INTRODUCING SUSTAINABILITY INTO INDUSTRIAL HOMOGENEOUS CATALYSIS

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By

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INTRODUCING SUSTAINABILITY INTO INDUSTRIAL HOMOGENEOUS CATALYSIS

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This thesis is dedicated to my family and friends, who with immeasurable love and incalculable patience have fostered in me a love for understanding.

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SUMMARY

This thesis describes four projects focused on the implementation of green chemistry and engineering in an industrial context. The first project describes efforts to transition Meerwein-Ponndorf-Verley reduction technology from a batch-wise production framework to a continuous-flow framework. This work was done in the context of improving the synthesis of HIV-protease inhibitor intermediates.

The second project describes a similar transfer of hydropyridoindole synthesis technology from batch processing to continuous-flow processing. In particular, a tandem synthetic pathway was developed for conducting cyclopropanation and ring-opening cyclization reactions in series.

The third project describes the development of a novel catalyst separation process incorporating the use of sulfur-containing additives and Organic-Aqueous Tunable Solvents. Specifically, this process is demonstrated on palladium catalysts that have been employed in Suzuki coupling reaction mixtures.

The fourth project describes the development of a recyclable catalytic system for use in Suzuki coupling reaction processes. The technology described incorporates the use of water-soluble ligands to generate hydrophilic palladium species that can be recovered via Organic-Aqueous Tunable Solvents and reintroduced as an active catalyst species.

CHAPTER 1 - INTRODUCTION

1.1 Principles of Green Chemistry and Engineering

In the half-century following the passing of the National Environmental Policy Act (1969)[1], the field of "Green Chemistry" has gained immense popularity as a tool for refining the benign interactions between the environment, the chemical industry, and the society that it serves. In the decades that followed, the world witnessed a number of changes in the political, societal, and industrial landscape concerning the development of green chemistry, ranging from the creation of the Environmental Protection Agency (EPA)[2], the passing of numerous pieces of environmental legislation, and a series of unfortunate chemical accidents[3]. However, the greatest steps weren't taken until nearly the end of the millennium.

In 1998, Paul Anastas and John Warner laid the groundwork for what would become the foundation of understanding of green chemistry applications by publishing *Green Chemistry: Theory and Practice*[4]. Within the text, Anastas and Warner provide 12 guidelines to be followed in order to encourage the development of sustainable chemistry. Those guidelines have come to be known as the 12 Principles of Green Chemistry, and are shown in Table 1-1.

Table 1-1: 12 Principles of Green Chemistry[4]

C1	It is better to prevent waste than to treat or clean up waste after it has been created.
C2	Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
C3	Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
C4	Chemical products should be designed to affect their desired function while minimizing their toxicity.
C5	The use of auxiliary substances, such as solvents and additives, should be made unnecessary wherever possible and innocuous when used.
C6	Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized.
C7	Whenever available and practicable, a raw material should be renewable.
C8	Unnecessary derivatization should be minimized or avoided if possible.
C9	Catalytic reagents are superior to stoichiometric reagents.
C10	Chemical products should be designed so that they break down into innocuous degradation products at the end of their function and do not persist in the environment.
C11	Analytical methodologies should be incorporated to allow for real-time monitoring and process control prior to the formation of hazardous substances.
C12	Substances and their applications should be chosen to minimize the potential for chemical accidents.

A similar code of conduct was made to define best practices for green engineering in 2003. This compilation of guidelines, known as the San Destin Declaration[5], exhibits

9 principles of green engineering, focusing on the development of processes in an industrial setting. The 9 principles of green engineering are shown in Table 1-2.

Table 1-2: 9 Principles of Green Engineering[5]

E1	Engineer processes and products holistically, use systems analysis, and integrate environmental impact assessment tools.
E2	Conserve and improve natural ecosystems while protecting human health and well-being.
E3	Use life-cycle thinking in all engineering activities.
E4	Ensure that all material and energy inputs and outputs are as inherently safe and benign as possible.
E5	Minimize depletion of natural resources.
E6	Strive to prevent waste.
E7	Develop and apply engineering solutions, while being cognizant of local geography, aspirations, and cultures.
E8	Create engineering solutions beyond current or dominant technologies.
E9	Actively engage communities and stakeholders in development of engineering solutions.

A brief comparison of the 12 Principles of Green Chemistry and the 9 Principles of Green Engineering reveals a few similarities that highlight the heart of the green chemical movement:

- Minimize waste
- Minimize resource depletion/utilize renewables
- Minimize toxicity of materials used
- Minimize exposure of people and environment to toxic materials

- Design processes to avoid hazardous conditions

These concepts are fundamental to the application of green chemistry and engineering, and are the impetus for research in the four topics discussed in this thesis. The first and second research projects present efforts to transition industrially-relevant chemistries from a batch-wise production framework to a continuous-flow production framework, thereby minimizing solvent via from batch-wise transferring (C1, E6), incorporating efficient heat-transfer via improved heating control (C6), and minimizing risk to personnel by the removal of workers from the workspace as well as the removal of large batches of dangerous compounds frequently employed in batch-wise chemistry (C12, E4). The third and fourth research projects discussed in this thesis present the development of processes useful towards the recovery and re-use of palladium catalysts in Suzuki coupling reactions, thereby minimizing the depletion of palladium feedstocks (C7, E5), reducing the amount of palladium lost to waste streams and the environment (C1, E3), and lowering the cost of operation for a chemical process (E9).

It is important to note here the relevance of Green Engineering Principle 9: "actively engage communities and stakeholders in development of engineering solutions". While the other principles discussed above have significant impact on sustainability and environmental stewardship, E9 is a principle that ensures cooperation between society and industry. This principle highlights the need for sustainable solutions to be economically preferable, rather than simply viable. Economic advantage of sustainable solutions guarantees that green chemistry and engineering will have industrial preference. It is for this reason that the work presented in this thesis targets chemistry that is important in the pharmaceutical and fine chemical industries.

The remainder of this chapter focuses on the background and motivation for the four research topics presented in this thesis. The first section discusses the benefits of continuous flow processing and compares the technology to batch-wise processing. The second section outlines the motivation for palladium recovery in an industrial setting and briefly explains the concept of Organic-Aqueous Tunable Solvents, a technology proposed for the recovery of palladium catalysts.

1.2 Implementation of Continuous-Flow Technology

In recent history, continuous-flow technology has drawn significant interest for the pharmaceutical industry as an alternate pathway for the productions of medicinally-active products[6]. The field of research committed to the transfer of technology from batch to flow has even been designated as the leading green engineering field of research by the American Chemical Society Green Chemistry Institute[7]. The reasons for the transfer stem from the benefits inherent to flow technology. In 2014, the American Chemical Society publication *Chemical & Engineering News* published an article outlining the advantages of a continuous flow methodology over a batch process, providing benefits such as low capital investment, less space required, safer with hazardous reactions, shorter processing times, possible novel chemistries, need for less inventory, potential cost savings, better product quality, improved environmental impact, and straightforward scale-up[6]. The benefits of scale-up are of particular interest, as continuous flow technology readily allows for the implementation of "scale-out" rather than "scale-up". "Scale-out" refers to the notion of production enhancement by simply multiplying the amount of reactors currently in use rather than developing a larger reactor via "scale-up", as shown in Figure 1-1.

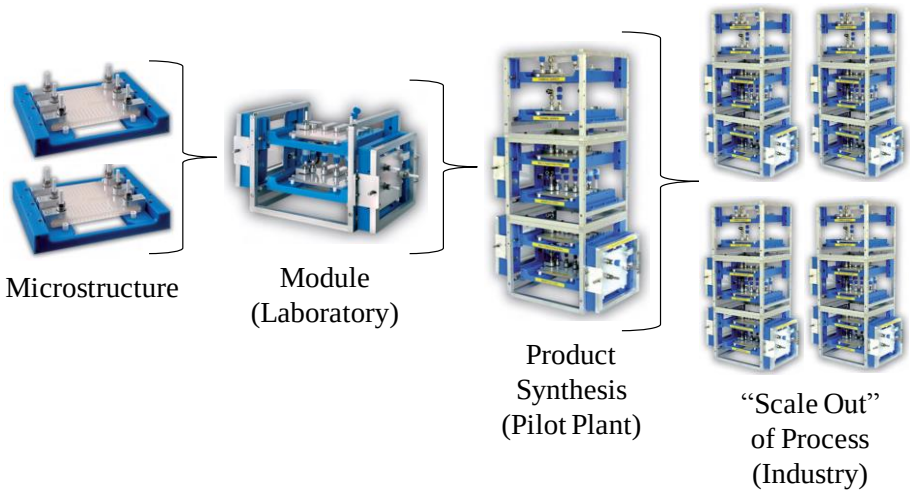

Figure 1-1: Concept of "Scaling-Out" a Continuous-Flow System

"Scale-out" is a significant benefit of continuous flow production in that excess research time is not needed to successfully increase production, as it is in a batch production framework. This savings in time provides a large impetus for industries to incorporate continuous flow for production of pharmaceutical compounds under time-sensitive patents.

In Chapters 2 and 3, separate batch syntheses are investigated and transferred to a continuous flow framework. In particular, each chapter targets a specific drug and addresses a challenge to continuous flow production. Chapter 2 focuses on the Meerwein-Ponndorf-Verley (MPV) reduction of carbonyls[8], targeting examples that are used as intermediates in the synthesis of a number of HIV-protease inhibitor drugs[9]. The resulting alcohol products are often insoluble in the reaction solvent. Work presented in

Chapter 2 demonstrates that MPV reductions may be performed under flow conditions, despite the formation of solid products. Chapter 3 addresses the notion of conducting multi-step reactions in flow, targeting molecular models for a known vasodilator[10]. The work in Chapter 3 demonstrates successful performance of tandem continuous flow reactions despite challenges caused by evolution of a second gas phase during reaction.

1.3 Use of Organic-Aqueous Tunable Solvents to Recover Palladium Catalysts

Platinum group metals (PGMs) are some of the most used catalysts in the chemical industry to date. Over the years, PGMs (platinum, palladium, rhodium, ruthenium, iridium and osmium) have found use in a number of valuable synthetic reactions, including hydrogenation, oxidation, hydroformylation and carbonylation reactions[11] as well as large number of coupling reactions such as the palladium-catalyzed Suzuki coupling reaction[12], which is the reaction of interest in chapters 4 and 5 of this thesis. Unfortunately, PGMs (including palladium) are rare in nature, and therefore are relatively expensive. The selling price of palladium in 2011 was $730 per troy oz., exhibiting a 174% increase from the price of Palladium in 2009, $420/troy oz[13]. The cost of palladium later spiked in 2014 to $911.50 in 2014[14]. In addition to the high cost of catalyst, chemical industries that employ palladium catalysts are subject to the ebbs and flows of market prices. In 2010, a deficit was observed between the amount of palladium produced and the amount consumed. In 2011, a report from Stillwater Mining Company[13] revealed that increasing demand for palladium in the auto sector would likely only cause the deficit to increase (prediction shown in Figure 1-2), with speculations suggesting that PGM prices would continue to climb.

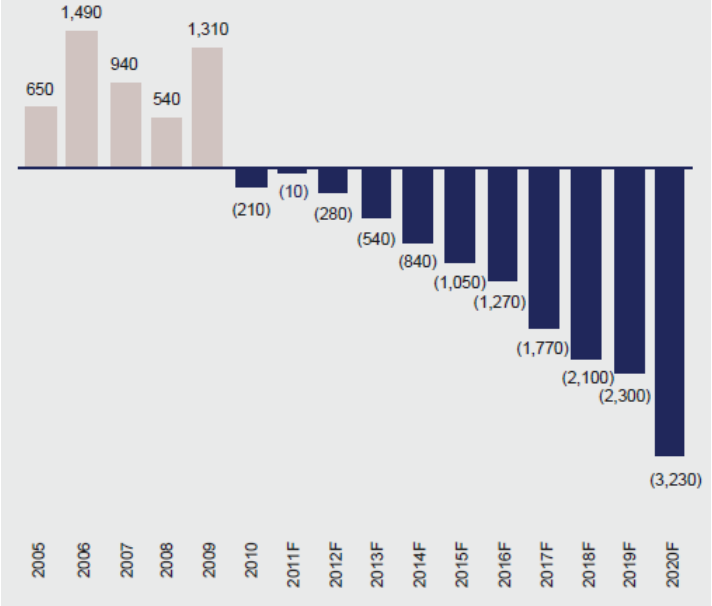

Figure 1-2: Market Deficit of Palladium (in '000s of oz), forecast to 2020

In addition to an impending rise in cost, industries are faced with further challenges concerning the removal of palladium from chemical waste streams. Government policies have been established that regulate the limits of PGM contamination in order to prevent harm to the public and environmental. In particular, limits of PGM (including palladium, platinum, and rhodium) exposure and consumption fall around 15 µg/day, or 5 ppm for oral ingestion[15].

In light of the increasing demand/supply ratio of palladium, as well as the low specification limits on environmental PGM concentration, there is a clear motivation to develop efficient, sustainable technologies to recover palladium from chemical waste streams for the goals of recycle or reuse. Chapters 4 and 5 propose strategies to separate and recycle palladium catalysts using Organic-Aqueous Tunable Solvent (OATS) technology[16]. OATS technology refers to a solvent system comprised of two miscible

liquids (such as acetonitrile and water) that can be made immiscible with the application of an antisolvent trigger, such as CO_2. By OATS, a process may undergo homogeneous reaction (achieving higher reaction rates) while retaining the benefits of heterogeneous separation (under application of CO_2)[17]. Furthermore, OATS systems exhibit tunability through the pressure-dependent absorption of CO_2, allowing the system solvent properties to be easily manipulated as a function of pressure. Finally, OATS constitutes a "green" process in that the additive employed to phase separation is relatively benign CO_2 that is easily removed via depressurization.

The work shown in Chapter 4 demonstrates a novel technique for the separation and recovery of palladium catalysts using OATS in combination with sulfur-based additives. The process allows for the majority of palladium to be removed from post-Suzuki reaction products without the generation of a large waste stream. Chapter 5 discusses work done towards the development of a recyclable palladium catalyst using water-soluble ligands and an OATS separation process. If implemented, the process would drastically reduce the rate of palladium consumption of the system, allowing catalyst to be recycled and reused in-house.

1.4 References

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CHAPTER 2 - IMPLEMENTATION OF CONTINUOUS FLOW TECHNOLOGY FOR USE IN THE MEERWEIN-PONNDORF-VERLEY (MPV) REDUCTION OF CARBONYLS

2.1 Introduction

Among the many chemical functional groups used in modern pharmaceutical chemistry, chloromethylketones (CMKs) stand out for their versatility and implementation[1]. One noteworthy use of CMKs is their use as synthetic intermediates for a variety of HIV treatment medications. An excellent example is the transformation pathways available from (S)-*tert*-butyl-(4-chloro-3-oxo-1-phenylbutan-2-yl)carbamate to form three distinct HIV-Protease Inhibitors (PIs)[2,3,4]. The transformation is highlighted in Figure 2-1.

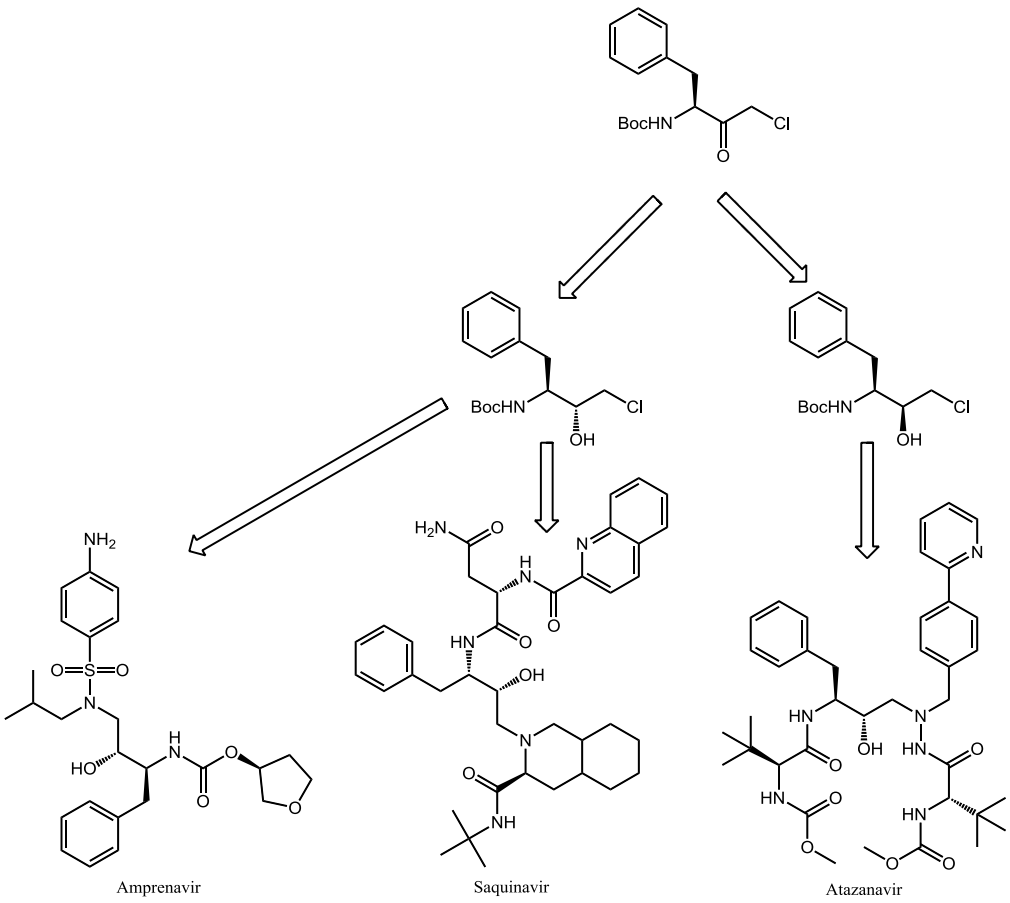


Figure 2-1: Syntheses of HIV-Protease Inhibitors from a Single Chloromethylketone

Given the significance of these compounds and the pharmaceutical chemicals that are derived from them, it is of considerable interest to optimize the synthesis and reaction of CMKs and CMK-derived drugs in a manner that is both economical and environmentally-conscious. One such optimization is the transition from batch processing technology to continuous-flow technology. Previous work has been done by Pollet *et al* studying the transition of technology for the production of (S)-*tert*-butyl-(4-chloro-3-oxo-1-phenylbutan-2-yl)carbamate from batch to continuous-flow processing[5]. Continuous flow reactions were implemented to produce the corresponding diazoketone

using the readily-available amino acid phenylalanine as a starting reagent. From this stage, the transition to the CMK is completed by treatment with hydrochloric acid. The complete reaction scheme is shown in Figure 2-2.

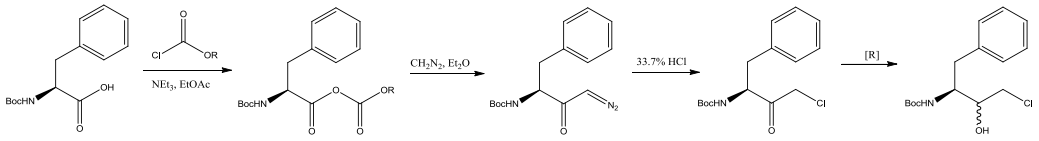


Figure 2-2: Synthesis of Chloromethylalcohol intermediate from Boc-phenylalanine[5]

While most of the steps have been shown and are well-understood, the reduction step has not, as of yet, been researched in a continuous flow framework. A number of reactions exist that can reduce the CMK to the appropriate chloromethylalcohol[6,7,8]. However, in order to reduce the CMK in a manner that maximized the yield of stereoisomeric products (such as those seen in Figure 2-1), a stereoselective reducing reaction is required.

The Meerwein-Ponndorf-Verley (MPV) reaction stands out as one of the most chemoselective pathways for reducing carbonyls to primary and secondary alcohols with the added benefit of using mild reaction conditions[9,10]. The MPV method involves the reaction of a carbonyl compound (aldehyde or ketone) with an aluminum alkoxide, usually in an alcoholic solvent. 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 hydride transfer from an aluminum-bound alkoxide ligand to the

carbonyl carbon via a six-membered ring transition state. The mechanism and transition state for the hydride transfer are illustrated in Figure 2-3.

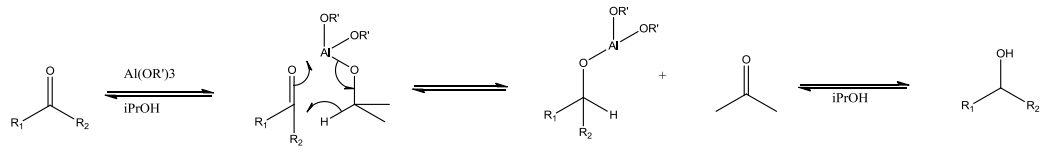


Figure 2-3: Reaction Mechanism for Meerwein-Ponndorf-Verley (MPV) Reduction of Carbonyls

In principle, catalytic amounts of aluminum alkoxide can be used since the active aluminum reagent is continually regenerated, but in practice, this usually results in very slow reaction rates. Additionally, small quantities of water can deactivate the aluminum species. In order to improve both the rate of reaction and the catalyst lifetime, large quantities of the aluminum catalyst are often employed (usually near-stoichiometric amounts)[11]. While large quantities of the aluminum catalyst are compatible with batch-mode processes, the potential for phase separation can be detrimental when transitioning to a continuous flow process.

Many conventional MPV reductions require reaction times on the order of hours. A significant rate enhancement of MPV reductions using aluminum tert-butoxide, $Al(O\textit{t}Bu)_3$ rather than the conventional $Al(OiPr)_3$ catalyst has been reported in literature[11]. $Al(O\textit{t}Bu)_3$ not only improved the reduction rate of both ketones and aldehydes, but is also commercially available and inexpensive. The enhanced activity of $Al(O\textit{t}Bu)_3$ allowed for catalyst loadings under 20 mol % and the inclusion of mixed

solvent systems with little hindrance to the rate. The research presented herein demonstrates that the enhanced activity of $Al(O\textit{t}Bu)_3$ (and subsequently, the reduced catalyst loading requirement) is conducive to a successful transfer of traditional batch MPV reductions to a continuous flow process. Six model compounds have been transferred from batch technology to continuous flow technology: benzaldehyde, acetophenone, cyclohexanone, dichloroacetophenone, (S)-*tert*-butyl-(4-chloro-3-oxo-1-phenylbutan-2-yl)carbamate, and (S)-*tert*-butyl-(4-chloro-3-oxo-1-(4-benzyloxyphenyl)butan-2-yl)carbamate (Figure 2-4).

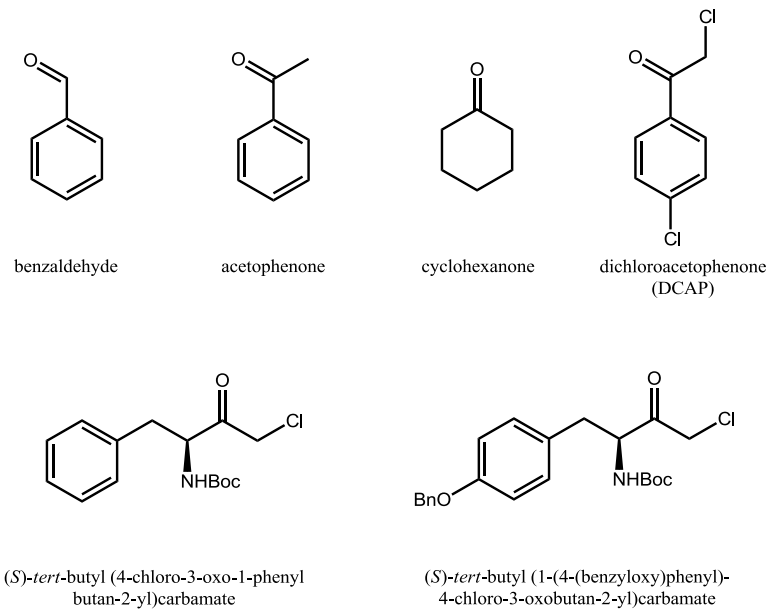


Figure 2-4: Structures of Model Carbonyls for Continuous-Flow MPV Reduction

The development of continuous processes has been identified as a key area of research toward sustainable manufacturing[12,13]. Currently, the pharmaceutical industry

primarily functions using batch processes, largely because of assets already installed[14]. Yet, there are widely recognized benefits of implementing continuous processes, including: (1) economics (scale "out" vs. scale "up"), (2) environmental (energy and atom economy), (3) product quality (greater, finer control of temperature and process parameters), and (4) safety (scale "out" vs. scale "up"). The "scale out" factor is of vital importance in the pharmaceutical industry as it can add years to the period of production during a patent lifetime.

2.2 Experimental Section

2.2.1 Materials

Benzaldehyde, acetophenone, cyclohexanone, and anhydrous isopropyl alcohol were purchased from Sigma-Aldrich and used as received. Aluminum *tert*-butoxide was purchased from Alfa Aesar and used as received. N-Boc-1-chloro-3-amino-4-phenylbutan-2-one was purchased from best of chemicals and used as received. N-Boc-4-(benzyloxyphenyl)-1-chloro-3-aminobutan-2-one was provided by American Pacific Fine Chemicals.

2.2.2 Experimental

2.2.2.1 Corning® Advanced-Flow Reactor Set-up

A Corning® Advanced-Flow glass reactor[15] with an operational pressure range of 0-18 bars and a temperature range of -60 to 200 °C was employed in this research. It is depicted in Figure 2-5.

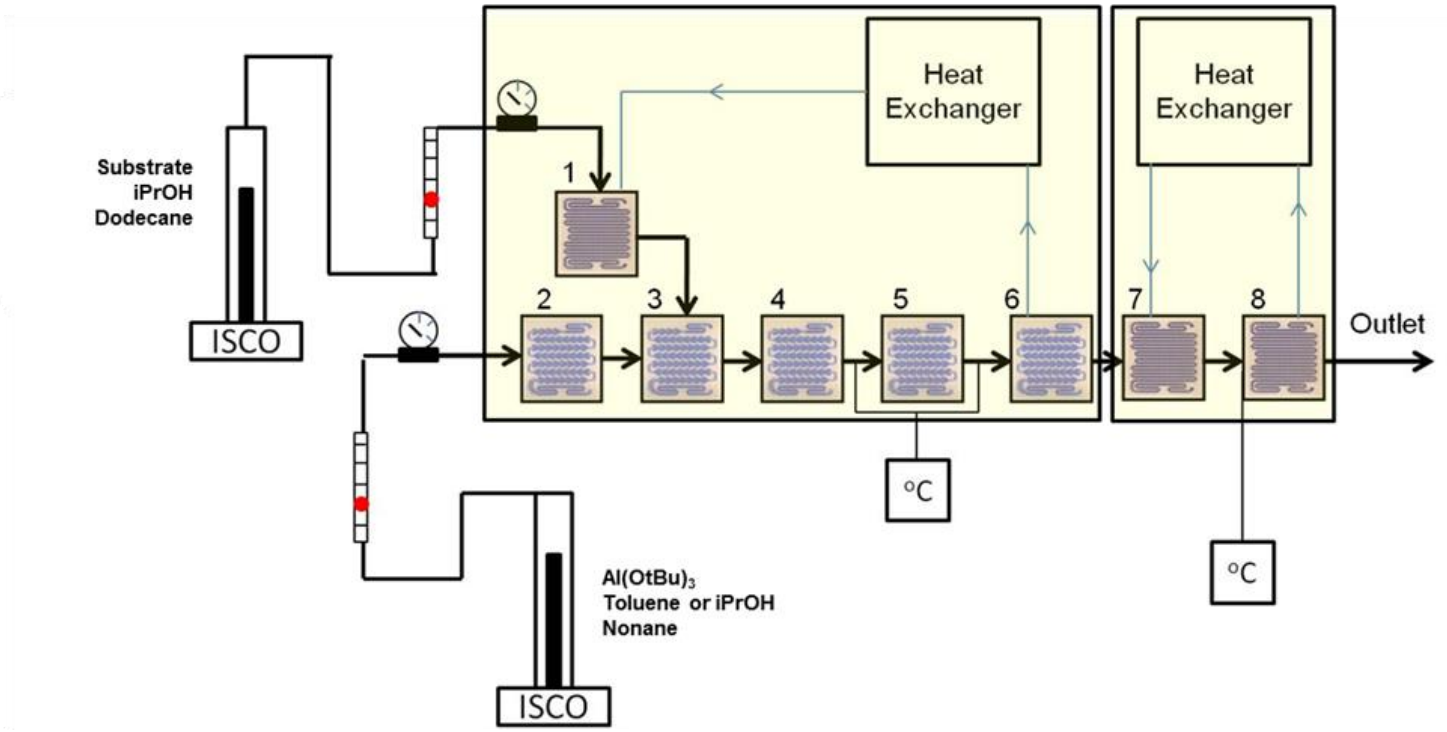


Figure 2-5: Schematic of Corning® Advanced-Flow Reactor

All modules were jacketed for thermal control. Two modules were used to preheat the reagents to the specified reaction temperature, and 6 modules were used for reaction: 4 modules specifically designed for enhanced mixing and 2 linear modules for additional residence time. The reagents were stored independently and pumped into the flow reactor with Teledyne ISCO 500D syringe pumps in a ratio of 3:2 toluene/isopropanol (benzaldehyde, acetophenone) or 9:1 catalyst:cyclohexanone (pure isopropanol). Rotameters at the inlet of the reactor were installed to measure the flow rates, which defined the residence time. Two heat exchangers, a LAUDA Integral XT150 and a Thermo Election Corp. NESLAB RTE7, controlled the temperature, which was monitored by thermocouples that were installed into the heat exchanger fluid modules.

2.2.2.1.1 Continuous Flow Reduction of Benzaldehyde

A stock solution of benzaldehyde (43 mL) was prepared in anhydrous isopropanol (500 mL) with dodecane (5.43 mL) added as an internal standard. Stock solutions of 5 mol % and 20 mol % $Al(O\textit{t}Bu)_3$ were prepared in anhydrous toluene (600 mL) using 3.8 g and 15.5 g of catalyst, respectively, with nonane (6 mL) added to each solution as an internal standard. The benzaldehyde solution was drawn into a 500D Model ISCO pump (Teledyne Isco, Inc.) and the $Al(O\textit{t}Bu)_3$ solution was drawn into a 500D Model ISCO pump equipped with a filter. The continuous flow reactor was brought to the appropriate reaction temperature (65 ^{o}C or 80 ^{o}C) and allowed to equilibrate. The pumps were set to flow at three total flow rates: 5 mL/min (3:2 toluene:isopropanol), 15 mL/min (9:6 toluene:isopropanol), and 30 mL/min (18:12 toluene:isopropanol). After flowing for two full reactor volumes (residence times), samples were collected at every residence time.

After the reactions were complete, the reactor and ISCO pumps were flushed with anhydrous isopropanol and toluene.

2.2.2.1.2 Continuous Flow Reduction of Acetophenone

A stock solution of acetophenone (49.3 mL) was prepared in anhydrous isopropanol (500 mL) with dodecane (5.5 mL) added as an internal standard. Stock solutions of 5 mol % and 20 mol % Al(O*t*Bu)$_3$ were prepared in anhydrous toluene (600 mL) using 3.8 g and 15.5 g of catalyst, respectively, with nonane (6 mL) added to each solution as an internal standard. The acetophenone solution was drawn into a 500D Model ISCO pump (Teledyne Isco, Inc.) and the Al(O*t*Bu)$_3$ solution was drawn into a 500D Model ISCO pump equipped with a filter. The continuous flow reactor was brought to the appropriate reaction temperature (65 ^{o}C or 80 ^{o}C) and allowed to equilibrate. The pumps were set to flow at three total flow rates: 5 mL/min (3:2 toluene:isopropanol), 15 mL/min (9:6 toluene:isopropanol), and 30 mL/min (18:12 toluene:isopropanol). After flowing for two full reactor volumes (residence times), samples were collected at every residence time. After the reactions were complete, the reactor and ISCO pumps were flushed with anhydrous isopropanol and toluene.

