PHOSPHONIUM SALT IONIC LIQUIDS

IN

ORGANIC SYNTHESIS

By

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ABSTRACT

A survey of substitution reactions conducted in a phosphonium bistriflimide ionic liquid is presented. The results demonstrate high selectivity favoring substitution over typically competitive elimination and solvolytic processes even when challenging secondary and tertiary electrophiles are employed. The first reports of Kornblum substitution reactions in an ionic liquid are described that proceed with very high chemoselectivity in favor of nitro over nitroso products and elimination side products. The structure- reactivity study indicates that these reactions proceed through a narrow spectrum of pathways ranging from straight S_N2 to a preassociation pathway along a saddle point that approaches the S_N1 limit. The lack of any basic entity in the phosphonium bistriflimide ionic liquid appears to prevent any potential base- mediated elimination reactions, which makes this a highly selective medium for use in general substitution reactions.

A general, high yielding procedure is described for the esterification of carboxylic acids through carboxylate alkylation in phosphonium salt ionic liquid. The product ester can be readily isolated using a standard extraction protocol or by direct solvent free-distillation allowing ionic liquid re-use. The reaction takes place at relatively low temperature in comparison to other processes reported in ionic liquids. Biologically important BZE (benzoate) esters were synthesized and a proposed solvolysis mechanism investigated in ionic liquids.

The Pd-mediated Buchwald-Hartwig amination reaction of aryl halides in phosphonium salt ionic liquid consisting of a trihexyl(tetradecyl)phosphonium cation with a range of anions has been investigated. A pronounced anionic effect was uncovered with the

reaction proceeding readily with weakly nucleophilic diarylamines only in the presence of non-coordinating anions. A mechanism is postulated to explain these results involving a rate limiting ligand exchange step that proceeds through a dissociative pathway.A novel non solvated crystal structure of tris(dibenzylideneacetone) palladium(0) in phosphonium salt ionic liquids is reported.. This research provided insights concerning the use of ionic liquids in palladium catalyzed Buchwald- Hartwig amination reaction. New synthetic methods were developed for the preparation of trialkyl (methyl) phosphonium ionic liquids, with this novel "green" protocol, the use of iodomethane is eliminated and oxidation of trialkyl phosphines can be reduced.

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This thesis is dedicated to my parents; **Sri. Anand Babu Cheekoori**, and **Smt. Vijaya Kumari Cheekoori,** whose love, prayers and faith in me have led me thus far and will continue to take me through the rest of my life.

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ABBREVATIONS

IL	ionic liquid
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et_3N	triethylamine
EtOAc	ethyl acetate
IR	infrared
HPLC	High Pressure Liquid Chromatography
HREIMS	High Resolution Electron Ionization Mass Spectroscopy
NMR	Nuclear Magnetic Resonance
$Pd_2(dba)_3$	palladium dibenzilidene acetone
PhMe	toluene
THF	tetrahydrofuran
THPC	trihexyl tetradecyl phosphonium chloride
DABCO	1,4-diazabicyclo[2.2.2]-octane
TLC	Thin Layer Chromatography
Emim	1-ethyl-3-methylimidazolium
bmim	1-butyl-3-methylimidazolium
mim	3-methylimidazolium
$scCO_2$	super critical carbon dioxide
triflimide	bis(trifluoromethylsulfonyl)imide
API	Active Pharmaceutical Ingredients
TON	turnover number

I Chapter 1: Introduction:

The discovery of ionic liquids has been met by scientists with much fascination and excitement, as is common with any new discovery. There has been a tremendous surge of research intensity over the last decade or so in an attempt to characterize and explain the properties, reactivity profile and potential applications associated with ionic liquids. Several definitions, along with vastly different characterizations have been assigned to these relatively newly discovered 'solvents'. A decade has passed between the initial article which was written by Michael Freemantle, describing ionic liquids by the much coveted title of 'designer solvents' in "Chemical and Engineering News"[1d].

Since the coining of the term 'ionic liquids' in this article its use has seen tremendous growth, with the term being used in over eight thousand articles pointing to the description of this new solvent class. This rush for a greater comprehension into the applicability of ionic liquids industrially and academically has been met with overwhelming vigour by scientists worldwide resulting in at least nine hundred patents to date[1].

There seems to be no limitation to the range of applications for which ionic liquids have been tested and consequently, the wide range of assigned utility resultantly discovered. The level of interest in fields other than chemistry has been equally matched accounting for the applications which ionic liquids have found, such as their use in sensors, solid state photocells and batteries, solar cells, lubricants, hydraulic cells and even in pharmaceuticals with their use being expanded outside the realm of just solvents[1].

These applications have been founded based on research targeted at finding the physical and chemical properties which can be associated with these novel and unique 'ionic liquids'. An insight into the properties has allowed the formulation of accepted definitions of ionic liquids to be defined as salts composed solely of ions with melting points below 100 °C, although more strict definitions have also been applied to account for other observed properties of ionic liquids. Depending on the specific need of the researcher, those associated properties would not only be investigated, but it has been discovered, that these properties which are desirable, can be isolated to a great degree of specificity to produce a desired result. This incredible ability of ionic liquids opens up the diverse scope of utility by which they could be used. Much like the designer capacity of popular brands, ionic liquids enjoy the same celebrity status over traditional solvents allowing for their new designation as 'designer solvents'[1].

Of significant concern not only in industry but also in academia is the need for cleaner technologies while there is the continual pursuit of finding alternatives to the use of damaging solvents. There are four strategies that can be implemented to fulfil this quest for cleaner methods by avoiding the excess use of organic solvents[1].

1. Developing new methods for solvent free synthesis.
2. Use of water as a solvent.
3. Use of supercritical fluids as solvents.
4. Use of ionic liquids as solvents.

Our intention was to explore the fourth strategy mentioned, which is the use of ionic liquids as solvents in organic synthesis. With the continual search for green alternatives on the horizon, ionic liquids possessing some fascinating properties and prospects have recently emerged. These liquids consist entirely of the ionic species and are often fluid at room temperature. Ionic liquids have an additional benefit since they are not, and do not emit any volatile organic compounds (VOC's), due to their having no measurable vapour pressure. Ionic liquids also have different and variable thermodynamic and kinetic properties for reactions carried out in them due to their tailorability, in contrast to conventional solvents. These ionic liquids therefore have the potential to give rise not only to greener technologies, but also lend towards the intrigue and fascination of new discovery.

The primary composition of an ionic liquid is that of ions. Its development dates back to 1914 with the synthesis of ethylammonium nitrate[2]. In 1948, researchers Wier and Hurley from the Rice Institute, Texas, were the first to develop chloroaluminate ions for the electroplating of aluminium as bath solutions [3]. It wasn't until the 1970's when Wilkes and Osteryoung rediscovered these ionic liquids and studied them for real applications [4]. This was the first time that liquid chloroaluminate melts were able to be prepared at room temperature. At this point in time, its role in electrochemical applications predominated the research of ionic liquids [5].

The use of tetra-n-hexylammonium benzoate as a solvent for kinetic and electrochemical applications was described by Swain et al. in 1967 [6]. This research was pointed in its significance since it was a quantitative determination of the ionization strength of the

ionic medium. The use of chloroaluminum melts (molten $AlCl_3$) as polar, non aqueous solvents for the investigation of transition metal complexes was started by Hussey and Seddon in the early 1980's [7].

For this investigation, complex chemistry experiments were done after studies dealing with electrochemical applications and research with relevant transition metal complexes. This work marked the beginning of ionic liquids ascending to the broader forum of mainstream chemistry research. Around the end of this decade, ionic liquids began being described as catalysts for organic synthesis and also as a new reaction media [1d]. For nucleophilic aromatic substitutions, phosphonium ionic liquids were being used successfully, while acidic ionic liquids with chloroaluminate ions were being effectively used as Friedel Craft's catalysts.

The term 'ionic liquid' has been coined to allow for its differentiation from that of classical molten salts. Unlike molten salts, which are very corrosive media with high melting points and high viscosity, ionic liquids have relatively low viscosity and are liquids at approximately less than 100 °C temperatures. Below 100 °C, the range of applications for liquid salts is much improved compared to molten salts. Also, below 100 °C, only liquid salts can be used for the substitution of conventional organic solvents as the reaction media, as some liquid salts have applications as reaction media below 100 °C, but cannot allow for solvent substitution. The basic physical properties of the ionic liquids that make them potential solvents for the organic synthesis are as follows [1]:

1. They are good solvents for both organic and inorganic materials; the reagents used can be brought to the same phase.

2. Ionic liquids are composed of non coordinating ions and have the capacity to be highly polar solvents.

3. Ionic liquids are immiscible with a number of organic solvents (hexane, toluene, etc.) and provide a non aqueous, polar media for two phase systems.

4. Ionic liquids are non volatile and the product can be distilled from the reaction mixture.

The quaternization of an amine or phosphine to form a cation is typically the key step in the synthesis of an ionic liquid. Depending upon the nature of the alkylating agent, salts with different anions are obtained by the quaternization reaction.

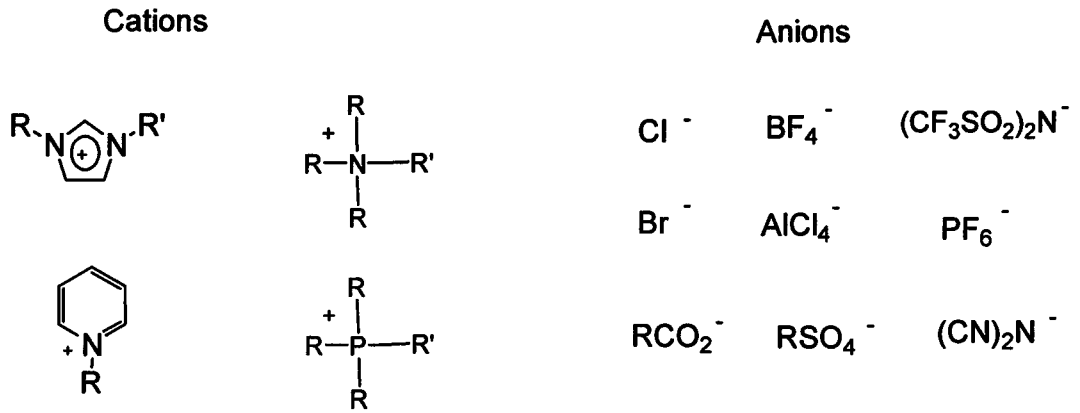
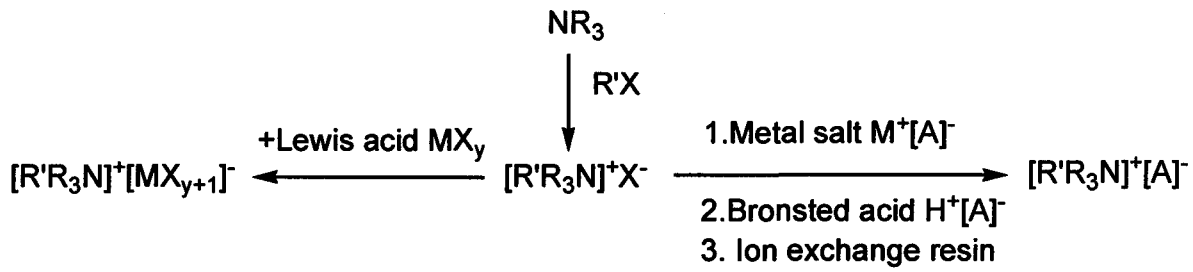


Figure 1.1: Commonly employed ionic liquid structural units.

For a large number of cation/anion combinations, melting points of less than 100 °C can be obtained. Whenever quaternization does not result in the desired anion being formed directly, a further ion-exchange step can be followed which would allow a variation of the anion to be formed [5].



Scheme 1.1: Synthesis paths for the preparation of ammonium salt ionic liquids

The most common method by which this is done is by substituting a halide ion for the desired anion. This can either be done by using a strong acid for the displacement of the halide or by the addition of metal salt or over an ion exchange column. One of the common solvent classifications is that of solvent polarity. This classification can be confusing and understood to a limited degree. The wide use of terms such as polarizabilities, dipole moments, dielectric constants and the description of solvents by terms such as polar, apolar and non polar have complex correlations. However, the most common and simplest definition to describe a polar solvent, which lends towards describing ionic liquids as being very polar solvents, is that they will stabilize dipolar or charged solutes through their dissolution [1b].

The ability of ionic liquid salts in the solvent phase to behave as a hydrogen bond donor and/or acceptor and the degree of localization of the charge on the anions helps to characterize ionic liquids as polar phases. There was not much difference in the delocalization of charge on the cation of the ammonium and phosphonium salts, which lends an important effect for other salts such as the imidazolium and pyridinium based ionic liquids. It was also interesting that the lipophilicity of the ionic liquids could be increased by increasing the chain length of the alkyl substituents on both the cations and

the anions. It is also noteworthy that by fluorinating the ionic liquid, the hydrogen bonding can be diminished [8].

One of the key and defining characteristics of an ionic liquid is its melting point. There exists a relationship between an ionic liquid's chemical and physical properties to the ionic liquid's structural features. Most importantly is the correlation between the melting point of the ionic liquid with its structure and chemical composition. For example the melting point of NaCl is 803 °C and KCl is 772 °C but an ionic liquid has melting points around 100 °C. The m.p. of 1, 3-dimethylimidazolium chloride is 125 °C and when methyl is substituted by an ethyl group the melting point of the ionic liquid drops to 87 °C. When this is substituted by n-butyl, the m.p. falls to 65 °C. Besides the cation, the anion also influences the melting point. For example, when we consider the 1-ethyl-3-methylimidazolium ion (emim) with different anions, the melting point decreases as there is an increase in the size of the anion in almost all cases. For example the melting point of [emim] Cl is 87 °C and [emim] NO_2 is 55 °C while the melting point of [emim] CF_3SO_3 is -9 °C [1].

The influence of the cation in these liquids can be clearly examined by taking a look at their different melting points. A melting point below 150 °C is observed and associated with chlorides which have such suitable organic cations, while alkali metal chlorides are characteristic for their high melting points.

The stability of the ionic liquids towards hydrolysis is imperative to their ability to be handled during work-up protocols, recycling and in-process chemistry. Ionic liquids that contain chloroaluminate anions are classified as labile towards hydrolysis and are very

hygroscopic. The ionic liquids which contain nitrate, benzenesulfonate and [bis(trifluoromethylsulfonly] amide ions are stable in water and air and may even be synthesized in water. The level of difficulty of using chloroaluminate melts increases when superacid protons are released when traces of water react in the chloroaluminate melts [1b].

Utilizing a non volatile reaction medium has tremendous advantages from an environmental perspective as well as from a safety perspective. Since ionic liquids have no vapour pressure, there is no loss of solvent through evaporation and no escape of dangerous volatiles into the environment thereby lending tremendously to this unique advantage of ionic liquids as a reaction medium.

The reduction in the use of catalysts is also a primary concern for developing green methods. Ionic liquids can allow for the catalysts to be isolated effectively from the product of a reaction and reused. This feature is due to the ability of ionic liquids to form a biphasic system or triphasic systems with water and/or organic solvents [9].

This biphasic system allows for the exploitation of the miscibility gap which exists between the product and the ionic catalyst phase allowing for catalyst recovery. This therefore allows for the desirable outcome of a reduction of the consumption of catalyst with respect to product formation as well as increasing the applications and total reactivity of the catalyst [9].

From another environmental perspective, the use of non volatile super acid ionic liquids for the substitution of HF is of tremendous significance and could be greatly promising if this gains impetus. Therefore, though the disposal and toxicity of ionic liquids have not

been completely explored, ionic liquids can definitely enjoy the classification of being a 'green solvent'.

I.1 Chloroaluminate(III) ionic liquids:

The acidic chloroaluminate (III) ionic liquid has chemical behaviour similar to that of a powerful Lewis acid [3]. Reactions which can be propagated by aluminium(III) chloride can be promoted by this ionic liquid but don't suffer from the adversity of low solubility as that experienced by aluminium(III)chloride in many solvents.

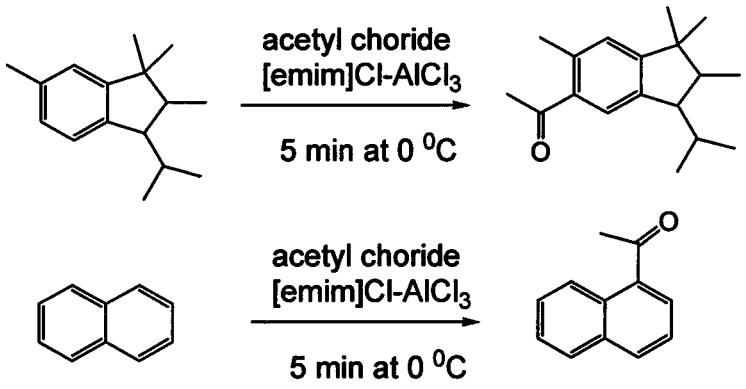
The toxic effects associated with halogenoaluminate (III) ionic liquids is still to be further explored. Ulceration as a result of skin irritation in the skin of rats is one observation which was made in a study on the effects of a basic [emim]Cl-$AlCl_3$ ionic liquid [10]. It was also observed that damage was done to the underlying cells as a result of penetration through the top layer of the skin by the toxic material, presumably $AlCl_3$. However, a reduction in the amount of damage which resulted could be minimized or reduced by washing the area of the skin in contact with the material with water. This demonstrated the potentially hazardous nature of halogenoaluminate (III) ionic liquids without providing treatment and safe exposure limits. The handling procedures which exist for the decomposition products as well as component materials would be similar for that of the ionic liquids since it can be assumed that the ionic liquids are of a similar hazardous nature.

A reaction that works with a high degree of efficiency in chloroaluminate(III) ionic liquids is the Friedel-Crafts reaction which is promoted by Lewis acids [11]. Because of the ease of preparation of binary mixtures of 1-methyl-3-ethylimidazolium chloride and

aluminium chloride (memCl-$AlCl_3$) combined with their favourable combination of physical properties, they are selected preferentially over other chloroaluminates for this reaction. These properties, which were highly favourable in this study, were not possessed by several other substituted imidazolium and pyridinium chlorides that form molten salts with aluminium chloride. Additionally, memCl-$AlCl_3$ is a convenient system for investigating Friedel-Crafts reactions since they have a wide range of Lewis acidity.

It is usual to have an inert solvent for the Friedel-Crafts alkylation and acylation reactions which are catalysed by dissolving $AlCl_3$ or by $AlCl_3$ suspension. A medium which acts as both a catalyst and a solvent at room temperature is provided for the Friedel-Crafts alkylation and acylation by the imidazolium chloroaluminate ionic liquid. $Al_2Cl_7^-$ is clearly identified as the catalyst for the Friedel-Crafts reaction since the Lewis acid species in the ionic liquid is well characterized, whereas just $AlCl_3$ on its own does not catalyze Friedel-Crafts reaction and requires two-fold loading for the promotion of the reaction

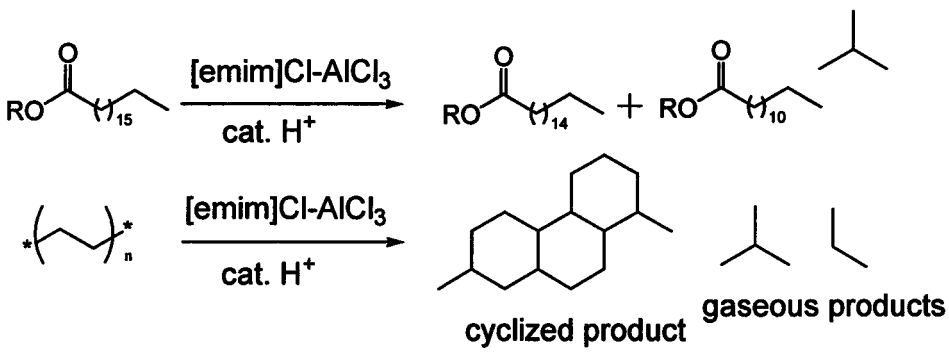
In these ionic liquids the Friedel-Crafts acylation reactions have been used for the synthesis of numerous important fragrance molecules of commercial importance on a large scale. For example in the ionic liquid [emim]Cl-$AlCl_3$, the compound Traseolide has been produced in high yields. The highest known selectivity of acylation of naphthalene in position 1 is achieved by the use of this ionic liquid.



Scheme 1.2: Acylation of 1,1,2,6-tetramethyl-3-isopropylindage and naphthalene in [emim]Cl-$AlCl_3$

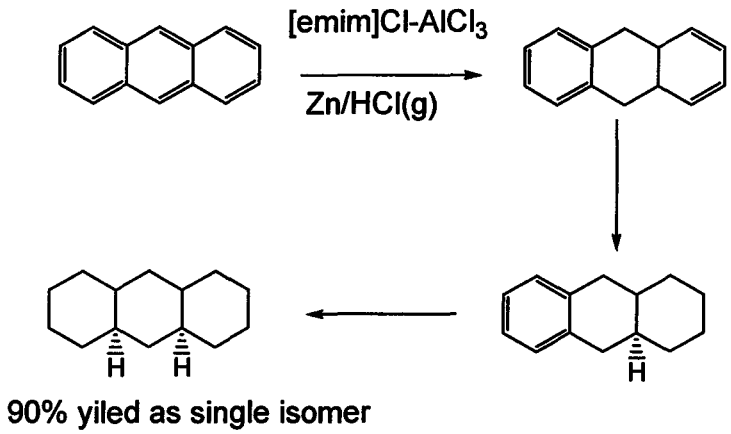
In acidic chloro(III)aluminate ionic liquids, cracking reactions occur with ease. The conversion of polyethylene into a mixture of gaseous alkenes and cyclic alkanes exemplifies this fact [12,13,14].

All other polyethylene reactions do not exhibit the formation of alkenes and aromatics in a significant concentration unlike this reaction in which the distribution of the products obtained is temperature dependent. Unlike conventional reactions which require extremely high temperatures in the range of 300 -1000 °C [15], reactions in ionic liquids occur at significantly lower temperatures, as low as 90 °C.



Scheme 1.3: Cracking reactions in ionic liquids.

Highly coloured paramagnetic solutions are formed when polycyclic aromatic hydrocarbons are dissolved in chloroaluminate (III) ionic liquid [16]. Selective hydrogenation of the aromatic compound results after a reducing agent such as an electropositive metal is added along with a proton source. An example of this is the reaction which occurs at ambient temperatures and pressures for the reduction of anthracene and pyrene to perhydro anthracene and perhydro pyrene [17]. In this reaction the product which is obtained is the most thermodynamically stable isomer which contrasts sharply with catalytic hydrogenation reactions in which an isomeric mixture of products results with high temperatures and pressures in the presence of an expensive platinum oxide catalyst [18].



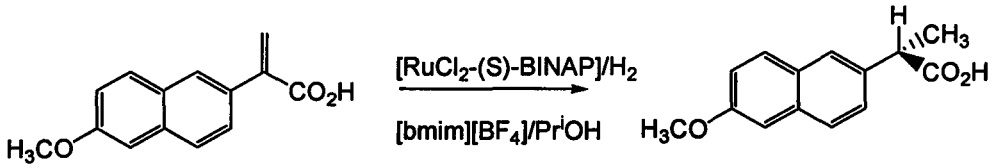
Scheme 1.4: Sequence in reduction of anthracene to perhydroanthracene

I.2 Neutral ionic liquids:

There are several disadvantages which chloroaluminate (III) ionic liquids suffer from, even though their use as catalysts and solvents are far superior. Their disadvantages include moisture sensitivity and difficulty in separating products containing heteroatoms from ionic liquids, without disrupting the liquid. Water stable ionic liquids are therefore of tremendous importance in order to further chemistry in ionic liquids and also for robustness of processes. With the exception of alkanes and alkylated aromatic compounds, many organic molecules readily dissolve in most ionic liquids though they have been found to be hydrophobic. One such ionic liquid which forms tri-phasic systems with alkanes and water is [bmin][PF_6]([bmin]=1-butyl-3-ethylimidazolium)[19]. This tri-phasic system can be compared to the use of the fluorous phase in some chemical processes and presents an important prospect for clean synthesis [20].

One key example to demonstrate this clean synthesis application is the exclusive ability of transition metals to dissolve in ionic liquids thereby allowing water or an organic solvent to be used for the removal of the products and the by-products from the ionic liquid. This application is of pivotal importance when using precious metal catalysts or expensive ligand catalysts which give the capability of recycling and reusing not only the ionic liquid, but also the catalyst. Since the ionic liquids also have no vapour pressure, volatile products can be removed from the catalyst and the ionic liquid by means of distillation. The extraction of naphthalene from [bmin][PF6] by using supercritical carbon dioxide demonstrates the ability for using supercritical solvents for extraction [21].

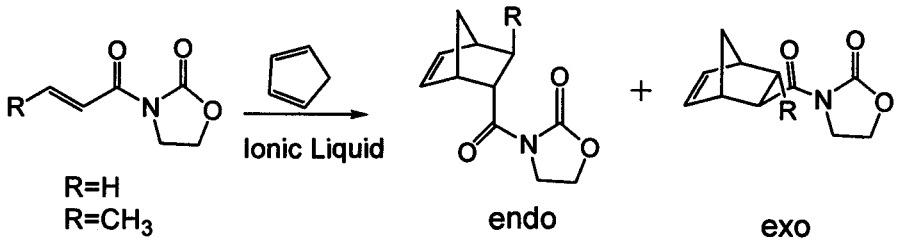
When reactions are being done in neutral ionic liquids like [bmim][PF_6], there is usually no requirement for any special conditions. For example, executing the reaction under an inert atmosphere or excluding water from the reaction is often unnecessary. The easy separation of the product from the ionic liquid as a result of this and the capacity to design the ionic liquid allows for such reactions to be tremendously simple. There has been much work done in studying the use of neutral ionic liquids as solvents for hydrogenation reactions. Of tremendous advantage for ionic liquids includes the fact that homogeneous transition metal catalysts can be used with great ease in separating the products of the reaction from the catalyst and ionic liquid. The complete hydrogenation of benzene rings along with the hydrogenation of cyclohexene are examples of this [22,23]. There have also been the asymmetric hydrogenation reactions as of recent. The synthesis of (S)-Naproxen in the ionic liquid [bmim][BF_4] [24].



Scheme 1.5: Asymmetric hydrogenation in ionic liquid.

