ABSTRACT

BRANNOCK, MOLLY CAROLINE. Investigating the Reactivity of Benzylic Nitriles in the Synthesis of a Multiple Cyano-Containing Polymer. (Under the direction of Dr. Christopher B. Gorman.)

Since the discovery of conducting organic polymers in the 1970's, researchers have investigated many types of materials for use in a variety of organic devices. Among these conductive materials is the class of aromatic ladder polymers. We have devised a route for obtaining a novel aromatic ladder polymer, and proposed a method that converts soluble precursor oligomers to cyclized isoquinoline-type conjugated products. The focus of the work presented here is the synthesis of the soluble precursor polymer. As shown below, this precursor material is comprised of multiple benzylic and aryl nitriles, both of which presented unique synthetic challenge. Palladium-catalyzed cross-coupling conditions were employed and multiple routes to form the carbon-carbon bond of the diarylmethane were tested. A model reaction was employed to optimize the conditions for the formation of this desired bond. We will describe the extension of this high-yielding model coupling to an initiator-assisted chain-growth polymerization. This method was utilized to obtain a polymeric material with a low polydispersity index and modest control over molecular weight.
Investigating the Reactivity of Benzylic Nitriles in the Synthesis of a Multiple Cyano-Containing Polymer

by
Molly Caroline Brannock

A dissertation submitted to the Graduate Faculty of North Carolina State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Chemistry

Raleigh, North Carolina

2012

APPROVED BY:

________________________________  ______________________________
Christopher B. Gorman    Elon Ison
Committee Chair

________________________________  ______________________________
Lin He        Walter Weare
DEDICATION

To my mother, Debbie, whose encouraging words have helped me through the difficult days, and loving support has made this journey easier. And to my father, Mark, whose work ethic and lack of complaining has motivated me to never give up. You have been with me every step of the way, and have made it possible for me to realize my dreams. Thank you for always reminding me of the goal.
BIOGRAPHY

The author was born Molly Caroline Brannock, the first-born daughter of Mark and Debbie Brannock, on a cold January morning in 1985. Reared in Mt. Airy, NC, better known as "Mayberry," Molly spent her early years surrounded by family and loving friends. Her maternal grandparents James Belton and Ruth Watson were constant sources of encouragement and love, while her paternal grandparents, Jack and Katherine Brannock, continually reminded her of how proud they were of their "little darling."

A new addition to the family came in July of 1992 with the birth of Molly's sister, Abigail, a true "miracle baby." The girls were inseparable, but had dramatically different personalities. While Molly was reserved and ambitious, always striving to please, Abigail was adventurous and independent, usually supplying the much-needed comic relief. Despite their differences, the girls enjoyed many of the same activities as children, and upon entering high school, both focused on tennis and piano. Participation in their church was also an integral part of their lives, and helped to mold them as compassionate, loving individuals.

At age 18, Molly graduated valedictorian of the North Surry High School Class of 2003, with numerous honors and awards. The most notable of these was a full-tuition scholarship to attend Salem College. Appreciating the historical aspects and advantages offered by a women's college, Molly enrolled at Salem, thankful that it was only 45 minutes from home. After a difficult first year in the pre-medicine program, Molly was recognized for receiving a 4.0 grade point average in her coursework. The following year was a struggle, however, as she questioned her career path and pursued many music classes as a
creative outlet. The summer of 2005 was a pivotal point in this young girl's life, as she was accepted into the summer intern program at R. J. Reynolds Tobacco Company. Because of her science background, she was placed in the flavor laboratory, as part of the applied research and development team. Here, Molly was surrounded by mentors Mike Dube, Cynthia Stokes, Bob Powell, and Al Gonzalez who instilled in her an appreciation for applied chemistry and the need for furthering her education. Upon returning to Salem, she changed her major to chemistry, and with a renewed sense of direction and purpose, continued her undergraduate studies. Over the next two years, she conducted research in the biochemistry lab and volunteered in the neonatal intensive care unit of the local teaching hospital, Wake Forest University Baptist Medical Center. She also continued to pursue her musical interests, but found that these talents were best used as a hobby and not a career. She graduated *magna cum laude*, with a Bachelor of Science degree in chemistry, and minors in biology and music, in May, 2007.

Feeling the need to continue her education, Molly applied to graduate school during her senior year at Salem. After being accepted to programs at the University of Michigan and NC State University, she visited both schools and found the research opportunities equally exciting. She opted to stay in North Carolina, and joined the Chris Gorman group in October, 2007. Molly enjoyed the concentration and focus of graduate work in comparison to the diversified liberal arts education she had received at Salem. The transition into research was full of challenges, however, and those first few months passed with many tears, but necessary lessons. Once adjusted to life as a bench chemist, she soon found the solitude
of late night reactions and purification techniques therapeutic, and developed the skills common to any good scientist: the ability to think critically and logically, and the need to question your own work, as well as the work of others. She was recognized for her accomplishments by winning the departmental poster session, and the Bereman Family Award for Excellence in Teaching. Molly also received a national travel grant from the American Chemical Society (ACS) Women Chemist's Committee to present the results of her research at the national meeting in Washington, D.C. She presented a second time at the national meeting in Boston, after receiving the ACS Organic Division travel award.

During Molly's final year of graduate school, she was offered a position in BASF's Professional Development Program, which consists of two nine-month rotations at various corporate locations, and is scheduled to begin in July, 2012. Full of faith, Molly hopes to enter this next phase of her life, relying on the foundation that has carried her thus far: an ever-present God, her supportive family and friends, and the knowledge that her life has a purpose.

"A man's heart deviseth his way: but the Lord directeth his steps."

-Proverbs 16:9
ACKNOWLEDGMENTS

At a recent graduation ceremony, the speaker asked the graduates to reflect upon their educational journey, and the people that had helped them along the way. He reminded them that "No one has made it here today by themselves." Truer words have never been spoken.

As I think back on the many individuals that have helped me on my journey, I am overwhelmed. Although there are far too many to name here, I would like to express my deep appreciation for the ones that went the extra mile to invest in my life. Many thanks to those few special teachers in elementary school that taught me to respect others and to take pride in my work, those in high school that stood by me when I was most vulnerable and would not settle for anything but my best effort, and the professors at Salem that patiently waited for me to find myself. I would have never had the courage to try this without you.

As for Dr. Gorman, I thank you for being patient with me, and for helping me realize my potential. When I think back to the time that you caught me painting my fingernails in the lab five years ago, I cannot believe how much I have changed, and so much of that is because of you. I am continually amazed that someone as distinguished and accomplished as you would devote so much time and energy to their students. For every page you proof-read, and every topic sentence you corrected, for catching all the typos in my oral presentations, and every letter of recommendation you wrote, I sincerely thank you. Selecting you as an advisor has been one of the best decisions I have ever made, and I hope to one day make you very proud.
I would also like to take this opportunity to thank my committee members, whose advice and guidance helped me reach this point. I am grateful that you agreed to serve on my committee, as I know your time is precious. As for the members of the Gorman group and students in Partners III that were always there to lend a hand or listening ear, I wish you all the very best. We've shared ideas, frustrations, and critiqued each other's work for so long that it will seem strange to work without you. You have made my days in graduate school more pleasant with occasional coffee breaks, funny stories, and warm smiles.

This work was supported in part by the Department of Energy (Grant DE-FG02-5ER46238). Additional funding was obtained from the North Carolina Biotechnology Center and the NCSU Department of Chemistry.
# TABLE OF CONTENTS

List of Tables ............................................................................................................... xii

List of Figures ............................................................................................................. xiii

List of Schemes ........................................................................................................... xv

1. **Chapter 1: Introduction** ................................................................................ 1
   
   A. Organic conducting materials ....................................................................... 2
   
   B. Proposed ladder polymer .............................................................................. 6
      
      1. Synthesis of the precursor polymer ............................................................ 6
      
      2. Conversion to the fused-ring ladder polymer ............................................. 9
      
      3. Outline of the thesis .................................................................................. 9
   
   C. References ..................................................................................................... 11

2. **Chapter 2: Overcoming challenges in the palladium-catalyzed synthesis of electron deficient ortho-substituted aryl acetonitriles** ........................................ 13
   
   A. Introduction .................................................................................................... 14
   
   B. Results and Discussion .................................................................................. 17
      
      1. Exploration of NAS pathway ...................................................................... 17
      
      2. Exploration of the Pd-catalyzed pathway .................................................. 19
      
      3. pKa determinations ..................................................................................... 21
      
      4. Optimization of base and solvent ............................................................. 22
5. Optimization of phosphine ligand ................................................................. 25

C. Conclusions ............................................................................................... 26

D. Experimental ............................................................................................. 27

1. Instrumental analysis .................................................................................. 27

2. pKa measurements ....................................................................................... 27

E. References .................................................................................................... 32

3. Chapter 3: Step-growth polymerizations using A-B monomers ............. 34

A. Introduction ............................................................................................... 35

B. Results & Discussion .................................................................................. 37

1. Effects upon variation of the polymerization conditions ....................... 43

2. Characterization of step-growth polymerization products by GPC, H-NMR, and MALDI ................................................................. 44

C. Conclusions ............................................................................................... 53

D. Experimental ............................................................................................. 54

E. References .................................................................................................... 64

4. Chapter 4: Use of protecting groups to replace the α-proton of the benzyl nitrile on the A-B monomer ................................................................. 65

A. Introduction ............................................................................................... 66
B. Results and Discussion .......................................................................................... 69

1. Trimethyl silyl as a protecting group ................................................................. 69

2. Ethyl ester as a protecting group ....................................................................... 74

C. Conclusions ........................................................................................................ 78

D. Experimental ..................................................................................................... 78

E. References ......................................................................................................... 82

5. Chapter 5: Attempts to form cyanodiarylmethanes using organozinc nucleophiles via Negishi couplings .......................................................... 84

A. Introduction ....................................................................................................... 85

B. Results and Discussion ..................................................................................... 87

1. Explorations of the method reported by Knochel et al.1 ................................... 87

2. Explorations of the method reported by Hartwig et al.14 ............................... 96

C. Conclusions ....................................................................................................... 99

D. Experimental ..................................................................................................... 99

E. References ......................................................................................................... 108

6. Chapter 6: Attempted polymerization using the palladium-catalyzed decarboxylation of cyanoacetate salts for carbon-carbon bond formation ..... 110

A. Introduction ....................................................................................................... 111

B. Results and Discussion ..................................................................................... 112
1. Shang method for monoarylation ................................................................. 112

2. Yeung method for diarylation ...................................................................... 119

C. Conclusions ................................................................................................. 123

D. Experimental ............................................................................................... 123

E. References .................................................................................................... 127

7. Chapter 7: Initiator-assisted chain-growth polymerizations .................... 129

A. Introduction ................................................................................................. 130

B. Results and Discussion ............................................................................. 143

C. Conclusions ............................................................................................... 151

D. Experimental ............................................................................................... 152

E. References .................................................................................................... 155
LIST OF TABLES

Table 1.1: Ladder polymers with calculated ionization potential (IP) in eV, and bandgap energy in eV. \textsuperscript{16-18} .................................................................4

Table 2.1: Results of coupling 5 with 4 under Pd-mediated coupling conditions. ........20

Table 2.2: Variation of Base. .........................................................................................23

Table 2.3: Variation of solvent and then further variation of base. ...............................25

Table 2.4: Variation of ligand. .........................................................................................26

Table 3.1: Polymerization of 5a under various conditions. ............................................40

Table 3.2: Comparison of trimer and polymer reactions. ................................................41

Table 3.3: Polymerization of 5b and 5c. .........................................................................43

Table 4.1: Unsuccessful model couplings to obtain 4 using various conditions. ............77
LIST OF FIGURES

Figure 1.1: Comparison of conductivities of several insulators, semiconductors, and metals as presented by Jain.5,15 .................................................................3

Figure 1.2: Illustration of direct writing. Conversion of an insulating material (precursor polymer) directly into a conducting material (fused-ring ladder polymer). ..6

Figure 3.1: Molecular weight based on % conversion of monomer in (a) chain polymerizations, (b) step-growth polymerizations, and (c) living polymerizations as presented by Odian.1 .........................................................................................36

Figure 3.2: Mechanical strength of a material based on molecular weight, as presented by Odian.1 ...........................................................................................................37

Figure 3.3: MALDI of MCB-II-82. ......................................................................................................................46

Figure 3.4: UV/Vis of deprotonated monomer 5a and resulting polymer. ......................48

Figure 3.5: Absorption spectra of the trimer, cyclized trimer and hexyl polymer. .........49

Figure 4.1: Proposed routes A, B, and C for synthesis of the silylated-monomer. .......71

Figure 4.2: Comparison of the reactions of two nitriles with lithium bases and TMSCl, benzyl cyanide (top)17 and ortho-cyano benzyl cyanide (bottom).3 .............73

Figure 6.1: 1H-NMR spectrum of MCB-VI-96 (THF layer)..................................................116

Figure 6.2: IR spectrum of MCB-VI-96 (THF layer)..............................................................117

Figure 6.3: Proposed route for the formation of diarylacetonitriles, as presented by Yeung et al.15 ........................................................................................................119
Figure 6.4: $^1$H-NMR (top) and IR spectrum (bottom) of MCB-VII-15. .........................123

Figure 7.1: Literature example of hindered coupling in the synthesis of polyamides, as presented by Yokoyama and Yokozawa. $^4$ .................................................................132

Figure 7.2: Schematic diagram of the initiator-assisted coupling with an A-B type monomer leading to a chain-growth condensation polymer, as presented by Yokoyama and Yokozawa. $^4$ ...........................................................................133

Figure 7.3: Top: Polymerization of 1 with 3 as presented by Sugi et al. Coupling conditions include 1.1 equiv of a lithium base in THF (initial concentration of 1=0.40M). Bottom: linear correlation of molecular weight ($M_n$) with respect to the feed ratio (left), polydispersity ($M_w/M_n$) for varying initiator ratios (right), and consistency of initiator to end group units with respect to feed ratio. ..............................................................................................................135

Figure 7.4: Comparison of the (a) resonance and (b) inductive effects in the polymerization of para- and meta-substituted monomers, respectively, as presented by Mikami et al. $^8$ ........................................................................................................................................137

Figure 7.5: Synthesis of polyesters from monomer 32 using an electron-withdrawing initiator and 18-crown-6 as phase-transfer catalyst (originally presented by Yokozawa and Suzuki. $^{10}$ .................................................................................................................................139

Figure 7.6: Comparison of aryl halides in the model coupling, step-growth coupling, and chain-growth coupling. The circled species highlight the aryl halide in each coupling scenario for ease of comparison.................................................................143

Figure 7.7: Adaptation of Yokozawa's biphasic polymerization using the ethyl cyanoacetate monomer derivative.................................................................150
### LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Scheme 1.1:</th>
<th>Proposed synthesis of an aromatic ladder material.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 1.2:</td>
<td>Self-reaction of alkyl nitriles in the presence of base as shown in the Thorpe reaction.</td>
</tr>
<tr>
<td>Scheme 1.3:</td>
<td>Resonance forms of deprotonated alkyl nitriles and routes to the thermodynamically-favored nitrile (right) and the kinetically-favored ketenimine (left).</td>
</tr>
<tr>
<td>Scheme 2.1:</td>
<td>Two possible methods of coupling to form a bis(o-cyanophenyl) acetonitrile (M = metal counterion, LG = leaving group).</td>
</tr>
<tr>
<td>Scheme 2.2:</td>
<td>Example of the conversion of a multiple-cyano containing oligomer to the fully cyclized, aromatic product.</td>
</tr>
<tr>
<td>Scheme 2.3:</td>
<td>Equilibrium between benzylic anions.</td>
</tr>
<tr>
<td>Scheme 2.4:</td>
<td>NAS reactions run to compare with previously reported, Pd-mediated couplings. Conditions: (CH₃)₂CHCN, sodium hexamethyldisilazide (NaHMDS), Toluene (i) 1a, 100°C, 1 h (ii) 1b, 90°C, 2 h.</td>
</tr>
<tr>
<td>Scheme 2.5:</td>
<td>Attempted formation of 6a via NAS.</td>
</tr>
<tr>
<td>Scheme 2.6:</td>
<td>Preparation of 5b.</td>
</tr>
<tr>
<td>Scheme 3.1:</td>
<td>Synthesis of the hexyl, tert-butyl, and methyl A-B monomer derivatives.</td>
</tr>
<tr>
<td>Scheme 3.2:</td>
<td>Possible pathways to the C- and N-arylated products resulting from resonance forms of the deprotonated benzyl nitrile.</td>
</tr>
<tr>
<td>Scheme 3.3:</td>
<td>Comparison of A-A + B-B and A-B coupling pathways.</td>
</tr>
</tbody>
</table>
Scheme 4.1: Shift of the benzyl proton during cyclization of the deprotonated monomeric nitrile in basic solution (top) and the coupled, doubly anionic species (bottom).

Scheme 4.2: Resonance structures of the deprotonated monomer showing delocalization of the anion through the ring and aryl nitrile.

Scheme 4.3: Proposed formation of cyclized product derivatives as presented by Behof. 3

Scheme 4.4: Representative coupling of an aryl halide with an alkyl silylated acetonitrile derivative. 7

Scheme 4.5: Proposed synthesis of the silyl-protected precursor and removal of the protecting silyl group.

Scheme 4.6: Proposed model coupling of 2-bromobenzonitrile with the protected cyano ester nucleophile 3 to obtain 4.

Scheme 4.7: Two unproductive routes to the cyano ester starting material: nucleophilic aromatic substitution (left) and palladium-catalyzed cross-coupling (right).

Scheme 4.8: Formation of 3 based on the methods of Deady et al. 24

Scheme 5.1: Routes to intermediates A, B, C, and D in the reaction of an isopropyl-metal (M) nucleophile and an aryl (Ar)-halide (X) in the presence of palladium (Pd) and ligand (L), as presented by Han and Buchwald. 5

Scheme 5.2: Coupling examples of alkyl zinc halide nucleophiles and aryl iodides containing acidic functionality. 1

Scheme 5.3: Proposed model coupling based on conditions optimized by Knochel for similar substrates.
Scheme 5.4: Adapted strategy for formation of the model nucleophile 1 based on the experimental details reported by Knochel.1 ................................................89

Scheme 5.5: Literature reaction for the formation of a similar derivative of the alpha-bromo benzyl nitrile.21 ...............................................................90

Scheme 5.6: Synthesis of the methoxy A-B monomer derivative.................................94

Scheme 5.7: Formation of a benzylic nitrile through the coupling of an alkyl nitrile and aryl bromide reported by Wu and Hartwig.14 ...............................................96

Scheme 5.8: Synthesis of the organozinc 1 for use in the model coupling to form 8. ....97

Scheme 5.9: Synthesis of the organozinc 1 for use in the model coupling to form 2. ...98

Scheme 5.10: Attempted polymerization of secondary nitrile A-B monomer 9a ..........99

Scheme 6.1: Proposed mechanism as presented by Goossen for decarboxylative synthesis of biaryls, where L is a ligand (phosphine, phenanthroline, or other), and R and R’ represent the multiple aryl halides and benzoic acids coupled.4 ....112

Scheme 6.2: Reference reaction for the formation of 2-phenylacetonitrile.3 ...............113

Scheme 6.3: Formation of cyanoacetate salts, M=Li, Na or K.3 ..............................114

Scheme 6.4: Model coupling of ortho-cyano bromobenzene and sodium cyanoacetate.115

Scheme 6.5: Attempted polymerization using Shang's method. ............................115

Scheme 6.6: Proposed decarboxylative coupling followed by subsequent deprotonation by the cyanoacetate salt and formation of the nucleophile. ......................118
Scheme 6.7: Reference reaction showing a mixture of mono- and diarylated products. 121

Scheme 6.8: Model coupling using the diarylation conditions.................................121

Scheme 7.1: Example of $S_N2$-type oxidative addition as presented by Crabtree.\textsuperscript{1}............131

Scheme 7.2: Proposed intramolecular catalyst transfer mechanism in the synthesis of oligothiophenes from monomer 31, as presented by Yokoyama and Yokozawa.\textsuperscript{4} ............................................................140
1. Chapter 1: Introduction
A. Organic conducting materials

Although much work remains to be done in the field of conducting organic materials, devices constructed of these carbon-based materials have several obvious advantages to traditional silicon or metal devices. Assuming a relatively efficient device, organic materials are superior from two perspectives. First, they are less expensive to make, requiring milder processing than their metal or metalloid counterparts, and thus are generally more environmentally-benign. For example, thin layers of organic molecules can be deposited by evaporating a solution onto a substrate. An analogous metal layer requires a high vacuum, often high temperature evaporation process. Secondly, they hold potential for flexible and lighter products and applications, some of which would be impractical with metals or metalloids. As devices decrease in size, the possibility that metals will electromigrate increases.\textsuperscript{1-3} Electromigration describes the process by which metals fail when a bias is applied.\textsuperscript{1-3} Carbon-based materials are envisioned to be superior in this respect as their covalent nature is not limited by size reduction.

Small molecules and conjugated polymers are two main types of organic materials currently used in devices.\textsuperscript{4} To differentiate, small molecules are discrete, generally with a molecular weight of ca. 100-500 Da, whereas conjugated polymers have higher molecular weights, and are polydisperse in weight. Films of both small molecules and polymers have reached conductivities equivalent to that of some metals. Figure 1.1 below shows organic materials in order of their relative conductivity, with the highest materials in the range of copper, and provides a basis of comparison for conducting organic polymers to insulators, semiconductors, and metals.\textsuperscript{5} Small molecules have currently not reached the equivalent
efficiency of polymers in devices like solar cells, but are rapidly gaining momentum as a result of their increased solubility, shorter synthesis times and easier characterization. Polymer materials, however, have been explored extensively, particularly as materials in photovoltaic devices, and have become the topic of many patent applications. Recently, researchers have reported several advantages of polymeric materials for use in devices (e.g. photovoltaics) such as solution processing, higher charge carrier mobilities, and the large number of options for controlling the morphology of a film through choice of solvent, annealing methods, and relative concentration of components in the depositing solution. Improvements in these areas has translated into more efficient devices, but additional factors may be optimized to realize the full potential of organic conducting materials.

Figure 1.1: Comparison of conductivities of several insulators, semiconductors, and metals as presented by Jain.
Within the field of conductive polymers is the class of fused-ring aromatic ladder polymers. These materials offer unique advantages and challenges. Efficient devices experience high electrical conductivity, and good electrical conductors have small bandgaps. A few examples of ladder polymers and their respective bandgaps and ionization potentials are shown in Table 1.1. In each case, a bandgap is predicted that is much lower than an analogous, unfused polymer. However, ladder polymers are inherently insoluble, resulting in precipitation of oligomers during synthesis limiting polymer growth. Therefore, they have limited commercial applications.

Table 1.1: Ladder polymers with calculated ionization potential (IP) in eV, and bandgap energy in eV.\textsuperscript{16-18}

<table>
<thead>
<tr>
<th>Structure</th>
<th>IP, eV</th>
<th>Eg, eV</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>5.8−6.0</td>
<td>0.0−0.2</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>8.1</td>
<td>0.0</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>4.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

A viable and direct route to ladder polymers is through a soluble precursor polymer that can be converted to the conductive ladder form. This route helps to avoid the problems caused from insolubility such as the difficulties in synthesis, characterization of the resulting
polymer, and processing. Optimally, this precursor should be soluble in a variety of solvents, and easily synthesized with low polydispersity. It should be able to be characterized by a variety of methods, and used to form durable films that are amenable to use in electronic devices such as thin film transistors and photovoltaics. Additionally, it must be able to undergo efficient conversion to the conductive form, preferably without the use of high temperatures or harsh chemicals.

To further highlight the conversion of a precursor polymer to the conductive ladder form, it should be noted that this step is often performed by a photolithographic method. By employing a mask, exposure to an energy source (i.e. laser) yields the conductive form. This is then followed by etching of the undesired material. Fabrication of this mask is tedious and time consuming, however. A more straightforward route would be advantageous, and make ladder polymers more accessible to commercial applications.

It is hoped that this conversion process could be facilitated by a single-step mask-less method, which we have referred to here as "direct writing." This process should be much more straightforward, only converting the desired material, without the need for a mask. An illustration of this is shown in Figure 1.2 below. The remaining precursor polymer on the surface can simply be washed away with solvent, leaving the patterned material behind. The solubility of this precursor also eliminates the need for the post-conversion etching steps.
Figure 1.2: Illustration of direct writing. Conversion of an insulating material (precursor polymer) directly into a conducting material (fused-ring ladder polymer).

B. Proposed ladder polymer

As part of this project, we attempt to synthesize a ladder polymer of the fused, isoquinoline structure shown below (Scheme 1.1) to serve as a potential semiconducting material in thin film devices. There are two key steps involved in obtaining this material. First, the synthesis of the precursor polymer with aryl nitriles and benzyl nitrile linkages should be optimized. Also, an efficient conversion method to the fused-ring form should be developed.