2.2.2.1.3 Continuous Flow Reduction of Cyclohexanone

A stock solution of cyclohexanone (31.1 mL) was prepared in anhydrous isopropanol (100 mL) with dodecane (6.5 mL) added as an internal standard. A stock solutions of 50 mol % Al(O*t*Bu)$_3$ was prepared in anhydrous isopropanol (400 mL) using 16.4 g of catalyst with nonane (2.6 mL) added as an internal standard. The continuous flow reactor was brought to 50 ^{o}C and allowed to equilibrate. Prior to loading the pumps for the reaction, the cyclohexanone solution was drawn into a 500D Model ISCO pump

(Teledyne Isco, Inc.) and pure isopropanol was drawn into a separate 500D Model ISCO pump. The pumps were set to flow at 5.091 mL/min (9:1 isopropanol:cyclohexanone). The reactor was allowed to equilibrate and a sample was taken after one residence time to accurately quantify the concentration of substrate exiting the reactor. Once complete, the $Al(O\textit{t}Bu)_3$ solution was drawn into a 500D Model ISCO pump and the pumps were set to flow at 5.091 mL/min (9:1 $Al(O\textit{t}Bu)_3$:cyclohexanone) to achieve an 11 minute residence time. After flowing for one full reactor volume (residence times), samples were collected every 11 minutes. After the reaction was complete, the reactor and ISCO pumps were flushed with anhydrous isopropanol.

2.2.2.2 Custom Tubular Reactor Set-up

The custom-built tubular reactor consists of a 30-mL tubular reactor (316 stainless steel) with an inner diameter of 3.2mm equipped with inlet and outlet thermocouples (1/8”), fit into the reactor via bored-through reducing unions (316 stainless steel) for temperature monitoring and control. Heating to the reactor and preheating lines is provided by heating tape and an array of Digisense temperature controllers. The reactor is supplied with reagent and catalyst via two Teledyne ISCO D-series syringe pumps capable of delivering highly accurate volume flow rates across a range of pressures. The syringe pumps are jacketed in order to provide preheating as well as improved solubility of the CMKs. As a matter of safety, a pressure relief valve was installed before the reactor in order to prevent the build-up of pressure above 200 psi in the event of channel blockage or plug formation. A schematic of the reactor is shown in Figure 2-6.

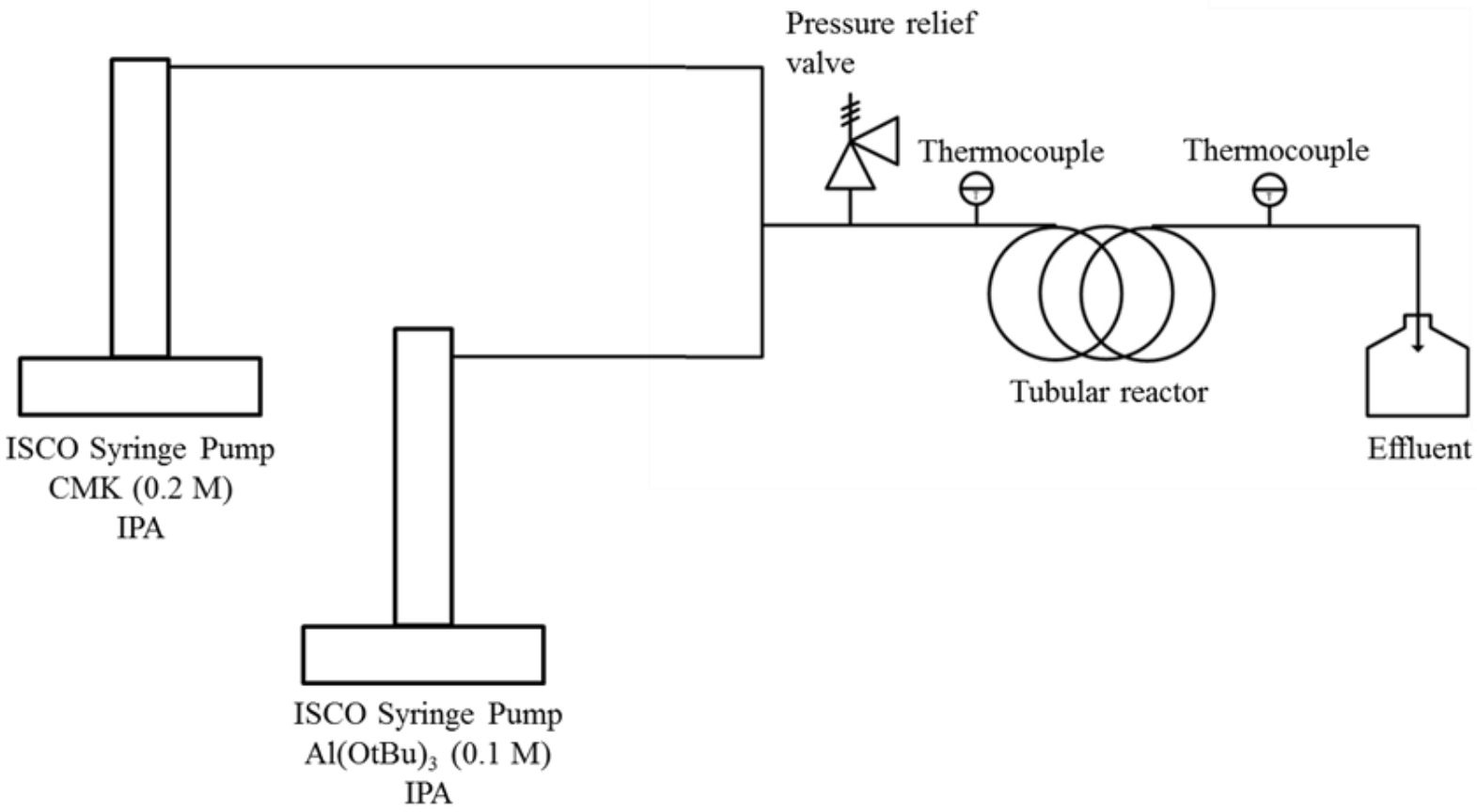


Figure 2-6: Schematic of Custom-Built Tubular Reactor

2.2.2.2.1 Continuous Flow Reduction of Chloromethylketones (CMKs)

A solution of 0.1 M or 0.05 M CMK substrate (4, 5 or 6) was prepared in anhydrous isopropanol 50 ml with about 0.72 g xylene added as an internal standard. The catalyst solutions of 50 mol % or 30 mol% $Al(OtBu)_3$ (based on substrate concentration) was prepared in another anhydrous isopropanol 50 ml. The house made tubular reactor and two ISCO pumps were preheated to 50 ^{o}C and allowed to equilibrate. Two prepared solutions were separately drawn into two ISCO pumps, and both pumps were set at the same volumetric flow rate 0.5 ml/min, in total 1 ml/min when two streams meet in tubular reactor. After flowing for one full reactor volume (resident time 30 min), samples were collected at 36 min, 60 min and 90 min. After the reaction was complete, the reactor and ISCO pumps were flushed with anhydrous isopropanol.

2.2.3 Instrumentation and Analysis

2.2.3.1 HPLC Analysis – Benzaldehyde & Acetophenone

For HPLC analyses, 1 mL aliquots were sampled, cooled to 0 ^{o}C in an ice bath, and diluted with 1 mL cold MeOH. After 1 minute, 0.4 mL 2M HCl were added followed by an additional 15 mL MeOH dilution. Finally, 0.1 mL of reaction mixture was further diluted with 0.9 mL MeOH and analyzed by HPLC. Calibration curves of benzaldehyde, benzylalcohol, acetophenone and *sec*-phenylethanol were prepared to quantify conversion and yields. Reaction samples were run on an HP 1100 series HPLC equipped with a UV detector set to λ = 210 nm and 254 nm, and used a Phenomenex Luna 5μ C18 reverse phase column equipped with a guard column. An isocratic method using water (0.1% TFA buffer) 52% and MeCN 48% as the mobile phases at a flow rate of 1.5 mL/min was used for the analysis. The column temperature was set to 40 ^{o}C.

2.2.3.2 GC-FID Analysis – Cyclohexanone

For GC analyses, 5 mL aliquots were collected from the continuous flow reactor and quenched on ice with 2M HCl (2 mL). These solutions were then quantitatively diluted to 25 mL using HPLC-grade THF. Calibration curves of cyclohexanone and cyclohexanol were prepared in the final solvent system (5 mL isopropanol, 2 mL 2M HCl, 17 mL THF) to quantify conversion and yields. Analysis was performed using an HP 6890 Series GC equipped with an FID detector and a HP-5 capillary column (30 m x 0.25 mm and 0.25 μm). Runs were conducted with the following temperature profile: 50 ^{o}C for 3 minutes followed by a 15 ^{o}C/min ramp rate to 300 ^{o}C and then held at 300 ^{o}C for two minutes.

2.2.3.3 HPLC Analysis – Chloromethylketones

For HPLC analyses, about 5 mL aliquots were sampled, cooled to 0 ^{o}C in an ice bath. After 1 minute, 2 ml 2M HCl were added, and then diluted to 50 ml in volumetric flask with MeOH. Finally, a 1 ml aliquot of the 50 ml solution was diluted to 10 ml with MeOH. The prepared 10 ml solution was analyzed with Waters HPLC. Calibration curves of CMK substrates and their corresponding reduction products were prepared to quantify conversion and yields. Reaction samples were run on an HP 1100 series HPLC equipped with a UV detector set to λ = 210 nm and 254 nm, and used a Phenomenex Luna 5μ C18 reverse phase column equipped with a guard column. An isocratic method using water (0.1% TFA buffer) 50% and MeCN 50% as the mobile phases at a flow rate of 1 mL/min was used for the analysis. The column temperature was set to 40 ^{o}C.

2.2.3.4 Flow Rate Analysis

In order to accurately determine the flow rates and concentrations of the combined reaction stream, two internal standards (dodecane and nonane) were employed as tracers for the catalyst and substrate streams and analyzed by GC. Calibration curves of dodecane and nonane were prepared independently. The internal standards were added in 1 vol % to the substrate solution (dodecane) and to the toluene/catalyst solution (nonane). The homogenous reaction mixture (reactants, products, and internal standards) was collected upon exiting the reactor and analyzed using a HP 6890 Series GC equipped with an FID detector and a HP-5 capillary column (30 m x 0.25 mm and 0.25 μm). Runs were conducted with the following temperature profile: 50 ^{o}C for 5 minutes followed by a 25 ^{o}C/min ramp rate to 300 ^{o}C and then held at 300 ^{o}C for two minutes.

2.3 Results and Discussion

2.3.1 MPV Reduction of Model Compounds: Benzaldehyde, Acetophenone, and Cyclohexanol

Experimentally, reaction progress was investigated as a function of catalyst loading, flow rate (residence time), and reaction temperature. It should be noted that accurate flow rates were accurately determined by GC analysis from the internal standards, dodecane and nonane, present in 1% vol in each stream. Reactions were conducted with catalyst loadings of 5 mol % and 20 mol% $Al(O\textit{t}Bu)_3$ at two temperatures: 65 ^{o}C and 80 ^{o}C. At each residence time, samples were collected into cold 2M HCl and subsequently diluted with MeOH. Three samples were taken for each data point. Disappearance of the carbonyl substrates and appearance of the corresponding alcohol products were quantified by HPLC.

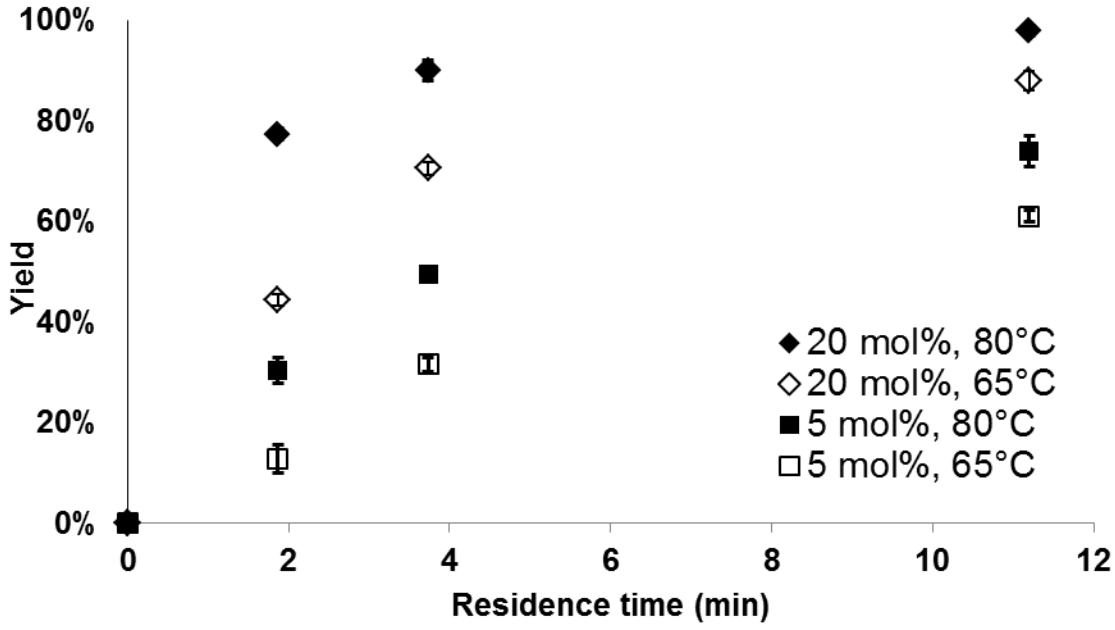


Figure 2-7: Yield of Continuous-Flow MPV Reductions of Benzaldehyde as a Function of Temperature, Catalyst Loading, and Residence Time

Figure 2-7 illustrates the production of benzyl alcohol in the continuous MPV reduction of benzaldehyde as a function of residence time. Independent reactions were performed at varied flow rates in order to observe the equilibrium yield at a given residence time. Reaction yields increased in conjunction with increasing residence time, with quantitative yields achieved at a residence time of 11 minutes using 20 mol % catalyst at 80 ^{o}C. The reaction performance at 20 mol % prompted investigation into lower catalyst loadings. At 5 mol % catalyst, the reaction proceeded efficiently with yields of 61% and 77% at 65 ^{o}C and 80 ^{o}C, respectively.

It has been previously reported that the batch reduction of acetophenone to 1-phenylethanol using 50 mol % $Al(OtBu)_3$ at 50 ^oC in isopropyl alcohol reached 80% completion in approximately 3 hours[11]. It was therefore anticipated that the reduction of acetophenone would require a long residence time in a continuous flow process in order to achieve complete reaction. The reduced quantity of aluminum reagent would reduce the reaction rate still further. Thus, even at the elevated temperature of 80 ^oC with a maximum residence time of approximately 11 minutes, a yield of only 18% was achieved. Figure 2-8 illustrates the yield as a function of residence time.

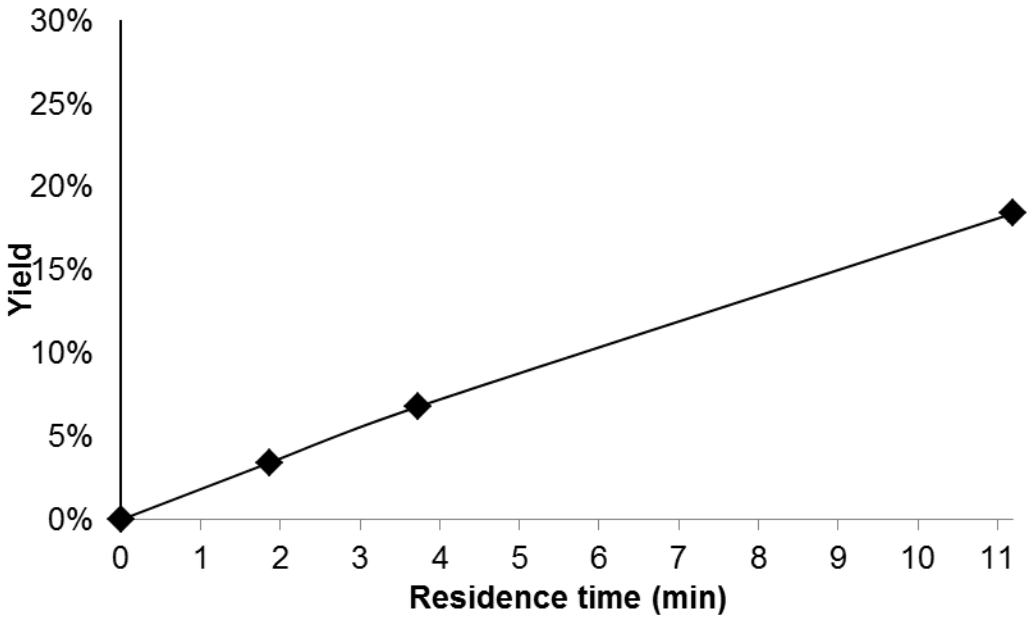


Figure 2-8: Yield of Continuous-Flow MPV Reduction of Acetophenone as a Function of Residence Time

Based on the measured rate of the corresponding batch process and extrapolation of the results derived from the continuous flow experiments, it is estimated that a 275-minute residence time would be necessary to achieve high yields of acetophenone in the continuous flow apparatus illustrated in Figure 2-5. Though acetophenone does not reflect an ideal substrate under these reaction conditions, it does serve as an illustrative example of how "scaling-out" of a process could be employed to allow for quantitative yields without "scaling-up" the reagents.

To provide a comprehensive evaluation of transitioning from batch reactions to continuous flow, the MPV reduction of cyclohexanone was screened as a function of time using 50 mol % of the rate enhancing enhanced catalyst, $Al(O\textit{t}Bu)_3$, in isopropanol at 50 ^{o}C (Figure 2-9).

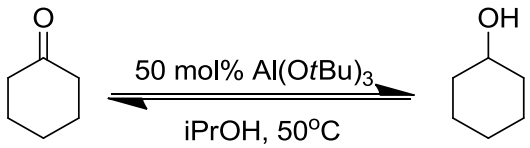


Figure 2-9: MPV Reduction of Cyclohexanone

Quantitative yields of cyclohexanol were achieved after 30 minutes. Under the same reaction conditions, only 50% yield was achieved after 1 hour when using $Al(O\textit{i}Pr)_3$. Figure 2-10 illustrates the yield of cyclohexanol as a function of time using $Al(O\textit{t}Bu)_3$ in a batch process.

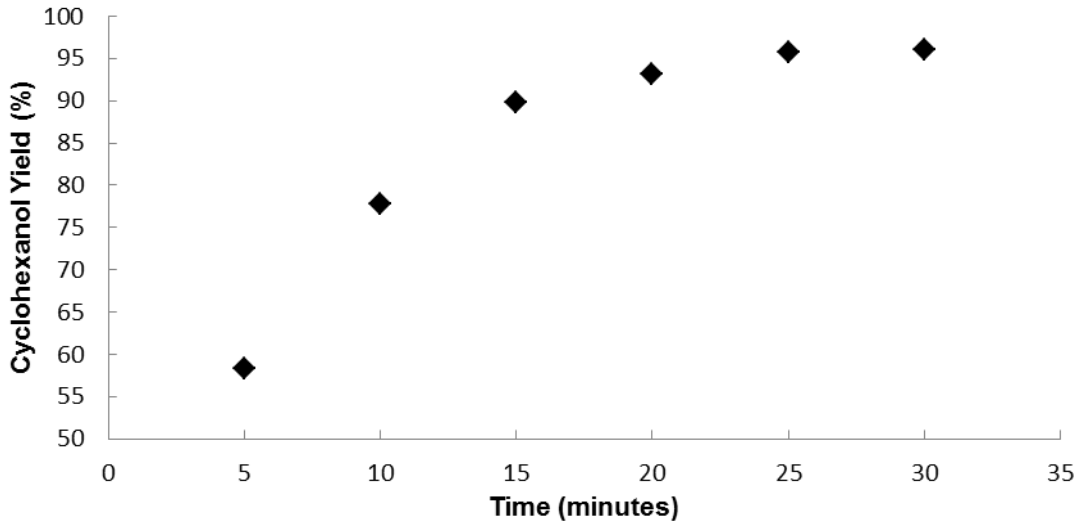


Figure 2-10: Yield of Batch-wise MPV Reduction of Cyclohexanone as a Function of Time

When transitioning to continuous flow, reaction conditions analogous to the batch process were used. Using a freshly prepared solution of $Al(O\mathit{t}Bu)_3$, solubility issues that are often encountered with degrading catalyst were mitigated, allowing for the use of 50 mol % catalyst in pure isopropanol to maximize reaction rate. Both catalyst and substrate stock solutions were prepared in anhydrous isopropanol with an internal standard (dodecane in the substrate solution and decane in the catalyst solution). The flow rates were adjusted to 9:1 catalyst:substrate, which allowed for a residence time of 11 minutes and a reaction concentration identical to the batch process.

Once the reaction was started, the reactor was allowed to equilibrate (1 full residence time) and samples were collected every 11 minutes and quenched with cold 2M HCl. Figure 2-11 illustrates cyclohexanol yield as a function of time in a continuous flow process.

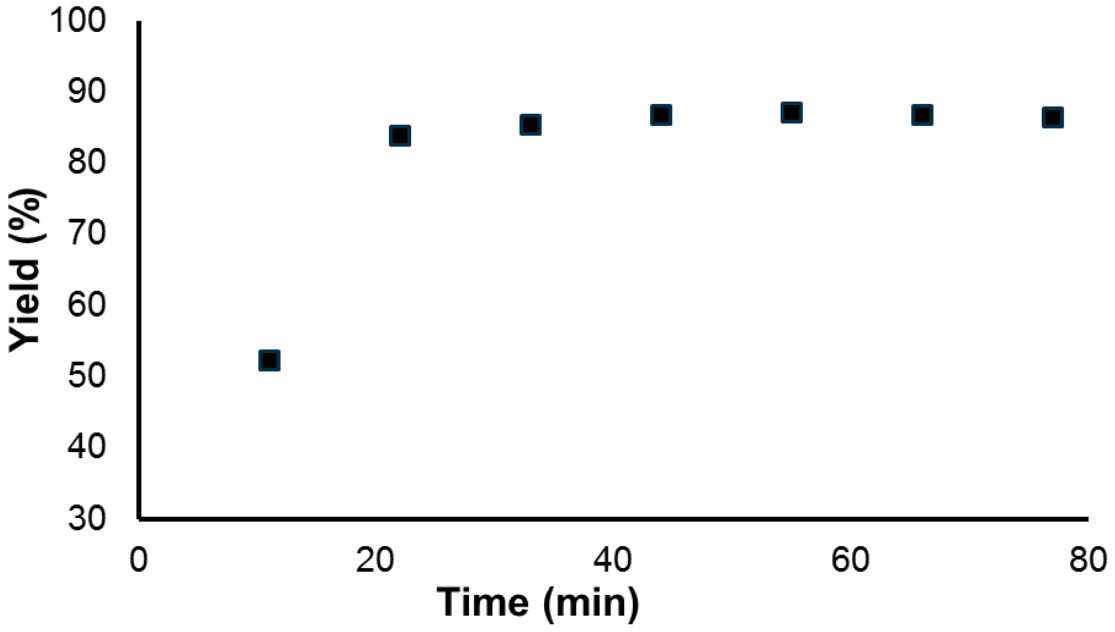


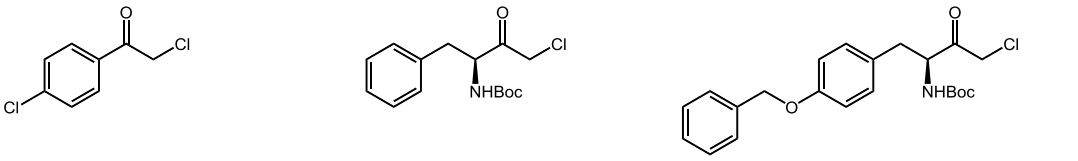
Figure 2-11: Yield of Continuous-Flow MPV Reduction of Cyclohexanone as a Function of Time. Residence Time = 11 min

As expected, the first sample (taken at 11 minutes) exhibits a "start-up" regime of diminished effectiveness. This yield (52%) is not indicative of the final, steady-state yield achieved by the reaction. However, by the second residence time (22 minute), the yield has increased to 84% and the reactor has reached steady state. The final steady-state yield of the reaction system is 83%, which is comparable to the yields seen in batch (77% at 10 minutes and 90% at 15 minutes). It is clear that the MPV reduction of cyclohexanone meets batch performances.

2.3.2 MPV Reduction of Chloromethylketones: Dichloroacetophenone, N-Boc-1-chloro-3-amino-4-phenylbutan-2-one, and N-Boc-4-(benzyloxyphenyl)-1-chloro-3-aminobutan-2-one

Unlike the model compounds discussed above, the MPV reductions of the CMKs targeted in this study tend to generate insoluble alcohol species upon reaction. The formation of these solids posed a problem for reaction within the small channels of the Corning® Advanced-Flow reactor. It was therefore necessary to design a tubular reactor with significantly larger inner diameter for the continuous-flow MPV reduction of CMKs. The reactor was designed and built in-house, and is described in detail in the experimental section. Reaction solutions were pumped within this custom-built reactor using the same ISCO syringe pumps that were used for the other model carbonyls.

Experimentally, continuous flow MPV reductions of CMKs largely mirrored the techniques used in the continuous flow reductions of model compounds described above. Catalyst and substrate streams were fed to the reactor at a 1:1 volumetric flow rate ratio (a 9:1 flow rate ratio is impractical due to the limited solubility of CMKs in IPA) at a total flow rate of 1 mL/min, yielding residence times of 30 minutes. Samples were taken at 36, 60, and 90 minutes, quenched with 2 M HCl at 0 °C, and diluted with MeOH for HPLC analysis in order to monitor the stead-state equilibration of the reaction. Three CMK substrates were examined at previously optimized conditions (50 °C, 50% catalyst loading): dichloroacetophenone, N-Boc-1-chloro-3-amino-4-phenylbutan-2-one, and N-Boc-4-(4’-benzyloxyphenyl)-1-chloro-3-aminobutan-2-one (Figure 2-12).



Dichloroacetophenone N-Boc-1-chloro-3-amino-4-phenylbutan-2-one N-Boc-4-(4'-benzyloxyphenyl)-1-chloro-3-aminobutan-2-one

Figure 2-12: Structures of Model Chloromethylketones

Figure 2-13 highlights the results of the MPV reduction of dichloroacetophenone in continuous flow at 0.1 and 0.05 M concentrations. For comparison, batch results are also given as dashed lines.

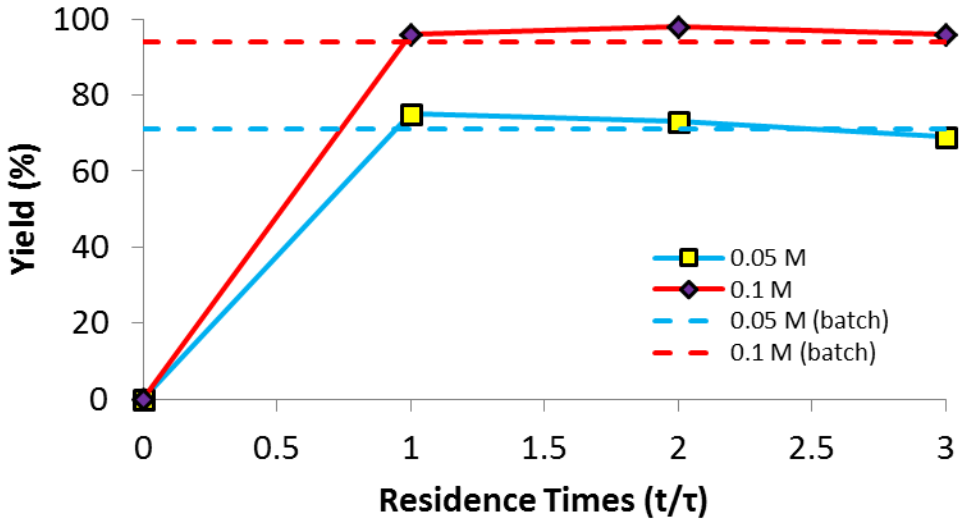
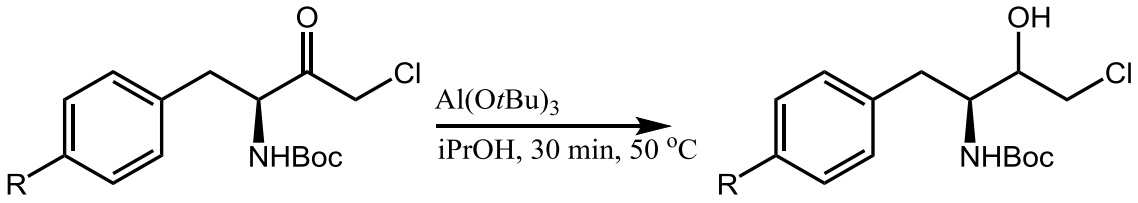


Figure 2-13: Yield of Batch and Continuous-Flow MPV Reductions of Dichloroacetophenone. Dotted lines indicate batch behavior, and solid lines represent yield of continuous-flow reductions as a function of time.

It is evident that continuous flow reduction in the tubular reactor effectively duplicates the reactivity seen in batch conditions. In the case where reaction is conducted at a substrate concentration of 0.05 M, the reactor has reached a steady-state regime within the first sampling period (36 minutes) that maintains an average yield similar to that of the same reaction conducted in batch mode (71%). Likewise, at 0.1 M the reaction has equilibrated within one residence to the steady-state yield of 96%, within experimental error of the batch yield (94%). It is perhaps interesting that the yield at 30 minutes (reaction time in batch or residence time in continuous operation) is approximately 20% higher at a higher concentration of substrate. However, this is readily explained by the bimolecular nature of the reaction kinetics, as well as the increase in catalyst concentration (locked at 50 mol%, based on substrate).

The continuous MPV reduction of two pharmaceutically-relevant CMKs was also investigated. Figure 2-14 is the reaction equation displaying the butanone backbone of each CMK undergoing MPV reduction to form the corresponding alcohol.



N-Boc-1-chloro-3-amino-4-phenylbutan-2-one: R = H
N-Boc-4-(4'-benzyloxyphenyl)-1-chloro-3-aminobutan-2-one: R = OBn

Figure 2-14: MPV Reduction of Pharmaceutically-Relevant Chloromethylketones

In particular, the effect of catalyst loading was investigated, as was the effect of temperature. Optimized reactions were also carried out for each substrate in both batch and flow conditions. The results are given in Table 2-1.

Table 2-1: Yields of Batch and Continuous-Flow MPV Reductions of Pharmaceutically-Relevant Chloromethylketones

R	Catalyst Loading (%)	Mode	Yield (%)
H	30	Batch	91 ± 1
H	30	Continuous	93 ± 1
H	50	Batch	98
H	50	Continuous	96 ± 1
OBn	50	Batch	94
OBn	50	Continuous	93

In general, it is clear that the custom-designed reactor is able to match the reactivity seen in batch mode operation. Near-quantitative yields are seen when N-Boc-1-chloro-3-amino-4-phenylbutan-2-one is used at optimized conditions of 50 ^{o}C and 50% catalyst loading (98% and 96% for batch and flow, respectively). Furthermore, due to the increased activity of Al(O-tBu)3, a decreased catalyst loading is able to be applied to MPV reductions of N-Boc-1-chloro-3-amino-4-phenylbutan-2-one in both batch and flow

conditions with no significant loss of yield, reaching 91% yield in batch and 93% yield in flow operation at 20 mol% catalyst loading. Additionally, it has been shown that both the Meerwein-Ponndorf-Verley reduction reaction as well as the transition from batch to flow technology are sufficiently robust for application to functionalized derivatives of N-Boc-1-chloro-3-amino-4-phenylbutan-2-one, namely N-Boc-4-(4'-benzyloxyphenyl)-1-chloro-3-aminobutan-2-one. This substrate was reduced in batch and continuous flow conditions to 94% yield and 93% yield, respectively, revealing the flexibility of MPV reductions in continuous flow to handle functionalized CMKs.

2.4 Conclusions

Overall, the enhanced catalytic activity of $Al(O\textit{t}Bu)_3$ played an instrumental role in successfully transitioning the Meerwein-Pondorf-Verley Reduction to a continuous process. This was demonstrated with three model compounds, benzaldehyde, acetophenone, and cyclohexanone. Benzyl alcohol was obtained quantitatively in an isopropanol/toluene solvent system at 80 ^{o}C with 20% catalyst loading in less than 12 min. Even when the catalyst loading was reduced by a factor of four from 20% to 5% a relatively high yield (77%) of product was realized. The reduction of cyclohexanone was achieved in 83% yield at a residence time of 11 minutes when using 50 mol % $Al(O\textit{t}Bu)_3$ in pure isopropanol at 50 ^{o}C. In contrast, the reduction of acetophenone was intrinsically slower. Although modest conversion was obtained with a residence time of about 12 min, this can, in principle, be improved by modifying and extending the reactor configuration ("scaling out").