Although the Diels-Alder reaction can be performed in water in an environmentally friendly way, moisture sensitive reagents cannot be used if water is used as a solvent. The first report on using ionic liquids as solvents for Diels-Alder reactions were reported by Jaeger's group using ethyl ammonium nitrate as the ionic liquid. Ethyl ammonium nitrate gave endo selectivity for the Diels-Alder reaction of cyclopentadiene with methyl acrylate and methyl vinyl ketone [25]. The reason behind this was the solvent effect of ionic

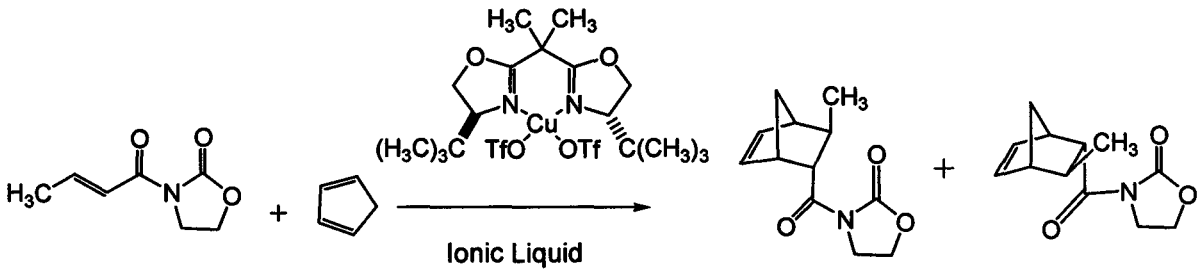
liquids on the reagents referred to as the "solvent cavity". But not until the late 90s was the stereoselective Diels-Alder reaction reported in ionic liquids. The ionic liquids used were hydrogen butyl imidazolium tetrafluoroborate (Hbuim) and 1, 3-dibutyl imidazolium tetrafluoroborate (dibuim). The reaction proceeds well in both ionic liquids with high stereo selectivities (*endo:exo*), but with poor yields. By addition of $ZnCl_2$ as the catalyst, the yields increased (scheme 1.6) [26].



Scheme 1.6: Diels-Alder reactions in ionic liquids.

When a chiral Lewis acid was used in the reaction, the stereochemical outcome of the reaction was tremendously increased compared to the traditional solvents.

For example, when the dienophile, in the presence of chiral catalyst was attempted and compared with DCM at room temperature, the reaction was fast in dbuim ionic liquid with high yields of 65% when compared to 4% in DCM. The endo:exo ratios were 93:7 in ionic liquids compared to 79:21 for the reaction in DCM, whereas the enantioselectivities were 96:4 in dbuim versus 76:24 in DCM (Scheme 1.7).

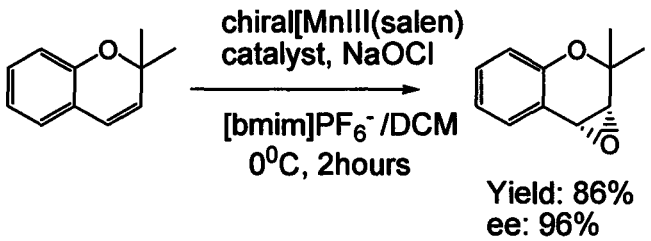


Solvent	endo:exo	Yield
DCM	79:21	4%
DiBuIm	93:7	65%

Scheme 1.7: Asymmetric Diels-Alder reactions in ionic liquid.

In conclusion, ionic liquids may give higher yields and greater selectivity when compared to the traditional solvents. Other advantages rest in the fact that in organic solvents the temperature of the reaction must be below 0 °C, whereas in ionic liquids the reaction proceeds at room temperature.

It has been shown by Song and Roh that using ionic liquids in selective oxidation reactions can be quite advantageous [27]. It was observed in the epoxidation of 2,2-dimethylchromene that with chiral salen complex (N,N'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] manganese (III) chloride in a mixture of [BMIM]PF_6 and DCM gave an 86% yield with 96% ee at 0 °C in 2hours (Scheme 1.8).



Scheme 1.8: Oxidation reactions in ionic liquid.

For this given reaction, when there was no ionic liquid, the exact conversion was obtained after 6 hours. The ee was 96% in either case. Whenever the ionic liquid solvent is utilized there is no need for any sort of catalyst modification and the catalyst is easily recycled. The ionic catalyst solution is recovered by washing the organic phase with water and subsequent extraction of the product with hexane. The recovered catalyst can be re-used. There is a decrease in the conversion to 53% compared to 83% yields after five recycles under identical conditions. The slow degradation of the [MnIII(salen)]complex can explain for the observed loss in activity.

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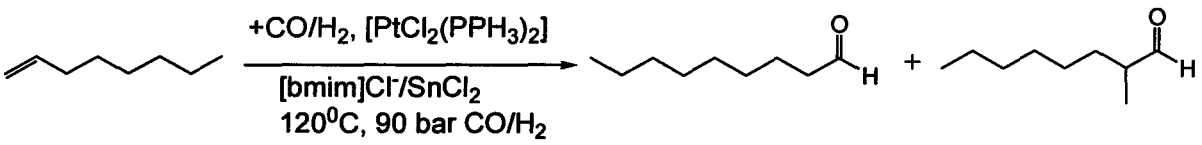
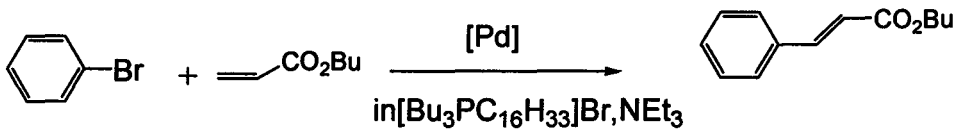
Tetraethyl ammonium trichloro stannate ionic liquid has been used in 1972 for the platinum catalyzed hydroformylation of ethene as reported by Parshall [28]. In this instance, the ionic liquid had quite a high melting point of 78 °C. The hydroformalation of 1-octene in [bmim]trichloro stannate occurred at room temperature with excellent n/iso selectivities. There was excellent activity of the Pt catalyst even though 1-octene was sparingly soluble in the ionic catalyst phase (Scheme 1.9) [29].



Scheme 1.9: Hydroformylations in ionic liquids

In this case, isolation of the product was very easy due to the biphasic nature of the reaction. The platinum catalyst did not leach into the product phase.

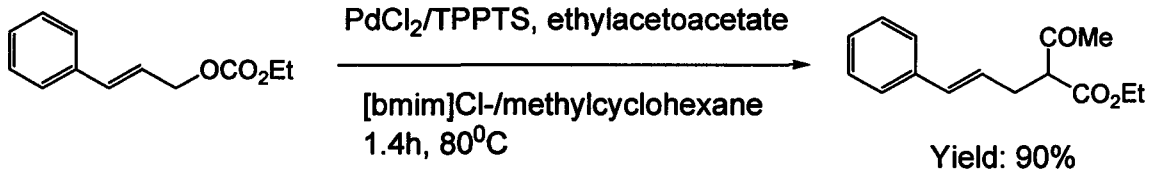
In 1996 Koffmann et al. initially published the utility of ionic liquids in palladium catalyzed Heck reactions as the reaction medium (scheme 1.10)[30]. There was a high yield of butyl-trans cinnamate by the reaction of bromobenzene with butyl acrylate in molten tetra alkyl ammonium and tetra alkyl phosphonium bromide salts (in our labs we use trihexyl(tetradecyl) phosphonium ionic liquids) .



Scheme 1.10: Heck reactions in ionic liquids.

The palladium catalyst experiences a stabilizing effect as a result of the use of the ionic liquid. With the complete conversion of the aromatic halide in almost all reactions, there was no precipitation of elemental palladium. Distillation of the non-volatile ionic liquids allowed for the isolation of the reaction products. There are clear advantages of using ionic liquids for applications in which organic solvents such as DMF would commonly be used. This is especially true in the case of the conversion of chloroarenes, which is of industrial importance.

One desirable way in which we could form C-C bonds in organic synthesis is by the nucleophilic, allylic substitution which is catalyzed by the Pd (0) complex. If ionic liquids are used in this reaction, it can be successfully executed. When 3-acetoxy-1,3-dipheyl prop-1-ene is reacted with dimethyl malonate in [bmim]BF_4 in a monophasic reaction, there is complete conversion after five hours keeping the reaction at 80 °C (Scheme 1.11)[31].

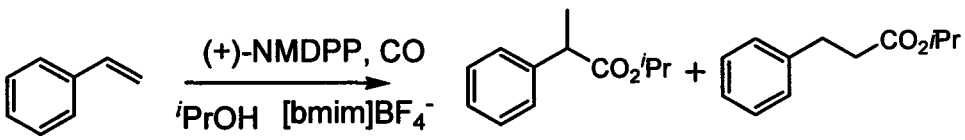


Scheme 1.11: Tsuji-Trost Coupling.

In this reaction, K_2CO_3 is used as the base, and the catalyst system is $Pd(OAc)_2PPh_3$. There was a 91% isolated yield of the desired coupling product.

Using the ionic liquid as a solvent in this reaction provides the unique advantage of generating the nucleophile in-situ. When ethyl cinnamyl carbonate is converted with ethyl acetoacetate in [bmim]Cl/methyl cyclo hexane via the biphasic Tsuji-Trost coupling reaction the result obtained was compared against the identical reaction in butyronitrile/water system. A tenfold enhancement in the catalytic activity was observed in the ionic liquid compared to the other system as a consequence of the more efficient solubility of the substrate molecules in the ionic liquid. There is also significant improvement of the selectivity in the ionic liquid reaction since the reaction of water as a nucleophile allows for the formation of cinnamyl alcohol while the formation of phosphonium salts is suppressed thereby being decreased in the ionic liquid [32].

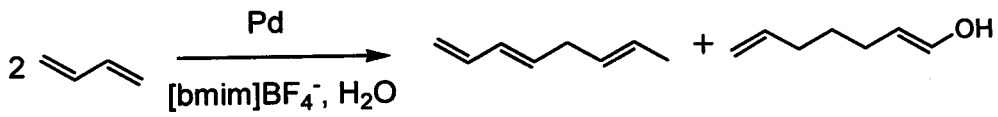
In a report which was published by Monteiro et al. [33], a biphasic example was specified in which styrene and its derivatives underwent a palladium catalyzed alkoxycarbonylation. For example, 2-isopropyl-phenyl propionate was produced in a system of [bmim] BF_4/cyclohexane, styrene, isopropyl alcohol and carbon monoxide. There was excellent regioselectivity and the product was produced in high yield when (+)-neomenthyldiphenylphosphane((+)-NMDPP) was used as the ligand. There was a very low asymmetric induction (ee < 5%) even though chiral phosphine ligands were used. As a consequence of bi-phasic reaction procedure, product isolation in the ionic liquid was easy to achieve (Scheme 1.12). The active palladium catalyst was observed to either partially or completely decompose following the complete conversion of the substrate.



Scheme 1.12: alkoxycarbonylations in ionic liquids.

Within [bmim] BF_4 ionic liquids, Dupont et al. [34] looked at the hydrodimerization/telomerization of 1, 3-butadiene with palladium (II) compounds (Scheme 1.13). They found that it was possible to obtain the telomere octa-2,7-dien-1-ol in addition to 1,3,6-octatriene. Utilizing CO_2 pressure, an increase in turnover frequency can be achieved for the activity of the catalyst to 204/hour compared to 118/hour. The ionic catalyst phase and the product phase can be induced by cooling the monophasic reaction system which is active at 70 °C to 5 °C,

This allows for the recovery of the ionic catalyst phase while allowing for a very simple isolation of the product.

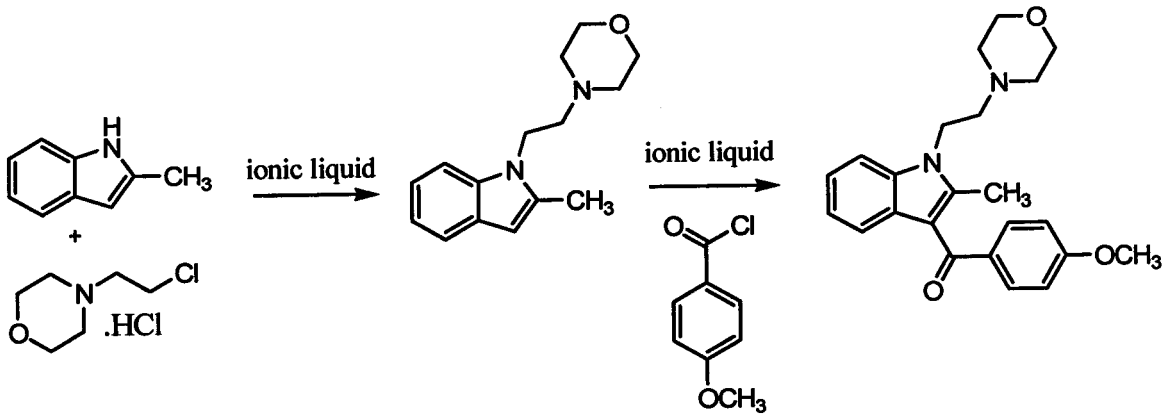


Scheme 1.13: Hydromerizations/Telomerizations in ionic liquid

I.3 The first total synthesis in ionic liquid:

Since Pravadoline combines both a nucleophilic displacement reaction and the Friedel-Crafts reaction, it was selected to showcase the complete synthesis of a pharmaceutical in an ionic liquid. By using potassium hydroxide as a base at room temperature, a 95% yield is obtained for the alkylation of 2-methylindole with 1-(*N*-morpholino)-2-cloroethane in ([bdmin][PF_6])[35].

If the ionic liquid 1-butyl-2,3-dimethylimidazolium hexafluorophosphate ([bdmin][PF_6]) is used, then the yield can be improved to 99%. The best results for the Friedel Crafts acylation from the nucleophilic displacement reaction can be obtained in ([bdmin][PF_6]) at 150 °C, though the reaction can be carried out in chloroaluminate (III) ionic liquid at 0 °C (Scheme 1.14).



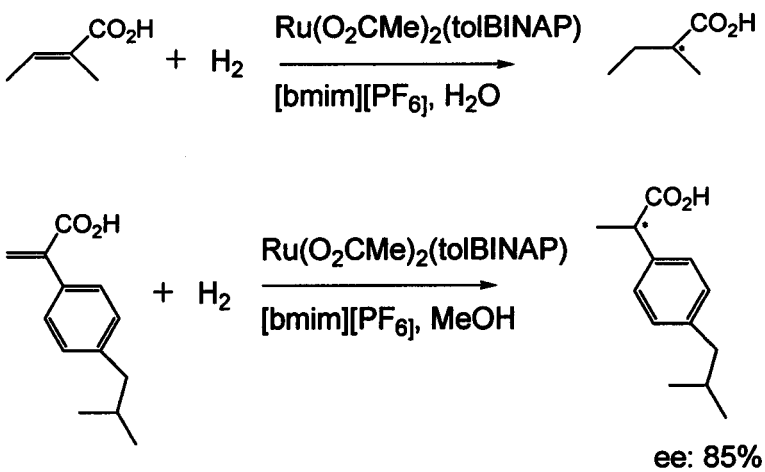
Scheme 1.14: Total synthesis of Pravadoline in ionic liquid.

The amount of waste that is produced from the Friedel Crafts reaction is minimal since no catalyst is utilized. Compared to the original synthesis which produces excessive amounts of acidic aluminium waste whilst utilizing dipolar aprotic solvents, only potassium chloride is produced as a waste product from the whole synthesis which uses KOH as the base in both steps of the reaction. The necessity for an inert atmosphere and strict anhydrous conditions are avoided when the ionic liquid process is used. Consequently, the entire process for the reaction sequence is more rapid, less laborious and more cost effective.

I.4 Applications of Room Temperature Ionic Liquid (IL)/Supercritical CO_2 systems:

In order to recover isolated reaction products from ionic liquids, often flammable molecular organic solvents and/or volatile solvents are employed. This may be seen to detract from the green credentials on the use of ionic liquids. Of tremendous need is an environmentally benign solvent that would be useful and efficient in isolating organic substrates. Much emphasis has recently been placed on the environmentally benign solvent; super critical carbon dioxide ($scCO_2$) for numerous applications, this solvent pairs easily with fairly polar ionic liquids as well as non volatile ionic liquids as a consequence of its high volatility and low polarity [36]. It is possible to have a two phase system utilizing $scCO_2$ and ionic liquids as a result of their difference in miscibility. This has been found to be useful for several applications. The ability by which this two phase system works is based on the insolubility of the ionic liquid in the $scCO_2$ and the solubility of the $scCO_2$ in the ionic liquid as a result of controlled pressure. By decreasing the viscosity of ionic liquids, the solubility of $scCO_2$ allows for mass transfer processes to

occur. The extraction of naphthalene from [bmim]PF_6 with $scCO_2$ allowed researchers to initially appreciate the benefit of combining these drastically different solvent types. In this reaction the ionic liquid was not only recovered but the aromatic hydro carbon was efficiently extracted by the $scCO_2$. Subsequently, the application of this was demonstrated by the effective recovery of a variety of polar and non-polar aliphatic and aromatic substrates from the ionic liquids using $scCO_2$ for the extraction. It was possible to establish a theoretical basis by which this phase behaviour of the IL/$scCO_2$ could be described. It was then possible for several metal catalyzed organic reactions to utilize this bi-phasic IL/$scCO_2$ system [37]. Using the [bmim][PF_6] IL the asymmetric hydrogenation of tiglic acid in the presence of $Ru(O_2CMe)_2$ ((R-*O*-tolBINAP) system produced an excellent yield and selectivity [38]. There was no contamination from the Ru complex or the ionic liquid during product extraction, in the pure form $scCO_2$. It was possible to re-use the catalyst for the subsequent four cycles without compromising the catalyst activity and obtaining the conversions of 99% combined with 90% ee. The authors also reported the asymmetric hydrogenation of isobutylatropic acid to give ibuprofen.

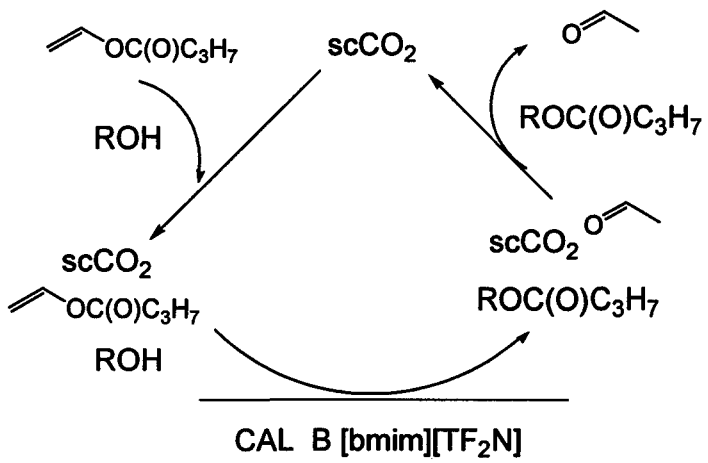


Scheme 1.15: Asymmetric hydrogenation reactions and product recovery in $scCO_2$

Of significant interest has been the possibility of using ionic liquids as a media for enzyme catalyzed transformations. When suspended in ionic liquids, lipases exhibit very high activity and stability. By looking at the kinetic resolution of 1-pheynylethanol there was an evident balance which existed between the identity of the enzyme and the structure of the ionic liquid. By extracting with hexane/propanal or by distillation it was possible to extract the products after the reactants were added to the IL/lipase mixture. Because of the level of ease of this approach it is very desirable. The major disadvantage of this method is the need for the product extraction to occur by using hazardous molecular solvents. There was also a significant decrease in the enzyme activity observed after the IL/enzyme mixture was re-used subsequent to isolating the product by distillation.

In a study of biocatalysts, the ionic liquids [emim]Tf_2N or mim[Tf_2N] was immobilized on glass wool while an aqueous solution of the biocatalyst *Candida Antarctica* lipase B (CALB) for transesterification, epoxidation reactions and ammoniolysis [39]. It was possible to recover the butyl butyrate product by the depressurization through a restrictor for the transesterification of vinyl butyrate and 1-butanol. In this process a twofold excess of the alcohol along with the solution of ester in hexane was injected into the $scCO_2$ system after which it was flowed over the immobilized IL/enzyme solution. The minimum amount of enzyme deactivation occurs for the lowest temperature as was found in reactions which were carried out at 15 MPa pressure and temperatures of 40, 50 and 100 °C. A aqueous enzyme solution was immobilized on Celite after being dissolved in emim[TF_2N] or bmim[Tf_2N] to produce the kinetic resolution of rac-1-phenyl ethanol. A

two fold excess of 1-phenyl ethanol in hexane alongside a solution of vinyl propionate was injected into $scCO_2$ and then flowed over an immobilize IL/enzyme layer. 99% ee of R-1-phenyl ethyl propionate was formed at 50 °C. For this reaction the activity was found to be eight times larger compared to when the enzyme was immobilized on Celite without the use of the ionic liquids. In the case of both ionic liquids, the efficiency was found to be identical[34]. The increase in activity can be attributed to the protection which the ionic liquid provided against enzyme denaturation-thermal and also through the action of the molecular organic solvent and $scCO_2$.



Scheme 1.16: Enzyme-catalyzed transesterification conducted in bmim[Tf_2N] and supercritical CO_2

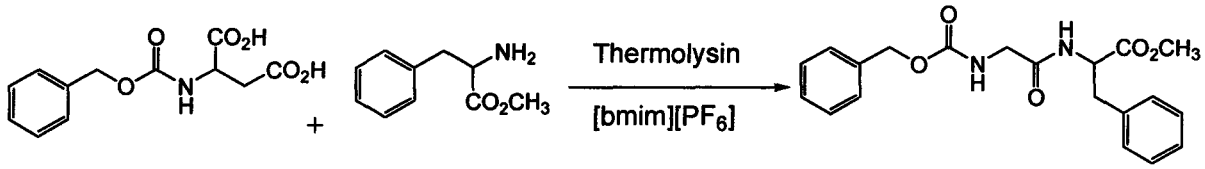
The biphasic/$scCO_2$ system would provide a very efficient system for future research. The solubility and stability of enzymatic catalysts or organo metallic catalysts in ionic liquids is a tremendous advantage of this system. The negligible solubility of these catalysts in $scCO_2$ is also advantageous. It is however true that the solubility of many organic reactants and products is fairly high in $scCO_2$. The simplicity of separation from

reaction products coupled with the non-toxic nature, recoverability and low costs provides the utilization of CO_2 with enormous advantages. In the past one of the difficulties associated with using ionic liquids included their lack of commercial availability. This factor is no longer an issue since the applications for ionic liquids are quite wide. In order to produce and handle $scCO_2$ and use these biphasic systems there is requirement for the equipment that is quite expensive. This is a significant disadvantage to these biphasic systems. The lack of information with regards to their toxicity and physiological effects forms the basis of yet another disadvantage use of ionic liquids.

I.5 Biocatalysis in ionic liquids:

The use of ionic liquids for bio catalytic applications in solvents is of tremendous intrigue. Though the amount of reported research in this field remains relatively small, the few results published have portrayed great promise. For the *Rhodococcus* 312 species, [bmim][PF6] was used as the solvent for the biphasic hydration of 1,3-dicyanobenzene [40]. Toluene solution has traditionally been used in this reaction. The known disadvantage of using toluene as the solvent for this reaction includes the fact that toluene has a very damaging effect on the cell wall of the biological catalyst. Other problems associated with the use of toluene include the fact that it is well known for its toxicity and flammability. When an ionic liquid system was used, the final yield was slightly higher than when the traditional H_2O-toluene solvent system was used. However, the initial rate of the reaction was lower in the ionic liquid compared to the toluene system. For this hydration reaction, the ionic liquid which was used is biphasic H_2O-[bmim][PF_6].

After the reaction was allowed to attain completion, it was observed that the H_2O-[bmim][PF_6] system allowed for much easier separation of the two phases. The cells exist in the aqueous phase while the ionic liquid holds the organic substrate effectively. By utilizing this [bmim][PF_6] system, it was subsequently found that it was possible to perform a liquid-liquid extraction of erythromycin. It was later reported in a successive research that [bmim][PF_6] could be further utilized for the application as a solvent for the formation of Z-aspartame from carbobenzoxy-L-aspartame and L-phenylalanine methyl ester hydrochloride by way of thermolysin catalysis [41].

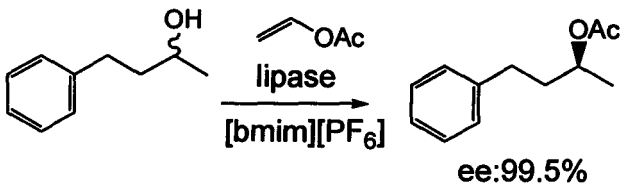


Scheme 1.17: Transesterification reactions in ionic liquids in bio catalysts.

The rates of reaction for 50 hour reactions conducted in conventional solvents such as ethyl acetate compared to that in ionic liquids is comparable. The main difference however lies in the capacity of the ionic liquid to be recycled for further reactions with no compromise to the rate of yield of the process. It is noteworthy that for this reaction, in order for there to be an increased efficiency, it was necessary to add a small (5%v/v) quantity of water. Another feature of this reaction is that at concentrations up to 3.2 mg/ml, the thermolysin dissolved in the ionic liquid but at this concentration, was absolutely inactive. From the observations thus made, it appeared as though the enzyme was only active when in suspension.

The kinetic resolution of rac-1-phenylethanol by transesterification with vinyl acetate was the initial example of enantioselective bio catalysis in ionic liquids [42]. In this study, nine lipase systems were screened against ten ionic liquids. One of the most popular solvents used in transesterification reactions is methyl tert-butyl ether (MTBE). The reactions in the ionic liquids were therefore compared to the reaction using MTBE. It was reposted that the patterns of reaction varied between these two systems. While [bmim][Tf_2N] gave some insight with regards to useful behaviour, it was difficult to assign a singular best ionic liquid for this process. For reactions in [bmim] there was a high conversion observed with two other enzyme systems. Of notable significance is that by using this ionic liquid system, it is possible to reuse the system at least three more times with little loss in activity (<10%) for every cycle. The products are easily removed by distillation under reduced pressure.

By using the ionic liquids [bmim][PF_6] and [bmim][BF_4] with four different alcohol substrates it was possible to investigate the transesterification reactions of vinyl acetate [43]. *Pseudomonas cepacia* and CaLB (immobilized) were the lipases which were employed in this study. The reactions which usually proceed in THF occurred with higher enantioselectivities. The hydrophobic [PF_6]- salt usually gives the best result. A preparative level of the PCL catalysed reaction of 1-chloro-3-phenoxypropan-2-ol with vinyl acetate. For this reaction, the acylated product was isolated in >99.5% ee in 42% yield. This reaction progressed to 46% completion and 50% completion after 48 hours of reaction, the latter producing substrates which were unreacted of >99.5% ee in 43% yield. Tf_2N], there was >98% ee values for five of the enzyme systems.



