Ionic Core Dependence of Ionophilic Thiourea Organocatalysis in Ionic Liquids

By

Katherine Parsons

A Thesis Submitted to

Saint Mary's University, Halifax, Nova Scotia

In Partial Fulfillment of the Requirements for

the Degree of Bachelor of Science

with Honours in Chemistry

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Approved:     Dr. Robert Singer

Supervisor and Chair of Chemistry
Department

Approved:     Dr. Jason Masuda

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**Abstract**

The Morita-Baylis-Hillman reaction forms a carbon-carbon bond between an electron-deficient alkene and an aldehyde in an atom economic, albeit slow, reaction in the presence of catalytic tertiary amine or phosphine.[1] Utilizing a methylpiperidinium derived ionic thiourea co-catalyst, **6**, in the Morita-Baylis-Hillman reaction between benzaldehyde and 2-cyclohexene-1-one with DABCO resulted in a rate acceleration and appreciable conversion to the product, 2-(hydroxyl(phenyl)methyl)cyclohex-2-enone, **1**, within two days. Additionally, recycling of the methylpiperidinium thiourea organocatalyst, **6**, was attempted in order to facilitate reuse of the catalyst by entrainment in two ionic liquids, [BMPyr][N(Tf)$_2$] and [BMPP][N(Tf)$_2$]. The percent conversions to the product of the first two trials were 89% and 88%, but on recycling, this decreased to 54% and 66% conversion respectively. The methylpiperidinium thiourea organocatalyst, **6**, was not able to be successfully recycled and did not maintain catalytic activity.

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## Abbreviations

| | |
|---|---|
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| [BMPyr][N(Tf)$_2$] | 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide |
| [BMPP][N(Tf)$_2$] | 1-butyl-1-methylpiperidinium bis(trifluoromethylsulfonyl)imide |
| kg | Kilogram |
| g | Gram |
| mL | Millilitre |
| L | Litre |
| DMSO-d$^6$ | Deuterated dimethylsulfoxide |
| CDCl$_3$ | Deuterated chloroform |
| ESI-MS | Electrospray ionization mass spectrometry |
| MP | Melting point |
| RT | Room temperature |
| ppm | Parts for million |
| CO$_2$ | Carbon dioxide |
| MW | Microwave Reactor |
| NMR | Nuclear Magnetic Resonance |
| ATR | Attenuated Total Reflection |
| IR | Infrared |
| MeCN | Acetonitrile |

## 1.0 Introduction

## 1.1 Green Chemistry

In 1991 Trost introduced the term "atom economy" to describe the efficiency of synthetic pathways and the inherent waste produced in the form of by-products. This approach takes precedence away from a singular focus on the yield and instead emphasizes the inclusion of reactants into the final product. The ideal "Atom Economy" should be 100%, indicating that each reactant used is present in the product.[2] The following year Sheldon introduced the E(nvironmental) factor to compare the waste produced as a consequence of the final product. The E factor is calculated such that the mass of waste is divided by the mass of product (in kg). Therefore, if minimal waste was produced in the formation of the product the E factor will reflect this in a value close to zero. Thus, when the E factor was calculated for the fine chemicals and pharmaceutical industries, large ratios of between 5-50 and 25 to over 100 respectively, serve to show the sheer scale of the waste produced and consequently the negative impact these industries have on the environment.[3]

Both atom economy and the E factor serve to highlight different aspects of the amount of waste that is produced in chemical processes, but do not account for everything. Atom economy is calculated based on a stoichiometric chemical equation and does not account for other sources of waste such as solvents. The E factor provides only information on the amount of waste and not the toxicity or biodegradability of the waste being generated.[3] Hence, in 1998 Anastas and Warner published the twelve principles of Green Chemistry which provide a framework for sustainability and efficiency while reducing negative health and environment impacts.[4]

One approach to mitigate the harmful consequences of waste on the environment is to prevent this waste from being released in the first place. This is the first principle of Green Chemistry. Green Chemistry provides guidelines and encourages avoiding and / or reducing waste rather than remediating waste once it has been created. Unwanted by-products get discarded as waste and the second principle is atom economy to promote the reduction of the inherent waste production within a reaction. Atom economy is formally calculated through dividing the molecular weight of the products by that of the reactants. The third, fourth and fifth principle of green chemistry are applicable to the different components of a reaction system, the third principle is to use a synthetic pathway that minimizes the inclusion of toxic materials, the fourth principle is to create products that are non-toxic, and the fifth principle is to use supporting components to the reaction, such as solvents, that are non-toxic.

Waste takes the form of useless chemical by-products but also as lost energy, the sixth principle is to reduce other types of waste. The seventh principle is to prioritize materials that are from renewable sources over materials from non-renewable sources, such as petroleum feedstock. The eighth principle is to design synthesis without the use of derivatives such as protecting groups. The ninth principle is to utilize catalysis and the tenth principle is to design products to be biodegradable. The eleventh principle is to analyze pollution without creating more waste in the process and the twelve principle is to minimize accidents.[4,5] The purpose of Green Chemistry is to reduce the associated hazard of the products of the chemical industry and also the waste that is produced in turn by incorporating thoughtful design that will be both environmentally and economically beneficial.

## 1.2 Green Solvents

The fifth principle of green chemistry refers directly to alternative solvent use in order to reduce the negative impacts of traditional volatile solvents.[4] Conventionally used organic solvents tend to be flammable and toxic. The volatile nature of these solvents increases the risk of harmful exposure to workers and contributes to environmental pollution, exacerbating problems such as global warming and ozone depletion. The main source of traditional organic solvents is petroleum, a source that is non-renewable and not sustainable.[6,7] There negative impacts are amplified due to the fact that solvents typically comprise the majority of the waste that is produced.[5] A facile solution to eliminate solvent waste is to perform neat reactions; however, solvents occupy many useful roles in the field of chemistry. Solvents allow reactants to interact in the same homogeneous phase facilitating molecular interactions, act as a means to moderate the temperature and are involved in the isolation and purification steps to yield final products.[7]

A green solvent would be categorized as non-toxic, safe, benign to the environment and obtained from sustainable sources.[6] Possible alternative solvents include water, supercritical $CO_2$ and ionic liquids.[5] Water is an applicable choice as a green solvent since it is recyclable, non-toxic, abundant and inexpensive. Supercritical $CO_2$, for example, is non-flammable, non-toxic and can be utilized as an effective solvent that can be easily removed as a gas when returned to ambient temperature and pressure.[7] However, pollution caused by organic solvents is a consequence of evaporation; therefore, a solvent that is not volatile will negate the production of this waste. A class of solvents that possesses a negligible vapor pressure are ionic liquids.[5,7]

## 1.3 Ionic Liquids

Ionic liquids have been arbitrarily designated to include all salts that melt below 100 C.[8] Ionic liquids that are liquidus at or below room temperature facilitate easy substitution for traditional organic solvents. However, the utility and application of ionic liquids goes beyond use as alternative solvents and extends into such area as catalysis, surfactants, use in extractions and batteries. Ionic liquids are composed of an organic cation, a few common choices are shown in Figure 1 below, and an inorganic anion such as a halide, $[BF_4]^-$, $[PF_6]^-$ or an organic anion such as $[CF_3COO]^-$ or $[N(Tf)_2]^-$.
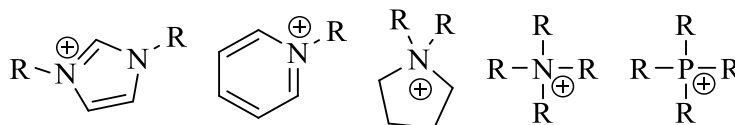


**Figure 1.** Common cations used in ionic liquids.

A judicious choice of substituents that result in a large and unsymmetrical cation are two general properties that result in a low melting salt.[8]

Modern ionic liquids stemmed from a temperature issue that the high melting point of an inorganic electrolyte salt caused in batteries; LiCl/KCl had a melting point of 355 °C. An electrolyte, $NaCl/AlCl_3$, with a lower melting point of 107 °C, was developed to address this issue. Replacement of the inorganic cation by an organic imidazolium or pyridiuium based cation resulted in salts with even lower melting points but were unstable in the presence of water. With the incorporation of a water stable anion such as tetrafluoroborate, hexafluorophosphate or nitrate, this resulted in low melting ionic salts that could now be easily handled on the bench top.[8]

Other common properties that ionic liquids possess include non-flammability and a large temperature range in which these compounds stay a liquid, with the upper temperature extent of the range typically marking the temperature at which the ionic liquid decomposed, usually between 250-450 °C.[9] This large liquidus range is indicative of the generally high thermal stability of ionic liquids.[8] However, due to the wide range of possible combinations of cations and anions, there are different properties that can be induced through altering the structure of the ionic liquid. The viscosity, melting point and even the solubility can be changed, for example creating a hydrophobic or hydrophilic ionic liquid by altering the anion.[9]

In order to be benign to the environment, chemicals must also be non-toxic and readily biodegradable, both characteristics that some ionic liquids were discovered to lack.[9] However, biodegradable ionic liquids can be synthesized.[10] Therefore, even though ionic liquids can be potentially harmful there is also the possibility of thoughtful design for future ionic liquids to satisfy the principles of Green Chemistry.

