HOMOGENEOUSLY-CATALYZED COUPLING REACTIONS IN SWITCHABLE SOLVENTS

by

Dev Raj Bhandari

A thesis submitted to the Department of Chemistry

in conformity with the requirements for

the degree of Master of Science

Queen's University

Kingston, Ontario, Canada

July, 2019

Copyright ©Dev Raj Bhandari, 2019

Abstract

Due to the increasing environmental impact of society, it is imperative that current industrial processes be modified and new industrial processes be implemented in order to reduce environmental harm. However, these new or modified processes must be more energy-efficient, materials-efficient, and cost-effective so that they are more economically beneficial than the other processes. The described research was inspired by these two ideas and is comprised of two projects, both focused on the creation of recyclable, CO_2-switchable methods of separating organic products, inorganic byproduct and catalyst.

For the first part of the project, Suzuki-Miyaura cross-couplings were tested in switchable water, concentrating on the activation of aryl chlorides and product separation techniques. Switchable water, which is an aqueous solution of an amine, was used as solvent with the amine functioning as the base for the palladium-catalyzed Suzuki-Miyaura cross-coupling of activated aryl chlorides with phenyl boronic acid, using TPPTS (a water-soluble phosphine ligand). The use of Schlenk techniques resulted in conversion of 99% and isolated yields of 87% with the absence of homocoupling.

For the second part of the project, the development of an easily prepared CO_2-switchable polymeric ligand is described. The polymeric ligand was used in the Suzuki-Miyaura cross-coupling reaction for the synthesis of a biaryl product using 4-iodobenzaldehyde and phenylboronic acid pinacol ester in water. With the help of this switchable polymeric ligand, organic product, inorganic byproduct, and catalyst were separated into three fractions. A catalyst recycling system was developed for the Suzuki-Miyaura cross-coupling reaction. The catalyst was able to be recovered and reused, albeit with lower activity.

Acknowledgements

I would like to express my sincere gratitude to my supervisor, Professor Dr. Philip Jessop, for his unrelenting inspiration, cohesive guidance and encouragement, which made my years of graduate study enjoyable and helped me complete my graduate degree.

I am also equally grateful to Prof. Dr. Michael Baird and Prof. Dr. David Zechel for serving on my supervisory committee. I would also like to thank internal examiner Prof. Dr. Donal Macartney and Prof. Dr. David Zechel for being in my examining committee.

I am thankful to all the Jessop group members. Their constructive suggestions, encouragement and support helped me to further my research with greater ease. I would also like to extend my sincere thanks to Dr. Ross Jansen-van Vuuren, Dr. Md Abu Affan, Dr. Ram Lamsal and Mr. Bidur Ghimire. I am also appreciative to all the technicians and staff in the Department of Chemistry for their support.

I'd like to thank my friends and family whom have been constantly supportive of me. I would especially like to thank my Mom and late Dad who implant me with a love of science and learning at a very young age.

Finally, I would like to thank my beautiful and inspiring wife, adorable daughters Simran and Abbu. You have been my biggest supporters and I will never be able to thank you enough for the sacrifices that you've made so that I could pursue my dreams.

I sincerely appreciate the Department of Chemistry and the financial support from the School of Graduate Studies and the Natural Science and Engineering Research Council (NSERC) of Canada.

Table of Contents

Abstract…….. ……ii
Acknowledgements..... iii
List of Figures..... vii
List of Tables viii
List of Schemes……..…….ix
List of Abbreviations xii
Chapter 1 Introduction…….1
1.1 Green chemistry……..……...1
1.1.1 The Idea And Principles……...……...1
1.1.2 Metrics…….…….....3
1.1.3 Green Solvents……...…….4
1.1.4 The Importance of Green Solvents……...……..5
1.2 Carbon Dioxide…….……..……...7
1.2.1 Reactivity of Carbon Dioxide……...……..8
1.3 Catalysis……..…….10
1.3.1 General Concept of Catalysis……..……..10
1.3.2 Homogeneously-catalyzed reactions……..……..13
1.3.3 Heterogeneously-catalyzed reactions…….……...14
1.3.4 Phase Switchable Catalyst……..…….....15
1.4 CO_2-switchable solvents……..16
1.4.1 Switchable Water (SW)…….……...…...17
1.4.2 Switchable Hydrophilicity Solvents (SHS)…….….20
1.4.3 Switchable-Polarity Solvents (SPS)……..…22

1.5 Research Objectives……..……..……23

1.6 References……..……...25

Chapter 2 Suzuki-Miyaura Cross-Coupling Reaction in Switchable Water……..……31

2.1 Introduction……..……31

2.1.1 Application of Switchable Water to Suzuki Reactions…….....35

2.2 Experimental Methods and Materials…..……...…….38

2.2.1 Materials…...……38

2.2.2 General Procedures……...……39

2.2.3 Reaction Procedure - Normal…….……..…...……..39

2.2.4 Reaction Procedure - Schlenk Technique…….……..……..39

2.2.5 Filtration and Recycling of the Aqueous Phase…….……..……41

2.3 Results and Discussions……..……...……..41

2.3.1 Experiments of Suzuki-Miyaura cross-coupling reaction in water……...……41

2.4 Conclusions…….…….……48

2.5 References…….…….……..49

Chapter 3 Synthesis of Phase Switchable Ligand and Its Application……..……....53

3.1 Introduction……..……54

3.2 Experimental Procedures……...……...55

3.2.1 Attempted Preparation of 4, 4′, 4″- Phosphinetriyltribenzoic Acid…..…….……...55

3.2.2 Synthesis of Tris[(p-carboxyl)phenyl]phosphine Oxide……..…..……57

3.2.2.1 Synthesis of Tris[(p-methoxycarbonyl)phenyl]phosphine Oxide……..58

3.2.2.2 Synthesis of Tris[(p-methoxycarbonyl)phenyl]phosphine……....58

3.2.2.3 Synthesis of Tris[4-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl-

phenyl)]phosphine……...……..….60

3.2.3 Synthesis of Tris[(p-chlorocarbonyl)phenyl]phosphine Oxide…….....61

3.2.3.1 Synthesis of Tris[(p-N,N-dimethylethylenediaminecarboxamido)phenyl] phosphine Oxide…….....….....62

3.2.4 Synthesis of Phase Switchable Polymer Ligand From 4-DPPS and DEAEMA…..62

3.3 Results and Discussions……...…64

3.3.1 Non-polymeric Phase Switchable Ligands……..…….64

3.3.2 Attempted synthesis of tris[(p-N,N-dimethylethylenediaminecarboxamido)phenyl] phosphine……...…….……..….65

3.3.3 Phase Switchable Polymeric Ligand.....66

3.3.4 Suzuki-Miyaura Cross-Coupling Reaction……...……68

3.4 Conclusion……..…….71

3.5 References……..……...73

Chapter 4 Conclusions and Future Work……..…….74

4.1 Conclusions……..……74

4.2 Future works……..……..76

Appendix……78

Appendix A (Supporting Information of Chapter 3)……...……78

List of Figures

Figure 1.1. The impact of the manufacture of solvents from biomass divided by the impact of manufacture from fossil fuels. A value greater than 1 indicates that manufacture from biomass is more harmful than manufacture from fossil fuels. CPME, cyclopentyl methyl ether; NMP, N-methylpyrrolidone……7

Figure 1.2. Conceptual model of switchable ionic strength water. The reversible change of the ionogen between a neutral state and a salt raises and lowers the ionic strength of the aqueous solution via the introduction or removal of CO_2…….....18

Figure 1.3. The use of switchable ionic strength water to control the solubility of an organic solute. The change of the ionogen into a salt raises the ionic strength of the water and forces out the organic solute as either a liquid (shown) or a solid (not shown)…….19

Figure 1.4. A conceptual scheme of a switchable hydrophilicity solvent (SHS)……..21

Figure 1.5. Switchable-polarity solvents…….....……22

Figure 2.1. The switchable miscibility of SW with THF…….....36

Figure 3.1. (a) A solution after the completion of Suzuki-Miyaura cross-coupling reaction using phase switchable polymer ligand; (b) a biphasic mixture after the addition of water into the Suzuki-Miyaura cross-coupling reaction mixture; and (c) the biphasic mixture after the addition of CO_2……69

Figure 3.2. (a) Aqueous solution of protonated SHS, catalyst and undesired inorganic by-product before passing argon gas through the mixture, (b) biphasic solution (upper layer deprotonated SHS and catalyst where as lower layer aqueous) after passing argon gas……70

List of Tables

Table 1.1. Binary solvent systems for biphasic catalytic transformations……....12

Table 2.1. Results of Suzuki-Miyaura cross-coupling reaction using different bases in normal conditions……...46

Table 2.2. Results of Suzuki-Miyaura coupling reaction with Schlenk technique……...47

Table 3.1. Conversions of 4-iodobenzaldehyde to biaryl product using phase-switchable polymer ligand followed by separation in a biphasic water/2-(dibutylamino) ethanol mixture. The switch between monophasic and biphasic was achieved using the CO_2-triggered phase separation of switchable water…….71

List of Schemes

Scheme 1.1. Chemical reaction showing addition of C1 using CO_2……...9

Scheme 1.2. Formation of carbamate salt using amine and CO_2……9

Scheme 1.3. Formation and dissociation of carbonic acid using CO_2……...10

Scheme 1.4. Hydroformylation of alkenes (R = C_6H_{13}, or CH_2OH) using a catalyst that can be switched and therefore change from preferentially partitioning in the organic phase (under CO_2) to partitioning in an aqueous phase (under N_2 or Ar)…….....…..16

Scheme 1.5. Examples of switchable-polarity solvents (a) amidine and alcohol mixtures (b) secondary amines (c) a diamine and (d) amidine and amine mixtures…….....….23

Scheme 2.1. General Suzuki-Miyaura cross-coupling reaction of aryl halides and aryl boronic acids……...32

Scheme 2.2. Korupensamine and Hippadine……...33

Scheme 2.3. Mechanism of the Suzuki-Miyaura cross-coupling reaction……34

Scheme 2.4. General Suzuki-Miyaura cross-couplings of aryl halides and aryl boronic acids. In the described experiments, X = Cl, Z = H, ligand = TPPTS, catalyst = $Pd(OAc)_2$ and heat = reflux……..……43

Scheme 2.5. Formation of biphenyl from phenyl boronic acid homo coupling……....43

Scheme 2.6. Suzuki-Miyaura cross-couplings reaction of 4-chlorobenzaldehyde and phenyl boronic acid……44

Scheme 2.7. Suzuki-Miyaura cross-couplings reaction of 4-chlorobenzaldehyde and phenyl boronic acid in water with palladium acetate, TPPTS and either 2-dimethylaminoethanol or K_2CO_3 as base……...…….45

Scheme 3.1. Conceptual scheme of a monophasic reaction followed by a biphasic separation using CO_2 in a liquid mixture of switchable hydrophilicity solvents, switchable catalyst and ligand. ……54

Scheme 3.2. Synthesis of tris(4-cyanophenyl)phosphine (compound **1**)……...…..56

Scheme 3.3. Attempted synthesis of 4,4′,4″-phosphinetriyltribenzoic acid…….56

Scheme 3.4. Synthesis of tris[(p-carboxy)phenyl]phosphine oxide……..57

Scheme 3.5. Synthesis of tris[(p-methoxycarbonyl)phenyl]phosphine oxide……...58

Scheme 3.6. Synthesis of tris[(p-methoxycarbonyl)phenyl]phosphine…….59

Scheme 3.7. Synthesis of tris[4-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl-phenyl)] phosphine..60

Scheme 3.8. Synthesis of tris[(p-chlorocarbonyl)phenyl]phosphine oxide…….……..61

Scheme 3.9. Synthesis of tris[(p-N,N-dimethylethylenediaminecarboxamido)phenyl] phosphine oxide……...62

Scheme 3.10. Synthesis of phase-switchable polymer ligand……...…63

Scheme 3.11. Planned synthesis of tris[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl-phenyl)] phosphine……..64

Scheme 3.12. Alternative synthesis of tris[4-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl-phenyl)] phosphine……..65

Scheme 3.13. Alternative synthesis of tris[(p-N,N-dimethylethylenediaminecarbo xamido) phenyl]phosphine…….65

Scheme 3.14. Poly-substituted tris[(*p-N,N*-dimethylethylenediaminecarboxamido)phenyl] phosphine oxide……..…….. 66

Scheme 3.15. Synthesis of switchable polymeric ligand……..……68

Scheme 3.16. Suzuki-Miyaura cross-coupling reaction of 4-iodobenzaldehyde and phenylboronic acid pinacol ester in water with palladium acetate in the presence of the phase switchable polymer ligand and 2-(dibutylamino)ethanol……..68

List of Abbreviations

AIBN	2,2′-azobis(2-methylpropionitrile)
CPME	cyclopentyl methyl ether
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCM	dichloromethane
DEAEMA	2-(diethylamino)ethyl methacrylate
2-DMAE	2-dimethylaminoethanol
DMSO	dimethylsulphoxide
4-DPPS	4-(diphenylphosphino)styrene
LCA	life cycle assessment
NMP	N-methylpyrrolidone
PBA	phenyl boronic acid
PEG	polyethylene glycols
RBF	round bottom flask
$scCO_2$	supercritical carbon dioxide
SHS	switchable hydrophilicity solvent
SPS	switchable-polarity solvent
SW	switchable water
THF	tetrahydrofuran
TLC	thin layer chromatography
TPPTS	trisodium salt of triphenylphosphine trisulfonate

Chapter 1

Introduction

1.1 Green Chemistry

1.1.1 The Idea And Principles

Green Chemistry is the branch of chemistry concerned with the design, development, and execution of chemical products and processes with the main focus being the reduction of negative environmental and health impacts,[1] for example by minimizing the creation of compounds which can significantly contribute to global warming, smog formation, ozone layer depletion, and bioaccumulation (among other impacts).[2] In the 1990s, the '12 Principles of Green Chemistry' were developed by Warner and Anastas to provide a preliminary guide for chemists and engineers when designing or redesigning a particular process.[3]

1. **Prevention**

   It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom Economy**:

   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Syntheses**:

   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the

environment.

4. Designing Safer Chemicals:

Chemical products should be designed to affect their desired function while minimizing their toxicity.

5. Safer Solvents and Auxiliaries:

The use of auxiliary substances (eg. solvents, separation agents, etc.) should be made unnecessary whenever possible and innocuous when used.

6. Designs for Energy Efficiency:

Energy requirements of chemical processes should be recognized for their environmental and economical impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks:

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce Derivatives:

Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalysis:

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation:

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time Analysis for Pollution Prevention:

Analytical methodologies need to be further developed to allow for the real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention:

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

The above principles, quoted directly from the work of Anastas and Warner, are a useful guide to the design or redesign of chemical processes or products to make them greener. However they are neither steadfast rules nor metrics for measuring environmental impact.

1.1.2 Metrics

To perform comparisons of the "green-ness" of two or more options (chemicals, products or processes), a number of metrics have been developed. The most popular metrics used to assign the "greenness" of a chemical reaction are atom economy and Environmental factor (or E-factor, for short). Atom economy, as developed by Trost,[4] reflects the percentage of atoms from reagents that appear in the left side of a balanced chemical reaction equation that are included into the desired product (Eqn. 1.1). Thus, a

high atom economy indicates an efficient chemical reaction.

$$\% \text{ Atom Economy} = \frac{\text{Molecular Weight of Desired Product}}{\text{Molecular Weight of All Reactants}} \times 100 \qquad (1.1)$$

The environmental factor or "E-Factor", developed by Sheldon,[5] is the ratio of the mass of the total waste generated by a reaction per unit mass of product produced (Eqn. 1.2). A low E-Factor therefore indicates minimal side reactions and minimal use of auxiliary materials like solvents, drying agents, etc.

$$\text{E Factor} = \frac{\text{Mass of Waste Generated}}{\text{Mass of Product Produced}} \qquad (1.2)$$

E-factor is an improvement upon atom economy as it better represents the total chemical process rather than a single chemical reaction. A reaction that is 100% atom-economical might, for example, produce a large amount of solvent waste, and therefore be less green than a reaction with a lower atom economy that does not use much solvent. Compared with the atom economy approach, the E-factor will reflect this difference in waste generation. Both metrics, however, fail to account for the fact that some wastes are more harmful than others. Life cycle assessment, which is far more complicated and is beyond the scope of this thesis, does take that into account.

1.1.3 Green Solvents

Green solvents are defined as solvents that combine minimal environmental impact during manufacture with a low risk to the health, environment and safety during

and after use, and this is usually expressed per kg of solvent. A certain solvent may be green for one application and may not be for another one; for example, water is a green solvent within consumer products such as paint because the solvent can completely dissipate to the environment during use, without causing harm; however, water is not a green solvent for the polymerization of tetrafluoroethylene because water is not able to dissolve that monomer and therefore requires the addition of a harmful surfactant (supercritical CO_2, $scCO_2$, is a green solvent for that polymerization as it dissolves the monomer well).[6] Therefore it is inaccurate to claim that any particular solvent is a "green solvent" or "not a green solvent" without specifying the application.

1.1.4 The Importance of Green Solvents

In most industrial processes or methods involving product formulation, the mass of solvent used is typically greater than the mass of the other compounds. Solvents are not usually the most harmful components per gram but large amounts of solvent used can have the greatest environmental impact. In industrial processes, the most commonly used solvents have low boiling points, which means that they are usually flammable and easily form smog; exceptions to this include water as well as halogenated solvents. However, even these solvents pose other risks to health and to the environment. In general, solvents can be: *carcinogenic* (benzene and chlorinated solvents), *neurotoxic* (hexane), *nephrotoxic* (toluene, ethylene glycol), *mutagenic* (benzene and trichloroethylene), *acid rain-forming* (CS_2), *environmentally persistent* (perfluorinated solvents), or prone to forming explosive peroxides (ethers and secondary alcohols).[7]

Solvents are also commonly used as reaction media or for separations or product

isolation. Organic solvents are mostly used in chemical manufacturing of products such as paints, personal care products, inks, and cleaning liquids. The choice of organic solvent used differs depending on the application.

