DEHYDRATION REACTIONS OF BENZYLIC ALCOHOLS AND PREPARATION OF PALLADIUM NANOCRYSTALS IN IMIDAZOLIUM AND PHOSPHONIUM IONIC LIQUIDS

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by

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ABSTRACT

Palladium catalyzed dehydrative etherification of benzyl alcohols in imidazolium ionic liquids (ILs) were studied. Several hydrophobic and hydrophilic imidazolium ionic liquids were employed and as expected, higher yields were obtained when hydrophobic ionic liquids were used as the reaction media. Among the transition metal complexes studied, $Pd(CH_3CN)_2Cl_2$ demonstrated the highest catalytic activity. $[BMMIm]PF_6$ ([BMMIm]= 1-butyl-2,3-dimethylimidazolium) was also used to study the possibility of N-heterocyclic carbene (NHC)-palladium complex formation. A catalytic cycle is proposed that supports the important roles of the ionic liquids and Pd in this reaction, in which ionic liquids stabilize the proposed ionic intermediates.

Phosphonium ILs were found to catalyze the above-mentioned reactions and an added metal was not needed. Benzyl ethers and alkenes were obtained from primary and secondary benzylic alcohols in good to excellent yields. Commercially available hydrophobic phosphonium ionic liquids containing the trihexyl(tetradecyl)phosphonium cation paired with six different anions were used for the reactions under microwave irradiation. NOESY NMR, in addition to some other NMR techniques, were used to study the interaction of substrates and ILs in order to gain insight into the reaction mechanism. The acidic properties of the phosphonium ionic liquids were also investigated in order to potentially correlate the pH of the ionic liquids and the reaction yield. There was no correlation.

Trihexyl(tetradecyl)phosphonium ILs were also found to support the formation of Pd(0) nanoparticles without the addition of reducing agents such as $NaBH_4$. Upon varying the Pd(II) sources and the anions of the phosphonium ILs, crystalline Pd nanoparticles grew as truncated octahedrons, octahedrons and trigonal plates with a narrow size distribution. No nanoparticle formation was observed when phosphonium ionic liquid with chloride anions were used. The presence of chloride anions is proposed to lead to oxidative etching of the particles and this process is reduced in the presence of certain anion partners including bis(2,4,4-trimethylpentyl)phosphinate. Two possible reduction mechanisms based on reactions of the phosphonium cation were suggested for the formation of the Pd(0) species. Different techniques such as TEM, XRD, FT-IR and TGA were employed to characterize the prepared nanocrystals and assess the role of the phosphonium ILs in their synthesis. The in situ prepared Pd nanocrystals in phosphonium ILs were used in a Suzuki coupling reaction and high yields were obtained.

To my wife, **SETAREH**, for all her support, understanding and motivation while I was writing this thesis.

&

To my parents for all their unconditional support in whole my life.

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LIST OF ABBREVIATIONS

ATR: attenuated total reflection

[BMIm]PF_6: 1-butyl-3-methylimidazolium hexafluorophosphate

[BMIm]BF_4: 1-butyl-3-methylimidazolium tetrafluoroborate

[BMMIm]PF_6: 1-butyl-2,3-dimethylimidazolium hexafluorophosphate

CAN: ceric ammonium nitrate

CWES: catalytic Williamson ether synthesis

DMC: dimethyl carbonate

DMS: dimethyl sulphate

DPM: diphenylmethyl

ECOENG^{TM}500: cocosalkyl pentaethoxy methyl ammonium methylsulfate

EDX: energy dispersive X-ray

[EMIm]Cl: 1-ethyl-3-methylimidazolium chloride

FWHM: full width at half maximum

GHS: globally harmonized system

GLC: gas-liquid chromatography

[HMIm][TfO]: 1-hexyl-3-methylimidazolium trifluoromethanesulfonate

HPA: heteropoly acid

HRMAS: high resolution magic angle spinning

IL: ionic liquid

ISM: industrial scientific and medical frequencies

LDA: lithium diisopropylamide

LHMDS: lithium bis(trimethylsilyl)amide

LL-PTC: liquid-liquid phase transfer catalyst

MW: microwave

NHC: N-heterocyclic carbene

NOESY: nuclear overhauser effect spectroscopy

$[NTf_2]^-$: bis(trifluoromethylsulfonyl)amide

$[OTf]^-$: trifluoromethanesulfonate

PEG: polyethylene glycol

PTC: phase transfer catalyst

PTFE: polytetrafluoroethylene

$[P_{666,14}]Cl$: trihexyl(tetradecyl)phosphonium chloride

RF: radio frequency

SCF: supercritical fluid

SLL-PTC: solid-liquid-liquid phase transfer catalyst

TEBAC: triethylbenzylammonium chloride

TEM: transmission electron microscopy

TGA: thermogravimetric analysis

TMSCl: chlorotrimethylsilane

TON: turnover number

VOC: volatile organic solvent

XRD: X-ray diffraction

Chapter 1

Introduction to ionic liquids

Introduction to ionic liquids

1-1 Definition and brief history

Ionic compounds composed of organic cations and inorganic or organic counterions that have melting points below the boiling point of water are called ionic liquids (ILs).[1,2] They have been called "neoteric solvents", however they can be traced back to 19th century (Table 1-1).[3] In the literature, these ionic compounds can be found with different names including "molten salts", "room temperature molten salts" and "liquid organic salts",[1] but if they have melting points lower than 100 °C, it is now generally accepted to call them

Table 1-1. Historical overview of ionic liquids[1-3]

Scientist	Time	Discovery
Unknown	Mid 19th century	Red oil was observed in Friedel-Crafts reactions. Later NMR showed that the red oil was a salt.
Paul Walden	1914	Liquid alkylammonium nitrate molten salts
John Yoke	1963	Mixtures of copper(I) chloride and alkyl ammonium chlorides
Jerry Atwood	1976	Ionic liquid clathrates
Robert Osteryoung	1978	$AlCl_3$-1-butylpyridinium chloride liquid systems at ambient temperature
John Wilkes	1982	Tetrachloroaluminate ionic liquids
Mike Zaworotko & John Wilkes	1992	Air and water stable imidazolium ionic liquids
Jim Davis	1998	Designer solvents or task-specific ionic liquids

ionic liquids.[1,4] Since water is partially dissociated to H_3O^+ and OH^- at ambient temperature, ionic liquids are sometimes called non-aqueous ionic liquids in order to differentiate them from water.[5]

1-2 Chemical and physical properties

Some of the common cations found in ionic liquids are imidazolium, phosphonium, pyridinium, ammonium, pipyridinium, triazolium (Figure 1-1) and examples of anions that they can be paired are hexafluorophosphate, tetrafluoroborate, dicyanamide, bromide, trifluoromethanesulfonate, bis(trifluoromethylsulfonyl)amide, alkylbenzenesulfonate (Figure 1-2). Based on various combinations of cations and anions thousands of ionic liquids have been reported to date.

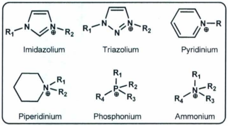


Figure 1-1. Some typical cations in ionic liquids[1,2]

Usually the physical properties of ionic liquids, such as solubility, viscosity and color, are controlled by the anion and the chemical properties are dominated by the cation;[6,7] however, this is not clear-cut. For example, 1-butyl-3-methyl imidazolium hexafluorophosphate, [BMIm]PF_6, is more hydrophobic than [BMIm]BF_4 and both of them are liquids at room temperature, while [BMIm]Cl has a melting point of around 70 °C. Therefore, the anion exchange is adjusting their physical properties.[5] In order to reach a lower melting point for the ionic liquid, the cation should have lower geometrical symmetry.[8] As another example, bis(trifluoromethylsulfonyl)-amide, tetrafluoroborate and triflate ($[OTf]^-$) containing phosphonium ionic liquids are much more thermally stable than the related trifluoroacetate ionic liquids.[9]

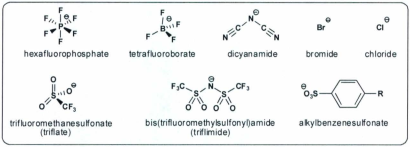
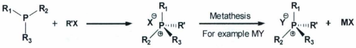


Figure 1-2. Some typical anions in ionic liquids[1,2]

1-3 Preparation of ionic liquids

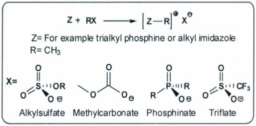
Since alkyl halides are comparatively inexpensive chemicals and chloride and bromide are good leaving groups, S_N2 reactions between nucleophiles (*e.g.* containing nitrogen, phosphorus or sulfur) and alkyl halides have been widely used to make ionic liquids.[10] In this process the leaving group (the halide) becomes paired with the resulting cation as the counter ion. Subsequently, through a metathesis process a wide variety of ionic liquids can be produced. Scheme 1-1 shows an example for the synthesis of phosphonium ionic liquids followed by a metathesis process using an alkali metal or silver salt.[11]



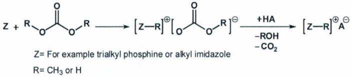
Scheme 1-1. Synthesis of phosphonium ILs followed by a metathesis substitution. "R" groups are alkyl chains, X is a halogen atom and MY is an alkali metal salt[11]

In 1992, Zaworotko and Wilkes introduced the first generation of air and water stable ionic liquids.[12] They reported the synthesis of a series of imidazolium based ionic liquids *via* a metathesis reaction of [EMIm]I and the corresponding silver salt in methanol or methanol-water media. Later, Carlin *et al.* treated [EMIm]Cl with the appropriate acid (protonated form of the desired anion) in the presence of excess Ag_2O.[13] Because these reactions were performed in aqueous media, silver compounds were used to precipitate out the halide as silver halide at the workup stage. The above mentioned method is expensive, because stoichiometric amounts of silver compounds are used and silver salts are produced as byproducts. Also silver contaminated products are inevitable. Fuller *et al.* developed a non-aqueous method to synthesize these hydrophilic ionic liquids.[14] They treated [EMIm]Cl with NH_4BF_4, instead of a silver salt, in acetone. The insolubility of NH_4Cl in acetone is the driving force for the production of [EMIm]BF_4. Alkali metal salts, like lithium triflimide, are also being used widely for this purpose.[11] The latter method is easier and cheaper than the silver salt method and it can be used for both hydrophilic and hydrophobic ionic liquids. Although in the aforementioned halogen salt methods a wide variety of ionic liquids can be prepared, halide contamination can be a problem when using these ionic liquids. For example, halides can poison metal-based catalysts, increase the viscosity of ionic liquids, affect their density and their ^{1}H NMR chemical shifts.[10,15] Therefore, halogen-free synthesis of ionic liquids has become a goal for researchers in recent years.[16]

Alkylating agents like organosulfates, trialkylphosphates, dialkylphosphonates, alkyl triflates and trifluoroacetates can be used to produce halogen-free ionic liquids.[10,17,18] In these methods the leaving groups can act as the desired anion in the ionic liquids. In these direct syntheses of the desired ionic liquid (Scheme 1-2), there is no need for the metathesis reaction. Dimethyl carbonate has been claimed to be a more environmentally friendly alkylating agent compared to the aforementioned examples.[10,19] It can be used as an alkylating agent to produce ionic liquids with a methyl carbonate anion. Subsequently different ionic liquids can be prepared through a metathesis reaction of the methyl carbonate salt and a Brønsted acid.[10] The only theoretical byproducts in this reaction are carbon dioxide and methanol (Scheme 1-3). Carbonate based ionic liquid precursors are now commercially available through Sigma-Aldrich for the synthesis of imidazolium, ammonium, phosphonium, pyrrolidinium, piperidinium and morpholinium type ionic liquids.[20] If a free acid for an anion is not available (for example HSCN), the ammonium salt can be used instead.[20]



Scheme 1-2. Halogen-free synthesis of phosphonium ionic liquids with different alkylating agents[10,19]



Scheme 1-3. Synthesis of a carbonate based ionic liquid followed by Brønsted acid anion exchange[10,19]

1-4 Uses and applications of ionic liquids

1-4-1 Introduction

There are advantages and disadvantages surrounding the applications of ionic liquids.[21,22] Are they green solvents? Are they really non-volatile? Should we use them at all? These are some questions that chemists should take into consideration before investigating ionic liquids in their research. The simple answer is that they do not perform magic, however they can be very useful tools for chemists in a range of fields. Ionic liquids have found applications in organic synthesis,[23-27] electrochemistry,[28] separation and extraction processes.[29] In addition to their use in academic research, some industrial uses of ionic liquids have been reported.[30-33] In the following two sections, more details about catalytic reactions and preparation of metal nanoparticles in ionic liquids are presented. These are the areas where contributions to the field of ionic liquid research have been made in this thesis.

1-4-2 Catalytic reactions in ionic liquids

The roles of ionic liquids in catalytic reactions can be discussed from three different perspectives. They can be used just as reaction media; however, they can also be employed as catalysts or co-catalysts. Either way, using ionic liquids in catalytic reactions can fulfil one of the most important principles of green chemistry, as generally catalysts in ionic liquids are recyclable. Ionic liquids can immobilize catalysts, while products and remaining starting materials can be removed by distillation or solvent extraction. The recycled ionic liquid and catalyst can be reused for another reaction by loading fresh substrate. This recyclability can make the reactions more environmentally friendly and also reduce expenses associated with the cost of the ionic liquid and catalyst. The above-mentioned uses will be discussed further with more emphasis on the special properties of ionic liquids in catalytic reactions rather than a survey of the types of reactions performed.

Because of the unique ionic nature of ionic liquids as solvents, they can dissolve a wide variety of ionic metal complexes. This property is often highlighted when ionic liquids are compared with classical solvents and can eliminate the ligand requirement when using ionic liquids for metal catalyzed reactions. In order to dissolve metal complexes in regular organic solvents, ligands with various functional groups are used to adjust the polarity of the complexes. The ability of ionic liquids to dissolve metal complexes has led to ionic liquids being widely used in homogeneous catalytic reactions. One of the pioneering works in this field was reported in 1972 by Parshall who was working at DuPont.[34] He reported platinum catalyzed hydrogenation and hydroformylation reactions of olefins in low-melting tetraalkylammonium salts of the $SnCl_3^-$ and $GeCl_3^-$. The low melting salt in this study acted as a good solvent for both substrates and the platinum catalyst ($PtCl_2$). Moreover, it worked as a ligand and it was proposed that it prevented the metal catalyst from being reduced to its metallic form.[34]

Various kinds of ionic liquids, which prevent catalyst decomposition and metal precipitation, have been reported. For example, several imidazolium, tetraalkyl phosphonium and tetraalkyl ammonium ionic liquids have been shown to stabilize metal complexes. Cocosalkyl pentaethoxy methyl ammonium methylsulfate (ECOENG^{TM}500) (Figure 1-3) in combination with dioxane was demonstrated to stabilize palladium catalysts and prevent the formation of palladium black in Suzuki cross coupling reaction.[35]

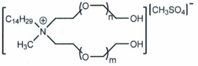
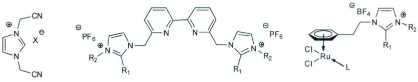


Figure 1-3. Chemical structure of ECOENG 500[35]

Figure 1-4 (compounds **1.1** to **1.3**) shows some examples of ionic liquids with functional groups that have been designed specifically to have a dual function of solvent and ligand in catalytic reactions.[36] Ionic liquids similar to the ones presented in Figure 1-4 can be highly efficient in the immobilization of metal catalysts. However, the immobilization of the metal catalysts in an ionic liquid phase has also been reported for simple imidazolium and phosphonium ionic liquids.[30,37-39] In these examples, the products or byproducts can be extracted in a suitable organic solvent, while the metal complex remains in the ionic liquid phase. This method is suitable for ionic liquids with very low solubility in an organic solvent, while the products or byproducts should have a good solubility in the organic solvent. In this way after the separation of organic and ionic liquid phases, the remaining organic solvent in the ionic liquid can be removed under vacuum. The ionic liquid phase, containing the catalyst, can be reused after loading with fresh reagent. These systems have advantages of both homogeneous and heterogeneous catalysis (catalyst efficiency in homogeneous and easy separation in heterogeneous systems). Some of the ionic liquids, *e.g.* $[P_{666,14}]Cl$, have the ability to make a ternary mixture with water and an organic solvent. For example, McNulty *et al.* reported cross-coupling Suzuki reactions in this ionic liquid.[40] After completion of the reaction, upon adding water and hexanes (1:3

volume ratio) to the mixture, salts and excess base went to the aqueous layer at the bottom while the product was extracted into the organic phase in the top layer. The central layer, which is the ionic liquid and the catalyst, could be reused after drying.



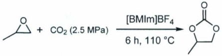
(1.1) **(1.2)** **(1.3)**

Figure 1-4. Some examples of functional ionic liquids with the potential use as a ligand and solvent[36]

Catalytic carbonylation, hydroformylation and hydrogenation using gaseous substrates have been studied in a variety of ionic liquids.[24,41,42] The solubility of gases such as CO_2, CO and H_2 is important for these reactions. Factors such as the polarizability of the gases or hydrogen bonding interactions between gases and solvents can change the solubility of gases in ionic liquids, however other parameters including the anions and cations of the ionic liquids are important too. For example, $[NTf_2]^-$ increases gas solubility compared to ionic liquids containing $[BF_4]^-$ and $[PF_6]^-$.[41,43] Taking into account all these factors, the solubility of gases in ionic liquids, is generally not much higher than in classical solvents.[41,42] However, in the aforementioned reactions, higher catalyst activities have been reported in ionic liquids compared with regular solvents. For example, in a rhodium catalyzed hydroformylation reaction of methyl-3-pentenoate, the catalyst was completely deactivated in regular organic solvents after its third use, but it retained its activity in

[BMIm][PF$_6$] for at least ten cycles. A TON* of 6640 was reported for the reaction in [BMIm][PF$_6$] after ten cycles, while this number for dichloromethane and toluene was 980 and 630, respectively.[41,44]

In addition to the role of reaction media, ionic liqids can also work as organocatalysts. In this way, the use of metal-containing catalysts can be eliminated. This is important as metal contamination of products can be an issue especially in the pharmaceutical industry. The selective cycloaddition of carbon dioxide to propylene oxide catalyzed by [BMIm]BF$_4$ has been reported (Scheme 1-4).[45] The propylene carbonate product was separated from the reaction mixture by distillation and the ionic liquid medium was reused four times and maintained good activity.[45] No clear mechanism for this reaction was proposed. It was claimed that in this reaction [BMIm]$^+$ activated the propylene oxide-CO$_2$ acid-base adduct. The possibility for the formation of the propylene oxide-CO$_2$ adduct was deduced based on the appearance of a new band in the UV spectrum of a saturated solution of CO$_2$ in propylene oxide at 260 nm.[45,46]



Scheme 1-4. Ionic liquid catalyzed cycloaddition of carbon dioxide to propylene oxide[45]

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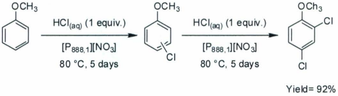
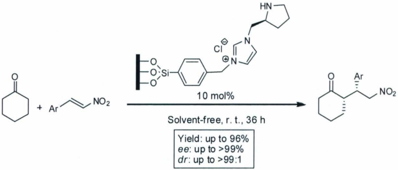
* TON (turnover number) is the number of moles (molecules) of a substrate that a mole (molecule) of a catalyst can convert into the product before the catalyst become deactivated.[5]

As organocatalysts, some phosphonium ionic liquids have been reported to possess catalytic behaviour in addition to their role as solvents.[47-49] The reports concerning the use of phosphonium ionic liquids as catalysts contain limited details about the mechanism of catalysis. For example, in oxychlorination reactions of arenes in $[P_{888,1}][NO_3]$ (Scheme 1-5), Perosa *et al.* proposed that the nitrate anion was acting as the catalyst.[48]



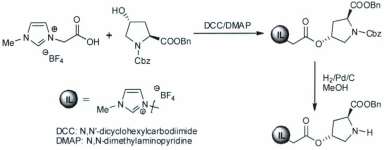
Scheme 1-5. $[P_{888,1}][NO_3]$ catalyzed two-step chlorination of anisole[48]

There is a growing interest in using organocatalysts anchored to solid supports in order to make them more convenient for recycling. From this point of view, ionic liquids are suitable candidates, since they can be functionalized with coordinating groups to be attached to solid supports. Furthermore, using chiral organocatalysts can induce chirality in the products. For example Wang *et al.* reported the enantioselective Michael addition of ketones with nitrostyrenes using a silica gel supported pyrrolidine-based chiral ionic liquid (Scheme 1-6).[50] The catalyst was reused six times without any significant loss of activity and selectivity. Each time it was separated through a simple filtration followed by washing with ethyl acetate and dichloromethane.

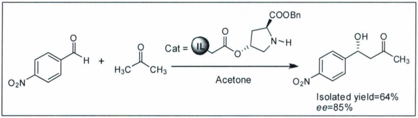


Scheme 1-6. Michael addition of ketones to nitrostyrene catalyzed by silica gel supported pyrrolidine-based chiral ionic liquid[50]

In the last example, (Scheme 1-6), the ionic liquid was supported on silica as the catalyst, while ionic liquids themselves can also be used as supports for organocatalysts.[51-53] Proline is an organocatalyst that has been incorporated into an ionic liquid so that it can be more readily recycled (Scheme 1-7). For example, asymmetric aldol reactions have been performed in an ionic liquid which has proline anchored to it and the catalytic system was recyclable at least four times (Scheme 1-8).[53] Ionic liquid supported proline showed the same activity as unsupported proline in these aldol reactions, however the ionic liquid supported proline showed up to 28% higher enantioselectivities.[53]



Scheme 1-7. Preparation of ionic liquid supported proline[53]



Scheme 1-8. Aldol reaction catalyzed by ionic liquid supported proline[53]

In the above examples, the cations played the role of catalyst. Anions have been reported to act as reagents or catalysts as well. *O*-acetylations of alcohols and carbohydrates have been conducted in imidazolium ionic liquids.[54] In these reactions, the anion (dicyanamide) of the ionic liquid, acted as a Lewis base catalyst to activate the alcohols.[54] In addition to the Lewis basicity of the anion activating the alcohols, the imidazolium cation through its Lewis acidity activates acetic anhydride in these reactions.[55]

Based on their functionalities, acidic, basic or neutral ionic liquids can be prepared. This property of ionic liquids can be very important in acid-catalyzed reactions. Deng *et al.* investigated the influence of the acidity of ionic liquids on some acid catalyzed reactions such as aldol condensations, etherification of alcohols and acetalization of benzaldehyde.[56] They mixed the ionic liquids (2 mmol) with distilled water (20 mL) and stirred the mixture for 2 min. After 30 min the pH of the aqueous phases were measured with a pH meter. Deng *et al.* claimed a good agreement between the results that were obtained in the above-mentioned reactions and the relative acidity of the ionic liquids that they used. However, just four imidazolium ionic liquids were employed as catalysts from the over 25 different ionic liquids that they studied through pH measurements. Among these four ionic liquids [BMIm]Cl (pH=6.98) showed the lowest conversions. [BMIm]PF_6 (pH=7.16) was also used and afforded an almost quantitative yield for the aldol reaction. However, for the ether synthesis although quantitative conversion was achieved, there was zero selectivity. As they mentioned in their paper, HF is released via hydrolysis of PF_6^- in [BMIm]PF_6 at their reaction temperature (120 °C) and this decreased the pH dramatically. Therefore, this ionic liquid was not a good choice for this study and a greater selection of the original 25 ionic liquids should have been screened in these catalytic reactions. Nevertheless, the pH of ionic liquids in acid-catalyzed reactions should not be ignored.

1-4-3 Ionic liquids as stabilizing and reducing agents in the preparation of metal nanoparticles

Ionic liquids, especially imidazolium ionic liquids have been reported widely as efficient immobilizing and capping agents in the preparation of metal nanoparticles.[57,58] Other ionic liquids, (*e.g.* quaternary ammonium and dialkylmorpholinium salts) have also been demonstrated to act as stabilizing agents for metal nanoparticles.[39,59,60] Santini *et al.* reported the preparation of Ru nanoparticles in several imidazolium ionic liquids. They used hydrogen gas as the reducing agent and (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene) ruthenium(0), Ru(COD)(COT), as the metal source. In this process, the only byproduct after the nanoparticle formation was cyclooctane that could be easily removed under vacuum. A linear correlation between the sizes of the particles and the length of the alkyl chain in the imidazolium cations was reported. They also proposed a direct relationship between crystal growth and the local concentration of the metal source which would be higher in the non-polar domains of the ionic liquids.[58,61]

In order to synthesize metal nanoparticles from metal salts, a wide range of reducing agents including organic molecules such as L-ascorbic acid,[62] citric acid,[62] DMF,[63] triphenyl phosphine,[64] and inorganic reagents like hydrogen,[65,66] $NaBH_4$[60,67] and carbon monoxide[68] have been used. Ionic liquids have also been reported to act as reducing agents in the preparation of metal nanoparticles. Some of these ionic liquids have been designed to have reducing agents incorporated in their cation. These ionic liquids can be considered as "task specific ionic liquids", since they have been designed to have some specific properties in these reactions. For example, ionic liquids with hydroxyl groups incorporated in the alkyl chains of their cations have reducing properties (Figure 1-5). Hydroxyl-functionalized imidazolium, morpholinium and quaternary ammonium ionic liquids have been used to prepare gold and silver nanocrystals. In these examples, ionic liquids have a dual role of reducing and stabilizing agent (Scheme 1-9).[69-71]

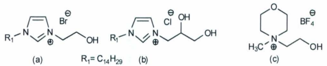
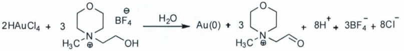


Figure 1-5. Hydroxyl-functionalized imidazolium (a and b) and morpholinium (c) ionic liquids as reducing agents[69-71]



Scheme 1-9. Preparation of gold nanoparticles in a hydroxyl-functionalyzed morpholinium ionic liquid as reducing and stabilizing agent[71]

More complex functional groups have also been employed to synthesize task specific ionic liquids to reduce metal cations and prepare metal nanocrystals. Ascorbic acid based ionic liquids (Figure 1-6) can reduce gold cations in an aqueous solution of $HAuCl_4$ to gold nanoparticles. In this process, the ascorbate anion acts as a reducing agent and the imidazolium cation acts as a capping agent.[72] Phosphorylated imidazolium ionic liquids (Figure 1-6) have been used for the preparation of palladium nanoparticles. In this example, a phosphinite group on the alkyl chain of the imidazolium cation acts as a complexing and reducing agent for Pd(II).[57]

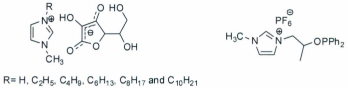


Figure 1-6. Ascorbic acid (left) and phosphinite (right) containing imidazolium ionic liquids[57,72]

Anions in ionic liquids can also have a significant effect on the formation and the crystal structure of nanoparticles. For example, a dark suspension of Pd nanoparticles is formed as soon as tetrabutylammonium acetate is added to a solution of palladium acetate in melted tetrabutylammonium bromide.[39,59] Also, Dyson *et al.* found that anion change in imidazolium and pyridinium-based ionic liquids can have a dramatic effect on the crystal structure and morphology of the prepared gold particles.[73] Different anions can stabilize different crystalline planes in gold nanocrystals. Therefore, the different coordination abilities of anions in the ionic liquids can result in different crystal structures or particle morphologies. Dyson also proposed that polar and non-polar microdomains in the ionic liquid network can act as templates for the nanoparticle formation. These microdomains change depending on the anions and cations and thus different crystalline structures can form.[73]

Electrochemistry is another well-known method for the preparation of metal nanoparticles. Ionic liquids with moderate viscosities are potentially suitable electrolytes for the electrochemical synthesis of metal nanoparticles. Ionic liquids have wider potential windows compared to regular organic solvents or water. As a result, electrochemical synthesis of metal nanoparticles in ionic liquids is sometimes more practical than in traditional organic solvents or aqueous solutions. For example, a potential window of more than four volts was measured for gold in [BMIm][PF_6], which is three times larger than the corresponding potential window in water under similar conditions. Furthermore, in aqueous solutions, hydrogen evolution can generate defects in the prepared nanocrystals due to adsorption, while this problem does not occur in ionic liquids.[74]

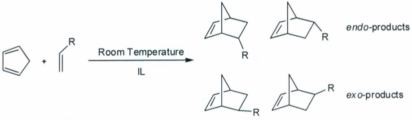
1-5 Analytical methods for characterizing ionic liquids and reactions in them

When monitoring reactions in ionic liquids, difficulties are sometimes encountered due to their higher viscosity and ionic properties compared to regular organic solvents. For example, electrochemical experiments are not recommended in viscous ionic liquids because of their low conductivities (see section 1-5-4).[28] Also, viscous samples or samples with highly ionic properties pose some potential difficulties in NMR experiments (see below). Usually, GC-MS analysis cannot be carried out directly on extracted samples because ionic liquids leach into the extracting solvent. After considering all of these problems, most routine analytical methods are still possible for characterizing reactions in ionic liquids provided careful sample preparation and optimization of experimental conditions under which the instruments are performed.