Additionally, it was shown that a custom-built tubular reactor was effective in conducting continuous MPV reductions of a selection of CMKs. It was seen that the reduction of dichloroacetophenone exhibits nonzero-order kinetics with respect to substrate and catalyst, with yields at 30 minutes (reaction time for batch conditions, residence time for flow conditions) increasing from 73% (flow) at 0.05 M to 97% (flow) at 0.1 M. Furthermore, continuous flow reductions of N-Boc-1-chloro-3-amino-4-phenylbutan-2-one revealed that no significant impact on reaction rate is seen when decreasing catalyst loading from 50% to 30%, achieving yields of 96% and 93%, respectively. Batch and continuous reductions of N-Boc-4-(4'-benzyloxyphenyl)-1-chloro-3-aminobutan-2-one were shown to be sufficiently similar (94% yield in batch vs. 93% yield in flow), demonstrating that the technological transfer from batch to flow is versatile towards functionalization of the medicinally-relevant N-Boc-1-chloro-3-amino-4-phenylbutan-2-one.

In summary, it has been shown that the Meerwein-Ponndorf-Verley (MPV) reduction of aldehydes and ketones is readily transferrable from batch-wise processing to continuous-flow processing. Furthermore, reductions of chloromethylketones have been demonstrated in flow, including a compound used as an intermediate in the synthesis of HIV-protease inhibitor medications. The flexibility of this system with regards to catalyst loading and substrate functionalization has been examined.

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CHAPTER 3 DESIGN OF A TANDEM, CONTINUOUS-FLOW PROCESS FOR THE PRODUCTION OF HYDROPYRIDO[1,2-*A*]INDOLES

3.1 Introduction

Indole alkaloids, or chemical species containing an indole moiety as well as basic properties, represent a relatively large group of natural products with biological and pharmaceutical importance[1,2]. Of particular interest is the hydropyrido[1,2-a]indole framework[3], shown below in Figure 3-1.

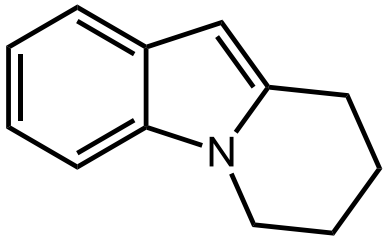


Figure 3-1: Structure of Hydropyrido[1,2-a]indole Framework

Such a framework is found in many naturally-occuring, physiologically-active species, one example being deethyleburnamonine (Figure 3-2, left), a derivative of a known vasodilator vinburnine[4] (Figure 3-2, right).

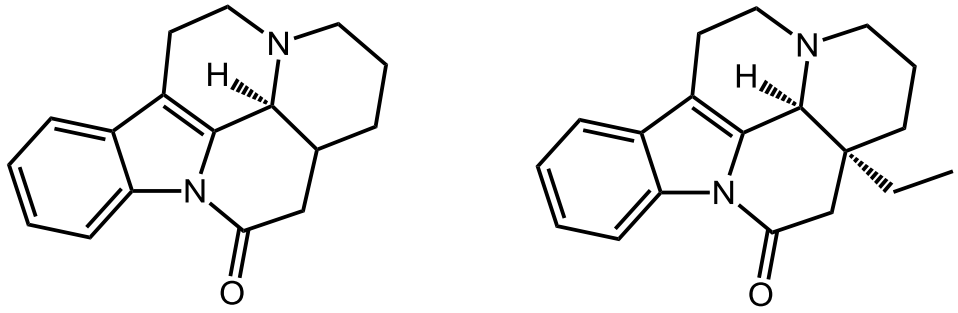


Figure 3-2: Structures of Deethyleburnamonine (left) and Vinburnine (right)

Given the importance and profusion of the hydropyridoindole framework in natural products, it is necessary to investigate the viability of industrial synthesis of similarly derived compounds. One particular area of research that offers a significant amount of promise towards industrial synthesis is the transition of hydropyridoindole production technology from batch-wise processing to continuous-flow processing. The transition of such a multi-step process is non-trivial and requires an understanding of reaction kinetics and behavior at each stage of processing.

Multi-step flow synthesis has seen a great deal of success in the literature. It has been used to demonstrate the viability of flow production of a variety of active pharmaceutical intermediates and products such as Oxomaritidine[5], Dumetorine[6], Ibuprofen[7], Grossamide[8], and Tamoxifen[9]. Many of these processes demonstrate advantages over batch production techniques that are common to continuous flow strategies due to superior control over mixing and heating. However, there are a number of challenges associated with the design of multi-step flow synthesis strategies. In particular, solvent-substrate compatibility, thermodynamic properties (solubilities, heats

of mixing/reaction), in-flow purification, and throughput management at each synthetic step are of greatest concern. These challenges require deliberate and effective reactor design. As a result, literature examples of multi-step flow processes are often limited to three- and four-step syntheses.

Despite these challenges, continuous flow processing offers a number of benefits over a traditional batch production process. The coupling of flow rate to heat transfer, mixing efficiency, and reaction time yields a great deal of control over reaction kinetics and thermodynamic behavior. Furthermore, continuous flow processes routinely demonstrate superiority over batch process in environmentally relevant metrics such as solvent use, and waste generation[10,11,12,13]. These trends, combined with the fact that flow processes are often easily scaled allow for superior economic performance, as well. Other advantages of continuous flow processing include increased product quality assurance and quality control, manifesting itself in enhanced selectivity due to increased control on reaction kinetics.

The synthetic pathway presented by France *et al* describing the batch synthesis of hydropyridoindoles[3] using simple indole precursors was chosen as a reaction model for technology transfer from batch to flow. The full reaction scheme is shown in Figure 3-3.

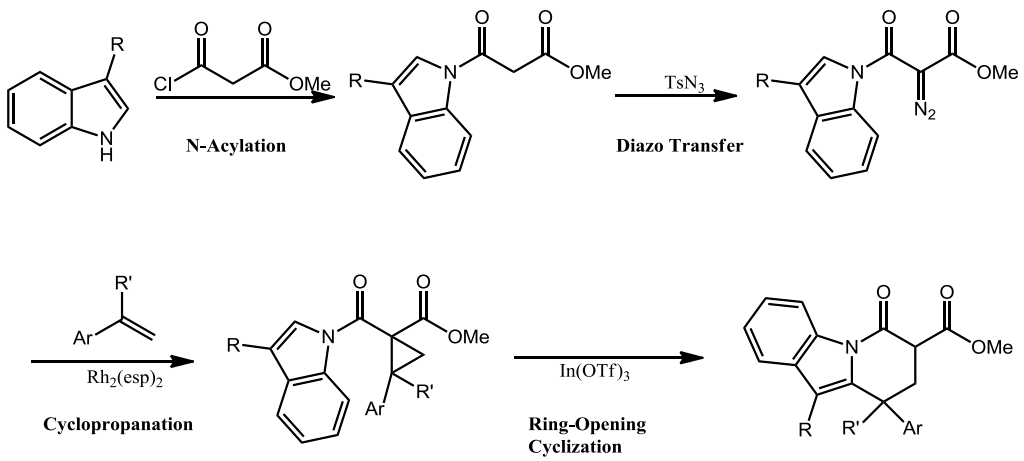


Figure 3-3: Total Synthesis of Hydropyridoindoles from Simple Indole Precursors

The synthesis begins with the reaction of a target indole with an appropriate acid chloride (e.g. methyl malonyl chloride) via N-acylation. A diazo transfer is then conducted using tosyl azide in order to generate a diazoester intermediate. The diazoester intermediate can then be reacted with a functionalized alkene (e.g. alpha-methylstyrene) via a rhodium(II)-catalyzed cyclopropanation reaction. Finally, the hydropyridoindole species is achieved via an indium-catalyzed intramolecular ring-opening cyclization reaction[14].

The work herein reports the success of technology transfer for the last two steps of the 4-step synthetic pathway, namely the cyclopropanation and ring-opening cyclization steps (Figure 3-4).

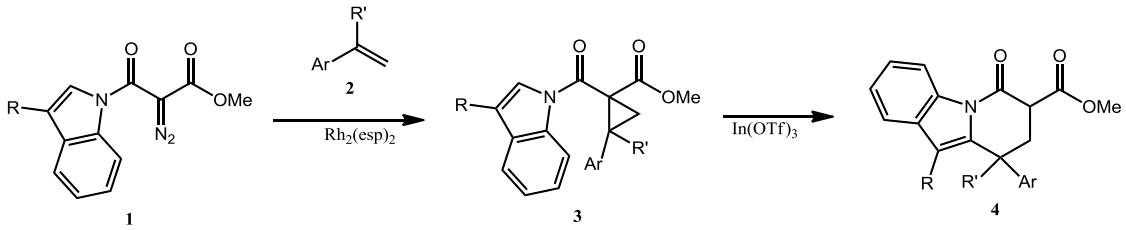
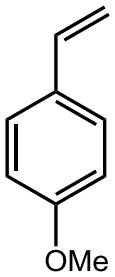
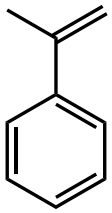


Figure 3-4: Sequential Cyclopropanation and Ring-Opening Cyclization of Diazoester 1

Studies of the cyclopropanation reaction cover the addition of two substituted alkenes (4-methoxystyrene **2a** and alpha-methylstyrene **2b**, Figure 3-5) to a model diazoketone intermediate (methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate **1**, Figure 3-6).

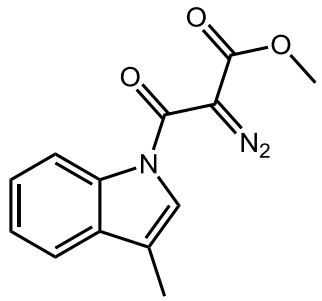


4-methoxystyrene
2a



alpha-methylstyrene
2b

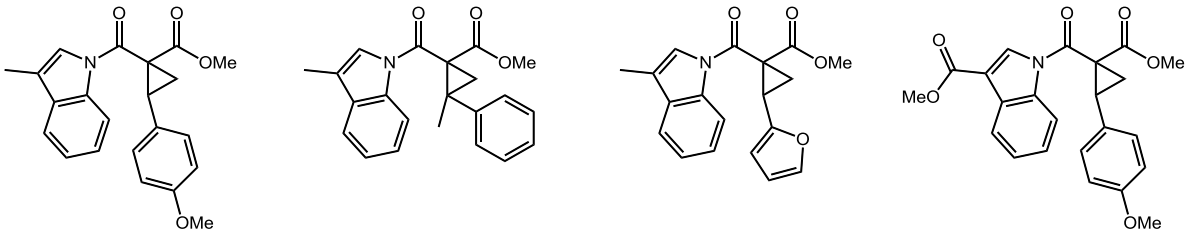
Figure 3-5: Structures of Alkenes Used in This Study. (Left) 4-methoxystyrene, 2a. (Right) alpha-methylstyrene, 2b.



methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)
-3-oxopropanoate
1

Figure 3-6: Structure of Target Diazoester

Studies of the intramolecular ring-opening cyclization focus on the continuous-flow cyclization of four model cyclopropanes, specifically methyl 2-(4-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate **3a**, methyl 2-methyl-1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropanecarboxylate **3b**, methyl 2-(furan-2-yl)-1-(3-methyl-1*H*-indole-carbonyl)cyclopropanecarboxylate **3c**, and methyl 1-(1-(methoxycarbonyl)-2-(4-methoxyphenyl)cyclopropanecarbonyl)-1*H*-indole-3-carboxylate **3d** (Figure 3-7), as well as the formation of their corresponding hydropyridoindoles, methyl 9-(4-methoxyphenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydridopyrido[1,2-*a*]indole-7-carboxylate **4a**, methyl 9,10-dimethyl-6-oxo-9-phenyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole **4b**, methyl 9-(furan-2-yl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate **4c**, and dimethyl 9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7,10-dicarboxylate **4d**, Figure 3-8.



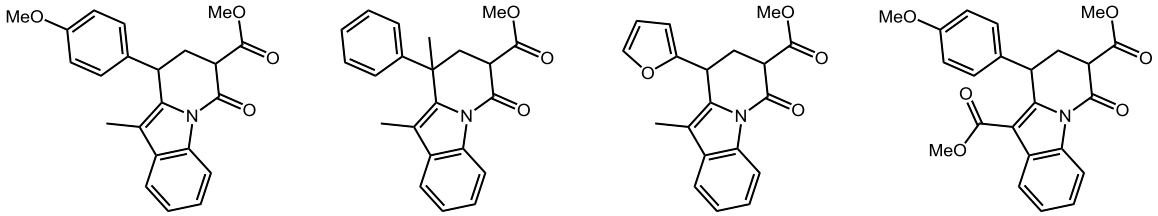
methyl 2-(4-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate **3a**

methyl 2-methyl-1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropanecarboxylate **3b**

methyl 2-(furan-2-yl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropanecarboxylate **3c**

methyl 1-(1-(methoxycarbonyl)-2-(4-methoxyphenyl)cyclopropane carbonyl)-1*H*-indole-3-carboxylate **3d**

Figure 3-7: Structures of Four Target Cyclopropanes Used in this Study



methyl 9-(4-methoxyphenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido [1,2-*a*]indole-7-carboxylate **4a**

methyl 9,10-dimethyl-6-oxo-9-phenyl-6,7,8,9-tetrahydropyrido [1,2-*a*]indole-7-carboxylate **4b**

methyl 9-(furan-2-yl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido [1,2-*a*]indole-7-carboxylate **4c**

dimethyl 9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido [1,2-*a*]indole-7,10-dicarboxylate **4d**

Figure 3-8: Structures of Four Hydropyridoindole Products Targeted in this Study

In addition to studies on the individual reactions, serial (or "tandem") reactions were conducted in which the cyclopropanation and ring-opening cyclization reactions were performed simultaneously with the use of a continuous flow reactor designed for multistep synthesis. In these experiments, the only feedstocks supplied to the reactor were the diazoketone intermediate **1**, substituted alkenes **2a** or **2b**, rhodium catalyst for the cyclopropanation reaction, and indium catalyst for the cyclization reaction, to produce hydropyridoindoles **4a** and **4b**.

This work was performed with a collaborative effort with Dr. Stefan France (GaTech, CHEM). The results of this collaborative research project can be explored in full in the manuscript titled "A Tandem, Bicatalytic Continuous Flow Cyclopropanation-Homo-Nazarov-Type Cyclization" by Joel Aponte-Guzmán *et al*, which was published on September 14, 2015 in the *Industrial and Engineering Chemistry Research*, volume 54, issue 39, pp 9550-9558. In order to fully elucidate the results of the technological transfer of hydropyridoindole production from batch to flow as well as their significance, this chapter refers regularly to the aforementioned publication.

3.2 Experimental Section

3.2.1 Materials

The diazoketone intermediate **1** and cyclopropanes **3a**, **3b**, **3c**, and **3d**, when used as feedstock materials were synthesized in-house by the France research group and used as received. 4-methoxystyrene **2a** and alpha-methylstyrene **2b** were purchased from Sigma-Aldrich and used as received. Rh_2esp_2 (used for the cyclopropanation reaction) was purchased from Sigma-Aldrich and used as received. $In(OTf)_3$ (used for the ring-opening cyclization reaction) was purchased from Strem Chemicals and used as received. Anhydrous acetonitrile (used as solvent for reactions) was purchased from Sigma-Aldrich and used as received.

3.2.2 Experimental

3.2.2.1 *Single-Stage Reactor Design*

A simple plug flow reactor was developed to conduct the individual ring-opening cyclizations and cyclopropanation reactions. A schematic of the reactor is shown in Figure 3-9.

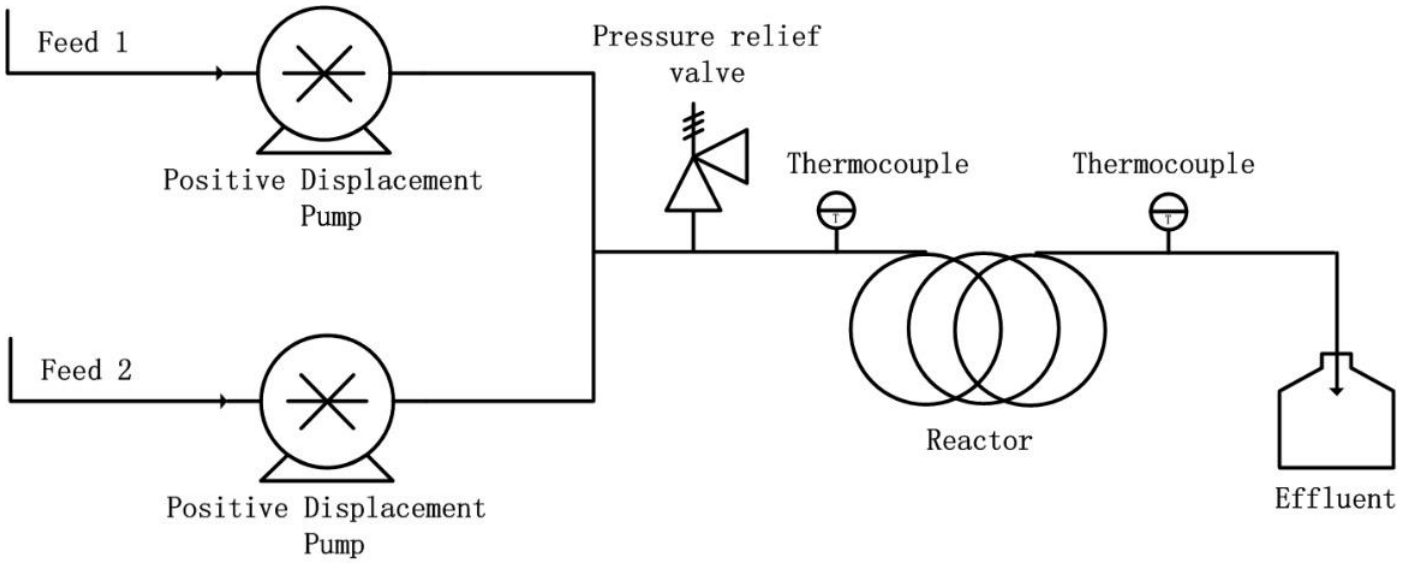


Figure 3-9: Schematic of Single-Stage, Custom-Built Tubular Reactor

The reactor featured a straightforward design with three principal components: (i) reagent/catalyst addition module consisting of reagent and catalyst reservoirs and two Eldex series 2000 ReciPro reciprocating pumps; (ii) a reactor module comprised of a 1/16" tee-joint where the solutions initially mix and proceed into the reactor coil (1/4" stainless steel tubing, Figure 2B) extending for a final reaction volume of 29.5 mL; and (iii) product collection module containing a reaction quenching agent. The system pressure and temperature were measured prior to entering the main body of the reactor. The reactor was heated (when necessary) with heating tape controlled by a Eutech Instruments Digi-Sense temperature controller and the effluent temperature was measured before emptying into a collection flask for analysis. The reagent/catalyst concentrations and flow rates were chosen to directly mimic conditions and reaction times of batch reactions. Samples were taken at residence time intervals (~every 15 min) to establish equilibrium composition and yield.

3.2.2.2 *Tandem Reactor Design*

To accomplish the two-step tandem reaction, the plug-flow reactor was re-designed to accommodate multiple solution inlets, proper mixing and the need for two reactor coils (Figure 3-10).

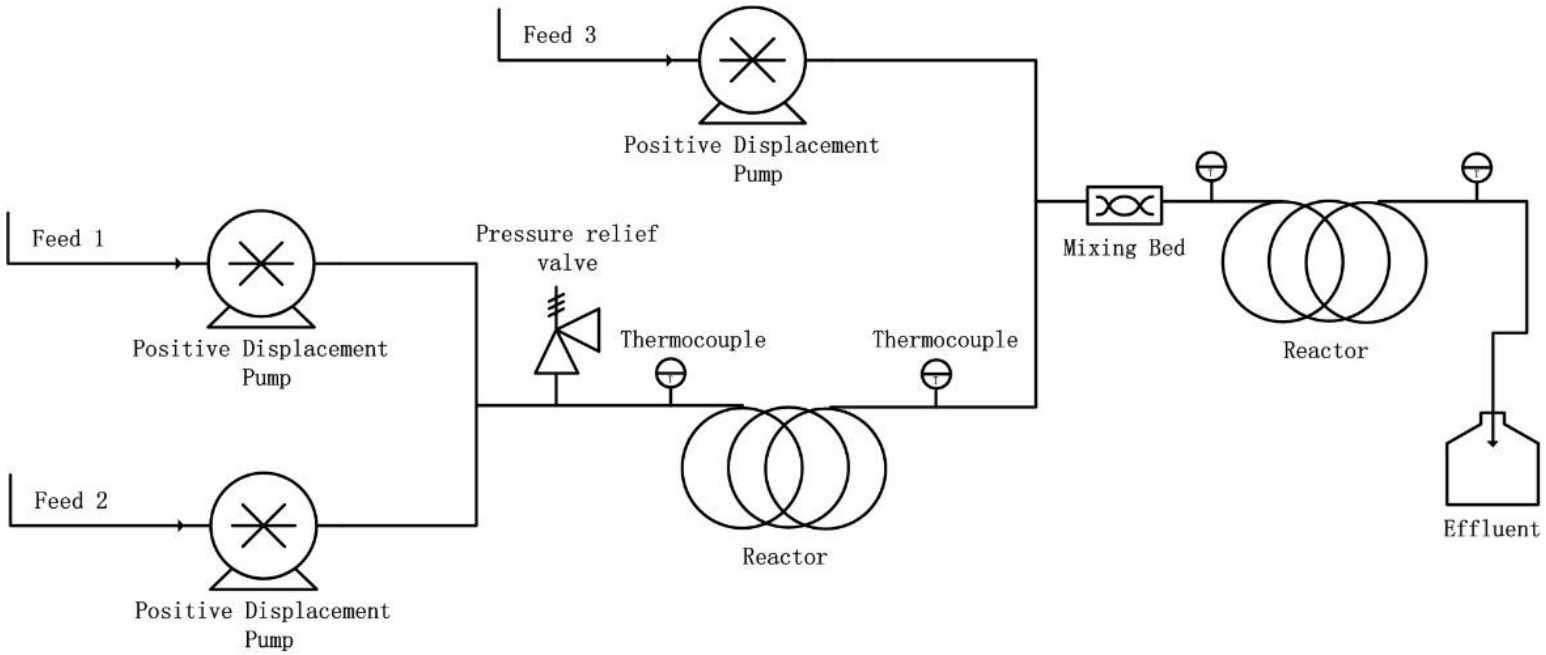


Figure 3-10: Schematic of Custom-Built Tubular Reactors used for Tandem Cyclopropanation/Cyclization Reactions

The new, tandem reactor apparatus consisted of two Teledyne Isco syringe pumps that feed solutions of diazoester **2** (pump 1) and a mixture of rhodium(II) catalyst, alkene **5** and internal standard *p*-xylene (pump 2) to the 30 mL single reactor 1 as described above. The effluent of this reactor is then mixed with an $In(OTf)_3$ feed stream (pump 3) by passing through a 6 mL mixing bed packed with 2 mm borosilicate glass beads. The mixed stream is then fed into a 30 mL reactor (316 stainless steel, 0.25" OD x 0.035" wall thickness, 3.5" diameter). Heating of the system to 50 ˚C was accomplished via heating tape wound about the reactor coil and controlled with a Digisense temperature controller. Samples were taken in 10 min intervals following the first residence time (50 min).

3.2.2.3 *Cyclization Reaction Procedure (Batch)*

An oven-dried round bottom flask was charged with $In(OTf)_3$ (5 or 15 mol%) and acetonitrile (2.5 mL). Once the mixture reached temperature, a solution of the cyclopropane (1.0 equiv., 0.5 mmol) in acetonitrile (2.5 mL) was added. The reaction was 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 an ^{1}H-NMR of the reaction mixture was acquired to determine the conversion. The product was extracted from the aqueous phase with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The organic layers were concentrated and separated via silica gel flash column chromatography.

3.2.2.4 *Cyclopropanation Reaction Procedure (Batch)*

An oven-dried round bottom flask was charged with Rh_2esp_2 (1.0 mol %), MeCN (2.5 mL) and the corresponding alkene (1.0 equiv., 1 mmol). Once the reaction mixture was heated to the indicated temperature, a solution of the diazoester (1 equiv.) in MeCN (2.5 mL) was added, keeping the reaction mixture at 50 °C. The reaction was monitored via TLC. After complete consumption of the diazo compound, the reaction was quenched with saturated aqueous thiourea (1 mL) and allowed to stir for 30 minutes. Solvent was then removed and the organic product was extracted with EtOAc (2x). The organic layer was washed with brine, dried with Na_2SO_4, and concentrated. Column chromatography was used to isolate the target cyclopropane.

3.2.2.5 *Tandem Cyclopropanation/Cyclization Reaction Procedure (Batch)*

The general cyclopropanation procedure was followed for the first step of the reaction. Once the diazo compound was consumed (monitored via TLC), a solution of $In(OTf)_3$ (50-150 µmol in 5 mL of MeCN) was added, keeping the reaction mixture at 50 °C. The reaction was monitored via TLC. After complete consumption of the cyclopropane compound, the reaction was quenched with saturated aqueous thiourea (2 mL) and allowed to stir for 30 minutes. Solvent was then removed and organic product was extracted with EtOAc (2x). The organic layer was washed with brine, dried with Na_2SO_4, and concentrated. Column chromatography was used to isolate the desired hydropyridoindole.

3.2.2.6 *Cyclization Reaction Procedure (Continuous Flow)*

A 0.2 M solution of cyclopropane was prepared by dissolving cyclopropane **3a**, **3b**, **3c**, or **3d** (15 mmol) into 75 mL of anhydrous MeCN. A solution of indium triflate

was prepared by dissolving 2.25 - 6.75 mmol $In(OTf)_3$ (5 mol% - 15 mol%) into 75 mL of anhydrous MeCN. These solutions served as feedstock reservoirs for the reciprocating pumps. Each pump was primed by detaching the pump outlet from the reactor, setting the flow rate to 5 mL/min and drawing ~5 mL through the pump chamber with a syringe. After the pumps were primed, they were reattached to the reactor and set to 0.984 mL/min in order to deliver a combined flow rate of 1.968 mL/min (residence time of 15 minutes). By combining the feedstocks at a 1:1 volume flow rate ratio, calculation of the concentration of reagents in the reactor is made by simply dividing the concentration of the reagents in their respective feedstock reservoirs by a factor of 2. Once the reactor reached temperature, the pumps were started. Reactor effluent was collected every 15 minutes (2-minute sample collection times) into a vial containing 2 mL of H_2O in order to quench further reaction and to establish steady-state yield. These samples were extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and evaporated to dryness with a rotary evaporator. Residues were then left to dry in a vacuum oven overnight in order to guarantee complete solvent removal. Yields and conversions were determined by weighing the solid residue and by ^{1}H-NMR analysis.

3.2.2.7 *Cyclopropanation Reaction Procedure (Continuous Flow)*

The continuous flow cyclopropanation reaction procedure was very similar to the procedure used for the continuous flow cyclization reaction, with a few distinct differences. A solution of alkene and rhodium catalyst was prepared by dissolving the target alkene **2a** or **2b** (20 mmol) and Rh_2esp_2 (0.2 mmol) into 50 mL of anhydrous MeCN. A 0.6 M solution of diazoketone **1** was prepared by dissolving 30 mmol of (1.5 equivalents) into 50 mL of anhydrous MeCN. These solutions served as feedstock

reservoirs for the reciprocating pumps. Each pump was primed by detaching the pump outlet from the reactor, setting the flow rate to 5 mL/min and drawing ~5 mL through the pump chamber with a syringe. After the pumps were primed, they were reattached to the reactor and set to 0.492 mL/min in order to deliver a combined flow rate of 0.984 mL/min (residence time of 30 minutes). Once the reactor reached temperature, the pumps were started. Reactor effluent was collected every 30 minutes (4-minute sample collection times) in order to establish steady-state yield. Samples were collected into vials containing 4 mL of saturated aqueous thiourea solution in order to quench any further reaction outside of the reactor. The mass of the samples collected was recorded and used to calculate yield (described below). The product cyclopropanes were isolated using the techniques described in the above synthesis. Due to the irregular effluent flow rates caused by production of N_2 gas during the cyclopropanation reaction, the below equations (Equation 3-1 and Equation 3-2) were used to calculate yield based on a mass balance and atom balance of the reagents:

$$yield = (m_{iso.} \times 100)/(\frac{m_{t2}}{m_2} \times m_{styr.} \times \frac{MW_{cycl.}}{MW_{styr}}) \quad \text{Eqn. 3-1}$$

$$m_{t2} = (\rho_2 v_2 m_t)/(v_1\rho_1 + v_2\rho_2) \quad \text{Eqn. 3-2}$$

where $m_{iso.}$ corresponds to the amount of isolated cyclopropane from a given sample, m_2 is the total mass of material used to generate the alkene feedstock solution, $m_{styr.}$ is the mass of alkene used to generate the alkene feedstock solution, $MW_{styr.}$ is the molecular

weight of the alkene used in the experiment, $MW_{cycl.}$ is the molecular weight of the target cyclopropane, m_t is the measured mass of the collected sample, v_1 and v_2 are the measured volume flow rates of pump 1 (diazoester feedstock) and pump 2 (alkene/rhodium feedstock), respectively, and ρ_1 and ρ_2 correspond to the measured densities of feedstock 1 (diazoester) and feedstock 2 (alkene/rhodium), respectively.

3.2.2.8 *Tandem Cyclopropanation/Cyclization Reaction Procedure (Continuous Flow)*

Three feedstock solutions were prepared in order to conduct the continuous tandem cyclopropanation/cyclization reactions. The first feedstock solution was generated by dissolving the target alkene **2a** or **2b** (20 mmol), Rh_2esp_2 (0.2 mmol), and p-xylene (2-4 mmol) into 50 mL of anhydrous MeCN. The second feedstock solution was generated by dissolving 30 mmol of (1.5 equivalents) of diazoester **1** into 50 mL of anhydrous MeCN. The third and final feedstock solution was prepared by dissolving 1–3 mmol (5-15%) of $In(OTf)_3$ into 100 mL of anhydrous MeCN. The flow rates of pumps 1 and 2 were set to 0.492 mL/min and the flow rate of pump 3 was set to 0.984 mL/min. This ensured that the nominal molarity of the limiting reagents in the cyclopropanation reaction (alkene) and the cyclization reaction (cyclopropane) were kept at 0.2 M and 0.1 M, respectively. Furthermore, this gives a unified residence time of 15 minutes (cyclization) + 30 minutes (cyclopropanation) = approximately 45 minutes. For this reason, the first sample was acquired from each tandem flow reaction at 50 minutes (samples collected for two minutes), and additional samples were taken every 10 minutes to monitor the steady-state yield until 90 minutes. Samples were collected into 6-dram vials containing 4 mL of water to quench further reaction. Hydropyridoindole products **4a** and **4b** were then isolated as described above in the tandem batch synthesis procedure.

Yields for the tandem flow reactions were calculated using p-xylene as an internal standard. The equation used to calculate yield is given below (Equation 3-3):

$$yield = m_{prod,iso} \times 100/(m_{std} \times \frac{m_{0,alkene}}{m_{0,std}}) \quad \text{Eqn. 3-3}$$

where $m_{prod,\,iso}$ is the mass of hydropyridoindole product isolated from a given sample, m_{std} is the mass of p-xylene contained in the same sample (measured by GC-FID), $m_{0,alkene}$ is the mass of alkene used to generate feedstock solution 1, and $m_{0,std}$ is the mass of p-xylene used to generate feedstock solution 1. The use of an internal standard mixed with the limiting reagent (alkene) ensures that the yield can be accurately calculated, despite the irregular flow rate caused by the generation of N_2 gas from the first reactor and any mixing anomalies caused by the combination of a liquid stream with a liquid-gas stream in the second reactor.

3.2.2.9 *Flow Rate Verification*

Volume flow rates of each positive displacement pump (reciprocating or syringe) were verified by calibration by measurement mass flow rate measurement. Deionized water was pumped at a constant rate for 5 minutes into 6-dram vials. The mass of water added within 5 minutes was measured and used, along with literature density values for pure water, to calculate the volume of water displaced. These volume flow rates were then confirmed by pumping water into a graduated cylinder.

3.2.3 Instrumentation & Analysis

In most cases, products of the batch and flow reactions were isolated via silica gel flash chromatography. Initial analysis of hydropyridoindole products from the cyclization reaction was performed using a Hewlett-Packard 1100 series HPLC with a Waters XBridge C-18 column (3.5 µm, 2.1 x 50 mm) in order to analyze the yield of a reaction as well as the stereoselectivity of the ring-opening cyclization. Quantifiable separation was achieved by analyzing HPLC effluent at 210, 254, and 280 nm wavelengths while using a linear gradient beginning at 5%/95% MeCN (+0.1% HCOOH)/H_2O (+0.1% HCOOH) and increasing acetonitrile concentration to 95%/5% at a rate of 3% per minute. An example chromatogram of a continuous flow synthesis of **4a** is shown in Figure 3-11.

