Daisy Chain Ligands for the Control of Layering in Pillared Metal-Organic Frameworks

Joseph Nicolas Sbrocca

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Daisy Chain Ligands for the Control of Layering in

Pillared Metal-Organic Frameworks

By

Joseph Nicolas Sbrocca

A thesis

submitted to the Faculty of Graduate Studies
through the Department of Chemistry & Biochemistry
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Windsor, Ontario, Canada

2015

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Daisy Chain Ligands for the Control of Layering in Pillared Metal-Organic Frameworks

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February 13, 2015
Declaration of Co-authorship

The initial project design in Chapter 2 was developed by Dr. Stephen Loeb and Dr. Kelong Zhu. The synthetic experiments were designed by the author, with additional input provided by Dr. Stephen Loeb and Dr. Kelong Zhu.

All experiments and characterization of compounds were performed by the author, with the exception of the attempted MOF synthesis, which was performed by Dr. Kelong Zhu, as well as the elemental analysis and MALDI mass spectrometry experiments, which were conducted by Dr. Janeen Auld.

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Abstract

Mechanically interlocked molecules (MIMs) have been studied extensively in solution for their ability to function as molecular motors, machines, and molecular muscles. Unfortunately, these systems lack organization in solution and the motions exhibited are incoherent. This has stimulated interest for the concept of installing MIMs as ligands into Metal-Organic frameworks (MOFs) to improve the molecular organization and coherency of these systems.

The material presented in this thesis describes the synthesis of two benzimidazole-crown ether (24C6) based cyclic daisy chains for the first time, one of which has the potential, upon further functionalization to be used as a pillaring ligand to separate 2D-layers in pillared MOFs.

Chapter 1 provides insight of various types of MIMs, in particular, a review of daisy chain compounds that have been reported, as well as an introduction to MOFs and the scope of MIMs that have been used as linkers in MOFs.

Chapter 2 describes the full synthesis of two cyclic daisy chain dimers containing rigid benzimidazole cores and crown ether (24C6) host moieties, as well as attempted metal-organic framework synthesis. All attempted synthetic routes are described, along with the relevant characterization data.

Chapter 3 provides an outlook on the potential improvements that can be made to the system, as well as the future directions that can be taken with this new family of cyclic daisy chain dimers.
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Abbreviations

\(^1\)H NMR = Proton Nuclear Magnetic Resonance Spectroscopy
\(^{13}\)C NMR = Carbon Nuclear Magnetic Resonance Spectroscopy

[a2] = acyclic daisy chain dimer
BBr\(_3\) = Boron tribromide
br = broad
[c2] = cyclic daisy chain dimer
CDCl\(_3\) = deuterated chloroform
CHCl\(_3\) = chloroform
CD\(_3\)OD = deuterated methanol
CD\(_3\)CN = deuterated acetonitrile
°C = degrees Celsius
d = doublet
DCM = dichloromethane
DCD = [c2]daisy-chain
DCD-1 = 34
DCD-2 = 42
DCD2-TA = [c2]daisy-chain # containing tetra-acid moiety (45)
DMAP = Dimethyl aminopyridine
DME = dimethoxy ethane
DMF = dimethylformamide
DMSO = dimethylsulfoxide
DMSO-d\(_6\) = deuterated dimethylsulfoxide
δ = chemical shift
eq = equivalent
EtOAc = ethyl acetate
EtOH = ethanol
Et₂O = diethyl ether

g = grams

Hex = hexanes

HBF₄ = tetrafluoroboric acid

HNO₃ = nitric acid

H₂SO₄ = sulfuric acid

Hz = hertz

IR = infrared spectroscopy

J = coupling constant

K₂CO₃ = potassium carbonate

K = kelvin

m = multiplet

MALDI = matrix-assisted laser desorption/ionization

MeCN = acetonitrile

mg = milligram

mL = millilitre

MIM = mechanically interlocked molecule

MOF = metal-organic framework

Mp = melting point

MS = mass spectrometry

nBuLi = n-butyllithium

NEt₃ = triethylamine

NMR = nuclear magnetic resonance spectroscopy

ppm = parts per million

q = quartet

s = singlet

sбу = secondary binding unit
SSNMR = solid-state nuclear magnetic resonance spectroscopy

\[ t = \text{triplet} \]

THF = tetrahydrofuran
Chapter 1: Introduction

1.1. Introduction to Supramolecular Chemistry

For many years, chemists have exhibited the competence to synthesize a variety of complex molecules and examine their chemical and physical properties. A unique field, known as supramolecular chemistry, has enhanced the creativity of researchers by enabling the design of molecular systems containing multiple components held together by intermolecular forces, instead of strictly through covalent bonding.\(^1\) Defined by Jean-Marie Lehn as “chemistry beyond the molecule”, supramolecular chemistry is a multidisciplinary field, so it requires a broad range of knowledge in organic and inorganic chemistry for synthetic purposes, and physical chemistry to acquire information about the properties.\(^2\) The innovative discoveries by Lehn, Donald Cram, and Charles Pedersen resulted in the Nobel Prize in Chemistry in 1987.

