Bis-Thiourea Based Ionic Organocatalysts

By
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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.

April, 2015, Halifax, Nova Scotia

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Date: April 24, 2014

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Abstract

Ionic liquids and organocatalysts serve as greener alternatives to conventional reaction solvents and catalysts. Recent research has found that pyrrolidinium tagged ionic organocatalysts enhance the rate of DABCO co-catalyzed Morita-Baylis-Hillman reactions and remain entrained in ionic liquid media. Three bis-thiourea based ionic organocatalysts have been synthesized. 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)pyrrolidinium hexafluorophosphate(V) was successfully employed in the DABCO co-catalyzed rate enhancement of the reaction between benzaldehyde and cyclohex-2-en-1-one. 95 % conversion to product was attained at 5 mol % catalyst loading. This room-temperature reaction used the ionic liquid *N*-butyl-*N*-methylpyrrolidiniumbis(trifluoromethane)sulfonamide, [BMPyr][$N(Tf)_2$], as the reaction solvent. Attempts at recycling the catalyst resulted in low conversion with no evidence of catalyst leaching. Microwave irradiation of the MBH reactions was attempted, with low conversion to product attributed to thermal degradation of the catalyst.

April 24, 2015

Acknowledgements

I would like to thank my supervisor, Dr. Singer, for his support and assistance, without whom this report would not have been possible. He allowed me to see my own potential in the field of chemistry and has offered invaluable guidance every step of the way.

This report would also not be possible without the support of both past and present members of the Singer group. Chris Lavoie and Trevor McGrath offered continuous support as I started out in the lab. A special thanks to Trevor should be noted for laying much of the groundwork necessary for this project to be possible in his own thesis. Bitu Hurisso continues to offer knowledge that has helped immensely in preparing this report. He is always willing to help no matter the time or place.

Support from the Saint Mary's University Chemistry Department faculty and staff played a major role in my research. Academic and technical support through my honours year and my entire university career has helped to produce all of my research to date. A special thanks goes out to Darlene Goucher, Elizabeth McLeod and Connie Clark for their technical support and Patricia Granados for providing ESI-MS characterization.

Lastly, I would like to thank my family and friends who have offered support throughout my past year at SMU, without whom I would not have been able to pursue my academic goals as enthusiastically. To my fellow honours classmate Marwa Yasmin I offer congratulations for all of her dedicated research and hard work.

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Abbreviations

$[BF_4]^-$	Tetrafluoroborate
$[bmim]^+$	1-butyl-3-methylimidazolium
$[BMPyr]^+$	N-butyl-N-methylpyrrolidinium
DABCO	1,4-Diazobicyclo[2.2.2]octane
DMSO-d_6	Deuterated dimethylsulfoxide
ESI-MS	Electrospray ionization mass spectrometry
IL	Ionic liquid
IR	Infrared
KIE	Kinetic isotope effect
MAOS	Microwave assisted organic syntheses
MBH	Morita-Baylis-Hillman (reaction)
mp	Melting point
NMR	Nuclear magnetic resonance
$[N(Tf)_2]^-$	Bis(trifluoromethane)sulfonamide
$[PF_6]^-$	Hexafluorophosphate
rpm	Rotations per minutes
rds	Rate determining step
RT	Room temperature
RTIL	Room temperature ionic liquid
S_N2	Bi-molecular nucleophilic substitution
TSIL	Task-specific ionic liquid

1. Introduction

1.1 Ionic Liquids

1.1.1—Introduction to Ionic Liquids

Ionic liquids (ILs) are typically defined as salts with melting temperatures below the boiling point of water, that is, 100°C.[1] Originally developed for use in specialized electrochemical applications, ionic liquids have since become prevalent in a wide array of chemical applications, such as reaction solvents, lubricants, surfactants and in biomass processing. Ionic liquids are known for possessing extremely wide liquid ranges, that is, the range in temperature between their melting and boiling points, with reports of ranges over 400K.[2] The chemical and physical properties of ionic liquids are known to vary enormously based on the identities of the typically organic cation and inorganic, polyatomic anion.[1] Some examples of common cationic and anion ionic liquid components are shown in Figure 1.

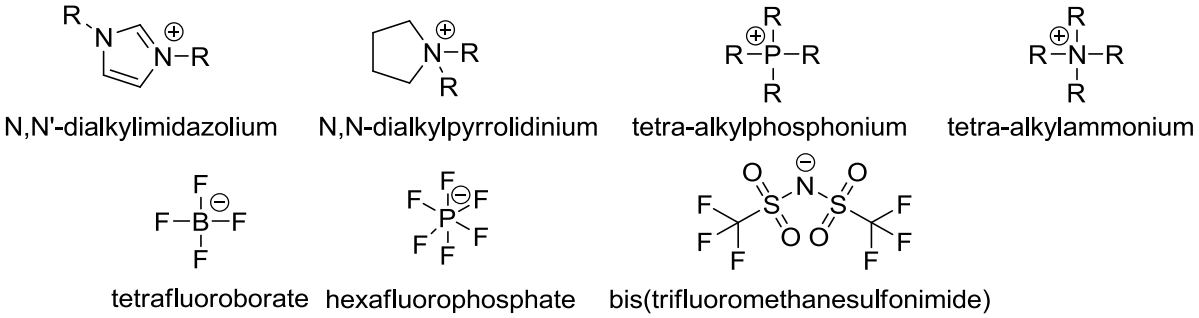

Figure 1. Common cations and anions of ionic liquids

1.1.2—History of Ionic Liquids

The earliest known ionic liquid material was described as a separate, liquid, "red oil" phase resulting from Friedel-Crafts reactions in the mid-19th century.[1] With the development of NMR, this "red oil" was later determined to be an ionic liquid, a heptachlorodialuminate salt. In 1914 Walden formed alkylammonium nitrate salts that were liquids at room temperature[3] and in the 1960s, John Yoke reported that mixtures of copper(I) chloride and alkylammonium chlorides often formed liquids.[4]

A major surge in the development of the field of ionic liquids came in 1963 as Major Dr. Lowell A. King at the US Air Force Academy initiated research projects designed to find replacements for the LiCl/KCl molten salt electrolyte used in thermal batteries, as 355°C temperatures tended to cause issues with materials inside the batteries and incompatibilities with other devices.[1] The research developed a $NaCl/AlCl_3$ solution with a eutectic composition with a significantly lower melting temperature (107°C).[5]

Through the 1970s and 1980s, studies mainly focused on the electrochemical applications of ionic liquids[2], but by the mid-1980s low melting point ILs had been proposed as solvents for organic synthesis reactions by Fry and Pienta[6] and Boon *et al*.[7] The prospect of creating ionic liquids even better suited for practical application than previous attempts led to a surge in IL research. For example, in 1990 Dr. Mike Zaworotko from Saint Mary's University took a sabbatical leave at the Air Force Academy where he developed so-called "second generation ionic liquids" with 1,3-dialkylimidazolium cations and anions such as tetrafluoroborate and hexafluorophosphate

stable to hydrolysis, thus solving the issue of the air-sensitivity and water-reactivity of previously developed ILs.[8]

1.1.3—Ionic Liquid Synthesis

The synthesis of ionic liquids may be broadly divided into two main components: (1) the formation of the desired cation and (2) anion exchange (metathesis).[1] A common method to prepare the cation is through the quaternization reaction of a phosphine or an amine with a haloalkane. By this method, the reaction tends to be increasingly facile in the order Cl → Br → I due to the nucleophilic substitution involved (with, understandably, no fluoride salts prepared) as well as reactivity decrease with increasing alkyl chain length.[1] Advantages of this method include the wide range of low-cost haloalkanes available and the ability of these reactions to run smoothly at relatively low temperatures. Formed halide salts are then easily converted into salts with a variety of different anions through salt metathesis reactions. Keeping in mind the vast array of compounds potentially used in the above reactions, the number of possible ionic liquids seems limitless. Earle and Seddon have estimated the number of salts with melting temperatures below 100°C to be of the order of 1 billion![9] As the field of ionic liquid chemistry has developed, an increasing amount of ILs have become commercially available from a range of suppliers.

1.1.4—Room Temperature Ionic Liquids

A specific class of salts that are liquid at or below room temperature are known as room-temperature ionic liquids (RTILs).[10] Such ionic liquids were a response to the demand for alternatives to more environmentally damaging chemicals that are often used

as solvents. Several typical, more conventional solvents are used in very high amounts and are often volatile liquids that are thus difficult to contain. RTILs offer several benefits in their use as reaction solvents. RTILs have proven to be effective solvents for a vast range of both organic and inorganic materials and are composed of poorly coordinating ions; thus, they have potential to be highly polar and yet non-coordinating in nature. The immiscibility of RTILs with several typical organic solvents provide an alternative to common aqueous two-phase systems, and due to their negligible volatility, they may be used in high-vacuum systems thus minimizing issues with regards to contaminants.[10] Most RTILs are, however, viscous liquids (comparable to oils), which may negatively effect mass transfers and alter the power requirements for stirring, such as in heterogeneous catalysis. Other concerns regarding RTILs include their biodegradability, toxicity, high cost, and thermal stability.

Ionic liquids are typically polar solvents with properties afforded to the ionic liquids based largely on their hydrogen bond donating or accepting ability as well as to charge localization of the anion.[11,12,13] Tuning of RTIL solvent properties is possible by, for example, alteration of alkyl substituent lengths forming more lipophilic solvents[14,15] or by decreasing hydrogen-bonding capabilities through IL fluorination.[16]An example of an ionic liquid as a reaction solvent is shown in the Diels-Alder cycloaddition reactions. This was first demonstrated by Jaeger and Tucker in the reaction of cyclopentadiene with methyl acrylate and methyl vinyl ketone in $[EtNH_3][NO_3]$.[17] The results showed a strong preference for the *endo* product and an acceleration of reaction rate when compared to non-polar organic solvents but poorer rates and selectivity compared to water. The advantage of using an IL in this case is the ability to use moisture-sensitive reagents.

Reversal of *endo/exo* selectivity (2:1 *endo:exo*) in Diels-Alder reactions of heteroaromatic diene furan by use of ionic liquids [bmim]BF_4 and [bmim]PF_6 has also been reported by the Singer group.[18] The enhanced isolated yields and *endo/exo* selectivity was attributed to the use of ionic liquids compared to conventional solvents, further evidence of the advantages ionic liquids may serve in synthesis.

1.2—Organocatalysis

1.2.1—Introduction to Organocatalysis

The term catalysis was first introduced in 1836 by Berzelius as he attempted to explain the "special powers" of certain chemicals able to influence the rates of specific reactions.[19] Ostwald noted that catalysts "accelerated a chemical reaction without affecting the position of the equilibrium."[20] It is now understood that catalysts lower the energy barrier (activation energy) of a chemical reaction through lowering the energy of the transition state of the rate determining step through alternative chemical pathways.

Organocatalysis refers to the use of small organic molecules to catalyse organic transformations and has become a relatively new and popular field in chiral molecule synthesis.[21] The first example of what is now known to be an organocatalytic reaction is that of Liebig in the synthesis of oxamide from dicyan and water with acetaldehyde serving as the organocatalyst.[22]

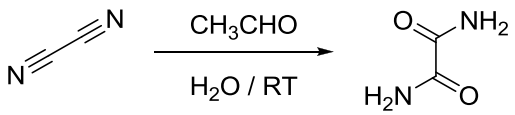

Figure 2. Synthesis of oxamide from dicyan and water

Between 1969 and 1997 a small number of studies reported the use of small organic molecules in asymmetric reactions, but were considered unique reactions rather than part of an overarching field of what is now known as organocatalysis.[21] By the end of the 1990s, Shi[23], Denmark[24] and Yang[25] showed the use of enantiomerically pure ketones as catalysts in enantio-selective epoxidation reactions of alkenes. Jacobsen[26] and Corey[27] shortly thereafter demonstrated hydrogen bonding catalysts that activated imine electrophiles in asymmetric Strecker reactions.