Scheme 1.18: Asymmetric transesterifcation in ionic liquids using bio catalysts.

Though there was almost no chiral resolution, when this reaction was compared with reactions utilizing organic solvents, it was found that the reactions, in which ionic liquids were used, occurred at a slightly slower rate. However, the ability of the ionic liquid and enzyme to be recycled and reused twice with absolutely no compromise or decrease in the reactivity or enantioselectivity for the CaLB catalysed reaction is of benefit. The range of reactions and enzymes which have been investigated within the area of biocatalysis utilizing ionic liquids is in its initial stages. Of primary concern based on the preliminary findings, is that the activity of enzymes remains the same in terms of their activity in ionic liquids. The greatest advantages which ionic liquids present at this stage of their investigations as biocatalysts is their capacity to be reduced and reused coupled with the enhancement which can be achieved in terms of enantioselectivity. However, though there are no drawbacks of using ionic liquids, rate enhancements using ionic liquids is yet to be shown. The salvation of enzymes in ionic liquids is an area of research that will likely emerge in the near future as a larger number of investigations are done.

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Chapter 2

Phosphonium Salts as Room-Temperature Ionic Liquids in Organic Synthesis [a]:

Applications of nitrogen-based, room-temperature ionic liquids,[1-5] including those based on ammonium, imidazolium or pyridinium cores, occupy centre stage in the rapidly expanding literature pertaining to their use as green solvents for a multitude of both catalytic and stoichiometric reactions.[6,7] This situation is due both to the historical development of the field of molten salts,[6] and the ready availability of quaternary nitrogen based systems. In contrast, few applications have been reported pertaining to the use of phosphonium salt ionic liquids, several of which are now readily available in industrially relevant quantities.[8] In this chapter the emphasis will be on the chemistry of phosphonium salts as benign and sustainable media for a variety of chemical transformations while highlighting some of their unique properties in comparison with nitrogen-based systems, and describing their interesting chemical reactivity uncovered so far.

Ionic liquids represent benign, non-volatile, non-flammable alternative media in which to conduct organic transformations. Ionic liquids not only allow the replacement of volatile, flammable and/or environmentally offensive solvents in chemical reactions; as the examples outlined below demonstrate, they offer a solution to the problem of sustainability in terms of catalyst recycling and re-use that is not achievable in conventional solvents. The inability to immediately recycle expensive transition metal

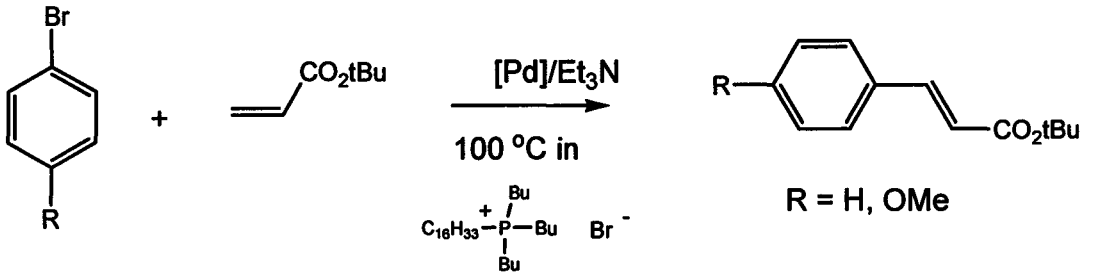
[a] Developed novel method for isolation of products from phosphonium salt ionic liquids.
Contribution to publication: 40%
McNulty, J.; Capretta, A.; Cheekoori, S.; Clyburne, J. A. C.; Robertson, A. J.; *Chim. Oggi.* **2004,** *22,* 13.

catalysts is a major disadvantage in conventional synthesis and also introduces a metals-disposal issue where catalyst recycling is not possible. In addition, the intrinsic nature of ionic liquids often allows for the discovery of unique and unusual chemical reactivity in comparison to standard solvents. Ionic liquids therefore not only represent a new medium in which to investigate interesting chemical reactivity, they also appear to meet the challenges of sustainability in the development of green chemical processes.[7a] Recently, the first multi-ton industrial process based on room-temperature ionic liquid technology involving an imidazolium salt as a hydrogen chloride scavenger was reported, representing a significant improvement in process chemistry.[7b] The rapid increase in this understanding regarding the scope of chemical reactivity possible with ionic liquids provides enlightenment from a fundamental viewpoint while benign and sustainable industrial applications are under development[7c] and those appearing on the near horizon continue to sharpen in focus.

Whereas phosphonium salts are well known as phase transfer agents and as precursors to ylides, the first reported use of a phosphonium salt as an ionic liquid solvent in a synthetic reaction was that of Kaufmann and co-workers.[9] In this work, the use of tributyl(hexadecyl) phosphonium bromide as a recyclable medium for the palladium mediated Heck coupling of aryl halides with acrylate esters was reported.[9] While these reactions proceeded without the use of an additive ligand, elevated temperatures (100 °C) were required and the process was most efficient only with more activated aryl halides, as shown in Scheme 2.1.

More recently,[10] use of trihexyl(tetradecyl)phosphonium chloride (Cyphos IL 101) has allowed for the successful Heck coupling of deactivated and more sterically-demanding aryl halides in high yields. For example, 2-iodotoluene was coupled with methyl acrylate in quantitative yield using Cyphos IL 101 in conjunction with $Pd(OAc)_2$ as a catalyst and sodium acetate as a base at only 50°C in two hours. In addition, the ionic liquid phase containing the active Pd-catalyst was shown to be still active and could be effectively re-used through several cycles.

Finally, it was shown that the counter anion to the trihexyl(tetradecyl)phosphonium cation plays a significant role on the outcome of the reaction. Screening of an ionic liquid library varying the anion revealed that the chloride and decanoate salts allowed for excellent turnover of the Heck catalytic cycle whereas other anions including hexafluorophosphate and tetrafluoroborate resulted in significantly lower isolated yields of the Heck-coupled product.



Scheme 2.1: Heck coupling in phosphonium salt ionic liquid.

The use of Cyphos IL 101 has been reported as a useful medium for the Suzuki cross coupling of aryl halides with boronic acid derivatives, Fig 2.1.[11] In this process, a soluble palladium catalyst precursor such as $Pd_2(dba)_3$-$CHCl_3$ was dissolved in the phosphonium salt producing a dark orange solution. This solution was stable in the absence of oxygen

for an extended period of time and could be recycled after solvent extraction of the biaryl reaction products. Two advantages of this system are the milder conditions under which the Suzuki coupling takes place in comparison to imidazolium based ionic liquids and the reactivity of economical, readily available aryl chlorides. The Suzuki cross-coupling reaction requires ultrasonic irradiation in order to proceed at 30 °C in imidazolium based ionic liquids.[12] In addition, inactive palladium black is deposited during the reaction resulting in lower yields of biaryl product even when reactive aryliodides and arylbromides are used and more so with aryl chlorides. The use of imidazolium-type ionic liquids in this manner is further compromised by the recent discovery that these solvents decompose when subject to ultrasonic irradiation.[13] The purely thermal Suzuki coupling reaction does not proceed with aryl chlorides even at 110 °C.[14] In contrast, the use of the phosphonium salt allows for very high conversion with aryl bromides and iodides and electron deficient chlorides at 50 to 70 °C. These results, in conjunction with the recyclability of the palladium catalyst/ionic liquid, indicate that the formation of a relatively stable and highly reactive palladium species occurs in this system. While *N*-heterocyclic carbene complexes have been identified as being formed *in situ* when palladium species are dissolved in imidazolium-based ionic liquids,[5] the nature of the active palladium catalyst formed in the phosphonium salt cases remains uncertain. Investigations are being done into the nature of the orange coloured active catalysts that is generated in Cyphos IL 101 with the expectiation that it will find application in other areas involving palladium catalysis given its succesful application in both Heck and Suzuki cross-coupling reactions.

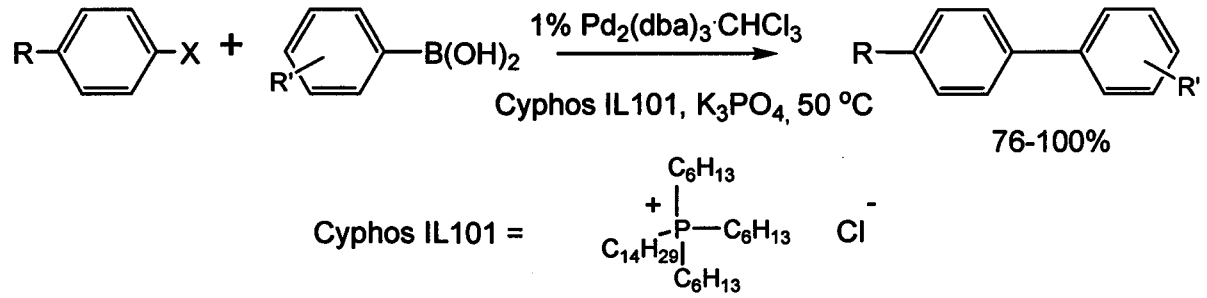


Fig 2.1: Suzuki cross-coupling in phosphonium salt ionic liquid.

In both the Heck and Suzuki processes described above, addition of hexane and water to the phosphonium salt reaction media results in the formation of a triphasic system. The non-polar organic product may be extracted into the hexane phase while salts can be removed in the aqueous phase. This leaves the active Pd catalyst in the ionic liquid phase that may be re-charged with reactants for further catalytic cycling. While continuous reactor designs can be contemplated, it was felt that there was the need to investigate the reaction work-up process chemistry in more detail, particularly for small to medium scale reactions, given the low solubility of many organic products in hexane or ether. Since the initial publications in this area, there has been numerous requests for guidance pertaining to situations where triphasic solutions were problematic or difficulty was encountered with the isolation of a polar organic product. Essentially two general protocols have been developed in the researchers' laboratories depending upon the overall polarity of the organic reaction product. In the first case, where the product is non-polar, partitioning between the ionic liquid, hexane and water is a very efficient process when Cyphos IL 101 containing the chloride counter anion is employed. For the other available phosphonium salts such as the decanoate and triflamide derivatives, partitioning between hexane and a 3:2 (v/v)

mixture of methanol:water was found to be most efficient. The methanol/water solution appears to lower the overall viscosity of the IL phase in these cases while still allowing clean, sharp definition of three phases as indicated in Figure 2.2. Extraction with several portions of hexane results in the removal of the non-polar organic product that generally contains only a trace of the IL. This may be quickly removed by filtration through a short silica-gel plug. In the case of a reaction producing a more polar organic product, it was found convenient to add dichloromethane and partition the ionic liquid-dichloromethane phase between the a 3:2 (v/v) solution of methanol:water. The precise ratio of water to methanol can be varied somewhat depending on the polarity of the organic product being separated. In general, the phosphonium salts are highly soluble in chlorinated solvents such as dichloromethane. Separation of the water/methanol phase and concentration allows recovery of the polar organic product cleanly. Removal of the dichloromethane from the ionic liquid phase allows re-use of the solvent and catalyst (if present).

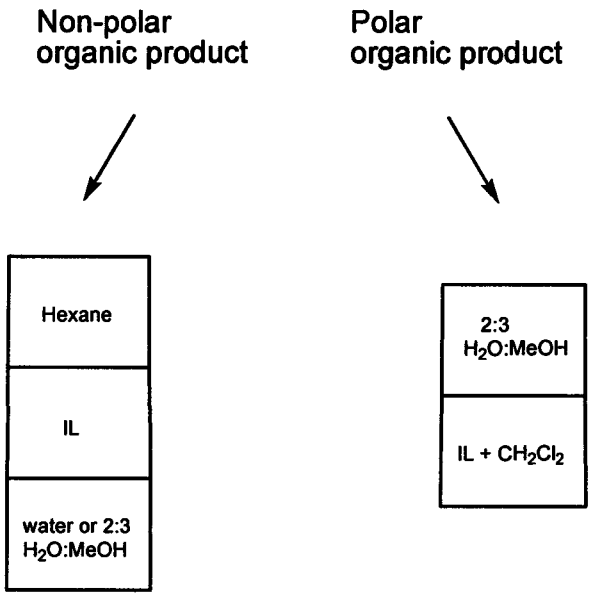
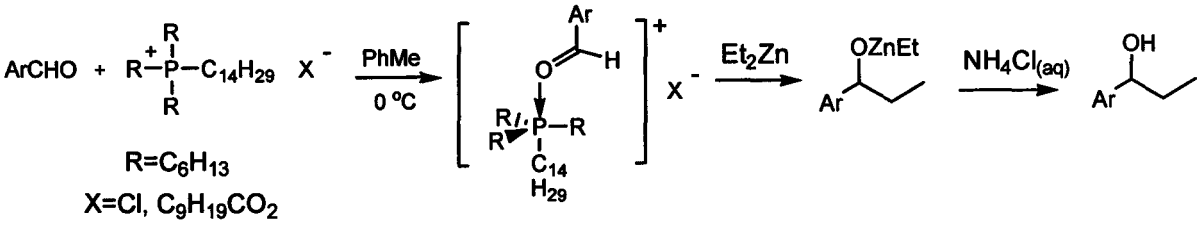


Fig 2. 2: Ionic liquid "Process Chemistry"

The above examples involving Heck and Suzuki cross-couplings illustrate how unique reactivity inherent in phosphonium salt ionic liquids in comparison to nitrogenous-based systems can be unravelled through reaction and phosphonium salt library screening. We have engaged in a more systematic attempt to evaluate potential unique applications for phosphonium salt ionic liquids. Our consideration of the nature and reactivity of phosphonium based salts as catalysts or media for organic reactions that differs from or are not possible with nitrogenous based systems led us to speculate that they might function as Lewis acids.[15] It was envisioned that due to the positive charge on phosphorus and the potential of phosphorus to adopt pentacoordinate structures, unlike nitrogen based counterparts, such species might be able to coordinate carbonyl compounds allowing activation of the carbonyl carbon towards nucleophilic addition,

as shown in Scheme 2.2. As a test case for this reaction, we investigated the addition of diethylzinc to benzaldehyde[16] in various phosphonium salt ionic liquids.



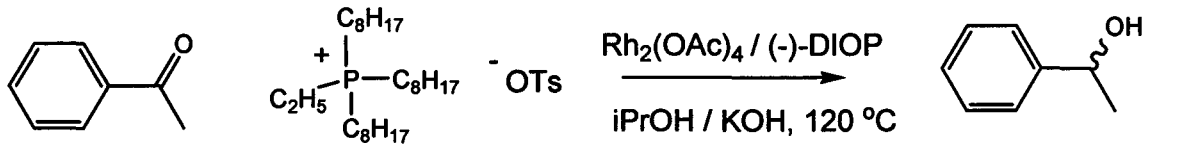
Scheme 2.2: Phosphonium salt mediated carbonyl activation.

The addition of two equivalents of diethylzinc to one equivalent of benzaldehyde in toluene at 0 °C results in less than 2% conversion after 24h. it was observed that addition of 0.1 equivalent (10 mol%) of Cyphos IL 101 results in a 47% isolated yield of the addition product under otherwise identical conditions. Through further screening of available phosphonium salt ionic liquids[8] it was determined that trihexyl(tetradecyl)phosphonium decanoate (Cyphos IL 103) was superior giving 71% isolated yield of the addition product.[17] Although it is not clear why the decanoate counterion is a superior catalyst, since this does not affect the solubility of the nucleophilic species (diethylzinc) present, phase transfer catalysis does not appear to be an option. It is more likely that the electronically diffuse decanoate couterion allows for further ion pair separation from the phosphonium ion resulting in increased Lewis acidity. It is clear that the phosphonium salt is able to function as a *mild* Lewis acid catalyst (7.1 turnovers) under these conditions. In comparison, the use of the stronger Lewis acid BCl_3-Me_2S resulted in 100% conversion in a matter of several minutes. A recent publication describing the addition of trimethylsilyl cyanide to aldehydes promoted by triphenyl(methyl) phosphonium iodide may also involve

Lewis acidic carbonyl activation, although no hypothesis as to the mode of action of the catalyst was forwarded.[18]

A wide variety of metal-mediated hydrogenation and hydroformylation processes have been reported in nitrogen-based room-temperature ionic liquids.[1,2,5] Phosphonium tosylates have now also been employed as solvents in the rhodium catalyzed hydroformylation of olefins.[19] In addition to the advantage of catalyst recovery demonstrated in this solvent-free process, these phosphonium salts exhibited unprecedented effects on the ratio of linear to branched aldehydes produced in the reaction. This ratio was also affected by the addition of further quantities of triphenylphosphine to the reaction. Given the need for hydroformylation catalysts that exhibit high regioselectivity this process may prove to be of great significance and appears to be worth a thorough investigation. The rhodium-catalyzed transfer hydrogenation of ketones has also been reported in phosphonium tosylates, as shown in scheme 2.3.[20] Once again the potential recyclability of the expensive catalyst and ability to perform the hydrogenation under solvent-free conditions alone are powerful incentives for the development of this process which does not appear to have been described in nitrogen-based ionic liquids. Although the yields reported could most likely be improved, these authors report that the addition of the chiral bidentate phosphine (-)-DIOP results in the transfer hydrogenation of acetophenone with 92% e.e. (50% yield), a remarkable result given that this reaction was performed at 120 °C. Lastly, it should be noted that the tetraalkyl phosphonium salt was required to effect asymmetric induction in this hydrogenation process as salts composed of phenyl and

p-tolyl phosphonium salts gave essentially racemic alcohols. Precisely how the phosphonium salt is involved in the asymmetric hydrogen transfer process in the presence of DIOP is a fascinating question to be explored.



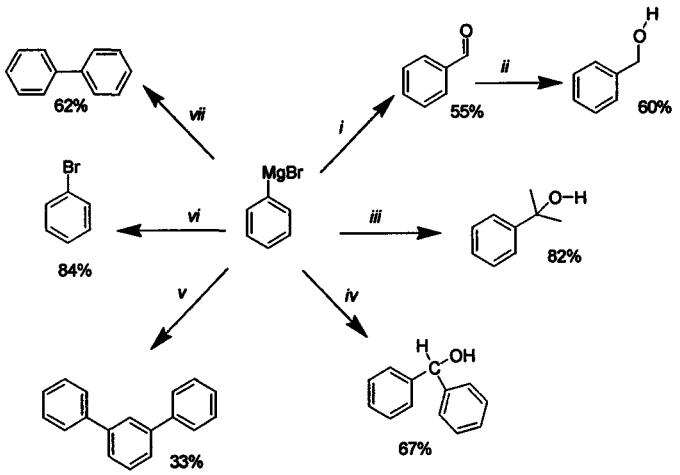
Scheme 2.3: Asymmetric transfer hydrogenation

The Diels-Alder reaction is another valuable transformation that has been actively investigated in a number of nitrogen-based ionic liquids[1,5,21] as well as phosphonium salts.[22,23] The reaction has been investigated with both acyclic 1,3-dienes as well as cyclopentadiene and with a variety of acrolein and acrylic acid dienophiles. Product yields are generally good to high in both the imidazolium and phosphonium salt ionic liquid classes, however *exo:endo* ratios are often low. High *endo* selectivities were achieved in imidazolium salt ionic liquid when an additional Lewis acid, such as ZnI_2 or BF_3-OEt_2, was added as a co-catalyst.[21] Asymmetric versions of the Diels-Alder reaction have also been attempted using chiral C_2-symmetrical imidazolium salts but have so far met with low asymmetric induction.[24] These results are of significance to the understanding of how such imidazolium ions activate the dienophile in the reaction and their possible involvement in the transition state. Overall, the advantages or disadvantages of using nitrogen-based or phosphonium salts as solvent for these cycloaddition reactions are not yet clear given the handful of publications that have appeared in the area. Considering the mild Lewis acidity of phosphonium salts

demonstrated in the catalysis of carbonyl addition reactions described above, there appears to be a lot of potential for phosphonium salts in general as both catalyst and solvent for the reaction and possibly chiral phosphonium salts in promoting asymmetric cyclo additions.

The stability of various reagents in phosphonium salt ionic liquids has also been explored. Recently it was found that *N*-heterocyclic carbenes (NHCs) are persistent in phosphonium based ILs, such as tetradecyl(trihexyl)phosphonium chloride.[25] NHCs are highly basic (pK_a = 22-24),[26] and it was surprising that deprotonation of the phosphonium ion to produce a phosphorane (ylide) did not occur. This observation led us to examine whether stronger bases would be *persistent* and *reactive* in phosphonium based IL's. One of the most basic classes of carbon centred nucleophiles is the Grignard reagents. These researchers first determined that anhydrous samples of tetradecyl(trihexyl)phosphonium chloride form clear solutions of low viscosity with commercially available PhMgBr in tetrahydrofuran.[27] These solutions showed no sign of degradation after two hours as demonstrated by ^{31}P NMR spectroscopy and subsequent reactivity studies. It was also found that complete removal of THF from the phosphonium ionic liquid/THF mixture results in the formation of biphenyl. The stability of such a strongly basic reagent in phosphonium salt media may be due to the steric hindrance of the CH's alpha to the phosphonium centre. We performed a survey of the reactivity of this solution of PhMgBr in tetradecyl(trihexyl)phosphonium chloride with standard electrophiles including addition to carbonyls, benzyne reactions, halogenation and coupling reactions, as

shown in scheme 2.4. All of these reactions were shown to provide the "normal" addition products confirming the integrity of the Grignard reagent in the phosphonium salt ionic liquid. The ability to perform these reactions in such a non-flammable, inert media offers considerable advantages over the use of traditional ether-type solvents.



Scheme 2.4:

Survey of reactions explored in tetradecyl(trihexyl)phosphonium chloride. Reaction conditions: i. DMF; ii. $NaBH_4$; iii. acetone; iv. benzaldehyde; v. 2,6-dibromo-iodobenzene vi. Br_2; vii. $CuCl_2$. Yields are reported as isolated yields.

In conclusion, it has been demonstrated that the investigation of phosphonium salt ionic liquids as solvents and catalysts can reveal advantages in comparison to nitrogenous based systems that may be rationally conceived or that may be unpredictable beforehand. It was demonstrated that an active, stable and recyclable palladium species is generated upon dissolution of $Pd_2(dba)_3$-$CHCl_3$ in phosphonium salt ionic liquids. This recyclable catalyst offers advantages in both Suzuki and Heck coupling processes and will no doubt find applications in other palladium-mediated processes as well. Furthermore, it has been

shown that phosphonium salts can act as mild Lewis acids resulting in the activation of carbonyl compounds toward nucleophilic addition reactions. The result with trihexyl(tetradecyl)phosphonium decanoate (Cyphos IL 103) is currently being extended to other carbonyl addition reactions, to cycloaddition reactions such as the Diels-Alder process and to the corresponding asymmetric variations. At present, it has been aptly demonstrated that phosphonium salts can furnish reactivity that is different or not generally accessible with the use of nitrogen based ionic liquids. Unusual effects on the regioselectivity of the hydroformylation reaction and an unprecedented catalytic asymmetric transfer hydrogenation protocol have also been demonstrated in phosphonium tosylate solvents, the latter process requiring a tetraalkyl phosphonium salt to achieve up to 92% ee.

The unique reactivity of phosphonium salt ionic liquids as both recyclable, solvent-free media for metal catalyzed reactions and as mild Lewis acids in catalytic processes represents fertile ground for research that is now in its infancy. The thermal stability[8] and demonstrated compatability of phosphonium salts IL's with a variety of reagents ranging from transition metal catalysts to Grignard reagents, demonstrates remarkable chemoselectivity. In addition, their intrinsic polarity and Lewis acidity bestows further versatility on this class of IL in organic synthesis. It can be postulated that the discovery and development of many new applications of this newer subset of ionic liquids will continue at an accelerated pace over the next few years leading to the introduction of benign and sustainable industrial processes.

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Chapter 3

3.1 Selective alkylations in phosphonium salt ionic liquids[b] :

Room temperature ionic liquids (ILs) have attracted considerable attention as novel reaction media over the last decade or so.[1,2] These liquids offer much potential for the development of cleaner, environmentally benign chemical reactions by virtue of their non-flammability, thermal stability, non-voaltility, and potential for reuse including the recycling of toxic and/or expensive transition metal catalysts. The ability of ILs to form three liquid phases, for example through the addition of water or methanol-water mixtures and a non-polar solvent such as hexane or ether, in conjunction with their thermal stability and non-volatility provides further advantages in chemical process control not possible with standard solvents. In addition, intrinsically novel chemical reactivities are being discovered in ILs at an increasing rate.[3] Not surprisingly, these materials have moved from being mere curiosites a decade or so ago to being commodity materials readily available on a large scale.[4] At least three large-scale industrial applications of Ils have been implemented and several others are in the pipeline.[5]

Structurally, most of the ILs that have been investigated thus far are based on quaternary nitrogen cores such as imidazolium, ammonium and pyridinium ions. In addition to the cationic core, further room exists for the engineering of these species through anionic exchange reactions allowing manipulation of properties such as density, viscosity, Lewis

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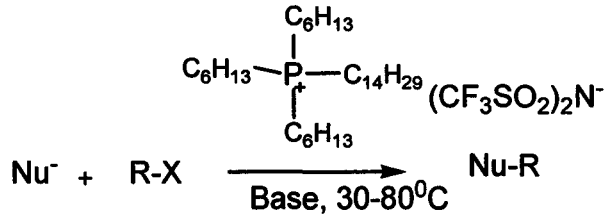
[b] Individually developed novel method and isolation protocol for Kornblum type substitution reactions in phosphonium salt ionic liquids.
Contribution to publication: 70%
McNulty, J.;Nair, J .J.; Cheekoori, S.; Larichev, V.; Capretta, A.; Robertson, A. J.;
Chem. Eur. J **2006**, *12*, 9314.

acidity, hydrophobicity, that allows tailoring the IL to the precise reaction or process of interest.[6] A pronounced example demonstrating the significant role of the anion on the solubility of carbohydrates in imidazolium ILs was recently described by Sheldon and co-workers.[7]



Scheme 3.1: General substitution reaction in phsophonium bistriflimide ionic liquid.