By examining the complementarity in a number of biological systems, supramolecular chemists can generate ideas for the design of molecular architectures for host-guest systems. An example of a biological system of this nature is valinomycin, a naturally occurring, macrocyclic antibiotic, which can transport potassium across mitochondrial membranes.\(^3\) In this example, potassium ions (guest) are complexed by the electronegativity of the oxygen atoms in the valinomycin (host).

Due to the fact that the strength of non-covalent interactions are much weaker than covalent bonds, this enables non-covalent interactions to be used in promoting strong
and selective recognition of guest molecules. Some of the most common non-covalent interactions utilized to hold molecules together are electrostatic interactions, hydrogen bonding, π-π stacking, van der Waals forces, and hydrophobic effects.

1.2. Self-Assembly

The ability of linked or separated components to spontaneously form ordered aggregates is known as self-assembly, as described by George Whitesides. In terms of molecular self-assembly, the molecules may be the same or different and the interactions between the molecular components are typically non-covalent interactions. The success of molecular self-assembly is also determined by reversibility, the environment, as well as mobility. The concept has been extremely useful in chemistry, in particular, for synthetic methodologies, the formation of molecular crystals, and self-assembled monolayers.

1.3. Mechanically Interlocked Molecules

1.3.a. Rotaxanes and Pseudorotaxanes

Rotaxanes and pseudorotaxanes are compounds that are composed of an electron poor axle, typically termed as “the thread” or “guest” and an electro-rich macrocycle, which is commonly coined as “the wheel” or “host”. The difference between rotaxanes and pseudorotaxanes is that rotaxanes contain stopper groups at each end of the thread to prevent the wheel from dethreading, whereas pseudorotaxane threads do not possess stopper group on the thread component, they are simply reported as interpenetrated species and are in equilibrium. The nomenclature of these MIMs is quite trivial; the sum of the number of wheel and axle components is recorded prior to the name of the compound. An example of a [2]rotaxane is shown below in Figure 1.1:
One of the attractive features of rotaxanes is the versatile and efficient synthetic methods available to generate them. The most efficient preparation of these compounds occurs under template directed control with molecular recognition in place between the components involved. To date, the most common synthetic methods used are capping\textsuperscript{11,12}, clipping\textsuperscript{11,12}, slipping\textsuperscript{11,12}, and active template.\textsuperscript{11-12} Various methods are depicted in Figure 1.2.
A great deal of interest has been placed on studying the potential of [2]rotaxanes being developed into artificial molecular machines by altering the position and motion of various components.\textsuperscript{13-14} Solution studies involving rotation of the ring component have been performed, which include influencing rotation by inducing an electric field\textsuperscript{15}, as well...
as measuring relative rotation rates of [2]rotaxanes containing α-cyclodextrin derivatives.\textsuperscript{16}


Additional work has been reported involving [2]rotaxanes with multiple recognition sites acting a molecular shuttle in solution, hence exhibiting translational motion.\textsuperscript{17-18} The translational motion observed has been initiated using electrochemistry\textsuperscript{19}, as well as acid-base chemistry causing changes in fluorescence upon translation.\textsuperscript{20}

\textbf{1.3.b. Catenanes}

Catenanes are mechanically interlocked molecules consisting of two or more macrocyclic rings interlocked.\textsuperscript{1} In order for the rings to be separated, a covalent bond must be broken. Optimal synthesis of catenanes typically requires preorganized non-covalent interactions, along with a ring closing reaction.\textsuperscript{12} Catenanes abide by the same naming system as rotaxanes, where the number listed in the name represents the number of components present, in this case rings.\textsuperscript{12}
Cases have been reported that involve catenanes acting as molecular rotors in solution, which involves a large parent ring containing multiple binding sites and a smaller ring rotating between multiple binding sites on the large parent ring.\textsuperscript{21-22} An example by Leigh is shown in Figure 1.5.

Figure 1.5: Movement of a macrocycle between three different binding sites in [2]catenane promoted by an external stimulus. Reproduced from Ref. 21.
1.3.c Daisy Chains

The term “daisy chain” is commonly defined as a string of daisies (the flowers) linked by stems to form a chain. For the purpose of supramolecular assemblies, the term was introduced by Stoddart, to describe a unique class of mechanically interlocked macromolecules that have the potential to exhibit switching on a molecular scale, as well as elongation capabilities. Structurally, Daisy Chains are composed of a sequence of identical molecules that contain an axle (guest) and a macrocycle (host) that are covalently bound. An early synthetic approach involved the use of a self-complementary monomeric species that had the ability to oligomerize or polymerize through non-covalent interactions in solution. Specific design requirements of the monomeric species need to be set in place in order to promote intermolecular recognition between the complimentary sites and prevent the possibility of self-complexation, which would proceed in an intramolecular fashion.

Figure 1.6: The concept of naming Daisy Chains is presented, illustrating that the number present in the name refers to the number of monomeric units present in the structure. The “a” stands for “acyclic” and the “c” stands for “cyclic”. Reprinted with permission from S.J. Cantrill, G.J Gilmer, J.F. Stoddart, J. Org. Chem. 2001, 66, 6857-6872. Copyright 2001, American Chemical Society.
The generated Daisy Chain monomeric species has the ability to self-assemble into a long acyclic oligomer\textsuperscript{25,27,28,29} or a cyclic structure.\textsuperscript{25,30,31} [c2]Daisy-chains are more thermodynamically stable in comparison to the acyclic species.\textsuperscript{23,25} The formation of long acyclic species is entropically unfavourable and can only be obtained using high monomer concentrations\textsuperscript{29} and strong binding affinities.\textsuperscript{24} Examples are shown in Figure 1.6.