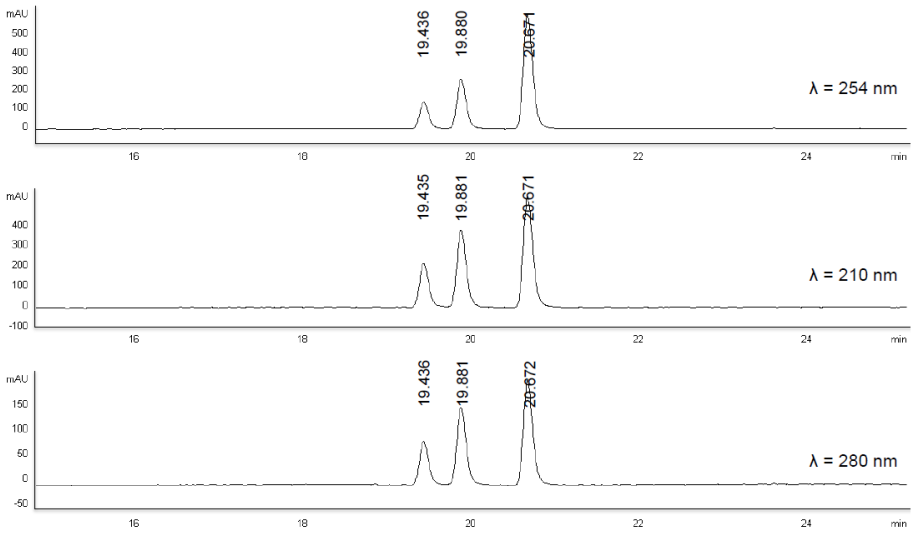


Figure 3-11: Liquid Chromatograph of Products from Cyclization of 3a

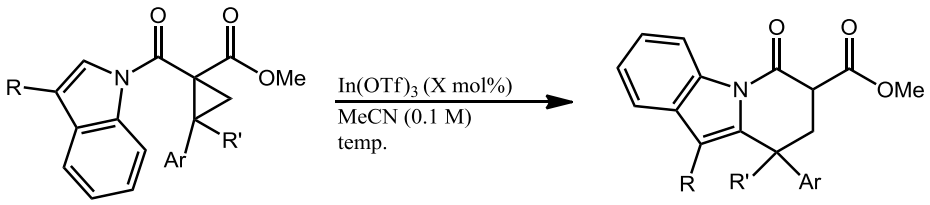
While the HPLC technique was useful in quantifying the yields of **4a**, it was rejected before analysis of **4b**, **4c**, and **4c** in favor of isolation and diastereomer quantification by NMR. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker 400 MHz NMR spectrometer. Concentrations of p-xylene used in tandem batch reactions were measured using a Shimadzu GC-2010 gas chromatograph-flame ionization detector (GC-FID).

3.3 Results and Discussion

While technology transfer of any synthetic transformation from batch processing to continuous flow generally requires some understanding of reaction kinetics and optimization, the transfer of a multi-step synthetic pathway from batch to flow inherently requires more consideration, simply because of the serial nature of the sequential steps. The approach taken in this work was to first optimize and transition the batch ring-opening cyclization to a continuous-flow framework. Once optimized parameters were found and the transition to continuous flow technology had been completed for the cyclization reaction, constrained optimization (optimization of a reaction process with some parameters necessarily fixed) was then performed for the cyclopropanation reaction. Using this approach, it was possible to quickly arrive at a set of optimal parameters for each reaction that can easily be implemented into a sequential continuous flow framework. The batch optimization for each reaction was performed in the France research group and is not included in this chapter, but is readily available in the *Industrial & Engineering Chemistry Research* article.

3.3.1 Ring-Opening Cyclization

First, the transfer of the ring-opening cyclization reaction from batch-wise processing to continuous flow processing was investigated. The reaction scheme of the cyclization is shown in Figure 3-12.



3a, 4a (R = Me; R' = H; Ar = C_6H_4 -4-OMe)
3b, 4b (R, R' = Me; Ar = Ph)
3c, 4c (R = Me; R' = H; Ar = 2-furyl)
3d, 4d (R = CH_2CO_2Me; R' = H; Ar = C_6H_4-4-OMe)

Figure 3-12: Indium-Catalyzed Ring-Opening Cyclization of Cyclopropanes

Table 3-1 shows the results of both batch and continuous flow cyclizations of cyclopropanes **3a**, **3b**, **3c**, and **3d**.

Table 3-1: Batch and Continuous-Flow Ring-Opening Cyclizations of Cyclopropanes

Entry	Cyclopropane	Temp (^{o}C)	Catalyst Loading (%)	Mode	Yield (%)
1	**3a**	rt	5	Batch	96
2	**3a**	rt	5	Continuous	99
3	**3b**	rt	15	Batch	34
4	**3b**	rt	30	Batch	44
5	**3b**	rt	15	Continuous	28
6	**3b**	50	15	Batch	99
7	**3b**	50	15	Continuous	93
8	**3c**	rt	5	Batch	79
9	**3c**	rt	5	Continuous	94
10	**3d**	rt	5	Batch	90
11	**3d**	rt	5	Continuous	96

Cyclization of **3a** proceeds in a straightforward manner in both batch and continuous flow processes, reaching yields of 96% and 99%, respectively (entries 1 and

2). Compound **3b**, however, proceeds much slower, reaching only 34% yield at 20 minutes, even with an elevated catalyst loading of 15 mol% in batch (entry 3). The reason for this is due to the steric and electronic effect caused by the additional group at the joining propyl carbon. The presence of this methyl group greatly reduces the activity of the cyclopropane compared to an equivalent molecule substituted with a hydrogen atom. At an increased catalyst loading of 30 mol%, batch cyclization of **3b** performs slightly better, proceeding to 44% yield in 20 minutes (entry 4). It is important to note that at 30 mol% indium loading, the reaction has become heterogeneous, with the acetonitrile saturated with $In(OTf)_3$. Rather than further increasing the catalyst loading, reaction temperature was explored as an independent parameter to increase the yield of the cyclization of **3b**. Using 15% catalyst loading and an elevated reaction temperature of 50 °C, a yield of 99% is able to be achieved within 10 minutes under batch conditions (entry 6). These same trends are seen in continuous flow conditions at the nominal 15 minute residence time, with reactions run at room temperature and 50 ^{o}C reaching yields of 28% and 93%, respectively (entries 5 and 7). Cyclization of **3c** proceeds smoothly in batch conditions, reaching a yield of 79% in 15 minutes (entry 8). The corresponding continuous flow reaction also performs very well, reaching a yield of 94% with a nominal residence time of 15 minutes (entry 9). Additionally, cyclization of **3d** performs well under the optimized conditions, giving a yield of 90% and 96% in batch and flow conditions, respectively (entries 10 and 11). Across the board, continuous flow processing meets or exceeds the standards set by batch conditions for ring-opening cyclizations, demonstrating the ease of which these technologies may be transferred to a continuous flow framework.

3.3.2 Cyclopropanation

After finalizing the technological transfer of ring-opening cyclizations from batch to continuous flow processing, the transfer of the cyclopropanation step was selected for investigation. A scheme of the reaction is given in Figure 3-13.

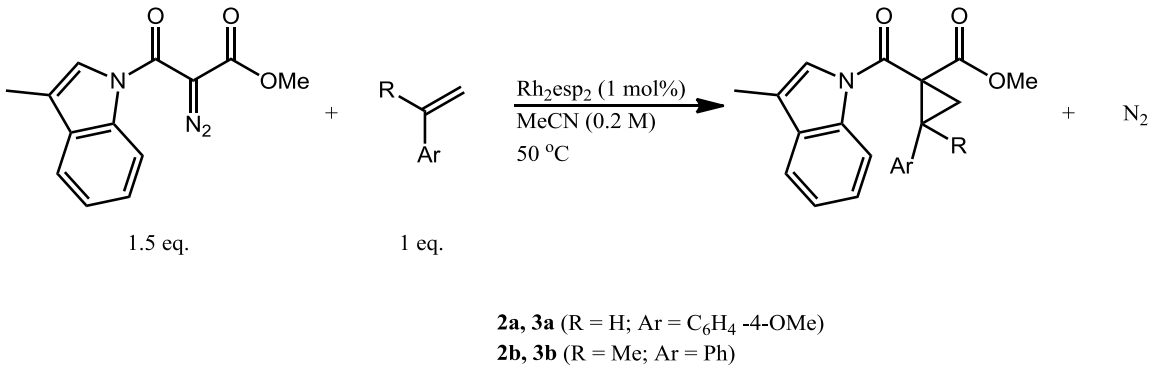


Figure 3-13: Rhodium-Catalyzed Cyclopropanation Reactions of Diazoester 1 with Alkene

One of the challenges encountered with the cyclopropanation reaction of diazoester **1** is the generation of N_2 gas from the removal of the diazo group in order to form the cyclopropane ring. The evolution of this gas leads to the formation of a distinct vapor phase within the reactor, increasing the total fluid volume flow rate within the reactor, thereby decreasing the physical retention time of the liquid reactant stream. In anticipation of the shortened residence times caused by the production of N_2 from the reaction, the nominal residence times of the continuous flow reactions were extended without the construction of a larger reactor by lowering the volume flow rates entering the reactor.

Table 3-2 gives the results of both batch and continuous flow cyclopropanations of diazoester **1** with alkenes **2a** and **2b** in the presence of rhodium catalyst.

Table 3-2: Batch and Continuous Cyclopropanations of Diazoester 1 with Alkenes 2a and 2b

Entry	Alkene	Mode	Yield (%)
1	**2a**	Batch	89
2	**2a**	Continuous	81
3	**2b**	Batch	73
4	**2b**	Continuous	57

The cyclopropanation of **1** with **2a** proceeds readily under batch conditions, reaching a yield of 89% (based on starting alkene) within 15 minutes (entry 1). Using a nominal residence time of 30 minutes, a similar yield is able to be reached under continuous flow conditions, achieving 81% yield of **3a** (entry 2). The cyclopropanation of **1** with **2b** proceeds smoothly, but at a considerably lower rate, reaching only 73% yield after 20 minutes under batch conditions (entry 3). The lowered activity of **2b** towards **1** afforded a yield of only 57% under flow conditions with a nominal residence time of 30 minutes (entry 4). The lower yields in entries 3 and 4 are consistent with the notion that slower reaction kinetics in a system requires longer residence times in order to

perform well in a continuous flow framework. This can be done by either decreasing flow rate or increasing reactor volume.

3.3.3 Tandem Cyclopropanation/Ring-Opening Cyclization

After the ring-opening cyclization and cyclopropanation reactions had been optimized independently, the two were combined into a tandem, multi-step process in which the crude reaction mixture from the cyclopropanation step ("effluent" in the case of continuous flow reaction) was introduced directly into the ring-opening cyclization reaction. The reaction scheme for this process is shown in Figure 3-14.

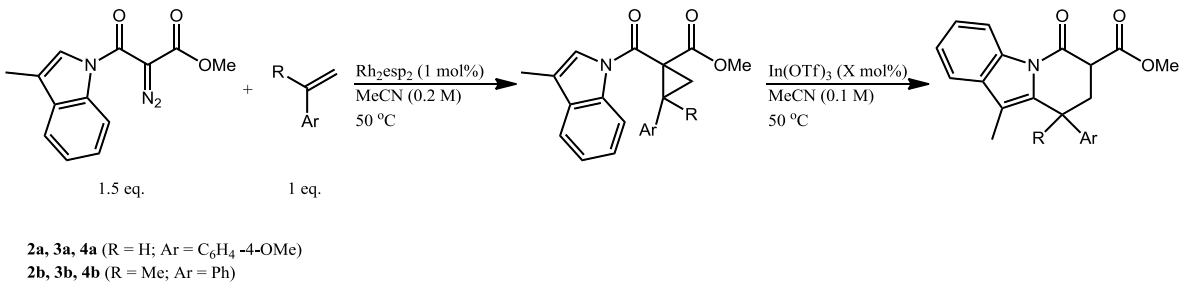


Figure 3-14: Tandem Cyclopropanation/Ring-Opening Cyclization Reactions

Just as in the case of the cyclopropanation reaction, the evolution of N_2 gas from the first stage of the tandem reaction presents a challenge for the tandem reaction under continuous flow conditions. At the union of the effluent stream from the first reactor and feedstock 3 (indium triflate solution), the two streams have dissimilar flow characteristics. Feedstock 3 is fed as a single-phase solution of indium triflate, whereas the effluent from the first reactor is a vapor-liquid biphasic mixture of irregular

instantaneous liquid flow rate. Unfortunately, this phase behavior would result in poor mixing of the first effluent stream and feedstock 3, yielding "packets" of unmixed indium triflate solution and concentrated cyclopropanation effluent. In anticipation of this challenge, a mixing bed was added to the tandem reactor system, comprised of 3/8" tubing packed with 2mm diameter borosilicate glass beads. The larger diameter tubing coupled with the bead packing was incorporated to allow lower linear velocities while simultaneously promoting turbulence in the liquid phase.

Table 3-3 gives the results of the tandem reaction process under both batch and flow conditions. The yield in the tandem flow is based on the amount of hydropyridoindole produced from the second reaction relative to the amount of alkene added into the first reaction.

Table 3-3: Batch and Continuous-Flow Tandem Cyclopropanation/Ring-Opening Cyclization Reactions

Entry	Alkene	Indium Loading (%)	Mode	Yield (%)
1	2a	5	Batch	88
2	2a	5	Continuous	98
3	2b	15	Batch	91
4	2b	15	Continuous	60

The one-pot batch synthesis of **4a** via cyclopropanation/cyclization occurs smoothly, proceeding to 88% yield within 30 minutes (20 minute cyclopropanation, 10 minute cyclization), (entry 1). Similarly, near-quantitative yields are seen for the tandem continuous flow synthesis of **4a** from **1** and **2a**, achieving 98% yield within a nominal 45-minute residence time (30 minute nominal residence time for cyclopropanation, 15 minute nominal residence time for cyclization), (entry 2). This result is a marked improvement over the expected yield based on the performance seen from individual continuous flow reactions, where a cyclopropanation yield of 81% of **3a** is achieved using a nominal 30 minute residence time (Table 3-2, entry 2) and a cyclization yield of 99% of **4a** is achieved using a physical 15 minute residence time (Table 3-1, entry 2). This suggests that a benefit to yield is seen when incorporating single-step reaction stages into a multi-step process, possibly resulting from the continued cyclopropanation of **1** and **2a** and subsequent cyclization within the second reactor.

The tandem synthesis of **4b** was also explored under batch and continuous flow conditions. One-pot batch synthesis of **4b** from **1** and **2b** resulted in 91% yield using a 40 minute batch reaction time (20 minute cyclopropanation, 20 minute cyclization), (entry 3). A distinct decrease in yield was seen under continuous flow conditions, achieving only 60% yield of **4b** using a 30-minute nominal cyclopropanation residence time and a 15-minute nominal cyclization residence time (entry 4). This result exhibits the same increase in yield compared to the expected yield based on individual continuous flow reactions (57% yield of **3b** from first step, Table 3-2, entry 4; 93% yield of **4b** from second step, Table 3-1, entry 7). The reason for the increase in actual yield compared to

expected yield of **4b** in a tandem continuous flow environment is likely continued cyclopropanation and cyclization within the second reactor, as was used to explain the same phenomenon present in the tandem continuous flow production of **4a**. A decrease in yield of **4b** from batch conditions (91%) to continuous flow conditions (60%) is not surprising, given that the generation of N_2 detrimentally affects the residence time and flow characteristics of the entire tandem process. This is inherent to any sequential, multi-step flow process, and greatly diminishes the actual residence time of the process as a whole. Such problems can be easily overcome, if necessary, by the removal of gas or by residence time extension via increased reactor size.

3.4 Conclusions

In conclusion, the transfer of hydropyridoindole technology from batch-wise processing to a continuous flow framework has been presented. By illustrating the multi-step continuous flow production of hydropyridoindoles from diazoesters and substituted alkenes, an important groundwork has been laid for the understanding of continuous flow production of hydropyridoindoles from simple molecular building blocks, such as indoles. Discussion has also been given concerning the approach to development and design of a multi-step continuous flow process.

Additionally, a number of revelations were made concerning the cyclopropanation of diazoesters, the ring-opening cyclization of cyclopropylesters, as well as the tandem reaction to generate hydropyridoindoles. It was shown that substitution of the cyclopropyl group has a significant effect on reactivity in batch-wise ring-opening cyclization, achieving yields of 96%, 99%, 79%, and 90% for reactions of **3a**, **3b**, **3c**, and **3d**, respectively. Attempts in continuous flow were met with similar success, providing

yields of 99%, 93%, 94%, and 96% for reactions of **3a**, **3b**, **3c**, and **3d**, respectively. Furthermore, cyclopropanations of **1** with alkenes **2a** and **2b** were explored in both batch and continuous flow conditions. Alkene **2a** provided the most reactive system, giving yields of 89% and 81% in batch and continuous flow modes, respectively. Alkene **2b** proved to be significantly less reactive, requiring an increased catalyst loading and elevated temperature to reach yields of 73% and 57% under batch and continuous operation, respectively. The reason for the decrease in yields compared to **2a** was due to the steric hindrance and electron-donating effect of the methyl group attached to the cyclopropyl ring in **2b**. Furthermore, it was postulated that the decrease in yield between batch and flow conditions was caused by the evolution of N_2 gas, thereby shortening the effective residence time experienced by the reactants in the reactor. Finally, the tandem reaction in which **1** and **2a/b** are reacted sequentially with rhodium and indium catalysts was explored. It was seen that formation of **4a** was very favorable in tandem, continuous flow conditions, achieving a yield of 98% compared to the yield of 88% achieved under batch conditions. The formation of **4b** proceeded less favorably in continuous flow conditions, reaching a yield of 60% compared to the batch-wise yield of 91%. The reason for this discrepancy is likely the shortened residence time caused by the evolution of gas coupled with the necessity of a longer residence time due to the inherently slower reactivity of alkene **2b**, as well as that of its derivative **3b**.

In summary, the transition of hydropyrido[1,2-*a*]indole production technology from a batch to continuous flow framework has been successfully demonstrated. Additionally, important observations concerning their synthesis have been made that are relevant to the transition from batch to flow technology.

3.5 References

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CHAPTER 4 - RECOVERY OF PALLADIUM FROM SUZUKI COUPLING MIXTURES USING ORGANIC/AQUEOUS TUNABLE SOLVENTS (OATS) AND SULFUR-CONTAINING ADDITIVES

4.1 Introduction

Among the many synthetic techniques available for the formation of C-C bonds, the Suzuki-Miyaura reaction (shown in Figure 4-1) stands out as a highly-desirable preparative route, largely due to the relative safety of reagents used in the reaction as well, the facile conditions under which the reaction is known to occur, and the large scope of functional groups that are inert to Suzuki chemistry[1,2,3,4,5]. It is unsurprising, then, that the Suzuki coupling reaction has found widespread use in the pharmaceutical and agroscience industries[6,7,8].

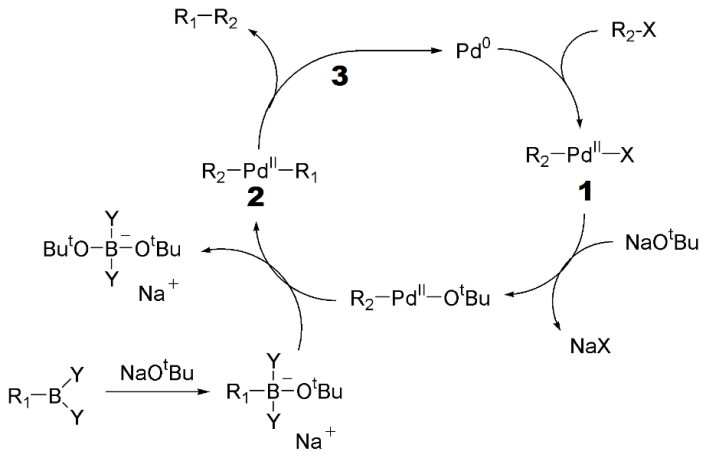


Figure 4-1: Catalytic Cycle of Suzuki-Miyaura Coupling Reaction

Such high-impact use requires a significant degree of accountability concerning the contamination of final products, specifically the contamination of palladium catalysts used in the coupling reaction. Furthermore, palladium is a highly-valuable metal, fluctuating between $20,000 and $30,000 per kg in 2014[9]. In this sense, palladium-rich waste streams are not only environmentally negligent, but also economically irresponsible. The motivation to remove palladium from valuable products is therefore two-fold: 1.) federal regulations limit the amount of platinum group metals (PGMs), including palladium, present in pharmaceutical and agriculturally-relevant compounds[10] and 2.) If recovered, palladium catalysts can be submitted to specialized recycling centers for credit towards reduced cost of new catalyst.

Intelligent process design then calls for the consideration of palladium separability while maintaining reactivity. Heterogeneous catalysis offers the advantage of facile separation, but is often hindered by lower reaction rates due to mass transfer limitations[11]. In the same sense, homogeneous catalysis is only partially beneficial,

offering increased reaction rates at the cost of catalyst separation. Water-soluble ligands may be employed to generate a soluble catalyst that maintains high activity and favorable separation, but these ligands are often expensive or difficult to synthesize[12,13].

Organic/Aqueous Tunable Solvents (OATS)[14,15] represent a class of solvents that offer solutions to the challenges described above. Within the OATS framework, a reaction may be conducted in a binary solvent system (often THF/H_2O or MeCN/H_2O) homogeneously, but separated heterogeneously with the application of a phase-split-inducing anti-solvent, such as CO_2. An example of such a process is shown by Eckert *et al*, wherein hydrophilic catalyst is recovered from the homogeneous hydroformylation reaction of 1-octene in THF/H_2O using moderate pressures of CO_2[16].

Application of OATS as a tool for removing palladium from Suzuki coupling mixtures requires a few modifications from its traditional implementation. While many Suzuki coupling reactions have been conducted using organic bases, the vast majority implement much cheaper inorganic bases such as potassium carbonate and potassium phosphate. These salts often initiate a phase split between the specified organic solvent and water prematurely, thus negating many of the tunable solvent systems benefits. It is therefore necessary to remove these salts before OATS processing in the cases where inorganic base is used.

Furthermore, many industrially-relevant Suzuki coupling reactions involve the use of heteroaromatic substrates, such as pyridines or imidazoles. Such systems are able to coordinate with palladium and hinder separation by extraction. While traditional adsorption methods such as treatment with activated carbon can reliably remove

complexed palladium from chemical streams[17], the affinity of many organic molecules towards activated carbon makes it unrealistic as a method of separating palladium from organic, hydrophobic products.

Figure 4-2 is a process flow diagram utilizing OATS for the removal of palladium from Suzuki coupling products. The process is broken into 3 primary steps: 1.) Suzuki coupling reaction with inorganic salts present, 2.) decantation of the organic palladium- and product-rich phase and subsequent treatment with water and additive, generating a single working phase, and 3.) addition of CO_2, formation of distinct product-rich and palladium-rich phases, and separation.

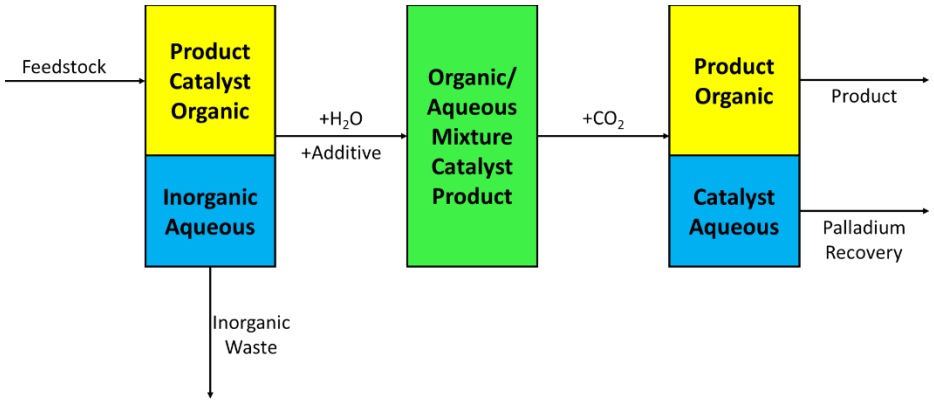


Figure 4-2: Process Flow Diagram for OATS Implementation in Suzuki Coupling Processes

Figure 4-3 describes the Suzuki coupling of 2-bromo-5-methylpyridine with phenylboronic acid in the presence of bis(triphenylphosphine)palladium chloride and potassium phosphate.

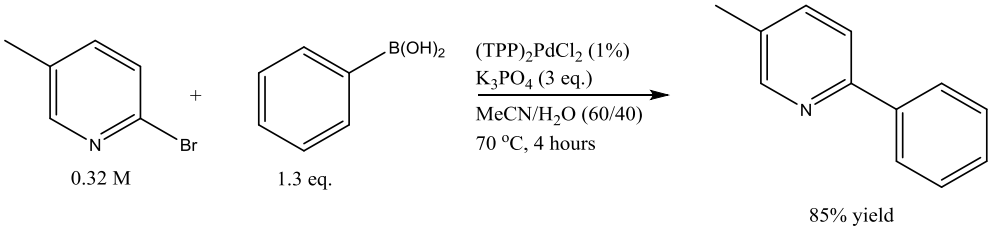


Figure 4-3: Suzuki Coupling Reaction of 5-methyl-2-bromopyridine with Phenylboronic Acid

This reaction was chosen as a model scaffold with which to investigate the application of OATS towards the recovery of palladium catalysts used in Suzuki couplings. A post-reaction system is given preference over model mixtures comprised of catalyst precursor and biaryl product due to the inherent difference in speciation of post-Suzuki palladium complexes. This system is characterized as an ideal template due to the intrinsic hydrophobicity of the product, the presence of a coordinative heteroatom, and the low solubility of palladium within the salt-rich aqueous phase following reaction (negligible at the conditions described above). This model exhibits further utility due to its use of readily available triphenylphosphine as a precursor ligand. This ligand is, in general, much cheaper than specialty ligands required in many Suzuki syntheses and is already employed as a preferred ligand at an industrial scale[18,19,20].

In order to effectively manipulate the hydrophilicity of palladium under application of CO_2, a variety of additives were screened as possible palladium chelants. The names and structures of these additives are given in Figure 4-4.

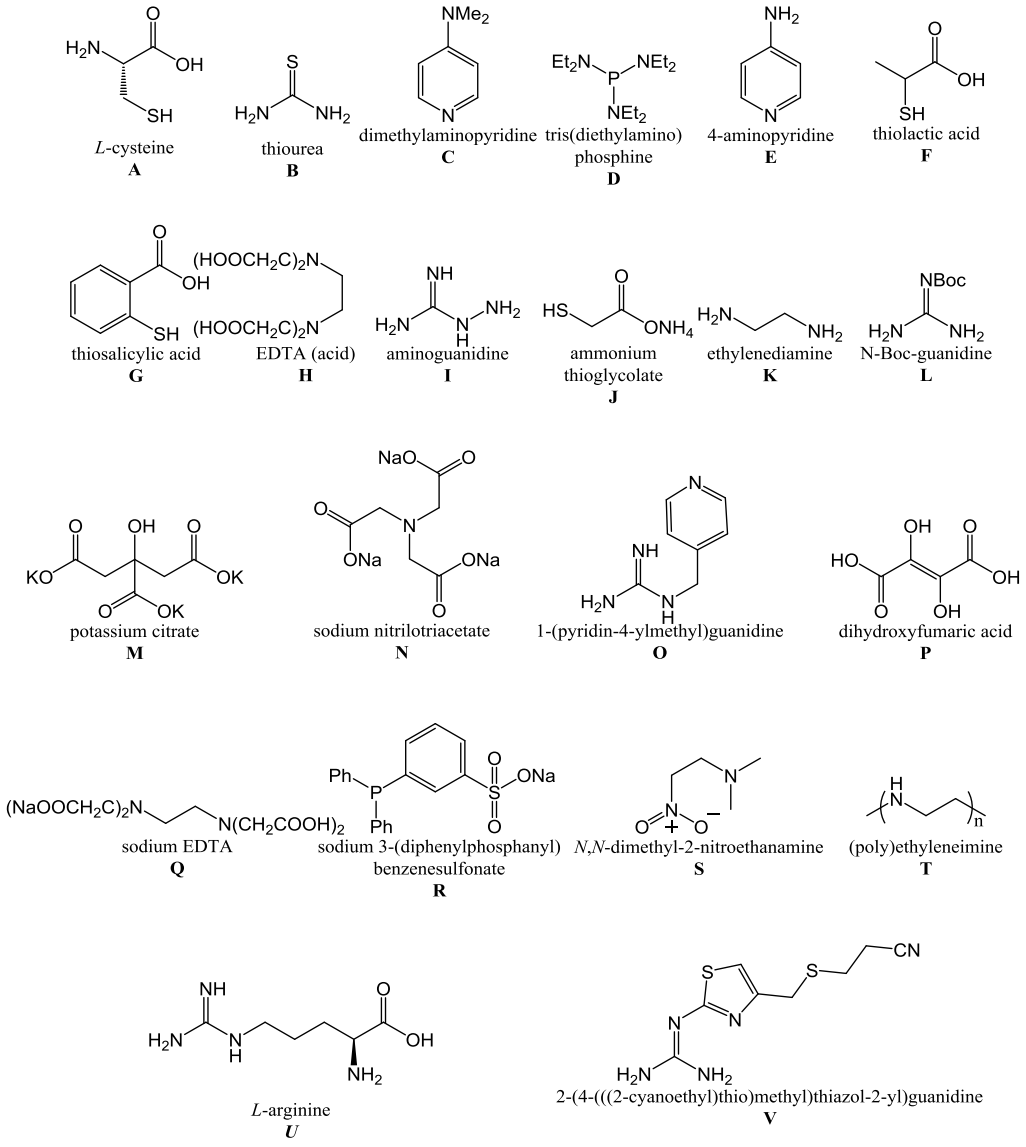


Figure 4-4: Additives Screened for Palladium Removal

Among the classes of compounds screened are: amino acids, guanidines, phosphines, polyamines, polyacids, thiols, pyridines and ionic salts. The separation case where no additive is present is also explored in order to determine the palladium separability without modification.

In order to investigate the substrate scope of the separation process, 4-amino-2-bromopyridine was selected for post-reaction treatment with sulfur-containing additives. As an electron-rich pyridine, it was thought that any coordinative effects seen in 2-bromo-5-methylpyridine-containing mixtures would be exaggerated with the aminopyridine presence. The reaction scheme is shown in Figure 4-5.

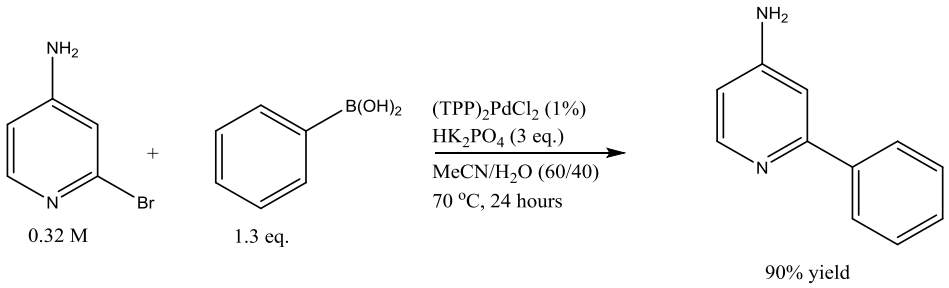


Figure 4-5: Suzuki Coupling Reaction of 4-amino-2-bromopyridine with Phenylboronic Acid

An important difference in this reaction is the use of dibasic potassium phosphate instead of the tribasic potassium phosphate used in the coupling of 2-bromo-5-methylpyridine. The weaker base was chosen in response to findings from Senter *et al*[5] concerning the effect of pH on the reactivity of pyridines in Suzuki coupling reactions.

4.2 Experimental Section

4.2.1 Materials

Deionized water was prepared in-house and used throughout the course of the described experiments. Before use, the water was degassed by sparging with N_2 for 30

minutes. Acetonitrile was purchased from Sigma-Aldrich and degassed by N_2 sparge before use. Bis(triphenylphosphine)palladium(II) dichloride, potassium phosphate, and phenylboronic acid were purchased from Sigma-Aldrich and used as received. 2-bromo-5-methylpyridine was purchased from Matrix Scientific and used as received. Throughout the course of this study, many additives were purchased from commercial chemical suppliers and used as received. SFE-grade CO_2 was purchased from AirGas and used as received.

4.2.2 Experimental

4.2.2.1 Design of Combinatorial Screening Apparatus

Large-scale screening of additives was conducted using a combinatorial apparatus built in-house, shown in Figure 4-6.