At this point in history, it became clear that the use of organic molecules as catalysts was a field in chemistry that posed great potential and deserved further investigation. An example of such potential for organocatalysis is noted among medicinal chemists who use organocatalysts in their search for therapeutic agents of a particular enantiomer.[28]

Organocatalysis poses several advantages in organic synthesis reactions, especially in cases such that the catalyst is recyclable. The reactions also tend to be easy and low cost. Due to the lack of metal centers typical of other catalysts, organocatalysts are insensitive to oxygen and moisture in the atmosphere, thus eliminating the need for expensive or complicated reaction vessels, storage containers, experimental techniques or ultra-dry reagents and solvents. Many organic reagents required are available in nature in massive amounts, thus making organocatalysts low-cost and accessible. The lack of metal centres also affords less toxic and thus more environmentally friendly products. Potential to reduce costly processes of removing toxic impurities from waste streams is also presented by the idea of non-toxic organocatalysis.[21] Organocatalytic processes are attractive to food and pharmaceutical industries due to the lack of toxic metal atoms.[29] This is not to

say organocatalysis is not without its disadvantages. Organocatalyst loadings tend to be much higher compared to metal-containing catalysts.[19] There also tends to be a more limited scope of substrates in which a certain organocatalyst can assist reactions compared to metal-containing catalysts.

1.2.2—Ionic Liquids in Organocatalysis

Biphasic catalysis is often used to aid the separation of products from the catalyst by separating them into two immiscible phases. The catalyst and substrate may be in two different phases at the beginning of the reaction and the mixture must be stirred vigorously for the interaction of catalyst and substrate to occur. Upon completion of the reaction, the immiscible phases re-separate into two layers, allowing easy separation of the products from the catalyst by, for example, simple decantation. Ionic liquids are composed of two molecular parts and thus possess a "synthetic flexibility" not possible by the use of single-molecule solvents.[30] Ionic liquids serve as possible solvents in the immobilization of ionic compounds with organocatalytic functionality, for example, thus allowing for removal of product and retention of the catalyst and IL medium for reuse.

1.3—Green Chemistry

In 1989, The World Commission for Environment and Development was formed by the United Nations in an attempt to prepare reports that outlined ways in which the world could continue to develop while conducting sustainable and environmentally conscientious practices. Sustainable development was defined by the Chairman, Norway's Prime Minister at the time, as "Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs".[31]

Around the same time, Anastas and co-workers coined the term "green chemistry". Green chemistry aims to promote new technologies that reduce or eliminate the requirement for hazardous materials in chemical processes, or in short, that products and processes are "benign by design." Anastas outlined twelve princples of green chemistry[32]:

> 1. Prevent waste, 2. Maximize atom economy, 3. Less hazardous chemical synthesis, 4. Safer chemicals and products, 5. Safe solvents and reaction conditions, 6. Increasing energy efficiency, 7. Use renewable feed stocks, 8. Avoid chemical derivatives (protecting groups), 9. Use catalysts, 10. Design chemicals and products to degrade after use, 11. Analyze in real time to prevent pollution, 12. Minimize potential for accidents.

Methods of quantifying how green a specific process is was developed in two systems. The E factor is defined as the ratio of waste produced to products desired in terms of mass (kilograms)[33] and atom economy describes the molecular weight of the product divided by the sum of those of the reactants given as a percentage.[34]

It is clear that ionic liquids and organocatalysts provide valuable routes to attain several of the goals outlined by green chemistry. Catalytic processes that are highly recyclable contribute to low E factor processes due to the lower amounts of waste generated upon recycling. Solvent loss is another major source of waste. Solvents may end up in the atmosphere or in ground water, which may lead to health and safety issues as well. The non-volatile and reusable nature of ILs certainly serves to alleviate this issue associated with conventional solvents.

1.4—Microwave Irradiation

The use of microwave-assisted organic synthesis (MAOS) has been on the rise following a series of publications by Gedye *et. al.* in 1986 dealing with the technique.[35] Early on, conventional microwave ovens were used in studies, but yielded poor reproducabilities and poorly controlled reactions. Since then, microwave reactors have been developed that allow for control and monitoring of irradiation, reaction temperature and pressure within reaction vessels.[35]

Advantages of microwave irradiation include reduced reaction time and increased product yield in comparison to conventional heating. The phenomenon largely responsible for such advantages is known as dielectric heating. This thermal effect is a result of an increase in the efficiency of energy transfer in the reaction medium. In this case, solvent or reagent molecules are able to convert micro-waves into heat through absorption of the waves. This "heating from the inside", or volumetric core heating, provides a reversed temperature gradient in comparison to conventional heating methods. Heat generated in the bulk of the microwave irradiated material results in the surface losing heat to the surroundings, opposite to conventional heating. In conventional heating, heat is applied to the surface and diffuses toward the lower-temperature inner-regions of the material. Some non-thermal effects leading to the advantages of microwave use have also been suggested.[35] These effects are suggested to be a result of activation energy reduction due to the changes in orientations of polar species in the electromagnetic field.

While several research efforts have dealt with microwave irradiation of metal-containing catalysts, microwave-assisted organic synthesis remains a relatively less-studied area of research. Thus, experiments in the following paper combining microwave irradiation techniques to organocatalytic reactions should serve to add to this developing field.

1.5—Thiourea Based Organocatalysts

Recently, the potential for *N*,*N*-dialkylthiourea derivatives to serve as organocatalysts in a wide range of synthetic reactions has been realized. These catalysts are useful specifically in reactions susceptible to general acid catalysis. *N*,*N*-dialkylthiourea catalysts are able to promote such reactions through stabilization of the transition state (TS) of the rate-determining step of the reaction by either hydrogen-bonding or a degree of proton transfer.[36] These thiourea catalysts are especially useful due to their high functional group tolerance and ability to doubly hydrogen bond (H-bond donating). An early example of the effectiveness of double hydrogen-bond donation is shown in the work of Hine *et al*.[37] who were able to promote the aminolysis of phenyl glycidyl ether by participation in two H-bonds with the conformationally rigid 1,8-biphenylenediol. The rate enhancement was determined by preparation of a Brønsted plot that found the efficiency of the conversion was comparable to a phenol 600 times as acidic as that of the diol.

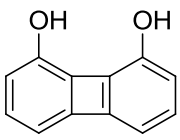

Figure 3. 1,8-biphenylenediol

Kelly *et. al*. later showed that double hydrogen-bond donation to carbonyl groups promoted Diels-Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes and ketones.[38] Further evidence of double hydrogen bond donation was implicated in the co-crystallization of *N*,*N*'-diarylureas with a range of compounds containing Lewis basic functional groups, including ethers and ketones, studied by Etter *et. al.*[39] Schreiner *et al*. tested the ability of diarylthioureas to catalyse Diels-Alder reactions between cyclopentadiene and α,β-unsaturated carbonyl compounds.[40] This reaction, which usually requires extended periods of heating, was assisted by double hydrogen bonding of a diarylthiourea catalyst with the transition state of the rate determining step.

Several structural features of the compound in Figure 4 make it an ideal catalyst in a variety of reactions. The trifluoromethyl moieties are poor hydrogen bond acceptors, thus limiting self-association of the molecules by interaction with the thiourea moieties. Thioureas (relative to ureas) are also poor hydrogen bond acceptors, further restricting the possibility of self-association. For hydrogen bonding catalysts to be effective they should bind preferably with the transition state of the rate determining step of the reaction and *not* with starting materials, products, or itself. The highly electron withdrawing nature of the $-CF_3$ groups also render the thiourea hydrogen atoms very acidic and thus benefits in hydrogen bond donation.[41] B3LYP/6-31G* computation studies have determined that the rotational barrier of the catalyst is quite high and this may be afforded to the rigidifying interactions developed by the polarized ortho-hydrogen atoms on the aryl ring with the Lewis basic sulfur hetero atom.[42] Entropy loss is thus minimized following the binding of the substrate to the catalyst, further facilitating promotion of the reaction. Such entropic

effects, dependent on the rigidity of the catalyst, are thought to contribute most to the observed strong complexation between thioureas and carbonyl compounds.[42]

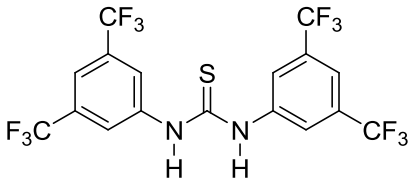

Figure 4. Schreiner's *N*,*N*-diarylthiourea catalyst

1.6—Morita-Baylis-Hillman Reaction

The Morita-Baylis-Hillman (MBH) reaction is an atom-economic carbon-carbon bond-forming reaction between electron deficient alkenes and an electrophile, such as an aldehyde (Figure 5). Atom economy refers to the efficiency of chemical processes in terms of atoms of reagents and atoms of products. This is measured by the ratio of molecular mass of the desired product to the molecular mass of all reagents involved. The allylic alcohols formed are synthetically useful building blocks that are obtained with the successful avoidance of by-products.[43] Morita initially reported the reaction by use of a phosphine catalyst in 1968 and in 1972 Baylis and Hillman reported a similar reaction by use of an amine catalyst: thus, each contributing to what is now known as the MBH reaction.[44] Tertiary amine catalysts such as 1,4-diazabicyclo[2.2.2]octane, DABCO are typically used to catalyze this notoriously slow reaction that may take days or weeks to complete, depending on the reactivity of the alkene and electrophile.[44] Zwitterionic aza-enolates formed by the use of tertiary amines, such as DABCO, have proven efficient in promoting subsequent steps in the MBH mechanism.

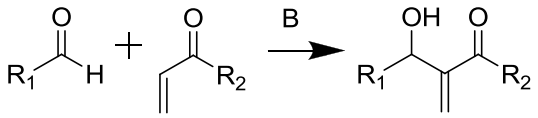

Figure 5. Morita-Baylis-Hillman reaction

The MBH reaction is attractive due to its use of low-cost and readily available starting materials as well as the atom-economic aspect of the reaction. Multifunctional adducts allow a wide range of functionalized products. For example, MBH reactions have been used to prepare key cyclic intermediates in the synthesis of several important molecules in medicine. One such molecule is Salinosporamide A, a proteasome inhibitor currently being studied as a potential anticancer agent.[45] The reaction is green due to the avoidance of heavy-metal pollution by the use of organocatalysts and the mild reaction conditions. Asymmetric product synthesis has also been proposed in MBH reactions.[44] Other than the time constraints, some other limitations outline the ways in which the MBH reaction may be problematic. For example, reactions between functional groups of starting materials may pose a problem. The competing reactions may prevail, making a final product with desired functional groups virtually impossible to prepare. Several activated alkenes may also prove problematic. For example, aryl vinyl ketone tends to add to another aryl vinyl ketone by a Michael addition, complicating the MBH reaction and the desired products.

Mechanistic aspects of the MBH reaction are often debated and have resulted in a number of kinetic studies aimed at determining the reaction mechanism. Hoffman[46] and Hill and Isaacs[47] proposed that the reaction begins with the conjugate addition of the tertiary amine to the electron deficient alkene, which generates a zwitterion (Figure 6).

This species then attacks the aldehyde in an aldol addition reaction, followed by an intramolecular proton shift from the α position to form the alcohol functional group in the final product releasing the amine catalyst in the final elimination step. Hill and Isaacs proposed the rate determining step to be the zwitterion attack on the aldehyde based on a low measured kinetic isotope effect (KIE = 1.03). KIE measures the rate of a reaction containing a hydrogen atom relative to the reaction using a deuterated form of the molecule. Cleavage of C-D bonds tend to require more energy than C-H bonds, and thus result in longer reaction times in the case that the rate determining step contains proton extraction, or a KIE greater than 2.

