Organocuprate Reactions in Phosphonium-based Ionic Liquids

By
Christian Boyd Kyle

A Thesis Submitted to
Saint Mary's University, Halifax, Nova Scotia
In Partial Fulfillment of the Requirements for the
Degree of Masters of Science in Applied Science

September 21, 2009, Halifax, Nova Scotia

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Abstract

Organocuprate Reactions in Phosphonium-based Ionic Liquids

By Christian Boyd Kyle

Submitted September 21, 2009

Ionic liquids (ILs) based on the trihexyl(tetradecyl)phosphonium cation were purified or synthesized in high yields (83.6-93.0 %) *via* salt metathesis. These were used as solvents for 1,4-congugate additions of lithium dibutylcyanocuprate [$Bu_2CuLi{\cdot}LiCN$] to *trans*-4-phenyl-3-buten-2-one; with and without tetrahydofuran co-solvent. Low conversion of substrate to product (4-phenyloctane-2-one) was achieved in 1 hour (0-59 %) in the IL alone while retaining the organic solvent offers better product formation (65-94 %) as determined by GC-MS analysis. Good stability of the cuprate in the ILs is experienced when the chloride anion is exchanged for bis(trifluoromethylsulfonyl)amide or dicyanimide, greatly reducing undesired alkenes formed *via in situ* generation of Wittig reagents from the cation. Methods to isolate the product and recycle the IL after reaction require further work. Three ether containing ILs were also synthesized in good yields (66.8-75.9 %); however, their hygroscopic nature proved deleterious to their role in the model reaction.

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First and foremost my deepest gratitude is extended to Dr. Robert Singer. I could match this document in length with the thanks I owe him for the opportunities given and the great memories shared. Without his understanding, support, and drive I would never have reached this stage, and I hope to carry with me forever the lessons he has shared. In this regard I would also like to thank Dr. Jason Clyburne, who always had an open door and with whom I shared many insightful discussions about chemistry and life. These two opened my eyes to the world of Green Chemistry and helped me not only to become a better researcher but also a better person.

I would also like to thank my external supervisor Dr. Ian Pottie of MSVU for unselfishly taking the time from his busy schedule to help me achieve this goal. My thanks are also extended to Dr. Jarda Dostal for his kind words, calming demeanor, and intelligent questions. To both I wish nothing but the best in the future. Also I would like to thank Dr. Kathy Singfield and Dr. Pawan Lingras for all the help along the way.

To the members of the Singer group from 2006 to present I thank you all. Special mention should be made to Alanna Durant for her help in the lab, and to Jeff Farrell, Ted Abraham, and Prashant Naik, with whom I enjoyed many a hot hectic day trying to please '*the boss*'. The Singer group has always been an intelligent and supportive bunch and I'm sure that will continue given the people coming through the ranks.

Special thanks are extended to Patricia Granados for her help with the analytical instrumentation, Darlene Goucher and Elizabeth McLeod for keeping the wheels of research in motion, and the Atlantic Regional Magnetic Resonance Centre for access to their instruments. Gratitude must also be extended to the faculty and staff of the Chemistry Department at Saint Mary's University, especially Dr. Marc Lamoureux for helping me to pursue this and other experiences. The future for Chemistry at Saint Mary's is bright and I am certain that with the core of people currently here that the reputation of the department and quality of research will continue to grow as it has since I first arrived.

To my parents I owe more than thanks, I owe everything. To my brother Erin and Colleen Peacock, the same. Please know that I love and will always love you all, no matter what, and I hope I've made you proud. I would also like to thank my friends who have been nothing but supportive and encouraging, giving me the distractions I needed to stay in touch with reality.

Not one thing or person has been more influential in this endeavor than my love Sarah Peacock. Words cannot express what you mean to me. The completion of this thesis is as much your accomplishment as it is my own. You are the most beautiful person in all regards, you complete me, and as we journey into our future please know that I will love and cherish you forever.

"Seeking to forget makes exile all the longer;
the secret of redemption lies in remembrance."

Richard von Weizsäecker

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List of Abbreviations

δ	NMR chemical shift downfield from a standard
amu	atomic mass unit
aq.	aqueous
$AgNO_3$	silvernitrate
$[BF_4]$	tetrafluoroborate anion
°C	degrees Celsius
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
CF_3	trifluoromethyl
$[n\text{-}C_9H_{19}CO_2]$	decanoate anion
$[CF_3CO_2]$	trifluoroacetate anion
[Cl]	chloride anion
cm^{-1}	wave number (IR frequency)
DMS	dimethlsulfate
EM	ethoxymethyl
Enone	α,β-unsaturated ketone
ESI-MS	electrospray ionization mass spectrometry
Et_2O	diethylether
eq.	equivalent(s)
FMO	Frontier Molecular Orbital theory
g	grams
GC-FID	gas chromatography flame ionization detector
GC-MS	gas chromatography mass spectrometry
h	hour
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HOE	Heteronuclear Overhauser Effect
HOMO	highest occupied molecular orbital
HSAB	Hard-Soft Acid-Base theory
Hz	Hertz
IL(s)	ionic liquid(s)
$kg\ y^{-1}$	kilograms per year
LUMO	lowest unoccupied molecular orbital
M^+	molecular ion
ME	methoxyethyl
min	minutes
mL	millilitre
m/z	mass-to-charge ratio
NHC(s)	*N*-heterocyclic carbine(s)
NMR	nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser Effect
$[N(SO_2CF_3)_2]$	bis(trifluoromethylsulfonyl)amide anion

$[N(CN)_2]$	dicyanamide anion
[*N*-Bu-3-EMPy]	*N*-butyl-3-(ethoxymethyl)pyridinium cation
[*N*-MEPy]	*N*-(methoxyethyl)pyridinium cation
[*N*-ME-3-EMPy]	*N*-(methoxyethyl)-3-(ethoxymethyl)pyridinium cation
OM	generic organometallic reagent
ov	overlapping
$[P^{6,6,6,14}]$	trihexyl(tetradecyl)phosphonium cation
$[PF_6]$	hexafluorophosphate anion
[Py]	pyridinium cation
ppm	parts per million
RLi	generic organolithium reagent
RMgBr	generic organomagnesium or Grignard reagent
R_2Zn	generic diorganozinc reagent
$R_2CuLi{\cdot}LiX$; X = I, CN	generic diorganocuprate, dialkylcuprate, or Gilman reagent
RTIL(s)	room temperature ionic liquid(s)
TSIL(s)	task-specific ionic liquids(s)
t_R	retention time
THF	tetrahydrofuran
sc-CO_2	supercritical carbondioxide
sc-H_2O	supercritical water
VOCs	volatile organic compounds

1 Introduction

Carbon-carbon bond forming reactions form the framework from which chemists build large and complex organic molecules.[1] Organometallic reagents are a fundamental and vital tool in this endeavor, offering chemoselective and regioselective stereogenic carbon-carbon bond forming pathways through transformations with a number of functionalities.[2] Simple organometallics including organolithium (RLi), organomagnesium (Grignard, RMgBr), diorganozinc (R_2Zn), and diorganocuprate reagents ($R_2CuLi{\cdot}LiX$; X = I, CN) are well studied in the literature and their applications are taught to all fledgling undergraduate chemists. The most commonly employed solvents for these organometallics, which are strong bases in general, are tetrahydrofuran (THF) and diethyl ether (Et_2O) which offer controlled use of these highly reactive and sensitive species. The health, safety, and environmental dangers associated with these ethereal solvents provided the motivation for this research into finding a more benign alternative solvent, specifically Ionic Liquids (ILs) based on the trihexyl(tetradecyl)-phosphonium [$P^{6,6,6,14}$] cation.

1.1.1 Solvent Considerations

In chemical manufacturing organic solvents are used in most steps of a chemical process, either as the reaction medium and/or in the separation (extraction, filtration) and purification (recrystalization, chromatography) of materials. By using an appropriate organic solvent one allows for the homogenization of a reactant mixture, providing faster rates of reactions through improved mixing compared to heterogeneous cases. Also the

solvent can be crucial in stabilizing reactive species, intermediates, and transition states, as well as acting as a heat sink for exothermic reactions, thus contributing to improved safety in such cases.

Volatile organic compounds (VOCs) comprise many of the more commonly used solvents. Being liquids at ambient temperatures and pressures, they offer the advantage of easy handling on a large scale for flow reactors using pipes and pumps. Also VOCs are popular solvents due to their ease of removal by evaporation, as VOCs possess a significant vapour pressure at room temperature. This property has played a significant role in the development of many useful products including ink, paint, and aerosol applications. However, VOCs contribute to air pollution as well as ground-level ozone formation, both factors which contribute to green-house warming and smog.[3] More than ever before, the environmental issues concerning VOCs must be addressed when selecting an appropriate solvent for a desired process. As previously mentioned, solvents are used in almost all stages of a chemical process and thus account for a large amount of the waste generated by the chemical and allied industries.[4] Recently a thorough Environmental, Health, and Safety assessment of 26 common organic solvents was performed by Fischer *et al.* and offers several suggestions as to which are the most and least hazardous.[5] Amongst the least recommendable solvents from an environmental perspective was THF, with Et_2O fairing better in their analysis due to its relatively clean production and low energy requirements for recycling by distillation. Notably THF and Et_2O are considered highly and extremely flammable respectively, both are mutagenic for mammalian somatic cells, and they may damage the central nervous system with prolonged exposure.[6]

1.1.2 Green Chemistry

The environmental legacy of the Industrial Revolution can be seen in the Great Smog of 1952 in London, the Union Carbide disaster in Bhopal, the 'burning' Cuyahoga river disaster, acid rain, and the discovery of holes in the polar regions of the atmospheric ozone-layer. In response to pressure from environmentalists and the public, as well as an increased scientific understanding of the negative impacts VOCs incur on the environment, Governments world-wide began to form legislation to curb VOC emissions. Early examples include the Clean Air Act 1956 of Great Britain, the Clean Air Act 1963 of the United States of America, and the Montreal Protocol 1989 of Canada, all of which have been amended with new more stringent guidelines.[4] The Kyoto protocol, an international agreement linked to the United Nations Framework Convention on Climate Change, is currently in effect with the aim to reduce green-house gas emissions produced by the most industrialized nations to 1990 levels by the end of 2012 and talks are underway to develop a successor.

Sustainable development, as defined by the United Nations Commission on the Environment and Development (Brundtland Commission, 1987), is a development that "*... meets the needs of the present without compromising the ability of future generations to meet their own needs.*"[7] It was in the early 1990s that the US Environmental Protection Agency coined the phrase *Green Chemistry* in an effort "*... to promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substances in the design, manufacture, and use of chemical products.*"[8]

This phrase has developed into both a methodology and a culture for chemists over the past 15 years and has even spawned a number of conferences and a self-titled journal devoted to its pursuit. Clearly the goal of today's chemical industry is to offer new and existing products while adhering to the ideals of environmental safety and sustainability. Two of the fathers of *Green Chemistry*, Paul T. Anastas and John C. Warner have listed *12 Principles of Green Chemistry*[9] as the key considerations one must address in optimizing a chemical process:

1. Prevent Waste
2. Atom Economy
3. Less Hazardous Chemical Synthesis
4. Designing Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-time Analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

Chemistry which addresses these aspects has the greatest potential to yield the most environmentally benign process. A major advantage to industry is that *Green Chemistry* can be perceived as a reduction process, leading to decreased material and energy consumption as well as reduced waste production. All of these factors evolve into lower operating costs for the process as a whole. Therefore industry should be inclined to view *Green Chemistry* as a means to increase rather than decrease profits.[10]

1.1.3 Alternative Solvents

Considering the relatively large amounts of solvents required for a chemical process as well as the flammability and toxicity of those most commonly employed, it is not surprising that solvent related issues arise in many of the *Green Chemistry* principles. There have been successful endeavours into solvent-free systems which greatly reduce the amount of materials going into and out of a chemical process.[11] Solvent-less synthesis however is not amenable to all chemical processes and use of a solvent is often unavoidable. Among the more studied alternative solvents are water,[12] supercritical fluids (*sc*-CO_2, *sc*-H_2O),[13] fluorous solvents[14] and ionic liquids (ILs).[15] Water is an ideal solvent as it is abundant, inexpensive, and innocuous in the environment. However, water can easily hydrolyze a number of functionalities and thus only compounds which do not react with water can be used efficiently. Many simple organometallics are highly reactive towards water and thus are employed under scrupulously dry conditions. Also, *sc*-CO_2 is reactive towards many organometallic species and thus is not a logical solvent alternative when such species are employed.[16] Fluorous solvents remain understudied, potentially due to their high cost and volatility, and the limited information available about their environmental persistence and toxicity. Along with water, ILs have been extensively studied as alternative solvents, with more than 15000 journal publications on ILs listed on SciFinder Scholar from 2004 to 2008 alone.

1.2 Ionic Liquids

Generally defined as salts having melting points below 100 °C that are liquids composed solely of ions, ILs are typically composed of large asymmetric organic cations such as imidazolium, pyrindinium, ammonium, or phosphonium cations with inorganic or organic anions (Figure 1).[17] The low melting point of ILs compared to inorganic salts can be attributed to the dispersed or protected charges in one or both ions, effectively reducing Coulombic attraction between them.[17] The asymmetry of the cation hinders efficient crystal packing, reducing the melting point of the salt. Further reduction of the melting point occurs with increased rotational degrees of freedom obtained by increasing the substituent alkyl chain lengths and/or branching. This trend continues to the point where Van der Waals interactions between ions dominate and the melting point increases.[18] To date, ILs containing unsymmetrical 1,3-dialkylimidazolium cations remain the most extensively studied, however some estimates suggest that as many as 10^{18} possible cation/anion pairs would produce room temperature-ILs (RTILs).[19]

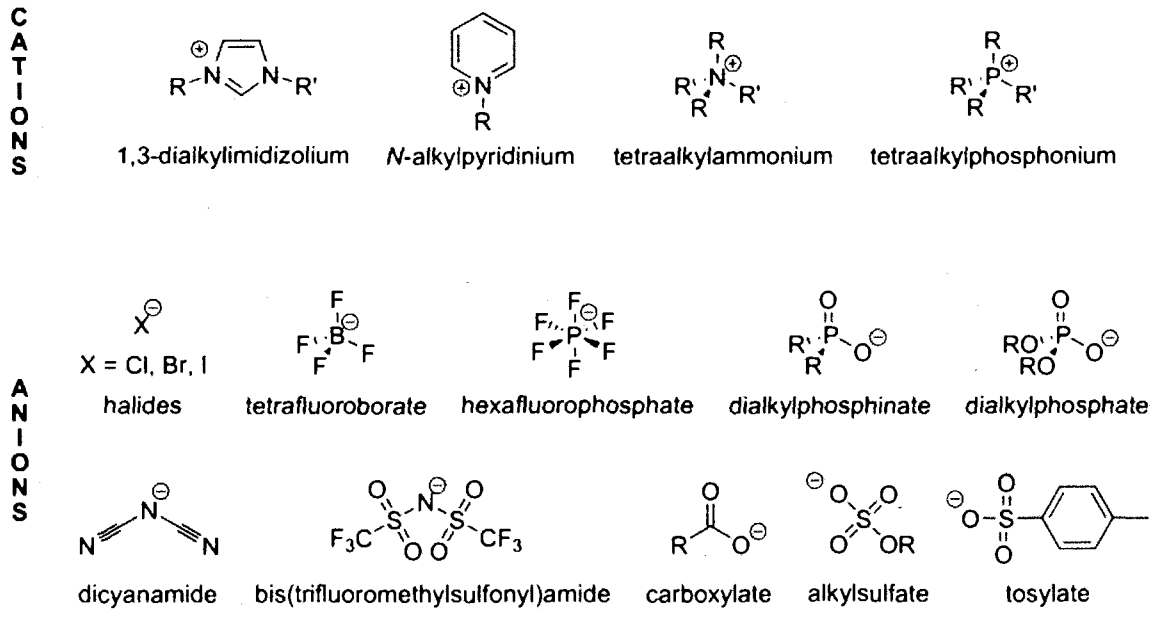
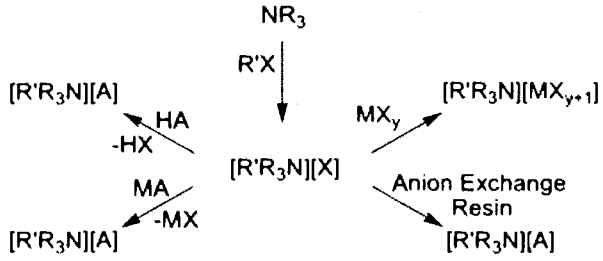


Figure 1: Some common cations and anions found in ILs.

The typical synthesis of ILs involves a two step process. First a quaternization reaction is performed to generate the bulky organic salt, usually containing a halogen anion. This is followed by an anion exchange reaction to provide the desired anion (Scheme 1). The anion exchange can be performed as the formation of eutectics from metal halides or through a salt metathesis pathway. Acid-base chemistry is another option as well as the use of anion exchange resins. As ILs cannot be purified by distillation like most organic solvents they are often washed with other solvents and dried under vacuum.[15]



Scheme 1: General Synthesis of ammonium-based ILs.

1.2.1 Brief History

The history of ILs has been told elsewhere and in greater detail.[15,16,20,21] It began more than a century ago when chemists speculated that the "red-oils" formed as a separate phase during some Friedel-Crafts reactions were in fact a stable intermediate organic salt. This was indeed confirmed with the development of NMR spectroscopy in the mid-20th century. Even before this Walden had reported in 1914 that ethylammonium nitrate produced by the reaction of ethyl amine and concentrated nitric acid, was liquid at room temperature (mp. 12-14 ^{o}C).[22] However, this discovery did not attract broad interest or attention towards ILs. The next half century produced reports on the use of ILs as media for electrochemical studies and infrequently for organic synthesis.[16] These studies mainly investigated eutectic mixtures of chloroaluminate-based salts (for example $AlCl_3$-NaCl) and pyrindinium hydrochloride.[23] The first ILs with chloroaluminate ions resulted from the work of Hurley[24] and Wier[25] who in 1948 developed chloroaluminate-based ILs as electrolyte solutions for aluminum electroplating. In 1967 Swain *et al.* published work on tetrahexylammonium benzoate as media for kinetic studies and electrochemical reactions including quantitative determination of the ionization strength of the medium.[26]

It was in the 1970s that ILs began to draw a more general audience, when the groups of Wilkes[27] and Osteryoung[28] developed the first chloroaluminate-based RTILs. The 1980s saw the groups of Hussey[29] and Seddon[30] extensively study these chloroaluminate melts as reaction media for transition metal complexes through electrochemical and spectroscopic studies. In 1986 the first report detailing the use of a low melting chloroaluminate-based IL as both solvent and catalyst for Friedel-Crafts reactions appeared.[31] This was followed by the first application of ILs as solvents for biphasic catalysis, where in 1990 Chauvin *et al.* successfully performed the dimerization of propene using nickel complexes in acidic chloroaluminate ILs,[32] while Osteryoung *et al.* reported ethylene polymerization using the Zeigler-Natta catalysts.[33] Application of 1-ethyl-3-methylimidazolium chloroaluminate-based eutectics for the acylation of ferrocene has been demonstrated by earlier work in our lab.[34]

One limiting factor for the number of applications for ILs containing chloroaluminate anions is the instability of the anion in the presence of air (O_2) and moisture (H_2O), as well as many organic compounds including alcohols and acetone.[16] Thus, the development of air and moisture stable imidazolium-based ILs with anions such as tetraflouoroborate [BF_4] and hexafluorophosphate [PF_6] by Wilkes and Zaworotko in 1992 was perhaps the most important breakthrough for ILs.[35] This resulted in a number of new ILs and also allowed for a number of functional groups which were not compatible with chloroaluminate anions to be investigated, further increasing the number of applications for ILs.

1.2.2 General Properties of Ionic Liquids

Significant attention is now being paid to ILs as potential environmentally benign alternative solvents as their bulk properties may offer much safer operating conditions compared to existing methods using VOCs.[16,20,36] Evaporation of VOCs results in waste, pollution and chronic exposure of workers to harmful chemical fumes. The risk of fire and explosion must also be considered for certain VOCs including THF and Et_2O. Conversely, ILs generally possess negligible vapor pressures under ambient conditions, are non-flammable and have the potential to be recycled.[15]

Other attractive properties of ILs include their high ionic conductivity, wide liquid ranges, high polarity, ability to solvate a wide range of inorganic and organic compounds simultaneously, and immiscibility with a number of organic solvents and water. This latter general property of ILs makes them useful in biphasic catalysis, which is an attractive method for the recycling of expensive or toxic transition metal catalysts.[16]

Recently, questions have been raised as to exactly how *Green* ILs are when all things are considered.[37] Indeed, the number of new ILs and applications for them has grown at a much greater rate than our understanding of their toxicity,[38] biodegradability,[39] bioaccumulation, disposal, and also the cost and waste involved in their synthesis and recycling processes.[40] Full life-cycle assessments are needed before final conclusions can be drawn on the *Green*-ness of any particular IL.[41]

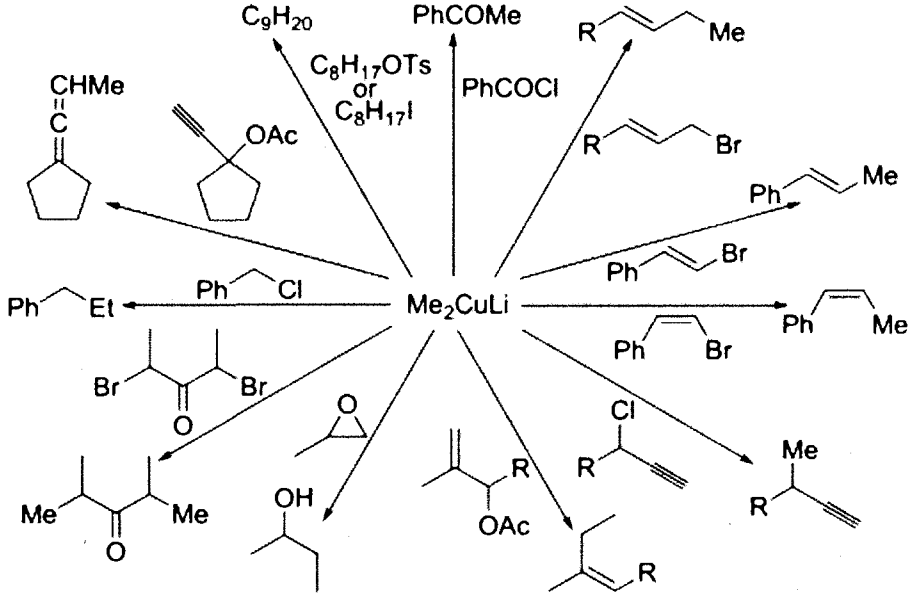
1.2.3 Applications of Ionic Liquids

The ability to tune the physicochemical properties of ILs (i.e. density, viscosity, conductivity, and solvent properties) by varying the cation and anion components for process optimization has lead to ILs often being referred to as *designer solvents*. The properties of ILs can be fine-tuned by variation of the substituents found on the ion components (i.e. alkyl chain lengths on the cation).[17] Also the ability of ILs to act as solvents, catalysts, co-catalysts, source of ligand, or combinations of said functions in certain applications may limit the amount of chemicals added to the reaction mixture, subsequently reducing the amount of waste from the process.[36] The ability to design ILs in a modular fashion and tune their physicochemical properties has resulted in their application in areas as diverse as CO_2 capture,[42] liquid crystals,[43] metal chelation,[44] lubrication,[45] electrodeposition,[46] desulfurization of fuel,[47] transportation of reactive gases,[48] dissolution of cellulose,[49] and as electrolytes for dye-sensitized solar cells (DSSC).[50] Often when an IL has been derivitized to perform a specific function in a chemical process it is termed a Task-Specific Ionic Liquid (TSIL).

