

# **A Survey of the Reactivity of Diphenylmagnesium in Polymeric Solvents**

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A Survey of the Reactivity of Diphenylmagnesium  
in Polymeric Solvents

By Marissa Louise Bender

**ABSTRACT**

Reactions with magnesium-based reagents are often performed in the solvent THF or diethyl ether, both of which are known to contribute to smog formation. A set of reactions with diphenylmagnesium was performed in the following 'greener' solvents: poly(ethylene glycol) dimethyl ether, poly(dimethylsiloxane) trimethylsiloxy terminated, diethylene glycol dimethyl ether, and 2-methyltetrahydrofuran. Products and yields in poly(ethylene glycol) dimethyl ether were expected to be the similar to those found in diethylene glycol dimethyl. The set of reactions included bromination, and hydrolysis of diphenylmagnesium. Additionally, the reaction of diphenylmagnesium with cyclopentanone was performed and the expected product, cyclopenten-1-yl-benzene, was found in very low yields when present at all. Instead, the products were dominated by 1-phenyl-1-cyclopentanol and 2-cyclopentylidene-cyclopentanone. diM-PEG was found to be a poor solvent for both Grignard and diorganomagnesium reagents, while TMS-PDMS as solvent produced high product yields despite not being able to dissolve the diphenylmagnesium.

August 29<sup>th</sup>, 2008

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## **DEDICATION**

To those who let me go.

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## LIST OF ABBREVIATIONS

2-Me-THF	—	2-methyltetrahydrofuran
Ac	—	acetyl
acac	—	acetylacetonate
BINAP	—	2,2'-bis(diphenylphosphino-1,1'-binaphthyl)
Bu	—	butyl
cP	—	centipoises
cSt	—	centistoke
DBU	—	1,8-diazabicyclo-[5.4.0]-undec-7-ene
DFT	—	density functional theory
diM-PEG	—	poly(ethylene glycol) dimethyl ether
DME	—	dimethoxyethane
DMF	—	dimethylformamide
DMSO	—	dimethyl sulfoxide
edta	—	ethylenediaminetetraacetic acid
<i>ee</i>	—	enantiomeric excess
Et	—	ethyl
GCMS	—	gas chromatography mass spectrometry
GRAS	—	generally recognised as safe
HPLC	—	high performance liquid chromatography
IL	—	ionic liquid
<i>i</i> Pr	—	isopropyl
IMIL	—	imidazolium-based ionic liquid

LD <sub>50</sub>	—	lethal dose 50%
Me	—	methyl
M <sub>N</sub>	—	number average molecular weight
MS	—	mass spectrometry
M <sub>W</sub>	—	weight average molecular weight
<i>n</i> Bu	—	<i>normal</i> -butyl
PDMS	—	poly(dimethylsiloxane)
PEG	—	poly(ethylene glycol)
Ph	—	phenyl
PMDTA	—	<i>N,N,N',N',N''</i> -pentamethyldiethylenetriamine
scCO <sub>2</sub>	—	super critical carbon dioxide
<i>t</i> Bu	—	<i>tert</i> -butyl
THF	—	tetrahydrofuran
TMEDA	—	<i>N,N,N',N'</i> ,-tetramethylethylenediamine
TMS-PDMS	—	poly(dimethyl siloxane) trimethylsiloxy terminated
TLV	—	threshold limit values
TRIZ	—	theory of solving inventive problems
VOC	—	volatile organic compound
VMS	—	volatile methyl siloxanes

## THESIS STATEMENT

Reactions involving Grignard reagents are synthetically useful as they impart new carbon-carbon bonds. They are used frequently in the large scale syntheses of fine chemicals such as drugs and food additives. These reactions, however, are often carried out in solvents such as tetrahydrofuran and diethyl ether, both of which are volatile organic compounds that are known to be toxic and can contribute to smog formation. In addition, they are both highly flammable and have low-to-moderate boiling and flash points. Tetrahydrofuran is also a suspected carcinogen. In some cases glycols like diethylene glycol dimethyl ether are used as solvent replacements because they are less volatile, less flammable, and have higher flash and boiling points. Diethylene glycol dimethyl ether can be considered a diethyl ether-type oligomer with three ether functional groups because they are structurally similar. Glycols are detrimentally toxic, however, and can cause breathing problems, sterility, and even death. Reactions with Grignard reagents cannot be performed solventless because they require electron donation from the solvent in order to prevent decomposition. As well, reactions involving Grignard reagents are very exothermic and the solvent plays a role in heat dissipation.

Liquid polymers have low to negligible volatility, dependent on the molecular weight, and have been recently investigated as possible solvents for reactions. Many are non-flammable and have very high boiling and flash points, conferring safety benefits. Poly(ethylene glycol) dimethyl ether, in particular, has a similar structure to both diethyl ether and diethylene glycol dimethyl ether. Indeed, Poly(ethylene glycol) may be considered a longer polymer version of both diethyl ether and diethylene glycol dimethyl ether. Poly(ethylene glycol), the polymer without methyl end-caps, is approved as a food

and drug additive and does not have any known negative health or environmental consequences. It is expected that the reactivity of Grignard reagents, or other reactants, performed in poly(ethylene glycol) dimethyl ether would be comparable to reactions carried out in diethyl ether and diethylene glycol dimethyl ether as they are all structural analogues. In other words, the molecular length of the solvent will not affect reactivity. The benefits to the use of this polymer would be increased safety and decreased health and environmental effects.

## **CHAPTER 1: SOLVENTS**

### **1.1 Preface**

Green Chemistry began as a philosophical movement that has since become an area of research in itself and is now considered a major scientific discipline<sup>1</sup> with several dedicated journals. The overall goals of green chemistry are to reduce waste, minimise the use of toxic substances, and to use materials derived from renewable resources.<sup>2,3</sup> These can be achieved through a variety of ways that have been described in the Twelve Principles of Green Chemistry, which can be found online<sup>4</sup> or in print.<sup>2</sup> The fifth principle, in particular, regards minimising or eliminating the use of auxiliary substances, such as solvents or separation agents, or choosing safer alternatives.

In a dilute solution, such as those found for typical organic reactions, only a very small number of molecules are solute molecules that are meant to react, while the vast majority are solvent molecules. When the product is removed the solvent molecules can be recycled, but very often they become waste because they are contaminated, and are thus treated and discarded. Solvents rarely comprise a portion of the final product, but are

conventionally used in excess. While this system is effective, it is clearly flawed and has room for improvement. The overuse of solvents is an absurd waste and one that is performed without thought, *de rigueur*.

Through further examination of the fifth Green Chemistry principle, one may question whether solvent is necessary whatsoever. While some reactions can be carried out in a solventless manner, others are dependent on properties derived from the solvent itself. In these cases, it becomes essential that less toxic, biodegradable, and recyclable solvent systems are investigated.

We cannot afford to let Green chemistry and environmental goals become a luxury during times of economic slowdown. The proper implementation of green goals through solvent choice will produce 'green' returns (money) through the reduction of energy, waste, and health costs.

The following sections will describe solvents, various properties of solvents, and then certain classes that have the potential to be 'greener' solvents.

## **1.2 Solvents and Solvent Types**

### **1.2.1 Solvent Overview**

When one is compelled to consider the necessary components of a chemical reaction, beyond the very obvious reagents, solvent is the often the next constituent that comes to mind. Given the sheer volume of solvent used each year, especially volatile organic compounds (VOCs)<sup>5</sup> such as toluene, methanol, hexane and dichloromethane,<sup>3</sup> it would appear that chemists, both in academia and industry, deem the use of solvent as essential. However, there are many examples of both solventless and non-VOC solvent

systems. The choice and use of solvent is of fundamental importance for certain reactions, as variation of solvent may lead to variation of product.

A solvent is the medium in which reagents exist, and is usually the component in largest quantity.<sup>6,7</sup> It will determine the state of matter in which the solution exists,<sup>8</sup> and can be the dissolving medium<sup>9</sup> although reactions need not be homogeneous to occur.<sup>10</sup> The purpose of solvent can be to facilitate a chemical reaction, extract substances, dilute concentrates, separate mixtures, clean reagents, disperse heat, or provide a medium for crystal growth, spectroscopic, or analytic methods.<sup>6</sup> By these definitions almost any compound can act as a solvent, especially those in the liquid and gaseous phases, so it is important not to limit solvent choices by commercial availability and convention.

It is imperative to recall that solvent is not a continuum characterised by physical constants, but a sea of discontinuum; of individual, mutually interacting, discrete molecules.<sup>7,11</sup> The reagents' interrelation with individual solvent molecules can dictate the course of a reaction. Furthermore, the solvent may react with the reagent itself in a process known as solvolysis, thereby affecting the yields of a reaction, examples *vide infra*.<sup>6</sup>

The ideal solvent would have a wide working range, be compatible with the reagents, have the desired solubility with respect to reagents and products, be free of contaminants, and have facile separation from the products.<sup>12</sup> In terms of facilitating chemical reactions, one of the most important purposes of solvent is to provide a means of close interaction between reactive species. This is usually done through dissolution of a solute in order to provide a higher reactive surface area. For solid-solid reactions, even of ultrafine powders, the surface area is much less than when dissolved in a liquid.<sup>6</sup>

Some physical constants that will affect solvent choice include the temperature ranges of the phases, volatility, density, viscosity, and dipole moment. Chemical properties include the stability of the reagents in the solvent, reaction rate and equilibrium effects, flammability, and the capacity for hydrogen bonding and donation of electron pairs. Other considerations involve expense and environmental effects, for both workers and the aquatic and atmospheric natural environments. Many solvents like benzene and carbon tetrachloride have found their use minimised or eliminated in recent years due to toxic and carcinogenic effects, ozone depletion, and the production of photochemical smog.<sup>5,13</sup> These attributes must be carefully assessed before solvent use, especially in large scale processes.

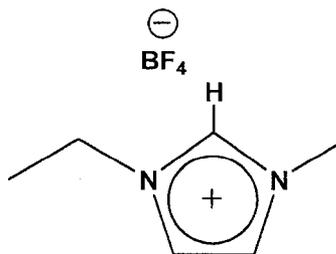
Solvents are often categorised according to certain contrary properties: protic versus aprotic, or polar versus non-polar; however, there are several other properties of solvents that can lead to additional classifications such as the propensity to hydrogen bond, in addition to physical properties such as boiling and melting points, actual functional temperature range, viscosity, density, conductivity, heat capacity *et cetera*.<sup>7,14</sup>

Characterisation and classification of solvents based on these easily measured physical constants can be found in several locations.<sup>7,15</sup> While density, temperature, and other physical characteristics will obviously affect reactions' outcome, the immediately following discussion will be centred more on chemical characteristics and how they can influence reactivity.

## 1.3 Properties of Solvents

### 1.3.1 Protic and Aprotic Solvents

A protic solvent is one that can donate an acidic hydrogen atom to form a hydrogen bond, while an aprotic solvent is one that cannot. In this way, protic solvents are also known as hydrogen bond donors or sometimes protogenic solvents.<sup>7,10</sup> This property arises from a hydrogen atom which is bonded to a sufficiently electronegative atom.<sup>6</sup> Examples of such solvents are alcohols, aldehydes, water, and imidazolium-based ionic liquids with a hydrogen at the C<sub>2</sub> position, of which a specific example is 1-ethyl-3-methylimidazolium tetrafluoroborate shown in Figure 1.3.1. Hydrogen bonding solvents tend to have high heat capacities and can easily transfer heat to an endothermic reaction, or can remove heat from an exothermic reaction. They are also ideal for systems that require that the solvent be brought to reflux.<sup>6</sup>



**Figure 1.3.1: 1-ethyl-3-methylimidazolium tetrafluoroborate: an ionic liquid with a hydrogen at the C<sub>2</sub> ring position.**<sup>16</sup>

In order to examine the role of proticity in solvent, it is necessary to consider hydrogen bonding itself. When a hydrogen bond forms, there are three atoms involved: the donor, the acceptor, and the proton.<sup>11</sup> In a protic solvent the donor and hydrogen atom are inherent, so there must be a source for the acceptor for it to be a factor in reactivity. When the acceptor is within the same solvent, then inherent are the high heat capacity and

other properties remarked upon in the paragraph above. On the other hand, the acceptor may instead be a reagent, which can be a benefit or a detriment, as will be later discussed.<sup>17</sup> There are instances in which a protic solvent will enhance a reaction. In general, these occur when an intermediate or transition state is stabilised by a proton.

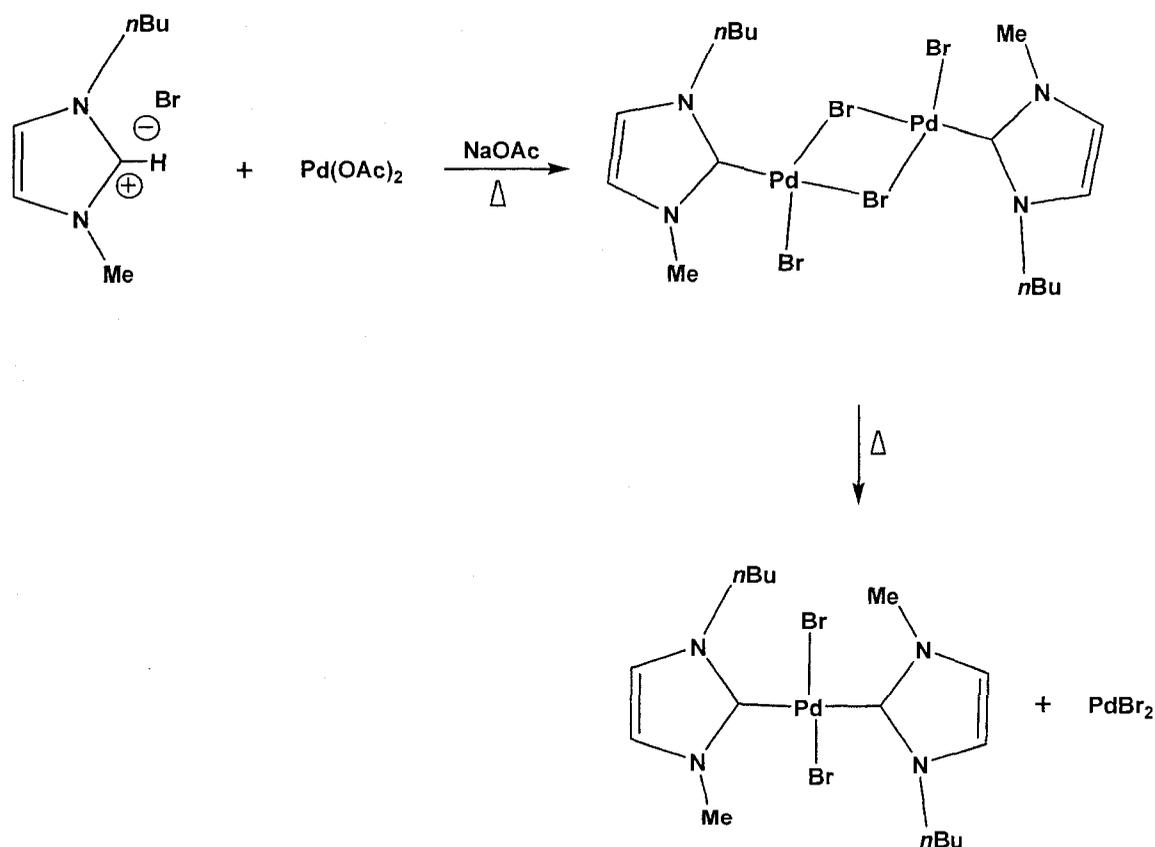
Proton acceptor solvents are cleverly known as hydrogen bonding proton acceptors or sometimes protophilic solvents.<sup>10</sup> Amines, ketones and ethers are hydrogen bond acceptors.<sup>7</sup> Amphiprotic solvents, such as water amides and alcohols, can act as either proton donors or acceptors.<sup>7,10</sup>

One example demonstrating the vital role of a protic solvent is that of asymmetric hydrogenation using a ruthenium catalyst, in which the nature of the solvent affected both the conversion and the enantioselectivity of the products. Methyl levulinate was successfully hydrogenated (or deuterated) asymmetrically with a Ru<sup>II</sup>-(*S*)-BINAP-HCl (where BINAP is 2,2'-bis(diphenylphosphino-1,1'-binaphthyl)) catalyst system, but this occurred only in protic alcohols and not in aprotic dichloromethane or tetrahydrofuran (THF).<sup>18</sup> It appears that the protic solvent facilitates the creation of a catalytically active ruthenium species through molecular hydrogen donation.<sup>18</sup>

Another instance that illustrates the necessity of protic solvent can be found with proteins and polypeptides in which surface-bound protic solvent molecules on the protein affects the rate and distribution of conformers. More specifically, Gramicidin A (a 15 amino acid polypeptide) forms conformational dimers that interconvert in solution. This interconversion is much faster in protic alcohols, and much slower in aprotic solvents such as dioxane or THF. The rate is so markedly different that High Performance Liquid Chromatography (HPLC) can be used to separate the conformers in dioxane, but not in

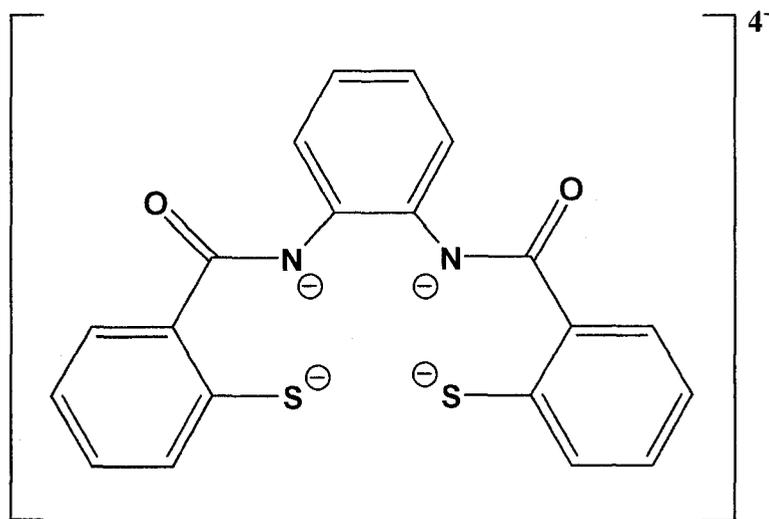
alcohol. The protic solvent is thought to catalyse the transformation between the higher-energy dimeric conformations.<sup>19</sup>

Imidazolium-based ionic liquids (IMILs) with an acidic hydrogen at the C<sub>2</sub> ring position have been seen to perturb reactions when used as solvent. The IMIL enhanced a palladium-catalysed Suzuki reaction through catalyst interaction,<sup>20</sup> and in another reaction formed a carbene complex via interaction with a palladium complex that became an effective catalyst in Heck reactions.<sup>21</sup> An imidazolium and aluminium chloride binary ionic liquid (IL) mixture was also seen to react with platinum chlorides to form new carbene complexes which may be useful as catalysts in their own right.<sup>22</sup>



**Scheme 1.3.1: The new complex formed through reaction of a palladium catalyst with an IMIL solvent. The dimer converts into the monomeric catalyst precursor for the Heck reaction, along with other conformers (Ac = acetyl).<sup>21</sup>**

Of course, the lack of a protic solvent may also be desired. An example of the importance of an aprotic solvent can be found in the case of NO reacted with  $(\text{Et}_4\text{N})_2\text{-}[\text{Fe}(\text{PhPepS})(\text{Cl})]$  (See PhPepS in Figure 1.3.2 below). In methanol, a protic solvent, the product was  $(\text{Et}_4\text{N})_2\text{-}[\text{Fe}(\text{PhPepS})(\text{NO})]$  whereas in the aprotic solvents MeCN or dimethylformamide (DMF), the result was a dimer:  $(\text{Et}_4\text{N})_2\text{-}[\{\text{Fe}(\text{PhPepS})\}_2(\text{NO})]$ . The protic solvent does not support the 5-membered intermediate that is necessary in the formation of the dimeric product.<sup>23</sup>



**Figure 1.3.2: PhPepS<sup>4-</sup> a ligand in enzyme modeling.**<sup>23</sup>

### 1.3.2 Dipolar, Apolar and Polarisable Solvents

Dipolar solvents, known largely as polar solvents, are those that have a permanent dipole moment such as alcohols and chloroform. Apolar solvents like liquid argon<sup>6</sup> have a spherical charge distribution and will not polarise in an electric field. Solvents that are neither dipolar nor apolar are, by default polarisable, because they will polarise in an electric field. These polarisable solvents, such as benzene, are more commonly referred to as non-polar<sup>6</sup> as most reactions are performed without the aid of a strong electric field.

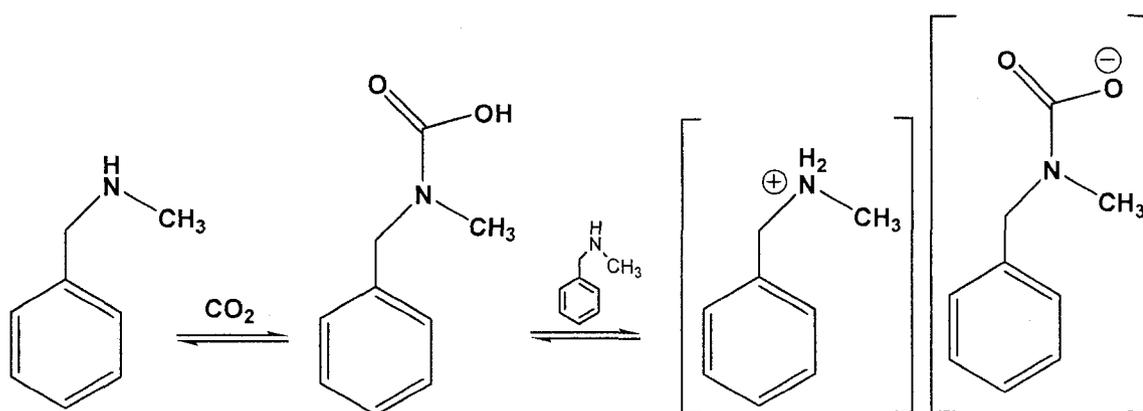
There are various methods to classify the polarity of solvents including the measurement of dielectric constants, the ability to accept an electron pair, the charge stabilisation of an indicator dye, and others.<sup>6</sup> One important implication of polarity is whether the desired reagents will dissolve in the selected solvent (or the related, which layer a desired product will migrate to in an extraction), as dipolar solvents will dissolve and stabilise dipolar solutes.<sup>10</sup> Further examples of dipolar solvents include dimethyl sulfoxide (DMSO), acetonitrile, ethers, and, by their ionic nature, ionic liquids, though these are not dipolar in the traditional molecular sense.<sup>12,24,25</sup> Polarisable or non-polar solvents include cyclohexane, carbon tetrachloride, and hydrocarbons.<sup>6</sup>

Dipolarity, or the lack of it, largely affects reaction rates by stabilising the transition state in the same way as hydrogen bonding although sometimes a dipolar solvent is useful solely through solvation. For instance, dipolar DMSO is one of the only solvents that is able to dissolve proteins; however the mechanism by which this occurs is not yet known (nor is the presumed effect on the protein).<sup>11</sup>

Dipolarity will also affect the miscibilities of solvents. At times, it is desirable to have systems which form separate layers such as biphasic reaction mixtures. Perfluorinated solvents are frequently used in biphasic systems because highly fluorinated molecules are often immiscible in both water and traditional organic solvents at room temperature. When heated, however, the fluorous and organic solvents will form a single phase, separating again when cooled. In these systems a fluorous compound, generally an organic molecule with a highly fluorinated domain, can be used as a catalyst or a reagent. Heating will cause the reaction to occur in the single phase; after cooling, the organic and fluorous products and catalysts automatically separate through diffusion into their preferred phases.<sup>26</sup> This kind of recyclable system works because fluorous compounds

have high chemical and thermal stabilities, and high density. Recycling of fluoruous solvent has been demonstrated for the oxidation of benzylic and aliphatic alcohols with a palladium catalyst.<sup>27</sup> In a further example, enzymes can be dissolved in an aqueous phase and their products can diffuse to an organic phase for simple separation.<sup>28</sup>

The introduction of a gas into certain solvents can cause them to expand and in turn affect their dipolarity. This can be seen in the switchable polarity solvent system DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene) with alcohol,<sup>29</sup> or in a single component system of secondary amines such as *N*-benzylmethylamine.<sup>30</sup> Both change to higher dipolarity upon exposure to carbon dioxide and are made polarisable again by bubbling nitrogen through the solvent while heating.