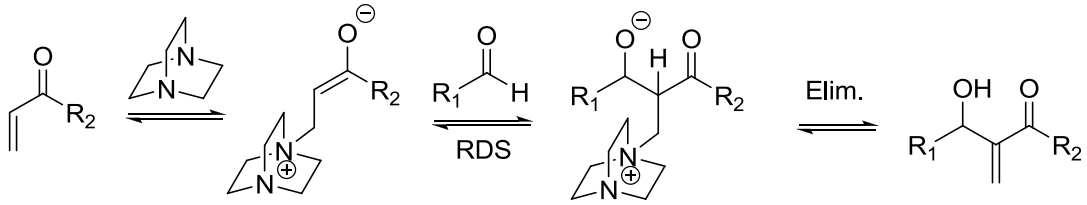

Figure 6. Hoffman, Hill, and Isaacs' MBH reaction mechanism using DABCO

McQuade et. al. proposed that the proton transfer step of the mechanism was the rate determining step based on a significant KIE (KIE = 5.2) in DMSO and KIE > 2 among other solvents tested, showing proton abstraction as the rate determining step. A new model was developed based on the findings of their kinetic studies:

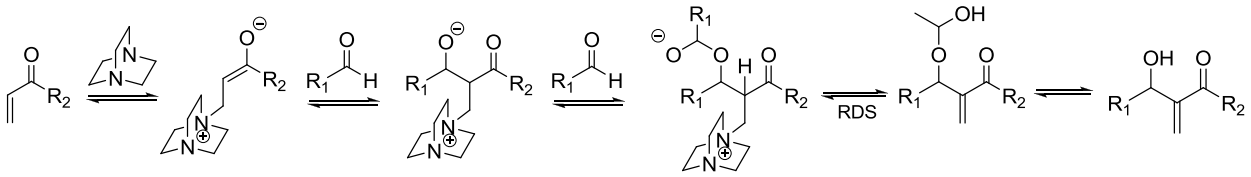

Figure 7. McQuade's MBH mechanism using DABCO

Several efforts have been made to overcome the slow rate of the MBH reaction. One method has been through the microwave irradiation of the reaction, which Bhat and co-workers have found to shorten the reaction time of several reactions from days to minutes.[48] Protic solvents are typically employed in MBH reactions, as they stabilize the enolate and activate the aldehyde, both through hydrogen bonding.[49] The use of organic co-catalysts has also proven an effective method of speeding up the MBH reaction including those of the bis-arylthiourea type, which have shown drastic enhancements in reaction rate.[45] Complexation of a bis-arylthiourea type organocatalyst with carbonyl moieties through hydrogen bonding in the transition state of the rate determining step allow such rate enhancement. Such a catalyst paired with a nucleophilic tertiary amine co-catalyst such as DABCO, necessary in the initial conjugate addition to the electron deficient alkene, have proven efficient in optimizing MBH reactions.

1.7—Singer Group Research

Recent research in the Singer group at Saint Mary's University conducted by McGrath *et al.* has focused on developing thiourea-based ionic organocatalysts for the rate enhancement of Morita-Baylis-Hillman reactions.[50] The catalyst McGrath prepared

contains a methylpyrrolidinium ionic tag as well as a 3,5-bis(trifluoromethyl)phenyl)thioureido moiety similar to Schreiner's catalyst.

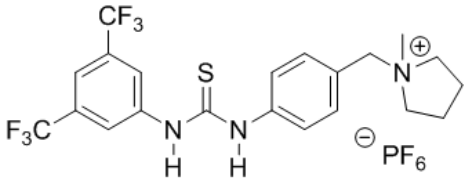

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Figure 8. McGrath's catalyst

McGrath's catalyst proved effective in catalyzing the MBH reaction between benzaldehyde and cyclohex-2-ene-1-one.

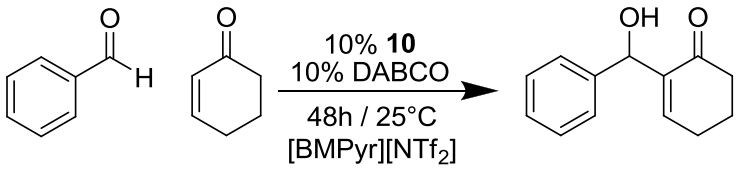


Figure 9. MBH reaction of benzaldehyde and cyclohex-2-ene-1-one.

McGrath was able to achieve 96% conversion to product (based on ^{1}H NMR analysis) following the conditions described in Figure 9. Optimized parameters were determined based on studies conducted on the effect of IL volume used (greater volumes led to lower conversion which is proposed to be due to a concentration effect), catalyst loading, and molar ratio of enone used. Microwave irradiation led to 78% conversion of reagents to desired product after only 6 hours and recyclability of the catalyst was verified by consistent conversions to products over a series of repeated trials using the same catalyst subsequently.

The research described in this thesis aims to prepare a catalyst that is bis-substituted with the thiourea moieties (Figure 10).

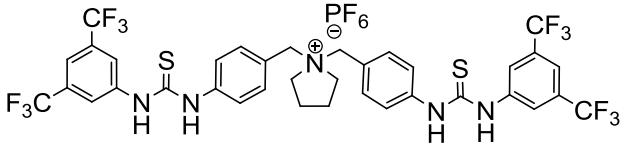


Figure 10. 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)pyrrolidinium hexafluorophosphate(V)

It is hypothesized that twice the amount of reagents will be converted to product per molecule of catalyst, compared to McGrath's, as hydrogen bonding will occur at two locations within the molecule. Accordingly, conversions to product in MBH reactions equal to McGrath's catalyst at half the catalyst loading are expected. Although this claim may ring true, it would mean little in practical terms, given that approximately the same amount of material will be required to produce one molecule of the bis-substituted catalyst compared to McGrath's mono-tagged catalyst. Regardless, the hypothesis that twice as much conversion to product per catalyst molecule will occur is certainly worth investigating. The desire to design green chemical reactions warrants testing of the recyclability of the proposed catalyst and effect of microwave irradiation on the MBH reactions as well.

2.0 Results and Discussion

The first step in attaining the desired catalyst, **3**, was the synthesis of 1,1-bis(4-nitrobenzyl)pyrrolidinium bromide, **1** (Figure 11). 4-nitrobenzyl bromide was dissolved in diethyl ether and pyrrolidine was added dropwise into the reaction flask in 1:1 ratio (4-nitrobenzyl bromide : pyrrolidine). At first glance, this method of synthesis seems problematic. One may wonder how one molecule of pyrrolidine and one molecule of 4-

nitrobenzyl bromide could produce one molecule of an *N*,*N*-bis(4-nitrobenzyl) pyrrolidinium bromide. The answer lies in the intermediate formed in the reaction that serves as a sacrificial base. It is proposed that following the formation of the mono-tagged pyrrolidine, another pyrrolidine molecule serves as a base, removing the remaining proton on the mono-tagged molecule, allowing a second S_N2 attack on the remaining 4-nitrobenzyl bromide, forming the desired bis-substituted product as well as a by-product of *N*-pyrrolidinium hydrobromide. Thus, the 1:1 ratio of reagents (4-nitrobenzyl bromide : pyrrolidine), is an appropriate ratio of reactants. ^{1}H-NMR analysis of solid by-product formed in the reaction provided evidence for the presence of the hydrobromide salt.

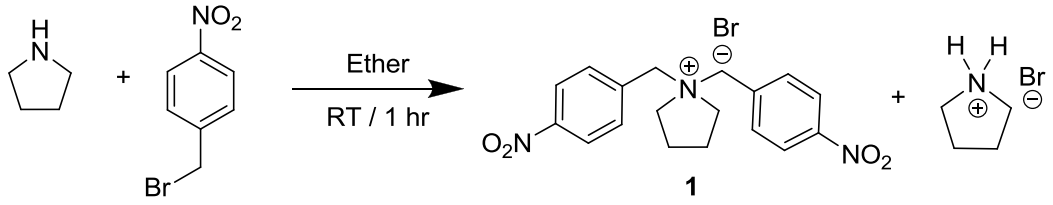


Figure 11. Synthesis of 1,1-bis(4-nitrobenzyl)pyrrolidinium bromide, **1**

The next steps in the procedure involved the reduction of the nitro functional groups to amine groups as well as the metathesis reaction to incorporate a PF_6^- anion into the desired **2** rather than a Br^- anion (Figure 12). The synthesis of 1,1-bis(4-aminobenzyl)pyrrolidinium hexafluorophosphate (V), **2**, first involved the reduction of the nitro group. The first step in this procedure involved the production of iron(0) particles. Iron sulfate and sodium citrate, as a co-reducing agent, were stirred in H_2O in a round bottom flask until the reagents dissolved. A measured mass of sodium borohydride was then added a spatula tip at a time, with black, solid Fe(0) immediately precipitating

from solution. The mixture was washed with water and decanted 3 times, and finally compound **1** was added on top of the solid Fe(0)-water mixture and stirred for 24 hours. The mixture was then poured through a medium pore frit, and prepared aqueous KPF_6 was added dropwise to the aqueous filtrate, forming a solid white product, compound **2**. The major issue regarding the synthesis of **2** was narrowing down the optimal ratio of compound **1**, iron sulfate, sodium citrate, and sodium borohydride. Instances arose in which the amount of iron(0) produced was simply present in too large quantities, as the decantation process invariably resulted in loss of iron(0), while too little iron(0) remained in the heterogeneous water phase, resulting in low yield of product. Time was also a factor: increasing reaction time from 24 to 48 hours resulted in virtually no increase in product yield. Following several trials of reaction optimization, a molar ratio of 1:6:0.5:12 (compound **1** : iron sulfate : sodium citrate : sodium borohydride) was found to be best.

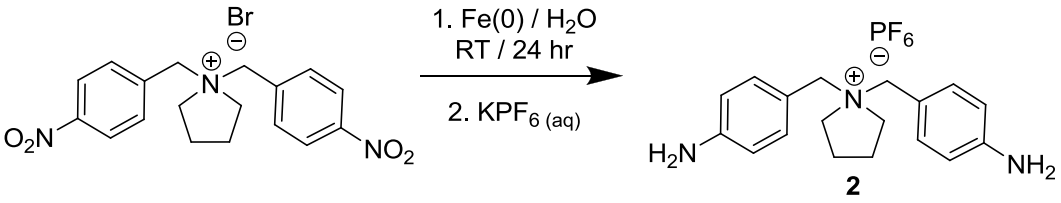


Figure 12. Synthesis of 1,1-bis(4-aminobenzyl)pyrrolidinium hexafluorophosphate (V), **2**

The above procedure is a variation on previous attempts to form compound **2**. In earlier trials, the metathesis step was conducted before the iron(0)-reduction step (Figure 13). In this procedure, **1** was first dissolved in hot water on a stir plate and gravity filtered while still hot into a round bottom flask while heating in an oil bath. This was necessary as **1** was only soluble in water at elevated temperatures (~70 °C). Anion exchange was

then completed by drop-wise addition of aqueous HPF_6 to the reaction flask, stirring for 1 hour, and subsequent cooling of the reaction flask to room temperature. Once this product was suction filtered and dried *in vacuo*, the iron(0)-reduction procedure ensued. In this instance, the compound did not easily dissolve or mix into the iron(0)-water mixture and much of it stuck to the sides of the reaction flask. After 24 hours of stirring, the solution was poured through a medium pore frit, the iron remaining in the frit was washed with acetonitrile, and the acetonitrile filtrate was concentrated *in vacuo* to produce the desired product, **2**. Clearly, this method was much more complex in terms of labour, time, and material utilized compared to the alternative procedure. The optimized procedure is beneficial in that heating and hot gravity filtration is avoided and the use of HPF_6, a highly toxic material, is avoided as well. The acetonitrile wash step is not necessary in this procedure and the product turned out to be cleaner by ^{1}H-NMR analysis. Lastly the bromide salt much more easily dissolves during the iron(0)-reduction step compared to the PF_6^- salt. Overall, great time and effort were saved by using the optimized method for the synthesis of **2**.

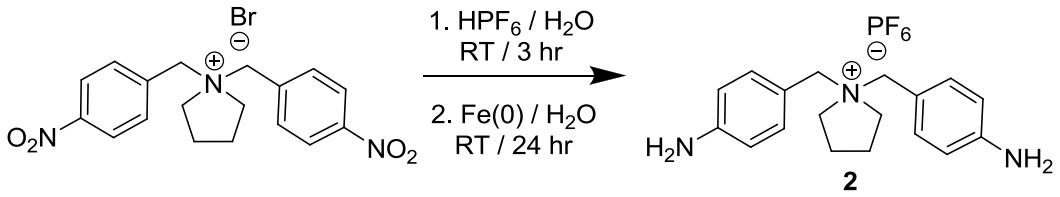


Figure 13. Synthesis of 1,1-bis(4-aminobenzyl)pyrrolidinium hexafluorophosphate (V), **2**, by the previously designed two-step process.

