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Efficient Iterative Synthesis of Oligophenylene Rods and Methodology Studies Involving Aryldiazonium Tetrafluoroborate Salts and Arylboronic Esters.

Douglas Macarthur Willis

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EFFICIENT ITERATIVE SYNTHESES OF OLIGOPHENYLENE RODS AND METHODOLOGY STUDIES INVOLVING ARYLDIAZONIUM TETRAFLUOROBORATE SALTS AND ARYLBORONIC ESTERS

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The Department of Chemistry

by

Douglas M. Willis
B.S., Texas Southern University, 1995
December, 2000
DEDICATION

This dissertation is dedicated to those who have supported me throughout the years. First, all honor and respect goes to almighty GOD, for without his power and guidance, none of this would have been possible. To the memory of my grandparents (Lee Prescar and Velma Willis), whose inspiration, compassion and determination drove me to succeed where others have faltered. To the memory of "Aunt Poochie" (Annie Ruth Williams), who I know really understands where my true love for science emanates. To my high school and college chemistry mentors (Drs. Pahlavan, Paul E. Thurston and Bobby Wilson), who exposed me to a world complete with endless challenges. To my Brothers In The Bond - you know who you are. To my (extended) family and friends - thanks for all of the support, encouragement and tolerance. To my siblings (Lemetha Willis, Byron Willis and Carl Willis) - yes, there is a "doctor" in the immediate family. Thanks for everything! To "Uncle Buddy" (Lavell Willis) and Aunt Francis - thanks for letting me impose. To my beloved son (Jerecq Marquis Willis), who I hope I have been a role model and an inspiration to since he has been one to me. Last, and most importantly, to my mother (Mary Lee Green), whose toil, strife and wisdom provided the means for my success. I will never be able to thank you enough. Thanks for the caring, love and "mother-wit". Thanks also for instilling in me the desire and faith to work hard and achieve no matter what. I Love You! Here's to twenty-two years of education and endurance.

Sincerely,

Douglas M. Willis
ACKNOWLEDGMENTS

I would like to express gratitude to Dr. Isaiah Warner, whose relentless recruiting efforts at Texas Southern University and other HBCU's, was partly responsible for my presence at Louisiana State University. Thanks for being a great mentor and showing concern. I am especially grateful to my esteemed advisor, Dr. Robert M. Strongin, who took a chance and provided me with the opportunity to work on a challenging research project as well as investigate some of my own novel ideas. I guess everything does work eventually! Thanks to our first postdoc, Dr. Marcelo Saraiva, who provided me with an excellent start in the laboratory and simply stated, "Don't worry, Douglas! One day you will get your Ph. D." Thanks to the National Consortium for Graduate Degrees for Minorities in Engineering and Science, Inc. (GEM), the Huel D. Perkins Foundation, the LSU Graduate School, the National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (NOBCChE) and Procter & Gamble for financial support at different stages of my graduate career. Your funds were well spent and appreciated. Thanks to Kodak for giving me an opportunity to excel in my first real industrial position. You will not be disappointed. Thanks to all of the past and present members of the Strongin Research Group (David Amspacher, Patricia Beck, Dr. Larry Cabell, Dr. Alfonso Davila, Claude Davis, Jorge Escobedo, Taiya Fabre, Ming He, Leticia Johnson, Rolanda Johnson, Patrick Lewis, Dr. Mark Read and Nadia St. Luce), my dissertation committee members (Drs. Frank K. Cartledge, William H. Daly and George G. Stanley), and other faculty and staff of the LSU Chemistry Department for their additional support and encouragement. All efforts were greatly appreciated.
This dissertation represents the 'termination' of twenty-two years of formal education and the inception of a new life and career. Throughout my years of matriculation, I have encountered many trials and tribulations for which I have sought various outlets and sources of inspiration. Furthermore, it became quite clear that sometimes laughter and humor were the appropriate medicines for certain events that occurred in graduate school. Accordingly, here is an interesting and facetious fable relevant to my experience in the Chemistry Department at Louisiana State University:

One sunny day a rabbit came out of her hole in the ground to enjoy the fine weather. The day was so nice that she became careless and a fox sneaked up behind her and cornered her.

"I am going to eat you for lunch!" yelled the fox.

"Wait!" replied the rabbit. "You should at least wait a few days."

"Oh yeah?" said the fox. "Why should I wait?"

"Well, I am just finishing my dissertation entitled *The Superiority of Rabbits over Foxes and Wolves!*" cried the rabbit.

"Are you crazy?" asked the fox. "I should eat you right now! Everybody knows that a fox will always win over a rabbit."

"Not according to my research," proclaimed the rabbit. "If you would like, you can come into my hole and read it for yourself. If you are not thoroughly convinced, then you can go ahead and have me for lunch."

"You really are crazy!" shrieked the fox.

However, since the fox was curious and felt it had nothing to lose, it followed the rabbit into the hole. The fox never came out. A few days later, the rabbit was enjoying a casual break from her writing. At that moment, a wolf came out of the bushes and was about to feast upon her.
"Wait!" exclaimed the rabbit. "You can't eat me right now."
"And why might that be?" asked the wolf.

"Well, I am almost finished writing my dissertation on *The Superiority of Rabbits over Foxes and Wolves,*" said the rabbit.

The wolf laughed so hard that it almost lost its grip on the rabbit.
"Maybe I shouldn't eat you," said the wolf. "You really are sick. You might even have something contagious."

"Okay, come and read it for yourself," said the rabbit. "You can eat me afterwards if you disagree with my conclusions."

So the wolf went down into the rabbit's hole...and never came out. The rabbit finally finished her dissertation and was out celebrating in the local lettuce patch when another rabbit came along.

"What's up?" asked the friend. "You seem very happy."

"Well, I just finished my dissertation," answered the rabbit.

"Congratulations! What's the topic of your dissertation?" asked the friend.

"*The Superiority of Rabbits over Foxes and Wolves,*" said the rabbit.

"Are you sure?" asked the friend. "That doesn't sound quite right."

"Oh yes, I'm sure," rebutted the rabbit. "But since you're a little skeptical, come into my hole and read it for yourself."

So together they descended into the rabbit's hole. As they entered, the friend saw the typical graduate student abode, albeit a rather messy one after completing a dissertation. The computer with the controversial work was in one corner. To the right of that, there was a pile of fox bones; to the left, a pile of wolf bones; and in the middle, a large well-fed lion.

**The moral of the story: The title of your dissertation doesn't matter. The subject doesn't matter. All that matters is who your advisor is.**

Other sources of personal motivation included the Good Book and various quotations by both celebrities and novices. The following includes several of the latter for your perusal:
"Optimism is the faith that leads to achievement. Nothing can be done without hope and confidence."
   - Helen Keller

"Nothing great is ever accomplished without enthusiasm."
   - Ralph Waldo Emerson

"The man who makes no mistakes does not usually make anything."
   - Bishop W. C. Magee

"He that is good for making excuses is seldom good for anything else."
   - Ben Franklin

"You can tell whether a man is clever by his answers. You can tell whether a man is wise by his questions."
   - Naguib Mahfouz

"I am enough of an artist to draw freely upon my imagination. Imagination is more important than knowledge. Knowledge is limited. Imagination encircles the world."
   - Albert Einstein

"I'd rather be a failure in something that I love than a success in something that I don't."
   - George Burns

"We are what we repeatedly do. Excellence is therefore not an act, but a habit."
   - Aristotle

"I shall allow no man to belittle my soul by making me hate him."
   - Booker T. Washington

"Never let your persistence and passion turn into stubbornness and ignorance."
   - Anthony J. D'Angelo

"The roots of true achievement lie in the will to become the best that you can become."
   - Harold Taylor

"The palest ink is better than the sharpest memory."
   - Chinese Proverb

"Wisdom begins in wonder."
   - Socrates

"One can never consent to creep when one feels an impulse to soar."
   - Helen Keller
"In the end, we will remember not the words of our enemies, but the silence of our friends."
- Rev. Dr. Martin Luther King, Jr.

"Vision without action is a daydream. Action without vision is a nightmare."
- Japanese Proverb

"Einstein's Three Rules of Work: 1) Out of clutter, find simplicity; 2) From discord, find harmony and 3) In the middle of difficulty lies opportunity."
- Albert Einstein

"I have learned that success is to be measured not so much by the position that one has reached in life, as by the obstacles which one has overcome while trying to succeed."
- Booker T. Washington

"The optimist sees opportunity in every danger; the pessimist sees danger in every opportunity."
- Sir Winston Churchill

"Genius is the ability to reduce the complicated to the simple."
- C. W. Ceram

"Zeal without knowledge is like fire without light."
- English Proverb

"Adversity is the first path to truth."
- Lord Byron

"Whether you believe you can do a thing or not, you are right."
- Henry Ford

"Tact is the art of making a point without making an enemy."
- Howard W. Newton

"Knowledge is power and enthusiasm pulls the switch."
- Steve Droke

"If you can't change your fate, change your attitude."
- Amy Tan

"It's how you deal with failure that determines how you achieve success."
- David Feherty

"The price of greatness is responsibility."
- Sir Winston Churchill
"It is better to deserve honors and not have them than to have them and not deserve them."
- Mark Twain

"I would rather fail with honor than succeed by fraud."
- Sophocles

"You can complain because roses have thorns, or you can rejoice because thorns have roses."
- Tom Wilson

"The true worth of a man is to be measured by the objects he pursues."
- Marcus Aurelius

"Obstacles are those frightful things you see when you take your eyes off the goal."
- Hannah More

"Luck is not chance, it's toil; fortune's expensive smile is earned."
- Emily Dickinson

"Change never helps those who do not help themselves."
- Sophocles

"Why do scientists call it research when looking for something new?"
- Anonymous

"The goal of science is to build better mousetraps. The goal of nature is to build better mice."
- Anonymous

"The great tragedy of science -- the slaying of a beautiful hypothesis by an ugly fact."
- Thomas Huxley

"Everything works...eventually!"
- Rob Strongin

"The only thing that is for sure is that nothing is for sure!"
- Escobedo's Law

"Diligence is the mother of good luck, and God gives all things to industry."
- Benjamin Franklin
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<table>
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<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Ar-B(OH)$_2$</td>
<td>Arylboronic acid</td>
</tr>
<tr>
<td>Ar-B(OR)$_2$</td>
<td>Arylboronic ester</td>
</tr>
<tr>
<td>Ar-$N_2$BF$_4$</td>
<td>Aryldiazonium tetrafluoroborate salt</td>
</tr>
<tr>
<td>Ar-OTf</td>
<td>Aryl triflate</td>
</tr>
<tr>
<td>DMA</td>
<td>N, N-Dimethylacetamide</td>
</tr>
<tr>
<td>FAB-MS</td>
<td>Fast Atom Bombardment Mass Spectrometry</td>
</tr>
<tr>
<td>GCMS</td>
<td>Gas Chromatography Mass Spectrometry</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>MALDI-MS</td>
<td>Matrix-Assisted Laser Desorption Mass Spectrometry</td>
</tr>
<tr>
<td>Na$_2$PdCl$_4$</td>
<td>Sodium tetrachloropalladate</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>OPP</td>
<td>Oligo($para$-phenylene)</td>
</tr>
<tr>
<td>Pd/C (30%)</td>
<td>30% Palladium adsorbed on carbon</td>
</tr>
<tr>
<td>PdCl$_2$</td>
<td>Palladium (II) chloride</td>
</tr>
<tr>
<td>PdCl$_2$(dpdpf)</td>
<td>Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II)</td>
</tr>
<tr>
<td>PdCl$_2$(PPh$_3$)$_2$</td>
<td>Dichlorobis(triphenylphosphine)palladium (II)</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>Palladium (II) acetate</td>
</tr>
<tr>
<td>Pd(PPh$_3$)$_4$</td>
<td>Tetrakis(triphenylphosphine)palladium (0)</td>
</tr>
<tr>
<td>PPP</td>
<td>Poly($para$-phenylene)</td>
</tr>
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</table>
Suzuki coupling protocols were applied towards the design and subsequent iterative synthesis of oligophenylene rods bearing polar functional groups. These well-defined, polar-functionalized rigid rods were ultimately constructed using an efficient iterative molecular doubling approach without using protecting groups, boronic acid isolations, Grignard or organolithium reactions or preparative chromatographic methods. Currently, these rods are being appended to resorcinarene macrocyclic scaffolds in efforts towards achieving a controlled synthesis of novel, uniform, three-dimensional, electronic directional materials with extended, highly functional lower aromatic cavities.

Unique methodology studies involving aryldiazonium tetrafluoroborate salts and arylboronic esters were also contrived and investigated. A novel procedure for the direct, palladium-catalyzed cross-coupling reaction of aryldiazonium tetrafluoroborate salts with arylboronic esters to provide functionalized, unsymmetrical biaryls in moderate yields was developed. Various aryldiazonium tetrafluoroborate salts bearing both electron-donating and electron-withdrawing groups were evaluated at relatively mild temperatures and in aqueous media.

Finally, a novel synthesis of arylboronic esters using bis(pinacolato)diboron and aryldiazonium tetrafluoroborate salts was also developed. The palladium-catalyzed borylation reaction proceeded efficiently under mild reaction conditions in the absence of base affording various functionalized arylboronic esters in moderate to high yields.
CHAPTER 1
INTRODUCTION

1.1 Materials Science: Studying Conjugated Oligomers

When polymers are made up of a large number of building blocks linked in a repetitive fashion, oligomers constitute their lower homologs. It is difficult to define a borderline between oligomers and polymers in terms of their molecular weights, but it is certainly a key feature that increasing the size of an oligomer changes its physical properties - until a convergence limit is reached. It follows that a major motive of oligomer research is to establish relations between chain length and physical properties. Oligomers can be polydisperse, but monodisperse oligomers allow a more precise structure-activity relationship to be determined as well as extrapolation of these relationships toward those expected for polymers. Researchers with different backgrounds are involved in the study of oligomers. Polymer scientists have prepared oligomers as models for polymers, while organic chemists have made oligomers as higher homologs of monomers.\textsuperscript{1,1}

1.2 Significance

Most synthetic processes that produce polymeric compounds afford polydisperse materials, containing mixtures of polymer chains of varying molecular weights.\textsuperscript{1,2} The heterogeneous nature of the polymeric mixture can be of little importance if the polymer is useful towards bulk applications. Heterogeneity can also be quite beneficial due to its retardation of crystallization. Thus, an interesting question may be raised. Can there be advantages of studying precisely defined or homogeneous systems?\textsuperscript{1,3}
Homogeneous oligomers or polymers can serve as prototypes for their related polydisperse macromolecular congeners.\textsuperscript{1,4,1.5} These homogeneous congeners usually offer unique knowledge relevant to the solution, electronic, photonic, thermal and morphological properties of their macromolecular counterparts and may also function as practical standards for polymeric structural and conformational analysis. (1.3)

Homogeneous synthetic approaches tend to address other important issues as well. It would be scientifically beneficial to know, for example, when an oligomer starts behaving like a polymer towards a certain task and also what degree of polymerization is required for a conjugated polymer to commence reacting like a conducting polymer. By building a sequence of oligomers and ascertaining their linear ($\lambda_{\text{max}}$ or band gap) and nonlinear optical responses, can the required minimum degree of polymerization needed to achieve a desired response from a polymer be obtained? Similarly, it may also be possible to determine polymer conformations in solution by studying the responses of a family of definitive, spectroscopically simple, smaller structures. Also, is there precise X-ray structural information of definitive oligomeric systems that may allow for prediction of morphological patterns of bulk polymeric materials? Indeed, the answer to these questions and others, can stem from analysis of homogeneous oligomers and polymers. Thus, precise data can be gathered that relates chain length and conformation to physical, electronic, and optical phenomena. (1.3)

The precise characterization of homogeneous materials is often simpler compared to that of the polydisperse congeners. NMR spectroscopic details are more
Readily resolved than with randomly distributed polymer samples; however, even on the homogeneous systems, the ability to make a truthful assignment becomes increasingly onerous with larger structures. With the use of matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS), molecular ions of synthetic polymers up to 200,000 Da range can be acquired. This information has proved useful for the characterization of large precise structures.

