WATER AND CARBON DIOXIDE FOR SUSTAINABLE SYNTHESIS AND SEPARATION OF PHARMACEUTICAL INTERMEDIATES

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For my family, who always supported and motivated me.

-In special, to my husband and daughter-

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LIST OF ABBREVIATIONS

Ac	Acetyl
ACD	Advanced chemistry development software
ACN	Acetonitrile
$Al(OEt)_3$	Aluminum ethoxide
$Al(O\textit{i}Pr)_3$	Aluminum *iso*-propoxide
$Al(O\textit{t}Bu)_3$	Aluminum tri-*tert*-butoxide
Ar	Argon
BHT	3,5-di-tert-butyl-4-hydroxytoluene
Boc	*Tert*-butylcarbamate
Boc_2O	di-*tert*-butyl dicarbonate
Br	Bromides
C	Carbon
CBz	Benzylcarbamate
$CDCl_3$	Deuterated chloroform
CHO	Formyl group
Cl	Chloride
CO	Carbon monoxide
CO_2	Carbon dioxide
COSMO-RS	Conductor-like screening model for realistic solvation
d	Doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	Diisopropyl ethylamine
DMSO	Dimethyl sulfoxide
eq	Equivalent
Et_2O	Diethyl ether
EtOH	Ethanol
GCMS	Gas chromatography – mass spectrometry
GXL	Gas-expanded liquid
H_2	Hydrogen
H_2O	Water
HCl	Hydrochloric acid
HPLC	High-performance liquid chromatography
I	Iodide

*i*PrOH	Isopropanol
K_2CO_3	Potassium carbonate
K_2HPO_4	Di-potassium phosphate
K_3PO_4	Tri-potassium phosphate
$K_4P_2O_7$	Potassium pyrophosphate
$KHCO_3$	Potassium bicarbonate
$KHPO_4$	Mono-potassium phosphate
LCMS	Liquid chromatography – mass spectrometry
m	Multiplet
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
mp	Melting point
MPV	Meerwein-Ponndorf-Verley
N_2	Nitrogen
NMR	Nuclear magnetic resonance (spectroscopy)
OATS	Organic-aqueous tunable solvents
OMe	Methoxy
OTf	Triflates
Pd	Palladium
$Pd(OAc)_2$	Palladium acetate
$Pd(TPP)_2Cl_2$	Palladium bistriphenylphosphine dichloride
$Pd(TPP)_4$	Palladium tetrakis
pH	measure of the acidity or basicity of an aqueous solution
Ph	Phenyl
$PhB(OH)_2$	Phenylboronic acid
$PhB(OH)_3^-$	Trihydrophenyl borate
Piv	Pivaloyl
pKa	acid dissociation constant at logarithmic scale
$Rh(acac)_3$	Rhodium(III) acetylacetonate
s	Single
TBME	*Tert*-butylmethylether
TEA	Triethylamine
THF	Tetrahydrofuran
TPP	Triphenylphosphine
TPPMS	Monosulfonated triphenylphosphine ligand
TPPTS	Trisulfonated triphenylphosphine ligand
UV-Vis	Ultraviolet-visible (spectroscopy)
WET	Water at elevated temperatures
X	Halogen

δ	NMR frequency
% v/v	Percent by volume
^{13}C NMR	Carbon NMR
^{1}H NMR	Proton NMR

SUMMARY

The research projects presented in this thesis are mainly focused toward green chemistry and engineering: developing innovative strategies to minimize waste, improve process efficiency and reduce energy consumption. Specifically, the work was centered on the design and applications of green solvents and processes for the sustainable production of pharmaceuticals.

The first research project investigated the use of CO_2 to enhance Suzuki Coupling reactions of substrates containing unprotected primary amines. The coupling reactions involving primary amine substrates suffer from low yields. The low catalyst activity in these reactions is attributed to the binding of the primary amines to the metal center and deactivating the catalyst. It has been shown that amines can react with CO_2 to form an ammonium-carbamate ion pairs, which can be used to temporarily protect primary amines. As a consequence, the use of CO_2 at a variety of pressures was evaluated as a reversible protecting/activating reagent for substrates containing primary amine groups. Detailed studies on the conditions necessary to perform Suzuki coupling reactions under CO_2 pressures, and a highly efficient and general Suzuki coupling reaction between phenylboronic acid and NH_2-unprotected halogenated pyridines under CO_2 are presented.

The use of water at elevated temperatures (WET) for the sustainable and selective removal of protecting groups was explored in the second project. Chemical processing in WET is possible because of the favorable changes that occur in the chemical and physical properties (*i.e.* density, dielectric constant and ionization constant) at high temperatures and pressures (125-275°C). Water is an attractive solvent for the development of

sustainable, environmentally green processes for the removal of protecting groups. The synthesis of pharmaceutical and natural product compounds and intermediates relies heavily on the use of protecting groups because of the inherent complexity and multifunctional nature of the target molecules. The water-mediated selective removal of protecting groups such as N-Boc, N-Acetyl and O-Acetyl from a range of organic model compounds was successfully achieved using only WET.

Organic-Aqueous Tunable Solvents (OATS) for the rhodium catalyzed hydroformylation of *p*-methylstyrene was investigated in the third project. OATS combine the benefits of homogeneous and heterogeneous catalysis while overcoming their respective limitations. This enables the reactions to be carried out efficiently under homogeneous conditions, followed by a carbon dioxide (CO_2) induced heterogeneous separation. Modest pressures of CO_2 induces the aqueous-rich phase (containing the catalyst) to separate from the organic-rich phase (containing the reactant), thus enabling an easy separation and the recycling of catalyst.

Continuous flow processes have gained considerable momentum in the recent years for the production of fine chemicals and pharmaceutical intermediates due to their economic and environmental benefits. The fourth project established that $Al(O\mathit{t}Bu)_3$ is a potent catalyst toward Meerwein-Ponndorf-Verley (MPV) reductions, thus enabling continuous technology as a viable approach. The MPV reduction of model compounds like benzaldehyde and acetophenone to their corresponding alcohols was investigated in continuous mode as a function of temperature and catalyst loading. These results establish a roadmap for the pharmaceutical industry to document the implementation of continuous flow processes in their manufacturing operations.

CHAPTER 1 - INTRODUCTION

Individuals and organizations are consistently becoming more aware of the growing need for more sustainable products and processes, and green chemistry and engineering has emerged as a definitive answer to that need. Green chemistry consists of chemicals and chemical processes designed to reduce or eliminate negative environmental impacts and risks to the human health [1]. It applies across the life cycle of a chemical product, including the design, manufacture, use and disposal. The use and production of these chemicals may involve reduced waste products, non-toxic components, and improved efficiency. Green chemistry is a highly effective approach for pollution prevention. It relies on the utilization of a set of twelve principles or guidelines that provide the framework to greener strategies and they can help to reduce or eliminate the use or generation of hazardous substances in the design, manufacture and application of chemical products (see Figure 1-1) [1, 2].

Green chemistry presents industry with incredible opportunities for growth and competitive advantage. Many environmentally benign alternative technologies have been proven to be economically superior and function as well or better than existing alternatives. The application of green chemistry to a process can reduce significantly the cost. For example, the removal of hazardous materials from a process will eliminate all the hazard-related costs such as those associated with handling, transportation, disposal and compliance. Environmentally benign alternatives to current materials and

technologies can be systematically introduced across all types of manufacturing to promote a more environmentally and economically viable future.

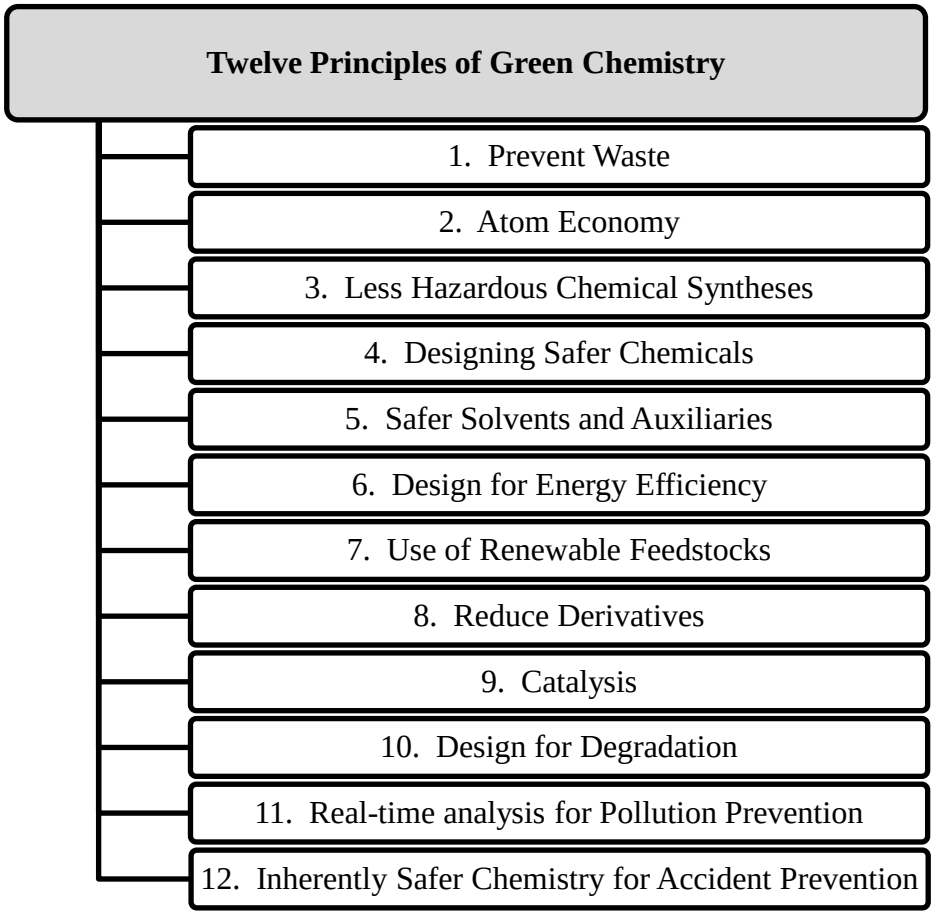

Figure 1-1 The twelve principles of Green Chemistry [1]

As engineers and chemists we have the responsibility and at the same time the ability to make significant changes in the materials that are used, the products made and in the development of processes, to make them safer for the human health and the environment. The green chemistry principles were an integral part in the development of

the four research projects presented in this thesis. Chapter 2 to 5 will discuss in detail the background, experimental work, analysis and conclusions of the different research projects. Among the principles of green chemistry, principles number three, six and eight are the most relevant to this work. Principle number three says that wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment. Principle number six discusses how the energy requirements should be recognized for their environmental and economic impacts and should be minimized; and principle number eight discusses how unnecessary derivatization like blocking groups and protection/deprotection steps should be avoided whenever possible. With these principles in mind, the research projects were mainly focused toward the development of innovative strategies to reduce waste, improve process efficiency and reduce energy consumption. The remainder of this chapter provides a brief background for each of the four research projects and highlights the motivation and goal for the different projects presented in later chapters.

Chapter 2 of this thesis work reports the first studies of progress of Suzuki coupling reaction as a function of CO_2 pressures. This palladium-catalyzed reaction between aryl halides with organoboronic acids allows for the construction of C-C bonds and is one of the most important of both academic and industrial interest [3]. Although this reaction tolerates a wide variety of functional groups, only a few reports can be found on successful Suzuki coupling reactions that possess unprotected amino groups on a heteroaryl substrate. It has been reported that for the success of the transformation and to prevent the possible competitive binding of the substrate with the palladium catalyst, either the primary amine group needs to be protected before the coupling process [4] or

highly active catalyst systems must be employed[5-10]. On the other hand, carbon dioxide (CO_2) can interact with certain functional groups such as amines to reversibly form carbamate or carbamic acid species that can be used to temporarily protect primary amines under CO_2 pressures and avoid the need of costly deprotection steps (see Figure 1-2) [11-14]. In Chapter 2, I shall discuss the different experiments performed to optimize the Suzuki reaction under CO_2 and also the results of the first highly efficient and general Suzuki coupling reaction between phenylboronic acid and unprotected amino halo pyridine substrates under CO_2.

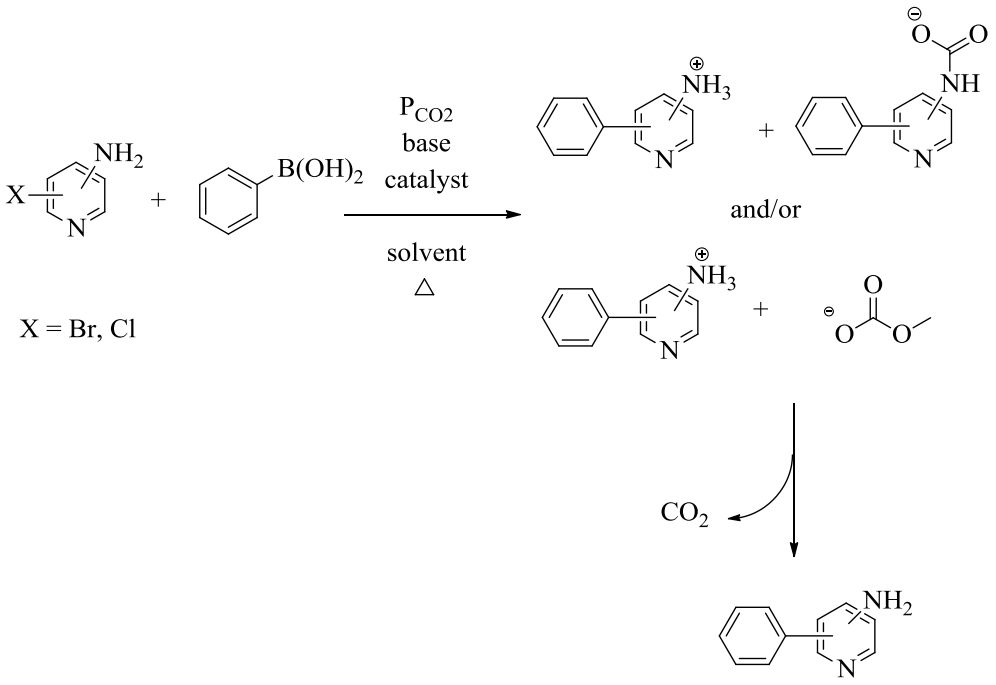

Figure 1-2 Suzuki coupling of CO_2 *in-situ* protected amine substrates

Chapter 3 explores the capabilities of water at elevated temperatures (WET) to act as a solvent, reactant and catalyst in the removal of protecting groups. The synthesis of

complex molecules like pharmaceuticals relies heavily in the use of blocking or protecting groups and their removal requires the addition of strong acids and bases. The excess of acid or base need to be subsequently neutralized and it can produce large amount of waste. While from a green chemistry point of view it would be preferable to develop selective reactions which do not require protecting groups, the reality is that this is not always possible. As a consequence, the development of green protocols for the protection and subsequent removal of these groups have become important considerations. The chemical and physical properties of water at elevated temperatures (WET) change drastically compared to common organic solvents; and also have a higher concentration of hydronium and hydroxide ions that are available to act as catalysts [15-17]. By simultaneously employing WET as the reaction solvent and catalyst, the need for environmentally hazardous solvents and acid catalysts are eliminated. This investigation provide insights into WET's capacity to be used for the deprotection of individual protecting groups as well as the competitive and selective deprotection of molecules containing two different protecting groups (see Figure 1-3).

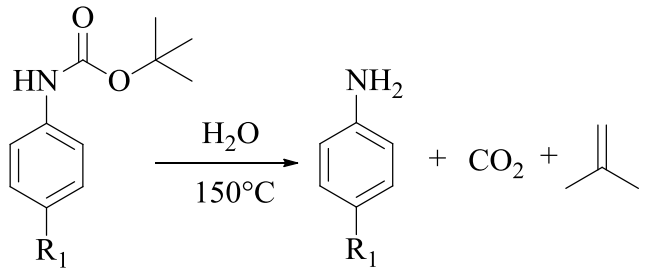

Figure 1-3 Removal of the N-Boc protecting group using WET at 150°C

In Chapter 4, I will discuss the use of organic-aqueous tunable solvents (OATS) for the hydroformylation of *p*-methylstyrene and the catalysts recycle [18]. OATS is a tunable solvent system that can offer an efficient, simple, and sustainable method for coupling homogeneous reactions with heterogeneous separations [19-26]. Their properties can often be varied by tuning the applied pressure or temperature of the system. Reactions are carried out under homogeneous conditions, followed by a CO_2-induced heterogeneous separation. Then, the polar protic component (aqueous-rich phase) containing the catalyst phase separates from the aprotic (relatively nonpolar) component (organic-rich phase, usually tetrahydrofuran or acetonitrile) containing the reactant, facilitating the separation and the recycle of catalyst. OATS can offer improved reaction rates, yields, and selectivity characteristics of homogeneous systems as well as simple catalyst separations and recycle characteristics of heterogeneous separations (see Figure 1-4). As an example, the Rh-catalyzed hydroformylation of an aromatic olefin, *p*-methylstyrene, was performed in OATS.

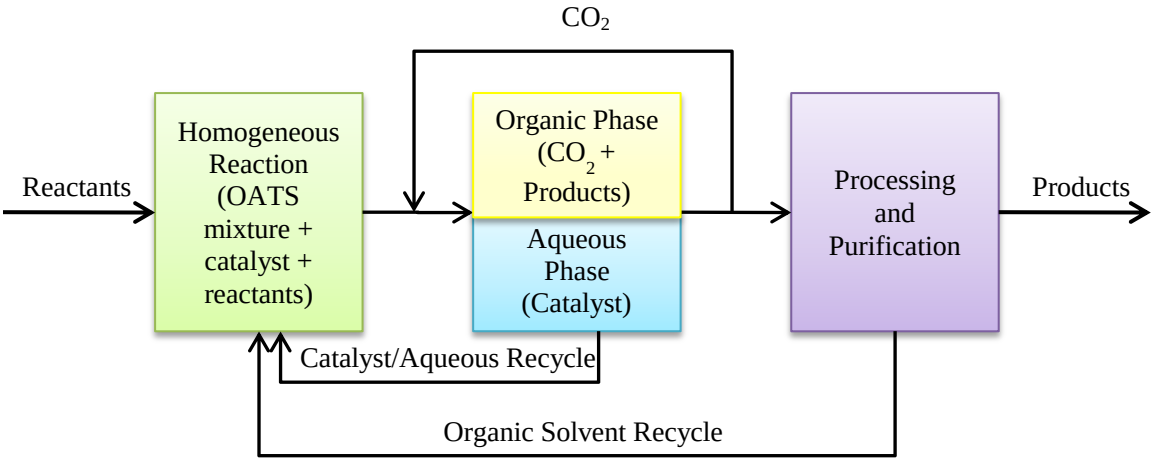

Figure 1-4 General scheme for reactions using OATS

The continuous Meerwein-Ponndorf-Verley (MPV) reductions of benzaldehyde and acetophenone will be discussed in Chapter 5. Although the pharmaceutical industry has long favored batch processing, continuous flow processes can offer a facile and fast reaction screening that will lead to the identification of promising drug candidates, optimum reaction conditions and to scale the reaction to manufacturing [27]. Continuous processing can also reduce costs, reduce the size of process equipment, improve product quality, reduce energy consumption, solvent utilization, and waste generation [28]. It can offer an improved product quality and consistency versus batch operations which are run dynamically. The Meerwein-Ponndorf-Verley (MPV) reduction is a chemical transformation that is currently run batch-wise by the pharmaceutical industry. This reaction is a commonly used pathway in the production of alcohols from ketones and aldehydes. The enhanced mass and heat transfer offered by continuous processing are beneficial to optimize the reaction in terms of concentration of reagents, catalyst and reaction time. The optimization and successful transfer of the MPV reduction of benzaldehyde and acetophenone from batch to continuous process will be presented in this chapter. A commercially available glass flow reactor, Corning® Advanced-Flow™ reactor was used for our experiments (see Figure 1-5).

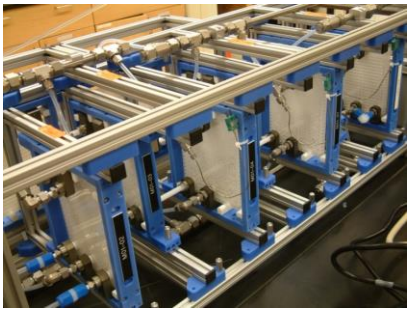

Figure 1-5 Corning® Advanced Flow™ Reactor

Finally, Chapter 6 provides a summary of the conclusions of this research work. It also includes recommendations made for exploring the opportunities offered from the various investigations presented herein.

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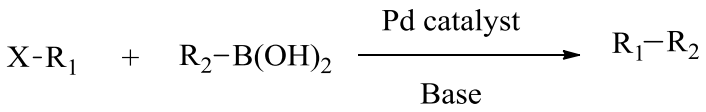
CHAPTER 2 - SUZUKI COUPLING REACTIONS AS A FUNCTION OF CO_2 PRESSURES

2.1 Introduction

Carbon-carbon bond formation reactions are important in chemistry, because they provide key steps in the building of complex, bioactive molecules developed as medicines and agrochemicals. The Suzuki coupling reaction has become one of the most widely employed carbon-carbon bond forming processes [1-3]. This palladium-catalyzed reaction between aryl halides with organoboronic acids allows for the construction of C-C bonds and is of both, academic and industrial interest (see

Figure 2-1). Its popularity is attributed to the stability and weak nucleophilic nature of the organoboron compounds. It tolerates a wide range of functional groups and is highly chemoselective. Furthermore, boron compounds are generally non-toxic, and the reaction can be run under very mild conditions [2]. Moreover, the inorganic by-product of the reaction is non-toxic and easily removed from the reaction. In addition, biaryl compounds play an important role in industrial chemistry, appearing in commercial products ranging from performance materials to pharmaceuticals.



X= I, OTf, Br, Cl

Figure 2-1 Generalized Suzuki coupling reaction

The Suzuki coupling reaction of an organoboron compound with an organohalide in the presence of a catalytic amount of palladium (0) complex leads to the formation of a new carbon-carbon single bond. The Suzuki coupling reaction was first published in 1979 by Akira Suzuki and the reaction also goes by the name of Suzuki-Miyaura reaction. The 2010 Nobel Prize in Chemistry was awarded in part to Suzuki for his discovery and development of this reaction [4]. His discovery had a great impact on academic research, the development of new drugs and materials, and is used in many industrial chemical processes for the synthesis of pharmaceuticals and other biologically active compounds. Figure 2-2 shows the mechanism of the homogeneous palladium-catalyzed Suzuki coupling reaction. The first step is the oxidative addition of the Pd(0) to the organic halide to form the organo-palladium halide species. The oxidative addition is often the rate-limiting step in the catalytic cycle and the relative reactivity of aryl halides decreases in the order of I > OTf > Br >> Cl. This reactivity is largely influenced by the proximity of electron withdrawing or donating groups. This is followed by metathesis, in which the base displaces the halogen on the palladium metal center. Base activation of the organoboron reagent as boronate intermediate facilitates the transfer of the organic group from boron to palladium, and this step is known as transmetallation. In this way the two organic groups are assembled on the same palladium atom via palladium-carbon bonds. In the final step, the two organic groups couple with one another to give a new carbon-carbon single bond, which subsequently is released from palladium. In the final step, Pd(II) is reduced to Pd(0), and is called reductive elimination. The energetics of the individual steps in this catalytic process are very dependent upon the specific reagents and conditions employed.

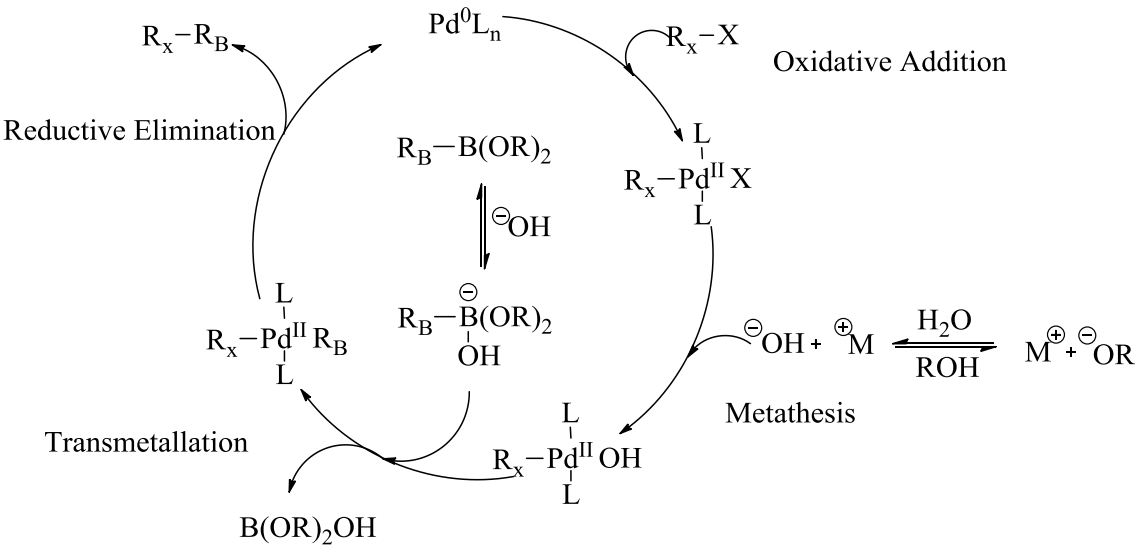


Figure 2-2 Catalytic cycle for Suzuki coupling of an organic halides and organoboranes in the presence of a hydroxyl base

The Suzuki coupling reaction rate can be influenced by several factors [2]. Some studies have shown that the reaction rate is influenced by the pH of the reaction mixture. As an example they showed that the use of K_2CO_3 instead of $KHCO_3$ increased the reaction rate [5]. In addition Smith et al. showed that the coupling was efficient when the base had a pKa close to 10, whereas it failed when the base had a pKa around 6 [6]. Considering the pKa of phenylboronic acid (pKa= 8.8), the authors explained that when the pH was greater than 9, phenylboronic acid was transformed into trihydrophenylborate ($PhB(OH)_3^-$). They believe this anion was the reactive species rather than the neutral boronic acid. They also proved that both, water and base are required to activate the boronic acid.

Despite the advances of the Suzuki coupling reaction, most of the reports of palladium-catalyzed coupling described the use of organic bromides, iodides and triflates. Organic chlorides are noticeably uncommon partners, despite the fact that among the halides, chlorides are arguably the most useful single class of substrates, because of their low cost and the wider diversity of available compounds [3]. Unfortunately, chlorides are generally unreactive under the conditions employed to couple bromides, iodides and triflates. The low reactivity of chlorides is usually attributed to the strength of the C-Cl bond (bond dissociation energies for Ph-X: Cl: 96 kcal mol^{-1}; Br: 81 kcal mol^{-1}; I: 65 kcal mol^{-1}) [7]. Also, byproducts such as self-coupling products, homocoupling products and coupling products of phosphine bound aryl are often formed [8]. The use of bulky ligand is sufficient to inhibit this type of side reactions and deliver high yields of the desired product. Also, the use of oxygen-free conditions prevents the formation of homocoupling products [9].

Several Suzuki couplings are carried out on intermediates which have an amine group that do not participate in the chemistry, but can interfere with the Suzuki reaction. Nitrogen based heterocycles are ubiquitous in the synthesis of pharmaceutical and agrochemical compounds, but the inclusion of these heterocyclic structures has been particularly detrimental to catalyst activity when palladium is used. The low catalyst activity in these reactions is due to the binding of the primary amine to the metal center and deactivating the catalyst. Therefore, coupling reactions involving primary amines suffers from low yields. Furthermore, the propensity for coordination to the palladium increased as the basicity of the substrate increased [10], making the 4-amino-2-halopyridine an exceptionally challenging substrates for Suzuki coupling reactions. Only

a few reports can be found on the successful Suzuki coupling reactions that possess unprotected amino groups on a heteroaryl substrate.

The success of the transformation requires preventing the competitive binding of the substrate with the palladium catalyst, so the primary amine group needs to be protected before the coupling process [11] or one must employ highly active catalyst systems [10, 12-16]. For substrates containing free amines, it is common practice to protect these functional groups prior to the coupling process and these must, correspondingly, be deprotected following the organometallic reaction. Thus, when a protecting group is used, a protection/deprotection sequence is required. These protection/deprotection steps add significantly to the processing, batch cycle times, material requirements, and consequently the overall cost of the manufacturing of these products. Similarly, the use of highly active catalyst systems adds significantly to the cost of the process.

Carbon dioxide (CO_2) is readily available, inexpensive, non-toxic, nonflammable, environmentally acceptable and chemically inert under many conditions. CO_2 does, however interact with certain functional groups and can thus impact the chemical transformation. For example, it is well known that amines react with CO_2 to form ammonium-carbamate ion pairs (see Figure 2-3) [17]. The reversible formation of the carbamate or carbamic acid can be used to protect temporarily primary amines under CO_2 pressures and avoid the need of costly deprotection steps [18-21]. If CO_2 reacts with the primary amine (NH_2) of substrates that will undergo Suzuki coupling reaction, it can dramatically reduce the possibility of the NH_2 group coordinating to the Pd catalysts, then, increasing the efficiency of the reaction. Herein, I report detailed studies on the conditions necessary to perform Suzuki coupling reactions under CO_2 pressures and the

first highly efficient and general Suzuki coupling reaction between phenylboronic acid and NH_2-unprotected halogenated pyridines under CO_2.

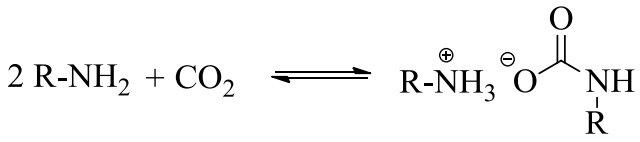


Figure 2-3 Reaction of an amine with carbon dioxide

2.2 Experimental Methods

2.2.1 General

All reagents were purchased from commercial sources as a reagent grade and were used without further purification. Solvents were degassed by sparging with nitrogen (N_2) or argon (Ar), or by conducting three cycles of freeze-pump-thaw method. Reactions were monitored by GCMS (HP6890 GC and a HP5973 MS) and by HPLC (HP1100 HPLC-UV instrument). All chromatographic data were quantified by using calibration curves of the standards. Proton and carbon NMR spectra were used to corroborate the results. NMR spectra were recorded on a 400 MHz Varian NMR.

2.2.2 Experimental Apparatus and Procedure

2.2.2.1 Typical procedure for reactions using $Pd(OAc)_2$ as the catalyst

The phenylboronic acid (1.2 eq), $Pd(OAc)_2$ (3 mol%), TPP (6.3mol%), K_2CO_3 (2.1 to 3 eq) were combined in a three-neck round bottom flask. The flask was purged with Ar for 15 minutes. A total of 25 mL of degassed solvent was added to the reaction flask in the appropriate ratio of THF:water. Bromobenzene (0.5M, 1 eq) was added to the reaction mixture which was then heated to 50°C. After 4 to 24 hours, the reaction mixture was cooled and an aliquot (100 μL) was taken for GCMS analysis. The reaction mixture was extracted with ethyl acetate (2 x 25 mL). The combined fractions were washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude organic product was analyzed by ^1H and ^{13}C NMR.

2.2.2.2 Typical procedure for reactions using $Pd(PPh_3)_4$ as the catalyst

The phenylboronic acid (1.2 eq), $Pd(TPP)_4$ (5 mol%), K_2CO_3 (3 eq), 4-bromotoluene (0.5M, 1 eq) were combined in a three-neck round bottom flask. The flask was purged with N_2 for 15 minutes. A total of 25 mL of degassed solvent was added to the reaction flask with the appropriate ratio of THF:water and was then heated to 50°C. After 4-24 hours, the reaction mixture was cooled and an aliquot (100 μL) was taken for HPLC analysis. The reaction mixture was extracted with ethyl acetate (2 x 25 mL). The combined fractions were washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude organic product was analyzed by ^1H and ^{13}C NMR.

2.2.2.3 Typical procedure for reactions using $Pd(TPP)_2Cl_2$ and K_3PO_4

The phenylboronic acid (1.3 eq), 4-amino-2-bromopyridine or 4-amino-2-chloropyridine (0.4 M, 1 eq), $Pd(TPP)_2Cl_2$ (5 mol%) and potassium phosphate (3-4 eq) were added sequentially to a reaction vessel (three-neck round bottom flask for N_2 reactions or the Parr reactor for CO_2 reactions). The vessel was then sealed and purged with N_2 or CO_2 for 15 minutes while stirring. Degassed acetonitrile was then added to the vessel and the reaction mixture was then heated to 50°C for 24 to 48 hours. After the reaction time, the reaction mixture was cooled to ambient temperature and depressurized. The total reaction mixture was then transferred to an external flask for work-up. Two different work-up procedures were employed, an acetonitrile/toluene/water and a methanol work-up. The acetonitrile/ toluene/water work-up consisted of the addition of some amount of water and acetonitrile to the mixture to fully transferred the solution, then small amounts of toluene were added to fully extract organic residues from the aqueous phase (liquid-liquid extraction). The methanol work-up consisted of the addition of methanol to the mixture for transferring and in addition the methanol used will cause the precipitation of any salt used or formed during the reaction and results in a single liquid phase (solid-liquid extraction). After the work-up, an aliquot of 1mL of the organic phase was taken for GC-FID or GCMS analysis. The remaining organic phase was concentrated under vacuum. The crude organic product was analyzed by ^{1}H and ^{13}C NMR.

2.3 Results and Discussion

The coupling of aryl halides with organoboronic acids is one of the most important palladium-catalyzed cross-coupling reactions. The Suzuki reaction has become one of the most widely employed carbon-carbon bond forming processes [1-3]. It has been shown in the literature that the coupling reaction involving primary amines suffered from low yields. The low catalyst activity in these reactions is due to the binding of the primary amine to the metal center. For substrates containing primary amines, it is common practice to protect these functional groups prior the coupling step [11] or use highly active catalyst systems [10, 12-14]. Our goal is to employ CO_2 to enhance the Suzuki coupling reactions of substrates containing primary amines in special halogenated amino pyridines. Detailed studies to understand better the optimum reaction conditions and the effect of CO_2 were performed. Several control reactions as well as reactions as a function of CO_2 pressures will be discussed in the following sections. The reaction progress of the different conditions was monitored by HPLC and/or GCMS.

2.3.1 Water Effect

The availability of the reagents and the mild reaction conditions contribute to the versatility of the Suzuki coupling reaction. The coupling reaction offers several additional advantages, such as being largely unaffected by the presence of water and oxygen, tolerating a broad range of functional groups and proceeding generally regio- and stereo selectively. In fact, Suzuki coupling reactions in aqueous media with different types of ligands and under ligandless conditions have been successfully reported in the literature [22, 23]. The amount of water added to the coupling is beneficial to enhance

the kinetics by reducing any mass transfer effects. Most of the bases that have been proven to be very successful for the Suzuki coupling reactions are inorganic bases, where the water will help to fully solubilize them. Moreover, water will serve as a source of hydroxide ions which could play multiple roles in the catalytic cycle. For example, it has been postulated that an increase in the hydroxide ion concentration will increase the rate of reductive elimination (reduction from Pd(II) to Pd(0)) [24]. However, the use of water with the addition of carbon dioxide (CO_2) to study Suzuki coupling reactions as a function of CO_2 pressures might be detrimental. CO_2 can react with water to form carbonic acid (see Figure 2-4). Then, carbonic acid can react with the inorganic base to form carbonate and bicarbonate and at the same time reduce the amount of available hydroxide ions. To understand the effect of added water in the Suzuki coupling reaction, we performed several baseline reactions using substrates which did not contain basic nitrogen atoms as a function of added water.

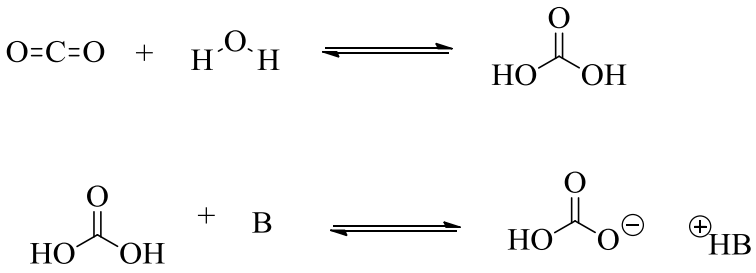


Figure 2-4 Formation of carbonic acid from the reaction of CO_2 and water

Initially, we investigated the effect of added water in the coupling reaction of bromobenzene with phenylboronic acid. In this reaction we used potassium carbonate (K_2CO_3) as the base, $Pd(OAc)_2$ and triphenylphosphine (TPP) as the catalyst in a mixture of tetrahydrofuran (THF) and water at 50°C for 4.5 hours (Figure 2-5). The reaction progress was monitored by HPLC and the results are summarized in Table 2-1. A significant increase in the reaction rate was observed when small amounts of added water ranging from 1 to 5% v/v were used, when compared to no added water conditions. The reaction was quantitatively completed in 4.5 hours using as low as 5% v/v added water.

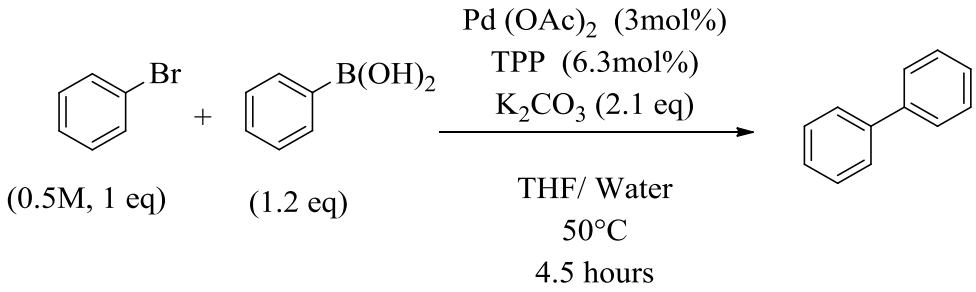


Figure 2-5 Coupling reaction of bromobenzene with phenylboronic acid

Table 2-1 Coupling reaction of bromobenzene with phenylboronic acid as a function of added water

Added Water (%v/v)	HPLC Yield (%)
0	1
1	84
2	87
5	100

Another reaction that was studied as a function of added water was the coupling reaction of 4-bromotoluene with phenylboronic acid, using $Pd(TPP)_4$ as the catalyst and K_2CO_3 as the base (see Figure 2-6). The reaction progress was monitored and quantified by HPLC and the results are summarized in Table 2-2. Similarly, we observed that the reaction rate and catalyst activity are significantly increased with the addition of small amounts of added water. In this specific case, the reactions with no added water achieved only a 9% yield after four hours, whereas quantitative yields were obtained using 2.5% v/v of added water at the same reaction time. These results indicate that small amounts of water are essential to increase the reaction rate and enhance the catalyst activity, but they need to be carefully selected to prevent any quenching of the base and/or consumption of the water. Water will facilitate the solubility of the inorganic base in the system, minimizing mass transfer effects and also will produce hydroxyl ions that have been shown to accelerate the catalytic cycle. It should be emphasized that this conclusion is specific for the substrates and reaction conditions employed in this study.

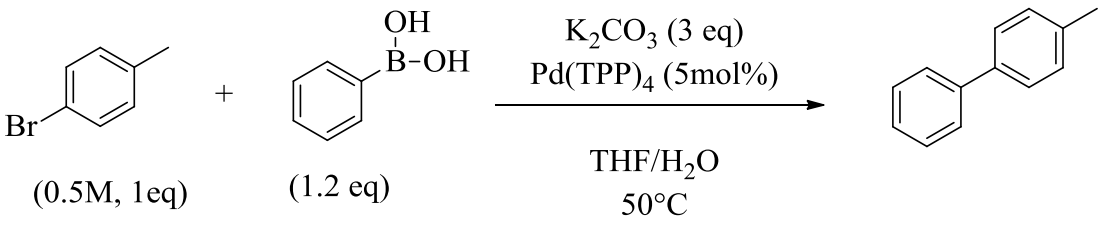


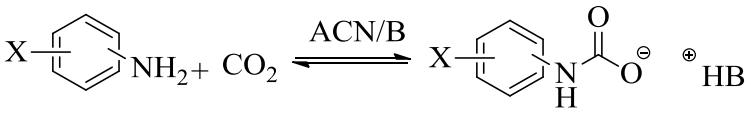
Figure 2-6 Coupling reaction of 4-bromotoluene with phenylboronic

Table 2-2 Reaction progress of the coupling of 4-bromotoluene with phenylboronic acid as a function of added water

Added Water (% v/v)	Time (hours)	HPLC Conversion (%)	HPLC Yield (%)
0	4	0	9
0	24	34	37
2.5	4	95	100
2.5	24	98	98

2.3.2 Base Screening

Experiments performed within our group and other groups showed that the solvent selection for the CO_2 *in situ* protection is very important, and it could even lead to the existence of stable carbamic acid species in the case of using a solvent like dimethyl sulfoxide (DMSO). Moreover, stable CO_2 *in situ* protected benzyl amines as carbamate species were found to be possible with the addition of an organic base like DBU [25]. The amount of base added will help to shift the equilibrium towards the protected compounds, making them less likely to reverse in solution (see Figure 2-7). In addition, the base plays an important role in the catalytic cycle, where two equivalents of the base are required (one equivalent for the metathesis and another equivalent for the transmetallation step). A series of experiments with different organic and inorganic bases were performed to find out the most suitable base system for the Suzuki coupling reaction and for the possible protection of the amine substrates.