The designed catalyst, 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido) benzyl)pyrrolidinium hexafluorophosphate(V), **3**, was synthesized by dissolving **2** in acetonitrile and adding 3,5-bis(trifluoromethyl)phenyl isothiocyanate in a 1:2.5 ratio (compound **2** : isothiocyanate) (Figure 14). The 1:2.5 ratio proved optimal following several trials in ensuring a high yield of **3**. While time constraints did not permit it, synthesis of **3** by microwave irradiation could prove beneficial in significantly reducing the reaction time from 7 days down to mere hours, as McGrath *et al.* have reported in the synthesis of their catalyst.[50]

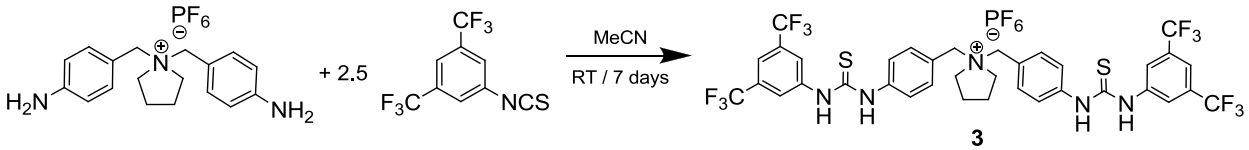


Figure 14. Synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido) benzyl)pyrrolidinium hexafluorophosphate(V), **3**

The synthesis of the imidazolium based catalyst, 1,3-bis(4-(3-(3,5-bis(trifluoromethyl) phenyl)thioureido)benzyl)-1H-imidazol-3-ium hexafluorophosphate (V), **6**, began with the synthesis of 1,3-bis(4-nitrobenzyl)-1*H*-imidazol-3-ium bromide, **4** (Figure 15). 4-Nitrobenzyl bromide was dissolved in acetonitrile and 1-(trimethylsilyl)imidazole was added in a 2:1 ratio (1-TMS-imidazole : 4-nitrobenzyl bromide). In this instance, the 2:1 ratio was necessary as the reaction proceeds *via* two S_N2 attacks without the use of a sacrificial base, as indicated in the synthesis of **1**. A condenser was attached to the reaction flask and the solution was stirred for 48 hours at 70 °C. Following the 48 hours,

solid precipitate was collected by suction filtration and recrystallized in water at 70 °C to obtain the desired product. The remaining filtrate was concentrated *in vacuo* and the crude solid obtained was recrystallized in water at 70 °C. This procedure proved problematic in that only a 35% yield was obtained. Various trials of synthesis of **4** yielded various, unpredictable observations: sometimes no solid would precipitate following 48 hours and the flask needed to be cooled on ice for product to form, and other times solid would form at the 70 °C stirring temperature. The difficulties that arose in the synthesis of **4** was one of the reasons the pyrrolidinium catalyst, **3**, was tested in the following experiments while the imidazolium catalyst, **5**, was not.

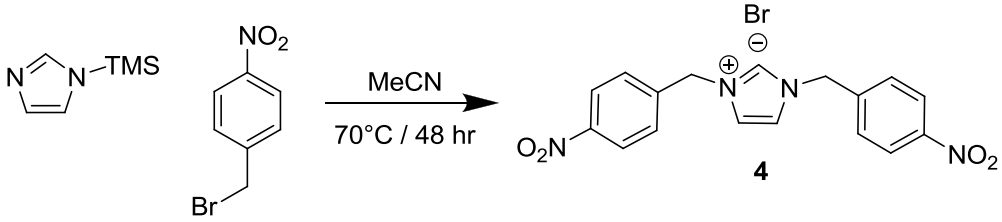


Figure 15. Synthesis of 1,3-bis(4-nitrobenzyl)-1*H*-imidazol-3-ium bromide, **4**

The remaining steps in the synthesis of **5** are identical to that of the synthesis of **3** (Figure 16).

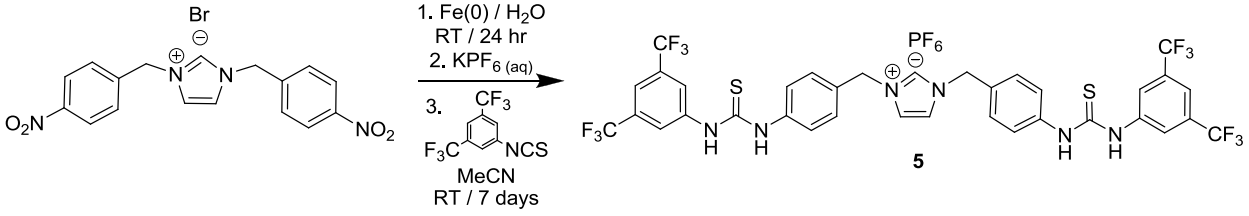


Figure 16. Synthesis of 1,3-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1H-imidazol-3-ium hexafluorophosphate (V), **5**

Optimistic that the MBH reactions would run smoothly with the synthesized catalyst, **3**, an analogous catalyst with a tetrafluoroborate anion rather than a hexafluorophosphate anion was designed to test the effect of alternate anions on the rate enhancement of MBH reactions. Synthesis of 1,1-bis(4-aminobenzyl)pyrrolidinium tetrafluoroborate, **6**, was the first step in the synthesis of this derivative catalyst (Figure 17). **6** was formed from compound **1** as described in the synthesis of compound **2**. This included an iron(0)-reduction step followed by an anion-exchange step. In this instance, rather than using aqueous KPF_6, an aqueous solution of $NaBF_4$ was used instead (1:1.25 mole ratio reduced product:$NaBF_4$). With the optimized reduction-then-metathesis procedure in mind, the synthesis of **6** was relatively simple, again dismissing several time-consuming and complicated steps originally proposed.

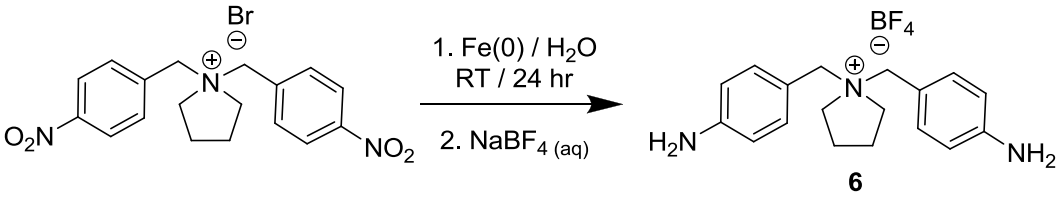


Figure 17. Synthesis of 1,1-bis(4-aminobenzyl)pyrrolidinium tetrafluoroborate, **6**

Synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benyzyl)pyrrol-

idinium tetrafluroroborate **7**, was conducted as described in the synthesis of catalysts **3** and **5** (Figure 18).

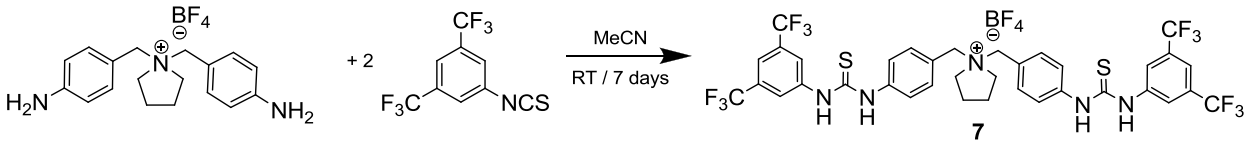
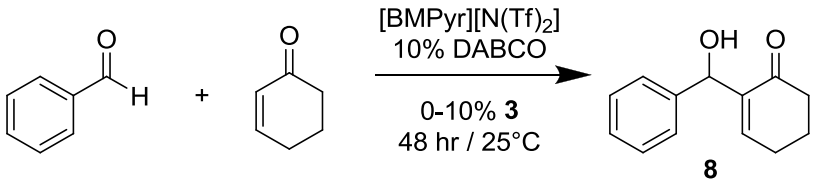


Figure 18. Synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido) benzyl)pyrrolidinium tetreafluroroborate, **7**

Following the synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-benzyl)pyrrolidinium hexafluorophosphate(V), **3**, its catalytic ability was tested in the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohex-2-en-1-one. DABCO was used as the tertiary amine co-catalyst in the reaction. 10 mol % each of **3** and DABCO were each used. The reaction was maintained at 25 °C and stirred for 48 hours. Percent conversion was determined by ^{1}H-NMR. Conversion was determined through normalization of the integrated proton peaks for the benzaldehyde proton (~10 ppm in $CDCl_3$) and the benzylic proton of 2-(hydroxyl(phenyl)methyl)cyclohex-2-enone, **8**, (~5.5 ppm in $CDCl_3$) using Topspin software. The singlet peaks in the spectrum were clearly distinguishable from all other peaks and thus serve as a good indication of conversion to the desired product, although more precise data would have been gathered if the relaxation rates of each proton were made equal. Results are shown in Table 1.

Table 1. Effect of catalyst loading of **3** on the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohex-2-en-1-one.



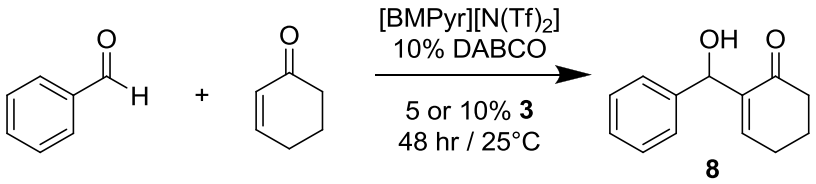
Entry	Benzaldehyde (mmol)	Cyclohex-2-en-1-one (mmol)	Catalyst loading (mol % benzaldehyde)	% Conversion to product
1	0.2	1.0	0.0	12
2	0.2	1.0	2.5	63
3	0.2	1.0	5.0	93
4	0.2	1.0	5.0	95
5	0.2	1.0	5.0	93
6	0.2	1.0	7.5	93
7	0.2	1.0	10.0	94

Following the success of catalyst loading at 10 mol % (94 % conversion, entry 7), lower catalyst loadings were tested. Using lower relative amounts of catalyst is beneficial from both an economic and green chemistry standpoint. Percent conversions remained consistent at 95% for 7.5 mol% loading and 93% for 5 mol% loading (entries 3-6). At loadings below 5 % (entries 1 and 2) conversion drastically dropped to 63% at 2.5 mol%. In the control reaction, with DABCO but no **3** present, 12 % conversion was obtained. It appears that catalyst activity ceases to improve below 5 mol% loading. This plateau may

represent the limit beyond which any additional catalyst would not be necessary to enhance the reaction. One would not employ **3** at 10 mol% loading when the same conversion can be obtain at 5 mol% loading. The exact loading of the catalyst at which this plateau occurs could be acquired with greater accuracy upon further trials of reaction optimization.

A useful feature of many catalysts is the ability to reuse (recycle) the catalyst. Thus, to fully exploit **3** as a catalyst, further experiments were required. In such recycling experiments, organic products and any remaining reactants were extracted using ethyl ether, with **3** remaining entrained in the ionic liquid due to its ionic-tag. The appropriate number of washings was determined to be the point at which no other organic molecules were observed in an H^1-NMR of the washings. This step in the procedure admitidly makes the reaction less green. Residual ether was taken off *via* concentration of products *in vacuo*. DABCO and the substrates, which had been extracted by the ether wash, were subsequently added in the same amounts as in the first run and the reaction stirred for 48 additional hours. Results of the recyclability experiments are presented in Table 2.

Table 2. Recyclability of **3** in the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohex-2-en-1-one.