**Scheme 1.3.2:** The reaction of *N*-benzylmethylamine with carbon dioxide to form a liquid carbamate salt, a solvent with switchable polarity through the addition of CO<sub>2</sub> or N<sub>2</sub>.<sup>30</sup>

### 1.3.3 Viscosity

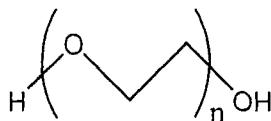
Viscosity, and the related thermal diffusion, is an essential consideration for solvents.<sup>31</sup> It is defined as the force that is necessary to maintain a velocity gradient between parallel planes<sup>14</sup> and is often higher in solvents with hydrogen bonding.<sup>14</sup> The opposite of viscosity is fluidicity. Viscosity is not usually directly measured but is instead

compared to a reference standard.<sup>14</sup> Viscosity is a useful property in model solvents when investigating diffusion patterns and rates,<sup>32</sup> or when diffusion rates need to be controlled.<sup>31,32</sup> It may be less desirable when liquids need to be pumped or transferred by pipet; high values will affect stirring quality as well.<sup>12</sup> Clearly, viscosity can be a problem in industrial processes as viscous solvents can require huge amounts of energy to handle and process.

Two general classes of solvents known for their high viscosities are polymers and ionic liquids, although this property can be highly variable. Great viscosity differences can be found in polymer solution systems, for example.<sup>31</sup> Polymers tend to become more viscous as chain length increases.<sup>33</sup> Similarly ILs generally become more viscous as the side chains lengthen, although this trend does not appear to extend directly to ionic liquids with methyl or ethyl side chains.<sup>34</sup>

Viscosity can have an effect on the course of reactions. Higher viscosity will limit diffusion rates within the solvent,<sup>25,35</sup> and can also reduce the rate of reactions.<sup>25</sup> For instance, the lifetime of a radical<sup>36</sup> or excited state<sup>37</sup> in a viscous liquid will be longer than in a liquid with greater fluidicity. Diffusion rates in ionic liquids increase when the side chains extend in the range of one carbon to four carbons, but the diffusion rates decrease at side chains of five carbons or more, as was demonstrated with molecular dynamic simulations.<sup>38</sup> Viscosity is also inversely proportional to conductivity.<sup>35</sup>

Differences in viscosities may even contribute to differences in crystal structures and yield. For example, branched lamellae and lower crystalline yields of poly(ethylene oxide) are found in high-viscosity urethane dimethacrylate, as opposed to the higher yields of irregular spherulites that were obtained in 1,6-hexanediol dimethacrylate, both under the influence of an electric field.<sup>39</sup>



**Figure 1.3.3: Poly(ethylene oxide), also known as poly(ethylene glycol).**

### 1.3.4 Volatility and Non-Volatility

Volatility refers to the capacity of a substance to vaporise and is usually measured in terms of vapour pressure. This is defined as the pressure at which the vapour in a system is in equilibrium with a liquid or solid phase.<sup>14</sup> Less commonly, the evaporation number may also be used to classify volatility with diethyl ether as the relative reference given an arbitrary evaporation number of 1.<sup>7</sup> Volatility is a specific enough physical property that it can even be used to characterise organic compounds.<sup>14</sup> VOCs, by definition, are highly volatile.

Volatility can be an extremely useful solvent property, but its usefulness can come at a cost, literally. When solvent escapes, if it is not in a closed system, then the solvent is lost and will have to be replenished from fresh stock. In a closed room without proper ventilation, toxic volatile chemicals can lead to acute or chronic health injuries.<sup>7</sup> In a room outfitted with proper safety devices, the solvents will escape into the atmosphere where they can lead to photochemical smog,<sup>5,13</sup> or for benign volatile chemicals like water, generalised 'hot spots' around industrialised land.<sup>40</sup> It is also more straightforward to create continuous flow reactor systems when the solvent is not continuously evaporating.<sup>13</sup>

Positive aspects of volatile solvents include distillations and refluxes that will occur at lower temperatures. Also, the slow, reasonably controlled, evaporation of solvent

can lead to the formation of solute crystals of quality and size suitable for X-ray diffraction. In terms of consumer applications, the evaporation rate is of utmost importance in the design of inks and paints and other products where the removal of solvent leaves behind the finished product.<sup>14</sup>

Non-volatile solvents have the benefit of not polluting the atmospheric environment through direct solvent evaporation; however, this does not automatically denote that these solvents are 'green' or environmentally friendlier as there are additional measures to consider.<sup>41</sup> They bring their own set of advantages and disadvantages. For instance, several ionic liquids are detrimentally toxic and disposal can be difficult.<sup>42</sup> However, non-volatile solvents that are also thermally stable to a high temperature can be vacuum distilled to remove reagents, products, and other waste. They can be left at atmospheric pressure without significant volume loss. Non-volatile solvents may also serve as a safer alternative for the transport of reactive gasses, if the solvent is non-flammable and the gas is reversibly bound to the solvent.<sup>17</sup>

One of the major disadvantages to non-volatile solvents is the process of the removal of product. One common extraction method involves the use of VOCs, but this defeats the purpose of using a non-volatile solvent in the first place.<sup>13</sup> It may be possible in the future to upgrade current systems incorporating a VOC extraction solvent such as dichloromethane to a more benign replacement solvent like supercritical carbon dioxide (scCO<sub>2</sub>). Unfortunately, these systems can be expensive and not all laboratories are equipped to run them safely.

In industry, a common class of volatile solvents that has been exempted from American federal VOC regulations are the Volatile Methyl Siloxanes (VMSs). This class gained their exemption by demonstrating that the vapours do not cause air quality

problems. Specifically, they do not appear to contribute to ozone degradation or global warming, and decompose into benign compounds in approximately one week through photodegradation. Animal toxicity studies also showed detrimental effects to be minor and short-term. VMSs are used in cleaners for oil and particulate removal, and as carrier fluids for precision water removal, which is a process used for flat-panel display screens, and other electronics, for spot-free finishes after aqueous cleaning.<sup>43</sup>

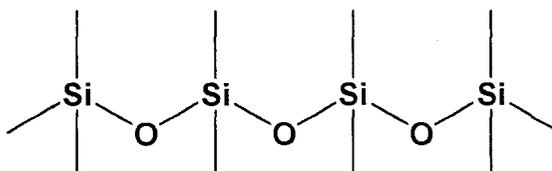


Figure 1.3.4: The VMS, decamethyltetrasiloxane.<sup>43</sup>

### 1.3.5 Density

Density is the mass of a substance per unit of volume, usually measured as grams per cubic centimetres or millilitres.<sup>14</sup> While knowledge of density is of utmost importance in industrial applications,<sup>25</sup> it is not always a consideration in academic research although it is often used to calculate other parameters such as the moles of a liquid substance.<sup>14</sup> Of course, of importance in extractions is whether the product will be found in the upper or the lower layer of the separatory funnel as these will separate based on their densities. It can also play a role in solvents that are compressed, such as supercritical fluids, although it may not affect such factors as equilibrium constants.<sup>44</sup>

### 1.3.6 Phase Change Temperatures: Melting Point and Boiling Point

Solvents are generally only useful in the liquid or gaseous phases, so the temperature and pressure at which these phase transitions occur will affect the reaction

set-up and process. Molecular solvents with low melting points, below that of water for instance, are most commonly used as solvents as they require no additional heat, *i.e.* energy, to be used. This means that reactions can be left to stir overnight, for example, without the necessity of an unattended hotplate, which can be a safety hazard. Low melting solvents can also be used for cooling baths of sub-zero temperatures such as acetone and dry ice. Molecular solvents do not tend to become detrimentally viscous when cooled to low temperatures, unlike certain polymers and ionic liquids.

Ionic liquids tend to be liquids at room temperature partially because they are made of large unsymmetrical ions.<sup>35</sup> The absence of symmetry, caused by non-symmetric side-chains usually situated on the cation, results in an inability to pack well which leads to liquidity at lower than expected temperatures.<sup>34</sup>

High melting solvents, or at least those that melt above ambient temperature, require heat or a pressure change in order to become liquid (or gaseous), the useful phases of solvents. On a large or continuous scale, this will palpably add to the expenditure of processes with each changing degree of temperature adding to the cost. A high melting solvent could be used, though, for solid storage. A rhodium catalyst,  $\text{RhCl}(\text{PPh}_3)_3$ , was successfully encapsulated in solid poly(ethylene) glycol and was still active for hydrogenation after sitting in the open atmosphere for one month.<sup>13</sup> Examples of high-melting solvents include polymers, ionic liquids and molten salts, and paraffin wax.<sup>13</sup>

The boiling point of a substance is the temperature at which the liquid vapour pressure is equal to the opposing pressure. In an open system, this would be the ambient pressure.<sup>14</sup> As pressure varies with altitude, the boiling point of a substance will change dependent on whether the matter is at sea level, or a dissimilar altitude. When transferring

technologies to different locales, regional air pressure should factor into the transfer calculations.

### **1.3.7 Conductance**

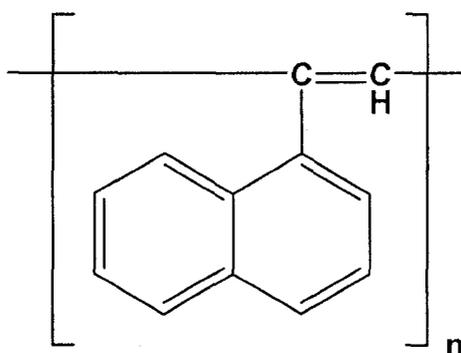
Conductance of a solvent is a useful property when dealing with electrochemical or electron-transfer processes<sup>7</sup> such as electroplating, as conductance is the reciprocal of resistance.<sup>14</sup> Most pure solvents have a low conductivity and consequently, this property can be used as a measure of purity in certain cases.<sup>14</sup> The conductivity of a solution will increase with the dissociation of the dissolved electrolyte and the inertness of the solvent towards the reaction intermediates.<sup>7</sup> For instance, if the solvent is to be used as an electrolytic solution in an electrochemical device, then it should be resistant to reduction and oxidation.<sup>35</sup> Practical solvents have a wide electrochemical window with high reduction and oxidation limits, although this is dependent on the nature of the solvent and electrolyte. Conductivity also increases with lower viscosity.<sup>7</sup> Even though ionic liquids are essentially molten salts, their conductivities are often measurably lower than typical aqueous electrolyte solutions<sup>35</sup> because the mobility of the ions in ionic liquids is limited.

### **1.3.8 Flammability and Non-flammability**

Non-flammability is a desirable property for solvents. The chance of a large-scale disaster increases with the amount of flammable substance that is used, so a reduction in the quantity of flammable solvents is a valuable goal as it follows the philosophies of Green Chemistry, and can save on insurance costs. Certain classes of solvents are widely revered for their resistance to inflammation even if it is not strictly true for all substances in that class. Some ionic liquids have been shown to be flammable under specific

conditions, although many are not.<sup>41</sup> When a flammable substance is dissolved in a non-flammable solvent, however, the risk of inflammation arises because the flammable substance such as a VOC, will burn even in the flame-resistant substance such as an ionic liquid.<sup>12</sup> Thus, it should be recognised that the inclusion of a non-flammable solvent does not necessarily preclude all fires.

Polymers can be flammable or non-flammable, dependent on their inherent properties. Often for polymers, non-flammability is induced through the introduction of a halogen atom in the repeating group, but it can also be accomplished in non-halogenated polymers such as poly(ethynylnaphthalene).<sup>45</sup>



**Figure 1.3.5: Poly(ethynylnaphthalene).**

The flash point of a solvent is a related parameter and describes the minimum temperature at which the vapours of the solvent (in air) will ignite from an external source and cause the surface of the solvent to inflame.<sup>14</sup> This has implications in open reactors as well as for shipping and storage.

### 1.3.9 Heat Capacity

The amount of heat required to raise the temperature of one gram of substance by one degree Celsius is known as the specific heat capacity.<sup>14</sup> In more practical terms and

with respect to solvents, it refers to how much energy the solvent will require to heat or cool it to the desired temperature, or how quickly the solvent will respond to energy perturbations from reactions carried out in them. So the knowledge of heat capacity is important as heat capacity will affect the heating or cooling of a reaction and will influence the thermal conductivity or ability of the same said solvent to dissipate heat from an exothermic reaction and to transfer heat to an endothermic reaction. The implications are scaled up with the reaction size as heating or cooling reactors can increase energy expenditures. Heat capacities and thermal conductivities are properties that receive little research attention nowadays, so this data is often not known for neoteric solvents.<sup>12</sup> Solvents with high heat capacities will maintain more stable temperatures during reactions but will require more energy to bring the reaction to the desired temperature. Solvents with hydrogen bonding tend to be those with higher heat capacity values.<sup>14</sup>

### **1.3.10 Toxicity**

Toxicity for all living species should be a prominent parameter when choosing a solvent, but is often not. Clearly, the least toxic solvent is desirable so that exposure to toxic chemicals can be limited or eliminated, especially as solvents tend to form a large component of the reaction mixture. Proper safety gear such as lab coats and fumehoods can minimise the risk, however risk need not be inherent. Water and Generally Recognised As Safe (GRAS) solvents are the best for workers and the environment and should be chosen when appropriate. GRAS solvents include acetic acid, acetone, methanol, piperidine, and paraffin wax.<sup>46</sup> Less toxic solvents often lead to less costly disposal. Solvents cannot be considered 'green' when they are highly toxic<sup>41</sup> even if they

have other properties that can be considered more environmentally friendly such as the prospect for recyclability.

Many countries and jurisdictions have their own safety guidelines, such as threshold limit values, (TLV)<sup>7,14</sup> to protect workers from chemical exposure. While these minimum standards must be abided by, finding processes with the lowest exposure risks, even well below industry standards, can prevent worker sickness and leave and can minimise the need for changes when technologies need to be expanded into new locations with possibly stricter toxicity standards.

#### **1.4 Choosing a Solvent**

Reactions tend to occur faster and with more control in solution so sometimes a solvent is necessary.<sup>47</sup> The consideration of alternative solvents, however, can facilitate the goals of Green Chemistry. Solventless systems should be the first consideration but in cases where these are unacceptable, solvent systems that are non-toxic and/or recyclable should be considered where appropriate with the 'greenest' choice utilised.

The industrial sector has shown creativity when choosing their solvent systems. For example, while non-molecular solvents like ionic liquids and polymers have been receiving attention in literature in recent years largely due to their often green-perceived property of low volatility, they have been used in industry for more than fourteen years.<sup>48</sup>

Ultimately, choosing a solvent is not a facile process. In addition to basic chemical and physical solvent properties, the inclusion of binary and higher order mixtures can lead to even more solvent variety as these mixtures can have unique properties unto themselves, which further adds to the complexity of choosing a solvent.<sup>49</sup>

## 1.5 Solvent Classes

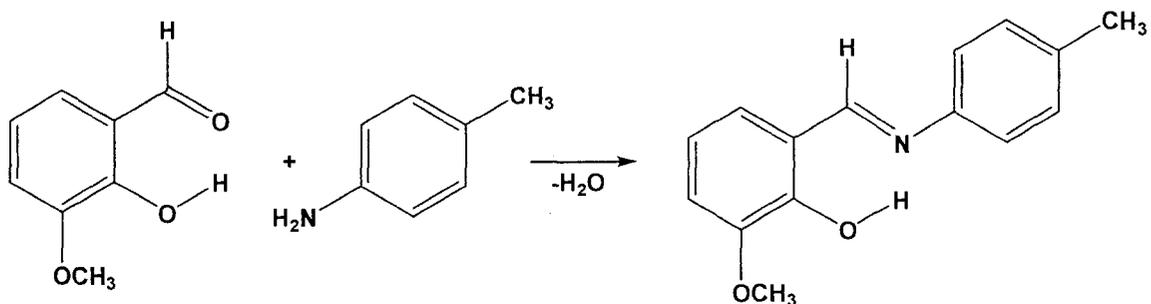
### 1.5.1 Solventless Systems

Solventless systems have received much attention, but even in these systems, one or more of the reagents often is a liquid so even though there is no solvent in the traditional sense, the reagent will perform some of the tasks usually carried out by the non-present solvent.<sup>3</sup> For instance, a eutectic melt may occur upon grinding which will create a liquid phase for the reaction, which would then not be considered a solid-state reaction.<sup>50</sup> Other solventless systems, for example solid-solid reactions, sometimes are condensation reactions and provide an aqueous layer in which the reaction can occur on the surface.<sup>6</sup>

Recently, mechanochemistry, or the mechanical grinding or milling of reagents to yield a reaction, has been highlighted as a consideration for organic reactions to acquiesce to the Green Chemistry philosophy as well as to save money through overall reduced energy costs.<sup>51</sup> There are several advantages to using solventless systems including fast kinetics, lower energy use, simplicity, and possible direct formation of substances with low impurity. Disadvantages include runaway reactions, hot spots, and solid material handling difficulties. Although solventless reactions reduce auxiliary materials, they still can have significant waste through poor atom economy or waste products.<sup>50</sup>

Many solventless reaction systems are known and some perform with more efficiency and selectivity than in the analogous solution-state reaction, as crystals are highly ordered and regular and can transfer these properties to the products.<sup>52</sup> Chiral recognition can even be used to form chiral products and separate racemic mixtures in solid-state reactions.<sup>52</sup> Examples of reactions that have been performed solvent-free are

the Knoevenagel condensation,<sup>51</sup> Aldol condensation,<sup>53</sup> and the reductive amination of *ortho*- or *para*-vanillin, both aldehydes.<sup>54</sup>



**Scheme 1.5.1:** The solventless reaction of *ortho*-vanillin with *para*-toluidine to form an imine.<sup>54</sup>

### 1.5.2 Water

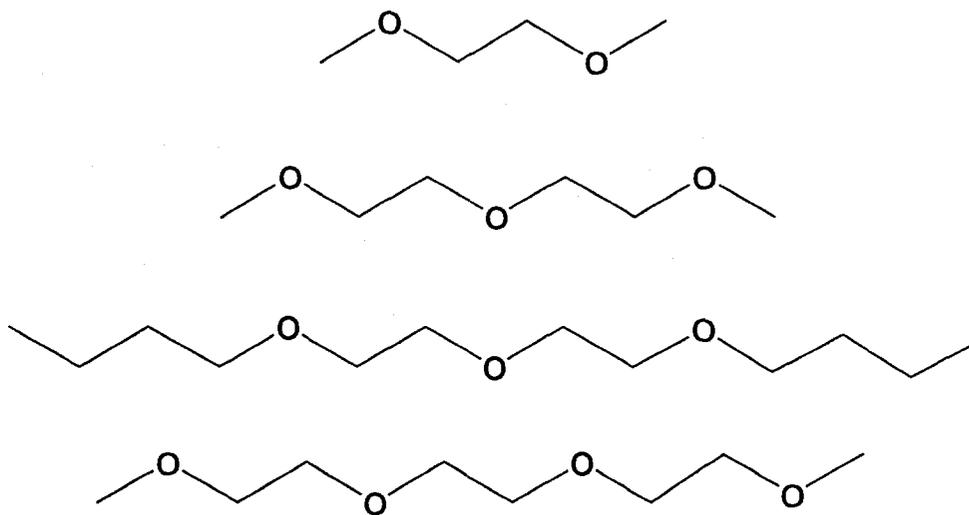
Water is widely recognised as the most available solvent on the planet and is considered to be benign, although wastewater treatment to remove all toxic impurities can be difficult.<sup>55</sup> Many reactions that originated in organic solvents have been shown to occur in water, including Diels-Alder, catalytic hydrogenations, and C-C bond forming reactions.<sup>56</sup> Super critical and near critical water have properties that differ from water at ambient pressure and temperature and can lead to further avenues for organic reactions.<sup>1</sup>

One of the set-backs for water-solvent research is that it is less lucrative than when using neoteric solvents as there are more limitations to intellectual property management.<sup>5</sup> Thus, there may be fewer opportunities for funding.

### 1.5.3 Glymes

Glycol ethers or 'glymes' were first used industrially in the 1920s and have found their place in coatings, for instance.<sup>57</sup> In addition to being a component of commercial products, glymes have also been shown to act as solvents for reactions. Butyl diglyme has

been suggested as an industrial alternative to THF and diethyl ether for reactions with Grignard reagents.<sup>58</sup> Glymes have high Lewis basicities, and are therefore better donors. They also have higher boiling points, and better chemical stability than the traditional Grignard solvents THF and diethyl ether. The high Lewis basicity is due to lone pairs on the ether oxygens.<sup>59</sup> In addition, certain glymes have limited water solubility<sup>57</sup> and do not swiftly form peroxides, which are quite hazardous in solvents.<sup>58</sup> Glymes are aprotic, chemically inert and have thermal stability above 120 °C.<sup>59</sup> They are stable in the presence of concentrated oxidants and bases such as sodium borohydride.<sup>59</sup> They have similar solubilities to ethers but have higher flash points and boiling points.<sup>59</sup> They can easily be dried with molecular sieves.<sup>49</sup> Systems of butyl diglyme may even be recyclable through simple distillation.<sup>58</sup> Butyl diglyme also has limited solubility in water, unlike many other glymes.<sup>59</sup>



**Figure 1.5.1: A selection of glymes: from top to bottom, dimethoxy ethane (monoglyme), diethylene glycol dimethylether (diglyme), diethylene glycol dibutylether (butyldiglyme), and tetraethylene glycol dimethylether (tetraglyme).<sup>59</sup>**

Glymes have been used for the preparation of Grignard reagents,<sup>59</sup> which will be later shown to be central to this thesis. When a water-insoluble glyme, such as butyl

diglyme is used, the reaction workup is facile and the solvent can be recycled.<sup>59</sup> There are at least two complexation sites between glymes and the Grignard compared to generally one in each THF or diethyl ether molecule. This leads to higher stability and reaction yields.<sup>59</sup> The addition of small amounts of glymes has been found to enhance the formation of Grignard reagents.<sup>59</sup> Glymes are also used for distilling fragrances from impurities, scrubbing gas streams, and as solvents for paint stripping.<sup>59</sup>

There is evidence of reproductive toxicity from glymes, especially in males. Glymes are also known to have teratogenic effects, and at high doses can cause respiratory arrest or renal failure. They affect the central nervous system, hematopoietic and renal systems and are able to penetrate the skin.<sup>60</sup> The acute toxicity of butyl diglyme is, however, higher than that of THF and ether with an LD<sub>50</sub> of 3900 mg/kg.<sup>58</sup>

#### **1.5.4 VOCs**

There are many reasons to consider the replacement of VOCs both in industry and academia. Some examples of harmful or toxic VOCs include toluene, benzene, hexane and dichloromethane.<sup>3,6</sup> Aqueous replacements would have the potential for reductions in cost, flammability, toxicity, and environmental risk in the case of accidental release.<sup>50</sup> Other alternatives to VOCs include polymers, ionic liquids, supercritical fluids, immobilised solvents, fluorinated solvents, and solventless systems.<sup>50</sup> When VOCs can't be replaced by non-volatile solvents, there are certain VOCs that can be considered 'greener' for secondary reasons.

