Progress Towards [2+2] and [3+3] Covalent Organic Polygons

by

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Abstract

Covalent organic polygons (COPs) are supramolecular structures that are held together by dynamic and robust covalent bonds. Due to the dynamic reversibility of their assembly, COP syntheses can be optimized through changing reaction conditions to favor the formation of a single, specific product. Additionally, covalent organic polygons are assembled through reticular synthesis, meaning the size and geometry of the building blocks can be used to create structures with predetermined polyhedral shapes. Because COP architectures are assembled through covalent bonds rather than noncovalent interactions, they have high thermal and chemical stability. This high stability allows COPs to have important applications in catalysis. In addition to catalysis, covalent organic polygons have applications in gas storage, drug delivery, membranes, and as liquid crystalline materials. Of the many dynamic covalent reactions that can form polygons, the boronate ester forming reaction is specifically intriguing because of boron’s empty p orbital which can extend conjugation between neighboring aromatic systems. The research outlined in this thesis investigates the synthesis of two bis-boronic acids and two organic tetra-ols, with the aim of synthesizing four covalent organic polygons. Once assembled, the four supramolecular structures are anticipated to have remarkable applications across many fields of chemistry.
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Chapter 1: Introduction and Background
1.1 Dynamic Covalent Chemistry

Supramolecular chemistry is defined by Lehn as “chemistry beyond the bond.” It aims to create complex, tunable, and reversible structures built from noncovalent interactions such as hydrogen bonding, van der Waals interactions, or π–π stacking. The specificity in the design of supramolecular materials has provided new molecular motifs with applications in regenerative medicine, photonics and electronics, and liquid crystals. Additionally, supramolecular chemistry plays an important role in biological materials design, such as in substrate binding, protein tertiary structure, and cellular recognition.

Traditionally, the self-assembly of supramolecular structures has relied on the reversible, intermolecular interactions between molecules. While this approach is useful, the noncovalent interactions that are thermodynamically stable tend to have rapid reversibility. Dynamic covalent chemistry (DCC) is a technique that is able to generate structures with both thermodynamic and kinetic stability. DCC works by creating a mixture of near isoenergetic structures that can exchange with each other because they are in equilibrium. This group of covalently interchangeable intermediates is called a dynamic combinatorial library (DCL). Therefore, DCC gives synthetic organic chemists a way to generate stable supramolecular structures that, like the self-assembly through noncovalent interactions, can always be modified due to their dynamic nature. Only reactions that meet specific requirements can be used in DCC. The reaction needs to be reversible on a reasonable timescale; it must be compatible with experimental conditions; the reaction conditions must be mild in order to not interfere with any noncovalent interactions that play a role in molecular recognition;
all library members must be soluble in the reaction solvent; and it should be possible to stop the reaction in order to isolate certain library members\(^9\). Examples of organic reactions that meet these criteria are imine formation, boronate ester synthesis, and disulfide exchange (Scheme 1).

**Scheme 1:** Examples of dynamic covalent reactions.

Because the library members are in equilibrium, it is possible to alter the reaction conditions such that a specific library member is amplified. It is this which makes DCC a powerful tool in synthetic chemistry; the dynamic nature allows for the changing of the reaction conditions that will favor a specific library member, and these conditions—such as pH, temperature, or the addition of a template—can be introduced at any time. The equilibrium gives way for an error checking mechanism, since the formation of a non-intended product can return to its intermediate precursor, to later be turned into the desired product\(^10\). This proof-reading helps favor the formation of one product at a high yield\(^10\).

The main factor that influences the ratios of product is the thermodynamic stability of the final products\(^10\). To favor the formation of an intended product, the reaction conditions can be altered such that the intended product will be the most stable library member. As an example, Sanders et. al. showed that increasing the
hydrophilicity of a solvent by increasing its salt concentration favors the formation of an organic trefoil knot over other macrocycles in its library\textsuperscript{11} (Scheme 2).

**Scheme 2.** The organic trefoil knot (right) is the most favored member of its DCL when the salt concentration is increased.

The reason behind the preference for the trefoil knot to be formed over other macrocycles is the hydrophobic effect. More than the other library members, the trefoil knot minimizes the amount of surface area between the hydrophobic parts of the building block and water. By increasing the salt concentration, the hydrophilicity increases, and the trefoil knot is the preferred library member under these conditions. The hydrophobic effect plays an important role in the folding of all biological proteins\textsuperscript{12}, and the example of the organic trefoil knot can help elucidate what specific factors influence protein folding, since this is an area of research that is currently not well understood.

In addition to changing the concentration, altering the pH of a DCL can favor the formation of a specific product. Wang et al. reported a toothbrush-type polymeric superamphiphile whose imine linkages can be assembled and disassembled in response to fluctuating the pH\textsuperscript{13} (Scheme 3). As shown, increasing the pH favors the formation of imine bonds, whereas lowering the pH has the opposite effect.
Another powerful way to favor a product distribution is the introduction of a template into a DCL. The template is designed to have favorable noncovalent interactions with the library member of interest. A generic representation of the addition of a template to a DCL is shown in Scheme 4.

**Scheme 4.** The addition of a template amplifies one product. The template accomplishes this by inducing favorable noncovalent host-guest interactions.

In template-directed syntheses, the template can be used to generate a given product and then later removed from solution, liberating the desired product. In other examples, the template can serve as a dock to get the molecule in the proper orientation,
and then the template becomes an integral part of the structure through covalent bonding. This type of template-driven synthesis is referred to as “covalent capture”\textsuperscript{14}.

A prominent type of template-directed synthesis is exemplified by Stoddart et. al. in the formation of a 3-fold symmetric tris-crown ether\textsuperscript{15} (Scheme 5). In order for the reaction to proceed with a high yield, the 3-fold multivalent template must be used so that it can interact with all three polyethylene glycol chains at once. This process places the chains in the proper orientation for the olefin ring-closing metathesis to occur.

**Scheme 5.** In order to produce the 3-fold symmetric tris-crown ether, the 3-fold multivalent template must be used.

In this example, the template can be removed, freeing the product. Stoddart et. al. also employed covalent capture techniques to demonstrate the second type of template-directed syntheses. In this article, they used covalent capture to mechanically interlock molecular bundles\textsuperscript{16} (Scheme 6).
**Scheme 6.** The template orients the three polyethylene glycol rings such that they can react with one another in the covalent capture steps. The three rings can be capped once or twice to form mechanically interlocked bundles. The template is captured within the structure by the imine bonds that are formed.

Dynamic covalent chemistry has been applied to the synthesis of many different supramolecular structures with varying applications. An area that is especially interesting is using DCC to form covalent organic frameworks (COFs).
1.2 Covalent Organic Frameworks

The use of dynamic covalent chemistry has been applied to the synthesis of supramolecular materials. An example is the use of DCC to synthesize covalent organic frameworks (COFs). First discovered by Yaghi et. al. in 2005\textsuperscript{17}, COFs are extended network materials with unique, porous structures that allow for applications in catalysis\textsuperscript{18}, optoelectronic devices\textsuperscript{19}, and membranes\textsuperscript{20,21}. Some examples of dynamic covalent reactions that have been used to synthesize COFs are imine condensation\textsuperscript{22}, boroxine anhydride formation\textsuperscript{18}, and the boronate ester synthesis\textsuperscript{23}. An example of COF formation, structure, and aggregation is outlined in Scheme 7.