In the early 1980’s, Fujita and coworkers studied the formation of cyclodextrin based Daisy Chains by substituting \(\beta\)-cyclodextrin with a tert-butylthiol group.\textsuperscript{32} By using high concentrations, the hydrophobic tert-butyl group became interpenetrated in the hydrophobic cavity of the macrocycle to generate linear acyclic daisy chain arrays.\textsuperscript{32} This initiated other studies to be performed utilizing the binding of hydrophobic aromatic groups to cyclodextrin to produce a variety of Daisy Chains.\textsuperscript{33-34}

![Figure 1.7](image_url) A linear, cyclodextrin based acyclic daisy chain. Reproduced from Ref. 24.

Kaneda \textit{et al.} developed a mechanically interlocked cyclic dimeric daisy chain through self-aggregation of a cyclodextrin based plerotopic monomer to generate a \([c2]\)daisy-chain and then adding 2-naphthol-3,6-disulfonic acid stopper groups to prevent deaggregation.\textsuperscript{35} This is shown in Figure 1.8.
Figure 1.8: The synthesis of a cyclodextrin based [c2]daisy-chain is presented. The synthesis proceeds through self aggregation, followed by stoppering to prevent deaggregation. Reproduced from Ref. 24.

Stoddart 36, Huang 37, and Ogashi 38 have prepared long acyclic Daisy Chains using monofunctionalized pillar[5]arenes utilizing the presence of a π-electron rich cavity that can act as a suitable host for electron poor guests, such as viologens. 36 The general trend observed for cyclodextrin based Daisy chains is that by functionalizing the 6-position, which is the smaller opening of the cavity, exclusively [c2]daisy-chains are formed. 24 Cyclodextrins decorated at the 3-position, which is the larger opening of the cavity, have been shown to lead to oligomerization and the formation of acyclic daisy chains when accompanied by a rigid guest component. 24

Crown ether based Daisy chain systems were first studied by Stoddart in 1998 using an ammonium based thread and a dibenzo[24]crown-8 (DB24C8) macrocycle in the
heteroditopic monomer. The presence of π-π stacking between host catechol moieties favoured the formation of daisy chain dimers.

Figure 1.9: A crown ether based daisy chain monomer that exhibits an aggregation number of 2 in solution.

By converting the thread to viologen paraquats, hence increasing the length, acyclic oligomers spanning from one to five monomeric units were formed (Figure 1.10). Gibson et al. discovered that by increasing the size of the macrocyclic cavity from DB24C8 to DB32C10 and using a rigid viologen thread, acyclic oligomers up to fifty monomeric units were formed.

Figure 1.10: A crown ether based daisy chain that exhibits an aggregation number ranging from 1–4 in solution, due to its longer thread portion invoking more flexibility.

The development of surrogate stoppered rotaxanes with t-butyl stoppers enabled the synthesis of [c2]daisy-chains at low concentrations and acyclic oligomers at higher concentrations. Synthetic methods such as “threading followed by swelling” and
anion-templating approaches followed by ring closing metathesis have invoked the production of mechanically interlocked [c2]daisy-chains.\textsuperscript{42-43}

![Diagram of synthesis of a [c2]daisy-chain using anion-templated ring closing metathesis method.]

**Figure 1.11:** Synthesis of a [c2]daisy-chain using and anion-templated ring closing metathesis method.

In comparison to cyclodextrin based daisy chains, deciphering the favourability behind the formation of cyclic or acyclic crown ether based Daisy chains is more complex.\textsuperscript{24} Typically, the formation of [c2]daisy-chains is observed with “threading followed by swelling” and anion template ring closing metathesis. Longer, more flexible threads may lead to self-complexed monomers.\textsuperscript{42} The studies behind the self-assembly of hermaphroditic crown ethers suggest that smaller macrocycles, lower solution concentrations, and lower temperatures favour the formation of [c2]daisy-chains, whereas larger macrocycles, higher concentrations, and higher temperatures favour the formation of acyclic oligomers.\textsuperscript{24} Characterization and differentiation between cyclic and acyclic
daisy chains is achieved through $^1$H NMR spectroscopy, mass spectrometry, as well as 2D $^1$H NMR spectroscopy.$^{23-24}$

**Molecular Muscles**

A [2]rotaxane that is pH dependent and contains multiple binding sites on the thread can act as a molecular shuttle exhibiting translational motion of the ring between recognition sites.$^{44}$ The same concept has been applied to daisy chains by developing threads with multiple binding sites and by applying an external chemical$^{45}$, electrochemical$^{46}$, or photochemical input$^{47}$; expansion and contraction motion can be generated mimicking an artificial muscle. Jean-Pierre Sauvage was the first to develop bistable daisy chain systems that portrayed extension and contraction properties, which involved a [c2]daisy-chain expanding and contracting with the exchange of coordinating ions.$^{48-50}$

Stoddart and coworkers were able to design an acid-base controllable [c2]daisy-chain by threading two heteroditopic monomers through each other and adding stopper groups to not only prevent dethreading of the macrocycles, but also to incorporate an additional binding site on each thread.$^{45}$ The linear [c2]daisy-chain fragment obtains maximum length in the extended state under acidic conditions, but becomes contracted upon deprotonation of the anilinium recognition site as the macrocycles move to the secondary pyridyl recognition site.$^{45}$ Further addition of acid promotes the reversibility back to the extended state.$^{45}$ This is illustrated in Figure 1.12.
Figure 1.12: Diagram displaying the extension and contraction states of a bistable [c2]daisy-chain under acid-base control. This system is often described as a molecular muscle. Reproduced from Ref. 45.