### 1.5.5 2-Methyltetrahydrofuran

2-Methyltetrahydrofuran (2-Me-THF) is touted as an environmentally friendly alternative to THF. It can be manufactured from agricultural waste by-products through the cyclisation to furfural of pentoses derived from corn cobs and sugar cane.<sup>61</sup> It is easier to extract than THF because it forms a separate layer from water and has a moderately high boiling point of 80.2 °C.<sup>62,63</sup> The separate layer implies that it may be useful in biphasic reactions.<sup>62</sup> It also entails a reduction in solvent use since another hydrophobic solvent does not have to be added when performing an extraction.<sup>61</sup> It can be used for organometallic reactions such as those with lithium aluminum hydride and *n*-butyllithium that require a strongly basic solvent.<sup>62</sup> The preparation of Grignard reagents in 2-Me-THF has also been demonstrated to have higher yields than in ether or THF, often exhibiting a difference of 15% or more.<sup>61</sup>

### 1.5.6 Non-Volatile Solvents

#### 1.5.7 Ionic Liquids

Ionic liquids (ILs) are deemed non-molecular because they consist of two distinct parts: an anion and a cation. One of the barriers to industrial deployment of ionic liquids is the significant economic investment, *i.e.* high cost.<sup>13</sup> The most touted property of ILs, and the source of their 'Green' appeal is their low- or non-volatility.<sup>64</sup> Some ILs are also non-flammable.<sup>35</sup> This means that unreacted reagents, impurities or even products could be distilled easily, allowing for recycling of solvent.<sup>35</sup> It also means less evaporation of solvent, which implies a lower cost and less waste. They dissipate heat well and the products can be extracted through biphasic systems.<sup>65</sup> Ionic liquids are, however, notoriously toxic.<sup>66</sup> There is some speculation that ILs are less toxic than some prominent

VOCs; however, this is dependent on the type of test and the type of ILs.<sup>12</sup> There is hope that ILs can be designed from the beginning to be non-hazardous by limiting inclusions of components that are known to increase toxicity.<sup>66</sup> The proper routes of disposal for ILs are also not well known.<sup>42</sup>

It is a widely erroneous notion that ionic liquids have not been used in industry. In fact, many have been used for more than fourteen years but have not been classified as ionic liquids as such, but merely salts that are liquid at or near room temperature.<sup>48</sup> Their enigmatic use may be a result of intellectual property rights and trade secrecy. Examples of current commercial applications include: ILs as solvent;<sup>67</sup> ILs to break up azeotropes to reduce separation costs; ILs for aluminium plating; ILs as scavengers; ILs as gas storage and transport media, ILs as paint additives, and many more.<sup>48</sup>

Ionic liquids may be excellent solvents for systems that require low VOC emissions, as well as easy removal or recyclability of a catalyst.<sup>68</sup> Such a system has been demonstrated for the polymerisation of acrylates and methacrylates.<sup>68</sup> ILs have also been studied as a protein denaturation medium.<sup>69</sup> There have been recent examples in the literature of novel employment of ILs with one such case being the inventive use of ionic liquids as the fluid in glass thermometers.<sup>70</sup> The ILs have a negligible vapour pressure and the expansion of the liquid from heat can be tuned for specialty applications.

The relatively slow reaction rates in ionic liquids as solvents may be attributed to their highly-ordered natures and hence their viscosities; the order of the media must be broken before the reagents can get into close contact for reaction.<sup>25</sup> Hydrogen bonding can be minimised in ionic liquids by introducing fluorinated groups.<sup>25</sup>

### 1.5.8 Liquid Polymers

Polymers tend to have very low volatile emissions, which can eliminate health and environmental effects due to volatility.<sup>13</sup> The lack of volatility, along with the useable liquid range, is dependent on average chain length and the nature of the polymer. Non-volatility is ideal for continuous-flow processes as little or none of the polymer is lost through repeated cycles.<sup>13</sup> The use of supercritical carbon dioxide is one of the extractant methods that has been demonstrated in continuous flow polymeric systems to remove products or reactants.<sup>13</sup> Some polymers are also non-toxic or possess low levels of toxicity.<sup>13,68</sup>

While the non-volatility of polymers gives them a 'Green' appeal, this property does cause challenges in terms of separations of products.<sup>13</sup> Many systems that use polymers as solvents end up extracting the products with a VOC, which defeats the purpose of using a non-volatile solvent in the first place unless the use of the polymer provides other additional benefits.

### 1.5.9 Poly(ethylene glycol)

Poly(ethylene glycol) or PEG has been receiving large amounts of interest in the literature as a solvent with similar physical properties to ionic liquids but with lower toxicity which can lead to damaging environmental effects.<sup>71</sup> Applications include use in the pharmaceutical, automotive, cosmetic, textile, and petroleum industries.<sup>72</sup> PEGs are stable under many basic and acidic conditions, as well as at high temperatures, and are non-volatile like many ionic liquids. The viscosities (dependent on the  $M_N$  or Number Average Molecular Weight) of PEGs are similar to ionic liquids as well.<sup>68</sup> PEGs also have low enough toxicity to be listed as 'generally recognised as safe', are used as a food

additive,<sup>73</sup> and also are non-halogenated and inexpensive.<sup>71,74</sup> A PEG with low  $M_N$  can be regarded as a protic solvent with aprotic ethylene oxide binding sites.<sup>73</sup> PEG is hygroscopic and room-temperature liquid PEG is readily miscible with water. Solid PEG is quite soluble in water.<sup>73</sup> PEG is also soluble in toluene, dichloromethane, alcohol and acetone but is not soluble in hexane, cyclohexane, diethyl ether, or other aliphatic hydrocarbons.<sup>73</sup>

Aqueous solutions of PEG are also considered to be 'greener' solvent systems and have been reviewed recently.<sup>73</sup> Aqueous solutions of PEG have been used as biphasic and extraction systems.<sup>68,72</sup> PEG has been demonstrated as a novel solvent for transition metal mediated radical polymerisation reactions to form both polystyrene and poly(methyl methacrylate) with significantly altered reaction rates compared to the same polymerisations in VOCs or ionic liquids.<sup>68</sup> Reaction rate enhancements were also found in Br/Mg exchange reactions upon addition of small amounts of ethylene glycol-type solvents like PEG and glymes.<sup>75</sup>

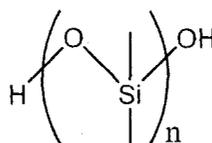
Poly(ethylene glycol) and Poly(ethylene glycol) dimethyl ether (diM-PEG) have been used successfully as solvents for the hydrogenation of aromatic ketones, enamides and acrylacrylic acids with ruthenium and rhodium catalysts, although the best results with the highest conversions and enantiomeric excesses (*ees*) were found with the addition of an alcohol cosolvent.<sup>71</sup> The solvent and the catalyst system were recyclable, although it involved an energy-intensive removal of the alcohol under reduced pressure, then extraction into VOCs.<sup>71</sup> PEG has also been used to hydrogenate styrene with  $\text{RhCl}(\text{PPh}_3)_3$  with facile catalyst recycling and extraction of product with  $\text{scCO}_2$ , which is viewed as a more environmentally friendly extraction step.<sup>13,74</sup>



**Figure 1.5.2: Poly(ethylene glycol) dimethyl ether (diM-PEG).**

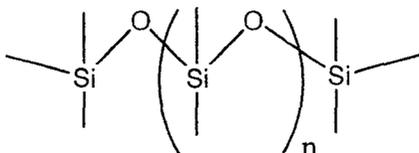
### 1.5.10 Poly(dimethylsiloxane)

Poly(dimethylsiloxane) or PDMS is the most common polymer from a class known as poly(organosiloxanes). They are viewed as having both organic and inorganic character with the type of organic substituents attached to the silicon atom influencing the chemical and physical properties of the polymer.<sup>76</sup>



**Figure 1.5.3: Poly(dimethylsiloxane) (PDMS).**

PDMS is not commonly used as a solvent but rather as a lubricant, cleaner, coating, surfactant, or when solid, as membranes,<sup>77</sup> contact lenses, or biomaterials.<sup>76</sup> PDMS is hydrophobic, although it is soluble in many organic solvents.<sup>13</sup> There appear to be no examples in academic literature of PDMS used as a solvent for organic reactions.



**Figure 1.5.4: Poly(dimethyl siloxane) trimethylsiloxy terminated (TMS-PDMS).**

In PDMS, the Si-O-Si bond is quite flexible and leads to elastic properties, even at low temperatures.<sup>76</sup> In addition, the Si-O-Si angle tends to be wider than that of the PEG C-O-C bond angle and this may contribute to solvation effects. These wider angles can be

seen in the crystal structures of short, non-polymeric siloxanes which have Si-O-Si angles ranging from around 140° up to 175°. <sup>78,79,80,81,82,83</sup> A partially condensed hydrosiloxane from the hydrolysis of *t*BuSiCl<sub>3</sub>, [*t*Bu(OH)<sub>2</sub>Si]<sub>2</sub>O, even has a Si-O-Si bond angle that is perfectly linear, although this may be partially attributed to inter-molecular hydrogen bonds.<sup>84</sup> Many of the siloxanes appear to be influenced by hydrogen bonding.<sup>84</sup> Hydrogen bonding is not a factor in PDMS although the average Si-O-Si bond angle is around 140°, which is still quite large when compared to the average C-O-C polymer angle around 111°. <sup>76</sup> In other words the donor solvent ability in siloxanes is weaker compared to glycol-type polymers, and this is reflected in both the ionic nature of the Si-O bond and wider bond angle which is attributed to electron pairs that have less repulsion.<sup>85</sup>

In PDMS, the siloxane (-Si-O-) bond has high dipolarity and considerable ionic character as well as a high dissociation energy making it more thermally resistant than the analogous carbon -C-O- bond in carbon-based polymers.<sup>76</sup> When thermally degraded, however, PDMS tends to form small cyclic, more thermodynamically stable, siloxane oligomers, usually with three or four repeating units, although they can be larger.<sup>86</sup> Strong bases, such as potassium hydroxide, will react with the siloxane and form byproducts.<sup>87</sup> These reactions appear to begin at the terminal sites of the polymer chain, not through “a random clipping of the siloxy chain.”<sup>88</sup> Solid PDMS is, however, tolerant of substances of high pH without degradation.<sup>89</sup>

## 1.6 Computational Studies

With the advent of inexpensive computational time, computational studies have become commonplace in contemporary research. It is imperative, then, that careful solvent considerations are made even for computational studies because solvation,

especially in the cases of donor and coordinating solvents, can drastically affect energy calculations and conformations, and certain models will better reflect the actual physical situations.<sup>90</sup> It may be impossible to ever fully describe the solvent effects with a computational model, but methods are constantly being developed that include explicit, rather than implicit, consideration of solvent molecules.<sup>91</sup> A theoretical system for describing complicated liquids, *i.e.* non-atomic liquids such as water, as a means to more fully depict the physical and thermodynamic properties of such liquids, can be found in the literature.<sup>11</sup>

Life cycle analysis software is also becoming more routine in literature and the concepts of cradle-to-grave or the improved cradle-to-cradle are becoming more important in academia and industry.<sup>5</sup> The introduction of a class or lab into the undergraduate curriculum that focuses on the life-cycle of chemicals could positively impact the next generation of chemists.

### **1.7 The Importance of Innovative Solutions**

The public and many chemists are aware of the growing trend of ‘greenwashing’ and the unfortunate shift from philosophical movement to marketing fad. While logical steps to improve a process are important and encouraging, only leapfrog innovations will bring true change, or perhaps even revolution, to chemistry. Genuine green changes will pay for themselves through lowered safety, disposal, and raw materials costs.

TRIZ (the Theory of Solving Inventive Problems)<sup>92,93</sup> is a valuable tool for innovative thinking and creativity that can be extended to chemical processes. First postulated by a Russian patent office employee, TRIZ stems from the idea that truly innovative products and processes either investigate the perceived problem and find a

new method or object to solve it, or develops a system to solve a new challenge that encompasses the original problem.<sup>93</sup> For instance, why spend time and money decaffeinating coffee beans through solvent means (methylene chloride or the more benign scCO<sub>2</sub>), when coffee beans can be grown ‘naturally’ decaffeinated, either through selective breeding or genetic modification?<sup>94</sup>

Higher levels of problem solving will often require information from outside of a given scientific discipline into other sub- and mixed-industries. Relevant data does not always traverse scientific borders although it can be used to approach a problem from a different angle.<sup>93</sup> Ideally, systems will evolve to a state that has no cost or harm.<sup>95</sup> Sometimes, visualising the ideal solution will lead to a new problem definition, often broader than the original problem.<sup>92,93</sup> Using a system of innovation is more efficient than simple trial and error in that it will save both time and money.<sup>93</sup>

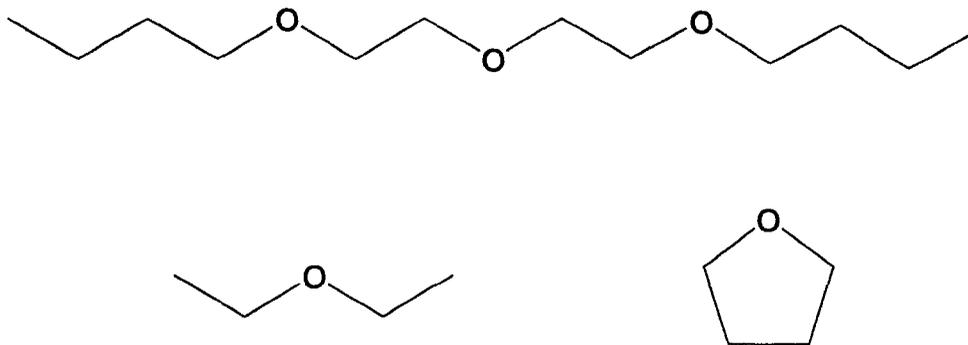
## CHAPTER 2: Organomagnesium Compounds

### 2.1 Magnesium

After the basics of solvents and their wide variety of physical and chemical characteristics, magnesium organometallic reagents are the subsequent topic. Magnesium compounds can be considered environmentally friendly as the resultant reaction products, magnesium dihalides, are known to be non-toxic. The electronegativities of magnesium and carbon atoms are 1.2 and 2.5, respectively, rendering carbon-magnesium bonds to be sources of formal carbanions.<sup>96</sup> Magnesium compounds are often among the first classes of basic reagents studied by undergraduates. In addition, magnesium organic compounds are common and practical organometallic reagents in synthesis<sup>97</sup> and indeed have been known as the most important reagents in organic and organometallic synthesis for the last hundred years<sup>98</sup> with Grignard reagents being the most prevalent. They are used in both industry and academia as alkylating and arylating agents.<sup>99</sup>

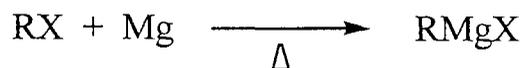
### 2.2 Grignard Reagents

Grignard reagents are an important tool for synthetic chemists as they are used to form carbon-carbon bonds,<sup>100</sup> and find extensive use in pharmaceutical and fine chemical manufacturing.<sup>62</sup> Reactions of this type are usually performed in volatile organic compounds (VOCs), namely THF or diethyl ether, although butyl diglyme<sup>101</sup> has been used industrially.<sup>102</sup>



**Figure 2.2.1: Typical solvents for Grignard reagents, clockwise from top: butyl diglyme, THF, diethyl ether.**

Grignard reagents, with the short-hand notation  $\text{RMgX}$ , are typically formed by a dropwise addition of a halo-substituted organic molecule (represented by  $\text{RX}$ , where  $\text{X}$  is usually  $\text{Br}$  but sometimes  $\text{Cl}$ ) to magnesium turnings in THF, followed by subsequent heating to reflux for one hour to form the Grignard reagent,  $\text{RMgX}$ .<sup>103</sup> The formation of Grignard reagents is known as the Grignard Reaction. Metal impurities in the magnesium, such as iron or manganese, can significantly affect reaction yields in a positive or negative manner.<sup>104</sup> Grignard reagents are straightforward to produce and their reactivity is largely predictable rendering them useful for alkylations; however, they have also been documented to act as bases and anionic polymerisation initiators.<sup>53</sup>

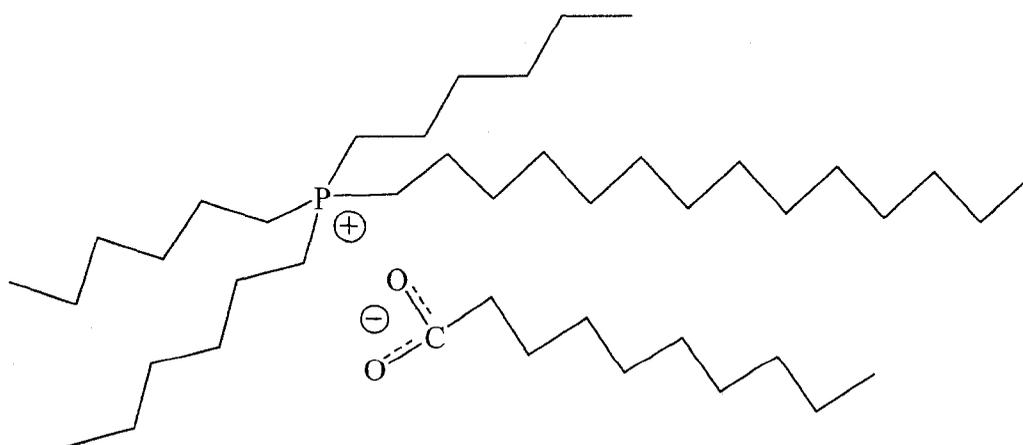


**Scheme 2.2.1: The Grignard Reaction.**

A Grignard reagent requires some form of stabilisation: in a solution of THF or diethyl ether, the oxygen atom provides this stability through electron donation, while in the ionic liquid trihexyl(tetradecyl)phosphonium decanoate (Figure 2.22), it is the carboxylate group of the anion that fulfills the role. Regardless of the source, the inclusion of oxygen or another kind of donor such as nitrogen appears to be a necessary

component of the solvent. Reactions with Grignard reagents are highly solvent-dependent.<sup>98</sup>

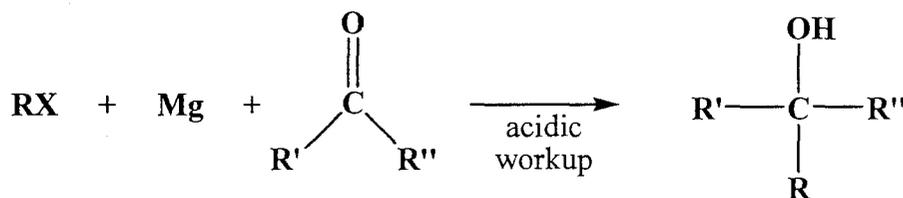
Grignard reagents have been shown to be persistent in ionic liquids (ILs), specifically in trihexyltetradecylphosphonium decanoate, trihexyltetradecylphosphonium chloride with an ethereal cosolvent,<sup>105</sup> pyridinium ionic liquids,<sup>106</sup> and various imidazolium<sup>107</sup> or imidazolium<sup>108</sup> ionic liquids with protection at the C<sub>2</sub> position. Of late, an example of a specially designed IL incorporating an ether component into the cation has been published.<sup>109</sup> Reactions with dissolved Grignard reagents have been performed to varying yields, but generation of the Grignard reagents themselves in the ionic liquids has been elusive in all but pyridinium ILs.<sup>106</sup> This may be due to a protective coating that forms on the surface of the magnesium upon contact with ionic liquids.<sup>110</sup> Other 'Green'-type reaction media such as water and supercritical carbon dioxide are unsuitable as they will react with the Grignard reagent;<sup>106</sup> however solvent-free conditions were successful for a system that involved Grignard-type reagents, namely catalytic C-H bond activation to form a carbon-carbon bond.<sup>100,111</sup>



**Figure 2.2.2:** The phosphonium IL, trihexyltetradecylphosphonium decanoate, which has been demonstrated as a suitable solvent for Grignard reagents.<sup>105</sup>

The reactivity of Grignard reagents is largely dependent on both the ligands and solvents used in each particular system.<sup>98</sup> Organomagnesium halides can be obtained in more than just ethers and ether-type solvents; they can be produced in non-polar hydrocarbons such as toluene, and not necessarily with the addition of small quantities of donor solvents like diethyl ether, although these are limited to primary alkyl- and aryl-magnesium compounds.<sup>103</sup> Toluene solutions have higher boiling and flash points compared to diethyl ether and can, in those ways, be viewed as a safer industrial alternatives.<sup>103</sup> Toluene is also non-hygroscopic and inexpensive.