1-5-1 NMR spectroscopy in ionic liquids

NMR experiments on ionic liquids can face two main problems. The first issue is the absorptivity of radiofrequency in ionic liquids due to their highly ionic nature. The second problem is signal broadening and lower resolution because of less molecular tumbling in viscous ionic liquids.[75,76] In spite of these problems, routine NMR techniques are possible with today's spectrometers.

NMR analysis has been widely used for reaction monitoring in ionic liquids as well as mechanistic studies and for monitoring the purity of ionic liquids. For example, the selectivity of products (endo:exo) in a Diels-Alder reaction between cyclopentadiene and methyl acrylate (Scheme 1-10) was studied based on ^{1}H and ^{13}C NMR spectra in different ionic liquids.[15] Dyson *et al.* predicted the selectivity in this reaction based on an empirical solvent parameter scale that they extracted from ^{1}H and ^{13}C NMR data.[15]



R= $COOCH_3$

IL: different imidazolium and pyridinium based ionic liquids

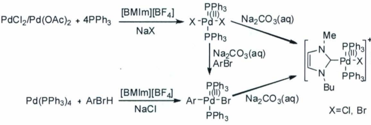
Scheme 1-10. Diels-Alder cycloaddition of cyclopentadiene and methyl acrylate[15]

Thermal stability and also inertness of ionic liquids in reactions can make them superior to regular organic solvents. In this regard, NMR analysis is a useful technique to monitor any possible decompositions in the ionic liquids. For example, ^{1}H and ^{13}C NMR studies have shown that [EMIm][TfO] and [HMIm][TfO] are stable in the presence of ceric ammonium nitrate (CAN) (10:1 IL/CAN ratio) at 100-125 °C for 6 h, which are typical reaction conditions for the oxidation of organic substrates.[77]

In addition to ^{1}H and ^{13}C NMR, other nuclei (*e.g.* ^{31}P, ^{19}F, ^{17}O, ^{27}Al, ^{2}H) can be used successfully in the NMR study of ionic liquids and reactions therein. Also, as many of the ionic liquids contain heteroatoms, NMR methods based on these nuclei can provide valuable insights into intermolecular interactions. For example, ^{19}F NMR is a useful tool to study ionic liquid-substrate interactions, since fluorine atoms are present in the anions of many ionic liquids (*e.g.* $[PF_6]^-$, $[BF_4]^-$, $[NTf_2]^-$, $[CF_3COO]^-$).[2,75] As another example of heteronuclear NMR spectroscopy, Welton *et al.* detected the intermediate complex,

$Pd(PPh_3)_2ArBr$, and the product palladium imidazolylidene complex, $[Pd(PPh_3)_2(BMIm)X][BF_4]$, based on ^{31}P NMR where X=Cl or Br.[78] Scheme 1-11 shows the different reaction routes and intermediates that produced the palladium imidazolylidene complex.

^2H NMR spectroscopy is a versatile method for monitoring chemical kinetics and mechanisms. The use of deuterated ionic liquids for this purpose is not economical and in many cases not practical.[79-81] As an alternative method commercially available deuterated substrates have been used to study reaction kinetics in ionic liquids.[82]



Scheme 1-11. Formation of palladium imidazolylidene and its phosphine-palladium intermediate complexes[78]

^2H is also used to lock the RF signal in NMR spectroscopy and therefore, deuterated organic solvents are used as lock solvents for solution NMR spectroscopy. Using these solvents directly in ionic liquids can have some impacts on the results. Because of the ionic properties of ionic liquids, dilution of these compounds in organic solvents can change their lattice structure.[75] Based on the polarity and polarizability of the molecules of organic solvents, solvation and therefore the interactions between the molecules of the organic solvent and ionic liquids can be different. Subsequently, different chemical shifts and resolution can be obtained for the NMR spectra of diluted ionic liquids in different deuterated solvents.[2,75,83] Although the use of diluted ionic liquids sometimes has drawbacks on the structural studies of ionic liquids and detection of intermolecular interactions, it has been widely used for reaction monitoring in ionic liquids.[15] In order to avoid these dilution effects, coaxial NMR tubes can be used. In these NMR tubes, the lock solvent is placed in the insert capillary and the ionic liquid in the outer NMR tube. Slightly better resolution can be obtained if the ionic liquid is used in the insert capillary, however this method is less practical due to difficulties in filling the capillary with the viscous ionic liquid and resulting air-bubbles.[75] Higher temperatures for the NMR experiments may be used to decrease the line width and increase the resolution when neat ionic liquids are used for NMR analysis with the lock solvent in the insert in a coaxial tube. Studies over the temperature ranges of 80 to 140 °C have been reported, however the boiling point of the lock solvent and pressure increase in the insert capillary must be taken into account.[75]

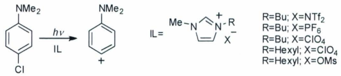
High resolution magic angle spinning (HRMAS) has been reported as an efficient NMR technique to monitor chemical reactions or investigate organic molecules in neat ionic liquids. Poletti and Caneva *et al.* have demonstrated 25 to 40% decrease in full width at half maximum height (FWHM) for ^{1}H HRMAS NMR of 4-methoxybenzyl acetate compared to regular ^{1}H NMR of the same sample in neat ionic liquids. Additionally, in this technique, there is no need for high solute concentrations, which is one of the problems usually encountered with NMR studies in neat ionic liquids.[84]

In addition to the aforementioned NMR methods, 2D NMR techniques have been used for reaction monitoring and also structural studies. For example, aggregation of ionic liquids has been studied using ^{1}H NMR spectroscopy. In this study based on 2D ^{1}H-^{1}H NOESY measurements a stair-like aggregation structure was proposed for a group of imidazolium ionic liquids in D_2O.[85]

In summary, NMR spectroscopy on ionic liquids, especially on neat ionic liquids, can be challenging. Several NMR techniques as well as some special hardware can be used to increase the quality of NMR data on ionic liquids. In spite of all these difficulties, this analytical method is one of the most powerful and practical techniques to study ionic liquids as well as monitoring reactions in these ionic media.

1-5-2 Some methods of measuring the polarity of ionic liquids

One of the common methods for measuring the polarity of ionic liquids is through the use of chemical probes. Chemical probes are usually organic molecules whose physical properties (*e.g.* UV absorption) change due to their interaction with the desired molecules. 4-chloro-N,N-dimethylaniline has been reported to generate the N,N-dimethylaminophenyl cation through photolysis as a chemical probe for solvent polarity in some imidazolium ionic liquids (Scheme 1-12).[86] Since the efficiency of this photochemical reaction depends on the polarity of solvent, the polarity of the examined ionic liquids was determined to be equivalent to medium polarity to polar organic solvents (approximately of the same order as acetonitrile or ethanol).[86,87]



Scheme 1-12. Photolysis of 4-chloro-N,N-dimethylaniline to N,N-dimethylaminophenyl cation in imidazolium ionic liquids[86]

Armstrong *et al.* used several imidazolium-based ionic liquids as liquid stationary phases in a gas-liquid chromatography (GLC).[88] They employed a range of probe molecules (*e.g.* 1-2-dichlorobenzene, phenol, xylenes, pyrrole) to characterize the ionic liquids based on different interactions between the probe molecules and the stationary phases. Ionic liquids have more complex structures compared with traditional organic solvents. Therefore, when they are used as solvents, different interactions (*e.g.* π-π, hydrogen bonding) with solute molecules are possible. Armstrong *et al.* used retention factors for the probe molecules to determine the interaction parameter coefficients to characterize the polarity of ionic liquids.[88] Later, they used the same method to study the solvation properties of phosphonium-based ionic liquids.[89] This GLC method is more applicable for phosphonium ionic liquids, since these ionic liquids are more thermally stable than nitrogen-based ionic liquids. In addition, the higher viscosity of phosphonium ionic liquids was an advantage for using them in GLC capillary columns. Based on their studies, Armstrong *et al.* reported that the anions in phosphonium ionic liquids were the source of hydrogen bond acceptor. Also greater hydrogen bond basic interactions were measured for phosphonium ionic liquids than nitrogen-based ionic liquids. More π and non-bonding electron interactions were detected for the phosphonium ionic liquids containing ether functional groups in their side chains. However, these types of interactions for phosphonium ionic liquids were generally lower than imidazolium ionic liquids.[89] Results from these studies (solvation properties), can be used to predict and explain the behaviour of these ionic liquids and have a better understanding of the reaction mechanisms in these ionic solvents. For example, larger hydrogen bond basicity was found in [BMIm]Cl compared to [BMIm][BF_4] and [BMIm][PF_6]. This factor could be a reason for the better solubility of cellulose in the former ionic liquid compared with the other two ionic liquids.[88]

1-5-3 Electrochemistry

Ionic liquids have been investigated as electrolytes in thermal batteries for decades.[3] They are conductive liquids that can be analyzed by electrochemical methods. However, electrochemical analysis is not applicable on neat bulky ionic liquids due to their high viscosities, which influence ionic conductivity.[7] Both anions and cations can influence viscosity and subsequently conductivity of ionic liquids. For example, phosphonium ionic liquids generally have lower viscosities than their ammonium counterparts. Also ionic liquids with bis(trifluoromethylsulfonyl)amide, $[NTf_2]^-$, as the anion have lower viscosities than halide ionic liquids due to weaker electrostatic anion-cation interactions.[7] Gao *et al.* studied the influence of alkyl chain, anion and water on the electrochemical behaviour of several imidazolium ionic liquids.[90] They demonstrated that the studied ionic liquids have higher conductivities in the presence of added water. Water molecules weaken the interactions between the cations and anions in the ionic liquids. Also lower conductivities were measured for ionic liquids having longer alkyl chains. Higher conductivities were reported at elevated temperatures, since the mobility of ions increased due to lower viscosities of ionic liquids at higher temperatures.[90] Wide electrochemical windows (-3.2 to +2.5 V *vs.* Fc/Fc^+) have been reported for ionic liquids including heavy and viscous phosphonium ionic liquids such as $[P_{444,8}][NTf_2]$ and $[P_{444,12}][NTf_2]$. Therefore, these ionic liquids can be employed in systems that require good electrochemical stabilities.[9] The electrochemical window of aliphatic quaternary ammonium systems are usually wider than the ionic liquids containing aromatic systems (*e.g.* pyridinium). Because of this wide electrochemical window, quaternary ammonium salts have been used as supporting electrolytes within conventional electrolytes.[28] Ionic diffusion coefficients, the degree of ionic association and the interaction between ions are some important parameters in the electrochemistry of ionic liquids that have not yet been clearly understood.[28,28]

1-6 Are ionic liquids "green"?

The right answer to this question is another question, "Compared to what?". We need all the details about a reaction or a procedure in hand in order to judge the greenness of the reaction or a compound in the reaction. For example, water is potentially a green solvent. However, in some reactions organic solvents can be greener than water, because they provide much higher yields and selectivities. Therefore, in order to make a reaction or procedure more environmentally friendly, we have to consider different parameters to make the procedure more compatible with the principles of green chemistry. In this section some aspects of ionic liquids that can make them more environmentally friendly as well as some of the problems and potential drawbacks of these ionic compounds are briefly discussed.

Since a large number of ionic liquids have been synthesized previously and potentially over one million of them exist,[33] not enough data has been obtained regarding their toxicity and biodegradability. However, efforts have been made to find and design less toxic and more biodegradable ionic liquids. Even if they are not toxic, these ionic compounds should be biodegradable in order to meet the complete requirements for green chemistry, because bioaccumulation of non-toxic materials can still cause some environmental problems.[11]

Docherty and Dixon *et al.* studied biodegradability of six imidazolium and pyridinium ionic liquids (Figure 1-7 (a) and (b)). They demonstrated that pyridinium ionic liquids are generally more biodegradable than their imidazolium counterparts.[91] In these ionic liquids longer alkyl chains showed faster biodegradation, which is maybe because of the presence of more degradation sites for the microorganisms. However, higher toxicity was reported for ionic liquids with longer alkyl chains. Therefore, in this case there is a trade-off between two parameters (degradation *vs.* toxicity).[91] Esteric side chains in imidazolium and phosphonium ionic liquids make them more biodegradable than linear alkyl chains (Figure 1-7 (c)).[11] Also, many quaternary ammonium salts and their phosphonium counterparts are potentially biocides for microorganisms, and therefore they show lower biodegradability than, for example, pyridinium salts.[11]

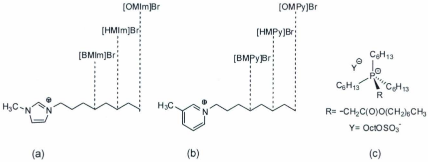
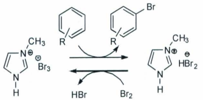


Figure 1-7. Chemical structure of three imidazolium (a) and three pyridinium (b) ionic liquids and phosphonium ionic liquids with an esteric side chain (c)[11,91]

Considering the biodegradability issues, ionic liquids do not usually cause acute problems for human health if they are used with proper protection.[5] In addition, they have some unique properties that make them appealing chemicals for chemists. Ionic liquids have negligible vapour pressures compared to regular organic solvents such as toluene or acetonitrile. However, some of the ionic liquids, for example [$P_{666,14}$]Cl, are less ionic. In this example, the cation and anion interact with each other more strongly than in other ionic liquids (*e.g.* [$P_{666,14}$][NTf_2]).[92,93] This leads to the ionic liquid having some characteristics more typical of molecular solvents, for example [$P_{666,14}$]Cl has a significant vapour pressure and can be vacuum distilled at 0.1 Torr at 80 °C.[93] However, for phosphonium ionic liquids enough data regarding their physical properties, such as their vapour pressures at different temperatures, are not available as well as imidazolium ionic liquids. Ionic liquids in general are less flammable than molecular organic solvents. Also, they have very good thermal stabilities, which make them suitable solvents for many organic reactions and particularly those performed at high temperatures.[5,6] However, lower thermal stabilities for imidazolium cations in the presence of nucleophiles, especially under microwave conditions, have been reported.[94] Because of their ionic nature, ionic liquids can dissolve and immobilize many polar substrates and metal complexes. Also based on different cations and anions in the ionic liquids they can have a variety of interactions with solutes and can dissolve a wide range of compounds.[2,5,7] The recyclability of ionic liquids is another added benefit for these neoteric solvents, which can reduce waste production and also the final cost of experiments.

Although many ionic liquids are commercially available, ionic liquids can be tailor-made solvents and designed for specific reactions. This property of these solvents can help to increase the selectivity, yield and safety of reactions. For example, trihalide-based ionic liquids have been reported to act as solvents and brominating agents for alkenes, alkynes and aromatics.[25,95-97] 3-Methylimidazolium tribromide was used as a reagent and solvent to brominate aromatic compounds (Scheme 1-13). Since this ionic liquid is a solid and easy to handle at room temperature, the method was claimed to be safer than using molecular bromine. After the reaction, the reacted ionic liquid, [HMIm][HBr_2] can be transformed to the original ionic liquid, [HMIm][Br_3], and re-used by adding the proper amount of molecular bromine.[95]



Scheme 1-13. Bromination of aromatic compounds in 3-methylimidazolium tribromide[95]

As a result of all of these different properties of ionic liquids, their use in research labs continues to increase. In order to use them on a large scale, more data are needed regarding their toxicity and biodegradability. Also, ionic liquids containing anions such as $[BF_4]^-$ and $[PF_6]^-$ are not suitable for large-scale purposes, since they cannot be incinerated easily.[5] Special facilities are needed for the incineration of fluorinated compounds, since most of the volatile fluorinated compounds that would form as combustion products are thought to be greenhouse gases and they have ozone-depleting properties.

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Chapter 2

Transformations of alcohols to ethers and alkenes

Transformations of alcohols to ethers and alkenes

2-1 Introduction

Ethers and alkenes are known as valuable compounds in research labs and also in industry. They are found in a range of substances including polymeric materials, pharmaceuticals, solvents, fragrances and cosmetics. Ethers and alkenes are normally obtained from petroleum-based feedstocks. They can be prepared by dehydration reactions of alcohols. Such reactions are becoming increasingly important in order to reduce the oxygen content of biomass feedstocks, including polyols or alcohols, and convert them into more valuable materials for chemical and allied industries. For example, if glycerol is directly added to fuel, due to the high temperatures created in the engine during combustion, it polymerizes and clogs channels in the engine.[1] It is also oxidized and produces toxic acrolein (2-propenal), which is released into the atmosphere. However, glycerol tertiary butyl ether, which is a derivative of glycerol, works as an excellent fuel additive.[1] If desired, acrolein which is an industrial chemical in high demand, can be produced in a controlled manner from dehydration of glycerol.[1]

In the pharmaceutical industry, ethers and alkenes can be used as building blocks for many biologically active materials and medicines. For instance, the Williamson ether synthesis[*] was used to synthesize guaifenesin, which is an expectorant.[2] The compound is

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[*] Different methods of ether synthesis including the Williamson method will be discussed in more detail later in this chapter.

used as a racemic mixture in syrup and tablet forms, however its (*S*)-(+) enantiomer is a more active expectorant than the (*R*)-(-) enantiomer (Figure 2-1).[2]

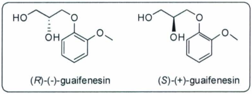


Figure 2-1. (*R*)-(-) and (*S*)-(+) enantiomers of guaifenesin[2]

Other anisole derivatives have UV absorption properties and are used in sunscreens. Ozone layer depletion has increased the demand for UV absorbent materials for skin protection and two examples of these materials are presented in Figure 2-2.[3]

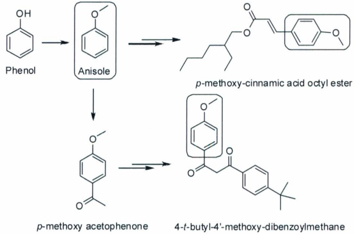
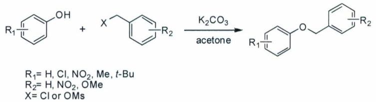


Figure 2-2. Anisole-based UV absorbers for skin protection[3]

Benzyl phenyl ethers have also been synthesized using the Williamson method (Scheme 2-1) and their activity as anti HIV-1 (human immunodeficiency virus-1) agents has been investigated. Among the studied compounds, 4-nitrobenzyl phenyl ether exhibited the highest activity.[4] Also, aromatic alkenes can have biological properties. For example, methoxy arylalkenes are building blocks of asarones, which have bactericide and pesticide activities and can be used to treat diphtheria and typhoid.[5]



Scheme 2-1. Williamson based synthesis of anti HIV-1 activated benzyl phenyl ethers[4]

Beyond the synthesis of pharmaceuticals, ethereal linkages have found some other applications. For example, the Williamson ether synthesis has been used to modify metal oxide surfaces. This process was performed via grafting of alkyl iodides to the hydroxyl groups on anatase nanocrystalline TiO_2 surfaces (Figure 2-3). These modified metal oxide surfaces have applications in catalysis, sensing, electronics and renewable energy (solar cells).[6]

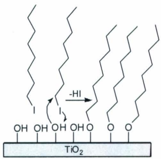
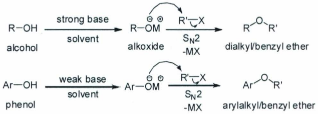


Figure 2-3. TiO_2 surface modification using Williamson method[6]

2-2 Classical methods for the synthesis of ethers and alkenes from alcohols

There are a number of methods used for the transformation of alcohols to ethers and alkenes. Some of these methods selectively produce one of the products, but most methods produce both ethers and alkenes with different ratios depending on the starting materials or the reaction conditions. A well-known method for ether synthesis is the Williamson reaction that was first introduced in 1851.[7] This method is suitable for the synthesis of different types of symmetric and asymmetric ethers, via an S_N2 reaction of aliphatic or aromatic alkoxides with alkyl, allyl or benzyl halides (Scheme 2-2). Generally, for reactions based on Williamson's method, E2 elimination occurs for tertiary or sterically hindered primary and secondary alkyl halides. Also, *C*-alkylation can happen for the alkali phenoxides in addition to the expected *O*-alkylation.[7] Another problem with the Williamson ether synthesis is the long reaction times. For example, Sanford *et al.* conducted some modifications on the classical method to make it convenient for students in undergraduate teaching labs to complete the reaction within the lab class's timeframe.[8] With regards to the principles of green chemistry and the Williamson reaction, waste production (mainly alkali metal salts) and use of toxic alkylating agents are disadvantages when the reaction is performed on a large scale.

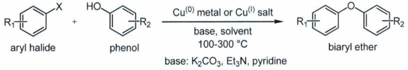


Strong base: alkali metals, liquid ammonia, metal hydrides, LHMDS, LDA
Weak base: NaOH, KOH, K_2CO_3, Cs_2CO_3
Solvent: usually dipolar aprotic such as DMSO, DMF

R: 1°, 2°, 3° alkyl, allyl, benzyl M: Li, Na, K, Cs
R': 1°, 2° alkyl, allyl, benzyl X: Cl, Br, I, OMs, OTs
Ar: aryl, heteroaryl

Scheme 2-2. Classical Williamson method for the synthesis of dialkyl/benzyl ethers and arylalkyl/benzyl ethers[7]

Another classical method for the synthesis of ethers, in particular biaryl ethers, was first introduced by Fritz Ullmann in 1905 based on a copper mediated reaction between an aryl halide and a phenol (Scheme 2-3).[7] The original Ullmann ether synthesis was performed in the presence of stoichiometric quantities of copper reagents at high temperatures (> 200 °C). Some common side reactions in this method in the presence of Cu(I) salts are reductive dehalogenation, Ullmann's biaryl homocoupling and halogen exchange reactions.[7,9] Figure 2-4 shows the proposed mechanism for the Ullmann Cu(I) catalyzed synthesis of biaryl ethers.



solvent: *e.g.* DMF, DMSO, pyridine, quinoline, nitrobenzene

R_1 & R_2: H, CN, NO_2, CO_2R, I, Br, Cl
X: I, Br, Cl, SCN

Scheme 2-3. Classical Ullmann method for the synthesis of biaryl ethers[7]

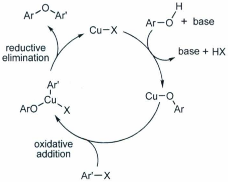
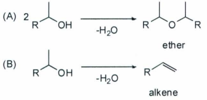


Figure 2-4. Proposed mechanism for Cu(I) catalyzed Ullmann ether synthesis[9]

Dehydration reactions can be considered as an alternative method towards the synthesis of ethers and alkenes from alcohols (Scheme 2-4). Low selectivity and use of harsh reaction conditions are the main problems associated with dehydration reactions of alcohols. For example, common strong mineral and organic acids, such as sulfuric and *p*-toluenesulfonic acids are used in these reactions,[10,11] which then require a neutralization process at the end of the pipeline. In order to avoid the neutralization process, heterogeneous acid catalysts have also been used with some success.[12,13] Advantages of dehydration reactions, where alcohols are used as feedstocks, for the preparation of ethers are reduction in waste production and avoidance of toxic alkylating agents.[10]



Scheme 2-4. Dehydration of alcohols to ethers (A) and alkenes (B)

Since the early days for these classical methods of ether synthesis, many modifications have been performed in order to improve the processes overall. Some of these changes will be presented in the following sections. These include reduction in energy consumption, use of safer alkylating agents, use of catalysts, use of solid acids and the use of alternative 'greener' solvents.

2-3 Modifications of the classical methods for the preparation of ethers and alkenes

2-3-1 Microwave-assisted synthesis of ethers and alkenes

Microwave (MW) heating is being used broadly instead of conventional heating as a method to improve the reaction conditions and outcomes in the above-mentioned processes. Therefore, a brief introduction about the mechanisms of heating under microwave conditions will be presented before addressing the microwave-assisted transformations of alcohols to ethers and alkenes.

Microwave radiation is a section of the electromagnetic spectrum with wavelengths between infrared and radiofrequency radiation. Microwave frequencies range from 300 GHz to 300 MHz (wavelengths between 1 cm and 1 m).[14,15] In order to avoid interferences with telecommunications and cellular phone frequencies, which are in the microwave region, domestic microwave ovens and laboratory reactor systems must work in the realm of Industrial Scientific and Medical frequencies (ISM). ISM frequencies are 27.12 MHz, 915 MHz and 2.45 GHz. Domestic ovens and laboratory microwave reactors work at 2.45 GHz.[14,15]

Heat generation in materials under microwave energy is due to the interactions from the electric component of the electromagnetic field with the molecules in the materials. These interactions and subsequent heat generation are based on two different mechanisms, dipolar polarization and ionic conduction mechanisms.[14]

The dipolar polarization mechanism involves the interactions between the electric field and the molecules that have a dipole moment (Figure 2-5). In this mechanism, the dipoles oscillate with the alternating electric field and they align themselves with the direction changes of the electric field. Therefore, heat is generated in these materials under microwave irradiation through friction and collisions between the molecules caused by realignment of the molecules with the electric field. The quantity of heat generated is directly related to the ability of the dipolar molecules to align themselves with the oscillating electric field.[14]

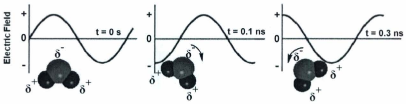


Figure 2-5. Dipolar polarization mechanism in microwave heating[14]

For ionic materials or materials containing ions, ionic conduction is the main heat generating mechanism. In the ionic conduction mechanism, ions move back and forth due to the oscillation of the microwave field (Figure 2-6). Collisions between the ions, as they move, is the main cause of heat generation in ionic materials under microwave irradiation.[14] Of the two heat generating mechanisms described above, the latter is much stronger, and hence makes ionic liquids very efficient microwave energy absorbers. Heat generation in ionic liquids, under microwave irradiation, is mainly based on the ionic conduction mechanism.

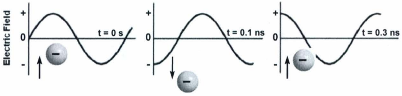


Figure 2-6. Ionic conduction mechanism in microwave heating. (Note: only anions shown for clarity. Cations will also oscillate through interactions and alignment with the applied electromagnetic radiation)[14]

Today it is generally accepted that microwave effects on reactions, such as decreases in reaction time, improvement in yields and selectivity, are all thermal and kinetic effects. Under microwave irradiation, in comparison to conventional heating (*e.g.* using an oil bath), a rapid increase in temperature is the main source of these effects. Therefore, microwave irradiation, by itself, does not cause any special effects (*e.g.* activation of bonds) on the reactions.[14,15] Another advantage of microwave heating over conventional heating is the homogeneity of the temperature in the reaction mixture. As was mentioned previously, heat generation in materials under microwave irradiation is based on the direct interactions of the microwave field and the molecules and ions in the reaction mixtures. Therefore, heat is generated internally in the reaction mixture and spreads out, while in conventional heating the reaction mixture in contact with the vessel walls is heated first and heat spreads through thermal conduction and via convection currents.

These differences in the heating mechanisms between the two systems causes a more homogeneous temperature in a reaction mixture under microwave conditions. In conventionally heated systems a temperature gradient is usually observed, especially at the beginning of the reaction, and 'hot-spots' can occur.[14] These phenomena can lead to side-reactions and a decrease in selectivity for conventionally heated reactions.

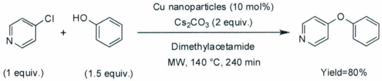
The first report of using microwave energy in organic synthesis was in 1986. Before inventing specially designed microwave reactors for chemical reactions, safety issues prohibited microwave energy becoming a common energy source in organic synthesis.[16] Online and accurate temperature and pressure control were two main factors that needed to be addressed before microwave-assisted chemistry became more common-place in laboratories. Also, homogeneous energy distribution in the microwave reactor cavity was an additional problem in the early days of this field.[16]

In the 1980s, open vessels were commonly used in domestic microwave ovens to heat the reaction mixtures. The flammability and volatility of organic solvents were two major safety concerns when using open vessels in this way. Some modifications were performed on the procedures to reduce the potential hazards. For example, reactions were reported under solvent-free conditions and in sealable pressure vessels made from PTFE (polytetrafluoroethylene).[17,18] Solid-supported reactions were also introduced as another solution for these problems.[19,20] However, these modified procedures still encountered some hazards including explosion of the vessel and charring of the reaction mixture. These problems occurred due to a lack of proper temperature control or heat transfer medium (solvent).[21] Therefore, it was necessary to have microwave instruments specially designed for chemistry to meet all the safety issues and make the results reproducible. Today, microwave reactors can provide online detection of pressure, temperature and power. These capabilities have made microwave-assisted reactions fast, reliable, reproducible and safe.

In the following section some examples of microwave-assisted transformations of alcohols to ethers and alkenes will be presented, in which a considerable difference between microwave heating and conventional heating was reported, particularly with regards to saving time and energy and improving the yield and selectivity. Long reaction times and high temperatures required are two problems usually encountered with classical Williamson and Ullmann ether synthesis methods. These can be overcome under microwave conditions. Also microwave heating can be a more energy efficient way of heating relative to conventional heating.