X= halogen
B= base

Figure 2-7 Protection strategy with added base

The coupling reaction of 4-bromotoluene with phenylboronic ester (see Figure 2-8) was investigated with the different organic and inorganic bases and the results are summarized in Table 2-3 and Table 2-4. The goal of these experiments was to determine the most suitable base system for (1) possible protection of amine substrates and (2) effective for Suzuki reaction. When an organic base was employed, a solid-liquid heterogeneous mixture was obtained. When an inorganic base was employed, a liquid-liquid heterogeneous mixture was obtained.

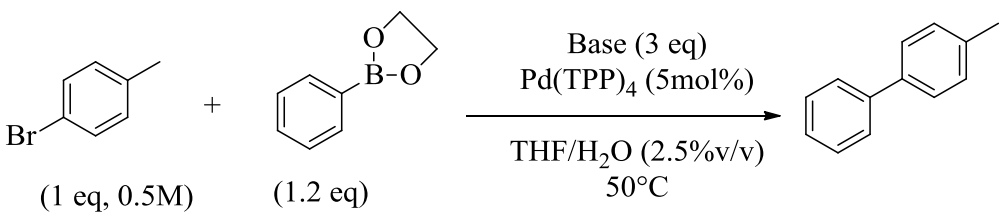


Figure 2-8 Coupling reaction of 4-bromotoluene with phenylboronic ester

Table 2-3 Suzuki coupling of 4-bromotoluene with phenylboronic ester using different organic and inorganic bases

Base	Time (hours)	HPLC Yield (%)
K_2CO_3	4	99± 1
DBU	4	2
Pyridine	4	7 ± 1
TMG	4	4 ± 1
DIPEA	24	2
TEA	24	75 ± 9

Table 2-4 Suzuki coupling of 4-bromotoluene with phenylboronic ester using a combination of bases

Base	Time (hours)	HPLC Yield (%)
K_2CO_3/DBU	4.5	1
K_2CO_3/TEA	4	96± 1

Table 2-3 showed a summary of the yields of 4-methylbiphenyl using different organic and inorganic bases. Potassium carbonate (K_2CO_3) as the base for the coupling reaction of 4-bromotoluene proved to be the most successful, even though the reaction was heterogeneous (solid-liquid equilibrium). The coupling reaction of 4-bromotoluene using 1, 8-Diazabicycloundec-7-ene (DBU) produced 4-methylbiphenyl in negligible yields. Also, the use of pyridine, 1, 1, 3, 3-Tetramethylguanidine (TMG) and N, N-di-*iso*propyl ethylamine (DIPEA) gave negligible yields: 7, 4 and 2% respectively. Another

organic base tested was triethylamine (TEA) and it resulted in a 75% yield of 4-methylbiphenyl. Table 2-4 showed the yield of 4-methylbiphenyl for the use of a combination of bases. The use of a combination of DBU and K_2CO_3 as the bases for the reaction resulted in low yields (1% yield). Based on these results, DBU seems to inhibit the coupling reaction. A combination of TEA and K_2CO_3 produced a high yield of 88% after only four hours, which is slightly lower than when K_2CO_3 was used alone. The use of the other organic bases like TMG, DIPEA and pyridine resulted in negligible yields. Factors such as steric hindrance and pKa of the bases are affecting the coupling reactions and the most successful option for the possible protection and coupling reaction steps could be the use of K_2CO_3 or a combination of TEA and K_2CO_3.

2.3.3 Baseline coupling reaction of amine substrates

Baseline reactions of different bromide and chloride halogenated aryl amines and pyridines substrates were performed under nitrogen. We have chosen the following set of substrates shown in Figure 2-9 which we will later utilize to demonstrate the benefits of CO_2 in different Suzuki coupling reactions as a function of CO_2. These substrates will couple with phenylboronic acid in the presence of K_2CO_3 and $Pd(TPP)_4$ in a tetrahydrofuran (THF) and water (14% v/v) solvent system (Figure 2-10).

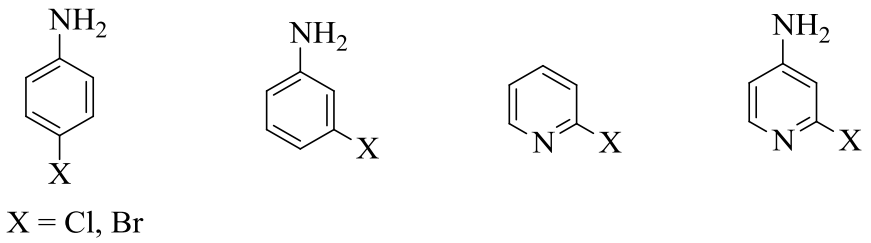
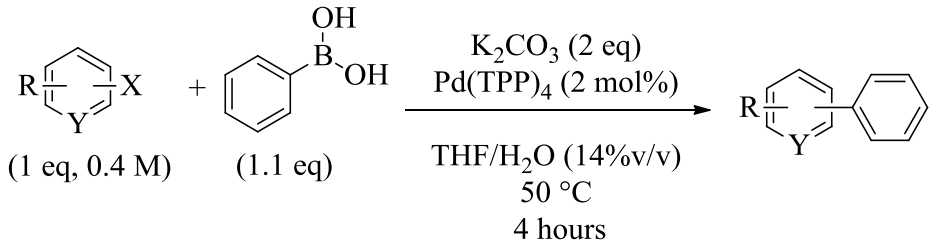


Figure 2-9 Amine and pyridine substrates for Suzuki reactions



X= Cl, Br
Y= N, C
R= NH_2, H

Figure 2-10 Reaction scheme of Suzuki coupling of different amine substrates

Table 2-5 and Table 2-6 summarizes the results for the different bromo- and the chloro-substrates, respectively. For the bromo-substrates, the reactions were run for 4 hours and for the chloro-substrates the reactions were run for 24 hours. Most of the reactions give a low yield, as expected for amine and pyridine substrates, except for the initial 3-bromoaniline reaction which yielded a moderate 43% of the 3-phenylaniline product. Reactions conditions such as reaction temperature, amount of added water and reaction time need to be studied in more detail for each substrate individually.

Table 2-5 Suzuki coupling of bromo-substrates for 4 hours

Substrate	Yield (%)
4-amino-2-bromopyridine	14
2-bromopyridine	7±2
3-bromoaniline	43
4-bromoaniline	14±1

Table 2-6 Suzuki coupling of chloro-substrates for 24 hours

Substrate	Yield (%)
4-amino-2-chloropyridine	19±1
2-chloropyridine	18±4
3-chloroaniline	13±4
4-chloroaniline	12±5

2.3.4 Suzuki coupling as a function of CO_2 Pressure

Generally, carbon dioxide (CO_2) is utilized as an inert reaction medium that undergoes no chemical reaction with either the catalyst or the substrate. However, CO_2 does react with certain functional groups such as amines to form carbamic acids or carbamates that can be used as a temporary protection and subsequently undergo a chemical transformation. A chemical reaction of great interest is the Suzuki coupling reaction. It has been shown that substrates containing primary amines suffered from low yields, due to the binding of the primary amine with the metal catalyst. Hence, the main goal of this project is to employ CO_2 gas-expanded solvents such as CO_2 dissolved in acetonitrile as a solvent and a protecting medium of primary amines groups. The CO_2 gas dissolved in the solvent at moderate pressures will *in situ* protect the primary amines as its carbamic acid, thus allowing the Suzuki coupling to proceed, and subsequent depressurization will return the coupled product with the primary amine intact (see Figure 2-11). The main advantage of employing CO_2 to *in situ* protect substrates with primary amines is that the conventional protection-deprotection steps are eliminated, greatly simplifying the process.

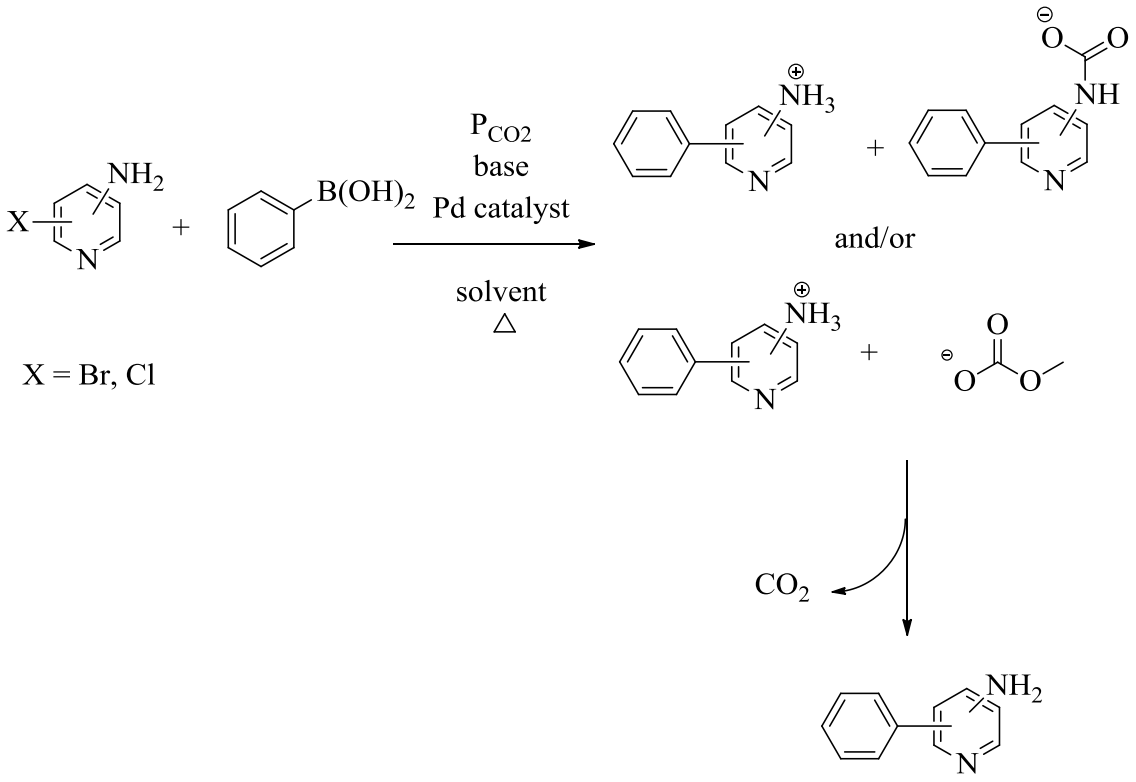


Figure 2-11 Suzuki coupling of CO_2 *in-situ* protected amine substrates

2.3.4.1 Suzuki couplings of 4-bromotoluene and 2-bromopyridine substrates using K_2CO_3 as a function of CO_2 pressures

Elevated pressures of CO_2 and optimum conditions for the possible protection and Suzuki reaction will improve the yields of the coupling reactions. Preliminary experiments to investigate the effect of CO_2 in a methanol (MeOH) and water solvent system (2.5% v/v water) were performed. The reaction investigated was the coupling of 4-bromotoluene with phenylboronic acid using K_2CO_3 at 50°C for 4.5 hours (Figure 2-12). The addition of different pressures ranging from 6.8 to 20.4 atm of CO_2 achieved lower yields compared to the one under N_2 atmosphere (Table 2-7).

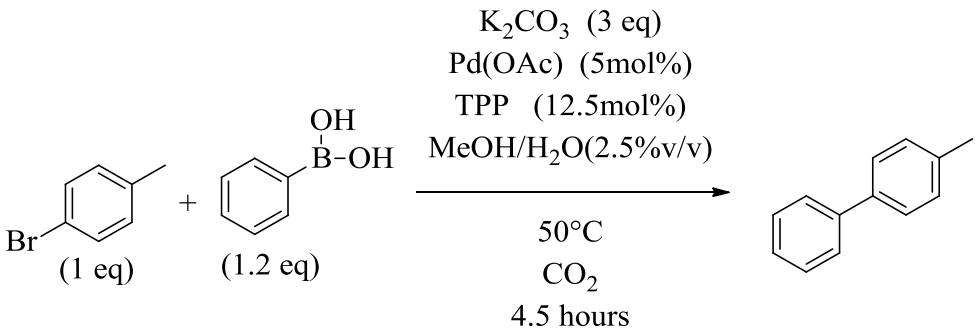


Figure 2-12 Coupling of 4-bromotoluene and phenylboronic acid in a methanol/water (2.5%v/v) solvent system

Table 2-7 Suzuki coupling as a function of CO_2 in a methanol/water (2.5%v/v) solvent system

Entry	Atmosphere	Yield (%)
1	1 atm N_2	38
2	6.8 atm CO_2	5
3	13.6 atm CO_2	9
4	20.4 atm CO_2	3

Additional coupling reactions in the presence of CO_2 were performed, in acetonitrile and water (14% v/v) solvent system (see Figure 2-13). This amount of water (14% v/v) represents the minimum quantity of water needed to ensure full solubility of the base in the aqueous phase, resulting in liquid-liquid heterogeneity. The results from these experiments were compared to the analogous coupling conducted under 1 atmosphere of nitrogen (N_2) and the results are summarized in Table 2-8. Significantly lower yields of 2-phenylpyridine were obtained in the presence of 30.6 atm of CO_2

compared to 1 atmosphere of N_2. The yield of the coupling reaction of 2-bromopyridine was decreased from 42% in the absence of CO_2 to 5% in the presence of 30.6 atm CO_2.

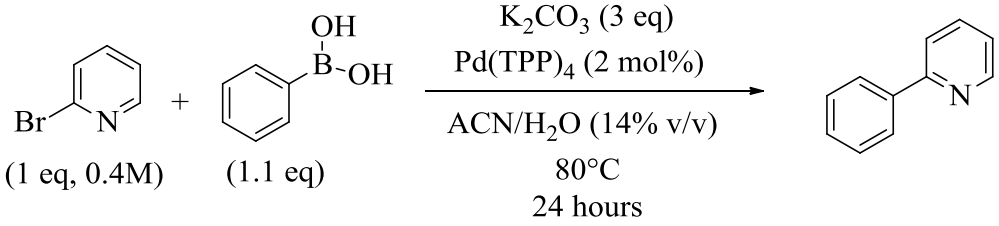


Figure 2-13 Coupling of 2-bromopyridine with phenylboronic acid in an acetonitrile/ water (14% v/v) solvent system

Table 2-8 Coupling 2-bromopyridine with phenylboronic acid in an acetonitrile/ water (14% v/v) solvent system in presence and absence of CO_2

Entry	Atmosphere	HPLC Yield (%)
1	1 atm N_2	42±1
2	30.6 atm CO_2	5±1

The lower yields in the reactions with CO_2 were attributed to three different factors. First, the addition of CO_2 to the acetonitrile/water or methanol/water system led to the formation of large quantities of bicarbonate, which is not as strong a base as carbonate and a far less reactive base in Suzuki coupling reactions (Figure 2-14). Secondly, the overall hydroxide ion concentration was substantially reduced. The formation of large quantities of bicarbonate resulted in the consumption of water and an accompanying formation of large quantities of solid. The initial liquid-liquid reaction system became a liquid-liquid-solid system. Third, a volume expansion of the organic

solvent (methanol (MeOH) or acetonitrile (ACN)) was expected as the CO_2 pressure was increased resulting in a dilution effect. Overall, the phase behavior became more complex, and it was difficult to determine the phase location of the reagents necessary for the coupling process.

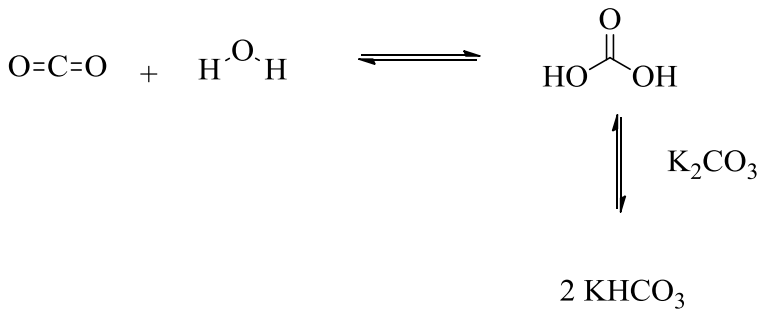


Figure 2-14 Potassium carbonate-carbonic acid equilibrium

Since the addition of CO_2 decreased the basicity of the reaction medium and the accompanying acid-base reactions of CO_2 also decreased the amount of water in the system, it appeared necessary to employ a stronger base and a greater quantity of water in order to facilitate the desired coupling reaction. As mentioned before water is critical to enhance the reaction rates because it serves as a solvent for the inorganic base and as a source of hydroxide ions that will facilitate the catalytic cycle. The literature contains several examples of tripotassium phosphate (K_3PO_4) as an effective base for promoting Suzuki coupling reactions. Its conjugate acid, dipothasium phosphate (K_2HPO_4) with a

pKa of 12.3, is two orders of magnitude more basic than bicarbonate ($KHCO_3$) with a pKa of 10.3. As a consequence, potassium phosphate (K_3PO_4) was used as the inorganic base for the following Suzuki coupling reaction. It is important to point out that, in the presence of CO_2, the resulting base system will be quite complex. An equilibrium mixture comprised of tribasic phosphate, dibasic phosphate, bicarbonate, carbonate, and hydroxide ions will be present. In addition, the concentration of each of the bases in this complex mixture will be a function of CO_2 pressure.

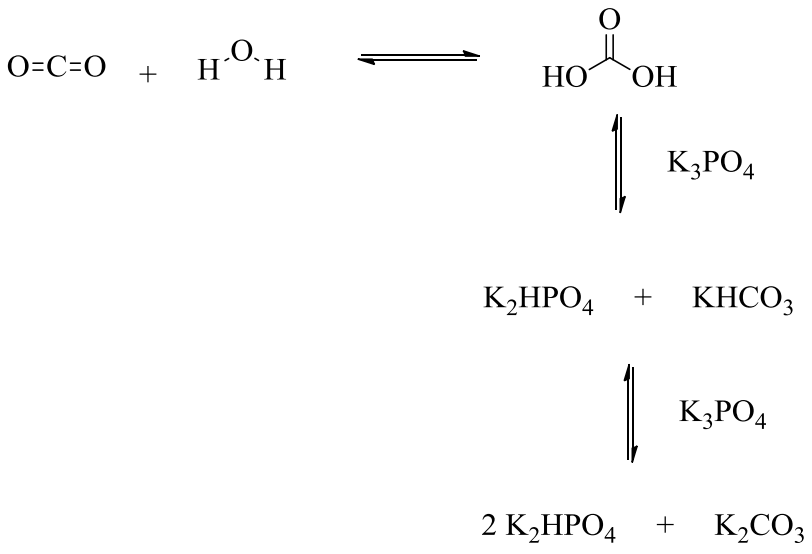


Figure 2-15 Potassium phosphate-carbonic acid equilibrium

2.3.4.2 Effect of added water under CO_2 pressure in the coupling of 4-amino-2-bromopyridine using K_3PO_4

To further investigate the effectiveness of potassium phosphate(K_3PO_4) as the base in Suzuki couplings as a function of CO_2 pressures, the coupling reaction of 4-amino-2-bromopyridine with phenylboronic acid using $Pd(TPP)_2Cl_2$ in an acetonitrile and water solvent system was investigated (Figure 2-16). The reaction progress was qualitatively monitored by GCMS and the estimated results are summarized in Figure 2-17. The results are represented as the ratio of the response of the product over the sum of the response of the product and substrate in the GCMS. The yield of 4-amino-2-phenylpyridine under 30.6 atm of CO_2 was investigated as a function of time and volume percent of water added. The amounts of added water investigated were 2.5% v/v and 25% v/v.

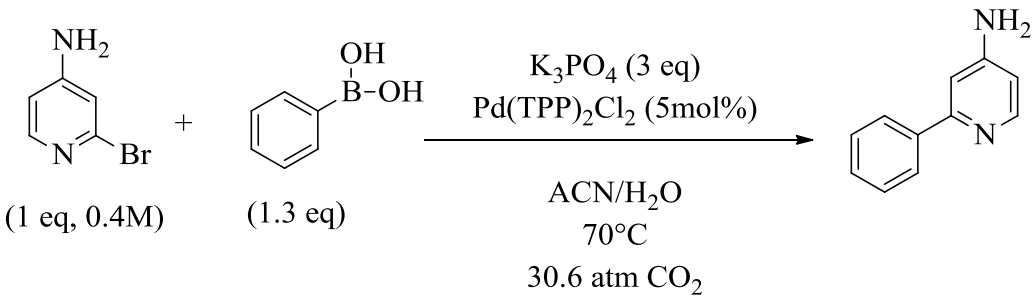


Figure 2-16 Suzuki coupling of 4-amino-2-bromopyridine using K_3PO_4

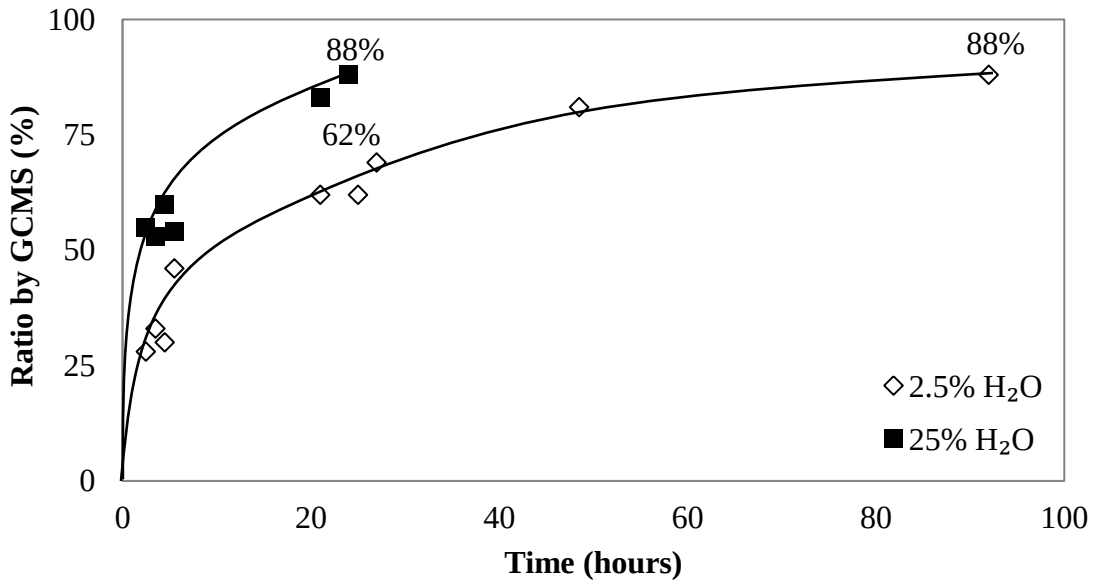


Figure 2-17 Yield of 4-amino-2-phenylpyridine at 30.6 atm of CO_2 as a function of time and amount of added water

The reaction with 25% v/v water displayed liquid-liquid heterogeneity; whereas, the reaction using 2.5% v/v water displayed solid-liquid heterogeneity. As can be seen in Figure 2-17, the reaction proceeds much faster with 25% v/v water than with 2.5% v/v water. Both reactions achieved an 88% yield of product; however the reaction with 2.5% v/v of added water was four times longer than the one using 25% v/v added water. This observation is consistent with trends observed in the water effect study reported previously (Section 2.3.1). More importantly, these reactions demonstrate that K_3PO_4 is a highly effective base for Suzuki coupling reactions in the presence of CO_2 and water.

2.3.4.3 Effect of CO_2 pressure in the coupling of 4-amino-2-bromopyridine using K_3PO_4

The coupling reaction of 4-amino-2-bromopyridine with phenylboronic acid was investigated as a function of CO_2 pressures (Figure 2-18). We monitored the progress of the reaction as a function of time as shown in Figure 2-19. The results are presented as the ratio by GCMS, which was estimated as the response of the product over the sum of the response of the product and the substrate. These experiments showed that when the reaction is carried out under atmospheric nitrogen, it achieved a plateau after approximately 24 hours giving a product ratio of approximately 25%. Alternatively, when 6.8 and 30.6 atm of CO_2 was used the ratio after 24 hours increased to 65% and 88% respectively. At 30.6 atm CO_2, the ratio is almost 3.5 times higher than with nitrogen. Moderate pressures of CO_2 ranging from 6.8 to 44.2 atm were found to increase significantly the yield of the coupling reaction of 4-amino-2-bromopyridine and phenylboronic acid.

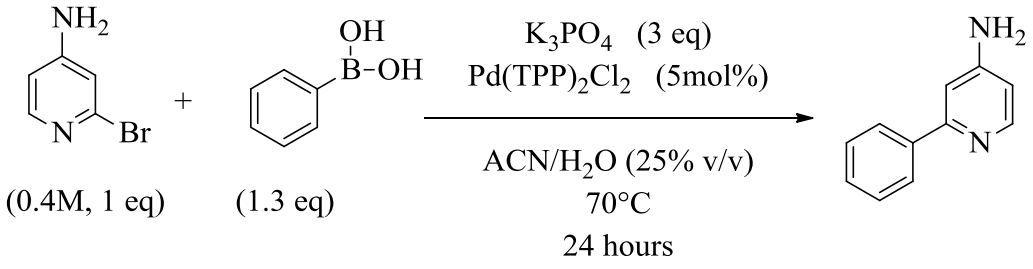


Figure 2-18 Reaction scheme for the coupling reaction of 4-amino-2-bromopyridine with phenylboronic acid using K_3PO_4 as the base

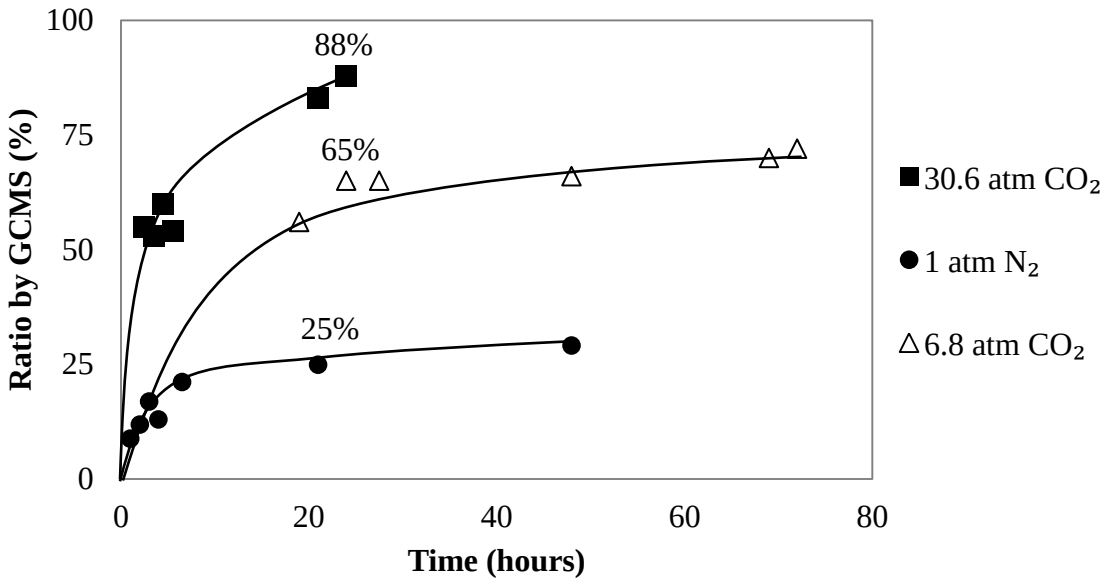


Figure 2-19 Product ratio estimated by GCMS for the coupling of 4-amino-2-bromopyridine as a function of CO_2 pressures

The coupling reactions of 4-amino-2-bromopyridine with phenylboronic acid using K_3PO_4 and 25% v/v added water under different pressures of CO_2 after 24 hours were fully quantified and the results are summarized in Table 2-9. The yield of 4-amino-2-phenylpyridine increased as the pressure of carbon dioxide was increased, going from 29% under nitrogen atmosphere up to 53% yield at 30.6 atm of CO_2.

Table 2-9 Yield of 4-amino-2-phenylpyridine from the coupling of 4-amino-2-bromopyridine and phenylboronic acid under different CO_2 pressures

Entry	Atmosphere	GC Yield (%)
1	1 atm N_2	29
2	6.8 atm CO_2	32
3	17.0 atm CO_2	39
4	30.6 atm CO_2	53

2.3.4.4 Effect of CO_2 pressure in the coupling of 4-amino-2-chloropyridine using K_3PO_4

The palladium-mediated Suzuki coupling reactions have some drawbacks. Mainly aryl bromides can be used, as the chlorides only react slowly. The low reactivity of chlorides is usually attributed to the strength of the C-Cl bond [7]. Herein, we discuss the successful coupling reactions of 4-amino-2-chloropyridine with phenylboronic acid using K_3PO_4 and 25% v/v added water under 30.6 atm of CO_2 (Figure 2-20). After 48 hours, the reactions were fully quantified and the results are summarized in Table 2-10. For comparison, the reaction was also carried out under nitrogen atmosphere. The yield of 4-amino-2-phenylpyridine increased as the pressure of carbon dioxide was increased, going from 43% under nitrogen atmosphere up to 86% yield at 30.6 atm of CO_2. As expected, the addition of CO_2 increased the reaction yield and the reaction of the chloride substrates was substantially slower than its bromide analogs. These results follow the expected reaction progress with the addition of CO_2. Also, the reaction time was set for 48 hours, because it has been shown that chloride substrates have a substantially lower reactivity compared to bromide substrates. Surprisingly in this case the reaction achieved a very high yield of 86% after the 48 hours under CO_2 pressures, even though most of the water or aqueous phase was consumed.

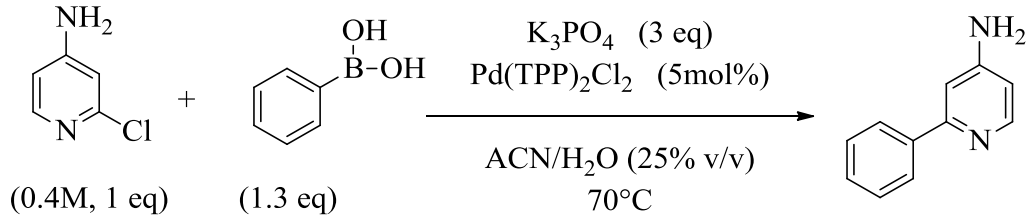


Figure 2-20 Reaction scheme for the coupling reaction of 4-amino-2-chloropyridine with phenylboronic acid using K_3PO_4 as the base

Table 2-10 Yield of 4-amino-2-phenylpyridine from the coupling of 4-amino-2-chloropyridine and phenylboronic acid under different CO_2 pressures

Entry	Atmosphere	Time	GC Yield (%)
1	1 atm N_2	48	43±1
2	30.6 atm CO_2	48	86±2
3	30.6 atm CO_2	72	95±4

2.3.4.5 Effect of CO_2 pressure in the coupling of 4-amino-2-bromopyridine using K_3PO_4 with two different work-up procedures

The coupling reactions of 4-amino-2-bromopyridine with phenylboronic acid using K_3PO_4 and at different pressures of CO_2 after 24 hours are presented in Table 2-10 and are graphically displayed in Figure 2-21. Figure 2-21 shows the reaction conversion and yield as a function of the different pressures of CO_2. There is a significant difference ranging from 30 to 50% between the conversion and the yield for the different systems' atmospheres. The significant difference was attributed to a poor recovery of the substrate and/or product or the loss of side products in the aqueous phase during the

acetonitrile/water/toluene work-up procedure. The work-up procedure consisted of the addition of acetonitrile and water to fully transfer the heterogeneous (liquid-liquid-solid) reaction mixture to an external flask. Toluene was then added to extract any organic residues from the aqueous phase and subsequently only the organic phase was analyzed by GCMS.

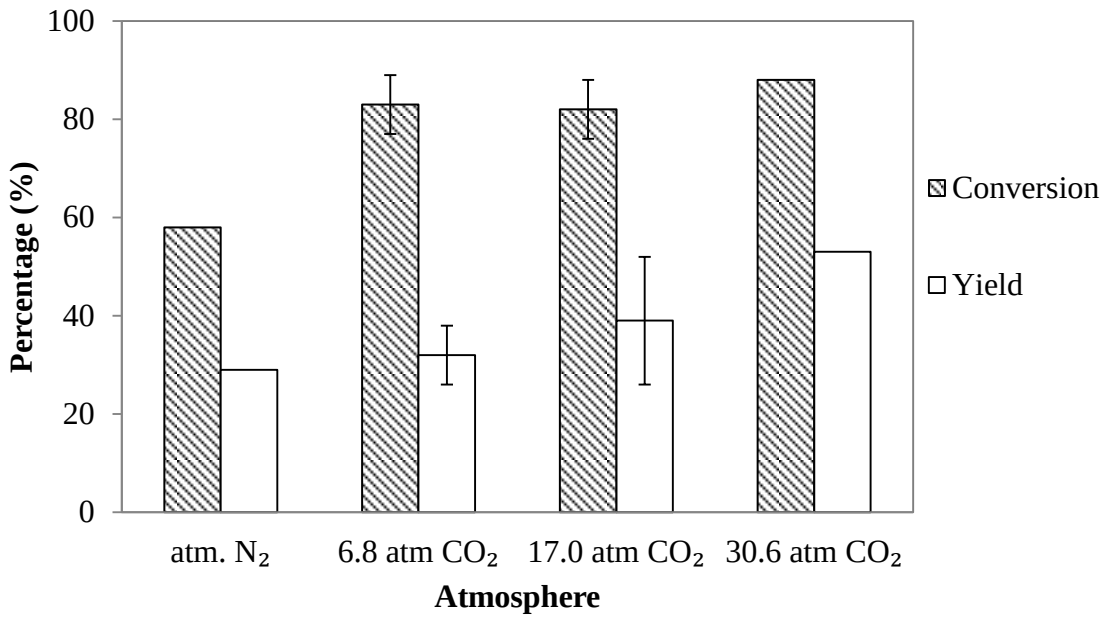


Figure 2-21 Conversion and yield for the coupling of 4-amino-2-bromo-pyridine with phenylboronic acid as a function of CO_2 pressures using an acetonitrile/water/toluene work-up procedure

As a result, the work-up procedure was then improved by the use of methanol (MeOH). The addition of methanol to the heterogeneous (liquid-liquid-solid) reaction mixture will cause the precipitation of all the salts from the solution, which leads to the formation of a single homogeneous phase that contains the solvents used in the reaction (acetonitrile and water), the methanol added during the work-up, the unreacted substrate and any products formed during the coupling reaction. The results using the improved

work-up procedure are graphically displayed in Figure 2-22. From the results, we again clearly noticed a significant difference from the reaction carried out under atmospheric nitrogen to the ones with CO_2. The yield of 4-amino-2-phenylpyridne went from 17% under nitrogen to approximately 57% under 44.2 atm CO_2. Interestingly, there was not a significant difference between the different pressures of carbon dioxide, resulting in yields a little over 50%. There was still a difference of approximately 20% in most of the cases between the conversion and yield of the reaction. The GCMS chromatograms showed only traces of side products and they do not account for the 20% difference. We believe the difference between the conversion and the yield is due to underestimation of the unreacted substrate during the GC analysis and as a result gave us higher conversions than the actual conversions of the coupling 4-amino-2-bromopyridine with phenylboronic acid.

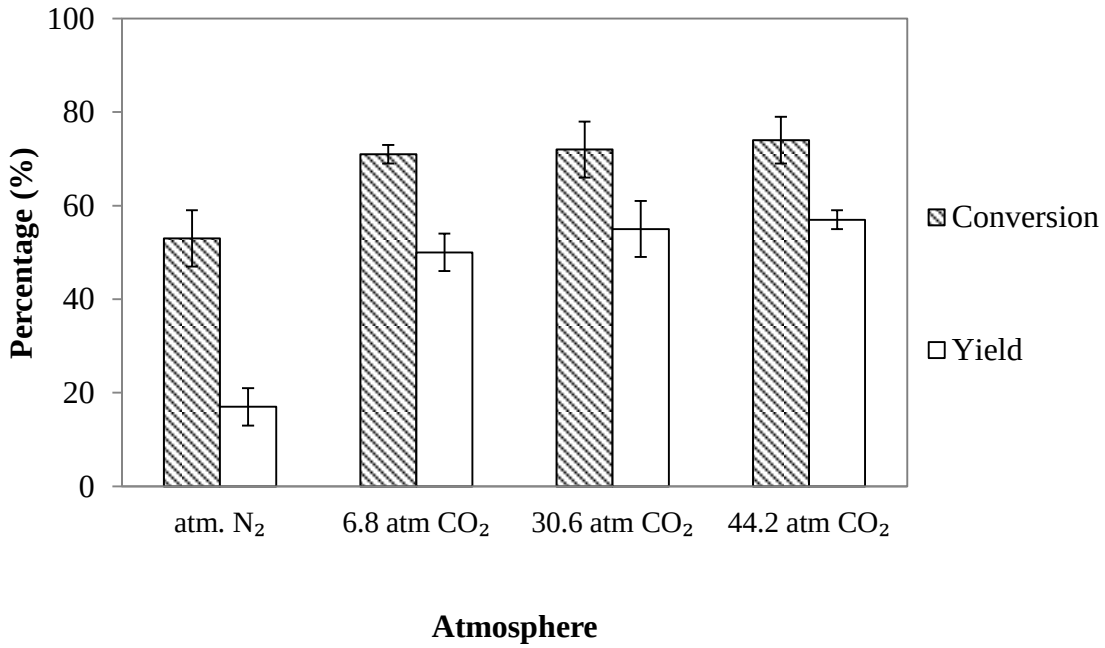


Figure 2-22 Conversion and yield for the coupling of 4-amino-2-bromopyridine with phenylboronic acid as a function of CO_2 pressure using a methanol work-up procedure

2.3.4.6 Water and base stoichiometry

The coupling reaction of 4-amino-2-bromopyridine with phenylboronic acid discussed in the previous section showed a significant enhancement in the reaction with the addition of CO_2. However, the reactions did not achieve completion after 24 hours. In addition, based on an experimental observation the 25% v/v of water added seems to be consumed during the reaction when CO_2 was employed. Based on these observations the coupling reaction was investigated using different equivalents of the base, potassium phosphate (K_3PO_4) and higher amounts of added water. The reaction investigated is the Suzuki coupling reaction of 4-amino-2-bromopyridine with phenylboronic acid in the presence of K_3PO_4 for 24 hours (Figure 2-23). The results are summarized in Figure 2-24.

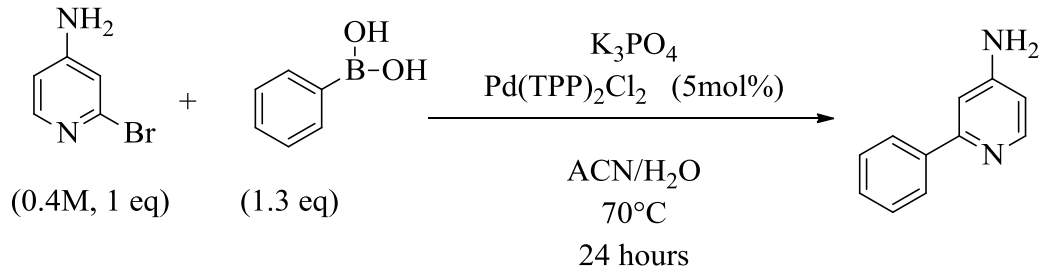


Figure 2-23 Coupling of 4-amino-2-bromopyridine with phenylboronic acid using K_3PO_4

Figure 2-24 graphically displays the reaction conversion and yield from the coupling of 4-amino-2-bromopyridine with phenylboronic acid using different equivalents of K_3PO_4 and different amounts of added water under 30.6 atm CO_2. The first set of data represent a 55% yield of 4-amino-2-phenylpyridine obtained using three

equivalents of K_3PO_4 and 25% added water. The use of four equivalents of base and 40% v/v added water, resulted in 72% yield, which is a 17% increment when compared to the conditions used in the previous section. The next two experiments looked at the effect of four equivalents of base and 40% added water independently. The use of an additional equivalent of base (4 equivalents total) and 25% added water resulted in 57%, whereas the use of 3 equivalents of base and 40% added water resulted in quantitative yields. For comparison, the reaction under nitrogen atmosphere was performed using the 40% added water and the reaction proceeded giving a 23% yield. A significant enhancement in the Suzuki coupling reaction of 4-amino-2-bromopyridine was observed. A 99% yield was obtained when 30.6 atm of CO_2 was used compared to 23% yield when the reaction was performed under nitrogen.