1.3 Organometallic Reagents

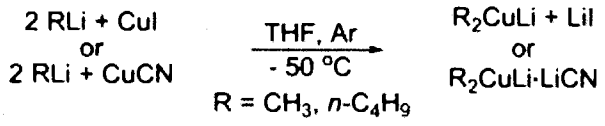
Organometallic reagents, simply compounds containing a carbon-metal bond, come in many variations with examples of both stoichiometric and catalytic organometallics being plentiful. Stoichiometric organometallics are often employed as a synthetic source of a carbanion, or carbon-based nucleophile. Lithium diorganocuprates were first prepared by Henry Gilman in 1952[51] and remain a commonly employed

reagent in many carbon-carbon bond forming reactions.[52] Extensive research into the utility of these species by the groups of House, Corey, Posner, Lipshutz, Woodward, Ullenius, and others has resulted in a plethora of possible transformations available through these organometallic species. These include a number of nucleophilic substitutions, coupling reactions, alkylations, 1,4-conjugate additions, carbocuprations, and enolate trapping reactions (Scheme 2).[53]



Scheme 2: Transformations offered by Gilman-type organocuprates.

Lithium diorganocuprates are commonly prepared by transmetallation of two equivalents of an alkyllithium compound using a copper(I) salt, typically CuI or CuCN (Scheme 3), and the resulting solution species consists of an aggregate, or aggregates, of diorganocuprate and lithium salt units. The exact nature of these aggregated species and



Scheme 3: Generation of Gilman and cyanocuprates *via* transmetallation.

their influence on the reactivity of the diorganocuprate has been the subject of much study and debate,[54] but is known to be highly dependent on the degree of solvent coordination/electron donation (Figure 2).[55] Clear trends, however, are not experienced. For example rates for 1,4-additions of Gilman cuprates to enones (α,β-unsaturated ketones) in Et_2O are increased upon addition of THF, while a decrease is experienced by cyanocuprates.[56] It has also been shown through low-temperature IR, ^{13}C NMR, and ^{31}P NMR spectroscopic studies that addition of a coordinating solvent such as HMPA alters the composition of organocyanocuprates in THF or DMS solutions. Evidence suggested higher-order cuprates exist as aggregates in THF or DMS alone whereas they exist as lower aggregates and lower-order Gilman-like organocuprates in THF with the presence of HMPA.[56]

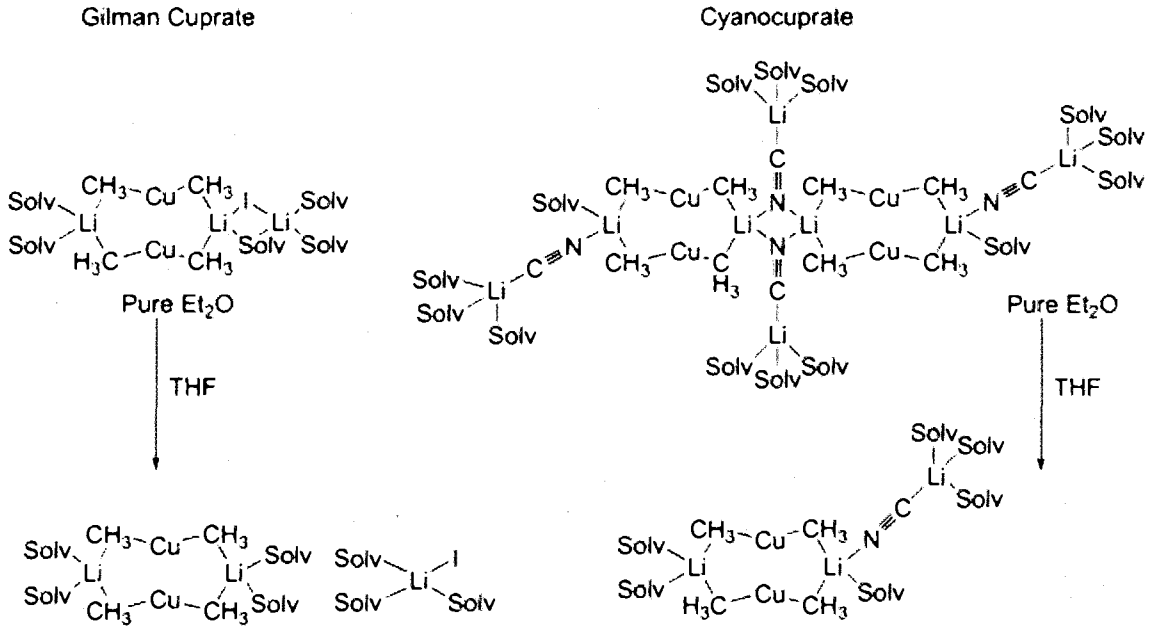
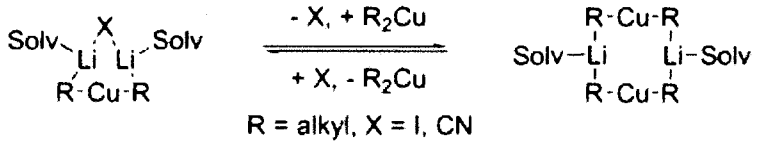


Figure 2: Postulated aggregate structures of Gilman and cyanocuprates in pure Et_2O and disaggregation upon addition of 4 eq. of THF determined by diffusion, NOE, and HOE NMR experiments.

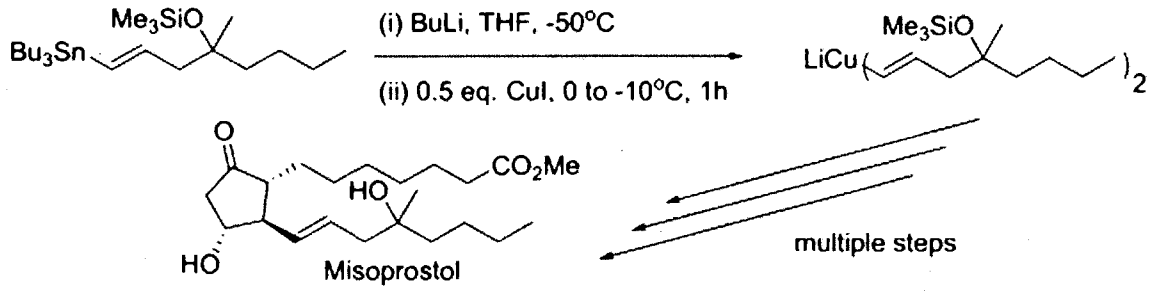
The solvent is not the only factor which alters the structure and reactivity of the cuprate species. Indeed it has been shown that the relative stoichiometry of the Cu(I) salt and alkyllithium reagents as well as the choice of Cu(I) salt can have a distinct effect on the structure of the aggregates.[57] Most spectroscopic studies suggest that the major species present is that in which Cu(I) is dicoordinated to two alkyl groups in a linear fashion with a bound or bridging lithium. This dialkylcuprate species is stabilized by solvent or anion coordination and in ethereal solvents the most stable structures for the cuprate is known as the neutral closed structures (Scheme 4).[58] This species however is in equilibrium with open clusters, minimum clusters, and free dialkylcuprates in solution.[53,59]



Scheme 4: Neutral closed structures of lithium dialkylcuprates.

Lipshutz *et al.* have long argued that the enhanced reactivity and selectivity of lithium dialkylcuprates derived from CuCN as opposed to CuI is a result of the formation of higher-order cyanocuprates wherein the reactive species contains a dianionic tricoordinate Cu(I) centre.[58(b)] While experimental evidence for tricoordinate Cu(I) species under certain conditions exist, most evidence suggests that in an ethereal solvent using one equivalent of CuCN with two equivalents of an alkyllithium, the expected dicoordinate $R_2CuLi{\cdot}LiCN$ species is the predominant species formed.[59]

The versatile chemistry of organocuprate reagents has resulted in their indispensable use in the synthesis of many natural products through carbon-carbon bond forming reactions. Copper-catalyzed reactions involving organocuprate intermediates have been successfully employed in a variety of syntheses, including the production of (-)-solavetivone[59]and prostaglandins.[60] Another example is the synthesis of the anti-ulcer agent misoprostol, which employs an organocuprate in a key stereoselective transformation and is produced in 50-200 kg y^{-1} quantities with a retail value exceeding \$7,000,000 y^{-1} (Scheme 5).[61]

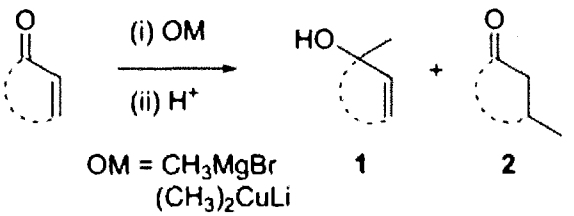


Scheme 5: Searle Pharmaceutical's Misoprostol procedure.

1.3.1 Mechanistic and Reactivity Properties of Organocuprates

Organometallic reagents such as RLi, RMgBr, R_2Zn, and $R_2CuLi{\cdot}LiCN$ are most commonly employed as synthetic sources of carbanions. These species exhibit varying but high degrees of basicity in part due to the electronegativity difference between the metal and its bound carbon(s). The smaller and less electronegative the metal the more carbanionic character the metal-carbon bond will exhibit and subsequently the carbon becomes more nucleophilic, basic, and reactive. The degree of carbanion character can also affect the selectivity of addition of the organic fragment as can be seen in the addition of an organometallic to an α,β-unsaturated ketone (enone) as shown in Scheme 6.[53]

The selectivity for 1,2-addition of a Grignard reagent compared to the 1,4-addition of a Gilman-type cuprate can be explained in terms of the Hard Soft Acid Base Theory (HSAB) and Frontier Molecular Orbital Theory (FMO).[62] Hard nucleophiles such as RLi and RMgBr reagents are typically highly polarized (not to be confused with



Scheme 6: Products of addition of organometallic to an enone: 1,2-addition **1** (CH_3MgBr) vs. 1,4-addition **2** ($(CH_3)_2CuLi$).

'polarizable' which they are not), with small ionic radii and thus high charge density at carbon and have a low lying HOMO. Soft nucleophiles like $R_2CuLi{\cdot}LiX$ are generally not polarized (but are 'polarizable'), with low charge density at the metal-bound carbon and posses a high lying HOMO with large molecular orbital coefficients at the reactive copper center. The metal-carbon bond character of hard nucleophiles is ionic in nature, tending towards covalent bond character for soft nucleophiles. Hard nucleophiles are selective for the 1,2-addition (**1**, Scheme 6) to enones whereas soft nucleophiles like cuprates give the 1,4-addition products (**2**, Scheme 6). The Klopman-Salem equation[63] for the interaction of a nucleophile and an electrophile (N and E respectively) combines the HSAB and FMO principles (Figure 3) to explain this selectivity.

For soft nucleophiles such as cuprates there will be a soft-soft interaction with the enone. The frontier orbital term is the dominant interaction because of the small $\Delta E(HOMO_N / LUMO_E)$ and small charge densities that reduce the Coulomb term. The

$$\Delta E = \underbrace{\frac{-Q_N Q_E}{\varepsilon R_{NE}}}_{\text{Coulomb term}} + \underbrace{\frac{2(c_N c_E \beta)^2}{E_{HOMO(N)} - E_{LUMO(E)}}}_{\text{Frontier Orbital term}}$$

Figure 3: Klopman-Salem equation: Q = charge density; ε = dielectric constant; R = distance (N-E); c = coefficient of MO; β = resonance integral; E = energy of MO.

largest LUMO-coefficient of the enone is located at the *β*-position to the carbonyl group, thus implying nucleophilic attack there according to the FMO theory giving the 1,4-addition product (Figure 4).

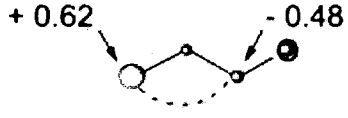


Figure 4: LUMO coefficients of an unsubstituted enone.

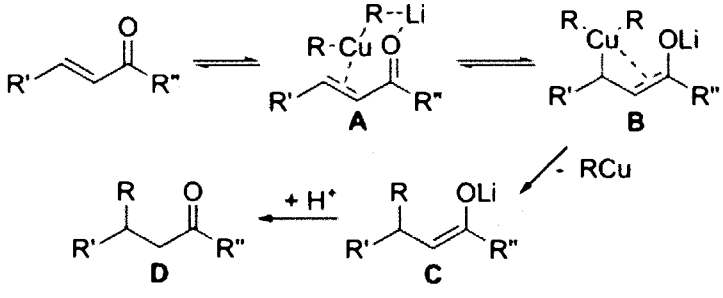
With hard nucleophiles such as RLi and RMgBr, the frontier orbital term of the Klopman-Salem equation is small because of the large $\Delta E(HOMO_N / LUMO_E)$. The dominant interaction is described by the Coulomb term and electrostatic interactions. The charge density on the enone indicates that the higher charge density is located at the carbon of the carbonyl group thus explaining the preferred attack of hard nucleophiles at that position to give the 1,2-addition product (Figure 5).

Figure 5: Charge densities of an unsubstituted enone.

The mechanism of copper-mediated 1,4-conjugate addition remains a subject of investigation. The proposal of single electron transfer has been rejected,[64] and more plausible mechanisms have been proposed over the last decade. Kinetic studies, NMR spectroscopy and theoretical calculations have led to a commonly accepted general mechanism. The simplest fundamental diorganocuprate unit is a linear [R_2Cu] anionic fragment (R = alkyl, aryl, etc.) and only one R group is transferred from the linear diorganocuprate, most often to an unsaturated organic molecule such as an enone.[65] The HOMO of the [R_2Cu] anion is the ligand-metal anti-bonding combination which uses the copper $3dz^2$ orbital. The LUMO(s) are the degenerate non-bonding copper $4p$ orbitals that are orthogonal to the axis of the molecule. The low lying empty $4p$ orbitals of the copper centre are both energetically and sterically inclined to act as σ-acceptors and the high lying unsaturated organic π orbitals as σ-donors. The copper $3d_{xz}$ or $3d_{yz}$ orbitals are also available to act as π-donors to the low lying empty π* of the unsaturated bond.

In the reaction of diorganocuprates with enones, the first step is the reversible coordination of copper on the enone, forming the π-complex **A** (Scheme 7). NMR-spectroscopic studies have shown that complex **A** is a reactive intermediate in the reaction and kinetic studies have shown that the reaction rate depends directly on the concentration of **A**.[66] Following the formation of the π-complex **A** two possibilities are generally considered for the transport of the organic fragment: (1) an organocuprate

intermediate is formed in which the formal oxidation state is copper(III); (2) a carbocupration intermediate in which the RCu-R adds across the double bond and the copper(I) formal oxidation state remains unchanged. The existence of the copper(III) intermediate is supported by the existence of compounds where the crystal structure shows square planar coordination of a formally *d8* copper and also by computational studies.[58(a)] Recently Cu(III) intermediates have been observed in 1,4-conjugate additions[59] as well as in direct alkylations.[67] Thus following the formation of the π-complex formal oxidative addition to form a σ-bound Cu(III) species occurs forming **B** and subsequent reductive elimination results in the formation of the enolate **C**, which can be transformed to the ketone **D** by addition of an electrophile such as H^+. The kinetic isotope effects in the 1,4-conjugate addition of Bu_2CuLi to cyclohexenone were determined by Singleton *et al.* with the conclusion that the rate-limiting step is carbon-carbon bond formation to give the enolate **C**.[68]



Scheme 7: Proposed mechanism for the addition of diorganocuprates to an enone.

Using the B3LYP/631A method for geometry optimization, the energy of the frontier molecular orbitals of the $[(CH_3)_2Cu]$ anion was examined for various C-Cu-C angles and the reactivity of lithium dialkylcuprates was reported to be correlated to the C-Cu-C angle (Figure 6).[69] Whereas a near linear geometry was found to be suited for S_N2 substitution reactions, a bent geometry was ideal for the formation of a π-complex with the enone.

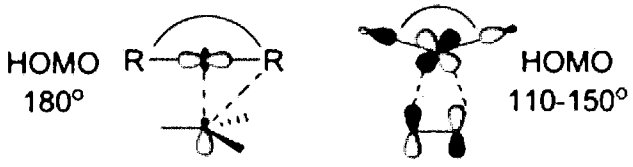


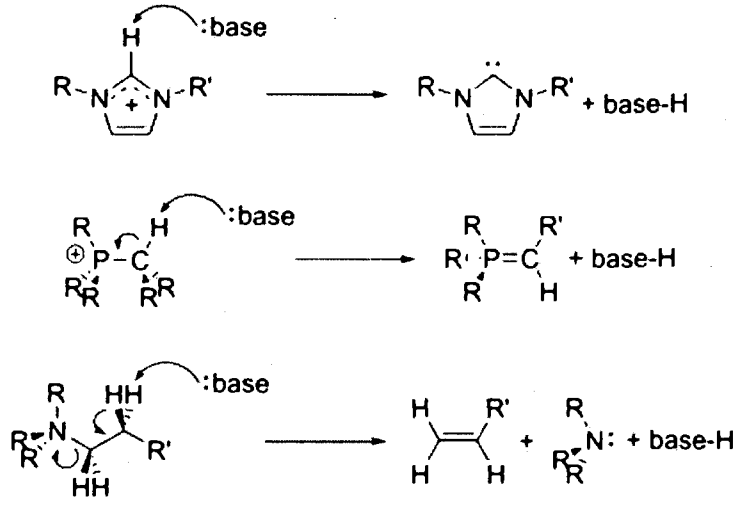
Figure 6: Effect of R-Cu-R angle on preferred reactivity. Linear R-Cu-R is the lowest energy structure for S_N2 additions and the bent geometry is optimal for forming the π–complex with an enone.

1.3.2 Ionic Liquids as Solvents for Stoichiometric Organometallic Reagents

Only recently have ILs demonstrated utility as solvents for stoichiometric organometallic reagents. While ILs are often thermally and electrochemically stable over broad ranges, there have been many examples of the chemical instability of the IL's cation in the presence of strong bases and active metals (Na, K). Deprotonation of the IL's cation is detrimental to the reaction as the solvent is destroyed along with the organometallic itself. For example imidazolium ions are easily deprotonated (typically at the C-2 position) under basic conditions.[70] This has been observed in the Baylis-Hillman reaction resulting in decreased yields since the *N*-heterocyclic carbene (*NHC*) formed is itself highly basic (pKa ~ 22-24)[71] and nucleophilic, reacting with carbonyls or aldehydes

giving decreased yields.[72] These *NHC*s can also be generated from imidazolium cations through oxidative addition of the carbon-hydrogen bond of the C-2 carbon to give an *NHC* metal complex.[73] In some cases, this *in situ* generation of *NHC*s can be favourable such as in palladium catalyzed carbon-carbon bond forming reactions where the catalytically active nanoparticle or low-oxidation state transition metal complex is believed to be stabilized by the newly formed *NHC* ligand(s).[74]

It is well known that quaternary ammonium cations with β-hydrogens undergo facile Hoffmann eliminations to give an alkene and an amine, while phosphonium cations with α-hydrogens can decompose to give a phosphorane (Wittig reagents) or under alkaline conditions can react with hydroxide ions to give a tertiary phosphine oxide and an alkane (Scheme 8).[75] Caution must therefore be taken when selecting the cationic components of an IL to be used in the presence of basic reagents such as simple organometallics.



Scheme 8: Deprotonation of: imidazolium cation to give a *NHC* (top); phosphonium cation to give a phosphorane (middle); ammonium cation to give an alkene and amine (Hoffman elimination, bottom).

In choosing an appropriate IL solvent for lithium dialkylcuprates the literature concerning reactions of similar reagents was examined. To date, no study has been reported for reactions of lithium dialkylcuprates in an IL solvent. Studies employing organocopper reagents in IL solvents are limited to Ullmann-type couplings[76,77] and copper-mediated 1,4-conjugate additions of diethylzinc reagents to enones.[78] The latter used a chiral IL based on α-pinene, however the IL was employed as an additive as opposed to a solvent. It has been shown that *N*-butylpyridinium [*N*-BuPy] and 1,2,3-trimethylimidazolium cations with the [BF_4] counter anion are suitable for alkylations of aldehydes with mono-[79] and diethylzinc reagents.[80] However, ILs suitable for Grignard chemistry may be more useful considering that a Grignard is more basic (harder) than its Gilman analogue. Thus it is likely that ILs suitable for Grignard chemistry should also find application with organocuprates. Figure 7 shows some of the ILs reported to date that have been shown to support Grignard reagents and chemistry. Albeit, these examples all required the presence of at least two residual THF molecules to stabilize the organometallic in the IL solution as there is a lack of coordinating/donor electrons in these ILs.