The two general methods for reducing the solvent-related environmental impact depend on volume reduction or impact reduction strategies. Volume reduction strategies include: (a) performing solvent-less syntheses, (b) using switchable solvents, (c) using higher concentrations of solute, and (d) selecting a solvent that is effective at higher concentrations of solute or lower solvent volumes. Impact reduction strategies mainly consist of selecting a solvent such that it reduces the environmental impacts of the process because the solvent is less environmentally damaging and more effective for the process than other solvents.

Most organic solvents are prepared from either petroleum or natural gas. Solvents prepared from biomass or CO_2 are more potentially sustainable but are not necessarily less harmful to the environment (Figure 1.1). Solvents that can be prepared from renewable feedstocks include ethanol, methanol, ethyl acetate,[8] and water may appear to be a very green solvent.

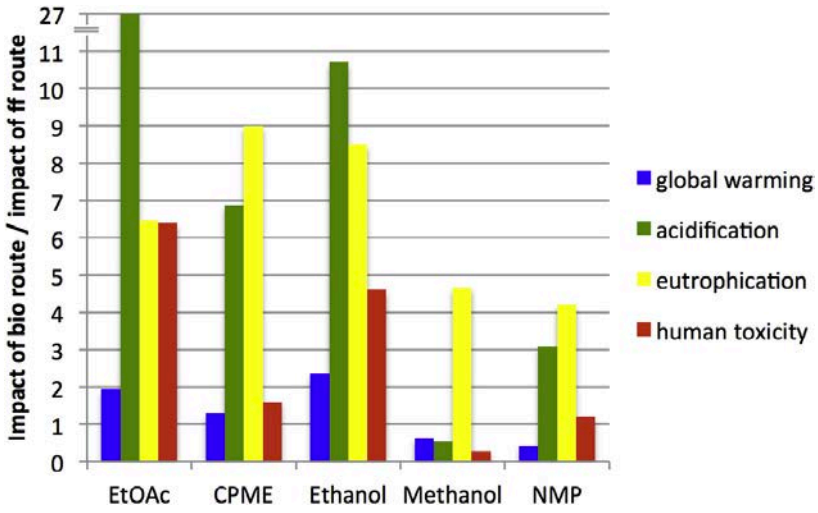


Figure 1.1. The impact of the manufacture of solvents from biomass divided by the impact of manufacture from fossil fuels. A value greater than 1 indicates that manufacture from biomass is more harmful than manufacture from fossil fuels. CPME, cyclopentyl methyl ether; NMP, N-methylpyrrolidone.[7]

However, in reality, this is sometimes not the case because in some chemical processes, water is a poor solvent or is difficult to remove post-reaction. It is true that water has many advantages in terms of environmental and health impacts compared with most organic solvents. However, the use and end-of-life disadvantages of water include high reactivity, poor solubilizing power for hydrophobic solutes, high energy required for separating solute from solvent, and high energetic cost for post-use purification.

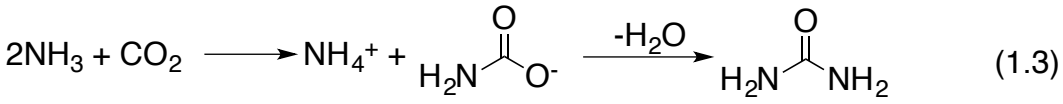
1.2 Carbon Dioxide

Carbon dioxide is a colorless gas, denser on its own than air. CO_2 was identified in the 16th century. CO_2 is produced as a by-product of charcoal production, fuel

combustion, and fermentation.[9] CO_2 is also produced by many other commercial processes for example, as a by-product of hydrogen production by steam-methane reforming, synthetic ammonia production, and limestone calcination. CO_2 is vital to the healthy operation of the environment. The earth is surround by CO_2 gas, which serves as a reagent in photosynthesis. However it is considered a greenhouse gas and is thought to be contributing to increasing global temperatures. The majority of research is currently devoted to methods of capture, isolation, and/or fixation of CO_2 into value-added products. CO_2 is also an important additive in process chemistry. CO_2 has become a popular medium for chemical reactions and extractions due to its low cost.

1.2.1 Reactivity of Carbon Dioxide

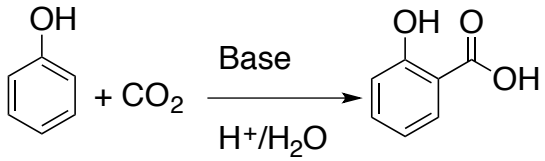
Generally, CO_2 is unreactive at room temperature and pressure in the absence of a catalyst or strong nucleophile. Industrial synthetic procedures which typically use CO_2 include the production of urea, where one mole of CO_2 reacts with two moles of ammonia, producing ammonium carbamate.[9] When the ammonium carbamate undergoes dehydration, urea is produced (Eqn. 1.3)



(1.3)

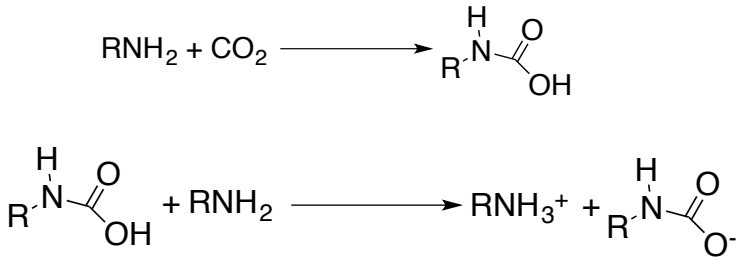
Similarly CO_2 is used in carboxylation reactions as a C1 source, which can later be transformed to a less-oxidized functional group. For example, phenol can undergo

carboxylation followed by an aqueous work-up to give 2-hydroxybenzoic acid via the Kolbe-Schmitt reaction (Scheme 1.1).[10]



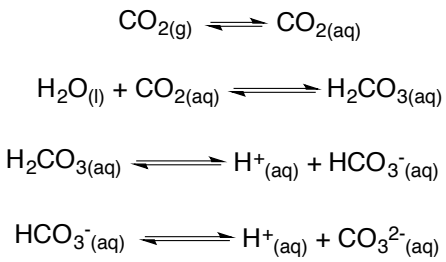
Scheme 1.1. Chemical reaction showing addition of C1 using CO_2

Similarly, CO_2 can react with primary and secondary amines to form carbamic acids, which can then react further with a second equivalent of an amine to produce a carbamate salt (Scheme 1.2)[11]



Scheme 1.2. Formation of carbamate salt using amine and CO_2

The dissolution of CO_2 in water affords a series of acid/base equilibria. When CO_2 is dissolved in water, a weak carbonic acid, H_2CO_3, is generated. This acid can further dissociate into bicarbonate and carbonate ions (Scheme 1.3). The dissociation of this compound acts to acidify water, which is a growing concern in large bodies of water due to the increasing atmospheric CO_2 concentration



Scheme 1.3. Formation and dissociation of carbonic acid using CO_2

The dissociation of carbonic acid results in the acidification of water, which is a growing concern due to the increasing atmospheric CO_2 concentration.[12] In the lab, this acid can be neutralized by common alkaline compounds such as amines, generating bicarbonate and carbonate salts in the process.

1.3 Catalysis

1.3.1 General Concept of Catalysis

Catalytic processes are key to industrial synthesis. The production of basic and fine chemicals via homogeneously-catalyzed reactions is a relatively well established field. For example, palladium-catalyzed coupling reactions have provided versatile synthesis approaches in organic chemistry over the last three decades due to the easy carbon-carbon bond formation that they facilitate.

Coupling reactions are very useful for reducing several stage steps of synthesis. However, challenges lie in the catalysis of the reactions. For example, the main challenges in homogeneous catalysis are the separation of the product, catalyst and byproduct from each other and rest of the reaction mixture. If a noble metal catalyst or an

expensive ligand is used, catalyst and ligand recycling is essential. Research is this area has attracted much interest but most published methods have focused on separation into two streams (catalyst versus product) rather than three streams (catalyst, product, and byproduct).

With environmental concerns driving the need for recyclability, new solvents are being sought which are non-toxic, non-volatile and can be reused, thus preventing waste rather than necessitating waste treatment. Therefore, our research groups focuses on the development of switchable hydrophilicity solvent (SHSs), ionic liquids, and supercritical fluids as support systems for homogeneous catalysts.[13] There are different approaches to catalyst recycling. However, recycling of catalysts used in coupling reactions has not been explored because of the inorganic byproduct, creating an extra level of difficulty to the separation process. The overarching objective of this work is therefore to separate the product, catalyst and ligand from the final reaction mixture, such that the catalyst and ligand could be reused. The novelty lies in the separation of the byproducts from the catalyst - this has not been previously reported.

Biphasic reaction systems consisting of a low-polarity organic solvent and water are promising systems for post-reaction removal of the catalyst and ligand, particularly for water-soluble catalysts.[14] In such a biphasic reaction medium, the water-soluble catalyst dissolves in the aqueous phase, whereas the reactant and product dissolve in the nonpolar solvent. The two-phase system allows for separation of the aqueous phase (containing the catalyst, ligand and any inorganic byproduct) and the organic phase (contains the organic product). The two solvents used for biphasic catalysis do not necessarily need to be a combination of water and an organic solvent. The choices for the

two immiscible solvents are listed in Table 1.1

Table 1.1 Binary solvent systems for biphasic catalytic transformations.[15]

Catalyst-bearing solvent[a]	Product-bearing solvent[a]	Catalyst modification	Reference[b]
Fluorous[c]	Organic	Fluorous[a]	15
Ionic liquid	Organic	None[d]	16
Liquid polymer	Organic	None[d]	17
Ionic liquid	H_2O	None	18
H_2O	H_2O	Water soluble	19
H_2O	$scCO_2$	Water soluble	20
Ionic liquid	$scCO_2$	None[d]	21
Liquid polymer	$scCO_2$	None[d]	22

[a]Note that inverted systems are possible, in which the two solvents switch roles.

[b]Not intended to be a comprehensive list of papers.

[c]Having high fluorine content, such as perfluorinated alkanes or amines.

[d]Although no catalyst modification is strictly necessary, leaching of the catalyst, if it occurs, could be reduced by using modified catalysts.

1.3.2 Homogeneously-catalyzed reactions

Approximately 20% of all industrial catalytic processes[23] are homogeneously-catalyzed; most of these are used for the production of fine chemicals and pharmaceuticals. The homogeneous catalysts are dissolved in liquid solvents (reaction media), in which the substrates and the product also dissolve. Such catalysts are often transition metal complexes, although the most common homogeneous catalysts are Bronsted acids like sulfuric acid, which do not contain transition metals. Homogeneously-catalyzed reactions performed in research typically employ one of dimethylformamide, toluene, acetonitrile, tetrahydrofuran or dioxane as the solvent,[23] whereas the most common solvent in the industrial sector is water. Each of these solvents allows for optimal solubility of the substrates as well as the catalyst. It follows therefore that high conversions can be obtained over short reaction times under mild conditions with higher selectivity. However, the above-mentioned solvents are either toxic or they are not easy to remove from the product due to their high boiling points. Using these solvents typically results in atmospheric emissions and pollution of ground waters. Another drawback of using homogeneous catalysis is the difficulty associated with the retrieval and reuse of the catalyst since all components of the reaction mixture dissolve in the reaction solvent. Therefore, complicated and energy-intensive processes such as distillation are necessary for removal of solvent from the various components of the reaction system. However, the harsh nature of these recovery steps typically results in the decomposition and deactivation of the catalyst. Furthermore, the reactions are not quantitative. With the development of water-soluble ligands for use in aqueous-based, biphasic, homogeneous metal-catalyzed reactions,[24] interest has grown in the use of more

environmentally friendly chemical processes. This includes the development of processes that use less toxic solvents and reagents while promoting waste prevention over waste treament.[25] The use of alternative "green" solvents, which allow for separation of the catalyst and ligand and their subsequent recycling are also garnering more interest.[26] The use of water as a solvent offers some key benefits, as it is non-toxic, nonflammable, and inexpensive. Thus, if a reaction is carried out in a biphasic reaction mixture - with the catalyst in the aqueous phase and the product in the organic phase, easy product separation and catalyst recycling is possible. Homogeneous catalysis offers several advantages: mild reaction conditions, high selectivity, and the fact that it is relatively well understood. These aspects can be combined with the advantages of heterogeneous catalysis (namely easy catalyst recycling) through the use of biphasic reaction conditions.

Cross coupling reactions are performed with either heterogeneous or homogeneous catalysts. Each of these offers unique advantages as well as limitations. The mechanism of homogeneously-catalyzed cross couplings likely follow the same steps as heterogeneous cross couplings; however, the mechanism of the heterogeneously-catalyzed reaction is not well understood.

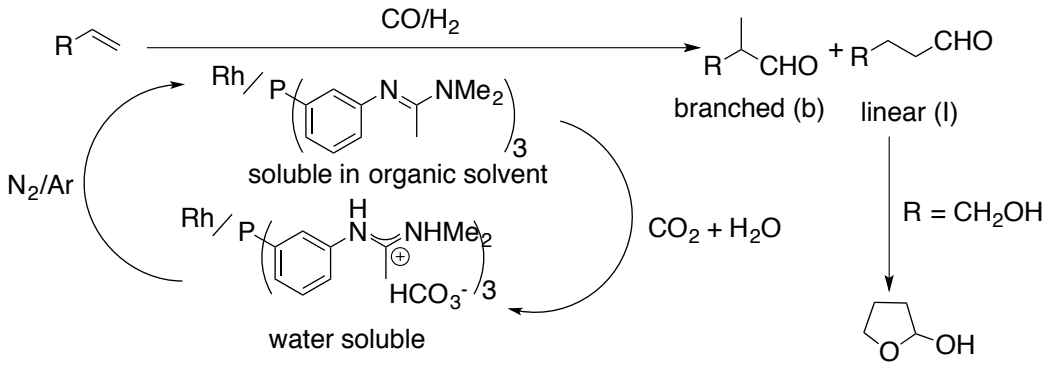
1.3.3 Heterogeneously-catalyzed reactions

Although a similar catalytic activity can be observed with heterogeneous catalysis compared to homogeneous catalysis, heterogeneous catalysts have significant drawbacks, especially, mass transfer limitations, and a lower selectivity especially for asymmetric synthesis. However, a key advantage of using a heterogeneous system is the facile post-reaction separation of catalyst from product and the ability to recycle the catalyst.

1.3.4 Phase Switchable Catalyst

To separate, recover and recycle homogeneous catalysts and ligands would be of great benefit industrially. One approach to achieving this involves performing catalysis in an aqueous/organic biphasic mixture.[24] Despite the fact that these aqueous/organic biphasic catalytic systems have the advantage of easy separation of the catalyst from the product, they generally experience slow reaction rates. This is because the catalyst and the reactants may be in different phases; in fact, when the reactant is highly hydrophobic, its concentration in the aqueous phase may be very low. There are two ways to solve this problem. 1. Merge the two liquid phases during the reaction by, for example, raising the temperature until the two liquids are miscible and then lowering the temperature after the reaction to make the system biphasic again,[6] or 2. Reversibly switch the hydrophilicity of the catalyst by protonation/deprotonation of the ligands, which allows a reaction to be run in an organic liquid phase, and the catalyst is later drawn into an aqueous phase, away from the products, using a pH change by introducing CO_2 in the aqueous phase.[27]

Desset et al.[28] solved the product-catalyst separation problem by carrying out the reaction in a single organic phase and switching the catalyst into a separate aqueous phase by bubbling with, and later removing, CO_2 (see Scheme 1.4).



Scheme 1.4. Hydroformylation of alkenes (R = C_6H_{13}, or CH_2OH) using a catalyst that can be switched and therefore change from preferentially partitioning in the organic phase (under CO_2) to partitioning in an aqueous phase (under N_2 or Ar).[28]

1.4 CO_2-Switchable Solvents

Water is the most common solvent in chemical industries. The other commonly used solvents in chemical industries are organic solvents, which are flammable and smog forming. Many organic solvents pose other risks to health and the environment including being carcinogenic, mutagenic, neurotoxic, and acid rain forming. Water is non-flammable, non-toxic and environmentally friendly. However the use of water as a solvent still causes environmental harm because the separation of water from solute by distillation, evaporation, extraction, or membrane filtration consumes energy and materials. The most common method is extraction of the product from the water by a volatile organic solvent but this is not a preferable because the volatile organic solvent can damage the environment as well as human health. Another common method used to separate organic solutes from water is salting out by adding electrolytes (kosmotropes) such as common salt (NaCl). When a common salt is added to an aqueous solution then

the ionic strength of the solution is increased, which decreases the solubility of many organic solutes and causes them to precipitate from the mixture. This method is quite feasible on a lab scale but is not reversible and the water can not be reused or discarded afterwards without desalination, which would be prohibitively expensive on an industrial scale.

1.4.1 Switchable Water (SW)

To overcome the above problems, the new concept of "Switchable Water" (SW) was introduced. Switchable water is an aqueous solution which can be reversibly changed between two states with distinct properties, such as between a state having high ionic strength and one having low ionic strength.[29–31] When a switchable ionogen is added into water, it allows reversible switchable changes in ionic strength. A switchable ionogen is a neutral (non-ionic) compound that can be made to switch into an ionic form upon application of a trigger. The switching of such additives can increase the ionic strength of the solution, which makes it easier to separate organic solute from the solution. Switching the solution back to a low ionic strength makes it possible to reuse the aqueous solution. The ionogens used in water are typically amines, diamines, or polyamines.[32,33] When a trigger such as CO_2 is introduced, a switch from low to high ionic ionic strength can be performed reversibly (Fig. 1.2).