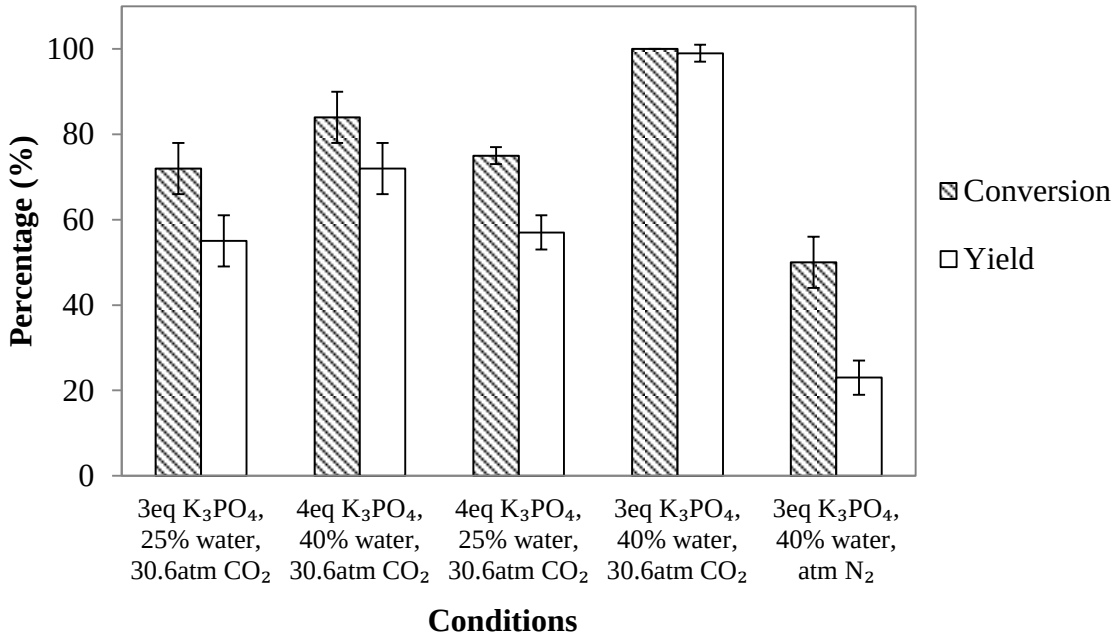


Figure 2-24 Reaction conversion and yield from the coupling of 4-amino-2-bromopyridine using different equivalents of bases and/or different amounts of added water

We found the optimum conditions and achieved quantitative yields by using CO_2 and K_3PO_4 for the coupling of 4-amino-2-bromopyridine and phenylboronic acid. Suzuki coupling reactions of amino pyridines are very complex and results in very low yields. There are few isolated examples in the literature of successful reactions in the presence of NH_2 groups, and many of them are low yielding. In particular, the reaction of 4-amino-2-bromopyridine due to its higher basicity results in low yields compared to other substituted amino pyridines. In the literature the use of bulky ligands or protected amines have helped in the coupling resulting in higher yields, but these two methods are very expensive and can produce large amount of waste. We have shown that the coupling reaction of a substrate bearing a primary amine group like 4-amino-2-bromopyridine is a suitable substrate for Suzuki coupling reactions with phenylboronic acid under standard conditions (a traditional base and catalyst like K_3PO_4 and $Pd(TPP)_2Cl_2$) just by the addition of CO_2 pressures, without the need for protection/deprotection steps.

2.3.4.7 Effect of CO_2 with the base

Potassium phosphate was identified as a good base for the Suzuki coupling of 4-amino-2-bromopyridine with phenylboronic acid under CO_2 pressures. Note that in the presence of CO_2, the resulting base system will be quite complex. An equilibrium mixture comprised of tribasic phosphate, dibasic phosphate, bicarbonate, carbonate, and hydroxide ions will be present (Figure 2-25). In addition, the concentration of each of the bases in this complex mixture will be a function of CO_2 pressure and the pH of the mixture could be possibly be very different. To investigate the effect of carbon dioxide with the base, different scenarios of possible bases formed during the reaction of CO_2,

water and the base were investigated. Once more, the reaction studied was the coupling reaction of 4-amino-2-bromopyridine with phenylboronic acid using different individual or combination of potassium bases (Figure 2-26) and the results are graphically displayed in Figure 2-27.

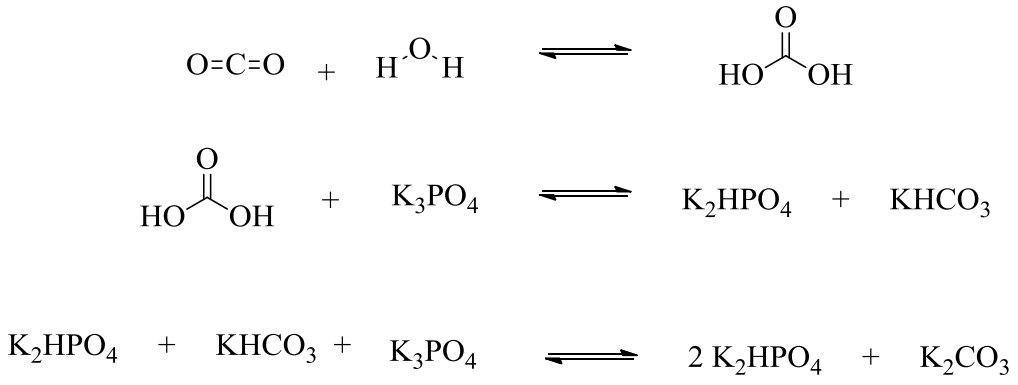


Figure 2-25 Possible potassium bases formed from the reaction of water, carbon dioxide and potassium phosphate

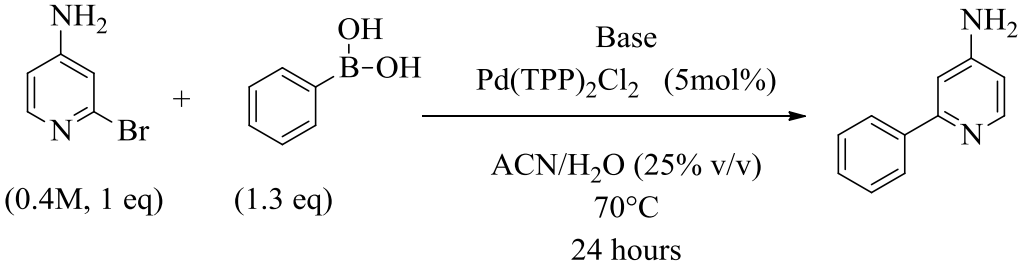


Figure 2-26 Coupling of 4-amino-2-bromopyridine with phenylboronic acid using different potassium bases

The individual and combination of bases such as K_3PO_4, K_2HPO_4, KH_2PO_4, K_2CO_3, $KHCO_3$ and $K_4P_2O_7$ were evaluated in the coupling of 4-amino-2-bromopyridine with phenylboronic acid under atmospheric nitrogen at 70°C. The results clearly show that KH_2PO_4 gave negligible yields (2%) after 24 hours. The use of other bases resulted in slightly higher yields. For example, the reaction yield increased with the other bases, especially in the cases using K_2HPO_4. The use of K_2HPO_4 alone resulted in 41%, the highest yield from all the base systems investigated. These results provide valuable insights into the possible effectiveness of potassium phosphate in the presence of CO_2. The addition of CO_2 decreases the basicity of the system resulting in the formation of K_2HPO_4 which, as indicated in Figure 2-27, is an effective base for this specific Suzuki coupling reaction. An experimental observation is that the amount of added water (25% v/v) is not consumed during the nitrogen experiments, while in the case of K_3PO_4 and 30.6 atm CO_2 the aqueous layer was reduced dramatically during the reaction. Previously we discussed that the reaction under 30.6 atm CO_2 achieved quantitative yields (99%) with the addition of a higher amount of added water (40% v/v).

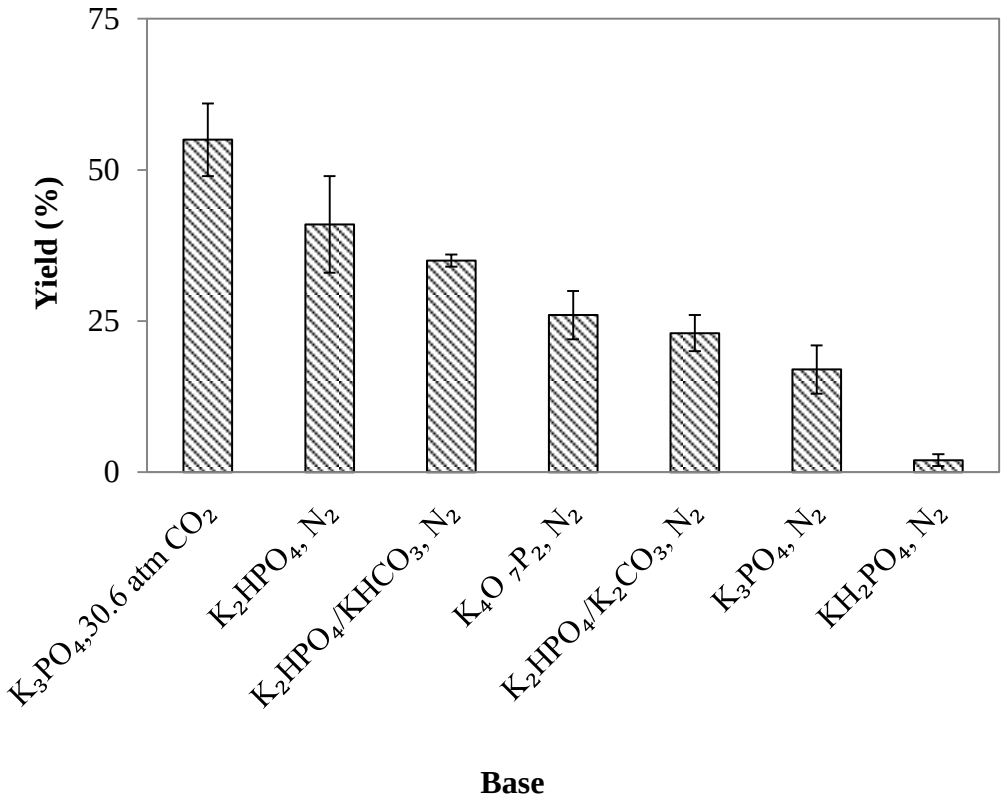


Figure 2-27 Yield of 4-amino-2-phenylpyridine using different potassium bases that could be formed when K_3PO_4 and CO_2 are used in the reaction

The pH measurements of the different bases systems investigated previously are summarized in Figure 2-28. There is possibly an inverse trend with the reaction progress and the pH of the mixtures. The pH of the reaction using K_3PO_4 under 30.6 atm CO_2 is about 8 and the pH of the reaction using K_2HPO_4 under nitrogen is about 9.44. It could be possible that it is a combination of the interaction of CO_2 with the primary amine and the complex base mixture formed which represents an effective system for the successful Suzuki coupling reaction at 30.6 atm CO_2 using K_3PO_4.

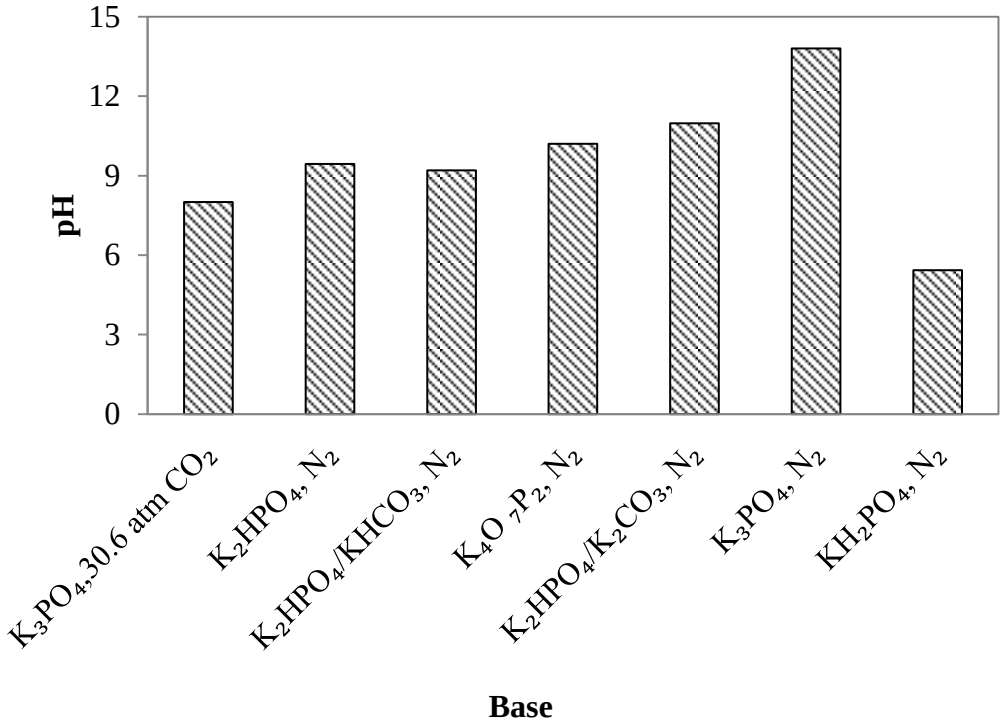


Figure 2-28 pH of reaction mixtures with different potassium bases

2.4 Conclusions

The goal of this project is to employ CO_2 gas-expanded solvents such as CO_2 dissolved in acetonitrile as a solvent and a protecting medium of primary amines groups. Control experiments first evaluated the effects of added water and the use of organic and inorganic bases on Suzuki coupling reactions containing no nitrogen centers and in the absence of CO_2 pressure. It was found that the addition of small amounts of water (2.5% v/v) significantly improves the rate and yield and is critical for an efficient Suzuki coupling reaction. It was found that K_2CO_3 and TEA were the most effective bases in the absence of CO_2. The results of the application of CO_2 pressures on Suzuki coupling

reactions of 4-bromotoluene and 2-bromopyridine with phenylboronic acid using K_2CO_3 resulted in lower yields than when N_2 was employed. This detrimental effect could be due to the formation of bicarbonate and the accompanying decrease in the amount of hydroxide and water when K_2CO_3 was employed. Therefore, careful selection of the base is essential and K_3PO_4 is the most effective base in the presence of CO_2 for the coupling of 4-amino-halopyridine substrates, resulting in quantitative yields (99% yield) in the presence of 30.6 atm of CO_2, compared to 23% yield in the absence of CO_2. The increment in the yield can result from multiple effects: 1) a change in the pH due to the formation of a complex base system, 2) interaction of CO_2 with the primary amine and 3) interaction of CO_2 with the catalyst.

This work establishes that exceptionally challenging substrates like halogenated amino pyridines bearing a primary amine group (NH_2) (4-amino-2-bromopyridine and 4-amino-2-chloropyridine) are suitable substrates for Suzuki coupling reactions under standard conditions using CO_2 pressures, without the need for protection/deprotection steps which are traditionally considered to be necessary for these reactions to proceed cleanly. This is the first study of such reactions in the presence of a primary NH_2 in the *para*- and the halogen in the *ortho*-position to the nitrogen of a pyridine substrate using traditional conditions under CO_2 pressures that achieved quantitative yields.

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CHAPTER 3 - WATER AT ELEVATED TEMPERATURES (WET): A REACTANT, CATALYST, AND SOLVENT IN THE SELECTIVE REMOVAL OF PROTECTING GROUPS

3.1 Introduction

In recent years, green chemistry has become an important research area and as defined it focuses on sustainable and environmentally friendly chemical processes that will minimize or eliminate the use or production of hazardous substances [1]. In addition, over the past years the number of regulations to which a chemical company must comply has increased dramatically [2]. The green chemistry is a strategy that will help the chemical industries to deal with the challenges of the future regulations. Among the Principles of Green Chemistry, principle number eight stated that the use of protection/deprotection sequences should be minimized or avoided if possible, because such steps require additional reagents and can generate waste[3]. As a greener alternative for the removal of protecting groups, I proposed the use of water for the selective removal of common protecting groups. Water is an inexpensive and environmentally benign solvent system for conducting a wide variety of synthetic transformations and subsequent separations [4-10].

The chemical and physical properties of water at elevated temperatures (WET) change drastically compared to common organic solvents. This change in the properties (*i.e.* polarity and density) is mainly due to a decrease of the hydrogen bonding [11], which ultimately results in enhanced solubility of nonpolar organic species. In addition, the density, the auto- ionization constant (K_w) and the dielectric constant (ε) change

substantially when compared to water at ambient conditions. Over the range of temperatures from ambient to 275°C: (1) the density [12] decreases from 1 g/mL to 0.76 g/mL, (2) the dielectric constant (ε) [13], decreases from 79 to approximately 25, and (3) the auto-ionization constant (K_w) [14], increases from 10^{-14} to 10^{-11} (See Figure 3-1, Figure 3-2 and Figure 3-3, respectively). The increment of the auto-ionization constant leads to an increase of three orders of magnitude of hydronium and hydroxide ions that are available to act as catalysts and the change of the dielectric constant gives water solvent properties similar to acetonitrile (ε=37.5). The changes of properties as a function of temperatures can be exploited to conduct acid or base reactions. The properties of water between ambient and elevated temperatures vary in a predictable continuous manner. Thus, the properties of water can be tuned by altering the temperature to meet specific solvent and reactivity needs. In addition, product isolation becomes more facile since mere cooling of the reaction mixture will result in phase separation of the organic products (Figure 3-4).

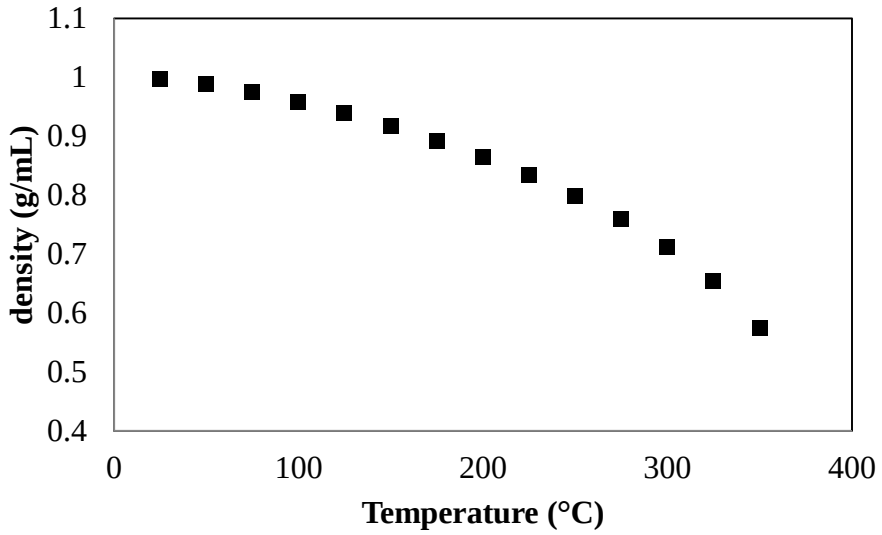


Figure 3-1 Density of water as a function of temperature [12]

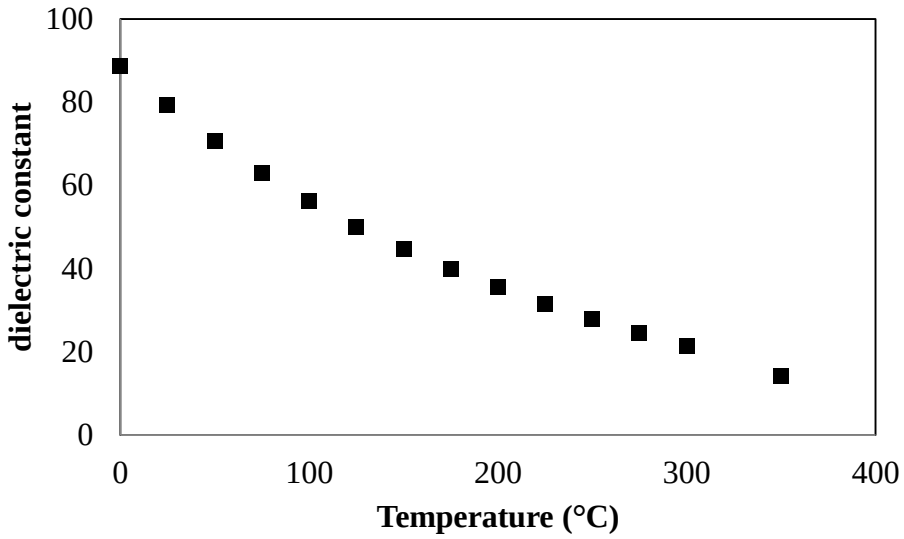


Figure 3-2 Dielectric constant (ε) of water as a function of temperature [13]

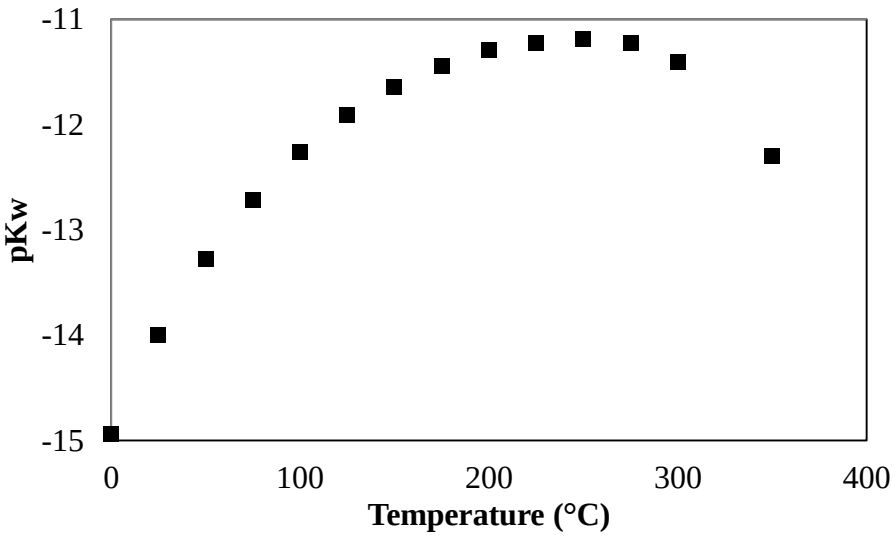


Figure 3-3 Auto-ionization constant (K_w) of water as a function of temperature [14]

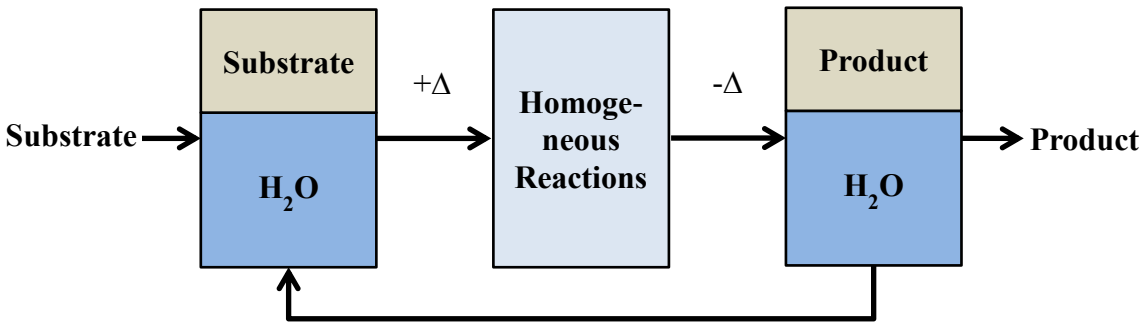


Figure 3-4 Processing: Facile separation of the product after reaction

Water is an attractive solvent for the development of sustainable, environmentally green processes for the removal of protecting groups. When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional molecule, other potentially reactive sites or functional groups must be temporarily protected. The synthesis of pharmaceutical and natural products compounds and intermediates relies heavily on the use of protecting groups because of the inherent complexity and multifunctional nature of the target molecule. A study presented by Carey *et al.* showed that 6% and 15% of the total reactions performed for the synthesis of pharmaceuticals are protection and deprotection reactions, respectively (Figure 3-5)[15].

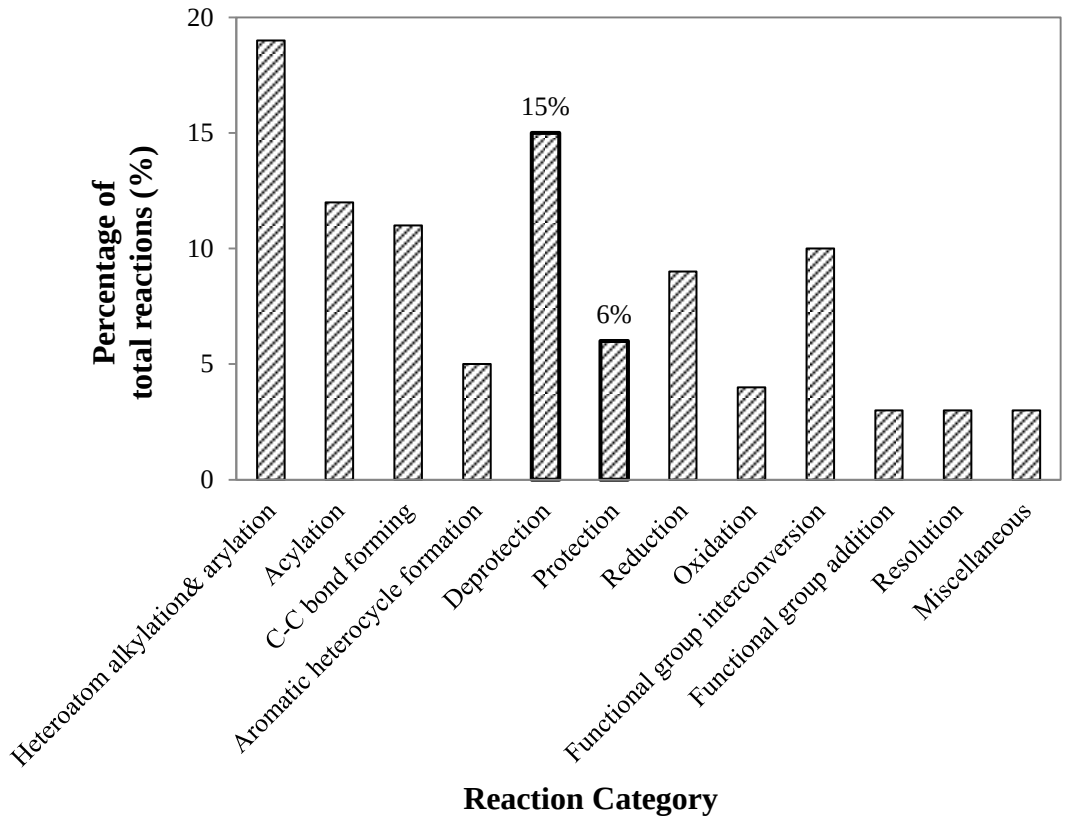


Figure 3-5 Percentage of total reactions in the synthesis of drugs molecules [15]

Protecting groups must fulfill a number of requirements; for example it must be introduce selectively in quantitative yield to give a protected substrate that is stable for the desired reactions. It must also be removed selectively and quantitatively under mild conditions that do not affect other functional groups [16]. This last requirement often requires strong acidic or basic reagents. Strong acids like hydrochloric, sulfuric, phosphoric or hydrobromic acid are frequently used for the removal of common protecting groups like the *tert*-butylcarbamate (Boc), benzylcarbamate (CBz) and *tert*-butylmethylether (TBME). The acid or base added are usually in excess and must be subsequently neutralized, significantly impacting the overall number of steps for the

synthetic procedure, as well as producing large amounts of salt and organic contaminated aqueous waste. While from a green chemistry point of view it would be preferable to avoid protecting groups, the reality is that this is not always possible. As a consequence the development of green protocols for the protection and subsequent removal of these groups have become important considerations.

The use of WET as the reaction solvent and catalyst, eliminates the need for environmentally hazardous solvents and acid catalysts. In fact, water has been used for a wide variety of applications at various temperatures ranging from its boiling point to above its critical point and successfully reported to mediate acid/base catalyzed hydrolysis [17-20], Claisen-Schmidt condensation reactions [21], and acid catalyzed Friedel-Crafts alkylation reactions [22]. In general each of these reaction types take place at dramatically different rates and therefore at substantially different temperatures. As a result, when using WET, the "strength" of the *in situ* acid can be tuned by altering the temperature. This is a versatile and reversible handle that does not require any added acid/base. Herein, I address the use of WET to selectively remove some typical protecting groups from amine and alcohol functionalities where just tuning the temperature of the water allows for the selective removal of one protecting group in the presence of a second. In addition, the kinetics and the associated mechanisms for the reactions in WET will be presented. Typical protecting groups for amines are the *tert*-butylcarbamate (Boc) and acetamide (Ac) derivatives and for alcohols the acetoxy and methoxy derivatives. I report the protocols for the deprotection of individual protecting groups as well as the competitive and selective deprotection of molecules containing two different protecting groups using WET at temperatures ranging from 125 to 275°C

3.2 Experimental Methods

3.2.1 Materials

The following reactants and reagents were purchased from commercial sources and were used without further purification: acetonitrile (Aldrich, HLPC Grade 99+%), water (Aldrich, HPLC grade), *tert*-butyl phenylcarbamate (Aldrich, 97%), aniline (Aldrich, ACS reagent grade), *p*-methoxyaniline (Aldrich, ACS reagent grade), *p*-chloroaniline (Aldrich, ACS reagent grade ≥99.5%), acetanilide (Aldrich, 97%), *p*-acetanisidide (TCI, 98%), 4'-acetoxyacetanilide (TCI, >98%), di-*tert*-butyl dicarbonate (Aldrich, 97%), ethanol (Aldrich), diethyl ether (Aldrich), magnesium sulfate (Aldrich, 98%). The deionized water was obtained in-house using a Barnstead B-Pure dual filter water filtration system, with a resistivity >18 MΩ. The following chemicals were synthesized as describe below:

1. ***tert*-Butyl (4-methoxyphenyl) carbamate:** *p*-Methoxyaniline (0.82g, 6.7mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 2.2g, 10mmol) were stirred in 25mL absolute ethanol overnight at room temperature. The solvent was removed by rotary evaporation. The resulting solid was dissolved in diethyl ether (Et_2O, 30mL) and washed three times with water (H_2O, 30mL). The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed on the rotovap. White solid, mp. = 95 – 96°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H), 7.33 (d, 2H), 6.81 (d, 2H), 3.68 (s, 3H), 1.44 (s, 9H). ^{13}C NMR: 153.96, 152.44, 132.09, 119.16, 113.30, 78.14, 54.52, 27.67.
2. ***tert*-Butyl (4-chlorophenyl)carbamate:** *p*-Chloroaniline (0.85g, 6.7mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 2.2g, 10mmol) were stirred in 25 mL absolute

ethanol overnight at room temperature. The solvent was removed by rotary evaporation. The resulting solid was dissolved in diethyl ether (Et_2O, 30mL) and washed three times with water (H_2O, 30mL). The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed on the rotovap. White solid, mp. = 102 – 103°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.49 (s, 1H), 7.46 (d, 2H), 7.27 (d, 2H), 1.45 (s, 9H). ^{13}C NMR: 152.18, 138.04, 128.00, 125.09, 119.03, 78.84, 27.58.

3. ***tert*-Butyl(4-acetamidophenyl)carbamate:** To 2g (0.00960 mol) of *tert*-butyl(4-aminophenyl)carbamate was added 200mL anhydrous DCM under nitrogen with stirring in an ice-water bath. 1.0mL (0.0124 mol) of anhydrous pyridine was added dropwise to the cold solution. The reaction mixture was stirred for 10 minutes and 1mL (0.0106 mol) of acetic anhydride was added dropwise. After 10 minutes of stirring, the ice-water bath was removed and the reaction proceeded at room temperature for 4 hours. The reaction mixture was neutralized with saturated sodium carbonate under vigorous stirring. Additional water and DCM were added and the organic layer separated, dried, and evaporated under reduced pressure. The product was recrystallized in toluene. The white solid was filtered, washed with toluene, and dried in a vacuum oven overnight yielding 0.903 g of product (82%), mp. 180-186°C. ^{1}H NMR (DMSO) δ 1.46 (s, 9H), δ 2.00 (s, 3H), δ 7.34 (d, 2H), δ 7.43 (d, 2H), δ 9.20 (s, 1H), δ 9.78 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 23.84, δ 28.14, δ 78.81, δ 118.50, δ 119.52, δ 133.89, δ 134.79, δ 152.85, δ 167.86. Elemental Analysis: Theoretical: C: 62.38%, H: 7.25%, N: 11.79%. Found: C: 62.35%, H: 7.36%, N: 11.07%. Mass (ESI+): 151.1 m/z.

4. ***tert*-Butyl (4-pivalamidophenyl)carbamate:** To 0.8g (0.00384 mol) of *tert*-butyl(4-aminophenyl)carbamate was added 65mL anhydrous DCM under nitrogen with stirring in an ice-bath. 0.350mL (0.0043 mol) of anhydrous pyridine was added dropwise to the cold solution. The reaction mixture was stirred for 10 minutes and 0.512mL (0.00416 mol) of pivaloyl chloride was added dropwise. After 10 minutes of stirring, the ice-water bath was removed and the reaction proceeded at room temperature for 4 hours. The reaction mixture was neutralized with saturated sodium carbonate under vigorous stirring. Additional water and DCM were added and the organic layer separated, dried, and evaporated under reduced pressure. The product was recrystallized from toluene. The white solid was filtered, washed with toluene, and dried in a vacuum oven overnight yielding 0.903 g of product (80%), mp. 214-220°C. ^{1}H NMR (DMSO-d_6) δ 1.21 (s, 9H), δ 1.47 (s, 9H), δ 7.36 (d, 2H), δ 7.49 (d, 2H), δ 9.07 (s, 1H), δ 9.22 (s, 1H). ^{13}C NMR (DMSO) δ 27.29, δ 28.17, δ 38.96, δ 78.79, δ 118.10, δ 120.90, δ 133.78, δ 134.96, δ 152.82, δ 176.09. Elemental Analysis: Theoretical: C: 65.73%, H: 8.27%, N: 9.58%. Found: C: 66.00%, H: 8.12%, N: 9.48%. Mass (ESI+): 193.3 m/z.
5. **4-((*tert*-Butoxycarbonyl)amino)phenyl acetate[23]**: A 25mL round bottom flask was charged with 0.75g (0.00496 mol) of 4-aminophenyl acetate[24] and 1.37g (0.00595 mol) of melted (about 40°C) of di-*tert*-butyl dicarbonate. 0.12g (5% mol) of ground $Bi(NO_3)_3{\cdot}5H_2O$ was added to the neat mixture. The mixture was stirred at 40°C for 10 minutes. Water was added to the mixture and the organics were extracted with ethyl acetate. The organic layer was dried with

$MgSO_4$, filtered and the solvent removed by rotary evaporation. The crude was purified with on a silica column with hexane:ethyl acetate (80:20, 50:50). 0.76g (61%) of product (white solid) isolated. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), δ 2.25 (s, 3H), δ 6.76 (broad, 1H), δ 6.99-6.95 (dt, 2H), δ 7.34-7.32 (d, 2H). ^{13}C NMR ($CDCl_3$) δ 20.98, δ 28.24, δ 80.48, δ 119.34, δ 121.81, δ 136.03, δ 145.84, δ 152.72, δ 169.66. Elemental Analysis: Theoretical: C: 62.14%, H: 6.82%, N: 5.57%. Found: C: 61.61%, H: 7.14%, N: 4.95%. Mass (ES+): 252 m/z.

3.2.2 Experimental Apparatus and Procedure

The reactions were performed in closed 3 mL titanium batch reactors. These reactors were designed and produced in-house and were sealed with titanium NPT plugs. Titanium was used as the material of construction due to the very low level of transition metals and corrosion resistance of the metal. 316 Stainless Steel reactors have been found to catalyze unwanted side reactions during investigations conducted within our research group. The reactors were loaded to have an approximate concentration of 0.033M with a volume of water of 1.5 mL. The titanium reactors were then placed in a thermostated aluminum heating block (Figure 3-6). The temperature of the heating block varied by ±1°C and was maintained using four cartridges heaters (Omega Technologies Co.) and a temperature controller (Omega Model CN76000). An over-temperature probe (I^2R Model OTP-1500) was also employed as safety precaution to prevent the block from overheating in the case of a temperature controller failure. The heating block was preheated to desire temperatures ranging from 125-275°C and the pressures in the individual reactors was generated

solely by the vapor pressure of the liquid medium (approximately 2 to 40 atm, see Figure 3-7). The reactors reached the reaction temperatures in less than 5 minutes (see Figure 3-8) and were withdrawn at various reaction times and quenched in a room temperature water bath and reached 25°C in less than 2 min. Upon completion, the reactor contents were diluted in acetonitrile in a single phase and separated and quantified using HPLC (HP 1100 with a UV detector using a Phenomenex Luna 5µm C18(2) reverse phase column) and LCMS (Waters Alliance 2965 Separations Module with a Waters 2998 PDA and a Waters 3100 SQD MS (ESI positive) using a Phenomenex Luna C18(2) column (3 µm, 4.6 x 75mm)).