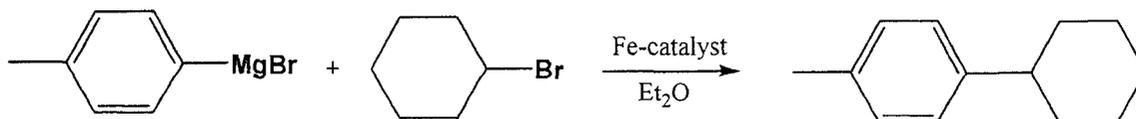
Reactions with Grignard reagents are similar to the Barbier reaction, which also involves a carbon attack by an organometallic substance. The Barbier reaction, however, occurs in one step with a carbonyl compound, alkylhalide, and a metal (lithium, magnesium, etc.).<sup>112</sup> Some Barbier-type reactions can be performed under aqueous conditions with a variety of metal centres including indium, zinc and tin.<sup>113</sup> The Barbier reaction yields are often higher than Grignard reaction yields.<sup>114</sup>



**Scheme 2.2.2: The general form of a Barbier reaction.**<sup>114</sup>

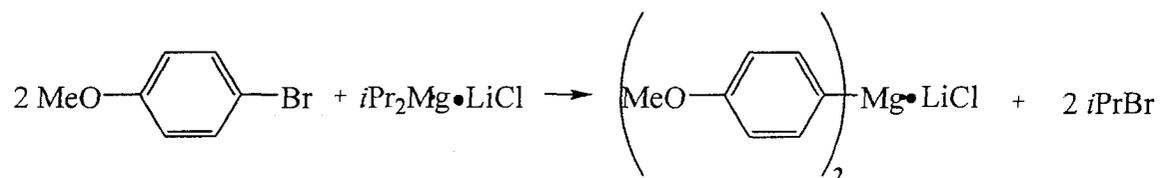
The reaction pathway of a Barbier reaction is not necessarily from reagents formed *in situ*, but can be via a radical pathway in which an anion radical is trapped directly by a carbonyl compound on the surface of the metal. The lifetime of the radical, and hence the viscosity of the solvent, will portend the chances of the reaction occurring by the radical or the organometallic route.<sup>114</sup>

Grignard reagents can be used in coupling reactions to form substituted phenyl C-nucleosides.<sup>115</sup> Cross-coupling reactions can also employ Grignard reagents, although these require a catalyst such as Fe(acac)<sub>3</sub> or iron nanoparticles (acac is acetylacetonate or 2,4-pentanedionyl).<sup>116</sup> The same catalyst system can also yield a tandem cyclisation/cross-coupling reaction.<sup>116</sup>



**Scheme 2.2.3: Iron-catalysed cross coupling reaction with a Grignard reagent.**

Halogen-magnesium exchange reactions have also been recently featured in the literature, that is, a reaction in which the magnesium and the bromine exchange places on two separate molecules. In these systems, increased electronic saturation at the magnesium center correlated with a decrease in the energy barrier to the reaction.<sup>75</sup> This increased electronic saturation can be achieved with strongly electron-donating ligands or a higher coordination number on magnesium.<sup>75</sup> Additions to Br/Mg exchange reactions of various chelating additives, such as PEG, crown ethers, dioxane, or tetramethylethylenediamine (TMEDA), were found to affect the reaction conversions in a positive way.<sup>75</sup> These effects have been attributed to coordination with the magnesium-centered reagents.<sup>75</sup>



**Scheme 2.2.4: An example of a magnesium bromine exchange reaction.**<sup>75</sup>

In industry, the high reactivity and therefore usefulness of Grignard reagents is eclipsed by their exothermicity in the usual highly volatile and flammable solvents diethyl

ether and THF.<sup>58</sup> Solvents such as butyl diglyme, a non-volatile, low water-miscible ether-type oligomer, can provide a medium that has less chance of combustion and more possibilities for processing and recycling.<sup>58</sup> Reactivity studies suggest that the effect on the Schlenk equilibrium (*vide infra*) by glymes is similar to that of THF.<sup>58</sup> The rate of reaction in glymes is, however, slower than in that of THF or diethyl ether, suggesting that the coordination of glymes is stronger than that of THF or diethyl ether and the displacement of such a donating solvent prevents fast reaction with adducts.<sup>58</sup> This slower reaction rate may yield higher selectivities.<sup>58</sup> Glymes also have higher Lewis basicities than diethyl ether or THF.<sup>58</sup>

Although Grignard reagents are dynamic and changing in solutions, some insight into their structure and subsequently their reactivity may be deduced through structurally characterised solids. Crystals of the Grignard reagent ethylmagnesium bromide with two solvating diethyl ether molecules were found to be monomeric,<sup>117,118</sup> a find which, at the time, refuted the supposed dimeric structure that was thought to be the favoured structure for Grignard reagents in the solid-state.<sup>117</sup> Crystals of the crown ether Grignard  $C_{14}H_{19}O_4MgBr$  or 2-(bromomagnesium)-1,3-xyllyl-15-crown-4 are known and were found to be also monomeric, although the degree of association could not be determined.<sup>119</sup>

### 2.3 The Schlenk Equilibrium

The composition of Grignard reagents in solution and in the solid-state is a dynamic and complex system of equilibria.<sup>120</sup> The central portion of the equation shown below is the best known portion of the Schlenk equilibrium, although the species that comprise the Schlenk equilibrium may also form dimers, trimers, and species of higher orders, which will shift quickly in solution.<sup>120</sup> In addition, electrical conductance

measurements demonstrate that Grignard reagents in solution contain anionic and cationic species, both of which include magnesium.<sup>58</sup>



**Scheme 2.3.1: The Schlenk Equilibrium.**<sup>120</sup>

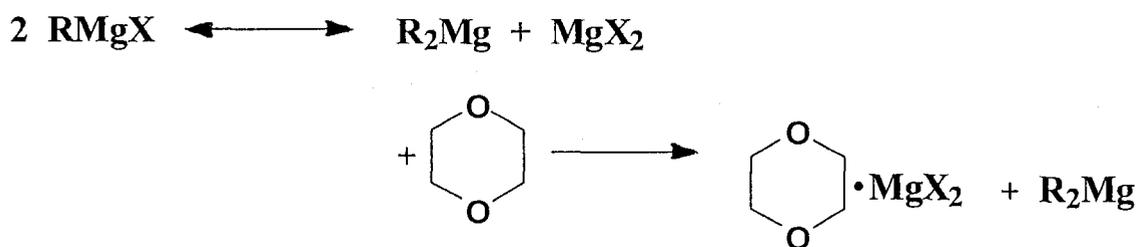
The position of the Schlenk equilibrium in solution is dependent on the nature of the X and R groups of the Grignard, as well as the concentration, temperature and nature of the solvent,<sup>98,120</sup> with the type of solvent and concentration being the most significant factors.<sup>120</sup> The effect of temperature can be of a kinetic or thermodynamic nature,<sup>120</sup> as increasing the temperature tends to allow faster magnesium ligand exchange which, in turn, results in faster equilibrium rates.<sup>120</sup> In addition, alkyl exchange rates are dependent on the structure of the alkyl group, intimating that methyl groups will exchange faster than *t*-butyl groups, for example.<sup>120</sup> It is generally recognised that a more coordinating solvent will favour the dimerisation ( $\text{R}_2\text{Mg}$  and  $\text{MgX}_2$ ) products,<sup>98</sup> however, solvent coordination that is too strong will adversely affect reaction rates by inhibiting the leaving of the solvent molecule.<sup>58</sup> Stabilisation by solvent molecules of the various organomagnesium species is greatest in  $\text{MgX}_2$  and weakest in  $\text{R}_2\text{Mg}$ , with  $\text{RMgX}$  intermediary.<sup>120</sup>

Diethyl ether is understood to favour  $\text{RMgX}$  while the symmetric product is slightly preferred in THF, although none of these equilibrium species have a long existence in solution.<sup>58</sup> This behaviour is ascribed to the relative Lewis basicities of the two solvents.<sup>120</sup>  $\text{N}_2\text{N}_2\text{N}'\text{N}'\text{N}''\text{N}''$ -pentamethyldiethylenetriamine, a strong donor is known to shift the products to the Grignard ( $\text{RMgX}$ ) side.<sup>98</sup>

There is some debate in the literature regarding the more reactive species of the Schlenk Equilibrium ( $\text{R}_2\text{Mg}$  or  $\text{RMgX}$ ).<sup>75,120</sup> A study involving the addition of rate-

enhancing substances to organomagnesium reagents found no reaction rate enhancement for Mg/Br exchange reactions with  $i\text{Pr}_2\text{Mg}$ , leading the researchers to conclude that the diorganomagnesium is the reactive species of the Schlenk equilibrium.<sup>75</sup> Moreover, the substances that did increase the reactivity of Grignard reagents appeared to do so by affecting the Schlenk equilibrium to the dismutation products.<sup>75</sup> Ethylene glycol-type additives, such as PEG and short ethers, were among those additives to increase the rates.<sup>75</sup>

The Schlenk equilibrium provides a facile route to diorganomagnesiums through dismutation; the dihalomagnesium can be selectively precipitated via the addition of 1,4-dioxane to a Grignard in solution.



**Scheme 2.3.2:** The selective precipitation of  $\text{MgX}_2$  with dioxane to render  $\text{R}_2\text{Mg}$  in solution.

## 2.4 Diorganomagnesium Reagents

As compared to Grignard reagents, diorganomagnesium compounds have more stoichiometric control, and produce reaction products that are easier to purify.<sup>97</sup> Sometimes, diorganomagnesiums are preferred to Grignard reagents simply because they contain no halogen atoms.<sup>121</sup>

Diorganomagnesiums were first prepared from Grignard reagents when Wilhelm Schlenk Sr. and Wilhelm Schlenk Jr. added 1,4-dioxane to a Grignard solution to force the equilibrium to the dismutation species, and selectively precipitated the magnesium

dihalide.<sup>98,122</sup> Indeed, this was the experiment that first brought to light the dynamic behaviour of Grignard reagents in solution.<sup>98</sup> After the precipitation and filtration of  $\text{MgBr}_2$ ,  $\text{R}_2\text{Mg}$  can be obtained by exhaustively removing ether and dioxane by heating the solid to 150 °C under an inert gas or vacuum.<sup>121</sup> Another route to diorganomagnesiums involves an exchange reaction between magnesium and a diorganomercury,<sup>122</sup> although this technique is no longer frequently used due to safety concerns with mercury.<sup>98</sup>



**Scheme 2.4.1: An obsolete preparation for diorganomagnesium reagents from diorganomercury reagents.**<sup>128</sup>

Grignard reagents require stabilisation by donor solvent molecules. The basicities of several solvents were determined via NMR based on their solvation ability for organomagnesiums:  $\text{Et}_3\text{N} < \text{Bu}_2\text{O} < \text{Et}_2\text{O} < \text{dioxane} < 2\text{-Me-THF} < \text{THF} < \text{diglyme} < \text{tetramethylethylenediamine} < \text{hexamethylphosphoramide}$ .<sup>123</sup> This can be viewed as a scale of donor solvents with the most electron-donating solvent at top of the scale. Some of these results were corroborated in a separate study.<sup>124</sup> When forming products for solid-state analysis, solvents with more donating ability are known to displace weaker donor solvents in a competition for solvation. For instance, diethyl ether is weakly coordinated to methylmagnesium bromide and will be replaced with THF or triethylamine if they are added to the solution. This applies for bi- and tridentate ligands as well so long as they are better electron donors.<sup>98</sup> Grignard complexes with better donors are less reactive, however, and it has been reasoned that the reaction can only occur when the strongly coordinating solvent has been displaced, which takes a greater amount of energy than with a weakly coordinating solvent molecule.<sup>125</sup>

Knochel *et al.* have noted that no rate enhancement is found for Br/Mg exchange reactions with  $R_2Mg$  as compared to  $RMgX$  (where  $R = iPr$  and  $X = Cl$  with  $R_2Mg$  prepared directly from  $RMgX$ ), suggesting that the reactive species of  $RMgX$  is actually  $R_2Mg$ , formed as a part of the Schlenk equilibrium.<sup>75</sup> However, organomagnesium reagents with an electropositive substituent on the organometallic carbon atom tend to have reduced reactivity.<sup>126</sup> Magnesiates ( $MgR_3^-$ ) are known to be more nucleophilic and have enhanced reactivity compared to diorganomagnesiums, from which they are usually generated.<sup>97</sup>

Some crystal structures for diorganomagnesiums are known. The dative bonds of ethers to diorganomagnesiums are less strong than in ordinary  $RMgX$  Grignard reagents.<sup>121</sup> Two-coordinate magnesium structures are generally not known at room temperature, as they are typically solvated by at least one donor molecule. If they are not solvated, then they tend to form insoluble polymers.<sup>127,128</sup> THF solvated molecules include  $Mg(2,4,6-MeC_6H_2)(THF)_2$ ,<sup>97</sup>  $Mg(2,4,6-i-PrC_6H_2)(THF)_2$ ,<sup>97</sup> diphenylmagnesium $\cdot(THF)_2$ ,<sup>128</sup> bis(*ortho*-vinylphenyl)magnesium $\cdot(THF)_2$ ,<sup>129</sup> and the interesting dimer [bis(*ortho*-anisyl)magnesium $\cdot THF$ ]<sub>2</sub> which contains both a four- and five-coordinate magnesium.<sup>127</sup> Diorganomagnesium reagents solvated by crown ethers include di-*p*-tolylmagnesium solvated by 1,3-xylyl-18-crown-5,<sup>130</sup> diphenylmagnesium, again solvated by 1,3-xylyl-18-crown-5,<sup>130</sup> bis(*p*-*tert*-butylphenyl)magnesium with 1,3-xylylene-18-crown-5,<sup>131</sup> the same with 1,3,16,18-dixylylene-30-crown-8,<sup>131</sup> diethylmagnesium solvated by 18-crown-6,<sup>132</sup> phenylmagnesium solvated 1,3-xylylene-15-crown-4,<sup>133</sup> and *p*-*tert*-butylphenyl-magnesium with a 1,3-xylylene-18-crown-5.<sup>125</sup> Crystal structures for the glyme-solvated diorganomagnesiums include bis(*p*-*tert*-butylphenyl)magnesium with both diglyme and tetraglyme.<sup>131</sup>  $N,N,N',N',-$

Tetramethylenediamine (tmeda) has successfully solvated diphenylmagnesium in the solid-state.<sup>134</sup> Diethylmagnesium has been crystallised with solvated dioxane which coordinates to two separate magnesium molecules and in effect, creates a polymeric chain.<sup>135,136</sup> Diphenylmagnesium<sup>128</sup> and di-*tert*-butylmagnesium<sup>99</sup> have both been isolated solvent-free. Dicyclopentadienylmagnesium has had its crystal structure determined, and it also appears to be a solvent-free molecule.<sup>137</sup>

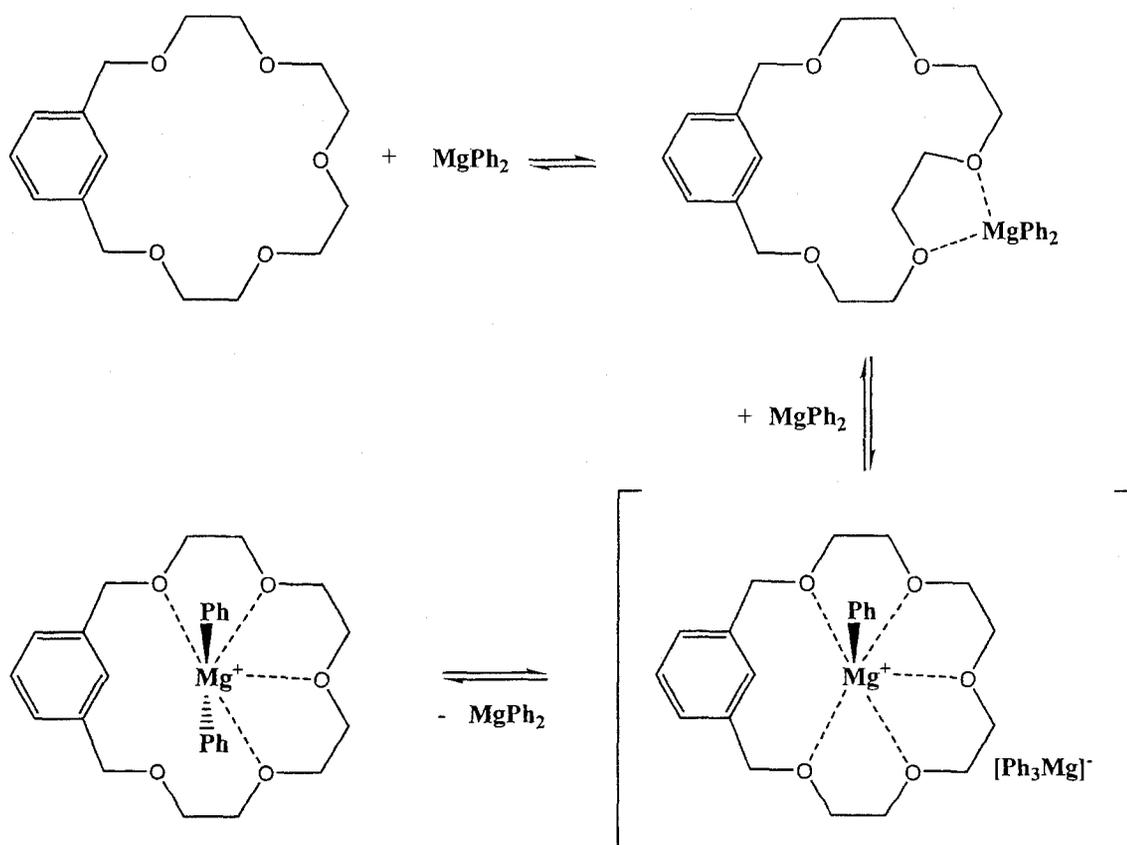
The preparation of many of the crown-ether and glyme crystals generally begins with diethyl ether adducts rather than THF as the strong donor ability of THF prevents the formation of many complexes.<sup>128</sup>

**Table 2.4.1 Some structurally characterised non-halo organomagnesium compounds.**

Organomagnesium	Solvated by	Reference
Ph <sub>2</sub> Mg • THF <sub>2</sub>	THF	128
Mg(2,4,6-MeC <sub>6</sub> H <sub>2</sub> )(THF) <sub>2</sub>	THF	97
Mg(2,4,6- <i>i</i> -PrC <sub>6</sub> H <sub>2</sub> )(THF) <sub>2</sub>	THF	97
( <i>p</i> -tolyl) <sub>2</sub> Mg(THF) <sub>2</sub> (monomer)	THF	128
[( <i>p</i> -tolyl) <sub>2</sub> Mg • THF] <sub>2</sub> (dimer)	THF	128
( <i>o</i> -vinylphenyl)Mg • (THF) <sub>2</sub>	THF	129
[Bis( <i>ortho</i> -anisyl)Mg • THF] <sub>2</sub>	THF	129
(Et <sub>2</sub> Mg) <sub>∞</sub> • dioxane	dioxane	135,136
Bis( <i>p</i> - <i>tert</i> -butylphenyl)Mg • diglyme	diglyme	131
Bis( <i>p</i> - <i>tert</i> -butylphenyl)Mg • tetraglyme	tetraglyme	131
Ph <sub>2</sub> Mg • tmeda	tmeda	134
PhMg • (1,3-xylylene-15 crown-4)	1,3-xylylene-15 crown-4	133
di- <i>p</i> -tolylmagnesium • 1,3-xylyl-18-crown-5	1,3-xylyl-18-crown-5	130
Ph <sub>2</sub> Mg • (1,3-xylyl-18-crown-5)	1,3-xylyl-18-crown-5	130
2-[( <i>p</i> - <i>tert</i> -butylphenyl)magnesium]-1,3-xylylene-18-crown-5	1,3-xylylene-18-crown-5	125
Bis( <i>p</i> - <i>tert</i> -butylphenyl)magnesium • 1,3-xylylene-18-crown-5	1,3-xylylene-18-crown-5	131
Et <sub>2</sub> Mg • (18-crown-6)	18-crown-6	132
Bis( <i>p</i> - <i>tert</i> -butylphenyl)magnesium • 1,3,16,18-dixylylene-30-crown-8	1,3,16,18-dixylylene-30-crown-8	131
[ <sup>t</sup> Bu <sub>2</sub> Mg] <sub>2</sub>	Solvent-free	99
(Ph <sub>2</sub> Mg) <sub>n</sub>	Solvent-free	128
Cp <sub>2</sub> Mg	Solvent-Free	137

An interesting multifarious crystal structure is that of bis[(*N,N,N',N'*-tetramethylethylenediamine)lithium][di- $\mu$ -phenyl-bis(diphenylmagnesiato)] which is a dimer with bridging phenyl groups.<sup>138</sup> Another unusual example is the two crystals obtained out of a solution of bis(*p*-tolyl)magnesium in a *n*-hexane/THF mixture. A monomer and a dimer co-crystallised in a ratio of 1:2. This dimer also contained bridging aryl groups.<sup>128</sup>

For crown ether-diorganomagnesium complexes in the solid-state, those that have a diameter that is sized appropriately to encompass the diorganomagnesium appear to have a rotaxane or 'threaded' structure with the nearly linear  $R_2Mg$  through the center of the crown ether.<sup>130,132</sup> This is true even when the R groups are too large and bulky to directly infiltrate the crown.<sup>130</sup> In solution, however, the organomagnesium appears to coordinate to both the inside and the outside of the crown.<sup>130</sup> As well, the introduction of crown ethers to diorganomagnesiums seems to induce disproportionation to a magnesiate and cationic monoorganomagnesium-crown substance (see Scheme 2.4.2 below), which serves as an intermediate for the crown-threaded structure.<sup>130,131,132</sup>



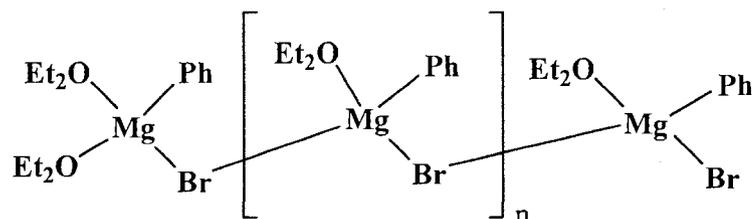
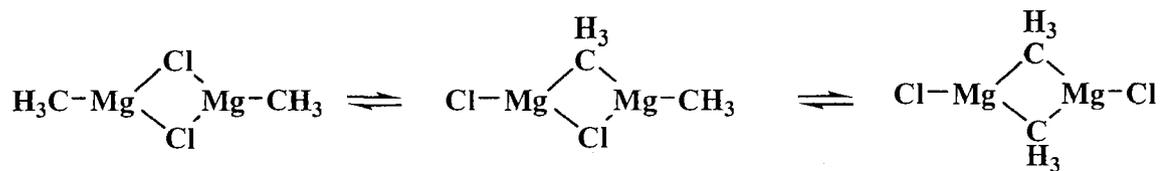
**Scheme 2.4.2:** An example of the addition of crown-ethers to induce disproportionation to magnesiate and cationic organomagnesium species (bottom right) as a transition state to the diorganomagnesium inclusion into the crown ether (bottom left).<sup>130,131</sup>

All of  $R_2Mg$ ,  $RMgX$  and  $MgX_2$  are solvated by electron donating portions of the solvents. In solid-state structures, the bond lengths between the magnesium center and the donor solvation sites are shorter for the dihalomagnesium than for the diorganomagnesium. For example, the bond distances in  $N,N,N',N',N''$ -pentamethyldiethylenetriamine (pmdta) complexes are on average more than 0.1 Å shorter in  $MgX_2$  (2.24 Å) than in  $R_2Mg$  (2.37 Å) for the same solvent. Otherwise, their structures are quite similar.<sup>98</sup> The differences are likely due to the fact that the bromo ligands are more electronegative,<sup>98</sup> and therefore more strongly bound to the Mg. This also implies a stronger bond interaction and that  $MgX_2$  is more acidic than  $R_2Mg$ . This trend has been demonstrated in gas-phase density functional theory (DFT) calculations as well, with the solvent-magnesium distance in  $RMgX$  found as intermediary between  $MgX_2$  and  $R_2Mg$ .<sup>98,120</sup> DFT calculations have also shown that magnesium compounds are solvated more strongly by THF than by diethyl ether and the solvent-Mg distances are longer for ether and shorter for THF.<sup>120</sup> Also, phenyl Grignard derivatives have calculated energies of solvation that are higher than for ethyl or methyl derivatives.<sup>120</sup>

In solution, the degree of association is dependent on the nature of R as well as the donor solvent.<sup>97</sup> The sterics of the R group as well as the solvent play a role in the solid-state structures.<sup>118</sup> The basicity of the solvent is established by the steric requirements as well as the electronic nature.<sup>118</sup> For instance, the dihalomagnesium species  $MgBr_2$  has been shown to be solvated by four THF molecules,<sup>120</sup> but only two diethyl ethers.<sup>118</sup> Optimised structures found using DFT calculations show diethyl ether exists in a 'propeller'-like shape leading to increased dimensions.<sup>120</sup> Solid-state structures may provide insight into their conformation in solution;<sup>97</sup> however, the solution structure may differ because of inter- and intramolecular forces in liquid phases.<sup>120</sup> Although many

aggregates are present in various equilibria in solution, the crystallisation conditions may selectively yield mono-, di-, or polymeric species.<sup>128</sup> The use of non-polar media may facilitate crystallisation of such isolates.<sup>128</sup> The concentration of such species in solution would also determine the ultimate crystal formed.<sup>118</sup>

For diarylmagnesiums, solutions in THF are associated with monomeric compounds even up to high concentrations.<sup>127</sup> The same is true for alkyl- and arylmagnesium halides even to concentrations as high as 3.5M,<sup>120</sup> whereas diorganomagnesiums in diethyl ether solutions have a varying degree of association dependent on the concentration. Higher concentrations lead to higher associations;<sup>128</sup> for example, solutions at concentrations below 0.1M are monomeric, while dimers are found between 0.5 and 1.0M.<sup>120</sup> This, in turn, shows that diethyl ether has a limited coordinating ability, as it cannot effectively compete with bridging groups at higher concentrations.<sup>128</sup> Whether these bridges are aryl or halide substituents, however, is unclear.<sup>120,128</sup> This appears to be at least partially dependent on the sterics of the organic groups. With respect to the formation of dimers and other aggregates, the difference between THF and diethyl ether for Grignard association behaviour is attributed to the difference in relative Lewis basicities of the VOCs.<sup>120</sup> These bridges effectively compete with the solvent molecules for solvation, and THF competes for these spaces better than diethyl ether.<sup>120</sup> The calculated solvation distances of THF or diethyl ether on RMgX compounds are shortest for X<sub>2</sub>Mg, longest for MgR<sub>2</sub>, and intermediate for RMgX, itself.<sup>120</sup>



**Scheme 2.4.3:** Two representations to demonstrate bridging halides: The upper in the form of a Schlenk equilibrium with bridging methyl groups as well;<sup>139</sup> the bottom a type of oligomer with donating solvent molecules inclusive.<sup>140</sup>

Magnesium compounds appear to prefer solvation by THF over diethyl ether as the calculated displacement reactions of diethyl ether by THF are all exothermic. The  $\Delta H$  was calculated at -3.8 kcal/mol for the first solvent molecule displacement and -9.2 kcal/mol for the second in diphenylmagnesium. The trends for other diorganomagnesiums organomagnesium halides, and dihalomagnesiums are similar.<sup>120</sup>

## **CHAPTER 3: The Thesis**

### **3.1 A Survey of Organomagnesium Reagents in Polymeric Solvents**

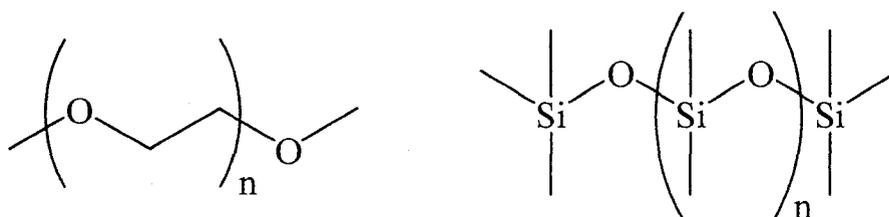
Hitherto, solvents and an important class of reagents, organomagnesium reagents, have been discussed. Hereafter the results of a survey-type study of diorganomagnesiums in certain 'greener' solvents will be presented and discussed as this area has been, until this point, surprisingly unexplored.