Grubbs was able to synthesize a [c2]daisy-chain employing the clipping method, which exhibited an impressive 48% increase in length by acylating the ammonium binding site (Figure 1.13) to enhance the steric bulk and force the crown to slip and hence increase the length.\(^{51}\)

Although the dynamics of rotaxanes, catenanes, and daisy chains have been studied as artificial molecular switches\(^{52}\), machines\(^{53}\), and muscles\(^{49}\) respectively, almost all of the reported systems have been analyzed in solution. The downside to this approach is the minimal organization in solution because the molecular devices are randomly dispersed and the motion is incoherent.\(^{54-55}\) This has stimulated interest in constructing metal-organic frameworks containing mechanically interlocked linkers to produce superior coherency and molecular organization.\(^{56}\)
1.4. Metal Organic Frameworks

1.4.a. Introduction

Metal-organic frameworks (MOFs) are robust crystalline materials composed of inorganic and organic linking units.\(^{57}\) The synthesis of MOFs involves combining metal containing secondary binding units (SBU’s) with organic linkers through reticular synthesis that will retain permanent porosity.\(^{58}\) Research involving MOFs has advanced in recent years due to the variety of SBU’s and organic linkers that can be used for synthesis\(^ {59}\), as well as the suitable attributes exhibited for applications such as high surface area\(^ {60}\), hydrogen storage\(^ {61}\), gas separation\(^ {62}\), and catalysis.\(^ {63}\)

The use of SBU’s promoting the production of directional, and thus rigid frameworks was first discovered by Yaghi and coworkers through the synthesis of MOF-2\(^ {64}\) and MOF-5.\(^ {65}\) The synthesis of MOF-2 and MOF-5 proved to be a blueprint for deriving reaction conditions that produce an SBU with predicted geometry \textit{in situ} and the generation of a pre-determined network using rigid organic linkers.\(^ {58}\)
Figure 1.14: The structure of MOF-5 is displayed with ZnO₄ tetrahedra and benzene dicarboxylate linkers. The yellow sphere represents the volume. Reproduced from Ref. 58.

1.4.b. Pillared Metal-Organic Frameworks

A family of MOF’s that has been extensively studied over the past decade is pillared-layered frameworks of the type [M₂L₂P]ₙ, where M is a metal, typically cobalt, nickel, copper, or zinc, L is a dicarboxylate linker, and P is a neutral pillar. The MOF structures obtained under these conditions include 2D-square grids, which contain M₂L₂ paddlewheel building units that are connected in the third dimension by a pillar. An example is shown in Figure 1.15.
An interesting characteristic of pillared MOFs that has been reported is the ability to exhibit a “shrinking and breathing” process\textsuperscript{66}, in which guest molecules are reversibly exchanged into and out of the layer spacings. When guest molecules are introduced into the cell, full extension of the pillars is observed, whereas once the guests are evacuated under an external stimulus, the pillars condense, causing the shrinkage of the architecture.
Kitagawa and co-workers first tested the flexibility of these systems using guests such as methane, methanol, and water.\textsuperscript{67} Other examples include the high breathing effect in chromium based, pillared MOFs\textsuperscript{68}, as well as the reversibility between large and narrow pore transitions upon adsorption and desorption of methanol (Figure 1.17).\textsuperscript{69-71}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure17.png}
\caption{Starting from the left, upon removal of DMF, the large pore (lp) shrinks to form a narrow pore (np). Upon addition of DMF, the narrow pore expands back to the large pore (lp). Reprinted with permission from S. Henke, A. Schneemann, A. Wutscher, R.A. Fischer, \textit{J. Am. Chem. Soc.}, 2012, 134, 9464-9474. Copyright 2012, American Chemical Society.}
\end{figure}

\textbf{1.4.c. Mechanically Interlocked Molecules in Metal-Organic Frameworks}

As was previously mentioned, solution studies have been performed on mechanically interlocked molecules, but in this phase, the molecules are dispersed and incoherent.\textsuperscript{56} A number of examples have been reported in which pseudorotaxanes have been used to generate coordination polymers of 1, 2, and 3-periodic crystalline lattices\textsuperscript{72},\textsuperscript{73}, but none of these exhibited the dynamics of the MIM component in the solid-state.