Scheme 1.1: Proposed synthesis of an aromatic ladder material.

1. Synthesis of the precursor polymer

The synthesis of such a precursor polymer is unprecedented, and an efficient method for synthesis should be developed. It was envisioned that palladium-catalyzed cross-coupling reactions could be employed to form the C-C bonds of the diarylmethane linkages. Catalytic
methods have been used to form diarylmethane linkages previously, even in the presence of nitriles. Although these couplings have proven to be successful, the reactivity of nitriles, particularly in the presence of base, has many documented challenges. One of these challenges is the potential to self-react to form enamines as shown in the Thorpe reaction below (Scheme 1.2).

Scheme 1.2: Self-reaction of alkyl nitriles in the presence of base as shown in the Thorpe reaction.

Additional issues encountered in the synthesis of alkyl/benzyl nitriles in the presence of base is the competition between C- and N- alkylation. This difference in reactivity is based on the resonance structures shown below (Scheme 1.3). The scheme also depicts how the thermodynamically-favored nitrile and the kinetically-favored ketenimine may result from the carbon and nitrogen anion resonance forms, respectively. There is precedence for this competition (c.f. C- versus O-alkylation of an enolate), and the ratio of isomeric products depends on conditions.
Scheme 1.3: Resonance forms of deprotonated alkyl nitriles and routes to the thermodynamically-favored nitrile (right) and the kinetically-favored ketenimine (left).

It has also been shown that some nitriles and ketenimines may exist as tautomeric pairs. Clarke et al. studied this equilibrium and suggested two main trends, both of which relate to the substituents on the alpha carbon. The first of these trends is related to the steric strain. As the bulkiness of the groups on the alpha-carbon increased, the ketenimine product was increasingly favored. This trend was illustrated by the addition of one, and then two pentamethylbenzene groups to alpha carbon. The second trend is related to electronic factors. Clarke observed that by adding electron-withdrawing groups to the alpha carbon the equilibrium shifted to favor the ketenimine product. In fact, researchers reported that by placing two highly electron withdrawing nitrile groups on the alpha-carbon to form the so-called cyanoform, that there is evidence to support the existence of both tautomers of the nitrile and ketenimine forms.

Many attempts to isolate this strong carbon acid have been made by researchers, however the structure has eluded most characterization methods to date. Bak and Svanholt examined the existence of HC₄N₃ over 30 years ago, and due to the highly polar nature and short lifetime of the compound, microwave spectroscopy was employed. This characterization
method provided evidence for a tricyanomethane structure that resulted from two, different, low-yielding synthetic methods. An ab initio calculation was also performed and the results presented in the same publication, suggesting a 10 kcal mol\(^{-1}\) preference for the tricyanomethane configuration as opposed to dicyanoketenimine.\(^{23}\) These findings will prove important in the synthesis of multiple cyano-containing molecules, as will be shown in the chapters that follow.

2. **Conversion to the fused-ring ladder polymer**

There is precedence for the conversion of similar small molecule derivatives via cyclization as presented by Tandel et al.\(^ {24}\) and expanded by Behof et al.\(^ {25-27}\) Conversion from the precursor polymer to the ladder polymer may present challenges, however. Issues with precursor solubility, or high temperature conversion steps to obtain the fused-ring ladder can prove problematic. Sometimes an alternative to heat can be used to convert the polymer (i.e. acids, light, chemical reagents). However, these alternatives are often harsh and can degrade the polymer. Also if the precursor or ladder polymer is unstable at any stage, the process will likely be unsuccessful in producing a useful, thin, semiconducting film. These issues will be explored in less detail in this thesis.

3. **Outline of the thesis**

The following chapters focus on the synthesis of the precursor polymer described above. Chapter 2 describes the process by which an optimized set of conditions were obtained for forming the diarylmethane C-C bond in a model coupling. This was done using excess base in the presence of nitriles, and employing a palladium catalyst. The next four chapters
explore attempted step-growth polymerizations using the optimum conditions found for the model coupling (Chapter 3), as well as a variety of alternate approaches, including the use of protecting groups (Chapter 4), alternate nucleophiles (also referred to as transmetallating reagents, Chapter 5), and base-free coupling conditions (Chapter 6). Finally, an initiator-assisted chain-growth polymerization was tested, and is discussed in Chapter 7.
C. References


2. Chapter 2: Overcoming challenges in the palladium-catalyzed synthesis of electron deficient ortho-substituted aryl acetonitriles

This chapter is the subject of a publication: “Overcoming the challenges in the palladium-catalyzed synthesis of electron deficient ortho-substituted aryl acetonitriles” Brannock, M. C.; Behof, W. J.; Morrison, G.; Gorman, C. B. *Org. Biomol. Chem.*, 2011, 9, 2661-2666.
A. Introduction

As part of an ongoing research program in the synthesis of cyano-containing polymers, we became interested in synthesizing oligomers and polymers with the general repeat unit shown in Scheme 2.1. We have recently reported the cascading cyclization of similar aryl and benzyl cyano-containing oligomers to form isoquinoline-type fused-ring molecules (Scheme 2.2). These conjugated materials may have potential for use in organic devices.

The key synthetic step here is the carbon–carbon bond formation of a benzyl/phenyl linkage to form a diaryl methane subunit. Scheme 2.1 shows the two logical bond deconstructions that could give rise to this linkage. The aryl group could be nucleophilic and the benzylic position would then be the electrophile (Scheme 2.1, top). Alternatively, these roles could be reversed (Scheme 2.1, bottom).

Using an aryl organometallic as a nucleophilic equivalent has been useful to prepare aryl–aryl and aryl–alkyl linkages. The use of aryl nucleophiles with ortho substituents, however, has had mixed results. In contrast, deprotonation of R\(_2\)CH\(_2\)CN or R\(_2\)CHCN and subsequent use as a nucleophilic equivalent has had several successful precedents. You and Verkade illustrated coupling of alkyl acetonitrile anions to aryl halides in the presence of a proazaphosphatrane ligand. Hartwig et al., Satoh et al. and Verkade et al. employed, with high efficiency, phenyl acetonitrile for monoarylations and acetonitrile for di-arylations. Culkin and Hartwig showed that the anion of alkyl nitriles could undergo a palladium-mediated coupling to aryl halides and studied the mechanism of this transformation in some detail. Wu and Hartwig later showed that an \(\alpha\)-silyl nitrile was an efficient palladium-mediated coupling partner to aryl halides in the presence of zinc fluoride.
Given these precedents, a cyanobenzyl nucleophile was selected for this coupling. Moreover, \( o \)-cyanophenyl acetonitrile is relatively acidic, (19.2 in dimethyl sulfoxide (DMSO))\(^{12} \) and thus easily deprotonated. The resulting carbanion would then be a suitable nucleophile in a carbon–carbon coupling reaction. The pK\( \alpha \) determination of similar molecules containing such groups will be reported below. Furthermore, the arene is relatively electron deficient which renders it a good electrophile.
Scheme 2.2: Example of the conversion of a multiple-cyano containing oligomer to the fully cyclized, aromatic product.

The examples given above suggest several challenges and raise several questions regarding the carbon–carbon bond forming reaction under study here. First, since our proposed arene is so electron deficient, can simple nucleophilic aromatic substitution compete with palladium-mediated coupling? This question may also be relevant in some of the examples shown above. Second, in the work above, limitations were observed when ortho cyano groups were present on the arene electrophile. The presence of o-cyano groups in our target might thus be an issue. Third, since the methine proton in the product (e.g. Ph$_2$(CN)CH) should be more acidic than the proton that must be removed in the starting material (e.g. Ph(CN)CH$_2$), can the reaction be driven forward in a reaction solution in which a less acidic proton must be removed in the presence of a more acidic proton? This issue is illustrated in Scheme 2.3.
Scheme 2.3: Equilibrium between benzylic anions.

In this chapter, nucleophilic aromatic substitution and palladium-mediated coupling reactions will be explored to determine how efficiently the reaction illustrated in the bottom half of Scheme 2.1 can occur. The relative efficacy of these two pathways will be compared. Choice of base, solvent, and catalyst/ligand will be shown to be key parameters in optimizing the palladium-catalyzed coupling. Finally, an optimal, high yielding route will be illustrated.

In the work of Hartwig et al.\textsuperscript{8, 10, 11} and You and Verkade\textsuperscript{6, 7} discussed above, both electron rich and electron deficient aryl halide substrates were explored. In the coupling of interest here, the aryl halide is electron deficient, begging the question as to whether, in this case, a nucleophilic aromatic substitution (NAS) reaction would be applicable. We tested this in three ways. First, a reaction from the literature was repeated under NAS conditions. Then from this, two new coupling reactions were explored.

**B. Results and Discussion**

1. **Exploration of NAS pathway**

Initially, the NAS pathway was investigated in the case of an electron deficient arene. Culkin and Hartwig reported formation of 2 from \( \rho \)-bromobenzonitrile (1a) in 99% yield in the presence of palladium acetate (Pd(OAc)\textsubscript{2}) and 2,2'-bis(diphenylphosphino)-1,1'-
binaphthyl (BINAP), and You and Verkade reported a similar reaction using \( p \)-chlorobenzonitrile (1b) to achieve 2 in 92\% yield in the presence of Pd(OAc)\(_2\) and a proazaphosphatrane ligand (Scheme 2.4).\(^6\) We repeated these reactions in the absence of palladium/ligand under the same conditions and obtained 42\% (X = Br) and 72\% (X = Cl) yield, respectively. Thus, palladium-mediated coupling does result in a higher yield. However, in this case, the results provide evidence for competition between NAS and the palladium-mediated pathway.

We then turned to the NAS of 2,6-dichlorobenzonitrile (3a) with \( o \)-cyanophenyl acetonitrile (4). When two equivalents of 4 were reacted with 3a in the presence of sodium tert-butoxide (NaO\(_\text{tBu}\)) (Scheme 2.5), only the mono-coupled product 5a was obtained in 91\% yield. When 5a was isolated and reacted with 4 for a longer period of time (72 h) and in excess (3.2 equivalents) base, only a small amount (13\%) of bis-coupled product 6a was isolated. This reaction was clearly inefficient for the formation of 6.
2. Exploration of the Pd-catalyzed pathway

Our strategy then shifted toward a palladium-mediated coupling given the poor results when attempting to prepare 6 via NAS. Culkin and Hartwig\(^8\) showed that Pd(OAc)\(_2\)/BINAP is an efficient palladium/ligand combination to couple phenyl acetonitrile anions with \(p\)-\(t\)Bu-bromobenzene. These conditions were used as the starting point to optimize the reaction for the formation of 6. Because it is the second coupling that is challenging, the reaction of 5 with 4 was explored. Since palladium-mediated couplings typically are more efficient on aryl bromides than chlorides, 3a was replaced with 3b, and 5b was synthesized in 93% yield using NAS in dimethyl formamide (DMF) (Scheme 2.6).

Scheme 2.6: Preparation of 5b.

Reaction of 4 and 5 under palladium-mediated conditions was then explored. The results are shown in Table 2.1. A maximum yield of 62% was obtained. Comparison of entries 1 and
2 in Table 2.1 indicates that use of the aryl bromide indeed does result in a higher yield. Comparison of entries 2 and 3 indicates that NAS is less efficient compared to palladium-mediated coupling. Comparison of entries 3 and 4 in Table 2.1 indicates that microwave heating was more efficient than thermal heating and gave a much higher yield of product. Moreover, extending the reaction time under thermal heating showed no further increase in yield when the reaction time was increased from 4 h to 6 h. For these reasons, microwave heating was used in all subsequent reactions. Also, poor yields were obtained when fewer than 3 equiv. of base were added. This point is treated below.

Table 2.1: Results of coupling 5 with 4 under Pd-mediated coupling conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. K-O/Bu</th>
<th>Heat Source</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>% 6b&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.2</td>
<td>Microwave</td>
<td>130</td>
<td>5 m</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>3.2</td>
<td>Microwave</td>
<td>130</td>
<td>5 m</td>
<td>33&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
<td>Microwave</td>
<td>130</td>
<td>5 m</td>
<td>62</td>
</tr>
<tr>
<td>4a</td>
<td>3.2</td>
<td>Thermal</td>
<td>80</td>
<td>2 h</td>
<td>17</td>
</tr>
<tr>
<td>4b</td>
<td>3.2</td>
<td>Thermal</td>
<td>80</td>
<td>4 h</td>
<td>37</td>
</tr>
<tr>
<td>4c</td>
<td>3.2</td>
<td>Thermal</td>
<td>80</td>
<td>6 h</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>Microwave</td>
<td>130</td>
<td>5 m</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>Microwave</td>
<td>130</td>
<td>5 m</td>
<td>5</td>
</tr>
</tbody>
</table>

Conditions: 0.3M THF, 1.2 eq. 4, 0.1 eq. Pd(OAc)<sub>2</sub>, 0.2 eq. BINAP. <sup>a</sup>Values obtained from HPLC with an estimated error of ± 5%. <sup>b</sup>Molecule 5a was used instead of molecule 5b. <sup>c</sup>No Pd catalyst or BINAP were added.
Palladium-catalyzed coupling can be greatly influenced by the base employed. Furthermore, the data above indicate that excess base is required. This requirement likely results because (1) both 5 and 6 are deprotonated preferentially to 4 and (2) any equilibrium between 5\(^{-}\) or 6\(^{-}\) and 4 favors 5\(^{-}\) or 6\(^{-}\). At first, we speculated that the opposite might be true. You and Verkade showed that the reaction between bromobenzene and benzyl cyanide to form diphenyl acetonitrile could be accomplished in 93% yield using 1.4 equivalents of sodium hexamethyl disilazide.\(^6\) The pK\(_a\) values of benzyl cyanide and diphenyl acetonitrile are 21.9 and 17.5, respectively.\(^{14}\) Thus, we speculate that there likely was some equilibrium between the anion of the product and that of the starting material in this case. However, in our case, the o-cyano groups likely have an important influence on the pK\(_a\) (and more importantly, the relative pK\(_a\)) values of our starting materials and product.

3. pK\(_a\) determinations

To determine the relative acidity of the protons on 4, 5 and 6, pK\(_a\) measurements in DMSO were performed using the procedure developed by Bordwell \textit{et al.}\(^{15}\) The pK\(_a\) of 4 was measured to be 19.2, consistent with that reported in the literature.\(^{12}\) Molecule 5\(_b\) had a pK\(_a\) of 13.6 and molecule 6\(_b\) had pK\(_{a1}\) and pK\(_{a2}\) values of 13.2. The similarity of the two pK\(_a\) values for 6\(_b\) is consistent with the findings of Streitwieser where unfused diprotic structures were determined to have indistinguishable pK\(_a\) values.\(^{16}\) Thus, if the anion of 4 is produced, it is likely in equilibrium with the anion of 5 (c.f. Scheme 2.3) and the (di)anion of 6. Given the values, this equilibrium is likely to be unfavorable, resulting in the need to use more than
one, or even two, equivalents of base. This need is in contrast to the results reported by You and Verkade above.

The pKa values may be only partially relevant, however. There are reports that suggest weak bases such as potassium carbonate (K$_2$CO$_3$)$^{17}$ and dimethylamino pyridine (DMAP)$^{18}$ are able to deprotonate 4. However, in THF the relative acidities of 4–6 might be quite different. Based on computations, Ding et al. suggest that neutral acids are typically eleven orders less acidic in THF than in DMSO.$^{19}$ Furthermore, even if the anions of 5 and 6 are produced, they may be innocent or unreactive. Their reactivity particularly depends on the solvent and counter-cation present.$^{20}$ Thus, some variation of base, solvent and counter-cation was explored.

4. Optimization of base and solvent

To explore variation of base in an efficient manner, reactions were conducted under otherwise identical conditions and analyzed by HPLC. Both the percentage of unreacted 5 and the percentage of 6 are given in Table 2.2. Weak bases (entries 1–5) clearly were ineffective. Potassium tert-butoxide yielded the greatest conversion. Addition of 18-crown-6, however, resulted in little recovered starting material or product. Thus, use of the larger potassium counterion favors product formation, but complexation of the potassium tends to produce side products (e.g. loss of starting material without formation of product).
Table 2.2: Variation of Base.

\[
\text{5b} \quad \text{pKa (DMSO)} = 13.6 \quad \text{4} \quad \text{pKa (DMSO)} = 19.2 \quad \text{6b} \quad \text{pKa (DMSO)} = 13.2
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield % of a Recovered 5b</th>
<th>Yield % of a Recovered 6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CsF</td>
<td>93</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
<td>nd&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Pyridine</td>
<td>97</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;NH</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>87</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>NaOMe</td>
<td>47</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>Na-OiPr</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Li-OtBu</td>
<td>100</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td>Na-OtBu</td>
<td>74</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>K-OtBu</td>
<td>15</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>K-OtBu/0.1 eq.</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>18-crown-6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conditions: 0.3 M in THF, 1.2 eq. 4, 3.2 eq. Base, 0.1 eq. Pd(OAc)<sub>2</sub>, 0.2 eq. BINAP, 130°C, µW, 100 W, 5 m. <sup>a</sup>Values obtained from HPLC with an estimated error of ± 5%.<sup>b</sup>Not detected by HPLC

As this reaction generates anions that must transmetallate to palladium, and as metallated nitriles form both complex aggregates with counterions<sup>21</sup> and also complex to palladium,<sup>7</sup> the choice of counterion and solvent is likely to have a large influence on the efficiency of this reaction. Thus, several solvents were explored for further optimization of the coupling. The results are presented in Table 2.3. The best conditions found above are reproduced as Entry 1. Inoh <em>et al.</em> used Cs<sub>2</sub>CO<sub>3</sub>/DMF to deprotonate <em>p</em>-nitro toluenes (pKa of 20.4 in DMSO),<sup>22</sup>
yet entries 2 and 3 in Table 2.3 indicate poor conversion and loss of starting material when DMF was used. When 6b was heated in DMF briefly, decomposition was observed indicating that DMF is not a suitable solvent for this reaction. N-Methylpyrrolidone (NMP) was tried as an alternative polar, aprotic solvent (Table 2.3, entry 4). The desired product was obtained in 20% yield with no starting material recovered. However, when mixed NMP/THF was used (Table 2.3, entries 5–9), excellent results were obtained. In 90/10 THF/NMP, in the presence of 0.1 eq. 18-crown-6, an 83% yield of product was obtained. Note that in the presence of NMP, 18-crown-6 increased the reaction yield. This behavior was not the case in pure THF.

To test the efficiency of a milder base in this solvent system, (Table 2.3, entries 10–13) several other, weaker bases than KOtBu were explored. The moderate conversion to 6b using potassium hydroxide (KOH) (Table 2.3, entry 10) indicates that KOH was strong enough for deprotonation, but this base was not efficient. It was suspected that the formation of water upon the protonation of hydroxide anion might be hindering the further formation of product by inactivating the palladium. To test the effect of water on the yield, reactions containing 0.22, 0.44, and 1.1 equivalents of water were run. Yields were found to change minimally from 71% to 77% when 0.22 eq. were added, and 77% to 71% when 0.44 equivalents were added, but decreased dramatically from 71% to 39% when 1.1 eq. were added. Carbonate bases were also explored but gave poor yields. The slightly less basic potassium methoxide and potassium iso-propoxide gave little advantage in yield. Furthermore, addition of tert-butyl alcohol (as a buffer) systematically decreased the yield of the desired product. Thus the relatively strong potassium tert-butoxide base was employed.
Table 2.3: Variation of solvent and then further variation of base.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ratio</th>
<th>Base</th>
<th>Recovered</th>
<th>Yield % of</th>
<th>5b</th>
<th>6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>THF</td>
<td>--</td>
<td>K-OtBu</td>
<td>15</td>
<td>5</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>--</td>
<td>K-OtBu</td>
<td>14</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>--</td>
<td>Cs₂CO₃</td>
<td>28</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NMP</td>
<td>--</td>
<td>K-OtBu</td>
<td>nd⁹</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>K-OtBu</td>
<td>5</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>THF/NMP</td>
<td>85/15</td>
<td>K-OtBu</td>
<td>24</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>THF/NMP</td>
<td>80/20</td>
<td>K-OtBu</td>
<td>nd</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>THF/NMP</td>
<td>50/50</td>
<td>K-OtBu</td>
<td>nd</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>K-OtBu+ 0.1 eq. 18-crown-6</td>
<td>nd</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>KOH</td>
<td>84</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>Cs₂CO₃</td>
<td>64</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>K₂CO₃</td>
<td>93</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>K₂CO₃ + 0.1 eq. 18-crown-6</td>
<td>94</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>KOCH₃</td>
<td>4</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>THF/NMP</td>
<td>90/10</td>
<td>KOiPr</td>
<td>76</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>THF/HOtBu</td>
<td>75/25</td>
<td>K-OtBu</td>
<td>6</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>THF/HOtBu</td>
<td>50/50</td>
<td>K-OtBu</td>
<td>18</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>THF/HOtBu</td>
<td>25/75</td>
<td>K-OtBu</td>
<td>21</td>
<td>61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conditions: 1.2 eq. 4, 3.2 eq. Base, 0.1 eq. Pd(OAc)₂, 0.2 eq. BINAP, 130°C, μW, 100 W, 5 m. ⁹Obtained from HPLC with an estimated error of ± 5%. ¹Not detected by HPLC. ²Entry 10 of Table 2.2 repeated for ease of comparison.

5. Optimization of phosphine ligand

Next, additional monodentate and bidentate phosphine ligands were tested for coupling efficiency (Table 2.4). The bidentate bisdiphenylphosphinoferrocene (dppf) was used both in the presence and absence of 18-crown-6 (entries 2 and 3 respectively). A slight increase in yield was observed in the absence of 18-crown-6, so subsequent reactions were run without
this additive. Use of the bidentate bis-diphenylphosphinobutane (dppb) and bisdiphenylphosphinoethane (dppe) resulted in good yields (entries 4 and 5). Three monodentate ligands were then explored (entries 6, 7, and 8). Of those tested, tricyclohexylphosphine (P(Cy)_3) provided the best results. The comparably poor yield obtained with P(tBu)_3 indicates sensitivity to the steric bulk of the supporting ligand.

Table 2.4: Variation of ligand.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield % of $^a$</th>
<th>Recovered $^b$</th>
<th>6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BINAP</td>
<td>5b</td>
<td>0</td>
<td>83$^{b,c}$</td>
</tr>
<tr>
<td>2</td>
<td>dppf</td>
<td>1</td>
<td>75$^c$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>dppf</td>
<td>2</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>dppb</td>
<td>1</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>dppe</td>
<td>50</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>P(tBu)$_3$</td>
<td>18</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>P(Cy)$_3$</td>
<td>7</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>P(Ph)$_3$</td>
<td>33</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

Conditions: 0.3 M THF/NMP 90/10 solvent, 1.2 eq. 4, 3.2 eq. K-OrBu, 0.1 eq. Pd(OAc)$_2$, 0.2 eq. Ligand, 130°C, µW, 100 W, 5 m. $^a$Values obtained from HPLC with an estimated error of ± 5%. $^b$Data from entry 9 of Table 2.3 repeated for ease of comparison. $^c$0.1 eq 18-crown-6

C. Conclusions

In palladium-mediated coupling to form diaryl acetonitriles, reaction conditions were varied in order to obtain high yields of the coupled product 6b. In the absence of palladium, NAS could form the products, but not as efficiently as under palladium-mediated coupling.
conditions. Microwave heating proved more convenient, and the higher temperatures seemed to the increased yield substantially when compared to thermal heating. KOtBu was found to be the best base in a 90/10 ratio of THF/NMP (0.3 M) with P(Cy)_3 as the supporting ligand.

D. Experimental

1. Instrumental analysis

A Grace Nucleosil C_{18} (5 micron, 4.6 mm ID, 250 mm length) column was used for HPLC analysis. The mobile phase was a 70:30 Acetonitrile/H_2O solvent system at a flow rate of 1.0 mL/m. Solvents were filtered HPLC-grade, and the H_2O was adjusted to a pH of 2.88 using glacial acetic acid. 3,5-Dimethyl anisole served as the internal standard. UV-Vis spectra were recorded on a JASCO V-550 spectrophotometer. LCMS data were collected from an Agilent Technologies 6210 LC-TOF mass spectrometer equipped with an Agilent SB-C18 1.8µm 2.1 x 50 mm column. Samples were diluted in methanol and analyzed via a 1 µL injection at 400 µL/min in a water:methanol gradient with 0.1% formic acid. The mass spectrometer was operated in positive-ion mode with a capillary voltage of 4 kV, nebulizer pressure of 30 psig, and a drying gas flow rate of 12 L/min at 350°C. The fragmentor and skimmer voltages were 210 and 65 V, respectively.