**Scheme 7.** COF-1, formed by the Yaghi group via the self-condensation of BDBA. The structure (middle) continues to polymerize outwards, creating a sheet of pores. The sheets aggregate to form the overall structure of the covalent organic framework (right).

COFs possess specific properties that are valuable in organic materials. Arguably most important is that the geometry and porosity of a COF can be tailored to its specific function. COF formation uses the principles of reticular synthesis, in which simpler molecular building blocks react to form predetermined, ordered structures. This control comes directly from the small, organic starting materials that make up these large, complex structures\textsuperscript{24}. Scheme 8 highlights some examples of the wide range of possible frameworks from differently shaped starting materials\textsuperscript{25}.
Scheme 8. The size and shape of covalent organic frameworks is dependent on the molecular components that make them up.

Exploiting the principles of reticular synthesis enables COFs to have applications in drug delivery. This is due to the ability to design a COF to have a certain affinity for a drug of interest. An example of COFs in drug delivery is shown by Yan et. al., who used 3D PI-COFs to entrap and release Ibuprofen in a controllable manner in vitro\textsuperscript{26} (Figure 1).

Figure 1. Ibuprofen fits comfortably in the pores of 3D PI-COF-5 and PI-COF-4 and can be controllably released in vitro.
Because COF formation uses DCC, the structures are held together by strong covalent bonds. Their robust, crystalline architectures give them high thermal and chemical stability. This high stability, combined with the ability to post-synthetically functionalize COFs make them ideal candidates for catalysis. Specifically, the high thermal and chemical stability allows for the recycling and reusing of COF catalysts, and the post-synthetic functionalization allows for metals that are important in catalysis—such as palladium—to be incorporated into COF architectures. Thus, COFs have been used as catalysts in organic and inorganic reactions without losing their crystallinity and porosity\textsuperscript{27}.

The Wang group designed a COF functionalized with palladium, Pd/COF-LZUI, to catalyze Suzuki-Miyaura coupling reactions. The COF catalyst proved to have excellent catalytic activity and achieved yields of 96-98\%\textsuperscript{28}. In the Wang paper, it is reported that Pd/COF-LZUI was dried after reacting, and then used directly without further treatment, showing the ease with which COF catalysts can be reused\textsuperscript{29}. The results of this recycle test are outlined in Figure 2.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{The recycle test of Pd/COF-LZUI1 in the Suzuki-Miyaura coupling reaction of \textit{p}-nitrochlorobenzene and phenylboronic acid.}
\end{figure}
In addition to having applications in Suzuki-Miyaura catalysis, COFs have been used to catalyze asymmetric Michael C-C formation reactions with high yields\textsuperscript{30} (Figure 3). In this paper, a specific framework is post-synthetically functionalized with organocatalytic sites. The COF is reported to be a highly efficient and easily recyclable catalyst with 92-95\% yields after repeated use\textsuperscript{31}.

![Figure 3. The Michael reactions catalyzed by the chiral COF. R: H, Cl, Br, Me, and OMe. The recycle test shown for the reaction when R = o-Cl.](image)

<table>
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<th>cycle number</th>
<th>time (h)</th>
<th>conversion (%)</th>
<th>yield (%)</th>
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<td>6</td>
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Just as COFs can be tailored to have large pore sizes that act as reaction sites, they can also be designed with small pores. Smaller pore size is an important feature for frameworks that aim to have selective gas adsorption. Zhu et. al. designed the smallest COF ever reported, with a uniform pore size of 0.64 nm\textsuperscript{32}. This COF, MCOF-1, is assembled from the boronate ester formation reaction. Its size gives MCOF-1 the ability to separate hydrocarbon mixtures because it is highly selective for C\textsubscript{3}H\textsubscript{8} and C\textsubscript{2} hydrocarbons over CH\textsubscript{4}\textsuperscript{33}. The structure of MCOF-1 and the results of its hydrocarbon gas adsorption are summarized in Figure 4.
Figure 4. The structure of MCOF-1. The graph displaying the MCOF-1 gas uptake for the hydrocarbons CH$_4$, C$_2$H$_4$, C$_2$H$_6$, and C$_3$H$_8$. As shown, MCOF-1 is selective for C$_3$H$_8$ and C$_2$ hydrocarbons over CH$_4$.

In addition to adsorbing gas, COFs are ideal membranes$^{34}$. Membrane separation is considered to be a useful technique for separating gases. Because of coal-fired power plants emitting around 2 billion tons of carbon dioxide every year, there has been recent interest in using membranes to capture CO$_2$$^{35}$. Qiu et. al. showed a covalent organic framework-metal organic framework (COF-MOF) hybrid that has a high selectivity for separating H$_2$/CO$_2$ gas mixtures (Figure 5)$^{36}$.

Figure 5. The COF-MOF hybrid membrane. When H$_2$ and CO$_2$ are filtered through the membrane, only H$_2$ can pass.

Covalent organic frameworks have many significant applications; however, they are limited by their large size, which makes them insoluble. This solubility issue
poses a hurdle in the characterization of COFs, and moreover the ability to understand the mechanisms and optimal reaction conditions for their formation\textsuperscript{37}. Consequently, there is a need to understand the underlying factors that achieve optimal COF formation. This need led to the study of discrete analogues of COFs, called covalent organic polygons (COPs). COPs are smaller, soluble structures that can elucidate ideal COF formation conditions.
1.3 Covalent Organic Polygons and Discotic Liquid Crystals

A covalent organic polygon (COP) is a discrete analogue of a covalent organic framework. Unlike COFs, COPs can be designed to be soluble and are therefore available to study using solution-phase techniques. Because covalent organic polygons are composed of similar starting materials, the study of COPs can elucidate ideal reaction conditions needed to optimize COF formation. Scheme 9 details the key differences between COPs and COFs.

**Scheme 9.** The general structures of covalent organic polygons (top) and covalent organic frameworks (bottom).

COPs and COFs are composed of similar starting materials, the only significant difference being that COPs contain –OR solubilizing groups, whereas COFs contain groups on the periphery that will continue to polymerize the framework outwards.
These different groups explain why COFs form sheets as they polymerize, and COPs are a discrete analogue. When covalent organic frameworks aggregate, there are many columns of pores connected covalently to each other. Conversely, covalent organic polygons form single columns where the discrete monomers stack cofacially.

Because of the similar aggregation patterns and starting materials, it is hypothesized that COPs possess many of the advantageous properties of COFs. Initially, COPs were investigated primarily with the aim to optimize reaction conditions for COF formation, and while these research efforts are still ongoing, it has been discovered that there are additional properties of COPs that COFs do not possess. Specifically, COPs are of great interest for their use as discotic (disc-like) liquid crystals.