For the first time, the Loeb research group showed the ability to use a [2]rotaxane as a linker in a MOF and to observe rotational motion of the ring upon activation of the material.\textsuperscript{56}
Additional studies have included incorporating an aniline based [2]-rotaxane as a pillar into a MOF, which revealed the ability to turn rotation of the wheel ON and OFF and reversibly change phases upon removal of the solvent and resolvation.\(^\text{74}\) This is possible due to the fact that prior to activation, the macrocyclic ring is trapped in the centre of the framework, thereby hindering rotation. Subsequently, once a thermal external stimulus is applied, guest molecules are evacuated from the framework generating, a change in layer spacing, freeing up the macrocycle to undergo rotational motion, which is characterized using \(^2\text{H}\) solid-state NMR (SSNMR). Further addition of solvent reverses the layer spacing back to the original framework leaving the macrocycle once again hindered in the framework. This can be observed in \textbf{Figure 1.19}.
Figure 1.19: Illustrated is the reversible conversion between the as synthesized form (left) of a [2]rotaxane pillared MOF and the structure obtained following desolvation (right), which releases the macrocycle into free volume to exhibit dynamic motion. Reprinted with permission from K. Zhu, V.N. Vukotic, C.A. O’keefe, R.W. Schurko, S.J. Loeb, J. Am. Chem. Soc., 2014, 136, 7403-7409. Copyright 2014, American Chemical Society.

A [2]catenane was first incorporated into a MOF when Stoddart and coworkers generated MOF-1011 by linking a bis-carboxylate strut to a trigonal Cu(I) unit. A 2D arrangement with sq1 topology was obtained75, but no attempts were made to observe rotational dynamics or switching.
**Figure 1.20:** A). Depiction of MOF-1011 layered structure with [2]catenanes bonded to the backbones of the grid. B). Displays a view down the b-axis between two layers and expressing the proximity of the catenanes in each layer. Reproduced from Ref. 75.

The synthesis of MOF-1030 was accomplished by extending the struts used in MOF-1011 with acetylene units, which resulted in the generation of MOF-1030 as a three-dimensional structure with nbo topology.\textsuperscript{76}
Unfortunately a complication was encountered during the synthesis of MOF-1030 due to \( \eta^2 \) binding of Cu(I) ions to the triple bonds of the acetylene units. This was overcome in the synthesis of MOF-1050 and MOF-1051 by lengthening the struts to heptaphenylene moieties. Copper-paddle-wheel based MOF-1050 and MOF-1051 formed 2D sheets held together by the acceptor and donor properties (Figure 1.22) of the [2]catenane linkers to form interpenetrated 3D architectures.
Investigations are still ongoing to determine whether MOFs containing catenane linkers can exhibit switchable motion in the solid-state. These studies provide insight into potentially incorporating daisy chain linkers into metal-organic frameworks, as a class of mechanically interlocked molecules that has not been explored to date.

1.5. Scope of Thesis

This thesis describes the synthesis of two benzimidazole-crown ether based (24C6) cyclic daisy chain dimers for the first time. Upon further functionality of DCD-1 (34) to Target 1, this has the potential to be used as a soft, yet rigid pillar in pillared metal-organic frameworks, which provides insight into the possible control of MOF layer spacing. The unique feature of DCD2-TA (45) also exhibits the characteristics to act as a soft, rigid MIM. The difference is that it provides a promising opportunity to produce a metal-organic framework in which all of the linkers contained are DCD2-TA (45). This initiates the potential to synthesize a family of cyclic daisy chain linkers that can be used for MOF synthesis.
The work presented in Chapter 2 encompasses the complete synthesis and characterization of DCD-1 (34) and DCD2-TA (45), as well as attempted MOF synthesis with DCD2-TA (45). Critical identification of both DCD-1 (34) and DCD2-TA (45) was required in order to determine whether a daisy chain monomer, acyclic dimer, or cyclic dimer was obtained. This was accomplished primarily through the use of NMR spectroscopy experiments, as well as Matrix-assisted Laser Desorption/Ionization mass spectrometry.

Chapter 3 proposes suitable solutions to improve the results obtained in chapter 2, as well as an outlook on additional benzimidazole-crown ether based daisy chains that can be synthesized and the potential of using the daisy chains as linkers to produce flexible metal-organic frameworks.
Chapter 2: Synthesis of Benzimidazole-Crown Ether (24C6) based

[c2]daisy-chain dimers

2.1. Introduction

Chemists have synthesized and characterized a variety of mechanically interlocked molecules (MIMS) such as rotaxanes\textsuperscript{20}, catenanes\textsuperscript{14}, and molecular knots.\textsuperscript{1} The fascinating aspect of mechanically interlocked molecules has been the potential use as molecular machines. In particular, a number of solution studies have been performed which involve the observance of translational and rotational motion in rotaxanes, and rotational motion catenanes. Daisy chains\textsuperscript{26} are another example of mechanically interlocked molecules that have been shown in solution to behave as molecular muscles, thereby exhibiting expansion and contraction properties.

The majority of these solution studies are quite interesting, but the problem that arises is that there is minimal organization in solution, so the molecular subunits are randomly dispersed, and the motion is incoherent. This has stimulated interest into placing MIMs into metal-organic frameworks (MOFs) as ligands in order to improve coherency and molecular organization of these systems.

A variety of Metal Organic frameworks have been synthesized over the years, in particular, some include utilizing ligands as pillars to separate 2D layers in the framework, therefore making a 3D network.\textsuperscript{66} Various ligands used as pillars have been shown to express flexibility upon removal of solvent from the framework.\textsuperscript{103} [2]Rotaxanes as the pillaring ligands\textsuperscript{74} in MOFs is known, but a case of incorporating daisy chain linkers in MOFs has not yet been reported. This resulted in the idea of
attempting to synthesize a rigid Daisy Chain linker that when neutral, could act as a soft, flexible, pillared linker between two layers in a Zn\textsuperscript{II} MOF.