2. pKa measurements

The procedure of Bordwell^{15} was followed for the pKa determination of mono-protic acids 4 and 5. DMSO was distilled under reduced pressure from sodium amide and a few milligrams of triphenylmethane without first being dried over molecular sieves. All solvents
and stock solutions were made and stored in the nitrogen dry box until removed for spectral analysis in a quartz cuvette capped with rubber septum and parafilm to minimize exposure to air and moisture. Unknown acids were first added (via syringe) to the potassium dimsyi solutions and then titrated with indicator acids. All indicators were purified as described in the literature. Toluene and tetrahydrofuran were distilled from sodium and benzophenone and were stored in a nitrogen filled dry box. The pKa value for the diprotic acid was obtained in the same way, assuming that only the dianionic species was formed (e.g. no spectral signature for the intermediate, mono-anionic species was observed during the titration).

**Synthesis of 4-(Cyano-dimethyl-methyl)-benzonitrile (2).** NaHMDS (256 mg, 1.4 mmol) and toluene (2 mL) were added to a Schlenk flask containing 4-chlorobenzonitrile (137 mg, 1 mmol). Under nitrogen, isobutyronitrile (83 mg, 1.2 mmol) was added drop wise and allowed to react at 90 °C for 2 h. The reaction was quenched using dilute HCl, extracted with EtOAc, and purified by column chromatography on silica gel (1:4 EtOAc/Hexanes) to give the desired product (123 mg, 72%) as a pale yellow solid: All spectral data matched reported values. Mp: 86-88 °C; ¹H NMR (CD₂Cl₂): δ=1.75 (s, 6H), 7.63 (d, J=8.6 Hz, 2H), 7.70 (d, J=8.6 Hz, 2H); ¹³C NMR (CD₂Cl₂): δ=29.0, 37.7, 112.2, 118.4, 123.5, 126.3, 133.0, 146.7; IR (KBr): 3040, 2985, 2920, 1608, 1505, 1475, 1468, 1454, 1404, 1390, 1368, 1288, 1237, 1198, 1181, 1102, 1021, 930, 766, 734, 631, 569, 551, 541 cm⁻¹.

**Synthesis of 2-Chloro-6-[cyano-(2-cyano-phenyl)-methyl]-benzonitrile (5a).** To a stirring solution of K-OtBu (246 mg, 2.2 mmol) in THF (4 mL) was added 4 (340 mg, 2.4 mmol) drop wise. Upon anion formation, the solution was added drop wise to a Schlenk
flask containing a stirring solution of 2,6-dichlorobenzonitrile (172 mg, 1.0 mmol) in THF (1 mL). The combined solution was allowed to react at 80 °C for 16 h. The reaction was quenched using dilute HCl, extracted with EtOAc, and purified by column chromatography on silica gel (1:2 EtOAc/Hexanes) to give the desired product (253 mg, 91%) as a yellow solid: Mp: 138-142 °C; $^1$H NMR (CDCl$_3$): $\delta$= 5.87 (s, 1H), 7.51-7.76 (m, 7H); $^{13}$C NMR (CDCl$_3$): $\delta$= 39.9, 112.8, 113.6, 113.7, 116.1, 116.4, 127.9, 129.8, 130.2, 130.8, 134.2, 134.4, 134.6, 135.9, 138.9, 139.0; IR (KBr): 2917, 2229, 1589, 1483, 1446, 1204, 1172, 1138, 889, 768, 632 cm$^{-1}$; Anal. Calcd for C$_{16}$H$_{18}$ClN$_3$ (277.04): C, 69.20; H, 2.90; N, 15.13. Found: C, 69.35; H, 2.87; N, 15.03.

**Synthesis of 2-Bromo-6-[cyano-(2-cyano-phenyl)-methyl]-4-methyl-benzonitrile (5b).**

To a stirring solution of K-OtBu (1.38 g, 12.3 mmol) in DMF (15.5 mL) was added 4 (1.91 g, 13.4 mmol). The solution was stirred for 30 m then added drop wise to a stirring solution of 3c (1.55 g, 5.6 mmol) in DMF (7.8 mL) in a Schlenk flask. The solution was heated to 85 °C and allowed to react under nitrogen for 12 h. The reaction was quenched using 2M HCl, extracted with EtOAc, rinsed with brine, and purified by column chromatography on silica gel (1:2 EtOAc/Hexanes) to give the desired product (1.75 g, 93%) as a white solid: Mp: 141-144 °C; $^1$H NMR (CDCl$_3$): $\delta$= 2.43 (s, 1H), 5.83 (s, 1H), 7.36-7.75 (m, 7H); $^{13}$C NMR (CDCl$_3$): $\delta$= 21.8, 39.7, 112.6, 112.7, 114.9, 116.0, 116.2, 127.1, 129.1, 129.5, 129.9, 133.9, 134.2, 134.3, 135.8, 138.4, 146.2; IR (KBr): 3072, 2921, 2229, 1598, 1551, 1485, 1451, 1290, 1255, 1213, 1099, 911, 863, 766, 732, 652 cm$^{-1}$; Anal. Calcd for C$_{17}$H$_{10}$BrN$_3$ (335.01): C, 60.73; H, 3.00; N, 12.50. Found: C, 60.68; H, 2.98; N, 12.33.
**Synthesis of 2,6-Bis-[cyano-(2-cyano-phenyl)-methyl]-benzonitrile (6a).** To 5a (80 mg, 0.29 mmol), 4 (50 mg, 0.35 mmol), and Na-OtBu (104 mg, 0.93 mmol) was added THF (1.5mL) in the dry box. The solution was allowed to react at reflux for 72 h. The reaction was quenched using dilute HCl, extracted with EtOAc, and purified by column chromatography on silica gel (1:1 EtOAc/Hexanes) to give the desired product (14.4 mg, 13%) as a white solid: Mp. > 240 ° (dec.); UV-vis (THF) λ_{max} (log ε): 225 (4.7), 278 (3.7) nm; ^1H NMR (CD2Cl2): δ= 5.88 & 5.89 (s, 2H, diastereotopic), 7.51-7.59 (m, 4H), 7.66-7.87 (m, 7H); ^13C NMR (CD2Cl2): δ=40.3, 40.3 (diastereotopic), 113.2, 113.3, 113.5, 113.8, 114.4, 116.4, 116.5, 116.7, 116.8, 130.1, 130.5, 130.5, 130.7, 130.7, 134.4, 134.5, 134.8, 135.0, 136.5, 139.2; IR (KBr): 3076, 2924, 2227, 1595, 1450, 1266, 763 cm⁻¹; ESI-MS (210 V, MeOH-0.1% formic acid) m/z (%): 406 ([MH+Na]^+, 100), 384 (49), 385 (12), 407 (26). HRMS (ESI) for C25H13N5 [M+H]^+ calcld 383.1171, found 383.1167.

**Synthesis of 2,6-Bis-[cyano-(2-cyano-phenyl)-methyl]-4-methyl-benzonitrile (6b).** To a microwave vial was added 5b (84 mg, 0.25 mmol), 4 (43 mg, 0.3 mmol), K-OtBu (90 mg, 0.8 mmol), Pd(OAc)_2 (5.6 mg, 0.025 mmol), P(Cy)_3 (16.8 mg, 0.050 mmol), THF (450 µL), NMP (50 µL), and 3, 5-dimethylanisole as an internal standard (350 µL). The mixture was allowed to react in the microwave reactor at 130°C, 100W, for a run time of 3 m, hold time of 5 m, and pressure limit of 150 psi. An aliquot was removed and diluted in a 70:30 acetonitrile/acidified H₂O (pH=2.88) solution, filtered, and analyzed by HPLC to yield converted product and recovered starting material. Mp. > 240 °C (dec.); UV-vis (THF) λ_{max} (log ε): 225 (4.8), 250 (4.1), 278 (3.8) nm; ^1H NMR (CDCl3): δ= 2.51-2.56 (s, 3H,
diastereotopic), 5.81-5.82 (s, 2H, diastereotopic), 7.49-7.61 (m, 6H), 7.68-7.79 (m, 4H); $^{13}$C NMR (CDCl$_3$): $\delta$ = 22.4, 22.5 (diastereotopic), 39.8, 39.9 (diastereotopic), 110.0, 110.5, 112.9, 113.1, 114.1, 116.0, 116.1, 116.3, 116.3, 129.7, 129.7, 130.0, 130.1, 131.0, 134.0, 134.0, 134.4, 136.1, 136.2, 138.5, 146.3, 146.4; IR (KBr): 3061, 2920, 2225, 1604, 1447, 1265, 1199, 1114, 873, 760, 736, 700 cm$^{-1}$; ESI-MS (210 V, MeOH-0.1% formic acid) $m/z$ (%): 420 ([MH+Na]$^+$, 100), 398 (43), 399 (11), 421 (27). HRMS (ESI) for C$_{26}$H$_{15}$N$_5$ [M+H]$^+$ calcd 397.1327, found 397.1320.
E. References


3. Chapter 3: Step-growth polymerizations using A-B monomers
A. Introduction

It was hoped that the optimal conditions found for the model coupling reaction could be extrapolated to provide the most efficient conditions for polymerization. Here, this hypothesis was tested on an ‘A-B monomer’ in which the ‘A’ and ‘B’ functionalities are an aryl bromide and a benzylic nitrile, respectively. It was envisioned that the benzylic nitrile could be deprotonated, and a carbon-carbon bond formed with the aryl bromide in a palladium-mediated coupling analogous to that presented previously. A-B type monomers, compared to A-A + B-B types, yield more monodisperse materials due to their inherent 1:1 stoichiometry. The dispersity of polymers can increase substantially if the ratio of monomers deviates from this stoichiometry.¹

Step-growth polymerizations techniques will be employed here, where monomers couple to form dimers, and dimers couple to form tetramers, and so forth. Polydispersities for standard step-growth mechanisms approach 2, while chain-growth mechanisms are often in the range of 2-5.¹ There are drawbacks to the step-growth method, however. Coupling yields higher than 98% are required to obtain high molecular weight products. The figure below depicts this disadvantage in contrast to chain-growth and living polymerization mechanisms (Figure 3.1).
Figure 3.1: Molecular weight based on % conversion of monomer in (a) chain polymerizations, (b) step-growth polymerizations, and (c) living polymerizations as presented by Odian.¹

For our final application, it was deemed more important to obtain less polydisperse samples rather than extremely high molecular weight samples. In fact, the ideal molecular weight for our precursor polymer was 10,000 Daltons. We anticipated that a material of this weight should theoretically yield polymeric properties such as viscosity and elasticity in the bulk material (Figure 3.2), which would be advantageous for application as a film.
Figure 3.2: Mechanical strength of a material based on molecular weight, as presented by Odian.¹

B. Results & Discussion

First, an A-B monomer for the desired polymerization was synthesized. This synthesis had been attempted several ways previously in the group. The most efficient route involves four steps and is shown in Scheme 3.1. This sequence was repeated as described previously to produce monomers with a hexyl (5a), tert-butyl (5b) and methyl (5c) group in the position para to the benzonitrile.² These groups were selected to mediate the solubility and solid-state morphology of the resulting polymers as discussed more fully below.
Scheme 3.1: Synthesis of the hexyl, tert-butyl, and methyl A-B monomer derivatives.

A reaction to synthesize the precursor polymer was first run with the optimized conditions found for the trimer coupling. The monomer with the hexyl functionality (5c) was polymerized, as the resulting polymer was speculated to be the most soluble. Then the conditions were altered to determine how the molecular weight of the resulting polymer changed as the concentration of monomer, ligand, time, and temperature were varied. The yield of polymer was determined by weighing the dried material that was precipitated into methanol (MeOH) at the end of the reaction. Molecular weights were obtained from gel permeation chromatography (GPC). These data are shown below in Table 3.1.

Polymerization for 5 minutes (entry 1) resulted in the highest observed molecular weight (~4100 Daltons). Reducing the time to 2.5 minutes or increasing the time to 10 minutes
resulted in lower molecular weight polymers (entries 2 and 3, respectively). Shorter reaction times in the microwave may not be sufficient to allow longer polymers to form by the step-growth mechanism, while irradiation beyond 5 minutes may result in conversion to undesired products as discussed below. Reducing the concentration of the monomer in solution from 0.3 M to 1.5 M resulted in a low molecular weight polymer (entry 4). A decrease in molecular weight was also observed when the reaction time was increased to 10 minutes while the temperature was lowered to 110°C (entry 5). Variation of phosphine ligands showed that both tricyclohexylphosphine (P(Cy)₃) and diphenylphosphinoferrocene (dppf) resulted in similar molecular weights (entries 1 and 6). Use of diphenylphosphinobutane (dppb), however, yielded a much shorter polymer (entry 7).
Table 3.1: Polymerization of 5a under various conditions.

<table>
<thead>
<tr>
<th>Polymer Rxn</th>
<th>Entry</th>
<th>Conc (M)</th>
<th>Ligand</th>
<th>Temp (°C)</th>
<th>Time (m)</th>
<th>M_{n} (Da)^{b}</th>
<th>M_{w} (Da)^{b}</th>
<th>PDI</th>
<th>% Yield(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCB-III-25</td>
<td>1</td>
<td>0.30</td>
<td>P(Cy)(_{3})</td>
<td>130</td>
<td>5</td>
<td>2000</td>
<td>4100</td>
<td>2.0</td>
<td>35</td>
</tr>
<tr>
<td>MCB-III-15</td>
<td>2</td>
<td>0.30</td>
<td>P(Cy)(_{3})</td>
<td>130</td>
<td>2.5</td>
<td>160</td>
<td>260</td>
<td>1.6</td>
<td>32</td>
</tr>
<tr>
<td>MCB-II-84</td>
<td>3</td>
<td>0.30</td>
<td>P(Cy)(_{3})</td>
<td>130</td>
<td>10</td>
<td>2600</td>
<td>3200</td>
<td>1.2</td>
<td>44</td>
</tr>
<tr>
<td>MCB-III-16</td>
<td>4</td>
<td>0.15</td>
<td>P(Cy)(_{3})</td>
<td>130</td>
<td>5</td>
<td>200</td>
<td>810</td>
<td>4.1</td>
<td>33</td>
</tr>
<tr>
<td>MCB-III-26</td>
<td>5</td>
<td>0.30</td>
<td>P(Cy)(_{3})</td>
<td>110</td>
<td>10</td>
<td>1300</td>
<td>2300</td>
<td>1.8</td>
<td>32</td>
</tr>
<tr>
<td>MCB-III-19</td>
<td>6</td>
<td>0.30</td>
<td>Dppf</td>
<td>130</td>
<td>5</td>
<td>2500</td>
<td>4000</td>
<td>1.6</td>
<td>37</td>
</tr>
<tr>
<td>MCB-III-24</td>
<td>7</td>
<td>0.30</td>
<td>Dppb</td>
<td>130</td>
<td>5</td>
<td>540</td>
<td>1300</td>
<td>2.4</td>
<td>32</td>
</tr>
</tbody>
</table>

Conditions: 3.2 eq. K-OtBu, 0.1 eq. Pd(OAc)\(_{2}\), 0.2 eq. ligand, 100 W, 150 psi. \(^{a}\)Obtained by precipitation from methanol and drying under reduced pressure. \(^{b}\)versus polystyrene standards.

The results of the polymerizations were compared to those found for the model coupling, as shown in Table 3.2. Entry one denotes the optimum reaction conditions, and then the subsequent entries provide yields for both the trimer and precursor polymer, as one condition was varied. When the time was reduced to 2.5 m, the trimer yield only dropped to 83% (within error), whereas the molecular weight of the polymer decreased significantly. Increasing the time to 10 m, however, appeared to have a more dramatic impact on the trimer by reducing the yield to 20% while slightly lowering the polymer molecular weight from 4100 to 3200 Da. Changing the reactant concentration to 0.15 M proved detrimental to both reactions, showing a 73% yield of trimer with an 810 Da molecular weight for the polymer. Dropping the temperature to 110 °C and holding for a longer time (10 m) decreased both
numbers moderately, as did substituting dppf for P(Cy)$_3$. Alternately, using dppb significantly lowered the weight of the polymer, but only moderately reduced the trimer yield. These data indicate that a change in conditions can have very different effects on the yield of the model coupling reaction and the molecular weight of the analogous polymerization. Thus, factors besides the efficiency of the coupling reaction are important in synthesizing a high molecular weight polymer.

Table 3.2: Comparison of trimer and polymer reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Trimer Rxn</th>
<th>Polymer Rxn</th>
<th>Variable Change</th>
<th>Trimer % Yield</th>
<th>Mn (Da)</th>
<th>Mw (Da)</th>
<th>PDI</th>
<th>Polymer % Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>MCB-III-48</td>
<td>MCB-III-25</td>
<td>-</td>
<td>92</td>
<td>2000</td>
<td>4100</td>
<td>2.0</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>MCB-IV-3</td>
<td>MCB-III-15</td>
<td>Time 2.5 m</td>
<td>83</td>
<td>160</td>
<td>260</td>
<td>1.6</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>MCB-IV-4</td>
<td>MCB-II-84</td>
<td>Time 10 m</td>
<td>20</td>
<td>2600</td>
<td>3200</td>
<td>1.2</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>MCB-IV-5</td>
<td>MCB-III-16</td>
<td>Conc. 1.5 M</td>
<td>73</td>
<td>200</td>
<td>810</td>
<td>4.1</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>MCB-IV-6</td>
<td>MCB-III-26</td>
<td>Temp 110°</td>
<td>81</td>
<td>1300</td>
<td>2300</td>
<td>1.8</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>MCB-II-07</td>
<td>MCB-III-19</td>
<td>Ligand Dppf</td>
<td>87</td>
<td>2500</td>
<td>4000</td>
<td>1.6</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>MCB-II-37</td>
<td>MCB-III-24</td>
<td>Ligand Dppb</td>
<td>83</td>
<td>540</td>
<td>1300</td>
<td>2.4</td>
<td>32</td>
</tr>
</tbody>
</table>

Optimum conditions found for both the trimer and polymer reactions using 3.2 equiv. K-OtBu, 0.1 equiv. Pd(OAc)$_2$, 0.2 equiv. P(Cy)$_3$, 0.3M THF/NMP (90:10), μWave heating at 100 W, 130°C, 150 psi, with a run time of 3 m, hold time of 5 m.

We hypothesized that the solubility of the resulting polymer might be the important factor governing its molecular weight. During synthesis, if the polymer aggregates or precipitates from solution, the reaction will be impeded or stopped, limiting the molecular weight that can be synthesized. To test this, monomers containing tert-butyl (5b) and methyl (5c) groups were synthesized and polymerized. The longer hydrocarbon chains are anticipated to have more degrees of freedom than the methyl group, and should therefore be more soluble in the
reaction solvent. Even though THF has a small dipole from the C-O bond, this difference in electronegativities is significantly smaller than that between the multiple C-CN bonds on the oligomers and polymers. Therefore, the addition of a hydrocarbon chain represents an attempt at making a more overall nonpolar material that will be more similar to the solvent. Solubility is often addressed as “like dissolves like” and so modifying the materials to better match the solubilizing medium is advantageous. Likewise with the tert-butyl group, the addition of hydrocarbons should allow for more interactions with the solvent, and the additional steric considerations of the spherical bulk may help to prevent aggregation, while limiting the intermolecular interactions present with the hexyl functionalities. If similar molecular weights were obtained when 5c and 5a were polymerized, this result would argue against solubility being an important factor. These monomers were polymerized according to the optimum conditions from above, and the results are shown in Table 3.3. Polymers were not obtained from these reactions, as molecular weights less than the weight of the monomers were computed. The results of these trials suggest that the coupling was not efficient for these monomers.
Table 3.3: Polymerization of 5b and 5c.

<table>
<thead>
<tr>
<th>Polymer Rxn</th>
<th>Entry</th>
<th>Monomer</th>
<th>Conc (M)</th>
<th>Ligand</th>
<th>Temp (°C)</th>
<th>Time (m)</th>
<th>Mn (Da)b</th>
<th>Mw (Da)b</th>
<th>PDI %</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCB-III-75</td>
<td>1</td>
<td>5c</td>
<td>0.3</td>
<td>P(Cy)3</td>
<td>130</td>
<td>5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>82</td>
</tr>
<tr>
<td>MCB-III-86</td>
<td>2</td>
<td>5b</td>
<td>0.3</td>
<td>P(Cy)3</td>
<td>130</td>
<td>5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>45</td>
</tr>
</tbody>
</table>

Conditions: 3.2 eq. K-OtBu, 0.1 eq. Pd(OAc)₂, 0.2 eq. ligand, 100 W, 150 psi. aPolymer yields obtained by precipitation from methanol and drying under reduced pressure. bVersus polystyrene standards. cND refers to a molecular weight that is not detected, or less than the weight of the monomer.

The previously stated hypothesis that solubility and the presence of solubilizing groups on the monomer are important factors in the coupling efficiency appears to be consistent with the data. Based upon the the molecular weights obtained from the polymerizations of monomers with hexyl, tert-butyl, and methyl functionalities, it is clear that significant polymer growth resulted only with the most solubilizing group.

1. Effects upon variation of the polymerization conditions
Upon further analysis of the differences between the model coupling and the polymerization, we noticed that only 2 equivalents of base should be required for coupling the monomers, as opposed to the 3 equivalents needed to deprotonate the 2 acidic starting materials and the product in the model example. Because we had shown the number of base equivalents to be integral to the coupling yield in the model example, we anticipated that this
excess could have detrimental effects on the polymerization reaction. When polymerizing 5a, reducing the number of base equivalents to 2 resulted in a 76% yield, compared to 56% when 3 equivalents of base were used. We maintained the use of 2 equivalents for future reactions.

The role of the solvent was also questioned, and polymerizations were tested both without NMP (THF only), and in acetonitrile (ACN). Polymers resulting from reaction in THF appeared to be more soluble and were the highest molecular weight we had obtained up to this point, 4200 Daltons (MCB-IV-28). Reaction in acetonitrile was first tested on the model coupling, which resulted in a 15% yield of product, while 58% of the aryl bromide starting material was recovered (MCB-IV-54). Acetonitrile should be superior to THF for dissolving the potassium salts that form upon deprotonation of the acidic protons, based on its higher dipole moment (3.92 and 1.75) and dielectric constant (36.64 and 7.52). Coupling was inefficient in this solvent, however, and the recovery of starting material suggested that a longer reaction time would be beneficial. Polymerization in acetonitrile was then attempted using 20 minutes in the microwave, but resulted in a modest 16% isolated yield, and only small oligomers were observed (MCB-IV-63).

2. Characterization of step-growth polymerization products by GPC, H-NMR, and MALDI

The molecular weight of a polymer can be determined by gel permeation chromatography (GPC) and end-group analysis, but should be reported with caution. GPC is a secondary measure of molecular weight as it provides values versus a standard (typically polystyrene). The accuracy of the retention times is extremely important, as small variation can result in significantly different molecular weights. Therefore, reproducibility of these times generates
concern, and many references cite the use of multiple columns to alleviate this issue. By adding additional columns, the retention time is dramatically increased for all eluting peaks. Errors in retention times thus have less impact on the molecular weight. However, experimenting with one- and two-column setups for the GPC generated the same results for our polymers. End-group analysis is similarly limited by the accuracy in which the end group and repeat unit peaks can be integrated. Broad peaks are common for polymers, as many similar species exist in a single sample. Multiple species result in signal overlap, or one broad peak. Our polymer has two specific $^1$H-NMR handles good for characterization. As the polymer grows, the number of methine protons increases in a 1:1 ratio for each additional monomer unit added. NMR studies have shown that the chemical shift for this proton lies around 5.8 ppm. This may then be compared to the peak corresponding to the two benzylic protons of the polymer “endgroup.” These protons appear in the spectrum around 4.0 ppm, and are related to the integration of the methine protons by a factor of two. We have found the calculated molecular weights to be consistent with those previously determined by other methods.

The molecular weight distribution of polymers can also be obtained using matrix-assisted laser desorption/ionization (MALDI) mass spectrometry. However, it has been shown that for polymers with polydispersity indices (PDI) greater than 1.2, the molecular weight assumptions may be biased towards lower weights.$^4$ A MALDI was performed on MCB-II-82 and is shown in Figure 3.3. Because the precursor polymer appears to consistently yield PDI values greater than 1.2, the molecular weight implied by MALDI may be lower than the actual weight by a factor of 1.5-2.
It was suspected that there was a cause for the smaller observed molecular weights than what was originally hypothesized. This hypothesis, that a polymer of moderate molecular weight would result, was based upon the improvements made in the model coupling efficiency. Behof was able to obtain a 6000 Da polymer under conditions that corresponded to a 73% yield in the model coupling. Therefore, it was anticipated that as the conditions for the palladium-mediated coupling were improved to yield 92% trimer, the corresponding polymerizations would result in polymers of higher molecular weight. We have seen from the multiple polymerization attempts, however, that higher molecular weight materials are not obtained from the optimized model conditions, but rather a colored product with limited solubility.
The precursor polymer was designed to maintain its solubility and processability before being converted to the cyclized ladder form. It was thought that the precursor polymer, repeating units of an alternating benzonitrile and methine bridge, would appear colorless due to its lack of conjugation through the bridge. Absorption in the visible region was not expected to appear until after cyclization, and experiments using ultra-violet/visible absorption spectroscopy (UV/Vis) were employed to explore the cause of the unexpected low molecular weight product and the observed color.