In 2010, Wheatley, Schouten *et al.* reported the first copper nanoparticle catalyzed Ullmann ether synthesis under microwave irradiation (Scheme 2-5).[22] They compared different copper sources including metallic Cu (3-75 μm), Cu(I), Cu(II) salts, Cu nanoparticles (10 nm) and Cu wires (20 and 50 μm) under oil bath heating and MW conditions. Under microwave conditions the best results were afforded in the presence of copper nanoparticles, while when Cu wires were employed, higher yields were obtained in an oil bath. The authors proposed that the copper wires acted as antennae under microwave conditions and decomposition occurred on the surface of the wires.[22]

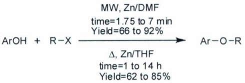
Wheatley, Schouten *et al.* also compared the energy consumption between heating using a microwave and an oil bath. 14.1 kJ of energy was consumed in 60 s to reach 140 °C under MW conditions. In order to reach this temperature in an oil bath, for the same reaction with the same volume, 1.4 MJ of energy was needed and 20 min required.[22] It should be noted that these researchers only measured the energy required to reach the maximum temperature (140 °C) under microwave conditions and in an oil bath. The energy difference would be much smaller if the total energy needed to complete the reaction was measured. In 2011, Kappe and Moseley investigated the greenness of microwave-assisted organic reactions from energy efficiency viewpoint.[23] Based on their studies the greenness of microwave-assisted reactions cannot be related to lower energy consumption by these reactors compared with conventional heating. Energy consumption for reactions under microwave conditions compared with conventional heating should be studied case by case and it depends on different parameters (*e.g.* type of microwave reactor, reaction vessels and reaction size). Therefore, sometimes conventional heating can be more energy efficient than microwave heating.[23]



Scheme 2-5. Copper nanoparticle catalyzed Ullmann ether synthesis under microwave irradiation[22]

The same reaction as the one presented in Scheme 2-5 was investigated previously using copper powder as the catalyst in combination with Cs_2CO_3 as base.[24] The Ullmann reaction between halo-heterocycles and phenols to produce heterocycle-aryl ethers under microwave irradiation has been reported. An increase in yield for electron deficient phenols was reported under microwave irradiation, while no trend related to the electronic properties of the reagents was observed using conventional heating.[24] Microwave irradiation has also been used to improve yields (due to faster heating) and decrease reaction times in the Williamson ether syntheses. Some examples are presented in Table 2-1, which demonstrate a comparison between microwave and conventional heating in terms of the reaction times and yields.[25]

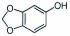
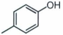
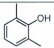
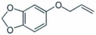
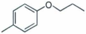
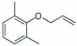
Zinc powder catalyzed Williamson ether synthesis has been reported using microwave (domestic) and conventional heating (Scheme 2-6).[26] This zinc catalyzed Williamson reaction could be used to produce alkyl-aryl, allyl-aryl, diaryl and aryl-benzyl ethers without any inorganic base or phase transfer catalyst. The zinc powder could be recycled up to six times and maintained reasonable activity after washing with diethyl ether and diluted HCl.[26]



$$\mathrm{ArOH} + \mathrm{R{-}X} \xrightarrow[\substack{\Delta,\ \mathrm{Zn/THF}\\ \mathrm{time}=1\ \mathrm{to}\ 14\ \mathrm{h}\\ \mathrm{Yield}=62\ \mathrm{to}\ 85\%}]{\substack{\mathrm{MW,\ Zn/DMF}\\ \mathrm{time}=1.75\ \mathrm{to}\ 7\ \mathrm{min}\\ \mathrm{Yield}=66\ \mathrm{to}\ 92\%}} \mathrm{Ar{-}O{-}R}$$

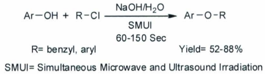
Scheme 2-6. Zinc powder catalyzed Williamson ether syntheses[26]

Table 2-1. Comparison between microwave heating and conventional heating for some examples of the Williamson reaction in ethanol[25]

Substrate			
Alkyl or allyl halide			
Base	NaOEt	KOH	KOH
MW temperature (°C)[a]	130	131	126
Time (conventional/MW)	60 min/1 min	35 min/3 min	3.5 h/4 min
Product			
Yield (%) (conventional/MW)	89/96	92/96	63/69

a) Conventional heating was performed at 78 °C (reflux condition) for all the samples

Simultaneous use of ultrasound and microwave irradiation has been shown to eliminate the need for phase transfer catalysts in a biphasic Williamson ether synthesis (Scheme 2-7).[27] Higher yields at shorter reaction times were observed for ultrasound agitation compared with magnetic stirring, even under reflux conditions. Ultrasound irradiation is known to increase reaction efficiency at liquid-liquid and solid-liquid interfaces in heterogeneous systems by microemulsification. Microwave irradiation coupled with ultrasound decreased the reaction time in these reactions.[27]



$$\text{Ar-OH} + \text{R-Cl} \xrightarrow[\text{SMUI}\ \ 60\text{-}150\ \text{Sec}]{\text{NaOH/H}_2\text{O}} \text{Ar-O-R}$$

R= benzyl, aryl Yield= 52-88%

SMUI= Simultaneous Microwave and Ultrasound Irradiation

Scheme 2-7. Simultaneous use of ultrasound and microwave irradiation in Williamson reactions[27]

2-3-2 Application of phase transfer catalysis in the synthesis of ethers and alkenes

Another modification of traditional Williamson ether synthesis is the use of phase transfer catalysts (PTC). In this regard, polyethylene glycol (PEG) with a molecular weight of 3000 (PEG3000) was used as the PTC in two liquid phases (LL-PTC), three liquid phases (LLL-PTC) and solid-liquid-liquid phases (SLL-PTC).[28] These systems were used to synthesize dibenzyl ether from benzyl alcohol and benzyl chloride. KOH was used as the solid phase in SLL-PTC and an organic solvent, dodecane, was used as one of the liquid phases (Figure 2-7).[28] Once PEG was added to the system, KOH was partially dissolved in the PEG and this PEG-KOH complex formed the second liquid phase. The reaction rate in SLL-PTC was reported to be eight times higher than the water containing PTC systems. In addition, higher base strength was reported in the SLL-PTC system than the other two liquid systems. Therefore, lower quantities of base were required in these systems. Moreover, PEGs are biodegradable, less toxic and cheaper than more common phase transfer catalysts such as quaternary ammonium salts or crown ethers. The proposed mechanism for these systems is presented in Figure 2-7. PEG forms a crown ether like structure, which can dissolve the KOH via coordination to the potassium cations. The hydroxide anion acts as a stronger base in the absence of water, since they are not hydrated with water molecules. Benzyl alcohol was transferred from the organic phase to the second liquid phase (PEG). Subsequently, in the presence of the PEG-KOH complex, the benzyl alcohol formed an alkoxide-PEG complex that was transferred to the organic phase and reacted with benzyl chloride to produce the dibenzyl ether.[28]

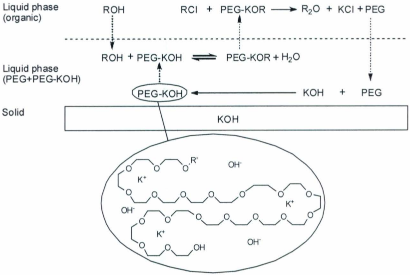
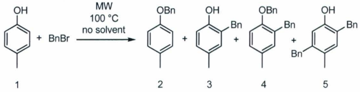


Figure 2-7. Reaction mechanism in a SLL-PTC system[28]

Using excess amounts of strong bases to remove weakly acidic protons from the alcohols is one of the potential problems with the Williamson method for ether synthesis. Strong bases, such as KOH, can react with sensitive functional groups on the substrate. The effects of base and PTC on the chemoselectivity of *O/C*-benzylation of phenols were investigated under microwave-assisted solvent-free reactions (Scheme 2-8, Table 2-2).[29] In these reactions, triethylbenzylammonium chloride (TEBAC) and K_2CO_3 were used as the PTC and base, respectively. In the absence of both of these reagents, low conversion was reported but high selectivity for the *C*-alkylation product was seen. When base was added, higher conversions were obtained but with low selectivities between *C*- and *O*-alkylation products. In the presence of 5 mol% TEBAC and one equivalent of K_2CO_3, benzyl aryl ethers were obtained with excellent yields.[29]

Phase transfer catalysts have been used in aqueous systems in order to increase the efficiency of extractions. However, separation of the phase transfer catalysts from the products can be a problem resulting from the use of PTC methods. *O*-alkylations were reported in the absence of PTC by using microwave and ultrasound irradiation simultaneously (*vide supra*).[27] Wagner *et al.* reported a non-aqueous Williamson ether synthesis under mild basic conditions without any phase transfer catalyst for the *O*-alkylations of phenols. They synthesized phenyl ethers under microwave conditions (100-140 °C and 15-30 min).[30] Wagner *et al.* used potassium carbonate, K_2CO_3, since it is partially soluble in solvents such as methanol and acetone and also it is a mild, cheap and an environmentally compatible base. In addition to avoiding the use of PTCs, the method is suitable for substrates that are sensitive to hydrolysis or strongly basic environments.[30]

Although methods using PTCs are greener than some traditional methods in terms of product selectivity and the efficiency of the reagents (*e.g.* bases), they still suffer from a relatively poor atom economy and require the use of halogenated reagents. In addition, product contamination with PTCs is another issue that is usually encountered in these systems.



Scheme 2-8. *O*- and *C*-benzylation of phenols[29]

Table 2-2. The effects of base and PTC on chemoselectivity of *O*- and *C*-benzylation of phenols[a29]

K_2CO_3 (equiv.)	TEBAC (mol%)	t (min)	1	2	3	4	5
–	–	35	58	0	32	0	7
1	–	40	9	52	27	6	6
1	5	35	0	96	0	4	0

a) 1, 2, 3, 4 and 5 were reported based on % yield

2-3-3 Metal-mediated reactions for the synthesis of ethers and alkenes

The use of different metal salts, complexes, metallic nanoparticles and metal powders has been reported for the catalytic dehydration and etherification of alcohols. Traditionally, Ullmann ether syntheses have been performed in the presence of stoichiometric quantities of copper salts.[7] As a modification of the traditional methods, metal complexes (*e.g.* various transition metal complexes) have been used in catalytic quantities to improve reaction conditions and efficiencies (*e.g.* decrease the reaction time, increase yield and selectivity).

As an inexpensive catalytic system, bis(acetylacetonato)copper(II), Cu(acac)$_2$, was used for the *O*-benzylation of primary alcohols and benzyl alcohols via the reaction of the alcohols with benzyl chloride.[31] The benzyl chloride and alcohol were heated to reflux in the presence of the catalyst (2.5 mol% to the alcohol). Good to excellent yields (60-94%) were obtained for the corresponding ethers for the reaction under neat conditions and very low yields (8-15%) were reported when the reactions were performed in THF. The lower yields in THF compared to the reactions under neat conditions were attributed to the lower boiling point of THF compared with the alcohol substrates.[31]

O-arylation of phenols and aliphatic alcohols was reported in a modified Ullmann ether synthesis using an air stable copper(I) catalyst.[32] Xu and Hu *et al.* used several copper(I) complexes (Figure 2-8), of which the air stable copper(I)-bipyridyl complex **2.3**, demonstrated the highest catalytic activity (Scheme 2-9). For example, 98% conversion was reported for a reaction between iodobenzene and phenol after 40 h at 90 °C in the presence of 5 mol% of copper (I) complex **2.3**, while 67% and 30% conversions were reported for this reaction in the presence of 5 mol% **2.1** and **2.2**, respectively. The reaction conditions were also applicable for *O*-arylation of primary alcohols and aryl iodides; however, attempts at reactions using aryl bromides were unsuccessful.[32]

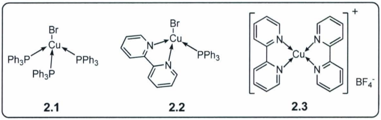
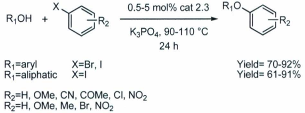


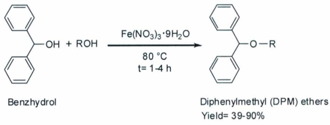
Figure 2-8. Air stable bidentate nitrogen or triphenylphosphine copper complexes[32]



Scheme 2-9. Ullmann reaction using copper(I)-bipyridyl complex[32]

Copper salts have also been used as catalysts in dehydration reactions. Such reactions are more atom-efficient than catalytic Ullmann and Williamson reactions, as the only byproduct is water and a halide leaving group is not required. For example, $Cu(OTf)_2$ was used as a dehydrating agent for the dehydration of primary, secondary and tertiary alcohols to alkenes. In this catalytic system, electron deficient copper(II) triflate was acting as a Lewis acid catalyst.[33]

Preparation of diphenylmethyl (DPM) ethers has been used to protect alcohols in chemical transformations.[34] An iron-catalyzed solvent-free method was introduced as a cheap and environmentally compatible process to convert various aliphatic and benzylic alcohols as well as phenols to the corresponding DPM ethers (Scheme 2-10). High yields (> 70%) were obtained when primary linear and benzylic alcohols were used, while lower yields (< 43%) were reported for secondary aliphatic alcohols. In this method iron(III) nitrate nonahydrate with a catalyst loading of less than 2 mol% compared to the substrate (ROH) was used in the absence of any solvent. [34]



Scheme 2-10. Iron-catalyzed preparation of diphenylmethyl ethers[34]

The preparations of alkyl benzyl ethers has also been reported via the reaction of benzyl bromides and different aliphatic alcohols in the presence of $FeSO_4$ in methanol under reflux conditions. In this method, an equimolar amount of ferrous sulfate compared with the benzyl bromide was used as a mediator. The researchers showed that the mediator was recyclable three times with only 8% drop in yield. This process was also a suitable method for the etherification of α,α'-dibromo-*o*/*p*-xylenes to afford α,α'-dialkyl benzyl ethers in high yields.[35]

Other less common metals have also been used to improve the process of ether synthesis or dehydration of alcohols to alkenes. Etherification of benzyl alcohols (using no halogen-containing reagents) has been reported using rhenium(I) complexes as catalysts.[36] $ReBr(CO)_5$ catalyzed asymmetric dehydrative etherification between primary benzyl alcohols and aliphatic alcohols (C1-C16) in high yields and selectivities. In these experiments, Re(I) complexes generally showed higher selectivities for the asymmetric ethers than Re(0) complexes (*e.g.* $Re_2(CO)_{10}$). Very low yields were observed when the dehydration was performed using n-octanol. Also the formation of rearrangement or elimination products was not detected via GC-MS analysis. However, dibenzyl ethers were obtained in yields higher than 70% (GC yield) when the dehydrations were performed on benzyl alcohols. Therefore, the formation of the benzylic cation was considered an important step in the proposed mechanism. Also the presence of oxygen is crucial in this catalytic system (Figure 2-9), since very low yields were obtained when the reactions were performed under an inert atmosphere.[36]

Niobium-based catalysts have also been used for the synthesis of benzylic and aliphatic ethers.[37,38] Quantitative conversion of benzyl alcohol to dibenzyl ether was reported under solvent-free conditions using microwave irradiation. In this method, a mixture of $NbCl_5$ and Al_2O_3 was used to catalyze the reaction. Quantitative yields could be achieved with catalyst loading as low as 5 mol% Nb.[37]

Microporous niobium silicate has been studied for the dehydration of ethanol, 1-propanol and 1-butanol. Using this catalytic system, alkenes could be obtained in high yields at 250-300 °C, while at lower reaction temperatures (< 200 °C), ethers were obtained with a lower total conversion value. These reactions were performed in the gas phase using a fixed-bed stainless steel reactor at atmospheric pressure.[38]

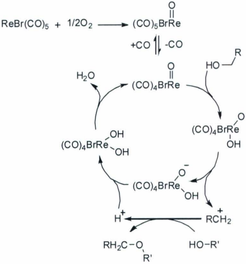
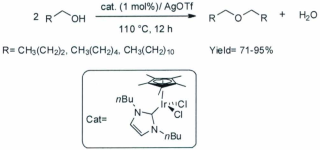


Figure 2-9. Rhenium(I) catalyzed halide-free starting material etherification of benzyl alcohols[36]

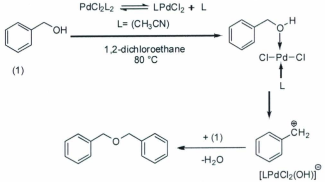
Molybdenum (metal-oxo species such as MoO_4^{2-}) impregnated aluminum hydroxide, $Al(OH)_3$, has also been used as a non-corrosive, environmentally friendly and inorganic solid acid catalyst for the selective conversion of benzyl alcohol to dibenzyl ether.[39] The activity of this catalyst was proposed to be highly dependent on the nature and method of the support's preparation. Likewise, catalytic activity was also affected by the pH of the metal salt solution and the drying process used for the solid support. Although high conversion (93%) and selectivity (82%) were reported for benzyl alcohol using this supported molybdenum catalyst, the method was not studied for substituted benzyl alcohols or other primary alcohols.[39]

[$IrCl_2Cp^*(I^{nBu})$] (Cp^*=pentamethyl cyclopentadienyl; I^{nBu}=1,3-di-n-butylimidazol-ylidene) has been reported to catalyze the condensation of aliphatic alcohols to the corresponding ethers in the presence of silver triflate, AgOTf, as a co-catalyst (Scheme 2-11). However, under these basic conditions, carbonylated products were observed instead of the predicted ethers. Identical reaction conditions were used for the cross-coupling of benzyl alcohols and primary/secondary alcohols and high selectivities were obtained for asymmetrical ethers.[40]



Scheme 2-11. Iridium catalyzed homo-coupling of aliphatic alcohols[40]

Among these catalytic systems, Pd(II) compounds have gained a special position, which has led to a recent review for the formation of ether linkages in the presence of palladium catalysts.[41] Muzart *et al.* investigated the effects of electronic properties of different Pd(II) complexes on the yields and selectivities of the products obtained for the dehydration of secondary benzylic alcohols.[42] An ionic intermediate was also proposed for Pd(II) catalyzed dehydration of benzylic alcohols (Scheme 2-12).[42]



Scheme 2-12. Proposed ionic intermediate in the Pd catalyzed etherification of benzyl alcohol[42]

Palladium(II) phosphine catalysts, with silver triflate as a co-catalyst, were able to selectively catalyze the etherification of secondary benzylic alcohols without any elimination products (Figure 2-10).[43] The reaction was demonstrated to be first order in alcohol, and so it was concluded that carbocation formation was the rate-determining step in these reactions (Figure 2-10).[43]

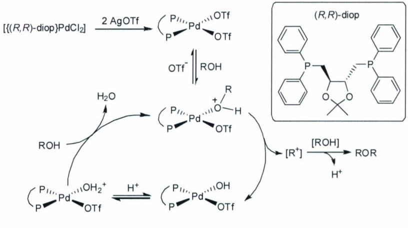


Figure 2-10. Proposed mechanism for the Pd catalyzed dehydrative etherification of alcohols using AgOTf co-catalyst[43]

The catalytic activities of different p-block metals (in the form of metal oxide nanoparticles or metal halides) were also investigated for the transformation of alcohols to ethers and alkenes. Goettmann *et al.* reported the condensation of benzyl alcohol based on a chlorine borrowing method.[44] In this work, they used chlorine functionalized SnO_2 nanoparticles prepared from $SnCl_4$ precursors. The use of chlorine-free nanoparticles yielded trace conversion for benzyl alcohol. This demonstrated the importance of the chlorine atoms on the nanoparticles' surface and they proposed that the chloride anion acted as the active species in the catalytic system (Figure 2-11). This method promotes the electrophilicity of alcohols through chlorinated intermediates. Although the reaction conditions required for this method are harsh (*e.g.* 80 h at 150 °C for the preparation of dibenzyl ether), the need for added alkylating reagents and noble metal catalysts has been avoided.[44]

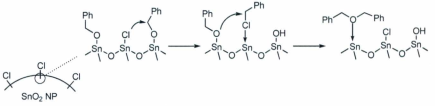
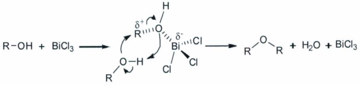
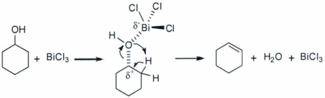


Figure 2-11. Proposed mechanism for the condensation of benzyl alcohol, catalyzed by chlorine functionalized SnO_2 nanoparticles (NPs)[44]

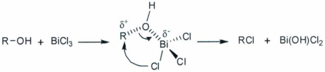
Bismuth compounds have also been studied in dehydration reactions. In particular, bismuth(III) halides were screened in halogenations, dehydrations and etherifications for a series of cyclic, acyclic and benzylic alcohols.[45,46] Boyer *et al.* used this Lewis acid in their studies since they considered bismuth to be the least toxic heavy element and a useful element in traditional medicine. Based on different reaction times and temperatures, chlorinated or dehydrated products were obtained (Schemes 2-13 to 2-15). For example, dibenzyl ether was obtained as the main product after 30 min from benzyl alcohol and $BiCl_3$ at room temperature. However, under reflux conditions in CCl_4, benzyl chloride was obtained in excellent yield after 5 min. It should be noted that $BiCl_3$ is a stoichiometric reagent in the chlorination reaction and can yield three equivalents of product. Therefore, 1/3 equiv. to equimolar amounts of $BiCl_3$ with respect to the substrate were used for the chlorination of alcohols while a catalytic amount (5 mol%) of $BiCl_3$ was used for etherification and dehydration reactions. Different mechanistic pathways were investigated for the etherification, dehydration and chlorination of alcohols with $BiCl_3$. Based on experimental evidence, four-coordinate bismuth intermediates were proposed.[45,46]



Scheme 2-13. Bismuth(III) chloride catalyzed etherification of aliphatic and benzylic alcohols[45,46]



Scheme 2-14. Bismuth(III) chloride catalyzed dehydration of cyclic alcohols[45,46]

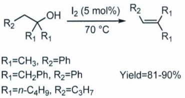


Scheme 2-15. Bismuth(III) chloride mediated halogenation of cyclic, acyclic and benzylic alcohols[45,46]

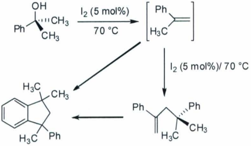
A combination of antimony(III) iodide, SbI_3, and phenylsilane, $PhSiH_3$, in dry tetrahydrofuran was demonstrated to facilitate etherification of different aliphatic, alicyclic and benzylic alcohols.[47] Moderate to excellent yields were obtained when these two reagents (equimolar with the alcohol substrate) were employed. However, other metal halides (*e.g.* NiI_2, TiI_4 or $MnCl_2$) under the same reaction conditions provided poorer yields.[47]

2-3-4 Non-metallic catalysts in the synthesis of ethers and alkenes

Non-metallic compounds have also been studied for the catalytic etherification of alcohols. For example, molecular iodine (I_2) and sodium bisulfite ($NaHSO_3$) were introduced as cheap and environmentally friendly catalysts for the aforementioned transformations. Iodine has some advantages over other Lewis acid catalysts, especially those bearing metals. Iodine is a water tolerant, environmentally friendly and comparatively cheap material. It also works exceptionally well under solvent-free conditions. A review article has recently been published on iodine-catalyzed reactions for oxygen functional group containing substrates (*e.g.* alcohols, phenols, ethers, esters and carbohydrates).[48] For example, iodine was used as an efficient catalyst to induce some transformations of alcohols under solvent-free conditions. Several solvents, such as acetonitrile, methanol and water were used for the experiments, however the best results were obtained without solvent. Under these conditions, phenyl substituted alcohols underwent dehydration, dimerisation and etherification, which was highly dependent on the structure of the substrate. In the presence of 5 mol% molecular iodine, I_2, primary and secondary benzyl alcohols were transformed to the corresponding ethers in high yields at 70 °C in less than 6 h. Under the same reaction conditions, tertiary alcohols underwent dehydration to form the corresponding alkenes (Scheme 2-16), while 2-phenylpropan-2-ol produced 1,1,3-trimethyl-3-phenylindane through a cyclodimerization process (Scheme 2-17).[49]

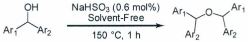


Scheme 2-16. Iodine catalyzed dehydration of tertiary alcohols[49]



Scheme 2-17. Iodine catalyzed cyclodimerization of tertiary alcohols[49]

As a cheap and mild catalyst, sodium bisulfite ($NaHSO_3$) can selectively catalyze the symmetric and asymmetric etherification of benzyl alcohols possessing β-hydrogens under solvent-free conditions.[50] Much lower selectivities were reported when more acidic sodium and potassium bisulfates ($NaHSO_4$ and $KHSO_4$) were used in the reactions. With these bisulfate salts, larger amounts of intramolecular dehydration products over the intermolecular etherification were observed. The reactions between an arylethanol, 1-(4-methoxyphenyl)ethanol, with several aliphatic alcohols in the presence of $NaHSO_3$, afforded the corresponding asymmetric ethers with high selectivities. Excellent yields were also reported with different electron rich or electron deficient benzhydrols employing this catalytic system (Scheme 2-18).[50] Low catalyst loadings (0.3-0.6 mol% to the substrates), solvent-free conditions, high yields and selectivities for the corresponding ethers over alkenes, the use of a cheap and weakly acidic catalyst are some of the highlights of this work. However, it should be noted that sodium bisulfite is considered a corrosive material in its MSDS (Material Safety Data Sheet).



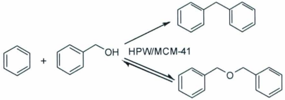
Scheme 2-18. Sodium bisulfite catalyzed etherification of benzyl alcohols[50]

2-3-5 Heteropoly- and solid-acid catalyzed synthesis of ethers and alkenes

Heteropoly acids (HPA) are solid inorganic acids composed of hydrogen, oxygen, metals (*e.g.* tungsten or molybdenum) and non-metals (*e.g.* phosphorus or silicon) in different combinations. They can be used either homogeneously or heterogeneously and can be combined with different solid supports in order to improve their properties (*e.g.* thermal stability or recyclability).

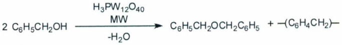
An aluminum salt of HPW, aluminumdodecatangstophosphate ($AlPW_{12}O_{40}$), has been reported to catalyze the self-condensation of benzyl alcohols at room temperature. $AlPW_{12}O_{40}$, is a heterogeneous, recyclable, cheap and water tolerant Lewis acid. Water tolerance is a very important property for catalysts in these dehydration reactions. The ability of this Lewis acid in catalyzing the conversion of highly electron deficient 4-nitrobenzyl alcohol to the corresponding ether is worthy of note. In this reaction, bis(4-nitrobenzyl)ether was obtained in 96% yield in refluxing 1,2-dichloroethane after 10 h. Asymmetric etherification of benzyl alcohols with various aliphatic alcohols in the presence of 5 mol% $AlPW_{12}O_{40}$ was reported under reflux conditions with high yields. In these experiments, primary, secondary and tertiary alcohols (*e.g.* methanol, 1-propanol, 2-propanol and *t*-butanol) were used as solvents and reagents. No conversion was observed for aliphatic and allylic alcohols to their corresponding symmetric ethers.[51]

Heteropoly acids (HPA) supported on mesoporous silica have been reported to catalyze the benzylation of aromatic compounds (Friedel-Crafts) through a halogen-free mechanism (Scheme 2-19).[52] Among the several HPA that were employed, the highest efficiency and turnover number was reported for tungstophosphoric acid ($H_3PW_{12}O_{40}{\cdot}xH_2O$) (HPW) supported on mesoporous silica, MCM-41. No benzylation was observed when nitrobenzene was used as the arene substrate, but instead, a quantitative yield for dibenzyl ether was obtained. When more electron rich arenes were used, the produced dibenzyl ether was proposed to act as a benzylating agent as well as the original benzyl alcohol starting material.[52]



Scheme 2-19. HPW/MCM catalyzed Friedel-Crafts benzylation of arenes and condensation of benzyl alcohols[52]

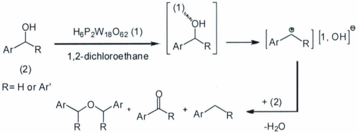
The same HPA, $H_3PW_{12}O_{40}$, was used in solvent-free etherifications of benzyl alcohol under microwave irradiation in an open Teflon vessel (Scheme 2-20). The maximum yield for the dibenzyl ether was reported at 0.06 mol% catalyst loading relative to the benzyl alcohol. Polybenzyl compound formation, as a byproduct, was reported at higher catalyst loading and also after prolonged reaction times and at higher microwave powers.[53]



$$2\ C_6H_5CH_2OH \xrightarrow[-H_2O]{H_3PW_{12}O_{40}\ MW} C_6H_5CH_2OCH_2C_6H_5 + -\!(C_6H_4CH_2)\!-$$

Scheme 2-20. Solvent-free, HPA catalyzed etherification of benzyl alcohol[53]

Ionic intermediates were proposed for the dehydration reaction of benzylic alcohols in the presence of Wells-Dawson tungsten heteropolyacid, $H_6P_2W_{18}O_{62}$ (Scheme 2-21). These experiments were carried out in 1,2-dichloroethane, which is considered to be a toxic and volatile solvent.[13] Therefore, 'greener' solvents (or solvent-free conditions) should be considered in future research.