The material presented in this chapter includes the full synthesis of the first benzimidazole-crown ether (24C6) based \([c2]\)daisy-chain (33 or DCD-1). This was accomplished by performing a double ring-closing metathesis (RCM) reaction using Grubb’s I catalyst, however low yields of the dimeric species were obtained. Both the \([c2]\)daisy-chain and the monomeric byproduct were characterized using various NMR spectroscopic techniques, as well as Matrix Assisted Laser Desorption-Ionization (MALDI) mass spectrometry. Upon further functionalization, this ligand has the potential to be used as a pillar in layered zinc MOFs.

![Chemical Structure of DCD-1](image)

In addition, another benzimidazole-crown ether (24C6) based \([c2]\)daisy-chain (45 or DCD2-TA) was synthesized using a double RCM reaction, followed by hydrogenation and hydrolysis. DCD2-TA contains isophthalic stopper groups and the yields obtained for
the RCM reaction were significantly higher than those for DCD-1 due to an improved template. Both the [c2]daisy-chain and the monomeric byproduct were characterized using various NMR spectroscopic techniques, as well as MALDI mass spectrometry. An attempt was made to synthesize a MOF containing copper paddlewheel nodes and DCD2-TA linkers, but unfortunately the solubility of DCD2-TA proved to be an issue. Further measures need to be taken to improve the solubility of DCD2-TA.

![Image of DCD2-TA structure](image-url)

45

DCD2-TA
2.2.a. Discussion and Analysis of Synthetic Strategy #1 for DCD-1 precursor (29)

Figure 2.1: Retrosynthetic Scheme #1 for the synthesis of the DCD-1 Precursor (29).
The retrosynthetic scheme in Figure 2.1 provides a layout of the first design for the synthesis of the DCD-1 (29) precursor. In order to obtain 29, compounds 28 and 8 needed to be synthesized.

Figure 2.2: Reaction Scheme for the synthesis of 8.

The synthesis of 8 was accomplished by first brominating 3, 5-dimethylaniline 5 with NBS to produce compound 6. Purification protocol involved recrystallizing 6 from hexanes to obtain a pure product in 80% yield. The $^1$H NMR data obtained for 6 was in direct correlation to literature reports. 6 was subsequently submitted to a Sandmeyer reaction in order to convert the amino functional group to an iodo group. Compound 7 was purified using column chromatography to produce yields greater than 90%.

Successful synthesis of the product was confirmed through $^1$H NMR data corresponding with literature values. The synthesis of compound 8 was promoted by performing a lithium halogen exchange reaction on 7. Yields obtained for this particular reaction were only 60% following purification with column chromatography. These moderate yields can be explained by the existence of two exchange sites in the starting material 7; it is possible that an exchange occurred at both the bromo and iodo sites of compound 7. The $^1$H NMR data for compound 8 indicated that the product was clean and identical to that previously reported. The complete reaction scheme is displayed in Figure 2.2.
Following the successful synthesis of the aldehyde 8, experiments were conducted in order to arrive at compound 28, which would enable the synthesis of the DC-1 precursor via a condensation reaction.

![Reaction Scheme](image)

**Figure 2.3**: Reaction Scheme #1 for the synthesis of 28.

As shown in **Figure 3**, veratrole 1 was nitrated to produce dintroveratrole 2 with a yield of 82%. The synthesis was confirmed with $^1$H NMR data. The following step involved the demethylation of compound 2 in order to generate a suitable compound for a nucleophilic substitution reaction. The demethylation was attempted using two different methods: one involving deprotection with hydrobromic acid at temperatures exceeding
150°C, with a percent yield of 50%, the other protocol utilizing boron tribromide as a de-
protecting reagent, resulted in a yield of 60%. The product 3, was characterized with \(^1\)H NMR\textsuperscript{82} spectroscopy, which clearly showed the absence of the methoxy groups present in 2.

An S\(_{N2}\) reaction was performed with 3 and 4 utilizing K\(_2\)CO\(_3\) to deprotonate the hydroxy groups of dinitrocatechol 3 and initiate attack of the electrophilic carbon adjacent to the chlorine in 4. Unfortunately, it was confirmed by analyzing \(^1\)H NMR data that no reaction occurred since only starting materials were observed in the spectrum. Although unsuccessful, additional attempts were made using increased reaction times and equivalents of 4. Potential explanations for the issue behind this lack of reactivity included the fact that chlorine may be too poor of a leaving group, or it could have been that the nitro groups present on the catechol may have been too strong as deactivating groups, thereby weakening the nucleophilic character of the hydroxy anions. Therefore, an alternative approach was derived to test whether chlorine was in fact too poor of a leaving group.
2.2.b. Discussion and Analysis of Synthetic strategy #2 for DCD-1 precursor (29)

Figure 2.4: Retrosynthetic Scheme #2 for the synthesis of DCD-1 precursor 29.
The modification made to improve the synthetic protocol for 28 involved installing a methyl-sulfonyl protecting group on 11 to give 12. The methane sulfonyl leaving group in 12 is a better leaving group than chlorine in 4 and a similar procedure had been performed by the Grubb’s research group in the past.\textsuperscript{51}

\textbf{Figure 2.5}: Reaction Scheme #2 for the synthesis of 28.