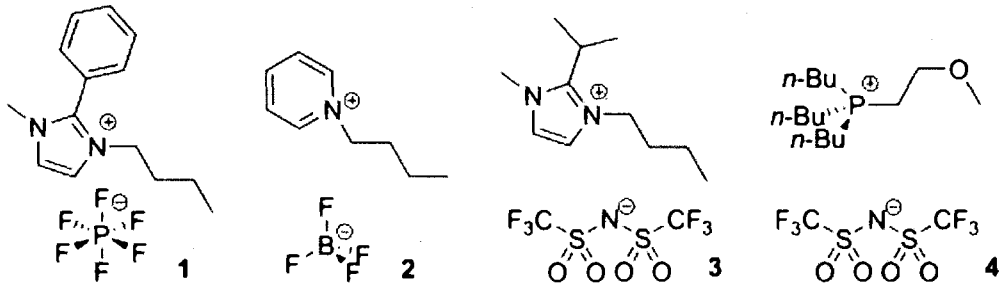


Figure 7: Potential IL candidates for lithium dialkylcuprates, previously found to form stable solutions with Grignard reagents (**1**[81],**2**[82],**3**[83],**4**[84]).

Clyburne *et al.* were the first to conduct Grignard chemistry in an IL solvent with absence of THF (as determined by ^{1}H NMR studies), showing that [PhMgBr] is persistent in long chained [$P^{6,6,6,14}$]-based ILs such as trihexyl(tetredecyl)phosphonium decanoate ([$P^{6,6,6,14}$][*n*-$C_9H_{19}CO_2$], Figure 8).[85] It was suggested that the coordinating/donor capacity of the [*n*-$C_9H_{19}CO_2$] anion stabilized the Grignard while the flexibility of the long alkyl chains located on phosphorous kinetically protects the phosphonium cation from deprotonation.

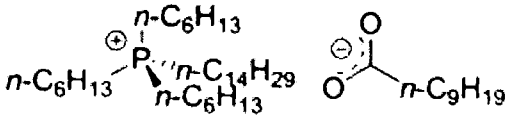


Figure 8: Trihexyl(tetradecyl)phosphonium decanoate, [$P^{6,6,6,14}$][*n*-$C_9H_{19}CO_2$].

1.4 Objectives

Our objective is to demonstrate that the chemistry offered by dialkylcuprates can be conducted in $[P^{6,6,6,14}]$-based IL solvents, thus minimizing or eliminating the use of THF and Et_2O. Through this we aim to show that conventional methods employed for cuprate chemistry can be improved upon in terms of reactivity, selectivity, and environmental friendliness, as well as to expand upon carbon-carbon bond forming reactions amenable to IL solvents. From a *Green Chemistry* perspective we hope to accomplish many goals through application of a number of the principles outlined by Anastas and Warner.[9] To truly achieve our goals our objectives must be:

(a) To determine an appropriate $[P^{6,6,6,14}]$-IL capable of forming stable ether-free solutions of dialkylcuprates by examining various anions.

(b) To develop a procedure to recycle the $[P^{6,6,6,14}]$-IL solvent.

(c) To show that the broad scope of transformations offered by cuprates in ethereal solvents can be achieved in the $[P^{6,6,6,14}]$-IL solvent.

The sensitivity of lithium dialkylcuprates to the reaction medium makes the choice of IL solvent incredibly important. We hope that in our efforts we can produce a more *Green* methodology for the utilization of diorganocuprates in carbon-carbon bond forming reactions by employing a $[P^{6,6,6,14}]$-based IL as an alternative to ethereal solvents.

2 Results and Discussion

The [$P^{6,6,6,14}$] cation was selected for this study as it has been shown to be stable in the presence of strong carbon-centered bases, including Grignard reagents.[88] As cuprates are less basic with a softer carbanion equivalent than their analogous Grignard species,[86] it should follow that the [$P^{6,6,6,14}$] cation is stable to deprotonation by the cuprate. The [$P^{6,6,6,14}$][Cl] salt was a convenient starting material from which we could synthesize *via* a metathesis reaction a series of [$P^{6,6,6,14}$]-based ILs to investigate as solvents for dialkylcuprates. However, commercially available [$P^{6,6,6,14}$][Cl] contains trace amounts of residual phosphines and HCl, trace amounts if phosphine oxides and isobutylnitrile, as well as retaining moisture. Therefore [$P^{6,6,6,14}$][Cl] was purified by a similar method as that described by Ramnial *et al.*[88(b)] prior to use in the synthesis of our other [$P^{6,6,6,14}$]-based ILs.

2.1 Purification of Trihexyl(tetradecyl)phosphonium-based Ionic Liquids

Saturated sodium bicarbonate (aq.) was used to neutralize excess HCl and the IL layer was washed thoroughly with water and extracted in a triphasic manner using hexanes and water. [$P^{6,6,6,14}$][Cl] was then dissolved in a small amount of hexanes and passed through a short column (silica gel/hexanes) to remove any phosphine oxides, which typically appear between 45-50 ppm in the ^{31}P NMR.[87] Trace organics are removed in the organic washes and under vacuum. Residual water was not removed from the bulk sample at this stage since water is used as co-solvent in the subsequent metathesis reactions. As reactions involving dialkylcuprates require completely

anhydrous conditions a portion of $[P^{6,6,6,14}][Cl]$ was dried *via* azeotropic distillation with toluene using a Dean Stark trap and further dried under high vacuum to yield a viscous, clear oil that is slightly yellow in colour.

The ^{1}H NMR spectrum of $[P^{6,6,6,14}][Cl]$ contains a broad multiplet at $\delta = 2.46$ ppm which integrates to 8 hydrogens corresponding to those located closest to the phosphonium centre $[P^{+}\text{-}(CH_2)_4\text{-}]$. At $\delta = 0.90$ ppm there are overlapping triplets integrating to 12 hydrogens corresponding to the terminal methyl groups of the alkyl chains. Between $\delta = 1.26$ and 1.51 ppm the remaining 48 hydrogens of the alkyl chains are found as broad overlapping multiplets. The ^{13}C NMR spectrum gives rise to 21 peaks as expected from the cation's structure, all appearing between $\delta = 32$ and 13 ppm. The ^{31}P NMR spectrum showed a single peak at $\delta = 32.1$ ppm and no other peaks verifying the removal of phosphine oxide impurities. The IR spectrum of $[P^{6,6,6,14}][Cl]$ is dominated by the C-H stretching frequencies appearing between 2855 and 2956 cm^{-1} and the P-CH_2 stretch at 1466 cm^{-1}. Analysis by ESI-MS in the positive mode confirmed the presence of the $[P^{6,6,6,14}]$ cation (m/z = 483.6) however the [Cl] anion (m/z = -35.5) was below the mass limit of the detector on the instrument in the negative mode (80 amu).

Attempts to remove the phosphine oxide from commercially available $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ *via* column chromatography (silica gel/hexanes) proved surprisingly counter-productive, with the relative amount of phosphine oxide (^{31}P $\delta = 48.4$ ppm) to the $[P^{6,6,6,14}]$ cation (^{31}P $\delta = 32.5$ ppm) increasing post-column (7.4 %) compared to pre-column (1.9 %).[88] Hence the IL was purified by the same process as used for $[P^{6,6,6,14}][Cl]$ with the exclusion of the column. A small amount of the phosphine oxide therefore

remains present in the $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$. Residual water was again removed by azeotropic distillation with toluene.

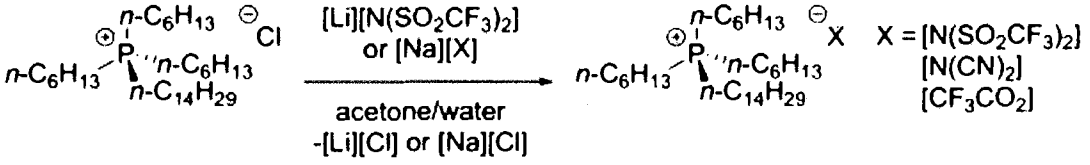
The ^1H NMR spectrum of $[P^{6,6,6,14}][n\text{-}C_9H_{19}\text{-}CO_2]$ is very similar to that of $[P^{6,6,6,14}][Cl]$ with two characteristic differences. One is a triplet at δ = 2.17 ppm corresponding to the 2 hydrogens next to the carboxylate moiety of the anion ($^3J_{H\text{-}H}$ = 7.5 Hz), the other being that the triplet of the terminal methyl group of the anion overlaps with those of the cation and that peak now integrates to 15 hydrogens (δ = 0.88 ppm). The multiplet for the 8 $[P^+\text{-}(CH_2)_4\text{-}]$ hydrogens are found at δ = 2.44 ppm and between δ = 1.26 and 1.49 ppm the remaining 62 hydrogens of the alkyl chains are found. The ^{13}C NMR spectrum contains 31 individual peaks as expected from $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$, mostly appearing between δ = 32 and 13 ppm. Of interest are the peaks outside this range, at δ = 179.27 ppm and 39.53 ppm corresponding to the carboxylate carbon and its α-carbon in the $[n\text{-}C_9H_{19}CO_2]$ anion respectively. The IR spectrum of $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ is again dominated by the C-H stretching frequencies appearing between 2855 and 2956 cm^{-1} and the P-CH_2 stretch at 1466 cm^{-1} and supports the presence of the anion displaying signals at 1579 and 1378 cm^{-1}, within the typical region for carboxylates. The presence of the $[P^{6,6,6,14}]$ cation (m/z = 483.6) and $[n\text{-}C_9H_{19}CO_2]$ anion (m/z = -170.8) was confirmed by ESI-MS analysis.

2.2 Synthesis of Trihexyl(tetradecyl)phosphonium-based Ionic Liquids

While ILs are typically considered to be non-coordinating, the anions in this study were chosen for the presence of potential electron donating lone-pairs. These are

considered to be essential for stabilization of the metal centre and dissolution of aggregated species in solution. The dicyanamide [$N(CN)_2$], trifluoroacetate [CF_3CO_2], and bis(trifluoromethylsulfonyl)amide [$N(SO_2CF_3)_2$] anions were also selected for their either hydrophobicity or low-viscosity, or both, the later property being important to ensure stirring at the low-temperatures required for the use of dialkylcuprate species.

The desired [$P^{6,6,6,14}$]-based ILs are easily synthesized by a metathesis reaction between the purified [$P^{6,6,6,14}$][Cl] and the sodium salt (lithium salt for [$N(SO_2CF_3)_2$]) of the desired anion in a procedure analogous to that described by Cieniecka-Roslonkiewicz *et al.* (Scheme RD.1).[89] The metathesis is carried out by dissolving [$P^{6,6,6,14}$][Cl] in acetone followed by addition of an excess of the alkali salt and subsequent stirring of the mixture at room temperature for 3 days. The acetone is then removed under vacuum and the newly synthesized [$P^{6,6,6,14}$]-based ILs are diluted with Et_2O and the organic layer is washed with deionized water to remove residual alkali and chloride salts until no precipitate forms upon addition of $AgNO_3$ to the washes. Removal of residual water *via* azeotropic distillation with toluene and subsequent removal of solvent affords pure [$P^{6,6,6,14}$]-based ILs in reasonably high yields (Table RD.1). The ILs, all of which were obtained as clear slightly-yellow oils, are stored under an inert atmosphere (Argon) in round-bottomed flasks sealed with greased glass stoppers to avoid absorption of water from the atmosphere.



Scheme RD.1: Synthesis of trihexyl(tetradecyl)phosphonium-based ILs by salt metathesis.

$[P^{6,6,6,14}]$-IL	Yield (%)
$[P^{6,6,6,14}][N(SO_2CF_3)_2]$	93.0
$[P^{6,6,6,14}][N(CN)_2]$	85.3
$[P^{6,6,6,14}][CF_3CO_2]$	83.6

Table RD.1: Results of the metathesis reaction to form trihexyl(tetradecyl)phosphonium-based ILs.

The ^{1}H NMR spectrum for $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ was found to be virtually identical to that of $[P^{6,6,6,14}][Cl]$ which would be expected given the absence of protons in the anion. The only notable difference is in the chemical shift of the 8 $[P^{+}\text{-}(CH_2)_4\text{-}]$ hydrogens now shifted to δ = 2.10 ppm. To confirm the presence of the $[N(SO_2CF_3)_2]$ anion we look at the ^{13}C NMR spectrum which contains the same 20 peaks between δ = 32 and 13 ppm as seen in $[P^{6,6,6,14}][Cl]$ as well as a quartet at δ = 120.0 ppm ($^{1}J_{C\text{-}F}$ = 321 Hz) resulting from the two equivalent CF_3 moieties found in the $[N(SO_2CF_3)_2]$ anion. Further confirmation of the anion's presence is the singlet found in the ^{19}F NMR spectrum at δ = -79.82 ppm, while the ^{31}P NMR spectrum shows only a singlet at δ = 32.6 ppm indicative of the $[P^{6,6,6,14}]$ cation and absence of any other phosphorous species. Analysis of the IR spectrum shows the same C-H and P-CH_2 frequencies seen in $[P^{6,6,6,14}][Cl]$ along with strong signals for the sulfonamide (N-S(O_2)-C; 1351 cm^{-1} and 1138 cm^{-1}) and the CF_3 moieties (1058 cm^{-1} and 1137 cm^{-1}). ESI-MS analysis confirms

the presence of both the [$P^{6,6,6,14}$] cation (m/z = 483.7) and the [$N(SO_2CF_3)_2$] anion (m/z = -279.6).

For [$P^{6,6,6,14}$][$N(CN)_2$] the chemical shift of the 8 [P^+-(CH_2)$_4$-] hydrogens is now shifted to δ = 2.20 ppm in the ^{1}H NMR. Confirmation of the [$N(CN)_2$] anion is seen as a singlet in the ^{13}C spectrum at δ = 119.96 ppm. Strong signals at 2127 cm^{-1} and 2225 cm^{-1} in the IR spectrum further confirm the anion's presence[90] in accompaniment with the typical C-H and P-CH_2 stretches associated with the [$P^{6,6,6,14}$] cation. The ^{31}P NMR spectrum confirms the presence of only one phosphorous species with a single peak appearing at δ = 32.5 ppm. The [$P^{6,6,6,14}$] cation (m/z = 483.7) was observed by ESI-MS however the [$N(CN)_2$] anion (m/z = -66.0) was again below the mass limit of the detector in the negative mode.

Lastly the ^{1}H NMR for [$P^{6,6,6,14}$][CF_3CO_2] has the 8 [P^+-(CH_2)$_4$-] hydrogens now shifted to δ = 2.29 ppm. Despite highly concentrating the sample the presence of the [CF_3CO_2] anion from the ^{13}C NMR spectrum is not as evident. Very low intensity peaks are seen as a singlet at δ = 160.26 ppm potentially corresponding to the carboxylate moiety and a possible doublet around δ = 117.50 ppm corresponding to the CF_3 moiety ($^1J_{C\text{-}F}$ = 295 Hz) however they are barely above the baseline and thus not definitive. This is likely due to the uneven Nuclear Overhauser Effect experienced in ^{13}C NMR, where the signals for the carbons of the [$P^{6,6,6,14}$] cation are enhanced by their bound hydrogens. As the carbons of the anion are not attached to any hydrogens the NOE enhancement is not as profound and thus the signals would be relatively weak. The inclusion of the [CF_3CO_2] anion is however confirmed by the presence of a singlet in the ^{19}F NMR spectrum at δ = -75.61 ppm. The IR spectrum again contains the C-H and P-CH_2 stretches

of the $[P^{6,6,6,14}]$ cation along with a signal at 1688 cm^{-1} corresponding to the carboxylate moiety and signals at 1117, 1159, and 1197 cm^{-1} corresponding to the CF_3 moiety. The ^{31}P NMR confirms the presence of only one phosphorous species with a single peak appearing at δ = 32.5 ppm. ESI-MS confirms inclusion of the $[CF_3CO_2]$ anion (m/z = -112.8) in the negative mode and the $[P^{6,6,6,14}]$ cation (m/z = 483.7) in the positive mode.

The variation of the chemical shift for the multiplet corresponding to the 8 [P^+-(CH_2)$_4$-] hydrogens suggest a possible anion effect, which may give insight into the strength of the attraction between the cation and anion in the $[P^{6,6,6,14}]$-based ILs (Table RD.2). Here it appears as though the more basic the anion the more shielded are the hydrogens closest to the phosphonium centre, as the anion donates electron density to the phosphorous atom. The trend of basicity of the anions ($[N(SO_2CF_3)_2]$ > $[N(CN)_2]$ > [*n*-$C_9H_{19}CO_2$] > $[CF_3CO_2]$ > [Cl]) closely matches the trend for the degree of shielding experienced by the [P^+-(CH_2)$_4$-] hydrogens save that [*n*-$C_9H_{19}CO_2$] and $[CF_3CO_2]$ are unexpectedly reversed in position. One would then expect that the ^{31}P NMR signal would also be affected however the signal varies very little in our series. This may be a result of inconsistent field drift as our ^{31}P NMR chemical shifts are reference to an external standard. Although the yields obtained for our series of $[P^{6,6,6,14}]$-based ILs is reasonably high, they could likely be improved upon by adding a larger excess of the alkali salt relative to $[P^{6,6,6,14}][Cl]$, although this would go against efforts towards atom economy in the preparation of these salts.[91] All of the IR spectra obtained for the $[P^{6,6,6,14}]$-based IL series were devoid of any signal in the region between 3300-3000 cm^{-1} indicating that water had been effectively removed by azeotropic distillation, supported by the absence of peaks for water in their respective ^1H NMR spectra.

$[P^{6,6,6,14}]$-IL	Chemical Shift of $P^+(-CH_2-)_4$- (^1H δ, ppm)	Chemical Shift of P^+ (^{31}P δ, ppm)
$[P^{6,6,6,14}][Cl]$	2.46	32.1
$[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$	2.44	32.5
$[P^{6,6,6,14}][N(SO_2CF_3)_2]$	2.10	32.6
$[P^{6,6,6,14}][N(CN)_2]$	2.20	32.5
$[P^{6,6,6,14}][CF_3\text{-}CO_2]$	2.29	32.5

Table RD.2: ^1H NMR chemical shift of the hydrogen closest to the phosphonium centre and ^{31}P NMR chemical shifts for the phosphonium centre.

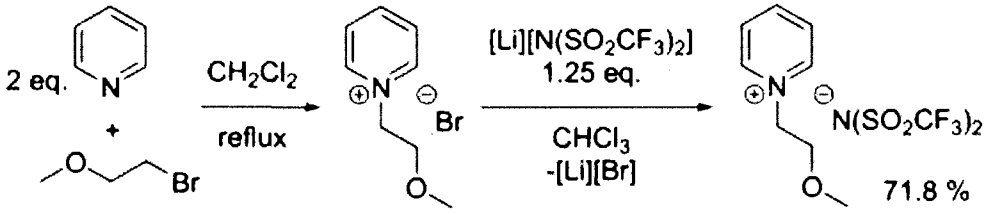
2.3 Synthesis of Pyridinium-based Ionic Liquids

Itoh *et al.* have recently shown that incorporation of an alkyl ether functionality onto the phosphonium centre generates phosphonium salts, notably methoxyethyl(tributyl)phosphonium bis(trifluoromethylsulfonyl)amide (Figure 7 example 4), that are capable of mediating reactions involving basic aliphatic Grignard reagents.[87] This is a logical design given the dependence of many simple organometallics on ethereal solvents for stabilization of the electropositive metal centre. Recently Scammells *et al.* have alternatively incorporated an ether functionality at the 3-position of a [Py]-based IL and showed that *N*-butyl-3-(ethoxymethyl)pyridinium bis(trifluoromethylsulfonyl)amide [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] is a suitable solvent for Grignard chemistry.[92] The following sections describe our attempts to access [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] and other ether containing [Py]-based ILs as potentially biodegradable,[93] low-viscosity ILs suitable for organometallic applications. Due to the hydrophilic nature of ether moieties incorporated into the cation the [$N(SO_2CF_3)_2$] anion

was selected for its hydrophobic nature and the relative reduction in IL viscosity compared to other anions.

2.3.1 Synthesis of *N*-(methoxyethyl)pyridinium bis(trifluoromethyl-sulfonyl)amide, [*N*-MEPy][$N(SO_2CF_3)_2$]

A Japanese patent from 2005 outlined the synthesis of [*N*-MEPy][$N(SO_2CF_3)_2$] and its potential use in electronic devices but has not been reportedly used as a solvent.[94] Since the patent was in Japanese we developed our own simple preparation of [*N*-MEPy][$N(SO_2CF_3)_2$] (Scheme RD.2) which involved gently heating a solution of 2-bromoethylmethylether and excess pyridine in CH_2Cl_2 at reflux for 5 h resulting in the solution changing from clear to brown-orange. A brown oil forms a separate layer at the bottom which solidifies when cooled to room temperature. The precipitate would not completely dissolve when reheated; however, crystalline [*N*-MEPy][Br] forms from both CH_2Cl_2 and acetone solutions.[95] As all materials used in the synthesis are readily volatile they are easily removed under vacuum to give [*N*-MEPy][Br] as a pure brown solid (white when ground into powder) in high yield (86.1 %; mp. 127-128 °C) and was characterized by NMR (^1H, ^{13}C) and ESI-MS.[96] This material is a convenient precursor for ILs through salt metathesis. Incomplete formation of [*N*-MEPy][Br] is likely due a percentage of the 2-bromoethylmethlyether (b.p 40-41 °C) remaining in the gas phase above the solution during the course of the reaction despite using a reflux condenser and keeping the system under a flow of argon.