It has been shown by other group members that cyclization can occur in relatively high yields in the presence of an effective nucleophile and counterion. This conversion has been shown to occur quite efficiently with excess BuLi at room temperature, but begs the question as to whether the benzylic nucleophile from K-OrBu, present in both the model coupling and polymerization, could act as an effective nucleophile for cyclization at elevated temperatures in the microwave. Further investigation by Gorman group members Dr. Behof and Menglong Hu revealed that butoxides were not efficient at cyclization when tested on the model oligomers, which suggests that it requires more than nucleophilic attack on the aryl and benzyl nitriles of the precursor materials to obtain the cyclized ladder structure.

Three hypotheses were generated to explain the observed color of the product, using the information obtained in the UV/Vis and IR spectra. The absorbance of both the polymer from 5a and the deprotonated monomer 5a are compared in Figure 3.4. The spectrum indicates absorbance in the red region upon polymerization. The first hypothesis is that multiple benzylic deprotonations occur and form a poly(anionic) polymer that is expected to have extended conjugation and a concomitant red shift. This hypothesis was ruled out,
however, when no observable color change appeared after exposure to concentrated HCl. Under these conditions, the anionic sites should be protonated, and the red color should disappear.

Figure 3.4: UV/Vis of deprotonated monomer 5a and resulting polymer.

Another possible explanation for the observed red color of the polymer could be a result of partial cyclization of the precursor to form the aromatic isoquinoline structure (as discussed in Chapter 1). It is inferred from the spectra that some degree of cyclization is taking place during polymerization. Just as the competing pathway for cyclization was thought to limit the growth of the polymers as stated above, the observed bathochromic shift in the visible region for the longer hexyl polymers, provided further evidence for increased conjugation,
most likely through cyclization to the isoquinoline structure, which has been documented by others in the Gorman group and will be discussed in more detail in later sections.5

Such a cyclization process should cause a red shift by extending conjugation. This theory was tested by comparing the model precursor oligomer to the cyclized oligomer, as shown below in Figure 3.5. Although the cyclized oligomer experiences a red shift from the deprotonated monomer, the fully cyclized trimer, as shown in Figure 3.5, is not as red-shifted as its deprotonated counterpart, or the hexyl polymer that tails off at more than 550 nm. This is therefore not a complete explanation of the observed color change in the polymer product.

Figure 3.5: Absorption spectra of the trimer, cyclized trimer and hexyl polymer.

Data from a fellow group member working to cyclize similar oligomeric groups (containing a succession of 1, 2, and 3 benzonitrile units) shows a general red shift with
increasing conjugation through additional cyclization.\textsuperscript{5} With this information, it is suspected that the polymer has greater than three fused isoquinoline units. We have also excluded the possibility of a fully-cyclized material, as such a material is expected to be inherently insoluble. We expect that the degree of cyclization of our polymer lies somewhere between these two points, based upon our UV/Vis data.

The final hypothesis with regard to the source of color is related to the reactivity of the monomer. Deprotonation and subsequent use of the benzylic nitrile as an organometallic nucleophile in the presence of palladium has documented problems. The resonance forms of the deprotonated nitrile explain possible pathways for formation of both C- and N-arylated products as shown in Scheme 3.2. Hartwig documented that the deprotonated benzyl nitrile complexed to palladium through the nitrogen in the presence of bulky phosphine ligands to form ketenimines.\textsuperscript{6} This finding was supported by crystal structures of the organometallic species and IR peaks arising in the ketenimine region (C=N bond assigned to the stretch at 2159 cm\textsuperscript{-1}).
Scheme 3.2: Possible pathways to the C- and N-arylated products resulting from resonance forms of the deprotonated benzyl nitrile.

Although we have presented multiple reasons for the observed color, it is important to remember that color can sometimes be deceiving. UV/Vis can be particularly valuable when answering questions concerning the amount of cyclization, since it appears to translate to a noticeable color change. Color is not represented by $\lambda_{\text{max}}$ only, but also contributing are the tails on the spectrum absorbing at higher wavelengths, which makes the color we observe with the naked eye often deceiving. For example, if the absorption spectrum of a cyclized oligomer tails into the red region, one could infer that the red color is due to the tails and not the $\lambda_{\text{max}}$ present at a much shorter wavelength. The phenomenon that allows more light to pass through objects absorbing near the infrared region, and less towards the ultraviolet, could also be related to our observed red color. A very small amount of material absorbing in the red region of the visible spectrum would overpower the other colors present, resulting
in an observed red color. We expect that the observed color may be implying more conjugation than is actually present, or no conjugation at all.

As the attempts to obtain high molecular weights from polymerization with the A-B monomers were not successful, couplings using an A-A + B-B monomer coupling strategy were considered. However, it was noted that the first coupling event of these new monomers would give the same result as coupling two A-B monomers (Scheme 3.3). Thus, there is no apparent benefit to this approach. However, focusing on the resulting dimer species, it was then considered whether it truly would behave as the model aryl halide used in the reaction to give the model trimer. If its reactivity is different, then the reactivity in the model coupling reaction is not a good comparison to the reaction to give the polymer. Indeed, it is assumed that this anionic monomer is likely to be much more electron-rich than the model aryl halide. If this is the case, then the monomeric aryl halide would be hesitant towards oxidative addition (prefers electron-deficient substrates), and likely to undergo side reactions to form alternate products. Some of these proposed side routes are discussed in the following chapters, while a possible solution for this problem is presented in Chapter 7.
Scheme 3.3: Comparison of A-A + B-B and A-B coupling pathways.

C. Conclusions

Ladder polymers have much potential for use in organic devices, but one must find a way around their insolubility for them to be a useful material. Our solution for this issue was the synthesis of a soluble precursor polymer that could be processed, and then converted to the ladder form in the desired regions. This method appears viable, but we experienced some challenges. We have not been able to obtain the pure precursor polymer in a high molecular weight. Instead, it appears that we obtain short, oligomeric pieces of partially-cyclized material, which is only moderately soluble. Multiple approaches have been tested, such as the addition of a hexyl chain to increase solubility, varying reactions conditions to promote chain growth, and optimizing the coupling conditions through the trimer model, but none have appeared to alleviate the problem. It is assumed that the formation of alternate products during the polymerization is leading to solubility issues, as well as a colored product. Improving the coupling efficiency during polymerization to favor the C-C bond forming reaction should help to minimize side products and improve both the molecular weight and physical characteristics of the polymeric material.
D. Experimental

A CEM Discover Microwave was used in the standard mode for all microwave reactions. Glass vials (7 mL capacity) with teflon snap caps were purchased from CEM and used with the closed-vessel attenuator graded to withstand 250 psi. Unless otherwise noted, stirring and cooling modes were applied. An International Equipment Company (IEC) Centra MP4 centrifuge was used to separate polymer precipitate from the monomer in solution. High performance liquid chromatography (HPLC) was performed using a Grace Nucleosil C\textsubscript{18} (5 micron, 4.6 mm ID, 250 mm length) column. The mobile phase was a 70:30 Acetonitrile/H\textsubscript{2}O solvent system at a flow rate of 1.0 mL/m. Solvents were filtered HPLC-grade, and the H\textsubscript{2}O was adjusted to a pH of 2.88 using glacial acetic acid. 3,5-Dimethyl anisole served as the internal standard. Ultraviolet-visible (UV-Vis) absorption spectra were recorded on a JASCO V-550 spectrophotometer. Liquid chromatography-mass spectrometry (LCMS) data were collected from an Agilent Technologies 6210 liquid chromatography, time-of-flight (LC-TOF) mass spectrometer equipped with an Agilent SB-C\textsubscript{18} 1.8\textmu m 2.1 x 50 mm column. Samples were diluted in methanol and analyzed via a 1 \mu L injection at 400 \mu L/min in a water:methanol gradient with 0.1% formic acid. The mass spectrometer was operated in positive-ion mode with a capillary voltage of 4 kV, nebulizer pressure of 30 psig, and a drying gas flow rate of 12 L/min at 350°C. The fragmentor and skimmer voltages were 210 and 65 V, respectively. Nuclear magnetic resonance (NMR) spectra were recorded on a 300 MHz Gemini 230 NMR spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer FT/IR Spectrum RX I on KBR discs. Number average molecular weights (M\textsubscript{n}), weight average molecular weights (M\textsubscript{w}) and polydispersity indices (PDI = M\textsubscript{w}/M\textsubscript{n}) values
were calculated from gel permeation chromatography (GPC) chromatograms obtained using a Lab Alliance pump with a flow rate of 1.0 mL/min, an Alltech Jordi-Gel divinylbenzene (DVB) 1000Å 250 mm, 10 mm I.D. column with a Phenomenex 50 x 7.80 mm, 5 micron linear/mixed guard column, a column heater set to 30.0°C, a JASCO RI-1530 refractive index (RI) detector, and a linear chart recorder, recording at a rate of 1 cm/min. The eluting solvent was either tetrahydrofuran (THF) (used in conjunction with a Waters Lambda-Max Model 481 LC Spectrophotometer) or dimethylformamide (DMF), and the calculation of molecular weight versus retention time was based upon the retention times of samples of EasiVial PS-L polystyrene standards for GPC obtained from Polymer Laboratories, a division of Varian Inc. THF was distilled from sodium and benzophenone. DMF was distilled under reduced pressure from 4Å molecular sieves. Ortho-cyano benzyl cyanide was purified by column chromatography prior to use in reactions. All other reagents were purchased from Aldrich and used without further purification.

**Synthesis of 2,6-Dibromo-4-hexyl-phenylamine (2a).** Notebook reference: MCB-II-72. To a stirring solution of 4-hexyl-phenylamine in a 50/50 mixture of methanol and dichloromethane (MeOH:DCM) (64.8 mL) bromine (138.0 mmol, 7.1 mL) in a 50/50 mixture of MeOH:DCM (26.2 mL) was added dropwise. This solution was allowed to stir at room temperature for 2 h. The crude product was rinsed with a saturated solution of sodium thiosulfate, and the solvents were evaporated under reduced pressure. The product was extracted with ethyl acetate, and rinsed with water and brine. The organic products were collected, dried over sodium sulfate (Na₂SO₄), and concentrated under reduced pressure. The crude material was purified by column chromatography (15-20% ethyl acetate
(EtOAc)/hexanes) to give 17.6 g (98%) of a white solid 2a. $^1$H-NMR, $^{13}$C-NMR and IR data matched the reported values.\textsuperscript{2, 7}

**Synthesis of 2,6-Dibromo-4-tert-butyl-phenylamine (2b).** Notebook reference: MCB-III-61. To a stirring solution of 4-hexyl-phenylamine (8.22g, 55.2 mmol) in a 50/50 mixture of MeOH:DCM (64.8 mL) bromine (138.0 mmol, 7.1 mL) in a 50/50 mixture of MeOH:DCM (26.2 mL) was added dropwise. This solution was allowed to stir at room temperature for 2 h. The crude product was rinsed with a saturated solution of sodium thiosulfate, and the solvents were evaporated under reduced pressure. The product was extracted with ethyl acetate, and rinsed with water, 20% NaOH, and brine. The organic products were collected, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. No further purification was needed to give 16.4 g (96%) of 2a. $^1$H-NMR, $^{13}$C-NMR and IR data matched the reported values.\textsuperscript{2, 6, 7}

**Synthesis of 2,6-Dibromo-4-hexyl-benzonitrile (3a).** Notebook reference: MCB-II-77.

Molecule 2b (1.00 g, 3.0 mmol), acetic acid (5.0 mL), and sulfuric acid (0.7 mL) were added to a round bottomed flask and heated to 60 °C. Once all of the material had dissolved, it was allowed to return to room temperature. In a separate round bottomed flask CuSO$_4$ (0.66 g, 4.2 mmol), and H$_2$O (2.6 mL) were added. Ice was added to the stirring solution of CuSO$_4$ and H$_2$O. To this mixture KCN (0.99 g, 14.9 mmol) in H$_2$O (2.2 mL) was added dropwise, while the temperature was kept below 20 °C by adding more ice. Finally, NaHCO$_3$ (5.00 g, 59.6 mmol) and hexanes (11.0 mL) were added. The KCN pot was heated to 55 °C, while the acidified aniline was cooled in an ice bath to 0 °C. Once cooled, a solution of NaNO$_2$ (0.25 g,
3.56 mmol) in H$_2$O (0.5 mL) was added dropwise with stirring. A yellow gas resulted upon addition. The cooled solution was then added dropwise to the KCN solution and was allowed to react for 2 h at 55 °C with vigorous stirring (larger scale reactions were stirred with mechanical stirrers). The reaction was cooled, extracted with toluene, and the combined organic layers were washed with a 20% solution of NaOH and brine. The organic material was dried over Na$_2$SO$_4$, concentrated, and the crude product was purified by column chromatography (10% EtOAc/hexanes) to give 0.43 g (42%) of 3a. $^1$H-NMR, $^{13}$C-NMR and IR data matched the reported values.$^2$

**Synthesis of 2,6-Dibromo-4-tert-butyl-benzonitrile (3b).** Notebook reference: MCB-III-67.

Molecule 2b (5.8 g, 18.9 mmol), acetic acid (30.4 mL), and sulfuric acid (4.8 mL) were added to a round bottomed flask and heated to 60 °C. Once all of the material had dissolved, it was allowed to return to room temperature. In a separate round bottomed flask was added CuSO$_4$ (4.20 g, 26.4 mmol), and H$_2$O (16.5 mL). Ice was added to the stirring solution of CuSO$_4$ and H$_2$O. To this mixture KCN (6.13 g, 94.3 mmol) in H$_2$O (14.3 mL) was added dropwise, while the temperature was kept below 20 °C by adding more ice. Finally, NaHCO$_3$ (31.69 g, 377.2 mmol) and hexanes (70.0 mL) were added. The KCN pot was heated to 55 °C, while the acidified aniline was cooled in an ice bath to 0 °C. Once cooled, a solution of NaNO$_2$ (1.56 g, 22.6 mmol) in H$_2$O (3.1 mL) was added dropwise with stirring. A yellow gas resulted upon addition. The cooled solution was then added dropwise to the KCN solution and was allowed to react for 2 h at 55 °C with vigorous stirring (larger scale
reactions were stirred with mechanical stirrers). The reaction was cooled, extracted with toluene, and the combined organic layers were washed with a 20% solution of NaOH and brine. The organic material was concentrated, and the crude product was purified by column chromatography (10-15% EtOAc/Hexanes) to give 3.62 g (61%) of 3b. $^1$H-NMR, $^{13}$C-NMR and IR data matched the reported values.$^2$

**Synthesis of 2,6-Dibromo-4-methyl-benzonitrile (3c).** Notebook reference: MCB-III-62.

Molecule 2c (5.00 g, 18.9 mmol), acetic acid (30.4 mL), and sulfuric acid (4.75 mL) were added to a round bottomed flask and heated to 60 $^\circ$C. Once all of the material had dissolved, it was allowed to return to room temperature. In a separate round bottomed flask, CuSO$_4$ (4.20 g, 26.4 mmol), and H$_2$O (16.5 mL) were added. Ice was added to the stirring solution of CuSO$_4$ and H$_2$O. To this mixture KCN (6.13 g, 94.3 mmol) in H$_2$O (14.3 mL) was added dropwise, while the temperature was kept below 20 $^\circ$C by adding more ice. Finally, NaHCO$_3$ (31.69 g, 377.2 mmol) and hexanes (70.0 mL) were added. The KCN pot was heated to 55 $^\circ$C, while the acidified aniline was cooled in an ice bath to 0 $^\circ$C. Once cooled, a solution of NaNO$_2$ (1.56 g, 22.6 mmol) in H$_2$O (3.1 mL) was added dropwise with stirring. A yellow gas resulted upon addition. The cooled solution was then added dropwise to the KCN solution and was allowed to react for 2 h at 55 $^\circ$C with vigorous stirring (larger scale reactions were stirred with mechanical stirrers). The reaction was cooled, extracted with toluene, and the combined organic layers were washed with a 20% solution of NaOH and brine. The organic material was concentrated, and the crude product was purified by column chromatography (10% EtOAc/Hexanes) to give 3.25 g (63%) of 3c. $^1$H-NMR, $^{13}$C-NMR and IR data matched the reported values.$^2$
Synthesis of (3-Bromo-2-cyano-5-hexyl-phenyl)-cyano-acetic acid ethyl ester (4a). Notebook reference: MCB-II-99. To a stirring solution of K-OtBu (2.04 g, 18.2 mmol) in DMF (20.4 mL) EtO$_2$CCH$_2$CN (2.0 mL, 19.1 mmol) was added dropwise. This solution was allowed to stir for 30 min in the nitrogen dry box, and was added dropwise to a Schlenk flask containing a stirring solution of 3a (1.57 g, 4.6 mmol) in DMF (6.3 mL). The flask was removed from the nitrogen dry box and was placed under nitrogen pressure in an oil bath at 100 °C for 18 h. The reaction mixture was cooled, quenched with 10% HCl, and extracted with ethyl acetate. The organic layers were collected, washed with water and a saturated brine solution. The organic layers were collected and combined, and were dried over Na$_2$SO$_4$ before they were concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, (10-15% EtOAc/Hexanes) to give 1.72 g (100%) of 4a. $^1$H-NMR, $^{13}$C-NMR and IR data matched the reported values.\textsuperscript{2}

Synthesis of (3-Bromo-2-cyano-5-tert-butyl-phenyl)-cyano-acetic acid ethyl ester (4b). Notebook reference: MCB-III-87. To a stirring solution of K-OtBu (1.34 g, 12.0 mmol) in DMF (14.2 mL) was added EtO$_2$CCH$_2$CN (1.42 g, 12.6 mmol) dropwise. This solution was allowed to stir for 30 min in the nitrogen dry box, and was added dropwise to a Schlenk flask containing a stirring solution of 3b (0.95 g, 3.0 mmol) in DMF (4.2 mL). The flask was removed from the nitrogen dry box and was placed under nitrogen pressure in an oil bath at 100 °C for 18 h. The reaction mixture was cooled, quenched with 10% HCl, and extracted with ethyl acetate. The organic layers were collected, washed with water and a saturated brine solution. The organic layers were collected and combined, and were dried over Na$_2$SO$_4$ before they were concentrated under reduced pressure. The crude product was purified by
column chromatography on silica gel, (0-25% EtOAc/Hexanes) to give 0.96 g (92%) of 4b.

$^1$H-NMR, $^{13}$C-NMR, IR and elemental analysis results matched the reported values.\(^2\)

**Synthesis of (3-Bromo-2-cyano-5-methyl-phenyl)-cyano-acetic acid ethyl ester (4c).**

Notebook reference: MCB-III-63. To a stirring solution of K-OtBu (1.21 g, 10.8 mmol) in DMF (12.8 mL) was added EtO$_2$CCH$_2$CN (1.29 g, 11.4 mmol) dropwise. This solution was allowed to stir for 30 min in the nitrogen dry box, and was added dropwise to a Schlenk flask containing a stirring solution of 3c (0.75 g, 2.7 mmol) in DMF (3.8 mL). The flask was removed from the nitrogen dry box and was placed under nitrogen pressure in an oil bath at 100 $^\circ$C for 18 h. The reaction mixture was cooled, quenched with 10% HCl, and extracted with ethyl acetate. The organic layers were collected, washed with water and a saturated brine solution. The organic layers were collected and combined, and were dried over Na$_2$SO$_4$ before they were concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, (10-30% EtOAc/Hexanes) to give 0.85 g (100%) of 4c.

$^1$H-NMR, $^{13}$C-NMR, and IR data matched the reported values.\(^2\)

**Synthesis of 2-Bromo-6-cyanomethyl-4-hexyl-benzonitrile (5a).**

Notebook reference: MCB-II-81. To a stirring solution of 4a (0.38 g, 1.0 mmol) in DMSO (0.7 mL) was added H$_2$O (0.036 g, 2.0 mmol). The reaction was placed into a microwave reactor and heated for 25 min at 165 $^\circ$C, 150 psi, and 300 watts. The reaction was cooled, diluted with ethyl acetate, added dropwise into an ethyl acetate/10% HCl solution and extracted with ethyl acetate. The organic layers were collected, washed with water and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column
chromatography on silica gel, (10% EtOAc/Hexanes) to give 250 mg (82%) of 5a. $^{1}$H-NMR, $^{13}$C-NMR and IR data matched the reported values.\textsuperscript{2}

**Synthesis of 2-Bromo-6-cyanomethyl-4-tert-butyl-benzonitrile (5b).** Notebook reference: MCB-III-69. To a stirring solution of 4b (105 mg, 0.3 mmol) in DMSO (0.2 mL) was added H$_2$O (11 mg, 0.6 mmol). The reaction was placed into a microwave reactor and heated for 25 m at 165 °C, 150 psi, and 300 watts. The reaction was cooled, diluted with ethyl acetate, poured into an ethyl acetate/10% HCl solution and extracted. The organic layers were combined, and washed with water and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The product was sufficiently pure after workup and no other purification was needed to give 79.2 mg (95%); Mp=162-164 °C; $^{1}$H-NMR (CDCl$_3$): $\delta$=1.35 (s, 9H), 4.01 (s, 2 H), 7.59 (s, 1H), 7.67 (s, 1H); $^{13}$C-NMR (CDCl$_3$): $\delta$=23.5, 30.9, 35.9, 112.7, 115.5, 115.9, 125.2, 126.6, 130.4, 135.8, 159.3; IR (KBr) 3169, 2965, 2877, 2223, 1570, 1543, 1463, 1401, 1167, 835 cm$^{-1}$; Anal. Calcd for C$_{13}$H$_{13}$BrN$_2$ (277.16): C, 56.34; H, 4.73; N, 10.11. Found: C, 56.29; H, 4.78; N, 9.90.

**Synthesis of 2-Bromo-6-cyanomethyl-4-methyl-benzonitrile (5c).** Notebook reference: MCB-III-64. To a stirring solution of 4c (0.31 g, 1.0 mmol) in DMSO (0.7 mL) was added H$_2$O (0.036 g, 2.0 mmol). The reaction was placed into a microwave reactor and heated for 25 m at 165 °C, 150 psi, and 300 watts. The reaction was cooled, diluted with ethyl acetate, poured into an ethyl acetate/10% HCl solution and extracted. The organic layers were collected, washed with water and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The product was sufficiently pure after workup and no
other purification was performed. Molecule 5c was isolated as a pale yellow solid to give 0.24 g (100%). \(^1\)H-NMR, \(^{13}\)C-NMR and IR data matched the reported values.\(^2\)

**Representative polymerization (MCB-III-25).**

To a microwave vial in a nitrogen-filled dry box was added 5a (91.5 mg, 0.3 mmol), Pd(OAc)\(_2\) (6.7 mg, 0.03 mmol), PCy\(_3\) (16.8 mg, 0.06 mmol), and K-OtBu (107.5 mg, 0.96 mmol). THF (0.9 mL) and NMP (0.1 mL) were then added. The vial was capped, removed from the nitrogen dry box, and immediately placed in a microwave reactor set to 300W, 150 psi, and 130 \(^\circ\)C with a run time of 3 m, and a hold time of 5 m. Immediately after the cooling period, the vial was removed from the reactor and was added dropwise to a centrifuge tube containing vigorously stirred methanol (10 mL). The tube was then placed in the centrifuge for 2 m at 3000 rpm. The solvent layer was decanted and the remaining solid was redissolved in THF (5 mL). This was transferred to a pre-weighed vial, concentrated under reduced pressure, and weighed to reveal a red-purple polymeric material. An aliquot for IR analysis was transferred in chloroform to a KBr disc. An additional aliquot was filtered through a 0.2 micron filter and injected onto the column for GPC analysis. Finally, the remaining sample was analyzed by NMR.

**Preparation of samples for UV/Vis analysis (Figure 3.4).** The two spectra were recorded separately, in 1 cm pathlength quartz cuvettes using spectroscopic-grade THF. The deprotonated monomer solution was prepared using excess K-OtBu (greater than 2 eq.) and molecule 5a. The hexyl polymer sample was prepared using an aliquot of MCB-II-82
(polymerization of 5a), which had previously been determined to have approximately a 4000 Da molecular weight by GPC.