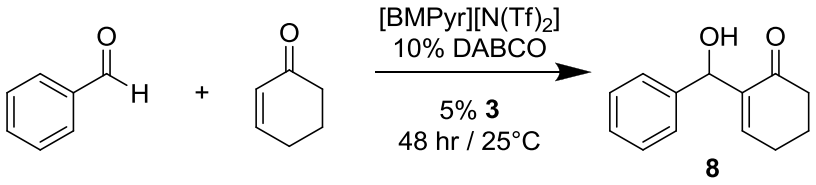


Entry	Benzaldehyde (mmol)	Cyclohex-2-en-1-one (mmol)	Catalyst loading (mol % benzaldehyde)	% Conversion to product	% Conversion to product (recycled)
1	0.2	1.0	5.0	93	12
2	0.2	1.0	5.0	95	6
3	0.2	1.0	10.0	80	42

The effect of the catalyst was significantly reduced in the recycling experiments. The % conversion to product in the recycled run were similar to the control run in Table 1 in which DABCO, but not **3** present, indicating little or no effect on rate enhancement from **3**. A possible explanation for such low conversion was the leaching of the catalyst from the ionic liquid layer into the ether layer. Low (or no) catalyst remaining in the ionic liquid layer would explain the lower conversion to product observed in the recycling study. This hypothesis was tested initially by a simple solubility test of the catalyst, **3**, in the ether. **3** appeared to be completely insoluble in diethyl ether. The hypothesis was further tested by analysis of ^{1}H-NMR spectra of the ether washes. Based on the ^{1}H-NMR of an authentic sample of **3**, no catalyst was present in the ether layer in both the first and

final washes. An alternative hypothesis was that the concentration of the substrates and catalyst may play a role. To test this, the general MBH procedure was conducted using 0.100 mL, 0.200 mL, 0.300 mL and 0.400 mL of the ionic liquid. The results are presented in Table 3.

Table 3. Effect of reaction component concentration on catalytic activity and recyclability of **3** in the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohex-2-en-1-one.



8

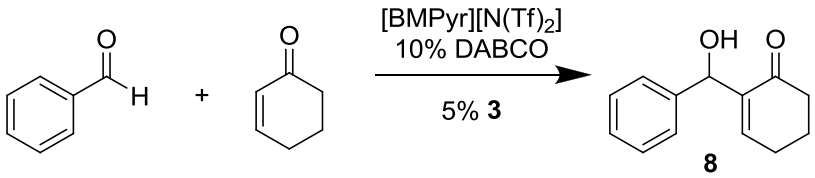
Entry	Catalyst loading (mol % benzaldehyde)	[**3**] (M)	% Conversion to product	% Conversion to product (recycled)
1	5.0	0.200	93	12
2	5.0	0.100	50	13
3	5.0	0.067	30	8
4	5.0	0.050	27	10

Increasing the volume of ionic liquid used in the reaction decreased the conversion to product. This is evident even upon decreasing the concentration of **3** to 0.100 M (entry 2). This effect may be explained by a concentration effect, that is, upon increasing the volume of the ionic liquid, the concentration of **3** and the substrates in the solution decreases and thus less incidents of interaction between the proposed catalyst and substrates actually occurs. Interestingly, there appears not to have been an effect of

concentration on the ability of DABCO to catalyze the reaction upon the recycling trial, with each % conversion around 10 %.

The results from the first three experiments indicated that further experiments should focus on the cause of the low recyclability of the proposed catalyst, **3**, but to wait 4 days for results from both the initial and recycling trials would be less feasible, time-wise. Microwave irradiation has been used previously in our group as a green approach to reducing the time requirements of reactions. Results from initial microwave trials of the MBH reaction are presented in Table 4.

Table 4. Effect of temperature, time, and reaction component concentration on the microwave irradiation of the Morita-Baylis-Hillman reaction between benzaldehyde and cyclohex-2-en-1-one.



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Entry	Catalyst loading (mol % benzaldehyde)	Temperature (°C)	Time (hours)	[**3**] (M)	% Conversion to product
1	5.0	50	2	0.100	15
2	5.0	80	2	0.100	25
3	5.0	100	4	0.100	31
4	5.0	100	6	0.100	31
5	5.0	100	4	0.067	21

Conversion to product was quite low at 50 °C under microwave irradiation, although the reaction only lasted 2 hours, a mere 1/24 the amount of time of the original (unassisted) reaction (entry 1). In the same amount of time, 2 hours, the conversion to product almost doubled when raising the temperature from 50 °C to 80 °C (entry 2). With this finding in mind, 100 °C was used as the reaction temperature in subsequent trials, which resulted in even greater conversion.

Time was the next variable tested. Reaction time was increased from 2 hours to 4 hours and then 6 hours in the microwave. No increase in conversion to product occurred following the 6 hour reaction compared to the 4 hour reaction, as each resulted in conversion to product of 31% (entries 3 and 4). Although further experiments attempting to optimize microwave irradiation conditions will be conducted at increased reaction times (8 and 12 hours) in future studies, the lack of significant increase in conversion to product from 2 to 6 hours led to investigations regarding the effect of concentration of reaction components on the conversion to product. Thus, before the continuation of time related trials, experiments concerning concentration were conducted.

Entry 5 in Table 4 indicates a positive correlation between reaction component concentration and conversion to product, as at a lower concentration of **3** of 0.067 M, conversion to product was 21%, lower than the 31% conversion at 0.100 M (entry 3). Another hypothesis regarding the low conversion to product was subsequently tested. Thermal degradation of the catalyst or ionic liquid may have occurred upon microwave irradiation. ^{1}H-NMR spectra were obtained for **3** alone in [BMPyr][$N(Tf)_2$], both before and after microwave irradiation. The ionic liquid, [BMPyr][$N(Tf)_2$], was not altered by

thermal degradation as shown in the stacked ^{1}H-NMR spectra in Figure 19. This region of the spectrum contained information regarding the protons of the ionic liquid and not the catalyst, **3**. Had the ionic liquid been chemically altered by thermal degradation, the unique ^{1}H-NMR peak assignments would vary from the spectrum obtained before microwave irradiation and the spectrum following microwave irradiation. In Figure 19 there is no indication of alteration of peaks among the three spectra and thus no indication of degradation of the ionic liquid.

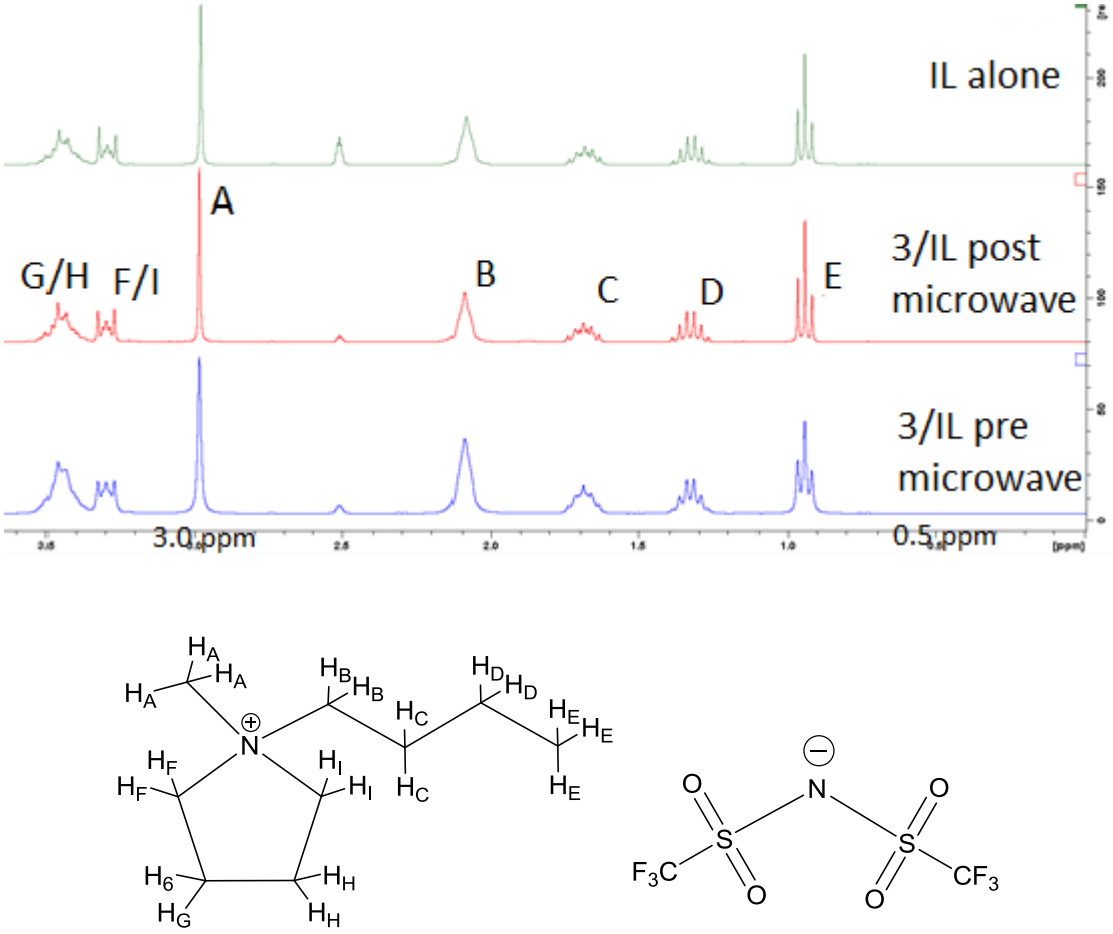


Figure 19. ^{1}H-NMR spectra for the [BMPyr][N(Tf)$_2$] (top), **3**-IL after microwave irradiation (middle), and **3**-IL before microwave irradiation (bottom).

The ^{1}H-NMR spectrum for **3** is presented in Figure 20. There were some notable changes in peaks of the ^{1}H-NMR spectra for **3** in the IL after microwave irradiation compared to **3**/IL before microwave irradiation and **3** alone, as shown in Figures 21 and 22. Note the peaks at 7.0 ppm, 7.2 ppm and 10.7 ppm in Figure 21 and the 3 doublet peaks between 4.0 and 4.5 ppm in Figure 22. These peaks only appear in the ^{1}H-NMR spectrum post microwave irradiation; this result suggests thermal degradation of the catalyst. If thermal energy caused **3** to break apart into smaller components, the protons on any fragment will no longer be in the same chemical environment they were before the degradation. With dissimilar chemical environments post microwave irradiation, different peaks will result in NMR spectra. These preliminary findings warrant supplemental investigations, such as thermal gravimetric analysis mass spectrometry (TGA-MS) to further support this hypothesis. Thermal gravimetric analysis will provide data on the physical and chemical changes of the catalyst as a function of temperature increase, such as phase transitions and decomposition.