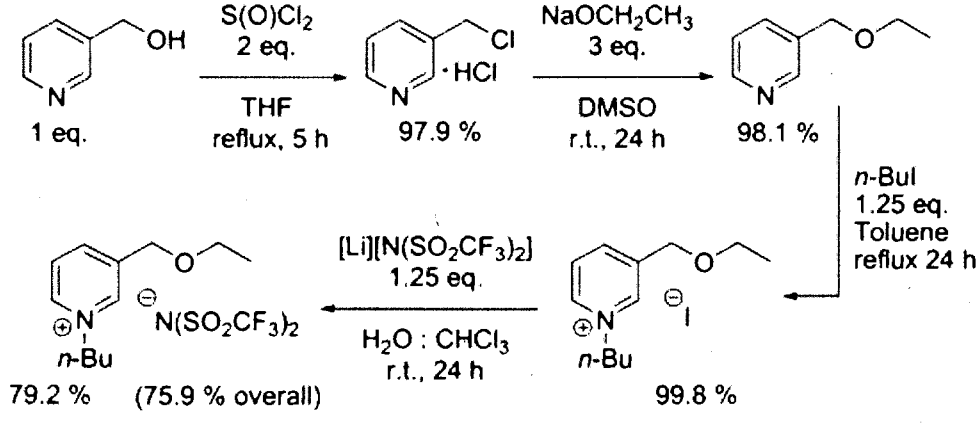
Scheme RD.2: Synthesis of *N*-(methoxyethyl)pyridinium bromide and *N*-(methoxyethyl)pyridinium bis(trifluoromethylsulfonyl)amide.

Metathesis of water soluble [*N*-MEPy][Br] with [Li][$N(SO_2CF_3)_2$] in a water/$CHCl_3$ binary solvent system at room temperature for 24 h affords [*N*-MEPy] [$N(SO_2CF_3)_2$] after extraction with $CHCl_3$ and washing with water until no precipitate formed when in the wash was tested with $AgNO_3$. After drying under high vacuum [*N*-MEPy][$N(SO_2CF_3)_2$] is isolated as a low-viscosity yellow oil in good yield based on 2-bromoethylmethylether (71.8 %). The ^1H NMR spectrum contains a singlet at δ = 3.33 ppm corresponding to the methoxy moiety, two triplets at δ = 3.84 and 4.76 ppm ($^3J_{H\text{-}H}$ = 4.4 Hz) respectively representing the O and N^+ terminated ethyl moiety. A multiplet at δ = 8.05 ppm, a triplet at δ = 8.55 ppm ($^3J_{H\text{-}H}$ = 7.6 Hz), as well as a doublet at δ = 8.79 ppm ($^3J_{H\text{-}H}$ = 5.8 Hz) represent the hydrogens of the pyridinium ring. The ^{13}C spectrum contains 7 peaks in total, 6 from the [*N*-MEPy] cation and notably a quartet at δ = 119.9 ppm ($^1J_{C\text{-}F}$ = 321 Hz, ^{19}F NMR δ = -80.2 ppm) indicative of the [$N(SO_2CF_3)_2$] anion. The IR spectrum contains some weak stretches around the 3000 - 2800 cm^{-1} region for the C-H stretches of the ether moiety along with medium intensity signals at 1638 and 1491 cm^{-1} characteristic of pyridine rings and strong signals for the sulfonamide (N-S(O_2)-C; 1352 cm^{-1} and 1137 cm^{-1}) and the CF_3 moieties (1191 cm^{-1} and 1057 cm^{-1}). Analysis of the

spectra obtained from ESI-MS confirmed our [*N*-MEPy] cation (m/z = 138.0) and $[N(SO_2CF_3)_2]$ anion pairing (m/z = -279.7).

2.3.2 Synthesis of *N*-butyl-3-(ethoxymethyl)pyridinium bis(trifluoromethylsulfonyl)amide, [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$]

The synthesis of [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] from 3-pyridinemethanol involved 4 steps as outlined in Scheme RD.3. Addition of 2 eq. of thionyl chloride to a THF solution of 3-pyridinemethanol at room temperature instantly results in the formation of a white powder in an exothermic reaction. After 5 h of stirring at reflux 3-(chloromethyl)pyridine hydrochloride is formed in near quantitative yields (step 1, 97.9 %). The remainder of the synthesis follows that described by Scammells *et al.* with addition of a DMSO solution of 3-(chloromethyl)pyridine hydrochloride to a separately prepared DMSO solution of sodium ethoxide producing 3-(ethoxymethyl)pyridine as a



Scheme RD.3: Synthesis of *N*-butyl-3-(ethoxymethyl)pyridinium bis(trifluoromethylsulfonyl)amide.

dark red oil in high yield (step 2, 98.1 %) after purification by column chromatography (silica gel/ethyl acetate). Quaternization of the pyridine ring is accomplished by heating 3-(ethoxymethyl)pyridine with an excess of 1-iodobutane in toluene at reflux. Simply removing the solvent under vacuum and excess 1-iodobutane under high vacuum offers pure [*N*-Bu-3-EMPy][I] as a brown solid again in near quantitative yield (step 3, 99.8 %). Finally, metathesis of [*N*-Bu-3-EMPy][I] with an excess of [Li][$N(SO_2CF_3)_2$], work up and drying under high vacuum provides [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] as a red-orange low-viscosity oil in an overall yield of 75.9 % based on 3-pyridinemethanol (step 4, 79.2 %). All intermediates have been characterized by ^1H and ^{13}C NMR with [*N*-Bu-3-EMPy][I] also being characterized by ESI-MS ([*N*-Bu-3-EMPy] m/z = 194.1; [I] m/z = -126.6) and elemental analysis (Calc: C 44.87 %, H 6.28 %, N 4.36 %; Found: C 45.20 %, H 6.49 %, N 4.35 %).

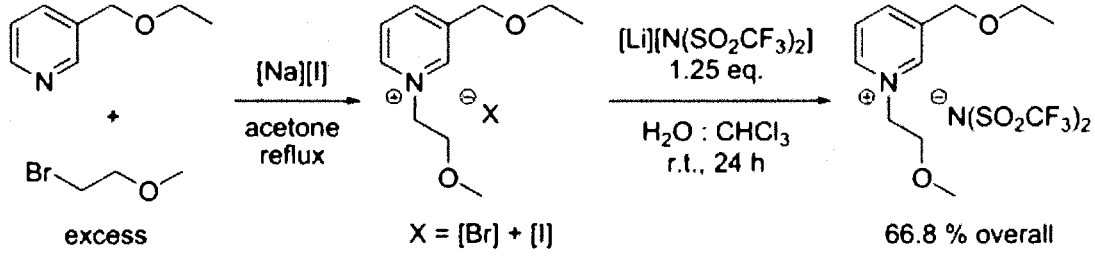
The ^1H NMR spectrum of [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] contains a triplet (δ = 0.97 ppm; $^3J_{H-H}$ = 7.4 Hz), a sextet (δ = 1.40 ppm; $^3J_{H-H}$ = 7.4 Hz), a quintet (δ = 1.40 ppm; $^3J_{H-H}$ = 7.5 Hz), and a triplet (δ = 4.58 ppm; $^3J_{H-H}$ = 7.4 Hz) representative of the Bu fragment. The ether fragment is represented by a triplet (δ = 1.28 ppm; $^3J_{H-H}$ = 7.0 Hz), a quartet (δ = 3.68 ppm; $^3J_{H-H}$ = 7.0 Hz), and a singlet (δ = 4.72 ppm). The pyridinium ring gives rise to an overlapping doublet of doublets which appears as a triplet (δ = 8.00), a doublet (δ = 8.44 ppm $^3J_{H-H}$ = 8.0 Hz), and a singlet (δ = 8.70 ppm) overlapping with a second doublet (δ = 8.44 ppm). The ^{13}C spectrum contains 13 signals as would be expected with 4 residing in the aliphatic region (δ = 13 – 34 ppm), the *N*-bound carbon of the butyl fragment appearing at δ = 62.36 ppm, while the two ethereal carbons appear at δ = 77.18 and 77.69 ppm. Between 128.20 and 143.61 ppm 5 peaks are found representing

the [Py] ring. The $[N(SO_2CF_3)_2]$ anion is observed in the ^{13}C spectrum as a quartet (δ = 119.85 ppm; $^1J_{C\text{-}F}$ = 321 Hz). A singlet in the ^{19}F NMR spectrum is observed for the CF_3 moiety at δ = -80.0 ppm. The IR spectrum contains weak C-H stretching between 3100-2800 cm^{-1} along with weak intensity signals between 1650 and 1450 cm^{-1} characteristic of pyridine rings and strong signals for the sulfonamide (N-S(O_2)-C; 1352 cm^{-1} and 1137 cm^{-1}) and the CF_3 moieties (1191 cm^{-1} and 1057 cm^{-1}) of the anion. The [*N*-Bu-3-EMPy] cation (m/z = 194.1) and $[N(SO_2CF_3)_2]$ anion (m/z = -279.7) pairing were confirmed by ESI-MS.

2.3.3 Synthesis of *N*-(methoxyethyl)-3-(ethoxymethyl)pyridinium bis(trifluoromethylsulfonyl)amide, [*N*-ME-3-EMPy][$N(SO_2CF_3)_2$]

After accessing 3-(ethoxymethyl)pyridine in the previous synthesis, we took advantage of fact that we could now incorporate a second ether moiety into our [Py] cation (Scheme RD.4). To achieve this 3-(ethoxymethyl)pyridine and excess 2-bromoethylmethylether (1.2 eq.) are dissolved in acetone and stirred at reflux overnight. After removing all volatiles the ^1H spectrum showed incomplete quaternization of the pyridine nitrogen (38 %). Addition of more 2-bromoethylmethylether (0.95 eq.) and overnight stirring at reflux increased the amount of quaternization (78 %). A final portion of 2-bromoethylmethylether (0.63 eq.) was added along with [Na][I] (1.501g, 10.00 mmol) to catalyze the reaction. The solution was heated and stirred at reflux for 6 h at which point the quaternization had not proceeded much further (86 %). Unreacted 3-(ethoxymethyl)pyridine was removed by column chromatography (silica gel/ethyl

acetate) and [*N*-ME-3-EMPy][X] (X = Br, I) eluted with MeOH. Removal of the solvent under vacuum and drying under high vacuum yields [*N*-ME-3-EMPy][X] as a viscous red liquid (3.75 g, 11.6 mmol or 69 % for [I], 13.6 mmol or 81 % for [Br]).[97] Metathesis of [*N*-ME-3-EMPy][X] with excess [Li][$N(SO_2CF_3)_2$] at room temperature in a water/acetone binary solvent system and subsequent work-up followed by drying under high vacuum yields [*N*-ME-3-EMPy][$N(SO_2CF_3)_2$] as a low-viscosity clear yellow-orange liquid (5.37 g, 66.8 % based on 3-(ethoxymethyl)pyridine).



Scheme RD.4: Synthesis of *N*-(methoxyethyl)-3-(ethoxymethyl)pyridinium bis(trifluoromethylsulfonyl)amide.

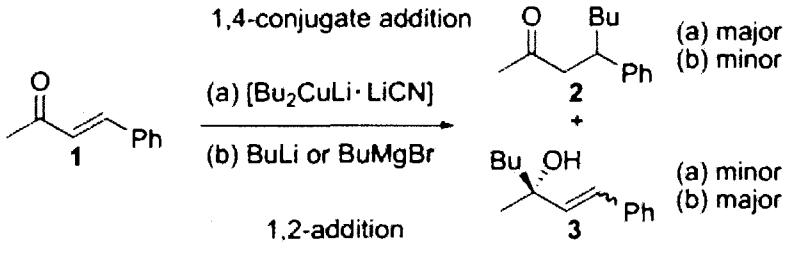
The ^{1}H NMR spectrum of [*N*-ME-3-EMPy][$N(SO_2CF_3)_2$] contains a triplet at δ = 1.28 ppm ($^3J_{H-H}$ = 7.0 Hz) and a quartet at δ = 3.67 ($^3J_{H-H}$ = 7.0 Hz) representing the 3-positioned ethoxymethylether moiety as well as a singlet at δ = 4.74 for the benzylic hydrogens. The *N*-methoxyethyl substituent is seen as a singlet at δ = 3.33 ppm, and two triplets at δ = 3.82 and 4.74 ppm ($^3J_{H-H}$ = 4.4 Hz). The pyridinium hydrogens are seen as a multiplet at δ = 7.98 ppm, a doublet at δ = 8.45 ppm ($^3J_{H-H}$ = 7.0 Hz), and a multiplet at δ = 8.67 ppm. The ^{13}C NMR spectrum contains 11 separate peaks for the [*N*-ME-3-EMPy] cation, mostly grouped between δ = 58-70 ppm (for the ether moieties) and δ = 127-144

ppm (for the pyridinium ring), and notably a quartet at δ = 119.77 ($^1J_{C\text{-}F}$ = 321 Hz) representing the anion. Again a singlet is observed (δ = -80.0 ppm) in the ^{19}F NMR spectrum representing the CF_3 moieties. The IR spectrum contains weak C-H stretching between 3100-2800 cm^{-1} along with weak intensity signals between 1650 and 1450 cm^{-1} characteristic of pyridine rings and strong signals for the sulfonamide (N-S(O_2)-C; 1353 cm^{-1} and 1136 cm^{-1}) and the CF_3 moieties (1194 cm^{-1} and 1058 cm^{-1}) of the [$N(SO_2CF_3)_2$] anion. Analysis of ESI-MS data confirms the [*N*-ME-3-EMPy] cation (m/z = 196.0) and [$N(SO_2CF_3)_2$] anion (m/z = -279.7) pairing. While the yield is fairly low, improvements can likely be made to the quaternization step for reasons similar to those given for the synthesis of [*N*-MEPy][Br].

2.4 Reactions of Organocuprates in Trihexy(tetradecyl)phosphonium and Pyridinium-based Ionic Liquids

With our series of [$P^{6,6,6,14}$] and [Py]-based ILs synthesized, purified, and characterized we now sought to explore their potential use in the 1,4-conjugate addition of dialkylcuprates to enones. We chose the addition of [$Bu_2CuLi{\cdot}LiCN$] to *trans*-4-phenyl-3-buten-2-one (**1**) to form 4-phenyloctan-2-one (**2**) as our model reaction as it is well studied in the literature offering us much comparative data (Scheme RD.5).[53] An authentic sample of **2** was prepared by conventional methods in THF and the product was characterized by ^1H and ^{13}C NMR as well as by its GC-MS retention time (t_R) and fragmentation pattern (M^+ = 204(1), 146(100), 147(48)). To identify any potential 1,2-addition products, namely 3-methyl-1-phenylhept-1-en-3-ol (**3**), we performed a separate

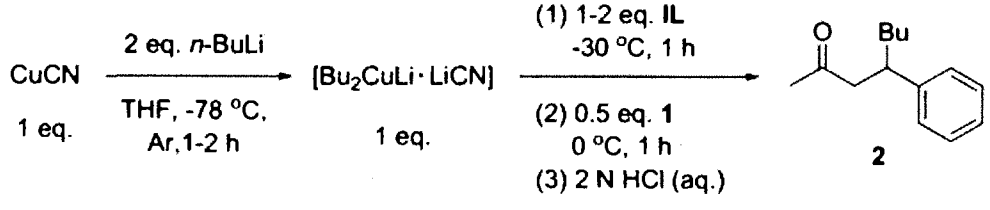
experiment involving the addition of *n*-BuLi to **1**. In this experiment the ^{1}H and GC-MS data confirmed **3** as the major product (61 %) with the 1,4-addition product **2** (18 %) and unreacted **1** also present in both forms of analysis.



Scheme RD.5: (a) 1,4-conjugate addition by using a dialkylcuprate reagent; (b) 1,2-addition by using an alkyllithium reagent.

2.4.1 Compatibility Experiments of Organocuprates in Trihexy(tetradecyl)phosphonium and Pyridinium-based Ionic Liquids: Preliminary Examination

In order to verify the stability of the [$P^{6,6,6,14}$] and [Py]-based ILs our model reaction was performed in THF in the presence of 2.5-2.75 mL of the IL under examination (Scheme RD.6). This equates to 1-1.3 eq. of the [$P^{6,6,6,14}$]-based ILs or 1.8-2.2 eq. of the [Py]-based ILs (Table RD.3) with respect to the amount of CuCN used to



Scheme RD.6: General procedure for compatibility experiments.

form the cuprate. The cuprate was prepared in THF and the IL under examination was added slowly to this solution at -30 °C. Typically the IL freezes and stops the stir bar, but eventually dissolves and forms homogenous clear yellow-orange THF/IL solutions of [$Bu_2CuLi{\cdot}LiCN$] after stirring for 60 min and warming to 0 °C. The exceptions being the [Py]-based ILs which form dark red solutions and [$P^{6,6,6,14}$][*n*-$C_9H_{19}CO_2$] which becomes a cloudy white-yellow mixture. After the addition of **1** at 0 °C and stirring at that temperature for 1 h the reaction is quenched with dilute HCl solution. Our GC-MS analysis involved comparison of the tR and fragmentation pattern of species present in the crude reaction mixtures from the compatibility experiments to those obtained for our authentic samples. The relative amounts of species present were calculated from the MS-

Ionic Liquid	**Density** g/mL [a]	**Vol** mL	**MW** g/mol	**Eq.** (w.r.t. to 4.00 mmol CuCN)
[$P^{6,6,6,14}$][Cl]	0.901	2.5	519.28	1.3
[$P^{6,6,6,14}$][*n*-$C_9H_{19}CO_2$]	0.897	2.5	655.11	1.2
[$P^{6,6,6,14}$][$N(SO_2CF_3)_2$]	1.07	2.75	763.97	1.0
[$P^{6,6,6,14}$][$N(CN)_2$]	0.904	2.5	549.88	1.0
[$P^{6,6,6,14}$][CF_3CO_2]	0.98 [b]	2.5	596.85	1.0
[*N*-MEPy][$N(SO_2CF_3)_2$]	1.5 [b]	2.5	418.33	2.2
[*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$]	1.2 [b]	2.5	474.44	1.8

Table RD.3: Volume of trihexyl(tetradecyl)phosphonium-based ILs used in compatibility experiments. (a) Density values acquired from Ionic Liquids Database (Merck)[98]; (b) density roughly calculated by taring a 1.00 mL syringe, drawing in some of the IL and dividing that volume by the new mass of the syringe.[99]

chromatogram integration values by dividing the area of a particular signal by the total area of all signals not found in the blank.[100]

Addition of **1** at 0 °C causes the [Py]-based IL solutions to change colour to near black and the reactions are quenched after 1 h with 2 N HCl. Disappointingly low conversion of **1** to **2** was observed for our model reaction in their presence. One major unexpected signal is observed in the GC-MS obtained for the reaction performed in the presence of [*N*-MEPy][$N(SO_2CF_3)_2$] (Table RD.4, entry 8; t_R 3.68 min, M^+ = 150(1), 148(95), 103(100)) and the same can be said for when [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] (entry 9; t_R 5.23 min, M^+ = 182, 131(100)) was examined. These signals are notably different both in t_R and fragmentation pattern, and thus are specific to the two different [Py]-based ILs. A possible structure has yet to be determined in either case, however these signals are not observed in any of the [$P^{6,6,6,14}$]-based IL compatibility experiments. The low conversion of **1** to **2** in our [Py]-based ILs may only be a result of slower reaction times in their presence however the dark colour of the reaction and unknown signals in the mass spectra suggest decomposition of the cuprate and/or the ILs. This could be a result of residual water being associated with the ether moieties found in the [Py]-cations despite the inclusion of the [$N(SO_2CF_3)_2$] anion and exhaustive drying of the IL under high vacuum at 60 °C prior to and just before their use. Scammells *et al.* reported that high vacuum was sufficient to remove residual water from [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] in their Grignard studies. In the case of [*N*-MEPy][$N(SO_2CF_3)_2$] the IL may decompose due to either oxidative addition of the N-C bond of the N^+-$CH_2CH_2OCH_3$ region of the IL to the copper centre of the cuprate or β-hydride elimination. Similar decomposition pathways are possible for [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$]. There is however insufficient evidence to support or disprove either such decomposition pathway at this time.

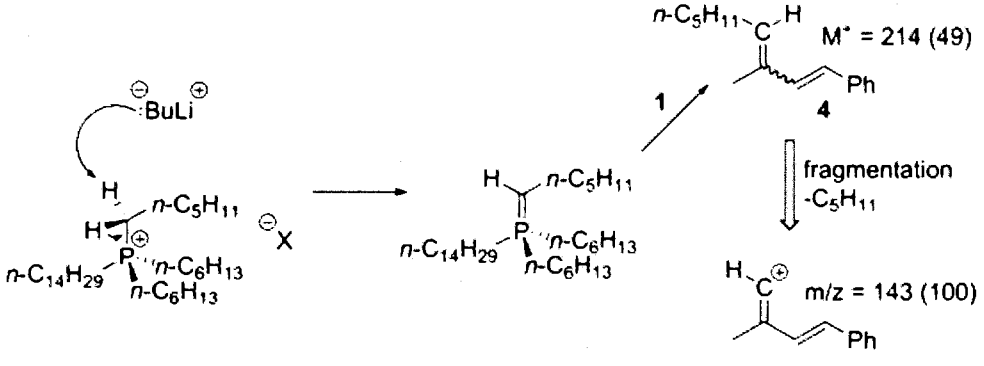
When **1** is added to the [$P^{6,6,6,14}$]-based IL/cuprate solutions at 0 °C the colour changes from yellow to orange. When the reactions are quenched the solutions form a solid very quickly that is white in colour which eventually dissolves and yields a yellow IL layer. Aliquots taken at 5 min and 1 h of reaction time in the presence of our [$P^{6,6,6,14}$]-based ILs show good to high conversion of **1** to **2** (Table RD.4, entries 1-7) with minimal formation of **3**. Multiple unexpected species appeared in many of our [$P^{6,6,6,14}$]-based IL compatibility experiments none of which appeared in the [Py]-based IL examples. Notably the unidentified peaks in each of the [Py]-based IL trials are not observed in the mass spectra obtained for the [$P^{6,6,6,14}$]-based IL compatibility experiments.