### **3.2 Research and Development**

Reactions with Grignard reagents are typically performed in THF or diethyl ether, both VOCs. While industrially these reactions have used less-volatile solvents such as butyl diglyme, it was unknown whether Grignard reagents would form persistent solutions with ether-substituent containing polymers. Some polymers can be perceived as 'greener' than glymes because their toxicities are lower and their volatilities, at a sufficiently high molecular weight, are negligible. This property could lead to recyclable systems with less overall waste. Finally, some polymers readily biodegrade as well.<sup>13</sup>

Poly(ethylene glycol) dimethyl ether (diM-PEG) and poly(dimethyl siloxane) trimethylsiloxy terminated (TMS-PDMS) were chosen for this study as they both are inexpensive polymers with low toxicity that are biodegradable under certain conditions. The end-capped versions are less biodegradable as that is where the microorganisms attack. These protected ends, however, are necessary when working with such strongly basic and reactive materials like organomagnesium reagents since capped polymers contain no obvious acidic protons. Both diM-PEG and TMS-PDMS contain the necessary

ether linkages to support organomagnesium reagents. Their inherent low cost and toxicities set these polymers apart from other ‘greener’ solvents such as ionic liquids.



**Figure 3.2.1: The polymers used in this study, diM-PEG and TMS-PDMS.**

PEG is a liquid up to an  $M_N$  of 800,<sup>73</sup> while PDMS is technically a liquid at an  $M_N$  of greater than 500 000, although the viscosity is extremely high. For a room temperature solvent, the useful viscosity maximum occurs for PDMS at a  $M_N$  around 60 000.<sup>87</sup> PDMS is sold by viscosity which is reflected in the abbreviated name. For instance TMS-PDMS T01.5 refers to a polymer with a kinematic viscosity of 1.5 centistoke (cSt). Kinematic viscosity is the liquid measure of volume flow.<sup>87</sup> The viscosity of the polymer can be determined by multiplying the kinematic viscosity by the density of the polymer.

The siloxane copolymers also used in this study were likewise chosen for their economical qualities but also to examine whether phenyl substituents along the backbone of the polymer would help to dissolve the organomagnesium, and to determine if copolymers had an inherent weakness at the end of each polymer block. Diethylene glycol dimethyl ether and 2-Me-THF are two additional solvents used in this thesis. They are also considered ‘greener’: diethylene glycol for being less volatile than ether or THF, and 2-Me-THF for having a higher boiling point and for being derived from a renewable resource. Diethyl ether was included for comparison.

**Table 3.2.1: List of solvents used in this survey.**

Name	Abbreviation
Poly(ethylene glycol) dimethyl ether $M_N$ 250	diM-PEG 250
Poly(ethylene glycol) dimethyl ether $M_N$ 2000	diM-PEG 2000
8-12%(phenylmethylsiloxane)-88-92%(dimethylsiloxane)copolymer	-
18-22%(diphenylsiloxane)-78-82%(dimethylsiloxane)copolymer	-
Poly(dimethylsiloxane) trimethylsiloxy end-capped T01.5	TMS-PDMS T01.5
Poly(dimethylsiloxane) trimethylsiloxy end-capped T1.5	TMS-PDMS T15
Diethylene glycol dimethyl ether	diglyme
2-Methyltetrahydrofuran	2-Me-THF
Diethyl ether	ether

Poly(ethylene glycol) can be dried through successive azeotropic distillations of the polymer with toluene to remove residual water.<sup>116</sup> This drying step has been demonstrated to enhance activity in reactions with Grignard reagents and iron nanoparticles when PEG was used as a stabilising agent in ethereal solvents.<sup>116</sup> PEG is hydrophilic and is soluble in water, toluene, ethanol, acetone and dichloromethane but insoluble in hexanes, diethyl ether, cyclohexane, and other hydrocarbons.<sup>73</sup> Diethylene glycol dimethyl ether was dried in an identical manner to poly(ethylene glycol), while the TMS-PDMS samples required the additional steps of a saturated sodium bicarbonate solution rinse, followed by a water rinse to ensure that all of the acid from the polymerisation had been removed. Failure to remove all of the acid could result in

reaction with the organomagnesium reagents. Three different kinematic viscosities of TMS-PDMS from two suppliers were used: 1.5cSt, 15cSt and ~5cSt (sold as  $M_w = 770$ ).

An attempt to formulate a solution of 3M PhMgBr in polymeric solvent was made. To do this, a Grignard solution of 3M phenylmagnesium bromide in diethyl ether was added dropwise to 50 mL of diM-PEG 250 under argon and at 0 °C. Over the course of the addition, the light yellow transparent polymer became green-grey and some precipitate was seen on the bottom of the flask. With more PhMgBr addition, the gel-like precipitate grew. After 25mL of PhMgBr addition, the congealed material in the flask had completely impeded stirring and had taken up most of the volume of the polymer. The precipitate was grey with a layer of yellow solution above it.

The polymer appeared to have cross-linked, and hence solidified, upon the addition of the ethereal Grignard reagent. Strongly donating solvents are known to shift the Schlenk equilibrium from the non-symmetric to the symmetric products, as is seen when dioxane is added to a Grignard reagent, for example. Solidification of the solution components of Grignard reagents does not occur, however, when the solvent is diethyl ether, THF, glymes or glycols, or the phosphonium IL, tetradecyl(trihexyl)phosphonium decanoate. Since the Grignard reagent only solidified in diM-PEG and not in the aforementioned solvents, it can be reasoned that the manner in which the molecules interact with the polymer is inherently different.

The polymer forms solvent-organomagnesium and solvent-halomagnesium complexes in a similar way as the other solvents. In the polymer however, all of the solvation sites are on long chains and when strongly coordinated to magnesium complexes, the polymers become entangled and lose their ability to flow. This contrasts the discrete molecular complexes of the Grignard reagent with ether, THF, diglyme and

IL which do not become detrimentally entangled, even at higher concentrations. In comparison, when diphenylmagnesium was added to the same polymer, diM-PEG 250, instead of forming a solid substance it dissolved into a light yellow solution.

The lack of bromine atom in diphenylmagnesium excludes the  $\text{RMgX}$  and  $\text{MgX}_2$  components of the Schlenk equilibrium and presents a less complicated system. As mentioned in previous sections, solvents bond more strongly to  $\text{MgX}_2$  than to  $\text{R}_2\text{Mg}$ , as is evidenced through shorter bond distances. The supposition that the solidification of diM-PEG 250 is caused by  $\text{MgX}_2$  was corroborated by the observation that the addition of a small amount of  $\text{MgBr}_2$  to diM-PEG 250 caused an observable increase in the viscosity of the polymer.

Grignard solutions were also added to trimethylsiloxy end-capped polydimethylsiloxanes and related copolymers in a similar manner, via dropwise addition, under argon at  $0^\circ\text{C}$ . These reactions, instead of solidifying, merely formed suspensions or bilayered mixtures, depending on the composition and viscosity of the polymer solvent. In the copolymers 8-12%(phenylmethylsiloxane)-88-92%(dimethylsiloxane)copolymer and 18-22%(diphenylsiloxane)-78-82%(dimethylsiloxane)copolymer, the addition of Grignard reagents caused grey-green suspensions to be formed in both. TMS-PDMS of weight average molecule weight ( $M_w$ ) 770 as well as TMS-PDMS T01.5 both formed two layers: a dark green bottom layer and a colourless, transparent upper layer while TMS-PDMS T15 formed a milky grey-green suspension. After the removal of ether via reduced pressure, all of the Grignard/polymer samples achieved a similar appearance, namely a dark gel in the bottom of the flask surrounded by transparent, colourless liquid polymer. Siloxanes do not donate electrons and stabilise the Grignard reagents as well as ether-type molecules,<sup>85</sup> which may also explain their reluctance to form a solution.

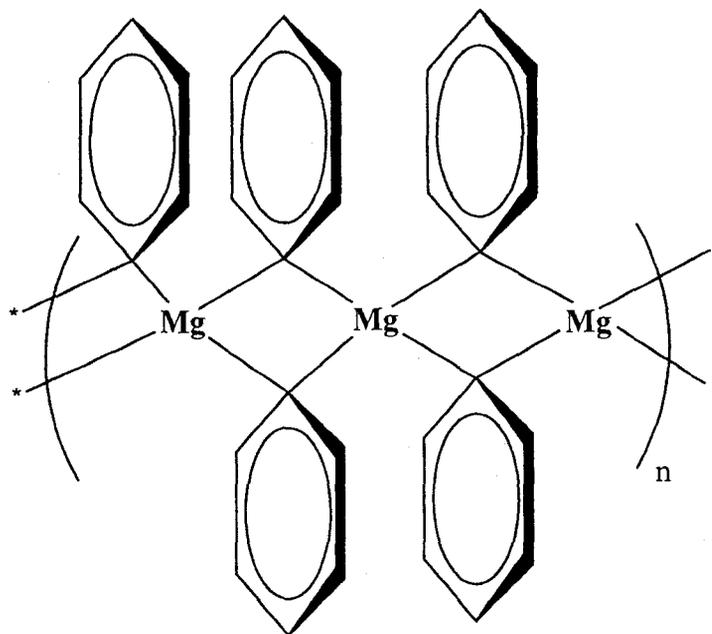
As Grignard reagents appeared to be unsuitable for further studies in polymeric solvents due to their propensity to form solids and layers, diorganomagnesium reagents were synthesised to determine if they would form solutions when added to the polymers. Diorganomagnesiums are one of the products on the symmetric side of the Schlenk equilibrium and are considered to be the reactive species of Grignard reagents in solution.<sup>75</sup> Diorganomagnesium reagents require a further synthetic step because they are often synthesised from Grignard reagents. This additional synthesis makes diorganomagnesium reagents more expensive.

Two prominent ways to prepare diorganomagnesiums are via a cross-coupling reaction with a diorganomercury, or the addition of a strongly donating reagent such as dioxane, to Grignard reagents to selectively precipitate and remove dihalomagnesium.<sup>98</sup> Mercury has been used less frequently in synthetic chemistry due to health concerns, so diorganomagnesiums were made by the use of dioxane precipitation.

Dioxane was added dropwise to a dilute solution of phenylmagnesium bromide in diethyl ether at 0 °C. After stirring for 24 hours, the grey-white precipitate was left to settle. After filtration, the pale yellow supernatant solution was put under reduced pressure to remove the solvent. The diphenylmagnesium remained as a light yellow powder. This was tested for halogen content with silver nitrate and was found to be halogen-free. Additionally, the diphenylmagnesium samples were analysed with <sup>1</sup>H NMR for residual ether.

As implied in earlier sections, in most crystal structures organomagnesium compounds have two or three solvent coordination sites; however, crystals for these studies are typically grown in a medium of excess solvent. If solvent is exhaustively

removed, the organomagnesium reagents form polymers in such a way to ensure the magnesium atom is four-coordinate, an ideal coordination number for magnesium.<sup>128</sup>



**Figure 3.2.2: The polymeric structure of solventless diphenylmagnesium.**<sup>128</sup>

The amount of the residual diethyl ether in the diorganomagnesium compounds was determined using  $^1\text{H}$  NMR.<sup>98</sup> All three samples used in this study were determined to have between 0.0176 and 0.790 ether molecules per magnesium center, substantially below the usual two ether molecules per magnesium found in crystal structures. The difference in ether solvation for the three samples is likely due to the lengths of time used to remove the solvent, the variation in strength of the vacuum pump, and the temperature of the water bath used to aid the solvent removal. These diphenylmagnesium samples were used in the following survey of reactions in alternative solvents.

### 3.3 Reactions of Diorganomagnesium Reagents in Alternative Media

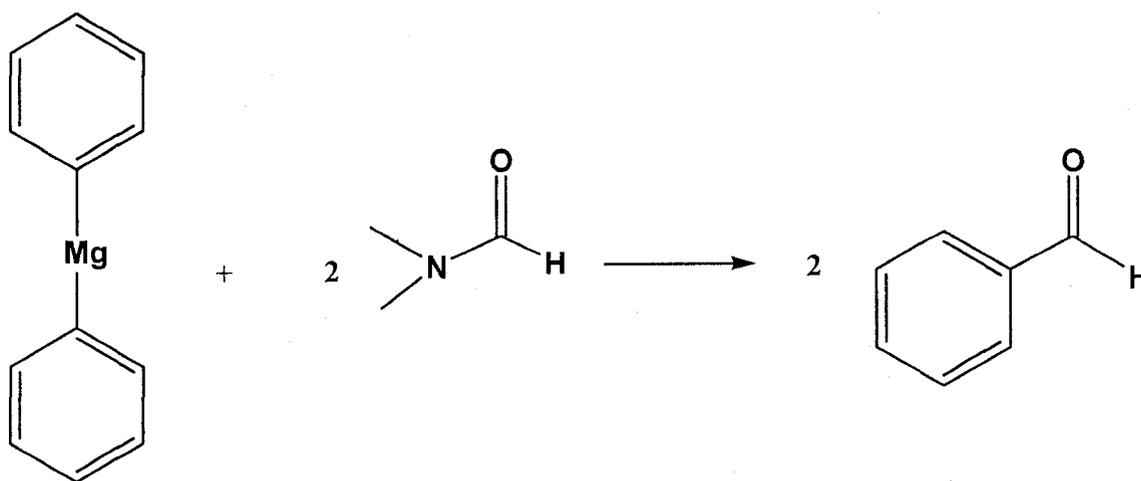
Reactions were performed with diphenylmagnesium in polymeric solvents and other alternative media. Following reaction completion, the products were extracted and

the organic extractant dried. Dilutions to a suitable concentration for quantitative analysis by Gas Chromatography Mass Spectrometry (GCMS) were performed. GCMS was used to analyse the reaction results for several reasons: the sample size is very small (approximately 1 mL) and the injected sample is measured in microlitres so there is less solvent waste than if a traditional column were to be used. As well, GCMS is very sensitive so even small amount of unexpected products can be detected while the mass spectrometer aids in identification. Even structural isomers can be detected and analysed by this method.

Diethyl ether was chosen as the extracting solvent as it was able to dissolve the predicted products, was inexpensive, and was compatible with the Polydimethylsiloxane column in the gas chromatograph. The ether solvent front eluted early from the GCMS, because of its low boiling point and molecular weight, so the large solvent peak did not cause a blind spot in an important area of the spectra. Diethyl ether is a VOC and moreover, possesses the poor health and safety-related qualities of high volatility and a low boiling point. With respect to Green Chemistry goals and the reduction of auxiliary substances such as extracting solvents, an organic solvent of some type was necessary to remove the products and unreacted reagents as polymers cannot be injected directly into a GCMS port. Processes can always be made 'greener', so in the future, a substance as  $\text{scCO}_2$  or another 'greener' solvent may replace the organic solvent and analysis may be done in a different manner.

The first test samples came from the reaction of diphenylmagnesium with dimethylformamide (DMF) in either diM-PEG or TMS-PDMS; however DMF eluted through the column very quickly and was found to reside in an unintegratable portion of the solvent front in the GCMS spectra. Although DMF was a reagent and not a product,

knowledge of the quantity of unreacted reagent would be useful for yield determinations. This particular study was abandoned in favour of one in which the leftover reagents could be better identified, even though based on initial olfactional indications, the reactions in TMS-PDMS were successful.



**Scheme 3.3.1: Diphenylmagnesium reacted with DMF to produce benzaldehyde.**

### 3.3.1 General Analysis Comments

To minimise variability, all reactions were performed three times and each extractant sample was injected into the GCMS thrice. Peak areas were analysed in an identical manner and were fitted to a calibration curve of peak areas and concentrations. The results of each run were averaged. Analytes in the mass spectrometer were characterised with a set of standards to match the fragmentation pattern and the retention times, unless otherwise noted. Benzene is the first compound of interest to elute off the GCMS column, and it lies on the tail end of the solvent front. While this position is integratable, it does make it difficult to measure reproducibly, resulting in higher standard deviations of repeated injections. In addition, unrepresented reactions that were quenched at

room temperature (not 0°C) suffered in terms of yields, with reduced quantities of desired product.

### **3.3.2 Extractions**

Each solvent was extracted once only and not necessarily into a solvent that was best suited for the extraction as ether was chosen mainly because it makes a satisfactory solvent for GCMS analysis, thus the overall yields were generally poor. To resolve this issue, tests of each solvent were made to extract known amounts of three analytes to determine the extraction coefficients. The analytes bromobenzene, benzaldehyde, and biphenyl were selected because they cover a range of the expected products in terms of molecular weight, dipolarity, and column retention times. A variety of extractant solvents were sampled and the systems with the best yields were the ones used to extract subsequent reactions.

**Table 3.3.1: Extraction of known amounts of analyte from alternative solvents.**

#	solvent	Extractant system	Bromobenzene			Benzaldehyde			Biphenyl		
			mmol added	mmol extracted	% recovered	mmol added	mmol extracted	% recovered	mmol added	mmol extracted	% recovered
1	diM-PEG 250	Ether / H <sub>2</sub> O	1.09	0.66	61	0.999	0.55	55	0.201	0.14	72
2	diM-PEG 250	0.5 ether, 0.5 hexanes/ H <sub>2</sub> O	1.10	0.52	48	1.03	0.37	36	0.214	0.12	55
3	diM-PEG 250	0.2 ether, 0.8 hexanes/ H <sub>2</sub> O	1.10	0.56	52	1.07	0.43	40	0.233	0.15	64
4	diM-PEG 250	hexanes/ H <sub>2</sub> O	1.13	0.74	65	9.60	0.44	46	0.182	0.13	72
5	diM-PEG 250	Ether / sat. NaCl soln.	1.13	0.73	65	1.04	0.670	64	0.240	0.17	69
6	diM-PEG 250	Ether / sat. NaCl soln.+ added Br <sub>2</sub>	1.15	0.66	58	0.971	0.48	49	0.220	0.15	67
7	diM-PEG 250	0.2 ether, 0.8 hexanes/ sat. NaCl soln.	1.21	1.1	90	0.942	0.77	81	0.246	0.26	1.1 E2
8	diM-PEG 250	0.2 ether, 0.8 hexanes / sat. NaCl soln. + added Br <sub>2</sub>	1.15	0.55	48	0.989	0.30	31	0.182	0.10	55
9	diM-PEG 250	Ether / 1M HCl	1.13	0.73	65	0.952	0.48	50	0.169	0.077	46
10	diglyme	Ether / sat. edta soln.	1.16	0.47	41	1.05	0.052	5.0	0.233	0.033	14
11	diglyme	Ether / 1M HCl	1.14	0.72	64	0.971	0.53	55	0.227	0.14	63
12	diglyme	0.2ether, 0.8 hexanes / sat. NaCl soln.	1.19	0.84	71	0.961	0.57	59	0.227	0.16	70
13	TMS-PDMS	Ether / sat. edta soln.	1.13	1.0	91	0.952	0.71	74	0.233	0.084	36
14	TMS-PDMS	Ether / 1M HCl	1.13	1.1	1.0 E2	0.999	0.86	86	0.188	0.19	1.0 E2
15	TMS-PDMS	0.2ether, 0.8 hexanes / sat. NaCl soln.	1.13	1.2	1.1 E2	0.961	0.87	90	0.214	0.20	94
16	2-Me-THF	Ether / 1M HCl	1.10	0.66	60	0.923	0.48	52	0.169	0.091	54
17	ether	Ether / 1M HCl	1.10	0.81	73	0.980	0.66	67	0.175	0.11	63

Note: edta = ethylenediaminetetraacetic acid

The extractant systems were analysed for their abilities to remove the desired analytes quantitatively. Products were most easily extracted from TMS-PDMS, likely

because it is hydrophobic and tends to have low solubility with many organic solvents. No fragmentation of solvents was found in the extraction tests.

The original extractions were rinsed with a solution of saturated sodium chloride solution to ensure that the aqueous layer was sufficiently ionic to encourage the organic molecules to migrate into the organic layer. This was later changed to 1M HCl as it was found to produce better extraction yields. As mentioned, these extraction tests were only performed once each, and were in most cases sampled by the GCMS once as well. This is in contrast to the reaction runs that were performed and sampled thrice each. So the precision in these numbers is diminished, however this test was designed to give only approximate values so that more comprehensive assessments for the reactions would be known.

The combination of diethyl ether and 1M HCl yielded the highest extraction values except in a few cases involving a 20/80 mixture of ether/hexanes with saturated sodium chloride solution. In the end, the ether and hydrochloric acid system was chosen for the remaining extractions for consistency. This prevented hexanes peaks in the GCMS spectra that might block analyte peaks, and was a simpler procedure overall.

**Table 3.3.2: The extractant systems and average recovery.**

Solvent	Extractant System	Average Recovery (%)
diM-PEG 250	Ether / 1M HCl	53.6
diglyme	Ether / 1M HCl	60.7
TMS-PDMS	Ether / 1M HCl	95.9
2-Me-THF	Ether / 1M HCl	55.3
ether	Ether / 1M HCl	68.0

The averages for the analyte recovery are given in the table above. It is clear that the recovery of different types of molecules is not identical. The average of recovery provides a rough estimate of how well compounds are removed from the solvents. It would have been impractical in this study to measure the recoveries of each analyte from each solvent.

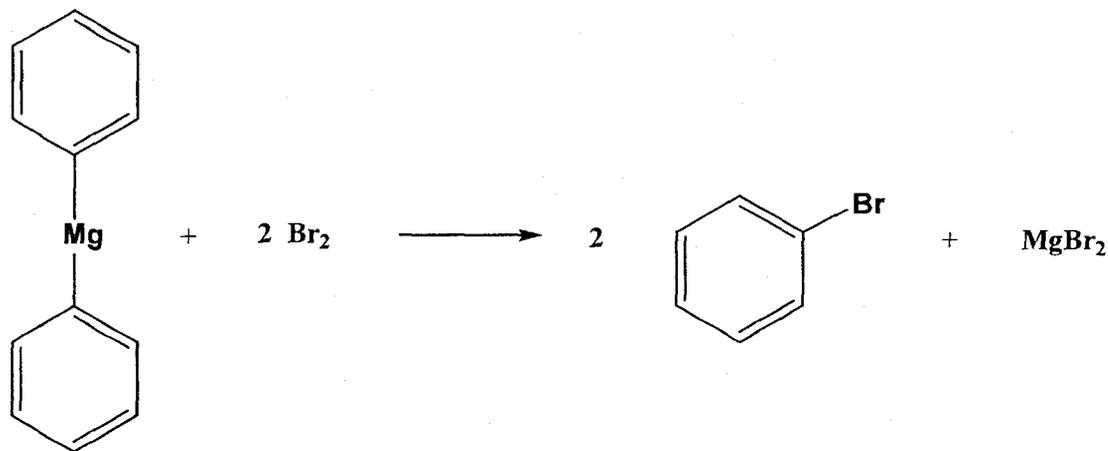
diM-PEG had the lowest recovery shown with the ether and hydrochloric acid extractant system. When PEG is dissolved in aqueous solution, it is considered a co-solvent and decreases the polarity of the solution.<sup>73</sup> In this way, the ether, and likely other organic molecules, will diffuse more easily into the PEG/aqueous layer. PEG is a known surfactant and may also encourage the transport of organics into the aqueous phase.<sup>72</sup> When PEG is dissolved in water, it may behave as a monophasic, homogeneously mixed solution, or as a biphasic mixture of free water and water-solvated polymer.<sup>73</sup>

In the cases of ether and 2-Me-THF, the products were initially in an organic phase so the addition of HCl was not strictly an extraction but rather a wash to remove any ionic molecules. Some product appears to have been lost in the washes reducing the overall yields.