Besides these homogeneous systems functioning as paradigms for higher congeners, there are unique advantages to applications involving precisely controlled length, size and shape compounds. Inhomogeneities can be deleterious in applications where the individual polymer chains are employed for molecular functions, for example, in catalysis (including enzymatic catalysis), host-guest interactions, and relative molecular recognition processes. Future nanoelectronic or nanophotonic processes will likely utilize monodisperse or homogeneous materials. Also, the design of large-pocketed organic crystals will likely require the assembly of large monodisperse frameworks. Thus, specific objectives are arising for many specialty oligomer and polymer syntheses, namely, precise control of molecular weight, composition, sequence, and stereochemistry. Likewise, one would like to build macromolecular architectures rapidly and efficiently with the capacity to employ a wide variety of monomer substrates. Therefore, versatility and efficiency in macromolecular construction are important goals. Consequently, these uniformed, precisely controlled length compounds are of great significance and their utility is on the rise.
The controlled synthesis of oligomers with well-defined end groups and chain lengths may be accomplished using various approaches. Consider, for example, the unequilibrated condensation reaction of terephthalic acid 1 with an alkanediol 2 to yield oligomers with the repeating unit 3. The first condensation step between the two bifunctional components requires one acid and one alcohol function, respectively, to carry different protection groups, say $P^1$ and $P^2$. What is important for further transformations of the resulting monoester 4 is that the protecting groups can be cleaved separately and the next condensation be initiated at either end. While this oligomer synthesis is conceptually straightforward, it becomes increasingly tedious for higher oligomers. Not surprisingly, therefore, oligomers are made using a random approach, for example, through the direct coupling of bifunctional starting compounds such as diols and diacids. While the stoichiometry of reactions can be varied to favor oligomer formation, the weakness of this protocol lies in the need to separate oligomers of different size and in the presence of different end groups. One
expects that increasing the size of the building blocks will render a separation of the oligomeric coupling products easier. (1.1)

The simplest conjugated oligomer is an oligoene chain consisting of an alternating sequence of double and single bonds with the \( \pi-\pi \) interaction extending over the whole molecule. Other examples include aromatic building blocks such as benzene, thiophene or pyrrole, or constitute hybrids of olefinic and aromatic units such as stilbene and higher phenylenevinylene. The general aspects outlined above for the synthesis of oligomers hold also for conjugated oligomers. A troublesome disadvantage arises from the rigid nature of the \( \pi \)-systems, which severely limits their solubility. While it is true that the materials science of oligomers is mostly centered around solid-state properties, sufficient solubility is important for synthesis, structure elucidation, and processing. Solubilization can be achieved by attaching alkyl substituents to the molecules and thus providing them with their own solvation shell. This approach, although having proved of great value, has several disadvantages. Alkyl substitution can weaken \( \pi \)-conjugation by inducing torsion about formal single bonds or inhibit a tight packing of molecules in the solid state. Further, alkyl substitution will dilute the electronically active function of the molecules. (1.1)

While structural homogeneity of the products is an important requirement of oligomer synthesis in general, this criterion is particularly severe for conjugated molecules. Consider, for example, the synthesis of an oligophenylenevinylene with C=C double bond formation through final elimination steps. A failure in this process leaves sp\(^3\)-hybridized centers in the chain, which will interrupt the \( \pi \)-conjugation and
give rise to smaller subunits. While such defects will not remain undetected in tests of the structure of oligomers, the situation may become troublesome in the related polymers. (1.1)

There seems to be uncertainty in the science of electronic materials; structures which arouse the most interest are the more poorly defined. Theory predicts, for example, that polymers with low bandgaps have attractive optical and electrical properties. One anticipates from the prevailing bonding situation, however, that such species, after having been formed, are readily susceptible to various kinds of follow-up reactions. This would, of course, destroy the desired structure. Also, a reliable optical detection of the bandgap would become impossible if some unwanted - and undetected - doping were to occur. There are many other examples of conjugated polymers in which wishful thinking rather than sound scientific reasoning has been the guideline of design and synthesis. (1.1)

It is obvious that oligomers adopt a key role in attempts to put materials science on a firm structural basis since a detailed analysis of their molecular structure is more straightforward than that of polymers. Further, the measurement of phenomena such as transport of charge carriers in photoconductivity and of excitons in photoluminescence requires scrupulous purification of samples, since impurities may produce false or, at least, misleading results. Oligomers are important, therefore, because they can often be purified more easily than polymers, whereby quite demanding techniques such as zone melting or vacuum sublimation have been used. The contribution of the end groups to the overall properties has to be taken into account appropriately. (1.1)
Work centered around oligomers can also stimulate advances in synthesis. Methods of C-C bond formation using organometallic intermediates, which were originally proposed for the synthesis of compounds with low molecular weight, have been tested in repetitive processes and then successfully incorporated into polymer synthesis. Key criteria among such design processes are the yield available in each elementary step, the occurrence of structural defects, and the nature of end groups. (1.1)

It is clear that the availability of a homologous series of monodisperse oligomers allows one to reliably follow their behavior as a function of size. Building homologs of conjugated oligomers is also among the fundamental concepts of organic chemistry. Questions such as achieving a bathochromic shift for a given class of chromophores, or increasing the number of interacting spins in redox-active molecules are closely related to progress in oligomer synthesis by which one makes the active component larger. (1.1)

1.4 Preparation

A significant research goal of the Strongin Research Group is the synthesis and study of novel, precise-dimensioned conjugated cylindrical compounds that can be obtained by regulated organic synthetic strategy. These compounds would encompass soluble and functionalizable precursors or analogs of the fullerene tubules (Figure 1).

One obstacle in investigating these materials as well as homogeneous oligomers and polymers stems from the difficulty of isolation in pure form. Previous work frequently addressed fractionation methods for obtaining oligomers or small
polymers. This involved starting with a bifunctional monomer and carrying out standard polymerization reactions; however, the reaction times were reduced and temperatures lowered for maximization of the formation of the lower molecular weight species. The yield of a desired product was typically low while separation methods generally were shown to be insufficient for the preparative fractionations required. Similarly, polymeric materials could be degraded and oligomeric compounds produced. However, the inefficiency of the necessary fractionation steps can inhibit the utility of this technique. (1.3)

![Diagram](image)

**Figure 1.** Proposed structure of the conjugated, cylindrical compounds.

Modern synthetic organic and organometallic strategies are establishing themselves as powerful towards the direct acquisition of the desired compounds by gradational methods. The gradational methods can take various forms. A monofunctional monomer can be added, successively, to the end of a growing chain.

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After the addition of each monomer unit, the material is often purified, the new end functionalized de novo, and another monomer unit affixed to the end of the chain. A comparable stepwise synthetic approach utilizes oligomers of known lengths, which are appended to the end or ends of a chain with the same purification and end group refunctionalization being required after each step. (1.4,1.5) Using this approach, the oligomer chain can increase by several monomer units per iteration. Purifications can be simplified since the differences in size between the reactants and products are usually several monomer units in length. However, even with this approach, there becomes a point where the differences in the homogeneous congeners are inadequate to allow facile separation from each other. Furthermore, low solubility of the larger intermediates can be a problem. The solubility problem generally manifests itself at early stages in the preparation of rigid, conjugated macromolecules. (1.3)

An extrapolation of this stepwise approach involves the use of an iterative divergent/convergent approach (Figure 2). A monomer M, with protective end groups X and Y, is separated into two reactants. One reactant is activated by converting X to X', while the other reactant is activated by converting Y to Y'. The two reactants are then combined to form the dimer XMMY with loss of X'Y'. Since the same protecting groups that were present in the monomer are now present in the dimer, the technique can be used repetitively resulting in exponential growth of molecular length at each iteration. Thus, the size of the oligophenylene, at any given interval, can be determined by Equation 1.

**Equation 1:** size of oligophenylene = $2^X$, where $X$ = # of iterations
Advantages of this technique include rapid proliferation of molecular chain length and simpler purification of desired products. Therefore, this iterative divergent/convergent approach is particularly attractive to modern synthetic organic chemists. (1.3)

![Diagram](image)

**Figure 2.** Iterative divergent/convergent approach to molecular length doubling.

Prominent examples using the iterative divergent/convergent approach include Whiting’s polymethylene giganta cycles\(^{1.8}\), Moore’s phenylacetylene macrocycles\(^{1.9}\), and Tour’s phenylacetylene rods.\(^{1.10}\) Inspired by these and other literature precedents, iterative divergent/convergent syntheses of functionalized monomeric and dimeric precursors were developed that should be effective towards the preparation of monodisperse, three-dimensional electronic organic materials.\(^{1.11}\)

### 1.5 Properties

The extended \(\pi\)-systems of conjugated oligomers qualify them as chromophores with a broad range of optical properties such as electrophores, with the ability to accept or donate extra charges. Interestingly, many physical properties relevant for materials science are related to the formation, transport, annihilation, or storage of charge. It is the challenge of oligomer research to systematically and comprehensively investigate these processes under structurally well defined...
conditions. It has been stressed that, by definition, the properties of oligomers are chain-length dependent - until one reaches a borderline length at which further extension will no longer affect their behavior. This aspect defines clearly the role of conjugated oligomers as models for the related polymers. At the heart of oligomer research lies the extrapolation of physical properties toward infinite chain lengths and the description of a conjugated polymer in its true state. Therefore, a major concern remains the synthesis and physical characterization of conjugated oligomers and of polymers at the highest possible level of structural precision and reliability. (1.1)

An oligomeric compound whose characterization is restricted to the recording of spectra because of lack of an efficient synthesis and therefore lack of quantity will never become a material. Accordingly, the active physical function of conjugated oligomers and polymers is a key prerequisite when proceeding from chemistry and physics to materials science. This transition also requires creation of a specific macroscopic state of matter, and this need highlights the crucial role of processing. It follows that the description of oligomers as electronic materials cannot be confined to properties of individual molecules in a dilute solution, but always deals with ensembles of molecules and their mutual interactions. It is clear that properties such as conductivity in macroscopic samples depend on charge-transport mechanisms between molecules and, subject to the morphology of the solid, between different structural organizations at various length scales. Thus, supramolecular ordering, which occurs under the influence of weak intermolecular forces and which depends upon the conditions of processing, must also be included when considering oligomers as electronic materials. (1.1)
If the limit of convergence of a particular physical property is already reached for a rather low oligomer size, and if oligomers have a high degree of structural homogeneity, one may regard oligomers as better materials. There are indeed cases where oligomers serve as electronic materials in their own right. Nevertheless, emphasizing the significance of oligomers should not be misunderstood as an argument against conjugated polymers, since discussing the competition between oligomers and polymers is debilitating. One obvious reason is that the performance of an electronic material as an active component of a device depends on a great variety of different, sometimes even conflicting requirements, not the least of which are chemical and morphological stability, as well as processability. (1.1)

1.6 References


CHAPTER 2
EFFICIENT ITERATIVE SYNTHESSES OF OLIGOPHENYLENE RODS:
A RESEARCH OVERVIEW

2.1 Introduction

Polyphenylenes often exhibit remarkable thermal stabilities. They have been considered for use in numerous applications requiring thermally robust organic materials including composites, lubricant additives, hydraulic fluids, heat transfer agents, coolants for nuclear reactors and thermoset precursors for high-performance aerospace materials applications.\(^{2,1,2}\) PPP is not the only constitutional form of the polyphenylenes that exhibits these excellent thermal properties. Appropriately substituted polyphenylenes or non-regiospecifically linked polyphenylenes are often soluble and they can, in some cases, exhibit thermal properties superior to that of PPP. Additionally, efforts to planarize PPP derivatives could lead to uses of soluble ladder polymers in electronic- and photonic-based nonlinear optical devices.\(^{2,2,2,3}\)

Over the past decade, considerable attention has been directed toward the synthesis of poly(p-phenylene) (PPP) and its derivatives. Their good thermal and chemical stability, electrical conductivity upon doping\(^{2,4}\) and optical properties\(^{2,5,2,6}\) make these rigid rod polymers attractive candidates for scientific and industrial applications.\(^{2,7}\)

Recent studies show that functional substitution on conjugated polymers can not only render solubility and processability, but also improve and/or modify electronic and optical properties of parent polymers.\(^{2,8}\) In order to increase the degree of polymerization, induce solubility, and obtain well-defined structure, the polymerization of substituted benzenes has received attention. Soluble poly-\(p\)-2,5-
dialkylphenylenes have been synthesized via palladium-catalyzed Suzuki coupling of 4-bromo-2,5-dialkyl-phenylboronic acid.\textsuperscript{2,9,10} The bulky alkyl groups on the benzene rings force them further out of coplanarity and significantly reduce the conjugation. PPP's with alkoxy substituents, which are more strongly electron donating and less bulky, show increased conjugation.\textsuperscript{2,11} As a further step in the structure-property studies in functionalized PPP's, it is very attractive to see the influence in electronic and optical properties by selectively introducing alkoxy substituents on the conjugated backbones.

Classical oligo- (OPP) and poly-p-phenylene chemistry is on stage as an important component molecule for photon electron cooperative novel advanced materials.\textsuperscript{2,12} To modify the electronic structure of OPP, the phenylene unit is replaced by a wide variety of $\pi$-systems, \textit{i.e.}, thiophene, carbazole, azulene, etc.\textsuperscript{2,13}

Aromatic rigid rod polymers play an important role in a number of diverse technologies including high-performance engineering materials\textsuperscript{2,14}, conducting polymers\textsuperscript{2,15}, and nonlinear optical materials.\textsuperscript{2,16} The synthesis of these interesting macromolecules has been historically difficult and will continue to face additional challenges in the coming decades as the design of superior materials, which may be synthesized and processed entirely under environmentally acceptable conditions, gains importance.\textsuperscript{2,17} It has long been our goal to develop routes to soluble and well-defined rigid rods that can be synthesized and processed in common organic or aqueous solvent systems.
2.2 Research Goals

Conjugated organic materials are the basis of the expanding molecular electronics field.\(^2\) Interactions deriving from \(\pi\)-systems are also of great importance in nature - playing integral roles in protein and nucleic acid structure and molecular recognition.\(^2\) Dissertation research entailed the synthesis and study of a unique class of three-dimensional conjugated \(\pi\)-materials which would allow me to attain discriminating biomimetic hosts with multipoint \(\pi-\pi\), ion-\(\pi\) and CH-\(\pi\) interaction sites as well as tunable functionality and molecular dimension. Contributions emanating from this research are the development of (1) new classes of enhanced, highly selective, versatile and fast-response visual chemosensors for biomolecules and (2) unique materials with extended binding pockets for improved separations, sensing and catalysis. Contributions towards these efforts included synthetic methods towards well-defined, responsive electronic organic architectures.

![Diagram of macrocycle coupling to conjugated rigid rods](image)

**Figure 3.** Generalized design of the proposed architecture.
A generalized design of the synthetic target is illustrated in Figure 3. It encompasses the coupling of the lower cavity of our resorcinarene macrocycle to conjugated aromatic rods. Ultimately, directional materials would be obtained. The extended, three dimensional $\pi$-cavities would have both fixed length (i.e. control over $n$ in I) and defined width. Aryl rings appended to the lower rims of resorcinarene macrocycles are known to lie virtually parallel to each other at 90° to the macrocyclic plane.\(^2\) Coincidentally, the diameter of the lower aromatic cavity of I is in the range of that of buckminsterfullerene and the smallest stable buckytube.\(^2\)\(^1\)

Conjugated rigid rods have been the focus of a worldwide research effort in polymer and materials chemistry and physics. They have exhibited a variety of electronic and optical properties\(^2\)\(^2\) towards potential applications in nonlinear optical\(^2\)\(^3\), sensory\(^2\)\(^4\) and luminescent devices.\(^2\)\(^5\) I synthesized one type of conjugated rigid rod, oligo($p$-phenylene)s, as functional, soluble, pure substances.

Both oligo- and poly($p$-phenylene)s are important redox and chromophore materials\(^2\)\(^6\) and have exhibited a variety of properties including electrical conductivity, radiation and chemical resistance, paramagnetism, luminescence and high mechanical strength.\(^2\)\(^7\) A recent report expresses the utility of oligophenylenes with appended hydroxyls as ion transport relays in lipid bilayers.\(^2\)\(^8\) Dissertation research embodied a new look at these materials as rigid cavity components for molecular recognition.

There has been much effort towards the synthesis of soluble poly($p$-phenylene)s of defined structure and dispersity.\(^2\)\(^9\) Iterative molecular doubling approaches have been proposed as a means to directly control the dispersity of rigid
rod conjugated materials.\textsuperscript{2,30} One example describes the synthesis of oligo(p-phenylene)s up to the 16-mer.\textsuperscript{2,31} My approach was similar but included important departures such as the synthesis of materials with side group functionalities that are polar and reactive. This not only allowed for control over solubility, but also might afford versatile sites to promote covalent and noncovalent interactions.

Resorcinarenes are a remarkable class of cyclic aromatic tetramers whose enormous impact in molecular recognition, materials science and supramolecular chemistry has been the focus of extensive study and recent review.\textsuperscript{2,32} Studies or proposals have suggested the potential utility of these materials as chemosensors\textsuperscript{2,32d}, catalysts, energy storage and drug delivery agents.\textsuperscript{2,32c} Research encompassing resorcinarene molecular containers (carceplexes, carcerands, hemicarcerands) has resulted in landmark achievements including the stabilization of encapsulated cyclobutadiene\textsuperscript{2,33} and benzyne.\textsuperscript{2,34} Multicomponent resorcinarene cavitands are materials of pronounced dimension and properties.\textsuperscript{2,35}

![Diagram](image.png)

**Figure 4.** Direct, fourfold conjugation extension of the resorcinarene lower rim.
Resorcinarene lower rim functionalization has attracted attention as a viable way to enhance the properties of the parent macrocycles.\textsuperscript{2,3,6} In 1989, a unique account described the extension of their lower cavity conjugation and involved a multistep process to incorporate a phenylacetylene moiety.\textsuperscript{2,3,3} Lewis\textsuperscript{2,3,7} (Figure 4) has recently performed direct, fourfold conjugation extension of the lower rim. These discoveries should lead to significant expansion of the scope and utility of the resorcinarenes and allow for the fabrication of rigid, heteropolyfunctional, directional molecular scaffolds. The construction of new heteropolytopic receptors and unique supramolecular materials could thus be realized.