## 1.4 Biphasic Catalysis using Ionic Liquids

Through the use of catalysts, reactions can potentially proceed under milder conditions of temperature and pressure, while reducing the reaction times and increasing selectivity. Catalysts are unchanged at the end of the reaction facilitating the opportunity to separate and reuse the catalyst in subsequent reactions. Ionic liquids facilitate an easier separation and reuse of the catalyst from the products by enabling a biphasic system in which the products can be extracted using an immiscible solvent while the catalyst remains in the ionic liquid phase. Improved solubility of the catalyst in the ionic liquid phase can

be achieved through the incorporation if an ionic tag into the catalyst. Thus, by a simple phase separation the products can be removed, and the catalyst recycled.[11]

Ionic liquids employed in this biphasic strategy are incorporating aspects of the two types of catalysis, heterogeneous and homogenous. Separation and reuse of the catalyst is easily accomplished using heterogeneous catalysis, wherein the catalyst and the reactants are not in the same phase. However, heterogeneous catalysis is characterized by lower selectivities and catalytic activity when compared to homogenous catalysis, (in which reactants and catalyst are in the same phase) which typically have higher rates and selectivities.[12] Thus, ionic liquids facilitate the high rates and selectivities while simplifying the separation of the catalyst from the products through immiscibility with the extracting solvent, thus combining aspects of homogeneous and heterogeneous catalysis.

## 1.5 Organocatalysis in Green Chemistry

The ninth principle of Green Chemistry is catalysis. Catalysts reduce waste by facilitating easier transformation from reactants to products without the need for stoichiometric amounts of reagents.[4] Additionally, waste is reduced through improving the selectively of a particular reaction and therefore eliminating unwanted by-products. The field of organocatalysis is relatively new and is considered to be established in the early 2000s, even though there have been a few publications concerning catalytic organic molecules earlier. What defines and separates organocatalysis as a field, when compared to the other fields such as organometallic and enzymatic catalysis, is the lack of a metal in a small catalytic organic molecule.[13]

When considering the twelve principles of Green Chemistry, organocatalysts possess several beneficial characteristics when compared to metal catalysts, with potential

to save in cost, time, and energy. The inclusion of metals can introduce toxicity into the catalyst and instability towards moisture and / or air. Certain metals are becoming increasingly scarce and can have a high acquisition and disposal costs due to this toxicity.[13,14] However, one notable drawback of utilizing organocatalysts are high catalyst loadings that are required for a particular reaction to proceed.[13]

## 1.6 Thiourea Organocatalysis

In 1994 Curran *et al*.[15] were the first to study the rate acceleration and selectivity of a urea organocatalyst incorporating the double-hydrogen bonding of the urea functional group. This catalyst was useful as a catalyst for the allyation of sulfoxides and later in a Claisen rearrangement.[16] Curran's urea, depicted in Figure 2, possessed two octyl ester groups in part to improve the solubility of this compound.
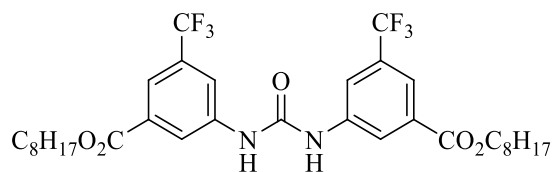


**Figure 2.** Curran's urea organocatalyst.

Alternatively, the thiourea functional group, with a sulfur atom instead of an oxygen atom, can also form double hydrogen bonds but possesses beneficial characteristics in comparison to the urea functional group. Thioureas are more soluble and easier to synthesize. Additionally, the incorporation of the less electronegative sulfur atom reduces the tendency for one thiourea functional group to double hydrogen bond to the sulfur atom of another molecule.[17]

In 2002 Schreiner and Wittkopp reported the successful rate acceleration of a Diels-Alder reaction between *N*-acyloxazolidinone and cyclopentadiene using two symmetric

diaryl thiourea organocatalysts at a 25 mol % catalyst loading. These two thiourea organocatalysts, differentiated by the number of trifluoromethyl substituents, gave inferior yields and stereoselectivity in chloroform to typical metal Lewis acid catalysts but could accelerate this reaction at room temperature under mild reactions conditions.[18] The thiourea functional group can interact with the substrate through the formation of two or more hydrogen bonds by the N-H groups with one or more Lewis basic site on the substrate.[18] Subsequently, an expanded library of symmetrical thiourea derivatives with various structures were investigated.[17] Studies demonstrated that the thiourea organocatalyst containing two 3,5-bis(trifluoromethyl)phenyl moieties had the best catalytic activity in the Diels-Alder reaction while the other investigated catalysts containing alkyl or less electron-withdrawing groups had reduced rate acceralations.[17] Schreiner's catalyst is depicted in Figure 3.
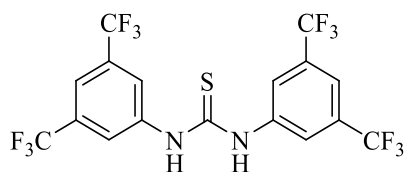


**Figure 3.** Schreiner's thiourea organocatalyst.

Schreiner and Wittkopp elucidated two important structural features that defined the most successful catalyst. The presence of the *meta-* and *para-* electron-withdrawing trifluoromethyl functional groups and a rigid catalyst. This rigidity is a consequence of the proximity of the *ortho*-hydrogen present on the aryl ring to the sulfur atom to hydrogen-bond.[17]
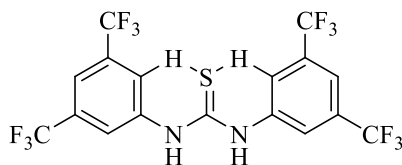
**Figure 4.** Rigidifying interaction between *ortho*-hydrogens and sulfur atom.

It would be later determined that the other *ortho*-hydrogens present on the 3,5-bis(trifluoromethyl)phenyl group, located adjacent to the N-H group of the thiourea, can also interact with Lewis basic molecules through hydrogen bonding.[19]

    Schreiner's catalyst contained only one thiourea functional group, but incorporation of additional structural features such as a tertiary amine or another thiourea moiety were also shown to be catalytically active. In 2003 Takamoto *et al*.[20] combined a chiral tertiary amine with a thiourea functional group, pictured in Figure 4 below, to synthesize the first bifunctional thiourea organocatalyst for use in a Michael reaction between *trans-β*-nitrostyrene and diethyl malonate.
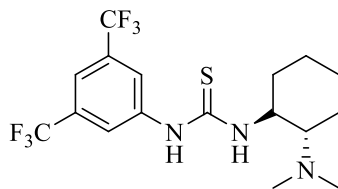


**Figure 5.** Takamoto's bifunctional thiourea organocatalyst.

    Takamoto *et al*. determined that the bifunctional catalyst outperformed the separated tertiary amine and thiourea components in terms of yield and enantioselectivity and proposed that the bifunctional thiourea catalyst was interacting with both reactants simultaneously.[21] The thiourea functionality interacting with the nitroolefin and the tertiary amine interacting with 1,3-dicarbonyl compound.[25] Furthermore, Nagasawa *et al*. incorporated two thiourea functionalities into the same catalyst, as depicted in Figure 5, in

the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohex-2-en-1-one, along other substrates. Nagasawa *et al.* proposed that the improved rate acceleration and selectivity were a consequence of the bis-thiourea organocatalyst interacting with both reactants.[22,23]
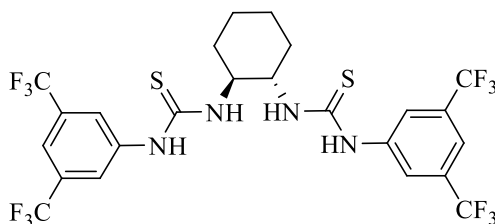


**Figure 6.** Nagasawa's bis-thiourea organocatalyst.

It would later be determined by Wang *et al.*[24] that Takemoto's bifunctional thiourea organocatalyst was not as effective when applied to different reactions, such as the Morita-Baylis-Hillman reaction. However, Wang *et al.* reported a novel chiral bifunctional thiourea organocatalyst, depicted in Figure 6, that was successful in catalyzing the Morita-Baylis-Hillman reaction without the need of a tertiary amine co-catalyst but was less effective when applied to aromatic aldehyde substrates.
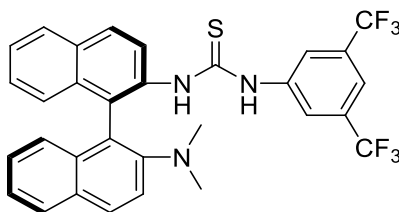


**Figure 7.** Wang's bifunctional organocatalyst.

It has been demonstrated that the thiourea functional group can be successfully utilized to accelerate the Morita-Baylis-Hillman reaction. An investigation by Coelho *et al.*[25] using ESI-MS(/MS) and theoretical calculations implicated that the double hydrogen

bonding of the thiourea functional group is able to participate in all steps of the mechanism, stabilizing the transition states.