Entry	Ionic Liquid	CuCN (mmol)	BuLi (mmol)	Vol IL (mL)	1 (mmol)	Time (min)	GC Yield of 2 (%)
1	[$P^{6,6,6,14}$]	4.02	8.8	2.5	2.01	5	40
	[Cl]	1 eq.	2.2 eq.	1.3 eq.	0.5 eq	60	65
2	[$P^{6,6,6,14}$]	4.02	8.0	2.5	2.01	5	23
	[Cl]	1 eq.	2 eq.	1.3 eq.	0.5 eq	60	80
3	[$P^{6,6,6,14}$]	3.94	7.7	2.5	2.01	5	44
	[*n*-$C_9H_{19}CO_2$]	1 eq.	1.9 eq.	1.2 eq.	0.5 eq.	60	94
4	[$P^{6,6,6,14}$]	4.00	8.6	2.5	2.00	5	23
	[$N(SO_2CF_3)_2$]	1 eq.	2.2 eq.	0.9 eq.	0.5 eq.	60	93
5	[$P^{6,6,6,14}$]	4.01	8.0	2.75	2.00	5	39
	[$N(SO_2CF_3)_2$]	1 eq.	2 eq.	1 eq.	0.5 eq.	60	84
6	[$P^{6,6,6,14}$]	4.03	8.8	2.5	2.01	5	13
	[$N(CN)_2$]	1 eq.	2.2 eq.	1 eq.	0.5 eq.	60	76
7	[$P^{6,6,6,14}$]	4.03	8.0	2.5	2.00	5	54
	[CF_3CO_2]	1 eq.	2 eq.	1 eq.	0.5 eq.	60	71
8	[*N*-MEPy]	4.02	7.7	2.5	2.00	5	/
	[$N(SO_2CF_3)_2$]	1 eq.	1.9 eq.	2.2 eq.	0.5 eq.	60	18
9	[*N*-Bu-3-EMPy]	4.00	7.8	2.5	2.00	5	/
	[$N(SO_2CF_3)_2$]	1 eq.	2 eq	1.8 eq.	0.5 eq.	60	5

Table RD.4: Experimental conditions and subsequent results for compatibility experiments of 1,4-congugate addition in ILs.

When an equimolar or slight deficiency of *n*-BuLi is used in the cuprate preparation the highest conversion of **1** to **2** after 1 h is achieved in the presence of $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ (94%, entry 3) supporting the findings of Raminal *et al.*[88(b,c)] that the $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ IL does not adversely affect the organometallic reagent, despite being unable to remove the phosphine oxide contaminant of that IL. Conversion of **1** to the desired product **2** was high in the presence of both $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ (84 %, entry 5) and $[P^{6,6,6,14}][Cl]$ (80 %, entry 2) while the lowest conversion was observed in the presence of $[P^{6,6,6,14}][CF_3CO_2]$ (71 %, entry 7). Multiple unexpected signals not present in the blank are consistently observed, however they fail to integrate for an appreciable value in these trials. When a slight excess of *n*-BuLi is used in the cuprate preparation we see increased conversion of **1** to **2** in the presence of $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ (93 %, entry 4) and good conversion was also achieved in the presence of $[P^{6,6,6,14}][N(CN)_2]$ (76 %, entry 6). However in the presence of $[P^{6,6,6,14}][Cl]$ while **1** has been almost completely consumed the relative amount of **2** present actually decreases (65 %, entry 1). It is an increase in the percentage of the unexpected peaks observed earlier, which are also observed in entries 4 and 6, that accounts for the decreased amount of **2** present. The increased presence of these unexpected species when an excess of *n*-BuLi is employed intuitively suggests decomposition of the $[P^{6,6,6,14}]$-cation, which would lead to the formation of a phosphorane or Wittig-type reagent (Scheme RD.7) which could then react with the carbonyl moiety of **1** to yield different *E* and *Z* isomers of 1-(3-methylnona-1,3-dienyl)benzene (**4**). This is not unexpected given that the $[P^{6,6,6,14}]$ cation is known to decompose in the presence of RLi reagents[88] and as such it becomes evident that caution must be employed not to use *n*-BuLi in excess

during the cuprate formation. Despite not being present in appreciable amounts for entries 2, 5, and 7 where *n*-Bu not used in excess, these unexpected signals are present in the base line of their respective GC-MS trace. We were encouraged by the complete absence of these signals for our model reaction in the presence of $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ (entry 3) and $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ (entry 5) where *n*-BuLi was not used in excess, and surprised by the very low amount of these species present for the $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ experiment where *n*-BuLi was used in excess (entry 4). Now let us side track biefly and try and understand what these unexpected peaks are and how they may be formed.

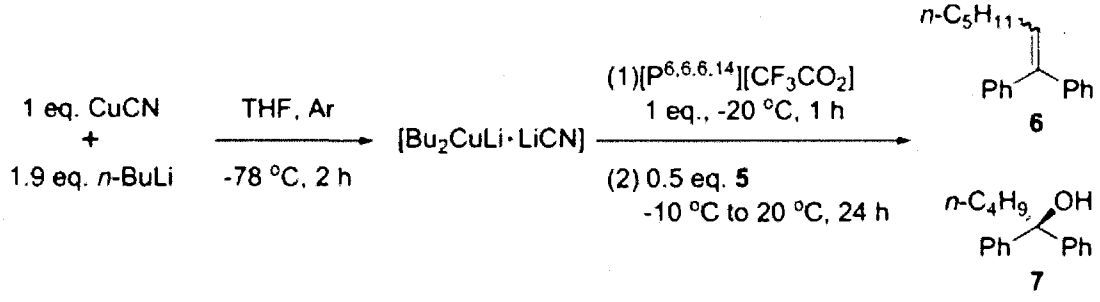


Scheme RD.7: Possible decomposition of $[P^{6,6,6,14}]$ cation to form a phosphorane Wittig reagent and subsequent reaction with **1** and fragmentation to the base peak.

2.4.2 Test for Wittig-type and 1,2-addition side reactions between $[Bu_2CuLi{\cdot}LiCN]$ and benzophenone in the presence of $[P^{6,6,6,14}][CF_3CO_2]$

In an effort to confirm or disprove the formation of any possible Wittig-type or 1,2-addition side reactions under our reaction conditions we prepared a

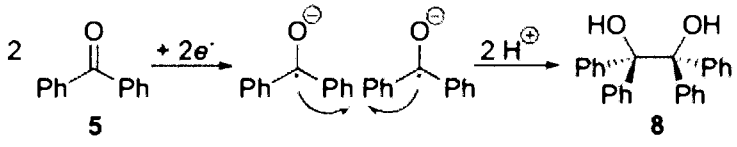
THF/$[P^{6,6,6,14}][CF_3CO_2]$/cuprate solution analogous to that prepared for entry 7. In this experiment addition of benzophenone (**5**) as opposed to **1** offers the potential for 1,2-addition of the cuprate to the carbonyl or formation of an alkene *via* transformation of the carbonyl moiety by a Wittig-type reagent (Scheme RD.8), with no possibility for 1,4-conjugate addition. The addition of **5** at -10 °C causes the solution to change colour from yellow to green as it stirs at this temperature for 3 h. Overnight stirring and warming to room temperature showed little change in colour. Samples for GC-MS analysis were prepared after 5 min, 1h, 3 h, and 24 h of reaction.



Scheme RD.8: Test for Wittig-type and 1,2-addition side reactions during compatibility experiments.

The signal for **5** under our method for GC-MS analysis has a t_R of 5.61 min and is characterized by its fragmentation pattern (M^+ = 182 (50), 105(100)). A Wittig-type reagent formed from the $[P^{6,6,6,14}]$ cation would likely occur by deprotonation of one of the three hexyl moieties and we would therefore expect the alkene produced after reaction with benzophenone to be 1,1-diphenylhept-1-ene (**6**, M^+ = 250). The possible 1,2-addition product, namely 1,1-diphenylpentan-1-ol (**7**, M^+ = 240), would be observed as the dehydrated fragment M^+-H_2O = 222. The significant colour change to green

suggests the formation of the ketyl radical of benzophenone. Our reaction was not protected from sunlight and thus the generation of the radical anion by UV irradiation is plausible.[101] Another possible mechanism for generation of such a radical would be one electron transfer from the cuprate.[88] If the radical is being generated we would expect to see some of the coupling product 1,1,2,2-tetraphenylethan-1,2-diol (**8**, Scheme RD.9) to appear in the mass spectrum.

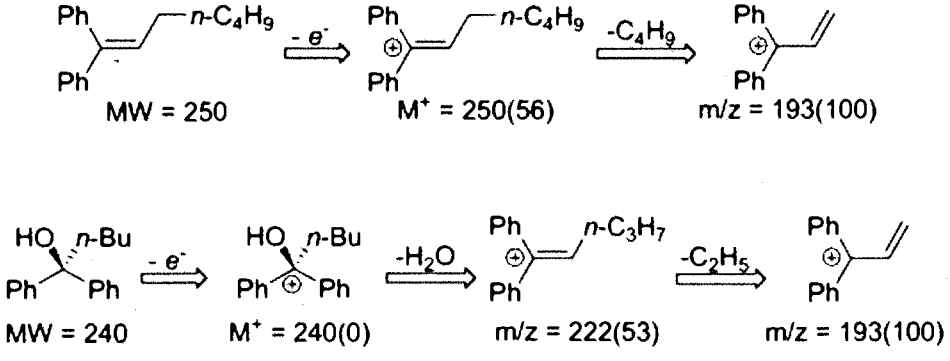


Scheme RD.9: Radical coupling of benzophenone forming 1,1,2,2-tetraphenylethan-1,2-diol.

After only 5 min we observe the formation of 2 new signals which grow in time over 24 h as the signal for **5** decreases. A signal appearing at t_R 6.80 min is thought to be **7** and is characterized by the fragments m/z = 222(53) and m/z = 193(100), the result of a rearrangement and subsequent loss of an ethyl fragment (Scheme RD.10). Examination of the fragmentation pattern for the signal at 6.80 min also strongly suggest the presence of **8,** with the characteristic fragments being m/z 183 (50) and 105 (31), where 183 is half of the molecular ion (M^+ = 366, not observed).

[102] The second signal at t_R 7.03 min is thought to be evidence for the formation of **6**, and is characterized by the M^+ m/z = 250(55). The base peak is again m/z = 193, the result of rearrangement and the loss of a butyl fragment in this case (Scheme RD.10). After 24 h of reaction the signal that we propose as **6** has become the dominant species.

Interestingly the peak we propose as a combination of **7** and **8** does not appear to grow between 3 and 24. Unfortunately the signals for **7** and **8** are unresolved and thus the relative amounts of **5**, **6**, **7** and **8** cannot be determined until our method is optimized; the integrated values from the MS for the signals are **5** (37 %), **6** (57%), and **7** + **8** (6%). Concrete conclusions cannot be drawn from this experiment as structural determination by fragmentation patterns alone are inconclusive and no effort was made to isolate the species produced in this reaction. It is believed however, based on our findings, that complex electron transfer processes between the substrate, the cuprate and the IL itself are leading to unexpected side reactions in our compatibility experiments. Due to the relative ease of formation of the benzophenone ketyl radical under UV irradiation it is not expected that single electron transfer by the cuprate is responsible for the formation of radicals.



Scheme RD.10: Proposed fragmentation patterns of 1,1-diphenylhept-1-ene (**6**) and 1,1-diphenylpentan-1-ol (**7**).

2.4.3 Compatibility Experiments of Organocuprates in Trihexy(tetradecyl)phosphonium and Pyridinium-based Ionic Liquids: Revisited

With strong evidence for the potential both Wittig-type and 1,2-addition side reactions being the possible source of the unexpected signals found in the mass spectra of our [$P^{6,6,6,14}$]-IL compatibility experiments we were fairly confident that we could assign a reasonable identity to a good number of them. Let us first quickly discuss the possible Wittig-type and 1,2-addition side reactions and products expected from them. If 1,2-addition of the cuprate with **1** were to occur we would expect to see *trans*-**3** and potentially a small amount of *cis*-**3** both characterized by the fragment M^+-H_2O = 186. If a phosphorane is generated then we could imagine potential *E* and *Z*-isomers of **4** both characterized by an M^+ = 214 (see Scheme RD.7), assuming only formation of the phosphorane as a result of deprotonation of one of the three hexyl substituents is observed. Now let us take a closer and more in depth look at the results of our [$P^{6,6,6,14}$]-compatibility experiments (Table RD.5).

Entry	Ionic Liquid	Time (min)	Relative amounts of Species present for Compatibility Experiments (%)				
			1[a]	**2**[b]	**3**[c]	**4**[d]	unknown[e]
1	$[P^{6,6,6,14}]$	5	54	40	3	1	2
	[Cl]	60	6	65	3	21	5
2	$[P^{6,6,6,14}]$	5	77	23	<1	<1	<1
	[Cl]	60	14	86	6	<1	<1
3	$[P^{6,6,6,14}]$	5	56	44	<1	<1	<1
	[*n*-$C_9H_{19}CO_2$]	60	1	94	5	<1	<1
4	$[P^{6,6,6,14}]$	5	72	23	<1	<1	1
	$[N(SO_2CF_3)_2]$	60	3	93	2	1	1
5	$[P^{6,6,6,14}]$	5	61	39	<1	<1	<1
	$[N(SO_2CF_3)_2]$	60	16	84	<1	<1	<1
6	$[P^{6,6,6,14}]$	5	85	13	<1	<1	2
	$[N(CN)_2]$	60	4	77	5	12	2
7	$[P^{6,6,6,14}]$	5	44	54	1	<1	<1
	$[CF_3CO_2]$	60	29	71	<1	<1	<1
8	[*N*-MEPy] $[N(SO_2CF_3)_2]$	60	71	18	<1	\	9[f]
9	[*N*-Bu-3-EMPy] $[N(SO_2CF_3)_2]$	60	72	5	1	\	20[g]

Table RD.5: Results of compatibility experiments for 1,4-conjuagte addition of $[Bu_2CuLi{\cdot}LiCN]$ to **1** in the presence of $[P^{6,6,6,14}]$ and [Py]-based ILs: **1** t_R 4.24 min, M^+ = 146(32), 103(100); (b) **2** t_R 4.92 min, M^+ = 204(1), 146(100); (c) *cis*-**3** t_R 5.14 min, *trans*-**3** t_R 5.48 min, both M^+ = 204(0), 186(52), 143(100); (d) *cis/trans*-**4** t_R 6.14 min, 6.51 min, both M^+ = 214(49), 143(100); (e) unk. t_R 5.68, base peak 105(100).; (f) unk. t_R 3.68 min, M^+ = 150(1), 148(95), 103(100); (g) unk. t_R 5.23 min, M^+ = 182, 131(100).

It should be noted that the relative percentages do not add up to 100 in all cases due to the presence of a small amount of cis-**1** found in most of the mass spectra obtained. The results here also are not as precise as they could be, given that the peaks in the mass spectra are not always fully resolved and thus our method of analysis requires optimization. The results do provide, at the very least, a general indication as to the progress of the model reaction and the associated side reactions taking place. Identification of by-products **4** resulting from Wittig-type side-reactions follow a similar

logical explanation based on the fragmentation patterns to that given in Section 2.4.2 save that the rearrangement is not as prevalent due to reduced resonance stabilization compared to the benzophenone experiment. When excess *n*-BuLi is used in our model reaction the highest amount of Wittig-type by-products **4** form in the presence of $[P^{6,6,6,14}][Cl]$ (21 %, entry 1) and $[P^{6,6,6,14}][N(CN)_2]$ (12 %, entry 6). It came as a surprise that in the presence of $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ the amount of species **4** remained very low (1%, entry 4) despite using an excess of *n*-BuLi. This suggests a marked anion effect on the amount and/or rate of side reactions taking place. The amount of **4** produced in the presence of $[P^{6,6,6,14}][Cl]$ was practically eliminated when a slight deficiency of *n*-BuLi was employed (entry 2). The amount of **3** formed resulting from 1,2-addition of the butyl fragment to **1** was reasonably small in entries 1-7 and the variations did not seem to follow any clear trends, the highest amount being formed in the presence of $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ (6 % **3**, entry 3). The most promising results were obtained for our model experiment performed in the presence of $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ (93 % **2**, entry 4; 84 % **2**, entry 5) and $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ (94 % **2**, entry 3) which offered the highest conversion of **1** to **2** with only small amounts of by-products **3** and **4** being formed.

Isolation of **2** had been achieved in earlier studies performed by Farrell in our group using column chromatography. Similar compatibility experiments performed in the presence of $[P^{6,6,6,14}][PhCO_2]$ and $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ achieved isolated yields of 91.9% and 79.5 % respectively, while the alkylsulfate anions studied performed moderately. Here we employed the same isolation technique as column chromatography (silica gel/9:1 hexanes ethylacetate) is required to separate **2** from unreacted **1** and we hoped that this would also remove the $[P^{6,6,6,14}]$-ILs. Unfortunately we were unsuccessful

in isolating pure **2** from any of the compatibility experiments. While column chromatography is one of the most useful and effective techniques for the separation of materials, it is perhaps not as applicable to separations from the ILs examined in this study. Both the [$P^{6,6,6,14}$] and [Py]-based ILs are polar and thus remain trapped at the top of the column. The relatively large volume of material introduced into the column and perhaps strong association of **1** and **2** with the IL leads to poor resolution and recovery of those two materials due to overloading. The reasonably large number of species present in crude reaction mixtures further complicated the separation of material, even when only found in trace amounts. Even with the ILs removed, a second column still did not yield pure **2**, and with each successive column the loss of material brought the mass of the still crude product well below the typically >90% isolated yields reported throughout the literature.[103] The identity of the impurity was not found in any of the solvents used and using fresh solvents did nothing to better the isolation. The identity of the impurity(s) is being investigated, but ^{1}H NMR shows that that the impurities reside in the aromatic and aliphatic regions which could be expected from compounds like those proposed to be **4**. Other separation techniques should be further explored including hexanes/[$P^{6,6,6,14}$]-IL/water triphasic extraction and perhaps sublimation, as using larger or numerous columns for isolation would generate much silica and solvent waste. It is also important to note that while some 1,2-addition of the cuprate to **1** was observed, the selectivity of the cuprate for 1,4-conjugate addition as the major pathway is retained in the presence of the ILs.

2.4.4 Experiments of Organocuprates in Trihexy(tetradecyl)phosphonium and Pyridinium based Ionic Liquids

Our compatibility experiments showed good potential for successful production of ether-*free* solutions of a dialkylcuprate in some of our $[P^{6,6,6,14}]$-based IL solvents as long as *n*-BuLi was used in a slight deficiency. The preparation of the IL/cuprate solutions was analogous to that of the compatibility experiments except that our molar ratios were adjusted to ensure that the IL was well in excess of $[Bu_2CuLi{\cdot}LiCN]$ (Table RD.6). The cuprate is formed in 5 mL of THF ensuring that *n*-Bu is not used in excess to avoid phosphorane formation. Ideally the cuprate should be formed with exactly a 2:1 ratio of *n*-BuLi to CuCN and the decision to use *n*-BuLi in slight deficiency was to ensure that no free *n*-BuLi would be present. After addition of the IL and stirring for 1 h warming to 0 °C the THF is slowly removed under high vacuum between -10 °C and 0 °C. If the solution is warmed past this or the THF evaporates too vigourously the solutions turn black, likely due to decomposition of the cuprate. Typically after 1 h bubbling has ceased and after an additional h under high vacuum a orange-yellow solution is obtained (slightly brown for $[P^{6,6,6,14}][N(SO_2CF_3)_2]$) which is so viscous that the solutions were difficult to stir. When the THF was removed from the $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ cuprate solution a clear gel-like substance was obtained. We cannot claim that all the THF is removed as the GC-

Entry	Ionic Liquid	CuCN mmol	BuLi mmol	Vol IL mL	TPBO mmol	Time min	GC Yield of 2 (%)
10	$[P^{6,6,6,14}]$ [Cl]	1.61 1 eq.	3.2 2 eq.	3.0 3.2eq.	1.00 0.6 eq.	60	40
11	$[P^{6,6,6,14}]$ [*n*-C_9H_{19}-CO_2]	1.61 eq.	3.2 2 eq.	3.0 2.5 eq.	1.00 0.6 eq.	60	0
12[a]	$[P^{6,6,6,14}]$ $[N(SO_2CF_3)_2]$	1.61 eq.	3.2 2 eq.	3.0 2.6 eq.	1.00 0.6 eq.	60	42
13	$[P^{6,6,6,14}]$ $[N(CN)_2]$	1.61 eq.	3.2 2 eq.	3.0 3.2 eq.	1.00 0.6 eq.	60	66
14	$[P^{6,6,6,14}]$ $[CF_3CO_2]$	1.61 eq.	3.2 2 eq.	3.0 3.0 eq.	1.00 0.6 eq.	60	35
15	[*N*-MEPy] $[N(SO_2CF_3)_2]$	1.61 1 eq	3.2 2 eq.	3.0 6.8 eq.	1.00 0.6 eq.	60	0
16	[*N*-Bu-3-EMPy] $[N(SO_2CF_3)_2]$	1.62 1 eq.	3.2 2 eq.	3.0 4.8 eq.	1.00 0.6 eq.	60	0

Table RD.6: Experimental conditions and subsequent results for ether-*free* experiments of 1,4-congugate addition in ILs: (a) Averaged for two trials.

FID chromatograms show a signal at 1.79 min which is present in all samples prepared where THF could possibly be present, and the blanks containing no THF did not show this signal. However this signal was smaller than the response to most other species present and the remaining volume in the flask is sufficiently small to say that the IL makes up the bulk volume of the solution, while residual THF is likely necessary to stabilize the cuprate. Also present in the GC-FID chromatograms is a signal at 5.48 min which is not observed in the MS-chromatogram and is thought to be the result of column bleeding exclusive to the GC-FID available to our experiments.

Addition of solid **1** causes the $[P^{6,6,6,14}]$-IL/cuprate solutions to change to an orange-red colour. As the $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ cuprate gel would not stir, **1** was added as a 0.4 M toluene solution to dissolve or lower the viscosity of the substance causing a

change to brown in colour. After 1 h the reactions were quenched with 2 N HCl with simultaneous addition of water and Et_2O to help the solutions mix more quickly. An aliquot of the crude reaction mixture was then obtained for analysis by GC-MS (Table RD.7). No attempts were made to isolate or separate materials from the crude reaction mixture due to the isolation problems alluded to earlier.