By far, most ionic liquids that have been investigated are based on imidazolium cations. Although beneficial in many cases, these cations have been shown to degrade under a variety of situations[8] including exposure to base and sonication. In addition, these aromatic rings have been shown to be susceptible to aromatic substitution reactions limiting their scope in electrophilic processes.[9] For these reasons we have been focussed on developing processes in phosphonium salt based ionic liquids over the last few years with the view of exploring their general scope and exploiting their unique capabilities. Examples include their use as recyclable media for Pd-mediated cross-coupling reactions,[10,11] and the ability of the quaternary phosphonium ion to expand valency and function as a mild Lewis acid.[12] Phosphonium-based IL's are very stable thermally,[13] stable towards strongly basic reagents including Grignard reagents,[14] and are not susceptible to aromatic substitution chemistry.[15] For these reasons they offer far greater scope than imidazolium ILs and deserve far more consideration as benign reaction media than has been afforded them in the Ils field thus far.

A further interesting consideration in the case of a standard phosphonium IL, such as trihexyl(tetradecyl)phosphonium bistriflamide, is the absence of a basic lone pair of electrons, or ease of formation a basic lone pair of electrons. It has been shown that ylid formation does not occur readily in the pure IL, even in the presence of strongly basic species such as a Grignard reagent.[14] It is well known that dipolar solvents such as DMF are valuable media for substitution reactions although proton shuttling and hence competitive elimination is clearly possible. Based on this consideration a working hypothesis in terms of simple substitution reactions involving secondary or tertiary elctrophiles capable of ionizing (halides, tosylates, mesylates etc) is that higher selectivity in favor of substitution over elimination is expected in the phosphonium salt. In other words, since the phosphonium salt IL cannot actively participate in proton removal from a carbonium ion intermediate and would have difficulty solvating a proton (E1 and E1cb processes unlikley) while the non-basic nature precludes the possibility of an E2 process, substitution reactions should be preffered. All of these indications led us to believe then that tetra-alkylphosphonium salt ILs carrying non-basic counter-anions should be ideal media for substitution reactions. Their polar and non Lewis-basic nature should allow high selectivity in favor of substitution over elimination. We recently reported the very general, mild alkylative esterification process in a phosphonium-based IL that offers wide scope in terms of substrate diversity, stereocontrol and processing advantages including solvent-free product isolation and IL recycling.[16] In this paper we report on the wider scope of general substitution reactions that are posssible in

phosphonium-based ILs in addition to the full details of the alylative esterification process.

To begin, we investigated the substitution reactions of challenging 2-phenylethyl electrophiles including the bromide, mesylate and tosylate derivatives with a range of nucleophiles in the phosphonium salt ionic liquid (trihexyl)tetradecyl-phosphonium bis-trilflamide.[17] The chosen nucleophiles ranged from the strongly nucleophilic azido and cyanide anions, a basic and nucleophilic primary amine to weakly nucleophilic phenolate, nitrite and carboxylate anions. The phenylethyl substrate was chosen as a challenging test-substrate since styrene formation is expected to occur in the event of any of the possible elimination pathways being operative and this would be readily detected. The results of this investigation are summarized in Table 3.1. The reaction with the strongly nucleophilc azido and cyanide anions with either the bromide, mesylate or tosylate derivatives proved to be straightforward, all reactions were complete at 80 °C in under 6 hours. The substitution product was obtained in about 90% isolated yield. These conversions are somewhat higher on average than similar nucleophilic displacements conducted in nitrogen-based ILs.[18]

Dibenzylamines are very useful protecting and modulating groups for primary amines, removable through hydrogenolysis.[19] It was thus desirable to attempt double alkylation of primary amines in the IL. The reaction with one half equivalent of benzylamine, provided the double alkyated amine in high yields with either the bromide or mesylate substrates (entries 3 and 6). These results demonstrate high selectivity for the substitution reaction, no styrene formation was detected under these conditions in the presence of basic amines

confirming the non-involvement of E2 or E1cb pathways. Recently, di-benzylation of primary amines with dibenzyl carbonate has been shown to be catalyzed with phosphonium salts catalysts.[20] In our case it is clear that the rate of substitution is much faster than any of the possibly elimination pathways.

We next extended the substitution reaction to weaker nucleophiles including nitrite, carboxylate and phenolate anions as indicated in Table 3.1, entries 9 to 14. Nitroalkanes are amongst the most versatile of intermediates in organic synthesis in view of their high reactivity and versatility in terms of subsequent conversions that are possible.[21] The Kornblum reaction involving the substitution reaction of an alkyl electrophile with potassium or sodium nitrite in a dipolar solvent such as DMF or DMSO is perhaps the most direct route to nitroalkanes.[22] Unfortunately, this route usually gives mixtures of nitro and nitroso substitution products through N-alklyation and O-alkyation of nitrite respectively.[23] We were thus delighted to find (entries 9-12) that the weakly nucleophilic nitrite anion participated in the reaction in the phosphonium salt IL without formation of any nitroso side product. We speculate that the high chemoselectivity in favor of nitro substitution may be manifest due to the oxyphilic-nature of the phosphonium ion. The substitution reaction proceeded with aliphatic primary bromides at 80 to 90 °C to give aliphatic nitro compounds in about 90 % isolated yield (entries 10 to 12). However, for the first time we noted some styrene formation in the case of the mechanistically challenging 2-phenyl bromoethane, but only if the reaction was performed at temperatures exceeding 85 °C. A respective 80% yield of the nitro substitution product (entry 9) was obtained when temperature was controlled at 80 °C. We speculate the

involvement of nitrite anion in an E1cb pathway as the weak bascicity of nitrite (and absence of any other appreciably basic species) appears to preclude an E2 pathway for this elimination. Although Kornblum substitution reactions have recently been described in aqueous media,[24] to the best of our knowledge, this is the first report of this type of substitution process in an ionic liquid. Finally, the reaction of a carboxylic acid and functionalized phenol with primary bromides proceeded without incident to give the ester and ether alkylation products in good isolated yields (entries 13 and 14).

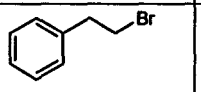
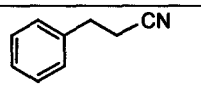
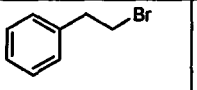
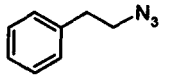
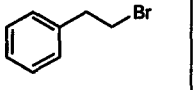
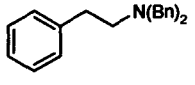
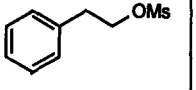
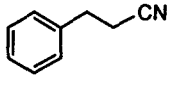
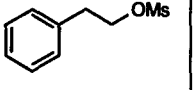
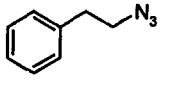
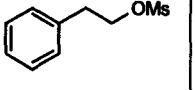
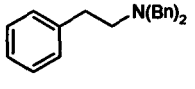
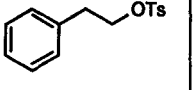
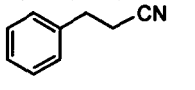
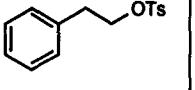
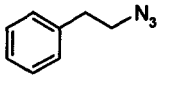
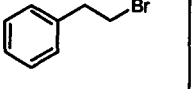
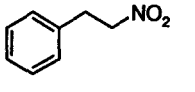
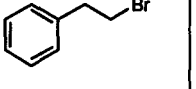
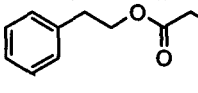
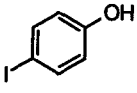
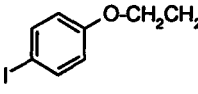
Entry	Electrophile	Nucleophile	T (C)	Product	Yield
1		KCN	80		92
2		NaN_3	80		95
3		Bn-NH_2	80		96
4		KCN	80		85
5		NaN_3	80		87
6		Bn-NH_2	80		90
7		KCN	80		84
8		NaN_3	80		86
9		$NaNO_2$	80		80
10	$CH_3(CH_2)_6$-Br	$NaNO_2$	90	$CH_3(CH_2)_6$-NO_2	90
11	$CH_3(CH_2)_7$-Br	$NaNO_2$	90	$CH_3(CH_2)_7$-NO_2	90
12	$CH_3(CH_2)_{11}$-Br	$NaNO_2$	90	$CH_3(CH_2)_{11}$-NO_2	90
13		$CH_3CH_2CO_2H$	75		98
14	$CH_3(CH_2)_3$-Br		70		87

Table 3.1: Alkylations in phosphonium salt ionic liquid.

3.2 General Procedure for alkylation

The electrophile (1 mmol) and nucleophile (2 mmol) were added to ionic liquid (0.5 g) followed by the addition of 0.3 ml water (for nitration, cyanylation and azidonation reactions only) and the reaction mixture stirred at 80 or 90 °C. After TLC indicated the reaction to be complete (in all cases within 6 hr), the mixture was poured into a methanol/water (3:2) solution (5 ml) and extracted with *n*-hexane (3 x 5 ml) which partitioned the ionic liquid layer between the upper organic and lower aqueous phases. The combined hexane fractions were dried over anhydrous Na_2SO_4, diluted with 5% ethyl acetate, filtered through a plug of silica gel and the solution concentrated under reduced pressure to give the alkylated product in 80-90% yield.

Table 3.1, entries 1, 4 and 7: 3-Phenylpropionitrile:^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.31 (5H, m), 2.96 (2H, t, *J*=7.4, 7.3 Hz), 2.62 (2H, t, *J*=7.4, 7.3 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 145.0, 135.7, 135.6, 135.1, 135.0, 134.1, 126.5, 38.4, 26.2. EIMS 70 eV, m/z (rel. int.): 131 [M^+] (20), 120 (100), 91 (50). HRMS (EI) calcd 131.0735 for C_9H_9N, found 131.0713. IR (NaCl) : 2927, 2248, 1604, 1559, 1456 cm^{-1}.

Table 3.1, entries 2, 5 and 8: 2-Phenyl azidoethane: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.29 (5H, m), 3.52 (2H, t, *J*=7.4, 7.3 Hz), 2.91 (2H, t, *J*=7.4, 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 145.0, 135.6, 135.5, 135.4, 135.3, 133.6, 59.3, 42.2. EIMS 70 eV, m/z (rel. int.): 147 [M^+] (5), 119 (42), 105 (32), 91 (100). HRMS (EI) calcd 147.0875 for $C_8H_9N_3$, found 147.0865. IR (NaCl): 2927, 2098, 1604, 1559, 1460 cm^{-1}.

Table 3.1, entries 3 and 6: Bis(2-phenylethyl) benzylamine: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.21 (15H, m), 3.76 (2H, s), 2.81 (8H, s). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 147.5, 147.4, 146.5, 135.7, 135.6, 135.5, 135.4, 135.3, 135.3, 135.2, 135.2, 135.1, 135.1, 135.0, 135.0, 133.7, 132.8, 132.7, 65.3, 62.5, 62.4, 40.4, 40.3. EIMS 70 eV, m/z (rel. int.): 315 [M^+] (5), 224 (10), 206 (10), 191 (40), 149 (5), 120 (8), 105 (100). HRMS (EI) calcd 315.4581 for $C_{23}H_{25}N$, found 315.4568. IR (NaCl): 2929, 1603, 1544, 1454, 503 cm^{-1}.

Table 3.1, entry 9: 2-Nitroethylbenzene: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.32 (t, J = 7.4 Hz, 2H), 4.61 (t, J = 7.4 Hz, 2H) δ 7.26 ppm (m, 5H); ^{13}C-NMR (50 MHz, CD_3OD) δ 33.4, 76.3, 127.4, 128.5, 128.9; MS-CI *m/z* 155.1, 152.06; Calculated Mass: 151.0633, Mass Observed: 151.0635. IR (neat) 2997, 2881, 1553, 1480, 1443, 1403, 1357 cm^{-1}

Table 3.1, entry 10: 1-Nitroheptane: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H); 1.27 (m, 8H), 2.00 (m,2H), δ 4.37 ppm (t, J = 7.0 Hz, 2H); ^{13}CNMR (50 MHz, $CDCl_3$) δ 14.1, 22.6, 28.1, 29.6, 31.5, 32.0, 75.6; MS-CI *m/z* 144; Calculated Mass: 144.1025, Mass observed : 144.1002. IR (neat) 2970, 2876, 2829, 1577, 1457, 1350 cm^{-1}.

Table 3.1, entry 11: 1-Nitrooctane: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.26 (m, 10H), 1.96 (m, 2H), 4.37 ppm (t, J = 7.0 Hz , 2H); ^{13}C-NMR (50 MHz, $CDCl^3$) δ 14.0, 22.5, 26.2, 27.4, 28.9, 29.6, 31.9, 75.7 ppm; HRMS-CI calcd 158.1181 for $C_8H_{17}NO_2$, found 158.1184; IR (neat) 2925, 2855, 1526, 1465, 1378 cm^{-1}.

Table 3.1, entry 12: 1-Nitrodocane: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.25 (m, 18H), 1.99 (m, 2H), 4.36 ppm (t, J = 7.0 Hz, 2H); ^{13}C-NMR (50 MHz,

$CDCl_3$) δ 14.1, 22.7, 26.2, 27.4, 28.8, 29.4, 29.5, 31.9, 34.1, 75.7 ppm; MS-CI *m/z* 214; Calculated Mass: 214.1807, Mass Observed: 214.1776. IR (neat) 2928, 2855, 1550, 1468, 1380 cm^{-1}.

Table 3.1, entry 14: 4-Iodo-butoxybenzene: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.96(t, *J* = 7.2 Hz, 3H); 1.45 (m, 2H), 1.75 (m, 2H), 3.90 (t, 2H), 6.65 (d, *J* = 6.9 Hz 2H), δ 7.52 ppm (d, *J* = 6.9 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 13.8, 19.2, 31.2, 67.8, 82.4, 116.9, 138.1, 159.0. MS-CI *m/z* 276; 219; Calculated Mass: 276.0011, Mass Observed: 276.0016. IR (neat) 2960, 2873, 1587, 1572, 1486, 1474, 1283, 1245, 1174, 1000, 819 cm^{-1}.

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Chapter 4

4.1 A mild esterification process in phosphonium salt ionic liquid[c] :

Esterification [1] is one of the most fundamental reactions in synthetic chemistry extensively employed for the protection and further manipulation of the carboxylic acid functional group. Esterification processes are widespread in the industrial synthesis of a variety of end-products such as fragrances, monomers, and plasticizers, many of which are classified as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemical targets are prominent, and often require more stringent coupling protocols to achieve the desired chemo and stereo-selectivity. In the latter case, situations that proceed with a high degree of inversion of configuration such as in the Mitsunobu reaction are specially sought. In view of their importance, esterification protocols should occupy a prominent place in the desire for advanced benign and sustainable chemical technologies into industrial process development [2]. The use of room temperature ionic liquids (ILs) as solvents for chemical reactions offer several advantages from this environmental perspective [3,4].

Several general, conventional methods are available for the esterification reaction of a carboxylic acid and alcohol often involving the use of stoichiometric activators and condensation or coupling reagents. The use of both imidazolium, a pyridinium based ILs in conjunction with the use of orthoacetate [5] and sulfuric acid catalyzed esterification [6]

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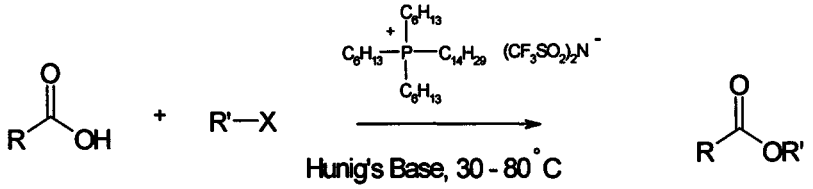
[c] Individually developed novel method and isolation protocol for esterification in phosphonium salt ionic liquids.
Contribution to publication: 70%
McNulty, J.; Cheekoori, S., Nair, J.J.; Capretta, A.; Robertson, A.J., *Tetrahedron Lett*, **2005**, 46, 3641;

have been recently reported. Consideration of the methods available and the nature of phosphonium salt IL's led us to believe that the alkylation of carbolxylic acid salts with alkyl electrophiles would be feasible in such media. Savelli and co-workers have recently reported on the use of imidazolaium ILs in the coupling of active alkylating agents with carboxylates [7].

The carboxylate alkylation reaction performed in conventional solvents outlined in Scheme 4.1 was first generalized by Mehta [8] based on the previous findings of Alvarez and Watt [9], and Raphel et al [10].

In general, this reaction takes place through the addition of an alkylating agent to the carboxylic acid in a dipolar aprotic solvent in the presence of a base. The reaction is most general for the preparation of methyl esters where iodomethane or dimethylsulfate is employed as alkylating agents [11]. Several variants of the processes have been shown to proceed with inversion of configuration where chiral secondary electrophiles are employed indicating the involvement of a general S_N2 process[12]. As such the reaction is sensitive to steric effects although cases involving separately, hindered acids, and teritiary alkyl halides have been reported.



Scheme 4.1: Esterification in Trihexyl (tetradecyl) phosphonium salt Ionic Liquids

In the present work, we began with an investigation of the reaction of propanoic acid with 1-bromooctane in the phosphonium salt ionic liquid (trihexyl)tetradecyl-phosphonium bis-trilflamide, containing diisopropylethyl amine (Hunig's base). From preliminary experiments a general process quickly evolved. The carboxylic acid (1.0 mmol) was dissolved in the ionic liquid at a concentration of 0.5M. To this was added the alkylbromide (2.0 mmol) and Hunig's base (2.0 mmol) and the mixture warmed to between 30 and 80 °C. The overall results from our study are reported in Table 4.1. Simple aliphatic and aromatic acids react with primary bromides to give the corresponding esters in high isolated yield. Entries 2 and 4 indicate that no competitive E2-type elimination occurs with the alkyl halide under these conditions. Electronic effects were investigated with a series of 4-substituted benzoic acids reacting with alkyl bromides (entries 5 to 13) and determined to be minor. Both primary and secondary bromides react without difficulty and even problematic[13] cyclohexyl halides such as bromocyclohexane provided a respectable yield of the cyclohexyl ester (entry 7). Steric effects were shown to be only slightly detrimental to the efficiency of the process (entries 14 to 17). Even the hindered 2,4,6-trimethylbenzoic acid reacted with the secondary halide 2-bromopropane to provide the ester in 85% isolated yield.[37] ß-Aryl acids, for which we have observed decarboxylation under Fischer esterification conditions, also reacted readily with primary and secondary bromides to give high yields of the ester (entries 18 and 19). In addition to bromides, we were delighted to find that tosylates readily entered into the reaction under similar conditions including the cyclic, secondary cyclohexyl-*p*-toluenesulfonate (entries 20 and 21). The use of potassium carbonate as

base was shown to be an effective substitute for Hunig's base (entry 22). The di-carboxylic acid phthalic acid also reacted with four equivalents of bromobutane to give the dibutyl ester in 86% isolated yield (entry 23). Dialkyl phthalates are HPV chemicals utilized both as insect repellents and plasticizers. The reaction was also successful using *t*-butyl bromide as electrophile (entry 24). The conventional esterification reaction generally fails[14] with tertiary halides when conducted in standard solvents. In one report, it was successful using a large excess (48 equivalents) of *t*-butyl bromide.[34] Using the standard IL protocol outlined here and employing only two equivalents of t-butyl bromide, an unoptimized 70% yield of the t-butyl-4-nitrobenzoate ester was realised. The success of this result with only two equivalents of t-butyl bromide indicates that little E1-type elimination takes place in the IL under these conditions. As expected, the reaction is slower when chloroalkanes are employed and particularly sluggish with secondary chloroalkanes.

For example, 2- bromohexane reacted with 4-nitrobenzoic acid (50°C, 3h) in the presence of Hunig's base to give the ester (81% yield) while under the same conditions 2-chlorohexane gave 12% conversion.

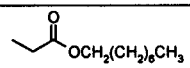
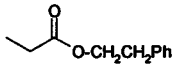
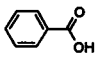
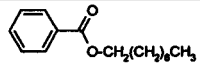
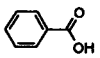
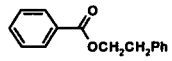
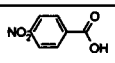
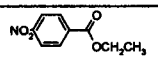
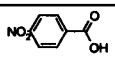
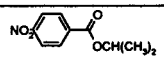
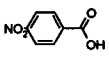
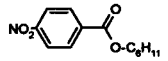
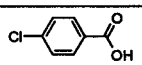
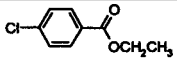
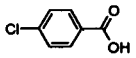
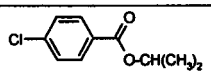
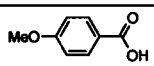
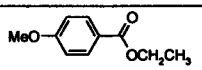
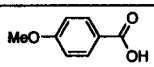
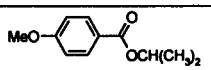
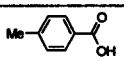
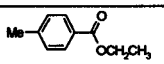
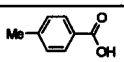
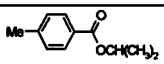
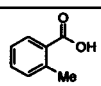
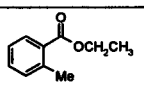
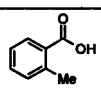
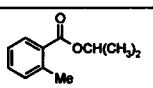
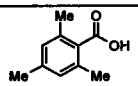
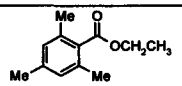
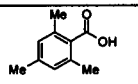
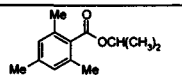
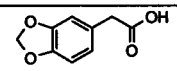
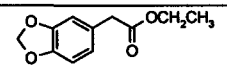
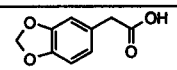
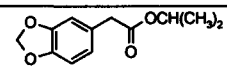
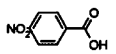
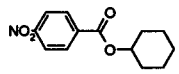
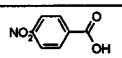
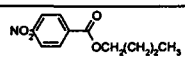
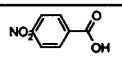
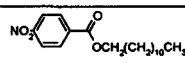
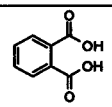
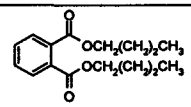
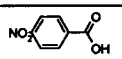
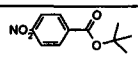
Entry	R-CO_2H	Alkyl-Agent	T (C)	Product	Yield
1		1-bromooctane	75		98
2		2-phenyl-1-bromoethane	75		98
3		1-bromooctane	75		98
4		2-phenyl-1-bromoethane	75		98
5		Bromoethane	30		95
6		2-bromopropane	40		94
7		Bromocyclohexane	70		80
8		Bromoethane	30		94
9		2-bromopropane	40		93
10		Bromoethane	30		94
11		2-bromopropane	40		92
12		Bromoethane	30		91
13		2-bromopropane	40		92
14		Bromoethane	30		89
15		2-bromopropane	40		88

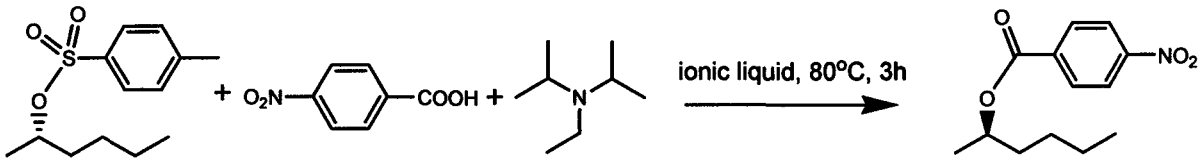
Table 4.1: Esterification in ionic liquids.

Table 4.1: Esterification in ionic liquids:

16		Bromoethane	30		86
17		2-bromopropane	40		85
18		Bromoethane	30		95
19		2-bromopropane	40		93
20		cyclohexyl-*p*-tosylate	80		77
21		1-butyl-*p*- tosylate	80		95
22		bromododecane	80		98*
23		1-bromobutane	80		86
24		*t*-butyl bromide	50		70

We next investigated the stereochemical outcome of the alkylative esterification using the tosylate derived from (2*S*)-hexanol in reaction with 4-nitrobenzoic acid, Scheme 4.2. The reaction proceeded in the bis-triflamide IL in the presence of Hunig's base at 80 °C for 3h to give the ester in 82% isolated yield with a high degree of inversion of stereochemistry (e.r. 4:96, retention:inversion). The reaction was slower at 50 °C but gave complete (>99%) inversion of configuration. These results are consistent with the involvment of essentially an S_N2-type process with some ionization (and racemization) occuring at

higher temperatures. This result is in agreement with earlier work carried out in conventional solvents.[10]



Scheme 4.2: Alkylative eseterification with (2S)-2-hexyl tosylate.

Finally, while the use of ionic liquid solvents offers many advantages over conventional solvents, one drawback is that often a volatile organic solvent is employed in the work-up or product isolation,[15] partially defeating the original purpose.[16] Having demonstrated the wide scope of the alkylative esterification method, we next investigated the possibility of a solvent-free product isolation and IL recycling protocol based on the low volatility of phosphonium salt ILs. To this end, the synthesis of the widely used commodity ester butyl acetate was investigated. The reaction of acetic acid (1.10 eq) and potassium carbonate (1.10 eq) with butyl bromide (1.0 eq) was conducted in the phosphonium salt IL under slightly modified conditions. Thin-layer chromatography indicated clean conversion to the ester which was isolated in 74% yield by direct distillation from the reaction mixture. The ionic liquid phase was washed with water, dried and a second esterification cycle conducted. Butyl acetate was isolated in 85% yield after the second cycle.