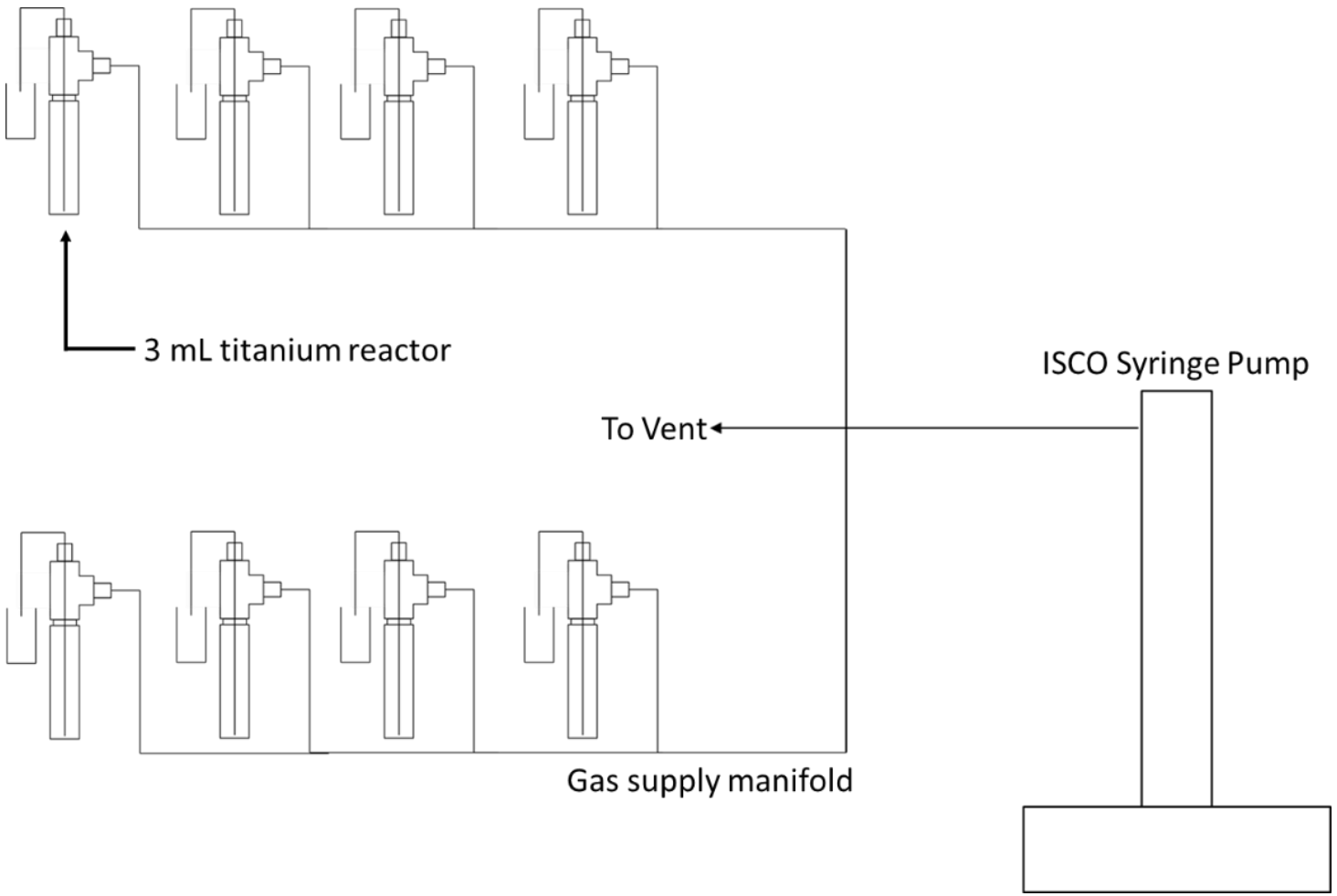


Figure 4-6: Schematic of Combinatorial Apparatus Built In-House for High-Pressure Sampling of Multiple Mixtures

The apparatus consists of eight 3-mL titanium cells, each with an ID of approximately ¼". Each cell is fitted with a 1/8" street tee. A 1/16" stainless steel tube was attached to the side of each tee in order to deliver a constant pressure of gas to the headspace. Each 1/16" gas supply tube was attached to a manifold constructed with 1/16" stainless steel tubing and 1/16" crosses purchased from High Pressure Equipment Company. The manifold was also equipped with a valve with which pressure can safely be relieved in the event of an emergency, as well as a transducer with which the system pressure can be monitored. The manifold was supplied with CO_2 via an ISCO Teledyne 260D syringe pump.

4.2.2.2 Design of High-Pressure Parr Sampling Apparatus

A 300 mL windowed Parr benchtop reactor was used to screen additives as a function of pressure. The schematic of this system can be seen in Figure 4-7.

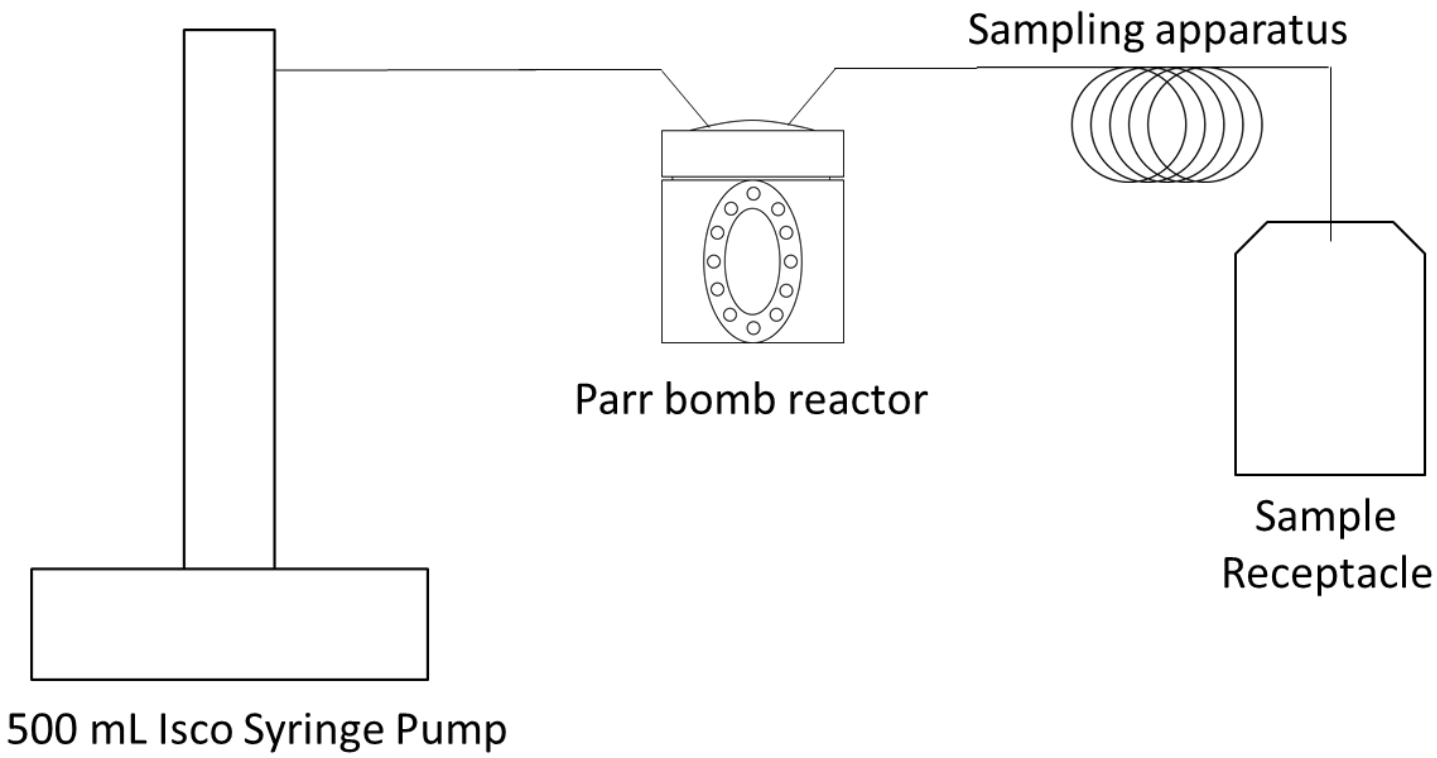


Figure 4-7: Schematic of Parr Reactor Sampling Apparatus

The apparatus consists of the 6-port windowed Parr reactor attached to an upstream Teledyne ISCO 500D syringe pump (for the delivery of CO_2 pressure) and a downstream Valco 6-port stainless steel HPLC sampling valve. This valve was used in conjunction with a sample loop composed of stainless steel tubing at a known internal volume (1.21 mL). Connections were made to the 6-port valve to allow sampling of each liquid phase within the reactor, isolation of a known volume of solution, and subsequent removal and rinsing of collected samples into a sample receptacle.

The Parr reactor itself was equipped with two ¾" quartz glass windows, three sampling ports equipped with 1/16" stainless steel tubing for sampling from various heights in the reactor (aqueous dip tube, organic dip tube, headspace), a Druck pressure transducer calibrated between 0 and 1000 psi, a thermocouple, as well as a burst cap (~2000 psi) to guarantee safety of the Parr operators. A cathetometer was used to measure liquid meniscus heights within the reactor in order to accurately determine volumes.

4.2.2.3 Suzuki Coupling of 2-bromo-5-methylpyridine

2-bromo-5-methylpyridine (16 mmol, 2.7523 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq, 2.5361 g), tripotassium phosphate (3 eq, 10.1890 g), and bis(triphenylphosphine)palladium(II) dichloride (1 mol%, 112.3 mg). The reaction flask was flushed with N_2 for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of

degassed H_2O were added using air-tight syringes. The mixture was then heated to 70 ^oC and allowed to react for 5 hours with magnetic stirring (85% yield by GC).

4.2.2.4 Suzuki Coupling of 4-amino-2-bromopyridine

4-amino-2-bromopyridine (16 mmol, 2.7682 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq, 2.5361 g), dipotassium phosphate (3 eq, 8.3616 g), and bis(triphenylphosphine)palladium(II) dichloride (5 mol%, 0.5615 g). The reaction flask was flushed with N_2 for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H_2O were added using air-tight syringes. The mixture was then heated to 70 ^oC and allowed to react for 24 hours with magnetic stirring (90% yield by GC).

4.2.2.5 CO_2-Induced Separation: Function of Pressure Studies

After reaction, the salt-rich aqueous phase is decanted using an airtight syringe and replaced with a solution of sulfur-containing additive (20 catalyst equivalents, 3.2 mmol) in 20 mL of degassed H_2O. The mixture is allowed to stir for 15 minutes and is then transferred to a 300 mL Parr bomb reactor (pre-flushed with 1 atm of CO_2) equipped with viewing windows. The mixture is then diluted with 42 mL of degassed acetonitrile and 28 mL of H_2O. The bomb reactor is brought to 100 psig using a 500 mL Teledyne ISCO syringe pump while being stirred mechanically. Once 100 psig is attained, stirring is allowed to continue for 15 minutes (until equilibrium is reached). Following equilibration, stirring is stopped and the mixture is allowed to stand unperturbed for 30 minutes in order to efficiently separate each liquid phase. Prior to sampling, liquid volumes are recorded using a cathetometer to measure differences in height of the organic meniscus and the organic-aqueous interface compared to that of a calibrated

reference point. Accurate-volume samples are taken of each phase via dip tube by allowing the phase samples to flow at low velocity through a sample loop of known volume (1.15 mL) before isolating the sample loop. The isolated sample loop is depressurized and rinsed with acetonitrile (2 mL) and water (1 mL) into a collection vial. The collected sample is then analyzed for organic product content by GC-FID and for palladium content by AAS. After organic and aqueous samples are collected, pressure on the system is increased and the above procedure is followed for 200 psig and 400 psig measurements.

4.2.2.6 CO_2-Induced Separation: Total Decant Studies

For total decant experiments, the same procedure described above is used to transfer post-reaction material to the Parr bomb reactor. Once the mixture has been transferred to the bomb reactor and diluted, the reactor is pressurized to the desired pressure via syringe pump and allowed to equilibrate with stirring for 30 minutes. Once equilibrium is reached, stirring is stopped and the mixture is allowed to stand unperturbed overnight to allow clear and distinct phase separation. After phase separation, the aqueous phase is removed at pressure using a dip tube positioned for full solvent recovery. Volumes of the depressurized aqueous and organic phases are recorded and each sample is measured for palladium and product content. After analysis, the aqueous phase is treated with activated carbon (20 g/L) and stirred as a slurry for 24 hours. Solid carbon was removed via gravity filtration and the remaining aqueous phase was measured for palladium content.

4.2.3 Instrumentation

Palladium concentration was measured using a Shimadzu AA-7000F Atomic Absorption Spectrometer, measuring as 247.6 nm. Background noise was removed from signal by self-reversal, with a current swing of 10 mA – 300 mA. Analysis occurred at a fuel gas flow rate of 1.8 l/min and an air flow rate of 15 l/min. Calibration curves were prepared by dissolving known amounts of bis(benzonitrile)palladium(II) dichloride into a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H_2O. Samples for analysis were dissolved in a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H_2O.

Concentrations of 2-bromo-5-methylpyridine and 2-phenyl-5-methylpyridine were measured using a Shimadzu GC-FID using calibration curves dissolved in 60/40 MeCN/H_2O with an initial oven temperature of 250 ^oC and a gradient of 10 ^oC/min.

4.3 Results and Discussion

4.3.1 2-bromo-5-methylpyridine

4.3.1.1 Additive screening

Figure 4-8 summarizes the results of palladium and product partitioning at 200 psig as a function of additive selection. The dashed 45^o line represents the "no separation regime" in which the percentage of solubilized palladium closely reflects the percentage of solubilized product retained in each phase, thereby offering no benefit to separation of palladium from product. The separation quality with no additive present is also given. Separation analysis returned an organic product retention of 90% or greater in every case, indicating the 5-methyl-2-phenylpyridine product is highly hydrophobic. Sulfur-containing compounds reliably provided the lowest organic palladium retention

percentages, relative to the initial amount of Pd charged to the reactor (cysteine – 26%, ammonium thioglycolate – 31%, TPPMS – 36%, CMT-guanidine – 46%, thiolactic acid – 51%). Amines, phosphines, and acids were also shown to be measurably beneficial for the removal of palladium from the organic phase (EDTA acid – 38%, Pyr-Me-guanidine – 61%, aminoguanidine – 64%, tris-diethylaminophosphine – 71%, DHF acid – 74%, DMA-nitroethane – 76%, N-boc-guanidine – 76%, thiourea – 82%). Acetate salts (Sodium EDTA – 95%, Sodium NTA – 95%, Potassium Citrate – 98%), polyamines (PEI – 95%, Ethylenediamine – 91%), aminopyridines (DMAP – 90%, 4-aminopyridine – 91%), arginine (92%) and thiosalicylic acid (>99%) provided the worst results for organic phase palladium removal.

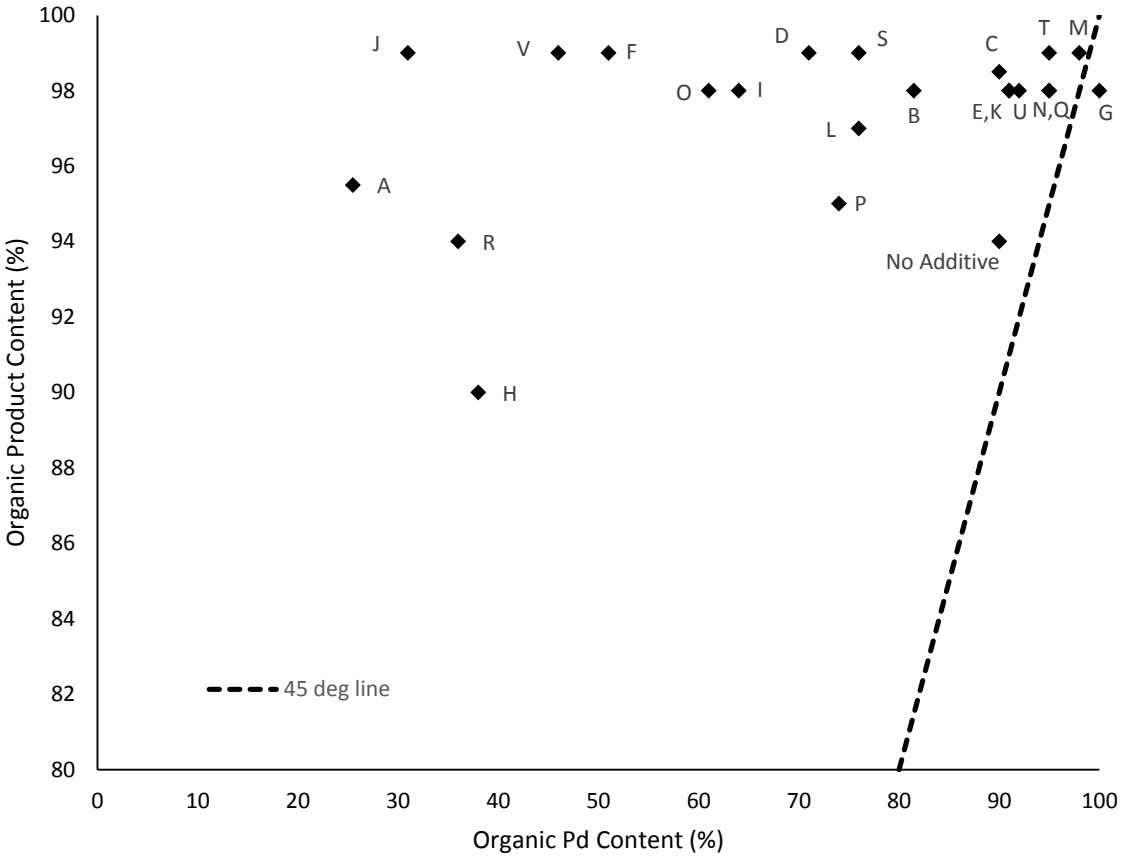


Figure 4-8: Scatter Plot of Organic Phase Retention of Palladium (X-axis) and 5-methyl-2-phenylpyridine (Y-axis) at 200 psig CO_2 as a Function of Additive Selection. Additives were introduced at 20 catalyst equivalents relative to catalyst loading. The dotted line is a reference line indicating a "No Separation Regime". Letters correspond to indices specified in Figure 4-4

Interestingly, not all sulfur-containing additives exhibit favorable palladium separation. Cysteine, for example, removes more than 70% of the Pd from the organic phase at 200 psig, whereas thiosalicylic acid fails to remove any, but instead seems to pull palladium away from the aqueous phase and sequester it within the product-rich organic phase. This is readily explained by the difference in hydrophilicity of the additives. Cysteine is a particularly hydrophilic compound with a log(Kow) = -2.49[21]. It is predictable from this behavior that cysteine would preferentially dissolve into a polar, protic solvent (such as water) rather than a non-polar, aprotic solvent (such as CO_2-expanded acetonitrile). However, thiosalicylic acid is distinctly hydrophobic, with a log(Kow) = 2.39[22]. Its preferential solubility would therefore be reversed, explaining the discrepancy between these sulfur-containing additives.

A further discrepancy is observed between the sodium salt and acidic derivatives of ethylenediaminetetraacetate (EDTA). Acidic EDTA removes approximately 60% of the process palladium and sequesters it into the aqueous phase. Surprisingly, sodium EDTA is largely indistinguishable from the case when no additive is used. This is perhaps explained by the production of a distinct aqueous phase upon addition of salt-derived additives (EDTA, NTA, citrate) before pressurization with CO_2. Despite diminished loading, the amount of salts present in these experiments forces heterogeneous behavior under N_2, possibly introducing a mass-transfer barrier to Pd-EDTA complexation. If the additive is unable to coordinate with the palladium, no separation will be seen, regardless of additive hydrophilicity.

4.3.1.2 Effect of CO_2 Pressure

Figure 4-9 summarizes the results of organic-phase palladium retention using multiple sulfur-containing additives as a function of CO_2 pressure. Organic palladium retention without the use of an additive is also given. While there is minimal change of organic palladium retention between 100 and 200 psig CO_2, there is a significant decrease in the amount of palladium retained in the organic phase when pressure is increased from 200 to 400 psig. This is likely due to a large increase in solubilized CO_2 at the higher pressure, resulting in swollen volumes and reduced effective solvent polarity.

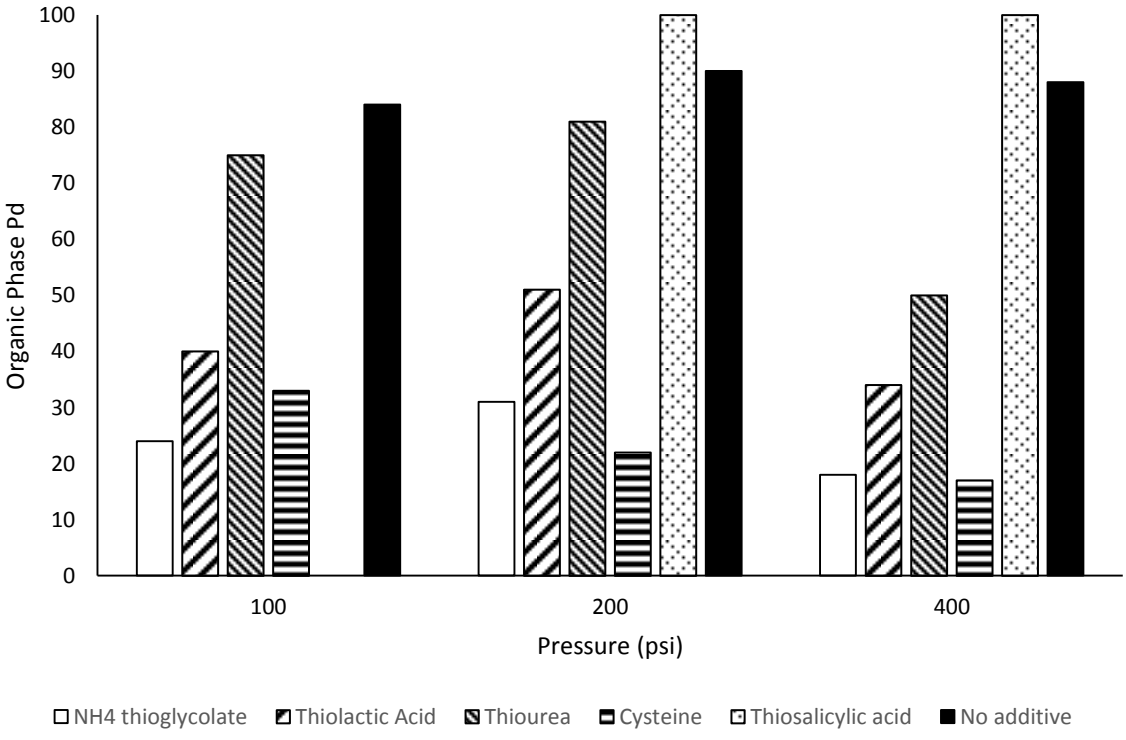


Figure 4-9: Organic Phase Retention of Palladium as a Function of Pressure Using Various Sulfur-Containing Additives

It is important to note a few observations concerning the phase behavior during this study. At 100 psig, there is no observable phase split when thiosalicylic acid is used as an additive. Furthermore, solid precipitates form at 400 psig when thiosalicylic acid and ammonium thioglycolate are used as additives. When these solids are present, a significant amount of system palladium is unaccounted for within either the organic or aqueous phases (thiosalicylic acid = 71% of system palladium unaccounted for, ammonium thioglycolate = 54%), suggesting that these solids are palladium complexes.

With the exceptions of thiourea and thiosalicylic acid, the sulfur-containing additives that were investigated each exhibit moderately hydrophilic palladium species, with cysteine under 400 psig CO_2 returning the most favorable results (~80% of system palladium removed from the organic phase). This constitutes a significant improvement over the case where no additive is used (~12% of system palladium removed). Such a drastic difference clearly decouples the effects of CO_2 pressure and additive selection on palladium partitioning and demonstrates the necessity for chemical additive to manipulate palladium hydrophilicity.

4.3.1.3 Effect of Additive Loading

In order to further understand the role of additive in OATS palladium separation, the effect of additive loading was investigated by conducting the separation at 200 psig with varied amounts of cysteine. The results are given in Figure 4-10.

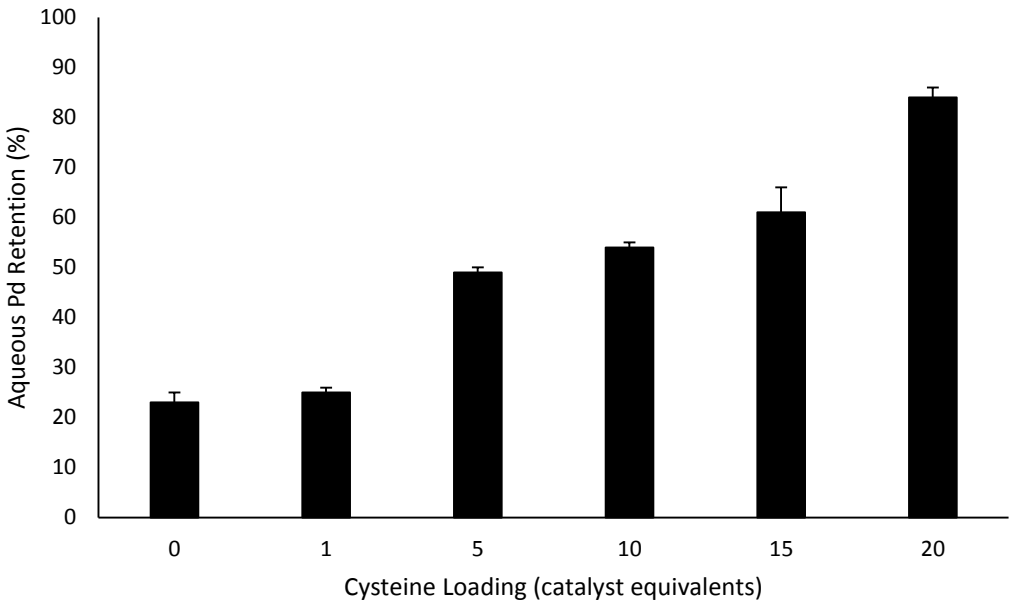


Figure 4-10: Aqueous Phase Palladium Retention as a Function of Cysteine Loading

Unsurprisingly, the amount of palladium sequestered in the aqueous phase increases as a function of cysteine loading. Little change is seen when increasing from no cysteine (23% aqueous palladium retention) to one catalyst equivalent of cysteine (25% aqueous palladium retention). However, aqueous palladium retention is greatly increased as the amount of cysteine present is elevated, increasing from approximately 50% using 5 equivalents of cysteine to >80% using 20 equivalents of cysteine.

4.3.1.4 Separation of Palladium from Product

It is important to note that manipulation of palladium is not, by itself, a sufficient technique for the removal of palladium from organic product: it is of equal importance to understand the partitioning of the desired product, particularly in a tunable solvent system such as OATS. Figure 4-11 shows the organic phase retention of both palladium and

post-Suzuki 5-methyl-2-phenylpyridine as a function of pressure when no additive is used. In every case, >80% of system palladium and system product are retained in the organic phase, retaining as much as 90% of the total palladium with 94% of the total product at 200 psig. No trend exists in the organic palladium retention as a function of pressure, suggesting that the pressure-tunable organic phase polarity is of negligible importance.

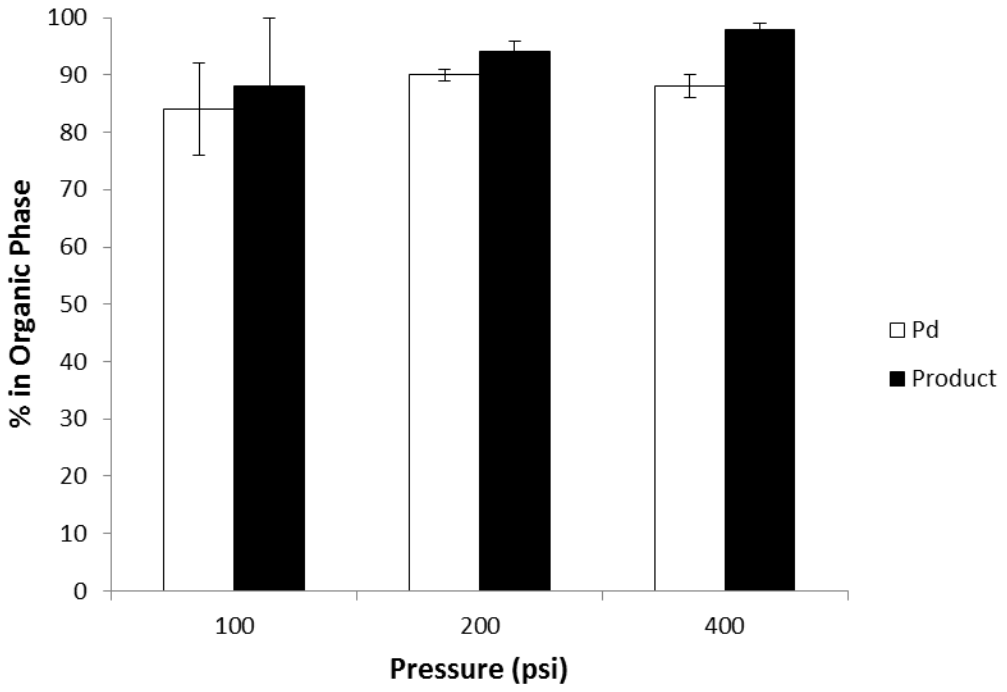


Figure 4-11: Organic Phase Retention of Palladium (white) and 5-methyl-2-phenylpyridine (black) as a Function of Pressure with No Additive Present

Figure 4-12 shows the organic phase retention of palladium and 5-methyl-2-phenylpyridine as a function of pressure when 20 equivalents of cysteine is employed as

an additive. The results are immediately distinguishable from the case when no additive is used (Figure 4-11). At pressures as low as 100 psig, up to 63% of system palladium has been removed from greater than 90% of the organic product. Trends in increasing hydrophilicity of palladium as well as hydrophobicity of product can be seen as a function of increasing pressure. Organic phase product retention increases to 97% at 400 psig, whereas organic phase palladium retention decreases to 20% at 400 psig.

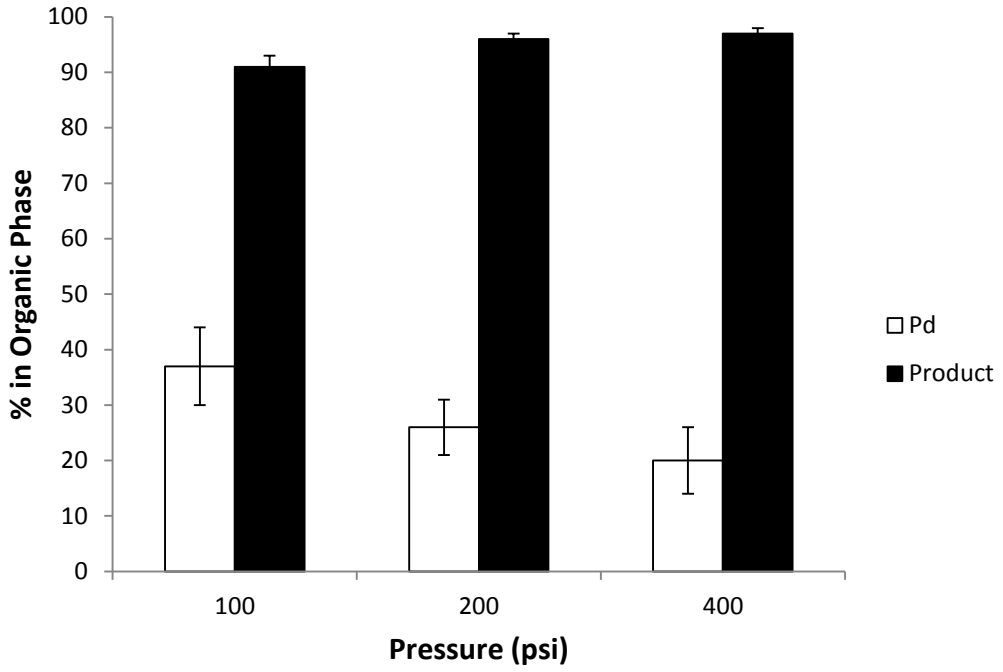


Figure 4-12: Organic Phase Retention of Palladium (white) and 5-methyl-2-phenylpyridine (black) as Function of Pressure with 20 Equivalents of Cysteine

Following separation, the palladium-rich aqueous phase was treated with activated carbon (20 g/L) in order to emulate common industrial catalyst recovery

processes and in order to uphold green engineering principles by avoiding the production of a high-volume aqueous palladium waste stream. It was found that, despite the presence of cysteine, effectively all of the solubilized palladium was able to be recovered via treatment with activated carbon. It was therefore seen that the OATS separation process coupled with activated carbon can provide a facile palladium removal procedure in which ≥80% of process catalyst can be removed and adsorbed in order to avoid the generation of high-volume waste.