## 1.7 Morita-Baylis-Hillman Reaction

The Morita-Baylis-Hillman reaction is useful in reacting cheap starting materials to yield products containing three different functional groups with high atom-economy. These products contain an alkene, hydroxyl and choice of electron-withdrawing group in which can be effectively used as intermediates for the synthesis of different natural products.[26] Examples of natural products synthesized with the assistance of the Morita-Baylis-Hillman reaction are Acaterin and Mycestercin E.[1]

However, the drawback of utilizing the Morita-Baylis-Hillman reaction is long reaction times, on the time scale of days. For example, the neat reaction between aldehyde and 2-propenoic acid takes 6 days to result in an 90% yield in the presence of the tertiary amine DABCO.[1] Utilizing a thiourea co-catalyst it is possible to accelerate the Morita-Baylis-Hillman reaction. However, alternative options to accelerate the Morita-Baylis-Hillman reaction exist such as Lewis Acids, proline or ionic liquids[26]; other methods include ultrasound or microwave irradiation.[1]

Scheme 1 depicts the Morita-Baylis-Hillman reaction consisting of two starting materials, an aldehyde and an electron-deficient alkene, and creating a new carbon-carbon bond to form an α-methylene-β-hydroxycarbonyl product.[1] Additionally, an electron-deficient imine can also undergo this carbon-carbon bond forming reaction, this is referred to as the aza-Morita-Baylis-Hillman reaction. This reaction is the culmination of the effort of two groups, Morita in 1968 then Baylis and Hillman in 1972, who demonstrated that this reaction could be catalyzed using a tertiary phosphine or amine.[1,26]

EWG = COR'', CHO, CN, CO$_2$R'', PO(OEt)$_2$, etc.
X = O, NCO$_2$Ar, etc.
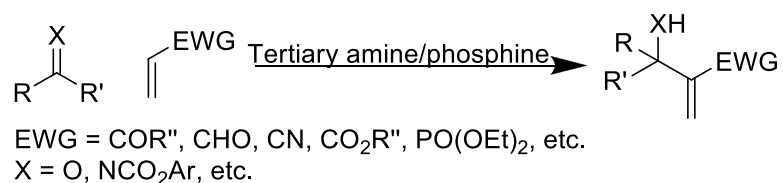
**Scheme 1.** The Morita-Baylis-Hillman reaction

An overview of the mechanism of the Morita-Baylis-Hillman reaction shows that it occurs in four steps as follows; the nucleophilic base creates an enolate by attacking the electron-deficient alkene, then this enolate will in turn undergo an aldol reaction with a molecule of an aldehyde. Thirdly, the hydroxyl group is formed when the hydrogen on the α-carbon transfers to the negatively charged oxygen and the nucleophilic base is eliminated.[26]
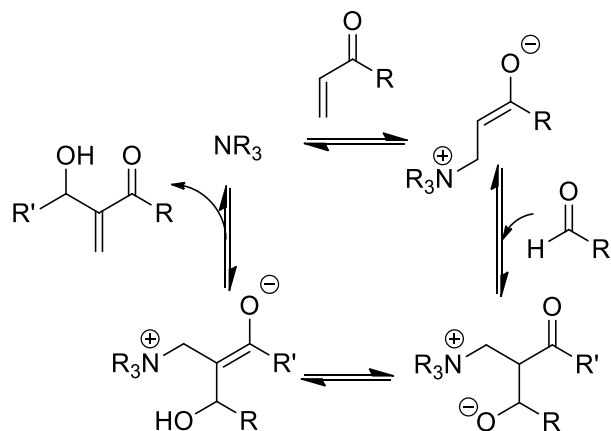


**Scheme 2.** Mechanism of Morita-Baylis-Hillman reaction

It was previously determined that the rate determining step was the aldol reaction with the addition of the aldehyde molecule but during a mechanistic investigation of the Morita-Baylis-Hillman reaction by McQuade *et al.*[27,28] a primary isotope effect was observed for the proton transfer step and that the reaction proceeded second-order with respect to the aldehyde. A new rate determining step was proposed, the proton transfer step,

that proceeded through an intermediate that involved two aldehyde molecules. Scheme 3 depicts the hemiacetal structure that facilitates the transfer of the proton that will ultimately lead to the final product of the Morita-Baylis-Hillman reaction.
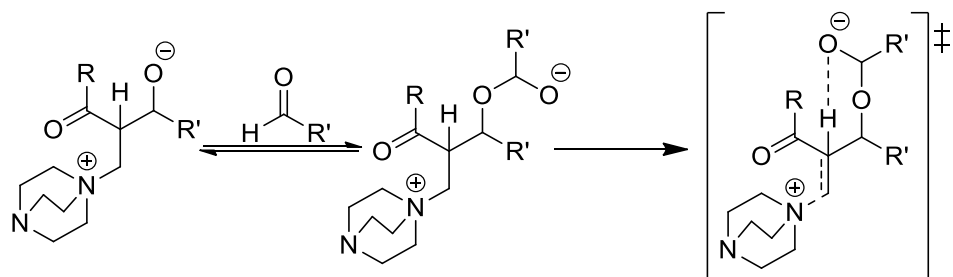


**Scheme 3.** Proposed intermediate of proton transfer step by McQuade

Aggarwal[28,29] using kinetic experiments and computational calculations supported the existence of this hemiacetal intermediate in the reaction pathway with the stipulation that this mechanism only occurred when no alcohol was present. Under reaction conditions involving an alcohol, either from an external source such as methanol or when enough of the product an alcohol had formed (approximately 20%) an alternative mechanism would involve the participation of an alcohol in the proton transfer step. This intermediate would form a six-membered ring and is depicted in Figure 9.
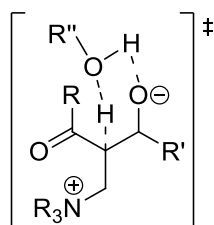


**Figure 8.** Proposed intermediate of alcohol-catalyzed proton transfer step by Aggarwal.[28,29]

Cantillo and Kappe investigated these two mechanisms and determined that both occur depending on the reaction conditions.[30]

## 1.8 Objectives

Ionic thiourea organocatalysis has been studied previously by the Singer research group. This thesis seeks to expand and build off of this preceding work. Earlier Singer group research investigated the catalytic activity of a methylpyrrolidinium derived ionic thiourea organocatalyst, **2** in Figure 10, in the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohexene-1-one using the tertiary amine 1,4-diazabicyclo[2.2.2]octane, DACBO, as the co-catalyst (Scheme 4). The use of a mono-substituted methylpyrrolidinium thiourea organocatalyst, **2**, was optimized using a ratio of 1:5 of benzaldehyde to 2-cyclohexene-1-one, 0.5 mL of the ionic liquid 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide, [BMPyr][N(Tf)$_2$], and a 10 mol % catalyst loading of both DABCO and the thiourea catalyst. [31]
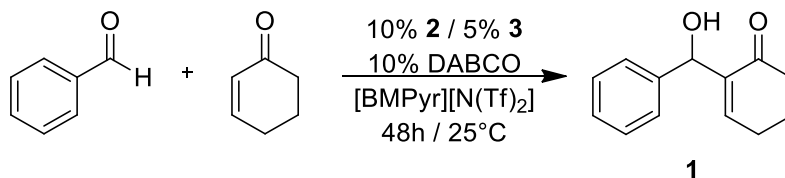


**Scheme 4.** Investigated Morita-Baylis-Hillam reaction

Under these optimized conditions a 96% conversion to the product, 2-(hydroxyl(phenyl)methyl)cyclohex-2-enone, **1**, was obtained after 48 hours. The ionic pyrrolidinium thiourea organocatalyst, **2**, was successfully entrained in the ionic liquid [BMPyr][N(Tf)$_2$] and recycled three times with minimal reductions in yield. Microwave irradiation was also proven to effectively promote the Morita-Baylis-Hillman reaction allowing elevated temperatures with reduced times.

A pyrrolidinium based bis-thiourea organocatalyt, **3**,[32] was also tested in the Morita-Baylis-Hillman reaction between benzaldehyde and 2-cyclohexene-1-one. Upon

investigation of the catalyst loading, the bis-thiourea organocatalyst **3** achieved a comparable conversion of 95% to product **1** using 5 mol %. Microwave irradiation utilizing the pyrrolidinium based bis-thiourea organocatalyst **3** could also effectivity promote the Morita-Baylis-Hillman reaction. However, the recycling studies of this catalyst in the ionic liquid [BMPyr][N(Tf)$_2$] were unsuccessful.
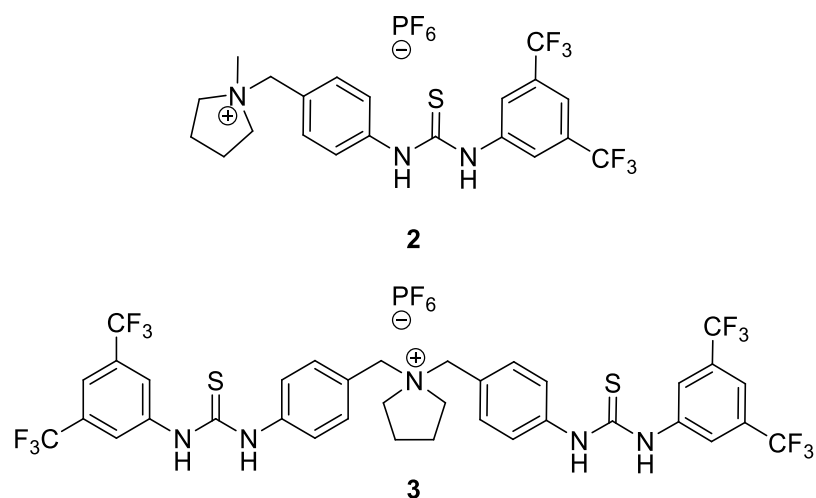


**Figure 9.** Previously studied pyrrolidinium based ionic thiourea organocatalysts.

The mono-substituted pyrrolidinium ionic thiourea organocatalyst **2** was successfully recycled three times while the bis-thiourea organocatalyst **3** was not but both studies only involved the one ionic liquid, [BMPyr][N(Tf)$_2$].[31,32] In order to investigate whether the ionic liquid has an effect on the recyclability of an ionic thiourea organocatalyst, a methylpiperidinium based ionic thiourea catalyst was tested in the Morita-Baylis-Hillman reaction and attempted to be recycled in two different ionic liquids [BMPyr][N(Tf)$_2$] and 1-butyl-1-methylpiperidinium bis(trifluoromethylsulfonyl)imide, [BMPP][N(Tf)$_2$].