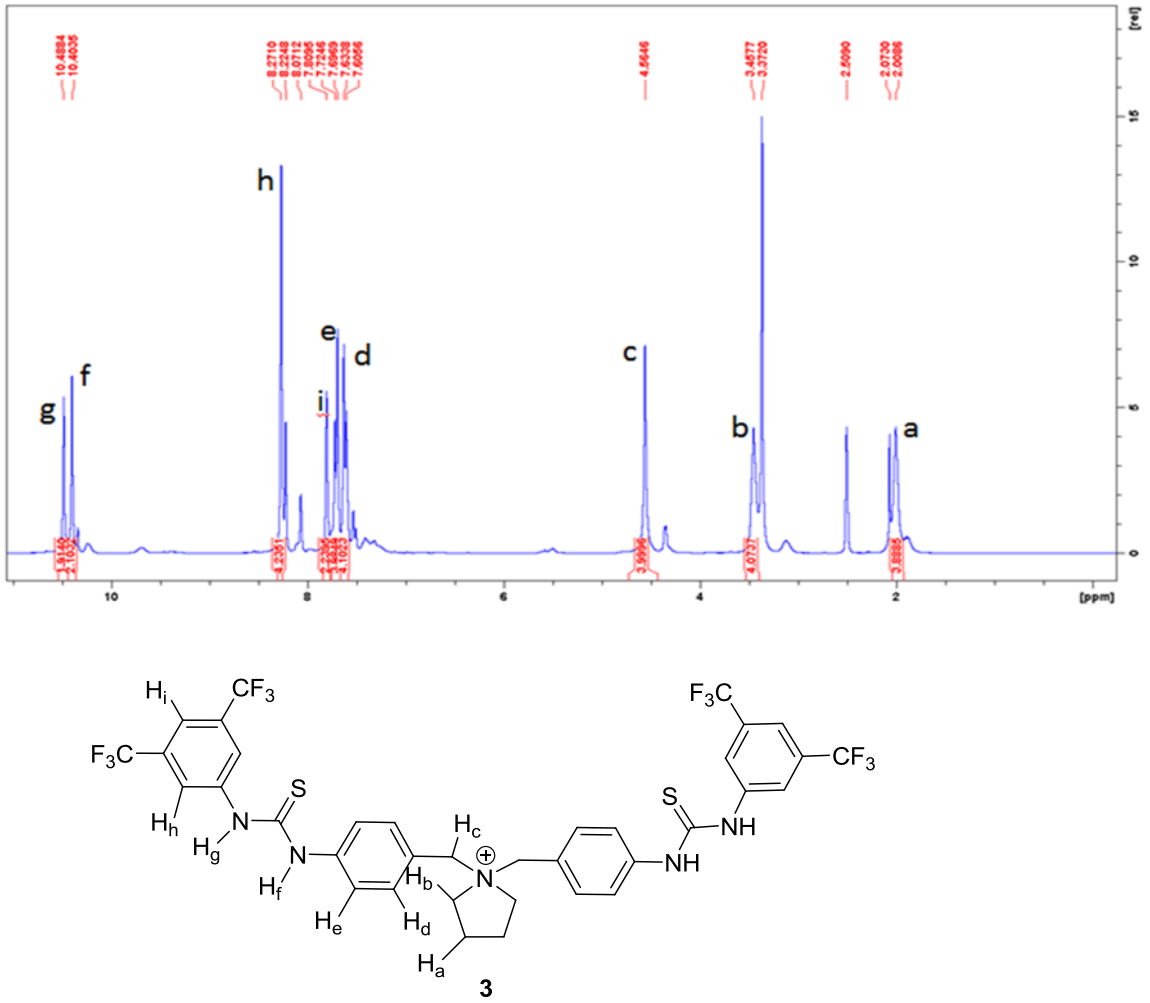


Figure 20. ^{1}H-NMR spectra for **3**.

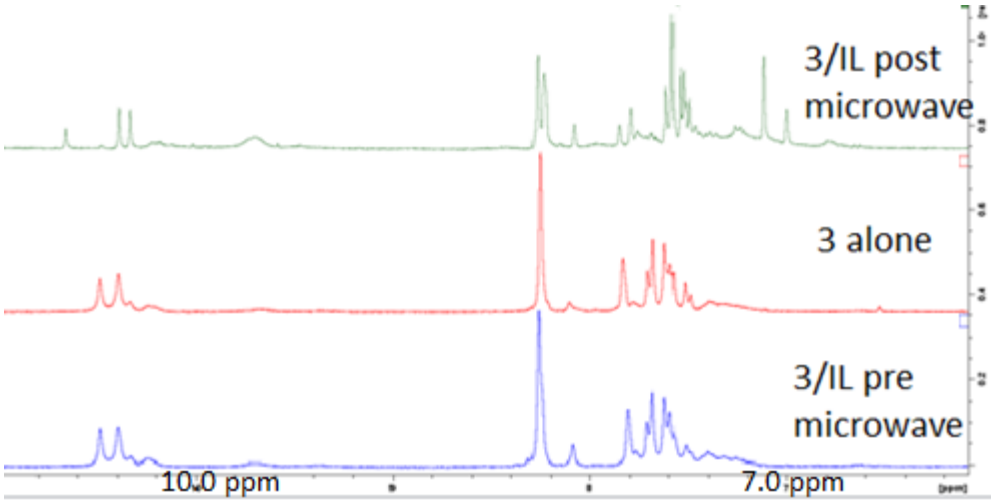


Figure 21. ^{1}H-NMR spectra from 6 to 11 ppm for **3**-IL after microwave irradiation (top), **3** alone (middle), and **3**-IL before microwave irradiation (bottom).

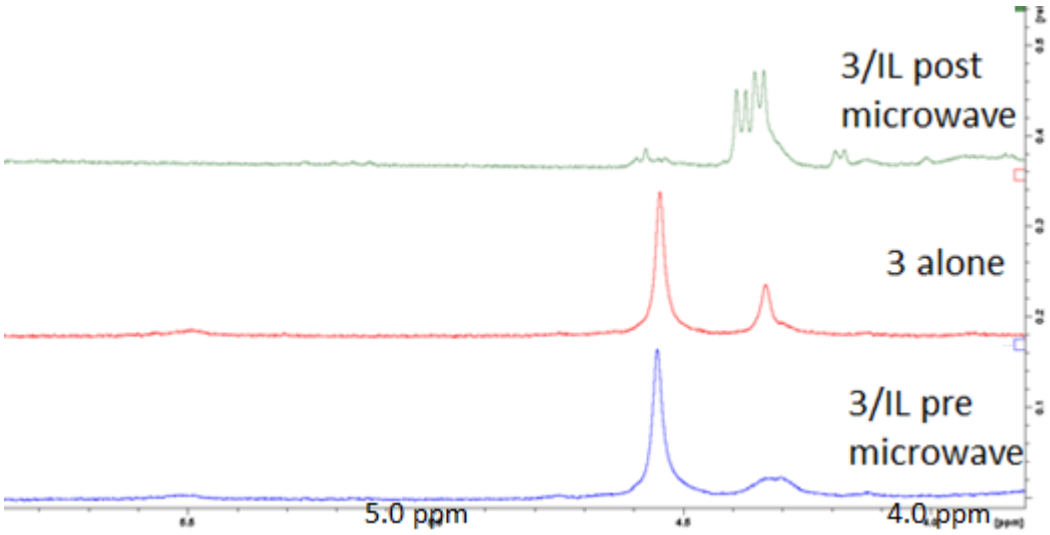


Figure 22. ^{1}H-NMR spectra from 4 to 6 ppm for **3**-IL after microwave irradiation (top), **3** alone (middle), and **3**-IL before microwave irradiation (bottom).

3.0 Conclusion

A series of bis-thiourea based ionic organocatalysts have been successfully synthesized and characterized. One catalyst, **3**, was employed in the rate enhancement of a Morita-Baylis-Hillman reaction between benzaldehyde and cyclohex-2-ene-1-one. Spectroscopic techniques used to characterize the catalyst included IR, ^{1}H- and ^{13}C-NMR, and ESI-MS. Use of the synthesized catalyst along with DABCO as a co-catalyst allowed nearly full conversionto the desired 2-(hydroxyphenylmethyl)-cyclohex-2-ene-1-one product at as low as 5% catalyst loading at room temperature over a period of 48 hours. Attempts at recycling of the catalyst were unsuccessful. Microwave irradiation of the reaction proved ineffective in attaining comparable conversions in the MBH reaction. While there was no evidence of catalyst leaching from the ionic liquid layer of the reaction, spectral analysis of the catalyst upon microwave irradiation suggested thermal decomposition of the catalyst, which may be further supported by TGA-MS analysis of **3**.

Synthesis and partial characterization of two analogous catalysts has also been achieved. One such catalyst contained an imidazolium rather than a pyrrolidinium ring. The other contained a BF_4^- rather than a PF_6^- anion. Catalytic activity of these derivatives has yet to be tested.

4.0 Future Directions

The main priority in further experiments of the synthesized catalyst should be to narrow down the explanation for both poor recyclability and poor response to microwave irradiation. Thermal gravimetric analysis mass spectrometry (TGA-MS) could be employed to measure physical and chemical changes of the catalyst as a function of increased reaction temperature. Should this issue be resolved, optimization of synthesis of starting material and microwave parameters for the MBH reaction should be investigated.

The two other catalysts prepared may also be studied for influence in reactions including the MBH and Diels-Alder reactions. Crystal structures of the catalysts would be very useful to fully characterize each catalyst. In the future, bi-functional derivatives of the synthesized catalysts should be investigated, such as bis-thiourea organocatalysts that contain the tertiary amine moiety necessary for MBH reaction rate enhancement, such as DABCO (Figure 22).

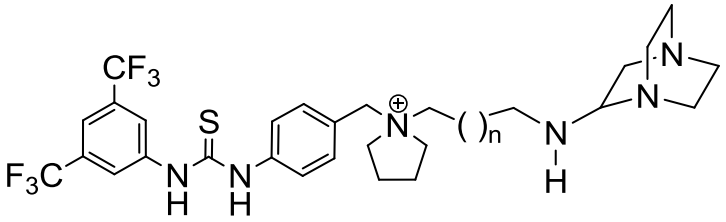


Figure 23. Hypothetical model of a thiourea organocatalyst that contains tertiary amine functionality.

5.0 Experimental

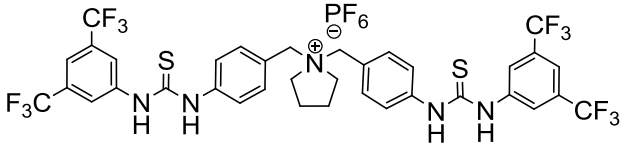
5.1 General Procedures

Glassware used in the synthesis of catalysts and in subsequent Morita-Baylis-Hillman reactions was cleaned in a Mandel Lancer dishwasher and oven dried at 110 °C before use. Solvents used in reactions were purchased from Sigma Aldrich and used directly from the bottle with no further purification steps.

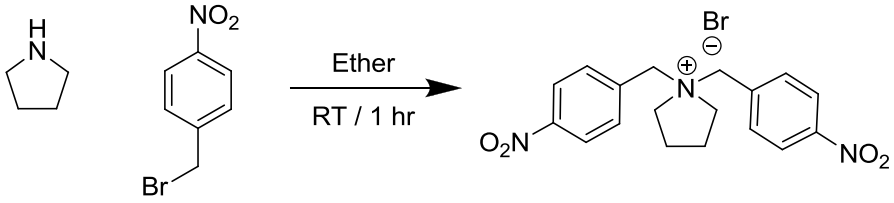
Nuclear Magnetic Resonance spectra were obtained from a Bruker 300 MHz Ultrashield spectrometer. The program Topspin was used to process and analyze spectra. Deuterated NMR solvents DMSO-d_6 and $CDCl_3$ were purchased from Cambridge Isotope Laboratories. These NMR solvents contained molecular sieves and were located in a chemical refrigerator.

Electrothermal Mel-Temp 3.0 melting point apparatuses were used to obtain melting point data. Electrospray ionization mass spectrometry samples were prepared in our research lab and sent to Patricia Granados at Saint Mary's University Center for Environmental Analysis and Remediation (CEAR) for processing using an Agilent 1100 LC/MSD Trap. IR spectra were obtained from a Bruker ALPHA Infrared Spectrometer by use of OPUS software. IR samples were prepared in the form of KBr pellets.