4.3.2 4-amino-2-bromopyridine

In order to further probe the use of a modified OATS separation process on multiple substrates, 4-amino-2-bromopyridine (Figure 4-13) was selected as an additional candidate for separation with cysteine.

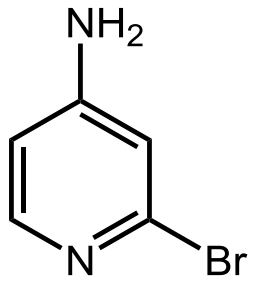


Figure 4-13: Structure of 4-amino-2-bromopyridine

Suzuki couplings of 4-amino-2-bromopyridines were performed as follows: 16 mmol of 4-amino-2-bromopyridine were weighed into a 3-neck 100-mL round bottomed flask along with 20.8 mmol of phenylboronic acid, 48 mmol of K_2HPO_4, and 0.8 mmol of

$(TPP)_2PdCl_2$. 30 mL of degassed MeCN and 20 mL of H_2O were added, the reaction was heated to 70 ^oC and allowed to mix for 24 hours at temperature. The reaction and conditions are described in Figure 4-5 (above).

Following reaction, the salt-rich aqueous phase was decanted away from the organic phase and replaced with 20 mL of degassed water. The mixture was transferred to a windowed Parr reactor via airtight syringe and pressurized using CO_2 as described above. Samples were taken as a function of pressure in order to observe the partitioning of palladium and product in the system. The results are shown in Figure 4-14.

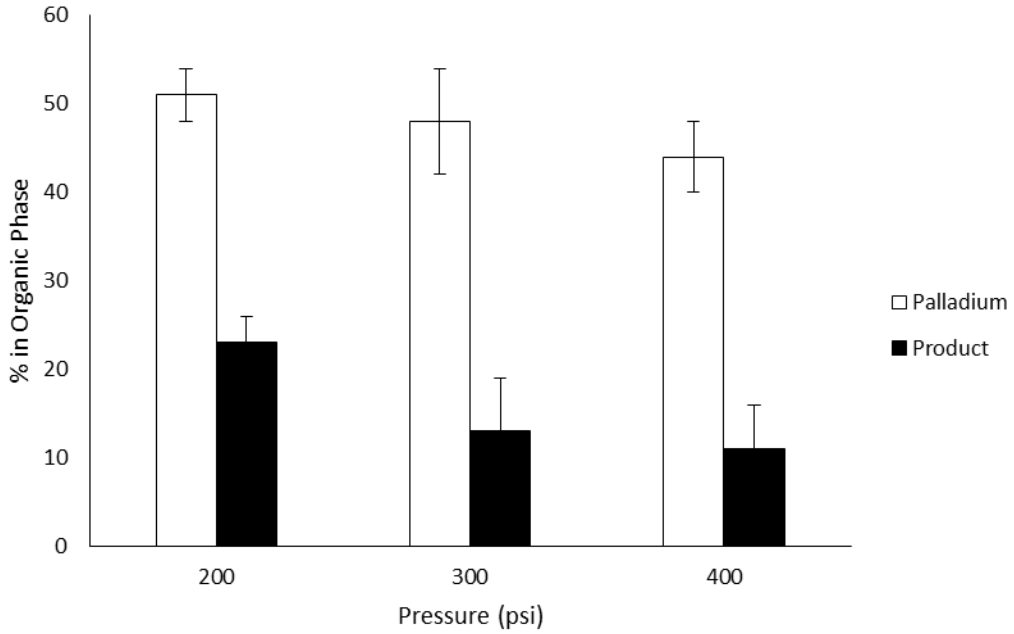


Figure 4-14: Organic Phase Retention of Pd and 4-amino-2-phenylpyridine as a Function of CO_2 pressure

Interestingly, the amount of palladium retained in the organic phase is lower when 4-amino-2-bromopyridine is used compared to 5-methyl-2-bromopyridine (51% compared to 90% at 200 psi). Furthermore, a slight trend of decreasing palladium retention in the organic phase is seen as a function of pressure, decreasing to 48% and 44% at 300 psi and 400 psi, respectively. More interestingly, it seems that a great deal less product is present in the organic phase when 4-amino-2-bromopyridine is used compared to when 5-methyl-2-bromopyridine is used (23% compared to 94% at 200 psi). Additionally, it is evident that product partitioning follows the same trend as palladium when 4-amino-2-bromopyridine is employed, with product percentage present in the organic phase decreasing as a function of pressure (23%, 13%, and 11% at 200, 300 and 400 psi, respectively). These trends are surprising when compared to results seen from 5-methyl-2-bromopyridine. However, the hydrophilicity of 4-amino-2-phenylpyridine in this system is likely explained by the basicity of the 4-aminopyridine functionality in the presence of carbonic acid produced by the absorption of CO_2 into the aqueous phase. A proposed reaction scheme is shown in Figure 4-15.

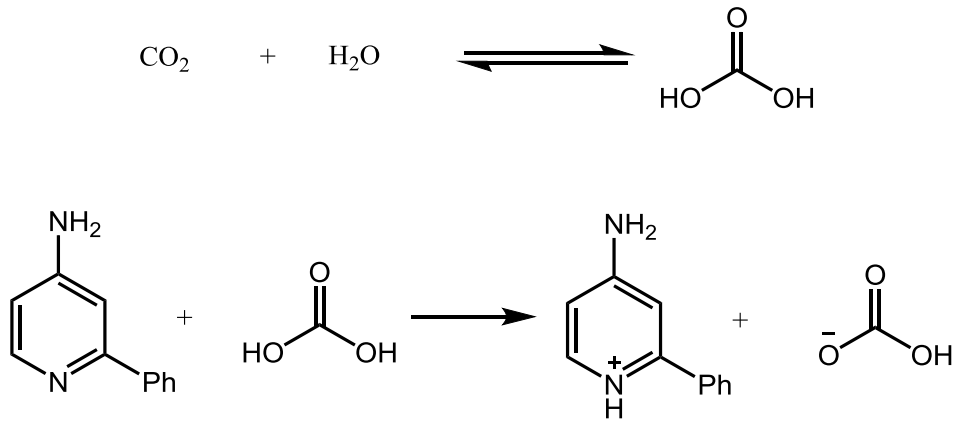
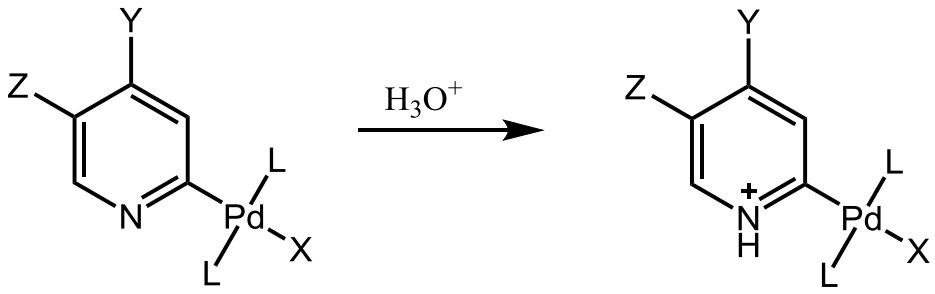


Figure 4-15: Formation of Carbonic Acid via CO_2 Addition to Water and Subsequent Proton Exchange with 4-amino-2-phenylpyridine

As CO_2 is added to the aqueous phase via elevated pressure, carbonic acid is formed by reaction with water. This carbonic acid can then undergo proton exchange with 4-amino-2-phenylpyridine. The 4-amino-2-phenylpyridine is expected to have a higher basicity due to the π-donating effect of the amino group at the 4-position on the pyridine ring. This added electronegativity, in turn, increases the likely hood of proton exchange, generating an ionic species that would be expected to have an increased solubility in water, compared to its non-ionized form. Additionally, it is possible that the increased solubility in the organic phase at higher pressures of CO_2 diminishes the solubility of 4-amino-2-phenylpyridine.

The lowered retention of palladium in the organic phase (when 4-amino-2-bromopyridine) exhibits a substrate dependence, and suggests that the substrate or product plays a role in the catalyst species. A proposed mechanism, based on the catalytic cycle and literature syntheses[23], for substrate-dependent catalyst speciation is shown in Figure 4-16.



L = TPP
X = Br, Cl, Ph
Z = H, Y = NH_2 (4-amino)
Z = Me, Y = H (5-methyl)

Figure 4-16: Proposed Catalyst Structure Explaining pH-Dependent Palladium Hydrophilicity

Cysteine was also used in an effort to enhance the separation of catalyst in mixtures generated from reactions with 4-amino-2-bromopyridine. Procedurally, 20 catalyst equivalents of cysteine (16 mmol) were added to the reaction mixture along with 20 mL of degassed H_2O after the initial salt-rich aqueous reaction phase was decanted away from the organic phase. From this point, the mixture was treated identically to the others, in that it was transferred to a windowed Parr via airtight syringe, pressurized with CO_2 and sampled in order to probe the effects of elevated CO_2 pressure on palladium partitioning. The results of these studies are described in Figure 4-17.

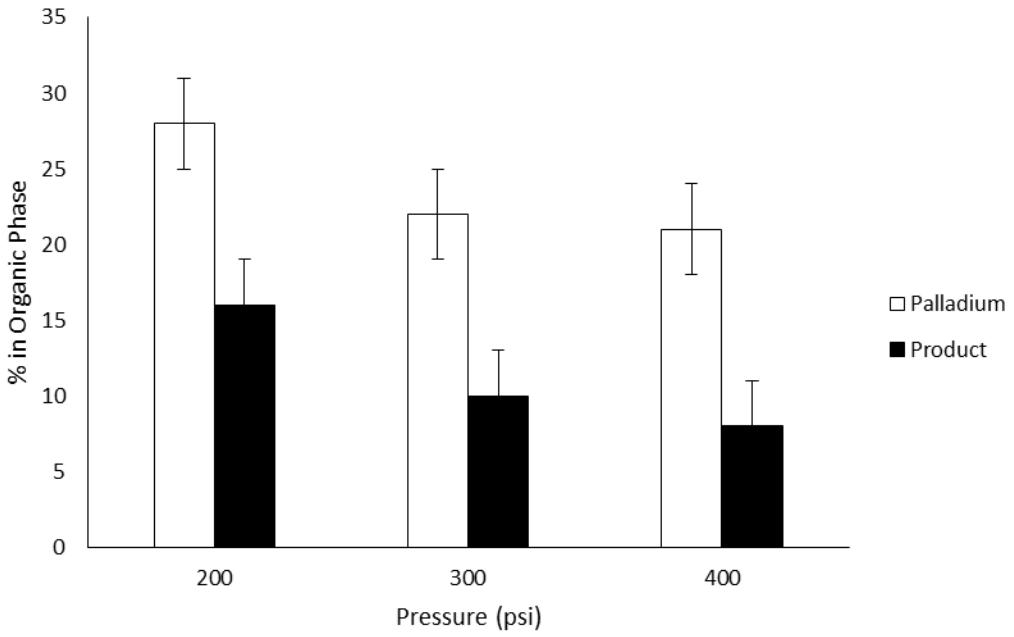


Figure 4-17: Organic Phase Retention of Pd and 4-amino-2-phenylpyridine as a Function of CO_2 Pressure in the Presence of Cysteine

It is clear that the use of cysteine does exhibit some benefit for removal of palladium from the organic phase in the presence of 4-amino-2-phenylpyridine under CO_2 pressures, with an organic phase palladium retention of 28% with the use of cysteine compared to 51% without the use of cysteine at 200 psi. The difference between the organic phase product content with and without cysteine is significantly smaller (16% with cysteine compared to 23% without cysteine), indicating that the presence of cysteine additive has minimal effect on product partitioning. The same pressure dependencies previously seen with 4-amino-2-bromopyridine mixtures can be seen with the addition of cysteine, as shown by the decrease of organic phase palladium content from 28% at 200 psig to 22% at 300 psig and 21% at 400 psig. The same slight trend is seen in product partitioning, with organic phase product content decreasing from 16% at 200 psig to 10%

at 300 psig and 8% at 400 psig. While it appears that cysteine is able to favorably alter the hydrophilicity of palladium in the presence of 4-amino-2-bromopyridine, the chemical properties of 4-amino-2-bromopyridine do not allow for a favorable separation, define as an equilibrium state where the majority of palladium is isolated away from the majority of organic product.

4.3.3 Effect of CO_2 Concentration of Product and Palladium Solubility

In order to further investigate the effects of CO_2 pressure on product and palladium solubility, a series of experiments were carried out in which the organic phase of a reaction mixture was decanted away from the aqueous phase and pressurized under CO_2 without the addition of degassed water. With less water present, distinct aqueous and organic phases are less likely to evolve with the addition of CO_2, allowing a more direct method of evaluating the relative solubilities of palladium and product in the organic phase without consideration of each species relative hydrophilicity. Figure 4-18 gives the results of these studies.

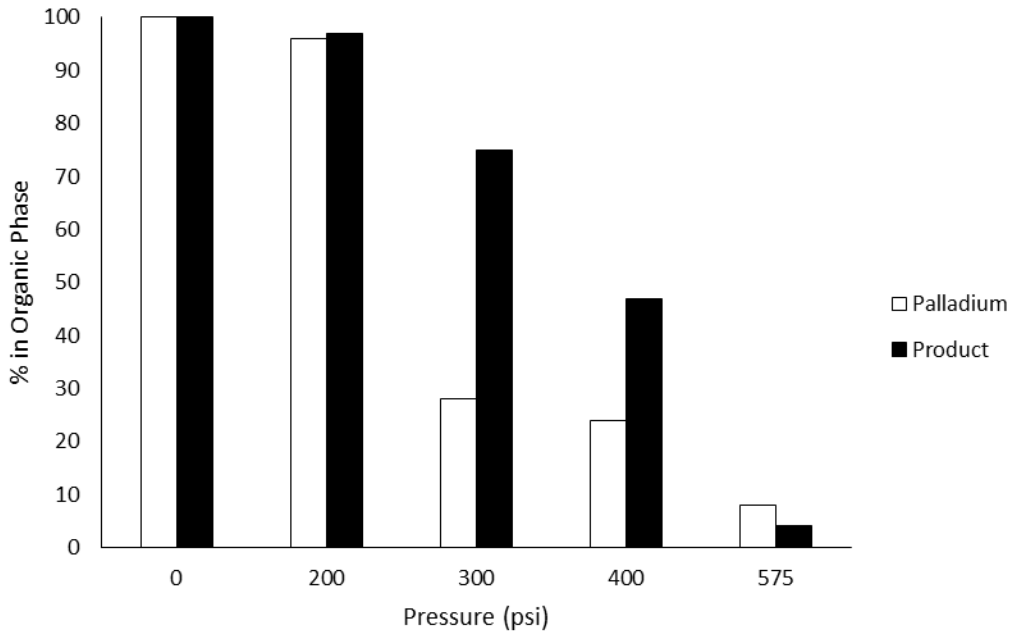


Figure 4-18: Pd and Product Content in Organic Phase as a Function of CO_2 Pressure. No Aqueous Phase is formed due to lack of water in system.

Interestingly, a gradual decrease is seen in the solubility of both palladium catalyst and 4-amino-2-phenylpyridine as CO_2 pressure is increased. At 0 psig of CO_2, effectively all of the catalyst and product (100%) is soluble in the organic phase. At low pressures of CO_2, this is still the case (96% of palladium, 97% of product soluble in the organic phase at 200 psig). However, as pressure is increased a drastic decrease in palladium solubility is seen, dropping to 28%, 24%, and 8% at 300, 400, and 575 psig, respectively. The reason for this pressure-dependent solubility is likely due to the increase of dissolved CO_2 as a function of pressure. CO_2 has a much lower dielectric constant (~1.6) compared to that of acetonitrile or water (37.5 and 80.1, respectively), which means that as the concentration of dissolved CO_2 is increased via increasing

pressure, the solvating power of the liquid phase is decreased, diminishing the ability of the solution to stabilize the polar, protic aminopyridine species.

In order to probe the reversibility of this behavior, the experiment was carried out in decreasing pressure, beginning from 575 psig and decreasing to 0 psig by venting the headspace. In order to prevent loss of solvent via depressurization, the Parr was cooled to 0 ^{o}C with an ice water bath before the headspace was vented. Following depressurization, the Parr was allowed to warm to room temperature before samples were taken from the mixture. Figure 4-19 gives the results of these experiments.

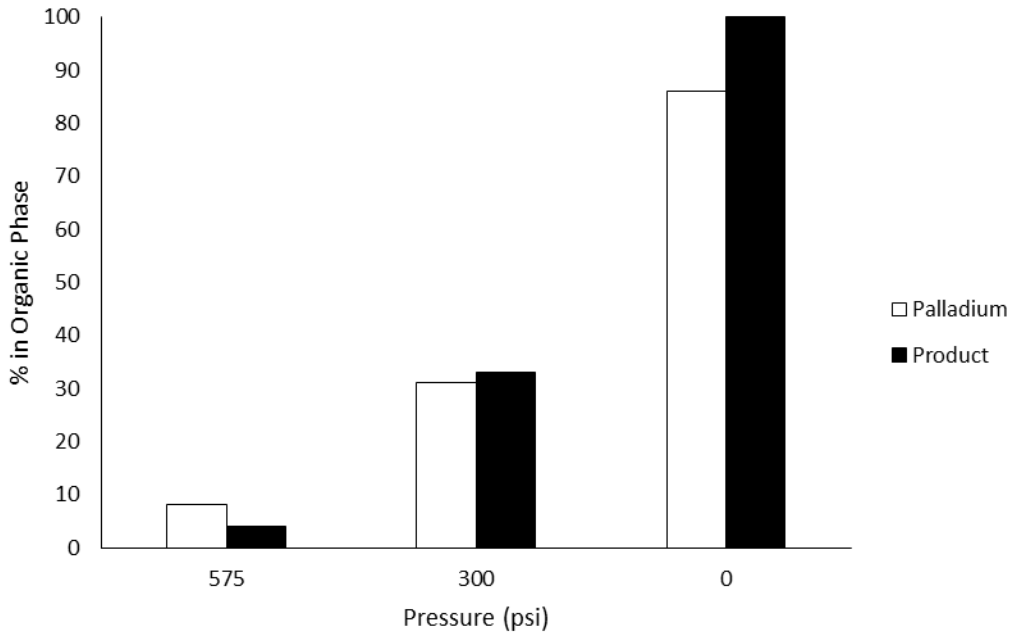


Figure 4-19: Pd and Product Content in Organic Phase as a Function of Decreasing Pressure. Trend exhibits reappearance of Pd and product, indicating re-dissolution.

It is clear that the previously seen decrease in solubility as a function of CO_2 pressure is reversible, with organic phase palladium content increasing from 8% at 575 psig to 31% and 86% at 300 and 0 psig, respectively. Additionally, the product appears to exhibit increasing solubility as CO_2 pressure is decreased, increasing from 4% at 575 psig to 33% and 100% at 300 and 0 psig, respectively. These results suggest that CO_2 concentration plays a major role in catalyst and product partitioning as a function of CO_2 pressure in OATS systems. Furthermore, these results indicate that the nature of the interaction between CO_2 and the species of interest is, at least in part, an equilibrium-based process and not an irreversible reaction between the CO_2 and catalyst or product.

4.4 Conclusions

The use of Organic/Aqueous Tunable Solvents has been found to be an effective method for the removal of homogeneous palladium from organic products of Suzuki coupling reactions when paired with the use of sulfur-containing additives. Among those screened, cysteine stands out as an additive agent for increasing the hydrophilicity of palladium. A dependence of palladium removal on additive loading has also been demonstrated, varying from 23% palladium removal with no cysteine to >80% palladium removal when 20 equivalents are used under 200 psig of CO_2. Furthermore, tunable separation has been demonstrated as a function of CO_2 pressure, varying palladium removal from 63% at 100 psig to 80% at 400 psig. Finally, the ability of activated carbon to extract the palladium from the catalyst-rich aqueous phase has been demonstrated, highlighting the capability of this process to be immediately implemented into existing technologies in a manner that adheres to the principles of green chemistry and engineering.

In addition to showing the benefit of OATS-like processes, an investigation into substrate scope expansion has also revealed important parameters that control the hydrophilicity of basic N-containing heterocycles in an OATS-like separation. It has been shown that the hydrophilicity of 4-amino-2-phenylpyridine is greater than that of 5-methyl-2-phenylpyridine under application of CO_2 pressure (23% of 4-amino-2-phenylpyridine contained in the organic phase at 200 psig compared to 94% of 5-methyl-2-phenylpyridine contained in the organic phase at 200 psig). Furthermore, it has been shown that the use of cysteine in 4-amino-2-phenylpyridine systems exhibits the ability to favorably partition palladium toward the aqueous phase, albeit with less benefit when compared to the 5-methyl-2-bromopyridine system (28% of 4-amino-2-phenylpyridine contained in organic phase when cysteine is employed at 200 psig compared to 51% of 4-amino-2-phenylpyridine contained in the organic phase when cysteine is not employed at 200 psig). It was proposed that pH and CO_2 solubility might play crucial roles in determining the partitioning of both catalyst and product in the organic phase. A model for pyridine protonation based on formation of carbonic acid and subsequent reaction with basic pyridines has been proposed, and the solubility of catalyst and product has been investigated as a function of pressure. It has been shown that both palladium catalyst and 4-amino-2-phenylpyridine lose organic phase solubility as a function of pressure (decreasing from 100% retention at 0 psi to 4% and 8% at 575 psi for product and palladium, respectively).

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CHAPTER 5 - HYDROPHILIC CATALYST RECOVERY AND RECYCLING USING ORGANIC-AQUEOUS TUNABLE SOLVENTS (OATS)

5.1 Introduction

Throughout the history of industrial chemistry, metal catalysis has played an integral role in the production of chemicals[1,2]. Metal catalysis allows reactions of organic molecules to proceed at faster rates (compared to uncatalyzed analogs), even at low (<1%) catalyst loadings (with respect to organic substrate)[3]. Of particular interest is the field of homogeneous catalysis, or catalysis that takes place within a single reaction phase. Homogeneous catalysis differs from heterogeneous catalysis in that the catalyst of interest in a particular homogeneous process is soluble in the reaction medium (e.g. solvent), whereas heterogeneous catalysts are insoluble, often existing as a solid or bound to a solid support.

While homogeneous catalysts are often superior to heterogeneous catalysts in terms of reactivity, they are often inferior in terms of catalyst recovery[4]. The solubility of the catalyst in the reaction medium becomes a burden when designing a homogeneous catalyst separation process. Heterogeneous catalysts afford more facile separations due to the fact that they are already constrained to a substrate-deficient phase (i.e. solid or solid support).

It is desirable to design a recyclable catalytic system that behaves as a homogeneous catalyst throughout reaction, but can be easily modified or "switched" to a heterogeneously catalytic system for facile separation. Such a design maximizes the return-on-investment of purchased catalyst, both maximizing the catalyst's effectiveness (homogeneous reaction) while minimizing separation costs and enhancing product quality by minimizing residual catalyst contamination. One example of such a switchable process is the Organic-Aqueous Tunable Solvents (OATS) system described by Pollet *et al*[5]. OATS systems are characterized as miscible solvent mixtures (e.g. THF/H_2O, MeCN/H_2O) that can be "switched" with the application of an external stimulus, or trigger, to exhibit immiscibility[6]. The trigger is an anti-solvent, generally one that exhibits high solubility in one of the selected solvents, and low solubility in the other. One example of an ideal anti-solvent is CO_2, which exhibits solubility in MeCN and THF, but is only marginally soluble in H_2O.

Figure 5-1 shows how an OATS process may be constructed in order to provide a system that utilizes homogeneous catalysis, heterogeneous separation, and subsequent catalyst recycle.

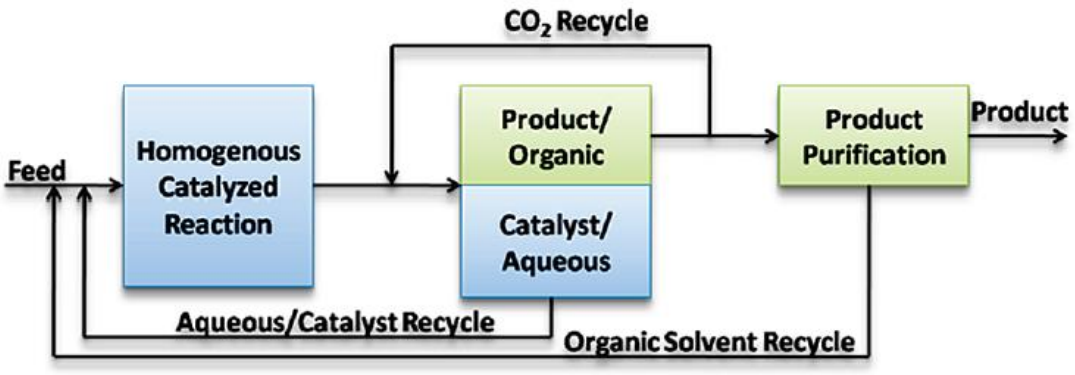


Figure 5-1: Process Flow Diagram of Homogeneously Catalyst Reaction Utilizing OATS Separation[5]

As depicted, OATS describes an optimum chemical process in which only raw materials enter the production line and only finished goods exit the production line: every ancillary material (solvent, catalyst, CO_2, etc.) is recycled. In order to realize this process, a few critical requirements are immediately obvious: 1.) organic solvent must be removable from the desired product (i.e. organic solvent must be recyclable), 2.) the anti-solvent must be easily removed from the organic phase post-separation (i.e. anti-solvent must be recyclable), and 3.) the catalyst must be preferentially soluble in the aqueous phase (away from the product) during the separation step. Organic solvent removal from final products is considered a downstream process and is not discussed in this work. However, the removal of anti-solvent from the organic phase is one of the most useful characteristics of OATS, in that one can achieve removal of CO_2 by simple depressurization. The final requirement (catalyst hydrophilicity) is of greater significance, and requires deliberate planning.

Such a hydrophilic, catalytic process was demonstrated by Hallett *et al*[7], applying the OATS process to the hydroformylation of 1-octene (Figure 5-2).

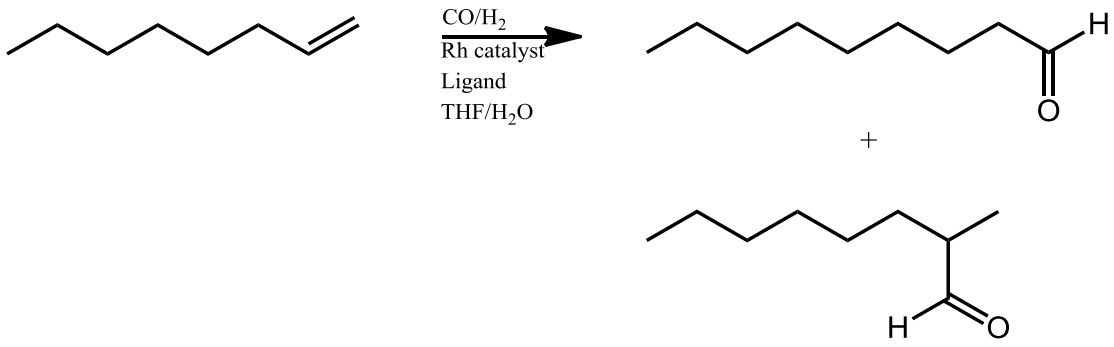
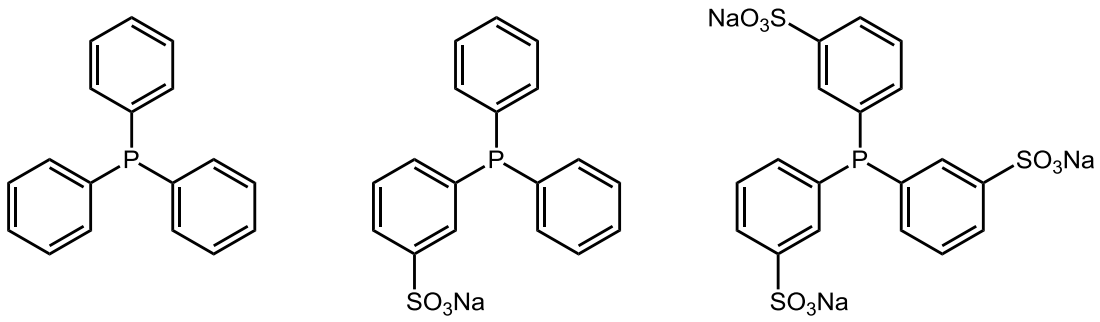


Figure 5-2: Rhodium-Catalyzed Hydroformylation of 1-octene

Hydroformylation reactions often employ phosphine ligand[8,9] due to a correlation between ligand loading and reaction rate and selectivity towards formation of linear aldehydes vs. branched aldehydes[10]. By using hydrophilic derivatives of triphenylphosphine (TPP, Figure 5-3, left), such as triphenylphosphine-monosulfonate (TPPMS, Figure 5-3, center) or triphenylphosphine-trisulfonate (TPPTS, Figure 5-3, right), the hydrophilicity of the catalyst can be manipulated[11].



Triphenylphosphine
TPP

Triphenylphosphine-monosulfonate
TPPMS

Triphenylphosphine-trisulfonate
TPPTS

Figure 5-3: Structures of Triphenylphosphine Derivatives. Triphenylphosphine (left), Triphenylphosphine-monosulfonate (center), and Triphenylphosphine-trisulfonate (right)

The relative solubilities of these water-soluble phosphines in THF/H_2O OATS mixtures were explored in order to better understand how they might be employed in an OATS catalyst recycle system. Ligand partitioning experiments conducted in THF/H_2O mixtures at various pressures of CO_2 are shown in Figure 5-4.

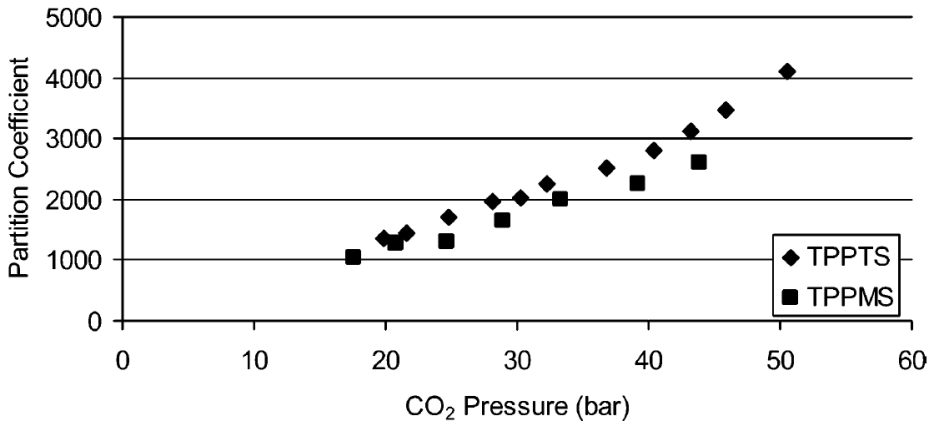


Figure 5-4: Partition Coefficient of TPPMS and TPPMS as Function of CO_2 Pressure[7]. Conducted in THF/H_2O OATS Mixture. Partition Coefficient defined as K = [Concentration in aqueous phase]/[Concentraion in organic phase].

A few things are obvious from the trends seen in water-soluble ligand partitioning as a function of pressure. In general, TPPTS exhibits greater hydrophilicity than TPPMS, reaching a partition coefficient (K_{TPPTS} = $[TPPTS]_{aq}/[TPPTS]_{org}$) of over 3000 at 43 bar of CO_2, compared to a K_{TPPMS} of 2700 at 44 bar of CO_2. Additionally, an increase in water preference is seen with increasing pressure, exhibited by the increase in partition coefficient of TPPTS from K_{TPPTS} = 1300 at 20 bar CO_2 to K_{TPPTS} = 4100 at 50 bar CO_2. From this previous work, it is obvious that both the choice of ligand as well as CO_2 pressure have a direct effect on partitioning behavior in an OATS system.

In addition to ligand separation, Hallett *et al*[7] probed the recyclability of rhodium catalysts used in conjunction with hydrophilic ligands (TPPMS) in an OATS process. Figure 5-5 gives the turnover frequency (TOF) from a series of three hydroformylation reactions in which the catalyst was recycled using an OATS separation process.