There was no magnesium hydroxide or magnesium bromide added to any of these extractions. Magnesium hydroxide and magnesium bromide are possible alternative products from diorganomagnesium reactions caused by hydrolysis or bromination of the metal. Magnesium compounds complex with solvent molecules and these complexes may complicate with extractions. Extraction tests that involved the addition of magnesium hydroxide to the polymer before analyte addition (not shown) did not show a significant diminishment in extractant yield. In the actual experimental situation, however, the magnesium compounds may be more complex.

### 3.3.3 Bromine Quench of Diphenylmagnesium

The next set of reactions involved a bromine quench of diorganomagnesium reagents. Bromination can impart a bromine functionality with which to perform further reactions as bromine is a good leaving group. The general procedure involved placing 0.10g of diorganomagnesium in a flask with 10mL of solvent. Over ice and under argon, this was reacted with an excess of Br<sub>2</sub> to yield the desired product of bromobenzene. Water was added to ensure the organomagnesium was no longer reactive; then the products were rinsed with 1M HCl or a saturated NaCl solution, and then were extracted into diethyl ether. These organic samples were dried over MgSO<sub>4</sub>, filtered, then diluted and analysed by GCMS. The solvents used were TMS-PDMS T01.5, diM-PEG 250, 2-Me-THF, and diglyme. The results were compared to those that used diethyl ether as the solvent. The reaction scheme is shown below with the results summarised in the table beneath:



**Scheme 3.3.2: Bromine quench of diphenylmagnesium to produce bromobenzene.**

**Table 3.3.3: Reaction yields from quench of Ph<sub>2</sub>Mg with Br<sub>2</sub>**

Solvent	Reaction		Results					
	Ph <sub>2</sub> Mg mmol	Br <sub>2</sub> mmol	bromobenzene mmol	%	benzene mmol	%	biphenyl mmol	%
10mL diM-PEG- 250	.42	1.4	.00062	.07	.93	1.1E2	.024	5.6
TMS- PDMS	.42	1.4	.58	68	.53	63	.0053	1.3
diglyme	.42	1.4	1.1	1.3E2	.19	23	.036	8.4
2-MeTHF	.42	1.4	.64	75	.33	40	.05	6.1
Ether	.42	.98	.60	72	.062	7.4	.012	2.9

From the results in the above graph, it is clear that the data are unusual. For instance, in the row for the results for diglyme, there is a yield for bromobenzene of 130%. As only 0.42 moles of the limiting reagent, diphenylmagnesium, were added, then the maximum possible amount of bromobenzene is 0.84 moles. It is not possible that matter has been created so the only explanation is that there is a problem with the data even though steps were taken to minimise this, as outlined in the previous sections.

There are a number of places where errors could have been introduced into this system. For instance, the use of diethyl ether as extractant meant that the solvent was extremely volatile, especially under warm lab conditions. Although samples were left in sealed vials, there is still the possibility for the volatile solvent to evaporate and increase the concentration of the sample. Another way in which errors could have been introduced was through the use of small masses of reagents. The absolute error in a balance is the same whether measuring 10 grams or 0.10 grams although that error may comprise a greater percentage error in the smaller masses. Measurement errors would have been increased for each mass or volume measurement and dilution. In addition, during the mole determination for diphenylmagnesium, it was found that there were between 0.17 and 0.79 ether molecules per magnesium center. The ether molecules may not have been

spread homogeneously throughout the diphenylmagnesium sample which may have led to erroneous mole calculations for experiments performed with diphenylmagnesium. Also, a small amount of benzene was found in the diethyl ether used in the extractions which would have led to an increased millimolar yield of benzene in each sample. Even still, with all errors from measurements and dilutions carried through, the percentage error is only 8% on average, not enough to account for a result that is 30% above expected. There is another source of error, then, that is more difficult to account for and that appears to be from the GCMS itself which had been used to determine peak areas of analytes that were then correlated to a concentration of sample.

GCMS is an extremely sensitive technique. Temperature fluctuations, humidity, and vibrations can all introduce errors into a spectrum. Unfortunately, due to circumstances beyond control, the GCMS was used in less-than-desirable conditions. This led to peak areas which fluctuated in unpredictable ways. In others words, the peak areas obtained from experimental runs could not be accurately correlated to calibration curves so could not be properly quantified. This occurred even though repetitive sampling techniques were used to minimise variation. For example in the bromine quench of diphenylmagnesium in diethyl ether, the three peak areas obtained for the same sample (injected thrice into the GCMS) were 10496, 35142, and 9761. As peak areas were averaged before comparison to the calibration, the average of these three numbers is 18466.3. A Q-Test to reject outliers could not be performed as the number of values in the sample was so small. Standard deviation of the above values, a measure of how close the data is to the mean or a measure of precision, is 11795; a value that is greater than two of the original data. As the number of values in the data set is quite small, a confidence interval can be calculated. This provides a numerical value for the percentage likelihood

that a certain range will contain the true mean that may have been calculated incorrectly due to the small data set. For these three values at a confidence level at 50%, the true mean is  $18466 \pm 5209$  meaning that a deviation from the calculated mean of 5209 only has a 50% chance of being the true mean, which would eventually be converged upon as the number of data points increased. For a confidence level of 95%, the true mean is  $18466 \pm 21669$ . In other words, the variability in peak area measurements is extremely high even from the same sample vial when injected into the GCMS in succession.

The solution concentration to peak area correlation on which the quantifications were based also appears to drift over time. As the number of injected analytes increases in the GCMS, the baseline of the analyte signal increases which can, in turn, cause peak areas to artificially inflate. This can sometimes be remedied through a bake-out (heating the column to a high temperature and holding it for several hours). Other sources of error include the loss of products into the aqueous extraction layer, products that were gaseous or eluted before or with diethyl ether from the GCMS column rendering them invisible in the spectrum, or products that had high enough boiling points that they did not elute at all from the column.

When quantification is performed with the use of a GCMS, it is recommended that all samples and standards be run in as short a time as possible. While an effort was made to minimise sample waiting time, the length of the method for analysis was simply too long to ensure samples and calibrations were performed even within the same week. The method was designed to ensure maximum peak separation for quantification and began at a low temperature of 24 °C. The method was 26 minutes long but with the time for the column to re-cool between samples included, each injection was a total of 40 minutes. This meant that for three reactions each sampled three times, one set of data took six

hours to obtain (provided all equipment was working properly). Calibration curves, on the other hand, consist of ten standards each sampled three times, so a full calibration curve required twenty hours of sample time. Each quantified analyte was sampled separately to minimise interference with other analytes which meant that a significant amount of time passed between the calibration curve and reaction sample runs. The column sensitivity generally drifted over time, thus the experimental peak areas, when compared to the calibrations, did not yield accurate results.

For the above reasons, the yields that were obtained for this and other reactions only provide useful information when viewed as a ratio of products. Over the 6 hours it took for a set of reactions to be sampled by the GCMS, the drift would be within an acceptable range. Thus viewed horizontally across rows, the relative yields provide relative results. As such, tables with the yields will be provided along with the approximate ratios of products for each reaction set. As these experiments were meant as a survey of the potential for the use of liquid polymers as a solvent for diorganomagnesium reagents, the focus was for qualitative results rather than strict quantification.

**Table 3.3.4: Ratio yields from quench of Ph<sub>2</sub>Mg with Br<sub>2</sub>**

Solvent	Reaction		Results					
	Ph <sub>2</sub> Mg mmol	Br <sub>2</sub> mmol	bromobenzene mmol	ratio	benzene mmol	ratio	biphenyl mmol	ratio
10mL								
diM-PEG-250	.42	1.4	trace	0	.93	38	.024	1
TMS-PDMS	.42	1.4	.58	109	.53	100	.0053	1
diglyme	.42	1.4	1.1	15	.19	3	.036	1
2-MeTHF	.42	1.4	.64	14	.33	7	.05	1
Ether	.42	.98	.60	20	.062	2	.012	1

The ratios for the bromine quench of  $\text{Ph}_2\text{Mg}$  can be seen in Table 3.3.4. In the diM-PEG solvent, there was practically no conversion to the desired product of bromobenzene. Most of the sample was protonated to benzene but a small amount of biphenyl Wurtz coupling product (formed through a radical mechanism) was found as well. Diglyme, 2-Me-THF and diethyl ether all showed the major product to be bromobenzene while the reaction in TMS-PDMS produced benzene and bromobenzene in near equal molar amounts. Biphenyl yields were always 5% or less than the total reaction yields.

There is no proper vertical comparison that can be made with the above table. For example, it does not make sense to compare the bromobenzene ratios from the diglyme and 2-Me-THF solvent because the mole amounts were different. The solvent extracted with different partition coefficients so in this case, ratios are useful constructs only when viewed horizontally.

In addition to the main expected products of bromobenzene, benzene, and biphenyl, some other chemicals were found in the extractant liquid. These are shown in the table below.

**Table 3.3.5: Other non-quantified extractants from the quench of  $\text{Ph}_2\text{Mg}$  with  $\text{Br}_2$**

Solvent	Other Products
All solvents	Toluene, BHT, xylenes
diM-PEG-250	2-bromotoluene, 4-bromotoluene, Br-ether fragments
TMS-PDMS	PDMS fragments, 2-bromotoluene, 4-bromotoluene, 1,4-dibromobenzene, 1,2-dibromobenzene
diglyme	diglyme, Br-glycol fragments 2-bromotoluene, 3-bromotoluene, 4-bromotoluene, $\alpha$ -bromotoluene
2-MeTHF	2-Me-THF, Br-THF
Ether	-

Toluene, BHT and xylenes were found in all samples. Xylenes (*p*-xylene, *o*-xylene and *m*-xylene) came from the diethyl ether used to make up the GCMS samples.

BHT (butylated hydroxytoluene) was found in both the GCMS grade diethyl ether and the diethyl ether that was used as extractant. BHT is often included as a stabiliser in ethers as it prevents the build-up of peroxides which can be explosively reactive. Toluene was found in small amounts in the ether used for extracting, but it was also in much larger volumes in diglyme, TMS-PDMS, and diM-PEG 250 as it was leftover from the drying step. In diglyme, TMS-PDMS, and diM-PEG 250, there was enough toluene that it reacted with the bromine and formed various bromotoluene products, albeit in low quality (based on approximate peak area). In TMS-PDMS, dibromobenzenes were also found. No benzene was found in the TMS-PDMS so this dibromobenzene had to come from bromobenzene that underwent a second bromination. Dibrominated benzenes were not seen in any other samples.

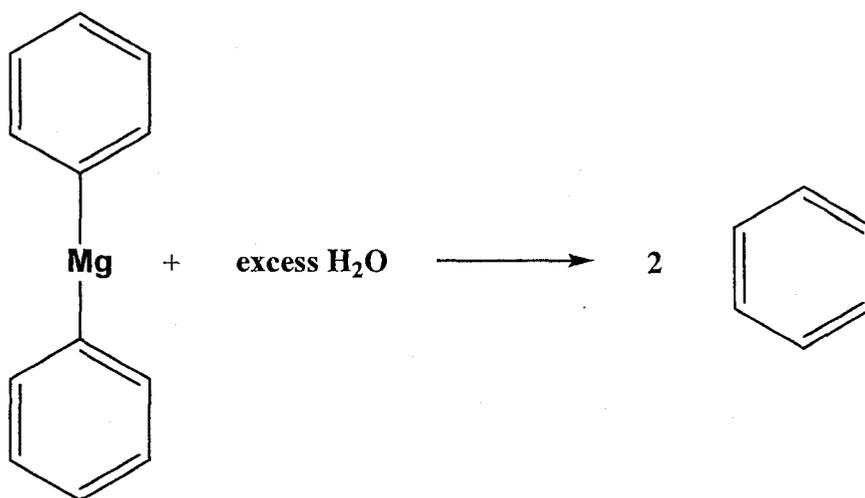
In addition to the brominated toluene and benzenes, some solvent fragmentation and bromination of solvents was also found. In the sample with diM-PEG as solvent, brominated ether fragments were found. In TMS-PDMS, there were both brominated and non-brominated siloxane fragments all between three and five repeating units in size. Finally in diglyme, there were brominated glycol fragments. These products were assigned through mass spectrum fragmentation patterns only, not through retention times and were not quantified. No solvent fragmentation was found in the 2-Me-THF or diethyl ether samples.

Recalling the previous extractant section, there was no solvent fragmentation in any samples. This indicates that the fragmentation is caused either by the bromine addition, or the diphenylmagnesium. The extractant system cannot be the cause of this solvent fragmentation because all samples were extracted in the same way and none of the extraction test samples showed solvent fragmentation.

At this point the cause of the solvent fragmentation was either the diphenylmagnesium, or the bromine. The next set of reactions, the water quench of diphenylmagnesium, was performed to determine the cause of the solvent breakdown. If the solvent continued to fragment in the polymers and diglyme, then the cause of the fragmentation would be at least partially from the diphenylmagnesium. If, however, no fragmentation occurred in the water quench reactions, then the source would be bromine.

### 3.3.4 Water Quench of Diphenylmagnesium

This set of reactions was devised to see if the diorganomagnesiums would have any effect on the solvents themselves: *i.e.* if they would cause fragmentation or coupling.



Scheme 3.3.3: Quench of diorganomagnesium with water to produce benzene.

Table 3.3.6: Reaction yields from the quench of diphenylmagnesium with water.

Solvent	Reaction		Results			
	Ph <sub>2</sub> Mg mmol	H <sub>2</sub> O mmol	benzene mmol	%	biphenyl mmol	%
diM-PEG-250	.48	Excess	.63	61	.017	4.1
TMS-PDMS T01.5	.48	Excess	.37	38	.017	3.6
diglyme	.42	Excess	.34	41	.011	2.5
2-MeTHF	.48	Excess	.54	56	.023	4.9
Ether	.48	Excess	.64	66	.014	3.0

The ratio results are provided in the table below.

**Table 3.3.7: Ratio yields from the quench of diphenylmagnesium with water.**

Solvent	Reaction		Results			
	Ph <sub>2</sub> Mg mmol	H <sub>2</sub> O mmol	benzene mmol	%	biphenyl mmol	%
diM-PEG-250	.48	Excess	.63	15	.017	1
TMS-PDMS T01.5	.48	Excess	.37	10	.017	1
diglyme	.42	Excess	.34	16	.011	1
2-MeTHF	.48	Excess	.54	11	.023	1
Ether	.48	Excess	.64	22	.014	1

All of the reactions produced the expected benzene as the major product. The coupling product, biphenyl, was seen as high as 9% of the total ratio value but was mainly a side-product. Of note are the products that were extracted beyond benzene and biphenyl. These results are in Table 3.3.8.

**Table 3.3.8: Other non-quantified extractants from the quench of Ph<sub>2</sub>Mg with water.**

Solvent	Other Products
All solvents	Toluene, BHT, xylenes
diM-PEG-250	-
TMS-PDMS	PDMS fragments
diglyme	diglyme
2-MeTHF	2-Me-THF, 2-phenylethanol
Ether	2-phenylethanol, phenol

The reactions in diethyl ether and 2-methyltetrahydrofuran produced some unexpected products. Phenol was found in the diethyl ether runs (average result: 0.0109 millimoles or 1.1%) and 2-phenylethanol. Both of these have been confirmed through retention times and the mass spectrometry fragmentation pattern. The origin of the 2-phenylethanol is unknown. The only other sample it was found in was from the addition cyclopentanone to diphenylmagnesium in diM-PEG 250. The peak areas for all three were quite small, bordering on being undetected, so it is possible that this is merely an extracting solvent or column impurity.

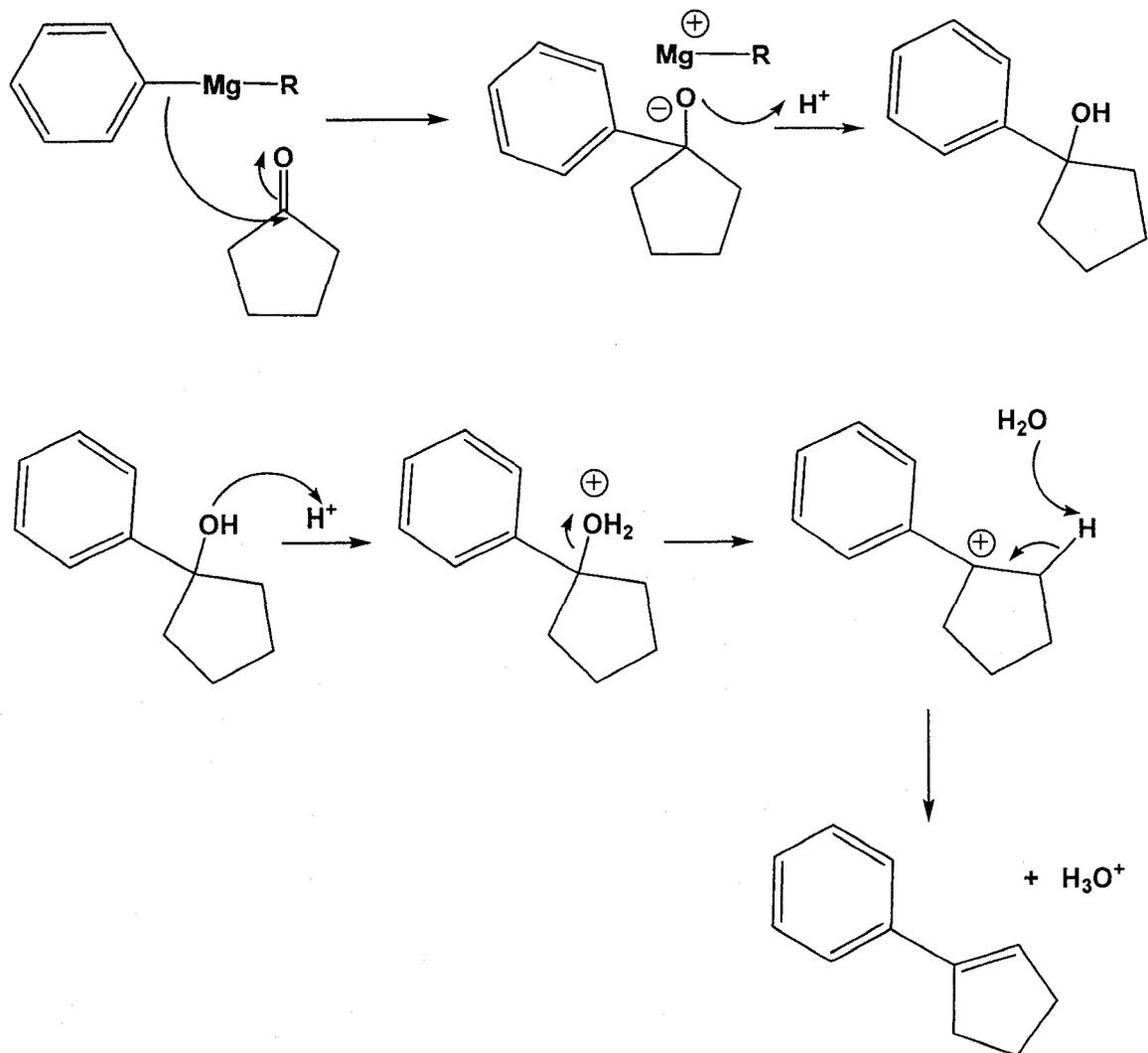
Phenol is likely produced from diphenylmagnesium upon exposure to oxygen. Phenol was found in all three samples with diethyl ether as solvent even though the ether was anhydrous and opened only within an atmosphere of argon.

The toluene in all extractions except diethyl ether can be sourced to the drying/distillation preparation steps, or the extractant ether, which was shown to contain some toluene and benzene. Some diglyme was also extracted with all diglyme reactions. This was not affected by the presence of magnesium. BHT and xylenes were found in all samples as well.

Of note is the lack of solvent fragmentation for diM-PEG 250 and diglyme. There were, however, fragments of TMS-PDMS similar to those found from the bromine quench reaction of diphenylmagnesium. This suggests that the fragmentation in the previous and subsequent PDMS reactions was caused by the diorganomagnesium itself and not the organic products, bromine, or extractant method.

### **3.3.5 Reactions of Diphenylmagnesium with Cyclopentanone**

Cyclopentanone is known to react with phenylmagnesium bromide to form the bicyclic molecule, cyclopenten-1-yl-benzene as shown in the scheme below.<sup>141</sup> Therefore, it was selected as a straightforward example of organomagnesium reactivity. This turned out to be not strictly true as several side reactions were found to have occurred which outperformed the desired main reaction in terms of yield. Some of the additional products, besides the anticipated benzene and biphenyl, were the entirely unexpected 2-cyclopentylidene-cyclopentanone, and what has been identified as 1-phenyl-1-cyclopentanol, an intermediate in the formation of cyclopenten-1-yl-benzene.



Scheme 3.3.4: Mechanism for the reaction of diphenylmagnesium with cyclopentanone and subsequent dehydration.

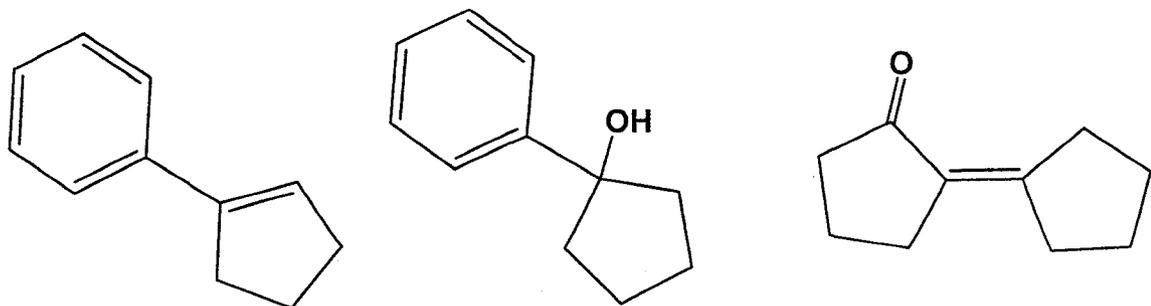


Figure 3.3.1: Products from the addition of cyclopentanone to biphenyl from left to right: cyclopenten-1-yl-benzene, 1-phenyl-1-cyclopentanol, and 2-cyclopentylidene-cyclopentanone.