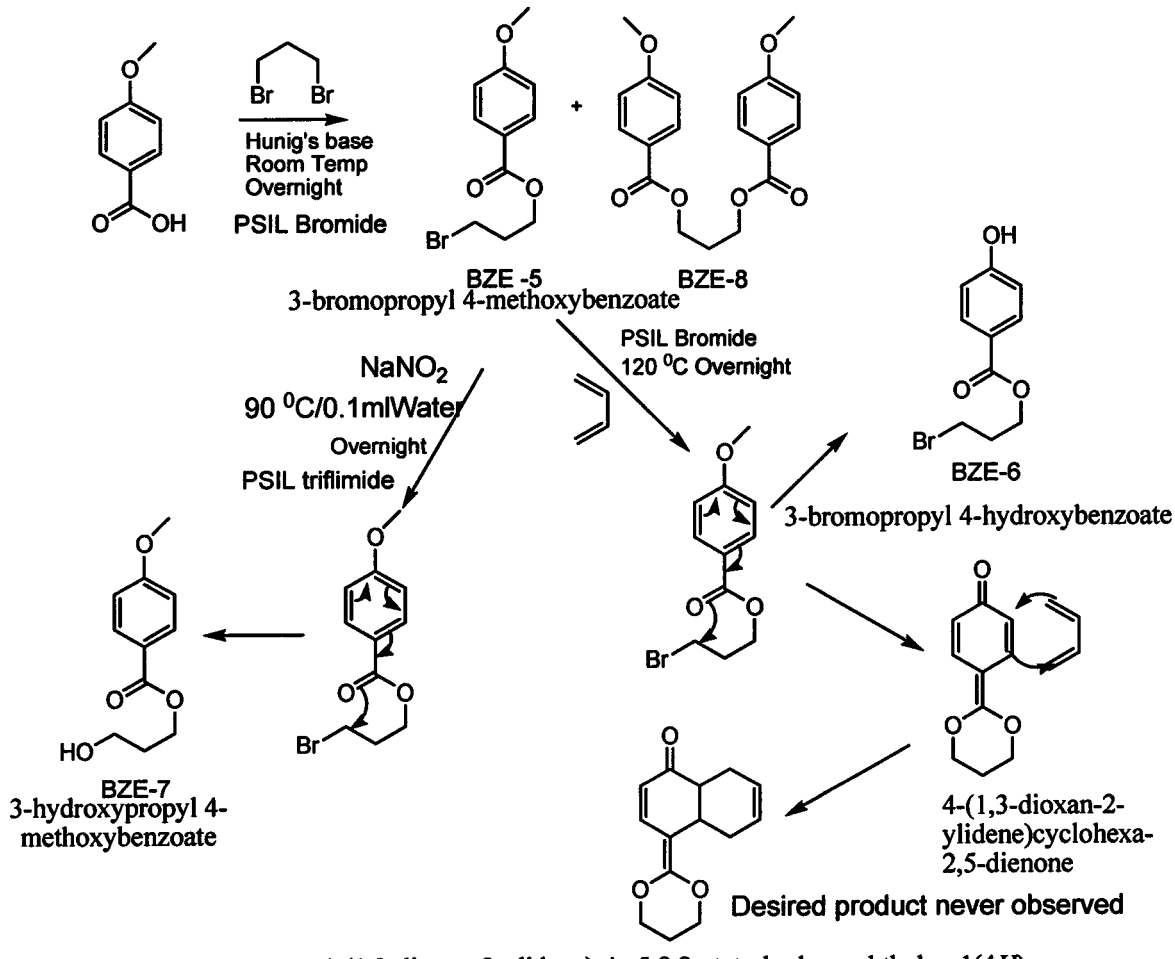
The high stereochemical inversion and generality demonstrated by this carboxylate alkylation process in the phosphonium salt IL using primary, secondary and tertiary bromides or primary and secondary tosylates with a large variety of hindered, electron

rich or electron deficient acids makes this process attractive from the structural viewpoint. No elimination from the electrophile or α–alkylation of any acid/ester has been observed in any of the cases described. The product ester can be readily isolated from these phosphonium salt ILs using either a standard extraction protocol,[38] or by direct, solvent-free distillation allowing IL re-use. Finally, the reaction takes place at a relatively low temperature in comparison to other processes reported in IL's.[6] Given these desirable features, we believe that this esterification protocol is a prime candidate for the development of economically viable, benign industrial processes for both HPV ester synthesis as well as lower volume, high-value targets.

4.2 Unusual reactions in esterification, novel synthesis of BZE esters:

During our research on esterification reactions in phosphonium salt ionic liquids, 3-bromopropyl 4-methoxybenzoate was synthesized. A Diels-Alder reaction with 1,3-butadiene sulphone was then tried in order to trap the intermediate 4-(1,3-dioxan-2-ylidene) cyclohexa-2,5-dienone as proposed in scheme 4.3, however, there was no product; 4-(1,3-dioxan-2-ylidene)-4a,5,8,8a-tetrahydronapthalen-1(4*H*)-one, as proposed. Instead 3-bromopropyl 4-hydroxybenzoate was observed. Although the reaction was not successful it was confirmed through the results that the intermediate 4-(1,3-dioxan-2-ylidene) cyclohexa-2,5-dienone was formed. This was deduced since a Kornblum type of reaction was experimented with in order to nitrate 3-bromopropyl 4-methoxybenzoate. It was thus observed that 3-hydroxypropyl 4-methoxybenzoate was formed instead of 3-nitropropyl 4-methoxybenzoate. The reason for the formation of the hydrolyzed product instead of the expected nitro substituted product could be as a result of the resonance

effect from the aromatic ring via the carbonyl group into the σ* orbital of the bromo-substituted carbon from 3-bromopropyl 4-methoxybenzoate resulting in the major solvolysis product rather than the nitro substituted product.



Scheme 4.3: Synthesis of BZE ester series.

4.3 General Procedure for esterification reactions (i.e. Table 4.1). Table 4.1, Entry 5: Ethyl 4-bromobenzoate. 4-Nitrobenzoic acid (40 mg, 0.24 mmol), Hunig's base (0.48 mmol) and tetradecyl(trihexyl) phosphonium bistriflimide ionic liquid (0.50 g) were

stirred at 30 °C under Ar for 10 min whereupon bromoethane (0.48 mmol) was added. After TLC indicated the reaction to be complete (in all cases within 12h), the reaction mixture was poured into a methanol/water (3:2) solution (5ml) and extracted with n-hexane (3x5 mL). The hexane fractions were dried over anhydrous sodium sulfate, diluted with 5% v/v Ethyl acetate and the solution filtered through a plug of silica gel. Concentration of the filtrate gave the ester product in 95% yield.

Ionic liquid recycling Recycling protocol: Synthesis of n-butyl acetate. Glacial acetic acid (1.10 g, 18.3 mmol) and K_2CO_3 (2.53 g, 18.3 mmol) were dissolved in ionic liquid (10.0 mL) and the solution stirred at 70 °C for 30 min under Ar when bromobutane (1.79 ml, 16.6 mmol) was added. After 6 hr the reaction was complete and the temperature was then raised to 130 °C and the n-butyl acetate distilled (127-128 °C) directly from the reaction mixture yielding 1.42g, 74%. The IL was subsequently cooled to rt, partitioned with water (3 x 20 ml) and dried under vacuum. A second identical reaction was then carried out in the recycled IL yielding butyl acetate in 85% yield after distillation.

Table 4.1, entry 1: Octyl propionate (pale yellow oil):

^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 4.03 (2H, t, *J*=6.6, 6.7 Hz), 3.37 (2H, t, *J*=6.8, 6.8 Hz), 2.27 (2H, m), 1.82 (2H, m), 1.59 (2H, m), 1.13 (3H, t, *J*=6.6, 6.7 Hz). 1.24 (12H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 174.3, 64.3, 33.7, 32.8, 31.7, 29.1, 28.6, 27.5, 25.8, 22.5, 13.9.EIMS 70 eV, m/z (rel. int.): 187 [M^+] (5), 112 (50), 205 (20), 83 (70), 57 (100). HRMS (EI) calcd 187.1698 for $C_{11}H_{23}O_2$, found 187.1682. IR (NaCl) : 2958, 2929, 1741, 1465, 1185, 1084 cm^{-1}.

Table 4.1, entry 2: Phenylethyl benzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.05 (2H, d, *J*=7.3 Hz), 7.43 (8H, m), 4.55 (2H, t, *J*=7.0, 6.9), 3.09 (2H, t, *J*=6.9, 6.9). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 166.4, 137.9, 132.9, 130.3, 129.5, 129.5, 128.9, 128.9, 128.5, 128.5, 128.3, 128.3, 127.8, 65.4, 35.2. EIMS 70 eV, m/z (rel. int.): 234 [M^+] (100), 211 (10), 183 (15), 178 (15), 176 (10).

Table 4.3, entry 3: Octylbenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.06 (2H, d, *J*=7.4 Hz), 7.51 (3H, m) , 4.34 (2H, t, *J*=6.6, 6.6 Hz), 1.76 (2H, m), 1.29 (10H, m), 0.96 (3H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 164.9, 133.1, 133.1, 128.9, 128.7, 127.9, 127.8, 63.4, 31.9, 30.1, 27.6, 27.1, 24.4, 21.0, 12.4.EIMS 70 eV, m/z (rel. int.): 234 [M^+] (5), 123 (100), 105 (90), 77 (75), 70 (20).HRMS (EI) calcd 234.1620 for $C_{15}H_{22}O_2$, found 234.1609. IR (NaCl): 2929, 2858, 1719, 1603, 1274, 1113 cm^{-1}.

Table 4.1, entry 4: Pheynylethyl propionate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.28 (5H, m), 4.29 (2H, t, *J*=7.0, 7.0 Hz), 2.94 (2H, t, *J*=7.0, 7.0 Hz), 2.33 (2H, q, *J*=7.5, 7.5, 7.5 Hz), 1.12 (3H, t, *J*=7.5, 7.5 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 174.3, 137.9, 128.9, 128.9, 128.4, 128.4, 126.5, 64.7, 35.1, 27.5, 9.1.EIMS 70 eV, m/z (rel. int.): 178 [M^+] (10), 104 (100), 91 (15), 57 (80), 51 (10).HRMS (EI) calcd 178.0994 for $C_{11}H_{14}O_2$, found 178.0988. IR (NaCl): 3030, 2349, 1738, 1498, 1384, 1349 cm^{-1}.

Table 4.1, entry 5: Ethyl 4-nitrobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.29 (2H, d, *J*=9.0 Hz), 8.21 (2H, d, *J*=9.0 Hz), 4.43 (2H, q, *J*=7.0, 14.1 Hz), 1.43 (3H, t, *J*=7.0, 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 172.2, 157.4, 142.7, 137.5, 137.4, 130.3, 130.2, 68.8, 21.1. EIMS 70 eV, m/z (rel. int.):195 [M^+] (31), 166 (42), 150 (100).

HRMS (EI) calcd 195.0532 for $C_9H_9NO_4$, found 195.0512. IR (NaCl) : 2993 , 1717 , 1605, 1526, 1474, 1457, 1368 cm^{-1}.

Table 4.1, entry 6: Isopropyl 4-nitrobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.28 (2H, d, *J*=9.1 Hz), 8.19 (2H, d, *J*=9.1 Hz), 5.29 (1H, m), 1.39 (6H, d, *J*=6.6 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 171.0, 157.8, 142.7, 137.5, 137.4, 130.3, 130.2, 76.5, 28.7, 28.6. EIMS 70 eV, m/z (rel. int.): 209 [M^+] (10), 173 (3), 150 (100). HRMS (EI) calcd 209.2020 for $C_{10}H_{11}NO_4$, found 209.2010. IR (NaCl): 2988, 1718, 1608, 1529, 1469, 1350 cm^{-1}.

Table 4.1, entry 8: Ethyl 4-chlorobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.99 (2H, d, *J*=8.4 Hz), 7.40 (2H, d, *J*=8.2 Hz), 4.37 (2H, q, *J*=7.1, 14.0 Hz), 1.38 (3H, t, *J*=7.0, 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 166.0, 138.1, 131.1, 131.0, 129.0, 128.8, 128.7, 61.3, 14.4. EIMS 70 eV, m/z (rel. int.):184 [M^+] (5), 164 (15), 135 (40), 119 (100). HRMS (EI) calcd 184.0291 for $C_9H_9ClO_2$, found 184.0302. IR (NaCl) : 2927, 1724, 1596, 1461, 1368 , 761 cm^{-1}.

Table 4.1, entry 9: Isopropyl 4-chlorobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.97 (2H, d, *J*=8.7 Hz), 7.40 (2H, d, *J*=8.7 Hz), 5.24 (1H, m), 1.36 (6H, d, *J*=6.5 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 172.0, 146.0, 137.7, 137.6, 136.2, 135.4, 135.3, 75.5, 28.7, 28.6. EIMS 70 eV, m/z (rel. int.): 198 [M^+] (5), 155 (19), 138 (48), 135 (100). HRMS (EI) calcd 198.0448 for $C_{10}H_{11}ClO_2$, found 198.0446. IR (NaCl): 2983, 1720, 1595, 1469, 1375, 762 cm^{-1}.

Table 4.1, entry 10: Ethyl 4-methoxybenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.99 (2H, d, *J*=8.1 Hz), 6.91 (2H, d, *J*=8.0 Hz), 4.33 (2H, q, *J*=7.0, 14.1 Hz), 3.86 (3H, s),

1.38 (3H, t, *J*=7.0, 7.1 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 173.0, 170.0, 138.4, 138.3, 130.0, 120.3, 120.2, 67.5, 62.2, 21.2. EIMS 70 eV, m/z (rel. int.) 180 [M^+] (5), 164 (50), 136 (10), 118 (100). HRMS (EI) calcd 180.0786 for $C_{10}H_{12}O_3$, found 180.0757. IR (NaCl) : 2982, 1713, 1608, 1512, 1464, 1368 cm^{-1}.

Table 4.1, entry 11: Isopropyl 4-methoxybenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.99 (2H, d, *J*=9.0 Hz), 6.90 (2H, d, *J*=9.0 Hz), 5.22 (1H, m), 3.85 (3H, s), 1.34 (6H, d, *J*=6.7 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm):172.5, 170.0, 138.3, 138.2, 130.2, 120.3, 120.2, 74.8, 62.2, 28.8, 28.7. EIMS 70 eV, m/z (rel. int.):194 [M^+] (15), 179 (5), 152 (37), 135 (100). HRMS (EI) calcd 194.0943 for $C_{11}H_{14}O_3$, found 194.0949. IR (NaCl): 2981, 1711, 1608, 1512, 1465, 1374 cm^{-1}.

Table 4.1, entry 12: Ethyl 4-methylbenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.94 (2H, d, *J*=8.1 Hz), 7.23 (2H, d, *J*=8.0 Hz), 4.35 (2H, q, *J*=7.0, 14.0 Hz), 2.40 (3H, s), 1.37 (3H, t, *J*=7.0, 7.0 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz), δ (ppm): 167.5, 144.7, 130.3, 130.2, 129.8, 129.7, 128.0, 61.5, 22.4, 15.1. EIMS 70 eV, m/z (rel. int.):164 [M^+] (5), 136 (47), 118 (100). HRMS (EI) calcd 164.2040 for $C_{10}H_{12}O_2$, found 164.2044. IR (NaCl) : 2958, 1735, 1618 , 1522 , 1459, 1385 cm^{-1}.

Table 4.1, entry 13: Isopropyl 4-methylbenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.92 (2H, d, *J*=8.2 Hz), 7.22 (2H, d, *J*=8.2 Hz), 5.23 (1H, m), 2.40 (3H, s), 1.35 (6H, d, *J*=6.7 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 166.5, 143.4, 129.6, 129.5, 129.1, 129.0, 128.0, 68.2, 21.7, 22.1, 22.0.EIMS 70 eV, m/z (rel. int.): 178 [M^+] (16), 136 (37), 119 (100). HRMS (EI) calcd 178.0994 for $C_{11}H_{14}O_2$, found 178.0986. IR (NaCl) : 2927, 1718, 1653, 1559, 1459, 1376 cm^{-1}.

Table 4.1, entry 14: Ethyl 2-methylbenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.90 (1H, d, *J*=7.5 Hz), 7.37 (1H, d, *J*=7.6 Hz), 7.25 (2H, m), 4.33 (2H, q, *J*=7.1, 14.0 Hz), 2.60 (3H, s), 1.39 (3H, t, *J*=7.0, 7.0 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 174.8, 147.0, 138.6, 138.5, 137.3, 137.1, 132.5, 67.5, 28.5, 21.2. EIMS 70 eV, m/z (rel. int.): 164 [M^+] (15), 135 (100), 119 (44). HRMS (EI) calcd 164.0837 for $C_{10}H_{12}O_2$, found 164.0836. IR (NaCl) : 2925, 1738, 1653, 1560, 1460, 1380 cm^{-1}.

Table 4.1, entry 15: Isopropyl 2-methylbenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.87 (1H, d, *J*=7.4 Hz), 7.36 (1H, d, *J*=7.4 Hz), 7.24 (2H, m), 5.24 (1H, m), 2.59 (3H, s), 1.32 (6H, d, *J*=6.5 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 167.7, 140.5, 131.9, 131.8, 131.8, 130.7, 125.9, 68.4, 22.2, 22.1, 22.0. EIMS 70 eV, m/z (rel. int.): 178 [M^+] (5), 155 (86), 138 (100). HRMS (EI) calcd 178.0994 for $C_{11}H_{14}O_2$, found 178.0993. IR (NaCl): 2926 (CH), 1735, 1653, 1559, 1461, 1379 cm^{-1}.

Table 4.1, entry 16: Ethyl 2,4,6-trimethylbenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.85 (2H, s), 4.36 (2H, q, *J*=7.0, 14.0 Hz), 2.28 (9H, s), 1.38 (3H, t, *J*=7.0, 7.0 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 177.4, 146.5, 141.2, 141.1, 137.7, 135.2, 135.1, 67.6, 27.9, 26.5, 26.4, 21.1. EIMS 70 eV, m/z (rel. int.): 192 [M^+] (38), 163 (20), 147 (100), 119 (26). HRMS (EI) calcd 192.1150 for $C_{12}H_{16}O_2$, found 192.1150. IR (NaCl) : 2981, 1727, 1613, 1449, 1366 cm^{-1}.

Table 4.1, entry 17: Isopropyl 2,4,6-trimethylbenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.84 (2H, s), 5.28 (1H, m), 2.29 (6H, s), 2.27 (3H, s), 1.35 (6H, d, *J*=6.5 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 146.2, 141.5, 141.4, 141.3, 138.2, 135.2, 135.1, 75.1, 28.7, 28.6, 27.9, 26.4, 26.3. EIMS 70 eV, m/z (rel. int.): 206 [M^+] (22), 164 (25), 147

(100), 119 (23). HRMS (EI) calcd 206.1307 for $C_{13}H_{18}O_2$, found 206.1301. IR (NaCl): 2980, 1723, 1613, 1559, 1457, 1376 cm^{-1}.

Table 4.1, entry 18, Ethyl 2-(3,4-methylenedioxyphenyl) acetate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.76 (2H, d, *J*=9.0 Hz), 6.68 (1H, s), 5.93 (2H, s), 4.14 (2H, q, *J*=7.0, 14.1 Hz), 3.51 (2H, s), 1.25 (3H, t, *J*=7.1, 7.1 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 178.0, 155.0, 153.0, 134.7, 129.2, 116.3, 115.1, 107.8, 67.7, 47.8, 21.0. EIMS 70 eV, m/z (rel. int.): 208 [M^+] (30), 180 (1), 159 (1), 135 (100). HRMS (EI) calcd. 208.0736 for $C_{11}H_{12}O_4$, found 208.0738. IR (NaCl) : 2984, 1735, 1610, 1504, 1446, 1368, 932 cm^{-1} .

Table 4.1, entry 19: Isopropyl 2-(3,4-methylenedioxyphenyl) acetate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.75 (2H, d, *J*=9.1 Hz), 6.72 (1H, s), 5.93 (2H, s), 5.00 (1H, m), 3.48 (2H, s), 1.22 (6H, d, *J*=6.3 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 177.8, 154.8, 153.0, 134.8, 129.2, 116.5, 115.1, 107.8, 75.0, 48.1, 28.6, 28.5. EIMS 70 eV, m/z (rel. int.): 222 [M^+] (15), 208 (12), 180 (1), 135 (100). HRMS (EI) calcd 222.0892 for $C_{12}H_{14}O_4$, found 208.0896. IR (NaCl) : 2984, 1735, 1653, 1506, 1446, 1370, 932 cm^{-1}.

Table 4.1, entry 20: Cyclohexyl 4-nitrobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.28 (2H, d, *J*=9.2 Hz), 8.20 (2H, d, *J*=9.2 Hz), 5.06 (1H, m), 1.96 (2H, m), 1.78 (2H, m), 1.57 (2H, m), 1.41 (4H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 170.9, 157.3, 143.2, 137.5, 137.4, 130.3, 130.2, 81.2, 38.4, 38.3, 32.2, 30.5, 30.4. EIMS 70 eV, m/z (rel. int.): 249 [M^+] (1), 233 (1), 194 (1), 168 (8), 150 (50), 120 (30), 104 (86), 82 (100). HRMS (EI) calcd 249.1001 for $C_{13}H_{15}NO_4$, found 249.1008. IR (NaCl): 2939, 1722, 1608, 1530, 1452, 1349 cm^{-1}.

Table 4.1, entry 21: Butyl 4-nitrobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.29 (2H, d, *J*=8.0 Hz), 8.20 (2H, d, *J*=8.0 Hz), 4.38 (2H, t, *J*=6.1, 6.2 Hz), 1.78 (2H, m), 1.50 (2H, m), 0.99 (3H, t, *J*=6.2, 6.3 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 172.0, 157.2, 142.6, 137.5, 137.4, 130.3, 130.2, 72.6, 37.4, 26.0, 20.5. EIMS 70 eV, m/z (rel. int.): 223 [M^+] (1), 207 (1), 168 (5), 150 (15), 119 (5), 83 (100). HRMS (EI) calcd 223.0845 for $C_{11}H_{13}NO_4$, found 223.0839. IR (NaCl): 2963, 1727, 1608, 1530, 1466, 1351 cm^{-1}.

Table 4.1, entry 22: Dodecyl 4-nitrobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.29 (2H, d, *J*=9.0 Hz), 8.20 (2H, d, *J*=9.0 Hz), 4.36 (2H, t, *J*=6.1, 6.2 Hz), 1.80 (2H, m), 1.26 (20H, m), 0.87 (3H, t, *J*=6.2, 6.3 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 172.0, 157.0, 142.5, 137.5, 137.4, 130.3, 130.2, 72.9, 38.7, 36.4, 36.3, 36.2, 36.2, 36.1, 36.1, 35.4, 32.8, 29.5, 20.9. EIMS 70 eV, m/z (rel. int.): 335 [M^+] (2), 305 (33), 289 (1), 278 (1), 169 (50), 137 (100), 119 (21). HRMS (EI) calcd 335.2097 for $C_{19}H_{29}NO_4$, found 335.2101. IR (NaCl): 2960, 1717, 1606, 1527, 1470, 1351 cm^{-1}.

Table 4.1, entry 23: Dibutyl phthalate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.70 (1H, d, *J*=3.2 Hz), 7.53 (1H, d, *J*=3.3 Hz), 4.29 (2H, t, *J*=6.5, 6.0 Hz), 1.71 (2H, m), 1.48 (2H, m), 1.13 (3H, m). ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 167.6, 167.6, 132.2, 132.2, 130.8, 130.8, 128.8, 128.8, 65.5, 65.5, 30.5, 30.5, 19.1, 19.1, 13.7, 13.7. EIMS 70 eV, m/z (rel. int.): 278 [M^+] (10), 223 (20), 205 (20), 150 (10), 149 (100), 31 (50). HRMS (EI) calcd 278.1518 for $C_{16}H_{22}O_4$, found 278.1523. IR (NaCl): 1750, 1600, 1290, 1122, 1075, 745 cm^{-1}.

Table 4.1, entry 24: Tert-butyl 4-nitrobenzoate: ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.26 (2H, d, *J*=9.0 Hz), 8.14 (2H, d, *J*=9.0 Hz), 1.61 (9H, s).^{13}C-NMR ($CDCl_3$, 50 MHz),

δ (ppm): 171.0, 157.5, 144.8, 137.3, 137.2, 130.2, 130.1, 89.8, 34.9, 34.8, 34.7. EIMS 70 eV, m/z (rel. int.): 223 [M^+] (5), 185 (1), 150 (100), 135 (5), 120 (10), 104 (40). HRMS (EI) calcd 223.0845 for $C_{11}H_{13}NO_4$, found 223.0838. IR (NaCl): 2982, 1717, 1607, 1527, 1460, 1350 cm^{-1}.

4.4 Procedure for synthesis of BZE-5 and BZE-8:

To a sample tube containing 1.0 g de-gassed trihexyl (tetradecyl) phosphonium bromide ionic liquid, was added *p*-anisic acid (100mg, 0.6mmol), 1,3 dibromopropane (144mg, 0.72mmol), Hunig's base (154.8mg, 1.2mmol), stirred the reaction mixture overnight at room temperature , TLC indicated the consumption of starting material and formation of two products. Products were isolated by using hexane/water protocol. The hexane layer was dried over Na_2SO_4 and solvent was removed under reduced pressure and columned to give two products BZE-5, 73.4mg, (45%) and BZE-8 88.7mg, (43%) of isolated yield.

BZE-5: 3-bromopropyl 4-methoxybenzoate: Brown oil; ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.96 (2H, d, *J*=4.73 Hz), 6.89 (2H, d, *J*=4.73 Hz), 4.42 (2H, t, *J*=2.36, 1.18 Hz), 3.85(3H, s), 3.53 (2H, t, *J*=4.72, 3.54 Hz), 2.33(2H, q, *J*=3.54, 3.54 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 166.1, 163.4, 131.6, 122.3, 113.6, 62.3, 55.4, 31.9, 29.5. EIMS 70 eV, m/z (rel. int.): 272 [M^+] (100). HRMS (EI) calcd 272.0048 for $C_{11}H_{13}BrO_3$, found 272.0040. IR (neat): 2976, 2840, 1717, 1383, 633 cm^{-1}.

BZE-8: pale yellow powder; ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.00 (4H, d, *J*=4.73 Hz), 6.87 (4H, d, *J*=4.73 Hz), 4.46 (4H, m), 3.85(6H, s), 2.24 (2H, m).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 166.2, 163.3, 131.6, 122.5, 113.5, 61.5, 55.4, 29.6. EIMS 70

eV, m/z (rel. int.): 344 [M^+] (100), 135 (5). HRMS (EI) calcd 344.1416 for $C_{19}H_{20}O_6$, found 344.1420 IR (neat): 2976, 2840, 1717, 1383 cm^{-1}.

4.5 Procedure for synthesis of BZE-6:

To a sample tube containing 1.0 g de-gassed trihexyl (tetradecyl) phosphonium bromide ionic liquid was added BZE-5 (60mg, 0.21mmol) and heated the mixture in a bomb at 120^0C for overnight, isolated the product by using hexane/water protocol. Dried the hexane layer over Na_2SO_4, solvent removed under reduced pressure and columned to give 25mg, 28% of isolated yield.