5.2 Synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl) pyrrolidinium hexafluorophosphate(V), 3



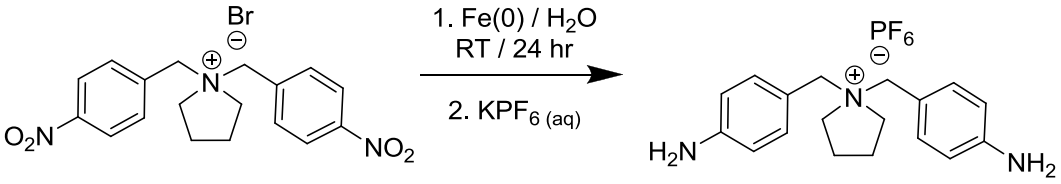
5.2.1 Synthesis of 1,1-bis(4-nitrobenzyl)pyrrolidinium bromide, 1



4-nitrobenzyl bromide was dissolved in the appropriate volume of diethyl ether (approx. 500 mL/g of 4-nitrobenzyl bromide) in a round bottom flask using a stir bar. The calculated volume of pyrrolidine necessary (1:1 ratio) was added to some ether to dilute. This solution was added dropwise to the dissolved 4-nitrobenzyl bromide, with stirring, from a syringe. Solid precipitated from the solution almost immediately. This solution was stirred at room temperature for 1 hour. The solution was gravity filtered and the solvent from the filtrate put on the rotovap. Chloroform was added to the resulting solid and stirred. The solid that did not dissolve was the desired product and was retrieved by suction filtration. The chloroform filtrate was put on the rotovap in case any product had been dissolved in it (residual ether allows for a solvent effect with the chloroform to dissolve some product if any ether remains). The solid was stirred once more in chloroform and suction filtered. The product was then dried *in vacuo*. (7.257 g, 74 % yield). MP 209-210 °C. IR (KBr): 1520.9, 1350.6 cm^{-1} (Nitro); ^{1}H NMR (DMSO-d_6, 300MHz) δ

8.35 (d, J=8.7 Hz, 4H), 7.97 (d, J=8.7 Hz, 4H), 4.88 (s, 4H), 3.53 (s, 4 H), 1.98 (s, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 149.0, 136.0, 135.3, 124.3, 62.2, 59.2, 21.2; ESI-MS: Positive Mode Found: m/z 342.2 [100% ($C_{18}H_{20}N^+$)]; Calc. 342.4.

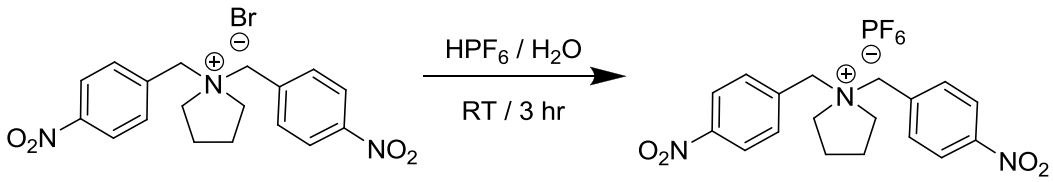
5.2.2 Synthesis of 1,1-bis(4-aminobenzyl)pyrrolidinium hexafluorophosphate (V), 2



1 (2 g or less) was measured and the appropriate masses of iron sulfate, sodium citrate, and sodium borohydride was calculated based on a 1:6:0.5:12 ratio respectively. Iron sulfate and sodium citrate was dissolved in distilled H_2O (approximately ½ of the round bottom with a large stir bar in it; the stir bar must be large for maximum attraction of the formed Fe(0)). Sodium borohydride was added a spatula tip at a time; reduced Fe(0) formed immediately (a black solid). This mixture was left to stir for a few minutes, the stirring was then stopped and the iron was allowed to settle to the bottom of the flask. As much water as possible was slowly and carefully decanted (without losing iron). The flask was filled half-way with distilled H_2O again, stirred, decanted and repeated once more. The dinitro pyrrolidinium bromide compound was added by a weigh paper funnel so as to allow as much of the solid as possible to land on the iron. The compound was slowly stirred into solution and the sides of the flask rinsed with water if necessary. The flask was capped. 24 hours later the mixture was poured through a medium pore frit by suction. Aqueous KPF_6 solution (1:1.25 mole ratio reduced product:KPF_6) was prepared

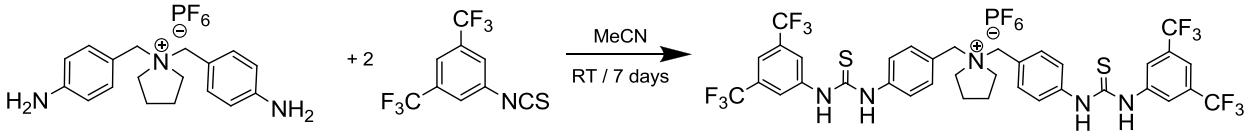
in a vial and added dropwise to the aqueous solution from the frit. A white solid precipitated out of solution and isolated by suction filtration and dried *in vacuo*. (0.58 g, 64 % yield; "one step" = 1.341 g, 63% yield). MP 134.0 – 135.2 °C. IR (KBr): 3507.2, 3406.3 (Primary amine) , 840.4, 558.0 (PF_6) cm^{-1}. ^1H NMR (DMSO-d_6, 300MHz) δ 7.17 (d, J=8.45 Hz, 4H) 6.61(d, J=8.45 Hz, 4H), 5.52 (s, 4H), 4.26 (s, 4H), 3.26 (bs, 4H), 1.92 (bs, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 150.9, 134.4, 114.6, 114.1, 63.7, 56.9, 21.2; ^{31}P NMR (DMSO-d6, 121 MHz) δ -144.2 (septet, *J*=712.2 Hz); ESI-MS: Positive Mode Found: m/z 282.2 [100.0% ($C_{18}H_{24}N_3^+$)]; Calc. 282.2; Negative Mode Found: m/z 144.6 [100% (PF_6^-)]; Calc 145.0.

The above procedure is a modification of a procedure followed in previous attempts at preparing the catalysts. In the earlier method, the metathesis step (bromide to PF_6 salt) came before the iron reduction step (below):



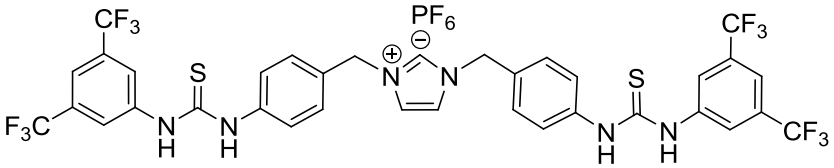
(2.275 g, 99 % yield). MP 224.2 – 225.6 °C. IR (KBr): 1526.6, 1350.8 (Nitro) , 833.7, 557.4 (PF_6^-) cm^{-1}. ^1H NMR (DMSO-d_6, 300MHz) δ 8.36 (d, J=8.80 Hz, 4H) 7.90 (d, J=8.80 Hz, 4H), 4.74 (s, 4H), 3.48 (s, 4H), 1.98 (s, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 149.1, 235.7, 135.3, 124.3, 62.5, 59.2, 21.2; ^{31}P NMR (DMSO-d6, 121 MHz) δ -144.2 (septet, *J*=712.5 Hz); ESI-MS: Positive Mode Found: m/z 342.3 [100.0% ($C_{18}H_{20}N_3O_4^+$)]; Calc. 342.4; Negative Mode Found: m/z 144.6 [100% (PF_6^-)]; Calc 145.0.

5.2.3 Synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl) pyrrolidinium hexafluorophosphate(V), 3

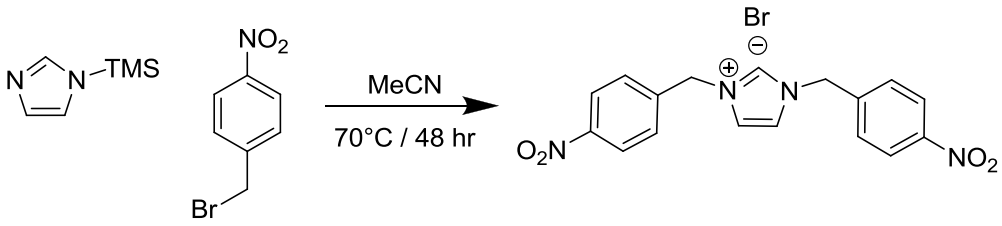


2 was dissolved in acetonitrile in a round bottom flask. The solution was stirred and the appropriate volume of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1:2.5 diamine:isothiocyanate compound) was added. The flask was capped and stirred for 7 days. The solution was placed on rotovap and the resulting solid was heated and dried *in vacuo*. (0.304 g, 65 % yield). IR (KBr): 3382.7 (Secondary amine) , 848.0, 557.1 (PF_6) cm^{-1} (expect thiocarbonyl stretch in 1050-1200 range and CF stretch in 1000-1400 range). ^1H NMR (DMSO-d_6, 300MHz) δ 10.49 (s, 2H) 10.40 (s, 2H), 8.27 (s, 4H), 7.81 (s, 2H), 7.71 (d, J=8.42 Hz, 4H), 7.62 (d, J=8.42, 4H), 4.56 (s, 4H), 3.46 (s, 4H), 2.01 (s, 4H); ^{31}P NMR (DMSO-d6, 121 MHz) δ -144.2 (septet, *J*=711.5 Hz); ESI-MS: Positive Mode Found: m/z 824.4 [62.1% ($C_{36}H_{30}F_{12}N_5S_2^+$)]; Calc. 824.2, 448.3 [100.0% ($C_{20}H_{20}F_6N_3S^+$)]; Calc. 448.1; Negative Mode Found: m/z 144.6 [100% (PF_6^-)]; Calc 145.0.

5.3 Synthesis of 1,3-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1H-imidazol-3-ium hexafluorophosphate (V), 6

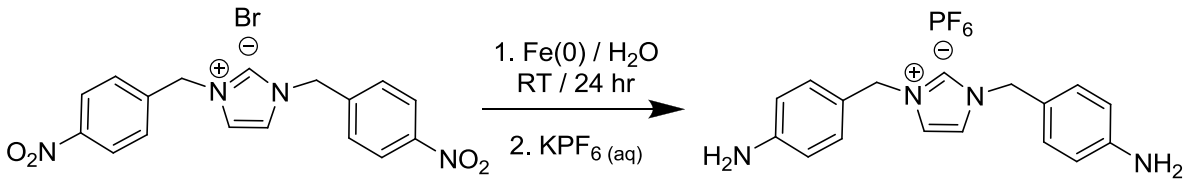


5.3.1 Synthesis of 1,3-bis(4-nitrobenzyl)-1*H*-imidazol-3-ium bromide, 4



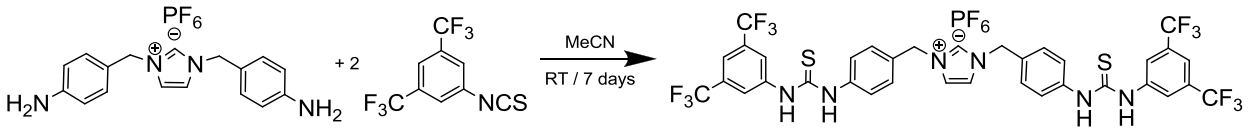
4-nitrobenzyl bromide was dissolved in the appropriate volume of acetonitrile (approx. 25 mL/g of 4-nitrobenzyl bromide) in a round bottom flask and stirred. The calculated volume of 1-(Trimethylsilyl)imidazole necessary (1:2 ratio) was added to the flask and stirring continued. A condenser was attached and the solution heated to 70°C. The solution was stirred for 48 hours. If any solid precipitated, it was collect by suction filtration and recrystallized in 70°C water to obtain the product. The remaining filtrate (or the original solution if nothing crashed out) was placed on the rotovap and the solid obtained was recrystallized as described above. The product was dried under high-vac. (3.36 g, 35 % yield). MP 212.5-214.4 °C, IR (KBr): 1346 & 1518 cm^{-1} (Nitro) ; ^{1}H NMR (DMSO-d_6, 300MHz) δ 9.62 (s, 1H), 8.29 (d, J=8.6 Hz, 4H), 7.97 (s, 2H), 7.73 (d, J=8.6 Hz, 4H), 5.69 (s, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 148.1, 142.4, 137.7, 130.2, 125.4, 123.7, 51.6.