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**Figure 5.** Model unification of resorcinarenes with conjugated rigid rods.

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The unification of resorcinarenes with conjugated rigid rods (Figure 5) should constitute a fundamental advance. It is also conceived that research endeavors would eventually lead to an entirely new class of functional, soluble, well-defined architectures impacting a variety of multidisciplinary research efforts. The fabrication of imaginative arrays of supramolecular materials, biosensors, composites, electronic devices, liquid crystals and host-guest, molecular transport and delivery systems could emanate from these studies. This statement is based on both the rich history of the component materials and the chemical transformability of our targets. The general synthetic design described herein could be readily extrapolated to include other electronic systems such as heteroaromatics and polyenes.

The functionalization of the molecular scaffold (Figure 5) with carboxylate side-groups should allow for binding of relatively complex $\pi$-interactive materials in aqueous media. The extended $\pi$-cavities should promote strong intercalation of such materials between the aryl pillars. Figure 6 exhibits an energy-minimized structure of the important anticancer drug doxorubicin bound in the lower cavity of the molecular scaffold having nine benzene rings attached.

Figure 6. Energy minimized structure of the molecular scaffold ($n = 4$) and doxorubicin (spacefill representation).
Figure 7. Proposed structure of 3-D electronic, organic materials.

The construction of conjugated rigid rods bearing hydroxyl and amine functional groups was also contrived and investigated. Particular interests involved devising methods to enhance the selective cross-coupling of aryl triflates over aryl bromides in palladium-catalyzed reactions via ortho-activation of the triflates with polar side chains followed by enhancement with various lithium chelating agents to induce subsequent oxidative insertion at that position. Furthermore, aryldiazenium tetrafluoroborate salts had recently proven to be powerful nucleofuges in palladium-catalyzed cross-coupling reactions; however, little attention had been paid to the reaction of arylboronic esters with aryldiazenium tetrafluoroborate salts using Suzuki coupling protocols. Efforts towards developing this protocol and applying it to novel
synthetic approaches aimed at the construction of conjugated, rigid π-materials were designed and implemented.

Figure 8. Molecular design of 3-D electronic, organic materials.

In the following chapters, the syntheses of functionalized monomeric and dimeric precursors using Suzuki protocols will be presented. These materials are being used for iterative divergent/convergent approaches towards polar, functionalized oligophenylenes and currently are being appended to resorcinarene macrocyclic scaffolds to create defined, unique three-dimensional electronic organic materials with extended, highly functional π-cavities (Figure 7). The broad scope of the Suzuki coupling protocol allowed for the design and implementation of several synthetic routes, illustrated in Schemes 1-5. Thus, the most promising method for the
preparation of our polar, functionalized oligophenylenes and extension of our highly functional π-cavities could be determined. Consequently, various synthesized electrophiles and boron nucleophiles were employed in the Suzuki cross-coupling reactions, including the aryl bromide and iodide (Schemes 1-4), aryl triflate (Scheme 3), aryldiazonium tetrafluoroborate salt (Scheme 5), arylboronic acid (Schemes 1-2) and arylboronic ester (Schemes 3-4). Figure 8 elaborates on the molecular design of these materials.

2.3 References


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CHAPTER 3
EFFICIENT ITERATIVE SYNTHESIS OF OLIGOPHENYLENE RODS:
SCHEME 1

3.1 Introduction

This strategy had the advantage that exponential growth could be obtained. Here, the Ar-B(OH)₂ and X (Br or I) functional groups were used to generate the oligophenylene rigid rod. The triazene function as the protecting group on the oligophenylene precursor promoted facile and clean transformation to the iodo function.³¹ Similarly, the X group could be converted to a boronic acid.³² The design was such that only one reaction was required to commence coupling and subsequent molecular doubling. We chose the Suzuki cross-coupling methodology using boronic acids and aromatic halides in the presence of base and Pd(0) catalysis.³³ This popular reaction was known to proceed regiospecifically and with high yields. Moreover, it was quite sensitive to the halogen used. Aryl iodides had been reported to couple significantly faster than aryl bromides.³⁴ Consequently, aromatics containing both bromo and iodo sites underwent coupling at the iodo site first. The manipulation of this feature of the Suzuki protocol was a design feature of strategic importance. For future solubility and materials studies, the conformationally rigid oligophenylenes were adorned with polar, interconvertable functional groups.³⁵

Scheme 1 indicates my initial iterative divergent/convergent growth strategy involving unsymmetrical precursors.
3.2 Results and Discussion

Scheme 1. Part 1: Synthesis of the bifunctional aryl electrophile.

Part 1 of Scheme 1 involved synthesis of the bifunctional aryl electrophile 3 in three steps. Commercially available 4-bromo-3-methylaniline was iodinated successfully to obtain 1 in 45% yield.\textsuperscript{3,6} Compound 1 was ultimately converted into its benzyl bromide derivative 2 in 64% yield using Wohl-Ziegler conditions.\textsuperscript{3,7} Finally, conversion of the benzyl halide 2 into the benzyl ether 3 was achieved in 99% yield using a Williamson ether synthesis.

Part 2 of Scheme 1 involved synthesis of the protected aryl electrophile 5 in two steps. Commercially available 4-bromoaniline was diazotized and trapped with
nucleophilic pyrrolidine to ultimately give the triazene derivative 4 in 93% yield. Initial attempts to make the triazene by trapping with diethylamine produced waxes rather than solids. Employing pyrrolidine gave the rigidity needed as crystalline solids were thus obtained. Afterwards, the triazene 4 was converted ultimately into its boronic acid derivative 5 in 88% yield. Using triisopropyl borate as the electrophile instead of trimethoxy borate gave better results. Due to cyclic boroxine formation, characterization after conversion to the corresponding pinanediol and pinacol (not shown) boronate esters was performed.

\[
\text{N} = \text{N} \quad \text{N}
\]

\[
\begin{align*}
1. \text{a}-\text{BuLi} \\
2. \text{Br(O-ipr)}_3 \\
3. \text{H}_2\text{O} \\
4 \quad 93\% \\
\end{align*}
\]

\[
\begin{align*}
1. \text{pinanediol} \\
2. \text{Na}_2\text{SO}_4 \\
3 \quad 83\% \\
\end{align*}
\]

Scheme 1. Part 2: Synthesis of the protected aryl electrophile.
Cross-coupling of the aryl iodide 3 and the arylboronic acid 5 using Suzuki protocols resulted in biphenyl 7 in 91% yield. The divergent synthesis of the biphenylboronic acid 8 and the biphenyl iodide 9 was then accomplished. The boronic acid derivative 8 was obtained from biphenyl 7 ultimately in 54% yield. Synthesis of the aryl iodide 9 by removal of the triazene function with methyl iodide was achieved in 95% yield.

Scheme 1. Part 3: Subsequent cross-couplings using Suzuki protocol.
3.3 Conclusions

Only one small-scale attempt was made to cross-couple the biphenylboronic acid 8 and the biphenyl iodide 9 using Suzuki protocol due to availability of material. The NMR spectrum seemed promising, but consistent and accurate mass spectral data could not be obtained. Efforts to abridge the iterative synthesis and remove the protecting group were to be designed and implemented.

3.4 Experimental

2-bromo-5-iodotoluene, 1. Finely crushed 4-bromo-3-methylaniline (215.1 mmol) was added to a reaction vessel, dissolved in 50% HCl(aq) and cooled to 0 °C. At 0 °C, 231 mmol of NaNO₂ (in 32 ml H₂O) was added dropwise over 20 min. After stirring for 10 min., 218 mmol KI (in 40 ml H₂O) was added dropwise and allowed to warm to room temperature while stirring. The solution was then heated to 50 °C for 15-30 min. to drive the reaction to completion, cooled to room temperature, and extracted with DCM/H₂O. The organic layer was dried with MgSO₄ and excess DCM removed in vacuo. Silica gel chromatography (hexane) afforded 28.8 g (45%) 1 as a pale orange liquid. ¹H NMR (200 MHz, CDCl₃): δ 7.56 (s, 1H), 7.32 (d, J = 6.7 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 2.34 (s, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 140.1, 139.3, 136.2, 133.8, 124.8, 92.3, 22.6. Analysis calculated for C₇H₆BrI (296.94): GCMS – 296 [M⁺], 298 [M⁺ + H⁺].

1-bromo-4-iodo-2-(bromomethyl)benzene, 2. 2-Bromo-5-iodotoluene 1 (67.36 mmol) was dissolved in CCl₄ and added, along with 67.36 mmol of 2,2’-azobisisobutyronitrile (AiBN) and 67.36 mmol N-bromosuccinimide (NBS), to a reaction vessel. The solution was allowed to reflux while stirring. Upon
determination of reaction completion by NMR, the solution was filtered, solvent removed in vacuo, and residue extracted with DCM/H₂O. The organic layer was dried with MgSO₄ and excess DCM removed in vacuo. Silica gel chromatography (hexane) afforded 16.3 g (64%) 2 as a crystalline white solid. \(^1\)H NMR (200 MHz, CDCl₃): δ 7.76 (s, 1H), 7.48 (d, \(J = 8.0\) Hz, 1H), 7.31 (d, \(J = 7.9\) Hz, 1H), 4.50 (s, 2H). \(^1\)C NMR (50 MHz, CDCl₃): δ 168.8, 166.5, 139.7, 138.9, 134.7, 92.5, 32.0. Analysis calculated for C₇H₅Br₂I (375.82): GCMS - 375 [M⁺], 377 [M⁺ + H⁺].

**1-bromo-4-iodo-2-(2,5,8,11-tetraoxatridecan-13-oxy)benzene, 3.** Under N₂, 30.19 mmol of 1-bromo-4-iodo-2-(bromomethyl)benzene 2 was added to a flame dried vessel containing 64.39 mmol NaH (dissolved in dry THF) and 80.49 mmol tetraethylene glycol monomethyl ether. The reaction was allowed to stir at room temperature until completion was determined by NMR. Upon reaction completion, the solution was slowly quenched with H₂O and excess THF removed in vacuo. Silica gel chromatography (70% EtOAc/Hex) afforded 16.1 g (99%) 3 as a yellow liquid. \(^1\)H NMR (250 MHz, CDCl₃): δ 7.81 (s, 1H), 7.44 (d, \(J = 8.0\) Hz, 1H), 7.19 (d, \(J = 8.0\) Hz, 1H), 4.55 (s, 2H), 3.4-3.7 (m, 16H), 3.36 (s, 3H). \(^1\)C NMR (62 MHz, CDCl₃): δ 140.4, 139.1, 139.0, 133.9, 122.3, 89.4, 72.6, 72.5, 70.6, 59.5. Analysis calculated for C₇H₅Br₂I (503.16): GCMS - 502 [M⁺ - H⁺], FAB MS - 502.80 [M⁺].

**2-pyrroolidinyl-1-(p-bromophenyl)diazene, 4.** 4-Bromoaniline (232.5 mmol) was added to a vessel and mixed with 120 ml 50% HCl(aq) and lowered to 0 °C. At 0 °C, 255.8 mmol NaN₃ (in 56 ml H₂O) was added to the solution while stirring. This solution was then transferred to a solution composed of both 348.8 mmol K₂CO₃ and 348.8 mmol pyrrolidine in 480 ml H₂O and the reaction stirred until completion. The
resulting solution was extracted with EtOAc/10% KOH, organic layer dried with MgSO₄ and excess EtOAc removed in vacuo. Silica gel chromatography (10% EtOAc/Hex) afforded 54.9 g (93%) 4 as a golden yellow solid. ^1H NMR (250 MHz, CDCl₃): δ 7.42 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 3.77 (br s, 4H), 1.99 (br s, 4H). ^13C NMR (62 MHz, CDCl₃): δ 150.3, 130.5, 121.8, 117.8, 23.5. Analysis calculated for C₁₀H₁₂BrN₃ (254.16): GCMS – 253 [M⁺ - H], 255 [M⁺ + H].

4-(2'-pyrrolidinylidiazene)phenylboronic acid, 5. 2-Pyrrolidinyl-1-(p-bromophenyl)diazene 4 (7.87 mmol) was added to a flame dried vessel and dissolved in dried THF. At -78 °C, 10.24 mmol 2.5 M n-BuLi was added over 15 min. via syringe. The temperature was allowed to rise to -10 °C, then lowered again to -78 °C, to complete anion formation. 23.6 mmol B(O-ipr)₃ was then added slowly and the reaction allowed to proceed at room temperature until completion was determined by NMR. The solution was quenched with H₂O, excess THF removed in vacuo and resulting aqueous solution extracted with EtOAc. Both layers were then removed in vacuo. Recrystallization using Me₂CO/Hex afforded 1.5 g (88%) 5 as a brick red solid. ^1H NMR (250 MHz, CDCl₃): δ 8.18 (br s, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 3.89 (br s, 4H), 2.18 (br s, 4H). Analysis calculated for C₁₀H₁₄BN₃O₂ (219.06): GCMS – 221 [M⁺ + 2H].

4-(2'-pyrrolidinylidiazene)phenylpinanendiolboronic ester, 6. 4-(2'-Pyrrolidinylidiazene)phenylboronic acid 5 (1.37 mmol) was added to a flame dried vessel containing dried THF and Na₂SO₄. Under N₂, 2.74 mmol of (+)-pinanediol was added and the solution was allowed to reflux, while stirring vigorously, until completion was determined by NMR. Upon reaction completion, excess THF was
removed in vacuo and the resulting residue extracted with EtOAc/H₂O. The organic layer was dried with MgSO₄ and excess EtOAc removed in vacuo. Silica gel chromatography (50% EtOAc/Hex) afforded 0.4 g (83%) 6 as an orange liquid. ¹H NMR (250 MHz, D₆-acetone): δ 7.70 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 4.52 (d, J = 7.1 Hz, 1H), 3.78 (br s, 4H), 2.06 (br s, 4H), 0.89–2.45 (m, 15H). ¹³C NMR (pinacol boronate ester, 62 MHz, CDCl₃): δ 163.4, 153.6, 135.5, 119.6, 83.4, 24.8, 23.7. Analysis calculated for C₂₀H₂₈BN₃O₂ (353.30): GCMS – 352.5 [M⁺ - H], 353.5 [M⁺], FAB MS – 354.2 [M⁺ + H].

4-bromo-4’-(2’’-pyrrolidinyldiazene)-3-(2’’’’,5’’’’,8’’’’,11’’’’-tetraoxatridecan-13’’’’-oxy)methylbiphenyl, 7. Under N₂, (0.006 mmol, 0.3 mol %) of tetrakis(triphenylphosphine) Pd(0) was added to degassed benzene, followed by 0.20 mmol 1-bromo-4-iodo-2-(2,5,8,11-tetraoxatridecan-13-oxy)benzene 3 and 0.40 mmol 2 M K₂CO₃. 4-(2’-pyrrolidinyldiazene)phenylboronic acid 5 (0.22 mmol) was added and the reaction, while stirring vigorously, was allowed to reflux until completion was determined by NMR. Upon cooling to room temperature, the solution was filtered and excess benzene removed in vacuo. The residue was dissolved and then extracted using EtOAc/H₂O. The organic layer was dried with MgSO₄ and excess EtOAc removed in vacuo. Silica gel chromatography (10% EtOAc/Hex) afforded 0.10 g (91%) 7 as an orange liquid. ¹H NMR (250 MHz, D₆-acetone): δ 7.90 (s, 1H), 7.65–7.70 (m, 3H), 7.49–7.60 (m, 3H), 4.70 (s, 2H), 3.91 (br s, 4H), 3.46–3.79 (m, 16H), 3.29 (s, 3H), 2.09 (br s, 4H). Analysis calculated for C₂₆H₃₆BrN₃O₅ (550.50): MALDI MS – 551.78 [M⁺ + H], FAB MS – 550.30 [M⁺].

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4'-(2''-pyrrolidinyldiazene)-3-(2''',5''',8''',11'''-tetraoxatridecan-13'''-oxy)methylbiphenyl-4-boronic acid, 8. 4-Bromo-4'--(2''-pyrrolidinyldiazene)-3-(2''',5''',8''',11'''-tetraoxatridecan-13'''-oxy)methylbiphenyl 7 (0.73 mmol) was added to a flame dried vessel and dissolved in dry THF. At -78 °C, 0.946 mmol 2.5 M n-BuLi was added over 15 min. via syringe. The temperature was allowed to rise to -10 °C, then lowered again to -78 °C, to complete anion formation. 2.18 mmol B(O-iPr)₃ was added slowly and the reaction allowed to proceed at room temperature until completion was determined by NMR. The solution was quenched with H₂O, excess THF removed in vacuo and aqueous layer extracted with EtOAc. The organic layer was dried with MgSO₄ and excess EtOAc removed in vacuo. Silica gel chromatography (5% MeOH/EtOAc) afforded 0.20 g (54%) 8 as a red-orange liquid.