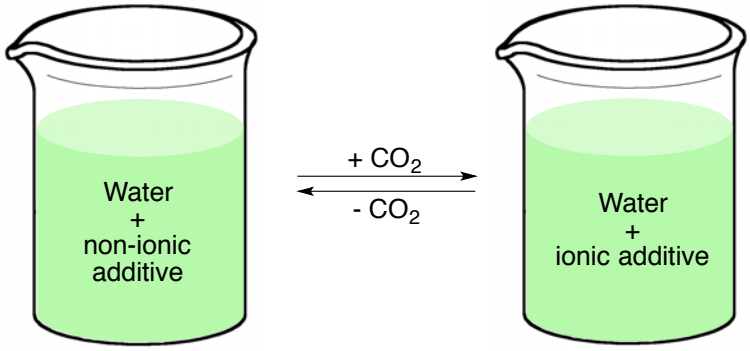


Figure 1.2. Conceptual model of switchable ionic strength water. The reversible change of the ionogen between a neutral state and a salt raises and lowers the ionic strength of the aqueous solution via the introduction or removal of CO_2.

Due to the reversible behavior of the ionogen, the versatility and attractiveness of water is greatly increased as an industrial solvent. After the Jessop[34,35] group invented this switchable solvent for the purposes of extraction, other potential applications of the concept became of interest.[29,36,37] The process of water switching is carried out by following reaction (Eqn. 1.4)

$$B + nH_2O + nCO_2 \rightleftharpoons BH_n^{n+} + nHCO_3^- \qquad (1.4)$$

where B is the amine, BHn^+ is the protonated amine and n is the average number of protons accepted by the amine in carbonated water. Due to presence of ionized BH_n^{n+} and $nHCO_3^-$ products, the ionic strength of water is increased. An aqueous solution of an organic, uncharged nitrogenous base ionogen has a low ionic strength. When CO_2 is removed by heating and/or exposure to a non-acidic gas such as argon, nitrogen or air,

the reaction reverses and the aqueous solution returns to a low ionic strength. Thus to make an aqueous solution of switchable ionic strength, there should be the combination of a nitrogenous base ionogen in water and the use of CO_2 as a trigger. This reversible change in ionic strength could then be used to expel or "salt out" organic liquids or solids from an aqueous solution (Fig. 1.3).

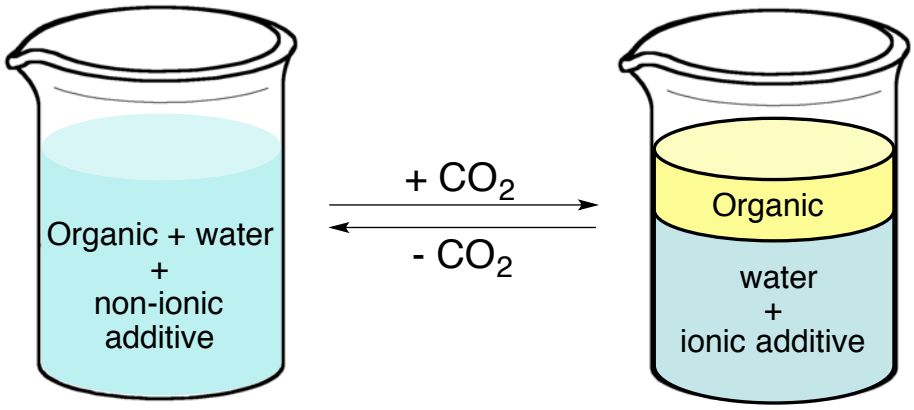


Figure 1.3. The use of switchable ionic strength water to control the solubility of an organic solute. The change of the ionogen into a salt raises the ionic strength of the water and forces out the organic solute as either a liquid (shown) or a solid (not shown).

It is reported that primary and secondary amines are superior to tertiary amines due to their greater CO_2 absorption capacity.[38] However, it is easier to remove CO_2 from aqueous solutions of tertiary amines than primary or secondary amines during recycling.[38] Because the performance requirements for SW ionogens are different from those of a CO_2 capture amine, the amines that are optimum for the one application are not necessarily optimum for the other. The requirements for a SW ionogen, are a) soluble, b) easy reversal, c) high ionic strength in the ionic form, and d) sufficient basicity to get

largely complete protonation in carbonated water. Literature studies of the related field of CO_2 capture also showed that alkanolamines are suitable additives for reversible reaction with CO_2 in water, due to their high water solubility, small molecular size, reactivity and basicity.

1.4.2 Switchable Hydrophilicity Solvents (SHS)

In industrial processes, organic solvents are generally removed from product by distillation. However, this method has many economic and environmental disadvantages. To remove the solvent by distillation, a volatile solvent is required. Volatile solvents contribute to smog formation, flammability, and inhalation and safety risks to workers. Additionally, distillation requires a large amount of energy, which is costly. To overcome these problems the concept of "switchable hydrophilicity solvents" (SHS) was introduced.[35] Such solvents can be removed from products without distillation. SHS can be reversibly switched from hydrophobic to hydrophilic making it possible to remove the solvent from organic product without distillation. A switchable hydrophilicity solvent is a solvent that is poorly miscible with water in one form and completely miscible with water in another form and can be switched between these two forms by a simple change in the system.[35] In literature it is reported that some liquid amidines and tertiary amines are good SHSs[35,14] and can be switched between their two forms when CO_2 is added or removed from the system. When CO_2 is added into the system then CO_2 reacts with water and produced carbonic acid (H_2CO_3), which reacts with SHSs and produces the corresponding hydrophilic bicarbonate (HCO_3^-) salt of SHSs (Eqn. 1.5, where B is the hydrophobic form of the SHS and $[BH^+][HCO_3^-]$ is the hydrophilic form). Due to this

behavior it is possible to use carbonated water to remove solvent from the desired organic product.

$$B_{(aq)} + H_2O_{(l)} + CO_{2(g)} \rightleftharpoons BH^+_{(aq)} + HCO_3^-{}_{(aq)} \qquad (1.5)$$

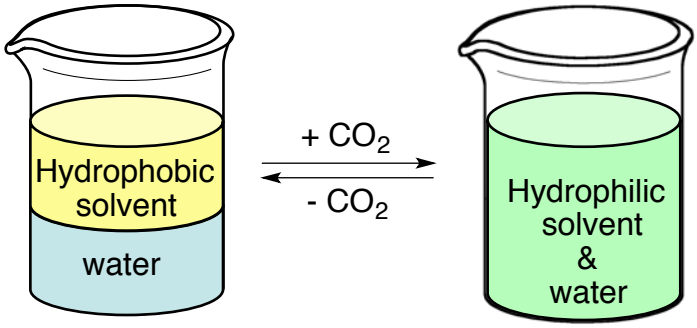


Figure 1.4. A conceptual scheme of a switchable hydrophilicity solvent (SHS).[14]

When CO_2 is removed from the solution by passing a non-acidic gas such as Ar or N_2 through the liquid, the nitrogenous base returns to its original hydrophobic form (reverse of equation 1.5).

$$BH^+_{(aq)} + HCO_3^-{}_{(aq)} \rightleftharpoons B_{(aq)} + H_2O_{(l)} + CO_{2(g)} \qquad (1.6)$$

The hydrophobic form of SHS is useful for extracting hydrophobic organic

substrates. Later, without distillation or filtration, the solvent can be washed out of organic product by carbonated water. When CO_2 is subsequently removed, the solvent separates from the water and can be re-used.

1.4.3 Switchable-Polarity Solvents (SPS)

Solvents which can be reversibly switched from one form to another form are called switchable solvents. The Jessop group invented the original concept of switchable polarity solvents triggered by CO_2.[35,39] These organic solvents reversibly switch between a low-polarity form and a high polarity form (Fig. 1.5) upon the addition of CO_2. When CO_2 is passed into the solution then the SPS becomes a high-polarity ionic liquid and when CO_2 is removed upon sparging with a non-acidic gas like Ar or N_2 then the SPS transforms into a lower polarity non-ionic solvent.

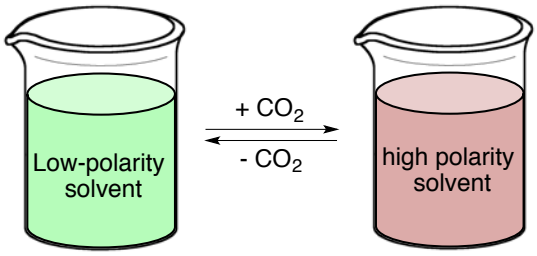
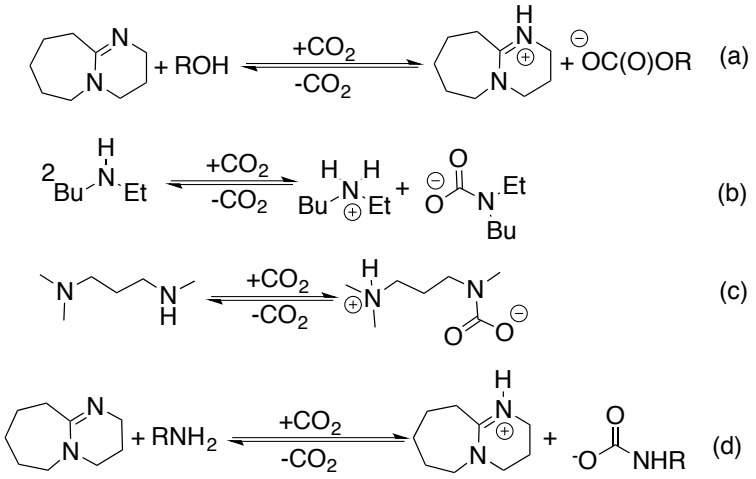


Figure 1.5. Switchable-polarity solvents.[35]

When CO_2 reacts with a mixture of an alcohol and an amidine or a guanidine base, then an ionic liquid with alkylcarbonate anions (Scheme 1.5a)[35] is formed. The alkylcarbonate-based SPS were the first switchable solvents. The first single-component SPS were secondary amines (Scheme 1.5b).[11] This cheaper SPS system requires only a

single organic compound without the costly amidine and guanidine bases. Other examples of switchable- polarity solvents are shown in Schemes 1.5c[39] and 1.5d.[40]



Scheme 1.5. Examples of switchable-polarity solvents (a) amidine and alcohol mixtures (b) secondary amines (c) a diamine and (d) amidine and amine mixtures.

Switchable-polarity solvents are very important for organic reactions because they facilitate post-reaction separations of catalyst from product including copolymerization of epoxide and CO_2,[11] activation of microcrystalline cellulose towards hydrolysis,[41] transesterification of soybean oil and other triacylglycerides,[14,42–44] and in biomass conversion by acylation of cellulose.[45]

1.5 Research Objectives

The main focus of this thesis is two fold. The first major objective of this thesis, as discussed in chapter 2, was the formation of C-C bonds between aromatic compounds

using aryl chloride and aryl boronic acid in a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction in which SW was used as the solvent with an amine functioning as the base. The second main objective of this work, as describe in chapter 3, was to develop a switchable ligand for a homogeneous catalyst, so that the catalyst, the organic product(s) resulting from the homogeneously catalyzed reaction can easily be separated from each other and from byproducts.

1.6 References

(1) Li, G. C.; Anastas, P.; Dunn, P. J. Green Chemistry Themed Issue The Importance of Green Chemistry in Process Research and Development W. *Chem. Soc. Rev* **2012**, *41*, 1452–1461.

(2) Kralisch, D.; Ott, D.; Gericke, D. Rules and Benefits of Life Cycle Assessment in Green Chemical Process and Synthesis Design. *Green Chem.* **2015**, *17*, 123–145.

(3) Anastas, Paul T, J. C. W. Green Chemistry: Theory and Practice; Oxford University Press: Oxford [England], New York, **1998**.

(4) Trost, B. M. Atom Economy A Search for Synthetic Efficiency. *Science.* **1991**, *254*, 1471–1477.

(5) Sheldon, R. A. Cutting-Edge Research for a Greener Sustainable Future The E Factor : Fifteen Years on. *Green Chem.* **2007**, *9*, 1273–1283.

(6) Capello, C.; Fischer, U.; Hungerbu, K. What Is a Green Solvent ? A Comprehensive Framework for the Environmental Assessment of Solvents. *Green Chem.* **2007**, *9*, 927–934.

(7) Jessop, P. G. "Green/Alternative Solvents", in Encyclopedia of Sustainable Technologies, M. Abraham, Ed., Chemical Reviews: American Chemical Society, USA, **2017**.

(8) Khoo, H. H.; Ee, W. L.; Isoni, V. Bio-Chemicals from Lignocellulose Feedstock: Sustainability, LCA and the Green Conundrum. *Green Chem.* **2016**, *18*, 1912–1922.

(9) Pierantozzi, R. Carbon Dioxide. *Kirk-Othmer Encycl. Chem. Technol.* **2003**, *4* (1),

803–822.

(10) Jeskey, Harold, A. S. L. The Kolbe-Schmitt Reaction Introduction. *Chem. Rev.* **1957**, *57*, 583–620.

(11) Phan, L.; Andreatta, J. R.; Horvey, L. K.; Edie, C. F.; Luco, A. L.; Mirchandani, A.; Darensbourg, D. J.; Jessop, P. G. Switchable-Polarity Solvents Prepared with a Single Liquid Component. *J. Org. Chem.* **2008**, *73* (1), 127–132.

(12) Loerting, T.; Bernard, J. Aqueous Carbonic Acid (H_2CO_3). *ChemPhysChem* **2010**, *11*, 2305–2309.

(13) Lemke, W. M.; Kaner, R. B.; Diaconescu, P. L. A Mechanistic Study of Cross-Coupling Reactions Catalyzed by Palladium Nanoparticles Supported on Polyaniline Nano Fibers. *Inorg. Chem. Front.* **2015**, *2*, 35–41.

(14) Jessop, P. G.; Phan, L.; Carrier, A.; Robinson, S.; Christoph, J. D.; Harjani, J. R. A Solvent Having Switchable Hydrophilicity. *Green Chem.* **2010**, *12*, 809–814.

(15) Cornils, B. Fluorous Biphase Systems-The New Phase-Separation. *Angew. Chem. Int. Ed.* **1997**, *36*, 2057–2059.

(16) Chauvin Y, Mussmann L, O. H. A Novel Class of Versatile Solvents for Two-Phase Catalysis: Hydrogenation, Isomerization, and Hydroformylation of Alkenes Catalyzed by Rhodium Complexes in Liquid 1,3-Dialkylimidazoliurn Salts. *Angew. Chem. Int. Ed.* **1995**, *107*, 2915–2917.

(17) Rosa, R. G.; Martinelli, L.; Silva, H. M.; Loh, W. Easy and Efficient Processes for Catalyst Recycling and Product Recovery in Organic Biphase Systems Tested in the Hydrogenation of Hex-1-Ene. *Chem. Commun.* **2000**, 33–34.

(18) Peng, J.; Shi, F.; Gu, Y.; Deng, Y. Highly Selective and Green Aqueous – Ionic

Liquid Biphasic Hydroxylation of Benzene to Phenol with Hydrogen Peroxide. *Green Chem.* **2003**, *5*, 224–226.

(19) Jessop, P. G.; Heldebrant, D. J. Green Biphasic Homogeneous Catalysis. In *Environmental Catalysis*; H.Grassain, V., Ed.; Marcel Dekker, NY, USA, 2005.

(20) Bhanage, B. M.; Ikushima, Y.; Arai, M. Multiphase Catalysis Using Water-Soluble Metal Complexes in Supercritical Carbon Dioxide. *Chem. Commun.* **1999**, 1277–1278.

(21) Brown, R. A.; Pollet, P.; Mckoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. Asymmetric Hydrogenation and Catalyst Recycling Using Ionic Liquid and Supercritical Carbon Dioxide. *J. Am. Chem. Soc.* **2001**, *123*, 1254–1255.

(22) Heldebrant, D. J.; Jessop, P. G. Liquid Poly (Ethylene Glycol) and Supercritical Carbon Dioxide : A Benign Biphasic Solvent System for Use and Recycling of Homogeneous Catalysts. *J. Am. Chem. Soc.* **2003**, *125*, 5600–5601.

(23) Nowothnick, H. Homogeneously Catalysed Suzuki Coupling Reaction in Microemulsion Systems with Recycling of the Catalyst, Technische Universität Berlin, Fakultät II, 2010.

(24) Obrecht, L.; Kamer, P. C. J.; Laan, W. Alternative Approaches for the Aqueous – Organic Biphasic Hydroformylation of Higher Alkenes. *Catal. Sci. Technol.* **2013**, *3*, 541–551.

(25) Devasher, R. B.; Moore, L. R.; Shaughnessy, K. H. Aqueous Phase Palladium-Catalyzed Cross-Coupling of Aryl Bromides under Mild Conditions Using Water Soluble Sterically Demanding Alkylphosphines. *J. Org. Chem.* **2004**, *69*, 7919–7927.

(26) R.A. Sheldon, I Arends, U. hanefl. Green Chemistry and Catalysis. *Appl. Organomet. Chem.* **2007**, *21*, 448–453.

(27) Mokhadinyana, M.; Desset, S. L.; Williams, D. B. G.; Cole-hamilton, D. J. Cooperative Ligand Effects in Phase-Switching Homogeneous Catalysts. *Angew. Chem. Int. Ed.* **2012**, *51*, 1648–1652.

(28) Desset, S. L.; Cole-hamilton, D. J. Carbon Dioxide Induced Phase Switching for Homogeneous-Catalyst Recycling. *Angew. Chem. Int. Ed.* **2009**, *48*, 1472–1474.