BZE-6: 3-bromopropyl 4-hydroxybenzoate :pale yellow oil; ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.97 (2H, d, *J*=4.73 Hz), 6.88 (2H, d , *J*=4.73 Hz), 5.52 (1H, s), 4.43(2H, t, *J*=2.36, 1.18 Hz), 3.54 (2H, t, *J*=4.72, 3.54 Hz), 2.27 (2H, q, *J*=3.54, 3.54 Hz).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 131.9, 115.2, 62.5, 31.8, 29.5. EIMS 70 eV, m/z (rel. int.): 257[M^+] (80). HRMS (EI) calcd 257.9892 for $C_{10}H_{11}BrO_3$, found 257.9850. IR (neat): 3388, 1690, 1312, 636 cm^{-1}.

4.6 Procedure for synthesis of BZE-7:

To a sample tube containing 1.0 g de-gassed trihexyl (tetradecyl) phosphonium bis (trifluoromethanesulfonyl) imide ionic liquid, was added BZE-5, (58mg, 2.12 mmol), sodium nitrite (37mg, 5.31mmol) and catalytic amounts of water, heated the reaction mixture at 90^0C overnight, isolated the product by using hexane/3:2 (MeOH:H_20) protocol. Dried the hexane layer over Na_2SO_4, solvent removed under reduced pressure and columned to give (13mg), 30% of isolated yield.

BZE-7: 3-hydroxypropyl 4-methoxybenzoate: pale yellow oil; ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.97 (2H, d, *J*=4.73 Hz), 6.92 (2H, d , *J*=4.73 Hz,), 4.49 (2H, t, *J*=3.54,3.54 Hz), 3.85 (3H, s), 3.75 (2H, t, *J*=3.54,3.54 Hz), 1.95 (2H,q, *J*=3.54, 3.54 H), 1.86 (1H,s).^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 131.6, 113.6, 61.4, 59.1, 55.4, 32.0, 9.7. EIMS 70 eV, m/z (rel. int.): 210 [M^+] (100). HRMS (EI) calcd 210.0892 for $C_{11}H_{14}O_4$, found 210.0874. IR (neat): 3435, 2926, 2854, 1711, 1318 cm^{-1}.

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Chapter 5

A Pronounced Anionic Effect in the Pd-catalyzed Buchwald-Hartwing Amination Revealed in Phosphonium Salt Ionic Liquids[d] :

The use of transition metal complexes to effect cross-coupling reactions between aryl and vinyl halides or their equivalents with amines has become a standard tool for the construction of complex amines.[1-5] Classic protocols utilizing copper salts (Ullmann reaction)[2] suffer from many drawbacks in terms of reactivity, often requiring high loadings of copper salt catalyst, high reaction temperatures and/or times, require the use of excess amine and result in the formation of side-products. Product purification and disposal of metal containing wastes highlight further environmental concerns over classic Ullmann reactions and the need for the development of "green" alternatives for this valuable transformation. Based on initial reports by Buchwald and Hartwig,[3] a plethora of methods utilizing Pd complexes (now known as Buchwald-Hartwig amination) coupled with a variety of electron rich, bulky ligands have appeared over the last few years.[4] A major impetus for these developments is the potential utility of efficient amination protocols in the synthesis of dyes, high-value pharmaceutical,[5] and functionalized triarylamines which are the key components in a variety of materials including organic photoconductors, light-emitting diodes and photovoltaic cells.[6] An expanding variety of aryl amines have now been prepared under mild conditions and in a controlled,

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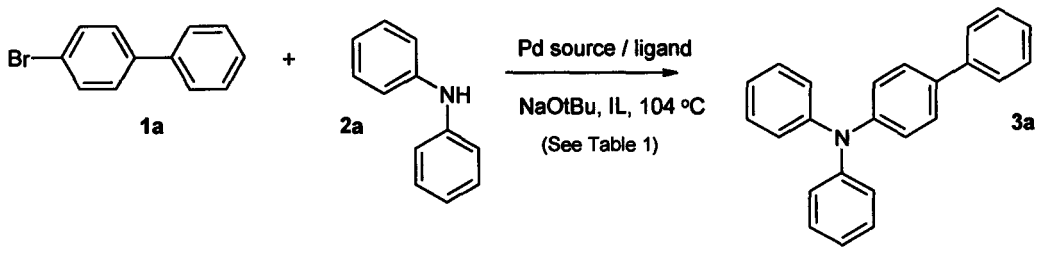
[d] Individually developed a novel protocol for Buchwald-Hartwig amination reactions in phosphonium salt ionic liquids and identified their anionic effects.
Contribution to publication: 90%
McNulty, J.; Cheekoori, S.; Bender, T. P.; Coggan, J. A.;*Eur. J. Org. Chem.*, **2007**, *9*, 1423.

chemoselective manner utilizing this methodology. Many factors contributing to the success of this reaction have been investigated including solvents effects,[7] where the superiority of non-coordinating solvents was demonstrated. To the best of our knowledge, no reports specifically on anionic effects have been reported.

Recently, we have been interested in developing applications of Pd-catalyzed[8] and other[9] cross-coupling reactions in phosphonium salt ionic liquids. Phosphonium based IL's are very stable thermally,[10] non volatile, economical and available on an industrial scale. Most ionic liquid research has been conducted in nitrogen-based solvents, especially alkyl imidazolium salts, and phosphonium species represent a largely unexplored area.[11] We have reported the efficient Suzuki cross-couplings of aryl halides, including chlorides, with a variety of boronic acids in the ionic liquid trihexyl(tetradecyl) phosphonium chloride. Efficient recovery and recycling of the palladium catalysts was demonstrated[8a] and this work has been extended to Suzuki and other Pd-mediated reactions employing an organic solvent nanofiltration technology.[12] In addition to the "green" potential of these processes, an interesting reactivity feature on the use of these IL solvents is the tunability that is available through altering the nature of either the anion or phosphonium cation. For example, trihexyl(tetradecyl)phosphonium bistriflimide ionic liquid proved to be the optimal choice in a series of alklyation reactions investigated,[9a,13] whereas, with this same cation, the chloride ionic liquid proved optimal in Suzuki[8a] and Heck[8b] cross-coupling reactions and finally the decanoate salt was optimal in catalyzing carbonyl addition reactions.[9b] As an extension of this work, we recently investigated a

Pd-mediated Buchwald-Hartwig amination reaction of an aryl bromide in the chloride ionic liquid and were surprised that little cross-coupling took place.



Scheme 5.1 : Screening Pd-sources and Ligand in trihexyl(tetradecyl)phosphonium bistriflimide IL

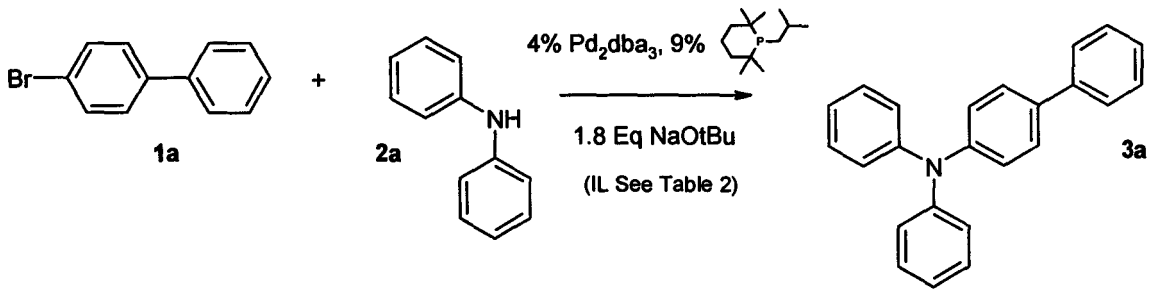
The target compound central to our investigation was the biphenyl-substituted triarylamine **3a**, Scheme 5.1. The most direct route for its synthesis and structural analogs would be from a diphenyl amine such as **1a** and 4-bromobiphenyl **2a** using a Buchwald-Hartwig amination protocol.[6] The cross-coupling shown (Scheme 5.1) did not proceed significantly in trihexyl(tetradecyl)phosphonium chloride ionic liquid however we quickly determined that it proceeded rapidly in the bistriflimide analog allowing for complete conversion of the aryl bromide. The reaction independently requires the addition of ligand and base. We screened two Pd^0 sources and several ligands (Table 5.1) in this ionic liquid solvent and determined that the source of the active palladium catalysts was not crucial although the combination of Pd_2dba_3-$CHCl_3$ with the tertiary phosphane 1-isobutyl-2,2,6,6-tetramethylphosphorinane proved optimal. We have recently found this ligand to be valuable in various Pd-mediated cross-coupling reactions including amination reactions conducted in toluene solvent.[15] Further experiments on the nature of the anionic effect were carried out with this optimal catalyst precursor combination.

Table 5. 1: Screening different palladium sources and ligands in bistriflimide IL:

Entry	Palladium source	Ligand	Temp °C	Time	%Conversion[a]
1	$Pd_2(dba)_3$	tri-^{t}-butylphosphine	104	15 hours	89
2	$Pd_2(dba)_3$	^{t}-Butyl phosphorinane	104	2hours	98
3	$Pd_2(dba)_3$	tri-*O*-toluylphosphine	104	2 hours	71
4	$Pd(OAc)_2$ [b]	tri-^{t}-butylphosphine	104	2 hours	90
5	$Pd(OAc)_2$	^{t}-Butyl phosphorinane	104	15 hours	36
6	$Pd(OAc)_2$	tri-*O*-toluylphosphine	104	15 hours	20

[a] Conversion determined by HPLC analysis.
[b] 5 mol % of palladium catalyst used.

The cross-coupling reaction was screened in nine different trihexyl(tetradecyl) phosphonium ionic liquids varying the electronic and to some extent steric nature of the anion, the results are summarized in Table 5.2. The superiority of the bistriflimide derivative is striking, this reaction went to completion within two hours, while even other partly successful anions, decanoate and tetrafluoroborate, provided only 57 to 59% conversion over 24 hours under otherwise identical conditions. The saccharide (imide) derivative was also successful but reacted slower to give 90% conversion over a 24 h reaction period. The inactivity of the chloride and bromide derivatives is also startling, particularly in view of the success of these media in promoting other Pd-mediated cross-coupling reactions.[8a,b]



Scheme 5.2: Screening Phosphonium based ionic liquids for standard amination reaction.

Entry	Ionic Liquid	Percent conversion (%)[a] Overnight	Isolated yield
1	Trihexyl(tetradecyl)phosphonium chloride	1	NA
2	Trihexyl(tetradecyl)phosphonium bromide	2	NA
3[b]	Trihexyl(tetradecyl)phosphonium dicyanamide	2	NA
4	Trihexyl(tetradecyl)phosphonium decanoate	57	42
5	Trihexyl(tetradecyl)phosphonium tosylate	2	NA
6	Trihexyl(tetradecyl)phosphonium-bis(triflouromethanesufonyl)imide	98[b]	73
7	Trihexyl(tetradecyl)phosphonium tetraflouroborate	59	35
8	Trihexyl(tetradecyl)phosphonium dibutyl phosphate	15	9
9	Trihexyl(tetradecyl)phosphonium saccharide	90	65

[a]Conversion determined by HPLC analysis.

[b]This reaction was complete in 2 hours.

Table 5.2: Phosphonium based ionic liquid screen for standard amination reaction.

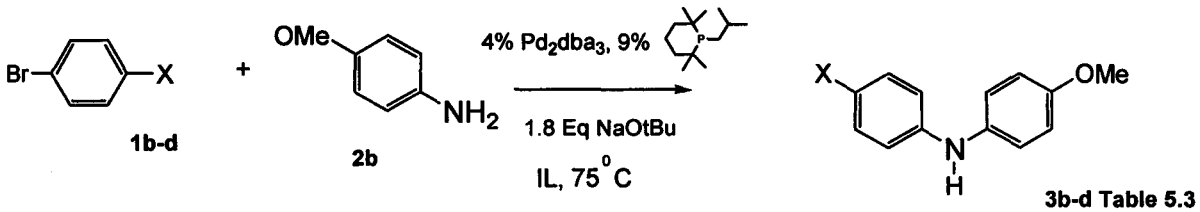
The Buchwald-Hartwig amination reaction in the tetradecyl(trihexyl)phosphonium bistriflimide was also successfully conducted using 4-methoxyaniline **2b** (Scheme 5.3) cross-coupling with bromobenzene derivatives **1b-1d** (Table 5.3). The reaction appears to be general and indicates that oxidative addition of the catalyst to both electron rich and electron deficient halides proceeds without difficulty.

In general, the results in Table 5.2 show that nucleophilic counter-anions are detrimental to the success of the reaction while diffuse, weakly or non-coordinating anions,

particularly the bistriflimide and saccharin derivatives, are superior. This result appears to be congruent to the solvent effect study recently reported in which donor solvents were seen to be inferior media.[7] It appears that the weakly nucleophilic nature of the diarylamine employed in the present study inhibits its participation in the Pd-mediated catalytic cycle where coordinating anions and/or solvent are present. These results contrast to the success of the chloride ionic liquid in the Suzuki cross-coupling reaction.[8a] Either a different Pd-catalyst is operative in the chloride ionic liquid or a different (associative) pathway is available for ligand exchange where good nucleophiles are present. This, and the generality of the above reaction to variously substituted aryl halides (Table 5.3) indicates that there is no problem with oxidative addition step in either catalytic cycle and that the explanation for the anionic effect rests upon the nature of the ligand exchange step with the weakly nucleophilic diarylamine.

Having uncovered the pronounced anionic effect in the phosphonium salt ionic liquids we desired to probe the affect in a typical organic solvent in order to ascertain if the anionic affect is general or just a manifestation of the overall polar and atypical nature of the medium. Further evidence for the general nature of the anionic effect described above was gained from the following reactions. The cross-coupling reaction between 4-bromobiphenyl **1a** (1 equivalent) and diphenylamine **2a** (1.05 equivalents) also proceeded smoothly in toluene as solvent with the same catalyst, ligand and base combination as shown in Scheme 5.1. The addition of trihexyl(tetradecyl)phosphonium bistriflimide in various proportions ranging from 1.0 to 5.0 equivalents (relative to 4-bromobiphenyl) to the amination reaction in toluene had no affect on the reaction, with

98% conversion being observed in the latter case. In contrast, the addition of trihexyl(tetradecyl)phosphonium chloride proved to poison the catalytic cycle operative in the cross-coupling reaction. Although 1.0 equivalent of the chloride ionic liquid was tolerated, the reaction did not proceed at all in toluene when 5.0 equivalents of this soluble chloride were added. Attempts to crystallize the active catalyst from the bistriflimide ionic liquid or toluene/IL blends have not so far been successful however it was clear that a different catalyst is formed in the non-coordinating media. For example, the active catalyst in the bistriflimide ionic liquid, or in toluene with or without added ionic liquid is a deep-purple colour. The soluble catalyst in the chloride ionic liquid is a distinct yellow-orange colour. The catalyst in toluene remains purple in colour with 1.0 equivalent of the chloride ionic liquid added but immediately becomes a distinct yellow colour when 5.0 equivalents of chloride ionic liquid are added. These results correlate precisely with the activity observed in the cross-coupling reaction as described purely in the ionic liquid solvent. In addition, excess salt can affect the process by simply increasing the polarity of the medium. These catalytic cycles also present an overall incongruity; whereas added halide may expedite the initial steps of the cycle, through the intermediacy of L_2PdX^- and rapid oxidative-addition to the Ar-X bond, a high concentration of halide is expected to hinder subsequent ligand exchange steps involving halide dissociation.



Scheme 5.3: Cross-coupling of 4-methoxyaniline with aryl bromides

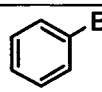
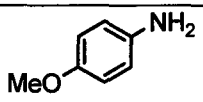
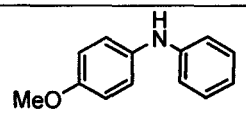
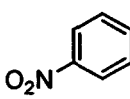
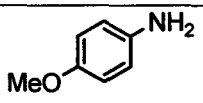
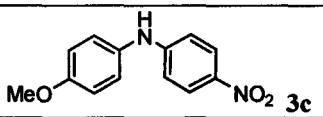
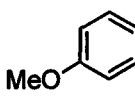
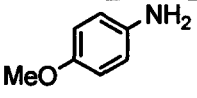
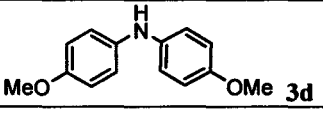
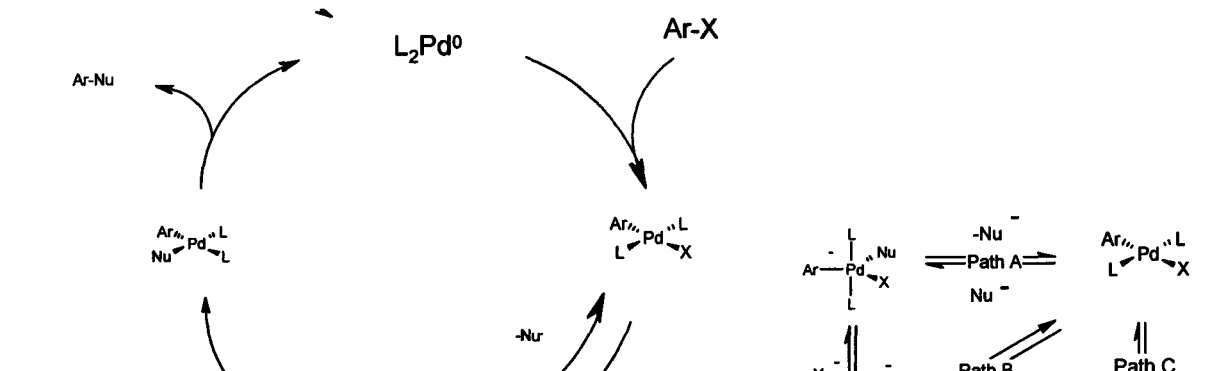
Entry	Aryl Halide	Aniline	Product	Time	Isolated Yield(%)
1			 **3b**	24 h	72
2			 **3c**	24 h	75
3			 **3d**	24 h	75

Table 5.3: Cross-coupling of 4-methoxyaniline with aryl bromides

Furthermore, since halide anions are released during many cross-coupling reactions, oxidative addition is expected to accelerate while ligand exchange should be self poisoning to the cycle as the reaction proceeds. The contributing affect of anions on a given catalytic cycle is therefore far from clear-cut and must depend on the nature of the active catalyst, the medium and intimate details of the contributing steps. In the present case, the bistriflimide ionic liquid is considered to be a dipolar, halide-free medium. Rapid cross-coupling takes place with a weakly nucleophilic diarylamine. When this reaction is performed in toluene, 5.0 equivalents of soluble chloride are enough to poison the catalytic cycle with this amine under conditions where stronger nucleophiles like arylboronic acids readily participate. The most likely explanation involves the nature of

the ligand exchange step. In principle, this may take place through either an associative, interchange or dissociative pathway.[20] In the case of the bistriflimide ionic liquid, the polar medium, absence of halide and excess of non-coordinating anion are likely to promote ionization of halide from the oxidative addition intermediate yielding a cationic L_2PdAr^+ complex[21] which can then combine with the weakly nucleophilic diarylamine providing the next intermediate which undergoes N-deprotonation[22] and finally reductive elimination to complete the cycle.



Scheme 5.4: Proposed catalytic cycle and dissociative ligand exchange (Path C) with weak nucleophiles in non-coordinating media.

Addition of excess halide or other coordinating ligand to the reaction conducted in a standard solvent such as toluene or ionic liquid coupled to coordinating anions will hinder the ionization step and thus not allow cross-coupling with weak nucleophiles. In

contrast, a strong nucleophile, such as aryboronic acid/base combination, could allow ligand exchange (or transmetallation) via a nucleophilically assisted process through either association to form an anionic palladium intermediate or directly through an associative pathway. A modification of the "textbook" catalytic cycle for halide free cross-coupling taking into account the details of the ligand exchange is presented in Scheme 5.4. This process also offers a satisfactory explanation for the successful Suzuki cross-coupling reactions reported in the chloride-containing ionic liquid and hence Scheme 5.4 describes a unified view of Pd-mediated cross-coupling reactions in phosphonium salt ionic liquids; the differences being accounted for by the nature of the ligand exchange process with strong or weak nucleophiles. While the Suzuki cross-coupling conducted in the chloride ionic liquid could take place *via* the involvement of the anionic complex (L_2PdCl^-), the lack of coordinating solvent and high chloride ion concentration are expected to retard subsequent ligand exchange process raising doubt that such a cycle is operative.

Taken together, the overall results of the amination reaction conducted in phosphonium salt ionic liquids and toluene with addition of soluble anions show that the general anionic effect uncovered in our investigations in ionic liquid media are also applicable to typical Buchwald-Hartwig amination reactions conducted in a standard solvent such as toluene. In retrospect, the use of the phosphonium salt ionic liquid media as solvent coupled with either coordinating or non-coordinating anions proved to be an ideal media in which to isolate, uncover and probe the anionic effect in this cross-coupling reaction. The use of a media consisting of a diffuse phosphonium cation coupled to anions varying

from non-coordinating to donor anion has provided insight into the nature of the Buchwald-Hartwig amination cycle. The anionic effects indicate ionization in non-coordinating media and the intervention of a cationic palladium intermediate with the weakly nucleophilic amine. Further investigations into the nature of the active catalyst described in the bistriflimide ionic liquid and its oxidative addition product as well as the synthesis of a variety of triarylamines via the cross-coupling of weakly nucleophilic diarylamines utilizing this process is under active investigation in our laboratories.

5.1 Experimental Section

General Considerations.

Reactions were carried out under an Argon atmosphere in oven-dried glassware. All Ionic Liquids used were obtained from Cytec Canada Inc., Niagara Falls, Ontario. Ionic liquids were de-gassed under high vacuum for at least one hour immediately prior to use. All other solids were dried under high vacuum. Toluene was distilled from sodium metal with benzophenone indicator. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (CI) were performed with a Micromass Q-Tof Ultima spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 or AV 700 spectrometer in $CDCl_3$ with TMS as internal standard, chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (J) are expressed in Hz.

General Procedure: To a vial containing degassed trihexyl(tetracdecyl)phosphonium bis(trifluoromethanesulfonyl) imide (1.00 mL) was added sequentially 4-bromobiphenyl (100 mg, 0.44 mmol), sodium *tert*-butoxide (77.5 mg, 0.79 mmol), $Pd_2(dba)_3.CHCl_3$

(18.46mg, 4 mol%), 2,2,6,6-tetramethyl-1-isobutyl-phosphorinane ligand HBF_4 salt (12.2mg, 9mol%) followed by diphenyl amine (90 mg, 0.46 mmol) under argon. The vial was capped and heated at either 75 or 104 ^{0}C for the duration specified. Reactions were terminated when TLC or HPLC indicated full consumption of the bromoarene. The reaction mixture was allowed to cool to room temperature. The product was isolated using a hexane/water protocol. This partitions the central ionic liquid phase between lower water and upper hexane layers with palladium complex remaining in the Ionic Liquid layer. The combined hexane fractions were dried over Na_2SO_4, solvent removed under reduced pressure and the product isolated from a silica column using hexane as eluting solvent to give desired product in 73% yield.

N-biphenyl diphenylamine 3a: The general procedure was followed throughout Table 5.2 with the various ionic liquids at 104 °C . White solid; ^{1}H-NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.57 (2H, d, *J*=7.49 Hz), 7.48 (2H, d, *J*=8.54 Hz), 7.41 (2H, t, *J*=7.57 Hz), 7.28 (6H, m), 7.14 (5H, d, *J*=8.37 Hz), 7.03 (2H, t, *J*=7.35 Hz), ^{13}C-NMR ($CDCl_3$, 125.7 MHz), δ (ppm): 147.7, 147.1, 140.6, 135.1, 129.2 (4C), 128.7 (2C), 127.7 (2C), 126.7 (2C), 126.6 (2C), 124.4 (4C), 123.9 (2C), 122.9 (2C). EIMS 70 eV, m/z (rel. int.): 321 [M^+] (100), 243 (15), 167 (10), 77 (10), 43 (10). HRMS (EI) calcd. for $C_{24}H_{19}N$: 321.1517, found: 321.1508.

4-Methoxydiphenylamine 3b (Table 5.3, entry 1): The general procedure was followed and the reaction was run at 75 ^{0} C. Yellow solid; M.p. 103-104^{0}C, lit. 104-105^{0}C, [23] ^{1}H-NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.26 (2H, t, *J*=8.4, 7.5 Hz), 7.12 (2H, d,

J=8.7 Hz), 6.86 (5H, m), 5.56 (1H, bs), 3.84 (3H,s). ^{13}C-NMR ($CDCl_3$, 125.7 MHz), δ (ppm): 155.3, 145.1, 135.7, 129.2 (2C), 122.2 (2C), 119.5 (2C), 115.6 (2C), 114.6, 55.5. CIMS 70 eV, m/z (rel. int.): 199 [M^+] (50), 184 (40), 105 (100). HRMS (CI) calcd. for $C_{13}H_{13}NO$: 199.0997, found: 199.0995.

4-Methoxy-4'-nitrodiphenylamine 3c (Table 5.3, entry 2): The general procedure was followed and the reaction was run at 75 ^{0} C. Orange solid; M.p. 152-153^{0}C, lit. 152-152.5^{0}C, [24] ^{1}H-NMR ($CDCl_3$, 500 MHz), δ (ppm): 8.10 (2H, d, *J*=9.2 Hz), 7.18 (2H, d, *J*=8.9 Hz), 6.96 (2H, d, *J*=8.9 Hz), 6.78 (2H, d, *J*=9.2 Hz), 6.15 (1H, s), 3.85(3H,s). ^{13}C-NMR ($CDCl_3$, 125.7 MHz), δ (ppm): 157.6, 151.9, 139.2, 132.2, 126.5 (2C), 125.6 (2C), 115.1 (2C), 112.6 (2C), 55.7.CIMS 70 eV, m/z (rel. int.): 244 [M^+] (35), 214 (100), 199 (60). HRMS (CI) calcd. for $C_{13}H_{12}N_2O_3$: 244.0848, found: 244.0854.

4, 4'-Dimethoxydiphenylamine 3d (Table 5.3, entry 3): The general procedure was followed and the reaction was run at 75 ^{0} C. Pale yellow solid; M.P. 102-103^{0}C, lit 99.5-101.5^{0}C,[24] ^{1}H-NMR ($CDCl_3$, 500 MHz), δ (ppm): 6.97 (4H, d, *J*=8.9 Hz), 6.85 (4H, d, *J*=9.0 Hz), 5.32 (1H, s), 3.79 (6H, s). ^{13}C-NMR ($CDCl_3$, 125.7 MHz), δ (ppm): 154.4 (2C), 138,1 (2C), 119.7 (4C), 114.9 (4C), 55.8 (2C). CIMS 70 eV, m/z (rel. int.): 229 [M^+] (100), 214 (90), 199 (10). HRMS (CI) calcd. for $C_{14}H_{15}NO_2$: 229.1103, found: 229.1102.