1H NMR (250 MHz, D₆-acetone): δ 8.29 (br s, 2H), 7.95 (s, 1H), 7.71-7.78 (m, 3H), 7.56-7.68 (m, 3H), 4.76 (s, 2H), 3.98 (br s, 4H), 3.51-3.84 (m, 16H), 3.37 (s, 3H), 2.11 (br s, 4H). Analysis calculated for C₂₆H₃₈BN₃O₇ (515.41): MALDI MS – 515.93 [M⁺].

4-bromo-4'-iodo-3-(2''',5''',8''',11'''-tetraoxatridecan-13'''-oxy)methylbiphenyl, 9. Iodomethane (46.7 mmol) and 4-bromo-4'-(2''-pyrrolidinyldiazene)-3-(2''',5''',8''',11'''-tetraoxatridecan-13'''-oxy)methylbiphenyl 7 (0.70 mmol) were combined in a pressure vessel and allowed to reflux for 6-7 hours under N₂ head space. The reaction vessel was depressurized, excess MeI removed in vacuo and residue extracted with EtOAc/H₂O. The organic layer was dried with MgSO₄ and excess EtOAc removed in vacuo. Silica gel chromatography (5% MeOH/EtOAc) afforded 0.40 g (95%) 9 as a golden yellow liquid. 1H NMR (250
MHz, CDCl$_3$): $\delta$ 7.77 (d, $J = 8.0$ Hz, 3H), 7.69 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 2H), 4.66 (s, 2H), 3.52-3.73 (m, 16H), 3.36 (s, 3H). $^{13}$C NMR (62 MHz, CDCl$_3$): $\delta$ 168.1, 166.5, 140.3, 133.4, 132.6, 131.4, 128.6, 127.8, 127.4, 127.2, 121.4, 114.6, 72.2, 71.6, 70.5, 70.0, 58.7. Analysis calculated for C$_{22}$H$_{28}$BrIO$_5$ (579.26): MALDI MS – 603.38 [M$^+$ + Na].

3.5 References


CHAPTER 4
EFFICIENT ITERATIVE SYNTHESSES OF OLIGOPHENYLENE RODS:
SCHEME 2

4.1 Introduction

Organoboronic acids are highly useful reagents for the Pd(0)-catalyzed cross-coupling of aryl halides. The compatibility of organoboronic acids with a broad range of functional groups permits them to be coupled with several electrophiles that are not susceptible to the organometallic reagents commonly employed in cross-coupling reactions. These reagents also possess the advantage of shelf-life stability and relatively low toxicity.\textsuperscript{4.1}

Many organic electrophiles participate in the cross-coupling reaction, with aryl halides being the most commonly used. Generally, aryl iodides and bromides lead to coupled products under mild conditions, while aryl chlorides usually require strong activation with electron-withdrawing substituents.\textsuperscript{4.2}

Snieckus established that arylboronic acids could be coupled with triflates catalyzed by palladium complexes in the presence of base.\textsuperscript{4.3} More importantly, a number of biaryls were obtained by this coupling in good to excellent yield without the addition of lithium chloride. (4.3) This was a remarkable contrast with organotin-triflate coupling reactions which required the addition of lithium chloride to the reaction mixture for satisfactory yields to be obtained.\textsuperscript{4.4} Similar reports further indicated that the triflate could be applicable towards the synthesis of arylboronates via the Pd(0)-catalyzed cross-coupling reaction with tetra(alkoxy)diborons.\textsuperscript{4.5}
Scheme 2 shows another iterative approach, using Suzuki protocol, that employs the triflate as a suitable electrophile in the preparation of monodisperse, three-dimensional electronic organic materials.

4.2 Results and Discussion

A rather abridged version of Scheme 1, Part 1 of Scheme 2 involved use of commercially available 5-iodosalicylic acid as the possible coupling partner to previously synthesized arylboronic acid 5. Using Fischer esterification methodology, the methyl ester 10 was ultimately synthesized in 97% yield. Compound 10 was then cross-coupled to arylboronic acid 5, using Suzuki protocol, to obtain biphenyl 11 in 92% yield.4,6

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Part 2 of Scheme 2 encompassed the subsequent divergent synthesis of biphenyl triflate 12 and biphenyl iodide 13. Initial attempts to obtain a high yield of compound 12 were unsuccessful due to the failure of conventional methods for the preparation of aryl triflates from phenols. (4.4) Biphenyl iodide 13 was synthesized in low yield (20%), resulting in the recovery of starting material. Biphenyl triflate 12 would then be converted into its arylboronic ester derivative using literature precedent and subsequently cross-coupled to biphenyl iodide 13. (4.5)

![Scheme 2. Part 2: Divergence using iterative synthetic strategy.](image)

4.3 Conclusions

No attempt was made towards the Suzuki coupling of 13 with the boronate ester of 12 due to availability of reagents and time constraints. Efforts to further
abridge the synthesis and ultimately remove the protecting group were still to be
designed and implemented.

4.4 Experimental

5-iodomethylsalicylate, 10. 5-Iodosalicylic acid (100.0 mmol), 110.0 mmol
concentrated sulfuric acid and 1.00 mol MeOH were combined in a vessel and
allowed to reflux in the presence of a calcium chloride drying tube and sand bath until
reaction completion was determined by NMR. The solution was cooled to room
temperature and excess MeOH removed in vacuo. The residue was recrystallized
from cold H₂O, crystals captured via suction filtration and washed repeatedly with
5% NaHCO₃ solution. Drying afforded 26.8 g (96%) 10 as a white solid. ¹H NMR
(250 MHz, CDCl₃): δ 10.69 (s, 1H), 8.09 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 6.77 (d, J
= 8.0 Hz, 1H), 3.94 (s, 3H). ¹³C NMR (62 MHz, CDCl₃): δ 169.1, 164.9, 161.0,
143.8, 138.1, 119.8, 114.3, 52.5. Analysis calculated for C₈H₇IO₃ (278.03): GCMS –
278 [M⁺].

3-carboxymethyl-4-hydroxy-4′-(2’’-pyrrolidinyldiazenelbiphenyl, 11. Under N₂,
(0.03 mmol, 0.3 mol %) of tetrakis(triphenylphosphine) Pd(0) was added to degassed
THF, followed by 1.08 mmol 5-iodomethylsalicylate 10 and saturated potassium
carbonate solution. 4-(2’-pyrrolidinyldiazenelphenylboronic acid 5 (1.19 mmol) was
added and the reaction, while stirring vigorously, was allowed to reflux until reaction
completion was determined by NMR. Upon cooling to room temperature, the
solution was filtered and excess THF removed in vacuo. The residue was dissolved
and then extracted using EtOAc/H₂O. The organic layer was dried with MgSO₄ and
excess EtOAc removed in vacuo. Silica gel chromatography (70% EtOAc/Hex)
 afforded 0.3227 g (92%) 11 as an orange solid. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 10.76 (s, 1H), 8.06 (s, 1H), 7.69 (d, $J = 6.1$ Hz, 1H), 7.50 (br s, 4H), 7.05 (d, $J = 8.0$ Hz, 1H), 3.95 (s, 3H), 3.80 (br s, 4H), 2.01 (br s, 4H). $^{13}$C NMR (62 MHz, CDCl$_3$): $\delta$ 166.7, 164.3, 160.5, 134.2, 127.7, 127.0, 120.7, 117.9, 114.1, 106.8, 105.6, 104.4, 103.6, 54.1, 29.7, 23.8. Analysis calculated for C$_{18}$H$_{19}$N$_3$O$_3$ (325.37): GCMS – 324 [M$^+$ - H].

3-carboxymethyl-4’-(2’’-pyrrolidinylidiazene)-4-triflylbiphenyl, 12. 3-Carboxymethyl-4-hydroxy-4’-(2’’-pyrrolidinylidiazene)biphenyl 11 (0.30 mmol) was dissolved in 3.10 mmol freshly distilled pyridine and added to a dried reaction vessel. Triflic anhydride (0.60 mmol) was added to the solution and heated gradually to 50 °C. The reaction mixture was filtered, solvent removed in vacuo and residue extracted with EtOAc/2 M NaOH. The organic layer was dried with MgSO$_4$ and excess EtOAc removed in vacuo. Silica gel chromatography (10% EtOAc/Hex) afforded 0.04 g (24%) 12 as an orange liquid. $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 8.18 (s, 1H), 7.61–7.82 (m, 5H), 7.17 (d, $J = 7.9$ Hz, 1H), 4.01 (s, 3H), 3.94 (br s, 4H), 2.10 (br s, 4H). Analysis calculated for C$_{19}$H$_{18}$F$_3$N$_3$O$_5$S (457.38): GCMS – 458 [M$^+$ + H], 456 [M$^+$ - H].

3-carboxymethyl-4-hydroxy-4’-iodobiphenyl, 13. Iodomethane (19.7 mmol) and 0.30 mmol 3-carboxymethyl-4-hydroxy-4’-(2’’-pyrrolidinylidiazene)biphenyl 11 were combined in a pressure vessel and allowed to reflux for 6-7 hours under N$_2$ head space. The reaction vessel was depressurized, excess MeI removed in vacuo and residue extracted with EtOAc/H$_2$O. The organic layer was dried with MgSO$_4$ and excess EtOAc removed in vacuo. Silica gel chromatography (5% EtOAc/Hex)
afforded 0.02 g (20%) 13 as an orange oil. $^1$H NMR (200 MHz, CDCl$_3$): δ 10.71 (s, 1H), 8.04 (s, 1H), 7.78 (d, $J = 8.0$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 1H), 3.99 (s, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$): δ 161.9, 160.4, 140.1, 138.0, 133.8, 132.6, 131.9, 129.3, 127.8, 127.4, 127.2, 121.4, 114.6, 67.4. Analysis calculated for C$_{14}$H$_{11}$O$_3$ (354.13): GCMS – 354 [M$^+$].

4.5 References


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CHAPTER 5
EFFICIENT ITERATIVE SYNTHESSES OF OLIGOPHENYLENE RODS:
SCHEME 3

5.1 Introduction

Snieckus and coworkers\textsuperscript{5,1} also reported that the relative reactivities of aryl halides and triflates in the coupling reaction are in the order of I, Br $>$ OTf. The discovery that arylboronic acids can be coupled with aryl triflates should be very valuable, since aryl triflates can be easily obtained from phenols. In contrast, more recent literature reports have suggested the following order of reactivity of electrophiles in cross-coupling reactions using Suzuki protocols:

$$\text{Ar-N}_2^+ > \text{Ar-I} > \text{Ar-OTf} \geq \text{Ar-Br} > \text{Ar-Cl}$$\textsuperscript{5,2}

Also, significant attention has recently been paid to arylboronic acids and esters due to their utility in organic synthesis\textsuperscript{5,3}, their biological activity\textsuperscript{5,4} and their molecular recognition properties\textsuperscript{5,5}. Various syntheses of boronic acids have been reported; however, the superlative procedures are based on the reaction of trialkyl borates with Grignard or lithium reagents\textsuperscript{5,6}. The transition metal catalyzed cross-coupling reaction of boron nucleophiles with aryl electrophiles is another route to such boronic acids and esters, but the lack of appropriate boron nucleophiles has restricted this protocol\textsuperscript{5,7}. Previous literature reports showed that the addition of tetraalkoxydiboron to alkynes to give cis-diborylalkenes was catalyzed by platinum (0) complexes\textsuperscript{5,8}. Since alkoxydiborons are thermally stable and easily handled in air, the reagent should be useful as a boron nucleophile for the cross-coupling with organic halides. Consequently, more recent literature reports have revealed the
palladium-catalyzed coupling reaction of bis(pinacolato)diboron and aryl halides\textsuperscript{5,9} and triflates.\textsuperscript{5,10} (5.9)

Scheme 3 demonstrates my modus operandi for the preparation of functionalized dimeric precursors and oligophenylene rods using these current literature precedents.

5.2 Results and Discussion

![Scheme 3. Part 1: Cross-coupling using Suzuki protocol.](image)

Part 1 of Scheme 3 utilized commercially available 4-bromophenylboronic acid as the boron nucleophile and coupling partner for previously synthesized aryl electrophile 10. The Suzuki cross-coupling reaction ultimately resulted in biphenyl 14 in 49\% yield.
Part 2 of Scheme 3 began with the subsequent divergent synthesis, which resulted in biphenyl triflate 15 and biphenylboronic ester 16. Ultimately, biphenyl triflate 15 was successfully obtained in 99% yield from functionalized biphenyl 14. Fresh 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was employed as the base with phenyl triflimide being used as the new triflating agent. In similar fashion, biphenylboronic ester 16 was prepared in 45% yield using current synthetic strategy.

Scheme 3. Part 2: Divergence using the iterative synthetic strategy.

5.3 Conclusions

To date, no attempt has been made towards the cross-coupling reaction which will provide an excellent opportunity to see whether the activated triflate site on
biphenyl 15 will selectively undergo differential palladium-catalyzed cross-coupling in the presence of the bromide site to give the desired functionalized tetraphenylenne product shown.

5.4 Experimental

4-bromo-3'-carboxymethyl-4'-hydroxybiphenyl, 14. Under N₂, (0.03 mmol, 0.3 mol %) of tetrakis(triphenylphosphine) Pd(0) was added to degassed MeOH, followed by 10.0 mmol 5-iiodomethylsalicylate 10 and 2.5 mmol K₂CO₃. 4-bromophenylboronic acid (11.0 mmol) was added and the reaction, while stirring vigorously, was allowed to proceed at 60 °C until reaction completion was determined by NMR. Upon cooling to room temperature, the solution was vacuum filtered and excess MeOH removed in vacuo. The residue was dissolved and extracted with EtOAc/H₂O. The organic layer was dried with MgSO₄ and excess EtOAc removed in vacuo. Silica gel chromatography (10% EtOAc/Hex) afforded 1.5008 g (49%) 14 as a white solid. ¹H NMR (250 MHz, CDCl₃): δ 10.80 (s, 1H), 8.03 (s, 1H), 7.53-7.68 (m, 3H), 7.42 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 3.98 (s, 3H). ¹³C NMR (62 MHz, CDCl₃): δ 170.5, 166.6, 165.0, 161.2, 138.7, 134.0, 131.9, 131.1, 128.5, 128.1, 127.9, 127.0, 121.2, 118.2, 112.5, 52.4. Analysis calculated for C₁₄H₁₄BrO₃ (307.12): GCMS – 306 [M⁺ – H].

4-bromo-3'-carboxymethyl-4'-triflylbiphenyl, 15. 4-Bromo-3'-carboxymethyl-4'-hydroxybiphenyl 14 (1.0 mmol) was dissolved in anhydrous THF and added to a flame dried reaction vessel. Upon purging thoroughly with N₂, 1.5 mmol DBU was slowly added to the vessel at room temperature and the solution was cooled to −78 °C. N-phenyltriflimide (1.5 mmol) was then added and the solution allowed to warm to
room temperature. The solvent was removed in vacuo and the resulting residue dissolved and extracted with EtOAc/H2O. The organic layer was dried with MgSO4 and excess EtOAc removed in vacuo. Silica gel chromatography (10% EtOAc/Hex) afforded 0.4352 g (99%) 15 as a yellow oil. 1H NMR (200 MHz, CDCl3): δ 8.31 (s, 1H), 7.40-7.81 (m, 6H), 4.06 (s, 3H). 13C NMR (50 MHz, CDCl3): δ 164.0, 147.6, 141.0, 140.4, 137.0, 132.0, 131.0, 128.7, 128.6, 127.6, 124.7, 123.3, 123.0, 116.2, 52.8. Analysis calculated for C15H10BrF3O5S (439.13): GCMS – 438 [M+ - H], 440 [M+ + H].

3'-carboxymethyl-4'-hydroxy-4-biphenylpinacolboronic ester, 16. Under N2, a vessel was charged with 1.1 mmol bis(pinacolato)diboron, 1.0 mmol 4-bromo-3'-carboxymethyl-4'-hydroxybiphenyl 14, 1.0 mmol of (0.03 mmol, 0.3 mol %) of dichloro[1,1-bis(diphenylphosphino)ferrocene] Pd(II) dichloromethane adduct and 3.3 mmol KOAc. Anhydrous DMF was added and the reaction allowed to stir at 50 °C until completion was determined by NMR. Upon completion, the solution was filtered and excess DMF removed in vacuo. The residue was dissolved and extracted with EtOAc/H2O. The organic layer was dried with MgSO4 and excess EtOAc removed in vacuo. Silica gel chromatography (10% EtOAc/Hex) afforded 0.1603 g (45%) 16 as a beige solid. 1H NMR (200 MHz, CDCl3): δ 10.80 (s, 1H), 8.09 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.54-7.74 (m, 4H), 7.10 (d, J = 8.0 Hz, 1H), 3.98 (s, 3H), 1.36 (s, 6H), 1.25 (s, 6H). 13C NMR (50 MHz, CDCl3): δ 169.2, 168.4, 166.9, 166.0, 161.2, 135.3, 134.5, 133.8, 128.2, 127.0, 125.8, 118.1, 104.0, 83.9, 52.4, 24.9. Analysis calculated for C20H23BO5 (354.19): GCMS – 354 [M+].