**Table 3.3.9: Reaction yields from the reaction of diphenylmagnesium with cyclopentanone.**

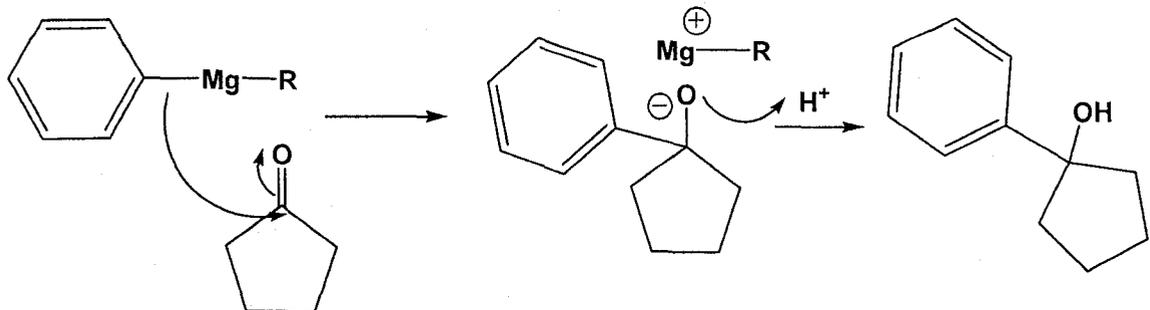
Solvent	Reaction		Results										
	Ph <sub>2</sub> Mg mmol	Cyclopentanone mmol	Benzene mmol	%	Unreacted cyclopentanone mmol	%	cyclopenten-1-yl-benzene mmol	%	Biphenyl mmol	%	1-phenyl-1-cyclopentanol	2-cyclopentylidene-cyclopentanone mmol	%
diM-PEG-250	.48	1.1	.75	78	.17	15	-	-	.014	3.0	-	-	-
TMS-PDMS	.42	1.1	.35	42	.27	24	.0060	.71	.021*	3.8*	yes	.16	28
diglyme	.42	1.1	.071	8.4	.16	14	.012	1.5	.043*	10	yes	.076	13
2-MeTHF	.48	1.1	.64	66	.17	15	-	-	small		yes	.091	16
Ether	.48	1.1	.58	60	.18	15	.0092	1.0	small		yes	.076	14
PEG 2000 80 °C	.48	1.1	.48	50	-	-	.093	9.6	.011	2.3	-	.20	35
PEG 2000 47 days of air exposure, 80 °C	.48	1.1	-	-	.20	17	-	-	.024	5.0	-	-	-
diM-PEG 250, 80 °C	.48	1.1	.42	44	.42	37	-	-	.024	4.9	-	-	-
diglyme, 80 °C	.42	1.1	.082	9.7	.022	1.9	.018	2.1	small		yes	.26	46
TMS-PDMS, 80 °C	.42	1.1	6.6	78	.013	1.2	-	-	.013	3.0	yes	.19	33

Some of the peaks in the GCMS spectra were too small to be integrated, and thus could not be quantitatively determined. These are noted in the table above as 'small'. There was also some peak overlap between the biphenyl and the 1-phenyl-1-cyclopentanol which could not be remedied. Attempts with slower GCMS runs in the disputed region would also not separate enough for quantitative determination. Results with asterisks in the table above are those that were estimated based on the total area of the mixed peak, and the portion that was comprised of biphenyl and 1-phenyl-1-cyclopentanol. 1-phenyl-1-cyclopentanol was, however, a major product in all of the reactions in which it was found.

**Table 3.3.10: Ratio yields from the reaction of diphenylmagnesium with cyclopentanone.**

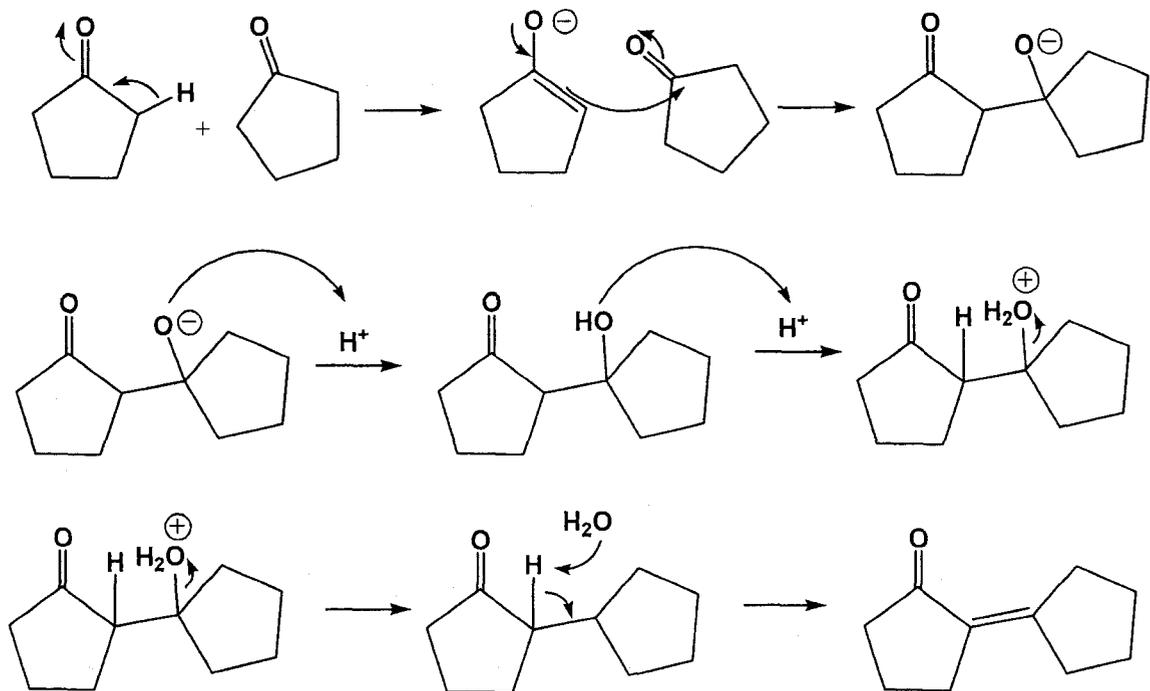
Solvent	Reaction		Results										
	Ph <sub>2</sub> Mg mmol	Cyclopentanone mmol	Benzene mmol	ratio	Unreacted cyclopentanone mmol	ratio	cyclopenten-1-yl-benzene mmol	ratio	Biphenyl mmol	ratio	1-phenyl-1-cyclopentanol	2-cyclopentylidene-cyclopentanone mmol	ratio
diM-PEG-250	.48	1.1	.75	26	.17	5	-	-	.014	1	-	-	-
TMS-PDMS	.42	1.1	.35	60	.27	34	.0060	1	.021*	5	yes	.16	40
diglyme	.42	1.1	.071	6	.16	9	.012	1	.043*	7	yes	.076	9
2-MeTHF	.48	1.1	.64	4.4	.17	1	-	-	small	0	yes	.091	1
Ether	.48	1.1	.58	60	.18	15	.0092	1	small		yes	.076	14
PEG 2000 80 °C	.48	1.1	.48	22	-	-	.093	4	.011	1	-	.20	15
PEG 2000 47 days of air exposure, 80 °C	.48	1.1	-	-	.20	1	-	-	.024	3	-	-	-
diM-PEG 250, 80 °C	.48	1.1	.42	9	.42	8	-	-	.024	1	-	-	-
diglyme, 80 °C	.42	1.1	.082	5	.022	1	.018	1	small		yes	.26	23
TMS-PDMS, 80 °C	.42	1.1	6.6	65	.013	1	-	-	.013	2	yes	.19	27

1-Phenyl-1-cyclopentanol was confirmed through retention time, and has been characterised through the MS fragmentation pattern. Unfortunately, as a standard in diethyl ether, 1-phenyl-1-cyclopentanol rapidly converts to cyclopenten-1-yl-benzene within a couple of hours. Therefore a calibration curve could not be made. The presence of this molecule is noted (by 'yes'), but not the quantity. As stated above, however, when found it was a major product. 1-Phenyl-1-cyclopentanol is the expected product that would be obtained in the reaction of cyclopentanone with diphenylmagnesium before dehydration.



**Scheme 3.3.5: The product of diphenylmagnesium with cyclopentanone without dehydration.**

In these reactions unreacted cyclopentanone was recovered. The fate of the cyclopentanone was to remain unreacted, to form cyclopenten-1-yl-benzene or 1-phenyl-1-cyclopentanol with the phenyl substituent from diphenylmagnesium, or to self-react to form 2-cyclopentylidene-cyclopentanone. The 2-cyclopentylidene-cyclopentanone was formed through an Aldol condensation as depicted in the scheme below. In some ways, it is not surprising, as heat and the presence of an acid or base tend to bring about these kinds of reactions.<sup>112</sup>



**Scheme 3.3.6:** The production of 2-cyclopentylidene-cyclopentanone via Aldol condensation.

For dimethyl-capped PEG 250, the major product was benzene. There was some biphenyl and unreacted cyclopentanone but none of the desired cyclopenten-1-yl-benzene product nor the alcohol or 2-cyclopentylidene-cyclopentanone coupling product.

The reactions in diglyme and TMS-PDMS both contained a very small amount of cyclopenten-1-yl-benzene, unreacted cyclopentanone, a small amount of biphenyl, and 2-cyclopentylidene-cyclopentanone and 1-phenyl-1-cyclopentanol as major products. TMS-PDMS also contained a substantial amount of benzene. Interestingly, the ratios (when compared horizontally) between 2-cyclopentylidene-cyclopentanone and unreacted cyclopentanone are similar.

The reaction in 2-Me-THF produced mainly benzene and 1-phenyl-1-cyclopentanol, which was similar to the results in diethyl ether although the reaction in 2-Me-THF contained none of the desired cyclopenten-1-yl-benzene product.

One of the interesting reactions from Table 3.3.10 was of that performed in diM-PEG 2000, which is a higher molecular weight polymer that is a waxy solid at room temperature and requires heating to 80 °C to be used as a reaction medium. In an analogous method to the rhodium catalyst encapsulation in PEG 1500 from the Jessop lab,<sup>13</sup> the diM-PEG 2000 was tested as a possible storage medium for diphenylmagnesium. In two separate reactions, approximately 10mL of diM-PEG 2000 was melted and then 0.10 g diphenylmagnesium was added to form a solution. One had cyclopentanone added to perform the desired organomagnesium reaction, while the other was left to cool with the diphenylmagnesium reagent dissolved inside. When it cooled to room temperature it resolidified. The flask was then opened to the atmosphere and was left exposed for 47 days, after which it was reheated under argon and reacted with cyclopentanone in the same way as the other samples had been previously. Both samples were extracted with hexanes and later diluted with diethyl ether as these systems required warm extractions that the low boiling diethyl ether would not tolerate in the liquid phase.

The diM-PEG 2000 polymer did not successfully encapsulate and protect diphenylmagnesium from atmospheric exposure. No phenyl-derived by-products other than biphenyl were observed. The most likely product from diphenylmagnesium exposure to the atmosphere is benzene, although none was found in the GCMS spectrum. Before heating the solid sample after the 47 days of exposure, it was placed under vacuum and purged with argon three times to ensure moisture removal. If, in the humid environment, hygroscopic PEG had absorbed enough water from the atmosphere, it may have become porous and the benzene could have been removed in the vacuum steps. Obviously, porosity is not a desirable trait for an encapsulation polymer.

diM-PEG 2000 was better than diM-PEG 250 in terms of solvent as it had a higher yield of the desired cyclopenten-1-yl-benzene product; the highest yield of all of the other solvents at 9.6%. To determine if the higher yield of cyclopenten-1-yl-benzene was brought about through the necessary heating of the solid-at-room-temperature polymer, the reactions with diglyme, diM-PEG 250, and TMS-PDMS were each repeated once at 80 °C. Only with diglyme as solvent at 80 °C was any cyclopenten-1-yl-benzene observed to speak of, present in 2.1% of anticipated yield. However, 1-Phenyl-1-cyclopentanol was found in both the TMS-PDMS and diglyme reaction samples in large yields. Essentially, TMS-PDMS and diglyme reacted similarly at room temperature and at 80 °C with the only difference being a slightly enhanced amount of benzene at the higher temperature.

As it turns out, while diM-PEG 2000 contained no 1-phenyl-1-cyclopentanol, the 80 °C samples from both TMS-PDMS and diglyme both contained this molecule in large amounts. (GCMS peak areas of ~130000 and 95000 respectively). If the peak response for these were the same as cyclopenten-1-yl-benzene, this would lead to yields of 0.42mmol and 0.16mmol respectively, which corresponds to approximately 50% and 38% yield before even taking into account deficiencies in extraction. As stated earlier, the attempt to form a calibration curve for 1-phenyl-1-cyclopentanol failed because in diethyl ether, it rapidly dehydrates to cyclopenten-1-yl-benzene before sampling can be completed.

It was postulated that 1-phenyl-1-cyclopentanol could have been a major product if the reactions were not made sufficiently acidic to bring about the dehydration step to turn 1-phenyl-1-cyclopentanol to cyclopenten-1-yl-benzene. While hydrochloric acid was used in the extraction steps it was thought that it may have been too late to affect

conversion from the alcohol to the bicyclic hydrocarbon. However, in reactions that were quenched with a saturated solution of ammonium chloride instead of water, (not presented here) there was virtually no difference in the ratios of reaction products. Quenching with either water or acid, in this case, appears to make no difference to the reaction products so there must have been an additional factor that prevented the 1-phenyl-cyclopentanol from dehydrating in the alternative solvent reactions as the dehydration occurs so readily in diethyl ether alone.

**Table 3.3.11: Other non-quantified extractants from the addition of cyclopentanone to Ph<sub>2</sub>Mg.**

Solvent	Other Products
All solvents	Toluene, BHT, xylenes
diM-PEG-250	-
TMS-PDMS	PDMS fragments
diglyme	diglyme
2-MeTHF	2-Me-THF
Ether	-
PEG 2000 80 °C	Hexanes
PEG 2000 one month of air exposure, 80 °C	Hexanes
diM-PEG 250, 80 °C	2-phenylalcohol
diglyme, 80 °C	diglyme
TMS-PDMS, 80 °C	PDMS fragments

There were some additional products found, namely the 2-phenylethanol in the sample run in diM-PEG at 80 °C of which the source is unknown, and hexanes which was used to extract the diM-PEG 2000 samples as they were only liquid at a high temperature so the use of low-boiling diethyl ether seemed unwise. Diglyme and 2-Me-THF were found in the extractions as well as TMS-PDMS fragments.

### 3.4 Discussion and Conclusions

Polymeric solvents are not simple replacement solvents that can be substituted for traditional molecular solvents in a straightforward manner, even though the structural

relationship between PEGs and diethyl ether and glymes is evident. The associations that occur between the solvent and organomagnesium reagents are acceptable when the complexes are between different discrete molecules, but appear to hinder reactions when these associations are with a polymer chain with many solvating sites.

Poly(ethylene glycol) performed very poorly with respect to all of the other solvents, even diglyme, which can be viewed as a very short PEG surrogate. It could be that the end-caps on the polymer were not complete exposing acidic protons that could react with the organomagnesium reagent. Infrared spectra were taken of the polymeric and diglyme solvents and OH absorptions were found in small amounts in all samples except TMS-PDMS which showed no absorption activity in that region. The reactions did tend to work in diglyme even though the infrared spectrum showed some hydroxyl groups but did not in diM-PEG 250. It is also possible that the diM-PEG contained water even after three flushes with toluene and evacuation with heat, although this process was taken from the literature and was found to be acceptable in an iron-nanoparticle and aryl – Grignard system.<sup>116</sup> As PEG is a viscous polymer, it could also be that the viscosity and likely chain entanglements prevented the reactants from reaching the magnesium centre for reaction. Perhaps a longer reaction time would have compensated for this although the diM-PEG 2000 polymer was significantly more viscous than diM-PEG 250 at 80 °C and the desired reactivity in the higher weight polymer was greater.

It is possible that PEG is simply unsuitable as a reaction medium for diorganomagnesiums: There is evidence from iron-catalysed cross-coupling reactions with Grignard reagents that too large an addition of PEG to an ethereal reaction solution reduces the yield to zero.<sup>116</sup>

The best solvents for Grignard reagents are not necessarily those with the highest levels of electron donation. Instead it is the ones that solvate enough to prevent the Grignard from decomposing while still binding loosely enough to allow the magnesium centre to bind elsewhere for reactions. For example, 1,4-dioxane is not a good solvent if one wishes to study a system with the full Schlenk equilibrium as dioxane will form an irreversible bond to  $MgX_2$  and eliminate it from solution as a precipitate. The solvation by solvents to  $MgX_2$  is much greater than to a diorganomagnesium, as has been evidenced in crystallographic and computational studies.<sup>98,120</sup>

The basicity and the donation ability of glyme is greater than THF, which itself is greater than ether. While the absolute donation ability of PEG is not known, if the trends between the number of solvation sites and basicity continue, PEG may solvate more strongly than diglyme in which case it would require more energy to displace the solvation for reaction. This can be seen in the case when PEG 250, dimethoxyethane(DME) and diglyme were added as reaction rate enhancers to a reaction mixture of  $iPrMgCl \cdot LiCl$  in THF.<sup>75</sup> In a reaction with 4-bromoanisole, PEG provided the smallest amount of conversion enhancement at 55% while glyme and DME provided 60 and 70% conversions, respectively.<sup>75</sup>

The mechanism for these enhancements was thought to be the selective complexation of the  $MgCl_2$  with the additive; however it is possible that the additive affected the non-halo compound as well. The amount of PEG in these systems was only 10% by volume whereas in a solution comprised almost exclusively of PEG, such as when PEG is used as the solvent, these effects may be enhanced.<sup>75</sup> It appears that the donating ability of PEG as well as the polymer structure influence the outcome of these

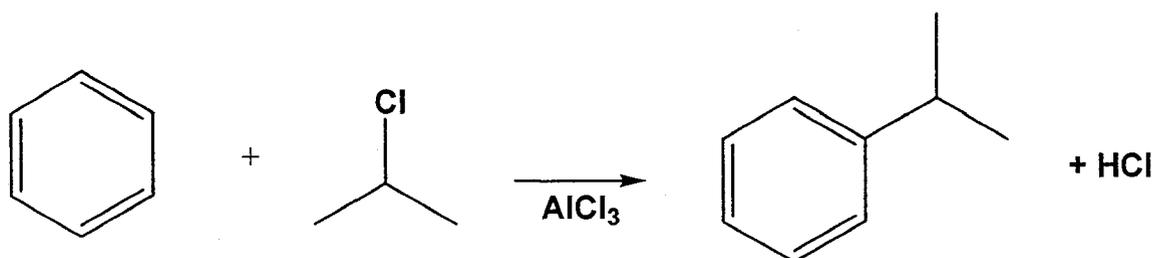
reactions as the sterics of the polymer may prevent reactive molecules from reaching the magnesium centre.

TMS-PDMS was a surprisingly good solvent for reactions with diorganomagnesium reagents, especially since they did not dissolve the reagent. Perhaps this was a contributing factor as to why it performed better than in diM-PEG, because the magnesium was simply more accessible for reaction, avoiding interaction with the polymer chain. The work-up from TMS-PDMS was facile and had the reagents not been so strongly basic, there would have been a lesser degree of polymer degradation, perhaps even a complete lack of it, which is necessary if the polymer is to be recycled, an ultimate goal for many Green Chemical systems.

### **3.5 Future Directions**

TMS-PDMS was the polymeric solvent that gave the most promise because extraction was simple and high yielding, and it possessed the properties of non-volatility and potential for biodegradability that made it appealing in the first place. It was unable to form solutions with the diorganomagnesium reagents but suspensions were persistent for several hours. The PDMS did suffer from some degradation and appears to degrade into cyclic siloxanes in the presence of other strong bases like sodium hydroxide and potassium hydroxide. Thus, PDMS would be more suitable as a solvent for acidic reactions such as the Friedel-Crafts reactions that use the Lewis-acid catalyst,  $\text{AlCl}_3$ . PDMS is hydrophobic, which is a useful solvent property when  $\text{H}_2\text{O}$  exclusion is necessary to prevent the formation of hazardous byproducts. Some siloxane polymers also contain groups along the polymer backbone that may assist in the dissolution of organic molecules: phenyl rings or straight-chain hydrocarbons. If the reagents are not strongly

complexed, dissolution in the polymer solvent could lead to greater reactivity through higher surface areas.



**Scheme 3.5.1: A general example of a Friedel-Crafts alkylation reaction.**

As diM-PEG was discovered to act as a decidedly poor solvent for Grignard and diorganomagnesium reagents, further exploration into different organomagnesium reagents (with different organic and halide groups) seems unnecessary. Rather, there are a variety of other reactions that could still be investigated with diM-PEG, or uncapped PEG as solvent. PEG is preferable to diM-PEG because it biodegrades faster and is less expensive. There are many organic reactions that have not been performed in polymeric solvents. Again, Friedel-Crafts reactions may be an interesting test reaction as this reaction has not been performed in polymeric solvents, according to SciFinder. PEG of higher molecular weight is easier to extract from, if using VOCs. Further, the extractant processes currently performed by VOCs could be replaced with a more benign solvent like  $\text{scCO}_2$ .

## **3.6 Methods and Procedure**

### **3.6.1 Chemicals and Equipment**

All solvents and reagents were purchased from commercial sources and used as received, with the following exceptions: the solvents poly(ethylene glycol), poly(dimethyl siloxane) and diethylene glycol dimethyl ether were dried according to the procedures

described below. Cyclopentanone was distilled and stored in an argon atmosphere. An atmosphere of argon was used for all reactions unless otherwise indicated.

A Varian 3800 Gas Chromatograph coupled to a Varian Saturn 2000 Mass Spectrometer with a Factor Four Varian capillary column (5ms, 5% poly(phenylmethyl siloxane) and 95% poly(dimethylsiloxane)) was used for analysis. This had a Varian CP 8400 autosampler. Split injection was used as well as a carrier gas of helium.

### 3.6.2 Experimental

#### *Drying of diM-PEG 250*

Dimethyl-capped poly(ethylene glycol) of  $M_N \sim 250$  (100 mL) was dried by adding 50 mL of toluene and removing it under vacuum. This was repeated two additional times then was left under dynamic vacuum at room temperature for 8 hours to ensure exhaustive removal.

#### *Drying of diM-PEG 2000*

The diM-PEG 2000 was solid at room temperature so required heating to 100 °C to liquefy. This was held under vacuum at 100 °C for 8 hours, then was allowed to cool and kept under dynamic vacuum overnight. It was stored under an argon atmosphere.

#### *Drying of TMS-PDMS*

100 mL of TMS-PDMS (T01.5, viscosity 1.5cSt) was placed in a beaker and 20 mL of saturated sodium bicarbonate was added. This was left to stir for 60 minutes. No foaming was observed. The polymer layer (top) was rinsed three times with 50 mL of water then was rinsed in opposing succession three times each with 40 mL hexanes, then

40 mL of water. Residual hexanes were removed *in vacuo*. Then 50 mL of toluene was added and again removed under reduced pressure. This was repeated twice more. The polymer was pumped overnight to yield a clear, colourless, non-viscous liquid.

#### *Drying of other polymeric solvents*

TMS-PDMS of higher viscosity T15 (viscosity 50cSt), a TMS-PDMS from a different chemical source ( $M_w = 770$ ), and two siloxy copolymers (8-12%(phenylmethylsiloxane)-88-92%(dimethylsiloxane)copolymer and 18-22%(diphenylsiloxane)-78-82%(dimethylsiloxane)copolymer) were dried in a similar manner.

#### *Drying of diethylene glycol dimethyl ether*

Approximately 400 mL of diethylene glycol dimethyl ether was placed in a 2 L, oven-dried Schlenk flask. To this flask was added 60 mL of toluene, which was then removed under reduced pressure. This azeotropic drying was repeated twice more with the final round of toluene elimination accompanied by heating in a hot water bath to aid in removal. The dried solvent was stored under argon.