Liquid crystalline substances are mesophases between a crystalline solid and an isotropic liquid\textsuperscript{38}. They are present in the natural world, such as in biological systems, and are also prominent in technology, such as with liquid crystal displays (LCDs). Liquid crystals generally fall under two distinct categories. Lyotropic liquid crystals form aggregates in different solvent systems. Some examples are cell membranes, bile salts, and myelin\textsuperscript{39}. Thermotropic liquid crystals occur under a specific temperature range. An example is cholesteric liquid crystals, which reflect different wavelengths of light at different temperatures. Cholesteric liquid crystals are what provide the altering colors in mood rings. These examples represent few of the many liquid crystal applications, and some additional uses, specifically for polymeric liquid crystals, are shown in Figure 6.
Figure 6. Some examples of potential liquid-crystalline polymer applications.

Under the umbrella of lyotropic and thermotropic, liquid crystalline materials can further be defined by categories that are based on composition: elongated rod-like (calamitic) or disk-like (discotic) organic molecules (Figure 7).

Figure 7. Example of calamitic (left) and discotic (right) liquid crystals.

The shape of these molecules allows them to possess orientational order that plays an important role in their liquid crystalline properties. While the molecules themselves are not cylindrical, their rapid thermal motion (on the order of $10^{-9}$ s) allows for them to be regarded as such. Because liquid crystalline materials are in between the crystal solid and isotropic liquid phase, the structures must have components that
are both rigid and flexible. This presents a balancing act between these two structural elements: if the molecules are too flexible, there will not be any orientational order; however, if they are too rigid, the molecule will transfer rapidly from the isotropic liquid to the crystalline solid phase. The right combination of flexibility and rigidity enables the slower transition between the two phases and allows for a compound to exhibit liquid crystalline properties. Calamitic liquid crystals accomplish this feat by having rigid aromatic bodies complemented with flexible hydrophobic tails. Similarly, discotic liquid crystals have an aromatic core and aliphatic tails that sprout outwards from the center. The variety of phases between crystal solid and isotropic liquid for discotic liquid crystals is demonstrated in Figure 8.

**Figure 8.** The liquid crystal phases between solid and liquid for disc-like molecules. The columnar and nematic phases are two liquid crystalline phases for disc-like liquid crystalline compounds.

The structural elements of covalent organic polygons align with the ideal liquid crystal composition. Therefore, COPs are of recent interest for these applications. COPs have aromatic cores, normally formed from benzene or a benzene derivative. This aromatic core allows for the covalent organic polygons to have a rigid component to their structure. The rigidity comes from the interactions between the aromatic rings. Benzene belongs to the $D_{6h}$ point group due to its symmetry, and therefore does not
have a dipole moment. The charge distribution in benzene, however, is not spherically symmetric, giving rise to a quadrupole moment \(^{41}\) (Figure 9).

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**Figure 9.** The quadrupole moment of benzene.

This quadrupole moment influences the favorable types of \(\pi-\pi\) stacking that can exist between two benzene rings. The most prominent types of \(\pi-\pi\) stacking are illustrated in Figure 10.

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**Figure 10.** Two \(\pi-\pi\) stacking modes: slip stacking and edge-on. The strong, favorable interactions in the \(\pi\)-conjugated core are important in holding together groups of discotic liquid crystals.

It is important, however, to counterbalance this rigidity with a structural component that adds flexibility. This counterbalancing force comes from the thermal motion of aliphatic chains. Therefore, the COP solubilizing (–OR) chains serve an essential purpose because they prevent the discotic structures from becoming crystalline solids.
The design of the aliphatic chains is integral to controlling the transition temperature from crystalline to liquid crystalline, and work has gone into figuring out what types of chains would best serve this purpose. Alkyl side chains are most commonly used, in part due to the availability of a broad range of alkyl halide starting materials. It was hypothesized that the transition temperature should lower with the addition of side chain branching, due to the increase in gauche interactions that prevent the aliphatic chains from packing together tightly\textsuperscript{42}. An illustration of these gauche interactions is shown in a Newman Projection in Figure 11.

![Newman Projection of a linear (left) and branched alkane (right). The gauche interaction is depicted by the steric markings in the Newman Projection on the right. An increase in gauche interactions introduces more kinks into the side chains, which prevents tight packing.](image)

While covalent organic polygons are composed of an aromatic core and aliphatic chains, in order for them to have applications as liquid crystal materials they must aggregate in a columnar fashion. Dichtel and Northrop reported the synthesis of discrete boronate ester macrocycles (Scheme 10) that stack cofacially in columns (Figure 12). This demonstrates that covalent organic polygons, such as boronate ester macrocycles, can have potential liquid crystal applications.
Scheme 10. A boronate ester macrocycle is formed from a bis-boronic acid and tetra-ol. The macrocycle aggregated cofacially (right).

To demonstrate that the discrete boronate ester macrocycles prefer this mode of aggregation, a solution of the columns was sonicated for one hour. The sonication broke apart the favorable interactions between the macrocycles, and then the solution was allowed to sit for twelve hours. After equilibrating, it was observed that the boronate ester macrocycles had returned to their columnar stacking mode (Figure 12). Thus, covalent organic polygons possess the ideal structural and stacking properties needed for discotic liquid crystalline materials.

Figure 12. Atomic force microscopy (AFM) images of the cofacially-stacked boronate ester macrocycles\textsuperscript{43}.

Covalent organic polygons assembled via the boronate ester forming reaction can be especially useful as liquid crystalline materials, since the boron is trivalent and can extend resonance between two conjugated systems. Given the importance of
dynamic covalent boronate ester formation in the self-assembly of COPs, it is important to consider the fundamental properties of boronic acids and their assembly in greater detail.
1.4 Boronic Acids and the Boronate Ester Synthesis

Boronic acids are enormously important in organic chemistry as chemical building blocks and intermediates. Their most profound application is arguably as a reagent in the palladium-catalyzed Suzuki cross-coupling with carbon halides, which was recognized for its significance by the Nobel Prize in 2010. Apart from organic synthesis, boronic acids play crucial roles in chemotherapeutic agents, self-healing materials, and carbohydrate sensors. The structure of boronic acids is derived from boric acid, where one of the hydroxyl groups is replaced with an \(-R\) group (Figure 14). Because boronic acids degrade to boric acid, they have a low toxicity and can be regarded as environmentally friendly.

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**Figure 14.** The structures of boric and boronic acid.

Boronic acids are trivalent compounds that are electrophilic due to their empty p orbital. The Lewis acid character is part of what makes boronic acids a particularly attractive class of synthetic intermediates. Because of the empty p orbital, boronic acids are sp\(^2\) hybridized. In arylboronic acids, the conjugated pi system can participate in resonance with the boron (Figure 15). This resonance gives the C-B bond some \(\pi\) character.
Figure 15. Phenylboronic acid electronic effects by resonance.

Boronic acids can condense with organic diols to produce boronate esters. Bis-boronic acids can react with tetra-ols to form complex, supramolecular structures such as rectangles (Scheme 11).

Scheme 11. The boronate ester forming reaction.