## 2.0 Results and Discussion

The synthesis of the monosubstituted piperidinium based thiourea organocatalyst, **6**, required a four step sequence. The first step involved the atom-economic $S_N2$ reaction of 1-methylpiperidinium with 4-nitrobenzyl bromide resulting in the ionic compound, 1-methyl-1-(4-nitrobenzyl)piperidinium bromide, **4**.
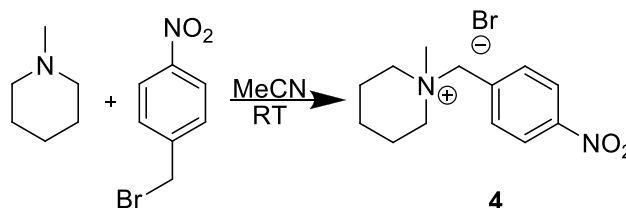


**Scheme 5.** Synthesis of 1-methyl-1-(4-nitrobenzyl)piperidinium bromide, **4**

4-Nitrobenzyl bromide was dissolved in acetonitrile and 1-methylpiperidinium was added dropwise to the solution in a 1:1 molar ratio. The reaction proceeded quickly and at room temperature (Scheme 5). Upon agitation of the solution a precipitate was formed. An equal amount of ethyl acetate was added to the reaction mixture in order to precipitate any remaining solid out of the acetonitrile. The solid was collected by filtration and rinsed with excess ethyl acetate to afford a white solid in a yield of 91%. The nitro functional group was evident in the infrared spectrum with two strong peaks at 1518 cm$^{-1}$ and 1344 cm$^{-1}$. In the aromatic region of the $^1$H NMR spectrum two doublets corresponded to a *para*-substituted aromatic ring and the methylene and methyl group were indicated by the two singlets at 4.77 ppm and 2.97 ppm, respectively. The multiplet peaks in the aliphatic region between 3.33-1.51 ppm corresponded to the piperidinium ring.

The second step involved the reduction of the nitro functional group on 1-methyl-1-(4-nitrobenzyl)piperidinium bromide, **4**, into a primary amine, followed by a metathesis

reaction in which the bromide anion was exchanged with a hexafluorophosphate anion, shown in Scheme 6.
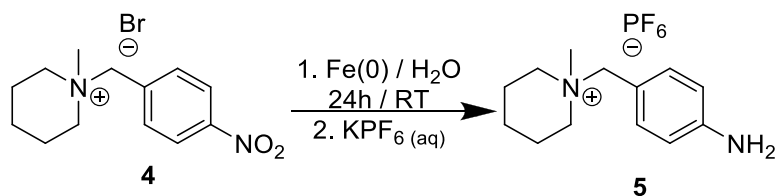


**Scheme 6.** Synthesis of 1-(4-aminobenzyl)-1-methylpiperidinium

hexafluorophosphate(V), **5**

The reduction was achieved using iron(0) nanoparticles in water, which is an effective reducing procedure for nitroarenes as demonstrated by Ranu *et al.*[33] The iron(0) nanoparticles were synthesized by dissolving iron(II) sulfate heptahydrate and sodium citrate in distilled $H_2O$. The iron(0) nanoparticles quickly precipitated out of solution with the slow addition of the reducing agent, sodium borohydride. When stirring was stopped the iron(0) nanoparticles settled on the stir bar and the bottom of the flask thereby simplifying the decantation of the water. The solid nanoparticles were then washed two more times, decanting the water in between. 1-methyl-1-(4-nitrobenzyl)piperidinium bromide, **4**, was transferred to the flask and left to react for 24 hours. The molar ratio of each component in this reduction reaction, iron(II) sulfate heptahydrate, sodium citrate, sodium borohydride and compound **4** were 6:0.5:12:1. The next day the solid iron was removed from the solution by filtration through a Celite bed. The obtained orange solution filtered through a second Celite bed afforded a clear and colourless filtrate.

Upon the dropwise addition of aqueous potassium hexafluorophosphate to the filtrate, in a 1.25:1 molar ratio with compound **4**, a white solid precipitated out of solution as a metathesis reaction took place while potassium bromide formed. This white solid was

the compound 1-(4-aminobenzyl)-1-methylpiperidinium hexafluorophosphate(V), **5**, and was collected by filtration obtaining a yield of 74%. The $^1$H NMR spectrum displayed an additional peak at 5.49 ppm that integrated to 2, corresponding to the addition of the two new hydrogens constituting the amine functional group. The infrared spectrum also supported the completion of the reduction reaction with the addition of two peaks at 3484 cm$^{-1}$ and 3398 cm$^{-1}$ corresponding to the primary amine and two peaks at 830 cm$^{-1}$ and 556 cm$^{-1}$ corresponding to the [PF$_6$]$^-$ anion.

The last step of this synthetic sequence is to add the thiourea group though the reaction of 1-(4-aminobenzyl)-1-methylpiperidinium hexafluorophosphate(V), **5**, with 3,5-bis(trifluoromethyl)phenyl isothiocycante in a 1:1 molar ratio. Compound **5** was dissolved in acetonitrile followed by a dropwise addition of 3,5-bis(trifluoromethyl)phenyl isothiocycante to afford compound **6** after stirring for 7 days at room temperature (Scheme 7). Afterwards, the solvent was removed *in vacuo* and silica gel column chromatography using an 85/15 chloroform/methanol mobile phase resulted in a pure catalyst. In the infrared spectrum there is one peak at 3372 cm$^{-1}$ corresponding to the presence of secondary amines. The addition of two singlet peaks in a 2:1 ratio in the aromatic region of the $^1$H NMR indicate the inclusion of the 3,5-(trifluoromethyl)phenyl ring and the peak at 179.81 ppm in the $^{13}$C NMR corresponded to the carbon bonded to the sulfur atom. Analysis by ESI-MS confirms the presence of the organic piperidinium based cation. It should be noted that the methylpiperidinium thiourea organocatalyst utilized in the investigation of the Morita-Baylis-Hillman reactions contained organic solvents that drying under high-vac and gentle heating under high-vac did not remove these solvent peaks in a significant and timely manner, after a few hours.
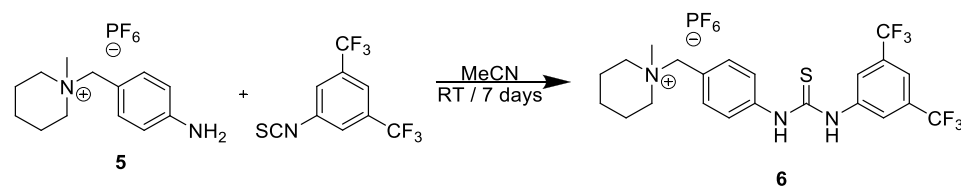
**Scheme 7.** Synthesis of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpiperidinium hexafluorophosphate(V), **6**

A second thiourea organocatalyst was also synthesized, this time with a DABCO based cationic core, the first step is shown in Scheme 7.
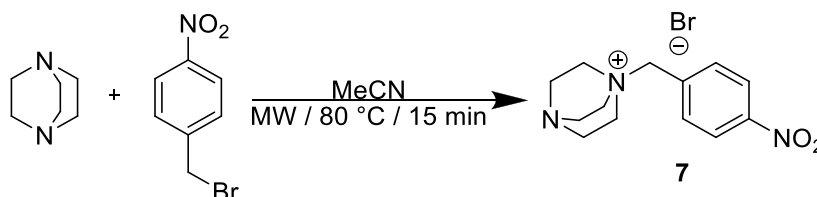


**Scheme 8.** Synthesis of 1-(4-nitrobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide, **7**

The two reactants, DABCO and 4-nitrobenzyl bromide, were dissolved in acetonitrile and heated at 80 °C for 15 minutes in the microwave reactor. An equal amount of ethyl acetate was added and the solid, **7** was collected and dried *in vacuo* and isolated in a 91% yield. The two peaks at 1518 cm$^{-1}$ and 1349 cm$^{-1}$ in the infrared spectrum correspond to the nitro functional group. The singlet in the $^1$H NMR spectrum at 4.80 ppm corresponded to the methylene functional group and two doublets in the aromatic region corresponded to the *para*-substituent aromatic ring. The two hydrogen environments constituting the DABCO ring are indicated by the two peaks at 3.40 ppm and 3.02 ppm.