Both of our [Py]-based ILs formed very dark solutions when the IL was added to the cuprate in THF and remained black and viscous when the THF was removed. Not surprisingly we observe no conversion of **1** to **2** in our GC-MS analysis, where **1** is the only species present for the reaction performed in [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] and for [N-MEPy][$N(SO_2CF_3)_2$] only **1** and the same unexpected peak experienced in the compatibility experiments are present. Again, due to the hydrophilic nature of the ether moieties found in the cation, perhaps the retention of water by these ILs is sufficiently strong that even at 60 °C high vacuum does not effectively remove residual water. For this reason [*N*-ME-3-EMPy][$N(SO_2CF_3)_2$] has yet to be investigated as the [Py]-based ILs should be dried *via* azeotropic distillation and re-examined as potential solvents for dialkylcuprate reagents. If azeotropic distillation fails to remove sufficient amounts of moisture we intend to determine the water content of the ILs once we obtain access to a Karl Fischer titrater.

A concern had been that with the THF removed the cuprate would decompose the [$P^{6,6,6,14}$] cation resulting in Wittig-type side reactions. Of the [$P^{6,6,6,14}$]-based ILs surveyed only [$P^{6,6,6,14}$][*n*-$C_9H_{19}CO_2$] did not show any conversion of **1** to **2** (entry 11). This was rather unfortunate as [$P^{6,6,6,14}$][*n*-$C_9H_{19}CO_2$] faired the best in our compatibility experiment. A large signal in the mass spectrum obscures the signal of **1**, however the

identity of the substance has yet to be deduced from its fragmentation pattern and **2** is only present in trace amounts. This suggests decomposition of the IL, and small amounts of **4** are present in the mass spectrum. The poor results are likely caused by the continued presence of the phosphine oxide we were unable to remove in our purification process, which would become more of a factor in the concentrated IL/cuprate solution.

Entry	Ionic Liquid	Time (min)	Relative amounts of Species present for Ether-*free* Experiments (%)				
			1[a]	**2**[b]	**3**[c]	**4**[d]	unknown[e]
10	$[P^{6,6,6,14}][Cl]$	60	41	27	5	11	16
11	$[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$	60	\	\	\	\	\
12	$[P^{6,6,6,14}][N(SO_2CF_3)_2]$	60	57	41	<1	2	<1
13	$[P^{6,6,6,14}][N(CN)_2]$	60	30	59	6	5	<1
14	$[P^{6,6,6,14}][CF_3CO_2]$	60	56	30	2	1	10

Table RD.7: Results of ether-*free* experiments for 1,4-conjuagte addition of $[Bu_2CuLi{\cdot}LiCN]$ to **1** in the presence of $[P^{6,6,6,14}]$ and [Py]-based ILs:(a) **1** t_R 4.24 min, M^+ = 146(32), 103(100); (b) **2** t_R 4.92 min, M^+ = 204(1), 146(100); (c) *cis*-**3** t_R 5.14 min, *trans*-**3** t_R 5.48 min, both M^+ = 204(0), 186(52), 143(100); (d) *cis/trans*-**4** t_R 6.14 min, 6.51 min, both M^+ = 214(45), 143(100); (e) unknown t_R 5.68, base peak m/z = 105; t_R 5.68 min, 6.24 min, base peak for both m/z = 111.

The other $[P^{6,6,6,14}]$-based ILs faired better but were not exceptional in all cases. After 60 min of reaction in $[P^{6,6,6,14}][Cl]$ only 27 % of the species present is our desired product **2** while what we propose as Wittig-type and as yet undetermined side reactions account for 11 % and 16 % respectively, the remainder being unreacted **1**. In our compatibility experiments we did not see this level of side-reactivity in the presence of $[P^{6,6,6,14}][Cl]$ after reducing the amount of *n*-BuLi employed and thus it appears that the [Cl] anion does not assist in stabilizing the cuprate once the THF is removed. For the

reaction performed in $[P^{6,6,6,14}][CF_3CO_2]$ the results suggest some stabilization of the cuprate as our undetermined and proposed alkene (**4**) by-products account for only 1 % and 10 % respectively (entry 14), with the relative amount of **2** present rising to 30 %. It appears here that in switching to the $[CF_3CO_2]$ anion we have marginally improved the stability of the cuprate. The highest conversion of **1** to **2** was experienced in $[P^{6,6,6,14}][N(CN)_2]$ (59 %, entry 13) with deleterious side reactions only accounting for 11 % of the species present. It may be the basicity of the $[N(CN)_2]$ anion and its similarity to the cyanide anion used in forming the cuprate that accounts for the degree of stabilization offered by this IL. The cleanest reactivity was observed for $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ (entry 12), which after 1 h of reaction time shows 41 % of the species present being **2**, while unreacted **1** accounts for 57 % and only 2 % is the result of side reactions. This suggests that the $[N(SO_2CF_3)_2]$ anion offers the best stabilization of the cuprate compared to our other $[P^{6,6,6,14}]$-based ILs and if the reaction were allowed to go longer we would expect to see higher conversion of **1** to **2**. $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ and $[P^{6,6,6,14}][N(CN)_2]$ also offer the advantage that they are the least viscous of the $[P^{6,6,6,14}]$-based ILs examined which helped to facilitate stirring of the cooled solutions. Given that the [Cl] content of our synthesized $[P^{6,6,6,14}]$-based ILs was only qualitatively verified, it would be interesting to see if $[P^{6,6,6,14}][CF_3CO_2]$ still contained an appreciable amount of $[P^{6,6,6,14}][Cl]$ due to incomplete metathesis, explaining the only partial stabilization of the cuprate by the $[CF_3CO_2]$ anion. Elemental analysis was not performed on our $[P^{6,6,6,14}]$-based IL series and should offer an answer to this question. All things considered, our findings suggest that both $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ and $[P^{6,6,6,14}][N(CN)_2]$ form reasonably stable ether-*free* solutions of dialkylcuprates, at least over the duration of our experiments. No attempt

was made to store [$Bu_2CuLi{\cdot}LiCN$] in any of our ILs and thus we cannot comment on prolonged stability of the cuprate in these solvents.

The low conversion achieved after 1 h is disappointing given that ILs are often shown to increase reaction rates. We experience the problem that the IL remains very viscous at low temperatures, which greatly reduces effective and efficient mixing of the solution. This leads to inefficient mass transport and the potential for exotherms or 'hot spots' resulting from high concentrations of reactants in remote areas of the solution. However if either $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ or $[P^{6,6,6,14}][N(CN)_2]$ form stable solutions of the cuprate then there is potential that with prolonged reaction times and/or improved mixing higher conversion of **1** to **2** would be observed.

3 Conclusions

Purification of $[P^{6,6,6,14}][Cl]$ allowed us to synthesize $[P^{6,6,6,14}]$-based ILs with either $[N(SO_2CF_3)_2]$, $[N(CN)_2]$, or $[N(SO_2CF_3)_2]$ as the counter ion *via* salt metathesis in reasonably high yields (83.6 – 93.0 %) and moisture is efficiently removed from these solvents *via* azeotropic distillation. Three [Py]-based ILs functionalized with one ([*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] and [*N*-MEPy][$N(SO_2CF_3)_2$]) or two ([*N*-ME-3-EMPy][$N(SO_2CF_3)_2$]) ether substituents were also synthesized in good yields (66.8 – 75.9). The [Py]-based ILs are believed to retain moisture in the ether substituents despite the inclusion of the hydrophobic $[N(SO_2CF_3)_2]$ anion and exhaustive attempts to remove water under high vacuum. This caused the [Py]-based ILs to perform poorly in our model reaction, the 1,4-conjugate addition of a dialkylcuprate to an α,β-unsaturated ketone, while $[P^{6,6,6,14}]$-based ILs showed promise.

Our results from both the compatibility and ether-*free* experiments suggest that $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ and $[P^{6,6,6,14}][N(CN)_2]$ form reasonably stable solutions of $[Bu_2CuLi{\cdot}LiCN]$ so long as the cuprate is formed with no excess *n*-BuLi being employed, and that improved mixing and longer reaction times will likely improve upon the low conversions achieved. The formation of phosphoranes when THF is removed from $[P^{6,6,6,14}][Cl]$ solutions of the cuprate results in Wittig-type side reactions not observed for $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ and $[P^{6,6,6,14}][N(CN)_2]$, suggesting that these anions help stabilize the cuprate in the reduced presence of ethereal solvents. While $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ performed well as an additive in THF solutions of the cuprate, removal of THF caused the solution to become near solid, and it is difficult to imagine how that particular IL can

be used without co-solvent in these reactions at reduced temperatures. However it is possible that the continued presence of the phosphine oxide caused the poor results achieved when THF was removed from the IL/cuprate mixture.

Looking back at our objectives the primary goals were to demonstrate that the chemistry offered by dialkylcuprates can be conducted in $[P^{6,6,6,14}]$-based IL solvents, and that use of these as opposed to ethereal solvents would offer *Green* advantages to existing methods. In this respect we can say that we have made progress showing that our model reaction proceeds in solutions where THF has been removed and replaced as the bulk solvent by $[P^{6,6,6,14}]$-based ILs; maintaining the selectivity of the cuprate for 1,4-addition. The high viscosity of the $[P^{6,6,6,14}]$-based ILs at reduced temperatures however has a deleterious effect on the rate of the reaction due to poor mass transport. As one of the criterion to improve the *Green*-ness of our model reaction we hoped to eliminate or reduce the amount of ethereal solvents employed we have yet to achieve this goal. Herein we formed our cuprate by traditional methods using THF as the solvent and *n*-BuLi as the source of the organic substituent and thus could not attempt to generate the cuprate in the $[P^{6,6,6,14}]$-based IL solvent in this manner. A potential solution to this problem could be to add CuCN to the IL then access the cuprate *via* transmetallation with an appropriate Grignard or dialkylzinc reagent either stoiciometrically or in catalytic copper(I) loadings. Also, in this study we investigated only dialkylcuprates, where diaryl- or diallylcuprates may have offered more positive results due to their increased stability resulting from electron sharing between the metal and organics (back bonding) for the latter two species not possible for dialkylcuprates.

Satisfied that ILs based on the [$P^{6,6,6,14}$] cation offer an alternative solvent for reactions involving dialkylcuprates when paired with an appropriate anion, much work is still needed to optimize our methodology before we can claim any improvements on existing methods. While the selectivity is retained, the rate of reaction is markedly slower and isolation of products is as of yet far more difficult to achieve. Specifically, the poor resolution of materials by column chromatography in an effort to remove the IL requires us to explore alternative techniques for isolation. Also we have yet to focus on potentially the greatest *Green*-asset that ILs have to offer, namely their potential to be recycled. Perhaps a triphasic extraction or sublimation/distillation technique will offer better recovery of materials than was experienced by column chromatography and in so doing simplify the recycling of the IL.

4 Future Directions

As $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ and $[P^{6,6,6,14}][N(CN)_2]$ seemingly form stable ether-*free* solutions of $[Bu_2CuLi{\cdot}LiCN]$ it is required that we re-examine these ILs allowing the reaction to progress past 1 h, despite the complete conversion of **1** to **2** over this period of time either by traditional methods or as experienced in our compatibility study. If these ILs do allow the reaction to reach completion, then other transformations offered by dialkylcuprates (Scheme 2) should be explored. Removal of the phosphine oxide from $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ is required before we can rule out this particular IL. As well, the [Py]-based IL series requires drying *via* azeotropic distillation and confirmation of dryness *via* Karl Fischer titration before being discredited.

Also, as one of our objectives was to eliminate or reduce the amount of ethereal solvents used, alternative methods to generate the cuprate in the IL solvent need to be explored. However, the issues that require immediate attention are isolation of materials from the IL and recycling of the solvent. As one of the basic principles of *Green Chemistry* is to reduce the amount of solvents used, sublimation or distillation of products would be preferred over extraction or column chromatography to isolate the product and if successful simplified purification of the IL solvent would be expected. Our GC-MS analysis also lacks the resolution of signals required to have 100% confidence in the integration values obtained therein. Hence, optimization of the analytical method should be addressed despite the fact that isolation of the product in high yield is the true benchmark on which we can gauge the viability of our methodology.

5 Experimental

5.1 General Experimental

Synthesis and reactions of dialkylcuprates were performed using glassware and equipment that was oven-dried at 115 °C overnight, vacuum cooled, and filled with argon prior to use. Anhydrous THF from an Innovative Technology PS-400-4 solvent system was collected in oven-dried, vacuum cooled glassware just prior to use. Solid *trans*-4-phenyl-3-buten-2-one was recrystalized from hexanes, filtered, and stored under argon after removal of the hexanes under vacuum. Copper(I)cyanide was obtained from Aldrich and handled under argon in a Vacuum Atmosphere Company ME-493 inert atmosphere glove box. The *n*-butyllithium used (1.6 M in hexane) was obtained from Aldrich and transferred using oven-dried glass syringes equipped with stainless steel needles cooled by flushing with argon before use. Low temperatures for synthesis and reactions of diorganocuprates were achieved using dry ice in acetone baths. The ILs $[P^{6,6,6,14}][Cl]$ and $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ were obtained from Cytec Industries Inc. and purified prior to use as described in *Section 5.2.1.* All other materials used in the synthesis of ILs were obtained from Aldrich and used without purification. Prior to use in reactions involving diorganocuprates, the ILs were dried under high vacuum at 60 °C for 3 h then cooled to room temperature. Column chromatography was performed using 60-240 mesh silica gel and was monitored by thin layer chromatography using ultraviolet light. Chromatographic plates were developed using 6% phosphomolybdic acid in ethanol (w/w). All ^{1}H, ^{13}C, and ^{19}F NMR data were obtained using a Bruker/Tecmag AC-250

NMR spectrometer at the Atlantic Regional Magnetic Resonance Centre while ^{31}P NMR spectra were obtained on an Anasazi Eft-60/Varian EM360L NMR spectrometer. Samples for NMR analysis were prepared using $CDCl_3$ and referenced to the appropriate nuclear standard (^{1}H and ^{13}C *vs.* TMS at $\delta = 0$ ppm, ^{31}P *vs.* 85 % H_3PO_4 at $\delta = 0$ ppm, ^{19}F vs. trifluorotoluene at δ = -63.88 ppm). All IR spectra were obtained using a Bruker Vector 22 spectrometer as thin films pressed between NaCl discs. Analysis by ESI-MS was performed using an Agilent 1100 Series LC/MSD ionic trap by direct injection in both positive and negative modes. The GC-FID and GC-MS data obtained was from a Varian 3800 GC and a Varian 2000 Saturn GC-MS/MS using EI as the mode of ionization (70 eV).

5.2 Purification and Synthesis of trihexyl(tetradecyl)phosphonium-based Ionic Liquids

5.2.1 Purification of trihexyl(tetradecyl)phosphonium-based Ionic Liquids

Purification of trihexyl(tetradecyl)phosphonium chloride, **$[P^{6,6,6,14}][Cl]$**

Saturated aq. sodium bicarbonate (20 mL) was added to 120 mL of $[P^{6,6,6,14}][Cl]$ in a 250 mL round-bottomed flask and the solution was stirred for 1 h. Foaming occurred for the first ½ h, then subsided. The solution was transferred to a 500 mL separatory funnel and washed with 4 x 125 mL deionized water. The $[P^{6,6,6,14}][Cl]$ was then extracted in a triphasic manner three times using 40 mL of hexanes and 40 mL of deionized water

simultaneously, where the water was drained and the hexanes layer removed using a pipette. The $[P^{6,6,6,14}][Cl]$ layer was then isolated in a 250 mL round-bottomed flask and any residual hexanes were removed under vacuum. The $[P^{6,6,6,14}][Cl]$ was then divided into ~ 20 mL portions, which were each dissolved in 10 mL of hexanes and passed through a short silica gel column using hexanes as eluent. Of these portions, five were combined and the hexanes removed under vacuum to afford $[P^{6,6,6,14}][Cl]$ as a clear slightly yellow oil for use in the synthesis of the $[P^{6,6,6,14}]$-based ILs used in this study. A 20 mL portion of $[P^{6,6,6,14}][Cl]$ was dried *via* azeotropic distillation with 100 mL of toluene. The toluene was removed under vacuum, residual toluene removed under high vacuum at 60 °C for 8 h, and the resulting clear yellow $[P^{6,6,6,14}][Cl]$ was stored under argon. ^{1}H NMR (δ/ppm, $CDCl_3$): 0.90 (m, 12*H*), 1.40 (*ov* m, 48*H*), 2.46 (m, 8*H*); ^{13}C NMR (δ/ppm, $CDCl_3$): 13.96, 14.15, 18.86, 19.60 21.86, 21.94, 22.37, 22.69, 28.98, 29.33, 29.36, 29.52, 29.62, 29.64, 29.68, 30.37, 30.61, 30.69, 30.93, 31.11, 31.91; ^{31}P NMR (δ/ppm, $CDCl_3$): 32.11; IR ν_{max} (cm^{-1}, thin film): 2956 (*s*), 2925 (*s*), 2855 (*s*), 1466 (*s*), 1414 (*w*), 1378 (*m*), 1300 (*w*), 1266 (*w*), 1215 (*m*), 1111 (*m*), 989 (*w*), 815 (*w*), 721 (*m*); ESI-MS: 483.6 (+ m/z), -35.5 (- m/z) not observed.

***Purification of trihexyl(tetradecyl)phosphonium decanoate,* $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$**

Saturated aq. sodium bicarbonate (25 mL) was added to 100 mL of $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ in a 250 mL round-bottomed flask and the solution was stirred overnight at room temperature. The solution was transferred to a 500 mL separatory funnel, dissolved in 100 mL of hexanes, and washed with 4 x 125 mL of deionized water. The hexanes

were removed under vacuum and a 20 ml portion of $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ was transferred to a 250 mL round-bottomed flask, dissolved in 80 mL of hexanes, and dried *via* azeotropic distillation with 80 mL of toluene. The toluene was removed under vacuum, residual toluene removed under high vacuum at 60 °C for 4 h to give clear slight yellow $[P^{6,6,6,14}][n\text{-}C_9H_{19}CO_2]$ which was stored under argon. ^{1}H NMR (δ/ppm, $CDCl_3$): 0.88 (m, 15*H*), 1.40 (*ov* m, 62*H*), 2.17 (t, 2*H*, $CO_2C\boldsymbol{H}_2CH_2$-, $^3J_{H\text{-}H} = 7.5$), 2.44 (m, 8*H*); ^{13}C NMR (δ/ppm, $CDCl_3$): 13.97, 14.15, 18.53, 19.27, 21.91, 21.99, 22.39, 22.71, 22.73, 27.43, 29.04, 29.35, 29.38, 29.46, 29.56, 29.64, 29.67, 29.70, 29.75, 29.85, 30.25, 30.44, 30.68, 30.76, 30.99, 31.17, 31.19, 31.94, 31.99, 39.53, 179.27; ^{31}P NMR (δ/ppm, $CDCl_3$): 32.50; IR ν_{max} (cm^{-1}, thin film): 2956 (*s*), 2925 (*s*), 2854 (*s*), 1579 (*s*), 1466 (*m*), 1378 (*m*), 1302 (*w*), 1111 (*w*), 721 (*w*); ESI-MS: 483.9 (+ m/z), -170.8 (- m/z).

5.2.2 Synthesis of trihexyl(tetradecyl)phosphonium-based Ionic Liquids

Synthesis of Trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)amide **$[P^{6,6,6,14}][N(SO_2CF_3)_2]$**

19.98 g (1 eq., 38.48 mmol) of $[P^{6,6,6,14}][Cl]$ was added to a 250 mL round-bottomed flask equipped with a stir bar and 25 mL of acetone was added to reduce the viscosity. To this solution 13.92 g (1.25 eq., 48.49 mmol) of lithium bis(trifluoromethylsulfonyl)amide was added along with 25 mL of deionized water. The solution was stirred for six days at room temperature at which point the stir bar was removed and the acetone removed under vacuum. The solution was then transferred to a 500 mL separatory funnel, 250 mL of

Et_2O was added and then water was drained. The ether layer was then washed with 6 x 50 mL portions of deionized water, filtered, and the ether removed under vacuum. A small amount of silver nitrate was added to the aq. extracts to insure all halides had been removed. The resulting oil was then dried under high vacuum at 60 °C for 7 h. $[P^{6,6,6,14}][N(SO_2CF_3)_2]$ was obtained as clear faint yellow oil which was stored under argon (27.33 g, 93.0 % yield). ^1H NMR (δ/ppm, $CDCl_3$): 0.89 (m, 12*H*), 1.31 (m, 32*H*), 1.48 (m, 16*H*), 2.09 (m, 8*H*); ^{13}C NMR (δ/ppm, $CDCl_3$): 13.88, 14.15, 18.22, 18.97, 21.43, 21.50, 22.34, 22.75, 28.81, 29.32, 29.43, 29.55, 29.68, 29.72, 29.75, 30.11, 30.34, 30.44, 30.68, 30.87, 31.99, 120.0 ($^1J_{C\text{-}F}$ = 321 Hz); ^{31}P NMR (δ/ppm, $CDCl_3$): 32.55; ^{19}F NMR (δ/ppm, $CDCl_3$): -79.82; IR ν_{max} (cm^{-1}, thin film): 2957 (*s*), 2928 (*s*), 2857 (*s*), 1467 (*m*), 1412 (*w*), 1351 (*s*), 1332 (*m*), 1225 (*m*), 1195 (*s*), 1138 (*s*), 1058 (*s*), 788 (*w*), 739 (*w*), 653 (*w*), 617 (*m*); ESI-MS: 483.7 (+ m/z), -279.6 (- m/z).