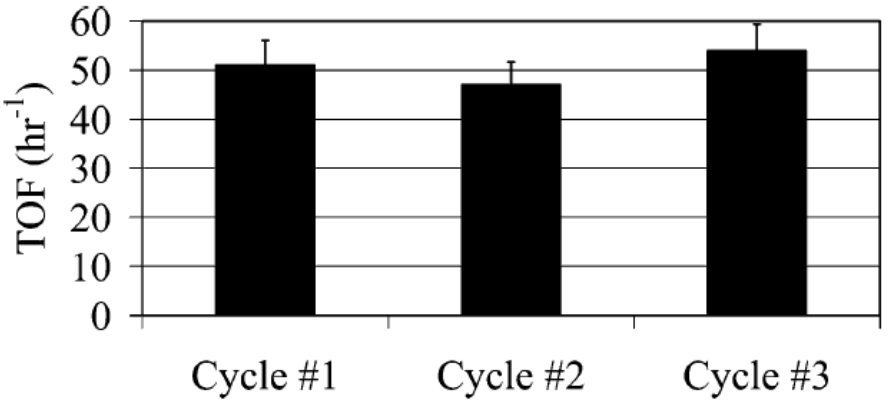


Figure 5-5: Turnover Frequency (TOF) of Catalysts in Hydroformylation Reactions Recycled Using OATS[7].

As is clear, the use of CO_2 has no significant effect on the reactivity of the rhodium catalyst used in the recycled hydroformylation reactions, with each reaction cycle returning a TOF of approximately 50 hr^{-1}. This preliminary work has established the foundation for OATS as a viable catalyst recovery/recycle technique.

The work presented in this chapter highlights the effort to develop a catalyst-recycle strategy for Suzuki coupling reactions using OATS technology. The Suzuki coupling reaction offers a number of challenges that are not present in the previously explored hydroformylation reaction, primarily due to the increased number of reagents used in a Suzuki coupling reaction and their respective effects on phase behavior. Not least among these challenges is the presence of base, usually inorganic, which invariably causes a phase-split in the presence of MeCN and H_2O.

The Suzuki coupling of 5-methyl-2-bromopyridine with phenylboronic acid in the presence of potassium phosphate and palladium catalyst was selected for use as a model

reaction throughout this work. TPPMS was used as a water-soluble ligand throughout this work. The reaction scheme is shown in Figure 5-6.

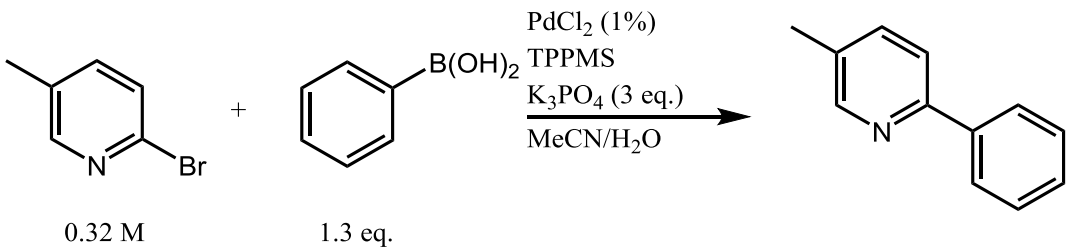


Figure 5-6: Suzuki Coupling of 5-methyl-2-bromopyridine with Phenylboronic Acid.

The use of 5-methyl-2-bromopyridine, as discussed in previous work (Chapter 4), affords the formation of a relatively hydrophobic product (5-methyl-2-phenylpyridine), which is useful in the design of a model system using a hydrophilic catalyst-ligand species. TPPMS was selected as a target ligand based on the success seen in the rhodium-catalyzed hydroformylation recycle experiments reported previously. Additionally, the MeCN/H_2O solvent system was chosen in order to leverage previous work on the removal of salts via aqueous decantation (Chapter 4).

5.2 Experimental Section

5.2.1 Materials

Deionized water was prepared in-house and used throughout the course of the described experiments. Before use, the water was degassed by sparging with N_2 for 30 minutes. Acetonitrile was purchased from Sigma-Aldrich and degassed by N_2 sparge

before use. Palladium(II) dichloride, potassium phosphate, and phenylboronic acid were purchased from Sigma-Aldrich and used as received. 2-bromo-5-methylpyridine was purchased from Matrix Scientific and used as received. Triphenylphosphine-monosulfonate (TPPMS) was purchased from TCI America and used as received. Throughout the course of this study, many additives were purchased from commercial chemical suppliers and used as received. SFE-grade CO_2 was purchased from AirGas and used as received.

5.2.2 Experimental

5.2.2.1 Pd-TPPMS Catalyzed Coupling of 2-bromo-5-methylpyridine

2-bromo-5-methyl pyridine (16 mmol, 2.7523 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq, 2.5361 g), and tripotassium phosphate (3 eq, 10.1890 g). The reaction flask was flushed with N_2 for 15 minutes prior to solvent addition. After flushing with inert gas, 25 mL of degassed acetonitrile and 15 mL of degassed H_2O were added using air-tight syringes. The mixture was then heated to 70 ^{o}C. Separately, palladium chloride (0.16 mmol, 28.4 mg) and TPPMS (3 cat. eq, 174.9 mg) were weighed into a round-bottomed flask and flushed with N_2 for 15 minutes. After flushing, 5 mL of degassed MeCN and 5 mL of degassed H_2O were added and the mixture was allowed to stir for 30 min, generating a yellow, homogeneous solution. This catalyst solution was transferred to the reaction flask, and the reaction was allowed to proceed for 120 minutes.

5.2.2.2 OATS Separation and Recycle

Following reaction, the salt-rich aqueous phase was decanted away. After decant, a solution of 174.9 mg TPPMS (3 cat. eq., unless otherwise noted) in 20 mL degassed

H_2O was added to the reaction organic phase. The mixture was then transferred to a windowed Parr reactor and pressurized to 400 psig CO_2 and allowed to stir for 30 minutes. After stirring, the pressurized mixture was allowed to settle overnight. The aqueous phase was then decanted into an N_2-flushed vessel, where the volume was measured and sampled for palladium and product content. Following palladium quantification, the aqueous phase was transferred to a 3-neck round-bottom flask containing 16 mmol of 2-bromo-5-methylpyridine, 1.3 eq. of phenylboronic acid, 3 eq. of potassium phosphate and 30 mL of MeCN at 70 ^oC

5.2.3 Instrumentation

Palladium concentration was measured using a Shimadzu AA-7000F Atomic Absorption Spectrometer, measuring as 247.6 nm. Background noise was removed from signal by self-reversal, with a current swing of 10 mA – 300 mA. Analysis occurred at a fuel gas flow rate of 1.8 l/min and an air flow rate of 15 l/min. Calibration curves were prepared by dissolving known amounts of bis(benzonitrile)palladium(II) dichloride into a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H_2O. Samples for analysis were dissolved in a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H_2O.

Concentrations of 2-bromo-5-methylpyridine and were measured using a Shimadzu GC-FID using calibration curves dissolved in 60/40 MeCN/H_2O with an initial oven temperature of 250 ^oC and a gradient of 10 ^oC/min

5.3 Results and Discussion

5.3.1 Reaction Optimization

Preliminary efforts were made to optimize the reaction conditions and catalyst-ligand state before pursuing a recycle strategy. By examining ^{31}P-NMR, it is possible to qualitatively monitor the state of the phosphine ligand with relation to palladium, observing oxidized phosphine, free phosphine, and Pd-bound phosphine. Figure 5-7 shows the ^{31}P-NMR of TPPMS. The peak at -4.95 corresponds to free phosphine while the peak at 34.61 corresponds to phosphine oxide. The large peak at 0 corresponds to an 85% phosphoric acid standard.

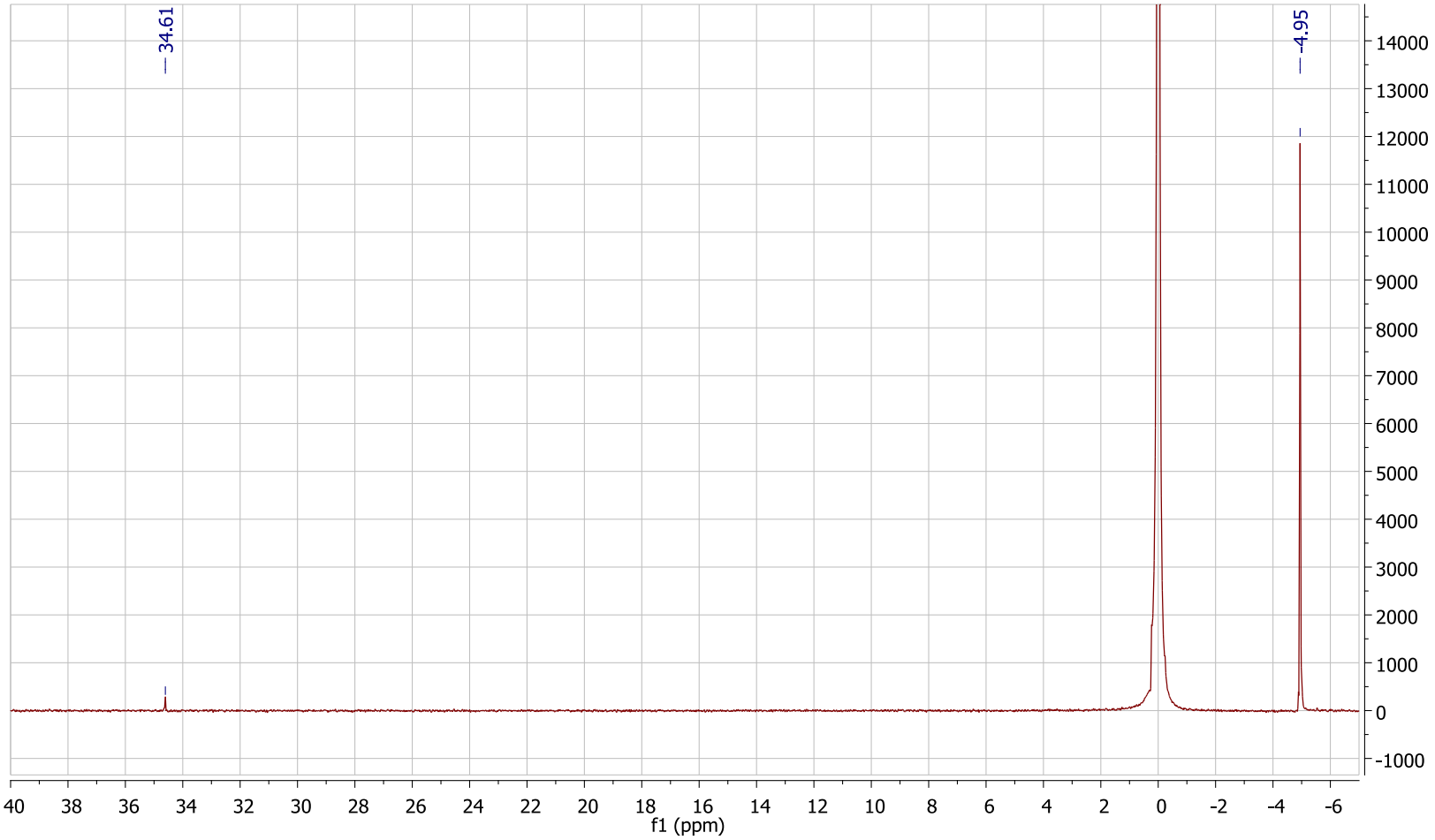


Figure 5-7: ^{31}P-NMR of TPPMS Ligand

Initial attempts to utilize TPPMS in Suzuki reactions were performed by combining all reagents into the same flask, adding degassed solvent, and heating to the desired temperature. However, these attempts resulted in the loss of catalyst via palladium black formation and the generation of TPPMS-oxide. This is due to the initially-unprotected state of the palladium catalyst (ligandless) in the presence of solubilized base. In order to avoid this, Pd-TPPMS catalyst was pre-prepared by combining $PdCl_2$ and TPPMS in 50/50 $MeCN/H_2O$ under N_2.

Figure 5-8 shows the ^{31}P-NMR of the preformed catalyst complex (procedure explained in the experimental section). The free phosphine peak has disappeared and the oxide peak (34.21 ppm) remains. Furthermore, two additional peaks have appeared (33.82 ppm and 30.32 ppm). These peaks correspond to Pd(II) complexes of TPPMS, based on literature results[12]. The continued presence of oxidized phosphine in pre-prepared catalyst mixtures suggests the presence of residual air in the system, leading to aerobic, palladium-catalyzed oxidation of TPPMS[13].

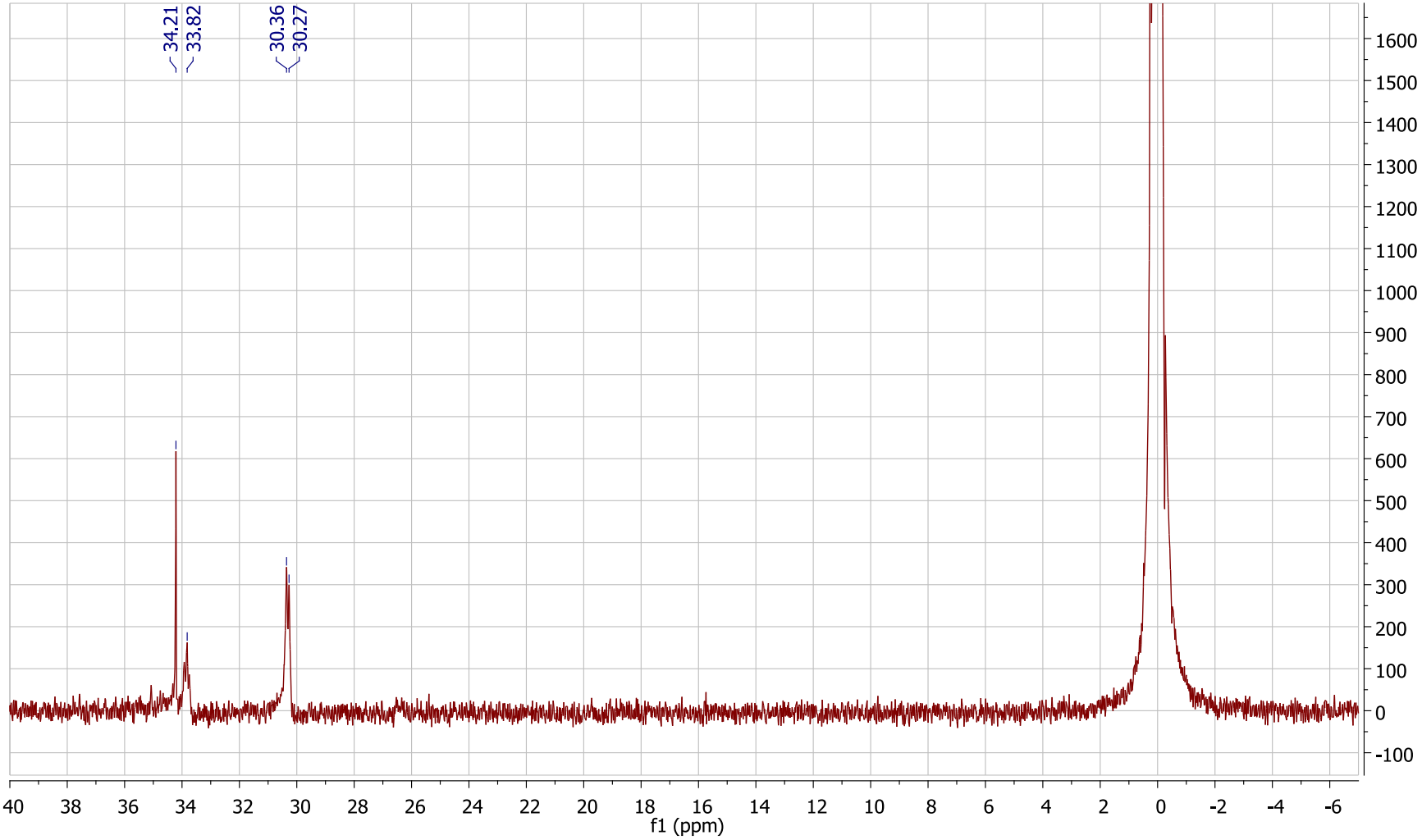


Figure 5-8: ^{31}P-NMR of Pre-prepared Catalyst $PdCl_2(TPPMS)_2$

After establishing a protocol with which stable Pd-TPPMS complex could be pre-prepared, experiments were conducted in order to observe the mass transfer limitations of the biphasic coupling reaction of 5-methyl-2-bromopyridine, given the insolubility of inorganic base in the organic phase and the insolubility of 5-methyl-2-phenylpyridine in the salt-rich aqueous phase (<1%). By conducting two reactions, one with poor stirring and one with effective stirring, it was possible to emphasize any mass transfer limitations on the reaction kinetics, which are manifest as reaction rates. Figure 5-9 shows the reaction rate profile of two such reactions over the course of 3 hours.

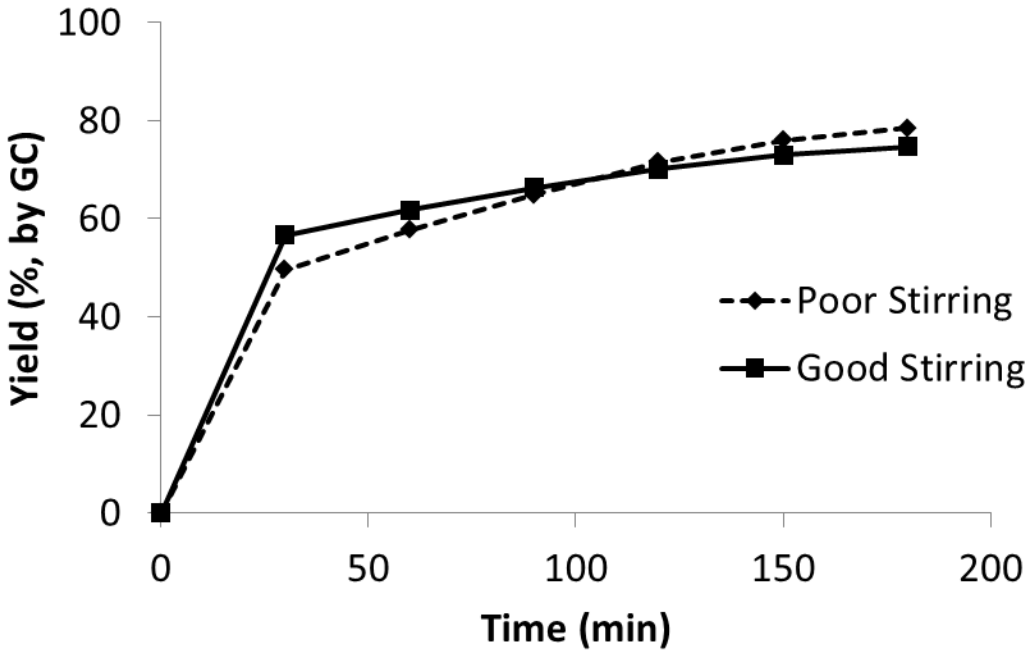


Figure 5-9: Yield of Suzuki Coupling Reactions at Varied Mixing Conditions

Both reactions exhibit relatively fast reaction rates compared to the reaction with triphenylphosphine (Chapter 4), with the poorly stirred reaction reaching 50% yield in 30 minutes and the well-stirred reaction reaching 57% yield in 30 minutes. Furthermore, both reactions slow after the initial 30 minutes, reaching 75% yield (good stirring) and 78% yield (poor stirring) at 180 minutes. This decrease in reaction rate is due partially to the depletion of starting material, but catalyst degradation may also play a minor role in the diminishing reaction rate. It is clear from the data, however, that there are minimal differences in reactivity caused by varying quality of mixing. This suggests that mass transfer limitations in the coupling reaction of 5-methyl-2-bromopyridine with phenylboronic acid at the described conditions are negligible. This is unsurprising, given the preferential solubility of both the catalyst and 5-methyl-2-bromopyridine in the organic phase (>95% of palladium and 5-methyl-2-bromopyridine are accounted for in the organic phase during reaction while salt is present in the aqueous phase).

In addition to mass transfer limitations, it was also important to understand the effect of temperature on reaction. Figure 5-10 shows the reaction kinetic profile at 70 ^{o}C and 50 ^{o}C.

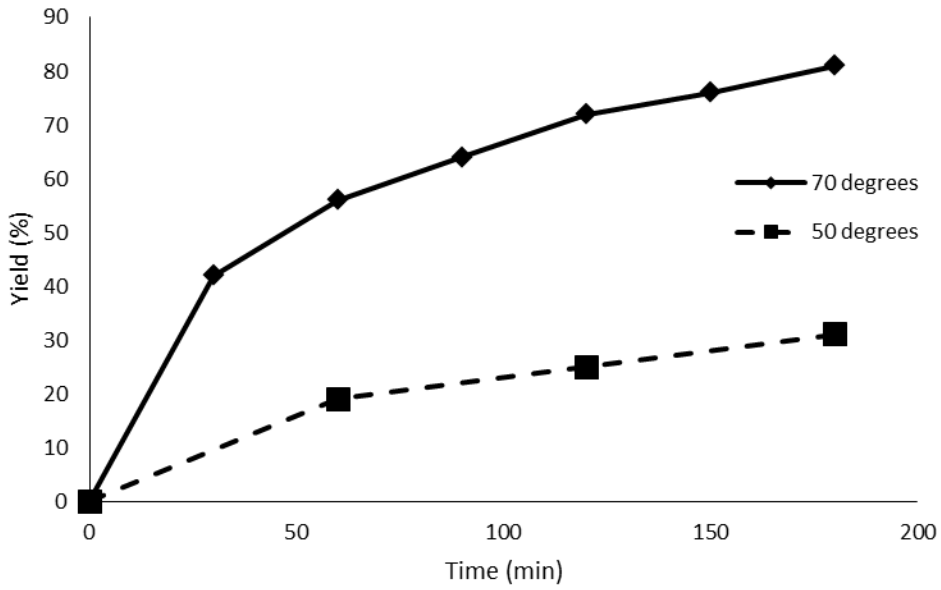


Figure 5-10: Suzuki Coupling Reactions at 50 ^{o}C and 70 ^{o}C

The fact that the reaction appears to proceed at a much higher rate at higher temperature is shown clearly in Figure 5-10. While the 70 ^{o}C reaction proceeds at a higher rate (56% yield at 60 minutes) compared to the 50 ^{o}C reaction (19% yield at 60 minutes), it is worth noting that both reactions proceed to completion within 24 hours. 70 ^{o}C was chosen as an optimal parameter in light of the apparent benefit to reaction rate with no obvious detriment.

Finally, experiments were conducted to understand the effect of ligand loading on the initial reaction. These experiments were conducted by pre-complexing $PdCl_2$ with varying amounts of TPPMS (2 equivalents, 3 equivalents, and 4 equivalents) and then using the precomplexed palladium species to conduct Suzuki coupling reactions. Figure 5-11 shows the kinetic profiles of reactions at these reactions at varied ligand loadings.

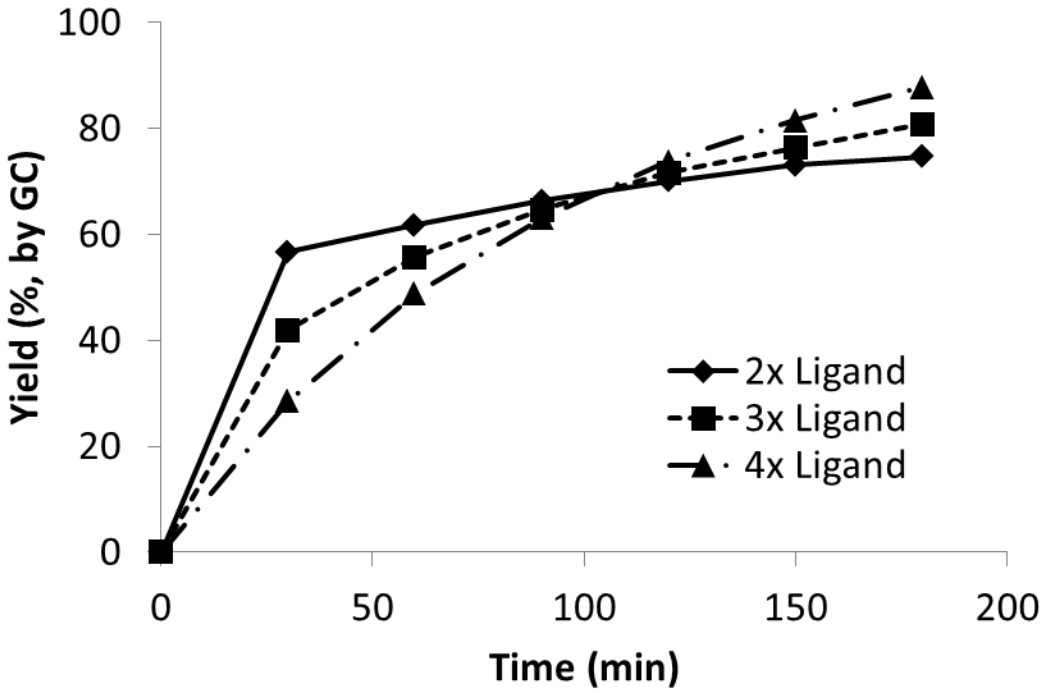


Figure 5-11: Effect of Ligand Loading on Reaction Rate

The results shown in Figure 5-11 largely exhibit expected behavior for a homogeneous catalyst-ligand system[14], in that the reaction with 4 equivalents of ligand yielded the lowest initial rates (28% yield at 30 minutes) compared to the reactions with 3 and 2 equivalents of ligand (42% and 57% at 30 minutes, respectively). However, at longer times the reaction with higher ligand loading achieves a higher reaction rate (88% yield at 180 minutes) compared to the reactions with 3 and 2 equivalents of ligand (81% and 75% yield at 180 minutes, respectively). It is clear that at lower ligand loadings, the reaction initially proceeds at a much higher rate. This is consistent with contemporary understanding of palladium-catalyst oxidative insertions in that less coordination promotes faster reaction with the aryl-halide bond. However, as ligand loading is

increased, higher yields are achieved at longer times, suggesting that increased ligand loading may play a role in stabilizing the palladium against degradation by increased coordination of phosphine to the metal center.

5.3.2 Catalyst Recycle Experiments

After probing reaction parameters and establishing an optimized reaction protocol, experimentation was conducted examining the separation and recyclability of Pd-TPPMS catalyst under CO_2 pressure in these post-Suzuki systems. In general, reactions were performed as shown in Figure 5-12.

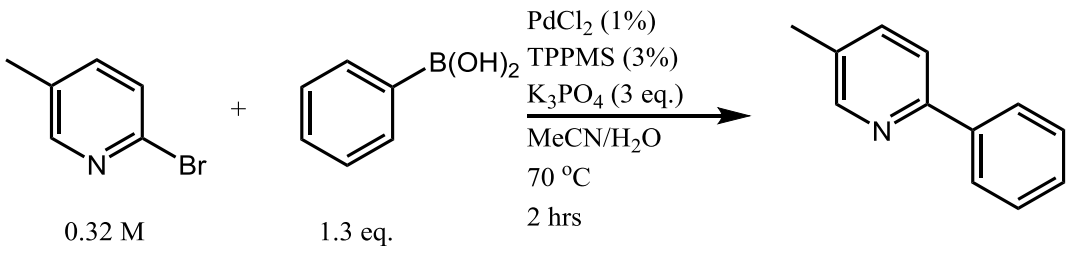


Figure 5-12: Optimized Reaction Conditions for the Suzuki Coupling Reaction of 5-methyl-2-bromopyridine with Phenylboronic Acid

Following reaction, a sample of the organic phase was taken in order to observe the state of the phosphine ligand post-reaction. Figure 5-13 shows the ^{31}P-NMR spectra after reaction.

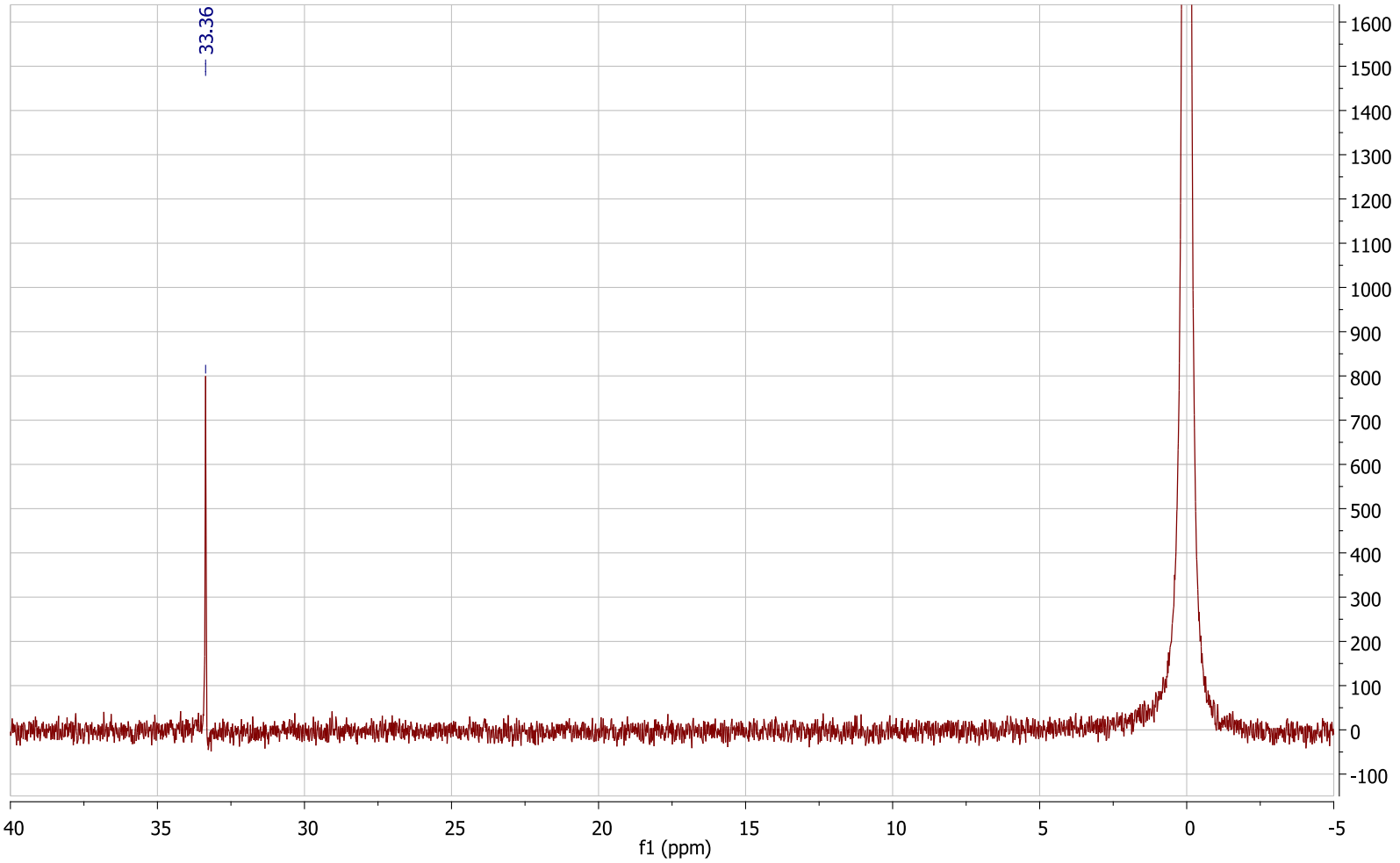


Figure 5-13: ^{31}P-NMR of Organic Phase Following Suzuki Coupling Reaction

It is obvious that a significant amount of phosphine present in the reaction has been oxidized, exhibiting a large peak at 33.36 ppm (relative to 85% H_3PO_4 standard at 0.00 ppm). This oxidation is likely caused by the high-pH environment of the reaction (pH = 13).

Following ^{31}P-NMR analysis, the salt-rich aqueous phase was decanted away from the organic phase. At this stage, <1 ppm of palladium is present in the salt-rich aqueous phase, even in the presence of TPPMS, suggesting that the aqueous decant step can be performed with minimal loss of catalyst while also removing most of the inorganic salts from the solvent system. Following decantation, a solution of TPPMS in degassed water (3% TPPMS relative to initial catalyst loading) was added to the organic phase in order to replace oxidized ligand. Afterwards, the mixture was transferred to a windowed Parr benchtop reactor and pressurized to 400 psig under CO_2.

Following pressurization under CO_2 (400 psig), the aqueous phase was recovered from the product-rich organic phase and collected under N_2. The recovered aqueous phase was subsequently used to conduct a recycle reaction. This was done by combining the recovered aqueous phase with a mixture of fresh 5-methyl-2-bromopyridine, phenylboronic acid, and potassium phosphate in MeCN. The recycle reaction was monitored by GC. The separation and recycle procedure was then repeated again in order to investigate the sustainability of the recycle process. Palladium content was tracked throughout the procedure using atomic absorption spectroscopy (AAS). Figure 5-14 shows the results of the recycle reaction experiments.