The reduction step (Scheme 9) followed the same procedure as stated for compound **6**; however, it was observed that 1-(4-aminobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane hexafluorophosphate(V), **8** is slightly soluble in water at room temperature. Therefore, before filtering the flask was cooled in an ice bath, reducing the solubility to obtain

compound **8** in a 41% yield. The appearance of the singlet at 5.50 ppm represents the successful reduction to the primary amine.
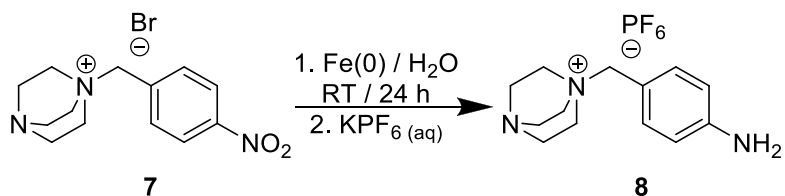


**Scheme 9**. Synthesis of 1-(4-aminobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane

hexafluorophosphate(V), **8**

In order to synthesize the thiourea organocatalyst, 1-(4-aminobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane hexafluorophosphate(V), **8** was dissolved in acetonitrile and 3,5-bis(trifluoromethyl)phenyl isothiocycante was added dropwise in a 1:1 molar ratio. The solution was heated to 50 °C for 2 hours in the microwave reactor. The solvent was removed and dried *in vacuo* to result in an impure catalyst (Scheme 10). The infrared spectrum shows the presence of the [PF$_6$]$^-$ anion with a peak at 833 cm$^{-1}$ and 584 cm$^{-1}$. The addition of the 3,5-(trifluoromethyl)phenyl functional group is apparent by the addition of two peaks in the aromatic region of the $^1$H NMR spectrum in a 1:2 ratio. The peak at 179.84 ppm in the $^{13}$C NMR corresponded to the carbon attached to the sulfur atom. ESI-MS revealed the presence of the organic DABCO based cation.
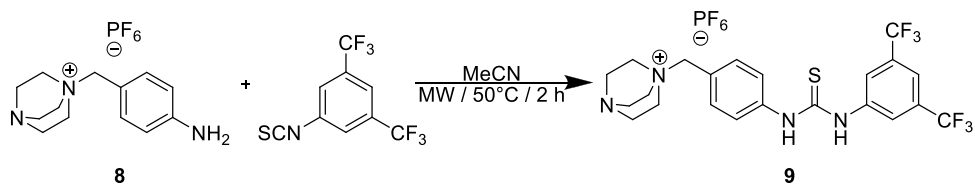
**Scheme 10.** Synthesis of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-4-

aza-1-azoniabicyclo[2.2.2]octane hexafluorophosphate(V), **9**

Once the methylpiperidinium ionic thiourea organocatalyst, **6**, was obtained the

catalytic activity was tested the Morita-Baylis-Hillman reaction between benzaldehyde and

2-cyclohexene-1-one with the co-catalyst DABCO in two ionic liquids [BMPyr][N(Tf)$_2$]

and [BMPP][N(Tf)$_2$]. The reaction was stirred for 48 hours at room temperature then the

organic components were extracted using 5 aliquots of diethyl ether. The organic layer was

dried using MgSO$_4$ then gravity filtered. The diethyl ether was removed *in vacuo* and the

mixture was analyzed by ^{1}H NMR with deuterated chloroform. The product of this reaction

was 2-(hydroxyl(phenyl)methyl)cyclohex-2-enone, **1**. This product contains a chiral center

located at the bridging carbon between the aryl and enone ring (investigating the obtained

chirality is beyond the scope of this research project); however, the methine hydrogen

bonded to this carbon provides a simple evaluation of the conversion from reactants to

products using ^{1}H NMR. By integrating the aldehyde proton located at approximately 10

ppm and the methine proton at approximately 5.5 ppm in CDCl$_3$ allows for the comparison

of the peak area and the percent conversion to be calculated.

The initial investigation into the catalytic activity of the methylpiperidinium

thiourea co-catalyst started with a 10% catalyst loading relative to the limiting reactant,

benzaldehyde, Table 1, Entry 2. In Table 1 all catalyst loadings are reported with respect

to 2-cyclohexene-1-one (thus a catalyst loading of 10 mol % with respect to benzaldehyde

is equivalent to 2 mol % with respect to 2-cyclohexen-1-one). Under this catalyst loading only a minimal 3% conversion to product was observed. When the catalyst loading relative to benzaldehyde was doubled to 20 mol % (4 mol % with respect to 2-cyclohexen-1-one), this also resulted in minimal conversion of marginal improvement to 8%, Table 1, Entry 2. When only the tertiary amine catalyst, DABCO, was present in a catalyst loading of 2 mol %, Table 1, Entry 1, there was no visible conversion after two days. Thus, even with small thiourea co-catalyst loadings of 2% and 4%, the combination of the thiourea and DABCO acting as co-catalysts successfully converted a fraction of the reactants into the product after 48 hours had passed. However, trivial conversions of only 3% and 8% was a major decline from the yields obtained in previous studies involving the methylpyrrolidinium thiourea co-catalyst, **2**, that, under optimized conditions, were above 90%.[31] In order to improve this catalytic system, the methylpiperidinium thiourea organocatalyst, **6**, was used as synthesized and both catalyst loadings were increased to 10 mol % relative to 2-cyclohexen-1-one. This resulted in a substantial increase in the conversion to the product, 89% conversion was obtained, Table 1, Entry 4. This new catalyst loading required five times the amount previously used in order for the product to be obtained in appreciable yields. The high catalyst loading emphasizes the benefit to be gained by being able to easily separate and recycle the thiourea co-catalyst and also illustrates the typical high catalyst loadings characteristic of organocatalysts.

**Table 1.** Evaluation of catalyst loading on the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohexene-1-one in the ionic liquid [BMPyr][N(Tf)$_2$].



| Entry | Benzaldehyde (mmol) | 2-Cyclohexene-1-one (mmol) | Catalyst loading of DABCO (mol % 2-Cyclohexene-1-one) | Catalyst loading of thiourea catalyst (mol % 2-Cyclohexene-1-one) | % Conversion to Product |
|-------|---------------------|----------------------------|-------------------------------------------------------|-------------------------------------------------------------------|-------------------------|
| 1 | 0.5 | 2.5 | 2 | 0 | 0 |
| 2 | 0.5 | 2.5 | 2 | 2 | 3 |
| 3 | 0.5 | 2.5 | 2 | 4 | 8 |
| 4 | 0.5 | 2.5 | 10 | 10 | 89 |

Upon the determination of a catalyst loading (10 mol % with respect to 2-cyclohexen-1-one) that provided adequate conversion to the product, 89% Table 1, Entry 4, a preliminary recycling study was undertaken using [BMPP][N(Tf)$_2$] as the ionic liquid and the catalyst without further purification.

**Table 2.** Recycling study of the thiourea co-catalyst in the ionic liquid [BMPP][N(Tf)$_2$].



| Cycle | Benzaldehyde (mmol) | 2-Cyclohexene-1-one (mmol) | % Conversion |
|-------|---------------------|----------------------------|--------------|
| 1 | 0.5 | 2.5 | 88 |
| 2 | 0.5 | 2.5 | 39 |
| 3 | 0.5 | 2.5 | 22 |

The solution containing DABCO and methylpiperidinium thiourea co-catalysts, benzaldehyde, 2-cyclohexene-1-one and the ionic liquid [BMPP][N(Tf)$_2$] was pale yellow. To facilitate the dissolution of the thiourea organocatalyst the liquid 2-cyclohexen-1-one was added to the mixture. This resulted in a significant decrease in the viscosity of the ionic liquid solution enabling it to be stirred. After 48 hours the solution was brown and an 88% conversion to product **1** was obtained, Table 2, Entry 1. The ionic liquid [BMPP][N(Tf)$_2$] was recycled after removing excess diethyl ether *in vacuo* then all the necessary reaction components were added in the same concentrations as before. After recycling the conversion to product **1** had significantly decreased to 39%, Table 2, Entry 2. Another 48 hours resulted in an even lower conversion to product **1** of only 22%, Table 2, Entry 3. It was evident during the extraction procedure that the intended premise of the project, wherein the ionic liquid and organic solvent neatly phase separate in order to provide ease in recycling the ionic thiourea, had not proceeded as expected. Upon the addition of the diethyl ether a white solid crashed out of the ionic liquid phase. The diethyl ether extracts

were removed as carefully as possible in order to ensure that this solid remained. Both the benzaldehyde, cyclohexene-1-one, 2-(hydroxyl(phenyl)methyl)cyclohex-2-enone and DABCO are soluble in diethyl ether. A simple solubility test demonstrated that the methylpiperidinium thiourea co-catalyst was not soluble in diethyl ether. At the end of the recycling experiment the ionic liquid was analyzed by ^{1}H NMR. A comparison of the ionic liquid phase to the extracted diethyl ether layer, depicted in Figure 10, revealed the presence of the [BMPP][+] cation thus indicating some leaching of the ionic liquid solvent.
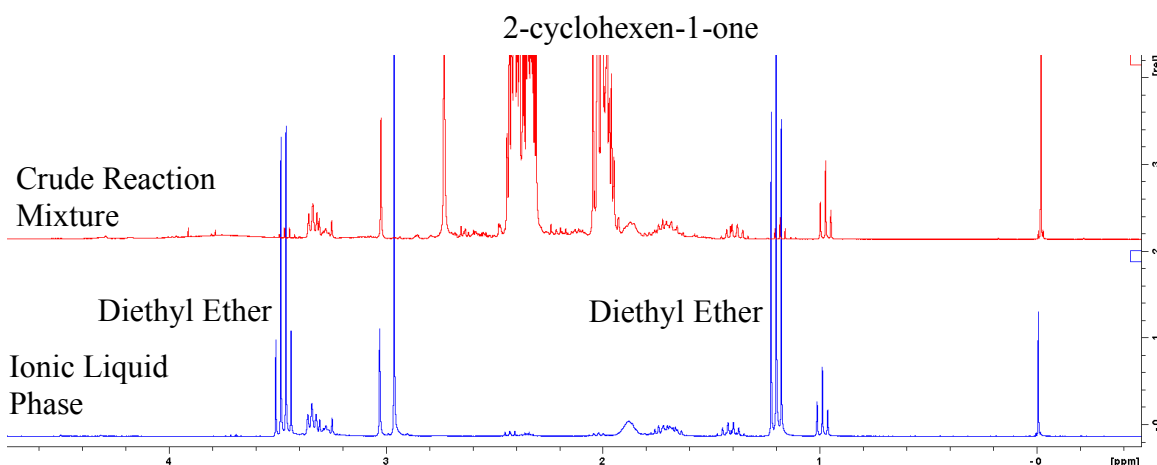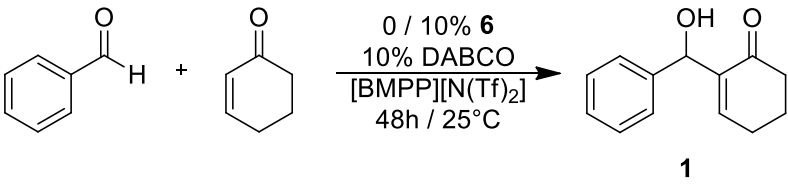