***Synthesis of Trihexyl(tetradecyl)phosphonium dicyanamide,* $[P^{6,6,6,14}][N(CN)_2]$**

20.01 g (1 eq., 38.53 mmol) of $[P^{6,6,6,14}][Cl]$ was added to a 250 mL round-bottomed flask equipped with a stir bar and 25 mL of acetone was added to reduce the viscosity. To this solution 4.42 g (1.25 eq., 49.64 mmol) of sodium dicyanamide was added along with 25 mL of deionized water. The solution was stirred for 5 days at room temperature at which point the stir bar was removed and the acetone removed under vacuum. The solution was then transferred to a 500 mL separatory funnel, 250 mL of Et_2O was added and the water was drained. The ether layer was washed with 6 x 50 mL portions of deionized water, filtered, and the ether removed under vacuum. A small amount of silver nitrate was added to the aq. extracts to insure all halides had been removed. The $[P^{6,6,6,14}][N(CN)_2]$ was

dried *via* azeotropic distillation with 100 mL of toluene. The toluene was removed under vacuum, residual toluene removed under high vacuum at 60 °C for 8 h to give clear yellow $[P^{6,6,6,14}][N(CN)_2]$ which was stored under argon (18.06 g, 85.3 % yield). ^{1}H NMR (δ/ppm, $CDCl_3$): 0.90 (m, 12*H*), 1.40 (*ov* m, 32*H*), 2.20 (m, 8*H*); ^{13}C NMR (δ/ppm, $CDCl_3$): 13.95, 14.14, 18.46, 19.21, 21.51, 21.59, 22.33, 22.69, 28.84, 29.30, 29.36, 29.52, 29.64, 29.68, 30.25, 30.49, 30.59, 30.82, 30.92, 31.91, 119.96; ^{31}P NMR (δ/ppm, $CDCl_3$) 32.54; IR ν_{max} (cm^{-1}, thin film): 2956 (*s*), 2927 (*s*), 2855 (*s*), 2225 (*s*), 2188 (*m*), 2127 (*s*), 1465 (*m*), 1412 (*w*), 1378 (*w*), 1305 (*m*), 1213 (*w*), 1111 (*w*), 990 (*w*), 900 (*w*), 809 (*w*), 720 (*w*); ESI-MS: 483.7 (+ m/z), -66.0 (- m/z) not observed.

***Synthesis of Trihexyl(tetradecyl)phosphonium trifluoroacetate,* $[P^{6,6,6,14}][CF_3CO_2]$**

19.99 g (1 eq., 38.50 mmol) of $[P^{6,6,6,14}][Cl]$ was added to a 250 mL round-bottomed flask equipped with a stir bar and 25 mL of acetone was added to reduce the viscosity. To this solution, 6.60 g (1.25 eq., 48.43 mmol) of sodium trifluoroacetate was added along with 25 mL of deionized water. The solution was stirred for 6 days at room temperature at which point the stir bar was removed and the acetone removed under vacuum. The solution was then transferred to a 500 mL separatory funnel, 250 mL of Et_2O was added and the water was drained. The ether layer was then washed with 6 x 50 mL portions of deionized water, filtered, and the ether removed under vacuum. A small amount of silver nitrate was added to the aq. extracts to insure all halides had been removed. The resulting oil was then dried under high vacuum at 60 °C for 8 h. $[P^{6,6,6,14}][CF_3CO_2]$ was obtained as a clear faint yellow oil which was stored under argon (27.33 g, 83.61 % yield). ^{1}H NMR (δ/ppm, $CDCl_3$): 0.89 (m, 12*H*), 1.40 (*ov* m, 48*H*), 2.29 (m, 8*H*); ^{13}C NMR (δ/ppm,

$CDCl_3$): 13.92, 14.14, 18.40, 19.15, 21.64, 21.72, 22.34, 22.71, 28.90, 29.31, 29.38, 29.52, 29.63, 29.67, 29.70, 30.28, 30.52, 30.84, 31.01, 31.94, 117.50 ($^1J_{C\text{-}F}$ = 295 Hz) 160.26; ^{31}P NMR (δ/ppm, $CDCl_3$): 32.46; ^{19}F NMR (δ/ppm, $CDCl_3$): -75.61; IR ν_{max} (cm^{-1}, thin film): 2956 (*s*), 2927 (*s*), 2856 (*s*), 1688 (*s*), 1466 (*m*), 1393 (*w*), 1379 (*w*), 1197 (*s*), 1159 (*s*), 1117 (*s*), 817 (*m*), 798 (*w*), 716 (*w*); ESI-MS: 483.6 (+ m/z), -112.8 (- m/z).

5.3 Synthesis of Pyridinium-based Ionic Liquids

***Synthesis of N-(methoxyethyl)pyridinium bromide,* [*N*-MEPy][Br]**

In an oven-dried 100 mL round-bottomed flask 10 mL of pyridine (2 eq., 9.82 g, 124.13 mmol) was dissolved in 20 mL of CH_2Cl_2. A stir bar was added along with 5.8 mL of 2-bromoethylmethylether (1 eq., 8.63 g, 62.07 mmol). The solution was stirred at 55 °C for 5 h and a dark red oil formed as a separate layer. The solution was then cooled to room temperature at which point a solid precipitated from the solution. All volatiles which include the solvent and unreacted starting materials were removed under high vacuum at room temperature after gently melting the solid with a heat gun. [*N*-MEPy][Br] was obtained as a very hard dense solid (11.66 g, 86.1 %). Mp. 127-128 °C; ^{1}H NMR (δ/ppm, $CDCl_3$): 3.27 (s, 3*H*, -O***CH***$_3$), 3.88 (t, 2*H*, -CH_2***CH***$_2$O-, $^3J_{H\text{-}H}$ = 4.8 Hz), 5.21 (t, 2*H*, -N^+***CH***$_2CH_2$-, $^3J_{H\text{-}H}$ = 4.8 Hz), 8.09 (dd, 2*H*, *Ar*), 8.56 (t, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 7.0 Hz,), 9.51 (d, 2*H*, *Ar*, $^3J_{H\text{-}H}$ = 6.1 Hz); ^{13}C NMR (δ/ppm, $CDCl_3$): 59.17, 61.38, 70.63, 128.04, 145.67; IR ν_{max} (cm^{-1}, KBr): 3036 (*w*), 2917, (*m*), 2848 (*m*), 2372 (*w*), 2857 (*s*), 1631 (*s*), 1577

(*w*), 1539 (*w*), 1486 (*s*), 1313 (*w*), 1174 (m), 1106 (*s*), 1014 (*m*), 978 (*w*), 782 (*m*), 685 (*s*); ESI-MS: 138.0 (+ m/z), -80.8 (-m/z).

Synthesis of N-(methoxyethyl)pyridinium bis(trifluoromethylsulfonyl)amide

[*N*-MEPy][$N(SO_2CF_3)_2$]

In a 250 mL round-bottomed flask equipped with a stir bar, 9.51 g of N-(methoxyethyl)pyridinium bromide (43.6 mmol) was dissolved in 75 mL of $CHCl_3$. To this 15.64 g of lithium bis(trifluoromethylsulfonyl)amide (1.25 eq., 54.5 mmol) was added along with 75 mL of deionized water. The mixture was stirred at room temperature for 3 days. The mixture was then transferred to a 500 mL separatory funnel and 150 mL of $CHCl_3$ was added. The IL/$CHCl_3$ layer was washed with 3 x 100 mL of deionized water at which point no precipitate was observed in the aqueous wash after addition of silver nitrate. The organic layer was then dried with magnesium sulfate and filtered into a 100 mL round-bottomed flask. [*N*-MEPy][$N(SO_2CF_3)_2$] was obtained as a clear, slightly yellow-brown liquid after the $CHCl_3$ was removed under vacuum and the IL was dried under high vacuum at 60 °C for 8 h (15.21 g, 83.4 %). ^{1}H NMR (δ/ppm, $CDCl_3$): 3.33 (s, 3*H*, -O***CH***$_3$), 3.84 (t, 2*H*, -CH_2***CH***$_2$O-, $^3J_{H\text{-}H}$ = 4.4 Hz), 4.76 (t, 2*H*, -N^+***CH***$_2$$CH_2$-, $^3J_{H\text{-}H}$ = 4.4 Hz), 8.05 (m, 2*H, Ar*), 8.55 (t, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 7.6 Hz), 8.79 (d, 2*H*, *Ar*, $^3J_{H\text{-}H}$ = 5.8 Hz); ^{13}C NMR (δ/ppm, $CDCl_3$): 58.93, 61.88, 70.00, 119.9 ($^1J_{C\text{-}F}$ = 321 Hz), 128.32, 144.99, 146.10; ^{19}F NMR (δ/ppm, $CDCl_3$): -80.2; IR ν_{max} (cm^{-1}, thin film): 3141 (*w*), 3096 (*w*), 2916 (*w*), 2358 (*w*), 1638 (*m*), 1491 (*m*), 1352 (*s*), 1191 (*s*), 1137 (*s*), 1057 (*s*), 951 (*w*), 775 (*w*), 740 (*w*), 638 (*m*) , 616 (*m*); ESI-MS: 138.0 (+ m/z), -279.7 (-m/z).

Synthesis of 3-(chloromethyl)pyridine hydrochloride

A 2-necked 100 mL round-bottomed flask equipped with a stir bar was fitted to a condenser. The system was put under an Argon atmosphere and 20 mL of anhydrous THF was added *via* syringe. To the THF, 2.4 mL of thionyl chloride was added (2 eq., 41.15 mmol) and the solution stirred. Then at room temperature, 2.0 mL of 3-pyridylmethanol (1 eq., 20.81 mmol) was added drop-wise *via* syringe. The mixture was then stirred at 66 °C for 5 h and subsequently cooled to room temperature. The THF and excess thionyl chloride were removed under vacuum, and the resulting white-yellow solid was titrated with 2 x 5 mL of anhydrous toluene. Residual toluene was then removed under high vacuum at room temperature for 2 h to yield 3-(chloromethyl)pyridine hydrochloride as a fine white-yellow powder (3.34 g, 97.9 %). ^{1}H NMR (δ/ppm, $CDCl_3$): 4.94 (s, 2*H*, ArC***H***$_2$O-), 8.09 (dd, 1*H*, *Ar*, $^{3}J_{H\text{-}H}$ = 5.5 Hz, 8.0 Hz), 8.60 (d, 1*H*, *Ar*, $^{3}J_{H\text{-}H}$ = 8.0 Hz), 8.95 (d, 1*H*, *Ar*, $^{3}J_{H\text{-}H}$ = 5.5 Hz), 9.21 (s, 1*H*, *Ar*), 13.77 (broad s, 1H, •*H*Cl); ^{13}C NMR (δ/ppm, $CDCl_3$): 41.08, 127.27, 138.37, 140.74, 141.06, 145.56.

Synthesis of 3-(ethoxymethyl)pyridine

In a 250 mL round-bottomed flask absolute ethanol (15 ml) was added drop-wise to freshly cut chunks of sodium (1.72g, 74.8 mmol) under aflow of argon. The mixture was subsequently heated to reflux until no solids could be observed. Excess ethanol was removed under reduced pressure and the white-brown solid was dried under high vacuum at 100 °C for 1 h. The resulting fine powder was suspended in 35 ml of DMSO. Meanwhile in a separate 100 mL round-bottomed flask 2.4 mL of thionyl chloride (41.15

mmol) was dissolved in 20 mL of dry THF and to this 2.0 mL of 3-pyridylmethanol (20.80 mmol) was added drop-wise at room temperature, with instant formation 3-(chloromethyl)pyridine hydrochloride as a white powder. The mixture was stirred at 65 °C for 1 h and then cooled to room temperature. The THF and excess thionyl chloride were removed under high vacuum at room temperature for 1 h and the resulting white solid was triturated with 2 x 5 mL of dry toluene. The 3-(chloromethyl)pyridine hydrochloride was then dissolved in 35 mL of DMSO and added drop-wise to the slurry of sodium ethoxide and the mixture was stirred overnight at room temperature and subsequently quenched with 90 mL of deionized water. The product was extracted with 3 x 50 mL of ethyl acetate, concentrated to 50 mL of ethyl acetate solution, and washed with 3 x 20 mL of deionized water. The organic layer was then dried with $MgSO_4$, filtered, and the solvents removed under reduced pressure. The red oil was further purified by column chromatography (silica gel) using ethyl acetate as the eluent to give 3-(ethoxymethyl)pyridine after removal of the solvent under vacuum (2.80 g, 98.1 %). ^{1}H NMR (δ/ppm, $CDCl_3$): 1.25 (t, 3*H*, -$OCH_2C\boldsymbol{H}_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 3.56 (q, 2*H*, -$OC\boldsymbol{H}_2CH_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 4.51 (s, 2*H*, $ArC\boldsymbol{H}_2O$-), 7.28 (m, 1*H, Ar*), 7.68 (d, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 7.0 Hz), 8.55 (m, 2*H*, *Ar*,); ^{13}C NMR (δ/ppm, $CDCl_3$): 15.17, 66.11, 70.15, 123.40, 133.95, 135.39, 149.02, 149.17.

***Synthesis of N-butyl-3-(ethoxymethyl)pyridinium iodide,* [*N*-Bu-3-EMPy][I]**

In a 100 mL round-bottomed flask equipped with a stir bar, 2.71 g of 3-(ethoxymethyl)pyridine was dissolved in 20 mL of dry toluene. To this 2.8 mL of 1-

iodobutane was added and the solution was stirred at 110 °C overnight. After 2 h a dark red oil can be observed forming at the bottom of the solution. The solvent and excess 1-iodobutane were removed under high vacuum at 60 °C for 1 h to give a dark brown solid (6.34 g, 99.8 %). ^{1}H NMR (δ/ppm, $CDCl_3$): 0.95 (t, 3*H*, -$CH_2CH_2CH_2C\boldsymbol{H}_3$, $^{3}J_{H\text{-}H}$ = 7.0 Hz), 1.26 (t, 3*H*, -$OCH_2C\boldsymbol{H}_3$, $^{3}J_{H\text{-}H}$ = 7.0 Hz), 1.40 (m, 2*H*, -$CH_2CH_2C\boldsymbol{H}_2CH_3$), 2.01 (m, 2*H*, -$CH_2C\boldsymbol{H}_2CH_2CH_3$), 3.66 (q, 2*H*, -$OC\boldsymbol{H}_2CH_3$, $^{3}J_{H\text{-}H}$ = 7.0 Hz), 4.79 (s, 2*H*, Ar$C\boldsymbol{H}_2$O-), 4.89 (t, 2*H*, N^{+}-$C\boldsymbol{H}_2CH_2CH_2CH_3$, $^{3}J_{H\text{-}H}$ = 7.0 Hz), 8.11 (m, 1*H, Ar*), 8.50 (d, 1*H*, *Ar,* $^{3}J_{H\text{-}H}$ = 7.0 Hz), 9.29 (s, 1*H*, *Ar*,), 9.37 (d, 1*H*, *Ar*, $^{3}J_{H\text{-}H}$ = 5.0 Hz); ^{13}C NMR (δ/ppm, $CDCl_3$): 13.60, 15.15, 19.35, 33.71, 61.82, 67.24, 67.77, 128.15, 140.98, 142.50, 143.50, 143.62.; ESI-MS: 194.1 (+ m/z), -126.6 (-m/z).

***Synthesis of N-butyl-3-(ethoxymethyl)pyridinium bis(trifluoromethylsulfonyl)amide,* [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$]**

In a 250 mL round-bottomed flask equipped with a stir bar, 4.80 g of N-butyl-3-(ethoxymethyl)pyridinium iodide (14.95 mmol) was dissolved in 200 mL of deionized water. To this 5.15 g of lithium bis(trifluoromethylsulfonyl)amide (1.2 eq., 17.94 mmol) was added and the solution was stirred overnight at room temperature. The mixture was then transferred to a 500 mL separatory funnel and extracted with 4 x 50 mL of CH_2Cl_2. The combined organic layers were transferred to a 500 mL separatory funnel and washed with 2 x 50 mL of deionized water until addition of silver nitrate to the aqueous wash produced no precipitate. The organic layer was then dried with magnesium sulfate, filtered, and the solvent removed under vacuum. The resulting red oil was dried under high vacuum at 50 °C for 4 h to give [*N*-Bu-3-EMPy][$N(SO_2CF_3)_2$] (5.62 g, 79.2 %). ^{1}H

NMR (δ/ppm, $CDCl_3$): 0.97 (t, 3*H*, -$CH_2CH_2CH_2C\boldsymbol{H}_3$, $^3J_{H\text{-}H}$ = 7.4 Hz), 1.28 (t, 3*H*, -$OCH_2C\boldsymbol{H}_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 1.40 (m, 2*H*, -$CH_2CH_2C\boldsymbol{H}_2CH_3$), 1.98 (m, 2*H*, -$CH_2C\boldsymbol{H}_2CH_2CH_3$), 3.68 (q, 2*H*, -$OC\boldsymbol{H}_2CH_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 4.58 (t, 2*H*, N^+-$C\boldsymbol{H}_2CH_2CH_2CH_3$, $^3J_{H\text{-}H}$ = 7.4 Hz), 4.72 (s, 2*H*, Ar$C\boldsymbol{H}_2$O-), 8.00 (m, 1*H, Ar,* $^3J^{H\text{-}\boldsymbol{H}}$ = 7.0 Hz), 8.44 (d, 1*H, Ar,* $^3J^{H\text{-}\boldsymbol{H}}$ = 7.0 Hz), 8.70 (m, 2*H, Ar*,), ^{13}C NMR (δ/ppm, $CDCl_3$): 13.22, 14.92, 19.28, 33.44, 62.36, 67.16, 67.69, 119.85 ($^1J_{C\text{-}\boldsymbol{F}}$ = 321 Hz), 128.20, 141.69, 142.00, 143.09, 143.61; ^{19}F NMR (δ/ppm, $CDCl_3$): -80.0; IR ν_{max} (cm^{-1}, thin film): 3080 (*bw*), 2971 (*w*), 2939(*w*), 2880(*w*), 1637(*w*), 1505(*w*), 1469(*w*), 1352(*s*), 1332(*m*), 1227 (*m*), 1194(*s*), 1137(*s*), 1058(*s*), 841(*w*), 789(*w*), 762(*w*), 740(*w*), 688(*w*), 654(*w*), 617(*m*); ESI-MS: 194.1 (+ m/z), -279.7 (-m/z).

***Synthesis of N-methoxyethyl-3-(ethoxymethyl)pyridinium bis(trifluoromethyl-sulfonyl)amide,* [*N*-ME-3-EMPy][$N(SO_2CF_3)_2$]**

In a 100 mL 2-necked round-bottomed flask 3-(ethoxymethyl)pyridine (2.315 g, 16.88 mmol) was dissolved in 20 mL of acetone. The flask was equipped with a stir bar, fitted to a condenser, and put under an Argon atmosphere. Through the side neck 2-bromoethylmethylether (1.9 mL, 1.2 eq., 20.25 mmol) added *via* syringe and the solution was stirred at 65 °C overnight. An additional portion of 2-bromoethylmethylether (1.5 mL, 0.95 eq., 15.96 mmol) was added and again the solution was stirred overnight. Then NaI (1.501g, 0.59 eq., 10.00 mmol) and more 2-bromoethylmethylether (1.0 mL, 0.63 eq., 10.64 mmol) was added and the solution was stirred for 6 h. The acetone was removed under vacuum and the crude product dissolved in 50 mL of DCM, filtered to remove inorganic salts, and the solvent removed under vacuum. Unreacted 3-

(ethoxymethyl)pyridine was removed by column chromatography (silica gel) by eluting the 3-(ethoxymethyl)pyridine with ethyl acetate then eluting N-methoxyethyl-3-(ethoxymethyl)pyridinium X (X = Br, I) with MeOH. A second column was required, which after removing the MeOH under vacuum and drying under high vacuum at 60 °C for 24 h yields N-methoxyethyl-3-(ethoxymethyl)pyridinium X (X = Br, I) as a viscous red liquid (3.75 g, 11.6 mmol for I, 13.6 mmol for Br).[104] Then 3.40 g of N-methoxyethyl-3-(ethoxymethyl)pyridinium X (X = Br, I) was transferred into a 250 mL round-bottomed flask equipped with a stir bar, dissolved in 30 mL of acetone and added [Li][$N(SO_2CF_3)_2$] (4.42 g, 15.39 mmol), stirring the solution for 48 h at room temperature. The solution was transferred to a 250 mL separatory funnel and extracted with 3 x 50 mL of DCM. The combined DCM fractions were dried with $MgSO_4$, filtered, and the solvent removed under vacuum. After drying under high vacuum at 60 °C for 15 h [*N*-ME-3-EMPy][$N(SO_2CF_3)_2$] was obtained as a low-viscosity clear yellow-orange liquid (5.37 g, 66.8 %). ^{1}H NMR (δ/ppm, $CDCl_3$): 1.28 (t, 3*H*, -$OCH_2C\boldsymbol{H}_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 3.33 (s, 3*H*, -$OC\boldsymbol{H}_3$), 3.67 (q, 2*H*, -$OC\boldsymbol{H}_2CH_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 3.82 (t, 2*H*, -$CH_2C\boldsymbol{H}_2O$-, $^3J_{H\text{-}H}$ = 4.4 Hz), 4.72 (ov s, 2*H*, Ar$C\boldsymbol{H}_2O$-), 4.74 (ov t, 2*H*, -$N^+C\boldsymbol{H}_2CH_2$-, $^3J_{H\text{-}H}$ = 4.4 Hz), 7.98 (ov dd, 1*H, Ar*), 8.45 (d, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 7.0 Hz), 8.69 (ov s+d, 2*H*, *Ar*,); ^{13}C NMR (δ/ppm, $CDCl_3$): 14.91, 58.98, 61.94, 67.13, 67.72, 69.97, 119.77 ($^1J_{C\text{-}F}$ = 321 Hz), 127.73, 141.17, 142.73, 143.60, 143.88; ^{19}F NMR (δ/ppm, $CDCl_3$): -80.0; IR ν_{max} (cm^{-1}, thin film): 3090 (*bw*), 2981 (*w*), 2939(*w*), 2881(*w*), 2359(*w*), 1638(*w*), 1506(*w*), 1477(*w*), 1353(*s*), 1332(*m*), 1194(*s*), 1136(*s*), 1058(*s*), 841(*w*), 789(*w*), 762(*w*), 740(*w*), 688(*w*), 654(*w*), 617(*m*); ESI-MS: 196.0 (+ m/z), -279.7 (-m/z).