5.3.2 Synthesis of 1,3-bis(4-aminobenzyl)-1*H*-imidazol-3-ium hexafluorophosphate (V), 5



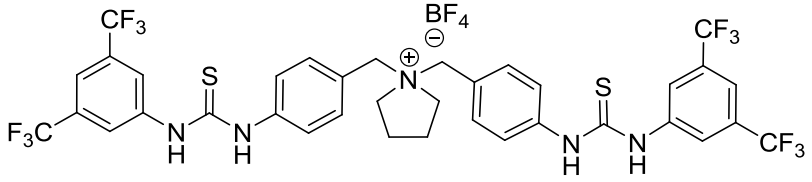
4 (2 g or less) was measured and the appropriate masses of iron sulfate, sodium citrate, and sodium borohydride was calculated based on a 1:6:0.5:12 ratio respectively. Iron sulfate and sodium citrate was dissolved in dH_2O (approximately ½ of the round bottom with a large stir bar in it; the stir bar must be large to allow for maximum attraction of the formed Fe(0)). Sodium borohydride was added a spatula tip at a time; reduced Fe(0) formed immediately (a black solid). This mixture was left to stir for a few minutes, the stirring was then stopped and the iron was allowed to settle to the bottom of the flask. As much water as possible was slowly and carefully decanted (without losing iron). The flask was filled half-way with dH_2O again, stirred, decanted and repeated once more. The dinitro pyrrolidinium bromide compound was added by a weigh paper funnel so as to allow as much of the solid as possible to land on the iron. The compound was slowly stirred into solution and the sides of the flask rinsed with water if necessary. The flask was capped. 24 hours later the mixture was poured through a medium pore frit by suction. Aqueous KPF_6 solution (1:1.25 mole ratio reduced product:KPF_6) was prepared in a vial and added dropwise to the aqueous solution from the frit. A white solid precipitated out of solution which was obtained by suction filtration and placed *in vacuo* for drying. (0.28 g, 64 % yield "1 step" method = 1.060g, 83% yield). MP 127.5-129.5 °C, IR (KBr): 3493 & 3395 cm^{-1} (Primary amine), 857 & 559 cm^{-1} (PF_6); ^{1}H NMR (DMSO-d_6, 300MHz) δ 9.17 (s, 1H), 7.68 (d, 2H), 7.10 (d, J=8.40 Hz, 4H), 6.56 (d, J=8.40, 4H), 5.27 (s, 4H), 5.16 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 149.8, 135.5, 130.2, 122.8, 121.4, 114.3, 52.6; ^{31}P NMR (DMSO-d6, 121MHz) δ -144.2 (septet, J=712.2 Hz); ESI-MS: Positive Mode Found: m/z 106.1 [100.0% ($C_7H_8N^+$)]; Calc. 106.1; 279.1 [75.5% ($C_{17}H_{19}N_4^+$)]; Calc. 279.4; 174.0 [69.1% ($C_{12}H_{10}N^+$)]; Calc. 174.1; Negative Mode Found: m/z 144.6 [100% (PF_6^-)]; Calc 145.0.

5.3.3 Synthesis of 1,3-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1H-imidazol-3-ium hexafluorophosphate (V), 6

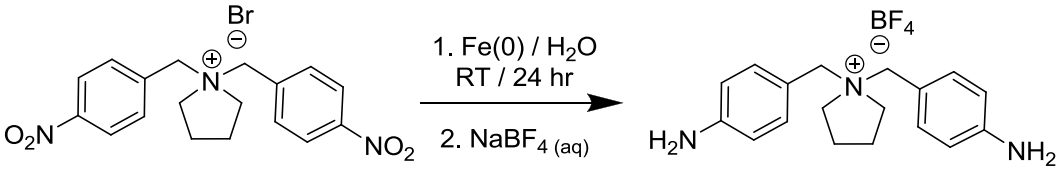


5 was dissolved in acetonitrile in a round bottom flask. The solution was stirred and the appropriate volume of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1:2.5 diamine:isothiocyanate compound) was added. The flask was capped and stirred for 7 days. The solution was placed on rotovap and the resulting solid was heated and dried *in vacuo*. (0.154 g, 68 % yield). ^{1}H NMR (DMSO-d_6, 300MHz) δ 10.34 (s, 2H), 10.29 (s, 2H), 9.42 (s, 1H), 8.24 (s, 4H), 7.84 (s, 2H), 7.80 (s, 2H), 7.54 (d, J=8.6 Hz, 4H), 7.44 (d, J=8.6 Hz, 4H), 5.42 (s, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 179.9, 141.7, 139.3, 136.2, 131.2, 130.3, 128.9, 125.0, 124.3, 123.4, 122.9, 121.4, 51.7; ^{31}P NMR (DMSO-d6, 121 MHz) δ -144.2 (septet, *J*=710.6 Hz); ESI-MS: Positive Mode Found: m/z 821.7 [100.0% ($C_{35}H_{25}F_{12}N_6S_2^+$)]; Calc. 821.7; Negative Mode Found: m/z 144.6 [100% (PF_6^-)]; Calc 145.0.

5.4 Synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl) pyrrolidinium tetreafluroroborate, 8

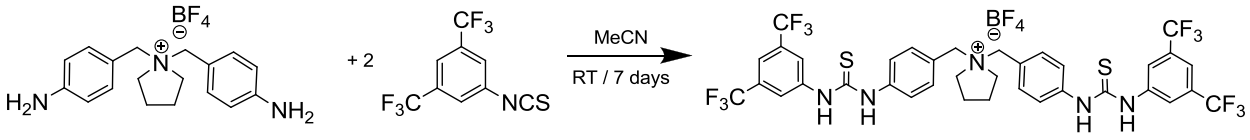


5.4.1 Synthesis of 1,1-bis(4-aminobenzyl)pyrrolidinium tetrafluoroborate, 7



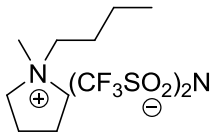
Synthesis of 1,1-bis(4-nitrobenzyl)pyrrolidinium bromide was conducted as described in 5.2.1. 1,1-bis(4-nitrobenzyl)pyrrolidinium bromide was iron-reduced as described in 5.2.2. Rather than using aqueous KPF_6, an aqueous solution of $NaBF_4$ was used instead (1:1.25 mole ratio reduced product:$NaBF_4$). Otherwise, procedure was followed as in 5.2.2. ^{1}H NMR (DMSO-d_6, 300MHz) δ 7.17 (d, 2H), 6.62 (d, 2H), 5.51 (s, 2H), 4.26 (s, 2H), 3.26 (s, 2H), 1.92 (s, 2H).

5.4.2 Synthesis of 1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl) pyrrolidinium tetreafluroroborate, 8



7 was dissolved in acetonitrile in a round bottom flask. The solution was stirred and the appropriate volume of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1:2.5 diamine:isothiocyanate compound) was added. The flask was capped and stirred for 7 days. The solution was placed on rotovap and the resulting solid was heated and dried *in vacuo*.

5.5 Synthesis of the ionic liquid 1-butyl-1-methylpyrrolidinium bis (trifluoromethylsulfonyl)imide [BMPyr][N(Tf)$_2$]

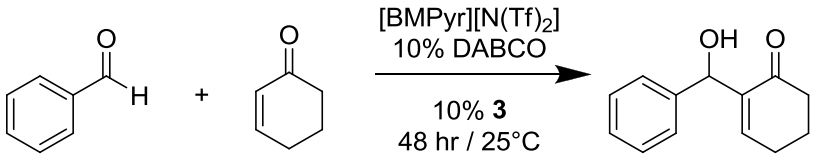


The procedure for the preparation of the ionic liquid was adapted from Cheng, J.P. *et al*.[51]10 mL of ethyl pyrrolidine, 20 mL of acetonitrile and 10.1 mL of 1-bromobutane were added to a 100 mL long neck round bottom flask and attached to a condenser. The reaction flask was placed in the microwave at 40 W power and stirred at 80 °C for 1 hour. The reaction mixture was then placed in a beaker and enough acetonitrile was added to dissolve the solid precipitate. An equal volume of ethyl acetate was added and solid product crashed out of solution. The resulting mixture was passed through a frit and washed with ethyl acetate. The resulting solid was transferred by a dry funnel to a pre-weighed round bottom flask. The flask was put under nitrogen and then under vacuum for further drying. The solid was dissolved in 100 mL of water and combined with 19.1 g of $LiNTf_2$ dissolved in water. The combined solution was stirred at room temperature for 48 hours. The resulting viscous liquid was washed in the round bottom with water. The washings were repeated until no more bromine remained in solution, indicated by negative results from a silver nitrate test.

5.6 Morita-Baylis-Hillman Reactions

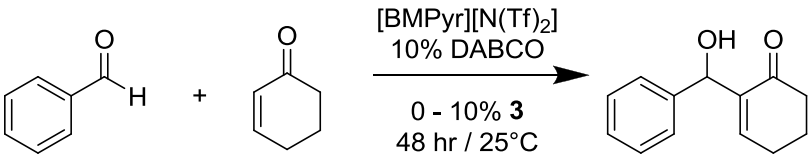
5.6.1 General Morita-Baylis-Hillman reaction procedure

1,1-bis(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)pyrrolidinium hexafluorophosphate(V), 3, was tested for catalytic ability in the Morita-Baylis-Hillman reaction.



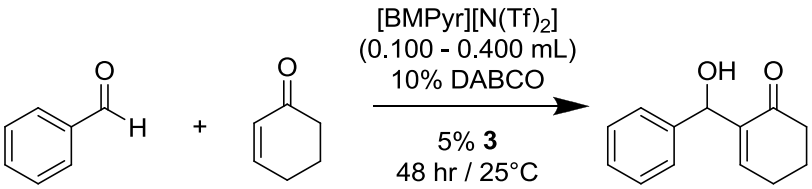
97 mg (10 mol %) of **3** was added to a 25 mL two-neck round bottom flask. 1 mmol (0.102 mL) of cyclohex-2-en-1-one and 0.100 mL of the ionic liquid [BMPyr][$N(Tf)_2$] were added to the flask and stirred at 100 rpm until (3) dissolved. 0.2 mmol of benzaldehyde was added (20.3 µL) to the stirring flask. 11 mg (10 mol %) DABCO was added, dissolved, sealed, and filled with nitrogen. The reaction was stirred for 48 hours at which point 2 mL of diethyl ether was added and stirred for 10 minutes to extract the organic products and any unreacted starting material. 5 drops of the ether layer were analyzed by ^{1}H-NMR. The % conversion to product was determined through normalization of the integrated proton peaks for the benzaldehyde proton (~10 ppm in $CDCl_3$) and the benzylic proton of 2-(hydroxyl(phenyl)methyl)cyclohex-2-enone (~5.5 ppm in $CDCl_3$). These singlet peaks in the ^{1}H-NMR are clearly distinguishable from all other peaks in the spectrum and thus serve as appropriate indication of conversion to the desired product.

5.6.2 Effect of catalyst loading procedure



This above description of the MBH procedure was repeated with a range of catalyst loadings. The catalyst loadings (and masses) were as follows: 7.5 % (73 mg), 5 % (48 mg) and 2.5 % (24 mg). A control reaction was conducted containing DABCO and no **3** as a co-catalyst.

5.6.3 Effect of concentration of reaction component procedure



The above description of the MBH procedure was repeated using 5 mol % **3** (48 mg) and a range of volumes of the ionic liquid, 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide [BMPyr][$N(Tf)_2$]. The volumes used included 0.100 mL, 0.200 mL, 0.300 mL, and 0.400 mL.

5.6.4 Recycling studies

Recycling studies were also conducted. Following the initial MBH reaction, the organic compounds were extracted with 5 x 2 mL volumes of diethyl ether with an understanding that the catalyst would remain entrained in the ionic liquid. Cyclohex-2-

en-1-one, benzaldehyde and DABCO were then added and the procedure followed as described in procedure for the initial test.

5.6.5 Microwave irradiation of MBH reactions

The catalyst, substrates, ionic liquid and DABCO were introduced to the microwave test-tube reaction vessel in the same order and manner as was with the round bottom flask described in the general MBH procedure section. The tube, containing a small stir bar, was capped and inserted into the CEM Discover SP microwave reactor. Synergy software was used to adjust reaction time, temperature, and power according to the parameters presented in Table 4 (Results).

5.6.6 Thermal degradation of the catalyst

To test the thermal stability of **3**, a small sample of **3** was first stirred in a microwave reaction tube in enough [BMPyr][$N(Tf)_2$] to dissolve. 5 drops were collected in a vial by pipette and a d-DMSO NMR sample was prepared. The **3** dissolved in [BMPyr][$N(Tf)_2$] was then placed in the microwave and heated at 100 °C for 4 hours. Following the reaction, 5 drops were collected in a vial by pipette and another d-DMSO NMR sample was prepared. The ^{1}H-NMR spectra obtained were then stacked on Topspin software in order to compare the spectroscopic features of the two samples.

6.0 References

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