(29) Mercer, S. M.; Robert, T.; Dixon, D. V; Jessop, P. G. Recycling of a Homogeneous Catalyst Using Switchable Water. *Catal. Sci. Technol.* **2012**, *2*, 1315–1318.

(30) Chem, G.; Mercer, S. M.; Robert, T.; Dixon, D. V; Chen, C.; Ghoshouni, Z.; Harjani, R.; Jahangiri, S.; Peslherbe, H.; Jessop, P. G. Design, Synthesis, and Solution Behaviour of Small Polyamines as Switchable Water Additives. *Green Chem.* **2012**, *14*, 832–839.

(31) Phan, L.; Andreatta, J. R.; Horvey, L. K.; Edie, C. F.; Mirchandani, A.; Darensbourg, D. J.; Jessop, P. G. Switchable-Polarity Solvents Prepared with a Single Liquid Component. *J. Org. Chem.* **2008**, *73*, 127–132.

(32) Jessop, P. G.; Mercer, S. M.; Heldebrant, D. J. CO2-Triggered Switchable Solvents, Surfactants, and Other Materials. *Energy Environ. Sci.* **2012**, *5*, 7240–7253.

(33) Phan, L.; Chiu, D.; Heldebrant, D. J.; Huttenhower, H.; John, E.; Li, X.; Pollet, P.; Wang, R.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. Switchable Solvents Consisting of Amidine / Alcohol or Guanidine / Alcohol Mixtures. *Ind. Eng.*

Chem. Res. **2008**, *47*, 539–545.

(34) Liu, Y.; Jessop, P. G.; Cunningham, M.; Eckert, C. A.; Liotta, C. L. Switchable Surfactants. *Science*; 2006; Vol. 313, pp 958–960.

(35) Jessop, P. G.; Heldebrant, D. J.; Li, X.; Eckert, C. A.; Liotta, C. L. Reversible Nonpolar-to-Polar Solvent. *Nature* **2005**, *436*, 1102–1102.

(36) Heldebrant, D. J.; Yonker, C. R.; Jessop, P. G.; Phan, L. Reversible Uptake of COS, CS2 , and SO2 : Ionic Liquids with Alkylxanthate, Alkylthiocarbonyl, and Alkylsulfite Anions. *Chem. Eur. J.* **2009**, *15*, 7619–7627.

(37) Holland, A.; Wechsler, D.; Patel, A.; Molloy, B. M.; Boyd, A. R.; Jessop, P. G. Separation of Bitumen from Oil Sands Using a Switchable Hydrophilicity Solvent. *Can. J. Chem.* **2012**, *90*, 805–810.

(38) Dubois, L.; Thomas, D. CO2 Absorption into Aqueous Solutions of Monoethanolamine, Methyldiethanolamine, Piperazine and Their Blends. *Chem. Eng. Technol.* **2009**, *32*, 710–718.

(39) Heldebrant, D. J.; Koech, P. K.; Ang, M. T. C.; Liang, C.; Rainbolt, J. E.; Yonker, C. R.; Jessop, P. G. Reversible Zwitterionic Liquids, the Reaction of Alkanol Guanidines , Alkanol Amidines , and Diamines with CO_2. *Green Chem.* **2010**, *12*, 713–721.

(40) Yamada, T.; Lukac, P. J.; Yu, T.; Weiss, R. G.; V, G. U.; May, R. V; Re, V.; Recei, M.; June, V. Reversible, Room-Temperature, Chiral Ionic Liquids. Amidinium Carbamates Derived from Amidines and Amino-Acid Esters with Carbon Dioxide. *Chem. Mater* **2007**, *19*, 4761–4768.

(41) Zhang, Q.; Oztekin, N. S.; Barrault, J.; Vigier, K. D. O. Activation of

Microcrystalline Cellulose in a CO_2-Based Switchable System. *ChemSusChem* **2013**, *6*, 593–596.

(42) Xue, D.; Mu, Y.; Mao, Y.; Xiu, Z. Kinetics of DBU-Catalyzed Transesterification for Biodiesel in the DBU–ethanol Switchable-Polarity Solvent. *Green Chem.* **2014**, *16*, 3218–3223.

(43) Cao, X.; Xie, H.; Wu, Z.; Shen, H.; Jing, B. Phase-Switching Homogeneous Catalysis for Clean Production of Biodiesel and Glycerol from Soybean and Microbial Lipids. *ChemCatChem* **2012**, *4*, 1272–1278.

(44) Saliu, F.; Orlandi, M. In Situ Alcoholysis of Triacylglycerols by Application of Switchable-Polarity Solvents. A New Derivatization Procedure for the Gas-Chromatographic Analysis of Vegetable Oils. *Anal. Bioanal. Chem.* **2013**, *405*, 8677–8684.

(45) Yang, Y.; Xie, H.; Liu, E. Acylation of Cellulose in Reversible Ionic Liquids. *Green Chem.* **2014**, *16*, 3018–3023.

Chapter 2

Suzuki-Miyaura Cross-Coupling Reaction in Switchable Water

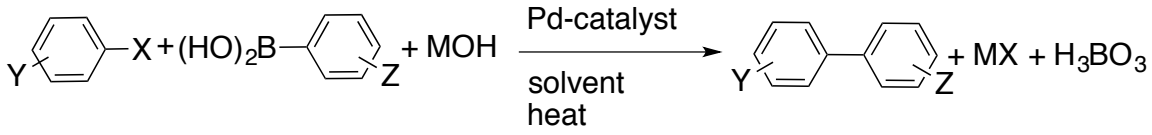
2.1 Introduction

Various coupling reactions can be employed to form new C-C bonds. These include Stille coupling, Heck coupling, Corriu-Kumada coupling, Negishi coupling, Himaya coupling, Liebeskind-Srogl coupling, and Suzuki-Miyaura cross-coupling reactions. The Suzuki-Miyaura cross-coupling reaction has become an important reaction over the past three decades to form carbon-carbon bonds, especially in biaryl compounds.[1] The main advantages of the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction over other coupling reactions are as follows: a) it can be carried out under mild conditions; b) the Suzuki-Miyaura cross-coupling reaction can tolerate several functional groups; c) organoboronic acids and their derivatives are generally stable and inert towards water and related solvents; d) the starting materials and byproducts are not only less toxic than those of similar coupling reactions but also more environmental friendly; and e) the starting materials are inexpensive and relatively easy to prepare.[2–7] This reaction is also versatile in nature and equally applicable in the synthesis of natural products, pharmaceuticals, fine chemicals and polymeric products. Due to the many applications of this reaction, Akira Suzuki along with Richard F. Heck and Ei-Ichi Negishi were jointly awarded the Nobel Prize in chemistry for "palladium-catalyzed

cross couplings" in organic synthesis in 2010.

However, one limitation of Suzuki-Miyaura cross-coupling reactions is the difficulty associated with separating the catalyst from the reaction mixture once the reaction has reached completion.[8] During large-scale homogeneously-catalyzed processes, the catalyst and solvent need to be recovered and re-used in order to make the reactions economically viable, unless the homogeneous catalyst is so active that very low loadings are sufficient. One option is to make the catalyst water-soluble, facilitating its separation from the products, which are typically soluble in organic solvents such as toluene or tetrahydrofuran (THF). A simple separation will therefore result in the catalyst remaining in the aqueous phase whilst the organic product can be filtered off or decanted.

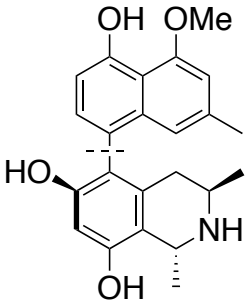
In the Suzuki-Miyaura cross-coupling reaction, aryl boronic acid and its derivatives are coupled with aryl halides forming biaryl compounds in the presence of a palladium catalyst,[9] as shown in Scheme 2.1.



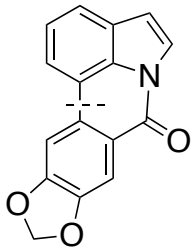
Scheme 2.1. General Suzuki-Miyaura cross-coupling reaction of aryl halides and aryl boronic acids.

In industrial chemistry, biaryl compounds have important roles ranging from performance materials to pharmaceuticals.[9] There are many applications of the Suzuki-Miyaura coupling reaction for the synthesis of useful natural products such as Korupensamine A, which can be used for anti-malarial activity as well as to make an

anti-HIV agent,[10] or hippadine which is used to decrease the blood pressure.[11]



Korupensamine A

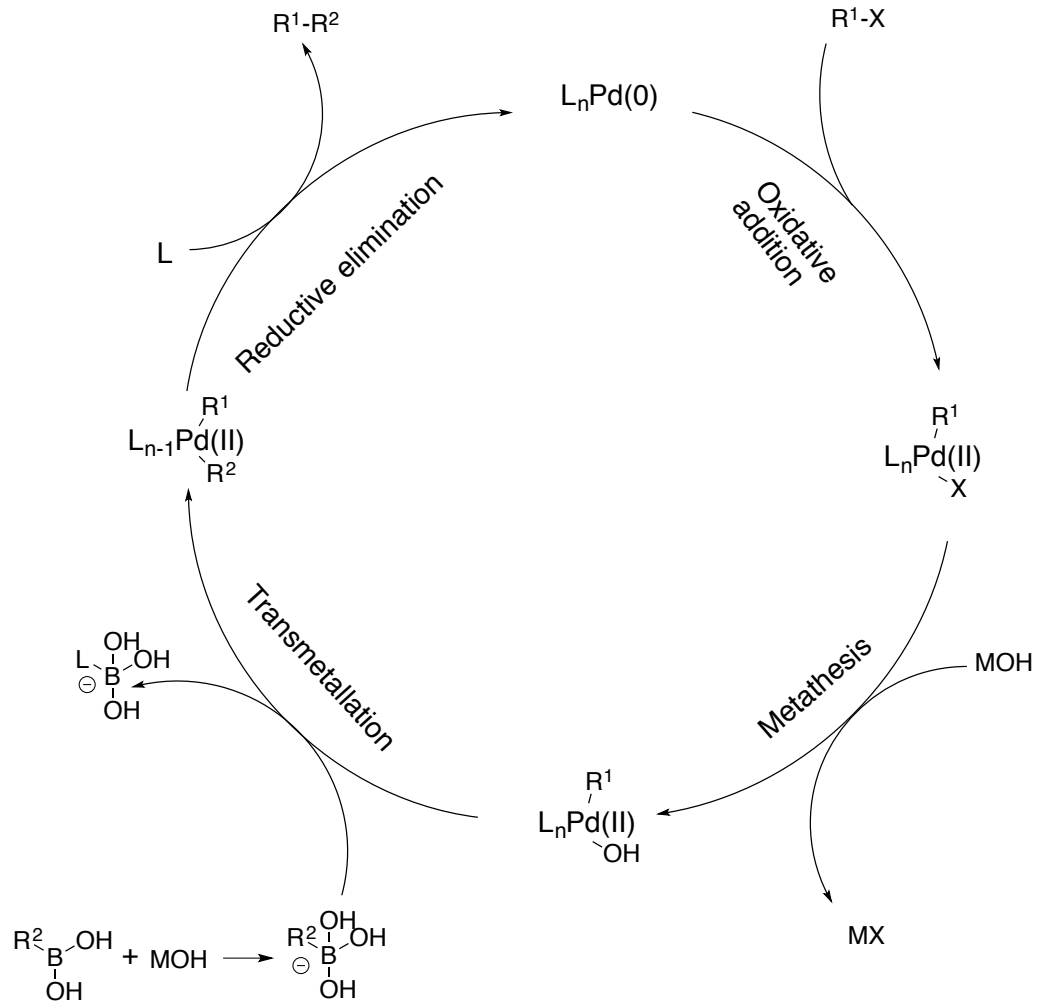


Hippadine

Scheme 2.2.[11]

In most cases, Suzuki-Miyaura reactions are generally carried out in organic solvents such as toluene, diethyl ether, THF or dioxane in the presence of a palladium(II) or (0) catalyst. Common bases used in this reaction are Na_2CO_3, $Ba(OH)_2$, and K_3PO_4. The function of these bases is in accelerating the transmetallation step of the reaction.

There are four main steps in the Suzuki-Miyaura coupling reaction to form the C-C bond between aryl halides and phenyl boronic acid.



Scheme 2.3. Mechanism of the Suzuki-Miyaura cross-coupling,[12] where M is a cation such as Na or trialkylammonium.

A) Oxidative addition step

I) The oxidative addition step is also the rate-determining step. The order of reactivity for the different aryl halides is as follows: I > OTf > Br >>> Cl. The reactivity of these groups depends upon the bond dissociation energy for C-X (X= halide or triflate). For example, the bond dissociation energy between C-Br is 339 kJ/mol and C-Cl is 402

kJ/mol. If an electron-withdrawing group is attached at the meta or para position (rather than an electron donating group), then it is easier to activate the aryl halides.[13,14]

II) The palladium catalyst is converted from palladium(0) to palladium(II) by inserting itself between the carbon and halide.[11]

B) Metathesis step

In this step, anion (X^-, OH^-, CO_3^{2-}) exchange takes place between the palladium catalyst and the base. In my experiment, the Cl^- ion is replace by the OH^- ion.

C) Transmetallation step

I) In this step, the organoborane nucleophile is activated by a base and forms a trans-sigma-palladium complex when the nucleophile binds to the palladium catalyst.[14]

II) An intermediate palladium(II) complex is formed when transmetallation occurs between the aryl boronic acid and the palladium-aryl complex.

D) Reductive elimination step

In the last step, reductive elimination take place, simultaneously giving the final biaryl product and regenerating the palladium(0) catalyst.[15]

2.1.1 Application of Switchable Water to Suzuki Reactions

As described in section 1, switchable water (SW) is an aqueous solution of select amines that has solution properties able to be "switched" by simply having CO_2 passed through it. For example due to the switchable properties of SW, organic compounds

(such as THF in Fig. 2.1) may dissolve readily in one form of the SW but be largely insoluble in the other form of SW.

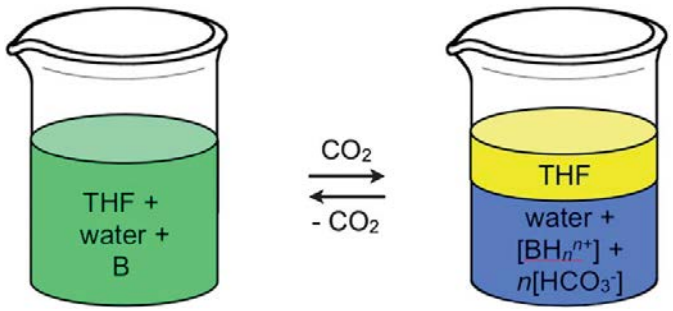


Figure 2.1. The switchable miscibility of SW with THF.[16]

Because SW is basic in its low ionic strength form, any homogeneously catalyzed reaction performed in SW must be compatible with basic conditions. Fortunately, Suzuki-Miyaura cross-coupling reactions are typically carried out in basic conditions, which make them a good test of the concept of using SW as a reaction solvent in order to facilitate the post-reaction separation of catalyst from coupling product. It was anticipated that the desired organic product could be separated by precipitation after the switching of SW triggered by the addition of CO_2.

A key objective of this research is to determine whether the use of SW as the solvent and base would enhance the reactivity of aryl chlorides for the Suzuki-Miyaura reaction and facilitate the recovery of the product. Due to their lower cost and greater availability, aryl chlorides were chosen over iodides and bromides although aryl chlorides have been reported to have lower reactivities compared with their bromide and iodide

analogues.[9] Aryl chlorides can give good yields but typically only with complicated catalysts and volatile solvents.[17] A catalyst often used for the Suzuki-Miyaura reaction is $Pd(OAc)_2$ because it is stable in air and can be easily reduced to Pd(0). The main problems of homogeneous catalysis are the post-reaction separation and recycling of the catalyst, both of which can be facilitated by using two-phase catalysis.[7] In such a biphasic reaction the catalyst is typically designed to reside in an aqueous phase whereas the desired products are in an organic phase. In order to ensure that the catalyst preferentially partitions into the aqueous phase, TPPTS (trisodium salt of triphenylphosphine trisulfonate) was selected as a ligand because it is hydrophilic and soluble in water. Due to the water-soluble nature of TPPTS, it has been commonly used in Suzuki-Miyaura cross-coupling reactions for all types of aryl halides.[18,19]

SW was therefore selected as the solvent, as it is able to act as both the solvent and the base. I hoped that the basicity of that solvent mixture would enhance the reaction with aryl chlorides and phenyl boronic acid and the switchable nature of that solvent would facilitate post-reaction separation of some products. Also, water is a non-toxic, non-flammable, environmental friendly, inexpensive and abundant solvent.[20]

The use of SW for the separation of catalyst from product should reduce the amount of cost and waste generated during the purification. The palladium catalyst used in Suzuki-Miyaura cross-coupling reaction is expensive, so recovering and reusing the palladium catalyst will decrease the economic costs for large-scale chemical synthesis.[21] The major products of the Suzuki-Miyaura reaction are organic products. To separate organic products, switchable water is better than regular water because the organic compounds have more solubility in switchable water than regular water during the

reaction, but less solubility upon CO_2 addition afterwards.[22]

However, having a facile post-reaction separation is useless if the reaction itself does not work. Therefore it was necessary to determine whether Suzuki-Miyaura reactions can proceed in SW. To the best of my knowledge, there is no record of Suzuki-Miyaura cross-coupling reactions which use water as the solvent and amines as the base. The literature does describe Suzuki-Miyaura cross-coupling reactions carried out in water but using different bases like Na_2CO_3 with PEG[23,24] rather than amines. For the preliminary study, I used 2-dimethylaminoethanol (2-DMAE) as the amine as it is soluble in water.