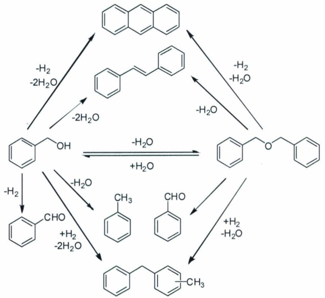


Scheme 2-21. Proposed ionic intermediate in the HPA catalyzed etherification of benzylic alcohols[13]

Carbon supported heteropolyacids (tungstophosphoric and molybdophosphoric acids) were also investigated for dehydration reactions of alcohols. These supported catalysts were made based on electrostatic interactions between HPA and carbon due to proton-transfer to the carbon support. These heterogeneous catalysts were non-corrosive and eased catalyst recovery and could therefore be considered as environmentally benign catalysts. In these systems, the pore sizes of the catalyst support and the molecular size of the alcohol dictated the conversion levels and selectivity (alkene/dimer). For larger molecules, lower conversions, but higher selectivities towards alkenes were reported. However, for smaller molecules (*e.g.* 1-indanol) dimer products were obtained predominantly.[12]

Beyond HPA, other solid-acids have also been investigated for alcohol to ether/alkene transformations. In this regard, Nafion-H, which is a sulfonated tetrafluoroethylene based polymer, was introduced to catalyze ether synthesis from alcohols. Ethers corresponding to different primary alcohols were obtained in high yields in the presence of this acidic resin catalyst. Similar results were obtained for cyclic secondary alcohols, however low conversions were reported for acyclic secondary alcohols. In this method, azeotropic distillation using toluene to remove water was necessary to achieve quantitative yields. Nafion-H was easily recyclable through simple filtration and it was regenerated by washing with acetone and water and drying at 105 °C overnight.[54]

A wide variety of transformations have been reported for benzyl alcohol in the presence of different types of zeolites (Scheme 2-22).[55] Toluene, benzaldehyde, anthracene, stilbene, *o*-benzyl toluene, dibenzyl ether (from benzyl alcohol) and benzyl alcohol (from dibenzyl ether) were obtained from the reaction of benzyl alcohol and dibenzyl ether over zeolites in the gas phase. For benzyl alcohol, these reactions were classified as dehydration, disproportionation and benzylation reactions and were discussed in detail in the paper by Pillai *et al.*[55] They found that various parameters, such as temperature and zeolite pore sizes played important roles in these reactions. For example, over zeolites with different pore sizes, dibenzyl ether was formed from the intermolecular dehydration of benzyl alcohol in higher yields at temperatures lower than 300 °C, while at higher temperatures (up to 500 °C) dibenzyl ether was not detected. Over zeolites with medium pore sizes, traces of anthracene was reported at 300 to 500 °C, however it was obtained as the major product when zeolites with large pore sizes were used.[55] Overall, low selectivities were reported for these reactions and the very high reaction temperatures needed could potentially limit the application of this method to a small number of substrates.



Scheme 2-22. Transformations of benzyl alcohol and dibenzyl ether in the gas phase over zeolites[55]

2-3-6 Alternative solvents in the synthesis of ethers and alkenes

As mentioned above, supported heteropoly-acids and polymeric solid-acids have been used in catalytic dehydration and etherification reaction of alcohols. They are recyclable and have less-impact on the environment than commonly used strong mineral acids.

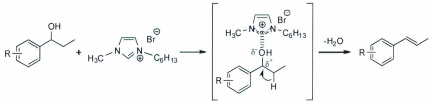
Further modifications have been performed on heterogeneous and homogeneous acid-catalyzed dehydration and etherification reactions in order to meet the requirements for green chemistry. In this regard supercritical fluids (SCFs) have been employed in combination with different heterogeneous or homogeneous acid catalysts.[56,57]

Supercritical fluids are considered useful solvents with some unusual physicochemical properties. Also, SCFs such as supercritical carbon dioxide, $scCO_2$, and supercritical water, scH_2O, are green solvents, because they are non-flammable and non-toxic. In some cases, increased catalyst stabilities have been reported in SCFs because of less coking.[56,58] Solid acids, such as Amberlyst 15 or Deloxan ASP, have been used for acid-catalyzed dehydration of alcohols to yield linear or cyclic ethers in continuous-flow $scCO_2$ reactors. In these reactors, cyclic ethers such as tetrahydrofuran or 1,4-dioxane were obtained in excellent yields (> 95%) from 1,4-butanediol and di(ethylene glycol), respectively. For the dehydration reaction of 1,4-butanediol, 100 atm pressure at 150 to 200 °C in a 10 mL fixed bed flow reactor was used with flow rates of 0.65 L/min and 0.5 mL/min for CO_2 and the substrate, respectively. The same reactors were employed to prepare 1,4-dioxane at 330 °C and 200 atm at the same flow rates. Similar conditions were used for the dehydration reactions of n-alcohols up to n-octanol, but lower yields (lower than 54%) were obtained. Unlike homogeneous acid-catalyzed dehydrations, the heterogeneous catalysts can be used under continuous flow conditions. In these heterogeneous processes, the acid separation and neutralization steps, that would be needed in homogeneous batch systems, are avoided. However, in the homogeneous catalytic systems fewer problems are encountered regarding mass and heat transfer. The low solubility of H_2O in $scCO_2$ has been suggested as the driving force for dehydration reactions of alcohols in this "green" solvent.[56]

Supercritical water has been used as the reaction medium for homogeneous-acid-catalyzed dehydration of some alcohols to alkenes.[57] Water acts as an ionic medium under supercritical conditions (*e.g.* 34.5 MPa and 400 °C for these experiments), thus it works as a suitable solvent for polar substrates. Negligible levels of decomposition for water and the substrate (ethanol) were detected in the presence of strong acids such as H_2SO_4 at 34.5 MPa up to 500 °C, as long as the walls of the reactor were clean and passivated properly.[57]

Ionic liquids have been used as solvents, reagents and catalysts in the dehydration of alcohols. For example, imidazolium ionic liquids, were used as solvents and reagents for the dehydration reaction of benzylic alcohols to yield alkenes.[5] The more hydrophobic the imidazolium ionic liquid the higher the yields obtained. In hydrophobic ionic liquids, water which is produced in the dehydration process, would leave the bulk ionic liquid layer and form a separate phase. This would occur since water is not soluble in hydrophobic ionic liquids. Higher yields were reported in 1-hexyl-3-methyimidazolium bromide, [HMIm]Br, than in 1-butyl-3-methylimidazolium bromide, [BMIm]Br. Also [BMIm]Br was more efficient than [BMIm][BF_4], as the former is a more hydrophobic ionic liquid than the latter. Microwave heating of reaction mixtures afforded short reaction times, less than 12 min, for these dehydration reactions. A polarization of the C-

O bond due to the interaction between the oxygen lone pair in the alcohol and the imidazolium cation followed by water abstraction was proposed as the possible mechanism for the preparation of aryl alkenes from benzyl alcohols (Scheme 2-23). A 5-6% decrease in activity was reported for the ionic liquids after recycling three times.[5]



Scheme 2-23. Dehydration of benzylic alcohols in imidazolium ionic liquid [HMIm]Br[5]

Imidazolium ionic liquids have also been used for Williamson and Ullmann ether syntheses as reaction media, promoters and base. For example, excellent yields were reported for the synthesis of alkyl aryl ethers from phenols and alkyl or benzyl halides in [BMIm][OH], in which the ionic liquid acted as solvent as well as base under moderately mild conditions (2 h at 70 °C).[59] While, for the same type of reactions using [BMIm]I in the presence of catalytic quantities of CuI moderate to excellent yields were reported for longer reaction times at higher temperatures (30 h at 110-130 °C).[60] In the reactions in [BMIm]I, K_2CO_3 was used as the base and the immobilized copper catalyst in the ionic liquid was recycled and reused several times.[60] Phenoxides have also been used as reagents for the preparation of diaryl ethers and diaryloxymethanes (Scheme 2-24) in a range of imidazolium ionic liquids.[61,62] For example, phenoxides were reacted with dichloromethane in [BMIm]Br to afford diaryloxymethanes based on the Williamson method. In these reactions, the ionic liquid could be recycled four times without a considerable change in activity.[61]

Scheme 2-24. Williamson type synthesis of diaryloxymethanes in imidazolium ionic liquid [BMIm]Br[61]

2-3-7 The role of bases in the Williamson method

Many dehydration and etherification reactions of alcohols are performed under acid-catalyzed conditions (*vide supra*), however, bases are an important reagent in the Williamson ether synthesis method. Usually strong bases are used to deprotonate the weak acidic protons on the hydroxyl groups of the alcohols. For example, Li *et al.* screened several bases in different solvents for the coupling of halides with alcohols under microwave irradiation. Very low yields (*e.g.* < 1% for the reaction of PhBr and benzyl alcohol) were reported in the presence of weak bases, such as K_2CO_3 in DMSO. For the same reaction a 63% yield was obtained when an equimolar amount (compared to the alcohol) of *t*-BuOK was used in DMSO.[63]

Taber *et al.* introduced potassium hydride in paraffin, KH (P), as an efficient and easy to handle base for Williamson ether synthesis and reported excellent yields for the condensation of tertiary benzyl alcohols and benzyl bromide.[64] Furthermore, high conversions and selectivities for the ether products were obtained even for alcohols that can potentially form elimination products. Although the base in this method was claimed to be easy to handle, the preparation of KH (P) requires pressurized hydrogen gas at 120 °C in contact with a large mass (50 g) of potassium metal in paraffin in a Parr reactor. Therefore, the preparation of KH (P) needs to be performed in a very safe environment and is potentially very hazardous.[64]

2-3-8 Weak alkylating agents in Williamson ether synthesis

In an attempt to obtain greener reaction conditions, Talbiersky *et al.* introduced the use of weak alkylating agents at high temperatures in Williamson ether syntheses.[3] In their method, use of a weak alkylating agent, such as methanol, and a catalytic amount of alkali metal benzoate means that the use of toxic and more expensive alkylating agents (*e.g.* alkyl sulfates and alkyl halides) can be avoided (Figure 2-12). Alkyl derivatives of Brønsted acids such as alkyl halides and alkyl sulfates are needed for Williamson ether synthesis at temperatures below 100 °C.[3] These strong alkylating agents are known to be highly toxic and usually carcinogenic materials. The efficiency of weak alkylating agents such as alcohols (*e.g.* methanol), esters of weak acids (*e.g.* acetic acid or benzoic acid) and dialkyl ethers can be increased at high temperatures and pressures. The authors introduced a catalytic Williamson ether synthesis (CWES), which has been used in an industrial plant to produce anisole from methanol and phenol at temperatures higher than 300 °C.[3] In this example they used in situ prepared potassium carboxylates from carboxylic acids (*e.g.* acetic acid, phthalic acid and benzoic acid) and KOH as the homogeneous catalysts and the only byproduct was water. The method, however, as they have mentioned cannot be a substitution for the classical Williamson method in the synthesis of more complex molecules, because of the limitations in the stability of many materials at such high temperatures.[3]

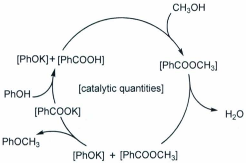


Figure 2-12. Proposed catalytic cycle for CWES using methanol as the alkylating agent in the presence of a catalytic amount of alkali metal benzoate[3]

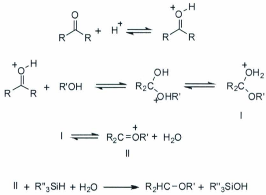
Selva *et al.* compared four methylating agents: dimethyl carbonate (DMC), dimethyl sulfate (DMS), methyl iodide (MeI) and methanol, in terms of toxicity, cost, safety and some other parameters in several reactions including *O*-methylation of phenols.[65] Methyl iodide and dimethyl sulfate are two highly toxic materials that are used in the synthesis of anisole from phenol based on Williamson reaction. Among these four alkylating agents dimethyl carbonate was introduced as the safest and a biodegradable alkylating agent, however it is classified as a flammable liquid. Methanol is considered as a toxic chemical, but it costs around 50% less than dimethyl carbonate. In terms of atom economy for the methylation reactions these reagents follow the trend: MeOH >> DMC $\geq$ DMS > MeI. Dimethyl carbonate showed higher activities at lower temperatures and is therefore a favourable alkylating agent compared with methanol.[65]

2-3-9 Oxidation-reduction method for the synthesis of ethers and alkenes

Reductive etherification is an alternative method to the Williamson ether synthesis and avoids the use of alkyl halides. Doyle *et al.* in 1972 reported the first reductive etherification of several aldehydes and ketones in a variety of alcoholic solutions.[66] Trialkylsilanes were used as reducing agents for the aldehydes and ketones in acidic alcoholic media. Various acids, such as sulfuric acid, trifluoroacetic acid and trichloroacetic acid were used in these reactions to activate the carbonyl groups in the aldehydes and ketones. Sulfuric acid provided a heterogeneous mixture with the silane reagent, while homogeneous solutions were obtained when trifluoroacetic and trichloroacetic acids were added to reaction mixtures containing the silane reagent. The proposed reaction mechanism for the reductive etherification of carbonyl substrates is given in Scheme 2-25.[66]

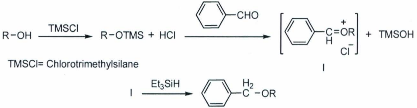
As a modification on the Doyle's reductive etherification, Oriyama *et al.* employed a catalytic amount of a Lewis acid instead of the excess amount of strong acid.[67] Iron(III) chloride was used to catalyze the reductive etherification of different alcohols in the presence of triethylsilane as the reducing agent in nitromethane at room temperature.

Benzyl alcohol, acyclic and cyclic secondary alcohols were used with a variety of aromatic and aliphatic aldehydes as well as ketones to afford the corresponding benzyl or alkyl ethers. Reductive etherification of benzaldehyde with the aforementioned alcohols gave the corresponding ethers in excellent yields (> 81%). When benzaldehyde and phenol were selected as the substrates, phenol did not participate in the reaction and dibenzyl ether was obtained in 92% yield.[67]



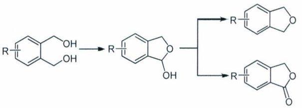
Scheme 2-25. Reductive etherification using aldehydes and ketones[66]

Chlorotrimethylsilane (TMSCl) has also been used as an acid source and a dehydrating agent in reductive etherification of benzaldehydes with Et_3SiH as the reducing agent (Scheme 2-26).[68] This method was used for the benzylation of benzyl alcohol and several partially benzylated glucose derivatives, such as 2,3,4-*O*-tribenzyl-*α*-D-glucopyranoside with good to excellent yields. However, the method was not suitable for substrates with 4-methoxybenzyl groups, since the combination of TMSCl and Et_3SiH selectively cleaved the 4-methoxy group in these substrates. The proposed mechanism consisted of several steps including HCl formation from the reaction of TMSCl (10 equiv.) and the alcohol. Subsequently, the reduction of the alcohol-aldehyde adduct intermediate was performed by the Et_3SiH (Scheme 2-26).[68]



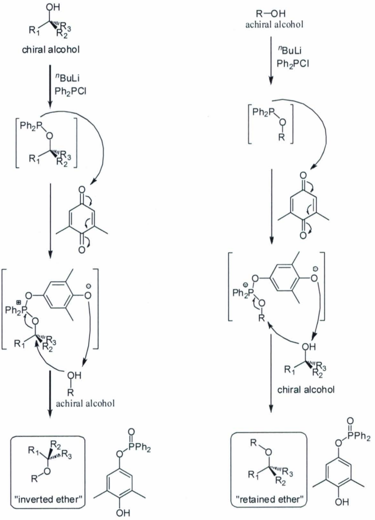
Scheme 2-26. Reductive etherification of benzaldehydes for benzylation of alcohols[68]

Cyclic and acyclic ethers have been prepared in high yields via an oxidation-reduction mechanism. In this process, MnO_2 (the oxidant) was added at -5 to 0 °C to the reaction mixture in DCM.[69] Subsequently, Et_3SiH was gradually added at room temperature as the reducing agent followed by the addition of CF_3COOH. In the oxidation step, *ortho* diols are oxidized to the corresponding lactols (Scheme 2-27). The lactols are converted to the cyclic ethers via the reduction of the oxonium ion intermediates.[69]



Scheme 2-27. Oxidation-reduction of alcohols in the presence of MnO_2 (the oxidant) and Et_3SiH (the reducing agent)[69]

Mukaiyama *et al.* introduced a method for the preparation of symmetric and asymmetric alkyl-aryl or dialkyl ethers through an oxidation-reduction condensation.[70,71] The method is applicable for carbon-oxygen bond formation at a chiral centre in secondary or tertiary alcohols with the ability to retain or invert the configuration (Scheme 2-28). The main step in this process was the in situ formation of alkoxydiphenylphosphines via the reaction of chlorodiphenylphosphine and alcohols in the presence of ^{n}BuLi. Subsequently, the reaction of the alkoxydiphenylphosphine (equimolar to the alcohol) with a mild oxidant (*e.g.* 2,6-dimethyl-1,4-benzoquinone, 1.2 equiv.) afforded the formation of a phosphonium salt. The last step in the mechanism is a S_N2 substitution to form the desired ether. For chiral secondary and tertiary alcohols the reaction of phenols or achiral alcohols with chiral alkoxydiphenylphosphines led to inversion of the configuration. In order to retain the same configuration in the synthesized ethers, achiral alkoxydiphenylphosphines should be reacted with chiral alcohols. This process is an efficient method for the preparation of a wide variety of symmetric and asymmetric ethers at room temperature in relatively short reaction times (0.5-3 h). However, dichloromethane was used as the solvent which is considered to be toxic and volatile.[70,71] In addition, in this method various types of benzoquinones (*e.g.* 2,6-dimethylbenzoquinone or tetrafluoro-1,4-benzoquinone) were used as oxidizing agents in over stoichiometric quantities (1.2 equiv.) relative to the alcoholic substrates. 2,6-dimethylbenzoquinone is not a dangerous substance according to GHS (Globally Harmonized System of classification and labelling of chemicals). However, tetrafluoro-1,4-benzoquinone (fluoranil) is a toxic material. Also these oxidizing agents cannot be considered cheap chemicals (over 45 Canadian Dollars per gram in September 2011), especially when they are used in more than stoichiometric quantities and they are not recyclable based on the reaction mechanism. Furthermore, no attempts were made by Mukaiyama *et al.* to reduce waste production (*e.g.* lithium chloride and phosphine compounds).



Scheme 2-28. Mechanism of oxidation-reduction condensation of alcohols with chiral centres with retention (right) and inversion (left) of the configurations[71]

2-4 Summary

Various classical methods for the synthesis of ethers and alkenes (including the Williamson and Ullmann methods) have been presented. Modifications on these methods to make them more environmentally compatible were also discussed. The emphasis for these modifications were on the waste reduction, use of safer reagents, use of more energy efficient methods, use of catalytic systems and the use of greener alternative media for these reactions. Although numerous efforts have been made to improve these reactions, there is still significant scope to make the reactions more compatible with the principles of green chemistry. In the next two chapters, research that we have performed on the dehydration transformation of alcohols to ethers and alkenes, with an attempt to solve some of the problems in the aforementioned examples, are presented.

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Co-Authorship Statement

This PhD thesis includes results of joint research that have been published in peer reviewed journals in the form of one communication and two full papers, as follows:

Chapter 3: Catalytic dehydrative etherification and chlorination of benzyl alcohols in ionic liquids

Authors: Hassan A. Kalviri, Chad F. Petten and Francesca M. Kerton

Journal: *Chem. Commun.*, **2009**, 5171-5173

The principal author (Hassan A. Kalviri) contributed to all aspects of the project as the main researcher including: literature review, performing 80% of the experiments, collecting and analyzing most of the data, designing some new experiments, presenting and discussing the data with the corresponding author, mentoring Chad F. Petten as an undergraduate summer student, writing the first draft of the manuscript and preparing answers to the questions and comments of the peer reviewers.

The co-author (Chad F. Petten) ran around 20% of the experiments and data analysis.

The corresponding author (Dr. Francesca M. Kerton) proposed the initial experiments and contributed to various aspects of the project including: data analysis, design of new experiments, revision of the draft manuscript and submission to the journal, supervision both of the principal author (H. A. K.) and co-author (C. F. P.).

Chapter 4: Dehydration of benzyl alcohols in phosphonium ionic liquids: synthesis of ethers and alkenes

Authors: Hassan A. Kalviri, and Francesca M. Kerton

Journal: Accepted in *Adv. Synth. Catal.,* on Aug 26, 2011 (Manuscript ID adsc.201100445.R1).

The principal author (Hassan A. Kalviri) contributed to all aspects of the project as the main researcher including: literature review, performing all the experiments, collecting and analyzing the data, designing new experiments, presenting and discussing the data with the corresponding author, writing the manuscript (first and final drafts), preparing answers to the questions and comments of the peer reviewers.

The corresponding author (Dr. Francesca M. Kerton) proposed the initial experiments and contributed to several aspects of the project including: data analysis, design of new experiments, revision of the draft manuscript and submission to the journal, supervision of the principal author (H. A. K.).

Chapter 5: Synthesis of Pd nanocrystals in phosphonium ionic liquids without any external reducing agents

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The principal author (Hassan A. Kalviri) contributed to all aspects of the project as the main researcher including: literature review, performing all the experiments, collecting and analyzing the data, designing new experiments, presenting and discussing the data with the corresponding author, writing the manuscript (first and final drafts), preparing answers to the questions and comments of the peer reviewers, and making the requested corrections to the article.

The corresponding author (Dr. Francesca M. Kerton) proposed the initial experiments and contributed to various aspects of the project including: data analysis, design of new experiments, revision of the draft manuscript and submission to the journal, supervision of the principal author (H. A. K.).

Chapter 3

Catalytic dehydrative etherification and chlorination of benzyl alcohols in ionic liquids

A version of this chapter has been published.
Hassan A. Kalviri, Chad F. Petten and Francesca M. Kerton
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Some modifications were made to the original paper for inclusion as a chapter in this thesis. For example, a reaction mechanism presented in this chapter was not in the original communication.

Abstract

Dibenzyl ethers and benzyl chloride can be obtained in moderate to excellent yields through Pd-catalyzed reactions in hydrophobic ionic liquids using microwave or conventional heating.

3-1 Objectives for chapter 3

- Establish whether ethers can be prepared in ionic liquids via catalytic dehydration.
- Explore the effect of hydrophobicity of ionic liquids on catalytic dehydrative etherifications.
- Study the effects of metal catalysts, and basic and acidic additives on the aforementioned reactions.
- Demonstrate whether there are any electronic effects with regards to substrate scope and reaction yields.
- Attempt to establish a mechanism for the dehydration reactions studied.

3-2 Introduction

Dehydrative reactions can be used for a wide variety of transformations including etherifications, esterifications and thioetherifications.[1] Generally, this route is more environmentally friendly than classical methods (Williamson and Ullmann) as the only byproduct is water, whereas the use of strongly basic alkoxides or phenoxides with alkyl or aryl halides in the Williamson method produces considerable amounts of salt byproducts. In etherification reactions, a wide variety of catalysts have been employed including alumina,[2,3] phase transfer catalysts,[4,5] Lewis acids,[6-8] and several transition metal complexes.[9-11]

Among these catalysts, Pd(II) compounds have a special position,[12-14] which has led to a recent review in this area.[15] It should be noted that dehydrative etherification of benzylic alcohols has been investigated to a lesser extent than phenols, however, such catalytic reactions could be useful in synthetic chemistry, *e.g.* for protecting alcohols.[8]

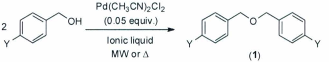
In the area of catalytic dehydration reactions, we thought that the use of hydrophobic ionic liquids (ILs) as reaction media could provide an added benefit to homogeneous catalytic systems by aiding in water abstraction from the reaction mixture. Water, which is produced in these reactions, would leave the bulk ionic liquid layer and form a separate phase. This would occur since water is not soluble in hydrophobic ionic liquids. It should be noted that a separate aqueous phase would not be expected to form if the reactions were performed in hydrophilic ionic liquids. Therefore, based on the Le Châtelier's principle, the reaction in a hydrophobic ionic liquid would proceed in the direction of product formation, as the water (byproduct) would leave the immediate surroundings of the reactants and not be present to inhibit the reaction (a separate phase of water from the ionic liquids was observed).

We have also employed microwave heating to reduce reaction times and energy consumption. In general, room temperature ionic liquids have attracted great attention during the last decade, since they are usually non-volatile, non-flammable, potentially recyclable and benign solvents with the ability to dissolve a wide variety of compounds.[16-19] In terms of ether synthesis, Ullmann and Williamson methods have been performed using ionic liquids as the reaction media,[9,20,21] as well as the promoter.[22,23] As far as we are aware, catalytic dehydrative etherification reactions have not been performed in ionic liquids previously.

3-3 Results and discussion

3-3-1 Solvent screening

In our preliminary studies, benzyl alcohol was selected as it is the simplest benzylic alcohol. Conventional heating (oil bath) as well as microwave irradiation was used as the energy source. Scheme 3-1 presents the general reaction conditions and the benzyl alcohol derivatives used in further studies. Environmentally-friendly systems, such as solvent-free (neat) conditions (Table 3-1, entry 1) and an aqueous medium (Table 3-1, entry 2), were not suitable for this reaction. Additionally, reactions in conventional polar, aprotic organic solvents (Table 3-1, entries 3 and 4) only gave low yields of the desired product. However, Table 3-1, entry 5 shows that ionic liquid [BMIm]PF_6, 1-butyl-3-methyl imidazolium hexafluorophosphate (Figure 3-4), provided a much better environment for the reaction and a much higher yield was obtained in this medium in the presence of $Pd(CH_3CN)_2Cl_2$. The increased yield obtained in the ionic liquid medium may be due to the unique highly ionic environment afforded by this medium that can support ionic intermediates that have been proposed for similar Pd-catalyzed reactions in conventional reaction media.[12]



(1)

Y= H, OCH_3, CH_3, Cl, Br, NO_2

Ionic liquid: [BMIm]PF_6, [BMMIm]PF_6, [BMIm]BF_4, [BMIm]Cl, [$P_{666,14}$]DBS

Scheme 3-1. General scheme for the dehydrative etherification of benzyl alcohols in ionic liquids

Table 3-1. Solvent screening for dehydrative etherification of benzyl alcohol [a]

Entry	Solvent	Yield [b] (%)	Time (min)/Temp (°C)	
			Microwave	Conventional
1	No solvent	0	7/90	24 h/90
2	H_2O	Trace	7/90	24 h/90
3	DMSO	5	9/130	
4	DMF	12	9/130	
5	[BMIm]PF_6	55	7/140	
6	[BMIm]PF_6	23		24 h/80

a) 0.05 equiv. of $Pd(CH_3CN)_2Cl_2$ with respect to benzyl alcohol. b) Yields were calculated relative to benzyl alcohol using ^{1}H NMR spectroscopy with acetophenone as the internal standard.

3-3-2 Study of the efficiency of several transition metal complexes

Various transition metal complexes were screened for catalytic activity in the reaction in the ionic liquid [BMIm]PF_6. The Pd complex, $Pd(CH_3CN_2)Cl_2$, afforded the highest catalytic activity amongst those screened for the dehydrative etherification of benzyl alcohol (Table 3-2). Control reactions were also performed and in the absence of a transition metal, no conversion of the benzyl alcohol was observed in $[BMIm]PF_6$ (Table 3-2, entry 8).

Table 3-2. Transition metal sources that were used in dehydrative etherification of benzyl alcohol in $[BMIm]PF_6$

Entry	**Metal source** [a]	**Yield** [b] **(%)**	**Time (min)/Temp (°C)**	
			Microwave	**Conventional**
1	$Pd(CH_3CN)_2Cl_2$	55	7/140	
2	$Pd(CH_3CN)_2Cl_2$	23		24 h/80
3	$Pt(COD)Cl_2$ [b]	0	7/125	
4	$RuCl_3{\cdot}xH_2O$	12	7/145	
5	$RuCl_3{\cdot}xH_2O$	23		24 h/80
6	$FeCl_3{\cdot}6H_2O$	24	9/130	
7	$FeCl_3{\cdot}6H_2O$	14		4 h/100
8	-	0	7/140	24 h/80

a) 0.05 equiv. of metal source with respect to benzyl alcohol. b) Yields were calculated relative to benzyl alcohol using ^1H NMR spectroscopy with acetophenone as the internal standard.

b) COD: 1,5-Cyclooctadiene

Dehydration products more complex than **1** were also observed when we performed reactions using $PdCl_2$ rather than $Pd(CH_3CN)_2Cl_2$. In these reactions **2** and **3** were observed based on GC-MS analysis (Figures 3-1 to 3-4). This demonstrates that acetonitrile is required and it coordination to the Pd may give control over the etherification reaction. **2**, **3** and their analogues were not observed by GC-MS upon extracting samples from other reaction mixtures and analysis under the same conditions. Furthermore, GC calibration samples of alcohols and ethereal products did not show **2, 3** and **4**. Therefore, it is highly unlikely that these compounds were formed within the GC-MS instrument and indeed did form during the microwave-assisted reactions.