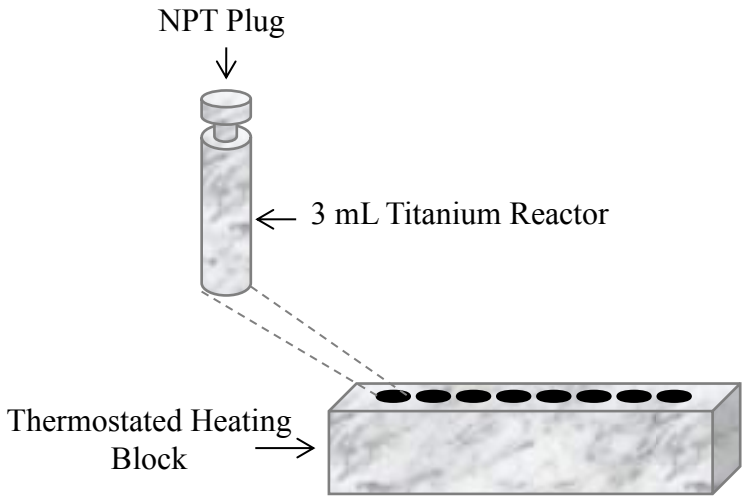


Figure 3-6 Titanium batch reactor and thermostated aluminum heating block

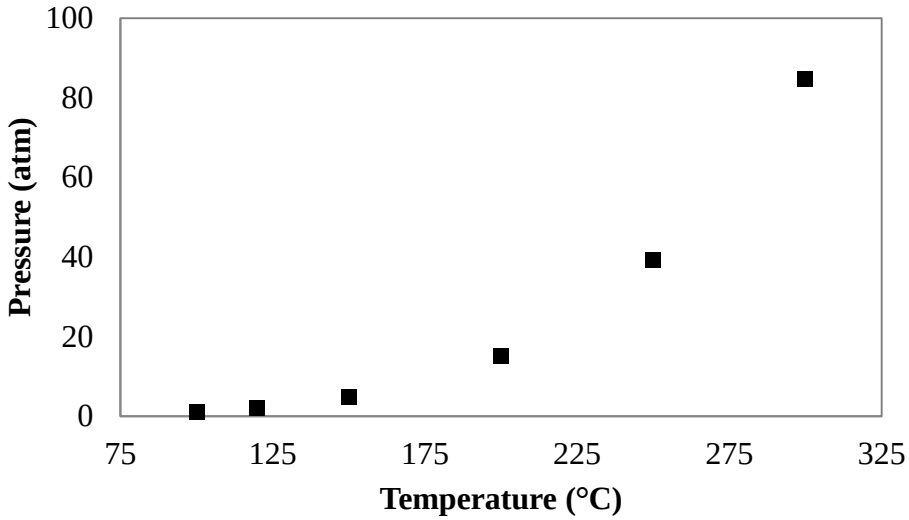


Figure 3-7 Pressure generated solely by the expansion or vapor pressure of the water

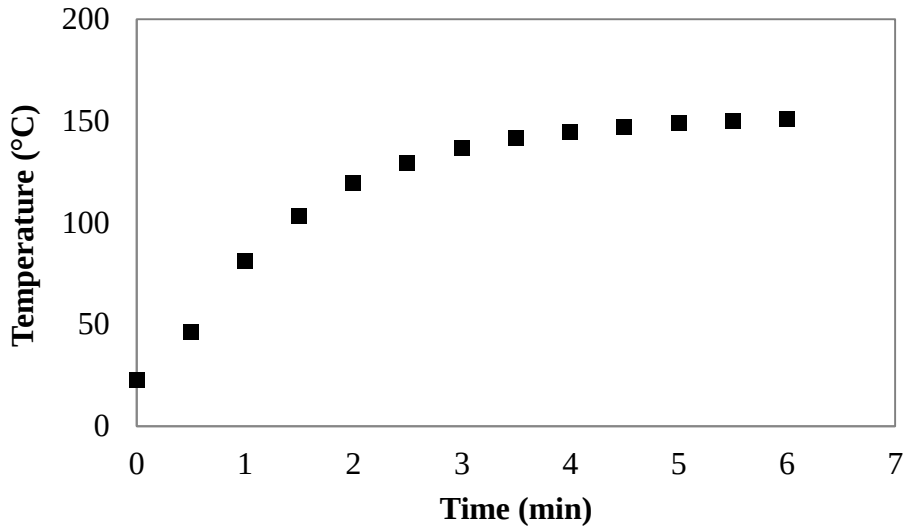


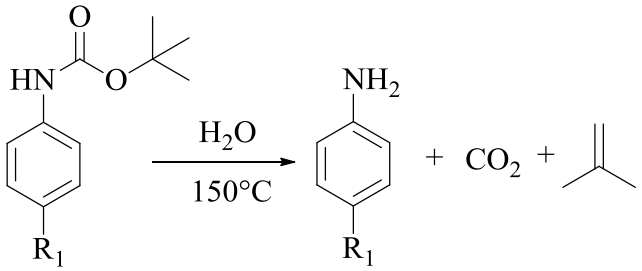
Figure 3-8 Reactors heating rate for the WET experiments (T_{set}=150°C)

3.3 Results and Discussion

3.3.1 Carbamates to amines

Amine protecting groups are frequently employed to decrease the nucleophilicity of an amino group in order to perform other transformations within the molecule. Among various amine protecting groups, the *tert*-butylcarbamate (Boc) group is perhaps one of the most widely used due to its stability towards a variety of reagents and reaction conditions. In addition, it can be easily cleaved with a strong acid, such as a solution of hydrochloric acid and ethyl acetate at 25°C for 30 minutes [25]. The removal of the N-Boc group was investigated using pure water at elevated temperatures (WET). Initial experiments for the removal of the Boc group from a model compound, *tert*-butyl phenylcarbamate, were performed at temperatures in the near critical region. Temperatures of 250°C and 200°C were examined; in both cases, the removal of the Boc group went to completion in very short reaction times. To investigate the kinetics and mechanism of the reaction, the temperature was lowered to give slower deprotection rates. A lower temperature of 150°C was further investigated with different *para*–substituted Boc protected anilines. The results for the removal of the Boc group or the transformation from carbamates to anilines using water at elevated temperatures (WET) at 125 to 150°C are summarized in Table 3-1. The general reaction mechanism for the WET-mediated removal of the *tert*-butylcarbamate (N-Boc) group from several protected anilines in WET at 150°C is given in the reaction scheme from Table 3-1. Along with the deprotected aniline derivatives, carbon dioxide (CO_2) and *iso*-butylene are also products formed during the reaction.

Table 3-1 Removal of the N-Boc group: Carbamates to anilines[a]



Entry	R_1	Time (min)	Yield (%)[b]
1	H	16	85
2	OMe	30	87
3	Cl	84	100
4	NAc[c]	10	98
5	NPiv[d]	45	89
6	OAc,[c,e]	90	78

[a] All the reactions were conducted using 0.5mmol of substrate in 1.5mL de-ionized water at 150°C in a closed vessel
[b] Calculated based on HPLC results and calibration curves
[c] Ac = Acetyl: $(C=O)CH_3$
[d] Piv = Pivaloyl: $(C=O)C(CH_3)_3$
[e] At 125°C to eliminate side reactions like the removal of the OAc group.

The ionization constant [14] of water significantly increases at elevated temperatures, resulting in a higher concentration of hydronium and hydroxide ions. As a result, these ions can acid or base-catalyze the reaction. I proposed that the mechanism for the removal of the Boc group goes through an acid-catalyzed mechanism in WET (See Figure 3-9). During the acid-catalyzed mechanism, you can distinguish that water clearly acts as a reactant, catalyst and solvent in the removal of protecting groups such as the Boc group. As discussed previously, the reaction will produce the deprotected aniline derivative, carbon dioxide (CO_2) and *iso*-butylene. Furthermore, the CO_2 formed during the reaction can potentially react with water to form carbonic acid and/or react with the aniline to form carbamic acid.

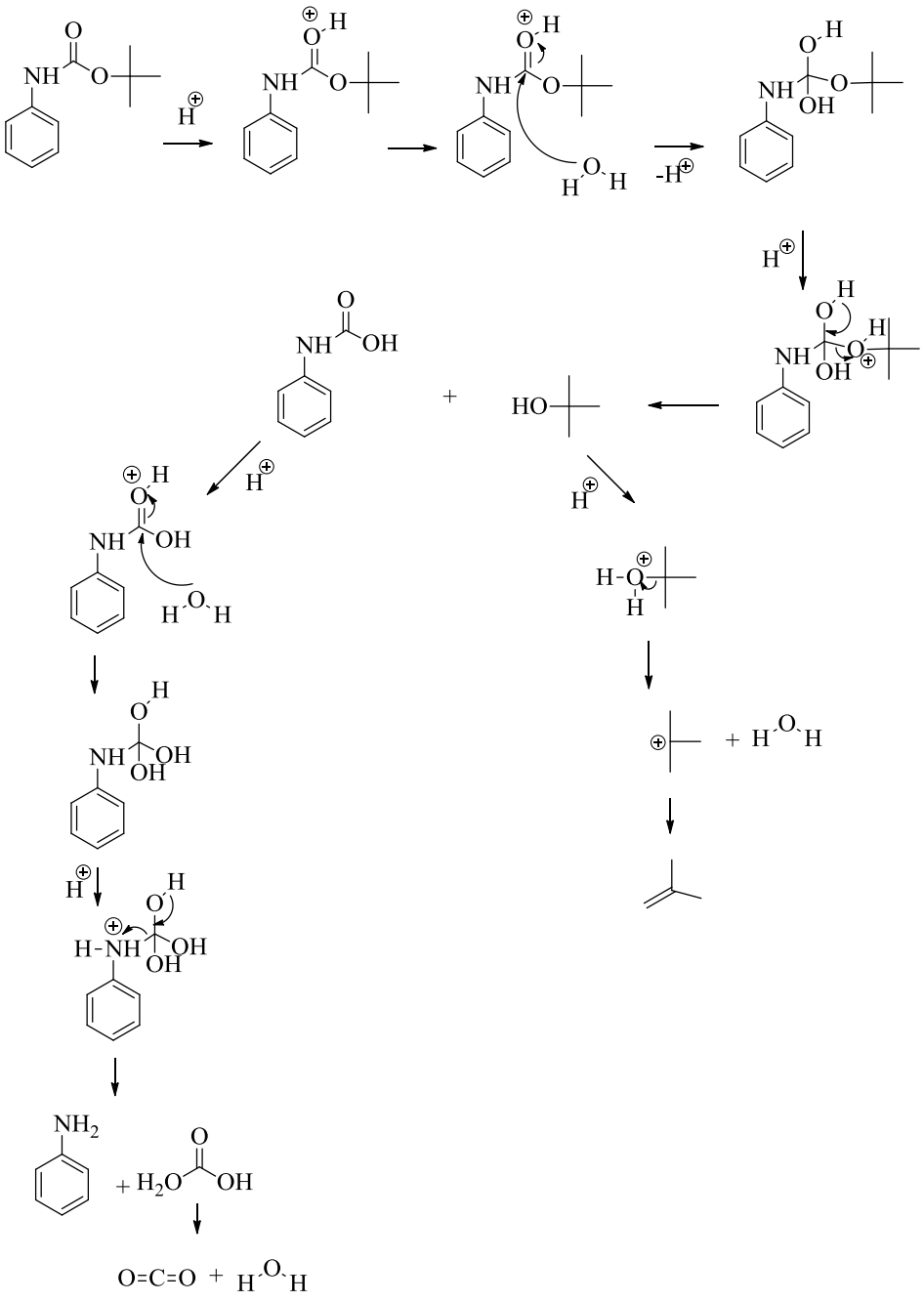


Figure 3-9 Acid-catalyzed N-Boc deprotection

The *tert*-butylcarbamate derivatives of aniline, *p*-methoxyaniline, and *p*-chloroaniline were subject to WET at 150°C (Table 3-1, Entries 1-3). These three substrates were chosen in order to explore the effect of electron-donating (*p*-OMe) and electron-withdrawing (*p*-Cl) substituents on the rates of hydrolysis. The yield as a function of time for each of these reactions is displayed graphically in Figure 3-10. The effect of substituent in the *para*-position (H, OMe, Cl) appears to be significant. If the electronic effect of the R_1 substituent were to be dominant, the electron withdrawing Cl-group would be expected to be the fastest reaction. However, the rates for hydrolysis of the Boc protecting groups follow the order: aniline > *p*-methoxyaniline > *p*-chloroaniline. Consistent with our findings, literature examples in which the deprotection was conducted in water attributed the difference in the reaction rates to the substrates solubilities [17, 20]. As a result the electronic effects are masked by the solubility of the substrates in water. In contrast, the results reported herein were conducted at a substantially higher temperature (150°C) in closed vessels such that the CO_2 generated cannot escape the reaction vessel. This is an important distinction since both carbonic acid [26] and carbamic acids would be present in the closed system to acid-catalyze the hydrolysis (Figure 3-11). The CO_2 produced during the removal of the Boc group will react with water to form carbonic acid and in addition the CO_2 can also react with the aniline derivative to form carbamic acid as shown in Figure 3-11.

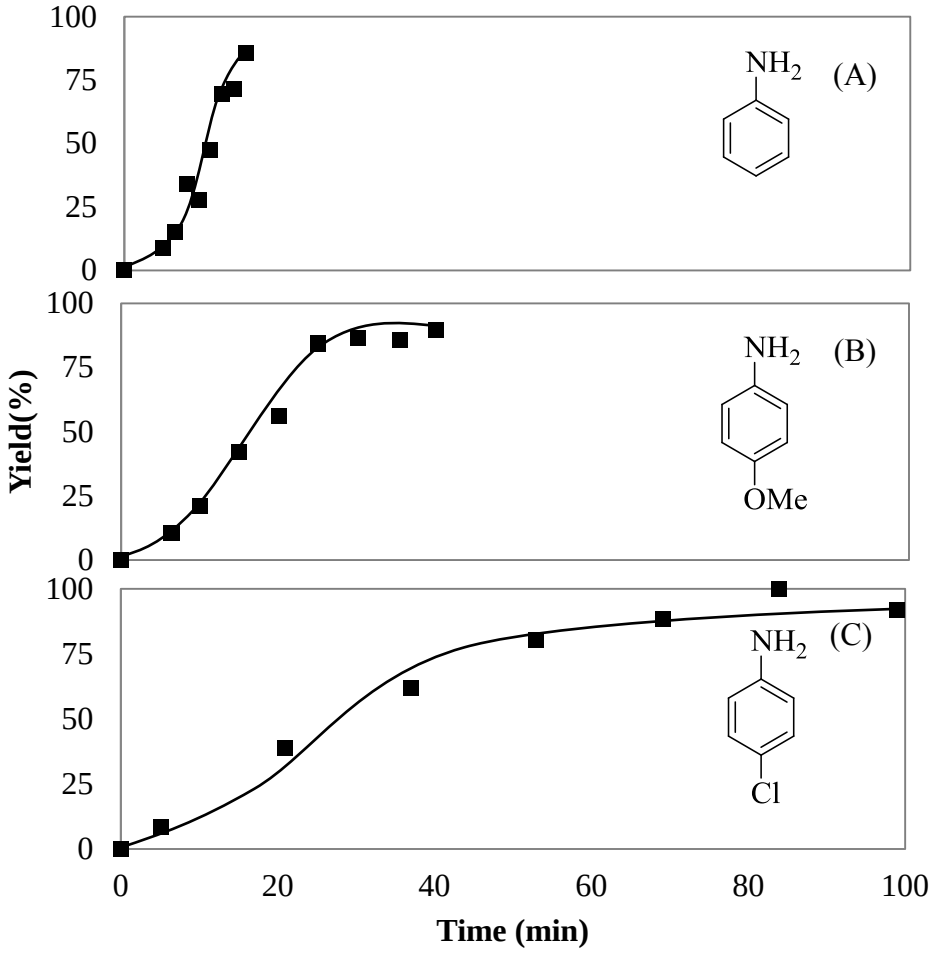


Figure 3-10 Removal of N-Boc group from different protected anilines as a function of time: (A) yield of aniline (Entry 1), (B) yield of *p*-methoxyaniline (Entry 2), (C) yield of *p*-chloroaniline (Entry 3)

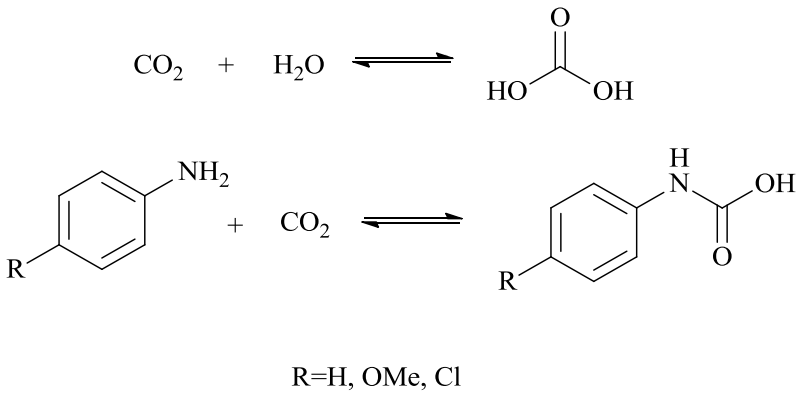


Figure 3-11 Formation of carbonic acid from water and the formation of carbamic acid from the aniline derivative with the CO_2 generated during the removal of the *tert*-butylcarbamate (Boc) group

In addition, Figure 3-12 shows the HPLC chromatograms as a function of time for the removal of the *tert*-butylcarbamate (Boc) protecting group from *tert*-butyl phenylcarbamate (Table 3-1, Entry 1). The deprotected aniline product (retention time of 1.7 minutes), and the protected *tert*-butyl phenylcarbamate (retention time of 9.5 minutes) are labeled as 1 and 3, respectively. However, an unknown peak was observed at a retention time of 5.3 minutes (labeled 2). Interestingly, the unknown was neither present at the beginning nor at end of the reaction, but remained relatively steady during the course of the reaction. This tends to suggest that it correspond to an intermediate product. A similar peak was observed for the chloro- and methoxy-substituted anilines (Table 3-1, Entries 2 and 3). Although the removal of the N-Boc group from different protected anilines in WET has been reported in literature, no documentation of an intermediate or possible mechanistic pathways were offered [17, 20]. The molecular weight of the intermediate in Figure 3-12 at 5.3 minutes was determined to be 212 g/mol by LC-MS, consistent with the structure of 1,3-diphenylurea shown in Figure 3-13.

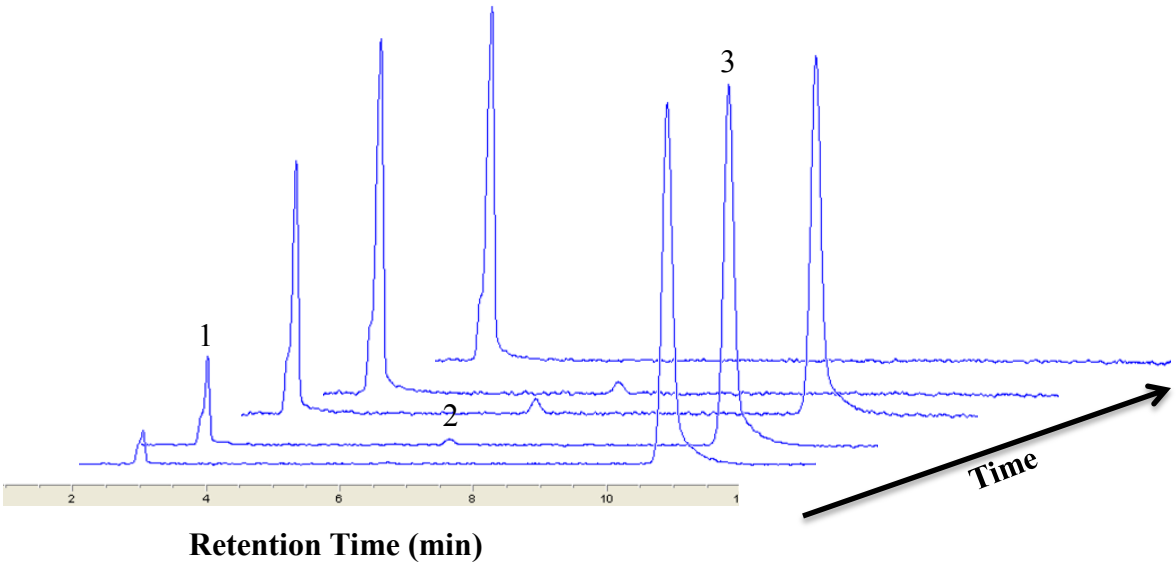


Figure 3-12 HPLC chromatograms for the removal of the Boc group from *tert*-butyl phenylcarbamate showing the appearance of aniline (1), the appearance of 1,3-diphenylurea (2) intermediate and the disappearance of *tert*-butyl phenylcarbamate (3)

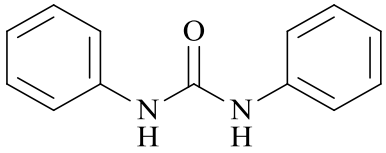


Figure 3-13 1,3-diphenylurea (2) intermediate structure

The 1,3-diphenylurea is a potential intermediate as shown in Figure 3-14. During the reaction the aniline derivative product can act as a nucleophile and attack the unreacted protected aniline to form the 1,3-diphenylurea intermediate. By analogy with the Boc-protected aniline, the urea intermediate can undergo hydrolysis to yield the corresponding aniline.

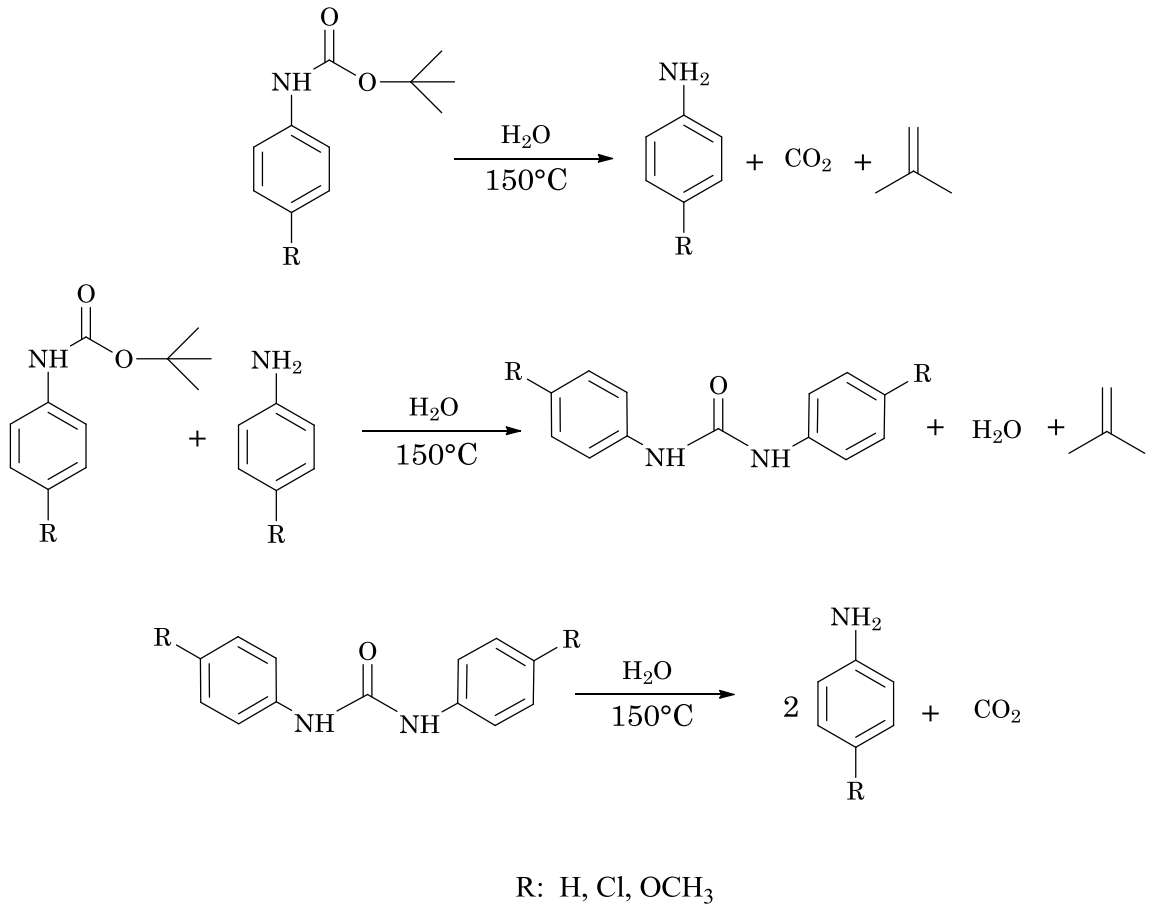


Figure 3-14 Mechanistic insight into the selective removal of N-Boc protecting group from different protected anilines

I also investigated the competitive and selective removal of an N-Boc protecting group in the presence of a second amine-protecting group (Table 3-1, Entries 4 and 5) and an alcohol-protecting group (Table 3-1, Entry 6). The removal of the Boc group from the protected aniline containing a second amine-protecting group was done in WET at 150°C. The yields as a function of time for each of these reactions are graphically displayed in Figure 3-15. The rates of hydrolysis of the Boc protecting groups follow the order: N-(4-aminophenyl) acetamide > N-(4-aminophenyl) pivalamide. In these cases of using WET at 150°C, the N-Boc groups were cleaved selectively to the corresponding

amines in high yields leaving the amides remaining intact. Since the pivaloyl (Piv) group is a more hydrophobic group than the acetyl group (Ac), the longer reaction time of Entry 5 was also expected due to its lower solubility.

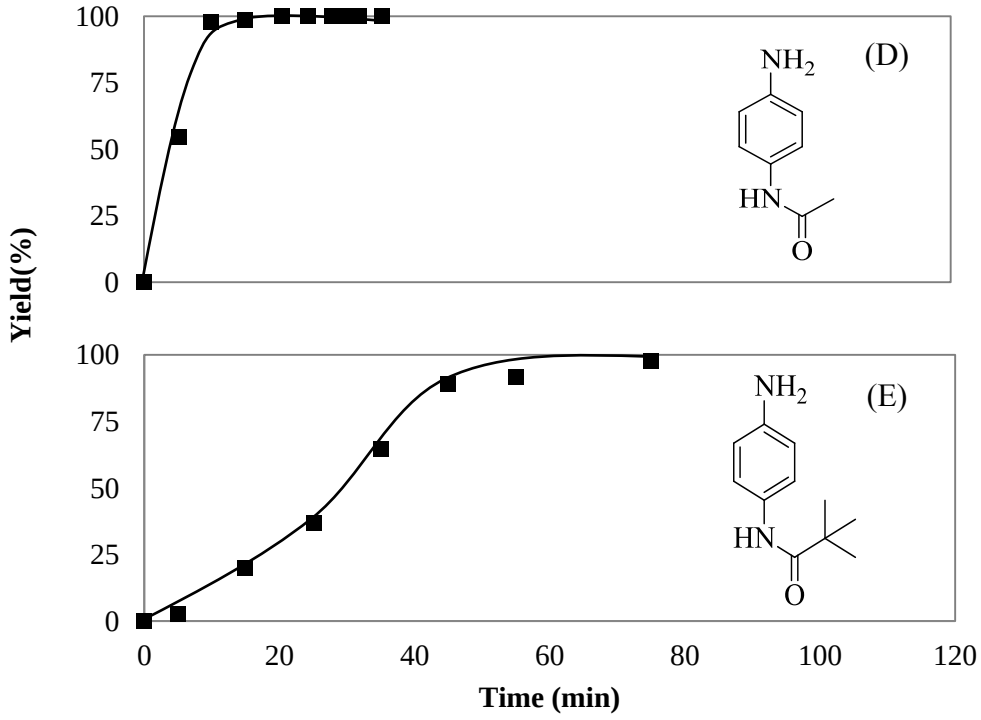


Figure 3-15 Removal of N-Boc group of different protected anilines containing a second amine-protecting group as a function of time: (D) yield of N-(4-aminophenyl)acetamide (Entry 4) and (E) yield of N-(4-aminophenyl)pivalamide (Entry 5)

The selective removal of the Boc group in the presence of an alcohol-protecting group (O-Ac) was also investigated (Table 3-1, Entry 6). In this case, the reaction was carried out at a lower temperature of 125°C and the results are summarized in Figure 3-16. By tuning the temperature, we were able to remove selectively the Boc group while leaving the O-Acetyl (O-Ac) group intact. A lower reaction temperature was

necessary to maintain high selectivity toward the removal of the Boc group. At 150°C, the O-Ac was partially cleaved (96% conversion and 70% yield after 40 min at 150°C).

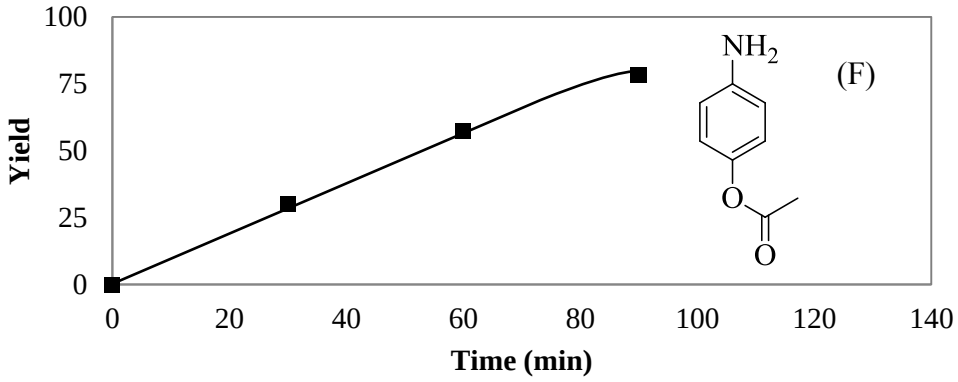


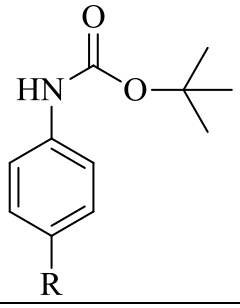
Figure 3-16 Removal of N-Boc group from protected aniline containing a second alcohol-protecting group as a function of time: (F) yield of 4-aminophenyl acetate (Entry 6)

3.3.1.1 Estimation of the solubility of tert-butylphenyl carbamates substrates

I suggest that the differences in the reaction rates for the removal of the Boc group from different *tert*-butyl phenylcarbamates are mainly due to the solubility, instead of any electronic effects from the *para*-substituents. This would be consistent with the suggestion of J. Wang et al. who reported the hydrolysis of Boc derivatives of nitrogen-containing heterocycles, aryl amines, and a variety of aliphatic and alicyclic amines in boiling water (100°C) open to the atmosphere [17], as well with G. Wang et al. who reported the N-Boc deprotection of variety of aromatic and aliphatic protected amines in water at 150°C [20]. Nevertheless, the studies reported here were conducted at a substantially higher temperature where the dielectric constant of water is approximately 45, similar to that of acetonitrile. As a consequence, I estimated the solubility of our substrates in water at 25°C in order to determine if the reaction rates were reflecting any

mass transfer limitation. Because the Boc substrates react rapidly with water at 150°C their solubilities could not easily be determined experimentally at higher temperatures. The solubility of the different substrates was predicted using COSMO-RS and ACD Software at 25°C. The results are summarized in Table 3-2 and the trend of the solubilities at 25°C follow the order: *tert*-butyl phenylcarbamate ≥ *tert*-butyl (4-methoxyphenyl) carbamate > *tert*-butyl (4-chlorophenyl) carbamate and *tert*-butyl (4-acetamidophenyl) carbamate > *tert*-butyl (4-pivalamidophenyl) carbamate. This same trend should be followed at higher temperatures, although the solubility of the substrates is enhanced as the temperature increases. The reaction rates followed the solubility trend estimated.

Table 3-2 Estimated solubilities at 25°C

Substrate: 		
	Estimated by COSMO-RS	Estimated by ACD Software
R	**Solubility (g/L water)**	
H	0.12	0.33
OMe	0.12	0.31
Cl	0.03	0.06
N-Ac	0.87	
N-Piv	0.06	

3.3.2 Amides to amines

Another common amine protecting group is the N-Acetyl (N-Ac) and its removal also requires heating in strongly acidic or basic solutions. For example, N-Ac groups could be hydrolyzed using a hydrochloric acid/water solution at reflux temperature for one hour[27]. The removal of the N-Ac group from N-phenyl acetamide at different temperatures was examined. The conversion of N-phenyl acetamide to aniline at 275°C proceeded faster than at 250°C, while at 200°C the reaction did not progress (Figure 3-17). As a result, the deprotection of aryl acetamide model compounds to their corresponding amines using WET was investigated at 275°C and the results are summarized in Table 3-3. The yield as a function of time associated with each of these reactions is graphically displayed in Figure 3-18. When the reactions were conducted in the presence of air (Entries 7 and 9), the conversion of the amide was high (almost quantitative) but the yields of the aniline products were comparatively low (35% and 46%, respectively). The liquid chromatography-mass spectroscopy (LCMS) analysis enables the identification of the major by-product as phenazine (an oxidation product) shown in Figure 3-19. We repeated the reactions with the exclusion of air (Entries 8 and 10) and obtained close to quantitative yields (97% and 92%, respectively). As anticipated, only traces of phenazine were then detected.

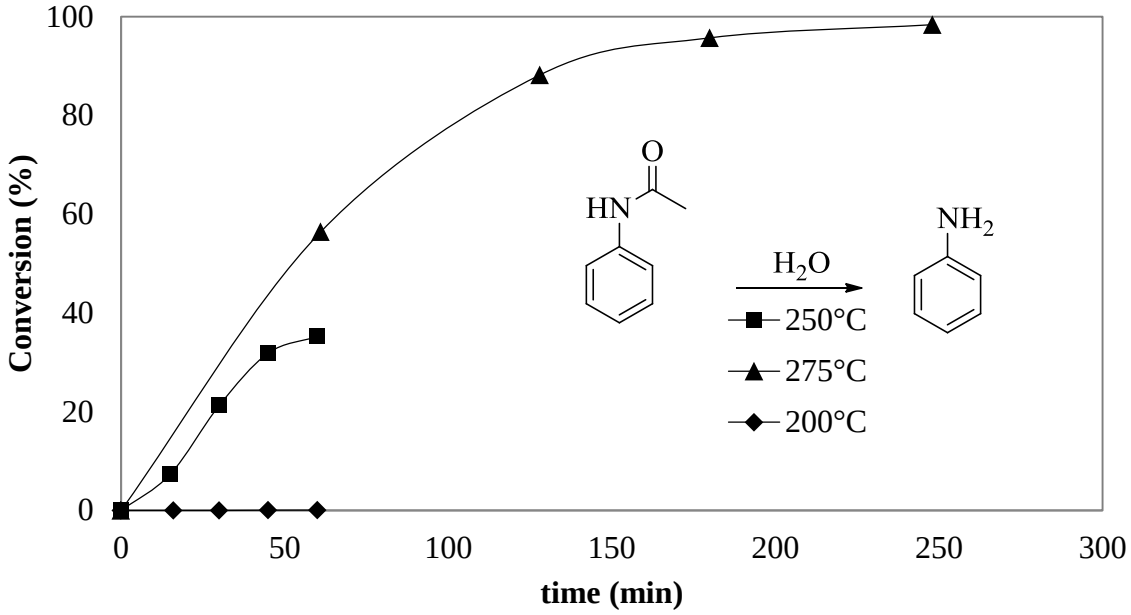
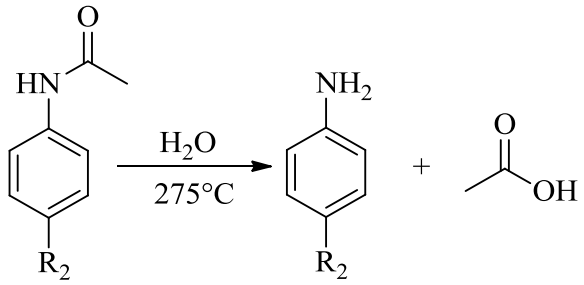


Figure 3-17 Removal of the N-Ac group: Conversion of N-phenyl acetamide to aniline as a function of time at different reaction temperatures

Table 3-3 Removal of the N-Ac group: Amides to anilines[a]



Entry	R_2	Time (min)	Yield (%)[b]
7	H	250	35
8[c]	H	250	97
9	OMe	400	46
10[c]	OMe	400	92

[a] All the reactions were conducted using 0.5mmol of substrate in 1.5mL de-ionized water at 150°C in a closed vessel

[b] Calculated based on HPLC results and calibration curves

[c] Reaction conducted with degassed water and under nitrogen atmosphere

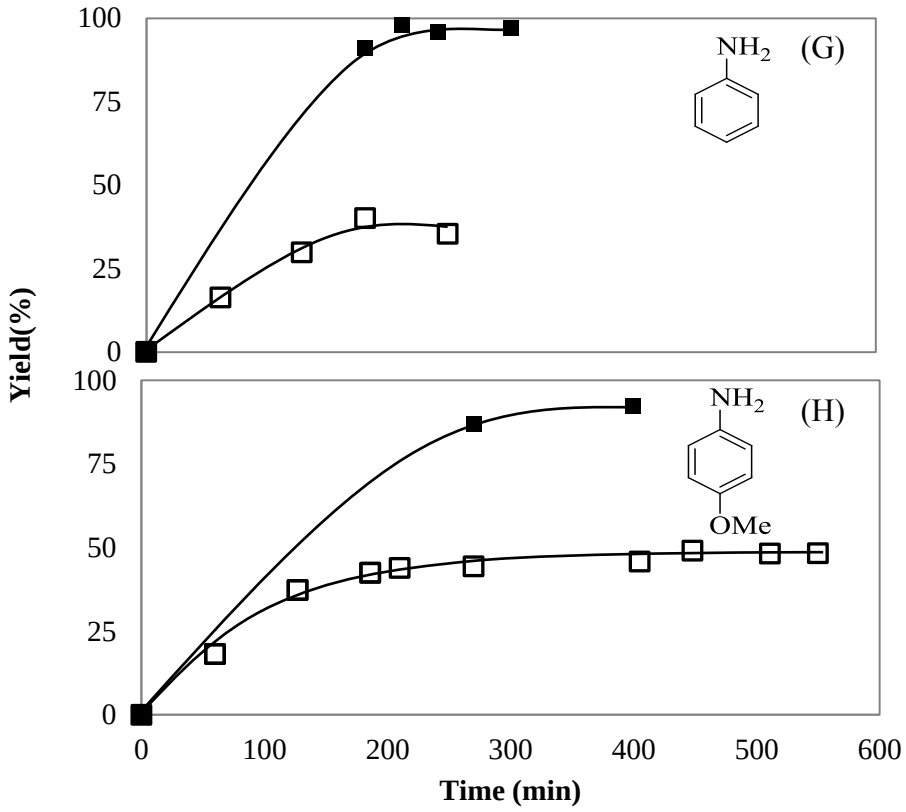


Figure 3-18 Removal an amide protecting group from different protected anilines as a function of time: (G) yield of aniline (Entry 7 and 8) under air atmosphere (□) and under N_2 atmosphere (■), (H) yield of 4-aminophenol (Entry 9 and 10) under air atmosphere (□) and under N_2 atmosphere (■)

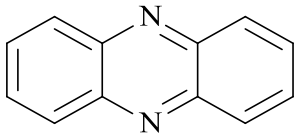


Figure 3-19 Structure of Phenazine (MW= 180g/mol)

3.3.3 Acetates to alcohols

A protecting group utilized in the protection of hydroxyl groups is the acetate ester (O-Ac). Generally, O-Ac can be cleaved under basic conditions, such as using potassium carbonate in a solution of methanol/water at 20°C for one hour. I investigated the deprotection of the phenyl acetate derivatives to their corresponding phenols using WET at different temperatures. As shown in Figure 3-20, at 250°C the reaction proceeded at a higher rate, than at 200°C and 150°C. As a result the removal of the O-Acetyl (O-Ac) group was conducted in WET at 250°C and the results are summarized in Table 3-4. Figure 3-21 shows the yield as a function of time for N-(4-hydroxyphenyl) acetamide (Entry 12). The reactions proceeded rapidly in less than 30 minutes. In the case of the phenyl acetate (Table 3-4, Entry 11), the deprotection was achieved in 20 minutes and 92% yield was obtained. In the case of the N-Acetyl (N-Ac) substituted compound (Table 3-4, Entry 12), complete selective deprotection of the O-Ac group was obtained in 30 minutes at 250°C, leaving the amide (N-Ac) group intact.