**Preparation of samples for UV/Vis analysis (Figure 3.5).** The three spectra were recorded separately, in 1 cm pathlength quartz cuvettes using spectroscopic-grade THF. The deprotonated trimer solution was prepared using excess K-OtBu (greater than 2 eq.) and the trimer molecule. The fully-cyclized trimer spectra was obtained from a previous group member for comparison purposes. The hexyl polymer sample was prepared using an aliquot of MCB-II-82 (polymerization of 5a), which had previously been determined to have approximately a 4000 Da molecular weight by GPC.
E. References


4. Chapter 4: Use of protecting groups to replace the α-proton of the benzyl nitrile on the A-B monomer
A. Introduction

To minimize the possibility of cyclization during coupling, which was discussed in the previous chapter, protecting groups were employed to replace the benzyl proton on the monomer prior to polymerization. Cyclization to the fused isoquinoline structure, as shown below, relies on the shift of this benzyl proton, so without it, the cyclization pathway is eliminated. As with other protecting groups, this reactive species is intended to be removed after the coupling step, to yield the precursor polymer. Although there are documented difficulties removing protecting groups from a polymer in high yields, methods to improve the efficiency of this process have been reported.1

Cyclization of the monomer from nucleophiles present in the reaction mixture (e.g. other deprotonated benzyl nitriles) have been shown by other researchers in the Gorman Group.2,3 Scheme 4.1 is a simplified, proposed cyclization mechanism, but at present has not been supported by mechanistic studies. To understand side product formation, it is helpful to follow the movement of the benzyl proton. Scheme 4.1 shows how the rearotation step of the cyclization pathway to the isoquinoline derivative is thought to result in a proton shift from the benzyl nitrile to the primary nitrogen for shorter oligomers (top) and the pyridine nitrogen for longer oligomers (bottom). Without this available proton, it was assumed that the route to the cyclized isoquinoline product would be hindered. Therefore, it was thought that a possible strategy for avoiding the cyclization pathway and side products was to replace the benzyl proton monomer and the methine proton of the coupled monomer with a "protecting group." Although this group would be used more as a hydrogen substitute that cannot be moved or shifted, it will be referred to as a protecting group, as it should be
removed after coupling occurs. By employing this group, it was thought that the proton shift would not be possible for the coupled monomers, preventing rearomatization and ultimate cyclization to the isoquinoline derivative.

Scheme 4.1: Shift of the benzyl proton during cyclization of the deprotonated monomeric nitrile in basic solution (top) and the coupled, doubly anionic species (bottom).

It should be noted that the monomer is presumed to be in the deprotonated form when the nucleophile is introduced. Considering the resonance structures for the deprotonated monomer, it is evident that nucleophilic attack would be disfavored by the added electron density of the monomer (Scheme 4.2). However, it has been shown that counterion complexation at the nitrile nitrogen, particularly to lithium ions, reduces the electron density and may encourage attack on the electrophilic carbon.3-6
Scheme 4.2: Resonance structures of the deprotonated monomer showing delocalization of the anion through the ring and aryl nitrile.

It is implausible to propose that nucleophilic attack would occur on a dianionic species, as suggested in Scheme 4.1. However, cyclization and the route to isoquinoline products has been studied and presented by previous group members, with efforts led by Dr. Behof. He presented the following explanation for the observation of cyclized products in his dissertation (Scheme 4.3). The difference in the scheme above and that presented by Dr. Behof is the ability of the product of the deprotonation reaction to remain formally neutral upon complexation with the Lewis acid (e.g. tert-butyl dimethyl silyl chloride or TBDMSCl). The electrophilic carbon of the resulting ketenimine is then susceptible to nucleophilic attack. Subsequent steps in Behof's proposed mechanism show loss of the Lewis acid as the cyclized isoquinoline product is formed. It was questioned whether ion complexation to the nitrogen of the deprotonated species in Scheme 4.1 would reduce the electron density enough to allow for nucleophilic attack and subsequent cyclization. Even though the details of the mechanism are not fully understood, it is important to eliminate this undesired route during the coupling reaction. The following reactions were designed to address this problem.
B. Results and Discussion

1. Trimethyl silyl as a protecting group

One suitable replacement for one of the two methylene protons on the monomer, as shown in Scheme 4.1, is the trimethyl silyl (TMS) protecting group. This group was attractive for two reasons. First, synthesis of TMS acetonitrile groups has precedence, and has been successfully coupled to aryl halides in the presence of nitriles.7 A representative coupling presented by Wu and Hartwig, is shown in Scheme 4.4 below.

Scheme 4.4: Representative coupling of an aryl halide with an alkyl silylated acetonitrile derivative.7
The second advantage of the silyl group is that it may be easily removed in quantitative yields, using mild conditions such as fluoride anion. Efficient post-polymerization modifications to a structure are critical to obtaining a homogenous polymeric material. It was even envisioned that a one-pot addition and removal of the silyl leaving group could be employed (Scheme 4.5).

Scheme 4.5: Proposed synthesis of the silyl-protected precursor and removal of the protecting silyl group.

Three routes to obtain the modified A-B monomer were then proposed. These routes are shown in Figure 4.1. There are, however, concerns with the use of silyl protecting groups. Because the most direct way to obtain the silylated monomer is to deprotonate TMS acetonitrile, as shown below in routes A and B, competition between N-silylation and C-silylation must be considered. Multiple binding modes of deprotonated alkyl nitriles are well documented and has been observed binding to metals through the carbon, nitrogen, and even as a bridge between two metals. Since bond formation through the alpha carbon is considered to be the more thermodynamically stable product, it was hoped that the C-arylated product could be favored over the N-arylated product by varying the conditions.
Figure 4.1: Proposed routes A, B, and C for synthesis of the silylated-monomer.

It was hoped that using a parallel approach to the thermodynamic versus kinetic control of similar enolate C- vs. O-alkylations would prove useful in obtaining the desired C-silylated product, as the N-silylated product is not suitable for polymerization. For example, Caron et al. documented more successful C-alkylation with potassium-complexed bases such as potassium hexamethyldisilylazide (KDA) over the lithium and sodium counterparts.\textsuperscript{16} Potassium-complexed bases, such as the non-nucleophilic KDA optimized by Caron, were thus employed in routes A and B of the proposed monomer synthesis (Figure 4.1). Couplings employing TMS-acetonitrile are not without precedence, and have been used with both traditional bases\textsuperscript{17,18} and fluorinated reagents.\textsuperscript{7,19,20} The choice of base and counterion, as well as the use of elevated reaction temperatures, should help to favor carbon bond formation.\textsuperscript{21}
The second possible challenge with the use of a silyl protecting group is the purification of the modified monomer before use in the polymerization. As designed, the protecting group must be intact during polymerization so that a neutral, coupled product may be formed. This may be challenging considering that silyl groups are oxyphilic and may be removed during chromatographic purification. Distillation methods are commonly used for purification of liquid silyl compounds, as chromatography of solid products has difficulties on silica gel. Chromatography on alumina may be used to help minimize loss of the silyl group, as well as recrystallization under a nitrogen atmosphere.

Results of the three attempts for making the TMS-modified monomer, as shown in Figure 4.1, are as follows. The crude $^1$H-NMR of the product from Route A revealed multiple peaks around 0 ppm (indicative of silyl peaks) indicating that a single, predominant product was not obtained. Purification was attempted using silica treated with small amounts of acetic acid, which was thought to help minimize desilylation, but no silylated products were recovered after purification.

Route B also resulted in a mixture of products (MCB-IV-43). When the A-B monomer was allowed to react with potassium hydride (KH) and trimethylsilyl chloride (TMSCl) at room temperature, analysis by thin layer chromatography (TLC) revealed more polar product spots. The $^1$H-NMR spectrum of the crude material showed a significant amount of recovered starting material, and did not reveal any peaks characteristic of silyl groups. Additionally, no downfield peaks indicative of cyclized products were observed.

The reagents and conditions used in Route B are very similar to those employed by Pi et al., who presented an efficient route to the C-silylated version of phenylacetonitrile through
the use of lithium hydride (LiH) and TMSCl (Figure 4.2, top). This resulted in a 78% of the C-silylated product, which was purified by distillation. Dr. Behof attempted to use similar conditions to form the C-silyl ortho-cyano benzyl cyanide (WJB-IV-10). The reaction is shown below in Figure 4.2 (bottom).³ This reaction was repeated without TMSCl, but only starting material was recovered. The following product resulted as the only product in quantitative yields. It is likely that a similar product resulted from Route B in Figure 4.1 above.

![Figure 4.2: Comparison of the reactions of two nitriles with lithium bases and TMSCl, benzyl cyanide (top)¹⁷ and ortho-cyano benzyl cyanide (bottom).³](image)

Finally, Route C of Figure 4.1 was attempted, and a mixture of organosilanes also resulted. This was evidenced by multiple peaks in the ¹H-NMR around 0 ppm. It was thought that recrystallization could have been used to purify the desired product, but due to the excess TMS-acetonitrile starting material, the mixture remained in liquid form. Separating the starting silane from the product was difficult, and pure product was never obtained.
Purification attempts on alumina were also unsuccessful. In conclusion, use of this protecting group was deemed impractical due to challenges obtaining pure samples of the desired monomer.

2. *Ethyl ester as a protecting group*

When the trimethyl silyl-derived monomer could not be purified, another protecting group was selected. For convenience, the ethyl acetate group was chosen. The final step of the A-B monomer synthesis is decarboxylation from the benzyl ethyl cyano ester, so the synthesis and purification details for this protected monomer are already known. It can also be formed and removed in quantitative yields. Another benefit associated with utilizing this specific protecting group is that it shortens the monomer synthesis by one step. Additionally, it was thought that its electron withdrawing ability could increase the rate of oxidative addition, which is likely the rate-limiting step during the palladium cycle.

Initial reaction with this modified monomer was tested using the same conditions optimized in the model study. The hexyl derivative of this protected monomer was synthesized and polymerized (MCB-VI-70, MCB-VI-71, MCB-VI-72). However, upon dropwise addition into methanol, no precipitate formed. Characterization of the reaction product by $^1$H-NMR revealed no peaks in the methine region (ca. 5.2-5.8 ppm), which would indicate recovery of starting material. However, because coupled product would lack the methine proton used as an NMR handle, other characterization methods were employed to monitor the reaction. IR spectroscopy revealed no signals in the stretching region for C=O, indicating a loss of the carboxylate group in the harsh microwave conditions.
A model coupling was thus proposed to better understand the limitations of this route (Scheme 4.6). It was hypothesized that the added steric bulk of the ester group was preventing transmetallation. Lower reaction temperatures were also favored, as a loss of the carbonyl stretching frequency in the IR spectrum, as well as the appearance of the two methylene protons at 4.0 ppm in the $^1$H-NMR spectrum seemed to indicate decarboxylation and recovery of the starting material. Fortunately, the high temperatures required for the model coupling to overcome the energy barrier of such an unfavorable oxidative addition on an anionic species should not be required here. The electron withdrawing ability of the ester group should help to stabilize the anion, and by replacing the methine proton in the product, would render a neutral coupled species.

Scheme 4.6: Proposed model coupling of 2-bromobenzonitrile with the protected cyano ester nucleophile 3 to obtain 4.

Initial attempts to synthesize the ethyl cyano ester starting material 3 for the model reaction were unsuccessful, however. Nucleophilic aromatic substitution on dibromobenzonitrile in the monomer synthesis resulted in $>90\%$ yield. However, when the same conditions were used on a monohalide, minimal coupled product was formed for the bromo, chloro and even
fluoro derivatives (Scheme 4.7, left). Palladium cross-coupling conditions were even tried to achieve the esterification product, but this attempt was also futile (Scheme 4.7, right).

Scheme 4.7: Two unproductive routes to the cyano ester starting material: nucleophilic aromatic substitution (left) and palladium-catalyzed cross-coupling (right).

At this point, we consulted the literature for routes to similar products, and noted that Deady et al. reported an efficient route to the desired ethyl cyano ester using ortho-cyanobenzyl cyanide and ethyl chloroformate with dimethylaminopyridine (DMAP). Coupling was tested in both tetrahydrofuran (THF) (MCB-VI-27) and dichloromethane (DCM) (MCB-VI-26). DCM performed better and resulted in quantitative yields of product. This conversion is illustrated in Scheme 4.8 below.

Scheme 4.8: Formation of 3 based on the methods of Deady et al.24

Once obtained, the cyano ester starting material 3 was used in the model coupling shown in Scheme 4.6. Results of varied reaction conditions are given in Table 4.1 below. Reaction
temperature in the microwave reactor was reduced to 45°C to help prevent decarboxylation of the protecting group. Potassium tert-butoxide was kept as the base, in addition to the 90:10 mixture of THF and NMP. However, coupling was not observed under these conditions. To favor oxidative addition, the aryl iodide was used in place of the aryl bromide, but still, no coupling was observed. Preforming the potassium salt of the benzyl nitrile and use of that in the reaction also proved unproductive. Noticing poor solubility of the anion once it was preformed prompted the addition of one equivalent of 18-crown-6 to the reaction mixture. The combination of 3, base, and crown ether resulted in a clear, fully-soluble, yellow solution. The aryl halide was then introduced, and the reaction was subjected to microwave heating. No coupling was observed, however, as evidenced by complete recovery of starting material. To conclude, this reaction was determined to be sufficiently different from the original coupling and polymerizations employing the ethyl cyano ester protecting group were not tested further.

Table 4.1: Unsuccessful model couplings to obtain 4 using various conditions.

<table>
<thead>
<tr>
<th>NB Page#</th>
<th>Aryl halide (X=)</th>
<th>Additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCB-VI-74</td>
<td>Br</td>
<td>-</td>
</tr>
<tr>
<td>MCB-VI-75</td>
<td>I</td>
<td>-</td>
</tr>
<tr>
<td>MCB-VI-76</td>
<td>Br</td>
<td>Preformed K-salt</td>
</tr>
<tr>
<td>MCB-VI-78</td>
<td>Br</td>
<td>1 eq 18-crown-6 ether</td>
</tr>
</tbody>
</table>
C. Conclusions

In conclusion, use of the trimethylsilyl and ethyl acetate protecting groups were both found to be unsuccessful as routes to the precursor polymer. The organosilane monomer was plagued by challenges in the synthesis and purification, and attempts to couple in the presence of fluoride also proved futile. Although the monomer with the ethyl acetate protecting group was easily synthesized, efficient coupling conditions were not identified. Even for the model reaction, this coupling was found to be sufficiently different from that optimized in Chapter 2.

D. Experimental

A CEM Discover Microwave was used in the standard mode for all microwave reactions. 7 mL glass vials with teflon snap caps were purchased from CEM and used with the closed-vessel attenuator graded to withstand 250 psi. Unless otherwise noted, stirring and cooling modes were applied. An International Equipment Company (IEC) Centra MP4 centrifuge was used to separate polymer precipitate from the monomer in solution. HPLC used a Grace Nucleosil C18 (5 micron, 4.6 mm ID, 250 mm length) column. The mobile phase was a 70:30 Acetonitrile/H2O solvent system at a flow rate of 1.0 mL/m. Solvents were filtered HPLC-grade, and the H2O was adjusted to a pH of 2.88 using glacial acetic acid. 3,5-Dimethyl anisole served as the internal standard. UV-Vis spectra were recorded on a JASCO V-550 spectrophotometer. LCMS data were collected from an Agilent Technologies 6210 LC-TOF mass spectrometer equipped with an Agilent SB-C18 1.8 µm 2.1 x 50 mm column. Samples were diluted in methanol and analyzed via a 1 µL injection at 400 µL/min in a
water:methanol gradient with 0.1% formic acid. The mass spectrometer was operated in positive-ion mode with a capillary voltage of 4 kV, nebulizer pressure of 30 psig, and a drying gas flow rate of 12 L/min at 350°C. The fragmentor and skimmer voltages were 210 and 65 V, respectively. NMR spectra were recorded on a 300 MHz Gemini 230 NMR spectrometer. IR spectra were recorded on a Perkin Elmer FT/IR Spectrum RX I on KBR discs. \( M_n \) and \( M_w/M_n \) values were calculated based on GPC results using a Lab Alliance pump with a flow rate of 1.0 mL/min, Alltech Jordi-Gel DVB 1000Å 250 mm, 10 mm I.D. column with a Phenomenex 50 x 7.80 mm, 5 micron linear/mixed guard column, column heater set to 30.0 °C, JASCO RI-1530 RI detector, and Linear chart recorder, recording at a rate of 1 cm/min. The eluting solvent was either THF (used in conjunction with a Waters Lambda-Max Model 481 LC Spectrophotometer) or DMF, and the MW curve was based upon a sample of EasiVial PS-L polystyrene standards for GPC obtained from Polymer Laboratories, a division of Varian Inc.

THF was distilled from sodium and benzophenone. DMF was distilled under reduced pressure from 4Å molecular sieves. Ortho-cyano benzyl cyanide was purified by column chromatography prior to use in reactions. All other reagents were purchased from Aldrich and used without further purification.

**Synthesis of Potassium trimethylsilylacetonitrile (1). (MCB-IV-68).** Potassium tert-butoxide (K-OrBu) (168 mg, 1.5 mmol), and THF (4 mL) were added to a Schlenk flask in a nitrogen dry box. The flask was removed from the dry box and placed under a nitrogen atmosphere in a -78 °C ice bath. Diisopropylamine (210 µL, 1.5 mmol) and butyl lithium (BuLi) (0.75 mL, 1.2 mmol) were added drop wise. This was allowed to stir for 15 m.
solution of TMS-acetonitrile (137 µL, 1.0 mmol) in THF (1.5 mL) was added to this dropwise, allowed to stir for 20 m, and was warmed slowly to 0°C. The resulting salt was used for the next step of the reaction without further purification.

**Synthesis of Cyano-(2-cyano-phenyl)-acetic acid ethyl ester (3).** (MCB-VI-26). Ortho-cyano benzyl cyanide (142 mg, 1.0 mmol) dimethylaminopyridine (DMAP) (317 mg, 2.6 mmol), ethyl chloroformate (229 µL, 2.4 mmol), and dichloromethane (DCM) (0.7 mL) were combined in a round bottomed flask with a reflux condenser. The flask was placed in an oil bath under a nitrogen atmosphere and was allowed to react at 40°C for 90 m. The reaction was quenched with a 10% aqueous solution of hydrochloric acid (HCl), extracted with ethyl acetate, and the organic layers were combined and dried over Na2SO4. The crude product was concentrated under reduced pressure and purified by column chromatography (0-35% EtOAc/hexanes) to give a quantitative yield of 3. 1H-NMR, 13C-NMR and IR data matched the reported values.24

**Representative model coupling (Table 4.1, Entry 1) MCB-VI-74: Synthesis of Cyano-bis-(2-cyano-phenyl)-acetic acid ethyl ester (4)** K-OrBu (40.3 mg, 0.36 mmol), Pd(OAc)2 (6.7 mg, 0.030 mmol), P(Cy)3 (16.8 mg, 0.060 mmol), 3 (77.1 mg, 0.36 mmol), 2-bromobenzonitrile (54.6 mg, 0.3 mmol), THF (0.9 mL), and NMP (0.1 mL) were combined in a 7 mL microwave vial in a nitrogen dry box. The vial was capped and removed from the dry box and placed immediately into the microwave reactor. The mixture was allowed to react in the microwave reactor at 45°C, 100W, for a run time of 3 m, hold time of 5 m, and pressure limit of 150 psi. The crude reaction mixture was quenched with a 10% HCl solution and extracted with ethyl acetate. The organic layers were combined, dried over Na2SO4, and
concentrated under reduced pressure. $^1$H-NMR and IR analysis of the crude product did not reveal signals characteristic of the desired product, and thus, purification was not attempted.
E. References


5. Chapter 5: Attempts to form cyanodiarylmethanes using organozinc nucleophiles via Negishi couplings
A. Introduction

In the last chapter, poor coupling efficiency was observed in the presence of trimethylsilyl and ethyl cyanoacetate protecting groups. It was suspected although not explicitly shown that carbon-nitrogen bond formation was competing with carbon-carbon bond formation. Here, an alternate, softer nucleophile is explored with the goal of favoring carbon-carbon bond formation over carbon-nitrogen bond formation. Several, soft transmetallating reagents have been used in conjunction with palladium-catalyzed cross-coupling. The most popular of these are likely the boronic acid derivatives used in Suzuki-Miyaura reactions. This is probably a result of their commercial availability, wide functional group tolerance, and breadth of applicability in coupling including alkyl, benzyl, and aryl substrates.

The literature provides limited examples, however, of efficient couplings using ortho-substituted or electron-rich aryl halides. Thus, Negishi couplings were explored, as organozinc reagents have been shown to tolerate a variety of functional groups and do not require elevated temperatures. Couplings that do not require the addition of a traditional base were also explored, since the desired diarylmethane product in this study contains acidic protons, and competitive deprotonation can result in unsuccessful couplings and alternate products. Some of these competitive routes are illustrated in Scheme 5.1 below, which shows the competition between β-hydride elimination, migratory insertion, and coupling pathways for the reaction of alkyl organozincs and aryl halides.
Manolikakes et al. has shown that Negishi coupling conditions tolerate acidic functionality on amines, alcohols and aryl anilines and phenols.\textsuperscript{1, 7-9} These groups are in the same acidity range as the benzyl nitriles of interest here. Researchers have also presented many examples of organozinc couplings in the presence of relatively acidic protons, specifically when employing the catalyst system developed by Buchwald and coworkers.\textsuperscript{10-13} Oganozinc species are softer and less basic than their lithium, potassium, and other alkali metal counterparts, and are thus tolerant for use with a wider variety of functional groups.\textsuperscript{14} Knochel found that only one equivalent of the organozinc was required for these reactions, and no base was needed for efficient coupling to aryl halides.\textsuperscript{1}
Hartwig et al. have also reported couplings of organozinc reagents to aryl halides, but they found limited success when the halide contained acidic protons. Secondary nitriles were found particularly well-suited for coupling to unsaturated halides, due to their increased solubility and inability to couple more than once, leading to diarylated products.

With so many potential advantages, simple routes for obtaining organozincs became of interest. Arylzinc iodides may be produced by employing Rieke-zinc, and this method is efficient for a large range of substrates, particularly when an electron-withdrawing ortho-substituent is present on the arene and higher temperatures are used. Recently, a report of zinc insertion into a wide variety of aryl bromides has been shown using commercially available zinc powder. Many of these experienced faster rates of coupling in the presence of ortho-substituted electron-withdrawing groups. These attributes hold promise for application to the synthesis of diarylmethanes in this study.

B. Results and Discussion

1. Explorations of the method reported by Knochel et al.

Use of zinc powder in the presence of lithium chloride to form organozincs has been used to subsequently synthesize diarylmethanes. Dong et al. reported that alkyl nitriles reacted with aryliodides containing acidic protons in high yields, as shown in Scheme 5.2 below. The reaction conditions are tolerant of alkyl nitriles, and are also efficient in the presence of ortho-substituents on the arene, as shown in examples A and B, respectively. The optimal catalyst system for these couplings was found to be palladium (II) acetate (Pd(OAc)₂) and 2-dicyclohexylphosphine-2',6'-dimethoxy-1,1'-biphenyl (SPhos). Base is not required for these
couplings, and researchers report that the bond forming reaction is faster than the competitive deprotonation of acidic protons on the phenol.

Scheme 5.2: Coupling examples of alkyl zinc halide nucleophiles and aryl iodides containing acidic functionality.\(^1\)

It may also be observed in example B above that the organozinc reagent is formed by preferential insertion of the zinc into the benzyl carbon-chlorine bond over the aryl carbon-chlorine bond. Because our system contains both aryl and benzyl halides, preferential insertion into the benzyl halide would be useful for obtaining a benzyl nucleophile that can couple to an unaffected aryl halide. It was envisioned that conditions similar to these could be used for our specific reaction, and a model coupling was proposed to mimic the bond forming step during polymerization (Scheme 5.3). Before this reaction can be tested, however, the organozinc 1 must be synthesized. The results of these attempts are described below.
Scheme 5.3: Proposed model coupling based on conditions optimized by Knochel for similar substrates.

To obtain the organozinc for the model coupling, the alpha-bromo benzyl cyanide derivative (3) was first formed from reaction of ortho-cyano benzyl cyanide and bromine as shown in Scheme 5.4 (MCB-V-40) and described more fully below. Although this organozinc was not formally characterized, a crude ¹H-NMR was taken of the organozinc in solution (THF) and revealed a single broad peak around 4.0 ppm. Peak broadening upon reaction with zinc has been observed in similar reactions by Dr. Behof.²⁰ The method described above was the same strategy used by Knochel to form the organozinc nucleophiles from zinc insertion into the alkyl halides.