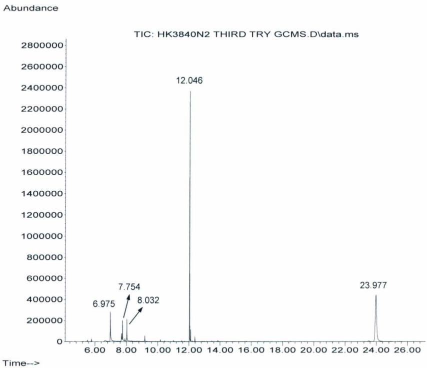


Figure 3-1. GC trace for the reaction of 4-methoxybenzyl alcohol with $PdCl_2$ as the catalyst. Retention times: t (12.05) for 4,4′-dimethoxydiphenyl methane (**2**) and t (23.98) for [4-methoxy-3-(4-methoxybenzyl)phenyl](4-methoxyphenyl)methane (**3**)

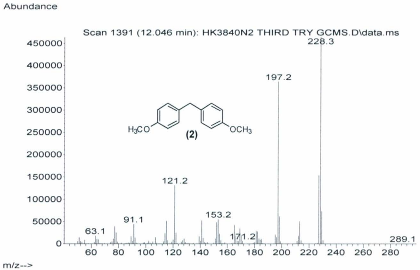


Figure 3-2. MS spectrum for 4,4′-dimethoxydiphenyl methane (**2**), related to Figure 3-1

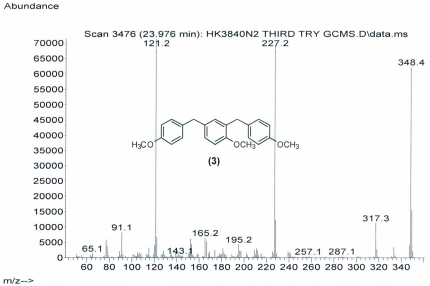


Figure 3-3. MS spectrum for [4-methoxy-3-(4-methoxybenzyl)phenyl](4-methoxyphenyl)methane (**3**), related to Figure 3-1

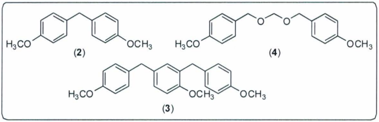
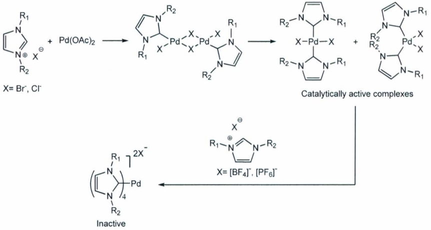


Figure 3-4. Byproducts formed upon prolonged heating of reaction mixtures

3-3-3 The effects of hydrophobicity of ionic liquids and the possibility of carbene complex formation

Two hydrophobic (Table 3-3, entries 1 and 2) and two hydrophilic ionic liquids (Table 3-3, entries 3 and 4) were used to conduct the reaction in the presence of $Pd(CH_3CN)_2Cl_2$. As expected for a dehydration reaction, hydrophobic ionic liquids, such as $[BMIm]PF_6$ and $[BMMIm]PF_6$ ([BMMIm]= 1-butyl-2,3-dimethylimidazolium) (Figure 3-5) gave the highest yields under microwave irradiation in combination with $Pd(CH_3CN)_2Cl_2$. However, ionic liquids with more hydrophilic properties, such as $[BMIm]BF_4$ and [BMIm]Cl were not suitable media for these reactions (Table 3-3, entries 3 and 4). Also, $[BMMIm]PF_6$ was used to assess whether an N-heterocyclic carbene (NHC) complex of Pd was the active species in this reaction. Previously, formation of imidazolylidene isomers (NHC complexes) of $PdX_2(BMImy)_2$ have been observed during Heck coupling reactions in [BMIm]X in the presence of $Pd(OAc)_2$, where X= Br or Cl (Scheme 3-2).[24] During attempted Heck coupling reactions, no N-heterocyclic carbene complexes of Pd were observed in the absence of any halide sources (*e.g.* in [BMIm]BF$_4$ or [BMIm]PF$_6$). When the catalytically active complexes, PdX$_2$(BMImy)$_2$, were immobilized in either [BMIm]BF$_4$ or [BMIm]PF$_6$, instead of [BMIm]Br lower activities were reported because of the formation of catalytically inactive tetrakis-carbene complexes (Scheme 3-2).[24,25]



Scheme 3-2. Generation of Pd-carbene complexes in imidazolium ionic liquids[24]

In [BMMIm]PF$_6$, the generation of the C2-carbene intermediate, which is very common for Pd catalyzed reactions in imidazolium ionic liquids, is impossible. However, carbene formation for the other carbon centres on the imidazolium ring cannot be completely ignored. Almost identical results compared with [BMIm]PF$_6$ were obtained when [BMMIm]PF$_6$ was used as solvent in the dehydrative etherification of benzyl alcohol in the presence of Pd(CH$_3$CN)$_2$Cl$_2$ under microwave irradiation (Table 3-3, entry 2). Therefore the active catalytic components in these reactions are probably not C2 N-heterocyclic carbene-Pd complexes. The slightly lower yield in this experiment (Table 3-3, entry 2) compared to the reaction in [BMIm]PF_6 was likely due to the higher viscosity of [BMMIm]PF_6 compared with [BMIm]PF_6.

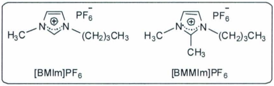


Figure 3-5. Chemical structures of [BMIm]PF_6 and [BMMIm]PF_6

Table 3-3. Dehydrative etherification of benzyl alcohol in different hydrophobic and hydrophilic imidazolium ionic liquids in the presence of $Pd(CH_3CN)_2Cl_2$[a]

Entry	Ionic liquid	Additive	Yield [b] (%)	Time (min)/Temp (°C)
1	[BMIm]PF_6	-	55 (**1**)	7/140
2	[BMMIm]PF_6	-	50 (**1**)	6/140
3	[BMIm]BF_4	-	0	10/135
4	[BMIm]Cl	-	Trace (**1**)	18/80
5	[BMIm]PF_6	KOH	0	15/158
6	[BMIm]PF_6	K_2CO_3	0	15/150
7	[BMIm]PF_6	CH_3COOH	36 (**1**) and 14 (**5**)	10/135
8	[BMIm]PF_6	NH_4Cl[c]	84 (**6**) and trace (**1**)	10/135

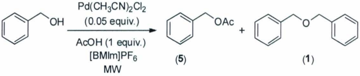
a) 0.05 equiv. of Pd with respect to benzyl alcohol. b) Yields were calculated relative to benzyl alcohol using ^1H NMR spectroscopy with acetophenone as the internal standard. c) 1 equiv. with respect to benzyl alcohol.

Since hydrophobic [BMIm]PF_6 afforded higher yields than hydrophilic ionic liquids ([BMIm]BF_4 and [BMIm]Cl) and PF_6^- was undergoing degradation (*vide infra*), an alternative hydrophobic ionic liquid was used. Trihexyl(tetradecyl)phosphonium dodecylbenzene sulfonate ([$P_{666,14}$]DBS) was employed but did not show a reasonable absorptivity for MW irradiation due to the large size of its cations and anions; however, under conventional heating (24 h at 90 °C), a 56% yield was obtained. This is comparable with results obtained using [BMIm]PF_6. Potentially, by doping the [$P_{666,14}$]DBS phase with a strong microwave absorber (*e.g.* an ionic liquid with lower viscosity or a polar solvent), the reaction could be performed using microwave heating.

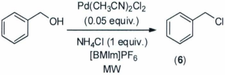
The results above were obtained with a Synthos 3000 microwave reactor. In later studies, phosphonium ionic liquids, including [$P_{666,14}$]DBS, could be effectively heated using a Biotage Initiator 2.5 microwave reactor. The Biotage microwave reactor uses monomodal (directed) microwave irradiation, which can provide a comparatively homogeneous and directed energy field. Therefore, in this reactor the maximum energy is focused on the sample. Whereas the Synthos 3000 reactor has a multimodal (multidirectional) microwave source and is specially suitable for scale-up synthesis by using different rotors. For example, it is possible to perform up to 64 reactions simultaneously using a 64MG5 rotor. However, in this reactor, the microwave energy is distributed in a large cavity and it is not as efficient as a monomode system. In the Biotage microwave reactor, the absorptivity was set on "high" when phosphonium ionic liquids were used as the reaction media, while lower microwave power could be used for imidazolium ionic liquids. The results for the dehydration reactions of alcohols in phosphonium ionic liquids are discussed in detail in chapter four.

3-3-4 Effect of pH and nature of additive

As many ether syntheses are pH dependent, the reactions were examined in the presence of several additives. Under basic conditions (Table 3-3, entries 5 and 6), no conversion was seen. Conducting the reaction in the presence of acetic acid led to the formation of benzyl acetate, **5** (Table 3-3, entry 7 and Scheme 3-3), while benzyl chloride, **6**, was obtained in excellent yield (84%) in the presence of NH_4Cl (Table 3-3, entry 8 and Scheme 3-4). NH_4Cl is less hazardous to human health and the environment than other common chlorinating agents including thionyl chloride and concentrated hydrochloric acid. Further studies on the halogenations of benzyl alcohols in imidazolium ionic liquids were performed by Chad F. Petten under the supervision of Prof. Francesca M. Kerton. Chad F. Petten completed his honours thesis on this subject in 2010.[26]



Scheme 3-3. Pd-catalyzed transformation of benzyl alcohol to benzyl acetate and dibenzyl ether in the presence of acetic acid as an additive



(**6**)

Scheme 3-4. Pd-catalyzed transformation of benzyl alcohol to benzyl chloride in the presence of NH_4Cl additive

3-3-5 Etherification reaction of *p*-substituted benzyl alcohol derivatives

Based on our initial studies, reactions using other benzyl alcohol derivatives were performed under microwave irradiation in $[BMIm]PF_6$ in the presence of catalytic quantities of $Pd(CH_3CN)_2Cl_2$ (Table 3-4). When 4-methoxybenzyl alcohol was used as the substrate (Table 3-4, entry 4), the highest yield was obtained. We propose that this is due to the higher stability of the benzylic carbocation formed from this reagent. All other alcohols, with the exception of 4-nitrobenzyl alcohol (Table 3-4, entry 7), were successfully coupled and yields of 50-60% were obtained. Furthermore, it should be noted that no precipitate formed during the transformation of 4-methoxybenzyl alcohol, whereas for other substrates, especially upon prolonged reaction times either thermally or in a microwave, quantities of a catalytically inactive solid were formed (*vide infra*). Initial recycling studies (Table 3-4, entries 5 and 6) using the ionic liquid (catalyst phase) from the transformation of 4-methoxybenzyl alcohol (Table 3-4, entry 4) were promising; yields were maintained or improved when the catalyst/ionic liquid was reused. Many Pd(II)-catalyzed reactions require or are enhanced by the presence of a copper co-catalyst.[27] Surprisingly, when $CuCl_2$ was used with the Pd for these reactions, the yield dropped from 57% to 8% (Table 3-4, entries 3 and 10).

TEM (Transmission Electron Microscopy) analysis of the reaction mixture (Table 3-3, entry 1) showed no evidence of the formation of colloidal Pd nanoparticles. Therefore, we propose that the catalyst is a homogeneous form of Pd such as L_2PdCl_2 (L = alcohol, CH_3CN or other species present in the reaction mixture).

Table 3-4. Dehydrative etherification of different benzylic alcohol substrates in $[BMIm]PF_6$ under microwave irradiation

Entry	Catalyst ^{a}	Y	Yield^b(%)	Time (min)/Temp (°C)^b
1	$Pd(CH_3CN)_2Cl_2$	H	55	7/140
2	$Pd(CH_3CN)_2Cl_2$	Cl	55	10/145
3	$Pd(CH_3CN)_2Cl_2$	CH_3	57	12/114
4	$Pd(CH_3CN)_2Cl_2$	OCH_3	71	9/113
5	Recycle 1 (reuse entry 4)	OCH_3	96	2×15/106
6	Recycle 2 (reuse entry 5)	OCH_3	78	8/116
7	$Pd(CH_3CN)_2Cl_2$	NO_2	0	10/115
8	$Pd(CH_3CN)_2Cl_2$	Br	6	12/170
9	Precipitate	Cl	8	11/131
10	$Pd(CH_3CN)_2Cl_2/CuCl_2 \cdot 2H_2O$	CH_3	8	10/115

a) 0.05 equiv. of catalyst with respect to benzyl alcohol. b) Yields were calculated relative to benzyl alcohol using ^1H NMR spectroscopy with acetophenone as the internal standard.

b) Optimum reaction conditions (time and temperature) were reported.

3-3-6 Possible reaction mechanism

A possible reaction mechanism for the palladium-catalyzed dehydrative etherification of benzyl alcohols in [BMIm]PF_6 is presented in Figure 3-5. This mechanism was inspired by the previously proposed mechanisms for the palladium catalyzed etherification of benzyl alcohols.[12,28] As demonstrated in Table 3-1 very low yields were obtained using regular polar organic solvents, however when hydrophobic ionic liquids were used as the reaction media, yields were dramatically increased. This suggests a role for ionic intermediates in the mechanism (Figure 3-6). The highly ionic environment of ionic liquids can stabilize the proposed benzylic cations as well as the hydroxyl palladium anionic species. Also, no catalytic activity was observed for the reaction under basic conditions (Table 3-3, entries 5 and 6). Although higher catalytic activity was seen under acidic conditions, the reaction was not purely acid catalyzed and the $Pd(CH_3CN)_2Cl_2$ was needed in order to achieve the best results. The acidic environment in the mechanism was provided by the inherent acidic properties of imidazolium ionic liquids.[29] Hydrophobic ionic liquids can also assist the water abstraction process in this mechanism. Since the reactions were performed under batch conditions in closed vessels, the released water accumulated in the system and based on the Le Châtelier's principle the reaction was prohibited from achieving completion and an equilibrium was established.

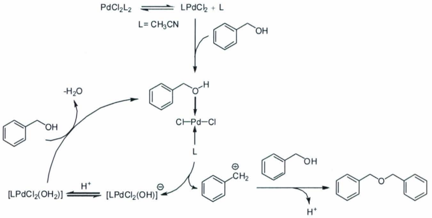


Figure 3-6. Possible mechanism for the Pd(II) catalyzed dehydrative etherification of benzylic alcohols in hydrophobic ionic liquid [BMIm]PF_6

3-3-7 Effects of reaction time and temperature on product formation

In attempts to further increase the yield of these reactions, the effects of increased reaction time and temperature were studied for the transformation of 4-methoxybenzyl alcohol in [BMIm]PF_6. When the reaction mixture (Table 3-4, entry 4) was heated for twenty minutes instead of nine, very little starting material but no ether was seen in the NMR spectrum. However, 4,4′-dimethoxydiphenyl methane (**2**) (Figure 3-4) was detected as the main product via GC-MS analysis (Figures 3-7 and 3-8). When the reaction was performed at a higher temperature (7 minutes at 125 °C), bis-(4-methoxybenzyl) acetal (**4**) was detected via GC-MS. As **2** and **4** are only seen after prolonged reaction times or at higher temperatures, one can assume that **1** is an intermediate in their formation. These products have been observed by other researchers in photochemical and acid-catalyzed reactions.[30,31]

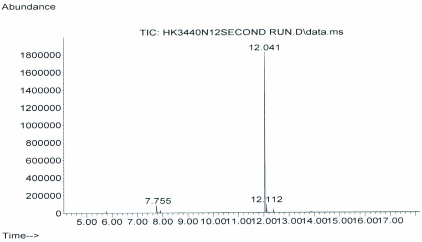


Figure 3-7. GC trace for the reaction of 4-methoxybenzyl alcohol with longer reaction time under MW condition (another 12 min for the sample mentioned in Table 3-4, entry 4). Retention times: t (7.75) for 4-methoxybenzyl alcohol and t (12.04) for 4,4′-dimethoxydiphenyl methane (**2**)

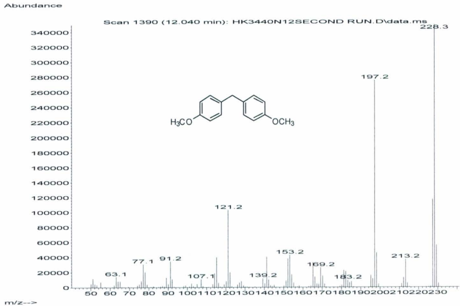
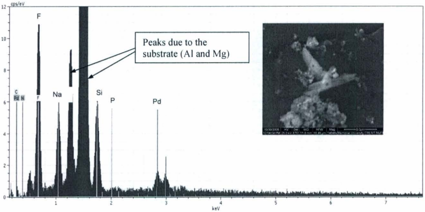


Figure 3-8. MS spectrum for 4,4′-dimethoxydiphenyl methane, related to Figure 3-7

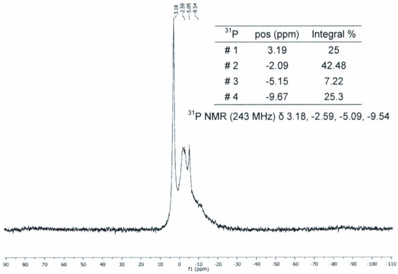
3-3-8 Problems due to hydrolysis of $[PF_6]^-$

As previously mentioned, in the absence of a transition metal, with and without additives, no conversion of the benzyl alcohol was seen. This indicates that although the hexafluorophosphate anion has a tendency to degrade and can potentially form HF in the reaction mixtures, the reactions were not purely acid catalyzed and the metal, ideally palladium, was an essential component of the catalytic system. The degradation of $[BMIm]PF_6$ was evident through the formation of a precipitate in many of the reactions especially upon prolonged heating. The precipitate contained significant amounts of Na and Si which could only have originated from the glass reaction vessels due to their sodium borosilicate content. Furthermore, mild etching of the vessels was seen after some reactions, presumably through in situ action of HF from PF_6^- degradation. EDX (energy dispersive X-ray) analysis of the precipitate showed the presence of Pd, F, Si, P and Na (Figure 3-9). Solid-state ^{19}F and ^{31}P NMR experiments also confirmed the presence of F and P (Figures 3-10 and 3-11). Attempts to use the precipitate as a catalyst (as it contained Pd) were made. It was separated, dried and used (Table 3-4, entry 9), but the yield was low.



Peaks due to the substrate (Al and Mg)

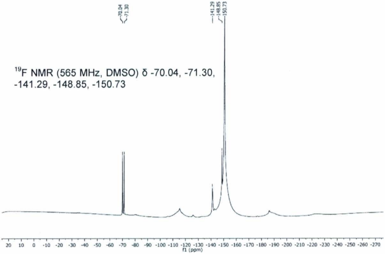
Figure 3-9. EDX analysis of the precipitates in the reaction mixture. The inset image is the precipitate's SEM image



^{31}P	pos (ppm)	Integral %
# 1	3.19	25
# 2	-2.09	42.48
# 3	-5.15	7.22
# 4	-9.67	25.3

^{31}P NMR (243 MHz) δ 3.18, -2.59, -5.09, -9.54

Figure 3-10. ^{31}P-NMR on the solid precipitate in the reaction mixture



^{19}F NMR (565 MHz, DMSO) δ -70.04, -71.30, -141.29, -148.85, -150.73

Figure 3-11. ^{19}F-NMR on the solid precipitate in the reaction mixture

3-4 Conclusions

We have shown that $Pd(CH_3CN)_2Cl_2$ in a hydrophobic ionic liquid affords a simple catalytic system for the direct condensation of substituted benzyl alcohols to afford their corresponding ethers. In the presence of NH_4Cl, benzyl chloride can be obtained in excellent yield. Control reactions revealed the necessity of the Pd catalyst in the reactions and conducting the reactions under acidic and basic conditions showed that the reactions were not purely acid catalyzed. Based on these evidences a possible mechanism for dehydrative etherification of benzyl alcohols was proposed, which shows the importance of ionic liquids in stabilizing the ionic intermediates.

3-5 Experimental

$PdCl_2$ and $RuCl_3 \cdot xH_2O$ were purchased from Precious Metals Online. All reagents and $[BMMIm]PF_6$ were purchased from Alfa Aesar, while the ionic liquid $[P_{666,14}]DBS$ was a gift from Cytec Inc. [BMIm]Cl, $[BMIm]BF_4$ and $[BMIm]PF_6$ were prepared using literature procedures.[32] The SEM (Scanning Electron Microscope) image was obtained using a *FEI Quanta 400* environmental SEM. The system has an Energy Dispersive X-ray (EDX) analytical system from Roëntec.^{1}H NMR spectra were acquired on a Bruker AVANCE 500 MHz spectrometer. Solid-state ^{19}F NMR and ^{31}P NMR spectra were obtained on a Bruker AVANCE II 600 spectrometer. All the chemical shifts are reported in ppm and all solution state NMR experiments were performed in acetone-D_6 except one experiment (using $[P_{666,14}]DBS$) in which chloroform-D was used as the deuterated solvent. An Anton Paar (Synthos 3000) microwave reactor was used to run the experiments under MW irradiation. In this reactor, a Rotor 64MG5 that is able to run reactions on a 0.3 to 3.0 mL scale (up to 20 bar and 200 °C) was used. GC-MS spectra were recorded on an Agilent 7890A GC system coupled with an Agilent 5975C MS detector that was equipped with a capillary column DB-5 (column length: 30.0 m and column diameter: 0.25 mm). All the products were previously reported in literature.

In a typical reaction, benzyl alcohol (0.56 mmol, 0.0610 g) and $Pd(CH_3CN)_2Cl_2$ (0.03 mmol, 0.0080 g) were added to $[BMIm]PF_6$ (2.0 mmol, 0.5408 g) in a vial and was sealed with a PTFE cap under a nitrogen blanket. The reaction mixture was heated under microwave irradiation for 7 min at 140 °C. Generally a microwave power of 150 to 200 W was used. Yields were calculated relative to benzyl alcohol using ^1H NMR, which were directly performed on aliquots of the reactions. In order to run GC-MS analysis the reaction mixture was extracted with diethyl ether.

In all quantification experiments, acetophenone was used as the internal standard (Figure 3-12). Table 3-5 shows the chemical shifts of the benzylic protons in the products that were documented in Table 3-4. GC-MS was used to confirm the identities of products and the selectivity of the reactions. For several reactions (using Pd or Ru), the reaction product was extracted and an isolated yield calculated. Isolated yields were generally in agreement with NMR yields. When $FeCl_3{\cdot}6H_2O$ was used as the catalyst, due to its paramagnetic nature, the reaction product was extracted using diethyl ether, concentrated and analysed using ^1H NMR spectroscopy and GC-MS.

Table 3-5. Chemical shifts of the benzylic protons in the ether products (Table 3-4) [a]

Entry	1	2	3	4	5	6	7
Y in different substrates	H	Cl	CH_3	OCH_3	Br	OCH_3 in $[P_{666,14}]$DBS	H in $[BMMIm]PF_6$
Chemical shifts for benzylic protons in ethers (ppm)	4.58	4.58	4.50	4.45	4.57	4.46	4.58

a) Deuterated solvent: acetone-D_6 except for $[P_{666,14}]$DBS, where chloroform-D was used

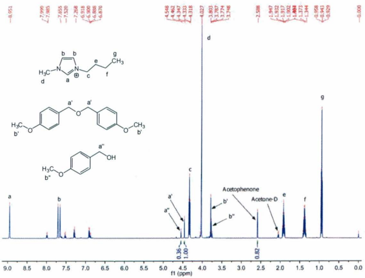


Figure 3-12. ^1H NMR spectrum of the reaction related to entry 4, Table 3-4

3-6 Acknowledgements

We acknowledge support from NSERC of Canada and the Canada Foundation for Innovation in the form of a Discovery Grant, a Research Tools and Instrument Grant, an Undergraduate Summer Research Award (C.F.P.) and a Leaders Opportunity Fund Award (F.M.K.). We would also like to thank Cytec Industries Inc. for samples of [$P_{666,14}$]DBS and Memorial University for funding.

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Chapter 4

Dehydration of benzyl alcohols in phosphonium ionic liquids: synthesis of ethers and alkenes

A version of this chapter has been published.
Hassan A. Kalviri and Francesca M. Kerton
Dehydration of benzyl alcohols in phosphonium ionic liquids: synthesis of ethers and alkenes
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Some minor modifications were applied to the original paper for inclusion as a chapter in this thesis.

Abstract

Dehydration of benzylic alcohols has been studied in several phosphonium ionic liquids in the absence of any metal catalysts. Benzyl ethers and alkenes were obtained from primary and secondary benzylic alcohols in good to excellent yields for these reactions. Commercially available hydrophobic phosphonium ionic liquids containing the trihexyl(tetradecyl)phosphonium cation paired with six different anions were used for the reactions under microwave irradiation. The interaction of the substrate with the ionic liquid was investigated using different NMR techniques, such as NOESY NMR. The effects of cation and anions on the behaviour of these ionic liquids in the reactions were studied in order to understand the mechanism. A catalytic cycle is proposed involving activation of the benzyl alcohol by the phosphonium cation.

4-1 Objectives for chapter 4

- Evaluate whether dehydration reactions of benzylic alcohols in phosphonium ionic liquids proceed via the same mechanism, as in imidazolium ionic liquids.
- Perform preliminary kinetics studies on benzyl alcohol dehydration reactions in phosphonium ionic liquids.
- Demonstrate whether there are any electronic effects with regards to substrate scope and reaction yields.
- Determine the pH of the phosphonium ionic liquids and stablish if there is any correlation between reaction yields and the acidity of the reaction medium.
- Explore the effect of hydrophobicity of the phosphonium ionic liquids on the reactions.
- Obtain NMR data regarding interactions between the alcohols and the ionic liquids to aid in proposing a possible mechanism for the reactions studied.

4-2 Introduction

Imidazolium ionic liquids have been widely studied and used in many types of reactions.[1] In some cases, imidazolium ionic liquids have acted as both catalyst and solvent.[2-4] Previously, we reported the dehydrative etherifications of benzylic alcohols in imidazolium ionic liquids, specifically, [BMIm]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate) in the presence of Pd catalysts.[5] We chose to study such reactions in ionic liquids, because these solvents display an exceptional ability to stabilize ionic intermediates. Phosphonium ionic liquids have been studied to a lesser extent although they possess some advantages over imidazolium ionic liquids. Phosphonium ionic liquids can be prepared without halide contamination, which is an important factor for halogen sensitive reagents.[6,7] Furthermore, phosphonium ionic liquids are more thermally stable than imidazolium and quaternary nitrogen salts.[8,9] Also, tetraalkylphosphonium salts are much less acidic than imidazolium ionic liquids.[10,11] Additionally, imidazolium ionic liquids are not completely inert in some reactions (reagents can potentially interact with the π-system and/or the acidic hydrogens on the ring periphery).[12] However, it has also recently been reported that phosphonium ionic liquids can participate in reactions.[13-15] We have seen this in our own research where Pd(II) salts can be reduced to yield Pd(0) nanocrystals in phosphonium ionic liquids without adding any reducing agents.[13] In this case, the phosphonium cation acts as the reducing agent.

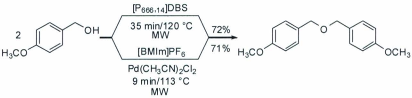
Many phosphonium ionic liquids are commercially available and have been successfully used as reaction media[8,10,16-29] and catalysts[30-32] in a variety of organic syntheses. They have also found industrial uses.[33,34] To the best of our knowledge, reports concerning the use of phosphonium ionic liquids as catalysts contain limited details about the mechanism of catalysis. For the oxychlorination reaction,[31] Perosa *et al.* proposed that the nitrate anion acts as the catalyst.

Dehydration reactions are becoming increasingly important in order to reduce the oxygen content of biomass feedstocks and convert them into more valuable materials for chemical and allied industries. Low selectivity and use of harsh reaction conditions are the main problems associated with dehydration reactions of alcohols. For example, sulfuric acid and *p*-toluenesulfonic acid are among the strong acids that are used for these reactions,[35,36] which need a neutralization process at the end of the pipeline. Heterogeneous acid catalysts have also been used with some success.[37,38] Furthermore, using alcohols as feedstocks for the preparation of ethers is desirable, as waste production (mainly alkali metal salts) and use of toxic alkylating agents are two hazards encountered in classical ether syntheses.[35]

Through our previous studies,[5] we became interested in using phosphonium ionic liquids as reaction media in the dehydration of benzylic alcohols to yield benzyl ethers and alkenes. Unlike our previous studies using imidazolium ionic liquids, we have since found that there is no need for Pd catalysts in phosphonium ionic liquids for these dehydration reactions and the phosphonium cation can catalyze these reactions.

Herein, dehydration reactions of benzylic alcohols are reported that can be performed within a short reaction time via microwave irradiation. The reaction conditions are very simple and highly atom economical, since there is no need for metal catalysts and alkylating agents, and the ionic liquids are recyclable. Also a catalytic cycle for the role of phosphonium ionic liquids in these dehydration reactions will be presented.

4-3 Results and discussion



Scheme 4-1. Dehydrative etherification reaction of 4-methoxybenzyl alcohol in $[P_{666,14}]DBS$ and $[BMIm]PF_6$

In our previous studies, very low conversions were observed in the absence of palladium for dehydrative etherification reactions in imidazolium ionic liquids,[5] however, we have since discovered that the reaction can be performed without any metal catalyst in phosphonium ionic liquids (Scheme 4-1). Furthermore, $[BMIm]PF_6$ was not completely stable under the reaction conditions, as HF was released via hydrolysis of the ionic liquid and our initial studies showed greater stability for phosphonium ionic liquids. As a starting point, 4-methoxybenzyl alcohol was used as the substrate. Several phosphonium ionic liquids containing $[P_{666,14}]^+$, trihexyl(tetradecyl)phosphonium cation, and six different counter ions were used as the reaction media (for their complete names and more information see Table 4-1). Among these phosphonium ionic liquids, $[P_{666,14}]DBS$ was revealed as having the greatest compatibility with the reactions studied in terms of higher yields and ease of product isolation.