When a boronic acid condenses to form a boronate ester, it loses its hydrogen bond donor ability, and as a result the esters are less polar and easier to handle. Boronic acids are widely used in organic and supramolecular synthesis because the strong B-O bonds yield materials with high thermal stability. This significant bond strength gives boronic acid-derived compounds use as flame retardants. B-O bonds
are covalent and exist under thermodynamic control. This affords chemists with the ability to use Le Chatelier’s principle to drive the reaction forward or in reverse with the removal or addition of water. Because the boron p orbital can participate in resonance, it works to extend the conjugation between neighboring aromatic systems. The conjugation extension lowers the bandgap by reducing the lowest unoccupied molecular orbital (LUMO) energy, giving way to intriguing optical and electronic properties.

Boronic acids are key starting materials for the syntheses of highly crystalline, porous materials like covalent organic frameworks (COFs) and covalent organic polygons (COPs). This thesis aims to synthesize four covalent organic polygons, with tetraethylene glycol and dodecyloxy solubilizing groups. The four target COPs, one [2+2] and one [3+3] assembly for each bis-boronic acid, are shown in Scheme 12. The assemblies are called [2+2] because two bis-boronic acids and two organic tetra-ols make up the final structure. Similarly, three bis-boronic acids and three organic tetra-ols make up the [3+3] assemblies.
Chapter 2: Results and Discussion
2.1 Synthesis of 2.6: The Hydrophilic Bis-Boronic Acid

**Scheme 13.** Full synthetic route to the hydrophilic bis-boronic acid (2.6).

The target [2+2] and [3+3] covalent organic polygons are composed of a bis-boronic acid that can be prepared following a multi-step synthesis starting with commercially available phenanthraquinone (Scheme 14).

**Scheme 14.** The synthesis of 2.6 starts with commercially available phenanthraquinone.

The solubilizing “-OR” groups were chosen specifically for their polarity. It is hypothesized that the tetraethylene glycol chains will allow for the overall [2+2] and
[3+3] COP architectures to be soluble in polar protic solvents, due to the hydrogen bond acceptor oxygens in the chain\(^6\) (Figure 16).

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**Figure 16.** Hydrogen bonding between water (solvent) and ethylene glycol. The dashed lines represent hydrogen bonds. Similar types of hydrogen bonding can occur between the tetraethylene glycol –OR chains and a polar protic solvent. The hydrogen bonds between water molecules are omitted to emphasize the interactions between ethylene glycol and water.

Phenanthraquinone was selected as the commercially available starting material since its structure gives the correct geometry for the resulting bis-boronic acid to form [2+2] and [3+3] assemblies.

The first reaction with phenanthraquinone was a free radical bromination to yield 2.1. The crude product was pure based on its \(^1\)H NMR spectrum (Figure 17).
Next, the di-brominated phenanthraquinone was reduced to a diol. The ketones must be reduced so that the subsequent substitution reaction between the diol (2.2) and 2.3 can occur. The reaction used sodium dithionite as the reducing agent and was run in a 25:18 ratio of tetrahydrofuran (THF) and water. This solvent system was used to solubilize both the inorganic reducing agent and the organic starting material (2.1). The reduced diol, 2.2, is oxidatively unstable, and consequently will convert back to its precursor upon exposure to air. To prevent oxidation, 2.2 was stored in the freezer under nitrogen. Additionally, the reduction was only carried out when 2.3 had been prepared. This way the subsequent reaction could be run within days of synthesizing 2.2. The $^1$H NMR spectrum of 2.2 is shown in Figure 18. The additional aromatic peaks represent residual starting material (2.1); however, due to the product’s oxidative instability, column chromatography cannot be performed.
In order to react the organic diol with the tetraethylene glycol “-OR” solubilizing groups, tetraethylene glycol monomethyl ether must be tosylated to turn the alcohol into a good leaving group (Scheme 15).

Scheme 15. Tosylation of tetraethylene glycol monomethyl ether.

This substitution reaction began by deprotonating the alcohol in tetraethylene glycol monomethyl ether using a sodium hydroxide / H$_2$O mixture in a round bottom flask. The acid base reaction between was run for three hours over an ice bath. Then, tosyl chloride dissolved in THF was added dropwise slowly through a dropping funnel over a period of 12 hours. The S$_{N}$2 reaction yielded 2.3. $^1$H NMR and thin layer chromatography (TLC) of the crude product showed unreacted tosyl chloride. Column
chromatography was performed with a 1:3 ethyl acetate (EtOAc):hexanes solvent system to elute excess tosyl chloride. 1:3 ethyl acetate:dichloromethane (DCM) was then used to retrieve the product, which was collected with 25 ml fractions in Erlenmeyer flasks. The $^1$H NMR of the isolated product is shown in Figure 19.

![Figure 19. $^1$H NMR spectrum of 2.3.](image)

Once 2.3 is synthesized, it can react with 2.2 in an S$_{N}$2 reaction. This reaction uses potassium carbonate as a base, and catalytic amounts of lithium bromide and 18-crown-6 in dimethylformamide (DMF). 18-crown-6 is used to help solubilize the potassium carbonate because its crown ether pore sequesters potassium ions with a 1.4 $\times$ 10$^6$ binding constant$^{57}$. The sequestering is favored because of the ion-dipole interactions between the positively charged potassium ion and the negatively-charged oxygens in the polyether ring$^{58}$ (Figure 20).
Figure 20. Potassium ions are favorably sequestered the crown ether pore. The dashed lines represent the ion-dipole interactions between the potassium ion and oxygen atoms. The space-filling model is shown in the right.

The potassium carbonate deprotonates the diol to give a di-alkoxide. The di-alkoxide species then reacts with 2.3 in an $S_N2$ reaction to produce 2.4. Because this reaction can substitute once, twice, or not at all, TLC and column chromatography must be used to isolate pure product. The column began with pure DCM, followed by 1:5 EtOAc:DCM, and 1:1 EtOAc:DCM. The $^1$H NMR of 2.4 is shown in Figure 21.

Figure 21. $^1$H NMR spectrum of 2.4.
The next reaction converts the two bromides into pinacol-based boronate esters. This reaction is called a Miyaura borylation, a palladium-catalyzed coupling reaction. Palladium acetate was used as the catalyst. This catalyst works to increase the rate of the transmetallation step by forming the (acetato)palladium(II) complex. This rate increase occurs because the Pd-O bond is more reactive than the Pd-Br bond, and the reason why the Pd-O bond is less stable is because it is between a hard Lewis base and a soft Lewis acid. The reaction mechanism for the Miyaura borylation is shown in Scheme 16.

**Scheme 16.** The Miyaura borylation mechanism.

The coupling reaction yields 2.5, a diborane ester. Column chromatography was performed to isolate the product. The solvent system was 3:1 EtOAc:DCM. Figure 22 shows the $^1$H NMR spectrum of 2.5.
The impurities at around 6.9 ppm, 5.0 ppm, 2.9 ppm, and 2.3 ppm are from residual dibutylhydroxytoluene (BHT), an antioxidant stabilizer that was added to the solvent used in this reaction.