**Figure 10.** Leaching of ionic liquid into the organic phase in CDCl$_3$.

Further investigation into the Morita-Baylis-Hillman reaction in the ionic liquid [BMPP][N(Tf)$_2$] was undertaken using the same 0.5:2.5 mmol ratio of benzaldehyde to 2-cyclohexen-1-one. Table 3, Entry 1 indicates that with increased catalyst loadings of DABCO (10 mol % with respect to 2-cyclohexen-1-one) the Morita-Baylis-Hillman reaction will be catalyzed to form the product, **1**, but very slowly with a small conversion of only 8% after 48 hours. In the presence of an equal catalyst loading of thiourea co-catalyst the conversion to product increased to 85% conversion, Table 3, Entry 2. Increasing the reaction time from 48 hours to 72 hours also caused an increased in the

conversion of the product to 93%, Table 3 Entry 3. After the Morita-Baylis-Hillman

reaction had proceeded for 72 hours the ionic liquid was recycled and left to react again for

72 hours. A lower conversion of 47% is indicative that this catalyst is not able to be

efficiently recycled, Table 3, Entry 3.

**Table 3.** Effect of different reaction conditions involving [BMPP][N(Tf)$_2$].



| Entry | Catalyst loading of DABCO (mol % 2-Cyclohexene-1-one) | Catalyst loading of thiourea catalyst (mol % 2-Cyclohexene-1-one) | Time (hours) | % Conversion | % Conversion (Recycled) |
|---|---|---|---|---|---|
| 1 | 10 | 0 | 48 | 8 | N/A |
| 2 | 10 | 10 | 48 | 85 | N/A |
| 3 | 10 | 10 | 72 | 93 | 47 |

The reaction of benzaldehyde and 1-cyclohexen-1-one in the ionic liquids

[BMPyr][N(Tf)$_2$] and [BMPP][N(Tf)$_2$] with DABCO and methylpiperidinium thiourea co-

catalysts were both effective in accelerating the Morita-Baylis-Hillman reaction within 48

hours. The reaction in two different ionic liquids gave comparable yields of 89% and 88%

respectively, (Table 4, Entry 1 and 2) indicating that the choice of ionic liquid had minimal

effect on the reaction. However, after extracting the organic components, the ionic liquid

was recycled and the same amounts of benzaldehyde, 1-cyclohexene-1-one and DABCO

were added. The second use of the ionic liquid/thiourea organocatalyst had a significant

decrease in the % conversion for both ionic liquids, down to 54% for [BMPyr][N(Tf)$_2$] and 66% for [BMPP][N(Tf)$_2$].

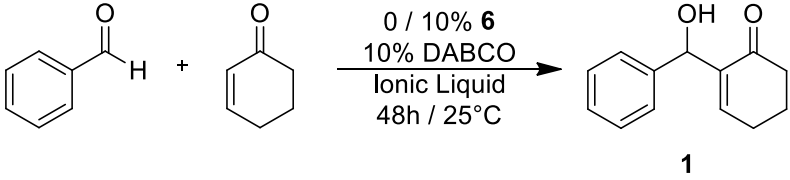**Table 4.** Comparing the recycling ability of two ionic liquids with the thiourea co-catalyst **6**.



| Entry | Benzaldehyde (mmol) | 2-Cyclohexene-1-one (mmol) | Ionic Liquid | % Conversion | % Conversion (Recycled) |
|-------|---------------------|----------------------------|--------------|--------------|-------------------------|
| 1 | 0.5 | 2.5 | [BMPyr][N(Tf)$_2$] | 89 | 54 |
| 2 | 0.5 | 2.5 | [BMPP][N(Tf)$_2$] | 88 | 66 |

Figure 11 and Figure 12 provides the aromatic region of the purified piperidinium thiourea organocatalyst **6** and that of the ionic liquid phases after two extractions superimposed. Clearly there are aromatic compounds present however, the distinctive doublets that correspond to the *para*-substituted aromatic ring and the singlet peaks that correspond to the 3,5-(trifluoromethyl)phenyl functional group are difficult to identify.
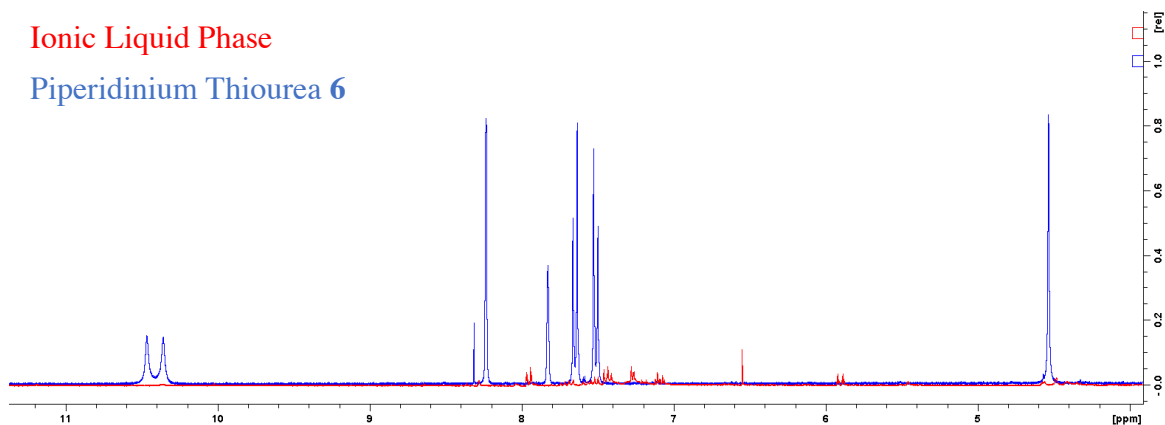
**Figure 11.** Ionic liquid phase of [BMPyr][N(Tf)$_2$] after two recycling trials in DMSO-d$^6$.
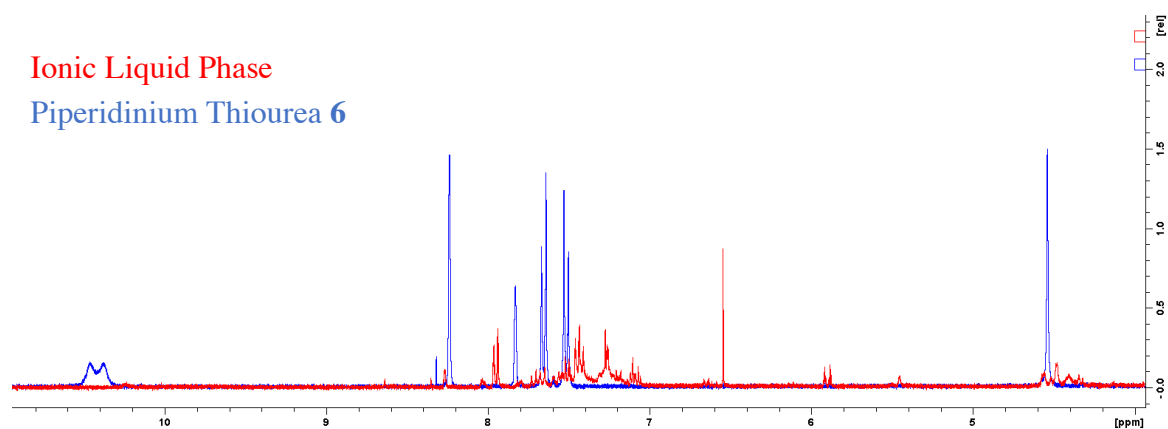


**Figure 12.** Ionic liquid phase of [BMPP][N(Tf)2] after two recycling trials in DMSO-d$^6$.

This would provide a possible answer to why the yields were decreasing upon recycling, the methylpiperidinium thiourea catalyst was decomposing under the reaction conditions. Since the yield for the second extraction was higher for the [BMPP][N(Tf)$_2$] ionic liquid rather than the [BMPyr][N(Tf)$_2$] ionic liquid, this would suggest that less methylpiperidinium catalyst decomposed in the [BMPP][N(Tf)$_2$] ionic liquid.

## 3.0 Conclusions

Through the use of the four-step synthetic sequence two ionic thiourea organocatalysts, one containing a methylpiperidinium cationic core, **6**, and the other a DABCO based cationic core, **8**, were successfully synthesized. This demonstrates the utility of this modular synthetic approach in creating novel ionic thioureas organocatalysts possessing alternative cationic cores by substituting different tertiary amines, such as 1-methylpiperidine and DABCO, into the first step.