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Chapter 6

6.1 A Novel Non-Solvated Crystal Structure of Tris(dibenzylideneacetone) palladium(0) in Phosphonium Salt Ionic Liquids

Among the transition metals, Pd catalysts play an important role in the formation of C-C bonds (Suzuki[1] and Heck[2] coupling) and C-N bonds (Buchwald-Hartwig reaction[3]). Palladium catalysts also have tolerance to a variety of functional groups such as carbonyl and hydroxyl groups, without the need of protection.[4] For the past few years we have been developing new "green" synthetic protocols by using phosphonium salt ionic liquids (PSIL's). Phsophonium salt ionic liquids are non-volatile, thermally stable and available in bulk quantity. Interestingly, phosphonium based ionic liquids are stable to strong bases, in contrast to pyridinium or ammonium based ionic liquids in which Hoffmann-type eliminations have been observed.[5] The products from these reactions can be isolated using a hexane/water mixture or hexane/MeOH water (3:2) protocol, giving a triphasic system wherein the upper hexane layer usually contains the product, while the ionic liquid is partitioned between the hexane and lower aqueous layer which contains inorganic salts.[6] It is possible to alter the physical and chemical properties of ionic liquids by either varying the length of the alkyl chain on phosphorous or changing the counter anion. We previously reported [7] the use of chloride phosphonium based ionic liquid in Suzuki coupling reactions and alkylation reactions in triflouromethane sulfonyl imide phosphosphonium based ionic liquids.[8] Recently we demonstrated the anionic effect of phosphonium salt ionic liquids on Pd-catalyzed Buchwald-Hartwig amination reaction.[9] No reaction was observed in tri(hexyl)tetradecyl phosphonium chlrodie ionic liquid. In this study, we observed that trihexyl(tetradecyl) phosphonium ionic liquids containing nucleophilic co-ordinating

counter ions such as chloride and bromide anions retard the reaction whereas non co-ordinating anions like bis(trifluoromethane sulfonyl)imide (triflimide) and saccharide do not have a marked effect on the palladium catalytic cycle. In these reactions, we used $Pd_2(dba)_3.CHCl_3$ as a palladium source and 1-isobutyl-2,2,6,6-tetramethyl phosphorinane HBF_4 salt as ligand. Since it is important to know the active palladium precursor present in the reaction mixture, two reactions were run, one reaction containing triflimide ionic liquid and the other in chloride ionic liquid. The active palladium precursor was isolated from triflimide ionic liquid only. We were surprised to observe a new non-solvated crystal of $Pd(dba)_3$. Only one report [10] of the crystal structure of $Pd(dba)_3$ exists in which it is solvated with benzene. $Pd_2(dba)_3.CHCl_3$ is a purple coloured needle shaped complex containing a molecule of $CHCl_3$. In $Pd_2(dba)_3$, dba behaves as two monodentate ligands, and each palladium co-ordinates with three double bonds of three molecules of dba giving a 16 electron complex. It was also reported [10] that the $Pd_2(dba)_3$ complex can dissociate to $Pd(dba)_2$ or $Pd(dba)_3$ in benzene. In the $Pd(dba)_3$ from triflimide ionic liquid it was found only one palladium for three dba molecules.

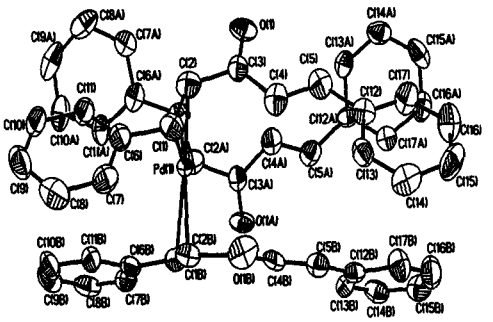

Fig:6.1 Crystal Structure of $Pd(dba)_3$ with palladium, Pd (1) probability of 83% is shown: thermal ellipsoids are set at the 30% probability level, with hydrogens omitted for clarity. Selected bond lengths (Å) : Pd(1)-C(1) 2.221(10), Pd(1)-C(2) 2.255(10), C(1)-C(2) 1.337(13), C(2)-C(3) 1.503(13), O(1)-C(3) 1.236(11).

The $Pd(dba)_3$ molecule consists of a trigonally coordinated Pd atom bonded to olefin groups of three dibenzylideneacetatone ligands. The structure of $Pd(dba)_3$ harvested from the phosphonium salt ionic liquid is remarkably different from that previously reported benzene co-ordinated structure. The structure determined here contains a palladium which is distributed at two sites, Pd(1) is 0.83% and Pd(2) is 0.17% resulting in the co-ordination of one palldium with three dba ligands. The three ligands have ideal *C3* symmetry. In this $Pd(dba)_3$ structure all double bonds have *trans* geometry and all the dba groups have s-*trans* geometry with respect to the position of the double bonds.

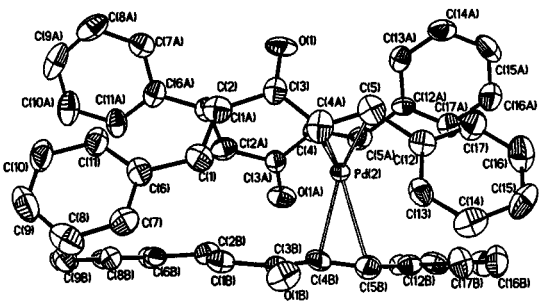

Fig : 6.2 Crystal Structure of $Pd(dba)_3$ with palladium, Pd(2) probability of 17% is shown: thermal ellipsoids are set at the 30% probability level, with hydrogens omitted for clarity. Selected bond lenghts (Å) : Pd(2)-C(4) 2.302(10), Pd(2)-C(5) 2.503(10), C(4)-C(5) 1.316(13), C(3)-C(4) 1.470(13).

The distance between palladium positions Pd(1) and Pd(2) reported here at 3.250(6) Å is comparable with that previously reported by Pierpont et al. [11] of 3.237(5) Å and also in agreement with the Pd-Pd bond distance reported by Ishii et al. [13] of 3.245(2) Å. However, it is 0.055(18) Å longer than the Pd-Pd distance reported by Pregosin et al in 1999 [14]. The average olefin C-C bond lengths reported [11,12,13,14] previously for both $Pd_2(dba)_3.CHCl_3$ and $Pd_2(dba)_3.CH_2Cl_2$ is 1.20(3) Å and for $Pd(dba)_3.C_6H_6$ is 1.38(2) Å, but in contrast the $Pd(dba)_3$ crystal from the phosphonium salt ionic liquid shows two different bond lengths at two different palladium sites, C1-C2 bondlength at Pd(1) is 1.337(13) Å and C4-C5 bondlength at Pd(2) is 1.316(13) Å. The average Pd-C bond length for both $Pd_2(dba)_3.CHCl_3$ [13] and $Pd_2(dba)_3.CH_2Cl_2$ [14] is 2.26(3) Å and 2.23(2) Å for $Pd(dba)_3$ [10] structure, but this new reported crystal structure has a Pd(1)-C distance of 2.238(10) Å and a Pd(2)-C distance of 2.4025(10) Å. The ratio of existance of 83% of

palladium on Pd(1) site over 17 % of palladium Pd(2) on the other site may be caused by the arrangement of the double bonds from three dba molecules. In the Pd(1) site three double bonds from the dba ligands lie further away from each other compared to the Pd(2) site where they are visibly closer. After the dissociation of $Pd_2(dba)_3.CHCl_3$ in trihexyl(tetradecyl) phosphonium triflimide to $Pd(dba)_2$ and then re-arranging itself to $Pd(dba)_3$, Pd(1) site must have been easier to form.

6.2 Experimental :

Crystal harvesting of $Pd(dba)_3$ in phosphonium salt ionic liquids: To a vial containing (169 mg) degassed trihexyl(tetradecyl)phsophonium bis(trifluoromethanesulfonyl)imide added Pd_2 $(dba)_3$ $CHCl_3$ (12 mg, 0.011 mmol), 1-isobutyl-2,2,6,6-tetramethylphosphorinane HBF_4 salt(8mg, 0.022 mmol), NaO^tBu (2 mg, 0.022 mmol) and 1 ml dry toluene which was allowed to evaporate through a needle in the vial cap in a glove box under nitrogen) was added. After three and a half weeks, a red crystal was harvested from the reaction mixture. The crystal was kept under paratone oil and frozen to a MiteGen. When a similar reaction was carried out by the addition of trihexyl(tetradecyl)phosphonium chloride (115mg), only palladium black was found in the ionic liquid. crystal data for C_{51} H_{42} O_3 Pd : M = 809.25, triogonal, space group R- 3c, a = 15.0031 (4), c = 60.050 (5) Å, U = 11705.9 (10) $Å^3$, Z = 12,

T = 173 (2) K, D_c = 1.378 mg/m^3, λ(Mo-Kα) = 0.71073 Å, μ(Mo-Kα) = 0.520 mm^{-1}, 16350 reflections collected. The maximum and minimum residual electron densities were 0.486 and –0.467 e $Å^{-3}$. The final agreement factors were R(F) = 0.0656 and $wR(F^2)$ = 0.1520, $I > 2\sigma(I)$ and all data, respectively (CCDC 652594).

Table 6.1. Crystal data and structure refinement for $Pd(dba)_3$.

Identification code	sc01	
Empirical formula	C51 H42 O3 Pd	
Formula weight	809.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	R -3 c	
Unit cell dimensions	a = 15.0031(4) Å	α= 90°.
	b = 15.0031(4) Å	β= 90°.
	c = 60.050(5) Å	γ = 120°.
Volume	11705.9(10) $Å^3$	
Z	12	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	0.520 mm^{-1}	
F(000)	5016	
Crystal size	.22 x .18 x .06 mm^3	
Theta range for data collection	1.71 to 22.99°.	
Index ranges	-16<=h<=16, -14<=k<=16, -56<=l<=66	
Reflections collected	16350	
Independent reflections	1818 [R(int) = 0.1838]	
Completeness to theta = 22.99°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.45	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1818 / 0 / 170	
Goodness-of-fit on F^2	1.289	
Final R indices [I>2sigma(I)]	R1 = 0.0656, wR2 = 0.1527	
R indices (all data)	R1 = 0.1520, wR2 = 0.1869	
Largest diff. peak and hole	0.486 and -0.467 $e.Å^{-3}$	

Table 6.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for sc01. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	-3333	3333	-164(1)	35(1)
Pd(2)	-3333	3333	-705(1)	39(3)
O(1)	-5807(5)	1702(5)	-454(1)	77(2)
C(1)	-4387(7)	3959(8)	-119(2)	68(3)
C(2)	-4975(8)	2990(9)	-189(2)	70(3)
C(3)	-5222(8)	2634(9)	-427(2)	57(3)
C(4)	-4786(8)	3395(9)	-608(2)	71(3)
C(5)	-5031(8)	3132(9)	-817(2)	72(3)
C(6)	-4282(9)	4289(11)	117(2)	63(3)
C(7)	-3809(8)	5340(9)	163(2)	67(3)
C(8)	-3665(9)	5709(10)	377(3)	86(4)
C(9)	-4012(11)	4991(14)	551(2)	101(5)
C(10)	-4491(8)	3958(12)	512(2)	87(4)
C(11)	-4607(8)	3636(9)	298(2)	70(3)
C(12)	-4666(8)	3859(9)	-1011(2)	55(3)
C(13)	-4181(8)	4913(10)	-987(2)	62(3)
C(14)	-3876(8)	5527(9)	-1166(2)	75(3)
C(15)	-4079(10)	5119(12)	-1376(2)	88(4)
C(16)	-4518(10)	4080(12)	-1398(2)	95(4)
C(17)	-4828(9)	3445(9)	-1219(2)	81(4)

Table 6.3. Bond lengths [Å] and angles [°] for $Pd(dba)_3$.

Pd(1)-C(1)#1	2.222(10)
Pd(1)-C(1)#2	2.222(10)
Pd(1)-C(1)	2.221(10)
Pd(1)-C(2)#1	2.255(10)
Pd(1)-C(2)#2	2.255(10)
Pd(1)-C(2)	2.255(10)
Pd(1)-Pd(2)	3.250(6)
Pd(2)-C(4)#1	2.302(10)
Pd(2)-C(4)	2.302(10)
Pd(2)-C(4)#2	2.302(10)
Pd(2)-C(5)#2	2.503(10)
Pd(2)-C(5)#1	2.503(10)
Pd(2)-C(5)	2.503(10)
O(1)-C(3)	1.236(11)
C(1)-C(2)	1.337(13)
C(1)-C(6)	1.486(13)
C(1)-H(1)	1.0000
C(2)-C(3)	1.503(13)
C(2)-H(2)	1.0000
C(3)-C(4)	1.470(13)
C(4)-C(5)	1.316(13)
C(4)-H(4)	1.0000
C(5)-C(12)	1.497(14)
C(5)-H(5)	1.0000
C(6)-C(11)	1.378(13)
C(6)-C(7)	1.396(13)
C(7)-C(8)	1.370(14)
C(7)-H(7)	0.9500
C(8)-C(9)	1.404(16)
C(8)-H(8)	0.9500
C(9)-C(10)	1.364(17)
C(9)-H(9)	0.9500

C(10)-C(11)	1.355(14)
C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
C(12)-C(17)	1.366(13)
C(12)-C(13)	1.378(13)
C(13)-C(14)	1.340(13)
C(13)-H(13)	0.9500
C(14)-C(15)	1.368(14)
C(14)-H(14)	0.9500
C(15)-C(16)	1.362(16)
C(15)-H(15)	0.9500
C(16)-C(17)	1.353(14)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(1)#1-Pd(1)-C(1)#2	118.56(12)
C(1)#1-Pd(1)-C(1)	118.56(12)
C(1)#2-Pd(1)-C(1)	118.56(12)
C(1)#1-Pd(1)-C(2)#1	34.8(3)
C(1)#2-Pd(1)-C(2)#1	87.4(3)
C(1)-Pd(1)-C(2)#1	153.0(3)
C(1)#1-Pd(1)-C(2)#2	153.0(3)
C(1)#2-Pd(1)-C(2)#2	34.8(3)
C(1)-Pd(1)-C(2)#2	87.4(3)
C(2)#1-Pd(1)-C(2)#2	119.55(7)
C(1)#1-Pd(1)-C(2)	87.4(3)
C(1)#2-Pd(1)-C(2)	153.0(3)
C(1)-Pd(1)-C(2)	34.8(3)
C(2)#1-Pd(1)-C(2)	119.55(7)
C(2)#2-Pd(1)-C(2)	119.55(7)
C(1)#1-Pd(1)-Pd(2)	96.9(3)
C(1)#2-Pd(1)-Pd(2)	96.9(3)
C(1)-Pd(1)-Pd(2)	96.9(3)
C(2)#1-Pd(1)-Pd(2)	86.1(3)
C(2)#2-Pd(1)-Pd(2)	86.1(3)

C(2)-Pd(1)-Pd(2)	86.1(3)
C(4)#1-Pd(2)-C(4)	113.8(3)
C(4)#1-Pd(2)-C(4)#2	113.8(3)
C(4)-Pd(2)-C(4)#2	113.8(3)
C(4)#1-Pd(2)-C(5)#2	130.2(4)
C(4)-Pd(2)-C(5)#2	114.4(4)
C(4)#2-Pd(2)-C(5)#2	31.4(3)
C(4)#1-Pd(2)-C(5)#1	31.4(3)
C(4)-Pd(2)-C(5)#1	130.2(4)
C(4)#2-Pd(2)-C(5)#1	114.4(4)
C(5)#2-Pd(2)-C(5)#1	113.0(3)
C(4)#1-Pd(2)-C(5)	114.4(4)
C(4)-Pd(2)-C(5)	31.4(3)
C(4)#2-Pd(2)-C(5)	130.2(4)
C(5)#2-Pd(2)-C(5)	113.0(3)
C(5)#1-Pd(2)-C(5)	113.0(3)
C(4)#1-Pd(2)-Pd(1)	75.3(3)
C(4)-Pd(2)-Pd(1)	75.3(3)
C(4)#2-Pd(2)-Pd(1)	75.3(3)
C(5)#2-Pd(2)-Pd(1)	105.6(3)
C(5)#1-Pd(2)-Pd(1)	105.6(3)
C(5)-Pd(2)-Pd(1)	105.6(3)
C(2)-C(1)-C(6)	124.4(12)
C(2)-C(1)-Pd(1)	74.0(6)
C(6)-C(1)-Pd(1)	106.1(6)
C(2)-C(1)-H(1)	114.7
C(6)-C(1)-H(1)	114.7
Pd(1)-C(1)-H(1)	114.7
C(1)-C(2)-C(3)	126.6(11)
C(1)-C(2)-Pd(1)	71.2(6)
C(3)-C(2)-Pd(1)	101.1(6)
C(1)-C(2)-H(2)	115.3
C(3)-C(2)-H(2)	115.3
Pd(1)-C(2)-H(2)	115.3

O(1)-C(3)-C(4)	124.7(10)
O(1)-C(3)-C(2)	115.9(10)
C(4)-C(3)-C(2)	119.4(11)
C(5)-C(4)-C(3)	121.7(12)
C(5)-C(4)-Pd(2)	82.7(7)
C(3)-C(4)-Pd(2)	102.7(6)
C(5)-C(4)-H(4)	114.7
C(3)-C(4)-H(4)	114.7
Pd(2)-C(4)-H(4)	114.7
C(4)-C(5)-C(12)	125.3(12)
C(4)-C(5)-Pd(2)	65.8(6)
C(12)-C(5)-Pd(2)	98.1(7)
C(4)-C(5)-H(5)	116.8
C(12)-C(5)-H(5)	116.8
Pd(2)-C(5)-H(5)	116.8
C(11)-C(6)-C(7)	116.6(10)
C(11)-C(6)-C(1)	125.2(12)
C(7)-C(6)-C(1)	118.2(11)
C(8)-C(7)-C(6)	121.9(11)
C(8)-C(7)-H(7)	119.1
C(6)-C(7)-H(7)	119.1
C(7)-C(8)-C(9)	117.8(12)
C(7)-C(8)-H(8)	121.1
C(9)-C(8)-H(8)	121.1
C(10)-C(9)-C(8)	121.8(13)
C(10)-C(9)-H(9)	119.1
C(8)-C(9)-H(9)	119.1
C(11)-C(10)-C(9)	118.0(13)
C(11)-C(10)-H(10)	121.0
C(9)-C(10)-H(10)	121.0
C(10)-C(11)-C(6)	123.9(12)
C(10)-C(11)-H(11)	118.0
C(6)-C(11)-H(11)	118.0
C(17)-C(12)-C(13)	119.2(11)

C(17)-C(12)-C(5)	117.6(11)
C(13)-C(12)-C(5)	123.3(11)
C(14)-C(13)-C(12)	120.7(11)
C(14)-C(13)-H(13)	119.7
C(12)-C(13)-H(13)	119.7
C(13)-C(14)-C(15)	120.6(11)
C(13)-C(14)-H(14)	119.7
C(15)-C(14)-H(14)	119.7
C(14)-C(15)-C(16)	118.1(12)
C(14)-C(15)-H(15)	120.9
C(16)-C(15)-H(15)	120.9
C(17)-C(16)-C(15)	122.0(12)
C(17)-C(16)-H(16)	119.0
C(15)-C(16)-H(16)	119.0
C(16)-C(17)-C(12)	119.1(11)
C(16)-C(17)-H(17)	120.5
C(12)-C(17)-H(17)	120.5

Symmetry transformations used to generate equivalent atoms:
#1 -y,x-y+1,z #2 -x+y-1,-x,z

Table 6.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $Pd(dba)_3$. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	33(1)	33(1)	39(1)	0	0	16(1)
Pd(2)	36(3)	36(3)	45(5)	0	0	18(1)
O(1)	57(5)	34(4)	113(6)	0(4)	-13(4)	3(4)
C(1)	61(8)	73(9)	77(8)	-4(7)	-9(6)	39(8)
C(2)	62(8)	71(8)	89(10)	-5(7)	4(7)	40(7)
C(3)	55(7)	78(9)	55(8)	3(6)	3(6)	46(7)
C(4)	81(9)	96(10)	72(9)	-1(8)	10(7)	72(8)
C(5)	76(8)	82(9)	77(9)	-8(8)	-3(7)	53(7)

C(6)	49(7)	89(10)	63(7)	-13(9)	-2(8)	43(6)
C(7)	60(8)	70(9)	78(9)	7(7)	6(6)	36(7)
C(8)	64(8)	88(10)	122(13)	-42(10)	-12(9)	49(8)
C(9)	72(10)	155(16)	81(12)	-58(11)	-17(8)	59(11)
C(10)	64(10)	138(13)	55(9)	-5(8)	11(6)	49(10)
C(11)	60(7)	99(9)	53(8)	3(7)	3(6)	42(7)
C(12)	59(7)	51(7)	71(9)	-1(7)	-2(6)	38(6)
C(13)	55(7)	82(9)	53(8)	-10(7)	-8(5)	39(7)
C(14)	74(8)	60(8)	103(10)	5(8)	16(8)	43(7)
C(15)	96(10)	100(12)	85(11)	49(9)	27(8)	63(9)
C(16)	131(14)	106(12)	63(9)	-7(8)	-5(8)	70(12)
C(17)	103(10)	67(9)	70(9)	2(8)	10(8)	41(8)

_ Table 6. 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3}) for $Pd(dba)_3$.

	x	y	z	U(eq)
H(1)	-4293	4497	-230	81
H(2)	-5457	2498	-75	84
H(4)	-4660	4096	-568	85
H(5)	-5603	2416	-847	86
H(7)	-3579	5814	43	81
H(8)	-3342	6426	405	103
H(9)	-3910	5232	701	122
H(10)	-4735	3479	632	104
H(11)	-4933	2917	271	84
H(13)	-4062	5207	-843	74
H(14)	-3515	6253	-1147	90
H(15)	-3920	5549	-1504	105
H(16)	-4608	3792	-1543	114
H(17)	-5153	2720	-1239	97

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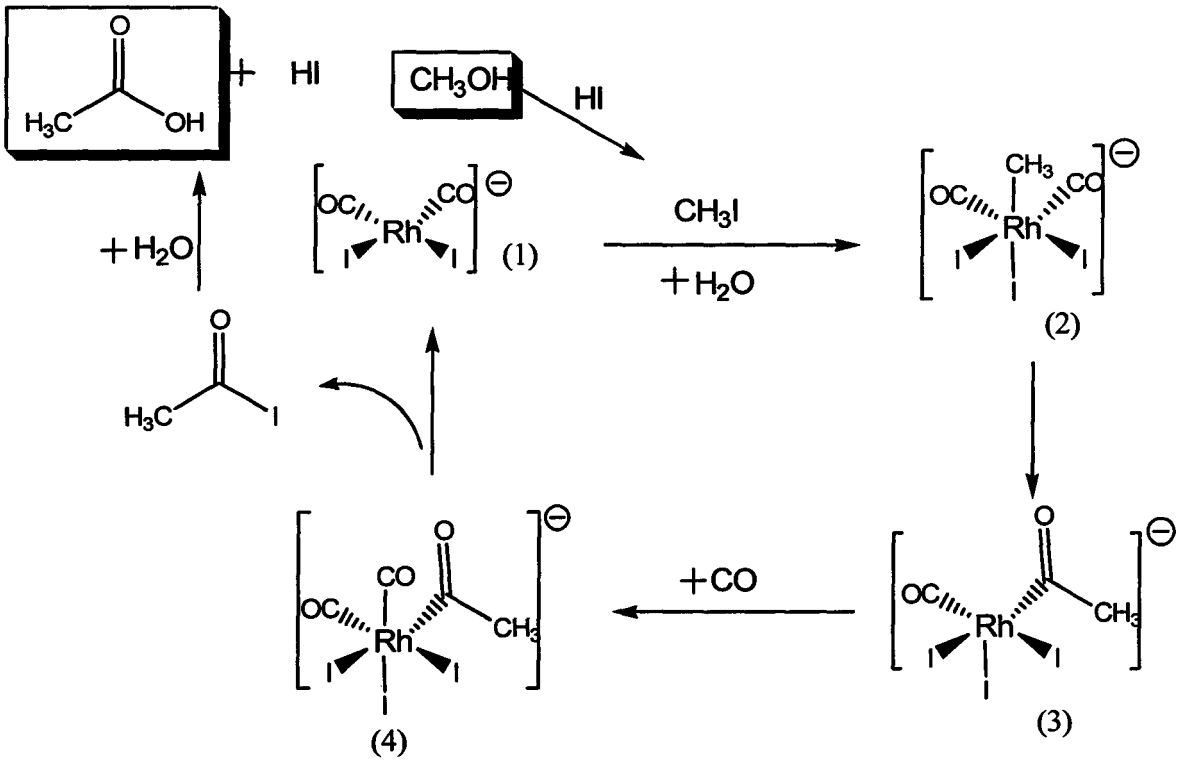
Chapter 7

7.1 New Synthetic method for the preparation of trialkyl(methyl)phosphonium ionic liquids:

The production volume of acetic acid utilizing the rhodium catalyzed carbonylation reaction between methanol and carbon dioxide was more than $8.3x10^6$ tons in the year 2000 [1]. Of this total production, more than 60% was based on using the $[Rh(CO)_2I_2]^-$ complex anion as the catalyst, in a homogeneous liquid phase Monsanto process [2]. The commercialization of a similar process has been recently reported, using iridium based process known as Cativa process [3].



Scheme 7.1: Monsanto Process for the preparation of acetic acid

For the catalytic cycle there are six important steps, the first step involves the oxidative addition of methyl iodide to *cis*- $[[Rh(CO)_2I_2]]^-$ in order to form $[[CH_3]Rh(CO)_2I_3]]^-$ which is a hexacordinate species. There is the migration of methyl group to the carbonyl ligand thereby transforming the anion and forming a pentacordinate acetyl complex $[[CH_3CO]Rh(CO)I_3]]^-$. The hexacoordinate dicarbonyl complex ((4), Scheme 7.1) is formed after the pentacoordinate complex reacts with carbon monoxide.

The six coordinate dicarbonyl complex then forms acyl-iodide (CH_3COI) by way of decomposition by reductive elimination. The active form of the catalyst is thus regenerated. Acetic acid is then formed from the hydrolysis of acyl-iodide.