5.4 Preparation of Authentic Samples

Synthesis of 4-phenyloctane-2-one (2) via 1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1)

In an inert atmosphere glove box 3.60 g (2 eq., 4.02 mmol) of Copper(I) cyanide was weighed into an oven dried 100 mL Schlenk round-bottomed flasks equipped with a stir bar. The flask was sealed with a septum, removed from the glove box and placed under a flow of argon. Then 10 mL of THF was added *via* glass syringe to the flask and cooled to -78 °C using a dry ice in acetone bath. 5.5 mL of *n*-BuLi (1.6 M in hexane, 4 eq., 8.80 mmol) was added drop-wise *via* glass syringe. The solution was stirred for 2 h to produce a clear, slightly yellow solution of [$Bu_2CuLi{\cdot}LiCN$]. In an oven-dried sample vial flushed with argon 0.2925 g of **1** was dissolved in 5.0 mL of dry THF (1 eq., 2.00 mmol) and was added drop-wise *via* glass syringe. The solution was stirred for 1 h at -78 °C then warmed to 0 °C over 1 h. The reaction was quenched with 10 mL of 2 N HCl, transferred to a 250 mL separatory funnel and extracted with 3 x 20 mL of Et_2O. The organic layers were combined, dried with magnesium sulfate, filtered, and the solvents removed under vacuum to give **2** as a clear yellow oil. (0.37 g, 91 % yield). ^{1}H NMR (δ/ppm, $CDCl_3$): 0.81 (t, 3*H*, -CH_2CH_3, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.20 (m, 4*H*, -$CH_2(CH_2)_2CH_3$), 1.58 (m, 2*H*, >$CHCH_2C_3H_7$), 1.99 (s, 3*H*, -C(O)CH_3), 2.77 (d, 2*H*, -C(O)CH_2CH<, $^3J_{H\text{-}H}$ = 7.5 Hz), 3.10 (quint. 1*H*, $(-CH_2)_2CH$-C_6H_5, $^3J_{H\text{-}H}$ = 7.5 Hz), 7.25 (m, 5*H*, ***Ar***); ^{13}C NMR (δ/ppm, $CDCl_3$): 14.20, 22.83, 29.81, 30.86, 36.42, 41.50, 51.16, 126.53, 127.70, 128.68, 144.84, 208.26; GC-MS: M^+ 204 (1), 146 (100), 147 (48).

Synthesis of 3-methyl-1-phenylhept-1-en-3-ol (3) via 1,2- addition of n-BuLi to trans-4-phenyl-3-buten-2-one (1)

An oven dried 100 mL Schlenk round–bottomed flask equipped with an oven dried stir bar was place under a flow of argon and 0.2928 g of **1** (2.00 mmol) was added. The solid was dissolved in 15 mL of THF added *via* glass syringe and the mixture was cooled to -78 °C using a dry ice/acetone bath. 2.4 mL of *n*-BuLi (1.6 M in hexane, 1.9 eq., 3.8 mmol) was added drop-wise *via* glass syringe. The solution was allowed to stir for 2 h warming to -30 °C at which point the solution was a clear faint yellow colour. The reaction was quenched after 2 h with 8 mL of 2 M HCl and extracted with 3 x 20 mL of Et_2O. The organic layers where combined, dried with magnesium sulfate and filtered. A sample for GC-MS analysis was prepared by passing 0.2 mL of the crude reaction mixture through a short dry silica plug using 9:1 hexanes:ethylacetate as eluent until the GC vial was filled to 1.5 mL. Analysis of the GC-MS chromatogram obtained for the crude reaction mixture confirmed the presence of **3** as the major product (61%, $M^+(-H_2O)$ = 186) with some of **2** (18%) and unreacted **1** also present. The ^1H NMR spectrum confirmed the presence of all three species with **3** being the major product. Specifically for **3** two doublets are observed (δ/ppm, $CDCl_3$: 6.28 and 6.58, $^3J^{H-H}$ = 16 Hz) which can be assigned as the allylic protons of **3** as they differ in chemical shift from those found in **1**. (GC-MS **3**: 186 (50), 143 (100).

Test for Wittig-type and 1,2-addition side reactions between [$Bu_2CuLi{\cdot}LiCN$] and benzophenone (5) in the presence of [$P^{6,6,6,14}$][CF_3CO_2]

In an inert atmosphere glove box 0.360 g of CuCN (1 eq., 4.02 mmol) was weighed into an oven dried 100 mL Schlenk round-bottomed flask equipped with an oven dried stir bar. The flask was sealed with a septum, removed from the glove box and placed under a flow of argon. 15 mL of THF was added *via* glass syringe and the mixture was cooled to -78 °C using a dry ice/acetone bath. 4.8 mL of *n*-BuLi (1.6 M in hexane, 1.9 eq., 7.7 mmol) was added drop-wise *via* glass syringe. The solution was allowed to stir for 2 h warming to -20 °C at which point [$Bu_2CuLi{\cdot}LiCN$] had formed as clear faint yellow solution. Meanwhile [$P^{6,6,6,14}$][CF_3CO_2] was dried under high vacuum for 3 h at 60 °C. After releasing the vacuum and cooling to room temperature 2.5 mL of [$P^{6,6,6,14}$][CF_3CO_2] (1.0 eq., 2.4 g, 4.1 mmol) was added slowly *via* syringe and the solution was stirred for 1 h, warming to -10 °C. The solution remained a clear yellow colour. In an oven dried sample vial 0.3657 g of **5** (2.00 mmol) was dissolved in 4.0 mL of THF (0.5 eq., 0.50 M solution) and this was added drop-wise *via* syringe to the Schlenk flask. The mixture was stirred for 3 h at 0 °C and then overnight warming to room temperature for a total of 24 h. At 5 min, 1 h, 3 h, and 24 h a sample for GC-MS analysis was prepared by quenching a 0.1-0.2 mL aliquot of the reaction with 0.5 mL of 2N HCl, extracting with 1.0 mL of Et_2O, and passing 0.5 mL of the Et_2O layer through a short dry silica plug using 9:1 hexanes:ethylacetate as eluent until the GC vial was filled to 1.5 mL. The results of this experiment suggest the formation of Wittig-type and 1,2-addition side reactions and are discussed in Section 2.4.2. The signal for (**5**) appears at t_R

= 5.61 min (M+ = 182(50), 105(100)) and decreases with time. After 5 min two new signals are present which grow equally over 1 h. The first peak with t_R = 6.80 min is proposed to be a mixtue of 1,1-diphenylpentan-1-ol (**7**, M^+-H_2O = 222, 193(100) and 1,1,2,2-tetraphenylethan-1,2-diol (**8**, ½ M+ = 183 (50), 105(31)), while the second peak appears at t_R = 7.03 min and proposed to be 1,1-diphenylhept-1-ene (**6**, M^+ = 250(55), 193(100)). After 1 h the signal at t_R = 6.80 min for the mixture of **7** and **8** does not increase any further and we experience conversion of **5** to **6** over the remainder of the 24 h reaction. The relative amount of species present after 24 h is **5** (37 %), **6** (57 %), **7** + **8** (6 %).

5.5 General Procedure for Compatibility Experiments of Ionic Liquids in the 1,4-conjugate addition of [Bu_2CuLi·LiCN] to *trans*-4-phenyl-3-buten-2-one (1); slight excess of *n*-BuLi

In an inert atmosphere glove box 0.358 g of CuCN (1 eq., 4.00 mmol) was weighed into an oven dried 100 mL Schlenk round-bottomed flask equipped with an oven dried stir bar. The flask was sealed with a septum, removed from the glove box and placed under a flow of argon. 20 mL of THF was added *via* glass syringe and the mixture was cooled to -78 °C using a dry ice/acetone bath. 5.5 mL of *n*-BuLi (1.6 M in hexane, 2.2 eq., 8.8 mmol) was added drop-wise *via* glass syringe. The solution was allowed to stir for 2 h warming to -30 °C at which point [Bu_2CuLi·LiCN] had formed as clear faint yellow solution. Meanwhile the IL under investigation was dried under high vacuum for 3 h at 60 °C. After releasing the vacuum and cooling to room temperature 2.5 mL of the IL (~ 1

eq. IL, see Table RD.4) was added slowly *via* syringe and the solution was stirred for 1 h, warming to 0 °C. Then, in an oven dried sample vial 0.292 g of **1** (0.5 eq., 2.00 mmol) was dissolved in 4.0 mL of THF (0.50 M solution) and this was added drop-wise *via* syringe to the Schlenk flask. The mixture was allowed to stir for 1 h maintaining the temperature at 0 °C. At 5 min and at 1 h a sample for GC-MS analysis was prepared by quenching a 0.1-0.2 mL aliquot of the reaction with 0.5 mL of 2N HCl, extracting with 1.0 mL of Et_2O, and passing 0.5 mL of the Et_2O layer through a short dry silica plug using 9:1 hexanes:ethylacetate as eluent until the GC vial was filled to 1.5 mL.

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [$P^{6,6,6,14}$][Cl] (Entry 1): Following the general procedure: The reaction was quenched after 1 h with 10 mL of 2 M HCl and extracted with 3 x 20 mL of Et_2O. The organic layers where combined, dried with magnesium sulfate, filtered, and the solvents removed under vacuum. The remainder was passed through a column (9:1 hexanes:ethylacetate, 50 g silica) by flash chromatography to give low purity 4-phenyloctan-2-one (**2,** 65 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [$P^{6,6,6,14}$][$N(SO_2CF_3)_2$] (Entry 4): Following the general procedure: The reaction was quenched after 1 h with 10 mL of 2 M HCl and extracted with 3 x 20 mL of Et_2O. The organic layers where combined, dried with magnesium sulfate, filtered, and the solvents removed under vacuum. The remainder was twice passed through a

column (9:1 hexanes:ethylacetate, 50g silica) by flash chromatography to give low purity 4-phenyloctan-2-one (**2**, 93 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [$P^{6,6,6,14}$][$N(CN)_2$] (Entry 6): Following the general procedure: The reaction was quenched after 1 h with 10 mL of 2 M HCl and extracted with 3 x 20 mL of Et_2O. The organic layers where combined, dried with magnesium sulfate, filtered, and the solvents removed under vacuum. The remainder was passed through a column (9:1 hexanes:ethylacetate, 50g silica) by flash chromatography to give low purity 4-phenyloctan-2-one (**2**, 77 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

5.6 General Procedure for Compatibility Experiments of Ionic Liquids in the 1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to *trans*-4-phenyl-3-buten-2-one (1); slight deficiency of *n*-BuLi

In an inert atmosphere glove box 0.358 g of CuCN (1 eq., 4.00 mmol) was weighed into an oven dried 100 mL Schlenk round-bottomed flask equipped with an oven dried stir bar. The flask was sealed with a septum, removed from the glove box and placed under a flow of argon. 20 mL of THF was added *via* glass syringe and the mixture was cooled to -78 °C using a dry ice/acetone bath. 4.8 mL of *n*-BuLi (1.6 M in hexane, 1.9 eq., 7.7 mmol) was added drop-wise *via* glass syringe. The solution was allowed to stir for 2 h warming to -30 °C at which point [$Bu_2CuLi{\cdot}LiCN$] had formed as clear faint yellow solution. Meanwhile the IL to be investigated was dried under high vacuum for 3 h at 60

°C. After releasing the vacuum and cooling to room temperature 2.5-2.75 mL of the IL (~ 1 eq for $[P^{6,6,6,14}]$-based ILs, ~ 2 eq. for [Py]-based ILs, see Table RD.4) was added slowly *via* syringe and the solution was stirred for 1 h, warming to 0 °C. Then, in an oven dried sample vial 0.292 g of **1** (0.5 eq., 2.00 mmol) was dissolved in 4.0 mL of THF (0.50 M solution) and this was added drop-wise *via* syringe to the Schlenk flask. The mixture was allowed to stir for 1 h maintaining the temperature at 0 °C. At 5 min and at 1 h a sample for GC-MS analysis was prepared by quenching a 0.1-0.2 mL aliquot of the reaction with 0.5 mL of 2N HCl, extracting with 1.0 mL of Et_2O, and passing 0.5 mL of the Et_2O layer through a short dry silica plug using 9:1 hexanes:ethylacetate as eluent until the GC vial was filled to 1.5 mL.

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [$P^{6,6,6,14}$][Cl] (Entry 2): Following the general procedure: The reaction was quenched after 1 h with 10 mL of 2 M HCl and extracted with 3 x 20 mL of Et_2O. The organic layers where combined, dried with magnesium sulfate, filtered, and the solvents removed under vacuum. The remainder was passed through a column (9:1 hexanes:ethylacetate, 50g silica) by flash chromatography to give low purity 4-phenyloctan-2-one (**2**, 80 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [$P^{6,6,6,14}$][n-$C_9H_{19}CO_2$] (Entry 3): The reaction was quenched after 1 h with 10 mL of 2 M HCl and extracted with 3 x 20 mL of Et_2O. The organic layers where

combined, dried with magnesium sulfate, filtered, and the solvents removed under vacuum. The remainder was passed through a column (9:1 hexanes:ethylacetate, 50g silica) by flash chromatography to give low purity 4-phenyloctan-2-one (**2**, 94 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [$P^{6,6,6,14}$][$N(SO_2CF_3)_2$] (Entry 5): Following the general procedure: The sample was lost and thus no attempt at isolation could be made and the mass spectra was used to determine the amount of 4-phenyloctan-2-one formed (**2**, 84 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [$P^{6,6,6,14}$][CF_3CO_2] (Entry 7): Following the general procedure: The reaction was quenched after 1 h with 10 mL of 2 M HCl and extracted with 3 x 20 mL of Et_2O. The organic layers where combined, dried with magnesium sulfate, filtered, and the solvents removed under vacuum. The remainder was passed through a column (9:1 hexanes:ethylacetate, 50g silica) by flash chromatography to give low purity 4-phenyloctan-2-one (**2**, 71 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [N-MEPy][$N(SO_2CF_3)_2$] (Entry 8): Following the general procedure: No attempt was made at isolation due to low conversion of starting material to 4-phenyloctan-2-one (**2**, 18 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in the presence of [N-Bu-3-EMPy][$N(SO_2CF_3)_2$] (Entry 9): Following the general procedure: No attempt was made at isolation due to low conversion of starting material to 4-phenyloctan-2-one (**2**, 5 % by GC-MS: M^+ = 204 (1), 146 (100), 147 (48)).

5.7 General Procedure for Ether-*free* Ionic Liquid Dialkylcuprate Experiments

In an inert atmosphere glove box 0.144 g of CuCN (1 eq., 1.61 mmol) was weighed into an oven dried 50 mL Schlenk round-bottomed flask equipped with an oven dried stir bar. The flask was sealed with a septum, removed from the glove box and placed under a flow of argon. 5.0 mL of THF was added *via* glass syringe and the mixture was cooled to -78 °C using a dry ice/acetone bath. 2.0 mL of *n*-BuLi (1.6 M in hexane, 2 eq., 3.2 mmol) was added drop-wise *via* glass syringe. The solution was allowed to stir for 1 h warming to -30 °C at which point [$Bu_2CuLi{\cdot}LiCN$] had formed as clear faint yellow solution. Meanwhile the IL under investigation was dried under high vacuum for 3 h at 60 °C. After releasing the vacuum and cooling to room temperature 3.0 mL (2.5-3.2 eq. for [$P^{6,6,6,14}$]-based ILs, 4.8-6.8 eq. for [Py]-based ILs, see Table RD.6) of the IL was added

slowly *via* syringe. The IL solidified, but dissolved and stirred at -10 °C for 30 min at which point the solution remained a clear yellow colour. The THF was then removed under high vacuum for 2 h at 0 °C at which point the solution had become very viscous and yellow-orange in colour (dark red for [Py]-based ILs). After releasing the vacuum 0.146 g of **1** (0.6 eq., 1.00 mmol) was added as a solid to the Schlenk flask. The solution was slowly stirred changing to orange in colour. After 1 h the reaction was quenched with 15 mL of 0.67 N HCl and quick addition of 15 mL of Et_2O to aid mixing. A sample for GC-MS analysis was prepared by passing a 0.5 mL aliquot of the Et_2O layer through a short dry silica plug using 9:1 hexanes:ethylacetate as eluent until the GC vial was filled to 1.5 mL to determine the amount of 4-phenyloctan-2-one (**2**) formed. No attempts were made to isolate **2** due to incomplete conversion by GC-MS and difficulties experienced during compatibility experiments.

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in [$P^{6,6,6,14}$][Cl] (Entry 10): After 1 h the relative amount of 4-phenyloctan-2-one (**2**) is present is 27 % by GC-MS (**2**, M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in [$P^{6,6,6,14}$][n-$C_9H_{19}CO_2$] (Entry 11): When the THF was removed from the IL/cuprate solution the mixture solidified, and after 1 h only trace amounts of 4-phenyloctan-2-one (**2**) was present by GC-MS.

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in [$P^{6,6,6,14}$][$N(SO_2CF_3)_2$] (Entry 12): After 1 h the relative amount of 4-phenyloctan-2-one (**2**) is present is 41 % by GC-MS (**2**, M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in [$P^{6,6,6,14}$][$N(CN)_2$] (Entry 13): After 1 h the relative amount of 4-phenyloctan-2-one (**2**) is present is 59 % by GC-MS (**2**, M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in [$P^{6,6,6,14}$][CF_3CO_2] (Entry 14): After 1 h the relative amount of 4-phenyloctan-2-one (**2**) is present is 30 % by GC-MS (**2**, M^+ = 204 (1), 146 (100), 147 (48)).

1,4-conjugate addition of [$Bu_2CuLi{\cdot}LiCN$] to trans-4-phenyl-3-buten-2-one (1) in [N-MEPy][$N(SO_2CF_3)_2$] or [N-Bu-3-EMPy][$N(SO_2CF_3)_2$]: In both of our [Py]-based ILs investigated the solution turned very dark after removal of THF and no conversion of **1** to 4-phenyloctan-2-one (**2**) was observed by GC-MS.

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[95] Unfortunately structure has yet to be resolved.
[96] Having a melting point of 127 °C [*N*-MEPy][Br] does not constitute an IL itself but is a convenient precursor for accessing [Py]-based ILs through metathesis.
[97] ^{1}H NMR (δ/ppm, $CDCl_3$): 1.29 (t, 3*H*, -$OCH_2C\boldsymbol{H}_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 3.35 (s, 3*H*, -$OC\boldsymbol{H}_3$), 3.69 (q, 2*H*, -$OC\boldsymbol{H}_2CH_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 3.96 (t, 2*H*, -$CH_2C\boldsymbol{H}_2O$-, $^3J_{H\text{-}H}$ = 4.8 Hz), 4.82 (s, 2*H*, Ar$C\boldsymbol{H}_2O$-), 5.15 (t, 2*H*, -$N^+C\boldsymbol{H}_2CH_2$-, $^3J_{H\text{-}H}$ = 4.8 Hz), 7.98 (dd, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 6.3 Hz, 8.3 Hz), 8.60 (d, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 8.3 Hz),

9.28 (s, 1*H*, *Ar*,), 9.33 (d, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 6.3 Hz); ^{13}C NMR (δ/ppm, $CDCl_3$): 15.12, 49.95, 59.16, 61.44, 67.10, 67.88, 70.48, 127.83, 140.42, 143.19, 143.91, 144.09.

[98] Ionic Liquids Database http://ildb.merck.de/ionicliquids/en/startpage.htm

[99] Density calculations for ILs: $[P^{6,6,6,14}][CF_3CO_2]$ d = (0.3126 g / 0.32 mL) = 0.98 g/mL; [N-EPy]-$[N(SO_2CF_3)_2]$ d = (0.9519 g / 0.63 mL) = 1.5 g/mL; [N-Bu-3-EPy]$[N(SO_2CF_3)_2]$ d = (0.3970 g / 0.32 mL) = 1.2 g/mL

[100] The mass spectra of the blank Et_2O and 9:1 hexanes/ethylacetate solutions used to elute our GC samples were checked both untreated and after being passed through a short silica gel plug akin to the sample preparation for the IL/cuprate experiments. Passing the solvents through the silica gel plug did result in very small amounts of contamination evident in the mass spectra. These peaks were ignored when calculating the relative percentages of species present in the crude sample. It was also observed that butylated hydroxytoluene (BHT) is present in all samples where Et_2O is used as it is an additive employed as an antioxidant in that solvent.. The BHT signal when fully resolved from **2** was eliminated from all calculations. Unfortunately BHT elutes from the GC column at a retention time just before **2**. The base peak of BHT is the molecular ion M+ = 205 which often complicated seeing the molecular ion of **2,** M+ = 204 (1%) and on occasion overlapped with 2 and thus was included in the area for that signal. Fortunatly BHT was observed as a relatively low intensity signal.

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[104] ^{1}H NMR (δ/ppm, $CDCl_3$): 1.29 (t, 3*H*, $-OCH_2C\boldsymbol{H}_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 3.35 (s, 3*H*, $-O\boldsymbol{CH}_3$), 3.69 (q, 2*H*, $-OC\boldsymbol{H}_2CH_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 3.96 (t, 2*H*, $-CH_2C\boldsymbol{H}_2O-$, $^3J_{H\text{-}H}$ = 4.8 Hz), 4.82 (s, 2*H*, $ArC\boldsymbol{H}_2O-$), 5.15 (t, 2*H*, $-N^+C\boldsymbol{H}_2CH_2-$, $^3J_{H\text{-}H}$ = 4.8 Hz), 7.98 (dd, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 6.3 Hz, 8.3 Hz), 8.60 (d, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 8.3 Hz), 9.28 (s, 1*H*, *Ar*,), 9.33 (d, 1*H*, *Ar*, $^3J_{H\text{-}H}$ = 6.3 Hz); ^{13}C NMR (δ/ppm, $CDCl_3$): 15.12, 49.95, 59.16, 61.44, 67.10, 67.88, 70.48, 127.83, 140.42, 143.19, 143.91, 144.09.