Scheme 5.4: Adapted strategy for formation of the model nucleophile 1 based on the experimental details reported by Knochel.¹

Initial conditions for this bromination reaction were based on the conditions reported in a Chinese patent for conversion of the similar ortho-chloro substrate, as shown in Scheme 5.5.
Experimental details for the bromination of the ortho-chloro benzonitrile substrate (a liquid) indicates neat addition of bromine.\textsuperscript{21} In our hands, however, upon addition of bromine to the dinitrile (a solid), efficient stirring was not achieved. Several solvents were thus employed to achieve better mixing. Solvent selection was restricted to aprotic options that lacked alkyl C-H bonds that could compete for bromination. Carbon tetrachloride (CCl\textsubscript{4}) was first tested (MCB-V-36), but with such a low boiling point, reaching the same 110 °C reaction temperature used in the literature was challenging. For this reason, benzene, with a slightly higher boiling point, was tested (MCB-V-39). Reaction in benzene resulted in mostly recovered starting material, with a minimal peak at 5.8 ppm in the crude \textsuperscript{1}H-NMR spectrum assigned to the product methine proton. However, more of the desired product resulted from reaction in CCl\textsubscript{4}, so further reactions were run in this solvent.

Scheme 5.5: Literature reaction for the formation of a similar derivative of the alpha-bromo benzyl nitrile.\textsuperscript{21}

\[
\begin{align*}
\text{Cl} & \quad \text{CN} \\
\text{Br} & \quad \text{CN} \\
\text{1.1: Br}_2, 3h, 110^\circ \text{C} & \quad \text{1.2: H}_2\text{O, 5 min, <30}^\circ \text{C} \\
\text{96% yield} &
\end{align*}
\]

Attempts to scale up this bromination reaction were largely unsuccessful. Large amounts of insoluble materials resulted, and diluting the reaction mixture were also unsuccessful (MCB-V-37). The best yield, 51\%, was obtained with bromination on the neat solid ortho-cyano benzyl cyanide (MCB-V-42). Purification by column chromatography was difficult
however, as the solubility of the product was limited. Yields were reduced to 30% when scaled up to 30 mmol (MCB-V-60).

Possible explanations for the observed low yields in the synthesis of 3, particularly when scaling up, may include side product formation from cyclization pathways. The by-product of the radical reaction is hydrogen bromide (HBr) gas, which is released in quantitative amounts. Thus, the larger the reaction scale, the more gas produced. It has been shown by previous group members\textsuperscript{22} that HBr is capable of invoking an acid-mediated cyclization pathway on ortho-cyano benzyl cyanide derivatives. This method was previously reported by Deady\textsuperscript{23} and Frohn,\textsuperscript{24} where HBr was introduced as 36 wt% HBr in acetic acid, allowing bromide anion to serve as the nucleophile for attack on the aryl nitrile to synthesize amino-iso-quinolines.

Once the alpha-bromo benzyl nitrile (3) was obtained, it was used to synthesize the organozinc nucleophile 1 with the method reported by Knochel (Scheme 5.4).\textsuperscript{1} Freshly distilled 1,2-dibromoethane and trimethylsilyl chloride (TMSCl) were added to activate the zinc powder, which is recommended for highly sensitive systems.\textsuperscript{25} The addition of lithium chloride is also important, as it reacts with the zinc to form a more soluble adduct. Although the exact role of the salt is not fully understood, it is thought that by forming the soluble Zn-LiCl adduct, the organometallic substrate is removed from the surface of the metal, making it available for subsequent insertion.\textsuperscript{19}

It was planned to determine the concentration of the organometallic in THF based on the titration method developed by Knochel.\textsuperscript{26} This is a colorimetric titration, and relies on the disappearance of color as the brown iodine in solution is consumed by the organozinc.
Although this worked well for many of the derivatives tested by Knochel, it was not transferable to our system, as the zinc reagent was not transparent, but slightly red-brown in color. Therefore, disappearance of color as all of the iodine was consumed, could not be distinguished.

Since the concentration could not be determined experimentally from the titration method, the concentration was assumed to be 0.9M (based on similar results from concentration determinations made by Knochel) and the model coupling reaction (from Scheme 5.3) was tested using an excess of the organozinc and conditions adapted from Knochel's procedure (MCB-V-64). This coupling attempt was unsuccessful, however, and no product formation was observed based on $^1$H-NMR characterization of the crude product, which should have given a peak at 5.8 ppm for the coupled product.

After no coupling was observed, possible explanations for this result were explored. Since it was not possible to characterize the organozinc, it is possible that it was never actually formed, and if it was formed, it could have self-reacted upon formation. The experimental details for forming the organozinc included neat addition of the alpha-bromo benzyl cyanide (3) to the activated Zn-LiCl solution in THF. It was observed, however, that the reaction pot got very hot during the addition of 3. Zinc insertion is expected to be slightly exothermic, however, and a dramatic increase in temperature could have encouraged coupling with the unreacted electrophile, rendering it unable to couple to the aryl halide in the next step.

Although attempts with the model coupling were unsuccessful, the strategy was extended to polymerization. First, a synthesis of the alpha-bromo derivative of the A-B monomer was planned. However, because the radical bromination reaction targets alkyl C-H bonds, the
methyl and even hexyl derivatives of the monomer were no longer useful due to the competition for bromination. For this reason, a suitable functional group was desired that would be similarly electron donating, but would lack the benzyl C-H groups. A methoxy group was therefore employed, having similar electron donating ability and steric parameters. Cyclohexane Å values for a methoxy group range from 0.55-75 compared to 1.74 for methyl groups, whereas the donating ability of these groups based on their Hammett values (sigma parameters) of -0.268 and -0.170 for methoxy and methyl groups, respectively.\textsuperscript{27}

A route to the methoxy monomer derivative was thus devised, and yields for each step are shown in Scheme 5.6. The four-step synthesis to reach the A-B monomer was comparable to that for the other monomer derivatives (see Chapter 3), with the exception of step 1. Because the amine and methoxy groups are both o/p directors with regard to electrophilic aromatic substitution, and the methoxy group provides more electron density to the ring than the methyl or hexyl groups used previously, multiple sites for bromination are possible. Initial attempts using the conditions from before resulted in a mixture of products. A total of 40% of the desired product was recovered, but the separation was very difficult because of multiple regioisomers.
Scheme 5.6: Synthesis of the methoxy A-B monomer derivative.

Conditions i: BTMA-Br₃, CaCO₃, MeOH/DCM ii: KCN/Cu₂SO₄, H₂O, NaNO₂, H₂SO₄, CH₃COOH, iii: CH₂CNCO₂C₂H₅, K-OtBu, DMF, iv: H₂O, DMSO, v: Bromine

The literature was thus consulted for optimized conditions for brominations on anisole derivatives. Kajigaeshi et al. reported a 78% yield of molecule 4 when the brominating agent benzyltrimethylammonium tribromide (BTMA-Br₃) was employed to synthesize bromomethoxyaniline derivatives. This was a superior method for the synthesis of 4, and scale-up reactions were successful.

Bromination attempts on the methoxy monomer derivative to produce 7a (MCB-V-54, MCB-V-73) revealed a mildly-soluble product that was difficult to purify and was therefore not fully characterized. An observed peak in the crude ¹H-NMR at 5.8 ppm was assigned to the methine proton of the brominated product. This product was used to form the organozinc, in the same manner as previously described with the model organozinc. The monomeric organozinc was also not able to be titrated because it was a colored material, and the color change could not be observed. Thus, as soon as it was formed, palladium catalyst and ligand were introduced so that the cross coupling reaction could occur. Knowing the exact concentration of the zinc reagent is not essential when dealing with the A-B monomer,
since quantitative conversion to the organozinc results in a product that is inherently in a 1:1 ratio of the coupling components. As purification of the organozinc monomer is not plausible, a quantitative conversion was assumed. Introduction of the same Pd(OAc)$_2$/SPhos catalyst system employed by Knochel to the organozinc did not result in efficient coupling, however. Also, dropwise addition of the crude product into methanol did not result in any precipitate, indicating that the attempted coupling did not produce high molecular weight, polymeric material (MCB-VI-18).

After attempts to polymerize the organozinc monomer failed, it was concluded that the Knochel method does not appear appropriate for the desired coupling. At least two factors could have proved detrimental to the coupling. Knochel did not report palladium-catalyzed cross couplings in the presence of ortho-nitriles, a group which has hindered similar couplings.$^{14}$ Also, Knochel indicated that the slow and consistent rate of addition of the organozinc was critical for efficient coupling to occur.$^1$ To ensure this, experimental details dictated use of a syringe pump that added the reagent over a 1 hour period. It was thought that this slow addition was required to minimize reaction with acidic protons present on the aryl halide. However, because acidic protons are present on the difunctional A-B monomer/organozinc, there is no way of introducing the two components slowly, because they exist as a single molecule. This variation from the literature protocol could have prevented coupling, and eventual polymerization.
2. Explorations of the method reported by Hartwig et al.\textsuperscript{14}

To avoid the tedious and inefficient synthesis of the alpha-brominated monomer, an alternate, zinc-mediated cross coupling was sought. An example was found in the literature where alkyl nitriles were coupled to substituted aryl bromides in high yields.\textsuperscript{14} This example, presented by Wu and Hartwig and shown in Scheme 5.7, reacts at room temperature and uses zinc chloride (ZnCl\textsubscript{2}) instead of the zinc powder-lithium chloride combination employed in Knochel's method. Wu and Hartwig found that secondary nitriles deprotonated with the non-nucleophilic LDA formed soluble organozinc nucleophiles when introduced to ZnCl\textsubscript{2}, and coupled efficiently to commercially available aryl bromides in the presence of palladium catalyst and bulky ligands, such as tri-\textit{tert}-butyl phosphine or adamantane/\textit{tert}-butyl phosphines.

Scheme 5.7: Formation of a benzylic nitrile through the coupling of an alkyl nitrile and aryl bromide reported by Wu and Hartwig.\textsuperscript{14}

A model coupling based on the procedure reported by Wu and Hartwig was proposed and attempted, as shown in Scheme 5.8. Because the nitrile to be used here is a primary nitrile as
opposed to a secondary nitrile, there were concerns about the solubility of the organozinc reagent. Couplings were attempted using lithium diisopropyl amide (LDA), but better results were obtained using K-OtBu. Also, it did not appear necessary to remove the conjugate acid formed from the base (in our case tert-butanol from use of K-OtBu), as was done under reduced pressure in the Hartwig couplings. The scheme includes the modified conditions for coupling the organozinc 1 to 4-bromoveratrole (MCB-VI-16) to obtain the coupled product 8.

Scheme 5.8: Synthesis of the organozinc 1 for use in the model coupling to form 8.

Reactivity of the nitrile nucleophile 1 with this specific aryl bromide can then be compared to the 68% yield reported by Hartwig et al. in Scheme 5.7. Although this yield is slightly lower than the example in Scheme 5.7, it is not unexpected, considering the reported yields\textsuperscript{14} were less than 50% when coupling acetonitrile anion derivatives.

The procedure used for forming the coupled diarylmethane 8 above was then adopted for the coupling of ortho-cyano benzyl nitrile with ortho-bromobenzonitrile as shown in Scheme 5.9 below. However, attempts to form 2 did not result in any coupled product (MCB-VI-19), even when using the alternate lithium tert-butoxide base (MCB-VI-20). Inefficient coupling to benzonitrile derivatives is not without precedence, though. Hartwig documented a modest 20% yield when coupling to 4-bromobenzonitrile, and noted that no reaction occurred "with
aryl halides containing ketones with enolizable hydrogens or free protic functionality. This is cause for concern, since both the adapted model coupling and A-B monomer for polymerization contain acidic protons on the starting materials and products.

Scheme 5.9: Synthesis of the organozinc for use in the model coupling to form 2.

Because the solubility of primary nitrile zinc reagents is limited, and issues coupling to benzonitrile derivatives had already been observed, a secondary nitrile zinc reagent was employed (Scheme 5.10, MCB-VI-18). The ethyl cyano ester group was retained on the monomer to prevent diarylation and to improve the solubility of the organozinc produced in situ. It was thought that this group could be removed after coupling occurred. However, even after longer reaction times than those reported by Hartwig et al., no precipitate formed upon addition to methanol, indicating that the coupling was inefficient, and no large molecular weight material resulted. GPC results also indicated that only small oligomeric/monomeric materials were present. The ^1H-NMR spectrum indicated that a moderate amount of starting material was recovered, which provides additional support for an inefficient coupling.
Scheme 5.10: Attempted polymerization of secondary nitrile A-B monomer 9a.

C. Conclusions

It was concluded that the routes explored in this chapter were not appropriate for the desired coupling. Solubility did not appear to be the limiting factor. It appears that the same issues Wu and Hartwig observed when attempting to couple to para-bromobenzonitrile also hindered our couplings. Coupling attempts to 4-bromoveratrole were successful, while the parallel reaction using the same nucleophile with 2-bromobenzonitrile was not.

D. Experimental

A CEM Discover Microwave was used in the standard mode for all microwave reactions. 7 mL glass vials with teflon snap caps were purchased from CEM and used with the closed-vessel attenuator graded to withstand 250 psi. Unless otherwise noted, stirring and cooling modes were applied. An International Equipment Company (IEC) Centra MP4 centrifuge was used to separate polymer precipitate from the monomer in solution. HPLC used a Grace Nucleosil C18 (5 micron, 4.6 mm ID, 250 mm length) column. The mobile phase was a 70:30 Acetonitrile/H2O solvent system at a flow rate of 1.0 mL/min. Solvents were filtered HPLC-grade, and the H2O was adjusted to a pH of 2.88 using glacial acetic acid. 3,5-Dimethyl anisole served as the internal standard. UV-Vis spectra were recorded on a Shimadzu UV-
LCMS data were collected from an Agilent Technologies 6210 LC-TOF mass spectrometer equipped with an Agilent SB-C18 1.8µm 2.1 x 50 mm column. Samples were diluted in methanol and analyzed via a 1 µL injection at 400 µL/min in a water:methanol gradient with 0.1% formic acid. The mass spectrometer was operated in positive-ion mode with a capillary voltage of 4 kV, nebulizer pressure of 30 psig, and a drying gas flow rate of 12 L/min at 350°C. The fragmentor and skimmer voltages were 210 and 65 V, respectively. NMR spectra were recorded on a 300 MHz Gemini 230 NMR spectrometer. IR spectra were recorded on a Perkin Elmer FT/IR Spectrum RX I on KBR discs. M_n and M_w/M_n values were calculated based on GPC results using a Lab Alliance pump with a flow rate of 1.0 mL/min, Alltech Jordi-Gel DVB 1000Å 250 mm, 10 mm I.D. column with a Phenomenex 50 x 7.80 mm, 5 micron linear/mixed guard column, column heater set to 30.0°C, JASCO RI-1530 RI detector, and Linear chart recorder, recording at a rate of 1 cm/min. The eluting solvent was either THF (used in conjunction with a Waters Lambda-Max Model 481 LC Spectrophotometer) or DMF, and the MW curve was based upon a sample of EasiVial PS-L polystyrene standards for GPC obtained from Polymer Laboratories, a division of Varian Inc.

THF was distilled from sodium and benzophenone. DMF was distilled under reduced pressure from 4Å molecular sieves. Ortho-cyano benzyl cyanide was purified by column chromatography prior to use in reactions. All other reagents were purchased from Aldrich and used without further purification.

Synthesis of organozinc lithium chloride adduct (1). Notebook reference MCB-V-40, MCB-V-56. Anhydrous LiCl (23.3 mg, 0.55 mmol) was added to a round bottomed flask in
a nitrogen-filled dry box. This flask was capped with a rubber septum, removed from the
box, and placed in a 150 °C oil bath under vacuum (600 mtorr). In this way, the solid was
allowed to dry for 30 min. The pot was then allowed to cool to 25 °C and zinc powder was
added under nitrogen. This mixture was allowed to dry in the same fashion under vacuum at
150 °C for an additional 30 min. The pot was allowed to cool to 25 °C, and the flask was
cycled between vacuum and nitrogen three times. THF (0.5 mL) was added, followed by
freshly distilled 1,2-dibromoethane (1.4 µL, 0.016 mmol) and TMSCl (2.1 µL, 0.016 mmol).
The mixture was cooled in a water bath with stirring. Molecule 3 (111 mg, 0.5 mmol) was
added neat, and the mixture was allowed to react for 2 h. After 2 h, stirring was stopped, and
the supernatant solution was gently removed from the solid beneath. This solution was
transferred to another dried, nitrogen-filled flask via syringe and needle. Titration of the
resulting Zn reagent was attempted with I₂ but was unsuccessful, and the concentration was
not determined. Putative molecule 1 was used for the next step without further purification.
A concentration of 0.9M was assumed, based on previous results by Knochel.¹

**Attempted Synthesis of 2,2’-(cyanomethylene)dibenzonitrile (2).** Notebook reference
MCB-V-64. A solution of 2-bromobenzonitrile (54.6 mg, 0.3 mmol), Pd(OAc)₂ (2.24 mg,
0.01 mmol), SPhos (8.22 mg, 0.02 mmol) in THF (0.3 mL) was prepared in a Schlenk flask
in a nitrogen-filled dry box. The flask was removed from the dry box and allowed to stir
under nitrogen while 1 equivalent of 1 (0.33 mL, 0.3 mmol), as prepared above, was added
extremely slowly. This mixture was allowed to stir at room temperature for 1 h. The
reaction was quenched by adding a saturated solution of ammonium chloride, and was
extracted in diethyl ether. The organic layers were combined, dried over Na₂SO₄, and
concentrated under reduced pressure. 1H-NMR analysis of the crude product did not reveal any peaks characteristic of the product and therefore, no purification methods were attempted.

**Synthesis of 2-(Bromo-cyano-methyl)-benzonitrile (3).** Notebook reference: MCB-V-42. To a round bottomed flask containing neat ortho-cyano benzyl cyanide (142.0 mg, 1.0 mmol) bromine was added dropwise (61.0 µL, 1.2 mmol). A reflux condenser was added and the round bottomed flask was placed in an oil bath at 110°C. The reaction was heated and stirred under nitrogen for 2 h, then cooled. The reaction was quenched by adding a saturated solution of sodium thiosulfate. The crude product was extracted with ethyl acetate, and washed with water and brine. Organic layers were combined, and dried over Na₂SO₄ before it was concentrated under reduced pressure. Purification by column chromatography (10% ethyl acetate/hexanes) resulted in a yellow solid (113.0 mg) to give 51% yield. Mp. 87-90°C; UV-vis (THF) λₑₓₘₐₓ (log ε): 226 (3.9), 280 (3.3) nm; ¹H-NMR (CDCl₃): δ=5.82 (s, 1H), 7.55-7.61 (t of d, J=7.8, 1.2 Hz, 1H), 7.73-7.79 (m, 2H); 7.93-7.96 (d of d, J=8.4, 1.2 Hz, 1H); IR (KBr): 2227, 1651, 1488, 1450, 768, 654, 554, 480, 460 cm⁻¹; HRMS (ESI) for C₉H₅BrN₂ [M+H]⁺ calcd 220.9709, found 220.9704.

**Synthesis of 2,6-dibromo-4-methoxy-aniline (4).** Notebook reference MCB-V-79. To a stirring solution of 3 in DCM (31.0 mL) and MeOH (11.5 mL) was added benzyltrimethylammonium tribromide (BTMA-Br₃) (2.59 g, 6.6 mmol), and CaCO₃ (1.24g, 12.4 mmol) at room temperature. The mixture was stirred for 30 m until the orange color diminished. The solid CaCO₃ was filtered off, the filtrate was concentrated, and H₂O was added to the remaining residue. The mixture was extracted with diethyl ether, and the
combined organic layers were dried over Na$_2$SO$_4$. The crude product was concentrated under reduced pressure and purified by flash chromatography (5-15% DCM/Hexanes) to give 0.78 g (90%) of 4. $^1$H-NMR, $^{13}$C-NMR, and IR data matched the reported values.\textsuperscript{20,28}

**Synthesis of 2,6-dibromo-4-methoxy-benzonitrile (5).** Notebook reference MCB-V-51. Molecule 4 (3.50 g, 12.5 mmol), acetic acid (21.0 mL), and sulfuric acid (3.2 mL) were added to a round bottomed flask and heated to 60 °C. Once all of the material had dissolved, it was allowed to return to room temperature. In a separate round bottomed flask was added CuSO$_4$ (2.96 g, 17.5 mmol), and H$_2$O (10.9 mL). Ice was added to the stirring solution of CuSO$_4$ and H$_2$O. To this mixture was added NaCN (3.06 g, 62.5 mmol) in H$_2$O (9.5 mL) dropwise, while the temperature was kept below 20 °C by adding more ice. Finally, NaHCO$_3$ (21.00 g, 250.0 mmol) and hexanes (46.3 mL) were added. The KCN-containing pot was heated to 55 °C, while the acidified aniline was cooled in an ice bath to 0 °C. Once cooled, a solution of NaNO$_2$ (1.04 g, 15.0 mmol) in H$_2$O (2.1 mL) was added dropwise with stirring. A yellow gas resulted upon addition. The cooled solution was then added dropwise to the KCN solution and was allowed to react for 2 h at 55 °C with vigorous stirring (larger scale reactions were stirred with mechanical stirrers). The reaction was cooled, extracted with toluene, and the combined organic layers were washed with a 20% solution of NaOH and brine. The organic material was concentrated, and the crude product was purified by column chromatography (5-25% EtOAc/Hexanes) to give 1.49 g (41%) of 5. $^1$H-NMR, $^{13}$C-NMR and IR data matched the reported values.\textsuperscript{20}

**Synthesis of (3-bromo-2-cyano-5-methoxy-phenyl)-cyano-acetic acid ethyl ester (6).** Notebook reference MCB-V-52. To a stirring solution of K-OtBu (0.45 g, 4.0 mmol) in
DMF (4.7 mL) was added EtO₂CCH₂CN (0.48 g, 4.2 mmol) dropwise. This solution was allowed to stir for 30 m in a nitrogen-filled dry box, and was added dropwise to a Schlenk flask containing a stirring solution of 5 (0.29 g, 1.0 mmol) in DMF (1.4 mL). The flask was removed from the dry box and was placed under nitrogen pressure in an oil bath at 100 °C for 22 h. The reaction mixture was cooled, quenched with 10% HCl, and extracted with ethyl acetate. The organic layers were combined, and washed with water and a saturated brine solution. The crude was dried over Na₂SO₄, concentrated under reduced pressure, and was purified by column chromatography on silica gel, (10-15% EtOAc/Hexanes) to give 297 mg (92%) of 6. Mp. 77-80 °C; UV-vis (THF) λₘₚ₉ (log ε): 227 (4.0), 280 (3.3) nm; ¹H-NMR (CDCl₃): δ=1.35 (t, J=7.5 Hz, 3H), 3.92 (s, 3H), 4.33 (q, J=4.0 Hz, 2H), 5.14 (s, 1H), 7.17 (d, J=2.1 Hz, 1H), 7.24 (d, J=2.4 Hz, 1H); ¹³C-NMR (CDCl₃): δ=14.1, 42.6, 56.6, 64.6, 108.1, 114.4, 114.8, 115.6, 119.5, 128.1, 163.2, 163.5; IR (KBr): 3086, 2985, 2941, 2908, 2844, 2254, 2227, 1748, 1598, 1557, 1475, 1439, 1425, 1393, 1368, 1303, 1276, 1303, 1276, 1254, 1103, 1035, 1022, 969, 860, 735, 496 cm⁻¹; ESI-MS (135.0 V, MeOH-0.1% formic acid) m/z (%): 345 ([MH+Na]+, 100), 347 (100).

Synthesis of 2-bromo-6-cyanomethyl-4-methoxy-benzonitrile (7). Notebook reference MCB-V-53. To a stirring solution of 6 (0.32 g, 1.0 mmol) in DMSO (0.7 mL) was added H₂O (0.04 g, 2.0 mmol). The reaction was placed into a microwave reactor and heated for 25 m at 165 °C, 150 psi, and 300 watts. The reaction was cooled, diluted with ethyl acetate, poured into an ethyl acetate/10% HCl solution and extracted. The organic layers were collected and combined, and were dried over Na₂SO₄ before they were concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel,
(10-15% EtOAc/Hexanes) to give 0.23 g (92%) of 7. Mp: 139-142 °C; UV-vis (THF) $\lambda_{\text{max}}$ (log $\varepsilon$): 226 (3.4), 281 (2.5) nm; $^1$H-NMR (CDCl$_3$): $\delta$=3.91 (s, 3H), 3.97 (s, 2H), 7.11 (d, $J$=2.4 Hz, 1H), 7.17 (d, $J$=2.1, 1H); $^{13}$C-NMR (CDCl$_3$): $\delta$=23.5, 56.5, 107.3, 114.5, 115.8, 118.5, 127.9, 137.6, 163.5, 175.9; IR (KBr): 3085, 2939, 2251, 2228, 1748, 1759, 1599, 1556, 1474, 1462, 1425, 1303, 1280, 1266, 1108, 1034, 960, 925, 882, 860 cm$^{-1}$; ESI-MS (135.0 V, MeOH-0.1% formic acid) $m/z$ (%): 273 ([MH+Na]$^+$, 100), 275 (95).