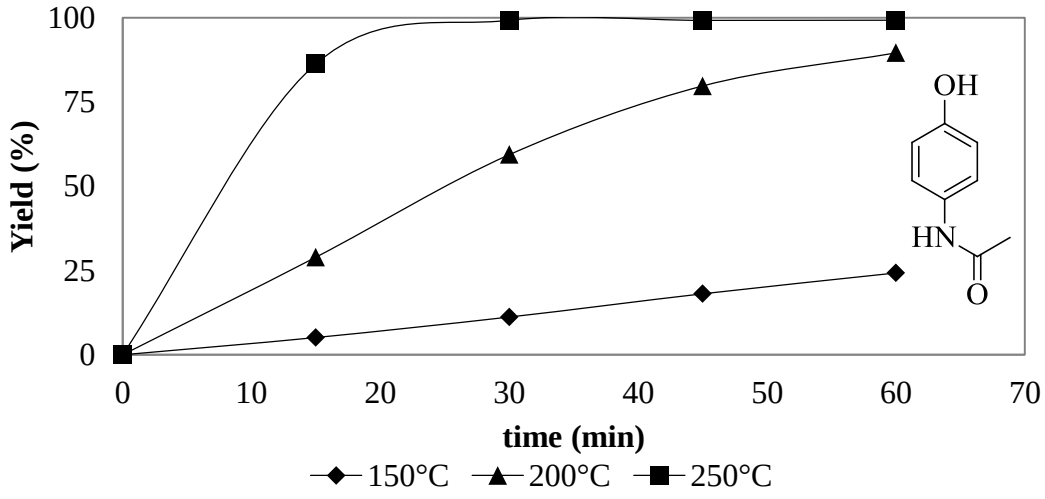
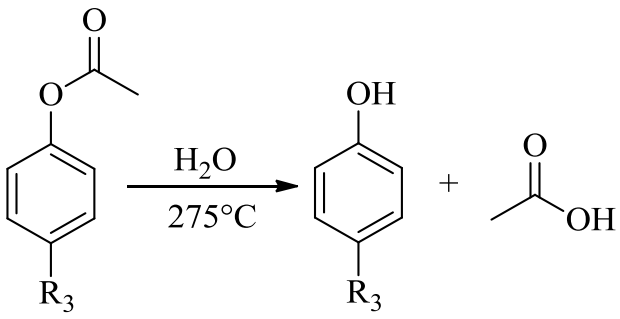


Figure 3-20 Removal of O-Ac group: yield of N-(4-hydroxyphenyl) acetamide as a function of time at different temperatures

Table 3-4 Removal of the O-Ac group: Acetates to alcohols[a]



Entry	R_3	Time (min)	Yield (%)[b]
11	H	20	92
12	NAc	30	99

[a] All the reactions were conducted using 0.5mmol of substrate in 1.5mL de-ionized water at 150°C in a closed vessel

[b] Calculated based on HPLC results and calibration curves

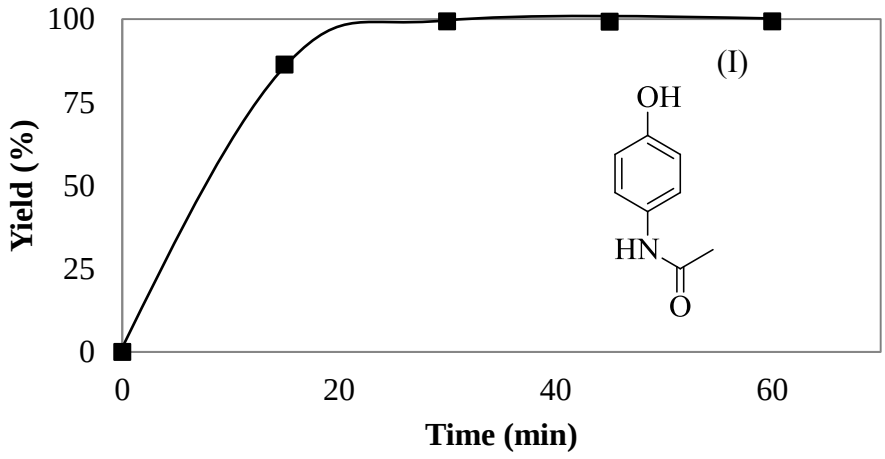


Figure 3-21 Removal of an ester group from a molecule containing an alcohol and an amine-protecting group as a function of time: (J) yield of N-(4-hydroxyphenyl) acetamide (Entry 12)

3.4 Conclusions

Water is an attractive solvent for the development of sustainable, environmentally greener processes. This study demonstrated its ability to act as the solvent, reactant, and catalyst for the selective removal of protecting groups such as carbamates, amides and esters. The N-Boc anilines derivatives were fully deprotected at relatively mild temperatures (125 to 150°C) and short reaction times (less than 2 hours). Amides and acetates were also successfully cleaved at higher temperatures, 275°C and 250°C respectively. I demonstrated that the reaction selectivity can be tuned by controlling "water's catalytic activity" by adjusting the temperature. Several scenarios were explored for proof of concept: 1) selective removal of a carbamate group (N-Boc) in the presence of amides (N-Ac and N-Piv) and acetates (O-Ac), and 2) selective deprotection of an acetate (O-Ac) group in the presence of an amide (N-Ac). In all cases, I achieved the selective and near quantitative deprotection of the targeted group. In addition, water is an *in situ*, reversible catalyst. Consequently, water-mediated deprotections are conducted without acids or bases and eliminate the subsequent neutralization step.

3.5 References

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CHAPTER 4 - ORGANIC-AQUEOUS TUNABLE SOLVENTS (OATS) FOR *p*-METHYLSTYRENE HYDROFORMYLATION AND CATALYST RECYCLE

4.1 Introduction

Generally, catalytic reactions can be achieved by using either homogeneous or heterogeneous organometallic complexes. Homogeneously catalyzed reactions are characterized by faster reaction rates and higher selectivities than their heterogeneously catalyzed counterparts. However, the difficulty of separating and recycling the homogeneous catalyst results in product contamination and in serious limitations for its applications. This problem arises because the separation of homogeneous catalyst is commonly done by thermal operations such as distillation, which requires elevated temperatures, but most of the catalysts used are temperature sensitive and very expensive and it will lead to thermal stresses on the catalyst and can cause possible decomposition reactions. On the other hand, heterogeneous catalyzed reactions allow easy and efficient separation of high value products from the catalyst. However, the selectivity and reaction rates are often limited by the multiphasic nature of this system and variations in active sites distribution from the catalyst.

Obtaining high yields alone are important in a chemical reaction process, but it is also greatly important to achieve product separation from the catalyst. Generally, in a chemical process the separation step consists of approximately three-fourths of the total number of unit operations and accounts for 60 to 80% of the overall cost [1]. In addition the solvents used for the reactions and separation steps can greatly influence the chemical processing. The solvent can affect reaction rates, dictate separation processes and impact

human health and the surrounding environment, in addition to playing an important role in process economics [2, 3]. For these reasons, heterogeneous catalysis is the more common type. The simple and complete separation of the product from the catalyst makes heterogeneous catalysis economically attractive because many catalysts are quite valuable and their reuse is demanded. But it is not the case for the hydroformylation process.

Hydroformylation reaction is one of the most important homogeneous transition metal catalyzed reaction in industry today for the production of aldehydes [4]. This chemical reaction involves the addition of a formyl group (CHO) and a hydrogen atom (H) to a carbon-carbon double bond (Figure 4-1). The process utilizes cheap and abundant syngas (H_2/CO) as a feedstock. Several metals have been described as catalyzing this reaction, but only systems based on cobalt (Co) and rhodium (Rh) are industrially applied. The oxygenated hydrocarbon compounds formed (*i.e.* aldehydes) are important building blocks for fine chemicals and pharmaceuticals. Since its discovery in 1938 by Otto Roelen, this reaction has gained significant interest from industry and academia [5]. Many efforts had led to development of more efficient catalysts and finding ways to increase the selectivity to linear or branched aldehydes, reduce the by-product formation, and achieve milder and more environmentally friendly reaction conditions.

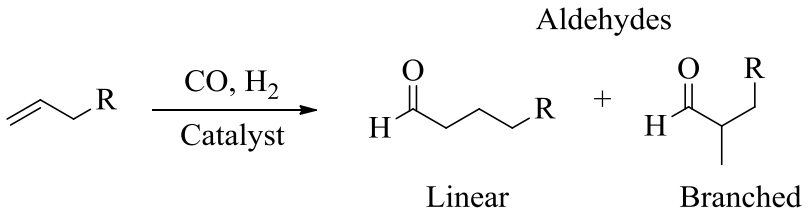


Figure 4-1 General Hydroformylation Reaction

A challenge in the development of new catalytic processes for the hydroformylation reaction is the full separation of the catalyst components (i.e. catalyst and ligand) from the products [6, 7]. Only extremely small residues of metals or ligands are often tolerated in the final product, particularly in the case of active pharmaceutical ingredients; additionally, environmental and cost considerations urge the development of processes that enable the separation and reuse of the catalyst [1]. The two processes under investigation for the hydroformylation process separation can be divided into two categories: (1) biphasic system, where the separation is performed by decantation (catalyst is soluble in one phase and the product in the other one) and (2) supported catalysts, where the separation is performed by filtration [7, 8]. A two phase hydroformylation process used industrially to sequester the catalyst and easy recycle is the Ruhrchemie-Rhône Poulenc process [9]. In this process, the catalyst uses a water soluble ligand, tris(3-sulfophenyl)phosphine trisodium salt (TPPTS), which will remain in the aqueous phase where the reaction occurs, while the products partition primarily into the organic phase. The reaction takes place under vigorous mixing to ensure maximum contact between the catalyst and the substrate. After the reaction is completed, the mixture is allowed to settle and the product is decanted, leaving the catalyst in the

aqueous phase for reuse and recycle. Although a commercial process, the Ruhrchemie-Rhône Poulenc process remains limited to short-chain olefins like propene because of the low solubility of higher olefins in water [10]. The other technique, which has been studied over the past years, is to immobilize complex catalysts on solid supports. These heterogeneous catalysts require harsher conditions than well-tuned homogenous catalysts and the continuous loss of the metal or catalyst leaching and low reaction rates are serious disadvantages.

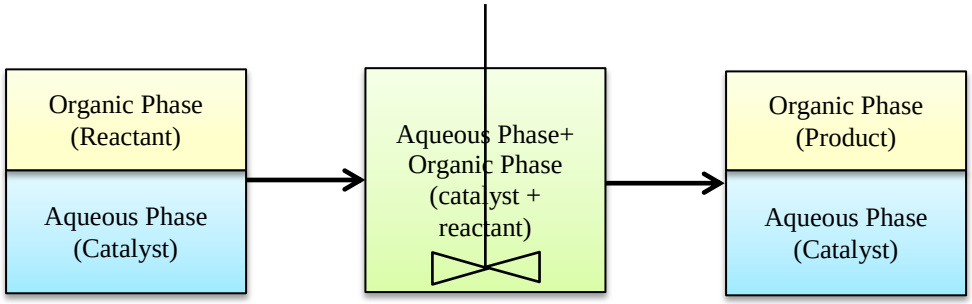


Figure 4-2 General principle of a two-phase hydroformylation process

To address these concerns our alternative tunable solvent system can offer an efficient, simple, and sustainable method for coupling homogeneous reactions with heterogeneous separations. Tunable solvents provide simple and efficient vehicles for conducting both reactions and separations [11-18]. Their properties can often be varied by tuning the applied pressure or temperature of the system. An example of a tunable solvent is a gas-expanded liquid (GXL). GXL combines the tunability of super critical fluids (SCFs) with the solvent power of traditional organic solvents (see Figure 4-3). The

addition of gaseous CO_2 to organic solvents to form gas-expanded liquids (GXLs) has been proven to be an effective means of improving mass transfer and gas solubilities in organic reactions [19]. GXLs have been applied to the development of organic- aqueous tunable solvents (OATS), a reaction process that combines homogeneous catalysis with heterogeneous separations.

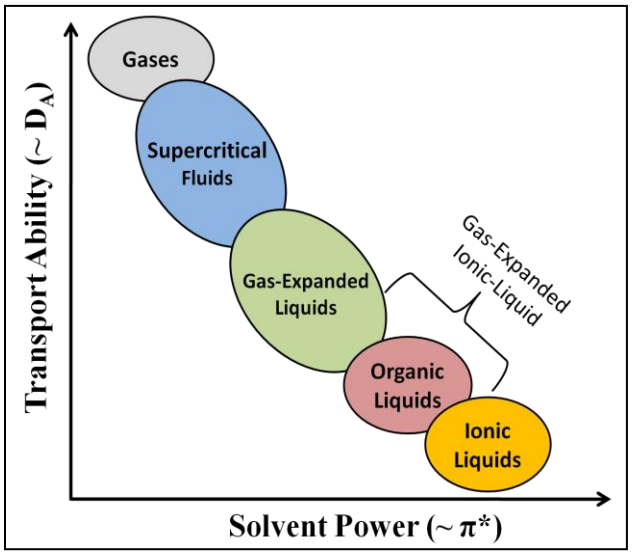


Figure 4-3 Solvent power and transport ability of different types of solvents

We have developed organic-aqueous tunable solvents (OATS) for reactions, which are homogeneous mixtures of a polar aprotic organic solvent (i.e. acetonitrile (ACN) or tetrahydrofuran (THF)) and water. Upon completion of the reaction, carbon dioxide (CO_2) is added to the reaction mixture to induce immiscibility. CO_2 is a cheap, safe, non-toxic, non-flammable additive used to replace a nonpolar organic extraction solvent. The resulting biphasic system consists of a gas-expanded organic phase and an

aqueous phase. Although little CO_2 dissolves in water, it is quite miscible with most organics, and radically lowers the solvent power of the organic phase for ions and other polar compounds. This facilitates the dissolution of hydrophobic substrates in the organic-aqueous mixture for reaction, and facile separation of hydrophobic products and unreacted substrate with the gas-expanded liquid after CO_2 addition by decantation. Subsequently, the CO_2 removal can be achieved by simply depressurization. The use of a hydrophilic catalyst permits facile recycle with the aqueous phase. We control the quality of the phase split and the partition values by adjusting the CO_2 pressure. Finally, after decantation of the gas-expanded organic phase, depressurization permits CO_2 recycle and simplified product purification (see Figure 4-4). Note that CO_2 will be present only during the separation stage of the OATS process. Therefore, any effects of CO_2 on system phase behavior, system pH or substrate/catalyst solubility will not affect the reaction chemistry. Additionally, the pressures required for separation (20-50 bar) are usually lower than those employed in the reaction (50-200 bar).

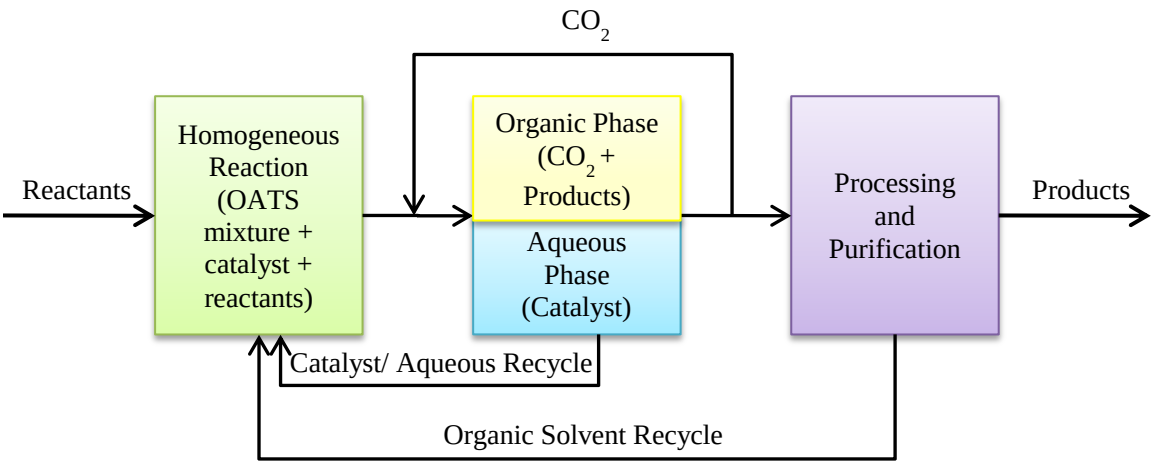


Figure 4-4 General scheme for reactions using OATS

The OATS process results in highly efficient reactions while reducing waste production and improving product quality by minimizing contamination. OATS also offer improved reaction rates, yields, and selectivity (characteristic of homogeneous systems) as well as simple catalyst separation and recycle (characteristic of heterogeneous separations). The OATS system was applied to a number of pharmaceutically relevant reactions with promising results [20-23]. Here we report a new method for performing hydroformylation processes, and show as an example the successful Rh-catalyzed hydroformylation of an aromatic olefin, *p*-methylstyrene[24] (Figure 4-5).

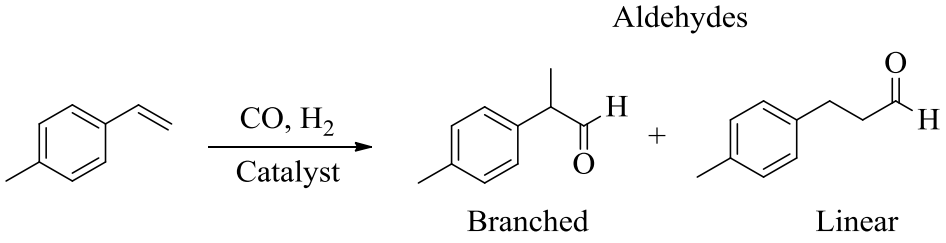


Figure 4-5 Hydroformylation of *p*-methylstyrene

4.2 Experimental Methods

4.2.1 Materials

The following HPLC grade solvents were degassed by the freeze-pump-thaw method for the hydroformylation reactions as received: HPLC grade acetonitrile (Sigma-Aldrich, ≥99.9%), 1,4-dioxane (Fischer Scientific, 99.9%), HPLC grade tetrahydrofuran (THF, Sigma-Aldrich, ≥99.9%, inhibitor free), BHT Stabilized THF (Sigma-Aldrich,

≥99.9%, 250 ppm BHT) HPLC grade water (Sigma-Aldrich), and *p*-methylstyrene (Alfa Aesar, >98%). Other HPLC grade solvents were used as received from Sigma Aldrich: acetone (99.9%), acetonitrile (99.9%), 1,4-dioxane (99%), tetrahydrofuran (99.9%), and water (99.9%). Carbon dioxide was supercritical fluid chromatography grade (SFC grade, Air Gas, 99.999%) and was further purified via a Matheson gas purifier and filter cartridge (Model 450B, Type 451 filter). Synthesis gas (syngas, Air Gas, 1:1 molar ratio of H_2:CO) was used as received. Also, the following materials were used as received and stored in a nitrogen-filled glove box: triphenylphosphine-3-sulfonic acid sodium salt (TPPMS, TCI America, >90%) and rhodium (I) dicarbonyl acetylacetonate (Rh(acac), Sigma-Aldrich, 98%).

4.2.2 Experimental Methods

4.2.2.1 p-Methylstyrene hydroformylation in OATS

Hydroformylations were performed in a 300 mL stainless steel Parr autoclave reactor (Parr Instrument Company, model 4561). The reaction pressure was monitored with a calibrated digital pressure transducer (Heise, model 901B) providing a precision of ± 0.07 MPa. A proportional-integral-derivative (PID) temperature controller and tachometer (Parr Instrument Company, model 4842) were used to control the temperature of the reactor to ± 2°C and the stirring speed to ± 5 rpm. The temperature inside the reactor was monitored with a type J thermocouple and heat was provided by an electric heating mantle. The catalyst solution was prepared by weighing the desired amounts of Rh(acac) and TPPMS in the glove box, adding 70/30 v/v organic/water OATS degassed

solution, and then stirring for at least 20 minutes and visually confirming complete solubility of the catalyst. The reactions were started by evacuating the Parr autoclave and flushing it with 0.3MPa of syngas. The degassed *p*-methylstyrene, the catalyst solution, and OATS solvents were added using gas-tight syringes (SGE Analytical Science). The total volume of the reaction mixture was 50mL with a *p*-methylstyrene concentration of 0.15M. The concentration of Rh(acac) and TPPMS were 0.0016 and 0.017 equivalents, respectively. The reactor was heated to temperature, stirred at 300 rpm, and subsequently pressurized with 3.1MPa of syngas. After the desired reaction period, a liquid phase sample was withdrawn, captured in acetone or methanol, and analyzed with an Agilent gas chromatography-flame ionization detector (GC-FID, model 6890) with an Agilent column (model HP-5MS). External standards of known concentrations were used to calibrate the FID response.

*4.2.2.2 **Partitioning experiments in OATS***

The partitioning experiments of the *p*-methylstyrene hydroformylation reaction were conducted after the hydroformylation reaction was completed. After an ice quench of the reaction, the syngas was vented and the reactor was flushed with CO_2 to remove any syngas and pressurized to 3.1 MPa of CO_2 using an ISCO syringe pump. After equilibrium (we determined independently that equilibrium was reached in 15 minutes of stirring and 30 minutes of settling), three samples each of the organic-rich and of the aqueous-rich phases were taken using dip tubes, as depicted in Figure 4-6. The dip tubes length was designed to be within the intended layer and away from the interface to prevent cross contamination of the samples. Each dip tube was connected to a six-way

port valve with a constant volume sample loop (Figure 4-7) that will allow for precise measurements of the sample volumes extracted from the two phases. Before and after sampling, the sample loop was flushed with at least three times its volume to rinse out any contaminants. Additional experiments corroborated that negligible reactants or catalyst were adsorbed on the walls of the sample loop. The samples from the organic-rich phase (top) were analyzed using the Agilent GC-FID described above to quantify the amount of reactants and products that portioned to that phase. The same mechanism to sample was used for the samples from the aqueous-rich phase, but instead these were analyzed by UV-Vis Spectroscopy to quantify the partition of the ligand (TPPMS) in the aqueous phase.

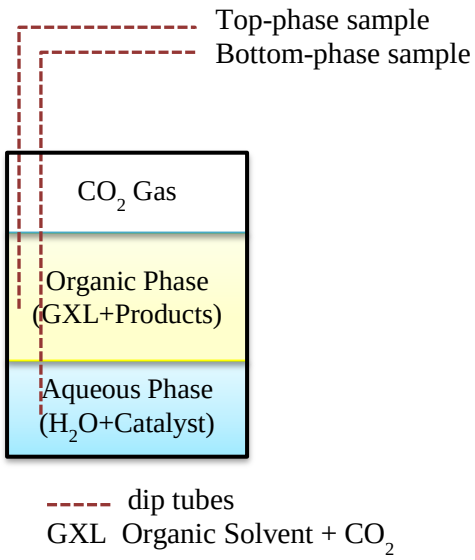


Figure 4-6 Experimental set-up for partitioning experiments under CO_2 pressures

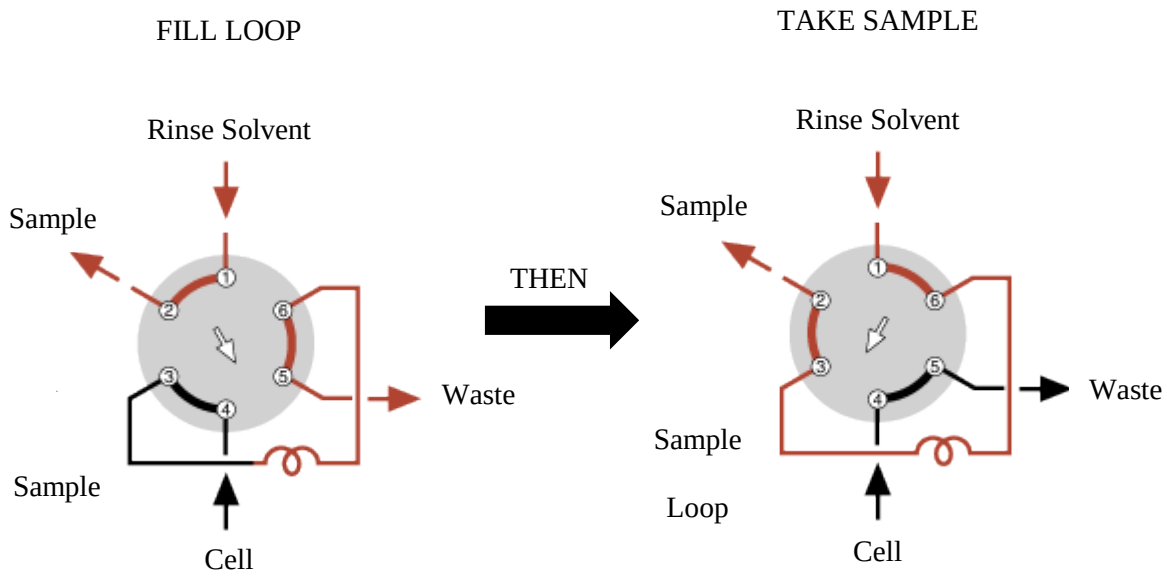


Figure 4-7 Sample loop using a six way port valve mechanism

4.2.2.3 Catalyst recycle experiments in OATS

To demonstrate catalyst recycle, we ran homogeneous hydroformylation reactions in ACN/H_2O OATS. The reaction was carried out with *p*-methylstyrene initial concentration of 0.15 M and with Rh:TPPMS:substrate ratios of 1:10:600 equivalents at 60°C for one hour and 3.1MPa syngas. Samples from the homogeneous reaction mixture were collected to analyze for conversion and selectivity. After an ice quench of the reaction, the syngas was vented and the reactor was flushed with CO_2 to remove any syngas and pressurized to 3.1MPa of CO_2. We were able to remove 85% of the organic-rich layer with the top phase dip-tube so that fresh *p*-methylstyrene and organic solvent could be added and the next reaction cycle started. Make-up catalyst was added to compensate for catalyst removed during sampling to maintain constant catalyst to substrate ratio.

4.3 Results and Discussion

4.3.1 Homogeneous hydroformylation of *p*-methylstyrene

The Rh-catalyzed hydroformylation of *p*-methylstyrene was investigated in organic-aqueous tunable solvents (OATS) in a Parr autoclave reactor. We chose *p*-methylstyrene as model compound, since the branched aldehyde product (2-(*p*-tolyl)-propanal) structurally mimics *p*-isobutylstyrene, a key synthetic precursor to ibuprofen [25, 26]. The rhodium-catalyzed hydroformylation reactions were carried out at a concentration of *p*-methylstyrene of 0.15 M and at 3MPa of syngas (CO/H_2) with the objective of understanding the effect of temperature in the conversion and branched product selectivity. Also, we investigated the effect of solvent in the reaction and on the separation. A summary of the reaction scheme and conditions for the hydroformylation of *p*-methylstyrene to produce the branched and linear aldehyde is shown in Figure 4-8. The hydroformylation reaction was performed using a rhodium catalyst ligated to a hydrophilic ligand, sodium 3-(diphenylphosphino)benzenesulfonate (TPPMS) (Figure 4-9).

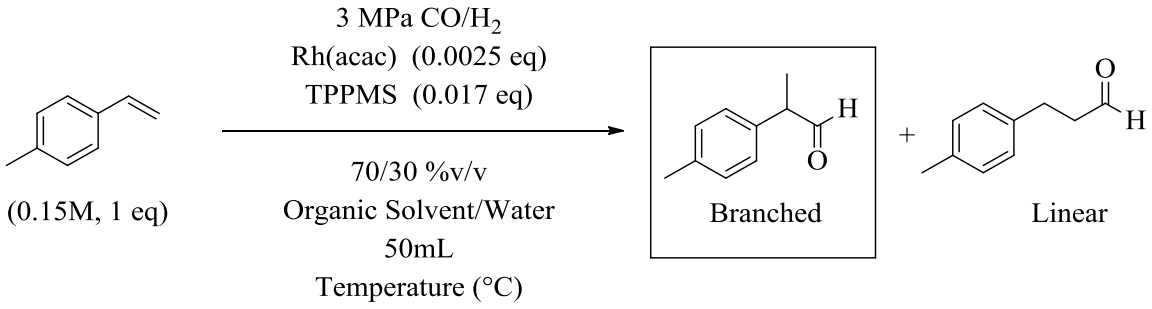
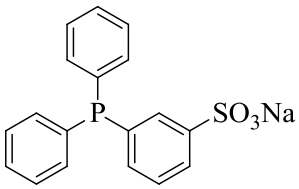


Figure 4-8 Rh-catalyzed hydroformylation of *p*-methylstyrene



TPPMS

Figure 4-9 Hydrophilic ligand for hydroformylation reactions (TPPMS)

4.3.1.1 Temperature effect

The effect of reaction temperature and organic solvent for the homogenous hydroformylation of *p*-methylstyrene to produce 2-(*p*-tolyl)-propanal (branched aldehyde) was investigated (Figure 4-8). The reaction was conducted in three different OATS systems: acetonitrile/water, dioxane/water and tetrahydrofuran/water at different temperatures and the results are displayed graphically in Figure 4-10, Figure 4-11 and Figure 4-12, respectively.

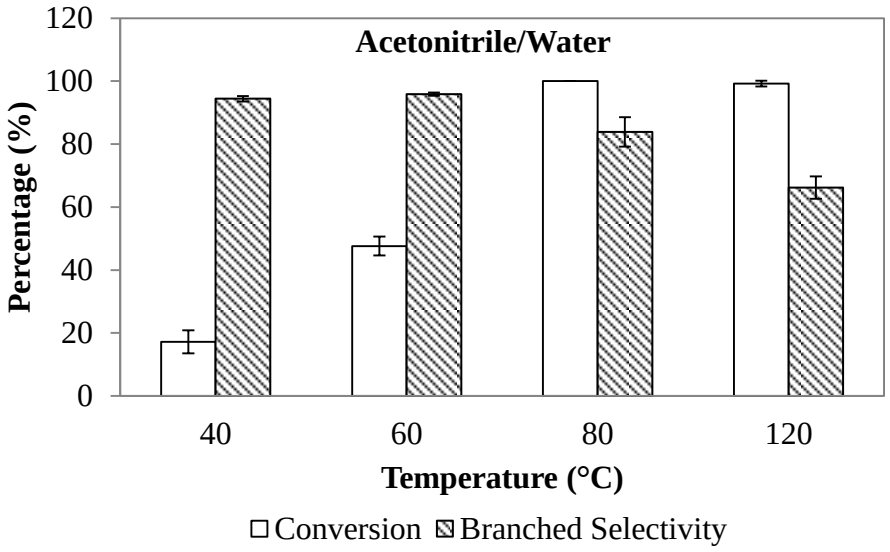


Figure 4-10 Effect of temperature on conversion and selectivity in the hydroformylation of *p*-methylstyrene using an acetonitrile/water OATS system after one hour

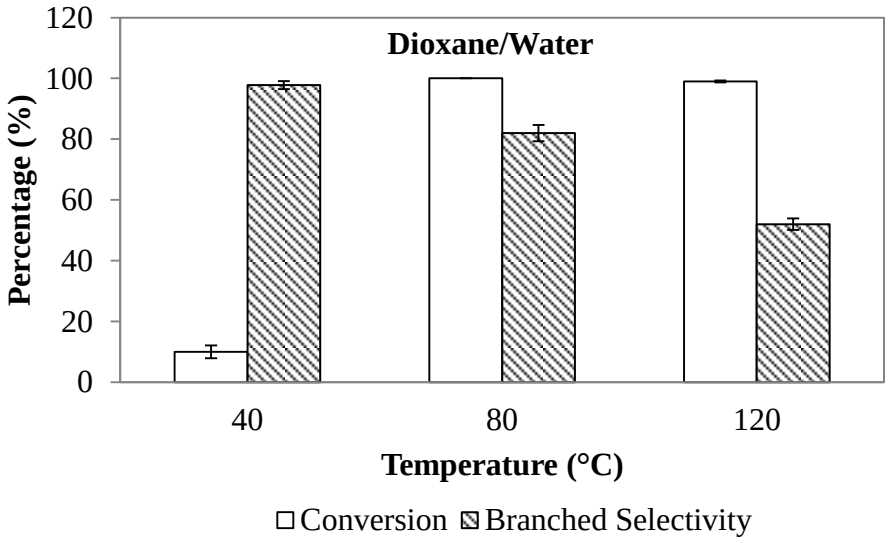


Figure 4-11 Effect of temperature on conversion and selectivity in the hydroformylation of *p*-methylstyrene using a dioxane/water OATS system after one hour

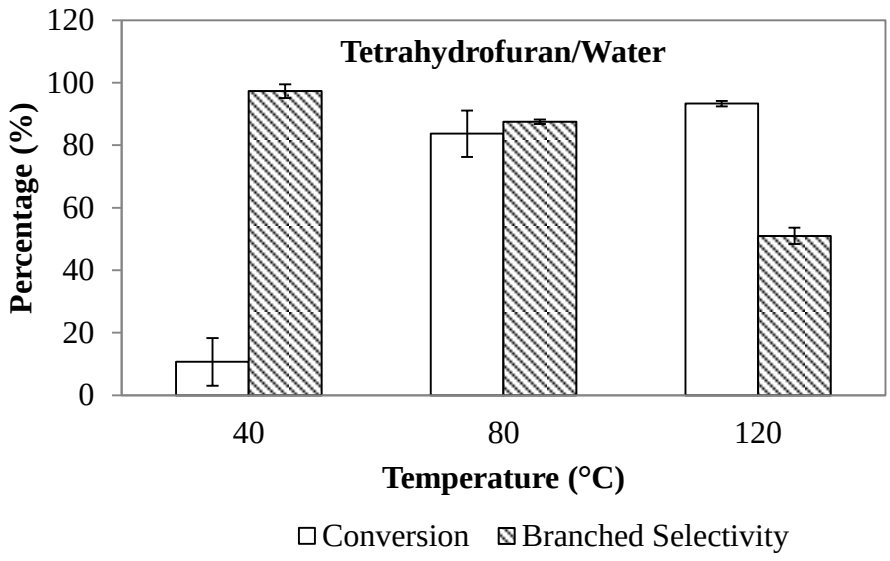


Figure 4-12 Effect of temperature on conversion and selectivity in the hydroformylation of *p*-methylstyrene using a tetrahydrofuran/water OATS system after one hour

The reaction rate and 2-(*p*-tolyl)-propanal selectivity of the hydroformylation of *p*-methylstyrene in acetonitrile/water and in dioxane/water OATS system were very similar. As shown in Figure 4-10 and Figure 4-11, the reactions proceeded slowly at 40°C with conversions of less than 20% after one hour and selectivities of about 95%. As expected, the reaction rate was increased at higher temperatures achieving completion after one hour at 80°C. However, increasing the reaction temperature further decreased the branched product selectivity of 2-(*p*-tolyl)-propanal. The selectivity dropped from approximately 84% at 80°C to 50% at 120°C. At low temperatures (*i.e.* 60°C) an increase in the selectivity of the branched product was observed indicating a significant reduction of side reactions.

In the case of the tetrahydrofuran/ water OATS system, the reaction proceeds at slower reaction rate compared to acetonitrile/water and dioxane/ water OATS systems. In addition, it was previously observed that the reactions in tetrahydrofuran/water OATS mixtures worked only for tetrahydrofuran stabilized with 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT). We speculate that the peroxides present in non-stabilized tetrahydrofuran were interfering with the reaction by causing catalyst poisoning. Also, when a stabilized tetrahydrofuran/water mixture was used to prepare the catalyst solution, we observed a color change of the solution that went from yellow to dark gray. Tetrahydrofuran was therefore not investigated further, and we chose to focus on the dioxane/water and acetonitrile/water systems.

The difference in reaction rates or conversion between the three OATS systems, especially in the case of acetonitrile/water and dioxane/water with respect to the tetrahydrofuran/water, could be due to solvent interactions. Solvent interactions with the catalyst are reported to induce changes in the rate and the selectivity of hydroformylation reactions; increasing the electron density on the metal enhances the linear aldehyde that in many cases is the desired [27, 28]. It is also known that rhodium-catalyzed hydroformylation of styrene and *p*-substituted styrenes give a prevalence of the branched over the linear aldehyde [29]. However, the results in Figure 4-10, Figure 4-11 and Figure 4-12 shows that as the temperature increases, the branched aldehyde product decreases. This decrease in the branched product selectivity at elevated temperatures is attributed to an increase of β-hydride elimination [30]. The intermediate complex of the branched product with the rhodium catalyst reverts to the starting material at reaction

temperatures greater than 60°C as observed in the reactions of the different OATS systems (see Figure 4-13).

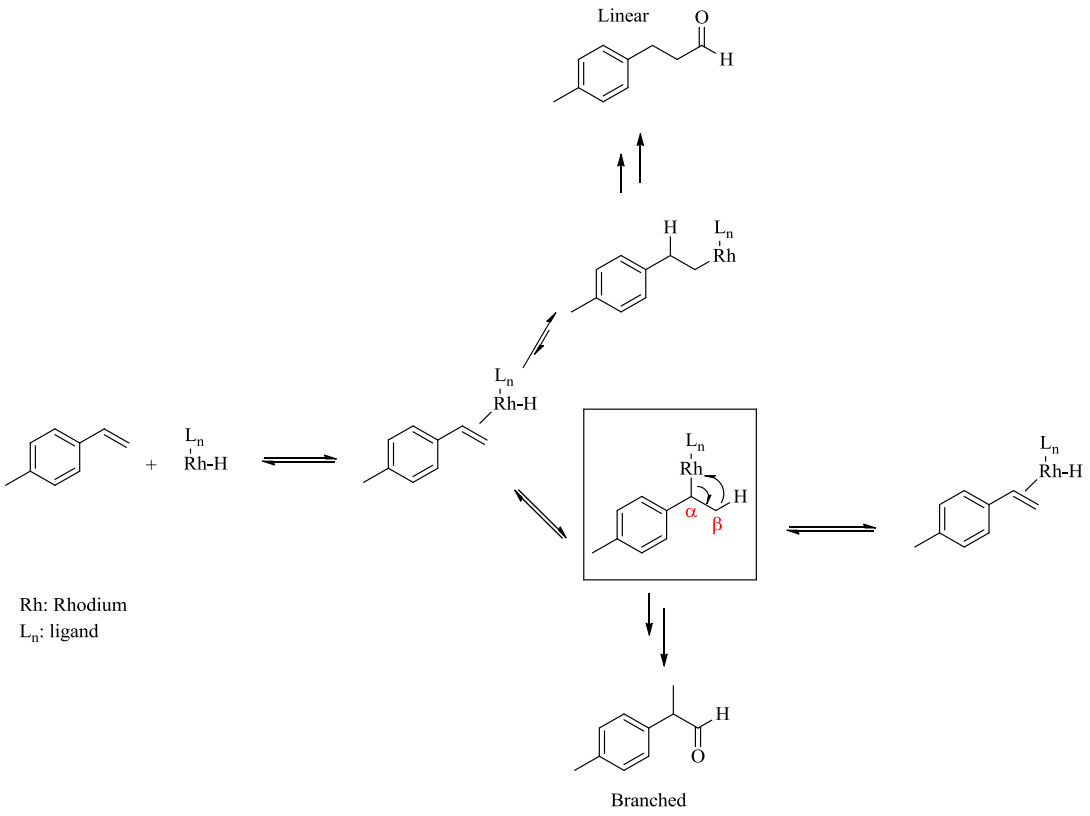


Figure 4-13 β-hydride elimination of the branched product at higher temperatures that reformed *p*-methylstyrene

The conversion rate of *p*-methylstyrene in OATS mixtures is comparable to or better than reactions homogeneously-catalyzed [31-34]. Kasinathan et al. reported the homogeneously rhodium-catalyzed hydroformylation of *p*-methylstyrene in a methanol/toluene mixture at 65°C in a continuous flow reactor and achieved 86%

conversion and 69% yield of the branched product in 58 minutes [31]. Rh-catalyzed hydroformylation of *p*-methylstyrene in OATS has higher reaction rates and is more selective than the analogous heterogeneous hydroformylation using polymer-supported catalyst [35], ionic liquid-confined silica sol-gel support [36, 37], supported rhodium nanoparticles [38] or inorganic supports [39]. The enhancement in the conversion and branched product selectivity could be due to the enhanced mass transfer which often characterized the homogeneous catalysis.

4.3.1.2 Effect of temperature as a function of time

To characterize further the β-hydride elimination and optimize the reaction, we ran the hydroformylation of *p*-methylstyrene in acetonitrile/water at 60°C and monitored the conversion and selectivity as a function of time, as shown in Figure 4-14. The conversion of *p*-methylstyrene increased exponentially with time. The reaction achieved completion after two hours at 60°C, and its selectivity went up to 94%. The observed conversion in this experiment was slightly higher than in the ones measured earlier, probably due to higher catalyst loading, temperature and mixing rate variations during the reaction. The 2-(*p*-tolyl)-propanal selectivity went up to 94% and remained almost constant during the rest of the experiment. The minimal effect in the branched product selectivity confirms that the side reactions (*i.e.* β-hydride elimination) were very slow at temperatures at or below 60°C.

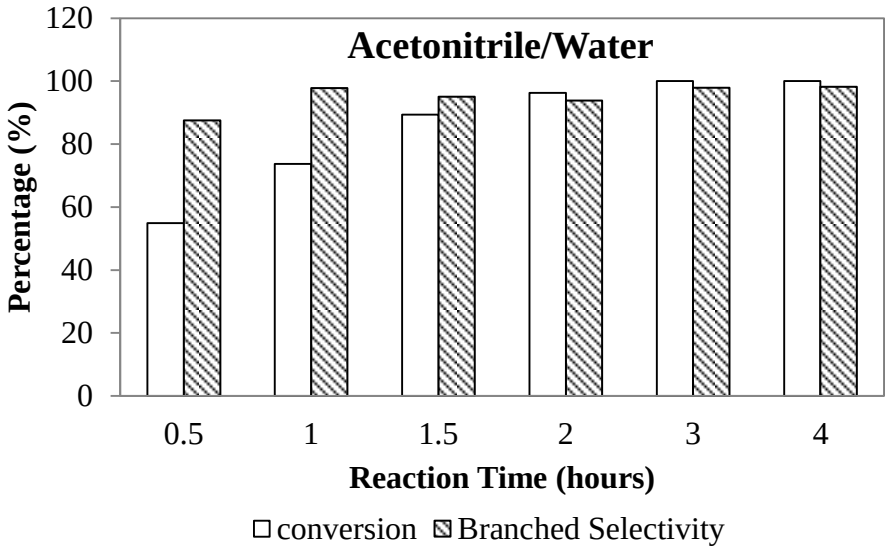


Figure 4-14 Effect of β-hydride elimination: *p*-methylstyrene conversion and selectivity as a function of time at 60°C

4.3.2 CO_2-induced heterogeneous separation

The OATS-mediated hydroformylation of *p*-methylstyrene allows the reaction to be conducted homogeneously, followed by a CO_2 –induced heterogeneous separation (Figure 4-15). After reaction completion, the excess of syngas was vented and the reactor was flushed with CO_2 and then pressurized continuously with 3.1MPa of CO_2. The efficiency of product separation and catalyst recovery was evaluated by measuring the concentration of the branched aldehyde, *p*-methylstyrene and the rhodium catalyst in the organic phase and in the aqueous phase. The results are represented with the partition coefficients.