Table 4-1. Names and some general physicochemical properties of the trihexyl(tetradecyl)phosphonium ionic liquids that were used in this work. Data were collected from the cited references

Ionic liquid	Anion name	Physical state at room temperature	Approximate thermal stability
$[P_{666,14}]Cl$	Chloride	Liquid, Tg=-56 °C[11]	335 °C[39]
$[P_{666,14}]Br$	Bromide	Liquid[18]	320 °C[18]
$[P_{666,14}][NTf_2]$	Bis(trifluoromethylsufonyl)amide	Liquid, Tg=-76 °C[11]	380 °C[39]
$[P_{666,14}]DBS$	Dodecylbenzene sulfonate	Liquid[18]	350 °C[40]
$[P_{666,14}][N(CN)_2]$	Dicyanamide	Liquid, Tg=-67 °C[11]	360 °C[39]
$[P_{666,14}][(i\text{-}C_8)_2PO_2]$	Bis(2,4,4-trimethylphenyl)phosphinate	Liquid[18]	340 °C[18]

Figure 4-1 shows the progress of dehydrative etherification of 4-methoxybenzyl alcohol in $[P_{666,14}]DBS$ in the presence and absence of $Pd(CH_3CN)_2Cl_2$ (5 mol% with respect to 4-methoxybenzyl alcohol). For this experiment, separate reaction mixtures were prepared with an alcohol to ionic liquid mole ratio of 0.65 (±0.05). The reaction mixtures were heated under microwave conditions at 120 °C for various reaction times as indicated in Figure 4-1. Higher yields were observed at shorter reaction times in the presence of palladium, however in the absence of palladium higher yields could be reached at longer reaction times. In the presence of palladium at prolonged reaction times product decomposition occurs[5] and benzyl chloride is formed presumably from the chloride present in the palladium precursor. Without palladium, the reaction progress can be seen to plateau. We attribute this to the increasing water content of the reaction mixture. Under the reaction conditions studied no considerable improvement in yields was observed in the presence of water scavengers, such as molecular sieves, and anhydrous sodium sulfate. Kappe *et al.* have previously noted that molecular sieves are not efficient water scavengers under microwave assisted reaction conditions.[41]

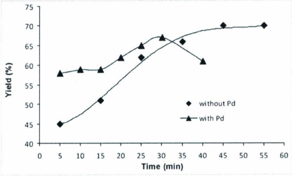


Figure 4-1. Reaction progress for dehydrative etherification of 4-methoxybenzyl alcohol at 120 °C in $[P_{666,14}]$DBS in the presence of 5 mol% $Pd(CH_3CN)_2Cl_2$ and with no palladium.

In the aforementioned experiments, the concentration of 4-methoxybenzyl alcohol was determined based on ^{1}H-NMR spectra of the reaction mixtures. For these experiments, a plot of ln[4-methoxybenzyl alcohol] *vs.* time gives a straight line (Figure 4-2). Therefore, the ionic liquid catalyzed dehydrative etherification reaction under these conditions is first order with respect to benzyl alcohol.

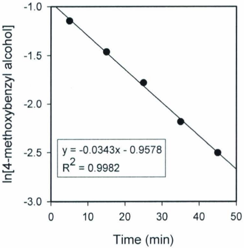


Figure 4-2. Plot of ln[4-methoxybenzyl alcohol] *vs.* time for dehydrative etherification in [$P_{666,14}$]DBS at 120 °C

The etherification reaction was also performed on reaction mixtures with different concentrations of 4-methoxybenzyl alcohol. These results were in agreement with the first order nature of the reaction (Table 4-2). Table 4-2 shows yields for dehydrative etherification reactions of 4-methoxybenzyl alcohol in [$P_{666,14}$]DBS. The reactions were performed at 120 °C for 35 min using four different mole ratios of alcohol to ionic liquid. This table demonstrates that higher yields were obtained at higher alcohol concentrations. Several substrates were screened for this reaction and the results are presented in Table 4-3. Table 4-3 shows that higher yields were obtained for electron rich substrates (entries 1-5). No conversion was observed for control reactions, neat alcohol and no ionic liquid, under these conditions. Since the reactions were performed under batch conditions in closed vessels, the released water accumulated in the system and based on the Le Châtelier's principle the reaction was prohibited from achieving completion. No etherification was observed for aliphatic alcohols or phenols. However, asymmetric etherification was possible between phenols and benzyl alcohols but with low yields and poor selectivities. For example, 16% yield was obtained for phenylbenzylether from condensation of 4-methoxybenzyl alcohol and 4-methoxyphenol at 150 °C (for GC-MS analysis see Figure 4-3).

Table 4-2. Dehydrative etherification reaction of 4-methoxybenzyl alcohol in $[P_{666,14}]$DBS at different alcohol/IL mol ratios

Alcohol/IL (mole ratio)	Yield [a)] (%)	CH_2 ether/CH_2 alcohol ^1H-NMR integral
0.3	54	1.00/0.43
0.6	61	1.00/0.28
1.1	70	1.00/0.16
1.9	72	1.00/0.13

a) Yields were calculated using ^1H-NMR spectroscopy with acetophenone as standard (The ratio of CH_2 ether to CH_2 alcohol resonances could also be used).

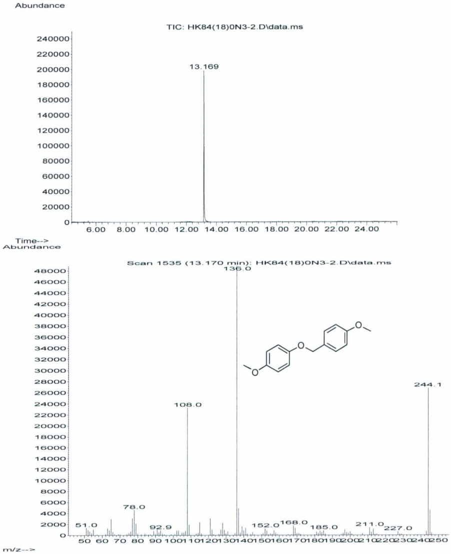
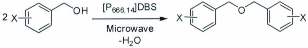


Figure 4-3. GC trace (top) and MS spectrum (bottom) of the ether from the condensation of 4-methoxybenzyl alcohol and 4-methoxyphenol. The sample for GC-MS was prepared from a TLC spot extracted with diethyl ether. Retention time, 13.2 min, 4,4'-dimethoxybenzylphenyl ether

Table 4-3. Etherification reactions of different benzylic alcohol substrates in [$P_{666,14}$]DBS under microwave irradiation



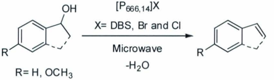
Entry	X	Yield $^{a)}$ (%)	Time [min]/Temp (°C)^{b}
1	4-MeO	72	35/120
2	3-MeO	53	25/200
3	4-EtO	50	20/140
4	4-Me	61	20/180
5	2-Me	63	20/180
6	H	34	60/180
7	4-Cl	26	45/170

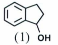
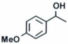
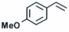
a) Yields were calculated using ^{1}H-NMR spectroscopy with acetophenone or mesitylene as standards.

b) Optimum reaction conditions (time and temperature) were reported. Maximum 2 min for temperature ramp to reach the reported temperature (Appendix 1, Figure 1).

Alkenes were produced as the major products for dehydration reactions of secondary benzylic alcohols which have *β*-hydrogens (Table 4-4). Various catalytic systems have been previously reported for this transformation. For example, recently Re_2O_7 or iodine under solvent-free conditions were reported as efficient catalysts for the dehydration of benzylic alcohols.[42,43] Also, aromatic alkenes can have biological properties. For example, some of the products in this work (methoxy arylalkenes) are building blocks of asarones, which have bactericide and pesticide activities and can be used to treat diphtheria and typhoid.[44] Since the alkene bond in indene is more stable than that in 4-methoxy styrene or styrene, (internal double bonds which are more substituted are more stable than terminal double bonds and in indene compared with the other two systems, more electron delocalization is obtained because of the rigidity of the ring)[35] higher yields were observed for the dehydration of 1-indanol than 1-(4-methoxyphenyl)ethanol and 1-phenylethanol. The lower yield in entry 5 compared to entry 6 is, possibly, because of polymerisation of styrene in [$P_{666,14}$]DBS. After reaction, most mixtures were transparent dark yellow-orange solutions while for entry 5 the reaction mixture was opaque. No attempt was made to fully characterize the insoluble byproduct. The product from the reaction mixture in Table 4-4, entry 2 was vacuum distilled (3 h, 70 mtorr and 110 °C) and when IL was reloaded with (**1**) a 99% yield of (**1'**) was obtained (Table 4-4, entry 3). For a picture of the vacuum distillation apparatus see Figure 4-4. This recycled ionic liquid was also used for dehydrative etherification of 4-methoxybenzyl alcohol and produced a 71% yield, which is comparable with the reaction in fresh [$P_{666,14}$]DBS (Table 4-3, entry 1). It is interesting that the ionic liquid can be re-used in a different dehydration to that which it was originally used in without any problems.

Table 4-4. Dehydration reactions of secondary benzylic alcohols that have *β*-hydrogens



Entry	Substrate	Alkene	Ionic liquid	Yield [a](%)	Time [min]/Temp [°C][c]
1	 (1)	 (1')	$[P_{666,14}]$DBS	96	30/120
2	(1)	(1')	$[P_{666,14}]$Br	99	30/120
3	(1)	(1')	$[P_{666,14}]$Br	99 [b)]	30/120
4	(1)	(1')	$[P_{666,14}]$Cl	30	30/120
5	 (2)	 (2')	$[P_{666,14}]$DBS	67	45/160
6	(2)	(2')	$[P_{666,14}]$Br	85	45/160
7	(2)	(2')	$[P_{666,14}]$Cl	16	45/160
8	 (3)	 (3')	$[P_{666,14}]$DBS	70	20/120
9	(3)	(3')	$[P_{666,14}]$Br	63	20/120
10	(3)	(3')	$[P_{666,14}]$Cl	58	20/120

a) Yields were calculated using ^{1}H-NMR spectroscopy with acetophenone or mesitylene as standards.

b) Recycled $[P_{666,14}]$Br was used. The reaction mixture from entry 2 was vacuum distilled and the IL reloaded with (1) and reused.

c) Optimum reaction conditions (time and temperature) were reported. Maximum 2 min for temperature ramp to reach the reported temperature (Appendix 1, Figure 1).

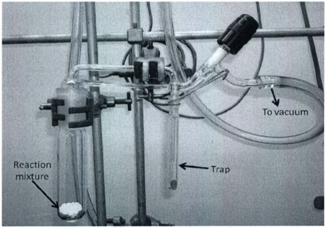


Figure 4-4. The apparatus that was used for the vacuum distillation of the samples. Coloured sample shown to clarify the image. During use the trap is immersed in a dewar containing liquid nitrogen to collect volatiles from reaction mixture

4-3-1 Effect of pH

Dehydrative etherification of 4-methoxybenzyl alcohol was also performed in five other phosphonium ionic liquids containing the same cation as $[P_{666,14}]$DBS but differing anions. The pH of these ionic liquids was measured to probe the effect of acidity on the reaction mechanism. A procedure similar to that reported by Deng *et al.* was used to measure the pH of the ionic liquids.[45] In each case, 5.00 mL deionised water was added to 0.5 mmol ionic liquid and the mixture was vigorously stirred for 2 minutes. The mixtures were passed through silica plugs and the pH of the aqueous phase was measured using a pH meter. The same procedure was used for a blank solution (deionised water) in order to eliminate the filtration and indicator's effects on the pH. The pH meter was calibrated using a buffer solution (pH= 4) before use. The results are summarized in Figure 4-5. Figure 4-5 shows that all these phosphonium ionic liquids have acidic properties. Although the acidic properties of these ionic liquids can come from possible impurities,[34] it has been shown that these ionic liquids have an inherent acidic nature (protons belong to the CH_2 adjacent to phosphorus in phosphonium cations have acidic properties).[15,45] ^1H and ^{31}P NMR spectra did not indicate the presence of any impurities in these ionic liquids. Surprisingly, high and low yields were observed for various ionic liquids across the pH range 2.1-6.2. These results highlight the point that there is no correlation between the pH of the ionic liquids and the reaction yield. Therefore, the reactions are not acid catalyzed. The method that was used for the pH measurements did not directly measure the acidity of the ionic liquids. However, it provides a reasonable estimate for the relative acidities of the ionic liquids. Also no correlation between the pH of the ionic liquids and yield was seen in the dehydration of secondary benzylic alcohols (Table 4-4). Significantly lower yields were obtained in $[P_{666,14}]Cl$ compared with the other two ionic liquids studied. As an alternative to measuring pH using a pH meter, aqueous solutions that were used for pH measurements were titrated with sodium hydroxide; since lower quantities of ionic liquids were consumed for titrations compared with using a pH meter. Solutions with the same concentrations of ionic liquids were prepared for all the samples. Their pH was calculated assuming a strong acid-base titration situation and the results are presented in Figure 4-6. The more acidic ionic liquids show smaller differences between the two methods, but the less acidic ionic liquids (*e.g.* $[P_{666,14}][N(CN)_2]$), show large differences between the two methods of measurement. However, this alternative method does confirm that all the ionic liquids studied were acidic and that there is no correlation between solution pH and yield.

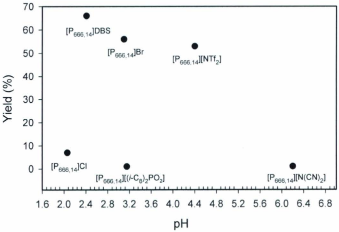


Figure 4-5. Percent yield for dehydrative etherification reaction of 4-methoxybenzyl alcohol in six different phosphonium ionic liquids. Horizontal axis shows the measured pH for the corresponding neat ionic liquids using a pH meter. [$P_{666,14}$]: trihexyl(tetradecyl)phosphonium; DBS: Dodecylbenzene sulfonate; Br: Bromide; [NTf_2]: Bis(trifluoromethylsulfonyl)amide; Cl: Chloride; [$(i\text{-}C_8)_2PO_2$]: Bis(2,4,4-trimethylpentyl)-phosphinate; [$N(CN)_2$]: Dicyanamide

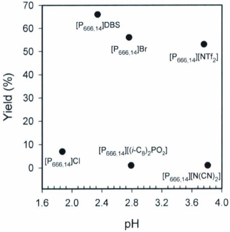


Figure 4-6. Percent yield for dehydrative etherification reaction of 4-methoxybenzyl alcohol in six different phosphonium ionic liquids. Horizontal axis shows the measured pH for the corresponding neat ionic liquids. The aqueous solutions were titrated with sodium hydroxide titrant. Each measurement was repeated three times.

4-3-2 Chloride ion levels

Seddon *et al.* have reported the importance of chloride impurities on the physical properties of ionic liquids.[46] We wondered if the low yield obtained using $[P_{666,14}]Cl$ was due to chloride ions and if the other two ionic liquids ($[P_{666,14}][(i\text{-}C_8)_2PO_2]$ and $[P_{666,14}][N(CN)_2]$) which gave low yields were contaminated with chloride ions. Therefore, chloride measurements were performed on the six phosphonium ionic liquids studied. All contained less than 0.3 wt% chloride, except $[P_{666,14}]Cl$ which contained 8.02 wt% chloride in agreement with its formulation.

4-3-3 Effect of water

All six phosphonium ionic liquids studied are hydrophobic, however their water capacities are not the same. Water solubility in some of the ionic liquids is increased due to the formation of reverse micelles. For example, a high water capacity, higher than 14 wt%, was reported for $[P_{666,14}][(i\text{-}C_8)_2PO_2]$ and $[P_{666,14}]Cl$, while for $[P_{666,14}]Br$, 4.5 wt% was reported.[18,47] However, we did not measure the water content of the ionic liquids in our study. Karl Fischer titration is generally used to quantify the water content of ionic liquids.[7] This factor could have a dramatic impact on the efficiency of the ionic liquids in dehydration reactions. In these reactions water is produced and the more hydrophobic the ionic liquid is, the higher yield should be obtained. In order to confirm the negative effects of water, the dehydrative etherification of 4-methoxybenzyl alcohol in $[P_{666,14}]DBS$ was performed in the presence of intentionally added 20 wt% water. The reaction was carried out under microwave conditions (15 min at 120 °C) with an alcohol to IL mole ratio of 0.7. A 24% yield was obtained for this reaction while, under the same reaction conditions, a 64% yield was achieved for the reaction without added water. Therefore, the use of hydrophobic ionic liquids appear to provide a significant driving force for enhancing the progress of the reactions towards the products.

4-3-4 Effect of ionicity

Another possibility is that the ionic properties of the ionic liquids affect these reactions via their ability to stabilize ionic intermediates. Some of the ionic liquids, for example $[P_{666,14}]Cl$, are less ionic than the others (*e.g.* $[P_{666,14}][NTf_2]$) and have a more closely packed network extended structure with the cations and anions interacting closely. In the former ionic liquid the cation and anion interact with each other more strongly than in the latter ionic liquid. This leads to $[P_{666,14}]Cl$ having some characteristics more typical of molecular solvent. On the other hand, some other anions, such as $[NTf_2]^-$ are less coordinating and can lead to more ionic properties within the ionic liquids,[48-50] *i.e.* the cation and anion are less closely associated with one another within the liquid phase.[48-50] Therefore, $[P_{666,14}][NTf_2]$ should be more suitable for reactions with polar intermediates than the chloride ionic liquid, as it will be better able to stabilize the ionic intermediates. The lower ionic nature of the chloride ionic liquid was confirmed when a reaction mixture of $[P_{666,14}]Cl$ was vacuum distilled at 80 mtorr (3 hours at 80 °C). The presence of this ionic liquid in the gas phase demonstrates that $[P_{666,14}]Cl$ can behave in a molecular fashion, where there is significant bonding between the chloride and phosphonium ions. The ^{31}P NMR spectrum (Figure 4-7) of the distilled material showed the presence of $[P_{666,14}]Cl$ in addition to the desired product. No considerable difference between ^1H NMR spectra of the distilled material and neat ionic liquid was observed (in the regions related to the ionic liquid). It can also confirm the presence of $[P_{666,14}]Cl$ in the distilled material. Under the same vacuum distillation conditions no peaks related to the ionic liquid were observed for samples prepared in $[P_{666,14}][NTf_2]$ or $[P_{666,14}]DBS$. Thus, these two ionic liquids are less volatile and more ionic in nature compared with $[P_{666,14}]Cl$. Therefore, they can provide more suitable environments for ionic reaction intermediates and yields are thereby enhanced.

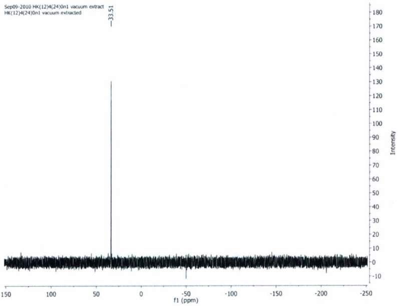


Figure 4-7. $^{31}P\{^{1}H\}$-NMR spectrum of material resulting from vacuum distillation of a reaction mixture using $[P_{666,14}]Cl$ as the reaction medium. Phosphorus peak shows the presence of $[P_{666,14}]Cl$ in the distilled sample

4-3-5 Interactions of substrate with phosphonium cation

NMR studies were performed on samples of the reaction mixtures and neat ionic liquids in order to collect more data to use in proposing a reaction mechanism. ^{1}H NMR spectra of the phosphonium ionic liquids were obtained with higher resolution when using deuterated acetone rather than $CDCl_3$ as the solvent (Figure 4-8). This demonstrates the proton exchange ability of all the methylene groups on the alkyl chains within the ionic liquids. The acidic nature of the protons on the methylene groups adjacent to the phosphorus atom has been reported previously,[15] but significant levels of exchange are also observed for protons farther from the phosphorus atom. In order to investigate the interactions of alcohols with phosphonium ionic liquids, NOESY (Nuclear Overhauser Effect Spectroscopy) NMR was used (Figure 4-9). The integrations in the NOESY spectrum showed the greatest interactions of the CH_2 benzylic protons with the methylene groups *d*, *b* and *c* and fewer interactions with the methylenes adjacent to the phosphorus *a* (Figure 4-9). Regarding the choice of ionic liquids used in this study and that afforded good yields (Table 4-3 and Table 4-4), $[P_{666,14}][NTf_2]$ has the lowest viscosity. Therefore, better molecular tumbling in this ionic liquid provides lower signal broadening and higher resolution NMR spectra, especially for the neat sample used in the NOESY NMR experiments. Furthermore, $[P_{666,14}][NTf_2]$ does not have alkyl chains within its anion, which simplifies its NMR spectra compared with $[P_{666,14}]$DBS.

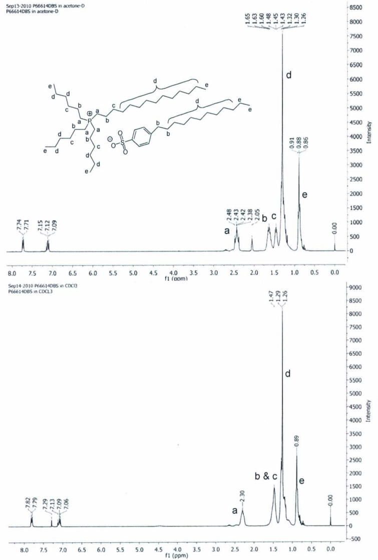


Figure 4-8. ^{1}H-NMR spectra of [$P_{666,14}$]DBS in deuterated acetone (top) and deuterated chloroform (bottom) as the NMR lock solvents

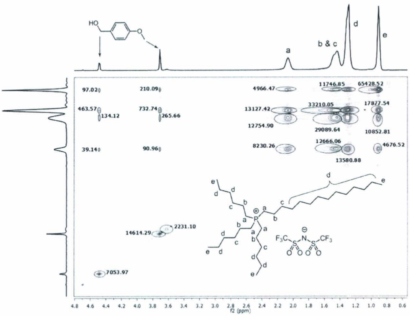


Figure 4-9. NOESY spectrum (selected region) of 4-methoxybenzyl alcohol in $[P_{666,14}][NTf_2]$. D_2O was used as NMR lock solvent in a coaxial NMR tube. Numbers on the contours in the figure indicate integrals for the cross peak resonances

^1H NMR spectra of neat $[P_{666,14}][NTf_2]$ with different concentrations of 4-methoxybenzyl alcohol (Figure 4-10) were in agreement with the results from NOESY NMR. The resolution of the ^1H NMR spectra decreased at higher alcohol concentration for the methylene groups farther from the phosphorus (Figure 4-10, spectrum 3), while for the methylene groups adjacent to the phosphorus, better resolution was obtained at higher alcohol concentrations. This means that in these systems, there are more interactions and exchange between the alcohol and the methylenes labelled *b, c* and *d* (Figure 4-9) than methylenes labelled *a*.

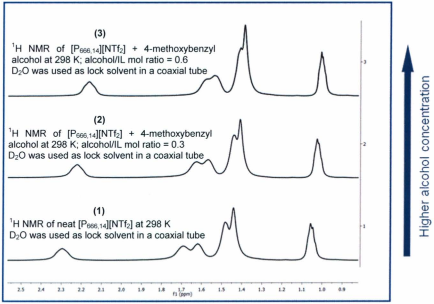


Figure 4-10. Selected region of ^{1}H NMR spectra of neat $[P_{666,14}][NTf_2]$ (spectrum 1) and of 4-methoxybenzyl alcohol at two different concentrations in $[P_{666,14}][NTf_2]$ (spectra 2 and 3). D_2O was used as the NMR lock solvent in a coaxial tube

All the aforementioned discussion has been summarised in a catalytic cycle that is proposed in Figure 4-11. Further support for the presence of ionic intermediates can be obtained by considering the resolution and chemical shifts of the protons in ^{1}H NMR spectra of the ionic liquids in the presence and absence of 4-methoxybenzyl alcohol (Figure 4-10). A significant shift (0.14 ppm) to lower frequency was observed in the presence of alcohol for the protons adjacent to the phosphorus (protons labelled *a*) than the other protons (0.08 ppm for protons labelled *b* and *c*). This demonstrates an increase in the partial electron density next to the above-mentioned protons with increasing alcohol concentration. This would be expected for ionic intermediates such as those proposed in Figure 4-11.

A similar mechanism could be followed by secondary alcohols with *β*-hydrogens. However, as intramolecular elimination is kinetically favoured for these molecules over intermolecular substitution, these reactions yield alkenes rather than ethers.

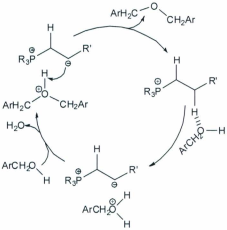


Figure 4-11. Proposed catalytic cycle for dehydrative etherification of benzylic alcohols in phosphonium ionic liquids. The counterion of the ionic liquid has been omitted for clarity. H^+ abstraction may also be occurring at the C α to the P atom.

A deuterium isotope exchange experiment was also performed on a sample of $[P_{666,14}][NTf_2]$, the same ionic liquid that was used for the NOESY NMR experiment. The procedure was modified from the method that was used by Chu *et al.* for $[P_{666,14}]Cl$.[15] The ionic liquid, 16.6 mg, was dissolved in 600 μL CD_3OD and D_2O (1:1 volume ratio) and a ^1H NMR spectrum obtained. A solution of NaOD (0.4 M, 50 μL) was added to the abovementioned solution and after 40 min a second spectrum obtained. The integral ratios for the different methylene groups were normalized relative to the terminal methyl hydrogens. The results showed that protons of the three methylene groups adjacent to the phosphorus, H_a, H_b and H_c in Figure 4-9, in the ionic liquid had undergone deuterium exchange (their integrals decreased over time). 10% of "H" had undergone exchange for each of these but was negligible for all other H environments.

The stability of phosphonium cations in phosphonium ionic liquids toward bases strongly depends on the size and strength of the base.[51,52] In the case of larger bases or reagents, the inner protons of the cation, H_a, are less accessible and the more accessible protons, H_c, *etc.* have significant interactions with these reagents. Therefore, in the case of benzylic alcohols and the mechanism proposed here it is plausible that because of steric hindrance, the inner protons, H_a, have lower interactions with the benzylic protons. The proposed mechanism matches with the NMR evidence, but more experimental and possibly theoretical evidence is needed to exclude the possibility of an ylide-catalyzed reaction, where H_a is abstracted by the alcohol. Ylides have been shown to act as reactive intermediates in a variety of organic reactions and they can also activate alcohols.[53] At this time we have obtained no evidence (*e.g.* ^{31}P NMR data) to support ylide formation, but it cannot be excluded. It is likely that any reactive intermediates, for example an ylide, would be present on a very short time scale before reacting and therefore would not be observed by NMR spectroscopy

4-4 Conclusions

A simple and atom economical method for the conversion of benzylic alcohols to their corresponding ethers and alkenes has been developed. The method is compatible with the principles of green chemistry, since alkylating agents and metal catalysts are avoided. Phosphonium ionic liquids, which are more thermally stable and occasionally cheaper than imidazolium ionic liquids have been used as both the reaction media and catalysts. Yields were reported based on ^{1}H NMR, however if products are isolated that would allow full characterization by ^{1}H, ^{13}C, MS, IR and EA. Both solvent screening and NMR studies support the formation of an ionic intermediate. The protons in β, γ and δ positions of the alkyl chains in the ionic liquids are seen via NOESY NMR to undergo ready exchange with the acidic protons of the alcohol. In the presence of NaOD, CD_3OD (a smaller alcohol) and D_2O, α, β and γ protons undergo deuterium exchange. These results show that phosphonium ionic liquids can act as the catalyst and reaction media in dehydration reactions. Therefore TOF/TON would appear very low. Further studies are needed in order to fully understand the mechanism and in order to scale up the reactions and increase substrate scope. One possible route for increasing yields and improving scale-up potential would be to use a supported version of these ionic liquids and perform dehydration reactions in a continuous-flow manner.

4-5 Experimental

4-5-1 General information and instrumentation

The ionic liquids [$P_{666,14}$]DBS (Cyphos phosphonium IL 202) and [$P_{666,14}$]Cl (Cyphos phosphonium IL 101) were gift samples from Cytec Industries and the other ionic liquids were purchased from Sigma-Aldrich. Alcohols were purchased from Alfa Aesar and used as received. A Biotage Initiator 2.5 microwave reactor was employed for the reactions. 0.5-2 mL microwave vials with PTFE seals were used for all the experiments. A Bruker AVANCE 500 MHz and a Bruker AVANCE III 300 MHz spectrometer equipped with XBB probe were used for the NMR experiments. ^{1}H-NMR spectra were referenced to tetramethylsilane as an internal standard and ^{31}P-NMR spectrum was referenced to external 81% H_3PO_4. A Thermo Scientific Orion 350 pH meter was used for pH measurements. GC-MS spectra were recorded on an Agilent 7890A GC system coupled with an Agilent 5975C MS detector that was equipped with a capillary column DB-5 (column length: 30.0 m and column diameter: 0.25 mm). Chloride ion measurements in the ionic liquids were performed by Canadian Microanalytical Service Ltd. (Delta, BC, Canada).