The monosubstituted methylpiperidinium based thiourea catalyst, **6**, was a successful co-catalyst in accelerating the Morita-Baylis-Hillman reaction within 48 hours. The percent conversion was calculated using $^1$H NMR to reveal that without this thiourea co-catalyst only 8% of the product had been converted after 48 hours compared to 85% with the thiourea co-catalyst. Yields of 89% and 88% were obtained in the two tested ionic liquids, [BMPyr][N(Tf)$_2$] and [BMPP][N(Tf)$_2$], respectively. Upon recycling these ionic liquids and the ionic thiourea organocatalyst resulted in conversions of 54% and 66%, indicating that the catalytic activity had decreased upon being recycled suggesting possible leaching, decomposition or degradation of the thiourea organocatalyst.

**4.0 Future Directions**

Further research directions in this project include attempting to obtain a crystal structure of the methylpiperidinium thiourea organocatalyst, **6**, in order to univocally determine the structure of this catalyst. Since a longer reaction time of 3 days corresponded to a higher conversion to products of 93%, it should be determined if this yield could be obtained from employing higher catalyst loadings with shorter reaction times. Isolated yields of the product of this Morita-Baylis-Hillman reaction, **1**, should be obtained.

The ionic liquids used in the recycling study were [BMPyr][N(Tf)$_2$] and [BMPP][N(Tf)$_2$]; both of these ionic liquids contain the same [N(Tf)$_2$]$^-$ anion and similar cations. Therefore, other alternative ionic liquids containing a larger diversity of structures should be investigated. The fate of the catalyst should be investigated and remedied if possible to improve recyclability. A purification method for the DABCO based thiourea organocatalyst **8** should be elucidated and this catalyst should be investigated for catalytic activity in the Morita-Baylis-Hillman reaction. Eventually, the library of the ionic thiourea organocatalysts should be expanded and then tested for recyclability and activity in a range of ionic liquids.

**5.0 Experimental**

**5.1 General Procedures**

Glassware used in Morita-Baylis-Hillman reactions were washed using Mandel Lancer dishwasher and dried in the oven at 120 ºC. The ionic liquid, [BMPyr][N(Tf)$_2$] was prepared previously by Kaitlyn Blatt-Janmaat in the Singer Research group and the ionic liquid [BMPP][N(Tf)$_2$] was purchased from Sigma-Aldrich. All other reagents and solvents were used as received without further purification from various suppliers. Deuterated solvents such as DMSO and CDCl$_3$ were obtained from Cambridge Isotope Laboratories. Topspin was used to analyze the spectra obtained from the Bruker 300 MHz Ultrashield spectrometer.

Infrared spectra were obtained by ATIR using a Bruker ALPHA Infrared Spectrometer. Electrospray ionization mass spectrometry were completed by Patricia Granados at Saint Mary's University Center for Environmental Analysis and Remediation using Agilent 1100 LC/MSD Trap. Electrothermal Mel-Temp 3.0 apparatus was used to obtain melting points of solids.

**5.2 Synthesis of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpiperidinium hexafluorophosphate(V), 6**.



**6**
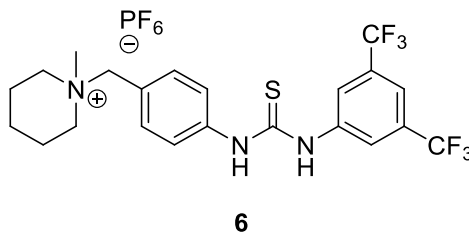
**5.2.1 Synthesis of 1-methyl-1-(4-nitrobenzyl)piperidinium bromide, 4**.
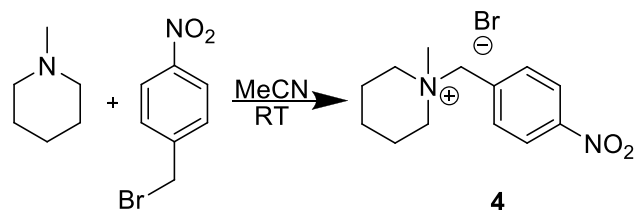
4-Nitrobenzylbromide (2.16g, 10 mmol) was dissolved in 30 mL of acetonitrile, N-methyl piperidine (1.22 mL, 10 mmol) was added dropwise and a solid precipitated out with swirling. An additional 30 mL of ethyl acetate was added then the solid was collected by vacuum filtration and dried under *vacuo*. (1.43g, 91%). MP 229.3-231.4 °C. IR(ATR) 1518, 1344 cm$^{-1}$ (nitro). $^1$H NMR (DMSO-d$_6$, 300 MHz) δ 8.35 (d, J=8.8Hz, 2H), 7.85 (d, J=8.8Hz, 2H), 4.77 (s, 2H), 3.33 (m, 4H), 2.97 (s, 3H), 2.07 (m, 4H), 1.60 (m, 1H), 1.51 (m, 1H). $^{13}$C NMR (DMSO-d$_6$, 75MHz) δ 149.0, 135.4, 135.1, 124.1, 65.1, 60.4, 46.4, 21.1, 19.8. ESI-MS: Positive Mode Found: m/z 235.1 [100.0% (C$_{13}$H$_{19}$N$_2$O$_2^+$)]; Calc. 235.14.
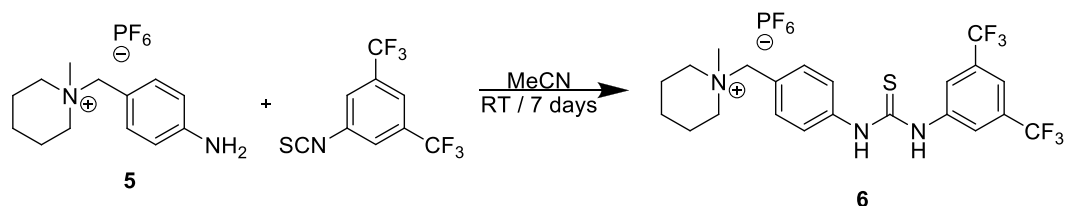
**5.2.2  Synthesis  of  1-(4-aminobenzyl)-1-methylpiperidinium hexafluorophosphate(V), 5**.
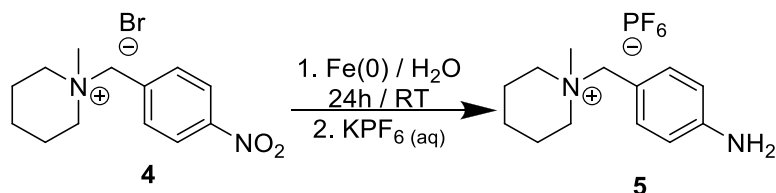


Iron(II) sulfate heptahydrate (6.67g, 24 mmol) and sodium citrate (0.59g, 2 mmol) were dissolved in deionized water in a round bottom flask. Sodium borohydride (1.81g, 48 mmol) was added slowly. The flask was left to stir until the evolution of gas had ceased. The water was decanted without removing the solid iron. Fresh deionized water was added, and the solid iron was stirred then the water was decanted again, this was repeated for a third time. 1-methyl-1-(4-nitrobenzyl)piperidinium bromide, **4** (1.26, 4 mmol) was added then the flask was capped and stirred for 24 hours. The solid iron was removed from

solution by filtration through a Celite bed. The orange filtrate was filtered through another Celite bed until a clear and colourless filtrate was obtained. Upon the addition of aqueous potassium hexafluorophosphate (0.92g, 5 mmol) a solid precipitated that was collected by filtration and dried *in vacuo*. (1.04g, 74%). MP 150.6-152.4 °C. IR(ATR) 3483, 3396 cm$^{-1}$ (Primary amine), 830, 556 cm$^{-1}$ (PF$_6^-$). $^1$H NMR (DMSO-d$_6$, 300 MHz) δ 7.13 (d, J=8.4Hz, 2H), 6.61 (d, J=8.5Hz, 2H), 5.49 (s, 2H), 4.32 (s, 2H), 3.19 (m, 4H), 2.82 (s, 3H), 1.83 (m, 4H), 1.58 (m, 1H), 1.48 (m, 1H). $^{13}$C NMR (DMSO-d$_6$, 75MHz) δ 150.92, 134.31, 114.0, 113.8, 67.69, 59.51, 46.03, 21.33, 19.78. ESI-MS: Positive Mode Found: m/z 106.2 [100.0% (C$_7$H$_8$N$^+$)]; Calc. 106.07, 205.1 [94.2% (C$_{13}$H$_{21}$N$_2^+$)]; Calc. 205.17. Negative Mode Found: m/z 144.6 [100.0% (PF$_6^-$)]; Calc. 144.96.

### 5.2.3 Synthesis of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpiperidinium hexafluorophosphate(V), 6.



1-(4-aminobenzyl)-1-methylpiperidinium hexafluorophosphate(V), **5** was dissolved in 10 mL of acetonitrile and 3,5-bis(trifluoromethyl)phenyl isothiocyanate was added dropwise. The flask was capped and left to stir for 7 days. The solvent was removed, and the catalyst purified using silca gel column chromatography (0.31g, 0.5 mmol) using an 85/15 CHCl$_3$/MeOH mobile phase. (0.22g, 71%) MP 113.1-117.1 °C; IR 3372 cm$^{-1}$ (Secondary amine), 1279, 1132, 838, 558 cm$^{-1}$ (PF$_6^-$); $^1$H NMR (DMSO-d$_6$, 300MHz) δ 10.48 10.36 (s,s 2H), 8.25 (s, 2H), 7.82 (s, 1H), 7.65 (d, J=8.5Hz, 2H), 7.52 (d, J=8.5Hz, 2H), 4.54 (s, 2H), 3.29 (m, 4H), 2.91 (s, 3H), 1.87 (m, 4H), 1.62 (m, 1H), 1.52 (m, 1H);

Crude Sample: $^{13}$C NMR (DMSO-d$_6$, 75MHz) δ 179.81, 141.61, 140.60, 133.48, 130.15 (q, $^3J_{CF}$=33Hz), 123.20 (q, $^1J_{CF}$=273Hz), 123.67, 123.48, 123.34, 177, 66, 59.72, 45.95, 20.82, 19.32 ESI-MS: Positive Mode: Found: m/z 476.3 [100% (C$_{22}$H$_{24}$F$_6$N$_3$S)$^+$] Calc: 476.16, 377.4 [71.7% (C$_{16}$H$_{11}$F$_6$N$_2$S$^+$)] Calc. 377.05; Negative Mode Found: m/z 144.6 [100.0% (PF$_6^-$)]; Calc. 144.96. High-Res-MS: Positive Mode: Found: m/z 476.1580 [100% (C$_{22}$H$_{24}$F$_6$N$_3$S)$^+$] Calc: 476.1590.