2.2 Experimental Methods and Materials

2.2.1 Materials

All the chemicals reagents used in Suzuki-Miyaura cross-coupling reaction were purchased from Alfa Aesar and Sigma-Aldrich. Except for 2-DMAE, all the chemicals were directly used without further purification. 2-DMAE was purified by distillation under argon. The progress of the reaction was monitored by thin layer chromatography (TLC) plates pre-coated with silica or alumina. The solvent used for TLC was a 4:1 v/v mixture of hexanes and ethyl acetate. To analyze the TLC plates, an ultraviolet lamp was utilized. Column chromatography was used to isolate the desired product.

2.2.2 General Procedures

The compounds were recognized using Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra or Carbon Nuclear Magnetic Resonance ($^{13}C\{^{1}H\}$ NMR) spectra. The chemical shifts are reported in parts per million (ppm).

2.2.3 Reaction Procedure - Normal

In general, 2.51 mmol of the aryl halide, 2.84 mmol of the aryl boronic acid and 6 ml of deionized water were added to a three-necked 50 ml round bottom flask in open air. To this solution, 8 μmol of palladium acetate, 24.4 μmol of TPPTS and 3.24 mmol of base were then added. The whole mixture was refluxed under an inert atmosphere with continuous flow of argon. To check the progress of the reaction, silica TLC (4:1 hexanes and ethyl acetate) was used. When the reaction was completed, the mixture was cooled in open air for 10 min.[11]

2.2.4 Reaction Procedure - Schlenk Technique

Palladium catalysts are generally air sensitive. To avoid the oxidation of the catalyst, the reaction was performed using Schlenk techniques. In this method all the reagents including the solvent but not the catalyst were added to a cleaned and oven-dried Schlenk flask with the positive flow of argon gas. The Schlenk flask was then connected to a high-vacuum pump and an inert argon gas. To remove the air from the Schlenk flask, it was slowly purged with vacuum and then filled with argon gas via a Schlenk line. This procedure was repeated three times. The palladium catalyst was immediately added to the flask under a positive flow of argon. The whole mixture was again slowly purged with

vacuum and refilled with argon gas. The mixture was refluxed under inert conditions until the reaction was complete, as determined by TLC.

After the completion of the reaction, the mixture was transferred to a clean separatory funnel. The Schlenk flask was rinsed with 15 mL of ethyl acetate, which was added to the separatory funnel. The mixture was vigorously shaken and allowed to stand for a few minutes. The organic phase was transferred to an Erlenmeyer flask. The aqueous phase was again washed with 10 mL ethyl acetate and the organic layer was separated and added to the previous Erlenmeyer flask (three washes in total). The organic phase was treated with anhydrous sodium sulfate for 10 min with continuous stirring. The solution was filtered, and the filtrate was collected. To isolate the product from the organic phase either recrystallization or column chromatography methods were used.

The recrystallization method involved first removing the solvent by evaporation in vacuo. The residue obtained from the rotary evaporation was first allowed to cool to room temperature. An appropriate solvent that does not easily dissolve the desired product at room temperature but does dissolve the product at elevated temperatures was selected. In this case methanol can be used. The methanol was added to the crude product until no further crude product could dissolve. The solution was slowly heated in a water bath at 70 °C until all solids were completely dissolved. The solution was slowly cooled to room temperature and left in a fridge overnight to grow crystals of the desired product. The precipitated crystals of product were separated from the solvent by vacuum filtration. The crystals were dried and the isolated yield was determined.

For the column chromatography method, a slurry of silica gel and eluent (4:1 hexanes and ethyl acetate) was prepared and poured into a chromatography column. A

thin layer of sand was added onto the top of the column and the extracted mixture after concentration was added to this stationary phase. The eluent was continuously but slowly added to the column and argon gas was used to push the solvent through the column. The eluent obtained from the column chromatography was collected in fractions, and the progress of the purification was monitored using TLC. The product was dried, and characterized using ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy.

2.2.5 Filtration and Recycling of the Aqueous Phase

After the aqueous phase had been washed with ethyl acetate, the aqueous phase was filtered. The filtrate, which contained the catalyst, could be reused for another Suzuki-Miyaura cross-coupling reaction by simply adding fresh aryl halide and phenyl boronic acid. In order to reuse the aqueous phase, the catalyst must be dissolved in the aqueous phase and should not have any black colloidal particles or black films of catalyst.

2.3 Results and Discussions

2.3.1 Experiments of Suzuki-Miyaura cross-coupling reaction in water

The main objective of this research is to determine whether the use of water as the solvent and base would enhance the reactivity of aryl chlorides for the Suzuki-Miyaura reaction and SW facilitate the recovery of the product.

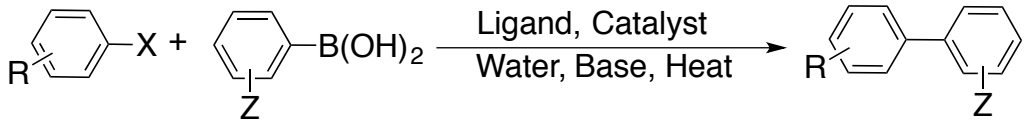
As a preliminary test, the common phosphine ligand 3,3′,3″-phosphanetriyltris(benzenesulfonic acid) trisodium salt and aqueous NaOH were used as

ligand and base, respectively. In this experiment, very little desired product was formed whilst significant biphenyl was produced. When the final reaction mixture was analyzed, it was found that most of the aryl chloride was unreacted. This implies that the aryl chloride bond in 4-chlorotoluene (first experiment) was difficult to activate. Thus, 4-chloronitrobenzene was used in the second experiment with the same catalyst, ligand and base to see if it improves the reaction progress. There was very little change in the desired product yield and, again, most of the reactant was still unreacted. Further test reactions were performed under identical conditions but varying the substrate to find out which activated chlorides provide the highest product yields. The activated chlorides tested were 4-chlorobenzoic acid, 4-chlorobenzaldehyde and 4-chloroacetophenone. In each of these cases, more than 50% conversion was observed but the desired products were not obtained in good yield. The majority of the phenyl boronic acid undergoes hydrolysis and is converted into benzene (Scheme 2.5). Among these different aryl chlorides, 4-chlorobenzaldehyde gave more of the desired product than other aryl chlorides. The reaction mixtures after these reactions were characterized by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy.

Aryl chlorides having different substituents were tested with different types of bases but with the same ligand, same catalyst, and same phenyl boronic acid. A water-soluble catalyst and ligand were selected because these need to be present in the aqueous phase when the reaction is complete.

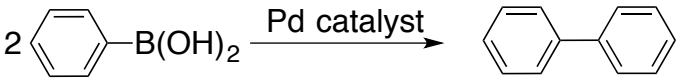
2-Propanol was added in the original literature procedure[25] to dissolve all the solid materials present in the reaction mixture but this was deemed to be unnecessary as it was found that the mixture was soluble after heating at 70 °C for 10 min without any propanol

present. In the original method, Na_2CO_3 was employed as the base, but in this study potassium carbonate, sodium hydroxide and 2-dimethylaminoethanol (2-DMAE) were explored as bases to identify the most suitable base for the Suzuki-Miyaura cross-coupling reaction using aryl chloride in water. K_2CO_3 and NaOH are not phase switchable bases but are often used in the Suzuki-Miyaura cross-coupling reaction. The initial goal was to compare 2-DMAE as a base to the more conventional bases than K_2CO_3 and NaOH for Suzuki-Miyaura cross-coupling reactions in terms of yield and separation, and second to obtain a good yield as well as facile separation of the desired product by switching of the SW.



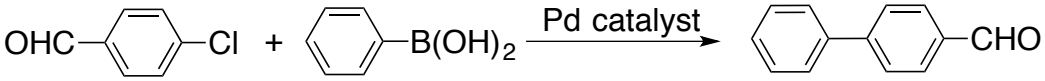
Scheme 2.4. General Suzuki-Miyaura cross-couplings of aryl halides and aryl boronic acids. In the described experiments, X = Cl, Z = H, ligand = TPPTS, catalyst = $Pd(OAc)_2$ and heat = reflux.

When reacted in the absence of an aryl chloride, phenyl boronic acid undergoes a homo-coupling reaction in the presence of a palladium catalyst to produce biphenyl (Scheme 2.5).



Scheme 2.5. Formation of biphenyl from phenyl boronic acid homo coupling.

To differentiate the desired products from the phenyl boronic acid homo-coupling product, aryl chlorides with different substituents in the para position were used (for example, as shown in Scheme 2.6).

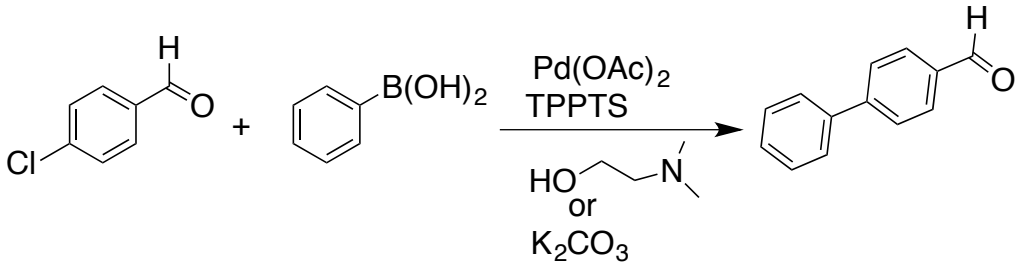


Scheme 2.6. Suzuki-Miyaura cross-couplings reaction of 4-chlorobenzaldehyde and phenyl boronic acid.

Further experiments were carried out using K_2CO_3 as the base. To test which activated chloride is able to provide the highest yield, 4-chloronitrobenzene, 4-chlorobenzoic acid, 4-chlorobenzaldehyde and 4-chloroacetophenone were selected in experiments 7-10, respectively. 4-Chlorobenzaldehyde, 4-chloroacetophenone and 4-chlorobenzoic acid showed more than 80% conversion. The use of 4-nitrobenzene resulted in very low conversion and product formation.

Similarly, more experiments were also carried out with 2-DMAE (2-dimethylaminoethanol) as the base in order to determine optimal reaction conditions and find out which would be the best aryl chloride for these experiments. In these experiments, 4-chloronitrobenzene, 4-chlorobenzoic acid, 4-chlorobenzaldehyde, and 4-chloroacetophenone were selected. Except for 4-chloronitrobenzene, all the activated aryl chlorides (listed in the previous paragraph) demonstrated > 95% conversion to the desired product. With 4-chloronitrobenzene, the conversion rate was very poor with very little desired product after 6 h. Among these different experiments, it was found that 4-chlorobenzaldehyde was transformed to the desired product in a quantitative yield

(Scheme 2.7).



Scheme 2.7. Suzuki-Miyaura cross-couplings reaction of 4-chlorobenzaldehyde and phenyl boronic acid in water with palladium acetate, TPPTS and either 2-dimethylaminoethanol or K_2CO_3 as base.

4-Chlorobenzaldehyde was therefore the aryl halide selected to be used for trial Suzuki-Miyaura cross-couplings with different bases to determine which of K_2CO_3 and 2-DMAE provides the greatest conversion to the desired product. The product of the reaction between 4-chlorobenzaldehyde and phenyl boronic acid was biphenyl-4-carboxaldehyde (Scheme 2.8), a white solid which precipitated when the reaction mixture was cooled to room temperature. Because the product precipitates, the use of CO_2-switching to induce product precipitation was not tested. The product was isolated by filtering the reaction mixture. During the filtration, a black film was collected as part of the residue, which is presumably from decomposition of the palladium catalyst. To overcome this problem (black film), the reaction mixture was filtered before being cooled to room temperature. When the filtration was carried out under these conditions, the catalyst could be recovered and added to the aqueous phase to reuse the catalyst. Then the reaction mixture could be cooled down to room temperature and filtered again to isolate the desired product.

The overall results of the reaction described in the previous paragraph (Scheme 2.7) in normal conditions can be seen in Table 2.1 below.

Table 2.1. Results of Suzuki-Miyaura cross-coupling reaction using different bases without using Schlenk techniques

Base	Isolated yield after 6 h, %	Isolated yield after 14 h, %	Isolated yield after 24 h, %
2-DMAE	87	85	84
K_2CO_3	44	55	53

Reaction conditions: 2.51 mmol of 4-chlorobenzaldehyde, 2.84 mmol of phenylboronic acid, 6.1 mL water, 8.1 μmol of $Pd(OAc)_2$, 24.4 μmol of TPPTS, 3.24 mmol of base and 100 °C.

It can be concluded that 2-DMAE is a more effective base than K_2CO_3 for Suzuki-Miyaura cross-coupling reactions of the substrates shown.

Different experiments were carried out with the Schlenk technique previously described (repeated vacuum-inert gas back-fill procedure). In this method, the water-base combination was initially degassed using a repeated vacuum-inert gas back-fill method. All other reagents except for the catalyst were then added to a cleaned and oven dried Schlenk flask which was connected to a high-vacuum pump and argon gas via a Schlenk line. To remove the air from the contents of the Schlenk flask, it was exposed to three cycles of vacuum inert gas back-fill before the palladium catalyst was added to the flask.

The whole mixture was again evacuated and refilled with argon gas to prevent the formation of the black particles as described earlier. However some black particles were formed during the reaction. This indicates the instability and sensitivity of the catalyst to air.

The results obtained using the above method (shown in Scheme 2.8) are shown in Table 2.2 below, comparing results from trials in which black particles were not observed and trials in which they were observed.

Table 2.2. Results of Suzuki-Miyaura coupling reaction with Schlenk technique

Black particles	Isolated yield after 6 h, %	Isolated yield after 14 h, %	Isolated yield after 24 h, %
Presence	87	85	84
Absence	65	61	62

Reaction conditions: 2.51 mmol of 4-chlorobenzaldehyde, 2.84 mmol phenylboronic acid, 6.05 mL water, 8.02 μmol of $Pd(OAc)_2$, 24.4 μmol of TPPTS, 3.24 mmol of 2-DMAE and 100 °C.

With the Schlenk technique, the highest yields were accompanied by the formation of black particles (compared to when no black particles were formed). Because the black particles are only formed when the catalyst solution is exposed to air, the particles may be caused by Pd metal precipitating after the phosphine ligand has been

oxidized. The fact that black particle formation improves rate and yield suggests that the true catalyst is heterogeneous. Black particle formation improves conversion rates and yields of the bi-aryl product. Moreover 2-DMAE was found to be a more effective base (Table 2.1) than NaOH and K_2CO_3, given that reactions with the organic base resulted in higher conversions and yields.

2.4 Conclusions

Suzuki-Miyaura cross-coupling reactions are commonly used in the synthesis of various natural and non-natural products. A major objective of this study was to explore the formation of C-C bonds between aromatic compounds using aryl chloride and aryl boronic acid in a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction in which SW was used as the solvent with an amine functioning as the base. Thus Pd-catalyzed Suzuki-Miyaura cross-coupling reactions of various activated aryl chlorides with phenyl boronic acid using TPPTS (water-soluble phosphine ligand) were carried out. Schlenk techniques resulted in conversions of 98 % and isolated yields of up to 87 % with 4-chlorobenzaldehyde in the presence of phenyl boronic acid and 2-DMAE. It was also found that 2-DMAE as a base enabled higher yields than aqueous NaOH and K_2CO_3. However, SW offers no product separation advantage for this reaction because the product precipitated at room temperature and could be separated by simple filtration. Other Suzuki-Miyaura cross-coupling products which have greater water solubility may benefit from this technique.

2.5 References

(1) Miyaura, N.; Yanagi, T.; Suzuki, A. The Palladium-Catalyzed Cross-Coupling Reaction of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth. Commun.* **1981**, *11* (7), 513–519.

(2) Suzuki, A. Organoboron Compounds in New Synthetic Reactions. *Pure Appl. Chem.* **1985**, *57*, 1749–1758.

(3) Martin, A. R.; Yang, Y.; Spinelli, D.; Frenna, V.; Consiglio, G.; Chanon, M.; Striley, C.; Weidlein, J.; Nasiri, A.; Okada, Y. Palladium-Catalyzed Cross-Coupling Reactions of Organoboronic Acids with Organic Electrophiles. *Acta Chem. Scand.* **1993**, *47*, 221–230.

(4) Suzuki, A. New Synthetic Transformations via Organoboron Compounds. *Pure Appl. Chem.* **1994**, *66*, 213–222.

(5) Stanforth, S. P. Catalytic Cross-Coupling Reactions in Biaryl Synthesis. *Tetrahedron* **1998**, *54*, 263–303.

(6) Miyaura, N. Synthesis of Biaryls via the Cross-Coupling Reaction of Arylboronic Acids. *Adv. Met. Chem.* **1998**, *6*, 187–243.

(7) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles. *J. Organomet. Chem.* **1999**, *576*, 147–168.

(8) Kotha, S.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki – Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, *58* (625), 9633–9695.

(9) Kostas, I. D.; Andreadaki, F. J.; Kovala-Demertzi, D.; Prentjas, C.; Demertzis, M.

A. Suzuki-Miyaura Cross-Coupling Reaction of Aryl Bromides and Chlorides with Phenylboronic Acid under Aerobic Conditions Catalyzed by Palladium Complexes with Thiosemicarbazone Ligands. *Tetrahedron Lett.* **2005**, *46* (12), 1967–1970.

(10) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki-Miyaura Coupling Reactions. *J. Am. Chem. Soc.* **2014**, *136* (2), 570–573.

(11) Callam, C. S.; Lowary, T. L. Suzuki Cross-Coupling Reactions: Synthesis of Unsymmetrical Biaryls in the Organic Laboratory. *J. Chem. Educ.* **2001**, *78* (7), 947.

(12) Laszlo, K.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Burlington, MA, USA, 2005.