As exhibited in Figure 2.5, compound 12 was synthesized over two steps, first requiring a nucleophilic substitution between 9 and 10. The product 11 was purified using column chromatography to give a 77% yield and characterized using \textsuperscript{1}H NMR spectroscopy, which indicated accurate values in comparison to literature reports.\textsuperscript{51} The alcohol 11 was then protected with a mesityl group to give compound 12 in 93% yield following purification by column chromatograph. This was confirmed by observing the sharp singlet for the methyl protons in the mesityl protecting group in the \textsuperscript{1}H NMR spectrum.\textsuperscript{51} At this point, compound 12 was suitable for use in a nucleophilic substitution.
reaction with dinitrocatechol 3. After employing the same reactions conditions that were used between 3 and 4 in Figure 2.3, once again, no reaction was observed as verified through $^1$H NMR spectroscopy. Therefore, since the reaction still did not proceed after improving the leaving group, a conclusion can be drawn suggesting that the nitro groups located meta to the hydroxy groups in dinitrocatechol 3 were too strong as deactivating groups, which hindered the nucleophilic strength of the hydroxyl anions. This resulted in the pursuit of another synthetic pathway developed for the synthesis of 28, which was to incorporate the alkoxy chains prior to the nitro groups on the aromatic ring.
2.2.c. Discussion and Analysis of Synthetic strategy #3 for DCD-1 precursor (29)

Figure 2.6: Retrosynthetic Scheme #3 for the synthesis of DCD-1 precursor 29.
Figure 2.7: Reaction Scheme #3 for the Synthesis of 28.

As the layout in Figure 2.7 suggests, the new synthetic strategy first involved protecting the alcohol 4 with an acetyl group. The product 14 was characterized using $^1$H NMR which clearly displayed the methyl protons corresponding to the acetyl group. By then taking catechol 15, a nucleophilic substitution was executed with 14 to produce compound 16, which was purified using column chromatography and characterized with $^1$H NMR. The next step required a nitration of 16, which produced 17, which was also purified using column chromatography and confirmed with proton NMR. The acetyl protecting groups were then removed using K$_2$CO$_3$ to give compound 18, for which the $^1$H NMR spectrum indicated the complete elimination of the acetyl protecting groups. An S$_N$2 reaction between 18 and 9 was first attempted using sodium hydride as a base. Only mild H$_2$ gas evolution was observed, and following the addition of 9, both TLC analysis and $^1$H NMR data were collected periodically, which indicated that the reaction
was not progressing. Upon using alternative bases\textsuperscript{85}, as well as incorporating phase transfer catalysts\textsuperscript{86}, there was still not reaction progress. Upon increasing the temperature, colour changes were observed in 18, along with changes in the “crown ether” region of the $^1$H NMR spectrum, which lead to the possibility that 18 may have decomposed.\textsuperscript{84} At room temperature, other than the possibility of moisture present in the reaction vessel and water acting as a nucleophile, no viable explanation is available as to why the reaction was not successful.
2.2.d. Discussion and Analysis of Synthetic strategy #4 for DCD-1 precursor (29)

Figure 2.8: Retrosynthetic Scheme #4 for the synthesis of DCD-1 Precursor 29.
Following a literature review, it was discovered that Jonathan Nitschke and coworkers at the University of Cambridge had very recently synthesized conjugated metal-organic polymers containing long alkyl chains\textsuperscript{87}. Upon reviewing the ligand synthesis, the alkoxy chains were added via a unique substitution reaction as shown in Figure 2.9.

![Figure 2.9: Synthetic method utilized by Nitschke to synthesize JN.](image)

Although both yields in the described reactions were reported to be understandably low, 38\% and 22\% respectively, this synthetic process was much more efficient in terms of atom economy than the previous attempts, which resulted in the work of Nitschke inspiring the development of the retrosynthetic scheme presented in Figure 2.8.
As displayed in Figure 2.10, 1,2-difluorobenzene 19 was nitrated to produce 20 in 35% yield. The successful formation was confirmed through $^1$H NMR spectroscopy and compared well with the data reported by Nitschke. The resulting compound 20 was used in an S_N2 reaction with the previously synthesized alcohol 11. The outcome was the production of both mono and disubstituted alkylation products, which were separated via column chromatography to give 21 for the first time with a yield of 33%. This synthesis was confirmed primarily using $^1$H NMR, which is shown in Figure 2.11. Once optimized, this turned out to be an excellent approach to synthesizing the 21, as this scheme is more efficient than the first three described in Figure 2.3, Figure 2.5, and Figure 2.7.
The next step involved determining a method to not only reduce the nitro functional groups to amino groups, but at the same time, prevent the reduction of the double bonds present on the alkoxy chains in 21. A commonly reported method is the use of tin chloride dihydrate reagents, which promote the reduction of nitro groups to amines, while leaving other susceptible reduction candidates such as alkenes in present.
functionality. Unfortunately, the results obtained using tin chloride dihydrate were unsuccessful, with the observation being only partial reduction of the nitro group, even after increasing the amount of tin chloride dihydrate. Attempts were also made with different solvents such as methanol and ethanol, as well as increasing reaction times and temperatures, but to not avail. Additional trials were attempted using reducing agents such as zinc$^{89}$, iron$^{90-91}$, and sodium sulfide$^{92}$, all of which generated no reduction. A promising reduction method was the use of hydrazine and a palladium on carbon catalyst.$^{93}$ The reaction with 21 resulted in the reduction of both the nitro groups and the alkenes to give 28B, which brought about another issue to work around. Adjustments were made to the solvent, such as using THF instead of ethanol and monitoring the progress of the reaction in ten minute intervals using $^1$H NMR. Unfortunately, the reduction occurred too rapidly to distinguish an optimal point under these conditions to successfully reduce the nitro groups in 21 and leave the alkenes untouched. The reduction of the alkenes can be observed in Figure 2.12, where the two multiplets typically present between 4.80 ppm and 5.90 ppm have vanished. The singlet at approximately 6.30 ppm is indicative of the more shielded aromatic protons due to the presence of the amino groups in comparison to the aromatic protons in 21.
Figure 2.12: $^1$H NMR spectrum of 28B displaying the reduction of alkenes present in 28. (See experimental section: Synthesis of 28B for complete labeling of $^1$H NMR spectrum).