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5.5 References


CHAPTER 6
EFFICIENT ITERATIVE SYNTHESSES OF OLIGOPHENYLENE RODS:
SCHEME 4

6.1 Introduction

Well-defined conjugated oligomers are of current interest as nondefected structures for catalysis and electronic device fabrication, as models for property and characterization studies of their larger polymeric congeners, and as components of large-pocketed organic crystals. These latter as well as related applications have inspired creative synthetic strategies and important property studies of a variety of conjugated oligomeric materials. Oligo(p-phenylene)s are an important class of conjugated redox and chromophore materials that have found use, for example, as chain stiffening building blocks in semiflexible polymers such as polyimides and aromatic polyesters and as models for rodlike polyaromatic and liquid crystalline materials. More recently, oligophenlenes have been transformed to planarized ladder-type materials and relatively large polycyclic aromatic hydrocarbons as well as novel macrocycles. Oligo(p-phenylene)s have also led to the discovery of a new mode of biomembrane recognition and depolarization as well as fascinating biomimetic barrel-like folds, ion channels and amphiphilic materials which form via supramolecular preorganization.

A barrier toward the realization of the full potential of soluble oligo(p-phenylene)s is their challenging synthesis, isolation and purification. A recent major advance toward well-defined, relatively long oligo(p-phenylene)s in multigram amounts is based on repetitive growth strategies. As part of our broader program, which involves the discovery of new palladium-catalyzed coupling reactions and
the creation of three-dimensional oligoaromatic architectures\textsuperscript{6,14} for optical and fluorescence bioanalytical sensing\textsuperscript{6,15}, we herein describe the synthesis of a new oligo(p-phenylene) rigid rod that possesses divergent end groups for potential telechelic applications as well as readily interconvertible carboxylate side groups. The molecular doubling approach involves no formal protecting groups or organolithium\textsuperscript{6,12a} or Grignard chemistry.\textsuperscript{6,12b} Each synthetic transformation is thus tolerant of pendant polar functional groups. The potentially troublesome isolation and characterization of arylboronic acids\textsuperscript{6,16} is avoided. All of the intermediates and the final target are purified without preparative thin layer or column chromatography.

6.2 Results and Discussion

Synthesis of the octameric oligo(p-phenylene) began with aryl electrophile 17 being ultimately synthesized in 94% yield via methyl esterification of the isatoic anhydride derived from 5-iodoanthranilic acid.\textsuperscript{6,17} Subsequent Suzuki coupling\textsuperscript{6,18} to commercially available 4-bromophenylboronic acid afforded biphenyl 18, after drying, in 89.7% yield (Scheme 4, Part 1).

Biphenyl 18 was first transformed to the corresponding biphenyl iodide 19 in 77.9% yield upon dissolution in anhydrous benzene in the presence of I\textsubscript{2} and t-BuONO\textsuperscript{6,19} and then biphenylboronic ester 20 in 91.5% yield via dissolution in a solution of anhydrous, degassed DMF along with commercially available bis(pinacolato)diboron and PdCl\textsubscript{2}(dppf) (Scheme 4, Part 2).\textsuperscript{6,20}


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The synthesis of tetrameric \(p\)-phenylene 21 was accomplished in 38.8% yield via the cross-coupling of biphenyl iodide 19 and biphenylboronate 20 in a degassed 4:1 DMF/H\(_2\)O solution (Scheme 4, Part 2). Subsequent divergent synthesis accomplished by Dr. Mark Read and Jorge Escobedo using tetraphenylene 21 afforded tetraphenyl iodide and tetraphenylboronate, respectively. The tetraphenylboronate was then functionalized with a lauryl moiety to enhance solubility and was subsequently coupled to tetraphenyl iodide to afford an octameric oligo\(p\)-phenylene as shown in Scheme 4, Part 3.
6.3 Conclusions

In conclusion, a highly functional octameric oligo(p-phenylene) was efficiently synthesized by the Strongin Research Group using a molecular doubling approach based on reactions I developed during the synthesis of 21. Transesterification of the side groups to, for instance, glycolate esters at the tetramer stage or earlier should allow the iterative synthesis to continue without end group functionalization with a solubilizing moiety, thereby affording longer rigid rods if needed. Decarboxylation to remove the side groups would furnish novel telechelic rigid rod phenylenes with unsubstituted repeat units. The use of bis(pinacolato)diboron in this scheme also allows for further synthetic streamlining via the application of one-pot arylborylation/cross-coupling methods. Further successful synthetic transformations and the incorporation of new rigid rod oligo(p-phenylene)s into unique, well-defined nanoscale oligoaromatic architectures has now also been achieved in our laboratory.

6.4 Experimental

5-iodomethylanthranilic acid, 17. 5-Iodoanthranilic acid (100 mmol), dissolved in dry THF, was added to a flame dried reaction vessel. Triphosgene (40 mmol) was dissolved in dry THF and slowly syringed into the reaction vessel. This solution was warmed to 60 °C and allowed to stir overnight. Upon cooling to 0 °C, the solution was filtered and afforded 91.7 mmol (92%) of the intermediate 5-iodoisatoic anhydride. A suspension of the 5-iodoisatoic anhydride was dissolved in dry DMF and treated with 917 mmol MeOH and 9.17 mmol 4-(dimethylamino)pyridine (DMAP). The resulting mixture was stirred at 60 °C for three hours. After cooling,
the solvent was removed in vacuo and residue extracted with EtOAc/H₂O. The organic layer was dried with MgSO₄ and excess EtOAc removed in vacuo. Vacuum drying afforded 25.4 g (92%) 17 as a tan solid. ¹H NMR (250 MHz, CDCl₃): δ 8.11 (s, 1H), 7.45 (d, J = 6.8 Hz, 1H), 6.45 (d, J = 8.0 Hz, 1H), 5.83 (br s, 2H), 3.84 (s, 3H). ¹³C NMR (62 MHz, CDCl₃): δ 167.2, 156.7, 149.7, 142.1, 139.4, 118.7, 112.7, 51.7. Analysis calculated for C₉H₇NCl (277.06): GCMS — 277 [M⁺].

4-amino-4′-bromo-3-carboxymethylbiphenyl, 18. 5-Iodomethylanthranilate 17 (0.0722 mol) was added to a reaction vessel along with 0.080 mol commercially available 4-bromophenylboronic acid, 0.163 mol K₂CO₃ and 1.72 mmol Pd(PPh₃)₄ and dissolved in anhydrous, degassed MeOH. The reaction mixture was heated at 60 °C for 12 h under N₂. After filtration, extraction and removal of the solvent in vacuo, the residue was dissolved in CH₂Cl₂ and passed through a short silica gel plug to afford, after drying, 19.8 g (89.7%) 18 as a light yellow solid, mp: 138-139 °C. ¹H NMR (250 MHz, CDCl₃): δ 8.09 (d, J = 2.28 Hz, 1H), 7.51 (dd, J = 2.31, 8.62 Hz, 1H), 7.51 (d, J = 8.59 Hz, 2H), 7.40 (d, J = 8.63 Hz, 2H), 6.78 (d, J = 8.56 Hz, 1H), 3.91 (s, 3H), 5.88 (br s, 2H). ¹³C NMR (62 MHz, CDCl₃): δ 149.9, 139.3, 132.5, 131.7, 129.3, 127.7, 120.4, 117.2, 110.8, 51.3. HRMS m/z calculated for C₁₄H₁₂BrNO₂: 305.0051, found 305.0063.

4′-bromo-3-carboxymethyl-4-iodobiphenyl, 19. 4-Amino-4′-bromo-3-carboxymethylbiphenyl 18 (0.99 mmol) was added to a reaction vessel and dissolved in anhydrous benzene in the presence of 5.94 mmol I₂ and 10.6 mmol 90% t-BuONO at 0 °C. After warming to 60 °C for 10 min., H₂O was added and the reaction mixture extracted, dried and concentrated. The residual solid was triturated with hexanes to
afford 3.18 g (77.9%) 19 as a brown solid. mp: 99.5-101 °C. $^1$H NMR (250 MHz, CDCl$_3$): δ 8.05 (d, $J = 8.25$ Hz, 1H), 7.98 (d, $J = 2.32$ Hz, 1H), 7.58 (d, $J = 8.41$ Hz, 2H), 7.44 (d, $J = 8.38$ Hz, 2H), 7.33 (dd, $J = 2.26$, 8.25 Hz, 1H), 3.96 (s, 3H). $^{13}$C NMR (62 MHz, CDCl$_3$): δ 156.8, 141.9, 140.0, 138.0, 135.6, 132.1, 130.8, 129.3, 128.4, 122.5, 93.0, 52.6. HRMS m/z calculated for C$_{14}$H$_{10}$BrIO$_2$: 415.8909, found 415.8914.

4-amino-3-carboxymethyl-4'-biphenylpinacolboronic ester, 20. 4-Amino-4'-bromo-3-carboxymethylbiphenyl 18 (9.86 mmol) was added to a reaction vessel and dissolved in a solution of anhydrous, degassed DMF along with 11.1 mmol commercially available bis(pinacolato)diboron, 33.0 mmol KOAc, and 0.290 mmol PdCl$_2$(dpdf). The mixture was heated at 60 °C for 12 h under N$_2$, filtered through celite, extracted and dried. The solid was redissolved in CH$_2$Cl$_2$ and filtered through a short silica gel plug, dried, triturated with hexanes and redried to furnish 3.17 g (91.5%) 20 as a white solid. mp: decomposed at 157.9-159 °C. $^1$H NMR (250 MHz, CDCl$_3$): δ 8.09 (d, $J = 2.23$ Hz, 1H), 7.78 (d, $J = 8.24$ Hz, 2H), 7.54 (dd, $J = 2.27$, 8.49 Hz, 1H), 7.48 (d, $J = 8.24$ Hz, 2H), 6.71 (d, $J = 8.55$ Hz, 1H), 3.84 (s, 3H), 1.29 (s, 12H). $^{13}$C NMR (62 MHz, CDCl$_3$): δ 168.5, 149.2, 142.9, 135.3, 132.9, 129.6, 129.5, 125.4, 117.5, 111.2, 83.7, 51.7, 24.9. HRMS m/z calculated for C$_{20}$H$_{24}$BNO$_4$: 353.1798, found 353.1780.

4-amino-4'''-bromo-3-carboxymethyl-3'''-carboxymethyltetraphenyl, 21. 4'-Bromo-3-carboxymethyl-4-iodobiphenyl 19 (7.19 mmol) and 7.93 mmol 4-amino-3-carboxymethyl-4'-biphenylpinacolboronic ester 20 were added to a reaction vessel, dissolved in a degassed 4:1 DMF/H$_2$O solution and heated to 60 °C for 12 h under N$_2$
in the presence of 15.1 mmol K$_2$CO$_3$ and 0.216 mmol Pd(PPh$_3$)$_4$. After filtration, extraction, and drying, the residual solid was redissolved in CH$_2$Cl$_2$ and passed through a silica gel plug to afford 1.44 g (38.8%) 21, after drying, as a white solid. mp: decomposed at 192-195 °C. $^1$H NMR (250 MHz, CDCl$_3$): δ 8.13 (d, $J$ = 2.22 Hz, 1H), 7.95 (d, $J$ = 1.96 Hz, 1H), 7.66 (dd, $J$ = 2.06, 8.03 Hz, 1H), 7.30–7.57 (m, 10H), 6.72 (d, $J$ = 8.54 Hz, 1H), 3.85 (s, 3H), 3.64 (s, 3H). $^{13}$C NMR (62 MHz, CDCl$_3$): δ 169.1, 168.5, 141.3, 138.9, 138.6, 132.8, 132.1, 131.9, 131.4, 129.5, 128.9, 128.8, 128.6, 128.3, 127.4, 127.2, 125.9, 122.1, 117.0, 111.4, 52.2, 51.7. HRMS m/z calculated for C$_{28}$H$_{22}$BrNO$_4$: 515.0732, found 515.0748.

6.5 References


6.3 First efficient palladium-catalyzed synthesis of relatively long oligophenylene rods and references on earlier property studies, see: Galda, P.; Rehahn, M. Synthesis 1996, 614.


6.11 The difficulties associated with the synthesis of multiply substituted phenylenes have been very recently noted: Robert, F.; Winum, J.-Y.; Sakai, N.; Gerard, D.; Matile, S. *Org. Lett.* 2000, 2, 37.

6.12 a) Liess, P.; Hensel, V.; Schlüter, A.-D. *Liebigs Ann.* 1996, 1037. b) A very different large scale synthesis of a sexiphenyl rod has also been reported: Kauffman, J. M. *Synthesis* 1999, 6, 918.


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CHAPTER 7
EFFICIENT ITERATIVE SYNTHESSES OF OLIGOPHENYLENE RODS:
SCHEME 5

7.1 Introduction

Miyaura and coworkers reported the synthesis of arylboronic esters from aryl halides using bis(pinacolato) diboron. They reported the synthesis of arylboronic esters from aryl halides using bis(pinacolato) diboron. The mild reaction conditions of the aforementioned synthesis and of the subsequent Suzuki coupling reaction allow for a broad range of functionalities on the phenyl ring. Similarly, recent reports of the emergence of aryldiazonium tetrafluoroborate salts as excellent coupling partners using Suzuki protocol has sparked our interests due to the economic advantage and availability of various substituted anilines.

Bart, who prepared phenyldiazonium tetrafluoroborate, as well as p-chloro-, p-nitro-, and p-ethoxyphenyldiazonium tetrafluoroborate, synthesized the first diazoniun tetrafluoroborates in 1913. He noticed the great stability of these compounds and alleged them to be functional as intermediates in the preparation of therapeutic agents and dyes. These salts, almost alone among the diazonium salts, are considerably stable and insensitive to shock, and many can be handled safely in quantities of several kilograms. Most of them have distinct decomposition temperatures, and the rates of decomposition, with few exceptions are easily managed. Generally, the overall yields are satisfactory. No special apparatus is required, and the inorganic fluoroborates necessary as intermediates may be purchased or easily prepared.

Presently, aryldiazonium tetrafluoroborate salts can be prepared by a variety of procedures. The most commonly used methods involve the diazotization of

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aromatic amines with sodium nitrite in 40-50% aqueous fluoroboric acid\textsuperscript{7,8} or diazotization in aqueous hydrochloric or sulfuric acid ensued by addition of sodium tetrafluoroborate or fluoro boric acid to precipitate the aryldiazonium tetrafluoroborate salt. Although these methods frequently give good yields of water insoluble diazonium salts, a large excess of fluoroboric acid or sodium tetrafluoroborate is necessary to precipitate the tetrafluoroborate salts and the procedure for obtaining the anhydrous salt is rigorous. Furthermore, aromatic amines that do not dissolve in aqueous mineral acid are not amenable to these procedures. Consequently, alternate processes that use either sodium nitrite in concentrated acids or nitrosonium tetrafluoroborate in anhydrous solvents have been developed.\textsuperscript{7,9}

Literature reports disclosed that nitrosyl chloride and nitrosyl bromide are formed by an efficient halide-alkoxide transfer between titanium tetrahalides and alkyl nitrites.\textsuperscript{7,10} Titanium tetrafluoride is not reactive with alkyl nitrites; however, boron trifluoride is and when combined with alkyl nitrites, offers convenient access to nitrosyl fluoride. When \textit{in situ} generated nitrosyl fluoride is produced in the presence of an aromatic amine and excess boron trifluoride, aryldiazonium tetrafluoroborate salts are formed in high yield. The diazotization reactions are carried out under mild conditions in an anhydrous solvent. Excess boron trifluoride, used as the appropriately stable etherate complex, traps the alcohol and water formed in this diazotization procedure, and the aryldiazonium tetrafluoroborates precipitate from the reaction solution as they are produced. The anhydrous tetrafluoroborate salts are procured after simple filtration. (7.9) This proved to be an outstanding method for
preparation of our functionalized biphenyldiazonium tetrafluoroborate salt directly from our functionalized biphenyl amine.

Recently, palladium-catalyzed cross-coupling has evolved as a powerful synthetic tool for the construction of unsymmetrical biaryls. The reaction, which is superior to prior biaryl syntheses, generally comprises an arylmetal species (ArM) reacting with an aryl electrophile (Ar'X) in the presence of a palladium catalyst. Many versions of this reaction are known today among which the aryltins and arylboronic acids have found extensive synthetic operations. However, for all practical purposes, the aryl electrophile component (Ar'X) in these reactions has been restricted to the conventional use of halides (Br, I) and the newly emerged triflates (OTf). Aryldiazonium salts, armed with an excellent nucleofuge (N_2), should offer a superior alternative to the aforementioned. (7.2)

Scheme 5 shows my initial novel iterative synthetic approach towards polar, functionalized oligophenylenes using the palladium catalyzed cross-coupling of aryldiazonium tetrafluoroborate salts with arylboronic esters.