**5.3 Synthesis of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-4-aza-1-azoniabicyclo[2.2.2]octane hexafluorophosphate(V), 9**



**9**
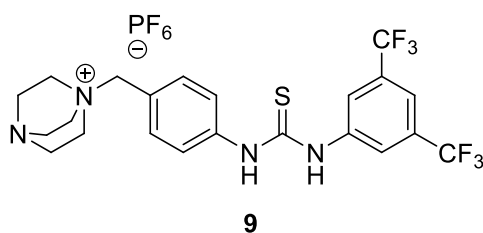
**5.3.1 Synthesis of 1-(4-nitrobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide, 7**



**7**
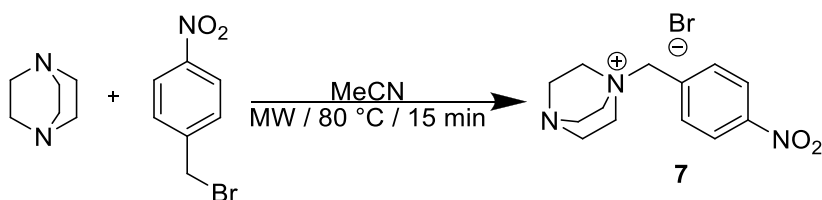
DABCO (0.67 g, 6 mmol) and 4-nitrobenzyl bromide (1.29g, 6 mmol) were dissolved in 12 mL of acetonitrile in a large microwave vessel, capped and heated at 80 °C for 15 minutes in the microwave reactor. An equal amount of ethyl acetate was added and the solid was collected by filtration and dried in *vacuo*. (1.79g, 91%). MP 219.6-225.1 ℃. IR(ATR) 1518, 1349 (Nitro) cm$^{-1}$. $^1$H NMR (DMSO-d$_6$, 300MHz) δ 8.34 (d, J=8.8Hz, 2H), 7.86 (d, J=8.9Hz, 2H), 4.80 (s, 2H), 3.40 (m, 6H), 3.02 (m, 6H). $^{13}$C NMR (DMSO-d$_6$,

75MHz) δ 148.51, 134.81, 134.45, 123.74, 64.61, 51.67, 44.64. ESI-MS: Positive Mode

Found: m/z 248.1 [100.0% ($C_{13}H_{18}N_3O_2^+$)]; Calc. 248.14.

### 5.3.2 Synthesis of 1-(4-aminobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane hexafluorophosphate(V), 8



**7**              **8**
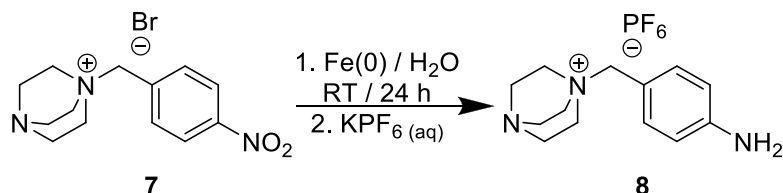
Iron (II) sulfate heptahydrate (30 mmol, 8.34g) and soldium citrate (2.5 mmol, 0.74g) were dissolved in deionized water in a round bottom flask. Sodium Borohydride (60 mmol, 2.27g) was added slowly. The flask was left to stir until the evolution of gas had ceased. The water was decanted without removing the solid iron. Clean water was added the solid iron was stirred then the water was decanted again, this was repeated for a third time. The 1-(4-nitrobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide, **7**, was added then the flask was capped and stirred for 24 hours. The solid iron was removed from solution through filtering through a celite bed. The metathesis reaction was completed with the dropwise addition of aqueous potassium hexafluorophosphate (1.15g, 6.25 mmol). The flask was cooled using an ice bath and the solid was collected through vacuum filtration. (0.7508g, 41%). MP 225.5-228.0 °C. $^1$H NMR (DMSO-$d_6$, 300MHz) δ 7.08 (d, J=8.4Hz, 2H), 6.61 (d, J=8.4Hz, 2H), 5.50 (s, 2H), 4.24 (s, 2H), 3.19 (m, 6H), 2.99 (m, 6H). $^{13}$C NMR (DMSO-$d_6$, 75MHz) δ 148.50, 134.82, 134.45, 123.75, 64.59, 51.66, 44.64. ESI-MS: Positive Mode Found: m/z 218.1 [100.0% ($C_{13}H_{20}N_3^+$)]; Calc. 218.17; Negative Mode Found: m/z 144.6 [100.0% ($PF_6^-$)]; Calc. 144.96.

### 5.3.3 Synthesis of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-4-aza-1-azoniabicyclo[2.2.2]octane hexafluorophosphate(V), 9
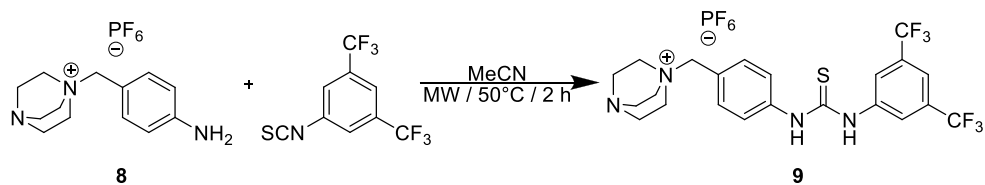
**8** + **9**

1-(4-aminobenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane hexafluorophosphate(V), 7 (0.3641g, 1 mmol) was dissolved in 10 mL of acetonitrile 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.183 mL, 1 mmol) was added dropwise. The mixture was heated at 50 °C for 2 hours in the microwave reactor. The solid was obtained using the rodovap and the catalyst was not purified. (0.64g) MP 116.5-120.7 ℃. IR(ATR) 3641 cm$^{-1}$ (Secondary amine) 831, 584 cm$^{-1}$ (PF$_6$). $^1$H NMR (DMSO-d$_6$, 300MHz) δ 10.46 10.34 (s,s 2H), 8.25 (s, 2H), 7.81 (s, 1H), 7.67 (d, J=8.6Hz, 2H), 7.48 (d, J=8.6Hz, 2H), 4.47 (s, 2H), 3.28 (m, 6H), 3.04 (m, 6H). $^{13}$C NMR (DMSO-d$_6$, 75MHz) δ 179.84, 141.63, 140.65, 133.61, 130.22 (q, $^3J_{CF}$=30Hz), 123.25 (q, $^1J_{CF}$=273Hz), 123.49, 123.18, 117.7, 66.26, 51.66, 44.70; ESI-MS: Positive Mode: Found: m/z 489.4 [100% (C$_{22}$H$_{24}$F$_6$N$_3$S)$^+$] Calc: 489.15.

### 5.4 General Procedure for Morita-Baylis-Hillman Reactions.
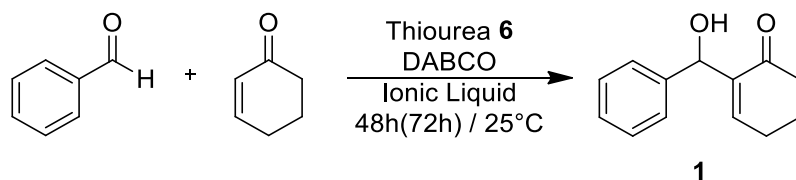


The appropriate amount of the methylpiperidinium thiourea catalyst, **6**, was weighed out into a conical vial containing a stir bar (for 10 mol % catalyst loading: 0.16g, 0.25 mmol). 0.25 mL of the applicable ionic liquid ([BMPyr][N(Tf)$_2$] or [BMPP][N(Tf)$_2$]) was pipetted into the vial along with 2-cyclohexen-1-one (0.242 mL, 2.5 mmol). The solution was stirred until all the thiourea catalyst **6** had dissolved. Then the benzaldehyde (0.0508 mL, 0.5 mmol) and DABCO (0.028g, 0.25 mmol) were added. A hotplate was utilized to ensure the temperature remained at 25 °C and once 48 hours (or 72 hours) had

elapsed 2 mL of diethyl ether was added to the vial. The mixture was stirred quickly, and the organic layer was collected in a small Erlenmeyer flask, this was repeated four more times. For Table 2 Entry 1 the extraction procedure was completed using approximately 2.4 mL of diethyl ether. The organic layer was dried using $MgSO_4$ and gravity filtered into a round bottom flask. The diethyl ether was removed using the rodovap and a NMR sample was prepared using $CDCl_3$. Integration of the peaks at approximately 10 ppm and 5.5 ppm resulted in the % conversion to product. The recycling studies were completed by attaching the conical vials to the high-vac to remove any remaining diethyl ether. Then the same amounts of 2-cyclohexen-1-one, benzaldehyde and DABCO were added and the experiment was repeated.

**6.0 References**

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