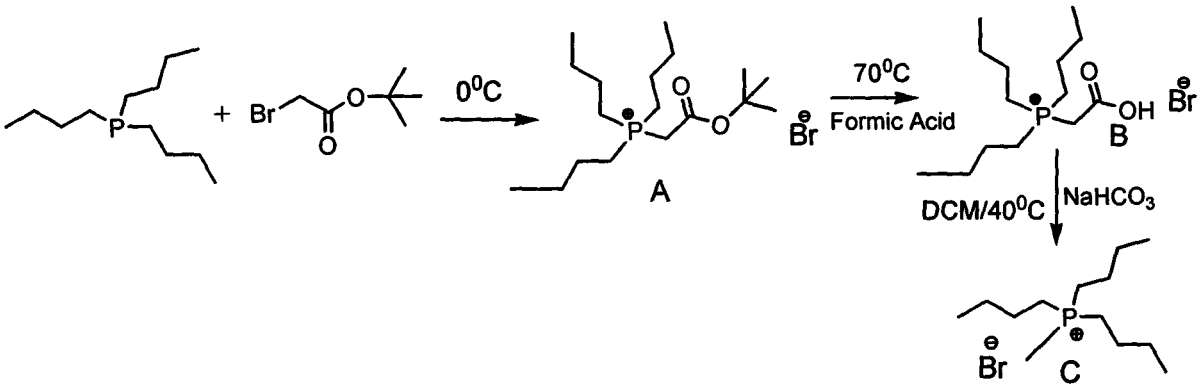
By using flash distillation under reduced pressure the reactants and products of the established Monsanto process continuous batch process are separated[4]. This process involves the recirculation of the catalyst, where the catalyst solution is returned to the reactor along with some of the reaction mixture. In order to prevent the formation of inactive species such as $[Rh(CO)_2I_4]^-$and the loss of rhodium in its insoluble rhodium(III)iodide form, the process needs to be controlled by reducing the through put of reagent per mole of rhodium. In order to have high production rates and minimize catalyst precipitation, the conditions in the reactor such as concentration of rhodium and water have to be well controlled (excess water produces corrosive HI and excess of Rhodium causes side reactions). There is much difficulty and cost associated with this process in plants since it also results in separation costs, higher corrosion rates as a result of hydrogen iodide formation and problems associated with the purification of the product. By anchoring rhodium iodide complexes on supports through ligand tethering or

ionic interactions, it is possible to use several heterogeneous catalyst systems for continuous flow liquid and gas phase processes, as an alternative to the Monsanto process[5]. One of the disadvantages of heterogeneous catalysts is their generally lower activity than homogeneous catalysts. As a result, there can be loss of metal carbonyl compounds by vaporization and insufficient reactant heat removal, rhodium metal leaching and even decomposition of the support material under high temperatures [6]. A high degree of stability and reactivity can be found on polymeric vinyl pyridine resins on which catalysts with $[Rh(CO)_2I_2]^-$ anions can be supported [7]. The commercialization of this catalyst system has been introduced for slurry phase methanol carbonylation.

Ionic liquids containing $[Rh(CO)_2I_2]^-$ catalyst for the production of acetic acid using a Monsanto type process can enable it to perform both gas phase [8]and liquid phase [9] carbonylation processes. A simple bubble column reaction system using a non-volatile catalyst solution which remains in the reactor for the duration of the process allows the gas phase process to proceed. Liquid phase processes are more complicated since they require the use of conventional continuous stirred batch reactors to allow for successive catalyst recycling and product flash separation. The heat generated from this reaction can be efficiently removed when the ionic liquid is used as the medium since it has high catalyst solubility. In order to recycle the recovered catalyst for a fresh cycle, the ionic liquid phase which contains the catalyst can be recovered and addition of methanol and iodomethane is necessary for the next catalytic cycle without the necessity of adding ionic liquid.

The above two methods using ionic liquids have been patented. Not only is the use of ionic liquids in the Monsanto process patented but also the method for the preparation of both nitrogen based and phosphonium based ionic liquids. In the patent it was also mentioned that the phosphonium or nitrogen based ionic liquids containing smaller chain lengths are quite useful. For example, tributyl(methyl)phosphonium halides are of greater utility as a result of the small chain(methyl) group. An obvious route for their synthesis from trialkylphosphines and iodomethane is also patented.

Methods to prepare trialkyl (methyl) phosphonium salts by anion exchange have also been patented. The following report describes a new unusual method for the preparation of trialkyl (methyl) phosphonium salts that appear to be applicable to any tertiary phosphine (Scheme 7.2).



Scheme 7.2: A novel synthetic route to trialkyl (methyl) phosphonium salts.

The synthesis of tributyl(methyl)phosphonium bromide features the addition of tributyl phosphine to *tert*-butyl bromoacetate at 0 °C to give the phosphonium ester (A, Scheme 7.2). This ester can then be hydrolyzed to form the corresponding acid (B, Scheme 7.2) at

70 °C in formic acid. Adding sodium bicarbonate to B results in neutralization to the desired product, (C, Scheme 7.2), accompanied by release of carbon dioxide.

7.2 Experimental:

Preparation of (tributyl phosphonium tertiary butyl acetate) bromide ionic liquid (Scheme 7.2, A):

Procedure: Into a two necked round bottomed flask fitted with a condenser is added tributyl phosphine (2.0691 gm, 10.093 mmol) under nitrogen, which was cooled to 0 °C and *tert*-butyl bromoacetate (2.0665g, 10.597 mmol) added drop wise. A white solid was formed. The product was dried under high vacuum for two hours and the yield was 3.941 gm (98% yield). White solid; ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 3.95 (2H, d, *J*=13.2 Hz), 2.56 (6H, m), 1.54 (12H, m), 1.46 (9H, s), 0.86 (9H, t, *J*=6.6 Hz), ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 164.1, 84.3, 28.6, 27.6, 23.8, 23.6, 23.5, 19.3(d, *J*=47.4 Hz), 18.2. ESMS 70 eV, m/z (rel. int.): 317 $[M-Br]^+$ (100).HRMS (ES+) calcd 317.2609 for $C_{18}H_{38}O_2P$, found 317.2622.

Preparation of (tributyl phosphonium acetic acid) bromide ionic liquid (Scheme 7.2, B):

To a round-bottomed flask was added tertiarybutyl-2-tributylphosphonium acetate (1.0 g, 2.5 mmol) and formic acid 5.0 ml added, the reaction mixture was heated at 70 °C overnight (16 hours) under nitrogen atmosphere. Removed the formic acid under vacuum, kept the resulted ionic liquid on high vacuum for two hours and the yield was 852 mg (quantitative yield) of the phosphonium bromide.

Viscous Liquid; ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 2.50 (6H, m), 2.41 (6H, m), 2.08 (3H, d, *J*=13.4Hz), 1.67 (12H, m), 0.89 (9H, t, *J*=6.8Hz) , ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 26.2(d, *J*=64.9 Hz), 22.9, 22.5, 22.2, 18.8 (d, *J*=49.0Hz), 12.1, 3.6(d, *J*=52.1 Hz).ESMS 70 eV, m/z (rel. int.): 217 $[M-Br]^+$ (100), 96.1 (15), 73.9 (20). HRMS (ES+) calcd 217.2085 for $C_{13}H_{30}P$, found 217.2075.

Preapartion of tributyl (methyl) phosphonium bromide (Scheme 7.2, C):

To a round bottomed flask was added (tributyl phosphonium acetic acid) bromide (1.0 g, 2.914 mmol), solid sodium bi carbonate (492.66mg, 5.865 mmol) followed by 5 ml of dry DCM and refluxed at 40 °C for 16 hours under nitrogen atmosphere. The resulting salt was filtered and the salts washed with 10 ml of DCM, evaporation of the DCM phase gave 830 mg, 98% of tributyl(methyl)phosphonium bromide ionic liquid. Viscous Liquid; ^{1}H-NMR ($CDCl_3$, 200 MHz), δ (ppm): 2.50 (6H, m), 2.41 (6H, m), 2.08 (3H, d, *J*=13.4Hz), 1.67 (12H, m), 0.89(9H, t, *J*=6.8Hz) , ^{13}C-NMR ($CDCl_3$, 50 MHz), δ (ppm): 26.2(d, *J*=64.9 Hz), 22.9, 22.5, 22.2, 18.8 (d, *J*=49.0Hz), 12.1, 3.6(d, *J*=52.1 Hz).ESMS 70 eV, m/z (rel. int.): 217 $[M-Br]^+$ (100), 96.1 (15), 73.9 (20). HRMS (ES+) calcd 217.2085 for $C_{13}H_{30}P$, found 217.2075.

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Conclusion:

The role of ionic liquids in industry has already risen in prominence replacing several hydrocarbon solvents of a polluting nature along with volatile solvents in a range of processes and synthetic applications for the production of a vast range of compounds; even nuclear fuels and the safe processing of nuclear wastes. Having the appropriate ionic liquid can directly result in higher yields and reduced wastes. This coupled with the recyclability of ionic liquids increases their utility and desirability tremendously.

Ionic liquids were originally discovered in the nineteenth century, although hidden under a different definition and with tremendously different applications. Molten salts were discovered and used in a variety of applications before the emergence of the term ionic liquid, in the modern sense. However, the distinctive difference which allowed for the differentiation of ionic liquids as a completely separate class of compounds from ionic salts lies in their low melting points, below the boiling point of water. These salts, which are liquid at room temperature, also have vastly different uses compared to 'molten salts'. Ionic liquid constitute organic cations and inorganic or organic anions. Practically, they can be used almost in the same way as organic solvents. They have many advantages over molten salts. One such advantage is with regard to the ability of ionic liquids to be used in the same reactions as molten salts but suffering from no ill effects associated with high temperatures, as is experienced by molten salts. Ionic liquids are therefore considered as neoteric (newly defined compounds which have previously existed within broad classification) liquids alongside other compounds such as supercritical fluids, which have existed for a while, but have newfound applications as solvents. If we

compare the use of ionic liquids to their previous classification, molten salts, we see that molten salts posses the advantages of having great stability electrochemically, chemically and thermally. Though they have these advantages, they are often not very practical reaction media. On the opposing side, ionic liquids are often excellent reaction media having the added advantage of operating at lower temperatures of below 100 °C compared to about 800 °C to 980 °C for a similar reaction in molten salts. Structurally, most of the ionic liquids that have been investigated to date contain quaternary nitrogen cores involving imidazolium, ammonium or pyridinium ions.

One of the first reported uses of phosphonium salt ionic liquid was its use in palladium mediated Heck coupling of aryl halides with acrylate esters (tributyl(hexadecyl)phosphonium bromide) was in this reaction as the recyclable medium. In addition to this, phosphonium salts are famous for their use as precursors to ylides and their use as phase transfer agents. Our interest was in the use of trihexyl(tetradecyl)phosphonium salt ionic liquids. Our motivation for using this ionic liquid was because of its thermal stability and inertness towards reactions with bases. The product isolation for the reactions conducted in phosphonium salt ionic liquids was from the tri-phasic system which is formed by the addition of hexane/ether and water to the phosphonium salt reaction media. The salts may be removed in the aqueous phase, while the non polar organic product could be extracted into the hexane phase. The major disadvantage of this process is that if the reaction contains a polar organic product, it is very difficult to get the product into the hexane layer. To overcome these limitations and to probe continuous reactor designs we decided to further investigate the work-up

processes in greater detail, especially with regards to small scale and medium scale reactions, since many organic products have low solubility in hexane and ether. One of the greater difficulties we were attempting to tackle is with regards to tri-phasic solutions where the isolation of the polar organic product was extremely difficult. To this end, we were able to develop methodologies in our lab which utilized the polarity of the organic reaction product. Two general methods were developed. The first method utilized the non-polar nature of the product in which case partitioning would occur between water, hexane and the phosphonium salt ionic liquid. When the chloride ions are used in the ionic liquid, then the separation process is very efficient. For the decanoate and triflimide derivatives which were the other available phosphonium salts, the most efficient method for their partitioning was found to be a 3:2(v/v) mixture of methanol and water. This allowed for sharp definition of three phases as a consequence of lowering the overall viscosity of the ionic liquid phase by the methanol/water solution. The non-polar organic product which contains only traces of the ionic liquid could be removed by extracting this with several portions of hexane. By utilising a short silica gel plug this may be quickly removed by filtration. For removal of polar products from the phosphonium salt ionic liquids, the addition of dichloromethane and a 3:2 (v/v) of methanol/water can be employed for the partitioning process. This ratio of methanol/water is not fixed and can be manipulated based on the organic product which needs to be separated. Chlorinated solvents such as DCM allow for a high degree of solubilization for phosphonium salts. The polar organic products produced can be easily and cleanly recovered by the

methanol/water phase. The solvent and catalyst which were both used in the reaction can be re-used upon the removal of DCM from the ionic liquid phase.

The use of phosphonium salt ionic liquids have the potential to be both unique and diverse and therefore one of our purposes in this research was to evaluate systematically how phosphonium salt ionic liquids could be utilized. One of the considerations into this research was to substitute the volatile, toxic solvents with phosphonium salt ionic liquids for a general use in mainstream reactions. In order to achieve this, we systematically developed a novel protocol for substititution reactions by replacing traditional organic solvents such as DMF and DMSO with trihexyl(tetradecyl) phosphonium bistriflimide ionic liquid. In this research we observed that as a medium, the standard phosphonium salt trihexyl (tetradecyl) phosphonium bistriflimde is an extremely efficient medium which allows for the promotion of various substitution reactions in an economical, chemo- and stereoselective fashion. High yields are obtained and the expected S_N2 substituted products are produced as a consequence of the reaction of primary electrophiles with a wide range of nucleophiles. When considering a β-phenyl substrate which is prone to elimination, the pathway which is preferred with basic and weak nucleophiles is substitution through the possible involvement of a phenonium ion. Both solvolysis and elimination products has been observed when using β-aryl primary halides in conventional media such as DMF. Often, it is assumed that ionic liquids are more polar than they actually are. This was highlighted during our study when polarity measurements indicated that the imidazolium bistriflimide ionic liquid has a polarity which was similar to that of acetonitrile which was a consistent result with the findings

that substitution reactions in solvents of high polarity prefer proceeding through borderline S_N1/S_N2 regions. From our observation in these substitution reactions, we found that free dissociated or solvent separated carbocations are not easily formed in phosphonium bistriflimide since there is a lack of racemization and elimination observed. In traditional solvents such as DMF and DMSO which are typical dipolar media, complete ionization would be hindered as a result of the presence of lone pairs. However, in our fairly polar solvent there are no basic lone pairs present and thus no hindrance to complete ionization. From our experiments we realized that unless forced, there would not be any formation of the free dissociated carbocations. As a result of this there is high chemoselectivity, which favours substitution reactions over elimination. Inversion reactions are also favoured as a result of stereoselectivity. We were therefore able to prove that the benefit associated with phosphonium bistriflimide ionic liquid is negligible in terms of carbocation stabilization unlike the standard dipolar solvents.

We next investigated Kornblum-type substitution for the preparation of nitroalkanes. Nitration may be considered to be a fundamental transformation in synthetic organic chemistry. Both aromatic and aliphatic compounds can be nitrated under different conditions. Usually, aromatic nitration is carried out in electrophilic fashion, while aliphatic nitration can proceed by free radical, electrophilic or nucleophilic pathways.

By using original Kornblum conditions, alkyl bromide was converted to nitroalkane by the reaction of silver nitrite as a nitrating agent in ethyl ether or DMF or DMSO.

The main disadvantage of this process lies in the reaction conditions. After addition of silver nitrite to alkyl halide in diethyl ether, the reaction mixture was stirred at 0 °C for

24 hours in the dark, followed by 36 hours at room temperature. Although by this procedure allowed for the nitrite ester side product to be reduced from 36% to 11-13%, maintaining the reaction temperatures was difficult. We overcame this practical difficulty and achieved an environmentally benign reaction. Our protocol eliminated the using of DMF or DMSO and also the formation of silver salts. The reaction time was decreased with a resultant increase in good yields of products that were simple to isolate. The formation of the nitro ester side product was also completely eliminated. We anticipated that the reason for the absence of the nitrite ester side product may be because of the formation of a weak bond between the positively charged phosphorous atom from the phosphonium salt ionic liquid with the negatively charged oxygen from the nitrite anion, which allows lone pairs of electrons on nitrogen to attack the α-carbon of alkyl bromide to give exclusively the desired nitro alkanes. We also reported the first examples of highly chemoselective Kronblum-type substitution reactions in ionic liquids that provide nitro-substitution products exclusively with aliphatic primary halides and problematic β-aryl halides.

One of the disadvantages associated with the use of ionic liquid solvents is that when they are employed in many reactions instead of conventional solvents, the work-up or product isolation stage still requires the use of volatile organic solvents. This defeats the purpose by which ionic liquids are supposed to completely substitute the conventional solvents. Since ionic liquids have been shown to demonstrate a wide range of applicability, our investigations therefore turned towards investigating the use of ionic liquids in reactions in which there would be solvent free product isolation along with

recycling protocols for the ionic liquid based on the low volatility of phosphonium salt ionic liquids. In order to achieve this, the synthesis of butyl acetate ester was investigated. The esterification was conducted in the trihexyl(tetradecyl)phosphonium bistriflimide ionic liquid where acetic acid and potassium carbonate were reacted with butyl bromide. 74% yield was isolated for the ester by direct distillation from the reaction mixture. During this process we also demonstrated the general application of this carboxylate alkylation product as well as the high stereochemical inversion which occurs when using phosphonium salt ionic liquids with primary and secondary bromides. Alternatively, primary and secondary tosylates can be used with a large variety of hindered electron rich or electron deficient acids. There has been no observation to support elimination from the α-alkylation of the acid ester or from the electrophile. By using direct solvent free distillation, the product ester was easily isolated while allowing the ionic liquid to be re-used. Alternatively, standard extraction protocols discussed above can be used to isolate the product ester from the phosphonium salt ionic liquids. When compared to other processes that have used ionic liquids, we find that this esterification occurs at a relatively low temperature by comparison, therefore provides us with sufficient evidence to confidently state that this esterification protocol can support the development of economically viable, benign industrial processes for the HPV ester synthesis and high value, lower volume targets.

Phosphonium salt ionic liquids can also be used as media for probing the reaction, by which fundamental reaction mechanisms can be understood. In this context we investigated the anionic effects of phosphonium salt ionic liquids for the fundamental

understanding of the disputed mechanism of Buchwald-Hartwig amination reactions. In this study, we discovered that in terms of the success of amination reactions, nucleophilic co-ordinating counter ions are quite detrimental. Anions such as bistriflimide and saccharide derivatives which are diffuse, weakly or non-coordinating are quite superior towards the success of amination reactions. This investigation allowed us to realize that our work is in good agreement with other studies where the solvent effect studies showed donor solvents to be inferior media. In the presence of co-ordinating anions or solvents the palladium mediated catalytic cycle will be inhibited. As a result of this, the diaryl amine which is weakly nucleophilic cannot participate in the ligand exchange step.

When these results were compared to the Suzuki cross coupling reaction, they were strikingly different to the outcome found with chloride containing ionic liquids. Since the reaction conditions are similar to the Suzuki process, it is unlikely that palladium catalysts would be operative in the chloride containing ionic liquid during the Suzuki process. To understand the basic mechanisms associated with these contrasting results from these anionic effects we used ionic liquids to probe the reaction mechanism. For example, when 4-bromobiphenyl and diphenylamine were reacted by a cross coupling reaction, the reaction progressed quite well when toluene was the solvent. For cross coupling reactions in toluene by the addition of trihexyl(tetradecyl)phosphonium bistriflimide, whether 5 equiv. or up to 10 equiv (relative to 4-bromobiphenyl) was used, there was no difference in terms of product formation, which was found to be 98% conversion to the desired product. For the cross coupling reaction in toluene, it was found

that addition of 5. 0 equiv of trihexyl (tetradecyl) phosphonium chloride (relative to 4-bromobiphenyl) poisoned the operative catalytic cycle. Although 1.0 equiv. of the chloride ionic liquid was tolerated, the reaction didn't proceed at all in toluene when 5.0 equiv. of soluble chloride ionic liquid was added. When these results are compared to that of the cross coupling reaction in the ionic liquid as a solvent, the generality of the ionic effect is confirmed since the results of both reactions correlate well. Bistriflimide ionic liquids are considered to be dipolar, halide free media. When weakly nucleophilic di-aryl amines are used, cross coupling occurs very efficiently. For this reaction, when performed in toluene using conditions that allow strong nucleophiles such as aryl boronic acids to participate, 5 equiv. of soluble chloride is enough to poison the catalytic cycle with this amine. The ligand exchange step of the mechanism provides an explanation for this; we were also able to provide mechanistic detail by using these phosphonium salt ionic liquids that demonstrated the ligand exchange step occurs by a dissociative pathway.

The results of our experiments show that the general anionic effects which we uncovered in phosphonium salt ionic liquids are applicable to Buchwald-Hartwig amination reactions which are conducted in standard solvents such as toluene. The general anionic effect is demonstrated by the amination reaction which took place in phosphonium salt ionic liquids and toluene along with the addition of soluble anions. The anionic effect in this cross coupling reaction can be effectively probed in the ideal media of phosphonium salt ionic liquids since the solvent couples with either the non-coordinating or co-ordinating anions. We have gained insight into the nature of the Buchald-Hartwig

amination cycle through the utilization of a diffuse, phosphonium cation coupled to anions which vary from Lewis basic to non-coordinating.

To continue our investigations on the active palladium precursor in the Buchwald-Hartwig amination reactions, we kept two reactions in toluene; one by addition of chloride ionic liquid to palladium precursor, namely $Pd_2(dba)_3CHCl_3$ along with1-isobutyl-2,2,6,6-tetramethyl phosphorinane HBF_4 salt and KO^tBu. The other reaction was kept with the addition of bistriflimide ionic liquid. We were able to isolate the active palladium precursor crystal for the Buchwald-Hartwig amination reactions only from the bistriflimide ionic liquid and we didn't observe any of the crystals in chloride containing ionic liquids. After the X-ray studies, we discovered the first non-solvated palladium dibenzylidene acetone in phosphonium salt ionic liquids. The crystal structure was also different from the previously reported crystals.

Future Work:

Since the properties of ionic liquids are easily and selectively tuned, it will be necessary to undertake toxicity studies to establish the appropriate range of their utility. That is, the biological properties which are associated with ionic liquids have not yet received due respect. For example, the similar natures of active pharmaceutical ingredients, pharmaceutical precursors, and many of the building blocks of ionic liquids could allow for a vast selection of pharmaceutically important products. Biologically active ions have been incorporated in some new ionic liquids. The motivation behind such work has been to utilize low toxicity ions to obtain the desired physical properties of the ionic liquid. An example of this is the use of quaternary ammonium cations for their anti microbial

properties [1]. Using these ionic liquids doesn't compromise the biological activity, since ionic liquids such as quaternary ammonium cations have been shown to retain their biological activity when used.

It is possible to use ionic liquids with the primary purpose of utilizing their biological activity. The active pharmaceutical ingredients (APIs) which are currently used in the pharmaceutical industry and many Government regulated industries are generally crystalline. These compounds are either solvates of neutral compounds or salts or neutral compounds. In order to produce the desired APIs, a pure pharmaceutical salt is obtained in the solid form after its selection by screening salts of pharmaceutically accepted counterions. In this process, the product solubility and control of crystal size assist in simplifying the manufacturing of these APIs. The disadvantages of using the solid forms of the APIs include factors such as low solubility, polymorphic conversion and limited bioavailability as a consequence of several other factors. The use, therefore, of certain new APIs is unsuccessful because of their bioavailability and solubility [2].

This problem could have a solution if targeted from an ionic liquid approach. From the investigations done on ionic liquids, it is apparent that salts which are produced by ionic liquids may be altered in such a way that allows the desirable properties to be enhanced or produced in the final drug. This can have a significant effect on improving the biological activity, efficacy, and even introducing a secondary biological activity. Many investigations have been specific towards the structural and physical properties which are optimal for ionic liquid formation. When an ionic liquid is being formed, the specific ions which are chosen have properties such as low symmetry, charge diffusion ions and

characteristics similar to that of APIs. An example of this is the nitrogen containing heterocycles which are common feature in many ionic liquids while being a component of typical APIs [1]. It is imperative that the ion pairs for the formation of the ionic liquid be given due consideration, since it will ultimately effect its end result.

The understanding of ionic liquids with regards to the dual functioning of salts is quite wide. However, this has found limited utility in terms of its application towards salts of API's and related systems. The problems being faced with APIs include bioavailability, solubility and polymorphism. If the pure liquid salt forms of the APIs are used, in addition to crystalline salt screening and the traditional API screening, many of the issued being faced may be negated. The characteristic of ionic liquids which allows them to be designed to suit the researcher needs seems to be very applicable in the pharmaceutical field. In addition to overcoming many of the issues which are as a consequence of the solid drug, ionic liquids have the capacity to provide viable new options and also to introduce new treatment options not previously available by way of traditional approaches or the use of solid APIs. The prospect of tuning IL-APIs which are specific to individual needs is as exciting as the potential to tune the ionic liquids' chemical and physical properties. The failure which is being faced by APIs can be completely eradicated if it is coupled with the appropriate anion or cation, thereby overcoming issues such as poor solubility. However, as with every technique there can be potential hazards. It may not be possible to predict the synergistic biological effects which could result from pairing two biologically active ions. Though the process by which IL-APIs could be prepared is relatively simple, it would probably require extensive testing before passing

regulatory agencies. While this can potentially be a serious hazard it could also be a completely new treatment option or a significantly enhanced drug efficacy which was never available from crystalline APIs [1].

The few examples of similar uses which were reported are for nitrogen based cations. It will be a tremendous significance if this study can focus on phosphonium based drugs. There are many phosphorous based pro drugs which are currently in use [3]. Converting these drugs to the corresponding phosphonium based ionic liquids will be of significant applicability in the future.

It is apparent that ionic liquids have potential use in the pharmaceutical industry, not only as solvents but as materials suitable for a variety of process options.

The evolution of ionic liquids is by no means limited to one particular industry or discipline. The applications to which ionic liquids can lend themselves are vast and fascinating. The chemistry of ionic liquids is presently on the verge of becoming mainstream, with several areas yet to be investigated and several latent new frontiers of discovery. Though this reaction medium will not solve every problem that exists within chemistry, its potential lies far beyond what presently exists, and therefore the burden of proof in terms of realizing the true capacity of ionic liquids lies with the initiative and imagination of researchers in every corner of science.

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