7.2 Results and Discussion

Scheme 5 involved, once again, commercially available 4-bromophenylboronic acid as our boron nucleophile. As mentioned previously, the aryl electrophile, 17, was ultimately synthesized in 92% yield via methyl esterification of the isatoic anhydride derived from 5-iodoanthranilic acid.\textsuperscript{7,11,7.12} The aryl iodide 17 was then cross-coupled to commercially available 4-bromophenylboronic acid using Suzuki protocol and resulted in biphenyl 18 in 89.7% yield. Subsequent, divergent syntheses produced the aryldiazonium tetrafluoroborate
salt 22 and the arylboronic ester 20. Aryldiazonium tetrafluoroborate salt 22 was ultimately obtained directly from biphenyl 18 in 94% yield as a reaction precipitant. It was notably stable at room temperature and was further purified via repeated recrystallization. Likewise, the biphenylboronate 20 was obtained in 91.5% yield. Preliminary palladium-catalyzed cross-coupling of the biphenyldiazonium tetrafluoroborate salt 22 and biphenylboronate 20 gave a low yield (10%) of desired product.

![Scheme 5. Initial iterative synthetic approach towards oligophenylene rods using arylidiazonium tetrafluoroborate salts and arylboronic esters as substrates.](image)

7.3 Conclusions

This reaction scheme spurred interest towards the investigation of optimal reaction conditions for the palladium-catalyzed cross-coupling involving
aryldiazonium tetrafluoroborate salts and arylboronic esters. As a result, a novel procedure was developed, reestablishing interest in this proposed iterative synthesis of functionalized oligophenylene rods.

7.4 Experimental

4-amino-4'-bromo-3-carboxymethylbiphenyl, 18. 5-Iodomethylanthranilate 17 (0.0722 mol) was added to a reaction vessel along with 0.080 mol commercially available 4-bromophenylboronic acid, 0.163 mol K$_2$CO$_3$ and 1.72 mmol Pd(PPh$_3$)$_4$ and dissolved in anhydrous, degassed MeOH. The reaction mixture was heated at 60 °C for 12 h under N$_2$. After filtration, extraction and removal of the solvent in vacuo, the residue was dissolved in CH$_2$Cl$_2$ and passed through a short silica gel plug to afford, after drying, 19.8 g (89.7%) 18 as a light yellow solid. mp: 138-139 °C. $^1$H NMR (250 MHz, CDCl$_3$): δ 8.09 (d, $J = 2.28$ Hz, 1H), 7.51 (dd, $J = 2.31$, 8.62 Hz, 1H), 7.51 (d, $J = 8.59$ Hz, 2H), 7.40 (d, $J = 8.63$ Hz, 2H), 6.78 (d, $J = 8.56$ Hz, 1H), 3.91 (s, 3H), 5.88 (br s, 2H). $^{13}$C NMR (62 MHz, CDCl$_3$): δ 149.9, 139.3, 132.5, 131.7, 129.3, 127.7, 120.4, 117.2, 110.8, 51.3. HRMS m/z calculated for C$_{14}$H$_{12}$BrN$_2$: 305.0051, found 305.0063.

4-amino-3-carboxymethyl-4'-biphenyolphosphinaboric ester, 20. 4-Amino-4'-bromo-3-carboxymethylbiphenyl 18 (9.86 mmol) was added to a reaction vessel and dissolved in a solution of anhydrous, degassed DMF along with 11.1 mmol commercially available bis(pinacolato)diboron, 33.0 mmol KOAc, and 0.290 mmol PdCl$_2$(dppf). The mixture was heated at 60 °C for 12 h under N$_2$, filtered through celite, extracted and dried. The solid was redissolved in CH$_2$Cl$_2$ and filtered through a short silica gel plug, dried, triturated with hexanes and redried to furnish 3.17 g
(91.5%) 20 as a white solid. mp: decomposed at 157.9-159 °C. ¹H NMR (250 MHz, CDCl₃): δ 8.09 (d, J = 2.23 Hz, 1H), 7.78 (d, J = 8.24 Hz, 2H), 7.54 (dd, J = 2.27, 8.49 Hz, 1H), 7.48 (d, J = 8.24 Hz, 2H), 6.71 (d, J = 8.55 Hz, 1H), 3.84 (s, 3H), 1.29 (s, 12H). ¹³C NMR (62 MHz, CDCl₃): δ 168.5, 149.2, 142.9, 135.3, 132.9, 129.6, 129.5, 125.4, 117.5, 111.2, 83.7, 51.7, 24.9. HRMS m/z calculated for C₂₀H₂₄BNO₄: 353.1798, found 353.1780.

4-amino-4‴-bromo-3-carboxymethyl-3‴-carboxymethyltetrapheny, 21. 4-Bromo-3′-carboxymethyl-4′-biphenyldiazenium tetrafluoroborate salt 22 (1.00 mmol), 1.10 mmol 4-amino-3-carboxymethyl-4′-biphenylpinacolboronic ester 20 and 0.100 mmol (10.0 mol %) Pd(OAc)₂ were added to a flame dried reaction vessel, dissolved in anhydrous, degassed THF and heated to reflux under N₂ until reaction completion. Upon cooling to room temperature, the solution was filtered and excess THF removed in vacuo. The residue was dissolved and then extracted using EtOAc/H₂O. The organic layer was dried with MgSO₄ and excess EtOAc removed in vacuo. Silica gel chromatography (20% EtOAc/Hex) afforded 0.0519 g (10%) 21, after drying, as a white solid. mp: decomposed at 192-195 °C. ¹H NMR (250 MHz, CDCl₃): δ 8.13 (d, J = 2.22 Hz, 1H), 7.95 (d, J = 1.96 Hz, 1H), 7.66 (dd, J = 2.06, 8.03 Hz, 1H), 7.30-7.57 (m, 10H), 6.72 (d, J = 8.54 Hz, 1H), 3.85 (s, 3H), 3.64 (s, 3H). ¹³C NMR (62 MHz, CDCl₃): δ 169.1, 168.5, 141.3, 138.9, 138.6, 132.8, 132.1, 131.9, 131.4, 129.5, 128.9, 128.8, 128.6, 128.3, 127.4, 127.2, 125.9, 122.1, 117.0, 111.4, 52.2, 51.7. HRMS m/z calculated for C₂₈H₂₂BrNO₄: 515.0732, found 515.0748.
4-bromo-3'-carboxymethyl-4'-biphenyldiazonum tetrafluoroborate salt, 22. A BF₃/THF etherate complex (7.5 mmol) was added to a flame dried reaction vessel. At -15 °C, 5 mmol 4-amino-4'-bromo-3-carboxymethylbiphenyl 18 was added and then, over 10 min, 6 mmol t-butyl nitrite. After stirring vigorously for 15 min., the solution was warmed to 5 °C over a 20 min. period. Hexane was subsequently added to the solution to induce precipitation and the precipitant was captured via filtration and washed repeatedly with cold hexane. Purification by repeated precipitation from reagent grade Me₂CO by the addition of hexane ultimately afforded 1.90 g (94%) 22 as a bright yellow-orange solid. ¹H NMR (200 MHz, D₆-acetone): δ 9.16 (d, J = 8.0 Hz, 1H), 8.85 (s, 1H), 8.70 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 6.1 Hz, 1H), 4.17 (s, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 166.5, 165.7, 164.1, 151.0, 135.7, 131.8, 131.7, 131.1, 129.7, 129.0, 125.0, 53.1. Analysis calculated for C₁₄H₁₀BBrF₄N₂O₂ (404.91): GCMS - 370 [M⁺ - (F + CH₃)].

7.5 References


7.5 Bart, Ger. Pat. 2S1,055 [C.A., 9 , 1830 (1915)].


7.12 Venuti, M. C. Georg Thieme Verlag 1982, 266.
8.1 Introduction

Biaryls (Ar-Ar') and their homologs such as teraryls, oligoaryls and polyaryls are a significant class of organic compound. The biaryl moiety is present in a number of compounds of interest including natural products, polymers, advanced materials, and molecules of biological and industrial value. Due to the extreme relevance of biaryls, many catalytic methods for constructing these molecules from two monoaryl precursors in a cross-coupling reaction have been contrived over the past two decades.\(^{8.1}\)

Biaryl synthesis is frequently based on palladium-catalyzed cross-couplings of aryl or alkyl electrophiles with aryl or alkyl boronic acids. The palladium-catalyzed cross-couplings involving vinyl-, aryl-, and alkylboronic acids with aryl and vinyl halides\(^{8.2}\) and triflates\(^{8.3}\), the cross-couplings of \(o\)-arylcarbamates\(^{8.4}\) and aryl sulfones\(^{8.5}\) with selected Grignards, and the nickel-catalyzed cross-couplings using aryl mesylates\(^{8.6}\) and arylboronic acids have previously been reported. Of recent interest is the palladium-catalyzed cross-coupling of aryldiazonium tetrafluoroborate salts with arylboronic acids\(^{8.7}\) and organotrifluoroborates\(^{8.8}\) to yield new syntheses of unsymmetrical biaryls. Suitable conditions for the successful direct, catalytic cross-coupling of aryldiazonium tetrafluoroborate salts to arylboronic esters, however, had not yet been found.\(^{8.9}\)

The diazonium electrophile, which can be synthesized from inexpensive, readily available anilines, is the most powerful nucleofuge used in differential cross-
Moreover, reaction times are generally short and high yields of desired product are usually obtained under mild conditions. Similarly, the relatively mild preparation of arylboronic esters tolerates a broad range of functional groups\textsuperscript{8,11} and affords access to one-pot conversion to cross-coupled products.\textsuperscript{8,12} The cross-coupling of aryldiazoniums with arylboronates would thus be of broad synthetic utility. Reaction times tend to be somewhat longer using arylboronic esters due to their cumbersome nature. Literature reports have suggested, however, that these reactions may be accelerated by and mediated using fluoride salts as a source of activation.\textsuperscript{8,13} The relatively weak basicity and poor nucleophilicity of the fluoride ion, the weakness of the palladium-fluoride bond, and the possibility of forming a boronate anion that is capable of effecting boron to palladium transmetalation due to the high affinity of fluoride ion for boron and the considerable stability of the product fluoroborate anion, all suggest that fluorides can be propitious to the success of a palladium-catalyzed cross-coupling reaction using arylboronic esters and aryldiazonium tetrafluoroborate salts as substrates.

As part of our program towards efficient syntheses of well-defined oligoaromatic materials\textsuperscript{8,14} for sensory applications\textsuperscript{8,15}, we decided to explore the palladium-catalyzed cross coupling of aryldiazonium tetrafluoroborate salts \textsuperscript{23} with arylboronic esters \textsuperscript{24} (Figure 9). Herein we report our preliminary findings concerning the synthesis of unsymmetrical biaryls in moderate yields in aqueous MeOH, at mild temperatures.
8.2 Results and Discussion

We initially screened the reaction of 23a (1.0 mmol) and 24a (1.5 mmol) in a variety of anhydrous solvents (2 ml) in the presence of CsF or KF (2 equiv.) at room temperature for 24 h, employing several palladium catalysts (5-10 mol %). Reaction progress and yields were determined by GCMS. As revealed in Table 1, the best results of 25a were obtained in the presence of both PdCl₂ and Pd(OAc)₂.

A meticulous examination of various reaction conditions revealed that polar, protic MeOH (entries 11-12) was the most suitable for this reaction using Pd(OAc)₂ as the catalyst. Ethereal 1,4-dioxane (entries 1-5) tended to severely retard or hinder the reaction in the presence of PdCl₂(dppf) (entry 1), PdCl₂(PPh₃)₂ (entry 2), Pd(OAc)₂ (entry 3), Pd/C (30%) (entry 4) and PdCl₂ (entry 5), ultimately resulting in the detection of an insignificant amount of 25a. On the other hand, polar aprotic solvents DMF (entry 9) and MeCN (entry 13) provided promising results, using
PdCl₂ and Pd(OAc)₂, respectively, but ultimately contributed to incomplete conversion into desired product 25a. Although fluoride activation was not essential for reaction success (entries 9 and 11), its presence afforded a cleaner and more efficient reaction (entry 12). Unexpectedly, PdCl₂ (entry 9) proved to be a very effective catalyst for the desired cross-coupling reaction at room temperature and was therefore chosen for future solvent studies due to its novelty and acceptable activity.

Table 1. Effects of catalyst on the cross-coupling of 23a and 24a.

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Solvent</th>
<th>Base (eq)</th>
<th>% 24a</th>
<th>% 25a</th>
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<tr>
<td>1</td>
<td>PdCl₂(dppf)</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂(PPh₃)₂</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Pd/C (30%)</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>PdCl₂(dppf)</td>
<td>DMF</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>PdCl₂(PPh₃)₂</td>
<td>DMF</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Pd/C (30%)</td>
<td>DMF</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>PdCl₂</td>
<td>DMF</td>
<td>-</td>
<td>44</td>
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<tr>
<td>10</td>
<td>PdCl₂(PPh₃)₂</td>
<td>MeOH</td>
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<td>Pd(OAc)₂</td>
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<td>-</td>
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<tr>
<td>12</td>
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<td>MeOH</td>
<td>CsF (2)</td>
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<tr>
<td>13</td>
<td>Pd(OAc)₂</td>
<td>MeCN</td>
<td>CsF (2)</td>
<td>70</td>
<td>11</td>
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</table>

* GCMS yields based on tetradecane internal standard.
Table 2 indicates the effects of various solvents on the cross-coupling of 23a with 24a conducted at room temperature over 24 h using 5-10 mol % PdCl$_2$ as the catalyst. The polar aprotic wonder solvent DMSO (entries 1-3) was shown to be ineffective in the absence (entry 1) and presence (entries 2-3) of fluoride base. Similar results were obtained in other polar, aprotic solvents in the presence of fluoride base including THF (entry 4), DMA (entry 5), and Me$_2$CO (entry 6). Water was also ineffective towards the cross-coupling of 23a with 24a (entry 7). However, polar aprotic, dimethylformamide, which was initially also shown to be ineffective towards the desired cross-coupling employing KOAc as base (entry 8), ultimately, resulted in some conversion into 25a, utilizing KF as base (entry 9), with optimal results being obtained in the absence of base (Table 1, entry 9). Similar results were obtained using polar aprotic MeCN in the presence of fluoride base (entry 10) with the best results being gathered employing polar protic MeOH as solvent in the presence (entry 11) and absence (entry 12) of fluoride base. Hydrous organic solvents (entries 13-18), resulted in complete conversion of 23a and 24a into 25a with the exception of MeCN (entry 16) and MeOH (entry 13). More importantly, the aqueous solutions formed with ethereal THF (entry 17) and polar aprotic Me$_2$CO (entry 18) in the presence of fluoride base now exhibited overwhelming activity towards the cross-coupling reaction of 23a and 24a. Previously, these solvents alone in the presence of fluoride base were shown to be ineffective (entries 4 and 6, respectively), suggesting that water could play a valuable role in accelerating the desired cross-coupling. Similar revelations were identified in entry 13, which also
suggested that the reaction was possibly retarded in aqueous solutions not mediated by fluoride base.\textsuperscript{8,17}

Table 2. Effects of solvent on the cross-coupling of 23a and 24a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base (eq)</th>
<th>% 24a</th>
<th>% 25a\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>KF (2)</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>CsF (2)</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>CsF (2)</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DMA</td>
<td>CsF (2)</td>
<td>100</td>
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</tr>
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<td>6</td>
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</tr>
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<td>CsF (2)</td>
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<tr>
<td>11</td>
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<td>CsF (2)</td>
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<tr>
<td>17</td>
<td>50% THF</td>
<td>CsF (2)</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>18</td>
<td>50% Me\textsubscript{2}CO</td>
<td>CsF (2)</td>
<td>-</td>
<td>57</td>
</tr>
</tbody>
</table>

\textsuperscript{a} GCMS yields based on tetradecane internal standard.
Based on these findings, the cross couplings of several aryldiazonium tetrafluoroborate salts with arylboronates were investigated using 75% MeOH as the solvent, CsF as the base and the more aqueous soluble and readily available sodium salt of PdCl$_2$, Na$_2$PdCl$_4$, as the catalyst (Table 3).

**Table 3.** Cross-coupling of aryldiazonium tetrafluoroborate salts 23 with arylboronic esters 24.

<table>
<thead>
<tr>
<th>Entry</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>% Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23a</td>
<td>24a</td>
<td>25a</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>23b</td>
<td>24a</td>
<td>25b</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>23c</td>
<td>24b</td>
<td>25c</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>23d</td>
<td>24a</td>
<td>25d</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>23e</td>
<td>24a</td>
<td>25e</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>23f</td>
<td>24a</td>
<td>25f</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>23g</td>
<td>24a</td>
<td>25g</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>23h</td>
<td>24b</td>
<td>25h</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>$N_2$BF$_4$</td>
<td>24a</td>
<td>25i</td>
<td>64</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield.
As shown in Table 3, the cross-coupling reactions, after 20-24 h at 40 °C under inert atmosphere, afforded unsymmetrical biaryls 25 in moderate yields. 