**2.5** was be converted to **2.6** in a hydrolysis reaction using diethanolamine and hydrochloric acid. The *H NMR was obtained in deuterated methanol (Figure 22).
Because boronic acids self-condense to form boronic anhydrides, column chromatography cannot be performed. Additionally, the self-condensation makes it challenging to characterize boronic acids via NMR spectroscopy, due to the many structures that can be formed (Scheme 17).

Scheme 17. Boronic acids self-condense, making their characterization difficult.

To obtain a useful NMR spectrum, the solvent must minimize the self-condensation reaction. Northrop et. al. reported that hydrophobic solvents such as
CH$_2$Cl$_2$ and CHCl$_3$ promote the formation of boroxine anhydride species, whereas polar solvents such as CH$_3$OH prevent self-condensation$^{51}$. This is the reason that the $^1$H NMR spectrum of 2.6 used CD$_3$OD as the NMR solvent.

It was hypothesized that the peak at 4.426 ppm in the 2.6 spectrum represents the boronic acid hydrogens; however, the chemical shifts cannot be compared to those in the starting materials because the spectra were obtained in different solvents. Because the bis-boronic acid cannot be characterized by NMR in deuterated chloroform, the acid groups were “capped” with organic diols. When the acid groups condense to boronate esters, they lose their ability to self-condense. Therefore, the esters can be characterized in CDCl$_3$. The results of the capping efforts are summarized in Section 2.3.
2.2 Synthesis of 3.4: The Hydrophobic Bis-Boronic Acid

**Scheme 17.** Full synthetic route the hydrophobic bis-boronic acid (3.4).

Just as 2.6, the hydrophobic bis-boronic acid has a multistep synthetic route beginning with phenanthraquinone. The first two reactions are carried out with the same reagents and under the same conditions detailed in Section 2.1. This section will begin where the hydrophobic and hydrophilic bis-boronic acid syntheses diverge: the substitution reaction with dodecyl bromide.

This $S_N2$ reaction uses potassium carbonate to deprotonate the diol, creating two alkoxide nucleophiles. The two newly-formed alkoxides nucleophilically attack on the dodecyl bromide, forming 3.3. Because the resulting structure is hydrophobic, TLC and column chromatography were run with pure hexanes. Since the byproducts—dodecyl bromide and the monosubstituted compound—are hydrophobic, they elute off of the column quickly. Dodecyl bromide doesn’t fluoresce under UV light, so 10 ml fractions were collected until NMR confirmed that there was no dodecyl bromide left
on the column. Then, Erlenmeyer flasks were used to collect the product in 25 ml fractions. The $^1$H NMR spectrum of 3.3 is in Figure 23.

![1H NMR Spectrum of 3.3](image)

**Figure 23.** $^1$H NMR Spectrum of 3.3.

Instead of the Miyaura borylation pathway, 3.3 was reacted with n-Butyllithium and triisopropyl borate to directly yield the bis-boronic acid. This alternate route is more cost effective and the overall synthetic scheme has one fewer step; however, it is limited by the fact that an intermediate cannot be isolated and characterized.

The n-butyllithium initiates lithium-halogen exchange with 3.3 in a single-electron transfer (SET) process. Then, the organolithium intermediate reacts with triisopropyl borate. Hydrochloric acid was added to liberate the bis-boronic acid (Scheme 18).
Scheme 18. An alternate synthesis gives 3.4.

The hydrophobic bis-boronic acid could not be characterized because the hydrophobic dodecane chains make it so that 3.4 is only soluble in nonpolar solvents that favor self-condensation. Therefore, the $^1$H NMR spectrum of 3.4 (Figure 24) was taken in CDCl$_3$.

Figure 24. $^1$H NMR Spectrum of 3.4.

Figure 24 demonstrates why it is challenging to characterize boronic acids in nonpolar solvents; when the different self-condensation products form, the spectrum is
impossible to resolve. This is especially the case for compounds with two or more boronic acids. To characterize 3.4, it is necessary to use the capping procedure. These capping efforts are outlined in the following section.
2.3 Capping the Bis-Boronic Acids

As stated in previous sections, boronic acids possess the ability to self-condense. The self-condensation of boronic acids makes them viable building blocks in self-assembling materials for sensing and separation\textsuperscript{61}. While advantageous, the self-condensation of boronic acids also makes them difficult characterize, since a boronic acid can exist in many different forms\textsuperscript{62} (Scheme 19). To overcome this issue, attempts were made to cap the two bis-boronic acids, 2.6 and 3.4, with organic diols such as catechol and pinacol. Unlike boronic acids, many boronate esters can be isolated via column chromatography and characterized by NMR spectroscopy.

**Scheme 19.** Boronic acids self-condense, making their structures difficult to characterize via NMR. When the acid groups are “capped” with a diol, the structures will not condense and are therefore available for study.

The stability of the resulting boronate ester is important to consider when choosing the right organic diol to use as a cap. Ideally, the boronate ester will be stable enough to not disassemble during column chromatography, while also sufficiently...
unstable to undergo hydrolysis to free the acid. Generally, rigid, pre-organized diols like the diol precursor to A (Figure 25) yield more robust esters. In addition, boronate esters produced from diethanolamine present a unique structure where the lone pair of the nitrogen atom can coordinate to boron’s empty p orbital, proving stability. It was also found that six-membered cyclic esters are generally more stable than five-membered cyclic esters. The reason for this is hypothesized to be that the six-membered ester provides better geometry for the coordination between the B-O bonds within the ring. Catechol-based boronic esters are more Lewis acidic due to the opposing conjugation between the phenolic oxygen rings and the benzene ring. Because they are more Lewis acidic, these esters are less stable to hydrolysis. Hydrolysis of acyclic or sterically unhindered boronate esters such as ethylene glycol is a rapid process. The relative stability of some boronate esters is summarized below in Figure 25.

---

\[
\begin{align*}
\text{A} & > \text{B} \cong \text{C} > \text{D} \cong \text{E} > \text{F} \\
\end{align*}
\]

**Figure 25.** Relative stability of a selection of arylboronate esters. A is most stable, and F is the least stable. In this figure, stability is defined in terms of the rate of hydrolysis to the boronic acid and organic diol precursors.

The first attempt to cap 2.6 was with catechol. Because catechol esters are relatively easy to hydrolyze they are a good option to characterize 2.6. The \(^1\)H NMR is below in Figure 26.
The reaction did not fully convert the acids to esters, which is evident from the many peaks that represent the self-condensation products. The capping reaction was run one more time on a larger scale to provide enough product for column chromatography. The column was run using dichloromethane to elute excess catechol, followed by 1:3 ethyl acetate:dichloromethane to retrieve the capped product. The column did not work. It is hypothesized that the boronate ester degraded on the column.

The next attempt to cap 2.6 was with diethanolamine (Figure 27).
Figure 27. $^1$H NMR spectrum of 2.6 capped with diethanolamine.

Because the $^1$H NMR spectrum of 2.6 was obtained in CD$_3$OD, it is difficult to compare the chemical shifts between the acid and the capped ester. Therefore, the $^1$H NMR spectrum of diethanolamine in CDCl$_3$ was used. Because the diethanolamine proton NMR spectrum has a triplet at 2.74 ppm$^{66}$, and this peak is not present in Figure 27, it is hypothesized that the capping of 2.6 with diethanolamine was successful.