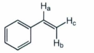
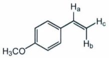
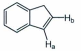
4-5-2 Experimental for dehydrative etherification reaction

In a typical reaction, [$P_{666,14}$]DBS (0.5070 g) was degassed under vacuum. 4-Methoxybenzyl alcohol (0.0979 g) was added to the ionic liquid in a 0.5-2.0 mL Biotage microwave vial and capped under nitrogen flow. The solution was stirred for a few minutes before putting in the microwave reactor. The reaction mixture was heated for 35 min at 120 °C. The absorptivity on the MW was set at "high" for all the samples and the microwave power reached 43-45 W (in this case) during the reaction. No colour change was observed in the reaction mixture upon heating, however droplets of a colourless, odourless liquid (assumed to be water) could be observed near the top of the microwave vial after reactions. Yields were calculated based on ^{1}H NMR spectra using mesitylene or acetophenone as standards. ^{1}H NMR chemical shifts related to CH_2 benzylic (in benzyl ethers) and alkene bonds (in alkenes) have been presented in Table 4-5 and Table 4-6 and the data are comparable with reported values.[5,54] In the case of styrene and 4-methoxystyrene, the products were compared with commercially available standards. The progress of the reactions was monitored using thin layer chromatography (TLC). GC-MS analysis could be performed on the TLC spots extracted with diethyl ether or direct extraction of the reaction mixture, if possible, to identify the products formed (*e.g.* Figures 4-12 to 4-17). Product separation can be performed either by solvent extraction or distillation. Solvent extraction is possible for $[P_{666,14}]Cl$ with 3:1 volume ratio of heptane-water. No degradation was observed for the ionic liquids during the reactions studied. ^{1}H NMR spectra of the ionic liquids, before and after the reactions, did not show any changes in the relative intensities and chemical shifts of the resonances assignable to the ionic liquids. The same procedure can be used for the dehydration reactions of alcohols 1-3 (Table 4-4) to yield alkenes. Yields were calculated relative to the alcohols using ^{1}H NMR spectroscopy with acetophenone (for $[P_{666,14}]DBS$) or mesitylene (for $[P_{666,14}]Br$ and $[P_{666,14}]Cl$) as the internal standards.

Table 4-5. Chemical shifts of the benzylic protons in the products from Table 4-3. $CDCl_3$ was used as the NMR solvent (300 MHz)

Entry	1	2	3	4	5	6	7
X in different substrates in Table 4-3	4-MeO	3-MeO	4-EtO	4-Me	2-Me	H	4-Cl
Chemical shifts for benzylic protons in the products (ppm)	4.45	4.53	4.49	4.49	4.57	4.56	4.51

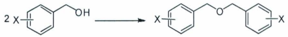
Table 4-6. Chemical shifts of the alkene protons in the products from Table 4-4. $CDCl_3$ was used as the NMR solvent (300 MHz)

Sample	**Chemical shifts (ppm) and couplings (Hz)**
	H_a: 6.71, dd, J(ab)=17.6, J(ac)=10.9 H_b: 5.75, dd, J(ba)=17.6, J(bc)=0.9 H_c: 5.24, dd, J(ca)=10.9, J(cb)=0.9
	H_a: 6.65, dd, J(ab)=17.6, J(ac)=10.9 H_b: 5.60, dd, J(ba)=17.6, J(bc)=0.9 H_c: 5.12, dd, J(ca)=10.9, J(cb)=0.9
	H_a: 6.88, td, J(ab)=5.5 H_b: 6.55, td, J(ba)=5.5

A comparison of reaction yields and conditions has been made (Table 4-7) for the systems reported in chapters 3 and 4 and the scientific literature. Apart from the use of volatile and toxic solvents (*e.g.* dichloromethane, dichloroethane and acetonitrile), many of the previously reported systems have a lower atom economy. However, in some cases higher yields have been reported.[56,57] In some literature studies, no temperature was reported, since the reactions were conducted in a domestic microwave. If the results from chapters 3 and 4 are compared, the reactions in phosphonium ionic liquids (chapter 4) are more compatible with the principles of green chemistry than the reactions in imidazolium ionic liquids. However, for some reactions higher yields were obtained for the reactions in imidazolium ionic liquids (Table 4-7, entries 5 and 6). No metal catalyst was needed for the dehydration reactions in phosphonium ionic liquids and the phosphonium ionic liquids are more stable than the imidazolium ionic liquids under the reaction conditions used. For previously reported Pd-catalyzed etherifications in chlorinated solvents,[60] very a low conversion and yield was reported for the ether product derived from benzyl alcohol and an oxidation by-product was reported with higher yield (12%). Under the reaction conditions that were reported in chapters 3 and 4 of this thesis, no oxidation products were detected. Long reaction times are a problem commonly encountered in such reactions, Table 4-7. For example, very long reaction times at high temperatures have been reported (entries 1, 5 and 6) previously but the yields obtained are not greater than those reported in this thesis.

A similar comparison has also been performed for the dehydration reactions of secondary benzylic alcohols that were reported in chapter 4 of this thesis (Table 4-8). Compared with the methods reported in literature, the method described in chapter 4 is more atom economical and much simpler. In entry 3 higher yields were reported by others, however our reaction was performed under more moderate conditions.

Table 4-7. Etherification reactions of different benzylic alcohols: a comparison between yield and reaction conditions reported in literature and our systems (reported in chapters 3 and 4)



Entry	X	Yield (%)	Time (min)/Temp (°C)
1	4-MeO	72[a]; 71[b]; 54[c]; 94[d]; 95[e]; 44[g]; 89[j]	35/120[a]; 9/113[b]; 24 h/r.t.[c]; 3 h/r.t.[d]; 7/unknown[e]; 48 h/120[g]; 20/r.t.[j]
2	3-MeO	53[a]; 80[e]; 87[j]	25/200[a]; 8/unknown[e]; 35/r.t.[j]
3	4-Me	61[a]; 57[b]; 91[d]; 41[f]; 88[j];	20/180[a]; 12/114[b]; 0.7/reflux[d]; 3 h/r.t.[f]; 30/r.t.[j]
4	2-Me	63[a]; 35[f]	20/180[a]; 3 h/r.t.[f]
5	H	34[a]; 55[b]; 95[g]; 81[e]; 6[h]; 72[d]; 63[c]; 84[i]; 90[j]	60/180[a]; 7/140[b]; 80 h/150[g]; 4/unknown[e]; 6 h/80[h]; 1 h/r.t.[d]; 72 h/80[c]; 5/r.t.[i]; 30/r.t.[j]
6	4-Cl	26[a]; 55[b]; 93[i]; 55[f]; 96[d]; 64[g]; 86[j]	45/170[a]; 10/145[b]; 5/r.t.[i]; 3 h/r.t.[f]; 1.2 h/reflux[d]; 20 h/130[g]; 25/r.t.[j]
7	4-Br	6[b]; 92[e]; 28[f]; 89[i]	12/170[b]; 8/unknown[e]; 3 h/r.t.[f]; 5/r.t.[i]
8	4-NO_2	0[b]; 85[e]; 98[d]	10/115[b]; 10/unknown[e]; 10 h/reflux[d]

a) This thesis (Chapter 4), Solvent and catalyst: $[P_{666,14}]$DBS, Microwave heating

b) This thesis (Chapter 3), Solvent: [BMIm]PF_6, $Pd(CH_3CN)_2Cl_2$ (5 mol%)

c) Solvent: Dichloroethane, $ZnCl_2$ (1 equiv.)[55]

d) Solvent: Dichloroethane, $AlPW_{12}O_{40}$ (7 mol%)[56]

e) Solvent: Solvent-free, CaS_2O_8, Silica gel, Microwave heating[57]

f) Solvent: Acetonitrile, Thianthrene cation radical perchlorate (1 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv.)[58]

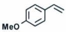
g) Solvent: Neat, SnO_2 NPs (25 mg NPs per 300 mg of alcohol)[59]

h) Solvent: Dichloroethane, $Pd(CH_3CN)_2Cl_2$ (0.1 equiv.)[60]

i) Solvent: Acetonitrile, Et_3SiH (1.2 equiv.), $BiBr_3$ (1-3 mol%), room temperature, aldehydes were used as substrates[61]

j) Solvent: CH_2Cl_2, polymethylhydrosiloxane (3 equiv.), I_2 (2.5 mol%), aldehydes were used as substrates[54]

Table 4-8. Dehydration reactions of secondary benzylic alcohols that have β-hydrogens: a comparison between yield and reaction conditions reported in literature and our systems (reported in chapter 4)

Entry	Product	Yield (%)	Time (min)/ Temp (°C)
1	 (1')	99[a]; 11[c]; 3[d]	30/120[a]; 110/reflux[c]; 10/80[d]
2	 (2')	85[a]; 79[e]	45/160[a]; 10/140[e]
3	 (3')	70[b]; 77[d]; 87[e]	20/120[b]; 24 h/100[d]; 7/140[e]

a) This thesis (Chapter 4), Solvent and catalyst: $[P_{666,14}]Br$, Microwave heating

b) This thesis (Chapter 4), Solvent and catalyst: $[P_{666,14}]DBS$, Microwave heating

c) Solvent: Chloroform, tungtophosphoric acid on activated carbon (0.5 equiv.)[37]

d) Solvent: Dichloroethane, $H_6P_2W_{18}O_{62}$ (0.004 equiv.), Dimer: 51%[38]

e) Solvent: [HMIm]Br, Microwave heating[44]

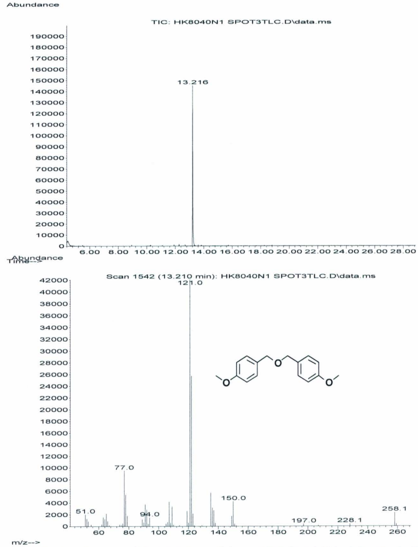


Figure 4-12. GC trace and MS spectrum of the product from Table 4-3 entry 1. The sample for GC-MS was prepared from a TLC spot extracted with diethyl ether. Retention time, 13.2 min, 4,4'-dimethoxydibenzyl ether

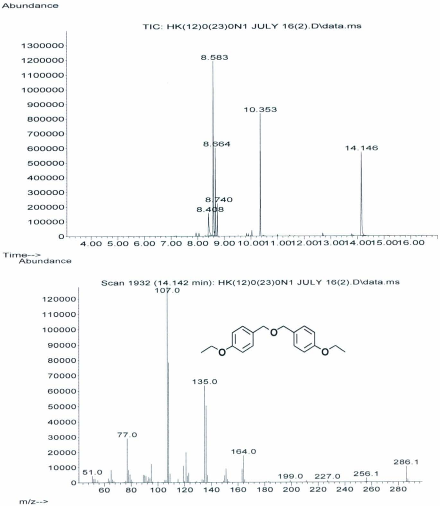


Figure 4-13. GC trace and MS spectrum of the product from Table 4-3 entry 3. The sample for GC-MS was prepared by extraction of the reaction mixture with heptane/water (3:1 volume ratio). Retention time 14.1 min, 4,4'-diethoxydibenzyl ether; 8.4 min, 4-ethoxybenzyl alcohol. Four other peaks in the GC trace 8.58, 8.66, 8.74 and 10.35 min are related to the long chain alkenes and alkyl chloride from partial decomposition of $[P_{666,14}]Cl$

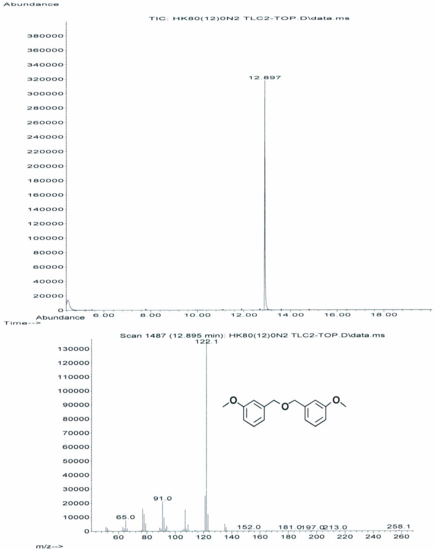


Figure 4-14. GC trace and MS spectrum of the product from Table 4-3 entry 2. The sample for GC-MS was prepared from a TLC spot extracted with diethyl ether. Retention time, 12.9 min, 3,3'-dimethoxdibenzyl ether

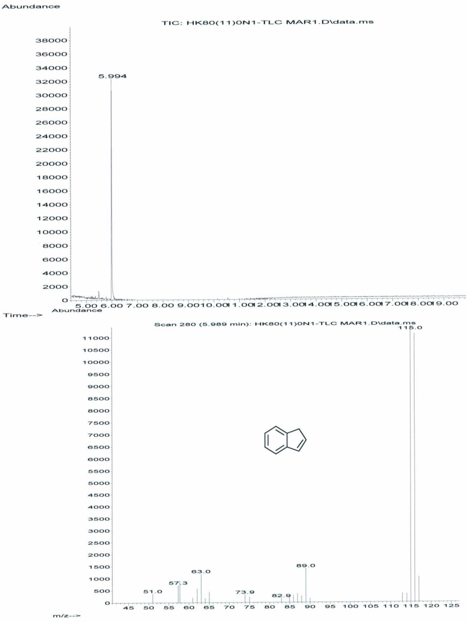


Figure 4-15. GC trace and MS spectrum of the product from Table 4-4 entry 1. The sample for GC-MS was prepared from a TLC spot extracted with diethyl ether. Retention time, 5.99 min, indene

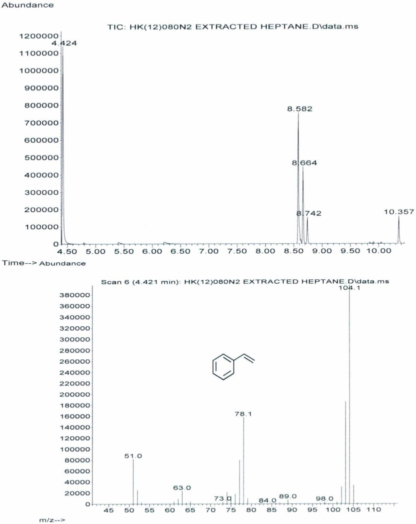


Figure 4-16. GC trace and MS spectrum of the product from Table 4-4 entry 5. The sample for GC-MS was prepared by extraction of the reaction mixture with heptane/water (3:1 volume ratio). Retention time, 4.4 min, styrene. Four other peaks in the GC trace, 8.58, 8.66, 8.74 and 10.36 min are related to the long chain alkenes and alkyl chloride from partial decomposition of [$P_{666,14}$]Cl

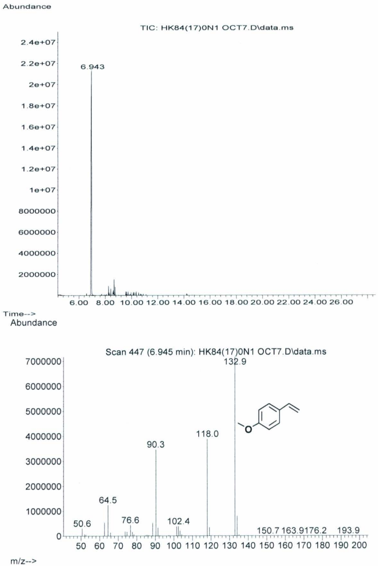


Figure 4-17. GC trace and MS spectrum of the product from Table 4-4 entry 8. The sample for GC-MS was prepared from a TLC spot extracted with diethyl ether. Retention time, 6.9 min, 4-methoxystyrene

4-6 Acknowledgements

We acknowledge support from NSERC and Canada Foundation for Innovation in the form of a Discovery Grant, a Research Tools and Instrument Grant and a Leaders Opportunity Fund Award (F. M. K.). We also thank Memorial University for funding and Cytec Industries Inc. for samples of [$P_{666,14}$]DBS and [$P_{666,14}$]Cl. Dr. Céline Schneider (C-CART) is thanked for assistance with some NMR experiments.

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Chapter 5

Synthesis of Pd nanocrystals in phosphonium ionic liquids without any external reducing agents

A version of this chapter has been published.
Hassan A. Kalviri and Francesca M. Kerton
Synthesis of Pd nanocrystals in phosphonium ionic liquids without any external reducing agents
Green Chem., **2011**, *13*, 681-686

Some modifications (including some additional images and a reaction scheme) were applied to the original paper.

Abstract

Trihexyl(tetradecyl)phosphonium ionic liquids (ILs) are found to support the formation of Pd(0) nanoparticles without the addition of reducing agents such as $NaBH_4$. The resulting particles are highly crystalline and have been characterized by a range of techniques including TEM and XRD. Their sizes are in the range 7 ± 2 nm. The particle formation process is highly dependent on the anion of the IL with no nanoparticles observed when the chloride derivative was used. Particle shape could be controlled through varying the anion of the IL and the Pd(II) precursor used. Palladium chloride reagents gave truncated octahedron shaped particles in trihexyl(tetradecyl)phosphonium dodecylbenzenesulfonate, whereas palladium acetate under the same conditions afforded a mixture of shapes including triangular plates. We propose that the presence of chloride anions in the reaction mixtures led to oxidative etching of the particles and that this process can be reduced in the presence of certain anion partners in the IL including bis(2,4,4-trimethylpentyl)phosphinate. Two possible reduction mechanisms based on reactions of the phosphonium cation are suggested for the formation of the Pd(0) species. The resulting nanoparticles are effective in catalyzing the Suzuki reaction of 4-bromotoluene and benzene boronic acid.

5-1 Objectives for chapter 5

- Investigate the stability of Pd(II) salts in ionic liquid solution via UV-Vis spectroscopy.
- Characterize the prepared Pd nanocrystals using a range of different techniques (TEM, XRD, FT-IR, TGA).
- Study the effects of Pd precursors and anions on the shape of the nanocrystals formed.
- Assess the effect of oxidative processes on the formation of Pd nanocrystals in phosphonium ionic liquids.
- Evaluate the effect of diluting the ionic liquid on the formation of Pd nanocrystals.
- Attempt to establish a mechanism for the reducing properties of phosphonium ionic liquids in the presence of Pd.

5-2 Introduction

Pd nanostructures have found many applications in science and engineering. Because of an increased surface area to volume ratio, nanostructures have more active sites compared with bulk materials. Therefore, nanomaterials are often more efficient in their applications, whether that be as catalysts,[1-3] sensors or in other fields. For example, Pd nanostructures have been employed for hydrogen gas detection based on a change in their resistivity.[4]

In catalysis, Pd nanostructures have been extensively employed in different fields. Pd nanowire arrays have been used as effective electrocatalysts for ethanol oxidation in direct alcohol fuel cells.[5] In organic synthesis, Pd nanoparticles are being used widely in catalytic C–C and C–N bond formation reactions.[6-11]

Noble metal nanostructures have been synthesized using a wide range of reducing agents including organic compounds such as citrate, DMF, ethylene glycol or ethanol and inorganic reagents like hydrogen, $NaBH_4$ and carbon monoxide.[12-15] Clearly, from a 'green' perspective, some of these reducing agents carry with them an inherent risk (*e.g.* $NaBH_4$ and carbon monoxide), while reagents such as citrate or ethylene glycol are more environmentally benign. Indeed, there has been growing interest in 'greening' nanoparticle synthesis. One way of doing this is by using naturally sourced and benign reducing agents and this has been particularly successful in the formation of Au or Ag nanoparticles. For example, $HAuCl_4$ has been reduced to Au(0) using glucose.[16,17] Another interesting example is the synthesis of Au nanoparticles in a continuous fashion using ascorbic acid as the reducing agent.[18] Silver nanoparticles have been prepared in aqueous solution using *Capsicum annuum* L. extract. It was proposed that proteins within the extract acted as the reducing agents.[19] However, in terms of Pd nanoparticle preparation, the most widely used reagents are sources of 'active' hydrogen, *e.g.* $NaBH_4$. Therefore, in order to reduce the risk of handling such reagents for the preparation of nanoparticles to be used in catalytic reactions, the nanoparticles are often formed in situ through reduction by reagents or solvent,[11,20,21] but this can lead to less control over the particle size and distribution.

In order to reduce the number of components (metal precursor, solvent, stabilizer, reducing agent) in the preparation of nanoparticles, in line with the principles of green chemistry, there is growing interest in the use of ionic liquids (ILs) as stabilizing agents and reaction media in their synthesis.[8,9,14,15,22] Modified ILs[22] have been prepared that contain a reducing moiety (*e.g.* hydroxyl containing ionic liquids), however, to the best of our knowledge there is no report of using commercially available phosphonium ILs as reducing agents in the synthesis of metal nanoparticles.

In this article, we report the synthesis of Pd nanocrystals with different shapes in phosphonium ILs composed of a trihexyl(tetradecyl)phosphonium ($[P_{666,14}]$) cation and different anions without any external reducing agents. One communication has been published concerning 'reductant-free' synthesis of Pd nanocrystals. In this example, it is likely that the solvent *N,N*-dimethylacetamide or carbon monoxide (present in the Pd precursor complex) were the reducing agents.[23]

The ILs studied were: $[P_{666,14}]$dodecylbenzenesulfonate ($[P_{666,14}]$DBS) **1**, $[P_{666,14}]$bis-(trifluoromethylsulfonyl)amide ($[P_{666,14}][NTf_2]$) **2**, $[P_{666,14}]$bis(2,4,4-trimethylpentyl)-phosphinate (($[P_{666,14}][(i\text{-}C_8)_2PO_2]$) **3**, $[P_{666,14}]$hexafluorophosphate ($[P_{666,14}]PF_6$) **4** and $[P_{666,14}]$chloride ($[P_{666,14}]Cl$) **5**. Phosphonium halide ILs have been used previously as media for Pd-catalyzed bond-forming reactions, however the presence of Pd nanoparticles was not reported.[24-27] We also report that the nanoparticles we have prepared can be used as effective catalysts in Suzuki cross-coupling reactions.

5-3 Results and discussion

5-3-1 Preliminary investigations

During our study of etherification reactions in ILs,[28] upon changing the IL from those containing imidazolium cations to $[P_{666,14}]$DBS (DBS = dodecylbenzenesulfonate) we discovered that the Pd(II)-IL mixtures would change colour over time in the absence of any reagents. We sought to discover the origin of this colour change. $Pd(CH_3CN)_2Cl_2$, as the Pd(II) source, was dissolved in a capped vial containing $[P_{666,14}]$DBS **1**. The initially orange-coloured solution was stirred at room temperature and after 1 h it had turned brown. UV-vis data for a sample showed good agreement with literature spectra for Pd nanoparticles (Figure 5-1).[12,29] Solutions containing Pd^{2+} show an indicative absorbance at above 400 nm.[12,29]

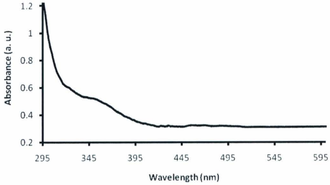


Figure 5-1. UV-vis spectrum of Pd nanocrystals prepared from reduction of $Pd(CH_3CN)_2Cl_2$ in $[P_{666,14}]$DBS. 60 mg of the reaction mixture was diluted in 5 mL of dichloromethane

Acetone was added to the solution and a black precipitate was separated by centrifuge. The precipitate was washed four times with acetone to remove excess **1** and dried, therefore any remaining organic groups were incorporated into the nanoparticle or on its surface. TEM images showed that the particles were truncated octahedrons (Figure 5-2a). Their powder XRD spectrum (Figure 5-2b) matched well to face-centered cubic (*fcc*) Pd (JCPDS card 05-0681) and the selected area electron diffraction pattern (Figure 5-3) confirmed the *fcc* crystalline structure of the product. ATR FT-IR spectra of the dry powder comprised of weak bands (symmetric and asymmetric C–H stretches) related to **1** (Figure 5-2 c and d). These results suggested that the IL maybe working as both the reducing and capping agent in the formation of the nanoparticles. Furthermore, a weight loss event below 400 °C was observed *via* TGA and is further proof for the presence of a capping agent on the surface of the nanocrystals. However, subsequent weight gain at above 530 °C is likely related to the oxidation of Pd (Figure 5-4) due to oxygen impurities in the nitrogen gas.[29]

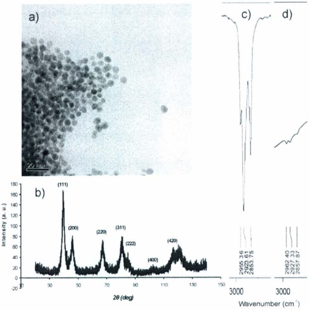


Figure 5-2. Characterization of Pd nanocrystals prepared in 1. (a) TEM image. (b) X-ray diffraction pattern. (c) and (d) Selected region of FT-IR spectra of 1 and the nanocrystals, respectively

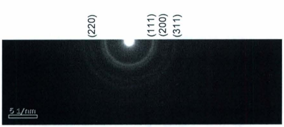


Figure 5-3. Selected area electron diffraction pattern of the Pd nanocrystals synthesized from dissolved $Pd(CH_3CN)_2Cl_2$ in $[P_{666,14}]$DBS

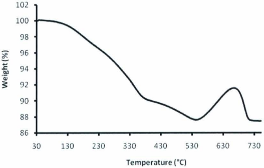


Figure 5-4. Thermogram of Pd nanocrystals. Sample was heated with a ramp of 20 °C/min under nitrogen flow. Approximately 10 wt% loss is seen between 30 °C and 350 °C

^{31}P NMR reveals a slight 0.20 ppm downfield shift and a slight broadening of the phosphorus peak after the reaction which may be significant (Figure 5-5) and an evidence for the formation of unsaturated bonds in the alkyl chains of the phosphonium cations. However, electrospray ionization mass spectra (both positive and negative modes) did not show any considerable differences for **1** before and after the reaction (Figures 5-6 and 5-7). Size distribution histograms of the images show that the majority of the particles have sizes smaller than 9 nm (Figure 5-8).

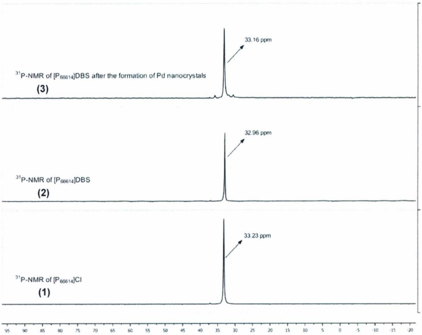


Figure 5-5. ^{31}P NMR of neat [$P_{666,14}$]Cl (spectrum 1, $\omega_{1/2}$= 60 Hz), neat [$P_{666,14}$]DBS (spectrum 2, $\omega_{1/2}$= 48 Hz) and [$P_{666,14}$]DBS after the formation of Pd nanocrystals (spectrum 3, $\omega_{1/2}$= 74 Hz)

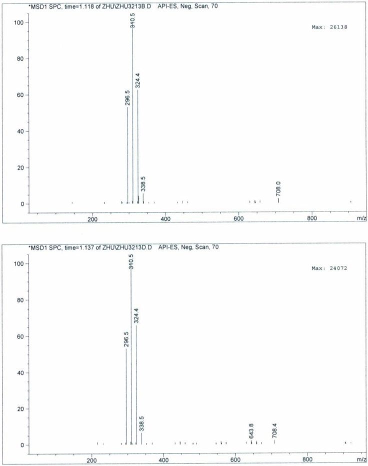


Figure 5-6. ESI-MS spectrum (negative scan) of [$P_{666,14}$]DBS before (top) and after (bottom) the synthesis of Pd nanocrystals

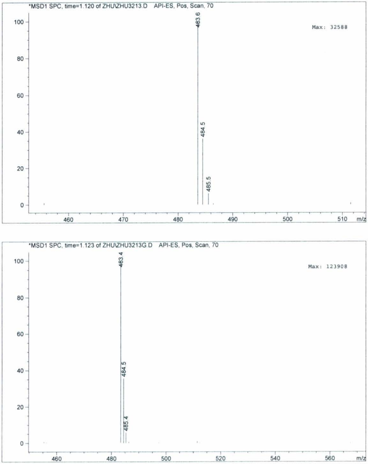


Figure 5-7. ESI-MS spectrum (positive scan) of [$P_{666,14}$]DBS before (top) and after (bottom) the synthesis of Pd nanocrystals

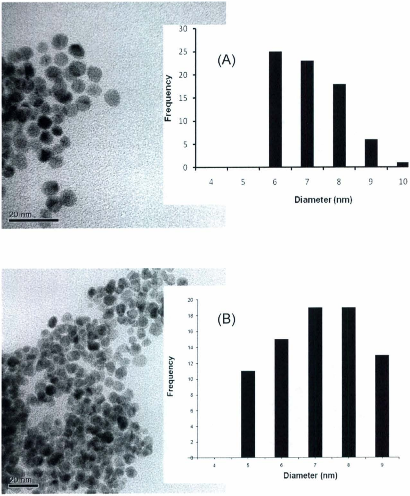


Figure 5-8. TEM images and size distribution histograms of Pd nanocrystals synthesized from the reaction of $Pd(CH_3CN)_2Cl_2$ in $[P_{666,14}]$DBS (A) and $[P_{666,14}][NTf_2]$ (B)

5-3-2 Mechanism

As no external inorganic or organic reagent was added to the ionic liquid solutions containing Pd(II) salts, the ionic liquid must be playing the dual role of reducing and stabilizing agent. Its role as a stabilizing agent is evident from the IR spectra of the particles (Figure 5-2 c and d) and the additional defects seen in the particles when the solution is diluted with a typical organic solvent (see below) and thereby contains less stabilizing agent. However, the possible reduction mechanism is still open to debate. We propose two possible routes. Several groups have previously studied the electrochemical stability of phosphonium salts.[30-32] The presence of current shoulder (+3.2 V *vs.* Fc/Fc^+) has been observed in their cyclic voltammograms.[32] These have previously been assigned to either the presence of water or a methoxy functional group in the IL. We also observe an irreversible current shoulder (oxidation) at +1.73 V *vs.* Fc/Fc^+ for **1** in CH_3CN (+2.20 V *vs.* SCE, Figure 5-9). This demonstrates that **1** is less electrochemically stable compared with the shorter alkyl chain phosphonium ILs studied by others, and that the shoulder observed in the cyclic voltammograms of some phosphonium salts is an inherent property of these species (not water or functional group dependent, since we used dry sample with no functional groups on the alkyl chains) and likely represents an oxidation process occurring within the alkyl chains. It is also worth noting that when the electrochemical oxidation of **1** is repeated in the presence of $Pd(CH_3CN)_2Cl_2$ this region of the voltammogram changes in appearance. Therefore, researchers should be aware that not all very similar ILs, *e.g.* phosphonium ILs with varying alkyl chain lengths, have the same useful electrochemical window and each one needs to be tested. Viscosity is an important factor in electrochemistry due to the necessary migration of species in solution. Phosphonium ILs with long alkyl chains (such as **1**) are not recommended for electrochemical purposes without a co-solvent as they are more viscous than their short-chain counterparts.