Aryldiazonium tetrafluoroborate salts 23 containing electron donating and electron withdrawing moieties furnished cross-coupled products. Acceptable yields of unsymmetrical biaryl were obtained even when 23 was adorned with a substituent in the ortho position (entry 7). 1-Naphthalenediazonium tetrafluoroborate salt seemed comparably reactive affording 1-phenynaphthalene in 64% yield upon cross-coupling with 24a (entry 9). Interestingly, a non-differentiated arylbisdiazonium tetrafluoroborate salt gave very low yield of substituted triphenyl product (entry 8). The reaction of 4-iodophenyldiazonium tetrafluoroborate salt 23c with 24b (entry 3) furnished 4-iodo-2'-methylbiphenyl 25c as the only cross-coupled product, highlighting the outstanding regioselectivity afforded by the diazonium moiety and suggesting that the reaction may be applicable towards the preparation of unsymmetrically disubstituted phenylenes by employing a sequential cross-coupling approach.

8.3 Conclusions

In conclusion, the current study demonstrates that readily available aryldiazonium tetrafluoroborate salts react with functional group tolerant arylboronic esters in aqueous solvents at mild temperatures to form isolable cross-coupled products. The reaction is operationally facile and employs anilines, which are usually more accessible and economical than many other typical electrophiles. Coupled with use of cheap and diverse palladium catalysts, differential cross-coupling applications and simplicity of the isolation and purification processes, these characteristics

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encourage broad implementation of this direct approach towards unsymmetrical biaryl synthesis. Our proposed catalytic cycle for the palladium-catalyzed cross-coupling of aryl diazonium tetrafluoroborate salts with arylboronic esters (Figure 10) involves: a) ligand dissociation, b) oxidative addition and formation of the zero-valent cationic palladium species, c) ligand addition of R-OH, d) transmetalation, e) reductive elimination of borate and f) reductive elimination of biaryl.\textsuperscript{8,19,8,20} Ongoing optimization studies are aimed at further elucidating the mechanism, scope and limitations of the reaction.

\begin{equation}
R\equiv\text{N}_2\text{BF}_4^- + \text{Ar-}B\equiv\text{O} \xrightarrow{\text{Na}_2\text{PdCl}_4} \text{Pd(II)} \xrightarrow{75\% \text{ MeOH}} \xrightarrow{40^\circ\text{C}} \text{Pd(0)}
\end{equation}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{Proposed catalytic cycle for the palladium-catalyzed cross-coupling of aryl diazonium tetrafluoroborate salts with arylboronic esters.}
\end{figure}

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8.4 Experimental

All reagents were purchased from Lancaster or Aldrich and used without further purification. Solvents were dried over potassium metal. All coupling reactions were carried out under inert atmosphere. Melting points were determined using a Fisher-Johns Melting Point Apparatus. Mass spectra were obtained using a Hewlett-Packard 5890 Series GCMS. $^1$H NMR spectra were obtained using either a Bruker AC 250 or 300 MHz instrument. Physical, spectral ($^1$H NMR) and GCMS data for aryldiazonium tetrafluoroborate salts 23, arylboronic esters 24, and unsymmetrical biaryls 25a-g, terphenyl 25h and naphthyl derivative 25i are disclosed.

General Procedure for the Preparation of Aryldiazonium Tetrafluoroborate Salts 23. To a flame dried vessel was added a BF$_3$/THF solution (1.5 mmol). At -15 °C was added Ar-NH$_2$ (1.0 mmol) and over ten minutes, tert-butyl nitrite (1.2 mmol). After stirring vigorously for 15 min., the solution was allowed to warm to 5 °C over 20 min. Hexane was added to the solution to induce precipitation and the precipitant was captured using suction filtration and washed repeatedly with cold hexane. Air drying afforded the respective aryldiazonium tetrafluoroborate salts. Repeated precipitation from reagent grade acetone by the addition of hexane was performed when additional purification was necessary.

4-bromophenyldiazonium tetrafluoroborate salt, 23a. Tan solid (95% from 4-Bromoaniline). $^1$H NMR (300 MHz, CD$_3$COCD$_3$): $\delta$ 8.77 (d, $J = 9.0$ Hz, 2H), 8.31 (d, $J = 9.0$ Hz, 2H)
4-methylphenyldiazonium tetrafluoroborate salt, 23b. White solid (96% from p-Toluidine). \(^1\)H NMR (300 MHz, CD\(_3\)COCD\(_3\)): \(\delta 8.75 (d, J = 9.0 \text{ Hz}, 2H), 7.92 (d, J = 9.0 \text{ Hz}, 2H), 2.69 (s, 3H)\)

4-iodophenyldiazonium tetrafluoroborate salt, 23c. Tan solid (93% from 4-Iodoaniline). \(^1\)H NMR (250 MHz, CD\(_3\)COCD\(_3\)): \(\delta 8.57 (d, J = 9.0 \text{ Hz}, 4H)\)

4-carboxymethylphenyldiazonium tetrafluoroborate salt, 23d. Almond solid (96% from Methyl-4-aminobenzoate). \(^1\)H NMR (250 MHz, CD\(_3\)COCD\(_3\)): \(\delta 9.00 (d, J = 9.0 \text{ Hz}, 2H), 8.58 (d, J = 9.0 \text{ Hz}, 2H), 4.01 (s, 3H)\)

4-methoxyphenyldiazonium tetrafluoroborate salt, 23e. Lavender solid (99% from p-Anisidine). \(^1\)H NMR (250 MHz, CD\(_3\)COCD\(_3\)): \(\delta 8.78 (d, J = 9.0 \text{ Hz}, 2H), 7.56 (d, J = 9.0 \text{ Hz}, 2H), 4.17 (s, 3H)\)

4-nitrophenyldiazonium tetrafluoroborate salt, 23f. Brown-orange solid (99% from 4-Nitroaniline). \(^1\)H NMR (300 MHz, CD\(_3\)COCD\(_3\)): \(\delta 9.21 (d, J = 9.0 \text{ Hz}, 2H), 8.88 (d, J = 9.0 \text{ Hz}, 2H)\)

4-bromo-2-methylphenyldiazonium tetrafluoroborate salt, 23g. Almond solid (96% from 4-Bromo-2-methylaniline). \(^1\)H NMR (250 MHz, CD\(_3\)COCD\(_3\)): \(\delta 8.71 (d, J = 9.0 \text{ Hz}, 1H), 8.23 (s, 1H), 8.13 (d, J = 9.0 \text{ Hz}, 1H), 2.95 (s, 3H)\)

1,4-phenylenebisdiazonium tetrafluoroborate salt, 23h. Tan solid (71% from 1,4-Phenylenediamine). \(^1\)H NMR (250 MHz, D\(_2\)O/CD\(_3\)COCD\(_3\)): \(\delta 9.32 (s, 4H)\)

1-naphthylidiazonium tetrafluoroborate salt, 23i. Lavender solid (94% from 1-Aminonaphthalene). \(^1\)H NMR (250 MHz, CD\(_3\)COCD\(_3\)): \(\delta 9.37 (d, J = 8.1 \text{ Hz}, 1H), 9.05 (d, J = 8.1 \text{ Hz}, 1H), 8.63 (d, J = 8.1 \text{ Hz}, 1H), 8.51 (d, J = 8.1 \text{ Hz}, 1H), 8.21 (dd, J = 8.1 \text{ Hz and 1.2 Hz}, 2H), 8.03 (dd, J = 8.0 \text{ Hz and 1.0 Hz}, 1H)\)
General Procedure for the Preparation of Arylboronic Esters 24. To a flame dried vessel was added PdCl₂(dppf) (0.03 mmol), anhydrous dioxane (5 ml), aryl halide (1.0 mmol), N(Et)₃ (3.0 mmol) and pinacol borane (1.5 mmol) under nitrogen, and the mixture was stirred at 80 °C until completion was determined by NMR. The reaction mixture was cooled to room temperature and solvent removed in vacuo. The residue was dissolved in EtOAc, decolorized, filtered through a celite cake and washed with water. After drying over MgSO₄, the solvent was removed in vacuo and product isolated by silica gel chromatography (0-10% EtOAc in hexanes), affording arylboronic esters 24a and 24b.

Phenylpinacolboronic ester, 24a. Yellow oil (97% from Iodobenzene). ¹H NMR (250 MHz, CDCl₃): δ 7.90 (d, J = 8.0 Hz, 2H), 7.37-7.53 (m, 3H), 1.41 (s, 12H)

2-methylphenylpinacolboronic ester, 24b. Orange oil (94% from 2-Iodotoluene). ¹H NMR (300 MHz, CDCl₃): δ 7.79 (d, J = 7.0 Hz, 1H), 7.36 (dd, J = 8.0 Hz and J = 8.0 Hz, 1H), 7.15-7.19 (m, 2H), 2.56 (s, 3H), 1.35 (s, 12H)

General Procedure for Cross-Coupling of Aryldiazonium Tetrafluoroborate Salts 23 and Arylboronic Esters 24. Aryldiazonium tetrafluoroborate salt (1.0 mmol), arylboronic ester (1.5 mmol), Na₂PdCl₄ (0.10 mmol) and CsF (1.5 mmol) were added to a reaction vessel and purged thoroughly with nitrogen in the dark. Degassed 75% MeOH/H₂O (2 ml) was added via syringe and the reaction was allowed to proceed at 40 °C in a sand bath until completion was determined by NMR. The solution was then cooled to room temperature, concentrated in vacuo, and residue extracted with EtOAc (3x10 ml). The organic layer was dried with MgSO₄, passed through celite and removed in vacuo. Silica gel chromatography (pentane or 0-10%
EtOAc in hexanes) afforded the respective biaryls, 25a-g, terphenyl 25h and naphthyl derivative 25i.

4-bromobiphenyl, 25a. White solid (56% yield). mp: 89-90 °C. TLC: Rf = 0.68 (pentane). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.54-7.59 (m, 4H), 7.37-7.48 (m, 5H). GCMS (m/z): 234 and 232 (M$^+$, 100%), 152, 126, 102, 76, 63

4-methylbiphenyl, 25b. White solid (62% yield). mp: 45-46 °C. TLC: Rf = 0.63 (pentane). $^1$H NMR (250 MHz, CD$_2$COCD$_3$): $\delta$ 7.71 (d, $J = 8.0$ Hz, 2H), 7.61 (d, $J = 9.0$ Hz, 2H), 7.51 (t, $J = 8.0$ Hz and $J = 8.0$ Hz, 2H), 7.45 (t, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 2.49 (s, 3H). GCMS (m/z): 168 (M$^+$, 100%), 152, 115, 82, 63

4-iodo-2'-methylbiphenyl, 25c. White solid (66% yield). mp: 103-104 °C. TLC: Rf = 0.58 (pentane). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.82 (d, $J = 8.0$ Hz, 2H), 7.28-7.35 (m, 4H), 7.14 (d, $J = 8.0$ Hz, 2H), 2.32 (s, 3H). $^{13}$C NMR (62 MHz, CDCl$_3$): $\delta$ 138.0 (2C), 137.2 (2C), 131.1 (2C), 130.4, 128.7 (2C), 127.6, 125.9, 93.5, 20.3. GCMS (m/z): 294 (M$^+$), 280, 165 (100%), 152, 127, 115, 83, 63

4-carboxymethylbiphenyl, 25d. White solid (61% yield). mp: 108-109 °C. TLC: Rf = 0.09 (hexane). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 8.13 (d, $J = 9.0$ Hz, 2H), 7.61-7.69 (m, 4H), 7.37-7.50 (m, 3H), 3.94 (s, 3H). GCMS (m/z): 212 (M$^+$), 181 (100%), 152, 126, 91, 76, 63

4-methoxybiphenyl, 25e. White solid (54% yield). mp: 87 °C. TLC: Rf = 0.23 (hexane). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 7.58 (d, $J = 6.0$ Hz, 2H), 7.54 (d, $J = 7.0$ Hz, 2H), 7.41 (t, $J = 5.5$ Hz, 2H), 7.30 (t, $J = 8.0$ Hz, 1H), 7.00 (d, $J = 9.0$ Hz, 2H), 3.85 (s, 3H). GCMS (m/z): 184 (M$^+$, 100%), 169, 152, 141, 115, 92, 76, 63

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4-nitrobiphenyl, 25f. Light yellow solid (64% yield). mp: 114-115 °C. TLC: Rf = 0.29 (hexane). 1H NMR (250 MHz, CDCl3): δ 8.33 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.61-7.65 (m, 2H), 7.44-7.54 (m, 3H). GCMS (m/z): 199 (M+, 100%), 169, 152, 141, 126, 115, 76, 63

4-bromo-2-methylbiphenyl, 25g. Light yellow oil (48% yield). bp: (0.7) 113-114 °C. TLC: Rf = 0.60 (pentane). 1H NMR (250 MHz, CDCl3): δ 7.42 (m, 2H), 7.39 (d, J = 7.0 Hz, 2H), 7.34 (s, 1H), 7.30 (m, 2H), 7.11 (d, J = 8.0 Hz, 1H), 2.25 (s, 3H). GCMS (m/z): 246 (M+), 165 (100%), 152, 139, 115, 102, 82, 63

2,3′′-dimethylerterphenyl, 25h. Almond solid (16% yield). mp: 145-146 °C. TLC: Rf = 0.42 (pentane). 1H NMR (250 MHz, CDCl3): δ 7.40 (s, 4H), 7.32 (m, 8H), 2.38 (s, 3H). GCMS (m/z): 258 (M+, 100%), 243, 228, 215, 165, 152, 141, 128, 115, 91, 77, 65

1-phenylnaphthalene, 25i. Colorless oil (64% yield). TLC: Rf = 0.58 (pentane). 1H NMR (250 MHz, CDCl3): δ 7.87-7.96 (m, 3H), 7.45-7.56 (m, 9H). GCMS (m/z): 204 (M+, 100%), 163, 150, 101, 69, 55

8.5 References


8.17 A mixture of desired product 28 and homocoupled by-products characteristically precipitates from these reactions under the described aqueous conditions.

8.18 Alkyl- and benzylidiazonium tetrafluoroborate salts were unreactive under these conditions.


9.1 Introduction

Boronic acids and esters are used in a wide variety of research applications.\(^{9.1}\) They also continue to attract attention as versatile functional group tolerant cross-coupling substrates in organic synthesis.\(^{9.2}\) Synthetic methodology allowing for the direct attachment of boron to aromatics to afford arylboronates is thus an important challenge.\(^{9.3}\) Arylboronic esters are generally purified more easily than arylboronic acids, can be synthesized without organolithium or Grignard reagents and promote one-pot cross-couplings.\(^{9.4}\) Since aryl borylation reactions, which directly afford arylboronic esters, have been successfully performed on aryl halides and triflates, it seems quite reasonable that aryl diazonium tetrafluoroborate salts may also be useful for this purpose. (9.3)

Aryldiazonium tetrafluoroborate salts are highly attractive synthetic alternatives to the corresponding halides and triflates. They can be prepared from relatively inexpensive, readily available anilines\(^{9.5}\) and are more reactive than halides or triflates in cross-coupling reactions.\(^{9.6}\) Recently, we demonstrated the first palladium-catalyzed cross-coupling of aryl diazonium tetrafluoroborate salts with arylboronic esters.\(^{9.7}\) As part of our program also entails the efficient synthesis of well-defined oligoaromatic materials\(^{9.8}\) for boronic acid-based sensory applications\(^{9.9}\), we herein report the first synthesis of arylboronic esters using aryl diazonium tetrafluoroborate salts as substrates (Figure 11).
9.2 Results and Discussion

We initially screened the reaction of 26a (0.50 mmol) and 27a (0.55 mmol) or 27b (0.75 mmol) in select organic solvents (2 ml) in the presence or absence of bases analagous to literature precedent (Table 4).93 Unfortunately, no reaction occurred using dialkoxyhydroborane as the borylation reagent (entries 6-8).93b,93d. However, promising results were obtained using KOAc and DMF - protocol that had been used previously in borylation reactions of aryl halides (entry 1).93a Adverse results were obtained using this protocol in the absence of KOAc (entry 2). Our best results were observed using MeOH rather than DMF as solvent (entry 3). In addition, we observed a comparable yield in the absence of base (entry 4). Commonly used dioxane93b-d was not suitable for converting 26a to 28a regardless of the borylation reagent employed (entries 5-6). We thus decided to further study the palladium-catalyzed coupling of 26a and 27a in MeOH without base.
Table 4. Effect of solvent and base on the borylation of 26a.\textsuperscript{a}

\[ \text{26a} + \text{R—B} \xrightarrow{\text{PdCl}_2(\text{dpff})} \text{solvent} \to \text{28a} \]

\( \text{a} \ R = \text{B(O}_2\text{C}_2\text{Me}_4) \)
\( \text{b} \ R = \text{H} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base (eq)</th>
<th>27</th>
<th>% 28a</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>KOAc (3)</td>
<td>27a</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>-</td>
<td>27a</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>KOAc (3)</td>
<td>27a</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>-</td>
<td>27a</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td></td>
<td>27a</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Dioxane</td>
<td>N(Et)_3 (3)</td>
<td>27b</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>-</td>
<td>27b</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>N(Et)_3 (3)</td>
<td>27b</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions were performed over 24 h at 60 °C using 3 mol % catalyst (dpff = 1,1'-bis(diphenylphosphino)ferrocene) and anhydrous solvents. Isolated yields are reported.