**Synthesis of 2-bromo-4-methoxy-6-(bromo(cyano)methyl)benzonitrile (7a).** Notebook reference MCB-V-73. To a round bottomed flask containing neat 7 (536.0 mg, 2.13 mmol) bromine was added dropwise (131 µL, 2.56 mmol). A reflux condenser was added and the round bottomed flask was placed in an oil bath at 110 °C. The reaction was heated and stirred under nitrogen for 2 h, then cooled. The reaction was quenched by adding a saturated solution of sodium thiosulfate. The crude product was extracted with ethyl acetate, and washed with water and brine. Organic layers were combined, and dried over Na$_2$SO$_4$ before it was concentrated under reduced pressure. Purification attempts by column chromatography (10% ethyl acetate/hexanes) resulted in an impure product that was subsequently used for the next step without further purification.

**Synthesis of 2-[Cyano-(3,4-dimethoxy-phenyl)-methyl]-benzonitrile (8).** Notebook reference MCB-VI-16. To a vial in a nitrogen-filled dry box was added K-OtBu (0.05 g, 0.4 mmol) and THF (0.3 mL). To this was added a solution of ortho-cyano benzyl cyanide (0.06 g, 0.4 mmol) in THF (0.8 mL) dropwise. This solution was then added to neat ZnCl$_2$ (0.06 g, 0.4 mmol) dropwise and was allowed to stir for 12 h. To a separate vial in the dry box was added Pd$_2$dba$_3$ (14 mg, 0.015 mmol), P(tBu)$_3$ (14 mg, 0.06 mmol), 4-bromoveratrole (65 mg,
0.3 mmol), and THF (0.2 mL). To this the zinc reagent was added dropwise. This mixture was allowed to stir in a capped vial in the dry box at room temperature for 15 h. The reaction was extracted with ethyl acetate. The organic layers were collected, washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, (0-30% EtOAc/Hexanes) to give 48 mg (58%) of 8. This compound was previously made as described by Sommer et al, but full characterization data was not provided.²⁹ UV-vis (THF) λ<sub>max</sub> (log ε): 229 (4.3), 283 (3.8), 387 (3.4) nm; <sup>1</sup>H-NMR (CDCl₃): δ=3.87 (s, 3H), 3.88 (s, 3H), 5.51 (s, 1H), 6.85-6.88 (d, J=8.4 Hz, 1H); 6.92-7.00 (t of d, J=9.5, 2.3 Hz, 2H), 7.45-7.51 (t of d, J=7.5, 1.7 Hz, 1H), 7.67-7.76 (m, 3H); <sup>13</sup>C-NMR (CDCl₃): δ=40.8, 56.2, 110.7, 111.0, 111.9, 117.1, 118.7, 120.4, 126.6, 128.3, 129.1, 134.0, 140.0, 149.6, 149.7; IR (KBr): 3466, 2929, 2225, 1636, 1517, 1465, 1448, 1419, 1242, 1144, 1024, 808, 762, 645, 558 cm⁻¹; HRMS (ESI) for C₁₇H₁₄N₂O₂ [M+H]<sup>+</sup> calcd 279.1128, found 279.1121.

**Synthesis of (1-(3-bromo-2-cyano-5-methylphenyl)-1-cyano-2-ethoxy-2-oxoethyl)zinc(II) chloride (9a).** Notebook reference: MCB-V-18. K-OtBu (34 mg, 0.3 mmol) and THF (0.3 mL) were placed in a vial in a nitrogen-filled dry box. A solution containing the protected monomer 9 (92.1 mg, 0.3 mmol) in THF (0.3 mL) was prepared in a separate vial and was added dropwise to the K-OtBu solution. This solution was allowed to stir for 30 m and then added dropwise to a vial containing ZnCl₂ (41 mg, 0.3 mmol). The resulting mixture was allowed to stir overnight (13 h) in the dry box. The organozinc product was formed in situ and used without further purification for the next step of the reaction.
Synthesis of the ethyl cyano acetate-substituted precursor polymer (10). Notebook reference MCB-VI-18. Pd$_2$dba$_3$ (13.7 mg, 0.015 mmol), tri-tert-butylphosphine (P(t-Bu)) (13.6 mg, 0.066 mmol), and THF (0.15 mL) were added to a vial in the dry box. The organozinc solution (9a) from above was added drop wise to the vial. The reaction was allowed to stir at room temperature for 24 h in the dry box. The resulting product was added drop wise into methanol, but no precipitate formed. The methanol solution was therefore concentrated under vacuum, but no yield was obtained. $^1$H-NMR and GPC results suggested monomeric products were recovered.
E. References


6. Chapter 6: Attempted polymerization using the palladium-catalyzed decarboxylation of cyanoacetate salts for carbon-carbon bond formation
A. Introduction

Based on our work optimizing the synthesis of the model trimer oligomer (discussed previously), we realized a potential problem associated with coupling benzylic nitriles in the presence of base. Upon deprotonation, benzylic nitriles exist in equilibrium with the nitrogen ylide of a ketenimine and arylation may occur through carbon- or nitrogen-based nucleophiles (these resonance forms with possible routes to C- and N-arylated products are discussed in Chapter 3).

Palladium catalyzed cross coupling reactions have several options for coupling materials without the need for a formal base. The Negishi and Stille couplings are two such examples. Cross-coupling reactions of this type have been referred to recently as the “work-horse” of the synthetic field, noting their high yields, short reaction times, and functional group tolerance. Palladium-catalyzed decarboxylation reactions are so-called because they undergo a loss of CO₂ during transmetallation, and likewise represent one of these "base-free" coupling scenarios.

Coupling carboxylic acids to halides in the presence of catalytic palladium and co-catalyst (e.g. copper salt) was first presented by Goossen, Deng and Levy and has since been explored by others alongside Goossen and other notable contributors such as Forgione, Glorius, Liu, Kwong, Myers and Tunge. Goossen and coworkers proposed a mechanism in the seminal paper for C-C bond formation with transmetallation occurring with the concomitant loss of CO₂ (Scheme 6.1). Optimized conditions included the use of molecular sieves to help remove water and improve the coupling yields of multiple aryl halides and benzoic acids. Much progress has been made since these early observations,
particularly involving the use of cyanoacetate salt coupling partners, as will be discussed below.

Scheme 6.1: Proposed mechanism as presented by Goossen for decarboxylative synthesis of biaryls, where L is a ligand (phosphine, phenanthroline, or other), and R and R’ represent the multiple aryl halides and benzoic acids coupled.4

B. Results and Discussion

1. Shang method for monoarylation

Synthesis of α-aryl nitriles using a decarboxylation approach was reported by Shang and coworkers.3 To optimize these conditions, several palladium catalysts, phosphine ligands, solvents, and metal cyanoacetate salts (e.g. lithium, sodium, and potassium) were examined. Use of allylpalladium chloride dimer ([Pd₂Cl₂(allyl)₂]) and 2-dicyclohexylphosphino-2’,6’-dimethoxy-1,1’-biphenyl (SPhos) in mesitylene resulted in the most efficient reaction
conditions when coupling chlorobenzene and sodium cyanoacetate. The reaction resulted in 86% of the monoarylated nitrile. Comparably, when the aryl bromide was used and all other variables were kept constant, the yield was slightly lower at 84% (Scheme 6.2).

Scheme 6.2: Reference reaction for the formation of 2-phenylacetonitrile.³

Several attempts were made to reproduce the yields obtained by Shang et al. The first step of this process was to synthesize the cyanoacetate salt (Scheme 6.3), which was done in quantitative yields following the literature procedure recorded by Shang.³ Yields for the coupling of chlorobenzene were slightly lower than that reported by Shang et al., resulting in a mixture of mono- (66%) and di-arylated (34%) products (MCB-VII-28). Efforts were taken to improve the yield of monoarylated product, but these attempts were unsuccessful. These efforts included extra precautions for nitrogen protection by keeping the reaction vials inside the nitrogen glove box for the duration of the reaction time, use of both thermal and microwave heating sources, and use of alternate palladium sources (e.g. Pd₂dba₃). The competition between monoarylation and diarylation was also noted by Shang et al., and attributed to lower yields in several instances. Our results were very similar to those reported
by Shang et al., however, diarylation proved to be more prevalent than was observed by that group.

Scheme 6.3: Formation of cyanoacetate salts, M=Li, Na or K.³

![Reaction scheme](image)

a) **Model coupling with an ortho-cyano aryl halide**

Although Shang et al. showed that this decarboxylative coupling method was applicable to a variety of substrates, no examples using ortho-cyano aryl halides as the starting material were presented. Because our goal is to synthesize a material with multiple aryl and benzyl nitriles, we devised a model reaction that would mimic the coupling conditions (electronic and steric) of the eventual polymerization. The results of this model reaction are shown below (Scheme 6.4), using the same conditions as the optimized reference reaction. Note that use of an aryl halide with the ortho-nitrile functionality resulted in formation of the diarylated product exclusively. Modifications were then made to these conditions to improve the coupling, such as the use of microwave heating, which showed a slightly higher yield (67%). However, the diarylated nitrile was still the only product recovered (MCB-V1-93).
Scheme 6.4: Model coupling of ortho-cyano bromobenzene and sodium cyanoacetate.

\[
\begin{align*}
\text{CN} & \quad \text{Br} & \quad \text{CN} & \quad \text{NC} & \quad \text{CO}_2\text{Na} \\
\text{Br} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} \\
\text{Mes} & \quad \text{SPhos} & \quad \text{[Pdiallyl]Cl}_2 & \quad \text{Mes} & \quad \text{SPhos} \\
\end{align*}
\]

\[
\text{MCB-V1-90}
\]

\[
\begin{align*}
0\% & \quad 57\%
\end{align*}
\]

b) Attempted polymerization using the Shang conditions

To obtain the desired precursor polymer, we extended this decarboxylative approach to polymerization with a dihalide monomer and cyanoacetate salt (Scheme 6.5). Several attempts were made using the best conditions found in the model coupling with one exception. An additional equivalent of the cyanoacetate salt was added in the event that it deprotonated the acidic methine proton found in each repeat unit of the product. We were concerned that, if there was an acid/base equilibrium that favored production of cyanoacetic acid, this species would not be an acceptable nucleophile for subsequent reaction. The cyanoacetate salt is likely more acidic than the methylene proton resulting from monoarylation, and even the methine proton of the diarylmethane (see Chapter 2). Therefore, the salt should be persistent and allow for coupling to occur.

Scheme 6.5: Attempted polymerization using Shang's method.
Attempts at polymerization gave poor isolated yields and low molecular weights as measured by GPC, even when using longer reaction times. Improvements in the polymerization were observed when the catalyst/ligand loading was increased from 2 mol% palladium to 10 mol%, while maintaining the ligand/catalyst ratio of 3:1. The addition of a hexyl chain to the monomer also improved the coupling efficiency presumably by making the growing chains more soluble in the reaction solvent. The comparable polymerization of the methyl monomer derivative resulted in over 50% recovered starting material and small, oligomeric products (MCB-VI-91). After allowing the hexyl monomer to react for 43 h, an oligomeric material was precipitated from methanol, redissolved in tetrahydrofuran (THF) and collected in a 46% yield. GPC indicated a $M_n$ of 3.5 kDa, $M_w$ of 7.0 kDa, and PDI of 2.0 (MCB-VI-96). The $^1$H-NMR of this oligomeric material lacked the peaks between 4.0 and 5.8 ppm, however, which are characteristic of the mono- and di-arylated products (Figure 6.1). These features suggested an alternative product to that sought.

Figure 6.1: $^1$H-NMR spectrum of MCB-VI-96 (THF layer).
Further characterization of this material with IR spectroscopy revealed possible amine (ca. 3400 cm\(^{-1}\)) and aryl nitrile stretches (ca. 2220 cm\(^{-1}\)). However, the IR spectrum lacked stretches in the alkyl/benzyl nitrile region (2260-2240 cm\(^{-1}\)) (Figure 6.2). These features also suggested a product different from that sought.

![IR spectrum of MCB-VI-96 (THF layer).](image)

Figure 6.2: IR spectrum of MCB-VI-96 (THF layer).

Although the desired benzyl nitrile linkages were formed in the model reaction as a product of diarylation, these conditions do not seem applicable to the polymerization. In rationalizing this statement, it is important to note here that the cyanoacetate salt acts both as
a coupling partner and a mild base that is potentially able to deprotonate the di-aryl acetonitrile formed. Once the cyanoacetate salt reacts with the dihalide and subsequently undergoes decarboxylation to form the first intermediate shown in Scheme 6.6, the anionic A-B dimer (discussed in previous sections) results. This anionic species is thought to be a poor electrophile for oxidative addition. Furthermore, once coupled, another equivalent of the salt may be used to deprotonate the more acidic product, as shown below.

Scheme 6.6: Proposed decarboxylative coupling followed by subsequent deprotonation by the cyanoacetate salt and formation of the nucleophile.

This deviation from the desired product is not unprecedented. It has been documented previously (Chapter 3) how this exact monomer leads to alternative products, even when using the optimized conditions from the model oligomer study. The model oligomer study also illustrates that many combinations of base and solvent do not result in the diarylmethane product. Because this method uses the cyanoacetate salt as both the coupling partner and base, it is concluded that this route will not result in the desired polymer under the given conditions.
2. Yeung method for diarylation

Yeung et al reported a related method for palladium-catalyzed, decarboxylative carbon-carbon bond formation.\textsuperscript{15} Although there are similarities in the conditions used by these researchers and by Shang et al.,\textsuperscript{3} it was hoped that these slight differences would significantly improve the coupling efficiency, and be applicable to a successful polymerization.

Yeung presented the following figure that illustrates the problems with obtaining the diarylated product from alpha-arylation of nitriles (Figure 6.3). Yeung and coworkers experienced challenges when trying to synthesis diarylacetonitriles using palladium and a mild base. When this proved unsuccessful, they increased the acidity of the acetonitrile derivatives by adding an activating group, in this case a carboxylate.

\textit{Initial failure}

\[
\begin{align*}
\text{ArCN} + \text{ArX} & \quad \xrightarrow{\text{Pd catalyst}} \quad \text{ArCN} \\
\quad \xrightarrow{\text{weak base}} \quad & \\
\end{align*}
\]

\textit{A new route proposal}

\[
\begin{align*}
\text{ROOC-CN} & \quad \xrightarrow{\text{ArX}} \quad \text{H Ar-CN} \\
\quad & \quad \xrightarrow{\text{[Pd], weak base}} \quad \text{ROOC-CN} \\
R = \text{K, Na} & \\
\end{align*}
\]

Figure 6.3: Proposed route for the formation of diarylacetonitriles, as presented by Yeung et al.\textsuperscript{15}
a) Reproducing the reference reaction

A number of attempts were made to reproduce the yield obtained by Yeung for the coupling of 4-chlorotoluene and potassium cyanoacetate. Yeung found that 92% of diarylated product was produced when palladium acetate (Pd(OAc)$_2$) and 2-(dicyclohexylphosphino)-2',4',6'-tri-isopropyl-1,1'-biphenyl (XPhos), were combined in xylene. Note the subtle differences in these conditions compared to the method by Shang et al., specifically the choice of ligand and solvent. Also unique to this method is the use of a 2:1 ratio of cyanoacetate salt to aryl halide, as discussed.

To reproduce this reaction, the cyano acetate salt was first prepared according to the literature procedure.$^3$ It was then reacted under the same conditions as above to give 75% of the diarylated nitrile (MCB-VII-20). The remaining material was the monoarylated product, which formed in a 1:3 ratio with the diarylated product (Scheme 6.7). Thus, the di-arylated product was the major product as reported by Yeung et al, but an appreciable amount of mono-arylated product was also produced, contrary to their reported results.
Scheme 6.7: Reference reaction showing a mixture of mono- and diarylated products.

\[
\begin{align*}
\text{Cl} & \quad + \quad \text{CN} \quad \text{CN} \quad \text{Pd(OAc)}_2/\text{XPhos} \\
& \quad \text{Xylene, 4h, 140}^\circ \text{C} \\
\rightarrow & \quad \text{CN} \quad \text{CN} \\
& \quad \text{25\%} \quad \text{75\%} \\
\end{align*}
\]

b) Model coupling

These same conditions were then applied to a reaction with \textit{ortho}-nitrile chlorobenzene to determine the effect of moving the cyano group from \textit{para} to \textit{ortho} to the aryl halide. This coupling resulted in diarylated product exclusively in an excellent 91\% yield, as shown in Scheme 6.8.

Scheme 6.8: Model coupling using the diarylation conditions.

\[
\begin{align*}
\text{CN} \quad \text{Cl} & \quad + \quad \text{CN} \quad \text{CN} \\
& \quad \text{Pd(OAc)}_2/\text{XPhos} \\
& \quad \text{Xylene, 12h, 140}^\circ \text{C} \\
\rightarrow & \quad \text{CN} \quad \text{CN} \\
& \quad \text{0\%} \quad \text{91\%} \\
\end{align*}
\]

c) Attempted polymerization

At this point, the diarylation method was extended to polymerization of a dihalide monomer and potassium cyanoacetate. Using 2 equivalents of the salt (the reaction may require an extra equivalent of base to deprotonate the acidic product formed), the reaction was allowed to run for 12 hrs using Pd(OAc)$_2$ and XPhos in xylene (MCB-VII-15). The resulting $^1$H-NMR spectrum again lacked peaks in the 4-5.8 ppm region, indicative of
coupled nitrile products. In accordance with this observation, no benzyl nitrile stretches were observed in the IR, but rather a significant stretch at 2159 cm\(^{-1}\), which are indicative of ketenimine derivatives (Figure 6.4).
C. Conclusions

Similar to the Shang method discussed previously, this method did not prove effective for producing the desired precursor polymer. Again, alternative products appear to rise from the deprotonation event and subsequent coupling. Although the Yeung conditions were slightly different from those presented by Shang, they still were not amenable to this polymerization.

D. Experimental

A CEM Discover Microwave was used in the standard mode for all microwave reactions. Glass vials (7 mL) with teflon snap caps were purchased from CEM and used with the closed-vessel attenuator graded to withstand 250 psi. Unless otherwise noted, stirring and
cooling modes were applied. An International Equipment Company (IEC) Centra MP4 centrifuge was used to separate polymer precipitate from the monomer in solution.

NMR spectra were recorded on a 300 MHz Gemini 230 NMR spectrometer. IR spectra were recorded on a Perkin Elmer FT/IR Spectrum RX I on KBR discs. \( M_n \) and \( M_w/M_n \) values were calculated based on GPC results using a Lab Alliance pump with a flow rate of 1.0 mL/min, Alltech Jordi-Gel DVB 1000Å 250 mm, 10 mm I.D. column with a Phenomenex 50 x 7.80 mm, 5 micron linear/mixed guard column, column heater set to 30.0°C, JASCO RI-1530 RI detector, and Linear chart recorder, recording at a rate of 1 cm/min. The eluting solvent was either THF (used in conjunction with a Waters Lambda-Max Model 481 LC Spectrophotometer) or DMF, and the MW curve was based upon a sample of EasiVial PS-L polystyrene standards for GPC obtained from Polymer Laboratories, a division of Varian Inc.

THF was distilled from sodium and benzophenone. DMF was distilled under reduced pressure from 4Å molecular sieves. Ortho-cyano benzyl cyanide was purified by column chromatography prior to use in reactions. All other reagents were purchased from Aldrich and used without further purification.

**Synthesis of cyanoacetate salts:** Notebook reference MCB-VI-86. Ethyl cyanoacetate (1.13 g, 10.0 mmol), \( \text{H}_2\text{O} \) (189 mg, 10.5 mmol), and 200-proof ethanol (20 mL) were added to a 100-mL, 2-neck round bottomed flask. A solution of K-OrBu (1.12 g, 10.0 mmol) in 200-proof ethanol (10 mL) was made in the vial in the nitrogen dry box and was added via addition funnel to the round bottomed flask over a period of 30 m. A white precipitate formed upon addition. The reaction mixture was then removed from the dry box, placed
under nitrogen, and heated to 60°C in an oil bath and allowed to react for 1 h. The reaction was cooled to room temperature, and concentrated under reduced pressure. The crude product was rinsed with 20 mL diethyl ether, and stirred vigorously with a glass rod. The solid was filtered, and washed sequentially with two, 2 mL portions of an ethanol/water mixture, followed by 3 successive 10 mL portions of diethyl ether. The remaining solid was transferred to another round bottomed flask and dried at 30°C under reduced pressure for 2 h. The salt was used for the next step of the reaction without purification.3

**Representative coupling with Shang conditions:** Notebook reference MCB-VI-90. Palladium allyl chloride dimer ((PdallylCl)_2) (3.7 mg, 0.01 mmol), SPhos (12.3 mg, 0.03 mmol), sodium 2-cyanoacetate (79.5 mg, 0.75 mmol), 2-bromobenzonitrile (91 mg, 0.5 mmol), and mesitylene (1.0 mL) were added to a Schlenk flask in a nitrogen dry box. This was removed from the dry box, placed in an oil bath, and was allowed to react under nitrogen at 130°C for 5 h. The reaction was quenched with 10% aqueous solution of HCl, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated under reduced pressure. Products from the reaction mixture were separated by column chromatography (0-50% ethyl acetate/hexanes) to give 24 mg of the diarylated product (57%).

**Representative coupling with Yeung conditions:** Notebook reference MCB-VII-20. Palladium acetate ((Pd(OAc))_2) (3.4 mg, 0.015 mmol), 2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl, (XPhos) (14.3 mg, 0.030 mmol), 1-chloro-4-methylbenzene (63.2 mg, 0.5 mmol), potassium 2-cyanoacetate (61.5 mg, 0.5 mmol), and xylenes (1.0 mL) were added to a crimp-sealed microwave vial in a nitrogen dry box. The sealed vessel was removed from the dry box and was placed in a 140°C oil bath. The reaction mixture was allowed to react
for 4 h, was cooled to room temperature, and was quenched with a 10% aqueous solution of HCl, and extracted with ethyl acetate. The organic layers were combined, dried over Na₂SO₄, and concentrated under reduced pressure. 60 mg crude material was recovered and product ratios of diarylated and monoarylated products were determined by ¹H-NMR to be 75 and 25%, respectively.
E. References


7. Chapter 7: Initiator-assisted chain-growth polymerizations
A. Introduction

In chapter 3, a difference in the reactivity of the model aryl halide and the A-B monomer was observed. Specifically, a two ring 'dimer' presenting an aryl bromide functionality could be coupled efficiently with a 'monomer' presenting a benzylic nitrile functionality to form a 'trimer', but the A-B monomer gave polymer in poor yield and with low molecular weight. Here, the source of this difference is investigated. Recalling that the step-growth polymerization attempts discussed previously resulted in alternative products (Chapter 3), even when using the same conditions that resulted in high yields of coupled products in the model reaction (Chapter 2), it became evident that there was either a steric or electronic difference between the model aryl halide and the monomer. Ruling out steric considerations, as the nucleophile/electrophile components are the same for both coupling scenarios, we turned our attention to electronic factors. Our goal was to find a better mimic of the model coupling, thereby obtaining better yields for the polymerization.

Searches in the literature for palladium cross couplings of formally anionic substrates revealed that such electron-rich systems are virtually unexplored. Although the inherent challenges of coupling such an electron-rich aryl halide should have been clear to us in the beginning, we were initially naive to the hurtles that our coupling entailed. While studying the model reaction, however, we observed better results using higher reaction temperatures and strongly electron-donating phosphine ligands, suggesting a rate-limiting oxidative addition step. An example of this catalytic step is shown in Scheme 7.1 below.
Although we were unable to find a case of highly electron-rich substrates undergoing catalyzed cross coupling, we did find a method presented by Yokoyama and Yokozawa that addressed a similar problem. These researchers studied polymerizations of acidic A-B monomers in the presence of base and observed that monomer-monomer coupling was inhibited by the added electron density from deprotonation of these acidic A-B monomers.