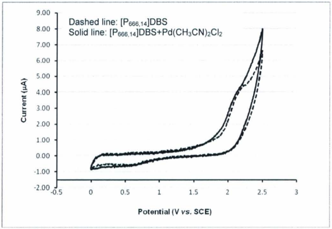
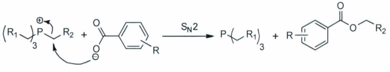
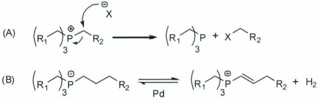


Figure 5-9. Cyclic voltammograms in CH_3CN for **1** (4.0 mmol L^{-1}) (dashed line), and **1** (4.0 mmol L^{-1}) with $Pd(CH_3CN)_2Cl_2$ (1.3 mmol L^{-1}) (solid line). Working electrode= Pt disk (0.0045 cm^2), counter electrode= high surface area Pt wire, and reference electrode= saturated calomel electrode (SCE). Scan rate, in both experiments, was 200 mV s^{-1}. The value *vs.* Fc/Fc^+ in CH_3CN can be calculated from the values *vs.* SCE by subtracting 0.47 V

Chu and co-workers have shown that $[P_{666,14}]Cl$ **5** can be deprotonated and undergo 'non-classical' Wittig reactions upon reaction with a suitable nucleophile.[33] A first step in this process was the formation of a trialkyl phosphine, Scheme 5-1. In organometallic chemistry, it is well known that reduced palladium, i.e. Pd(0) nanoparticles or colloids, can be formed *via* oxidation of phosphine ligands by oxygen from an anion (*e.g.* acetate or in our case DBS) or adventitious water or oxygen.[34,35] Therefore, a trialkyl phosphine (phosphorus(III) species) produced in situ (Scheme 5-2 (A)) in the reactions reported here could be reducing Pd(II) to Pd(0) and in the process be oxidized itself to a phosphorus(IV) compound. Furthermore, via GC-MS analysis of the volatile components from reaction mixtures, we have observed the formation of hydrocarbon and halogenated hydrocarbon chains (Scheme 5-2 (A)). However, we have not observed the presence of the intermediate phosphines or product phosphine-oxides by ^{31}P NMR. Also, no distinctive odour indicative of phosphine presence was noted during the preparation of the nanoparticles. Although, it should also be noted that both trialkyl phosphines and phosphine oxides can be used as stabilizing (or capping) agents in nanoparticle syntheses. If the phosphorus-containing species has become adsorbed onto the Pd nanoparticle surface (as potentially indicated by TGA and IR data above), we would not expect to see a corresponding resonance in the solution NMR spectra of the IL after its use (Figure 5-5). Another possible mechanism, given the microscale reversibility of many reactions, is the dehydrogenation of alkyl chains in the presence of palladium (Scheme 5-2 (B)) and subsequently the hydrogen formed acts to reduce the Pd(II). Mechanism (B) may lead to the slight broadening of the resonance that we see in the ^{31}P NMR of **1** after formation of nanoparticles but at this stage mechanism (A) or other possible mechanisms (*e.g.* simultaneous routes such as A + B) cannot be ruled out.



Scheme 5-1. Nucleophilic substitution reaction of sodium benzoate and phosphonium ionic liquid **5** as part of proposed mechanism for the non-classical Wittig reaction[33]



Scheme 5-2. Some possible reactions of trihexyl(tetradecyl)phosphonium ionic liquids

5-3-3 Effect of varying the palladium precursor

Under the same reaction conditions, $Pd(OAc)_2$ and $PdCl_2$ also afforded nanocrystals (Figures 5-10 and 5-11). Interestingly, $Pd(OAc)_2$ yielded particles with a variety of different crystalline forms including octahedrons and triangular plates in addition to truncated octahedrons (Figure 5-10, indicated by arrows). Since in $Pd(OAc)_2$ there is no chloride ion source, less oxidative etching can occur and this results in the formation of more diverse nanocrystalline shapes. Metal nanoparticles have been reported to "re-dissolve" from solution to form metal cations,[12] *e.g.* Pd^{2+}, due to oxidative etching effects. This can happen in the presence of oxygen or chloride ions. Oxidative etching can change the redox equilibrium during the process of metal nanoparticle formation and cause undesirable oxidation to occur. Therefore, it prevents or slows down the formation of metal nanoparticles. Chloride ions act as ligand for the palladium cations and form $PdCl_2$ or $PdCl_4^{2-}$ complexes and help the oxidative etching process.

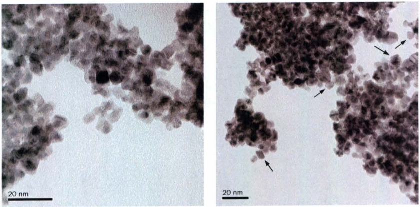


Figure 5-10. TEM images of the Pd nanocrystals prepared from dissolved $Pd(OAc)_2$ in $[P_{666,14}]$DBS

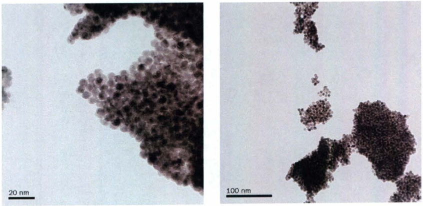


Figure 5-11. TEM images of the Pd nanocrystals prepared from dissolved $PdCl_2$ in $[P_{666,14}]$DBS

5-3-4 Effect of varying the anion of the ionic liquid

Several other phosphonium ILs were screened for Pd nanocrystal formation using $Pd(CH_3CN)_2Cl_2$ as the Pd precursor. $[P_{666,14}]$bis(trifluoromethylsulfonyl)amide **2** yielded truncated octahedrons (Figure 5-8 (B)) with a narrow size range. In contrast, under the same room temperature reaction conditions no colour change was observed when using $[P_{666,14}]$bis(2,4,4-trimethylpentyl)phosphinate **3** and $[P_{666,14}]PF_6$ **4**, however, after 5 h at 100 °C octahedrons and triangular plates of Pd were the major products in **3** (Figure 5-12) and after 15 h at 80 °C a mixture of truncated octahedrons and octahedrons of Pd were formed in **4** (Figure 5-13).The need to heat **3** and **4** to achieve nanoparticle formation is due to the comparatively high viscosity of **3** and because **4** is a solid at room temperature. **4** melts and **3** becomes less viscous upon heating and thus allows palladium seed particles to migrate through the IL phase and from nanocrystals. For a *fcc* structure octahedron or tetrahedron shapes have the lowest total surface energy. This is despite a truncated octahedron, which has a semispherical shape, having a smaller surface area with more {111} and {100} facets and lower interfacial free energy.[12,36]

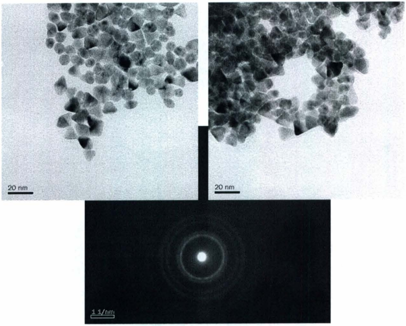


Figure 5-12. TEM images of the Pd nanocrystals prepared in $[P_{666,14}][(i\text{-}C_8)_2PO_2]$ and the corresponding selected area electron diffraction pattern, which confirms the *fcc* crystalline structure of the product

Oxidative etching of Pd can happen in the presence of O_2 and Cl^-, and twinned particles (octahedrons) are known to be etched faster than single crystals (truncated octahedrons).[37,38] Therefore truncated octahedron structures are those most likely to form under our reaction conditions, unless a stabilizing agent can attach to {111} facets (in the case of an octahedron) and prevent the oxidative etching from occurring (Figure 5-12). As when **3** is used, octahedron-shaped structures are seen, the bis(2,4,4-trimethylpentyl)phosphinate anion must also be involved in the stabilizing process and prevents etching. Etching may also be the reason why no nanoparticles were observed when the reaction was performed in $[P_{666,14}]Cl$ **5** even at elevated temperatures, while the anions in the other ILs can stabilize the nanocrystal seeds and slow down any oxidative etching.

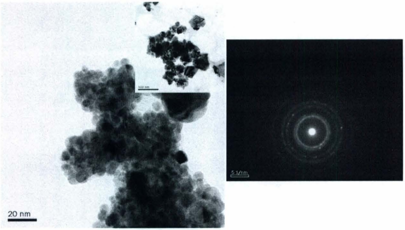


Figure 5-13. TEM images of the Pd nanocyrstals (and the corresponding selected area electron diffraction patterns) prepared from dissolved $Pd(CH_3CN)_2Cl_2$ in $[P_{666,14}]PF_6$

5-3-5 Effect of oxygen levels

Although Cl^- was present in most of the reaction mixtures, reactions were repeated under oxygen-free conditions in order to assess any oxidative etching effects. For example, two reaction mixtures were prepared using dried and degassed **1** and $Pd(CH_3CN)_2Cl_2$. One of the samples was transferred to a glove box under a nitrogen atmosphere and the other was kept in a capped vial (it was not sealed) on the benchtop. The sample in the glove box changed colour much faster than the sample outside (Figure 5-14) indicating that oxygen has inhibitory effect on the formation of Pd nanocrystals. However, it should be noted that suspensions of nanoparticles in **1–3** are stable (showing no evidence of precipitate formation) upon storage in capped vials on a benchtop for at least 3 months.

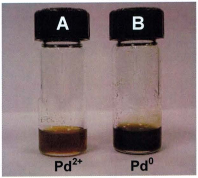


Figure 5-14. Oxidative etching effect on the reaction. In this study, the same amount of $Pd(CH_3CN)_2Cl_2$ was dissolved in dried and degassed $[P_{66614}]$DBS. The solutions were stirred with the same speed on the benchtop (A) and in glove box (B) for 18 h

5-3-6 Effect of ionic liquid concentration

As ILs are quite expensive, we wanted to see if smaller amounts of ILs could be used in solution to yield nanoparticles. A $Pd(CH_3CN)_2Cl_2$ solution composed of a 1:1 mole ratio of **1** and THF yielded 'merged' Pd nanocrystals (Figure 5-15). Since coalescence of particles in the less viscous reaction solution (THF+IL) is more probable and also there is a lower concentration of stabilizer, more stacking faults were observed in TEM images of these samples (one of these faults has been highlighted by an arrow in Figure 5-15 a).

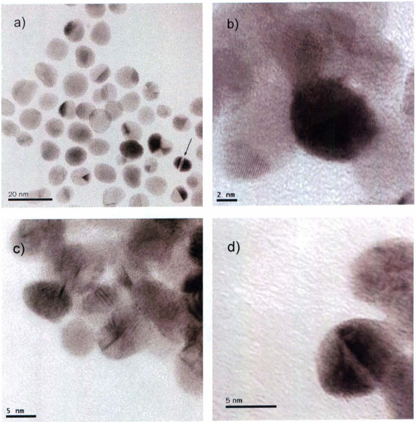
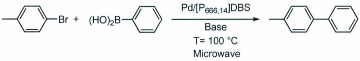


Figure 5-15. TEM (a) and HRTEM (b, c and d) images of the Pd nanocrystals prepared from $Pd(CH_3CN)_2Cl_2$ in a 1:1 mole ratio of $[P_{666,14}]$DBS and THF at room temperature. Stacking defects are observable in the images

5-3-7 Preliminary results using phosphonium-stabilized Pd nanoparticles as catalysts

As an important use of Pd nanoparticles is in catalysis, a Suzuki reaction was carried out using in situ prepared Pd nanocrystals in **1** under microwave irradiation. A high yield was obtained when 4-bromotoluene was reacted with benzene boronic acid in the presence of potassium hydroxide (Table 5-1). TEM images of the Pd nanocrystals after the Suzuki reaction showed that the reaction does not affect the shapes and the sizes of the nanoparticles (Figure 5-16). However, no tests were performed in situ on the catalytic reaction mixtures to definitely prove the nature of the active catalytic species. The active species might not be the nanocrystals themselves but the nanocrystals may be acting as a reservoir of soluble Pd. Nanocrystals with different shapes based on their crystal facets can have different catalytic activities and selectivities in a chemical reaction.[12,37]

Table 5-1. Suzuki coupling reaction of 4-bromotoluene and benzene boronic acid in $[P_{666,14}]$DBS using Pd nanocrystals and different bases



Entry	Base	Base/Bromotoluene (mole ratio)	Time (min)	Yield [a] (%)
1	KOH	1.1	10	50
2	KOH	1.1	15	60
3	Triethylamine	1.1	10	9
4	$K_2CO_3 \cdot H_2O$	1.6	15	78
5	KOH	1.8	15	90
6	Cs_2CO_3	2.0	15 (2×15)	43 (75)

a) Yields were calculated relative to 4-bromotoluene using ^{1}H NMR spectroscopy with acetophenone as the internal standard.

Therefore, future work will involve preparing Pd nanocrystals with different shapes based on this method in order to investigate the relationship between shape and reactivity.

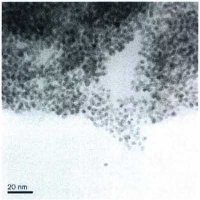


Figure 5-16. TEM image of the Pd nanocrystals after the Suzuki reaction

5-4 Conclusions

We have described a simple method for preparing Pd nanocrystals with different shapes without using any external reducing agents. In this method, phosphonium ILs have been used as both reducing and stabilizing agents. This work provides further evidence of the useful nature of phosphonium-derived ILs in reduction chemistry.[39] This method circumvents the need for additional reagents in the formation of the particles as the IL acts as the medium, reducing agent and stabilizer for the process. This in some way reduces the risk and hazards associated with the preparation of Pd nanoparticles. However, it cannot be ignored that phosphonium ILs themselves are known to be toxic,[40] and therefore the quest for truly benign syntheses of Pd nanoparticles continues. The in situ prepared Pd nanocrystals showed good catalytic activity in a Suzuki cross-coupling reaction.

5-5 Experimental

5-5-1 General information and instrumentation

$PdCl_2$ was purchased from Precious Metals Online. The ionic liquids $[P_{666,14}]$DBS (Cyphos phosphonium IL 202) and $[P_{666,14}]$Cl (Cyphos phosphonium IL 101) were gift samples from Cytec Industries and the other ILs were purchased from Sigma-Aldrich. Nanoparticles were prepared using ILs as they were received and ILs purified using a literature method,[39] but the same results were obtained using purified and 'as received' batches of ILs.

TEM images were obtained using a JEOL 2011 high resolution (200 kV) Scanning Transmission Electron Microscope (STEM) with EDAX (Genesis) Energy Dispersive X-ray system at the University of New Brunswick. Samples were shipped to New Brunswick as suspensions in acetone that had been reconstituted from nanoparticulate dry powders. The suspensions were sonicated before sampling in order to have a homogeneous dispersion of particles. TEM images were taken by putting a drop of nanoparticle suspension in acetone on a carbon coated copper grid. ImageJ software was used to obtain size distribution histograms.

Infrared spectra were obtained using a Bruker TENSOR 27 infrared spectrometer equipped with a MIRacle ATR (Attenuated Total Reflection). ^{31}P NMR spectra were obtained on a Bruker AVANCE II 600 spectrometer (referenced with respect to 85% H_3PO_4 at 0.00 ppm). An Ocean Optics UV-vis spectrophotometer was used for UV-vis spectroscopy and the IL-nanoparticle suspensions were diluted in dichloromethane. X-Ray diffraction analyses were performed on a Rigaku Ultima IV with cross-beam optics (CBO). Bragg-Brentano mode was used for the analysis. Cu was used as the X-ray source (40 kV and 44 mA). For the TGA analysis, a TA Instruments Q500 was used and the sample was loaded onto a platinum pan. The experiment was performed under 60.0 mL min^{-1} nitrogen flow with a temperature increase rate of 20 °$Cmin^{-1}$. An Agilent 1100 MSD instrument was used for the electrospray ionization spectrometry (ESI-MS) and all samples were diluted in acetone prior to analysis. A Biotage Initiator 2.5 microwave reactor was employed for the Suzuki reactions. 0.5-2 mL microwave vials with PTFE seals were used for all the experiments.

5-5-2 Preparation of Pd nanocrystals

$Pd(CH_3CN)_2Cl_2$ (0.0072 g, 0.028 mmol) was dissolved in degassed IL (0.500 g) in a vial capped under nitrogen flow. For **1** or **2**, the solution was stirred for 18 h at room temperature. For ILs **3** and **4**, the reaction mixtures were heated to 100 °C for 5 h and 80 °C for 15 h, respectively. The reaction mixtures were monitored using UV-Vis spectroscopy for the disappearance of Pd^{2+}. Acetone (3 × 3 mL) was added to the brown reaction mixture to precipitate the Pd nanoparticles and remove the IL. The resulting fine black powder was isolated from acetone *via* centrifuge and dried under vacuum for 18 h prior to analysis using FT-IR, TGA and XRD. Nanoparticles were redispersed in acetone for TEM sample preparation. The ILs were recovered from the acetone washings and analysed *via* ESI-MS and NMR spectroscopy. ESI-MS and NMR experiments were also performed on the reaction mixtures themselves.

5-5-3 Experimental for the Suzuki reactions

In a typical reaction, $Pd(CH_3CN)_2Cl_2$ (0.0058 g, 2.7 mol%) was dissolved in degassed $[P_{666,14}]$DBS **1** (0.563 g) in a vial capped under nitrogen flow. The solution was stirred until it turned deep brown in colour indicating that Pd nanocrystals had formed. $Pd(CH_3CN)_2Cl_2$ could also potentially be the pre-catalyst for this reaction. However, UV-Vis analysis of the nanoparticle/IL suspension confirms the absence of this Pd precursor in the IL. 4-Bromotoluene (0.141 g, 0.825 mmol), benzeneboronic acid (0.130 g, 1.07 mmol) and KOH (0.082 g, 1.47 mmol) was added to the reaction mixture (KOH was ground to a powder before addition). This reaction mixture was capped again and sealed under a nitrogen blanket. The reaction was heated in a Biotage MW system for 15 min at 100 °C (the absorptivity on the MW was set at "high"). The vial was opened and the product isolated from the $[P_{666,14}]$DBS/Pd/base mixture by vacuum distillation. (Note: For other ionic liquids, solvent extraction of the products could be performed.)

5-6 Acknowledgements

We acknowledge support from NSERC and Canada Foundation for Innovation in the form of a Discovery Grant, a Research Tools and Instrument Grant and a Leaders Opportunity Fund Award (F. M. K.). We would also like to thank Memorial University for funding and Cytec Industries Inc. for samples of $[P_{666,14}]$DBS and $[P_{666,14}]$Cl. Dr Louise Weaver (University of New Brunswick, Canada) is thanked for obtaining TEM images and Prof. Peter Pickup and Mr Rodney Smith (Memorial University) for access to electrochemical equipment.

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Chapter 6

Conclusions and future research

In the first two chapters (introduction to ionic liquids and transformations of alcohols to ethers and alkenes), literature reviews related to our research were presented. It was attempted to highlight the green perspectives of the presented methods. Also, potential problems encountered when using some of the methods were discussed and some possible modifications were presented to make the processes more compatible with the principles of green chemistry.

As a conclusion to chapter two, dehydrative etherification reactions are discussed. Such reactions are usually more environmentally friendly than classical ether syntheses (Williamson and Ullmann), since the only byproduct is water. Consequently these reactions should have lower *E*-factors compared to the classical methods and also water as a byproduct is not harmful to the environment. Palladium complexes had been used previously as efficient catalytic species for dehydration reactions of alcohols,[1] and ionic liquids have been used for decades as substitutes for VOCs (Volatile Organic Solvents).[2] Therefore, catalytic dehydrative etherification of alcohols in imidazolium ionic liquids using Pd catalysts was studied (Chapter 3).[3] $Pd(CH_3CN)_2Cl_2$ in hydrophobic ionic liquids afforded a simple catalytic system for the direct condensation of substituted benzyl alcohols to prepare their corresponding ethers.[3] Several polar aprotic organic solvents were also used, however yields were highly increased when the hydrophobic ionic liquid $[BMIm]PF_6$ was used as the reaction medium. Since dehydration reactions has been reported under acidic conditions[4] and imidazolium ionic liquids are inherently acidic,[5] the reactions were likely performed under acidic conditions. Although in this case, no direct or indirect pH measurements were made, in an attempt to adjust pH, NH_4Cl was used as an additive. In the presence of NH_4Cl, benzyl chloride was obtained in excellent yield. NH_4Cl is a more environmentally benign compound compared with traditional chlorinating reagents (*e.g.*, thionyl chloride). Therefore, this chlorination reaction was the starting point for another project and Chad F. Petten completed his honours thesis on this subject under the supervision of Prof. Francesca M. Kerton in 2010.[6] Control reactions revealed the necessity of the Pd catalyst for the dehydration reactions in imidazolium ionic liquids. Based on the evidence obtained, a possible mechanism for dehydrative etherification of benzyl alcohols was proposed, which shows the importance of ionic liquids in stabilizing ionic intermediates.

PF_6^- and BF_4^- anions in ionic liquids such as $[BMIm]PF_6$ and $[BMIm]BF_4$ hydrolyse, especially at high temperatures and in contact with water. Since water was produced in the above mentioned dehydration reactions, hydrolysis of PF_6^- occurred and HF was released. The released HF caused some problems, such as corrosion of the reaction vessels. Therefore, phosphonium ionic liquids were used to avoid these problems. It was found that the dehydration reactions of benzyl alcohols can be performed without any metal catalyst in phosphonium ionic liquids.[7] Several phosphonium ionic liquids containing $[P_{666,14}]^+$, trihexyl(tetradecyl)phosphonium cation, and six different counter ions were used as the reaction media. The method was simple and atom economic, since the need for the metal catalyst and alkylating agents were avoided. The phosphonium ionic liquids were stable under the reaction conditions and their recyclability was demonstrated for several reactions. Compared with imidazolium ionic liquids, in literature, less information was available for the behaviour of phosphonium ionic liquids in reactions. Therefore, several NMR techniques were employed to investigate the interactions of substrates with the phosphonium ionic liquids. NOESY NMR was used in this regard and interactions between the protons in α, β, γ and δ positions of the alkyl chains in the ionic liquids with benzylic protons were observed. In the presence of NaOD, CD_3OD (a smaller alcohol compared with benzyl alcohol) and D_2O, α, β and γ protons underwent deuterium exchange. These results show that phosphonium ionic liquids can act as the catalyst and reaction media in dehydration reactions of benzyl alcohols. Further studies are needed in order to fully understand the mechanism and in order to scale up the reactions and increase substrate scope.

During the course of this research, a few experiments were performed on the condensation of benzyl amines to dibenzyl amines and imines, however not enough data were collected to publish the results. Reactions were performed in phosphonium ionic liquids under similar conditions to the benzyl alcohol dehydration reactions. Production of dibenzyl amines were detected via GC-MS analysis of reaction mixture extracts, however very weak signals were detected by in situ NMR analysis of reaction mixtures. Therefore, future work should also be dedicated to amination reactions. Condensation reactions of benzyl mercaptans have also been suggested as a future avenue for exploration in this field.

In order to increase yields and improve scale-up potential for the dehydration reactions, one possible route would be to use a supported version of these ionic liquids and perform dehydration reactions in a continuous-flow manner. Ionic liquids are generally more expensive than common organic solvents, therefore in order to minimize the use of ionic liquids, supported ionic liquids have been suggested as an alternative by several researchers.[8] In addition, this method would have less impact on the environment via bioaccumulation (smaller quantities of ionic liquids are used and less would potentially end up in the environment). Also such a method would combine the advantages of homogeneous catalysis (higher catalytic activity) and heterogeneous catalysis (easy catalyst separation).[8]

In chapter five, the preparation of Pd nanocrystals with different shapes in the presence of phosphonium ionic liquids as stabilizing agents in the absence of any external reducing agents was reported.[9] The stabilizing properties of the anions of the phosphonium ionic liquids in the formation of Pd nanocrystals were studied. Also, it was shown that oxygen and chloride ions have oxidative etching effects on the nanocrystals and no nanocrystal formation was observed in $[P_{666,14}]Cl$, because of the high chloride concentration. Two possible routes for the reduction mechanism in the phosphonium ionic liquids were also presented. The in situ prepared Pd nanocrystals showed good catalytic activity in a Suzuki cross-coupling reaction. TEM images of the Pd nanocrystals after the Suzuki reaction showed that the reaction did not affect the shapes and the sizes of the nanoparticles and they were still crystalline. TEM images showed that nanocrystals employed for the Suzuki reaction had truncated octahedron shapes. Nanocrystals with different shapes based on their crystal facets can have different catalytic activities and selectivities in a chemical reaction.[10] Therefore, future work could involve studying the effect of nanocrystal shape on the outcome of C-C coupling reactions.

Ionic liquids were used as substitutes for regular organic solvents in the aforementioned reactions not just because they have very low vapour pressures. In addition to this advantage, by performing the reactions in ionic liquids we were able to avoid the use of alkylating agents and in phosphonium ionic liquids both alkylating agents and metal catalysts were avoided. In the formation of Pd nanoparticles in phosphonium ionic liquids, the ionic liquids were used as stabilizing agent, solvent and reducing agent. Therefore, the method is potentially safer than other methods that use, for example $NaBH_4$, a reducing agent. Furthermore, it was demonstrated that the ionic liquids are recyclable in these reactions and also they are suitable reaction media under microwave conditions.

Although these reactions meet several requirements of the twelve principles of green chemistry, they can still be improved. For example, imidazolium ionic liquids other than $[BMIm]PF_6$ (*e.g.* $[BMIm][NTf_2]$) should be employed for the reactions (reported in Chapter 3) to avoid the hydrolysis of the anion. Furthermore, ionic liquids containing PF_6^- and BF_4^- are not suitable for reactions on a large scale, since special facilities are needed for their incineration.[8a] The phosphonium ionic liquids studied, generally, do not suffer from this hydrolysis problem and they are more stable than imidazolium ionic liquids. However, product extraction from these ionic liquids is not as easy as imidazolium ionic liquids, since generally they have good solubilities in organic solvents. For these ionic liquids, distillation was used to separate the product and recycle the ionic media. Esteric side chains in imidazolium and phosphonium ionic liquids make them more biodegradable than their analogues containing linear alkyl chains.[11] Therefore, phosphonium ionic liquids bearing these biodegradable functional groups in their side chains could be studied as a future research area for dehydration reactions of alcohols.

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Appendix 1

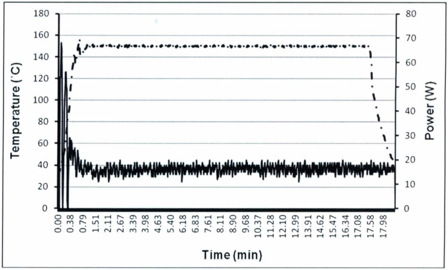

Figure 1. Temperature and power profiles for a typical dehydrative etherificaion in a phosphonium ionic liquid under microwave conditions. (Dashed line = Temperature; Solid line = Power)