Optimization studies began with the investigation of the effect of stoichiometry and temperature on the course of the reaction (Table 5). The use of 1 equiv of 26a to 27 resulted in a 56% conversion to 28a at 60 °C (entry 1). Adding additional aliquots of 26a (0.5 eq) in 1h intervals resulted in 65% and 75% conversion into 28a respectively; however, adding 2 equiv of 26a at once did not improve the conversion and afforded partial decomposition of 26a (entry 2). Couplings conducted at rt with varying amounts of 26a (entries 3-6) afforded conversions comparable to the runs at 60 °C. We thus decided to allow the borylation...
to proceed at rt for 1h and then add aliquots of 26 at slightly elevated temperature to push the reaction to completion.\textsuperscript{9,10}

Table 5. Effect of temperature and stoichiometry on the borylation of 26a.\textsuperscript{a}

\[
\begin{array}{cccccc}
\text{Entry} & \text{Eq. 26a Used} & \text{Temp. (°C)} & \text{Time (h)} & \% 28a\textsuperscript{b} \\
1 & 1.0 & 60 & 1.75 & 56 \\
2 & 2.0 & 60 & 1.00 & 75 \\
3 & 1.0 & rt & 1.25 & 56 \\
4 & 2.0 & rt & 1.25 & 60 \\
5 & 3.0 & rt & 1.25 & 56 \\
6 & 4.0 & rt & 1.25 & 54 \\
\end{array}
\]

\textsuperscript{a} Reactions performed in 2 ml of anhydrous MeOH under N\textsubscript{2} using 0.125 mmol 27.

\textsuperscript{b} Conversion yields based on NMR integration.

As shown in Table 6, the borylation reactions, performed in the absence of added base, afforded arylboronic esters 28 in moderate to high yields.\textsuperscript{9,11} Sterically encumbered aryldiazonium tetrafluoroborate salt 26h (entry 8) furnished multi-substituted arylboronic ester 28h in moderate yield. Direct borylation of \(\alpha\)-naphthyl diazonium tetrafluoroborate salt (entry 9) afforded naphthylboronate 28i in high yield. Aryldiazonium tetrafluoroborate salt 26f (entry 6) provided only a moderate yield of functionalized arylboronic ester 28f. Successful regioselective borylation at the diazonuim site was accomplished in the presence of both C-I (entry}
4) and C-Br (entries 2 and 8) bonds, affording two novel functionalized arylboronates 28d and 28h respectively.

**Table 6. Synthesis of arylboronic esters 28.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-N$_2$BF$_4$</th>
<th>Eq 26 Used</th>
<th>Time (h)</th>
<th>Product 28</th>
<th>% Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_5$N$_2$BF$_4$</td>
<td>3.0</td>
<td>3.0</td>
<td>28a</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>4-BrC$_6$H$_5$N$_2$BF$_4$</td>
<td>3.0</td>
<td>5.0</td>
<td>28b</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>4-MeC$_6$H$_5$N$_2$BF$_4$</td>
<td>3.0</td>
<td>5.0</td>
<td>28c</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>4-IC$_6$H$_5$N$_2$BF$_4$</td>
<td>3.0</td>
<td>5.0</td>
<td>28d</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>4-CO$_2$MeC$_6$H$_5$N$_2$BF$_4$</td>
<td>4.5</td>
<td>8.0</td>
<td>28e</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>4-OMeC$_6$H$_5$N$_2$BF$_4$</td>
<td>4.5</td>
<td>8.0</td>
<td>28f</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>4-NO$_2$C$_6$H$_5$N$_2$BF$_4$</td>
<td>3.5</td>
<td>6.0</td>
<td>28g</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>4-Br, 2-MeC$_6$H$_5$N$_2$BF$_4$</td>
<td>3.0</td>
<td>5.0</td>
<td>28h</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>$\alpha$-C$_{10}$H$_7$N$_2$BF$_4$</td>
<td>3.0</td>
<td>5.0</td>
<td>28i</td>
<td>73</td>
</tr>
</tbody>
</table>

$^a$Isolated yield.

**9.3 Conclusions**

In conclusion, we have introduced a novel procedure, using aryldiazonium tetrafluoroborate salts and bis(pinacolato)diboron, for directly transforming carbon-nitrogen bonds into carbon-boron bonds. The current work demonstrates that aryldiazonium tetrafluoroborate salts, which are easily synthesized from economical and readily available anilines, may serve as suitable substrates for the facile synthesis of arylboronic esters using bis(pinacolato)diboron. The new methodology features relatively mild conditions, an environmentally benign alcohol solvent and no added base. This, coupled with the outstanding chemoselectivity and differential borylation capabilities afforded by employing aryldiazonium tetrafluoroborate salts as
substrates, may effect widespread implementation of this procedure. Our proposed catalytic cycle for the synthesis of arylboronic esters via the palladium-catalyzed borylation of aryl diazonium tetrafluoroborate salts (Figure 12) involves: a) ligand dissociation, b) oxidative addition and formation of the zero-valent cationic palladium species, c) ligand addition of R-OH, d) transmetallation, e) reductive elimination of borate and f) reductive elimination of arylboronic ester.9,12,9,13 Ongoing studies are aimed at further broadening the scope and elucidating the mechanism of the reaction.

![Proposed catalytic cycle for the synthesis of arylboronic esters via the palladium-catalyzed borylation of aryl diazonium tetrafluoroborate salts.](image)

**Figure 12.** Proposed catalytic cycle for the synthesis of arylboronic esters via the palladium-catalyzed borylation of aryl diazonium tetrafluoroborate salts.
9.4 Experimental

Bis(pinacolato)diboron was purchased from Frontier Scientific and used without further purification. All other reagents were purchased from Lancaster or Aldrich and used without further purification. All borylation reactions were carried out under inert atmosphere. Melting points were determined using a Fisher-Johns Melting Point Apparatus. Mass spectra were obtained using a Hewlett-Packard 5890 Series GCMS. $^1$H and $^{13}$C NMR spectra were obtained using a Bruker AC 250 MHz instrument. Physical, spectral and GCMS data for arylboronic esters 28a-h and naphthylboronic ester 28i are available.

General Procedure for the Borylation of Aryldiazonium Tetrafluoroborate Salts (26). Bis(pinacolato) diboron 27 (1.0 mmol), aryldiazonium tetrafluoroborate salt 26 (1.0 mmol) and PdCl$_2$(dppf) (0.03 mmol) were added to a reaction vessel which was purged thoroughly with N$_2$. Deoxygenated anhydrous MeOH (2-10 ml) was added via syringe and the reaction was allowed to proceed at rt for 1h. Additional 0.5 eq. and 0.0075 eq. aliquots 26 and PdCl$_2$(dppf), respectively, were then added in 1.00 h intervals and the solution was heated to 40 °C in a sand bath until reaction completion was determined by NMR. The solution was then cooled to room temperature and concentrated. The residue was dissolved in 0-20% EtOAc/Hex, decolorized, passed through celite and concentrated. Kugelrohr distillation or silica gel chromatography (0-20% EtOAc/hexanes) afforded the respective arylboronic esters 28.

Phenylpinacolboronic ester, 28a.$^{9,14}$ Pale yellow oil (96% from Phenyldiazonium tetrafluoroborate salt). $^1$H NMR (250 MHz, CDCl$_3$): δ 7.80 (d, $J = 8.0$ Hz, 2H), 7.34-
7.49 (m, 3H), 1.35 (s, 12H). GCMS (m/z): 204 (M⁺), 189 (100%), 161, 147, 131, 118, 105

4-bromophenylpinacolboronic ester, 28b. Pale yellow oil (80% from p-Bromophenyl diazonium tetrafluoroborate salt). ¹H NMR (250 MHz, CDCl₃): δ 7.67 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 1.37 (s, 12H). GCMS (m/z): 282 (M⁺), 267, 196, 183 (100%), 161, 117, 103

4-methylphenylpinacolboronic ester, 28c. Pale yellow oil (87% from p-Tolyldiazonium tetrafluoroborate salt). ¹H NMR (250 MHz, CDCl₃): δ 7.70 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.0 Hz, 2H), 2.38 (s, 3H), 1.35 (s, 12H). GCMS (m/z): 218 (M⁺, 100%), 203, 161, 146, 132, 119

4-iodophenylpinacolboronic ester, 28d. Pale almond solid (58% from p-Iodophenyl diazonium tetrafluoroborate salt). mp: 86-89 °C. ¹H NMR (250 MHz, CDCl₃): δ 7.70 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 1.33 (s, 12H). ¹³C NMR (62 MHz, CDCl₃): δ 136.9, 136.3, 98.8, 84.0, 24.8. GCMS (m/z): 330 (M⁺), 315, 244 (100%), 230 (100%), 161, 117, 104

4-carboxymethylphenylpinacolboronic ester, 28e. Almond solid (81% from p-Methylbenzoated diazonium tetrafluoroborate salt). ¹H NMR (250 MHz, CDCl₃): δ 8.00 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 3.92 (s, 3H), 1.35 (s, 12H). GCMS (m/z): 262 (M⁺), 247 (100%), 231, 219, 205, 176, 163, 145, 131, 117, 103

4-methoxyphenylpinacolboronic ester, 28f. Pale yellow oil (51% from p-Anisolediazonium tetrafluoroborate salt). ¹H NMR (250 MHz, CDCl₃): δ 7.75 (d, J = 7.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 3.83 (s, 3H), 1.31 (s, 12H). GCMS (m/z): 234 (M⁺, 100%), 219, 203, 176, 161, 148, 135
4-nitrophénylpinacolboronic ester, 28g. (9.14) Pale yellow solid (61% from p-Nitrophenyl diazonium tetrafluoroborate salt). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 8.11 (d, \(J = 8.0\) Hz, 2H), 7.89 (d, \(J = 9.0\) Hz, 2H), 1.31 (s, 12H). GCMS (m/z): 249 (M\(^+\)), 234 (100%), 206, 192, 163, 150, 104

4-bromo-2-methylphenylpinacolboronic ester, 28h. bp: >200 °C. Pale yellow oil (42% from 4-Bromo-2-methylphenyl diazonium tetrafluoroborate salt). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 7.59 (d, \(J = 8.0\) Hz, 1H), 7.31-7.33 (m, 2H), 2.50 (s, 3H), 1.32 (s, 12H). 13C NMR (62 MHz, CDCl\(_3\)): \(\delta\) 147.0, 137.3, 132.6, 127.8, 125.5, 83.6, 24.8, 21.9. GCMS (m/z): 255 (M\(^+\), 100%), 239, 210, 196, 182, 168, 155

1-naphthylpinacolboronic ester, 28i.\(^{9.16}\) Pale yellow oil (73% from \(\alpha\)-Naphthyl diazonium tetrafluoroborate salt). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta\) 8.81 (d, \(J = 9.0\) Hz, 1H), 8.13 (d, \(J = 8.0\) Hz, 1H), 7.94 (d, \(J = 9.0\) Hz, 1H), 7.84 (d, \(J = 7.0\) Hz, 1H), 7.46-7.61 (m, 3H), 1.45 (s, 12H). GCMS (m/z): 255 (M\(^+\), 100%), 239, 210, 196, 182, 168, 155

9.5 References


9.10 Inert atmosphere was essential for reaction success.

9.11 The borylation of 1,4-phenylenebisdiazonium tetrafluoroborate salt was unsuccessful to date, affording phenylboronic pinacol ester and a trace amount of bisborylated product.


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I. Differential palladium-catalyzed cross-coupling of activated aryl triflates in the presence of aryl bromides.

- A possible application for these materials may stem from a recent report that describes the utility of oligophenylene rods with appended hydroxyls as ion transport relays in lipid bilayers. (ref. 2.28)
- Scheme 3 showed a unique approach towards the synthesis of these oligophenylene rods. (Section 5.2)
II. Iterative synthesis of higher order oligophenylenes using the palladium-catalyzed cross-coupling of aryldiazonium tetrafluoroborate salts with arylboronic esters.

- Scheme 5 represented my initial attempt towards the synthesis of these materials using this strategy. (Section 7.2)
- may be streamlined using one-pot syntheses
III. Physical properties and materials studies of higher order oligophenylenes before and after attachment to the macrocyclic scaffold.

- How would varying $n$ affect molecular functions (e.g. chemosensing and host-guest interactions)?
- Would electronic or optical properties be enhanced by cooperativity or varying $n$ and substituents?

IV. Proof of proposed catalytic cycles for:
- Palladium-catalyzed cross-coupling of aryldiazonium tetrafluoroborate salts with arylboronic esters. (Appendix 2)
- Synthesis of arylboronic esters via the palladium-catalyzed borylation of aryldiazonium tetrafluoroborate salts. (Appendix 3)

V. The use of heterocycles in the palladium catalyzed cross-coupling of aryldiazonium tetrafluoroborate salts with arylboronic esters:
- Example (using possible nucleophiles)
VI. One-pot synthesis of unsymmetrical and symmetrical biaryls.

- **Unsymmetrical**

\[
\begin{align*}
\text{R-N}_{2}\text{BF}_4 & \quad \overset{\text{PdCl}_2(\text{dppf})}{\text{MeOH}} \quad \text{X-N}_{2}\text{BF}_4 \\
\text{R} & \quad \text{O} & \quad \text{B} & \quad \text{O} & \quad \text{R} & \quad \text{X} \\
\end{align*}
\]

- **Symmetrical**

\[
\begin{align*}
\text{R-N}_{2}\text{BF}_4 & \quad \overset{\text{PdCl}_2(\text{dppf})}{\text{MeOH}} \quad \text{R-N}_{2}\text{BF}_4 \\
\text{R} & \quad \text{O} & \quad \text{B} & \quad \text{O} & \quad \text{R} & \quad \text{R} \\
\end{align*}
\]

VII. Mild synthesis of arylboronic acids from anilines:

\[
\begin{align*}
\text{R-N}_{2}\text{BF}_4 & \quad \overset{\text{PdCl}_2(\text{dppf})}{\text{MeOH}} \quad \text{hyd.} \\
\text{R} & \quad \text{O} & \quad \text{B} & \quad \text{O} & \quad \text{OH} & \quad \text{OH} \\
\end{align*}
\]

- no anion chemistry
- versatile via widespread functional-group toleration
- employs readily available anilines and diboron reagents [bis(neopentyl glycolato)- or bis(hexylene glycolato)diboron]
- simple isolation and purification
VITA

Douglas M. Willis was born May 26, 1973, in Houston, Texas. He attended Jack Yates Senior High School in Houston, Texas, and graduated as the Valedictorian of his class in 1991. He then matriculated at Texas Southern University in Houston, Texas, where he graduated in 1995 *Summa Cum Laude* with a bachelor of science degree in chemistry. He began his studies for the doctoral degree in 1995 at Louisiana State A&M University in Baton Rouge, under the direction of Professor Robert M. Strongin and will obtain the degree of Doctor of Philosophy in December 2000.

During his graduate studies, Doug gained extensive experience in the application of Suzuki coupling protocol and designed novel iterative synthetic strategies towards obtaining uniform, three-dimensional electronic organic materials with highly functional $\pi$-cavities. In addition, Doug synthesized higher order oligophenylene rigid rods, designed and implemented a procedure for the direct, palladium-catalyzed cross-coupling of aryldiazonium tetrafluoroborate salts with arylboronic esters, developed a facile synthesis of arylboronic esters via the palladium-catalyzed borylation of aryldiazonium tetrafluoroborate salts and composed and delivered several oral and poster presentations at local and national meetings.

Doug has received numerous awards, honors and fellowships, including the Procter & Gamble Award, LSU Dissertation Fellowship, and Huel D. Perkins Fellowship. Furthermore, Doug holds membership in various organizations including Phi Lambda Upsilon (PLU), the American Association for the Advancement of
Science (AAAS), the American Chemical Society (ACS), the National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (NOBCChE) and Kappa Alpha Psi Fraternity, Inc. (KAΨ).

DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Douglas M. Willis

Major Field: Chemistry

Title of Dissertation: Efficient Iterative Syntheses of Oligophenylene Rods and Methodology Studies Involving Aryldiazonium Tetrafluoroborate Salts and Arylboronic Esters

Approved:

[Signature]
Major Professor and Chairman

[Signature]
Dean of the Graduate School

EXAMINING COMMITTEE:

[Signatures]

Date of Examination:

October 10, 2000