A specific example of this chain-growth method, as seen in the synthesis of polyamides, was presented by Yokoyama and Yokozama and is shown in Figure 7.1 below. Deprotonation of A-B monomer 1 with base results in the electron-rich monomer 2. The delocalization of electron density from the formal nitrogen anion in molecule 2 renders the electrophilic carbonyl inactive, as evident in the resonance structure 2'. Molecule 3 is thus introduced as an electron-withdrawing initiator molecule that will couple to the deprotonated monomer 2, rendering a neutral 4 with an active site that can undergo subsequent coupling to produce the polymer product.
Figure 7.1: Literature example of hindered coupling in the synthesis of polyamides, as presented by Yokoyama and Yokozawa.\textsuperscript{4}

The schematic diagram, as presented by Yokoyama and Yokozawa and reproduced in Figure 7.2, illustrates more generally the problem encountered when using an A-B type monomer, where the active site can be deactivated upon an event such as deprotonation. Their solution for this deactivation was the incorporation of an electron-withdrawing molecule to which they referred to as an initiator. Coupling the deprotonated monomer to this electron-poor initiator reduces the electron density, transferring the reactive site from the initiator to site B of the coupled monomer. This method fixes the problem of an unreactive
'A' site and also parallels the coupling pattern of chain-growth polymers. Specifically a single chain results from a single initiator.

![Figure 7.2: Schematic diagram of the initiator-assisted coupling with an A-B type monomer leading to a chain-growth condensation polymer, as presented by Yokoyama and Yokozawa.](image)

Additional benefits of this method include the ability to obtain low polydispersities and control over molecular weight. Sugi et al. illustrated these attractive features by varying the amount of initiator added in the polyamide example below. The amount of initiator present relative to the monomer is described in this method as the "feed ratio." It is varied across the polymerization attempts to give samples of different molecular weights. Polydispersity values (Mw/Mn) were found to be at or below 1.1 in these trials, which is especially attractive for chain-growth polymerization methods. Molecular weight was also controlled by the amount of initiator added, and correlated well to the theoretical molecular weight calculated assuming one chain was produced from each initiator molecule. Figure 7.3 below shows the
positively-sloped linear correlation for $M_n$ as the feed ratio is increased (or the amount of initiator is decreased). Also shown is the polydisperity index (PDI) of each sample as well as support for a chain-growth mechanism, as the initiator:end group ratio is maintained at 1.0 for each entry.
Figure 7.3: Top: Polymerization of 1 with 3 as presented by Sugi et al. Coupling conditions include 1.1 equiv of a lithium base in THF (initial concentration of 1=0.40M). Bottom: linear correlation of molecular weight (M_n) with respect to the feed ratio (left), polydispersity (M_w/M_n) for varying initiator ratios (right), and consistency of initiator to end group units with respect to feed ratio.
Another crucial feature of the coupling in Figure 7.3 is the highlighted inductive effect. Because the resonance effect is traditionally the main means of electron delocalization, it was originally thought that these findings were not applicable to our system. However, Sugi et al. showed that not only resonance effects, as seen with *para*-substituted aryl polyamides, may hinder coupling, but also inductive effects, arising from *meta* substitution.  

Inductive effects may be quantified by the Hammett equation and are defined as $+I$ and $-I$ for electron donating and electron withdrawing substituents, respectively. Considering the acidity of benzoic acid derivatives, a comparison of inductive and resonance effects can be made based on the pKa values of regioisomers. For instance, *p*-nitrobenzoic acid has a pKa of 3.44 compared to 3.45 for the *meta-* derivative. If the *para-* version is representative of the resonance effect ($-R$) and the *meta-* version representative of the inductive effect ($-I$), it is clear that the inductive effect can be as substantial as the resonance effect. This should also be the case in the reverse direction, when considering electron-donating substituents as opposed to withdrawing ones. This distinction is illustrated in Figure 7.4, as presented by Mikami et al. This parallels our coupling, where the aryl bromide electrophile is *meta* in relation to the benzylic nitrile anion nucleophile.
Inductive effects stemming from a negatively-charged substituent are shown to be just as effective at preventing self-condensation of the deprotonated monomer. The impact of this inductive effect was explored further by comparing the activation energies of monomer-monomer coupling (propagation) as opposed to monomer-chain coupling (self-condensation). This was done through a comparison of reaction rates in the synthesis of polyamides. Activation energies for propagation and self-condensation steps for the reaction
were calculated using density functional theory (DFT) methods as 21.6 and 27.0 kcal/mol, respectively. Using these values to calculate the corresponding rate constants of $1.1 \times 10^{-3}$ s$^{-1}$ for propagation and $1.3 \times 10^{-7}$ s$^{-1}$ for self-condensation, the preference for the chain-growth mechanism is evident with a $8.6 \times 10^3$ fold increase in the rate constant.9

Incorporation of a phase-transfer catalyst into the initiator method helps to minimize monomer-monomer interaction by introducing a biphasic system. The formation of alternate products in the coupling of interest here, occurred as a result of monomer-monomer coupling (Chapter 3). By hindering the reaction of the deprotonated monomer with itself, it was hoped that routes to undesired side products would be avoided. This shows the need for a method that minimizes undesirable monomer-monomer coupling, and encourages coupling to the growing chain. This method involves the introduction of catalytic amounts of 18-crown-6 ether to help keep the majority of the deprotonated monomer in the solid phase. As the potassium salt version of the monomer is insoluble in the selected solvent, it must be transferred to the solution-phase, where the growing chain (non-anionic) is available for coupling. An example illustrating how the phase-transfer catalyst is employed is shown in Figure 7.5, and the use of this method with our monomer will be presented in the results section below.
Yokozawa's method has also been adapted to the synthesis of π-conjugated polymers. Yokozawa and Yokoyama refer to this process as catalyst-transfer condensation polymerizations, but it is not used with monomers of the type above. Scheme 7.2 shows the synthesis of oligothiophenes that Yokoyama and Yokozawa obtained in the attractive head-to-tail orientation with polydispersities as low as 1.15 and molecular weights that could be controlled by the catalyst to monomer ratio. It was proposed that the molecular weight control was related to the intramolecular catalyst transfer along each chain; one catalyst molecule per chain. This theory was supported by MALDI characterization, where a bromine atom and hydrogen atom were found at the two ends of these homogenous samples, which contained only one set of peaks.¹¹
Scheme 7.2: Proposed intramolecular catalyst transfer mechanism in the synthesis of oligothiophenes from monomer 31, as presented by Yokoyama and Yokozawa.\textsuperscript{4}

Yokozawa et al. optimized several variables that helped to improve their polymerizations. First, using meta-substituted monomers as opposed to the para- examples increased the solubility of the product.\textsuperscript{4} Also, they found that certain side reactions could be avoided by varying temperature. For example, higher temperatures favored transesterification in the polyester synthetic example.\textsuperscript{12} Finally, they employed a phase-transfer catalyst to limit the ability of the monomer to self-react. Each of these strategies should be applicable to our coupling, as the first two have already been exploited in the model reaction by using a meta-substituted substrate and exceeding the boiling point of our solvent in a pressurized reaction vessel to achieve the optimized reaction temperature. The third approach would require
slight modification of the current conditions and monomer, but could prove very rewarding if it eliminated side reactions.

Another experimental detail that was found to be integral to this method was the order of addition of the coupling components. The monomer was deprotonated prior to being added to the catalyst/initiator solution, and was added drop wise at the set reaction temperature a single drop at a time, until the color from the presence of the anion disappeared. This disappearance of color (or color change) indicates that the added monomer had totally been consumed, or coupled, to the growing chain, and more monomer could be added without running the risk of monomer-monomer coupling to form undesired products.

It is worth pointing out that these details may not all be relevant to the coupling of interest in our work. The first difference is the addition of the monomer at the reaction temperature. Because the original model coupling reaction conditions were optimized in a sealed vessel in the microwave reactor, THF was able to be used above the boiling point without loss of solvent. However, current microwave technology does not allow for additions after the pressure device is sealed. It was eventually found that the best results were obtained when the monomer was added at the reflux temperature of the solvent (THF), and then put immediately into the microwave reactor.

Another detail not reproduced in our case was the color change that signaled that it was acceptable for further addition of the deprotonated monomer. Since the polymer product is more acidic than the starting material, it is deprotonated by the extra equivalent of base once coupled (see Chapter 2 for details on the pKₐ values of the starting materials and products). Therefore, the deprotonated product is expected to be colored as well, and therefore, color in
the reaction vessel will never "disappear." A slow, drop wise addition should thus be used instead of this color indicative method.

In our coupling, the model aryl halide contains an additional benzonitrile, which likely results in differential reactivities between the model aryl halide and the monomeric aryl halide. With an acidic proton on the diarylmethane linkage (Figure 7.6), it is thought that deprotonation would happen quickly, and subsequent coupling would have to occur on a formally anionic species. This anion is, however, able to be delocalized by the additional electron withdrawing benzonitrile, resulting in a substrate that is electron-poor enough to undergo oxidative addition. The figure below highlights the difference in the electrophilic components for each type of coupling. It is clear from the figure that this initiator-assisted chain-growth method provides a more comparable electrophile to that used in the model reaction.
Figure 7.6: Comparison of aryl halides in the model coupling, step-growth coupling, and chain-growth coupling. The circled species highlight the aryl halide in each coupling scenario for ease of comparison.

### B. Results and Discussion

Taking into consideration the many benefits of the initiator-assisted chain growth polymerization method, we applied it to our specific coupling. An electron-withdrawing initiator was selected to mimic the aryl halide of the model coupling. *Ortho*-cyano benzyl cyanide was selected as the initiator and was first employed in a 10% mol ratio with the monomer, while the other conditions from the optimized model remained the same. The order of addition was altered, however, to better match the experimental details of the chain-growth method, minimizing monomer-monomer interaction.
Initial workup methods were based on optimized conditions found by Miyakoshi, Yokoyama and Yokozawa in the synthesis of oligothiophenes and included quenching with 5 M hydrochloric acid to obtain a more homogeneous product with a lower polydispersity.\textsuperscript{13} Initial attempts polymerizing with 10 mol\% initiator and the methyl monomer derivative resulted in complete conversion of starting material to polymer with an $M_n$ of 1690, but PDI ($M_w/M_n$) of 2.2, and yield of 78\% (MCB-VI-33). This molecular weight correlated fairly well to the theoretical molecular weight of 1550, which was calculated based on the amount of initiator used. Attempts lowering the amount of initiator to obtain larger oligomers and materials closer to our goal weight of 10,000 Daltons, were unsuccessful, however. Using only 2 mol\% initiator to obtain an expected molecular weight of 7,750 Daltons resulted in some unconverted starting material and GPC results indicated only small oligomeric material (MCB-VI-34). Attempts with 5 mol\% initiator also showed unreacted monomer (MCB-VI-35).

It was noted during these polymerizations that yields were sometimes above 100\%, and the reason for this was not initially apparent. The initiator molecule is the only additional component when compared to the step-growth polymerization method presented in Chapter 3, and this small difference should not dramatically affect the yield. Yields for these polymerizations are calculated by obtaining the weight of the dried solid after precipitation from methanol. This weight excludes monomers and small oligomers, as they are soluble in the methanol layer. It was thought that the source of this additional product weight was from something other than the monomer and initiator.
Solvent removal is a crucial part of determining accurate reaction yields. THF was not of concern since it would be removed under reduced pressure, and it was thought that the 100 μL of NMP in the THF/NMP reaction solvent would remain in the methanol layer upon precipitation. In fact, this was supported by the 1H-NMR spectra of the dried methanol layer which showed peaks characteristic of NMP. However, it became clear that a small amount of NMP was retained in the THF layer, and as it was not removed on the vacuum line, it therefore contributed to the weight of the product, and thus falsely inflated the yield. At this point, additional precipitations were done in methanol to remove the residual NMP to obtain more accurate yields.

Multiple precipitations to remove residual solvent was tested on step-growth polymerizations done previously, but due to the insolubility of the side products formed, removing all of the NMP left a completely insoluble product that was difficult to characterize by NMR and GPC. Because NMR characterization provided great insight into the product formed, and the GPC was integral in determining the weight of the product as well as serving as an indirect measure of the efficiency of the coupling, yield determination was sacrificed for these two methods of characterization. It was found, however, that the initiator method resulted in a more soluble product that could be redissolved even after multiple precipitations to remove NMP. Yields were again obtainable, and are reported below.

Strategies based on examples from the initiator methods described above were employed to improve the efficiency of the coupling and the molecular weight distribution. First, attempts using equimolar amounts of catalyst and initiator were tested since researchers had obtained better results using this ratio in the biphasic phase-transfer coupling example.
However, because the model coupling was optimized with 10 mol% palladium, reducing this to match the 5 and even 2 mol% initiator loadings were unsuccessful, and unconverted starting material was recovered. Returning to the model coupling to improve the yield using lower catalyst loadings proved futile as well.

The next strategy was to use the hexyl monomer derivative instead of the methyl derivative to improve the solubility. Yokozawa and Yokoyama documented that solubility limitations of the resulting polymer product could broaden the molecular weight distribution.\textsuperscript{4} Solvent selection and the addition of solubilizing chains to the monomer were used to alleviate this issue.\textsuperscript{14}

It was found that solubility was also a key factor in obtaining adequate characterization of the precursor polymer. \textsuperscript{1}H-NMR results were drastically improved when using the polar aprotic DMSO-d\textsubscript{6} over the more common chlorinated options, deuterated chloroform (CDCl\textsubscript{3}) and deuterated dichloromethane (CD\textsubscript{2}Cl\textsubscript{2}), and dimethylformamide (DMF) was found to be a superior solvent to THF for the GPC analysis. Because of the UV/Vis cutoff of DMF that extends into the visible region, however, refractive index detection was necessary.

Polymer synthesized with the hexyl monomer, 1 mol% initiator, and 10 mol% palladium catalyst with other conditions held constant, were precipitated into methanol, and for the first time, a viscous material resulted (MCB-VII-35). In fact, the material was so viscous that removal from the reaction vessel was challenging, and characterization data was not recorded. The reaction was therefore repeated using two times as much solvent (2 mL). This resulted in an M\textsubscript{n} of 60 kiloDaltons (kDa), M\textsubscript{w} of 66 kDa, a PDI of only 1.1, in 77% yield.
(MCB-VII-36). This is, however, much higher than the theoretical molecular weight of 22.5 kDa for 1 mol% initiator. Because the material was so viscous that it was clumpy in appearance and unable to stir, it was thought that poor mass transport could be the reason for the deviation from the expected molecular weight. Therefore, the solvent volume was increased to 3 mL, but this lower concentration decreased the rate of reaction, and the coupling efficiency decreased giving a product that did not form a precipitate in methanol, and therefore no yield or molecular weight was calculated (MCB-VII-37). Returning to a 2 mL reaction volume and 0.5 mol% initiator produced a polymer with a $M_n$ of 129 kDa, a $M_w$ of 146 kDa, PDI of 1.1, in 30% yield (MCB-VII-38). These values are again higher than the theoretical molecular weight of 45 kDa, but are similar to the results obtained previously (MCB-VII-36). It is assumed that the polymerization resulted in higher than expected molecular weights because not all of the initiator reacted to form polymer. This is likely the result of errors in the experimental technique with addition of very small volumes of the initiator solution into relatively large reaction vessels. Attempts to obtain more molecular weight data using alternate methods were made, however.

MALDI was used to reveal information about both the molecular weight and chain distribution in Yokozawa's examples. However, MALDI requires that the solute be dissolved in a solvent and incorporated with the matrix before being added to the target, where the solvent evaporates, leaving behind the mixed matrix and solute. This process presented challenges when we applied it to the characterization of our polymer product. Because it had limited solubility in THF, but was fully soluble in DMF and DMSO, MALDI was attempted using these solvents. However, because they have high boiling points, they
did not evaporate from the target, even after applying a modest heat source to the surface of the target. High boiling point solvents are not recommended for use with MALDI.

Also a challenge with MALDI characterization is the possibility of reaction between the trifluoroacetic acid (TFA) and solvent. TFA is commonly used in MALDI to help solubilize the organic salts, and samples were prepared with and without this additive. Overall, it was determined that this method of characterization was not appropriate for our system.

Endgroup analysis was also not extremely helpful in this case as the ratio of the integrals of the protons at the end group to the protons in the backbone was too small to make accurate calculations of the molecular weight. This method is also heavily dependent on the solubility of the material, as higher molecular weight fractions will not be included in the spectrum if they are not in the solution.

To further limit the ability of the monomer to react with itself and to couple preferentially to the growing chain, the phase-transfer catalyst 18-crown-6 ether was introduced. As emphasized by Yokozawa and Suzuki, this strategy requires the use of a potassium base (that may be encapsulated by this specific crown ether), and a solvent that selectively solvates the growing chain and not the deprotonated monomer. The feed ratio was redefined as a comparison of the amount of initiator relative to that of the monomer and it was thought that the optimum ratio would be equimolar, since this was observed by Suzuki and Yokozawa.10

To ensure that the growing polymer was fully soluble in the reaction solvent, the initiator method was tested using a more substituted monomer where a carboxylate replaced the acidic, methine proton. The resulting polymer should not be deprotonated and thus should be neutral rather than anionic. The adaptation of Yokozawa's biphasic polymerization using our
system is illustrated in Figure 7.7 below. Acetone met the solubility requirements for our specific coupling and polymerization was attempted at with a 90/10 ratio of acetone and NMP at 130 °C for 5 minutes in the microwave (MCB-VI-65). Characterization of the crude product by $^1$H-NMR revealed unreacted starting material, and products from decarboxylation of the ethyl cyanoacetate group, which can result at these high temperatures. The temperature was therefore decreased to 100 °C and held for a longer time of 10 minutes in the microwave to help prevent decarboxylation. The 10% NMP was also removed, and this polymerization attempt likewise resulted in unreacted starting material (MCB-VI-66).

This more substituted monomer was thought to lead to a more soluble product, and is the same derivative used previously in the protecting group section of Chapter 4. After several attempts polymerizing the substituted monomer did not result in materials of high molecular weight (MCB-VII-70, 71, 72), it was thought that a model coupling could be employed. However, upon further analysis, it was realized that the reaction coupling this initiator to the secondary nitrile is the same coupling that was previously found to be unsuccessful (Chapter 4). For this reason, a model coupling and optimal coupling conditions were not explored.
It was thought that incorporating an initiator followed by the decarboxylation method presented in Chapter 6 could be beneficial. However, after some consideration, it was determined that this would not likely result in the desired product. Work done previously by Yokozawa and Yokoyama with electron-withdrawing initiators show that slow, drop wise addition of a previously-formed anionic monomer is essential for achieving monodisperse polymers. The decarboxylation method discussed here forms the anionic monomer in situ from the coupling of two separate species, the dihalide and cyanoacetate salt. Thus, there is no plausible way of controlling the rate at which the deprotonated monomer is introduced to the initiator. This reaction also requires an extra equivalent of base (the cyanoacetate salt), which could also prove detrimental to the initiator. Furthermore, this electron-withdrawing additive would be a better electrophile than the monomer. Noting that the initiator is only used in catalytic amounts, it is safe to assume that it would be consumed readily in the
presence of excess salt. In summary, the initiator method is worthy of further exploration, but not in conjunction with decarboxylative couplings.

We thus returned to the successful initiator-assisted polymerizations done previously to attempt to scale up the reaction size in the microwave. After experiencing problems with the reproducibility of the microwave reactor, we turned to thermal heating options. The problems we encountered when optimizing the model coupling was the same for polymerizations: solvent loss at higher temperatures. For this reason, a sealed reaction vessel was employed, and was tested using the same optimized set of conditions. Polymerization using 2 mol % initiator to obtain an 11 kDa material was attempted (MCB-VII-61). Characterization of the thermal reaction revealed a successful coupling with a product that precipitated into MeOH, could be redissolved in THF, and contained the indicative product peak at 5.2 ppm in the $^1$H-NMR. GPC results revealed a bimodal distribution: $M_n=9.6$ kDa, $M_w=35.1$ kDa, and a PDI of 3.6 in 19% yield.

C. Conclusions

By employing 2-bromobenzonitrile as an electron-withdrawing initiator in the polymerization of interest, we have been able to efficiently apply palladium cross-coupling conditions to monomers with acidic functionality. The electron-rich monomer that was hesitant to couple in a step-growth fashion, as discussed in Chapter 3 and presented here in Figure 7, was successfully polymerized using the initiator-assisted chain-growth polymerization presented by Yokozawa et al. Increasing the temperature during the addition of the deprotonated monomer to the initiator/catalyst mixture, allowed for both thermal and
microwave heating methods to be employed. By lowering the electron density of the deprotonated monomer, the conditions optimized in Chapter 2 for the model oligomer synthesis were able to be applied to the polymerization. Low polydispersities and modest control over molecular weight were also achieved.

D. Experimental

A CEM Discover Microwave was used in the standard mode for all microwave reactions. Glass vials (7 mL capacity) with teflon snap caps were purchased from CEM and used with the closed-vessel attenuator graded to withstand 250 psi. Unless otherwise noted, stirring and cooling modes were applied. An International Equipment Company (IEC) Centra MP4 centrifuge was used to separate polymer precipitate from the monomer in solution. HPLC used a Grace Nucleosil C_{18} (5 micron, 4.6 mm ID, 250 mm length) column. The mobile phase was a 70:30 Acetonitrile/H_{2}O solvent system at a flow rate of 1.0 mL/m. Solvents were filtered HPLC-grade, and the H_{2}O was adjusted to a pH of 2.88 using glacial acetic acid. 3,5-Dimethyl anisole served as the internal standard. UV-Vis spectra were recorded on a JASCO V-550 spectrophotometer. LCMS data were collected from an Agilent Technologies 6210 LC-TOF mass spectrometer equipped with an Agilent SB-C18 1.8µm 2.1 x 50 mm column. Samples were diluted in methanol and analyzed via a 1 µL injection at 400 µL/min in a water:methanol gradient with 0.1% formic acid. The mass spectrometer was operated in positive-ion mode with a capillary voltage of 4 kV, nebulizer pressure of 30 psig, and a drying gas flow rate of 12 L/min at 350°C. The fragmentor and skimmer voltages were 210 and 65 V, respectively. NMR spectra were recorded on a 300 MHz Gemini 230 NMR
spectrometer. IR spectra were recorded on a Perkin Elmer FT/IR Spectrum RX I on KBR discs. \( M_n \) and \( M_w/M_n \) values were calculated based on GPC results using a Lab Alliance pump with a flow rate of 1.0 mL/min, Alltech Jordi-Gel DVB 1000Å 250 mm, 10 mm I.D. column with a Phenomenex 50 x 7.80 mm, 5 micron linear/mixed guard column, column heater set to 30.0°C, JASCO RI-1530 RI detector, and Linear chart recorder, recording at a rate of 1 cm/min. The eluting solvent was either THF (used in conjunction with a Waters Lambda-Max Model 481 LC Spectrophotometer) or DMF, and the MW curve was based upon a sample of EasiVial PS-L polystyrene standards for GPC obtained from Polymer Laboratories, a division of Varian Inc.

THF was distilled from sodium and benzophenone. DMF was distilled under reduced pressure from 4Å molecular sieves. Ortho-cyano benzyl cyanide was purified by column chromatography prior to use in reactions. All other reagents were purchased from Aldrich and used without further purification.

**Initiator-assisted synthesis of precursor polymer (representative polymerization):**

Notebook reference MCB-VII-36. Pd(OAc)\(_2\) (6.7 mg, 0.03 mmol), PCy\(_3\) (16.8 mg, 0.06 mmol), 2-bromobenzene (30 µL of a 0.1 M stock solution in NMP) and NMP (170 µL) were placed in a 7 mL microwave vial in a nitrogen dry box. This was allowed to warm to 78°C in the dry box with stirring. A solution of K-OtBu (74.0 mg, 2.2 mmol) and THF (0.9 mL) was made in a separate vial. A solution of monomer (91.5 mg, 0.3 mmol) in THF (0.9 mL) was made in another separate vial. The base solution was added drop wise to the monomer solution, and the combined mixture was then added drop wise to the catalyst solution. The microwave vial was removed from heat, capped, and immediately removed from the dry box
and placed in the microwave reactor, and was allowed to react at 100W, 130 °C, 150 psi, for a run time of 3 m, and hold time of 5 m. After the cooling cycle, the vial was removed from the reactor, and the crude reaction mixture was added drop wise to methanol (20 mL) in a centrifuge tube with stirring. A light yellow-brown precipitate settled to the bottom of the tube after 2 m in the centrifuge. The methanol layer was decanted into a pre-weighed vial and was concentrated under reduced pressure. The remaining precipitate was redissolved in THF (5 mL) and transferred to a pre-weighed vial. This layer was concentrated under reduced pressure, and was characterized by NMR, GPC, and IR. 52 mg polymeric material was recovered from the second precipitation in methanol to give a 77% yield. ¹H-NMR ((CD₃)₂SO): δ=0.68 (b, 3H), 1.13 (b, 6H), 1.65 (b, 4H), 5.28-5.30 (m, 1H); 6.95-7.80 (b, 2H); GPC (DMF): Mₙ=60 kDa, M_w=66 kDa, PDI=1.1; IR (KBr): 3321, 2955, 2931, 2226, 2130, 1666, 1441, 1367, 1344, 1322, 1304, 1191, 1121, 1068, 1037, 965, 926, 850, 755, 569 cm⁻¹.
E. References