(13) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95* (7), 2457–2483.

(14) Nowothnick, H. Homogeneously Catalysed Suzuki Coupling Reaction in Microemulsion Systems with Recycling of the Catalyst, Technische Universität Berlin, Fakultät II, 2010.

(15) Littke, A. F.; Fu, G. C. A Convenient and General Method for Pd-Catalyzed Suzuki Cross- Couplings of Aryl Chlorides and Arylboronic Acids. *Angew. Chemi Int. Ed.* **1998**, *37*, 3387–3388.

(16) Mercer, S. M.; Jessop, P. G. "Switchable Water": Aqueous Solutions of Switchable Ionic Strength. *ChemSusChem.* **2010**, *3*, 467–470.

(17) Div, M.; Littke, A. F.; Fu, G. C. A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids.

Angew. Chem. Int. Ed. **1998**, *37*, 3387–3388.

(18) Galland, J.-C.; Monique, S.; Gentt., J.-P. Cross-Coupling of Chloroarenes with Boronic Acids Using a Water-Soluble Nickel Catalyst. *Tetrahedron Lett.* **1999**, *40*, 2323–2326.

(19) Galland, J.-C.; Savignac, M.; Gentt., J.-P. Suzuki Cross-Coupling of Arylboronic Acids Mediated by a Hydrosoluble Pd(0) / TPPTS Catalyst. *Tetrahedron Lett.* **2001**, *42*, 6523–6526.

(20) "What Is Green Chemistry? " https://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry.html (accessed Oct 12, 2018).

(21) Shaughnessy, K. H. *Metal-Catalyzed Cross-Couplings of Aryl Halides to Form C-C Bonds in Aqueous Media*; Markono Print Media Pte Ltd, Singapore, 2013.

(22) Liu, L.; Zhang, Y.; Wang, Y. Phosphine-Free Palladium Acetate Catalyzed Suzuki Reaction in Water. *J. Org. Chem.* **2005**, *70*, 6122–6125.

(23) Vanderveen, J. R.; Burra, S.; Geng, J.; Goyon, A.; Jardine, A.; Shin, H. E.; Andrea, T.; Dyson, P. J.; Jessop, P. G. Characterizing the Effects of a " Switchable Water " Additive on the Aqueous Solubility of Small Molecules. *ChemPhysChem.* **2018**, *19*, 2093–2100.

(24) Leadbeater, N. E.; Marco, M. Ligand-Free Palladium Catalysis of the Suzuki Reaction in Water Using Microwave Heating. *Angew. Chem. Int. Ed.* **2002**, *41*, 2973–2976.

(25) Zafarani-Moattar, M. T.; Hamzehzadeh, S. Salting-out Effect, Preferential

Exclusion, and Phase Separation in Aqueous Solutions of Chaotropic Water-Miscible Ionic Liquids and Kosmotropic Salts: Effects of Temperature, Anions, and Cations. *J. Chem. Eng.* **2010**, *55*, 1598–1610.

Chapter 3

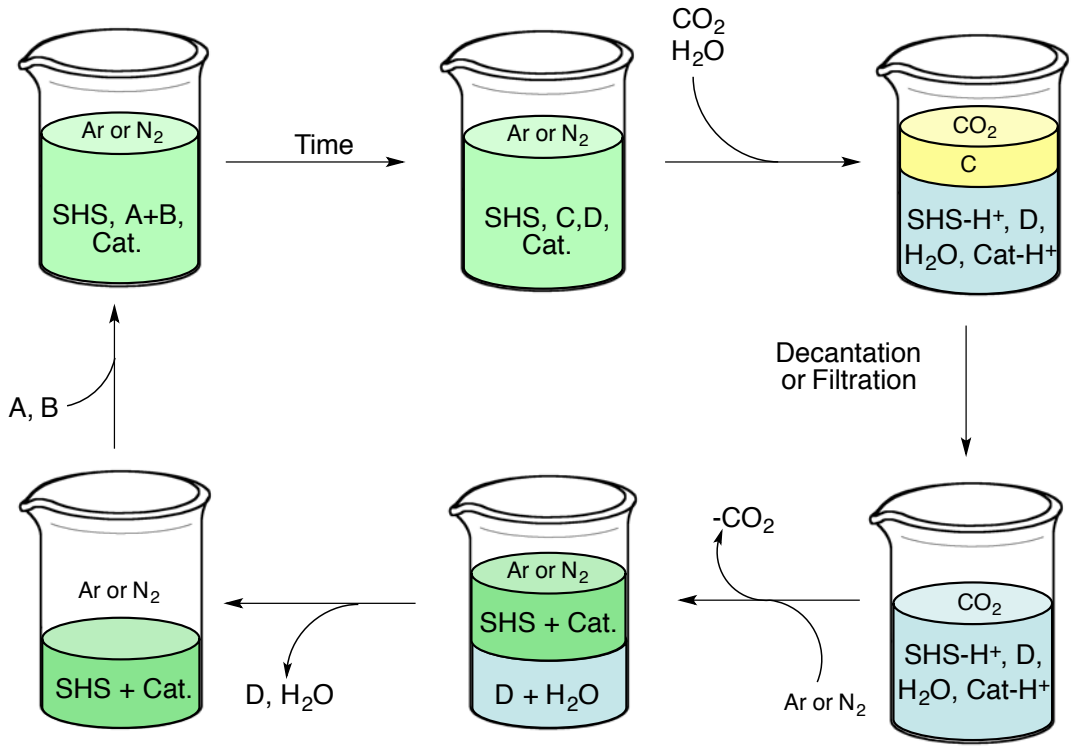
Synthesis of a Phase Switchable Ligand and Its Application

3.1 Introduction

The main objective of this work is to develop a CO_2-switchable ligand for a homogeneous catalyst, so that the catalyst and the organic product(s) resulting from the homogeneously catalyzed reaction can easily be separated from each other and from byproducts. If the aqueous phase consists of "switchable water" then switching between a monophasic system (in the absence of CO_2) and a biphasic organic/aqueous system (in the presence of CO_2) can be performed under ambient conditions. The catalytic process being developed involves homogeneous catalysis within the aqueous/organic monophasic mixture (in the presence of CO_2 gas). When CO_2 is bubbled through the solution of the amine, the ionic strength of the solution increases as the amine sites become protonated. This triggers the salting out of the product and organic solvent from the aqueous phase. If the catalyst is hydrophilic it remains in the aqueous phase. The desired organic product can then be separated by filtration or decantation. Following separation of the organic product, CO_2 can be removed from the aqueous phase by passing Ar or N_2 gas, reducing the ionic strength of the aqueous phase, resulting in separation of the catalyst and ligand from the aqueous phase and any undesired inorganic byproduct. Thus, the catalyst and ligand are regenerated for future use. For this concept we, consider the following general chemical reaction (equation 3.1) where A and B are organic or organometallic reagents, C is the desired organic product, and D is an undesired inorganic byproduct. Assuming that A and B are entirely consumed, the remaining materials C, D, and catalyst could

hypothetically be separated from each other by exploiting CO_2-switchable materials as shown in Scheme 3.1.

$$A + B \xrightarrow[SHS]{Cat.} C + D \qquad (3.1)$$



Scheme 3.1. Conceptual scheme of a monophasic reaction followed by a biphasic separation using CO_2 in a liquid mixture of switchable hydrophilicity solvent, switchable catalyst and ligand.

The Suzuki-Miyaura cross-coupling reaction results in the protonation of one equivalent of the SHS and this reaction is irreversible, meaning that it would not be reversed by flushing the CO_2 away from the system. To meet this goal first I decided to synthesize a phase switchable ligand so that we can separate out the catalyst from the desired organic product as well as from undesired inorganic byproduct.

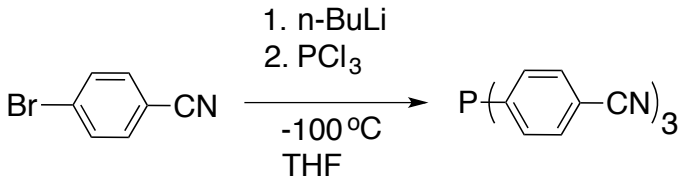
3.2 Experimental Procedures

All chemicals and solvents were obtained from Sigma Aldrich, TCI or Fisher Scientific and were used as received, except as noted below. Tetrahydrofuran (THF) was dried with Na and distilled before use. n-BuLi (1.6 M solution in hexane) and PCl_3 were each slowly degassed separately under vacuum before argon gas was continuously passed through each for at least 6 h. NMR spectroscopy was performed using Bruker 300 and 400 MHz spectrometers. All reactions were carried out under argon using Schlenk techniques.

3.2.1 Attempted Preparation of 4,4',4''-Phosphinetriyltribenzoic Acid

Following a previously reported method,[1] 2.5 g (0.014 mol) of 4-bromobenzonitrile was mixed with 10.64 mL of dry and degassed THF in a 100 mL three necked round bottom flask (RBF) under a continuous flow of argon gas. The mixture was cooled to -100 °C using a liquid nitrogen and diethyl ether mixture before 8.60 mL (0.0137 mol) *n*-butyllithium (1.6 M solution in hexane) was added dropwise. A solution of 0.40 mL (0.0046 mol) phosphorus trichloride in 6.96 mL THF was also added dropwise to the above mixture under argon gas whilst the mixture was held at -100 ^{o}C. The reaction mixture was slowly allowed to warm to room temperature. The resulting

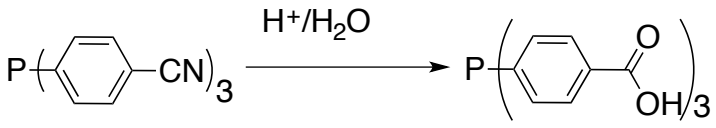
viscous and purple solution was then filtered under argon. The filtrate, containing mainly tris(4-cyanophenyl) phosphine, was concentrated under reduced pressure to yield a purple semisolid residue.



Scheme 3.2. Synthesis of tris(4-cyanophenyl)phosphine (compound **1**).

Compound **1** was analyzed using ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy (in $CDCl_3$). The NMR spectra matched those reported in the literature.[1] ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.15-7.95 (m, 12H, Ar-H) ppm; $^{31}P\{^{1}H\}$ NMR (121.5 MHz, d_6-DMSO): δ -3.9 ppm.

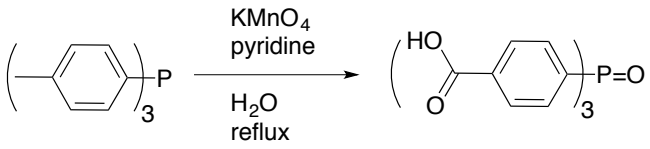
The conversion of compound **1** into 4,4′,4″-phosphinetriyltribenzoic acid was attempted (Scheme 3.2) but compound **1** was insoluble in dilute as well as concentrated HCl.



Scheme 3.3. Attempted synthesis of 4,4′,4″-phosphinetriyltribenzoic acid.

3.2.2 Synthesis of Tris[(p-carboxyl)phenyl]phosphine Oxide

About 2.0 g of tris(p-tolyl)phosphine was dissolved in 32 mL of water and 16 mL of pyridine in a 250 mL round-bottomed flask.[2] This mixture was refluxed in an oil bath set at 120 °C for 24 h, before being allowed to cool to room temperature. About 20 g of $KMnO_4$ was added to the mixture and it was brought to reflux (oil bath set at 120 °C) for 48 h. The hot mixture was filtered and washed with hot water to remove any residual MnO_2. The filtrate was acidified with semi-concentrated (N/2) H_2SO_4 until a white precipitate formed.[3] The white precipitate was separated by filtration and dissolved in 6 N NaOH before being washed with an ethyl acetate-THF mixture to remove any residual starting material. The aqueous phase was again treated with semi-concentrated H_2SO_4 to precipitate the desired product. The solid compound was dried at 70 °C under vacuum to form 1.5 g of solid white tris(*p*-carboxyphenyl) phosphine oxide.

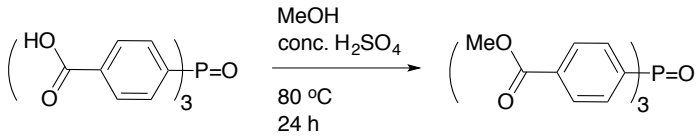


Scheme 3.4. Synthesis of tris[(p-carboxy)phenyl]phosphine oxide.

Tris(*p*-carboxyphenyl) phosphine oxide was characterized by ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectroscopy. The NMR spectra matched those reported in the literature.[2] ^{1}H NMR (300.13 MHz, d_6-DMSO): δ 7.75-8.15 (m, 12H, Ar-H) ppm; $^{13}C\{^{1}H\}$ NMR (121.49 MHz, d_6-DMSO): δ 135.06, 131.02, 129.75, 132.85, 167.21 ppm; $^{31}P\{^{1}H\}$ NMR (121.5 MHz, d_6-DMSO): δ 25.6 ppm.

3.2.2.1 Synthesis of Tris[(p-methoxycarbonyl)phenyl]phosphine Oxide

In this method,[2] 1.0 g of tris(p-carboxyphenyl)phosphine oxide was added to a solution of 20 mL methanol and 1.5 mL concentrated H_2SO_4. The mixture was refluxed at 80 °C for 24 h and then allowed to cool to room temperature. About 20 mL water was added to the mixture before the mix was extracted with 30 mL benzene (3 times). The combined organic fractions were evaporated under reduced pressure to obtain dry tris[(p-methoxycarbonyl)phenyl]phosphine oxide. The compound was purified by crystallization using benzene as a solvent. The mass obtained of tris[(p-methoxycarbonyl)phenyl]phosphine oxide was 0.25 g.



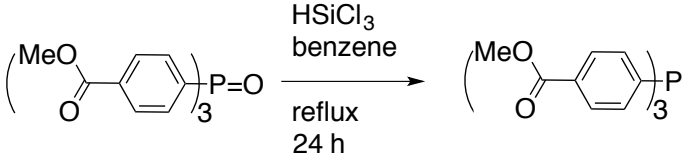
Scheme 3.5. Synthesis of tris[(p-methoxycarbonyl)phenyl]phosphine oxide.

The compound was characterized by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy. The NMR spectra matched those reported in the literature.[2] ^{1}H NMR (300.13 MHz, d_6-DMSO): δ 4.10 (s, 9H, $-CH_3$), 7.76-8.12 (m, 12H, Ar-H) ppm; $^{31}P\{^{1}H\}$ NMR (121.5 MHz, d_6-DMSO): δ 24.6 ppm.

3.2.2.2 Synthesis of Tris[(p-methoxycarbonyl)phenyl]phosphine

In this method, 0.20 g of tris[(p-methoxycarbonyl)phenyl]phosphine oxide was

added to the 4 mL dry benzene under inert conditions (continuous flow of argon). About 0.70 mL of trichlorosilane was added dropwise into the mixture under the same conditions. The mixture was refluxed for 24 h at 85 °C under a continuous flow of argon gas before being cooled to 0 °C and an excess of pre-cooled 2 M NaOH added to neutralize the unreacted trichlorosilane. Following the neutralization, the organic component of the mixture was extracted with benzene (3x8 mL) and the organic solvent was evaporated under the reduce pressure. The crude product was further purified using column chromatography, with silica as stationary phase and $CHCl_3$ as eluent, enabling the isolation of 0.10 g of tris[(p-methoxycarbonyl)phenyl]phosphine.



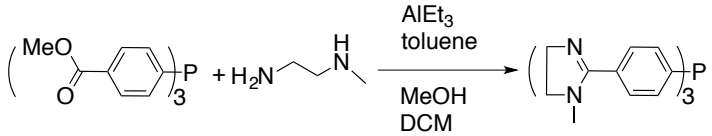
Scheme 3.6. Synthesis of tris[(p-methoxycarbonyl)phenyl]phosphine.

The compound was characterized by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy. The NMR spectra matched those reported in the literature.[2] ^{1}H NMR (300.13 MHz, d_6-DMSO): δ 4.12 (s, 9H, $-CH_3$), 7.27-8.08 (m, 12H, Ar-H) ppm; $^{31}P\{^{1}H\}$ NMR (121.50 MHz, d_6-DMSO): δ -4.8, 25.1 ppm. Most of the phosphine oxide was reduced to phosphine because there was only a small peak of phosphine oxide. An attempt to purify the solid by column chromatography using DCM/hexane (1:1) was unsuccessful. I repeated this method many times but got the same result. This indicates that the tris[(p-methoxycarbonyl)phenyl]phosphine oxide is not completely reduced to tris[(p-

methoxycarbonyl)phenyl]phosphine.

3.2.2.3 Synthesis of Tris[4-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl-phenyl)]phosphine

In the first step, 0.20 mL of N-methylethylenediamine was mixed into 5 mL dry toluene and this mixture was added in a dropwise fashion to a strenuously stirred solution of 0.30 mL triethyaluminium in 4 mL dry toluene at 0 °C under continuous flow of argon gas. The mixture was then stirred at room temperature for 1 h. The solution was again cooled at 0 °C and the solution of tris[(p-methoxycarbonyl)phenyl]phosphine (0.10 g) in dry toluene (2 mL) was added in a dropwise manner.[4] The reaction mixture was reflux for 6 h and cooled at 0 °C. The mixture was carefully quenched by dropwise addition of 4 mL MeOH followed by 4 mL water. Again 6 mL dichloromethane (DCM) was added in to the mixture and refluxed for 1 h at 70 °C to ensure complete precipitation of the aluminum salts. The product was extracted with DCM and H_2O. The solvent was evaporated in vacuum and pale-yellow semisolid was obtained which was purified on a silica gel column using DCM/MeOH (7:3) as an eluent.