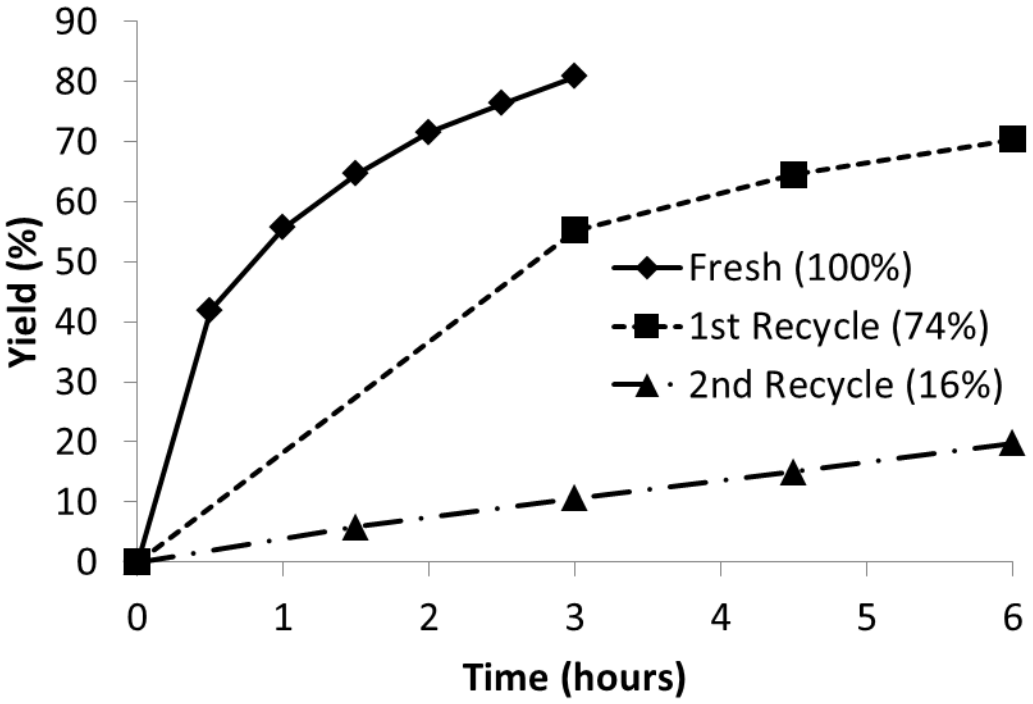


Figure 5-14: Suzuki Coupling Recycle Reaction Profiles. "Fresh" refers to a reaction that has been run wthout recycled catalyst. "1st Recycle" refers to a reaction utilizing catalyst that has been recycled from a "fresh" reaction. "2nd Recycle" refers to a reaction utilizing catalyst that has been recycled from a "1st Recycle" reaction.

From Figure 5-14 it is evident that recycled catalyst retains activity. The first separation/recycle yielded 74% palladium recovery (relative to the initial loading of palladium). The decreased palladium loading in the second reaction fully explains the discrepancy in yield between the fresh reaction and first recycle reaction (81% yield for a fresh reaction at 3 hours compared to the 55% yield achieved by the first recycle reaction in the same time).

The separation and recycle of the previously-recycled reaction led to a recovery of 16% of the initial palladium charge, which was transferred to a new recycle reaction. It is worth noting here that the lowered catalyst loading again explaining the discrepancy in yield (81% yield for a fresh reaction at 3 hours compared to 11% yield for the second recycle reaction). TOFs for each run are consistent, giving values of 27 h^{-1}, 25 h^{-1}, and 23 h^{-1} for the fresh reaction, first recycle reaction, and second recycle reaction, respectively. This indicates that the largest factor governing reaction rate is the amount of catalyst recycled (specifically, 74% recovered in the first separation and 16% recovered in the second separation). The discrepancy in palladium recovery from the first and second separation/recycle processes is possibly due to the build-up of reagents that were not accounted for in the recycle process (e.g. excess phenylboronic acid). Such build-up represents a challenge to be addressed in any recycling strategy.

After preliminary catalyst recycling trials were conducted, a number of experiments were designed to probe the effect of the excess ligand that was added following reaction in order to replace the TPPMS oxidized during reaction. The experiments were conducted by measuring the rate of formation of product in a recycle reaction in which various amounts of ligand had been added following initial reaction and salt-rich aqueous phase decant (0 eq., 1.5 eq., and 3 eq., relative to initial catalyst loading). Figure 5-15 shows the kinetic profiles of these recycle reactions.

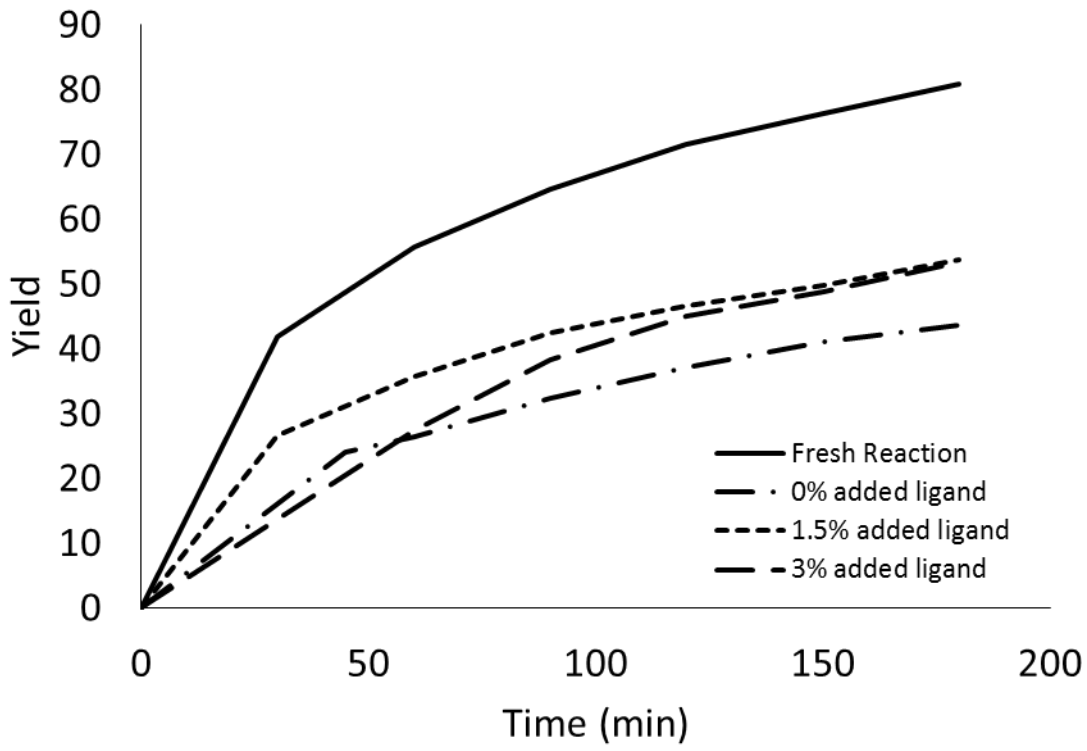


Figure 5-15: Recycle Reaction Profiles of Suzuki Coupling Reactions Using Make-Up Ligand. Percentage indicated refers to the loading of TPPMS added post-reaction, relative to the substrate, 5-methyl-2-bromopyridine.

No major trends can be seen in palladium recovery as a function of make-up TPPMS loading, with 45%, 62%, and 64% of palladium recovered (relative to 100% initial charge in fresh reaction) when using 0, 1.5, and 3 catalyst equivalents (0%, 1.5%, and 3% with respect to 5-methyl-2-bromopyridine loading) of make-up TPPMS, respectively. The greatest trend seems to be the dependence between catalyst recovery and recycle reaction rate. With 0% added ligand (45% catalyst recovery), a yield of 44% was reached at 180 minutes. With 1.5% and 3% added ligand (62% and 64% catalyst recovery, respectively), a yield of 53% was reached in the same amount of time. By examining the TOF of each of these recycle reactions (33 h^{-1}, 28 h^{-1}, and 28 h^{-1} for 0%,

1.5%, and 3% added make-up ligand) it becomes obvious that no appreciable difference can be observed in catalyst activity, indicating that the most important factor in determining recycle reaction rate is the amount of catalyst recovered. The fact that more palladium is recovered with the use of make-up TPPMS suggests that make-up ligand can be used to increase recycle reaction rates by increasing the amount of palladium recovered. This makes intuitive sense with the understanding that the increase in free TPPMS concentration should increase coordination of the water-soluble phosphine to the metal center. Additionally, these results suggest that the deleterious effects of TPPMS oxidation on palladium separation can be overcome with the use of make-up ligand added after reaction.

In addition to post-reaction ligand addition experiments, studies were conducted in which the organic phase from a fresh reaction mixture was extracted multiple times using OATS in order to examine the ability of a Suzuki coupling reaction to be extracted using a multi-stage OATS process. In principle, catalyst partitioning is an equilibrium-limited process. If a species exhibits solubility in both phases of a separation step, the total amount of material separated may be enhanced by the use of multiple extraction steps, or "stages". These studies were performed by conducting a standard 5-methyl-2-bromopyridine Suzuki coupling reaction, decanting the aqueous phase as discussed previously, addition of a solution of TPPMS (3%) in degassed water, and pressurization/separation under 400 psig of CO_2. After separation of the catalyst-rich aqueous phase, the Parr reactor was depressurized and charged with an additional 20 mL of degassed H_2O and re-pressurized to 400 psig, at which time a second separation was conducted. Both aqueous phases were then used to conduct individual recycle reactions

following the same protocol discussed earlier. Figure 5-16 shows the results of these experiments.

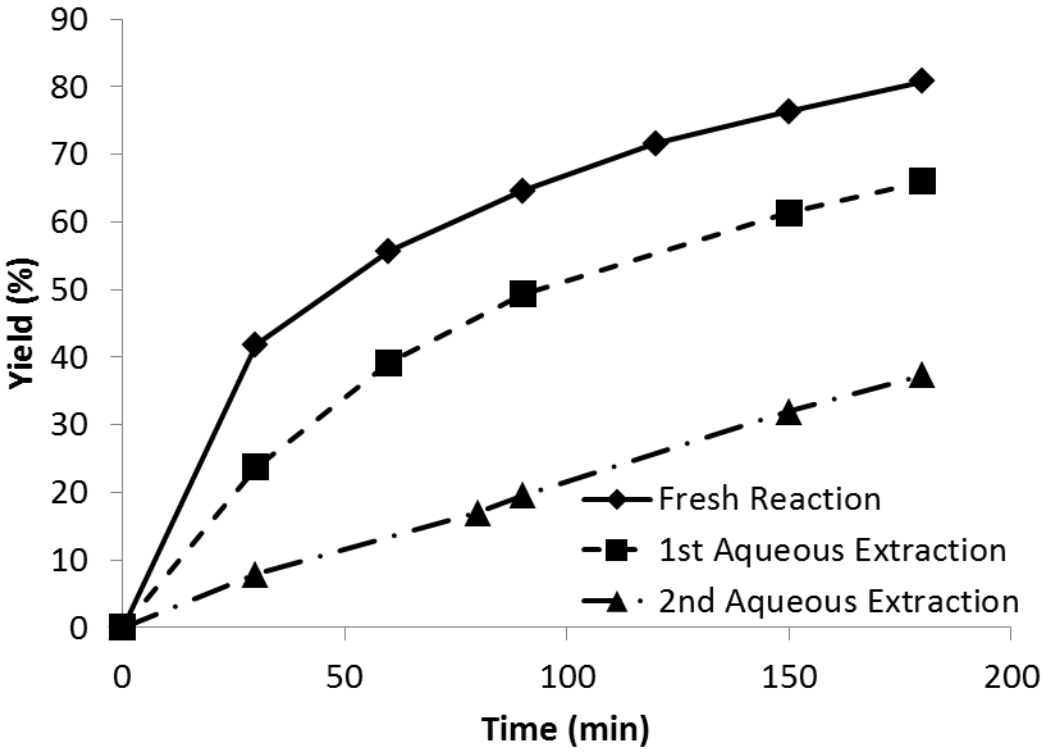


Figure 5-16: Reaction Profile of Staged Suzuki Coupling Recycle Reactions. "1st Aqueous Extraction" refers to recycle reactions using catalyst recovered from OATS separation of a fresh reaction. "2nd Aqueous Extraction" refers to recycle reactions in which catalyst was recovered from an organic phase that previously been separated with OATS.

The data from fresh reaction kinetics and 1st aqueous extraction recycle kinetics (70% catalyst recovered relative to initial charge of Pd) indicate similarly active catalysts in these reactions, with a TOF of 82 h^{-1} for the fresh reaction and a TOF of 81 h^{-1} for the 1st extraction recycle reaction. Furthermore, the first extraction exhibits relatively high

amounts of recovered catalyst (70%). However, the 2nd aqueous extraction recycle reaction exhibits remarkable differences, in that a great deal less catalyst was recovered (5% relative to initial catalyst loading). Furthermore, the 2nd extraction seems to yield a catalyst species of significantly improved activity, giving a TOF in excess of 200 h^{-1}. These differences are likely caused by variation in solvent composition caused by the extraction procedure (e.g. removal of residual phosphate ions from initial reaction, depletion of acetonitrile dissolved in aqueous phase under CO_2 pressure, etc.). These changes in solvent compositions could have an effect on important reaction parameters, such as starting pH and ionic strength, which in turn could change the solubility and activity of the palladium catalysts.

5.4 Conclusions

In conclusion, it has been shown that Pd-TPPMS catalysts show promise as hydrophilic species capable of Suzuki chemistry and subsequent catalyst separation and reuse. The Suzuki coupling reaction of 5-methyl-2-bromopyridine with phenylboronic acid has been explored as a model reaction for a recyclable Pd-TPPMS reaction system. The reaction itself exhibits predictable dependence on ligand loading, with lower loading leading to faster initial rates and higher loadings leading to longer-lived catalyst. Additionally, it has been shown that temperature plays an important role in increasing reaction rate, with reaction at 70 ^{o}C achieving 81% yield within 3 hours, compared to a yield of 31% achieved in 3 hours when reacted at 50 ^{o}C.

The separation and recycle of Pd-TPPMS catalysts have also been investigated and discussed. It was shown that catalyst recycled under 400 psig of CO_2 exhibit similar activity compared to fresh catalysts (average TOF of = 25 h^{-1}). It has been observed that

phosphine oxidation occurs readily under the reaction conditions, suggesting the necessity of added, or "make-up" ligand following reaction. It has been shown that the use of make-up ligand greatly affects the recovery of palladium via CO_2 separation, yielding a recovery of 64% of the initial charge of palladium when 3 extra equivalents of TPPMS is employed, compared to the recovery of 45% of initial palladium seen when no make-up ligand is added. Finally, it has been shown that a multi-stage approach to separation of palladium from organic product may be of some use, allowing the recovery of an additional 5% of initial palladium exhibiting an increased reactivity (TOF > 200 h^{-1}).

In addition to the results discussed above, significant light has been shed on the challenges inherent to the design of a recycling process. Examples of such challenges discussed here are the necessity of "make-up" ligand, the composition of phases upon separation, and the build-up of chemical species over time. Each of these challenges requires deliberate effort and design, and are the current focus of the ongoing research for which the work presented here has built a foundation.

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CHAPTER 6 - CONCLUSIONS AND RECOMMENDATIONS

6.1 Continuous-Flow Meerwein-Ponndorf-Verley (MPV) Reduction of Alcohols

6.1.1 Conclusions

In Chapter 2, the successful continuous flow MPV reductions of 6 model compounds were demonstrated. Three of the model compounds (benzaldehyde, actophenone, and cyclohexanone) were reduced using the Corning® Advanced-Flow reactor, which demonstrated the inherent advantages of continuous flow reactions over batch reactions. Some of the advantages displayed were the ability of the reactor to conduct reactions to high yields in relatively short residence times. Furthermore, the high degree of temperature control and mixing efficiency present in the Corning® Advanced-Flow reactor allowed yield equal to or greater than those seen under batch conditions.

In addition to the three model compounds discussed above, three chloromethylketones (CMKs) (1,4'-dichloroacetophenone, N-Boc-1-chloro-3-amino-4-phenylbutan-2-one, and N-Boc-4-(4'-benzyloxyphenyl)-1-chloro-3-aminobutan-2-one) were continuously reduced using a custom-built tubular reactor. It was shown that the custom reactor was able to overcome the challenge of solid formation inherent to the reduction of these CMKs, allowing for high yields comparable to those seen in batch conditions. The custom-built tubular reactor also was shown to be an effective tool in optimizing reaction conditions by exploring the yield of dichloroacetophenone as a function of substrate loading.

Finally, another step of the synthesis of HIV-protease inhibitor has been demonstrated in a continuous-flow framework. With the completion of this work, a majority of the continuous-flow synthesis of N-Boc-1-chloro-3-amino-4-phenylbutan-2-one from simple building blocks such as phenylalanine has been successfully documented as a precedent for process development (Figure 6-1).

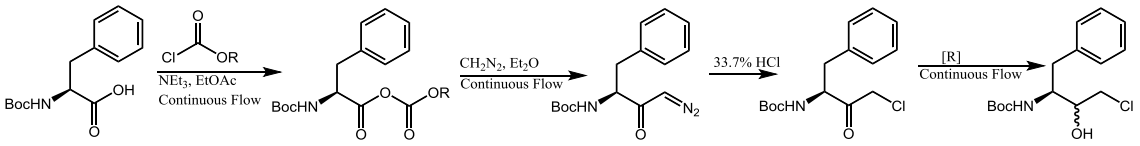


Figure 6-1: Synthesis of Chloromethylalcohol Intermediate from Boc-protected Phenylalanine

6.1.2 Recommendations

As shown in Figure 6-1 above, the only step of the continuous-flow chloromethylalcohol synthesis that has not been explored is the chlorination of the diazomethylketone, shown in Figure 6-2.

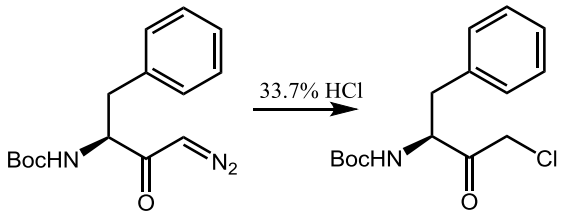


Figure 6-2: Chlorination of Diazomethylester Intermediate

The conversion of this reaction to continuous-flow conditions offers a few opportunities for innovative development, primarily due to the challenge of conducting an acidic reaction that produces N_2 gas. As discussed in Chapter 3, the production of N_2 gas has a deleterious effect on continuous-flow reactions conducted in tubular reactors, increasing the total fluid flow rate within the reactor and diminishing the effective residence time of the reagents. In addition, the generation of gas is a source of concern regarding the possible build-up of pressure. The possibility of high-pressure generation necessitates a design for high-pressure safety, including pressure relief valves and strong materials capable of withstanding elevated pressures. The custom-built tubular reactors discussed in Chapters 2 and 3 are composed of such materials (316 stainless steel). However, 316 stainless steel is incompatible with high concentrations of HCl[1], thereby rendering the custom-built tubular reactors useless in this application. Polymers such as (poly)tetrafluoroethylene (PTFE) are resistant to HCl, but possess heat transfer characteristics that are drastically different from 316 stainless steel. Alternatively, the nickel-based alloy Hastelloy C-276 possesses an excellent resistance to corrosion from HCl and thermal conductivities far superior to PTFE. However, Hastelloy is more expensive than stainless steel, so an economic analysis should be performed in tandem with material compatibility tests.

In addition to the challenges offered by the chlorination reaction itself, significant attention must be given to downstream processing of the HCl waste. Neutralization or removal is necessary due to the acid-base reactivity between HCl and Al(OtBu)3. This process must be done with the use of minimal water, as it also degrades the aluminum

catalyst downstream. The addition of an organic base may prove useful in the elimination of harmful HCl without the generation of large amounts of inorganic waste.

It seems clear that further research is needed for material selection and reactor design before the synthesis of the HIV-protease inhibitor intermediates discussed in Chapter 2 can be completely generated in flow. Attention must be given to acid neutralization/removal processes and their effect on downstream chemistry. In addition to possible deleterious chemistry, the generation of N_2 gas must be considered during the design process.

6.2 Continuous Tandem Cyclopropanation/Cyclization Reactions

6.2.1 Conclusions

In Chapter 3, the successful transfer of hydropyridoindole production technology from batch-wise to continuous-flow methodology has been demonstrated. By developing a continuous-flow, tandem cyclopropanation/ring-opening cyclization process, an important foundation has been established for understanding the production of hydropyridoindoles from simple building blocks such as indoles under continuous-flow conditions. Breadth of scope was demonstrated for the cyclization reaction in continuous flow, allowing for the high conversion of four distinct cyclopropanes to their respective hydropyridoindoles at relatively gentle conditions ($T \leq 50\ ^{o}C$) in short residence times (15 minutes). Furthermore, the transfer of the cyclopropanation reaction to a continuous-flow framework was demonstrated successfully, despite the generation of N_2 gas and its deleterious effects on the residence time of the flow reactions.

The construction of a tubular reactor for the tandem continuous-flow cyclopropanation/cyclization reaction allowed for high yields of hydropyridoindole in the case of highly reactive cyclopropanes (4-methoxystyrene-derived cyclopropane), but only modest yields in the case of deactivated cyclopropanes (alpha-methylstyrene-derived cyclopropane). The reason for the decreased yields in alpha-methylstyrene reactions was proposed to be the generation and presence of N_2 gas throughout the tandem reaction process. Despite the challenges presented by the generation of N_2 gas, the final two steps of the synthesis of hydropyridoindole compounds from simple indole precursors (Figure 6-3) has been demonstrated in a continuous-flow framework with the completion of the work described in Chapter 3.

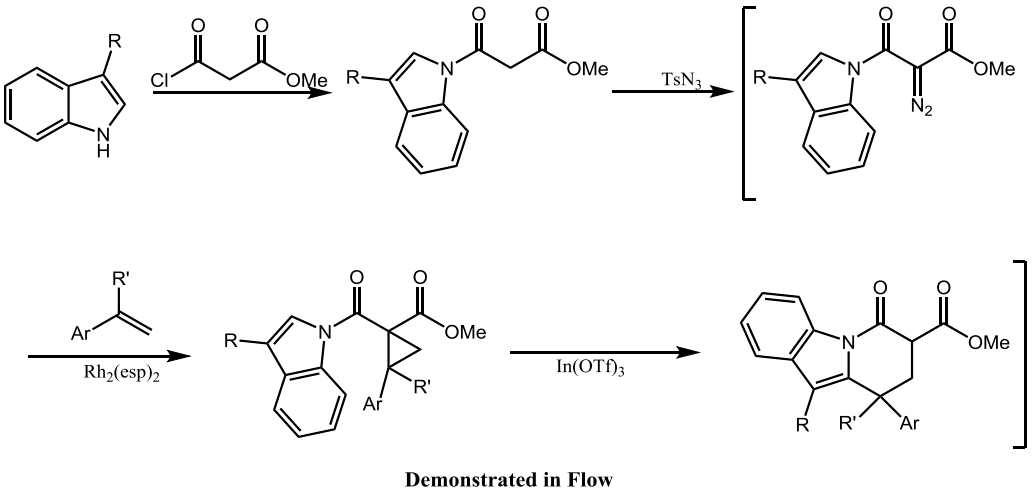


Figure 6-3: Complete Synthetic Pathway for Production of Hydropyridoindoles from Indole Precursors

6.2.2 Recommendations

While significant progress has been made in understanding the continuous-flow production of hydropyridoindoles from simple precursors, no effort has been made as of yet to recover the catalysts used in these processes. The greatest incentive for catalyst recovery in this process is the cost of rhodium, which has historically often peaked at prices higher than that of gold[2]. Given the high cost of rhodium relative to the indium used in the tandem reaction process, research should be focused on recovery and reuse of rhodium while simply pursuing removal of indium catalyst from the product-rich effluent stream.

Given the historic success of OATS (discussed in Chapters 4 and 5) to recover and recycle rhodium catalysts in hydroformylation reactions, it seems reasonable that a similar approach could be implemented in the production of hydropyridioindoles. However, a direct use of OATS would present many difficulties upon implementation, primarily due to the introduction of water in the system. The indium catalyst used in the ring-opening cyclization is very sensitive to the presence of water, which immediately hydrolyzes the triflate groups away from the metal center. Application of OATS as discussed in Chapters 4 and 5 ($MeCN/H_2O$ systems under CO_2 pressure) would introduce significant amount of water (~10 mol% or greater) upon separation, effectively shutting down the downstream indium chemistry. A possible alternative separation strategy is a modified, version of OATS, called POTS (PEG-Organic Tunable Solvents)[3], where water has been replaced with polyethylene glycol. More research is required to understand the stability of $In(OTf)_3$ in PEG solutions, but the field holds promise. Once a separation strategy has been selected that does not interfere with downstream chemistry,

cyclopropanation reaction optimization will be needed in order to understand the rhodium chemistry in the presence of the ligands necessary for separation.

6.3 Palladium Recovery Using Sulfur-Based Additives and Organic-Aqueous Tunable Solvents (OATS)

6.3.1 Conclusions

In Chapter 4, OATS was shown to be an efficient method for the removal of palladium catalysts from post-Suzuki reaction mixtures when combined with the use of sulfur-containing additives. Cysteine was shown to be particularly effective at removing palladium from an organic phase upon the application of CO_2 pressure. It was shown that the loading of cysteine plays an integral role in the removal of palladium. Furthermore, the tunable nature of these OATS-additive systems was explored as a function of CO_2 pressure. Additionally, recovery of palladium from the OATS process was demonstrated with activated carbon in order to avoid the generation of a large stream of aqueous, palladium-rich waste. These findings constitute a flexible process that can be directly applied to existing industrial Suzuki coupling systems. The prospect of catalyst recovery promises to be appealing for industrial application based on the economic advantage of catalyst recycling/regeneration. Furthermore, the OATS-sulfur additives separation process meets the requirements of a "green process" in that it prevents harmful contamination (removal of palladium) and encourages recycle of solvent (minimize material consumption).

In addition to these findings, the substrate scope of the OATS-sulfur additives process has been examined by looking at alternative halopyridines (4-amino-2-

bromopyridine). It was shown that product solubility plays a significant role in determining the separability of palladium in post-Suzuki mixtures. A mechanism has been proposed to explain the hydrophilicity of aminopyridine products compared to that of methylpyridine products, invoking the formation of carbonic acid from dissolved CO_2 as a protonating agent for the pyridines in question. This suggests that pH could be used in addition to CO_2 pressure as a tunable parameter for the partitioning of palladium in the presence of basic, N-containing heterocyclic products.

6.3.2 Recommendations

While the OATS-sulfur additive separation is an innovative solution to the problem of homogeneous palladium catalyst recovery, there is no strategy in place at this point for point-of-use catalyst regeneration and recycling. Suzuki coupling reactions carried out in the presence of cysteine afford negligible yield, indicating that cysteine complexes with and effectively "poisons" the palladium catalyst. While this behavior is useful toward the generation of a hydrophilic catalyst species, it greatly shortens the lifetime of the catalyst compared to a process that incorporates catalyst recycling.

It is of interest, then, to consider the design of a process that can regenerate active Pd catalyst from a solution of Pd-cysteine complex. One possible solution may be the oxidation of cysteine to cystine, shown in Figure 6-4.

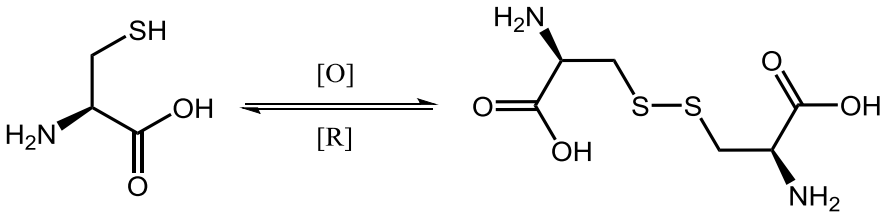


Figure 6-4: Oxidation of Cysteine to Cystine

Some success has been seen in literature using hydrogen peroxide to oxidize cysteine to cystine[4]. Additionally, other oxidants exist that may be leveraged for their affinity towards carboxylic acid groups (such as that of cysteine), such as calcium hypochlorite. Additional research is needed to fully understand the stability of Pd-additive complexes discussed in Chapter 4 before design of a catalyst regeneration process can be effectively designed.

6.4 Hydrophilic Catalyst Recycle Using Organic-Aqueous Tunable Solvents (OATS)

6.4.1 Conclusions

In Chapter 5, Pd-TPPMS complexes were shown to be effective Suzuki catalysts for recovery and recycle using OATS technology. The effect of ligand loading on reaction rate was explored, revealing a balance between catalyst stabilization and suffocation with ligand. In addition, reactions with the catalyst complex were briefly optimized as a function of temperature, revealing catalyst stability at elevated temperatures (70 ^{o}C).

Furthermore, separation and recycle of the Pd-TPPMS species has been investigated under OATS conditions. It was shown that catalyst recycled using OATS

technology following a reaction exhibited comparable reactivity to that of a fresh reaction. Additionally, due to the formation of TPPMS-oxide during reaction, it was shown that post-reaction addition of "make-up" ligand can be useful in increasing the amount of palladium catalyst recovered during the separation step. Finally, it was shown that an OATS separation can be performed in multiple stages, enhancing the overall recovery of active catalyst from a post-Suzuki reaction mixture.

The recyclable catalytic process designed in Chapter 5 offers several benefits toward industrial application, including the possibility of reduced catalyst cost and lowered consumption of raw materials. However, the oxidation of TPPMS presents a significant challenge, requiring the addition of "make-up" ligand in order to achieve palladium recoveries greater than 50%. Additional investigation is required for the Pd-TPPMS system. This work is the focus of on-going research in the Liotta group laboratory.

6.4.2 Recommendations

The loss of TPPMS to TPPMS-oxide represents a significant challenge to the sustainability of the catalyst recycling process. Ligands as expensive as TPPMS are cost-prohibitive, and must be integrated as a recyclable species in order to avoid unnecessary waste and loss of profit. It is speculated that the oxidation of TPPMS occurs in the high-pH environment of the Suzuki reaction via reaction of hydroxide anion with the palladium-bound phosphine[5], shown in Figure 6-5.

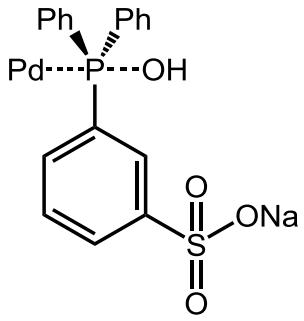
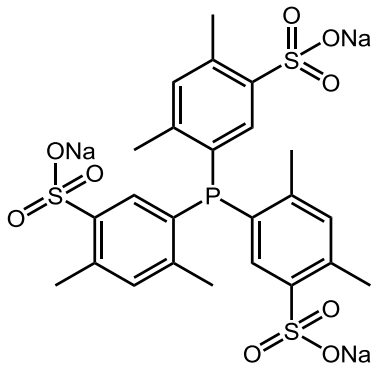


Figure 6-5: Transition State of Phosphine Oxidation Process in the Presence of Base

The problems of oxidation may be solved by selection of alternative ligands for recycling with Pd. Literature results report success using other water-soluble phosphines in Suzuki coupling reaction mixtures[6]. Of particular interest is the ligand trixylylphosphine-trisulfonate (TXPTS), shown in Figure 6-6.



Trixylylphosphine-trisulfonate
TXPTS

Figure 6-6: Structure of TXPTS

This ligand may be employed as a water-soluble phosphine to produce a recyclable catalyst species in Suzuki coupling reactions. Additionally, the presence of methyl groups on the aromatic rings adds some electron density to the pi-networks, possibly stabilizing the phosphine against oxidation via hydroxide addition.

A number of challenges need to be addressed when investigating new ligands for recyclable Suzuki coupling processes using OATS. First, ligand loading optimization must be done in order to maximize catalyst activity. As discussed in Chapter 5, a loading too high may shut down chemistry, while a loading too low may not offer enough stability against catalyst degradation. In addition to reaction optimization, the solubility of the catalyst-ligand complex must be well documented at each step of the process. Preliminary data suggest that Pd-TXPTS catalysts, in the presence of non-coordinating substrates, partition favorably into the salt-rich aqueous phase during reaction, thereby rendering the separation process as proposed in Chapter 5 useless for palladium recycling. This demonstrates that further research is required to understand the effects of system parameters such as salt loading, pH, CO_2 pressure, and substrate selection on catalyst partitioning when new ligands are investigated.

6.5 References

1. Chemical Resistance Chart
http://www.usplastic.com/catalog/files/charts/LG%20CC.pdf

2. Data courtesy of Xignite. InfoMine., Ed.

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