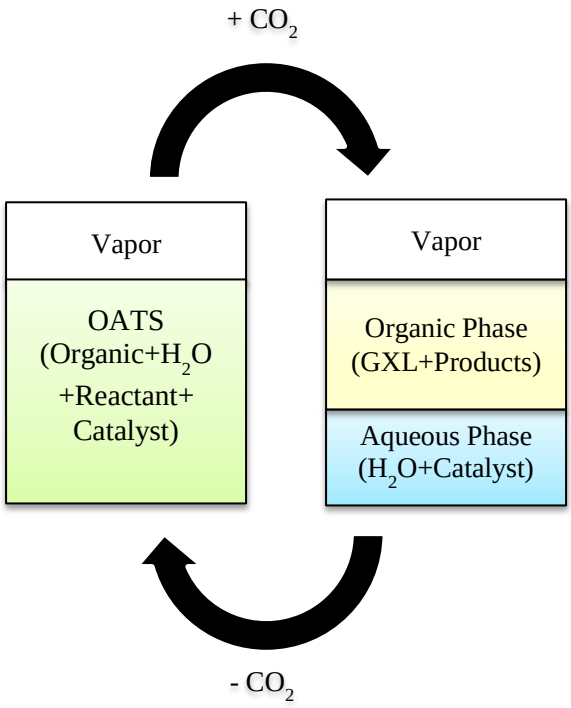


Figure 4-15 CO_2-induced heterogeneous separation

4.3.2.1 Partitioning of the product

The ratio of the branched product concentration in the organic phase to that in the aqueous phase (partition coefficient) is shown in Figure 4-16 for dioxane/water and acetonitrile/water OATS systems at 20°C. The partition coefficient of *p*-(2-toly)-propanal in acetonitrile/water OATS systems increased exponentially as CO_2 pressure increased and more than 99% of the desired product was separated in the organic phase at CO_2 pressures around 2.5 MPa. The partition coefficient in dioxane/water shows a similar trend but more CO_2 pressure (about twice) was required to achieve comparable efficiency to that of acetonitrile/water system. For example, at CO_2 pressures of 4 MPa of CO_2 99% of the branched product was separated in the dioxane rich-phase. The

difference in separation efficiency between acetonitrile/water and dioxane/water OATS systems can be explained by examining the molecular interactions between water with dioxane and water with acetonitrile. Goats *et al*. [40] investigated interactions between dioxane and water and reported the possibility of H-bonded complexes. The favorable interactions between dioxane and water can explain the need for greater amounts of CO_2 to achieve efficient phase separation. In acetonitrile/water OATS mixture, the interactions are lower [41] and thus the separation of acetonitrile from water with CO_2 is achieved with relatively low pressures.

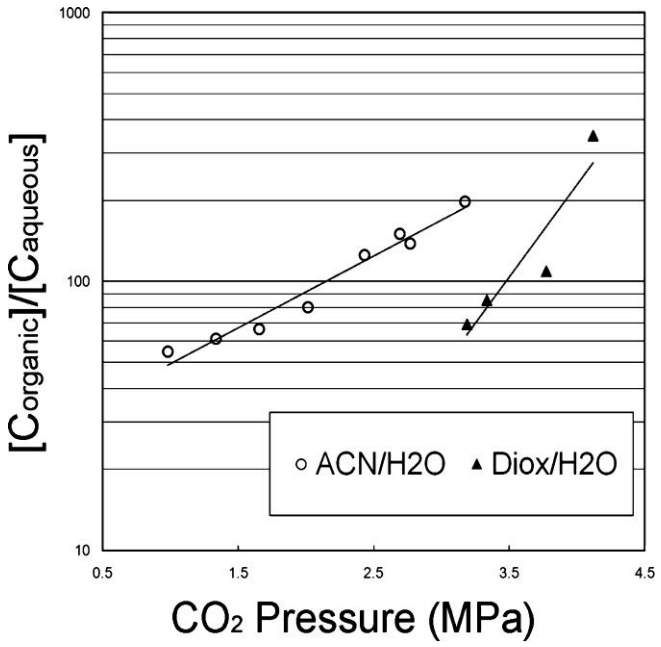


Figure 4-16 Differences in OATS on the separation of 2-(*p*-tolyl)-propanal in the organic phase as a function of CO_2 pressure

The separation of *p*-methylstyrene and 2-(*p*-tolyl)-propanal were measured and are displayed graphically in Figure 4-17. The separation of both compounds increased exponentially as CO_2 pressure was increased. The partition coefficient of *p*-

methylstyrene was larger than the partition coefficient of 2-(*p*-tolyl)-propanal. For example, at 1.5 MPa of CO_2, *p*-methylstyrene has a partition coefficient of about 100 while the branched product has a partition coefficient of about 65. This was anticipated as the more hydrophobic nature of *p*-methylstyrene results in lower water solubility than the aldehyde product. The carbonyl oxygen in the product may result in hydrogen-bonding with the water to make this compound more water soluble than the styrene molecule. These partitioning results are in agreement with reported partitioning results for 1-octene and 1-nonanal in tetrahydrofuran/water OATS [23].

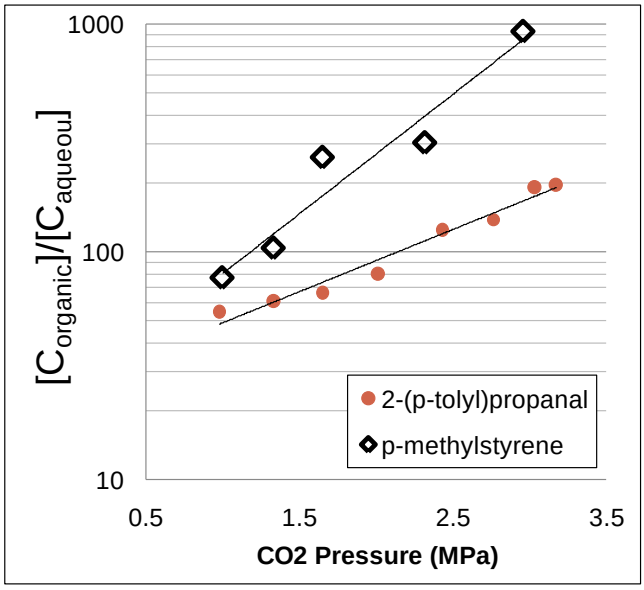


Figure 4-17 Separation of branched product (2-(*p*-tolyl)-propanal) and *p*-methylstyrene in acetonitrile/water OATS system as a function of CO_2 pressure

The separation efficiency of the water soluble ligated catalyst (TPPMS as the ligand) in the aqueous phase is graphically displayed in Figure 4-18. We measured the concentration of the water soluble ligand, TPPMS, in both the aqueous-rich and the

acetonitrile-rich phases. The partitioning of TPPMS in the aqueous phase increases exponentially with CO_2 pressure. At 4 MPa of CO_2, 99.9% of the TPPMS was in the aqueous phase and the concentration of TPPMS in acetonitrile phase was below 1 ppm at 3.5MPa of CO_2. At the same pressure, the calculated amount of the maximum possible rhodium leaching was around 100 ppb (rhodium leaching was calculated by assuming that one rhodium molecule coordinates with three molecules of TPPMS—we used excess TPPMS in these reactions). The measured TPPMS retention and calculated Rh leaching are similar in magnitude to those reported by Hallett *et al.* in tetrahydrofuran/water OATS system [23]. Also, the catalyst leaching is similar or better than reported heterogeneous systems using Y-zeolites (Rh leaching <0.01%) [42], hydrotalcites (Rh leaching ~ 1.5%) [43]. Also, compared to schemes that utilize temperature as a phase separation switch (thermomorphic, Rh leaching > 2.8%) [44], CO_2-OATS provides a significant reduction in the amount of rhodium leaching.

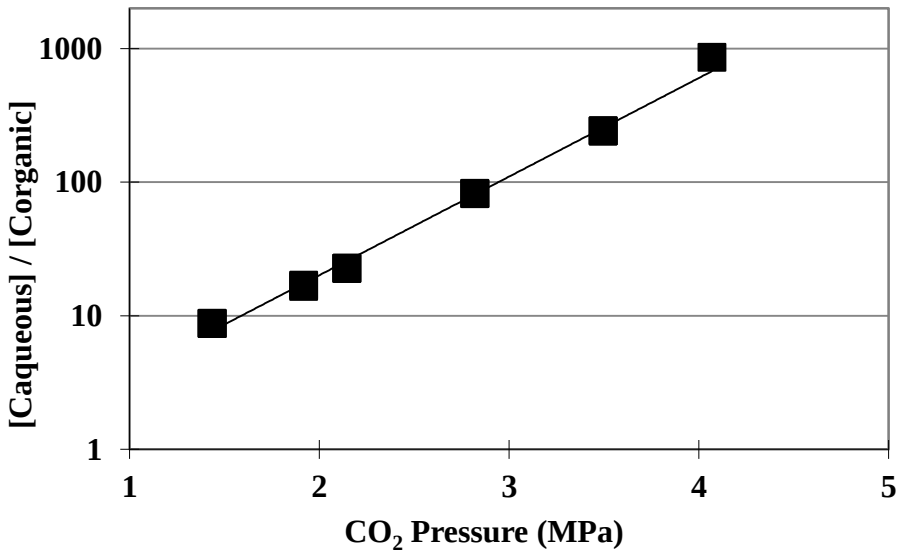


Figure 4-18 Ligand partitioning (TPPMS) in acetonitrile/water OATS system as a function of CO_2 pressures

4.2.3 Recycling Experiments

The recycling experiments of the Rh-TPPMS catalyst for five consecutive hydroformylations were carried out in ACN/H_2O OATS and the results are summarized in Figure 4-19. After carrying out the reaction for 1 hour at 60°C, 3.1 MPa of CO_2 (same as reaction pressure) was used to cause phase separation and 85% of the organic-rich layer was decanted under pressure. Fresh starting material and acetonitrile were added to start the next reaction. The average conversion of the five recycles experiments is 47.6±3.0% and the selectivity is 95.9±0.5%. The recycle experiments reflect constant catalytic activity with an average turnover frequency of 193.2±12.3 h^{-1} per reaction.

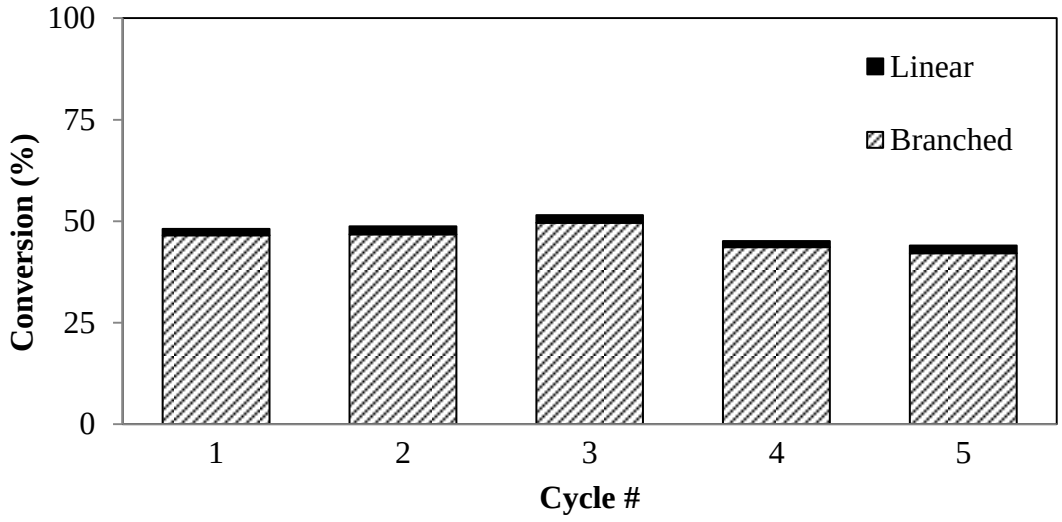


Figure 4-19 Catalyst recycling experiments in acetonitrile/water OATS mixture with 3.1 MPa of CO_2

4.4 Conclusions

We used the tunable solvents to develop organic-aqueous tunable solvents (OATS) that couple homogeneous reactions with heterogeneous separations. We investigated the OATS-mediated hydroformylation of *p*-methylstyrene, which mimics the pharmaceutical precursor of ibuprofen. The homogeneous reactions using OATS provided fast reaction rates with excellent selectivity at lower temperatures. For example, the reaction reached completion after two hours with 94% selectivity of the branched aldehyde at 60°C. After the reaction was successfully carried out, a CO_2-induced heterogeneous separation was further investigated. The partitioning of p-methylstyrene, 2-(*p*-tolyl)propanal and the Rh-TPPMS catalyst were studied. The separation of the product from the catalyst provides an efficient and simple way to remove 99% of the product, retain 99.9% of catalyst, and to recycle the Rh-TPPMS catalyst for five consecutive reactions without significant loss of activity.

4.5 References

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CHAPTER 5 - CONTINUOUS MEERWEIN-PONNDORF-VERLEY (MPV) REDUCTIONS OF BENZALDEHYDE AND ACETOPHENONE

5.1 Introduction

The pharmaceutical industry is continually searching for controllable, information-rich, high-throughput and environmentally-friendly methods of producing compounds with a high degree of chemical selectivity [1]. Finding the optimal operating conditions like reaction temperature, time and reagent concentration is critical for the success of a process. Traditionally, batch experiments are used to determine the optimal conditions and require considerable amounts of labor and expensive starting materials. Furthermore, results from batch experiments can be constrained by mass transfer limitations, making the scale-up of the reactions difficult. Alternatively, the use continuous flow processes can accelerate the efficiency and the speed of optimization. In addition it allows for the advantage of the scale out (*i.e.* running a reasonable number of reactors in parallel for mass production) instead of the scale up generally performed for batch processes, resulting in no loss of time (see Figure 5-1). Although the pharmaceutical industry has long favored batch processing, continuous flow processes can offer a facile and fast reaction screening that will lead to the identification of promising drug candidates, optimum reaction conditions and to scale the reaction to manufacturing [2].

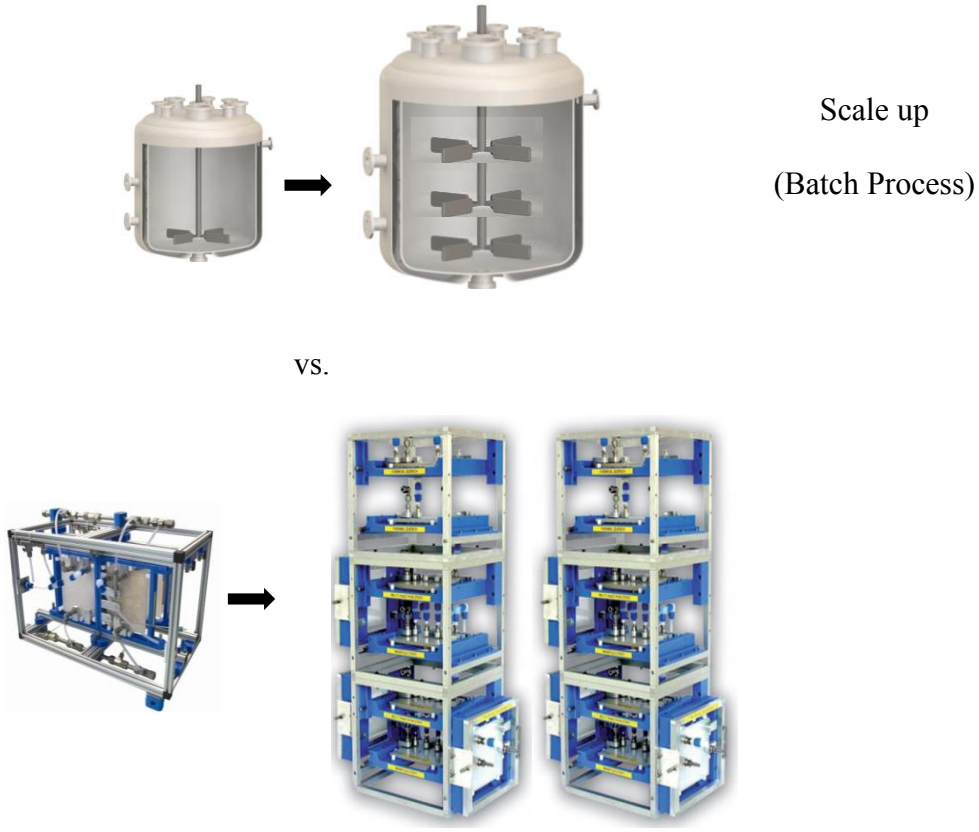

Figure 5-1 Scale-up versus scale-out processing approach

Continuous flow processes have the ability to control reaction parameters very accurately. For instance, the regulation of temperature and concentration is crucial to maintaining control over reactions that need very short residence times and/or fast mixing and enables performing greener, more economical, and safer processes. For example, in traditional large scale batch reactors, fluctuations in temperature are difficult to correct, as any alteration takes time to have an effect on the reactor as a whole; in comparison, changes are observed almost instantaneously within flow reactors [3]. Along with increasing the rate of mixing, decreasing the channel diameter results in an inherently high surface to volume ratio, allowing rapid dissipation of any heat generated over the

course of a reaction. As a result, continuous flow technology is especially useful for reactions involving a temperature sensitive and/or a highly reactive intermediate [4], reactions with hazardous reagents [5], and reactions of biphasic systems; preventing thermal degradation or explosive evolution [6] through improving mass and heat transfer. Attributed to the enhanced mass and heat transfer rates, improvements in reaction yields in continuous flow reactors have been demonstrated for a wide variety of applications [1, 4, 7-14].

Continuous processing can reduce costs, reduce the size of process equipment, improve product quality, reduce energy consumption, solvent utilization, and waste generation [15]. It can offer an improved product quality and consistency versus batch operations which are run dynamically. More precise controls of variable such as temperature, pressure and heat transfer can improve yields and selectivity and can reduce process variance. Another advantage of continuous processing is the potential for solvent reductions since the reaction can be run neat in a flow reactor or at least more concentrated. The design and development of fully integrated continuous processes requires detailed understanding of the process so that the resultant knowledge can be used to run at steady state, providing consistent, high-quality product. Thus, in this chapter we shall discuss the optimization and transfer of the Meerwein-Ponndorf-Verley (MPV) reduction from batch to continuous process.

The Meerwein-Ponndorf-Verley (MPV) reduction is an important transformation in organic synthesis. It consists of the reduction of ketones and aldehydes to their

corresponding alcohols utilizing aluminum alkoxide catalyst in the presence of a sacrificial alcohol. The interest in the MPV reduction lies in its high selectivity and its use of a cheap environmentally friendly metal catalyst. The MPV reduction was first discovered independently by Verley and by Meerwein in 1925 and later was optimized by Ponndorf in 1926[16]. Verley and Meerwein found that an aldehyde can be reduced to the corresponding alcohol with aluminum ethoxide ($Al(OEt)_3$) in ethanol (EtOH) (Figure 5-4)[17, 18]. In 1926, Ponndorf applied the reaction to ketones and upgraded the catalyst to aluminum isopropoxide ($Al(O\textit{i}Pr)_3$) in isopropanol (*i*PrOH) (Figure 5-3)[19]. The accepted mechanism for the reduction involves: (1) coordination of the aluminum reagent with the carbonyl oxygen of the aldehyde or ketone, and (2) subsequent transfer of a hydride from the alkoxide attached to the aluminum, to the carbonyl carbon of the aldehyde or ketone via a six-membered ring transition state. The mechanism and transition state for the hydride transfer are illustrated in Figure 5-4.

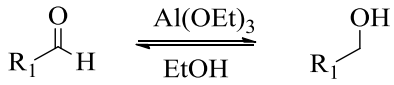

Figure 5-2 Reduction of an aldehyde using $Al(OEt)_3$ in ethanol

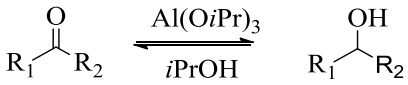

Figure 5-3 Reduction of a ketone using $Al(O\textit{i}Pr)_3$ in isopropanol

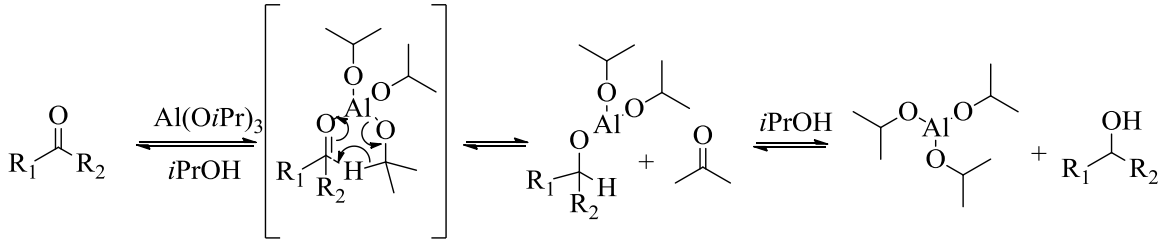

Figure 5-4 MPV reduction mechanism with Al(O*i*Pr)$_3$ using isopropanol as both the solvent and hydride source

The Meerwein-Ponndorf-Verley (MPV) reduction is currently run batch-wise by the pharmaceutical industry. This reaction is a commonly-used pathway in the production of pharmaceutical intermediates, and generally large quantities of the aluminum reagent are employed to improve the reaction rate and the catalyst lifetime [20]. The enhanced mass and heat transfer offered by continuous processing could be very beneficial to optimize the reaction in terms of concentration of reagents, catalyst and reaction time. There are only few reports discussing the continuous MPV reductions [21-23]. Herein, we report the continuous MPV reduction of two model compounds benzaldehyde and acetophenone using a commercially available glass flow reactor (Corning® Advanced-Flow™ reactor, See Figure 1-5).

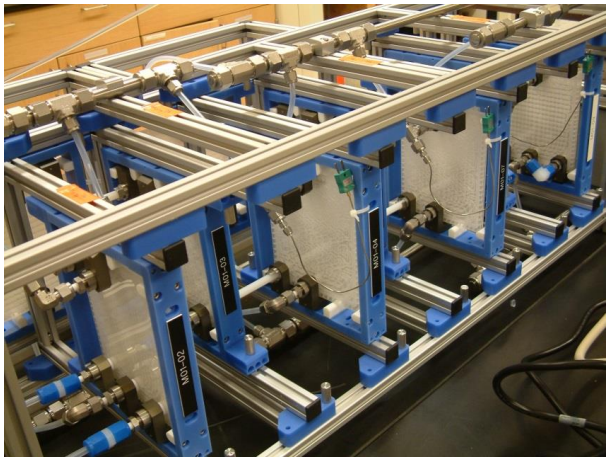

Figure 5-5 Corning® Advanced Flow™ Reactor

5.2 Experimental Methods

5.2.1 Materials

All the solvents including toluene, isopropanol and methanol were purchased in their anhydrous form from Sigma Aldrich. Acetophenone and benzaldehyde were distilled prior the MPV reductions. All other chemicals such as nonane, dodecane and hydrochloric acid were purchased from Sigma Aldrich and used as received.

5.2.2 Continuous Flow Reactor

We utilized a commercially available modular design continuous flow reactor, the Corning® Advanced-Flow™ glass reactor. This reactor is a versatile glass continuous flow reactor constructed of standard borosilicate glass and is compatible with a wide range of chemicals and solvents. The continuous flow reactor is capable of pressures from 0 to 18 bars and temperatures ranging from -60 to 200°C. The continuous reactor in our laboratories has a total of nine modules and each of them is jacketed to enhanced thermal control (see Figure 5-6). It is also capable of having a maximum of six inlets and

three temperature regions which are displayed in a simplified schematic of the reactor in Figure 5-7.

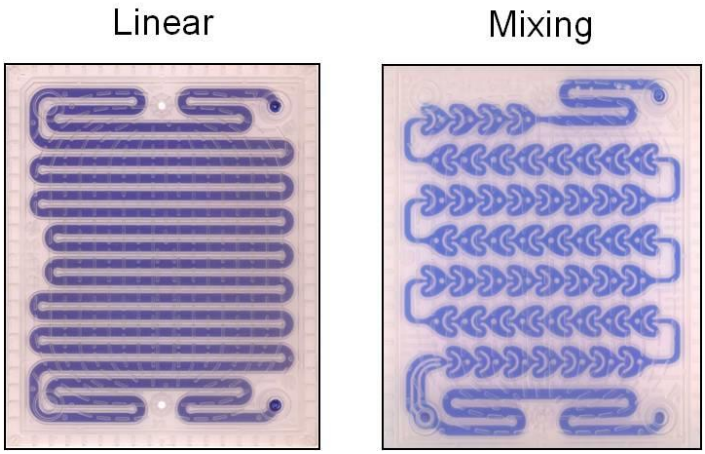

Figure 5-6 Mixing and Linear Modules

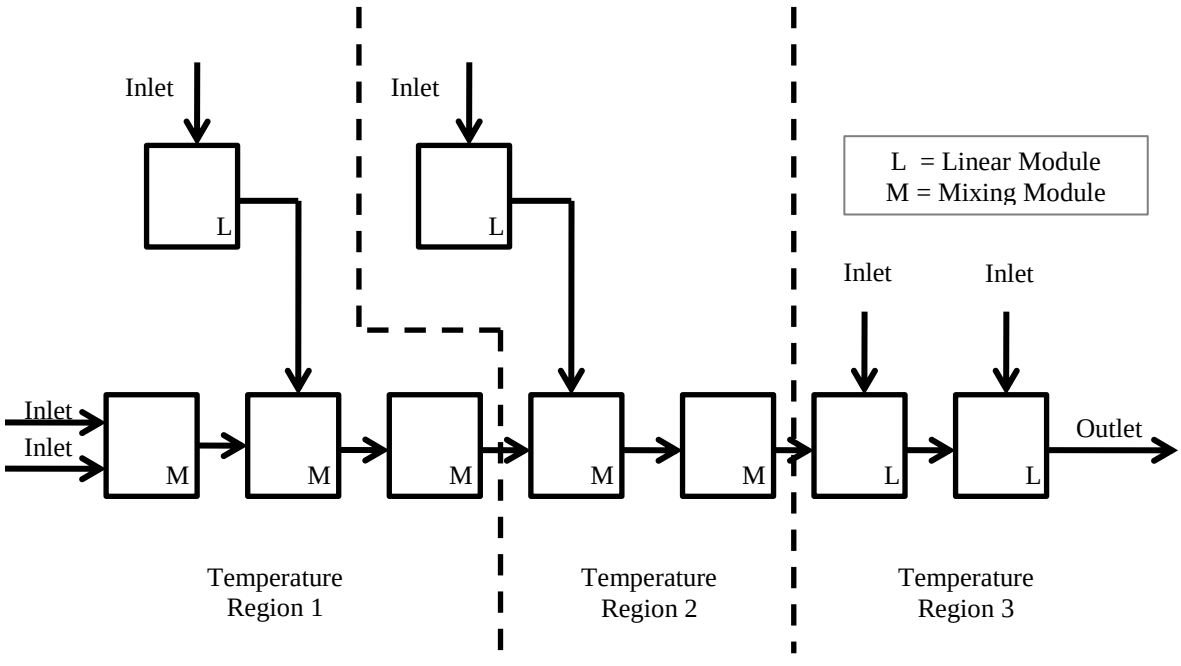

Figure 5-7 Schematic of the continuous flow reactor with multiple inlets and temperature regions

From the nine total modules, eight modules were used for the MPV reduction (labeled 1 to 8) and they were specifically equipped with pressure gauges, rotameters, thermocouples, and pressure relief valves, as represented in Figure 5-8. The configuration implemented two preheating modules (1 and 2) and a mixing module (3) that will combine the two streams containing reactants and catalyst. Overall, the reaction takes place in four mixing modules (3 to 6) and two linear modules (7 and 8) for an extended residence time. The two reactant streams, (1) benzaldehyde or acetophenone in anhydrous isopropanol and (2) Al(O*t*Bu)$_3$ in anhydrous toluene were independently controlled and introduced to the reactor using two different ISCO syringe pumps. The residence time of the reactions were controlled by changing the flow rates. Specifically, residence times of 1.87, 3.73 and 11.20 minutes corresponded to flow rates of 30, 15 and 5 mL/min, respectively.

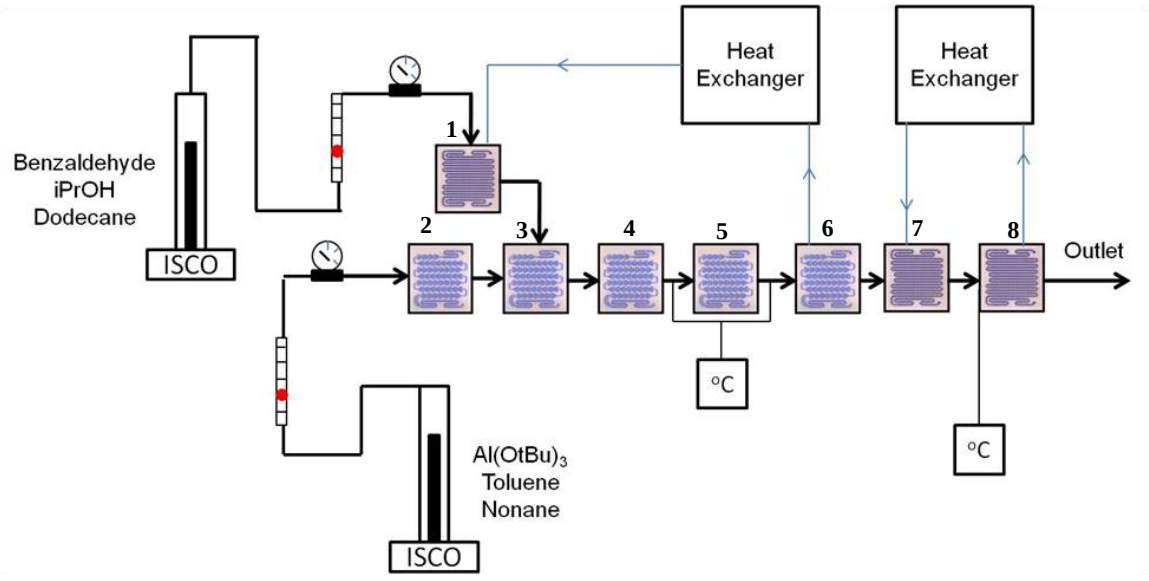

Figure 5-8 Schematic continuous flow reactor configuration for MPV reductions

5.2.3 Continuous Flow Reductions

For all the reactions, we used a mixed solvent system of 3:2 toluene and isopropanol (*i*PrOH) to enable full solubility of the catalyst and the reactant. The two reactant streams, (1) benzaldehyde or acetophenone (0.84M) in anhydrous isopropanol (500mL) with a 1% v/v dodecane (5mL) as an internal standard and (2) $Al(O\textit{t}Bu)_3$ (5 to 20mol%) in anhydrous toluene (600mL) with a 1% v/v nonane (6mL) as an internal standard were independently controlled and introduced to the reactor using two different ISCO syringe pumps. Special precautions were taken for the introduction of the catalyst solution to the reactor, where a filter was placed to prevent insoluble aluminum species from clogging the reactor and/or the syringe pumps. The residence time of the reactions were controlled by changing the flow rates (5, 15 and 30mL/min). The continuous flow reactor was brought to the appropriate reaction temperature and allowed to stabilize. To ensure steady-state data collection, the system was flushed for a period of approximately two residence times before collecting samples for GC/HPLC analysis. Experimentally the reaction progress was investigated as a function of catalyst loadings (5 and 20mol% $Al(O\textit{t}Bu)_3$), residence time (Flow rates: 5,15 and 30mL/min) and reaction temperatures (65 and 80°C). Three samples were taken for each data point and were quenched upon exiting the reactor with 2M hydrochloric acid (HCl) and diluted with methanol (MeOH). In all cases, the disappearance of the starting carbonyl substrates (benzaldehyde and acetophenone) and the appearance of the corresponding alcohol products, benzyl alcohol and 1-phenylethanol respectively were monitored by HPLC. Although the reaction quench was conducted outside of the reactor in this particular study, this step could be conducted continuously by incorporating an inlet acid stream within the reactor

configuration. After the reactions were complete, the reactor and ISCO pumps were flushed with anhydrous isopropanol and toluene to clean any residue left from the reaction and the heat exchangers were cooled to room temperature.

5.2.4 Reaction analysis

The homogenous reaction mixture containing the substrate, product, and internal standards was collected upon exiting the reactor, and analyzed by GC-FID/HPLC. To ensure steady-state data collection, the system was flushed for a period of approximately two residence times before collecting samples for analysis. Internal standards, dodecane and nonane, were used to verify the flow rates of the two streams and the analyses were performed by GC (HP 6890 Series GC, with a FID detector and a HP-5 capillary column (30m x 0.25 mm and 0.25 μm)). The GC-FID method consisted of a temperature profile as follows: 50°C for five minutes followed by a 25°C/minute ramp rate to 300°C and allow equilibrating for two minutes. The reaction progress such as conversion and yield for the different sets of reaction conditions were monitored by HPLC (HP 1100 series HPLC equipped with a UV detector set to λ = 210 nm and 254 nm, and used a Phenomenex Luna 5μ C18(2) reverse phase column). An isocratic HPLC method was used for the analysis (52% water with 0.1% trifluoroacetic acid buffer and 48% acetonitrile as the mobile phases at 1.5 mL/min and 40°C). Calibration curves of the substrate and product were experimentally generated to determine their actual concentration after the desired reaction conditions.

5.3 Results and Discussion

We have selected benzaldehyde and acetophenone as model compounds to demonstrate the feasibility of the Meerwein-Ponndorf-Verley (MPV) reductions in

continuous mode. The main advantage in the MPV reduction lies in its high chemo-selectivity, and its use of a relatively cheap, environmentally friendly aluminum alkoxide catalyst. Previous research in our group reported significant rate enhancement of MPV reductions using $Al(O\textit{t}Bu)_3$, an inexpensive, air stable alternative to the conventional $Al(O\textit{i}Pr)_3$ in the reduction of benzaldehyde and acetophenone. Batch experiments showed an enhancement in the reaction rate, two to three times higher when $Al(O\textit{t}Bu)_3$ was used when compared to $Al(O\textit{i}Pr)_3$ (Figure 5-9 and Figure 5-10). The difference in the aggregation state is believed to contribute to the superior activity of $Al(O\textit{t}Bu)_3$, where a lower aggregation state compare to $Al(O\textit{i}Pr)_3$ led to faster reductions. The structures of the two aluminum complexes and their aggregation states are illustrated in Figure 5-11. The enhanced activity of $Al(O\textit{t}Bu)_3$ allowed for catalyst loadings of 20mol% or less as well as the use of mixed solvent systems.

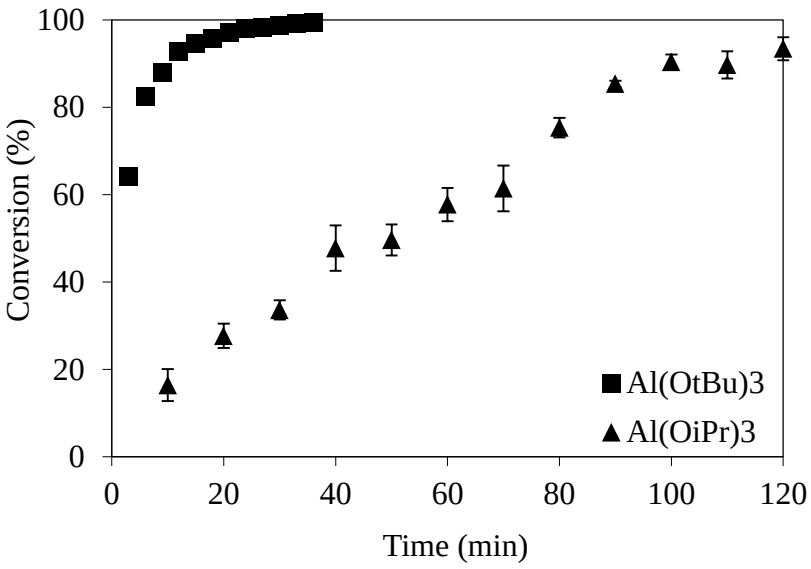

Figure 5-9 Reaction conversion as a function of time for the MPV reduction of benzaldehyde in a solvent ratio of 9:1 toluene/isopropanol in batch reactors, catalyzed by 50 mol% catalyst ($Al(O\textit{i}Pr)_3$ or $Al(O\textit{t}Bu)_3$) at 40°C[24].

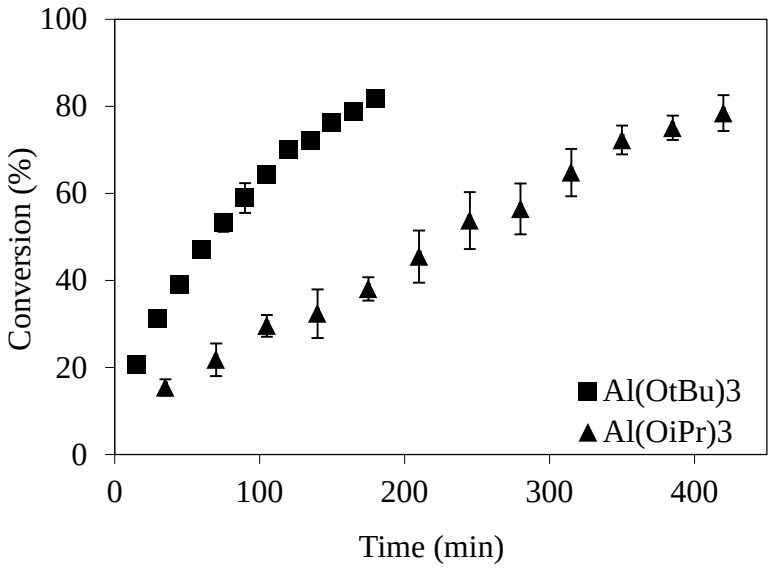

Figure 5-10 Reaction conversion as a function of time for the MPV reduction of acetophenone in a solvent ratio of 9:1 toluene/isopropanol in batch reactors, catalyzed by 50 mol% catalyst (Al(O*i*Pr)$_3$ or Al(O*t*Bu)$_3$) at 40°C[24].

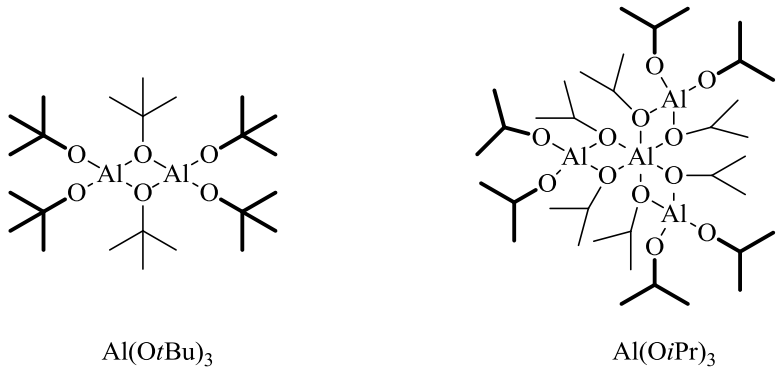

Figure 5-11 Structures of the dimeric Al(O*t*Bu)$_3$ and tetrameric Al(O*i*Pr)$_3$ aggregation states. (Exchangeable ligands are shown in bold)[24]

Now we report the continuous MPV reductions of benzaldehyde and acetophenone to benzyl alcohol and 1-phenylethanol, respectively. The reactions were carried out using a Corning® Advanced-Flow™ reactor. The continuous flow reactor

had a total of eight reactor modules and was specifically equipped with pressure gauges, rotameters, thermocouples, and pressure relief valves, as represented in Figure 5-12. To ensure homogeneity, toluene was used as a co-solvent accounting for the limited solubility of $Al(O\textit{t}Bu)_3$ in pure isopropanol. It should be emphasized that isopropanol was used as a solvent and as a reactant in the MPV reductions. Different temperatures, catalyst loadings and residence times (flow rates) were investigated to optimize the continuous MPV reactions of benzaldehyde and acetophenone. In all cases, the disappearance of the substrate and the appearance of the alcohol product were monitored by HPLC. Samples were taken in triplicates for each data point and averages of the results are presented in the following sections.