As shown in Figure 25, diethanolamine based boronate esters are more stable than boronate esters made from catechol because of the internal coordination between the lone pair on nitrogen and boron’s empty p orbital (Figure 28). This reason might explain why the capping reaction was successful with diethanolamine.
Figure 28. The interaction between the nitrogen (purple) and the boron (yellow) stabilizes the diethanolamine boronate ester\textsuperscript{67}.

Once 2.6 was capped, focus was shifted to capping 3.4. Because the last isolated precursor to the hydrophobic bis-boronic acid is the dibrominated 3.3 product, initial capping used the 3.3 structure to directly make the boronate ester. The first attempt used a Grignard reaction with an ethylene glycol cap. Like catechol, ethylene glycol boronate esters are relatively easy to hydrolyze and were therefore of interest. The experimental set-up was followed according to a literature precedent, which reported near quantitative yields\textsuperscript{68}. The reaction did not work with 3.3, however. The $^1$H NMR spectrum showed unreacted starting material.

The reaction was tried again using n-butyllithium in place of the Grignard, and the $^1$H NMR spectrum of the product is shown in Figure 29.
The appearance of new aromatic peaks indicates that some amount of product was formed, however there is also starting material present. Because ethylene glycol based boronate esters are rapidly hydrolyzed, column chromatography cannot be performed to isolate the product.

The next attempt used the Miyaura borylation (Scheme 20). This reaction was carried out with the same experimental conditions used for 2.5.

**Scheme 20.** The Miyaura borylation reaction.
The $^1$H NMR spectrum of the pinacol capped boronate ester is shown in Figure 30.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure30.png}
\caption{$^1$H NMR of the pinacol based boronate ester made using the Miyaura borylation.}
\end{figure}

This reaction worked to give the pinacol based boronate esters, which was determined by the presence of the pinacol peak and the shifting of the aromatic peaks from the chemical shift values in the starting material.

With the spectrum in Figure 30 as a reference point, the pinacol based boronate ester was attempted to be synthesized from 3.4. If this boronate ester formation worked, then the Miyaura borylation (which uses a palladium catalyst) would not be necessary and the synthesis would be much more cost effective.

This alternate route reacted pinacol with 3.4. The $^1$H NMR spectrum is shown in Figure 31.
The abundance of peaks signifies some amount of unreacted bis-boronic acid that formed self-condensation products. Because pinacol based boronate esters are robust, it might be possible to perform column chromatography to isolate the boronate ester, however this has not been attempted yet.

In addition to the bis-boronic acids, two organic tetra-ols needed to be synthesized to enable the formation of the [2+2] and [3+3] covalent organic polygons. Their synthesis is outlined in the following section.
2.4 Synthesis of the Organic Tetra-ols

In order to form the [2+2] and [3+3] covalent organic polygons, the bis-boronic acid and the organic tetra-ol must first be synthesized. The tetra-ol used in the [3+3] COPs is made from the reducing 2,5-dihydroxy-1,4-benziquinone (Scheme 21). This reaction has not been carried out because the product is oxidatively unstable. Once the [3+3] covalent organic polygons are ready to be assembled, this tetra-ol will be made.

Scheme 21. Synthesis of the tetra-ol for the [3+3] assemblies.\(^{69}\)

When benzene-1,2,4,5-tetrol and the bis-boronic acids are available, the [3+3] polygons can be assembled (Scheme 22).

Scheme 22. The condensation of the bis-boronic acids and benzene-1,2,4,5-tetrol to yield the [3+3] assemblies.

Unlike, the [3+3] assemblies the tetra-ol in the [2+2] COPs is not oxidatively unstable. The tetra-ol, 4.1, was synthesized from an aryl methyl ether that had previously been prepared in the Northrop Lab. The aryl methyl ether synthesis is outlined in Scheme 23.
Scheme 23. Synthesis of the aryl methyl ether.\textsuperscript{70}

\begin{align*}
\text{Scheme 24. The aryl methyl ether cleavage to give 4.1.}
\end{align*}

The product was isolated via column chromatography with 10% EtOAc in DCM followed by pure EtOAc to retrieve the product. Figure 32 shows the \textsuperscript{1}H NMR spectrum of 4.1, and Figure 33 shows a zoom-in of the aromatic region.
Figure 32. $^1$H NMR Spectrum of 4.1.

Figure 33. A zoom-in on the aromatic region of the $^1$H NMR Spectrum of 4.1.
Once the two bis-boronic acids are synthetized, 4.1 will be used to assemble the [2+2] covalent organic polygons (Scheme 25).

**Scheme 25.** The condensation of the bis-boronic acids and 4.1 to yield the [2+2] assemblies.
Chapter 3: Conclusion and Further Work
Covalent organic polygons (COPs) have made a remarkable impact on developments in catalysis, gas storage, drug delivery, and liquid crystalline materials. COPs that are synthesized through boronate ester forming reactions are particularly interesting because of boron’s empty p orbital that extends resonance between neighboring aromatic groups. This thesis details research that aimed to synthesize two types of [2+2] and [3+3] covalent organic polygons held together through boronate ester linkages. The two types of polygons are hydrophilic and hydrophobic. The hydrophilic COPs have tetraethylene glycol solubilizing groups on the periphery of the bis-boronic acid, while the hydrophobic COPs have peripheral dodecyloxy solubilizing chains.

The hydrophilic bis-boronic acid (2.6) was made and the details of its synthesis are outlined in Section 2.1. It is hypothesized that the [2+2] and [3+3] covalent organic polygons made with 2.6 will be hydrophilic, since the tetraethylene glycol chains can participate in hydrogen bonding with polar protic solvents.

The hydrophobic bis-boronic acid (3.4) was made and the details of its synthesis are outlined in Section 2.2. It is hypothesized that the [2+2] and [3+3] covalent organic polygons made with 3.4 will be hydrophobic due to the greasy dodecyloxy chains.

In order to assemble [2+2] and [3+3] architectures, two tetra-ols must be synthesized. The tetra-ol corresponding to the [2+2] assembly (4.1) was successfully synthesized. The details of this reaction are outlined in Section 2.3.

Both bis-boronic acids, 2.6 and 3.4, were successfully capped and characterized by ¹H NMR spectroscopy. 2.6 was capped with diethanolamine through a condensation reaction with 2.6. 3.4 was capped with pinacol through a Miyaura borylation reaction.
with 3.5. The details of these capping efforts are summarized in Section 2.4. Future work on this research will involve fully characterizing the hydrophobic and hydrophilic bis-boronic acids by $^1$H NMR and $^{13}$C NMR spectroscopy, mass spectrometry, Ultraviolet-Visible (UV/Vis) and fluorescence spectroscopy.