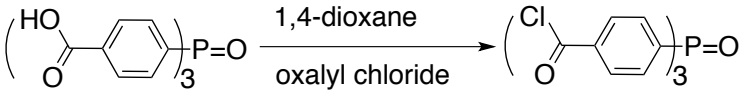
Scheme 3.7. Synthesis of tris[4-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl-phenyl)] phosphine.

The compound was characterized by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy. The

NMR spectra matched those reported in the literature.[4] ^{1}H NMR (300.13 MHz, d_6-DMSO): δ 2.72 (s, 9H, N-CH_3), 3.40-3.80 (m, 12H, N-CH_2-CH_2-N), 7.33-7.58 (m, 12H, Ar-H) ppm; $^{31}P\{^{1}H\}$ NMR (121.5 MHz, d_6-DMSO): δ -5.9, 25.6 ppm.

3.2.3 Synthesis of Tris[(p-chlorocarbonyl)phenyl]phosphine Oxide

About 0.82 g (2 mmol) of tris[(p-methoxycarbonyl)phenyl]phosphine oxide was added into 10 mL dry 1,4-dioxane under argon in a 50 mL Schlenk flask and degassed with argon. The Schlenk flask was then connected to a high-vacuum pump and an argon gas. To remove the air from the Schlenk flask, it was slowly purged with vacuum and then filled with argon gas via a Schlenk line. This procedure was repeated three times. Then, 0.55 mL (6 mmol) oxalyl chloride was added dropwise to the reaction mixture at room temperature.[5] The mixture was stirred for 4 h at 70 °C in a preheated oil bath and was cooled at room temperature. The solvent was removed under reduced pressure. The crude product was washed with diethyl ether to remove the leftover 1,4-dioxane. The product was again washed with pentane and dried under vacuum.

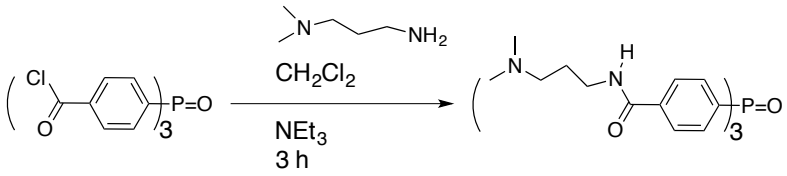


Scheme 3.8. Synthesis of tris[(p-chlorocarbonyl)phenyl]phosphine oxide.

The compound was characterized by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy. ^{1}H NMR (300.13 MHz, d_6-DMSO): δ 7.75-8.20 (m, 12H, Ar-H) ppm; $^{31}P\{^{1}H\}$ NMR (121.5 MHz, d_6-DMSO): δ -5.9, 25.8 ppm.

3.2.3.1 Synthesis of Tris[(p-N,N-dimethylethylenediaminecarboxamido)phenyl] phosphine Oxide

In this method,[6] 0.76 g of tris[(p-chlorocarbonyl)phenyl]phosphine oxide was taken into the 100 mL Schlenk flask and dry degassed DCM (15 mL) was added under argon. After that, 0.91 mL of triethylamine was added at 0 °C. A solution of 0.66 mL of *N*,*N*-dimethyl-1,3-propanediamine in 10 of mL pure and dry DCM was added dropwise to the above mixture under a continuous flow of argon. The mixture was stirred for 4 h at 40 °C, after which the solvent was removed under reduce pressure. The product obtained after the evaporation was taken in DCM and washed with 1 N HCl and then with 1 N NaOH. The organic phase was extracted and dried over anhydrous Na_2SO_4. The solvent was evaporated to dryness to reveal the crude product.

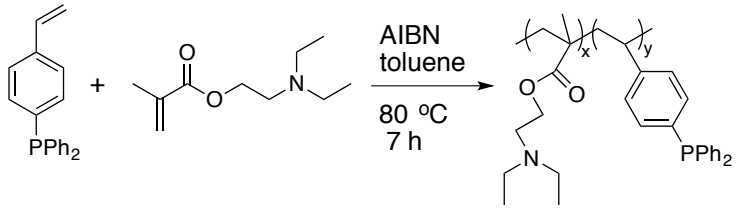


Scheme 3.9. Synthesis of tris[(p-N,N-dimethylethylenediaminecarboxamido) phenyl]phosphine oxide.

3.2.4 Synthesis of Phase Switchable Polymer Ligand From 4-DPPS and DEAEMA

In this method, 4 mmol (1.15 g) of 4-(diphenylphosphino)styrene and 80 mmol (16.00 mL) of 2-(diethylamino)ethylmethacrylate (in a mole ratio of 1:20 monomers) were mixed in a round bottom flask in 34 mL of toluene. Approximately 0.18 g (0.11

mmol) of 2,2′-azobis(2-methylpropionitrile) (AIBN) was added to the mixture. The mixture was heated at 80 °C for 7 h before being allowed to cool to room temperature. To precipitate the polymer, the cooled mixture was added dropwise to a beaker containing water at 25 ^{o}C being stirred continuously. The precipitated polymer was collected by filtration and dried under vacuum.



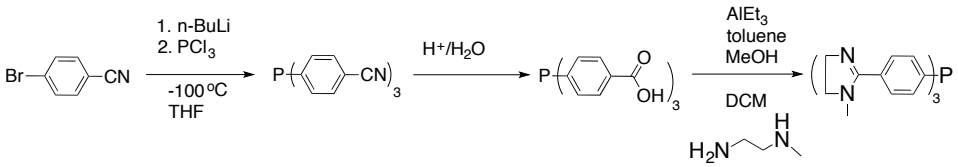
Scheme 3.10. Synthesis of phase-switchable polymer ligand.

The polymer was purified by repeated precipitation of a THF solution of polymer in cold (0 ^{o}C) water. The polymer was collected, dried, and characterized by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.01 (3H, N-CH_2-CH_3) 1.78 (3H, C-CH_3) 2.5 (2H, N-CH_2) 4.01 (s, 2H, O-CH_2) 7.16-7.26 (m, 14H, Ar-H) ppm whereas ^{31}P{^{1}H} NMR (121.5 MHz, d_6-DMSO): δ -6.5 ppm.

3.3 Results and Discussions

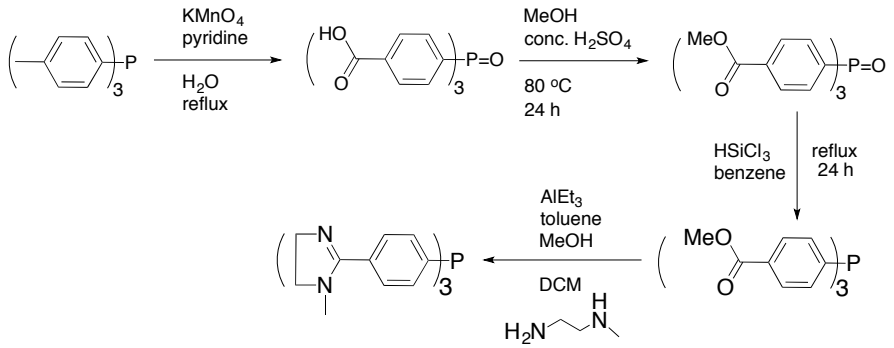
3.3.1. Non-polymeric Phase Switchable Ligands

During the synthesis of phase switchable ligands I attempted to synthesize the previously unknown phosphine ligand tris[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl-phenyl)]phosphine as shown in Scheme 3.11. This particular amidine phosphine ligand, was targeted, rather than putting a NMe_2 group in the para position, because although the latter option would have probably been easier it would have made an amine-phosphine that would not be sufficiently basic to be CO_2 switchable.



Scheme 3.11. Planned synthesis of tris[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl-phenyl)]phosphine.

The tris(4-cyanophenyl)phosphine was insoluble in dilute as well as hot and cold concentrated HCl so I decided to try another synthetic route to obtain the same amidinophosphine, via tris(p-tolyl)phosphine as shown in Scheme 3.12.

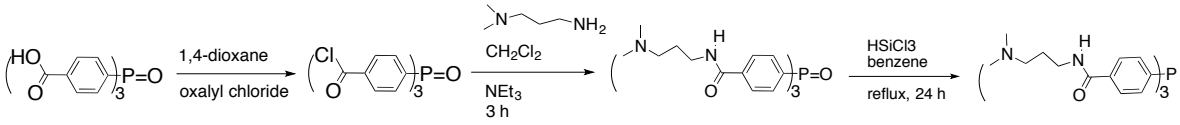


Scheme 3.12. Alternative synthesis of tris[4-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl-phenyl)]phosphine.

In this route, the first two steps proceeded as planned but the third step failed. Tris[(p-methoxycarbonyl)phenyl]phosphine oxide was not completely reduced to tris[(p-methoxycarbonyl)phenyl]phosphine. I tried to separate this mixture by column chromatography, but did not succeed.

3.3.2 Attempted synthesis of tris[(p-N,N-dimethylethylenediaminecarboxamido) phenyl]phosphine

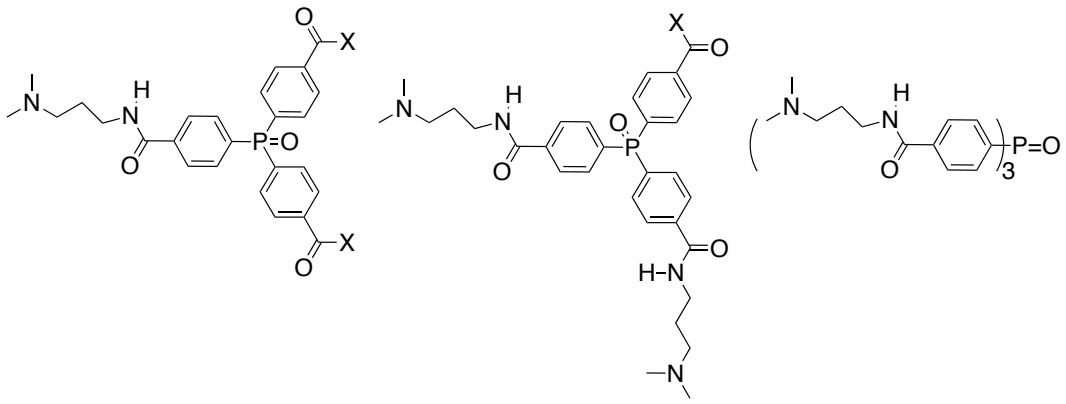
Similarly I attempted to synthesize the tris[(p-N,N-dimethylethylenediaminecarbo xamido)phenyl]phosphine as shown in Scheme 3.13.



Scheme 3.13. Alternative synthesis of tris[(p-N,N-dimethylethylenediaminecarbo xamido)phenyl]phosphine

In this route, the first two steps proceeded as planned but the third step failed. The

small amount of tris[(p-N,N-dimethylethylenediaminecarboxamido)phenyl]phosphine oxide (steps 3) was dissolved in d_6-DMSO and a $^{31}P\{^1H\}$ NMR spectrum was acquired. There were three different peaks which clearly indicates the presence of more than one product; most likely a mixture of mono-, di- and tri-substituted products[6] as shown as below.



Scheme 3.14. Poly-substituted tris[(*p-N,N*-dimethylethylenediaminecarboxamido)phenyl] phosphine oxide**,** where X could be Cl or OH.

Attempts to separate the above amides by column chromatography were unsuccessful, always producing mixtures that exhibited three peaks in the $^{31}P\{^1H\}$ NMR spectrum. Thus, these amides were not suitable for use as a phase switchable catalyst.

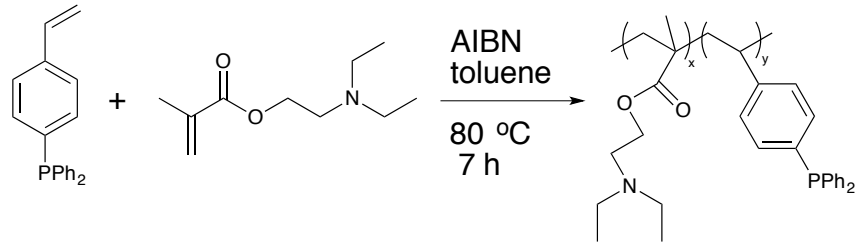
3.3.3. Phase Switchable Polymeric Ligand

I hypothesize that polymeric ligands are likely to be more complete partitioning into the aqueous phase under CO_2 and more complete partitioning into the organic phase in the absence of CO_2, due to presence of a greater number of switchable amino group

per molecule as compared to ligands that only have 1 to 3 switchable groups as shown in Scheme 3.13. Moreover it would be easier to make and hypothesized that it would switch better. For this reason, we decided to synthesize a phase switchable polymeric ligand made by a copolymerization of 4-(diphenylphosphino)styrene (4-DPPS) and 2-(diethylamino)ethyl methacrylate (DEAEMA).

During the synthesis of polymeric ligand, 4-(diphenylphosphino)styrene and 2-(diethylamino)ethyl methacrylate (in a mole ratio of 1:20 monomers) were mixed with toluene in a round bottom flask. 2,2′-azobis(2-methylpropionitrile) (AIBN) was added to the mixture and heated at 80 °C for 7 h before being allowed to cool to room temperature. The polymer was precipitated in water at 25 ^{o}C being stirred continuously. The precipitated polymer was collected by filtration, purified repeated precipitation of a THF solution of polymer in cold (0 ^{o}C) water, and dried under vacuum.

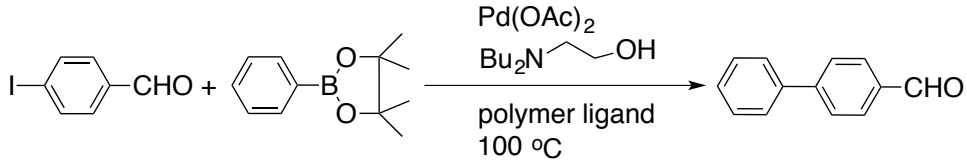
Finally I was successful in synthesizing the polymeric ligand, which was in a pure state. The molecular weight of the polymeric ligand was determined by GPC method and to be 53000. The observed average ratio of monomers was 1:33 (4-DPPS:DEAEMA). (see the Appendix for details of this calculation and for relevent spectra.) This polymeric ligand was in pure state without any starting monomers, phosphine oxide, and residual solvent. This polymeric ligand was far easier to synthesis than the ligands I attempted to prepare earlier.



Scheme 3.15. Synthesis of switchable polymeric ligand, where the ratio of x:y is 33:1

3.3.4 Suzuki-Miyaura Cross-Coupling Reaction

To analyze whether the phase-switchable polymer is able to function as a switchable ligand and able to facilitate the post-reaction separation of the desired organic product from catalyst and undesired inorganic byproduct, I tested it as a ligand in a Suzuki-Miyaura cross-coupling reaction. In this case, the reagents consisted of 4-iodobenzaldehyde and phenyl boronic acid pinacol ester with palladium(II) acetate acting as a catalyst, and the SHS 2-(dibutylamino)ethanol being used as the solvent and base. It was found that the synthesized polymer (acting as a ligand) provides good conversion to the desired product.



Scheme 3.16. Suzuki-Miyaura cross-coupling reaction of 4-iodobenzaldehyde and phenylboronic acid pinacol ester in water with palladium acetate in the presence of the phase switchable polymer ligand and 2-(dibutylamino)ethanol.

The above reaction was carried out under argon. When the reaction was

completed, it was allowed to cool to room temperature and the mixture was transferred into a vial under the same conditions as shown as in Fig. 3.1.a

a b c

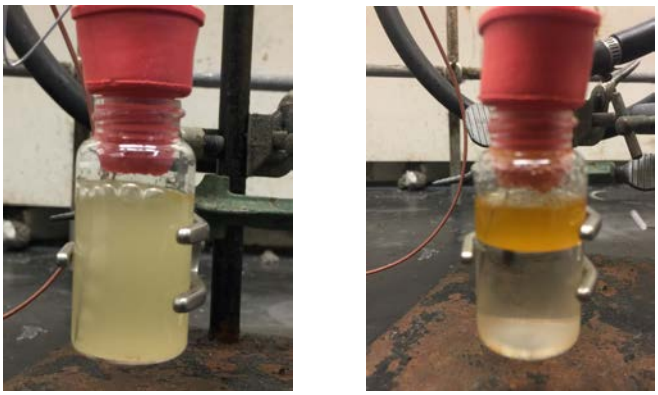
Figure 3.1. (a) A solution after the completion of Suzuki-Miyaura cross-coupling reaction using phase switchable polymer ligand; (b) a biphasic mixture after the addition of water into the Suzuki-Miyaura cross-coupling reaction mixture; and (c) the biphasic mixture after the addition of CO_2

Once in the vial, a volume of deionized water twice that of the reaction mixture was added under argon, creating a biphasic mixture as shown in Fig. 3.1 b.

When CO_2 was passed into the solution, the ionic strength was increased and a biphasic system was generated in which the catalyst and switchable hydrophilic solvent (SHS) were protonated and therefore resided in the aqueous phase, whilst the desired organic product was separated (Fig. 3.1 c). The organic phase could then be removed by

filtration or decantation depending upon whether the product is solid or liquid. In this experiment the organic product was separated by filtration.

After the desired organic product had been separated from the aqueous phase, the aqueous solution was transferred to another vial and argon gas was passed through it. When the CO_2 had been completely removed from the solution, the deprotonated SHS and catalyst now formed a biphasic mixture consisting of an aqueous layer (water, undesired inorganic byproduct) and an organic layer (SHS and catalyst), as shown as in Fig. 3.2 (a) and (b) below.



a b

Figure 3.2. (a) Aqueous solution of protonated SHS, catalyst and undesired inorganic by-product before passing argon gas through the mixture, (b) biphasic solution (upper layer deprotonated SHS and catalyst where as lower layer aqueous) after passing argon gas.