Figure 5-12 Corning® Advanced Flow™ Reactor Setup

5.3.1 Continuous MPV Reduction of Benzaldehyde

The continuous MPV reduction of benzaldehyde to benzyl alcohol utilizing $Al(OtBu)_3$ in the presence of an isopropanol/ toluene mixture was investigated (Figure 5-13). To optimize the continuous flow reduction of benzaldehyde, studies with different reaction temperatures, catalyst loadings and residence times were performed. The yield of the reaction was analyzed by HPLC as a function of residence times and the results are summarized in Figure 5-14 and Figure 5-15.

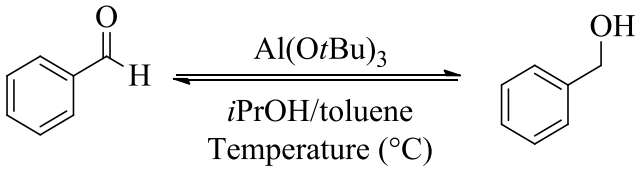

Figure 5-13 MPV reduction of benzaldehyde showing using $Al(OtBu)_3$ in an *i*PrOH/toluene mixture

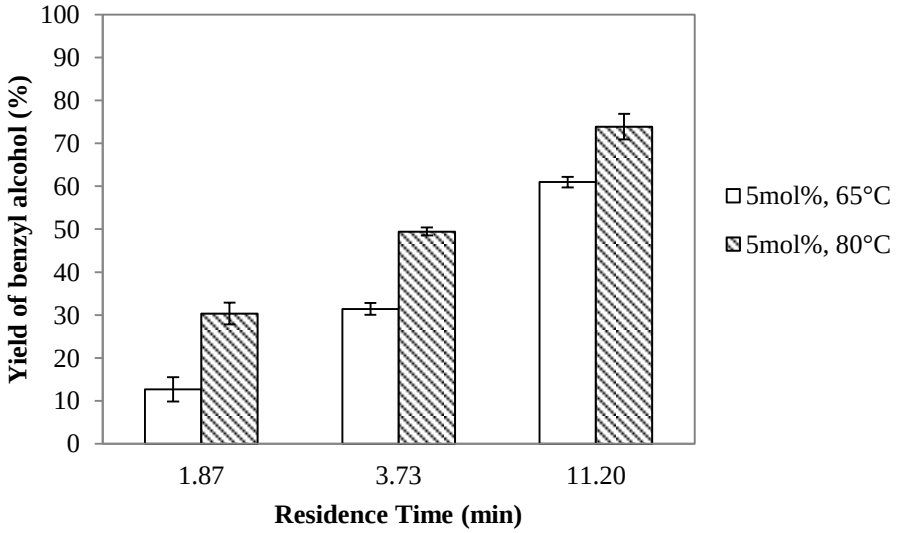

Figure 5-14 Yield of benzyl alcohol as a function of residence times at 65°C and 80°C using 5mol% $Al(OtBu)_3$

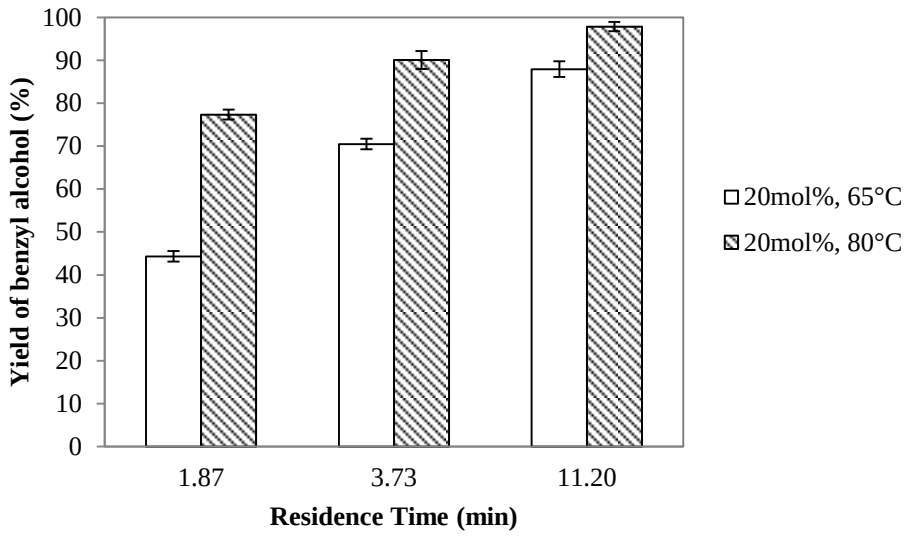

Figure 5-15 Yield of benzyl alcohol as a function of residence times at 65°C and 80°C using 20mol% Al(O*t*Bu)$_3$

Figure 5-14 displays the yield of benzyl alcohol in the continuous MPV reduction of benzaldehyde as a function of residence time using 5mol% Al(O*t*Bu)$_3$. Under these conditions and at the longest residence time of 11.2 minutes (5mL/min) achieved by the continuous flow reactor, the reaction yield went up to 61% and 74% at 65°C and 80°C, respectively. As expected the yield of the reaction increased with higher residence times and higher temperatures. Note that the reaction achieved a 77% yield at 80°C in 11.2 minutes using only 5mol% catalyst.

To achieve completion, a higher catalyst loading of 20mol% was used and the results are summarized in Figure 5-15, which displays the yield of benzyl alcohol in the continuous MPV reduction of benzaldehyde as a function of residence times. In this case 20mol% Al(O*t*Bu)$_3$ after 11.2 minutes resulted in 88% and 98% at 65°C and 80°C,

respectively. As expected, the 20mol% catalyst loading at the two different temperatures resulted in faster reaction rates than at 5mol% catalyst loading.

The reduction of benzaldehyde was indeed achievable with the current Corning® reactor configuration. The results demonstrate that Al(O*t*Bu)$_3$ enable the successful transfer of MPV reductions from batch to continuous processing. For the optimization for the reduction of benzaldehyde, we took into consideration several factors such as the reaction temperature, catalyst loading and residence times.

5.3.2 Continuous MPV Reduction of Acetophenone

The continuous MPV reduction of acetophenone to 1-phenylethanol using Al(O*t*Bu)$_3$ in the presence of an isopropanol/ toluene mixture was investigated (Figure 5-16). The MPV reductions of ketones are slower than their aldehyde counterparts; therefore the reaction was carried out at the optimum conditions, 80°C and 20mol% catalyst loading in the continuous flow reactor as a function of different residence times. The progress of the reactions was analyzed by HPLC and the results are summarized in Figure 5-17.

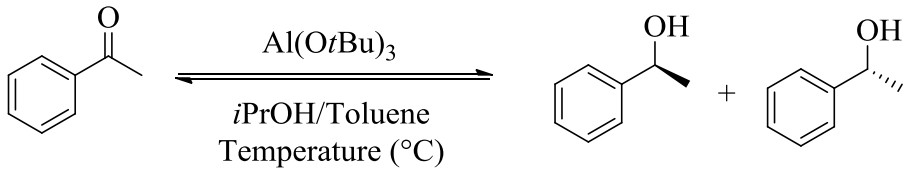

Figure 5-16 MPV reduction of acetophenone using Al(O*t*Bu)$_3$ in an *i*PrOH/toluene mixture

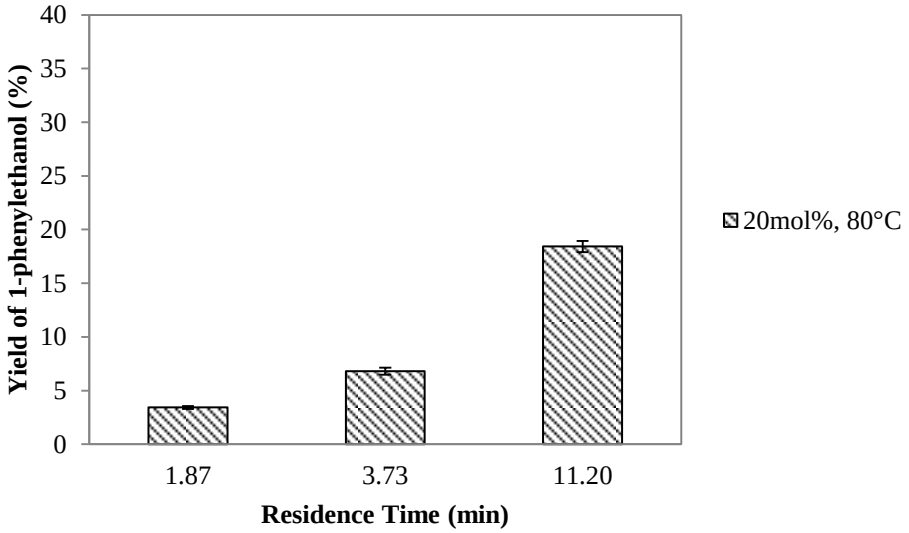

Figure 5-17 MPV reduction of acetophenone to 1-phenylethanol in the continuous flow reactor at 80°C and 20mol% Al(OtBu)3 at different residence times

Figure 5-17 displays the yield of 1-phenylethanol in the continuous MPV reduction of acetophenone as a function of residence times. The reaction at 20mol% catalyst loading and 80°C at the longest residence time of 11.2 minutes achieves only 18% yield of the 1-phenylethanol, probably due to the fact that acetophenone has a more sterically hindered carbonyl. However, it must be recognized that the extent of reaction was only limited by our set-up. Unfortunately, this reaction is very slow and our continuous flow reactor setup will not allow it to go to completion. In theory it should take 59.52 minutes to go to completion at our conditions (20mol% $Al(O\textit{t}Bu)_3$ and 80°C).

It was found that the reduction of acetophenone was slower compare to the reduction of benzaldehyde. The current Corning® reactor configuration cannot achieve

completion in the acetophenone reductions, where longer residence times will be required.

5.4 Conclusions

The MPV reduction is a commonly-used pathway in the synthesis of important pharmaceutical intermediates. The enhanced catalytic activity of $Al(O\textit{t}Bu)_3$ played an important role in successfully conducting the continuous MPV reductions using the Corning® Advanced-Flow™ Glass Reactor. This was demonstrated with two model compounds, benzaldehyde and acetophenone. Benzyl alcohol for instance was obtained quantitatively in iPrOH/toluene solvent at 80°C with 20% catalyst loading in 11.2 minutes. The use of a lower catalyst loading of 5mol% $Al(O\textit{t}Bu)_3$ resulted in 77% yield after 11.2 minutes at 80°C. The reduction of acetophenone is intrinsically slower. Although modest conversion was obtained with a residence time of about 11.2min, this can easily be improved by modifying the reactor configuration. For instance, adding modules for longer residence time (the modular nature of the continuous reactor is one of their marked advantage) and increased temperature will permit a viable continuous strategy. Unquestionably, enabling continuous $Al(OtBu)_3$ catalyzed MPV reductions can significantly contribute to moving forward synthetic strategies from batch to continuous manufacturing.

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CHAPTER 6 - CONCLUSIONS AND RECOMMENDATIONS

The green chemistry principles presented in Chapter 1 have served as a guide for the four industrially-relevant projects presented in Chapter 2 through 5. The main focus of this thesis was to develop innovative strategies to reduce waste, improve process efficiency and reduce energy consumption. It involved the use of green solvents and processes for the sustainable production of pharmaceuticals and fine chemicals. For each of the projects presented below, a summary of the conclusions and recommendations are given.

Suzuki coupling reactions as a function of CO_2 pressures (Chapter 2)

The work presented in Chapter 2 is part of a multi-year project in collaboration with Dow Chemical Co. and the project just completed its 6^{th} quarter of research. The goal of the project is to explore the effect of CO_2 for conducting Suzuki Coupling of substrates containing unprotected primary amines groups. First, we carried out baseline Suzuki coupling reactions in the absence of CO_2 to evaluate the effects of added water and we found that small amounts of added water (2.5% v/v) significantly increase the reaction rate and yield. Different organic and inorganic bases were screened and showed different level of success without CO_2. However, K_3PO_4 was significantly superior in the presence of CO_2. For example, the coupling reaction of 4-amino-2-bromopyridine with phenylboronic acid using K_3PO_4 and 40% v/v added water, achieved a 99% yield in the presence of 30.6 atm of CO_2, compared to 23% yield in the absence of CO_2. The yield

increase can result from multiple effects: (1) change in the pH: inorganic chemistry yield a complex mixture of bases, (2) interaction of CO_2 with the primary amine group and (3) interaction of CO_2 with the catalyst. These will be further investigated. This preliminary work establishes that exceptionally challenging substrates like halogenated amino pyridines bearing a primary amine group (NH_2) (specifically 4-amino-2-bromopyridine and 4-amino-2-chloropyridine) are suitable substrates for Suzuki coupling reactions under standard conditions (K_3PO_4, 70°C and $Pd(TPP)_2Cl_2$) using CO_2 pressures, without the need for protection/deprotection steps which are traditionally considered to be necessary for these reactions to proceed cleanly.

The reaction rates and yields of Suzuki coupling reactions vary with temperature, solvent, concentration, catalyst and base, and are highly substrate dependent. Therefore, it is very important to investigate these parameters as a function of substrate and pressure of CO_2. Future experiments should address the following:

- Optimization of the reaction conditions for the coupling of 4-amino-2-bromopyridine with phenylboronic acid under CO_2 pressures in terms of:
    1) *Catalyst loading (0.5 to 2mol% catalyst loading)* - Currently a 5mol% catalyst is employed; and a lower catalyst loading would be desirable. It would be very important to monitor the progress of the reaction at lower catalyst loadings (0.5 to 2mol %) as a function of CO_2 pressures.
    2) *Reaction temperature (100°C)* - First, the reaction progress as a function of time needs to be measured for the optimum conditions achieved so far (40% water, 5mol% catalyst, 70°C). With those results in mind, a higher temperature can be studied as a function of

time. The higher temperature should help to increase the reaction rate and consequently reduce the reaction time. Careful analysis of possible side products needs to be performed.

3) *Base equivalents (2 equivalents)* - We are currently using 3 equivalents of base and the reaction theoretically needs only two equivalents; so a lower amount of base used in the reaction will be preferable.

- Establish the effect of CO_2 on substrates like 4-bromotoluene, aniline and pyridines
- Establish the effect of CO_2 on typical amine protected substrates (*tert*-butylcarbamate (N-Boc), acetamide (N-Ac))
- Understand the effect of CO_2 in the Suzuki coupling reaction by spectroscopic studies (e.g. NMR, IR, and UV-VIS)
    1) Investigate the interaction of CO_2 with pyridines, anilines, and aminopyridines as a function of CO_2 pressure may provide insight as to the role of CO_2.
    2) Identify the complex mixture of basic species in the reaction system formed in the presence of CO_2. Specifically ^{31}P NMR and IR can be used to identify them.
- Investigate the effect of CO_2 in the Suzuki Coupling using other bases such as triethylamine (TEA) and potassium fluoride (KF), where there will be no interaction of the base with CO_2.

Water at Elevated Temperatures (WET): a Reactant, Catalyst, and Solvent in the Selective Removal of Protecting Groups (Chapter 3)

This study demonstrated the ability of water at elevated temperatures (WET) to act as the solvent, reactant, and catalyst for the selective removal of protecting groups such as carbamates, amides and esters. The N-Boc aniline derivatives were fully deprotected at relatively mild temperatures (125 to 150°C) and short reaction times (less than 2 hours). Amides and acetates were also successfully cleaved at higher temperatures, 275°C and 250°C respectively. We also demonstrated that the reaction selectivity can be tuned by controlling "water's catalytic activity". Practically, this was done simply by adjusting the temperature. Several scenarios were explored for proof of concept: 1) selective removal of a carbamate group (N-Boc) in the presence of amides (N-Ac and N-Piv) and acetates (O-Ac), and 2) selective deprotection of an acetate (O-Ac) group in the presence of an amide (N-Ac). In all cases, the selective and near quantitative deprotection of the targeted group was achieved without the need of added acids or bases and thus eliminated the subsequent neutralization step.

The rate of reaction of the different substrates seems to be related to the solubility of the substrates in water. Future experiments to estimate the solubility at higher temperatures of the different substrates should be performed. In addition, future work can be expanded to the use of WET for carbonyl deprotections (i.e. protected ketones, aldehydes, and carboxylic acids). The selective removal of protecting groups such as N-Boc, N-Ac, O-Ac on an actual pharmaceutical compound can be investigated to understand the effect of temperature on a complex molecule. An analysis of the efficiency of the separation after cooling would be necessary to address any

contamination effect of the organic reactants in the water and evaluate the possible recyclability of the water. Finally, an economic analysis of the use of WET vs. traditional acid/bases for the deprotection needs to be performed to understand the actual benefits that water can offer in a process.

Organic-Aqueous Tunable Solvents (OATS) for *p*-Methylstyrene Hydroformylation and Catalyst Recycle (Chapter 4)

Homogeneous catalysis is a powerful tool for yielding impressive reaction rates and selectivities in any organic transformation. However recovery of toxic or expensive catalysts often limits the implementation of homogeneous catalysis to high-value products. Heterogeneous catalysis has found widespread use due to the easy catalyst recovery. The combination of these two methods has been the focus in this chapter. Homogeneous catalysis, coupled with heterogeneous separations, has the potential to be a powerful tool for industrial organic chemistry. Organic-aqueous tunable solvents (OATS) can couple homogeneous reactions with heterogeneous separations. We investigated the OATS-mediated hydroformylation of *p*-methylstyrene, which mimics the pharmaceutical precursor of ibuprofen. The homogeneous reactions using OATS provide fast reaction rate with excellent selectivity at lower temperatures. After the reaction was carried out successfully, a CO_2-induced heterogeneous separation was further investigated. The partitioning of *p*-methylstyrene, product and of the Rh-TPPMS catalyst was studied. Excellent separation (> 99%) of the catalyst in the aqueous phase and the reactants in the organic phase was achieved; and in addition, it allowed for the recycling

of the Rh-TPPMS catalyst for five consecutive reactions without significant loss of activity.

It was proven that OATS is an efficient solvent system to perform homogeneous reactions with heterogeneous separations. Although the incorporation of moderate pressures of CO_2 into industrial processes is expensive due to the cost of the specialized high pressure equipment needed, some of the cost can be recovered through the ease of separation that is achieved. Additionally, the types of synthesis that involved metal catalyst often yield high-value-added products, such as pharmaceuticals, in which the high purity obtained could justify the additional cost. Moreover, an expensive catalyst can be recycled. OATS affords advantages that cover both process and environmental aspects for metal-catalyzed reactions. These OATS systems can be extended to other homogeneously metal-catalyzed reactions such as coupling reactions (*i.e.* Heck, Suzuki and Stille). Most of the coupling reactions use a mixture of water and organic solvents. The aqueous phase helps to fully dissolve the inorganic base and allows the easy separation of a hydrophilic catalyst in aqueous-rich phase and the hydrophobic reactants in the organic-rich phase with the application of CO_2 pressures.

Continuous Meerwein-Ponndorf-Verley (MPV) Reductions of Benzaldehyde and Acetophenone (Chapter 5)

The MPV reduction is a mild, and chemoselective protocol commonly used in the synthesis of pharmaceutical intermediates. The enhanced catalytic activity of $Al(O\textit{t}Bu)_3$ compare to $Al(O\textit{i}Pr)_3$ was essential to successfully conducting the continuous MPV

reductions using the Corning® Advanced-Flow™ Glass Reactor. This was demonstrated with two model compounds, benzaldehyde and acetophenone. Successful MPV reductions were achieved, and the catalyst loading and reaction temperature were optimized. Unquestionably, enabling continuous $Al(O\textit{t}Bu)_3$ catalyzed MPV reductions can significantly contribute to moving forward synthetic strategies from batch to continuous manufacturing.

We have successfully demonstrated the continuous MPV reduction of a model aldehyde and a ketone which are one-step reactions. A detailed study of other substituted aldehydes and ketones will help us understand the effect of substituent on the reaction rate. In addition, multi-step syntheses in continuous flow mode are desirable. A two-step model reaction can be carried out to prove the advantages of continuous flow reactors. Although the longest residence time achieved is 11.2 minutes in the Corning® Advanced-Flow™ Glass Reactor, it offers the capability to add other streams throughout the total residence time. This feature will enable the successful multi-step reaction.

APPENDIX A - ACCEPTED PROPOSAL FOR THE ACS-GCI PHARMACEUTICAL ROUNTABLE AWARD 2012

I have been instrumental in developing collaboration between our sustainable, green chemistry group (Eckert/Liotta) and Dr. Stefan France's synthetic organic chemistry group. This collaboration led to the idea of integrating Dr. France's groups work in Homo-Nazarov based approaches for the synthesis of functionalized heterocycles to continuous flow. Because this work is particularly of interest to the pharmaceutical community, we envisioned optimization and conversion of batch multi-step reactions to continuous flow operations, of which the advantages have been described in Chapter 5. The accepted grant proposal is shown below. The ACS-GCI award was received by our collaborative group and will continue through 2014.

A.1 Green and effective continuous flow multi-step synthesis of heteroaromatic ring-fused cyclohexanes

A.1.1 Abstract

Green chemistry and engineering are creating a culture change for the future directions of industry. As the needs of industry change, innovation becomes a necessity. Continuous process technologies have already been identified as vehicles for its environmental and economic advantages by enabling superior mixing, heat transfer and notably lower cost through the "scaling out" strategies as opposed to the traditional "scaling up". Also central to pharmaceutical-oriented synthetic strategies are

heteroaromatic-fused ring systems since they are present in biologically active molecules and are building blocks for complex pharmaceutical synthesis. Recently, the synthesis of heteroaromatic fused cyclohexyl compounds was reported via the catalytic homo-Nazarov cyclization. Unfortunately this ground-breaking strategy utilizes 1) a reactive diazoketone intermediate, 2) a relatively high loading (up to 30 mol %) of an expensive Lewis acid catalyst for high yield and 3) a chlorinated solvent.

We propose to develop continuous and sustainable Lewis acid-catalyzed homo-Nazarov cyclization processes involving reactive donor-acceptor cyclopropanes for the production of biologically active molecules. In these instances, transfer of critical technology variables from batch to continuous flow can maximize performances in term of reaction yield and product selectivity while minimizing solvent and catalyst needs. The goal is to ultimately eliminate chlorinated solvents. By taking advantage of the high mixing and heat transfer performances of our glass continuous flow reactor, we propose to establish the benefits of continuous process technology for pharmaceutical industry to conduct multistep synthesis, namely (1) the Lewis-acid catalyzed homo-Nazarov to yield heteroaromatic-fused cyclohexyl rings and (2) the synthesis of the diazoester and cyclopropane precursors. We propose to concretely assess the benefits of continuous process technology for the homo-Nazarov cyclization using Aspen for process optimization and cost analysis. Finally, we propose to deliver a realistic roadmap for technology transfer from batch to continuous mode.

The Eckert-Liotta group is a combination of chemical engineers, physical and synthetic chemists with extensive experience in working with industrial partners to develop processes that are both environmentally benign and economically viable. The

research group has expertise in demonstrating the superiority of a continuous process in terms of reaction control and efficiency (higher atom economy). The France group is a well-recognized synthetic chemistry group with expertise in synthetic methodology development. They have established $In(OTf)_3$ as a batch process catalyst for homo-Nazarov cyclizations in maximizing product yield, activity and selectivity-opening a new, unexplored synthetic avenue for the key pharmaceutical heteroaromatic-fused cyclohexanone motifs.

A.1.2 Background

A.1.2.1 *Homo-Nazarov Cyclization*

Six-membered rings are extremely important structural subunits for the vast majority of natural products and pharmaceuticals. Given this prevalence, synthetic chemists have continuously been interested in the development of stereoselective methodologies for their preparation. Some of the most efficient protocols include the Diels-Alder reaction (which remains the standard bearer for the formation of six-membered rings), polyene cyclizations,[1] intramolecular ene-reactions,[2] Robinson annulations,[3] and other transition-metal mediated annulations.[4] Yet, a viable, but underexplored approach to six-membered carbo- and heterocycles has been exemplified by the homo-Nazarov cyclization (Figure A-1). In this reaction, cyclopropyl vinyl ketones are converted into unsaturated cyclohexenones. The proposed mechanistic steps involve acid-promoted ring opening of the cyclopropane ring to afford a 1,3-dipole. This species then undergoes intramolecular attack by the adjacent vinyl electrons to afford a

cyclic oxylallyl cation. Elimination to quench the cation followed by tautomerization of the enol affords the cyclohexenone product.

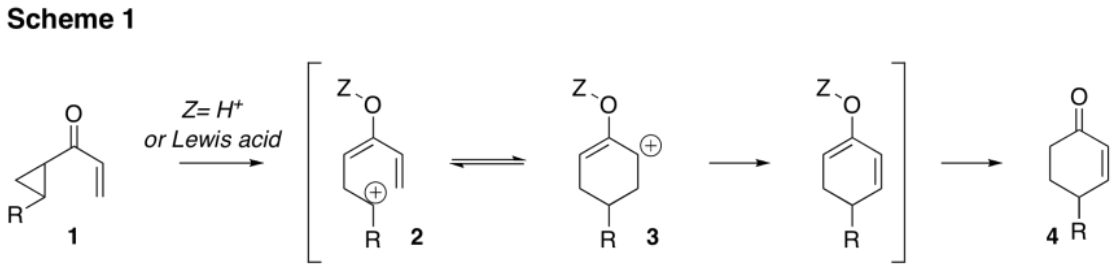
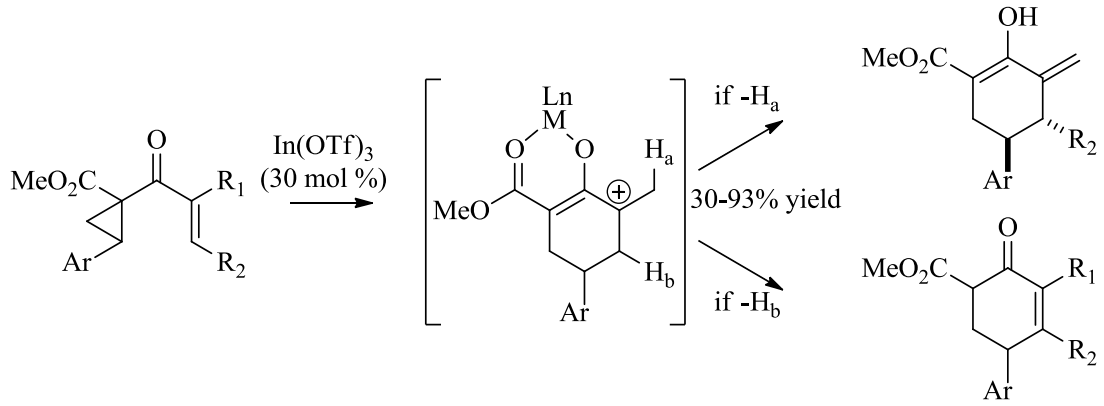


Figure A-1 Homo-Nazarov Cyclization

The France lab has recently pioneered several novel homo-Nazarov technologies catalyzed by Lewis acids using donor-acceptor cyclopropanes containing a secondary acceptor group that "polarizes" the resulting cyclic oxyallyl cation by localizing charge density. We first demonstrated that $In(OTf)_3$ effectively catalyzes the homo-Nazarov cyclizations of alkenyl cyclopropyl ketones to afford methylene cyclohexenols and/or cyclohexenones in good to high yields (Figure A-2).[5] This general method also works for cyclopropyl heteroaryl ketones where treatment with $In(OTf)_3$ similarly provides 2,3- and 3,4-heteroaryl-fused cyclohexanones in good to high yields (56-91%) with modest diastereo selectivities (1:1 to >20:1 dr, Figure A.2).[6] This method is amenable to a variety of heteroaromatics, including furan, thiophene, pyrrole, indole and benzofuran. Furthermore, the method tolerates a wide range of functional groups and substituents.

Scheme 2



Scheme 3

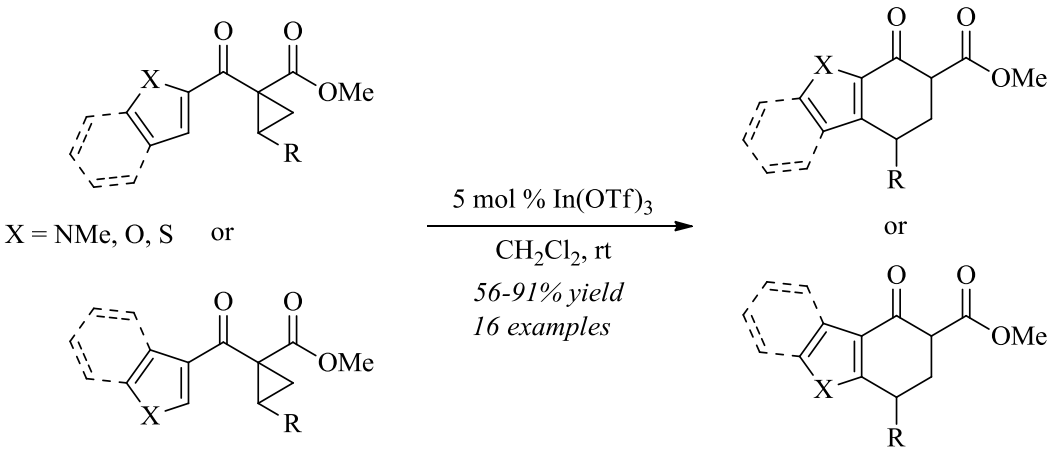


Figure A-2 Catalytic Homo-Nazarov and Fused Heteroaromatics

A.1.2.2 ***Continuous flow Technology***

Although the pharmaceutical industry has long favored batch processing, the advantages of continuous flow processing technology are now being documented, due to mounting economic competition and commercial production benefits [7,8]. When *scaling up* batch processes, pilot scale units must be built and operated to ascertain accurate heat and mass transfer mechanisms; this is hardly sustainable and subtracts substantially from

the marketable patent life of the product. In contrast, continuous flow processing allows for the advantages of *scale out*, eliminating the pilot plant and engineering associated with production scale—a clear financial incentive. Continuous flow technology also enables greener processes in terms of energy, solvent consumption, atom efficiencies and as a result waste generation. For instance, enhanced mixing improves the mass transfer of biphasic systems, which leads to better yields, catalyst recovery and subsequent recycling schemes. The ability to accurately control the reaction temperature leads to exact control of reaction kinetics and product formation. This increases product quality and reproducibility by eliminating unfavorable selectivity (by-product formation), which is impactful both from an environmental and a financial stand-point.

We have experience in converting pharmaceutically-relevant, batch processes to continuous flow processes. We successfully designed, built and used a continuous flow reactor to carry out a two-step reaction sequence for the preparation of the key HIV protease inhibitor intermediate, 1-benzyl-3-diazo-2-oxopropylcarbamic acid *tert*-butyl ester (Figure A.3).[9]

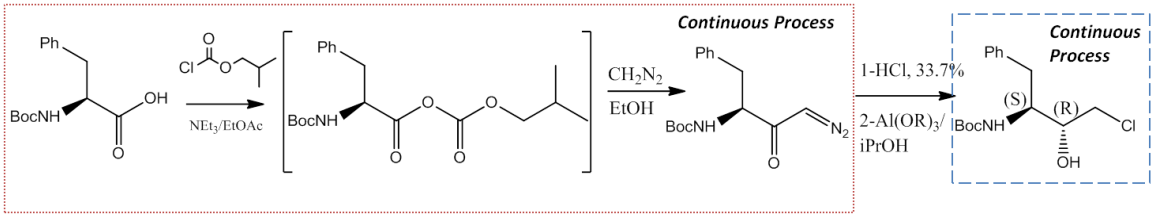


Figure A-3 Continuous Formation of (S)-CMK through a diazoketone

Indeed, continuous technology was regarded—and demonstrated—as beneficial in this particular synthesis since it involves the formation of a temperature sensitive mixed anhydride intermediate and its subsequent reaction with trimethylsilyldiazomethane (a highly reactive reagent) to yield the diazoketone isolable intermediate. By modifying the chemistry and maximizing the mixing and heat transfer, the continuous flow process enabled superior (in fact quantitative) yields at milder reaction temperature (4^{o}C instead of -20^{o}C). Subsequently, we aimed at developing Meerwein-Ponndorf-Verley (MPV) reductions of model compounds in the Corning® glass reactor. As a result, we pioneered continuous MPV reductions of the model compounds acetaldehyde and acetophenone (a simple analogue for *N*-Boc-(*R*)-benzyl-2-oxo-3-chloropropylamine) by (1) establishing Al(O*t*Bu)$_3$ as an highly active, efficient and cost-effective catalyst for MPV reductions of aldehydes and ketones and (2) implementing Al(O*t*Bu)$_3$ as catalyst for continuous reductions processes of ketones and aldehydes to their corresponding alcohols (upon optimization of solvent, temperature, catalyst loading for example).

Continuous flow processing technology has been used in industry for large-scale synthesis for almost 30 years. Within the past 10 years, the technology has become more widespread due to the commercial-availability of microreactors and bench-top continuous flow systems. Despite this growth, only a handful of multi-step flow syntheses have been reported.

A.1.3 Objectives

(1) Design and optimize experimental protocols to conduct the Lewis-acid catalyzed homo-Nazarov cyclizations in continuous mode

As a batch, the homo-Nazarov reaction was demonstrated with two different solvents (dichloromethane and acetonitrile) and Lewis-acid catalysts at loading up to 30 mol %. Unquestionably, continuous flow strategy can contribute to the optimization of the process to maximize performances in term of reaction yield and product selectivity while minimizing solvent (ultimately eliminating chlorinated solvents) and catalyst needs.

(2) Establish an experimental protocol to prepare the diazoester and cyclopropane precursors in continuous mode

It is not sufficient to perform one step in continuous mode. In reality, enabling multi-step synthesis will be essential for the continuous technology to meet its promises and be truly innovative. We will investigate the synthesis of the homo-Nazarov precursors as shown in Figure A-4. Each of these steps will be first optimized individually in the reactor as they can benefit from a continuous process design (they involve highly reactive intermediate and reagent).

(3) Develop a multistep strategy that enables the complete process to be conducted continuously

We will integrate each of the steps into one, continuous process. The optimization of the process will be performed and provide the basis for economic and environmental assessment.

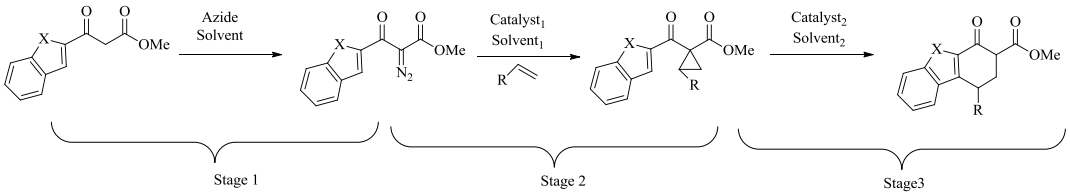


Figure A-4 General heteroaromatic homo-Nazarov multistep synthesis

(4) Definite economic and environmental assessment of the benefits and viability of the continuous approach

Through the use of the Aspen software suite, a detailed process model will be shaped, allowing for an accurate economic and environmental analysis and process optimization.

A.1.4 Project Approach

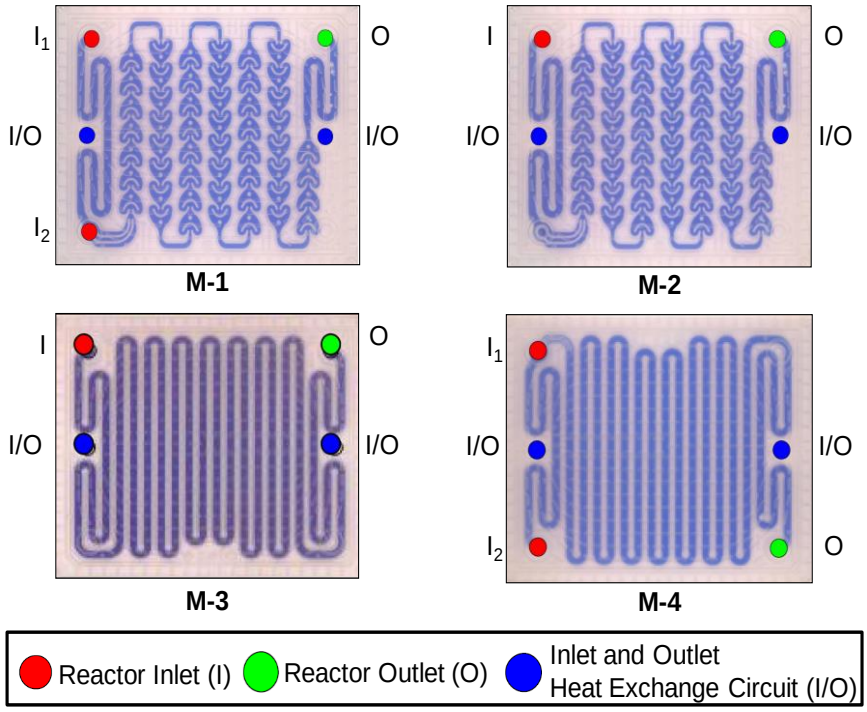


Figure A-5 Corning® Glass Flow Reactor Plates

We propose to utilize the glass Corning® continuous flow reactor for the proposed research (Figure A-5). The assembly of microstructures (161mm x 131mm x 8mm) made of glass is compatible with a wide range of chemicals and solvents and corrosion-resistant over a wide range of temperatures (-25^{o}C to 200^{o}C) and pressures (up to 18 bar). The Corning microstructures was designed for our needs and optimized for specific operations including, but not limited to: multi-injection, mixing, residence time, and heat transfer. All of the microstructures are equipped with two fluidic layers (-25^{o}C to 200^{o}C, up to 3 bar) for heat exchange on either side of the reaction layer. Heat transfer rates are proportional to heat transfer surface area and inversely proportional to volume. These microstructures facilitate an optimum surface-to-volume ratio for improved heat transfer.

Aim 1: Technologic transfers from Batch to Continuous to conduct the Lewis-acid catalyzed homo-Nazarov cyclizations and Optimization (solvent, catalysts loading, temperature, etc.)

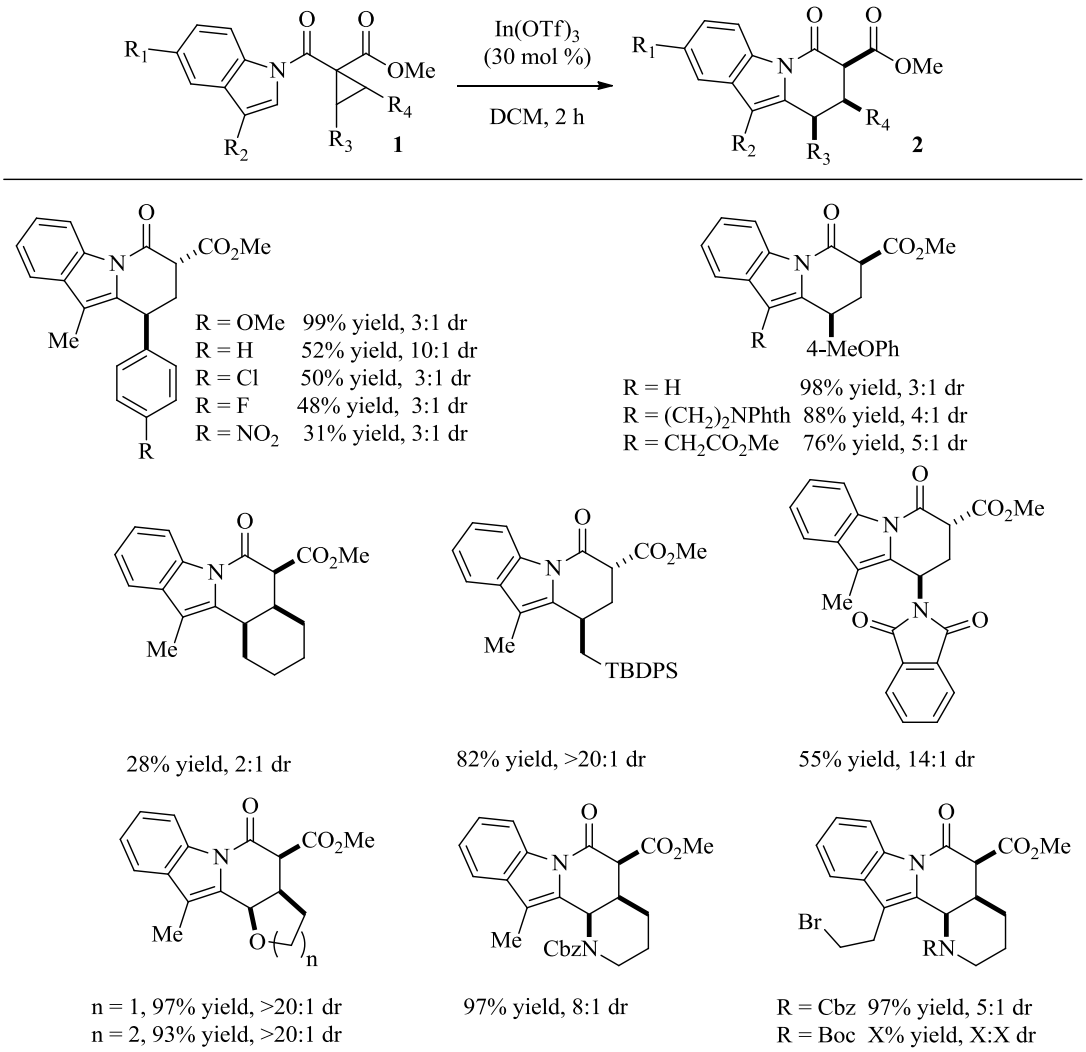


Figure A-6 Breadth of the homo-Nazarov cyclization for pharmaceutically relevant heterocycles

We recently disclosed an efficient and modular approach to hydropyrido[1,2-*a*]indole-6(7*H*)-ones via the $In(OTf)_3$-catalyzed homo-Nazarov cyclizations of methyl 1-(1*H*-indole-carbonyl)-1-cyclopropane carboxylates (Figure A-6). Mechanistically, the protocol involves cyclopropane ring-opening in the presence of a Lewis acid catalyst, followed by an intramolecular Friedel-Crafts alkylation of the indole. This transformation specifically generates the lactam ring portion of the hydropyrido[1,2-*a*]indole-6(7*H*)-

ones. The hydropyrido[1,2-*a*]indole skeleton is a key structural motif that appears in the core structures of an impressive number of naturally-occurring indole alkaloids and pharmaceutically-relevant compounds. When cyclopropanes **1** were subjected to 30 mol% $In(OTf)_3$ in CH_2Cl_2 at 25˚C, the anticipated homo-Nazarov cyclizations readily occurred and afforded dihydropyrido[1,2-*a*]indole-6(7*H*)-ones **2** in good to excellent yields (55-99% yield) with some diastereoselection (from 2:1 *trans*:*cis dr* to >20:1 *dr*). To date we have applied this method to a diverse set of *N*-acyl indolyl substrates to determine the scope and limitation of the reaction (Figure A.6).[10] The method is amenable to a variety of functionalities including alkyl and aryl halides, protected alkyl amines, ethers, silyl groups, and nitro groups. This method is highly modular and can be easily carried out on a multi-gram scale.