After the two bis-boronic acids are characterized, this research will assemble the four [2+2] and [3+3] architectures. To accomplish this, the organic tetra-ol in the [3+3] assembly must be synthesized. Once the COP assemblies are synthesized with both the hydrophobic and hydrophilic bis-boronic acids, all four structures will be characterized. The COPs will also be characterized using $^1$H NMR and $^{13}$C NMR spectroscopy, mass spectrometry, and UV/Vis and fluorescence spectroscopy. It is noteworthy that these analytical techniques are not amenable to the characterization of Covalent Organic Framework (COF) materials, further highlighting one of the benefits of soluble and solution-processable COPs relative to insoluble COF materials.

Another extension of this research is to include thiol-Michael “click” chemistry to functionalize the bis-boronic acid with many different solubilizing chains. This can be accomplished by putting a Michael acceptor in the –OR position that can react with a thiol (Scheme 26). The thiol-Michael reaction has been studied in the Northrop Lab and conditions for different thiol-Michael reactions have been optimized.$^{71}$

**Scheme 26.** A Michael acceptor such as an acrylate moiety can be added in the –OR position. Then, a thiol can be used in the thiol-Michael reaction to produce many bis-boronic acids with selectively-targeted solubility.
Dynamic covalent chemistry allows for the synthesis of COPs with remarkable applications. With the incorporation of many –OR groups with varying solubility, the [2+2] and [3+3] COPs could be useful in many different areas of materials chemistry.
Experimental
Materials

The solvents used in this thesis were purchased from Fischer Chemical and Pharmco-AAPER. When applicable, solvents were dried with 3 angstrom molecular sieves. Any mention of water that was used was deionized. Chemical reagents were purchased from commercial suppliers such as Sigma Aldrich, Acros Organics, and Alfa Aesar. Thin layer chromatography was run using Agela Technologies 60 angstrom, pH 5, silica gel plates. Column chromatography was run using Silicycle silica gel.

The \textsuperscript{1}H NMR spectra were acquired using a Varian 300 MHz and 75 MHz spectrometer and the Varian 500 MHz and 125 MHz spectrometer.

The above materials were used in the synthesis of both bis-boronic acids and organic tetra-ols. Methods for these syntheses are outlined in the subsequent sections of the experimental.
The Hydrophilic Bis-Boronic Acid Methods

**Scheme 26. Synthesis of 2.1.**

Preparation of 2.1: To a 250 ml three neck round bottom flask was added 2 g phenanthraquinone (9.61 mmol) and 0.1 g benzoyl peroxide (catalytic amount). The flask was fit with a condenser and the flask was then evacuated and filled with nitrogen three times and 30 ml of nitrobenzene was added. 2 ml bromine (38.43 mmol) was added slowly and the reaction was stirred at room temperature for three hours under a Tungsten lamp. The reaction was stirred for an additional three hours at 60 °C under the Tungsten lamp. Heat and the Tungsten lamp were removed and the reaction was cooled to room temperature overnight. Isopropyl alcohol was added to the reaction mixture, and then the orange product was filtered and rinsed with isopropyl alcohol. The remaining solvent was removed under reduced pressure and the solid product was dried, yielding 2.1 (3.250 g, 92%).

$^1$H NMR (300 MHz, acetone-$d_6$): \( \delta \) 8.630 (s, H\text{Ar}), 8.046 (d, J = 8.1 Hz, H\text{Ar}), 7.812 (d, J = 8.1 Hz, H\text{Ar}).
Preparation of **2.2**: To a 500 ml round bottom flask was added 2.24 g **2.1** (6.11 mmol). **2.1** was dissolved in 203 ml of tetrahydrofuran and 146 ml of water. 4.26 g sodium dithionite (24.44 mmol) was added to the round bottom, and the reaction stirred for three hours at room temperature. The tetrahydrofuran was removed under reduced pressure, and the resulting mixture was extracted using ethyl acetate. The organic layer containing the product was dried using magnesium sulfate, filtered, and the solvent was removed under reduced pressure and dried. The round bottom flask containing **2.2** (2.036 g, 90%), a green solid, was evacuated and filled with nitrogen three times, and then placed in the freezer until further use.

$^1$H NMR (300 MHz, acetone-$d_6$): $\delta$ 8.965 (s, $H^{Ar}$), 8.319 (s, ArOH), 8.1855 (d, $J = 8.7$ Hz, $H^{Ar}$), 7.7795 (d, 8.7 Hz, $H^{Ar}$).
**Scheme 28. Synthesis of 2.3.**

![Scheme 28](image)

Preparation of 2.3: To a 250 ml round bottom flask was added 3 g tetraethyleneglycol monomethyl ether (14.41 mmol) and 1.7 g NaOH pellets (43.22 mmol) dissolved in 30 ml water. The mixture was stirred over an ice bath for three hours. Then, the reaction flask was fit with a dropping funnel containing 6.2 g tosyl chloride (32.42 mmol) dissolved in 60 ml tetrahydrofuran. The dropping setting was set to low, and the reaction was allowed to run overnight. The reaction mixture was placed into a 250 separatory funnel and the product was extracted with 2x dichloromethane washes. The organic layer containing 2.3 was removed under reduced pressure and dried. Thin later chromatography was performed and it was decided for the column that 1:3 ethyl acetate:hexanes is best to remove excess tosyl chloride, and then 1:3 ethyl acetate:dichloromethane should be used to collect 2.3. Column chromatography was used following this solvent system. 2.3 was eluted from the column (3.661 g, 70%). The $^1$H NMR spectrum chemical shifts correspond to literature reports$^{72}$. 
Preparation of 2.4: To a 50 ml three neck round bottom flask was added 0.929 g 2.2 (2.525 mmol), 3.661 g 2.3 (10.1 mmol), 2.094 g potassium carbonate (15.15 mmol), and catalytic amounts of 18-crown-6 and lithium bromide. The flask was evacuated and filled with nitrogen three times, and then a minimum amount of dry dimethylformamide was added. The reaction was allowed to stir at 80 °C overnight. The reaction mixture was filtered through a Buchner funnel set up with a water aspirator. The product was rinsed with dichloromethane, and the filter flask solution containing 2.4 was poured over 15 ml of water, inducing a color change from purple to brown. The product was then extracted three times with dichloromethane, and the combined organic layers were washed three more times with water to get rid of any excess dimethylformamide. The organic solvent was removed under reduced pressure and dried. Thin layer chromatography and column chromatography were performed, used a solvent system of 100% dichloromethane, then 20% ethyl acetate in dichloromethane, then 1:1 ethyl acetate:dichloromethane, and then 3:4 ethyl acetate: dichloromethane until the product eluted (1.3329 g, 51%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.6345 (J = 1.5 Hz, H$_{Ar}$), 8.2385 (d, J = 8.7 Hz, H$_{Ar}$), 7.706 (d, J = 8.7 Hz, H$_{Ar}$), 7.015 (s, H$_{Ar}$).
Hz, $^1H^\text{Ar}$), 4.385 (t, $J = 4.5$ Hz, 4H), 3.821 (t, $J = 4.35$ Hz, 4H), 3.651-3.536 (multiplet, 24H), 3.362 (s, 6H).

Scheme 30. Synthesis of 2.5.