Once the aqueous layer had been separated from the deprotonated SHS and catalyst, a fresh supply of organic substrate was added and the reaction repeated. A yield of 95 % of the biaryl compound (first run) was obtained. Due to the solubility of inorganic byproduct in water it remained in water during the separation of organic

product.

The organic product was dried and characterized by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy. The product was found to be quite pure. The NMR spectra match those reported in the literature. There were no peaks corresponding to SHS, catalyst, polymer, or starting materials.

Table 3.1 Conversions of 4-iodobenzaldehyde to biaryl product using phase-switchable polymer ligand followed by separation in a biphasic water/2-(dibutylamino) ethanol mixture. The switch between monophasic and biphasic was achieved using the CO_2-triggered phase separation of switchable water.

Cycle	% conversion	% biaryl yield
1	100	95
2	60	50

The catalyst/SHS mixture was able to be recycled for only two runs. After two runs the conversion rate and biaryl product rate was very low which may be due to the loss of catalyst or poisoning of the polymer ligand.

3.4 Conclusion

From this experiment, it can be concluded that phase-switchable polymer ligand can also be used to separate the desired organic product, inorganic byproduct, SHS and catalyst in a general Suzuki-Miyaura cross-coupling reaction. In the second run the

conversion was significantly lower, suggesting that either much of the catalyst was lost in the separation or the catalyst was insufficiently stable. Future work should evaluate these possibilities. Spectrophotometric methods could be used to evaluate the partitioning of the ligand or its complexes between an aqueous and an organic phase. On the other hand, if instability was the cause then probably the polymeric ligand dissociated from the metal atom. To enhance the strength of coordination of the ligand, it may help to make the phosphine-containing repeat units closer together, like in a block copolymer, so that chelation is facilitated. This ligand could also be studied for other aryl halides such as aryl bromides and aryl chlorides.

5. References

(1) Ravindar, V.; Hemling, H.; Schumann, H.; Blum, J. A New Synthesis of Hydrophilic Carboxylated Arylphosphines. *Synth. Commun.* **2006**, *22* (6), 841–851.

(2) Chou, W.; Pomerantz, M. N-Phenyl-P,P,P-Triarylphospha-.lambda.5-Azenes, Triarylphosphines, and Triarylphosphine Oxides. Substituent Effects on Nitrogen-15, Phosphorus-31, and Carbon-13 NMR Spectra. *J. Org. Chem.* **1991**, *56* (8), 2762–2769.

(3) Däbritz, F.; Jäger, A.; Bauer, I. Synthesis, Derivatisation and Structural Characterisation of a New Macrobicyclic Phosphane Oxide Cryptand. *Eur. J. Org. Chem* **2008**, *2008*, 5571–5576.

(4) Ferretti, G.; Dukat, M.; Giannella, M.; Piergentili, A.; Pigini, M.; Quaglia, W.; Damaj, M. I.; Martin, B. R. Homoazanicotine : A Structure-Affinity Study for Nicotinic Acetylcholine (nACh) Receptor Binding. *J. Med. Chem.* **2002**, *45* (21), 4724–4731.

(5) Boersch, C.; Merkul, E.; Müller, T. J. J. Catalytic Syntheses of N-Heterocyclic Ynones and Ynediones by In Situ Activation of Carboxylic Acids. *Angew. Chem. Int. Ed.* **2011**, *50*, 10448–10452.

(6) Safer, D.; Bolinger, L.; Leigh, J. S. Undecagold Clusters for Site-Specific Labeling of Biological Macromolecules ; Simplified Preparation and Model Applications. *J. Inorg. Biochem.* **1986**, *26*, 77–91.

Chapter 4

Conclusions and Future Work

4.1 Conclusions

In the second part of thesis, the work was begun with the aim of designing and synthesizing a phase switchable ligand and using this ligand to separate the desired organic products, inorganic byproducts, catalyst and ligand in three fractions so that the overall economic and environmental cost of the chemical reaction and separation could be minimized. During the synthesis of the phase switchable ligand, however, many methods were unsuccessfully attempted.

The first method was to synthesize tris[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl-phenyl)]phosphine. To synthesis this compound I started with 4-bromobenzonitrile as discussed in chapter 3. The tris(4-cyanophenyl)phosphine was insoluble in cold and hot concentrated HCl and was not converted to 4,4′,4′′- phosphinetriyltribenzoic acid so this method was abandoned.

Another attempted method was to synthesized tris[(p-N,N dimethylethylenediaminecarboxamido)phenyl] phosphine oxide. To synthesized this ligand tris(p-tolyl)phosphine was chosen. This approach successfully led to the synthesis of tris[(p-methoxycarbonyl)phenyl]phosphine oxide, but when this compound was reduced, mixtures of tris[(p-methoxycarbonyl)phenyl]phosphine and tris[(p-methoxycarbonyl)phenyl]phosphine oxide were obtained. The separation of these mixtures was unsuccessfully attempted using column chromatography (DCM/hexane, 1:1) because the major product in these mixtures was the desired tris[(p-

methoxycarbonyl)phenyl]phosphine, I tried to synthesized tris[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl-phenyl)]phosphine using the above mixture. This produced mixtures of tris[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl-phenyl)]phosphine and tris[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl-phenyl)]phosphine oxide. Attempts to separate this mixture using column chromatography failed. No doubt further modification and testing of this approach would eventually produce the desired ligand, but the synthetic difficulties encountered prompted a reconsideration of the design of the switchable ligand. It seemed that another design, specifically a polymer, would better offer the desired combination of ease of synthesis with effective switching.

Therefore another method was used to synthesize a phase switchable polymer ligand from 4-DPPS and DEAEMA. The preliminary results, especially those from 4-DPPS and DEAEMA, represent a good starting point for the development of phase switchable polymeric ligands, an approach which is now being pursued by a new student in the Jessop group. The phase switchable polymer ligand was synthesized and the synthesis of a new polymer ligand has been confirmed by NMR characterization. An appealing feature of this ligand was stability. The ligand, in the solid state, was highly stable even when kept for a long time in open air. This ligand was successfully tested for Suzuki-Miyaura cross coupling as shown in chapter 3. The desired biaryl products were obtained and more importantly the switching procedure with this ligand made it possible to separate the desired organic product, the inorganic byproduct, as well as the catalyst into three fractions. Such a three-way post-reaction separation should have utility for homogeneously-catalyzed reactions that generate hydrophobic products and hydrophilic byproducts or, potentially, the reverse.

4.2 Future work

Future work on the first project should further investigate the apparent relationship between palladium nanoparticle formation and successful conversion of aryl halides. Would conditions or additives that stabilize such nanoparticles or promote their formation enhance the rate of the coupling reaction? The conversions and yields could also be improved by a screening of reaction conditions, and the proposed procedure for recycling the aqueous phase should be explored. The prevention of PBA hydrolysis should be studied by using a drop-wise mechanism to slowly add the PBA in order to avoid its rapid hydrolysis to form benzene and to maintain its availability to react with the aryl halide.

Future work on the second project should further investigate how the polymer ligand could be improved. The molecular weight of synthetic polymer ligand was 53,000 but a lower molecular weight of about 10-15,000 might be more appropriate. Moreover the ratio of monomers was 1:20 4-(diphenylphosphino)styrene : 2-(diethylamino)ethyl methacrylate but the ratio of monomers actually incorporated into the polymer might differ from the ratio used. In addition, varying the ratio would make it possible to find the best balance between cost, catalyst stability, and switching ability. Increasing the content of the amino group in the polymeric ligand would enhance its switching properties due to the increase in the number of protonatable sites but would add to the mass and cost of the ligand. I tried the Suzuki-Miyaura cross coupling reaction using aryl iodide as a starting material. In future one could try other aryl halides such as bromides and chlorides.

Future work on the catalyst recycling system describe in chapter 3 should include the continued optimization of conditions, catalyst, and the screening of more polymeric

ligands for the Suzuki-Miyaura cross-coupling reaction.

In closing, the phase switchable ligand and separation of desired organic product, inorganic byproduct and catalyst project has proven to be a quite fruitful research project. The versatility of the concept has opened a vast amount of future research with potential industrial utility. As stated previously, the purpose of researching green chemistry-based concepts, such as phase switchable ligand, is to move future green technologies towards industry where they can have the greatest impact both economically and environmentally. I hope that in the future, the research presented here will assist in bringing about the incorporation of phase switchable ligands, in addition to other CO_2-switchable technologies, into current and new industrial processes.

Appendix A: Supporting Information for Chapter 3

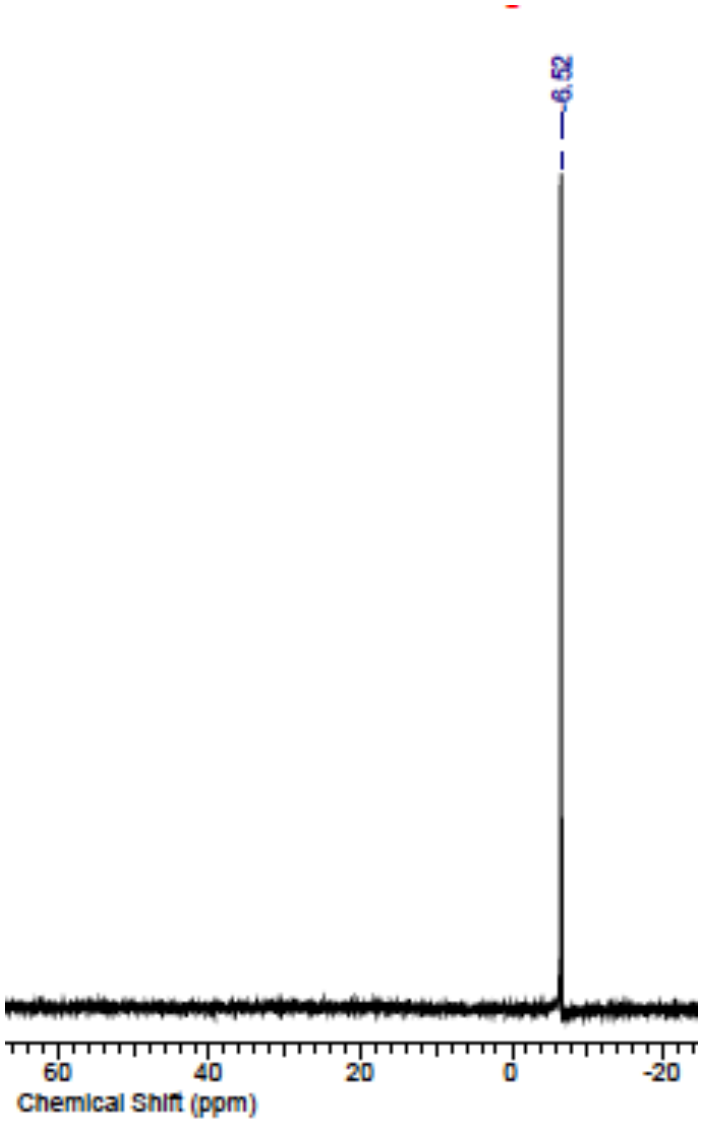


Figure A.1. $^{31}P\{^{1}H\}$ NMR spectrum of the polymeric ligand

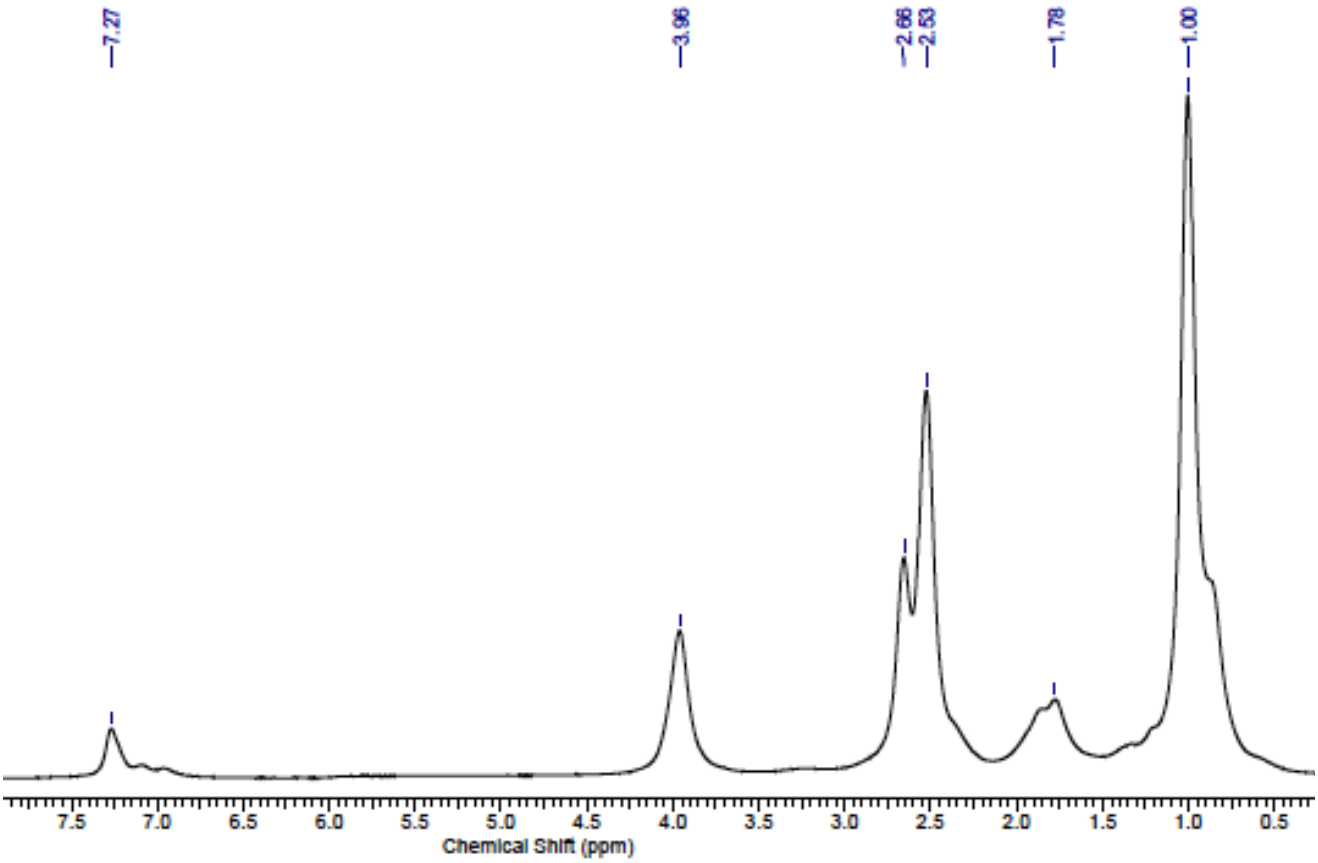


Figure A.2. ^{1}H NMR spectrum of the polymeric ligand

Table A.1. Monomers ratio of polymeric ligand

Integration of phosphorus monomers	1.04	**Integration of DEAEMA**	4.52
Number of hydrogen	14	Number of hydrogen	2
Ratio	0.074	Ratio	2.26
The ratio of monomers (4-DPPS:2-DEAEMA) is	3.17≈3	The ratio of monomers (4-DPPS:2-DEAEMA) is	97.18≈97

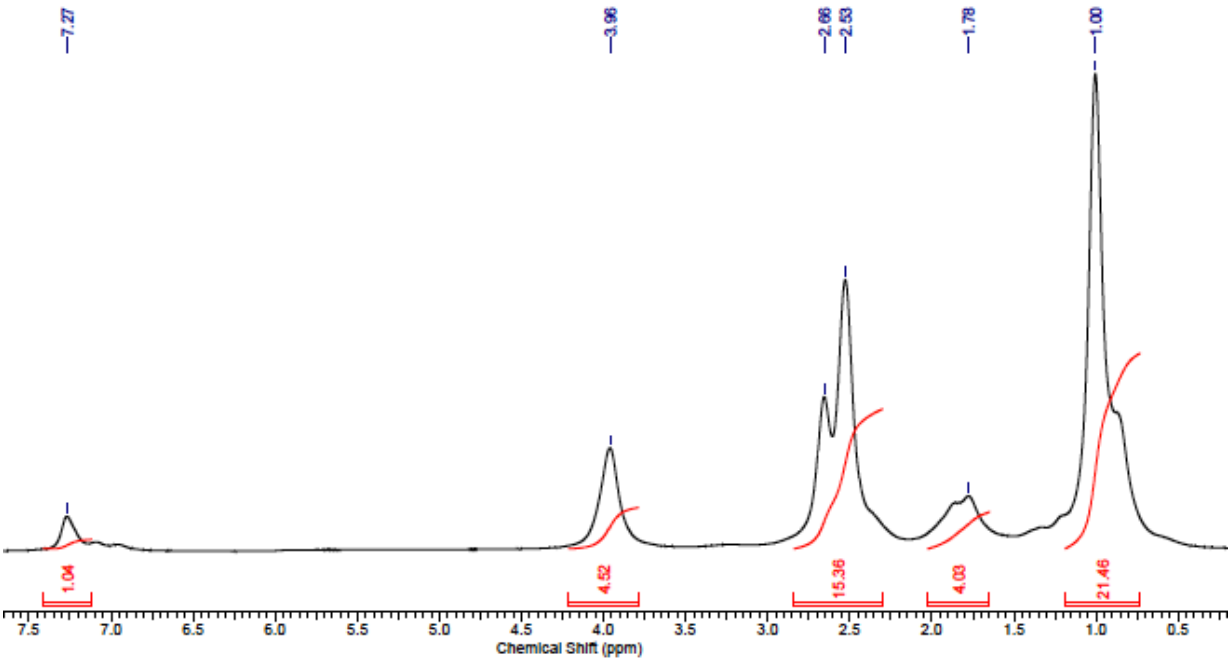


Figure A.3. Integrated ^{1}H NMR spectrum of the polymeric ligand