#### *Addition of PhMgBr to diM-PEG 250*

50 mL of dried dimethyl-capped poly(ethylene glycol) of  $M_N \sim 250$  was placed in a 250 mL Schlenk-type flask and was placed under argon in an ice bath. Phenylmagnesium bromide (3M in diethyl ether) was added dropwise. At an addition of 8mL, a white precipitate was visible in the bottom. Addition continued and the precipitate grew until 25 mL of PhMgBr had been added, at which time the precipitate had grown to

a large grey gel-like mass which impeded stirring. A transparent yellow layer of liquid was visible on top.

#### *Addition of MgBr<sub>2</sub> to diM-PEG 250*

Dibromomagnesium (0.10 g) was placed in 10 mL of dried dimethyl-capped poly(ethylene glycol) of M<sub>N</sub> 250 in a 100 mL Schlenk-type flask. The solution became cloudy and slightly yellow and a precipitate was seen on the bottom of the flask. Although this was left stirring for several days, the viscosity of the polymer increased immediately upon addition and did not change over time.

#### *Addition of PhMgBr to TMS-PDMS and siloxy copolymers*

10.0 mL of dried TMS-PDMS T01.5 was placed in a 100 mL Schlenk-type flask and was placed under argon in an ice bath. 5.0 mL of phenylmagnesium bromide (3M in diethyl ether) was added dropwise. This formed two layers with the bottom being dark green and the top, colourless and transparent. Upon exhaustive ether removal via vacuum, the bottom layer gelled (became solid) while the upper layer was unchanged. This procedure was identical to those used for TMS-PDMS T15, TMS-PDMS M<sub>w</sub>, 770, 8-12%(phenylmethylsiloxane)-88-92%(dimethylsiloxane)copolymer and 18-22%(diphenylsiloxane)-78-82%(dimethylsiloxane)copolymer. After the vacuum step to remove ether, all had solid green gels with a colourless polymer or copolymer above.

#### *Synthesis of diphenylmagnesium<sup>142</sup>*

Into a 250 mL Schlenk flask was placed 100 mL of anhydrous diethyl ether. 21.0 mL of PhMgBr (3M in diethyl ether) was added by syringe to form a dark green solution.

The flask was cooled with an ice bath and 1,4-Dioxane was added with the aid of a dropping funnel. A grey-white precipitate formed immediately. This was stirred overnight, then filtered through a fine frit. The resulting liquid was a light yellow solution that was pumped down to a very sticky, light-yellow mass. Further evacuation with the aid of a warm-water bath (~40 °C) left a dry, light yellow solid, mp >350 °C. <sup>1</sup>H NMR: (500 MHz, benzene-*d*<sub>6</sub> with THF co-solvent): δ 1.15 (t, 2.30H, ether CH<sub>3</sub>), δ 3.23 (q, 1.53H, ether CH<sub>2</sub>), δ 6.91 (t, 2H, *p*-Ph-H), δ 7.00 (t, 4H, *m*-Ph-H), δ 7.68 (d, 4H, *o*-Ph-H). The 6:2.3 ratio of calculated to found ethereal methyl hydrogens lead to the conclusion of 0.38 diethyl ether molecules per diphenylmagnesium molecule. This excess was incorporated into the M<sub>w</sub> of the diorganomagnesiums in successive calculations, in this case, 206.962 g/mol.

Ph<sub>2</sub>Mg was tested qualitatively for excess halogen with silver nitrate: 0.1 g Ph<sub>2</sub>Mg was put in a vial with 1 mL of ethanol. This formed some precipitate. An aliquot of the liquid from the vial was transferred to a vial containing 1 mL of a 2% AgNO<sub>3</sub> solution in ethanol. Cloudiness indicated residual halogen. Diorganomagnesiums were not used if they were found to contain halogens.

#### *Test of diM-PEG 250 extraction method*

Known amounts of bromobenzene (~0.17 g), biphenyl(~0.03 g), and benzaldehyde(~0.10 g) were placed in separate vials. The contents of these vials were transferred to flasks each containing 10.0 mL diM-PEG 250 and were stirred for at least 10 minutes. If there was an additive in the polymer, such as bromine, it was added before the contents of the vials. They were extracted with an organic solvent or solvent mixture, and washed twice with an aqueous solvent or solvent mixture, in accordance with the

table below. The organic layer of each was dried with magnesium sulphate, filtered and diluted by a factor of 100 for a sample appropriate for GCMS.

**Table 3.6.1: Aqueous and organic solvent extracting systems.**

Vial	Organic Solvent(s)	Aqueous Solvent	Additive to polymer
1	diethyl ether	Water	-
2	50% diethyl ether/ 50% hexanes	Water	-
3	20% diethyl ether/ 80% hexanes	Water	-
4	hexanes	water	-
5	diethyl ether	Sat NaCl solution	-
6	diethyl ether	Water	Br <sub>2</sub>
7	20% diethyl ether/ 80% hexanes	Sat NaCl solution	-
8	20% diethyl ether/ 80% hexanes	Water	Br <sub>2</sub>

*Diphenylmagnesium with bromine quench in diM-PEG 250*

0.10 grams of Ph<sub>2</sub>Mg was placed in a 100 mL Schlenk flask with 10.0 mL of diM-PEG 250 to form a pale yellow viscous solution upon stirring. Over ice and under argon, 0.05 mL of bromine was added via syringe. This caused the solutions to become orange, although they lightened over time. After two hours of stirring, they were quenched with water in an ice bath which caused the liquids to turn cloudy. These were extracted with diethyl ether and rinsed twice with a saturated aqueous NaCl solution. The diethyl ether layer was dried with magnesium sulphate the solids were removed by filtration. 1mL of the dried diethyl ether solution was diluted to 10mL, and 1mL of this sample was diluted to 10 mL to yield a sample for GCMS.

#### *Diphenylmagnesium with cyclopentanone in diM-PEG 250*

Into a 100 mL Schlenk flask was placed 0.10 g diphenylmagnesium. 10.0 mL dimethyl-capped poly(ethylene glycol) ( $M_N \sim 250$ ) was added and this was stirred to form a light yellow solution. Under argon in an ice bath, distilled cyclopentanone (0.10 mL) was syringed in. This was stirred at room temperature for two hours, and then was quenched at 0 °C with ~5 mL of water. The diM-PEG was extracted with diethyl ether and rinsed with a solution of saturated NaCl. The organic layer was dried with  $MgSO_4$ , filtered, and diluted 100-fold for a GCMS sample.

#### *Diphenylmagnesium with water quench in diM-PEG 250*

A 100 mL Schlenk flask had 10.0 mL diM-PEG 250 and 0.10 g of diphenylmagnesium added which formed a slightly yellow solution upon stirring. After 30 minutes,  $H_2O$  was added while the flask was in an ice bath. This was stirred for two hours, then was extracted with diethyl ether and washed twice with a saturated sodium chloride solution. The diethyl ether portion was dried with magnesium sulphate, filtered, and the remaining organics were diluted by a factor of 100 for GCMS.

#### *Dibromomagnesium in diM-PEG 250*

0.10 g of dibromomagnesium was added to 10.0 mL diM-PEG 250. An increase in viscosity was noticed immediately and became cloudy and slightly yellow with a noticeable precipitate over five days.

#### *Diphenylmagnesium with bromine quench in diethyl ether*

Diethyl ether (10 mL, anhydrous) was added to 0.10g of  $\text{Ph}_2\text{Mg}$  in a 100 mL Schlenk flask. This formed a solution with a very slight yellow hue. 0.5 mL of bromine was added under argon which caused the solution to turn bright orange. This was stirred for two hours over which the orange colour lessened, even though the flask was sealed. After two hours, a small layer of brown solution was found to have formed in the bottom of the flask. 5 mL of  $\text{H}_2\text{O}$  was added to quench any remaining diorganomagnesium which caused some smoking and made the liquid become a single cloudy layer. This was rinsed three times with a saturated sodium chloride solution and the diethyl ether layer was dried with  $\text{MgSO}_4$ , and diluted by a factor of 100 which was used as a GCMS sample.

#### *Diphenylmagnesium with cyclopentanone in diethyl ether*

0.10 g of  $\text{Ph}_2\text{Mg}$  was added to a flask containing 10 mL of anhydrous diethyl ether, in which it dissolved. At  $0^\circ\text{C}$ , distilled cyclopentanone (0.10 mL) was added via syringe to no immediate visible change. This was stirred at room temperature for two hours, upon which a cream coloured precipitate was seen in the flask. It was quenched with 2 mL 1M HCl and the precipitate redissolved. The diethyl ether was rinsed twice with more 1M HCl, then dried with magnesium sulphate and diluted by a factor of 100 to yield a GCMS sample.

#### *Diphenylmagnesium with water quench in diethyl ether*

Ten millilitres of anhydrous diethyl ether were added to 0.10 g  $\text{Ph}_2\text{Mg}$  to form a solution. With the flask in an ice bath, 5 mL of water was added to the ethereal solution which caused cloudiness to occur. After 2 hours, the diethyl ether was rinsed twice with

1M HCl, then was dried with magnesium sulphate and filtered. The organic layer was then diluted 100 to 1 for GCMS.

*Diphenylmagnesium with bromine quench in 2-methyltetrahydrofuran*

Diphenylmagnesium (0.10 g) was put into a flask with 10.0 mL of anhydrous 2-methyltetrahydrofuran which formed a solution upon stirring. 0.05 mL of bromine was added via syringe while the solution was at 0°C. This yellow solution was stirred for two hours and then quenched in an ice bath with 4mL of 1M HCl. The organic layer was rinsed twice with further 1M HCl and was dried with magnesium sulphate. Diethyl ether was added to boost the volume, and then the solution was diluted by a factor of 100 to yield samples suitable for GCMS.

*Diphenylmagnesium with cyclopentanone in 2-methyltetrahydrofuran*

0.10 g of diphenylmagnesium was placed in a 100 mL Schlenk flask and had 10.0 mL of anhydrous 2-Me-THF added. Within minutes this formed a solution. This solution was put in an ice bath under argon and had 0.10 mL of distilled cyclopentanone syringed in. It was left to stir at room temperature for two hours at which point it was quenched at 0 °C with 2mL of 1M HCl. The organic layer was rinsed twice more with 1M HCl and diethyl ether was added to increase the organic volume, which was then dried with MgSO<sub>4</sub> and filtered. The 2Me-THF/ether was diluted 100-fold with more diethyl ether in preparation for GCMS.

*Diphenylmagnesium with water quench in 2-methyltetrahydrofuran*

A flask had 10.0 mL of 2-Me-THF syringed in. 0.10 g of diorganomagnesium was added and with stirring, this formed a solution with a slight yellow colour. Over an ice bath, an excess of H<sub>2</sub>O was added which caused a second layer to form. After two hours, this was rinsed twice with 1M HCl and diethyl ether was added to the organic layer to increase the volume. This was dried with MgSO<sub>4</sub> and filtered, then was further diluted to 0.01 for a sample for GCMS.

*Diphenylmagnesium with bromine quench in TMS-PDMS T01.5*

Diphenylmagnesium (0.10 g) was placed in a flask with 10.0 mL of TMS-PDMS (T01.5) This was stirred but did not form a solution; the slightly yellow Ph<sub>2</sub>Mg formed a suspension in the clear, colourless polymer. The flask was placed in an ice bath and 0.05 mL of Br<sub>2</sub> was syringed in under argon. This caused the liquid to turn orange, which faded to grey-brown over time. After two hours, this was quenched with 5 mL H<sub>2</sub>O over an ice bath. Two layers formed, and the upper was yellow. The mixture was extracted with diethyl ether, and rinsed twice with saturated sodium chloride solution. The organic layer was dried with MgSO<sub>4</sub> and was filtered, then diluted twice by a factor of 10 for a sample for GCMS.

*Diphenylmagnesium with cyclopentanone in TMS-PDMS T01.5*

TMS-PDMS (T01.5, 10.0 mL) was placed in a flask with 0.10 g of diphenylmagnesium. With stirring, this did not form a solution but rather remained a suspension. At 0 °C under an atmosphere of argon, 0.10 mL of cyclopentanone was syringed in and the mixture was allowed to stir at room temperature for two hours. At this

time it was quenched with water at 0 °C. The organics were extracted with diethyl ether and rinsed twice with aliquots of 1M HCl. The diethyl ether was dried with magnesium sulphate, and then gravity filtered. A 1.0 mL aliquot was diluted to 10.0 mL, and then 1.0 mL of this dilution was further diluted to 10.0 mL for a sample that was dilute enough for GCMS analysis.

*Diphenylmagnesium with water quench in TMS-PDMS T01.5*

A portion (10.0 mL) of TMS-PDMS was syringed into a 100 mL Schlenk type flask. Diphenylmagnesium (0.10 g) was added and even with vigorous stirring, would only form a suspension. With an ice bath, an excess of water was added and this now-cloudy mixture was allowed to stir for two hours, upon which it was extracted into diethyl ether, and rinsed twice with 1M HCl. The organic layer was dried with magnesium sulphate and this was removed with gravity filtration. The dried organic layer was then diluted 100-fold for a GCMS sample.

*Diphenylmagnesium with bromine quench in diethylene glycol dimethyl ether*

10.0 mL of diethylene glycol dimethyl ether was placed in a flask with 0.10 g of diphenylmagnesium. With stirring, this formed a faint yellow solution. Over an ice bath and under argon, 0.05 mL of bromine was added via syringe. This caused the solution to become bright orange. After two hours of stirring at room temperature, the orange colour had disappeared and then H<sub>2</sub>O was added at 0 °C. This was extracted with diethyl ether and rinsed twice with saturated sodium chloride solution. The organic layer was dried with MgSO<sub>4</sub> and this was filtered. The remaining organic layer was diluted by 100% for a GCMS sample.

*Diphenylmagnesium with cyclopentanone in diethylene glycol dimethyl ether*

Into a flask was placed 0.10 g diphenylmagnesium. 10.0 mL of diethylene glycol dimethyl ether was added which, upon stirring, formed a solution with a slight yellow colour. This solution was put into an ice bath and under a flow of argon, and had 0.10 mL of cyclopentanone added by syringe to no visible change. This was stirred for two hours and then extracted into diethyl ether and washed with 1 M HCl. The organic layer was dried with magnesium sulphate, and was diluted by a factor of 100 for a sample suitable for GCMS analysis.

*Diphenylmagnesium with water quench in diethylene glycol dimethyl ether*

A flask was filled with 10.0 mL of diethylene glycol dimethyl ether and to this 0.10 g of diphenylmagnesium was added. With stirring, this became a light yellow viscous solution. An excess of water was added at 0 °C and was allowed to stir for two hours before extraction into diethyl ether with washes of 1M HCl. The diethyl ether extractant was dried with MgSO<sub>4</sub>, filtered, and diluted through two successive dilutions of 1 mL to 10 mL. This twice diluted sample was submitted to GCMS.

*Diphenylmagnesium with cyclopentanone in diM-PEG 2000 (80°C)*

Dried chunks of diM-PEG 2000 were placed in a Schlenk flask to an approximate volume of 10 mL. Then 0.10 g of diphenylmagnesium was added while the polymer was still solid. This was heated to 80 °C to melt the solid and with stirring, the Ph<sub>2</sub>Mg dissolved into the polymer. After temperature stabilisation, 0.10 mL of distilled cyclopentanone was syringed in. This was stirred under Ar at 80 °C for two hours,

removed from the oil bath, then was quenched with 4 mL H<sub>2</sub>O followed by 4 mL 1M HCl. After a few moments, hexanes was added. These liquid additions were enough to make the PEG no longer solid. The mixture was extracted with diethyl ether, and the diethyl ether layer was washed twice with 1M HCl. The discarded aqueous layer was quite cloudy. The ether/hexanes were dried with MgSO<sub>4</sub>, then diluted by a factor of 100 and submitted as a GCMS sample.

*Diphenylmagnesium with cyclopentanone in diM-PEG 2000 (80°C) after 47 days*

Pieces of previously dried diM-PEG 2000 were placed in a Schlenk flask to make up a volume of approximately 10 mL when melted. 0.10 g of diphenylmagnesium was also placed in the flask. This was heated under argon to 80 °C upon which the polymer melted and the diphenylmagnesium dissolved into the polymer. This was stirred for one hour, then was removed from heat and left to solidify under argon. After the flask had cooled to room temperature, the stopcock on the flask was opened and was left exposed to the atmosphere on the benchtop for 47 days.

After 47 days, the flask was put through a vacuum-pump-fill cycle three times to remove the air. Then under argon, the flask was heated to 80 degrees and the polymer remelted. 0.10 mL of cyclopentanone was added to this melt and was stirred at 80 °C for two hours. At this time, the products were quenched with water, extracted into hexanes and rinsed with 1M HCl. The hexanes layer was dried with MgSO<sub>4</sub>, filtered, and diluted with diethyl ether by a factor of 100. This sample was analysed by GCMS.

*Diphenylmagnesium with cyclopentanone in diM-PEG 250 (80°C)*

A flask had 10.0 mL of diM-PEG 250 placed in it along with 0.10 g of diphenylmagnesium. Stirring caused a solution to be formed which then had 0.10 mL of cyclopentanone added. This reaction mixture was heated to 85 °C for two hours, then was quenched with H<sub>2</sub>O and left to cool. The products were extracted into diethyl ether and rinsed with 1M HCl. The diethyl ether layer was dried with magnesium sulphate, and then was filtered. This filtered layer was then diluted twice by a factor of 10. This twice diluted sample was submitted to GCMS for analysis.

*Diphenylmagnesium with cyclopentanone in diglyme (80°C)*

A 100 mL Schlenk flask had 10.0 mL of diethylene glycol dimethyl ether placed in it along with 0.10 g of diphenylmagnesium. A light yellow solution was formed upon stirring. Cyclopentanone was added (0.10 mL) and the solution was then heated to 80 °C for 2 hours. After 40 minutes, the solution appeared cloudy. After two hours, the reaction was quenched with water, then was extracted with diethyl ether and rinsed with 1M HCl. The organic layer was dried with MgSO<sub>4</sub>, and then was diluted 100-fold to a concentration suitable for a GCMS sample.

*Diphenylmagnesium with cyclopentanone in TMS-PDMS T01.5 (80°C)*

TMS-PDMS (10.0 mL, T01.5) was placed in a flask along with 0.10 g of diphenylmagnesium. This did not form a solution. Cyclopentanone was syringed in under argon, and then the flask was placed in a bath at 80 °C and was left to stir for two hours. After this time, the mixture appeared cloudy. It was quenched with water, extracted with diethyl ether, and rinsed with 1M HCl. The diethyl ether was dried with magnesium

sulphate, then was filtered and diluted by a factor of 100 so that it could be sample with GCMS.

#### *GCMS Calibration Standards*

Standards were made for GCMS by successive dilution of a known amount of analyte. Ten different concentrations were made for each, although some fell outside of the range of proper detection via mass spectrometry by being too concentrated, or too dilute. A known amount of analyte (from 0.019 g to 0.039 g) was placed in a 10mL volumetric flask and was filled to the mark with GCMS grade diethyl ether. This made a sample that was approximately 2000  $\mu\text{g/mL}$ . The series of dilutions was made according to the following table:

**Table 3.6.2: Dilutions for calibration curves.**

To make:	take	of	Dilute to
200 $\mu\text{g/mL}$	1 mL	2000 $\mu\text{g/mL}$	10 mL
100 $\mu\text{g/mL}$	5 mL	200 $\mu\text{g/mL}$	10 mL
50 $\mu\text{g/mL}$	5 mL	100 $\mu\text{g/mL}$	10 mL
25 $\mu\text{g/mL}$	5 mL	50 $\mu\text{g/mL}$	10 mL
20 $\mu\text{g/mL}$	1 mL	100 $\mu\text{g/mL}$	5 mL
10 $\mu\text{g/mL}$	1 mL	50 $\mu\text{g/mL}$	5 mL
5 $\mu\text{g/mL}$	1 mL	25 $\mu\text{g/mL}$	5 mL
2.5 $\mu\text{g/mL}$	1 mL	25 $\mu\text{g/mL}$	10 mL
1 $\mu\text{g/mL}$	1 mL	10 $\mu\text{g/mL}$	10 mL
0.5 $\mu\text{g/mL}$	5 mL	1 $\mu\text{g/mL}$	10 mL

For example, to make a solution of  $\sim 20 \mu\text{g/mL}$ , one would take 1mL of the 100  $\mu\text{g/mL}$  sample and dilute that to 5 mL.

The exact concentrations were calculated and these values were used in conjunction with the peak areas obtained from the mass spectrometer to form a calibration curve for the determination of reaction yields. Each analyte concentration was sampled in the GCMS three times and the resultant signals were averaged.

*GCMS Method Details*

**Table 3.6.3 Oven temperatures of GCMS method.**

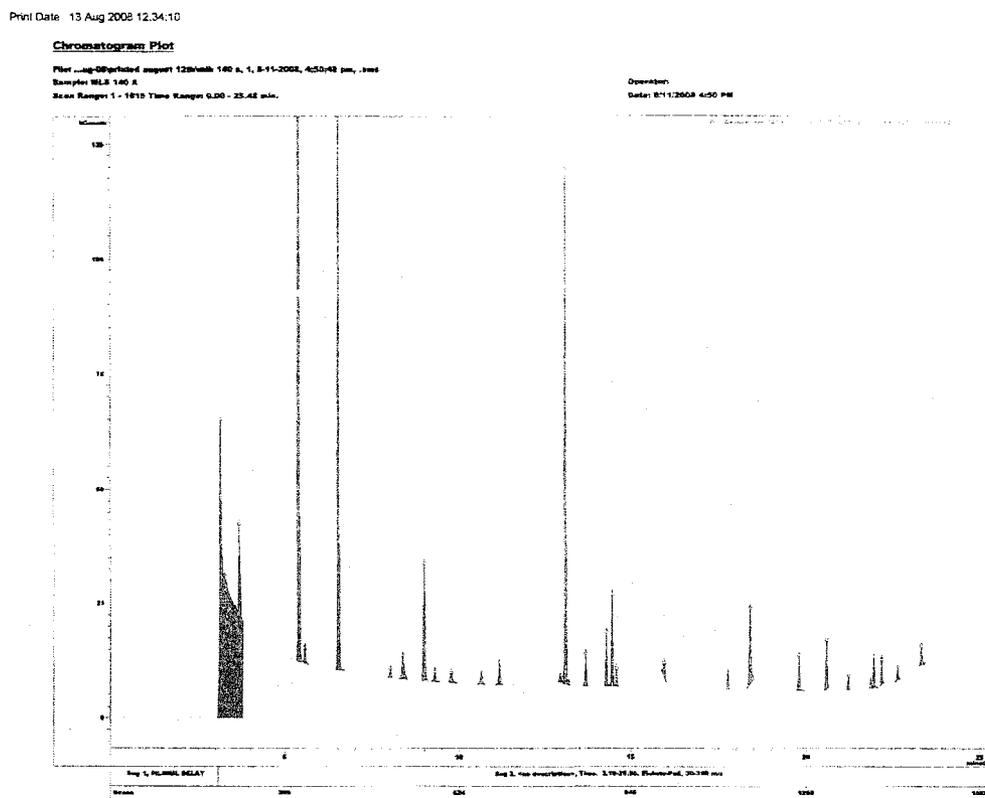
T (°C)	Rate (°C/min)	Hold (min)	Total time (min)
24	-	3.00	3.00
46	30.0	-	3.73
52	5.0	-	4.93
58	1.0	-	10.93
85	12.0	-	13.18
100	20.0	-	13.93
170	10.0	-	20.93
270	50.0	3.50	26.43

**Table 3.6.4 Oven temperatures for slow method to separate biphenyl and 1-phenyl-1-cyclopentanol product peaks.**

T (°C)	Rate (°C/min)	Hold (min)	Total time (min)
50	-	1.00	1.00
150	50.0	0.50	3.50
151	0.1	-	13.50
270	100	1.00	15.69

# Appendix

Figure A.1: A sample GCMS trace from the bromine quench of diphenylmagnesium in diM-PEG 250.



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