Preparation of 2.5: To a pressure flask was added 0.5 g 2.4 (0.486 mmol) and 0.37 g bis(pinacolato)diboron (1.46 mmol). Quickly was added 0.413 g (1.94 mmol) $K_3PO_4$, 0.00798 g SPhos (0.01944 mmol), and 0.0065 g Pd(OAc)$_2$ (0.00972 mmol) in that order. The pressure flask was evacuated and filled with nitrogen three times. 0.972 ml toluene and 0.1 ml water was added. The pressure flask was capped and the reacted was stirred at 110 °C for twenty four hours. 10 ml of water was added and the reaction mixture was extracted three times with dichloromethane. The organic layer was removed under reduced pressure and dried. Thin layer chromatography and column chromatography were performed with a solvent system of 3:1 ethyl acetate:dichloromethane was used. 2.5 was eluted off the column (193.4 mg, 42%).

$^1H$ NMR (300 MHz, CDCl$_3$): $\delta$ 9.206 (s, $H^\text{Ar}$), 8.321 (d, $J = 8.4$ Hz, $H^\text{Ar}$), 8.005 (d, $J = 8.7$ Hz, $H^\text{Ar}$), 4.411 (t, 4H), 3.857 (t, 4H), 3.682-3.539 (multiplet, 24H), 3.362 (s, 6H), 1.436 (s, 24H).
**Scheme 31. Synthesis of 2.6.**

Preparation of 2.6: To a 10 ml round bottom flask was added 160 mg 2.5 (1.899 mmol), 58.8 mg diethanolamine (0.570 mmol), and 2 ml diethylether. Diethyl ether was replaced as it evaporated over a period of twenty four hours. The reaction mixture was placed in 3 ml tetrahydrofuran and 3 ml 1 M HCl. The reaction was allowed to stir for three hours. The reaction was diluted with 20 ml water. The product was extracted twice with ethyl acetate. The combined organic layers were extracted two times with 2 NaOH pellets dissolved in 50 ml water. The basic extracts were acidified to pH 1 with 1 M HCl added dropwise. The acidic layers were extracted two times with ethyl acetate. The combined organic layers were washed once with brine, dried with magnesium sulfate, filtered, and dried. 2.6 was obtained (50.5 mg, 34%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.994 (s, H$_{Ar}$), 8.3555 (d, J = 8.1 Hz, H$_{Ar}$), 7.862 (d, J = 7.8 Hz, H$_{Ar}$), 4.867 (t, 4H), 4.426 (s, 4H, OH), 3.885 (t, 4H), 3.693-3.304 (multiplet, 30H).
Preparation of 2.6: A 100 ml Schlenk flask was flame dried and cooled. 809.3 mg of 2.4 (0.787 mmol) was mixed with a minimal amount of dry tetrahydrofuran and the mixture was transferred to the Schlenk flask. The THF was removed under reduced pressure and 2.4 was dried. The flask was evacuated and filled with nitrogen three times. 2.6 ml of dry tetrahydrofuran was added, and the flask was placed in a dewar containing dry ice and acetone (-78°C). 0.737 ml of n-butyllithium (1.18 mmol) was added dropwise. The reaction was allowed to stir for thirty minutes. 0.27 ml of triisopropyl borate (1.18 mmol) was added. The reaction was allowed to warm to room temperature overnight. The reaction placed in an ice bath, and to the reaction mixture was added 10% HCl(aq) until pH 2-3 was achieved. 7 ml water was added, and an extraction was carried out twice with ethyl acetate. The combined organic layers were washed with water, and then brine. The solvent in the combined organic layers was dried with magnesium sulfate and filtered. The solvent was removed under reduced pressure, and the product was dried (0.560 g, 104%).

*The 104% yield indicates the presence of excess solvent or an impurity, but column chromatography cannot be performed successfully on boronic acids because of their
tendency to self-condense. The $^1$H NMR chemical shift data is the same as the first route to 2.6.
The Hydrophobic Bis-Boronic Acid Methods

The preparation of 3.1 and 3.2 are identical to the preparation of 2.1 and 2.2, which is detailed in the previous section.

Scheme 33. Synthesis of 3.3.

Preparation of 3.3: The experimental methods are identical to those outlined in the preparation of 2.4, with the exception of 2.3 being replaced with dodecyl bromide. Thin layer chromatography and column chromatography was performed with 100% hexanes. 3.3 was eluted off the column (762.9 mg, 39%).

\[^1\text{H NMR}(300 \text{ MHz, CDCl}_{3})\): \(\delta\) 8.647 (s, \(\text{H}^{\text{Ar}}\)), 8.092 (d, \(J = 9.0 \text{ Hz, H}^{\text{Ar}}\)), 7.702 (d, \(J = 7.2 \text{ Hz, H}^{\text{Ar}}\)), 4.172 (t, \(J = 6.6 \text{ Hz, 4H}\)), 1.873 (q, \(J = 7.35 \text{ Hz, 4H}\)), 1.267 (multiplet, 36H), 0.879 (t, 6.9 Hz, 6H).
Scheme 34. Synthesis of 3.4.

Preparation of 3.4: A 100 ml Schlenk flask was flame dried and cooled. To the 100 ml Schlenk flask was added 300 mg 3.3 (0.42573 mmol). The flask was evacuated and filled with nitrogen three times. 1.5 ml of dry tetrahydrofuran was added, and the flask was placed in a dewar containing dry ice and acetone (-78°C). 0.53 ml of n-Butyllithium (0.85146 mmol) was added dropwise. The reaction was allowed to stir for thirty minutes. 0.2 ml of triisopropyl borate (0.85146 mmol) was added. The reaction was allowed to warm to room temperature overnight. The reaction placed in an ice bath, and to the reaction mixture was added 10% HCl\(_{(aq)}\) until pH 2-3 was achieved. 7 ml water was added, and an extraction was carried out twice with ethyl acetate. The combined organic layers were washed with water, and then brine. The solvent in the combined organic layers was dried with magnesium sulfate and filtered. The solvent was removed under reduced pressure, and the product was dried (0.2307 g, 85%).

A definitive \(^1\)H NMR spectrum could not be obtained in CDCl\(_3\) due to self-condensation of the bis-boronic acid (see Scheme 19).
Preparation of 4.1: To a round bottom flask was added 0.221 g aryl methyl ether (0.633 mmol). The flask was evacuated and filled with nitrogen three times. 10 ml of dry dichloromethane was added to the flask. The reaction flask was put into an ice bath. 0.36 ml boron tribromide (3.799 mmol) was added dropwise. The reaction was allowed to stir for three hours. The dichloromethane was removed under reduced pressure, and the product was extracted to times with ethyl acetate. The organic layers were dried with magnesium sulfate and filtered. The solvent in the combined organic layers was removed under reduced pressure, and the product was dried. Column chromatography was performed with 10% ethyl acetate in dichloromethane for one column volume, and then 100% ethyl acetate to collect the 4.1 product (0.182 g, 76%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.443 (q, J = 3 Hz, H$_{Ar}$), 8.376 (s, Ar-OH), 8.080 (s, H$_{Ar}$), 7.877 (s, H$_{Ar}$), 7.514 (q, J = 3.15 Hz, H$_{Ar}$).
References


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