Although this represents a ground-breaking strategy, this multi-step synthesis utilizes reactive diazo species, a rather high catalyst loading (up to 30 mol %) of an expensive Lewis acid catalyst and chlorinated solvents in enable high yield. As a consequence, we propose to first investigate the $In(OTf)_3$-catalyzed homo-Nazarov cyclization methyl 1-(1H-indole-carbonyl)-1-cyclopropanecarboxylates (Figure A-7) in the continuous flow reactor as a function of (1) catalyst loading, (2) temperature, (3) solvent and (4) concentration. Although dichloromethane will be first investigated in a preliminary phase (to compare performances with the batch results), our aim is to move toward non-chlorinated solvents such as toluene and THF. Extension to other Lewis acid catalysts, such as Al^{3+}, Sc^{3+} and Zn^{2+} salts, will also be considered.

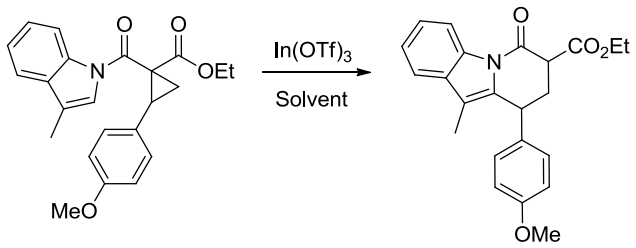


Figure A-7 Homo-Nazarov of methyl 1- (1H- indole- carbonyl)- 1- cyclopropanecarboxylates

Aim 2: Technologic transfers from Batch to Continuous to prepare the diazoester and cyclopropane precursors

The preparations of the precursors to the homo-Nazarov are deemed to benefit from being run in continuous mode as they involve heterogeneous catalysis and/or energetic reagents and intermediates. Indeed, the 1-(1H-indole-carbonyl)-1-cyclopropanecarboxylate is synthesized using the following four-step sequence starting with the requisite indole: (1) *N*-acylation with commercially-available methyl malonyl chloride to give the 1,3-dicarbonyl intermediate; (2) diazo transfer to provide the □-diazoester; (3) rhodium-catalyzed cyclopropanation in the presence of an alkene to afford the desired cyclopropyl *N*-acyl indole; and (4) $In(OTf)_3$-catalyzed homo-Nazarov cyclization (Figure A-8). The preparation of the diazoester and cyclopropane intermediates will be investigated in the continuous reactor as a function of (1) temperature, (2) solvent, (3) catalyst loading and (4) concentration.

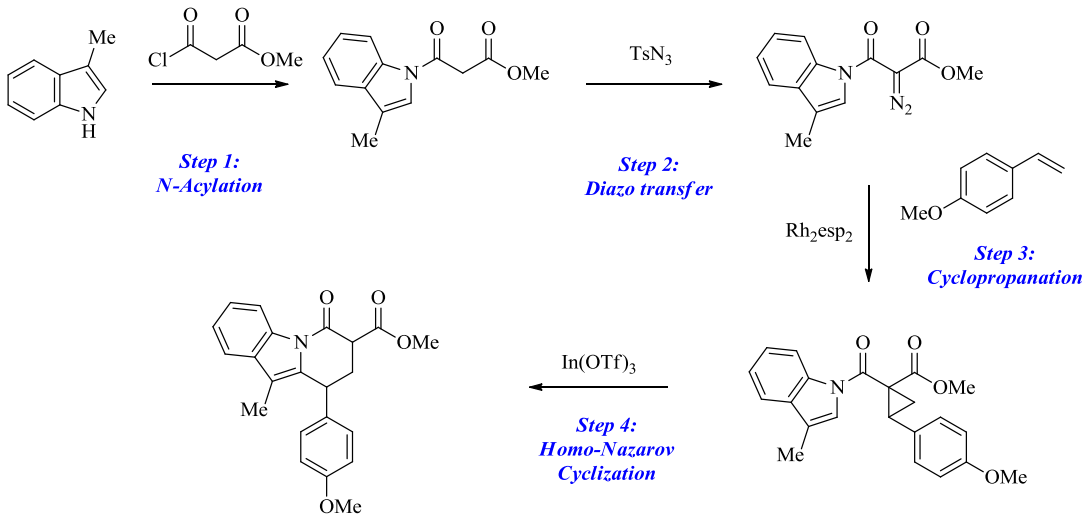


Figure A-8 Multi-step synthesis to ethyl 9-(4-methoxyphenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-7-carboxylate

Aim 3: Develop a multistep strategy that enables the multi-step process to be conducted continuous mode.

Combining the previous steps into a multi-step continuous synthesis will finally be demonstrated, providing a roadmap to the pharmaceutical industry for the synthesis of heteroaromatic ring-fused cyclohexanones. The configuration shown in Figure A-9 will be used for multistep synthesis. M-3 and M-1 will be used as heating and cooling units whereas M-2 will be used for residence time and both M-4's will be used for sequential reagent introduction and mixing.

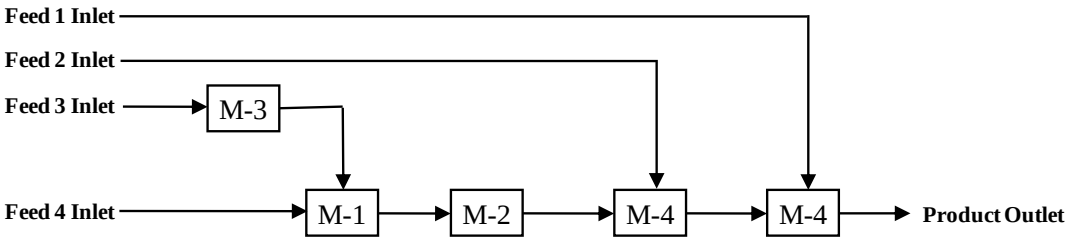


Figure A-9 Proposed microstructure assemblies that will be used for the multistep synthesis reaction

Aim 4: Process Assessment

Through the use of the Aspen software suite, a detailed process model can be created that will allow for an accurate economic analysis and process optimization to be performed. The Aspen software suite is an extremely powerful tool that makes use of high order thermodynamic calculations in order to design various process operation units (e.g., reactors, distillation columns, strippers, etc.). The thermodynamic calculations are performed based on a user-defined equation of state (e.g., Peng-Robinson, Soave-Redlick-Kwong, NRTL, UNIFAC, UNIQUAC, etc.) that is best able to predict the specific material species at the potential operating conditions. Once a process model has been developed and optimized, using up-to-date economic information (e.g., raw material costs, capital/equipment costs, and operating costs) Aspen is capable of providing a life-cycle analysis of the designed process model. The ability to perform this level of process design and economic analysis is absolutely crucial to the development of new technology and intellectual property.

A.1.5 Conclusions/Impact

We propose to design and optimize a far-reaching, unexplored approach to the synthesis of fused heterocyclic rings, a pharmaceutical prevalent motif, for continuous flow processes. By integrating flow technology early on in the development of the synthetic strategy, we propose to contribute in establishing the continuous multistep synthesis as a transformative technology. Unquestionably, this research will be a milestone from which we can build-upon to develop flow-processes; for example, stereoselective, green synthetic schemes toward pharmaceutical applications.[11]

A.1.6 Summary of Project Aims and Progress

Aim 1: Optimize Lewis acid-catalyzed heteroaromatic homo-Nazarov cyclization to produce cyclohexanone **5** in both batch and continuous flow reactions.

Aim 2: Optimize production of amidoester **2**, diazoester **3**, and cyclopropane **4** in both batch and continuous flow mode.

Aim 3: Develop a strategy that enables the multi-step process shown in Scheme 1 to be conducted in continuous flow mode.

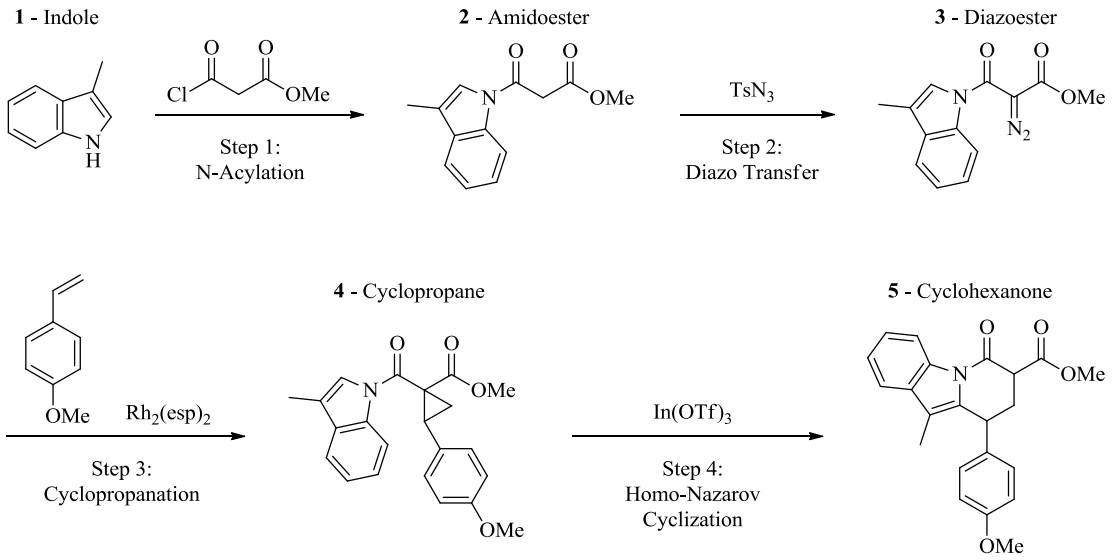


Figure A-10 Multi-step synthesis of the model heteroaryl-fused cyclohexanone

A.1.7 Preliminary Results

A.1.7.1 *Preliminary Optimize Lewis acid-catalyzed heteroaromatic homo-Nazarov cyclization to produce cyclohexanone 5 in both batch and continuous flow reactions*

Cyclopropane **4** was synthesized on a large scale (55 g) according to the literature procedure reported by France and coworkers[1] and subsequently used for reaction optimization in terms of solvent and catalyst loading (Table 1). All experiments were carried out in oven-dried glassware under N_2 atmosphere and care was taken to keep moisture out of the reaction vessel. Cyclopropane **4** and indium (III) trifluoromethanesulfonate ($In(OTf)_3$, 0.5 to 30 mol%) in a given solvent were stirred at the indicated temperature. The reactions were monitored by thin layer chromatography

(TLC) every 15 minutes until the starting material could no longer be detected. The reaction was then quenched with 1.0 mL of water and the ^{1}H-NMR acquired. This standard batch procedure, analysis, and calculation of the conversion remained consistent during the investigations to optimize solvent and catalyst loadings.

The NMR spectra (using acetonitrile as the lock solvent) of the purified cyclopropane **4** and cyclohexanone **5** are shown in Figure A-11 and Figure A-11, respectively. The conversion of the cyclopropane **4** was calculated from the crude reaction mixture using ^{1}H-NMR. The ratio of the 3-methylindole peak of the cyclohexanone **5** (1.70 and 1.94 ppm in Figure A-12, as diastereomers) to the 3-methylindole peak of the cyclopropane 4 (2.28 ppm in Figure A-11) in the crude reaction mixture was used as an approximate measure of conversion.

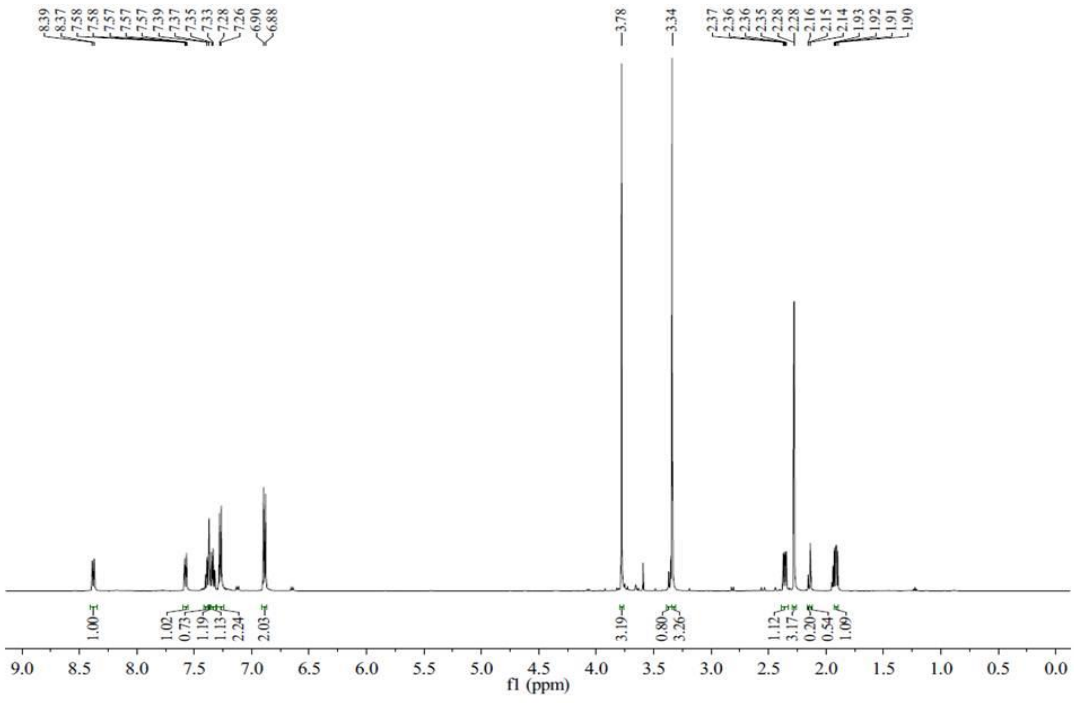


Figure A-11 ^{1}H NMR spectrum of the purified cyclopropane 4

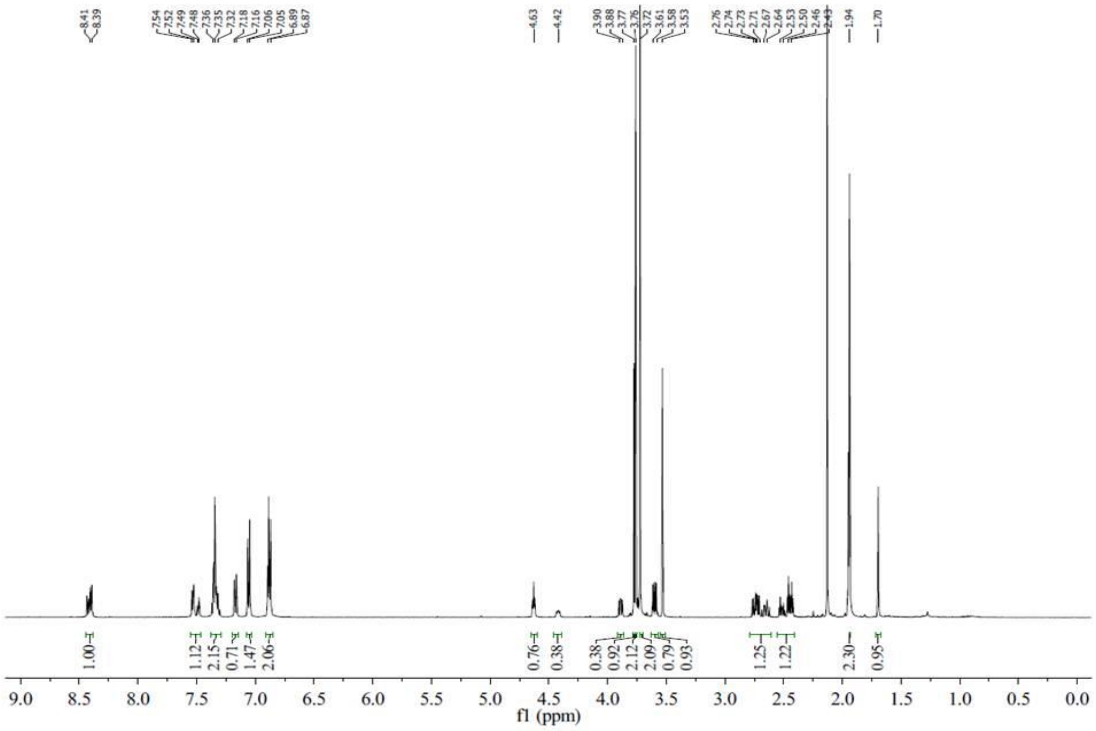


Figure A-12 ^{1}H NMR spectrum of the purified cyclohexanone 5

The solvent study for the homo-Nazarov cyclization step was accomplished utilizing the different pharmaceutically and/or industrially suitable solvents listed in Figure A-13. Solvents such as acetonitrile (CH_3CN), toluene ($PhCH_3$), acetone, and ethyl acetate (EtOAc) gave conversions comparable to those observed in dichloromethane (DCM). Solvents containing an ether moiety, such as tetrahydrofuran (THF) or methyl *tert*-butyl ether (MTBE), were excluded from further studies due to long reaction times even when high catalyst loadings were used. Alcohols were also excluded because no reaction was observed within a 24 hour time frame. This lack of reactivity could be attributed to the insolubility of both the $In(OTf)_3$ and cyclopropane **4** as well as

a potential interaction between the solvent and Lewis acid. Based upon these results, an effort was made to optimize reaction temperature and catalyst loadings in the optimal solvents of ACN and EtOAc (toluene studies are planned).

Figure A-13 Solvent screening study for the homo-Nazarov cyclization of cyclopropane 4 (NR – No Reaction)

Solvent	Temperature (°C)	Catalyst Loading (mol %)	Time	Conversion (%)
DCM	20	30	15 min	100
THF	20	30	12 hrs	100
MTBE	20	30	9 hrs	100
MeOH	20	30	24 hrs	NR
*i*PrOH	20	30	24 hrs	NR
CH_3CN	20	30	15 min	100
$PhCH_3$	20	30	15 min	100
Acetone	20	30	30 min	100
EtOAc	20	30	15-30 min	100

Different reaction temperatures and catalyst loadings in our optimal solvents of CH_3CN and EtOAc were explored in an effort to optimize the reaction. The results are summarized in Figure A-14 and show that in CH_3CN at reflux, the catalyst loading could be lowered to 1 mol% and that the reaction time and conversion were not significantly altered. The results obtained from the optimization are exciting: the reaction can reach full conversion in 15 min at room temperature in acetonitrile with a relatively low catalyst loading. This is especially conducive to the transfer from batch to continuous flow.

Figure A-14 Indium triflate loading study for the Lewis acid-catalyzed homo-Nazarov cyclization of cyclopropane 4.

Solvent	Temperature (° C)	Catalyst Loading (mol %)	Time	Conversion (%)
CH_3CN	20	10	15 min	100
CH_3CN	20	5	15 min	100
CH_3CN	20	1	20-30 min	95
CH_3CN	20	0.5	18 hrs	90
CH_3CN	80	1	15 min	95
EtOAc	20	10	12 hrs	90
EtOAc	20	5	24 hrs	<10
EtOAc	77	10	20-30 min	100
EtOAc	77	5	30-40 min	95

A simple continuous plug flow reactor was designed to transfer the homo-Nazarov reaction from batch to continuous technology. A schematic of the reactor is shown in Figure A-15. Two Eldex (ReciPro Series 2000) positive-displacement pumps feed individual solutions of the cyclopropane **4** and the $In(OTf)_3$. They mix at a tee-joint and where they can begin reacting. For safety concerns, a pressure-relief valve was installed in case of any significant increase in pressure. Two thermocouples monitor the temperature shortly after the reactant and catalyst mix and before the exit of the reactor. The internal volume of the reactor is approximately 29.5 mL. The entire body of the reactor is stainless steel to prevent any additional catalytic effect. The reactor effluent is collected for analysis. The reactor will be submerged into a controlled temperature bath to perform studies at elevated temperatures.

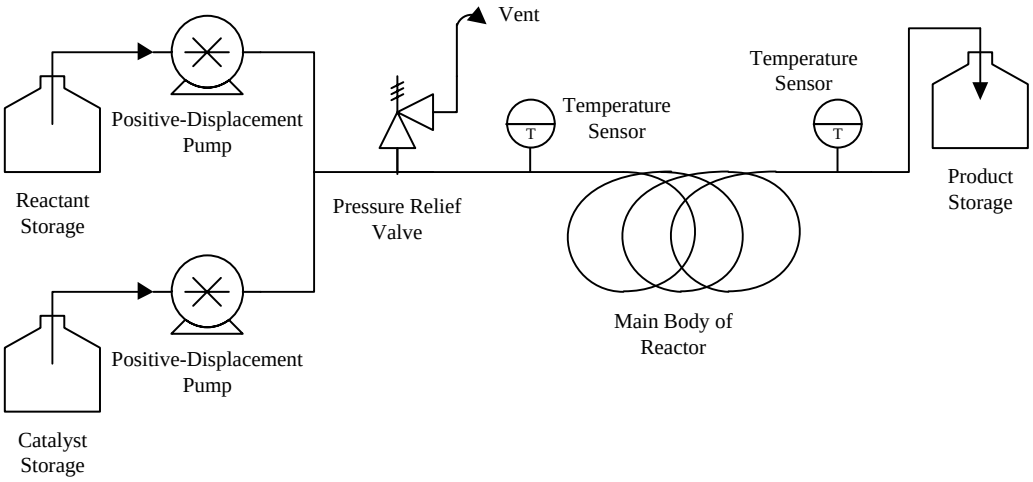


Figure A-15 Schematic of the continuous flow reactor

The first homo-Nazarov reaction performed in this reactor was conducted as follow: a 0.2 M solution of cyclopropane **4** in acetonitrile was reacted with a 0.01 M

solution of $In(OTf)_3$ in acetonitrile. The pumps were set to deliver a volumetric flow rate of 1.135 mL/min each (2.270 mL/min total). This provided a reaction mixture that was 0.1 M cyclopropane and 5 mol% $In(OTf)_3$ which has been shown to reach completion in less than 15 minutes (see Figure A-14). The flow rate (2.270 mL/min) provided an approximate residence time of 15 minutes which allowed for a direct comparison of the batch reaction to the continuous reaction. In order to quench the catalyst and prevent further reaction upon exiting the reactor, the effluent was quenched into water and collected. Every 15 minutes, a sample of the effluent was collected for one minute (~2.3 mL) into 1 mL of water. This reaction mixture was analyzed by high performance liquid chromatography (HPLC).

Reverse phase chromatography was used in the analysis of the reaction solutions. Method development was completed using a Waters XBridge C18 column (3.5 µm, 2.1 x 50 mm) installed in a HP 1100 series HPLC equipped with a degasser, binary pump system, autosampler, column heater, and UV-VIS detector. The analytes were monitored at 210, 245, and 280 nm and a linear gradient was employed. The gradient was optimized using water and acetonitrile as the mobile phase and by reducing the slope of the gradient from a change of 6% (CH_3CN) per minute to 3% per minute. At the optimum conditions, the cyclopropane **4** has a retention time of 20.7 minutes while the cyclohexanone **5** eluted at 19.4 and 19.9 minutes (as diastereomers) show in Figure A-16. Naphthalene was chosen as the internal standard because it does not interfere in cyclization reaction, is soluble in acetonitrile, and has a significantly different retention time (16.8 minutes) than the starting material and products as shown in Figure A-17.

After method optimization and the internal standard was chosen, calibration curves for each compound were made so that a quantitative analysis of each reaction could be performed.

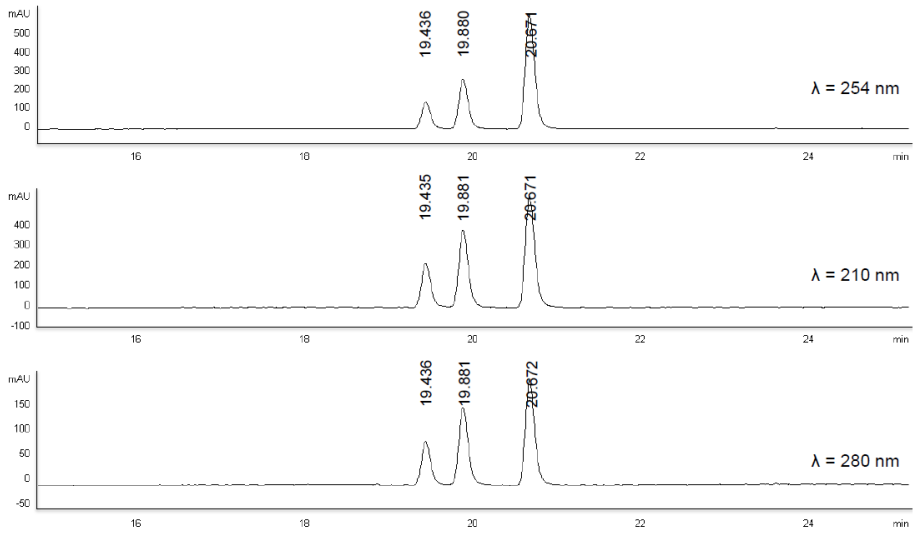


Figure A-16 Optimized separation of starting material (retention time = 20.7 min) and products (retention times = 19.4 and 19.9 min).

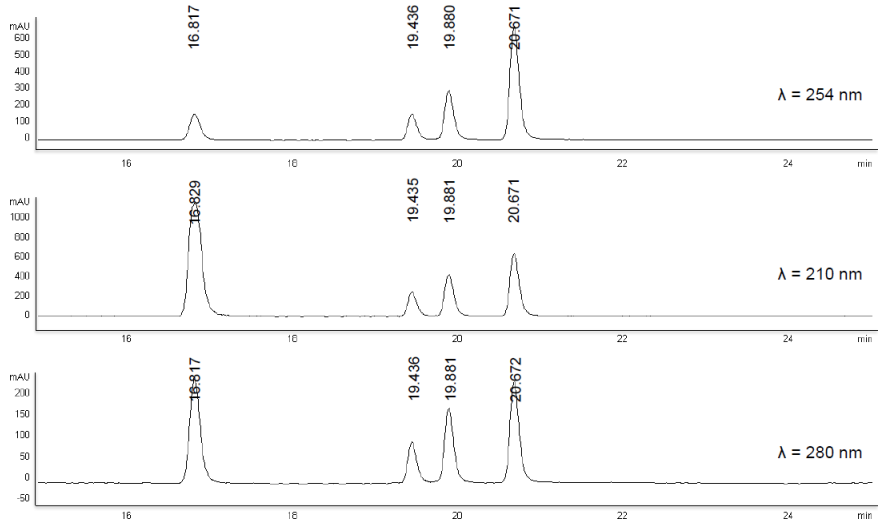


Figure A-17 Optimized separation of the internal standard (retention time = 16.8 min), starting material (retention time = 20.7 min), and products (retention times = 19.4 and 19.9 min)

The first continuous flow reaction was performed at an uncontrolled room temperature (~18°C) and reached full conversion and yield of approximately 80%. Initial concentrations of the cyclopropane 4 and $In(OTf)_3$ upon mixing were 0.1 M and 0.005 M, respectively. Naphthalene was used as an internal standard in the cyclopropane solution at a concentration of 0.05 M. The concentration of the cyclopropane in the effluent was below the detection limit of the HPLC and no additional side-products were detected. Additional experiments with the reactor are planned to reproduce these results and investigate the impact of catalyst loading, flow rates, and solvents. In addition, a second internal standard (biphenyl) will be used to improve the analysis.

A.1.7.2 ***Optimize production of amidoester 2, diazoester 3, and cyclopropane 4 in both batch and continuous flow mode***

Following the procedure reported by France and coworkers[1], large scale batch reactions were performed to synthesize 20 g of diazoester **3.** The cyclopropanation reaction was optimized for batch operation prior to the transfer to continuous operation. All reactions were carried out under anhydrous conditions. One tenth to one mol% of Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] ($Rh_2(esp)_2$) was dissolved in DCM and then 4-vinylanisole (1.0 equivalent) was added to the solution. Next, diazoester **3** (1.1 equivalents) was added to the reaction mixture and allowed to stir

at ambient temperature. The reactions were monitored via TLC every 5 minutes until the starting material could no longer be detected. The original protocol calls for dichloromethane as the solvent; however, as we proposed to move away from chlorinated solvents and optimize a multi-step continuous synthesis, we optimized the reaction conditions with acetonitrile and toluene as solvents (EtOAc studies are also planned).

This study investigated concurrently the solvent (acetonitrile vs. toluene) and catalyst loading as summarized in Figure A-18. The reaction at 23°C in acetonitrile requires more than 2 hours to reach completion. An increase in the reaction rate was observed when the reaction was refluxed in acetonitrile (82°C): the reaction reached completion in less than 5 minutes with a catalyst loading of 0.5 mol%. Studies at lower temperatures and lower catalyst loadings are underway using acetonitrile as the solvent. Toluene was also tested and resulted in faster reaction times when compared to acetonitrile at 23°C. Other studies at different temperatures using toluene as the solvent are underway in order to reduce the catalyst loading

Figure A-18 Solvent and catalyst loading study for the rhodium(II)-catalyzed cyclopropanation.

[a]Conversion estimated by TLC, [b]Product was not isolated, [c]Isolated yield.

Solvent	Temperature (°C)	Catalyst Loading (mol %)	Time	Conversion[a] (%)	Yield (%)
CH_3CN	23	0.1	>24 hrs	40-50	-----[b]
CH_3CN	23	0.5	>2 hrs	90-95	-----[b]
CH_3CN	23	1.0	>2 hrs	100	82[c]
CH_3CN	82	0.1	15-20 min	90	-----[b]
CH_3CN	82	0.5	≤5 min	100	-----[b]
CH_3CN	82	1.0	≤5 min	100	77[c]
$PhCH_3$	23	0.1	15-20 min	100	-----[b]
$PhCH_3$	23	0.5	≤5 min	100	-----[b]
$PhCH_3$	23	1.0	≤5 min	100	86.4[c]

The batch cyclopropanation procedure makes use of a rhodium(II) catalyst which is typically quenched with saturated thiourea. Translating this quenching procedure to the continuous flow reactor would add an additional complicated separation. For this reason, a tandem protocol is being considered in which the homo-Nazarov cyclization is performed immediately after the cyclopropanation without quenching or removing the rhodium catalyst. In this protocol, the $In(OTf)_3$ (5 mol%) was added once the diazoester was completely consumed and the reaction monitored via TLC every 5 minutes. Figure A-19 summarizes the preliminary data for the tandem protocol.

Figure A-19 Tandem protocol for the synthesis of the model heteroaryl-fused cyclohexanone starting from the diazoester compound 3. [a]Temperature and loading of $Rh_2(esp)_2$, [b]Time for complete consumption of diazoester 3, [c]Temperature and loading of $In(OTf)_3$, [d]Time for complete consumption of cyclopropane 4, [e]Isolated yield.

Solvent	Cyclopropanation Conditions[a]	Time[b]	Cyclization Conditions[c]	Time[d]	Yield[e] (%)
CH_3CN	82°C, 0.5 mol%	≤5 min	23°C, 5 mol%	1 hr	42.6
CH_3CN	50°C, 0.5 mol%	40 min	50°C, 5 mol%	10 min	65.0
$PhCH_3$	23°C, 0.5 mol%	≤5 min	23°C, 5 mol%	>1 hr	64.1

When the cyclopropanation was performed in acetonitrile at 82°C, the diazo compound was completely consumed in less than 5 minutes. The reaction mixture was cooled to 23°C and $In(OTf)_3$ was added to the reaction. Complete consumption of the cyclopropane was observed after 1 hour and the product was isolated in 43% yield. The tandem reaction protocol was performed at 50°C (without cooling between reaction steps) in order to decrease the reaction time for the homo-Nazarov cyclization. The cyclopropanation took 40 minutes to reach completion and the cyclization step took 10 minutes (isolated cyclohexanone **5** yield of 65%). Reactions with a higher loading of rhodium and a higher temperature are underway in order to obtain a reasonable reaction time for the cyclopropanation.

Toluene was also used for the tandem protocol since the cyclopropanation requires shorter reaction times and lower loading of the catalyst in toluene. When the $In(OTf)_3$ was added to the reaction (once the diazo was completely consumed) the

cyclization reaction took more than one hour for full completion (isolated cyclohexanone **5** yield of 64%). Reactions at higher temperatures are underway in order to obtain a reasonable reaction time.

A.1.8 Future Directions

A.1.8.1 *Homo-Nazarov Cyclization*

With the homo-Nazarov cyclization reaction optimized and the continuous flow reaction demonstrated to be a viable method, additional continuous flow experiments will be performed to further investigate catalyst loadings, flow rates, and temperature effects. These additional reactions will provide significant amounts of kinetic information that will be used to aid process development of the continuous technology

A.1.8.2 *Diazo Transfer and Cyclopropanation*

The cyclopropanation reaction will be further investigated in order to optimize the reaction as well as the tandem protocol that will enable the facile transfer to continuous technology. The continuous flow reactor will be modified to allow for additional reaction steps by including additional pumps, safety measures, temperature sensors, heating capabilities, and sampling points. The cyclopropanation and tandem protocol (cyclopropanation + homo-Nazarov) will then be demonstrated respectively using the modified continuous flow reactor.

A.1.9 References

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APPENDIX B - TUNABLE ORGANIC-IONIC LIQUID SOLVENTS (TOIS)

B.1 Introduction

Ionic-liquids (ILs) have gained significant importance as alternative solvents for catalysis applications, particularly in cases where water can interact with the transition metal catalyst or substrates that have very low solubility in water. This has led to research activities mainly on the development of new catalyst/solvent systems for various reactions [1-3]. Ionic-liquids offer a low vapor pressure, thermal and chemical stability. They can also offer new opportunities for the development of improved biphasic systems. For example, ionic-liquids can represent an interesting alternative to substitute water in biphasic hydroformylation reactions. Ionic-liquids are reported to enhance the catalytic activity for some chemical transformation. In aqueous biphasic systems, low reaction rates are usually obtained because of phase transfer limitations caused by the low solubility of the substrate in the catalyst phase. On the other hand, ionic liquids are good solvents for a wide range of both organic and inorganic species without undesirable interactions with the metal center. Also, homogeneous mixtures of ILs and organics have been reported to phase-separate under CO_2 pressures and therefore, could be beneficial for separating nonpolar products from ionic catalysts [4, 5]. Tunable Organic-Ionic Liquids Systems (TOIS) can be seen as a complimentary solvent system to OATS that may be beneficial for these types of reactions.

B.2 Results and Discussion

In this study we report a new approach to performed hydroformylation reaction of *p*-methylstyrene by using TOIS. In the first series of experiments, we performed the hydroformylation of *p*-methylstyrene in two different commercially available imidazolium based ionic liquids ([BMIM][BF_4] and [BMIM][PF_6] shown in Figure B-1) and acetonitrile. The reactions were carried out in a Parr reactor at 60°C and using the same reaction conditions described in Chapter 4 for using OATS. The results are summarized in Figure B-2. The hydroformylation of *p*-methylstyrene using tunable organic-ionic liquids (TOIS) resulted in lower reaction rates compared to the traditional OATS systems. The lower reaction rate is attributed to the low solubility of syngas (H_2/CO) in the ionic liquid. The two imidazolium based ionic liquids ([BMIM][BF_4] and [BMIM][PF_6]), exhibited low syngas solubility which are not suitable for hydroformylation kinetics, although they can achieve completion after approximately 20 hours. In addition a lower selectivity was observed when TOIS was used.

1 **2**

Figure B-1 Structure of [BMIM][BF_4] (1) and [BMIM][PF_6] (2)

Figure B-2 Hydroformylation of *p*-methylstyrene in TOIS

IL	Temperature (°C)	Time (hour)	Conversion (%)	Selectivity to Branched Product (%)
[BMIM][PF_6]	60	1	58	93
[BMIM][BF_4]	60	1	9	100
[BMIM][PF_6]	80	20	97	82
[BMIM][BF_4]	80	20	100	77

B.3 Conclusion and Recommendations

The hydroformylation reaction of *p*-methylstyrene using [BMIM][BF_4] and [BMIM][PF_6] and acetonitrile mixtures achieved lower reaction rates compared to the traditional OATS solvent system discussed in Chapter 4[6]. The slow reaction rates are attributed to the low solubility of syngas (CO and H_2) in the ionic liquid. However, the reaction using tunable organic-ionic liquid solvents can be improved by the use of other ionic liquids. For example, ionic-liquid [MMIM][BF_4] exhibited a higher (almost 4.7 times higher) carbon monoxide solubility than [BMIM][BF_4][1].

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VITA

Wilmarie Medina-Ramos was born in Puerto Rico on June 2, 1986. She graduated from high school in 2004 and then pursued an undergraduate degree in Chemical Engineering at the University of Puerto Rico- Mayaguez Campus. While pursuing her undergraduate degree, she conducted research under the direction of Dr. Samuel Hernández at the University of Puerto Rico, and held a summer internship at Rensselaer Polytechnic Institute under the research direction of Dr. Marc Olivier Coppens. After graduating in 2009, she decided to pursue an advanced degree in Chemical Engineering. She began her doctoral study at the Georgia Institute of Technology in the Chemical & Biomolecular Engineering department in 2009. During that time, she has completed research as a member of the Eckert-Liotta research group. She will complete her Ph.D. in Chemical Engineering in July 2013. Selected publications and presentations follow.

PUBLICATIONS

Medina-Ramos, W. ; Mojica, M.; Hart, R.; Pollet, P.; Cope, E.D.; Liotta, C.L; Eckert, C.A.; Water at Elevated Temperatures: A Reactant, Catalyst, and Solvent in the Selective Catalyzed Hydrolysis of Protecting Groups (Manuscript in preparation).

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Davey, E.; **Medina-Ramos, W.;** Flack, K.; Marus, G.; Dzenis, O.; Saunders, S.; Pollet, P.; Liotta, C.L; Eckert, C.A.; Continuous Flow Processing: Enabling a Meerwein-Ponndorf-Verley (MPV) Reduction (Manuscript in preparation).

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PRESENTATIONS

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Medina-Ramos, W. ; Mojica, M.; Andrews, J.O.; Pollet, P.; Jha, R.; Cope, E.D.; Liotta, C.L; Eckert, C.A.; *"*Water at Elevated Temperatures: A Reactant, Catalyst, and Solvent in the Selective Catalyzed Hydrolysis of Protecting Groups" (10^{th} ISSF 2012, San Francisco, CA, May 2012)

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