In order to resolve this issue, a different avenue was taken. The new retrosynthetic presented in Figure 2.13 suggested synthesizing a benzimidazole, followed by attachment of the alkoxy groups via an $S_N2$ reaction. In order to prevent alkylation onto the nitrogen atoms of the imidazole, Boc protecting groups would be installed to prevent this from occurring.
2.2.e. Discussion and Analysis of Synthetic strategy #5 for DCD-1 precursor (29)

Figure 2.13: Retrosynthetic Scheme #5 for the synthesis of DCD-1 precursor 29.
Compound 2 had been synthesized in previous experiments, so the nitro groups were reduced using an already familiar method with hydrazine and palladium on carbon to give quantitative yields of 22, with the purity being confirmed by $^1$H NMR spectroscopy. The next step involved the dehydration reaction between 22 and the previously synthesized aldehyde 8, which was catalyzed by zirconium tetrachloride to give the benzimidazole 27. Compound 27 was obtained in 60% yield and purified using column chromatography. The moderate yield can be attributed to the additional formation of 27B due to a double dehydration reaction, which is shown in Figure 2.15.
The benzylic protons from 27B were clearly identified in a \(^1\)H NMR spectrum displaying the mixture of 27 and 27B. As shown in Figure 2.14, experiments continued with the demethylation of 27 with boron tribromide, but unfortunately the reaction was unsuccessful due to poor solubility of 27 in chloroform at -78°C. In order to accommodate for the solubility issue, the reaction was attempted at 0°C in chloroform with boron tribromide, but precipitation of 27 was still observed upon cooling. The same reaction conditions were also attempted using THF, but solubility still remained as an issue. Alternative protocols used for demethylation reactions such as hydrobromic acid\(^{95}\) under harsh reaction conditions were also attempted, but brought about no success.
2.2.f. Discussion and Analysis of Synthetic strategy #6 for DCD-1 precursor (29)

Figure 2.16: Retrosynthetic Scheme #6 for the synthesis of DCD-1 precursor 29.
As shown in Figure 2.16, an additional retrosynthetic scheme was devised, which entailed forming a benzothiadiazole moiety with the alkoxy chains intact and performing a sulfur extrusion reaction on the thiadiazole to obtain the desired compound 28. The reasoning behind using the sulfur extrusion reaction was because it is commonly used in the Loeb research group for the synthesis of benzimidazole based [2]rotaxanes and bisbenzimidazole based [2]rotaxanes. This procedure involves decorating a benzothiadiazole substrate with the required functionality, followed by performing a sulfur extrusion reaction to generate a diamino substrate suitable for a dehydration reaction. An example is shown in Figure 2.17.

![Figure 2.17: Sulfur extrusion reaction carried out with sodium borohydride (R = H, Ph).](image-url)
Compound 22 was used as the starting substrate with thionyl chloride to produce a benzothiadiazole 23 in 77% yield. The purity of the product was confirmed with $^1$H NMR spectroscopy and compared to reported literature values. A demethylation reaction was then performed using hydrobromic acid and temperatures exceeding 150°C to produce 24 with a yield of 68%. The product was characterized using $^1$H NMR spectroscopy. The key distinguishing factor between the product 24 and starting material 23 was the disappearance of the protons from the methoxy groups. The alcohol 11, which had been previously synthesized, was protected with a tosyl group to give 25, which would serve as a good leaving group for the subsequent S$_N$2 reaction.

The process was continued as displayed in Figure 2.18, by performing an S$_N$2 reaction with 24 and 11, which produced 26 in 65% yield. The moderate yield can be
attributed to the mixture of mono and disubstituted products, which were separated using column chromatography. The most useful characterization technique to confirm the isolation of the disubstituted product was proton NMR due to the sharp singlet observed in the aromatic region in Figure 2.19, whereas the mono-substituted product would have consisted of two separate singlets in the aromatic region in addition to lower integration values corresponding to the protons from the alkoxy chains. This also provided more supporting information as to why the substitution reactions in Schemes 1 and 2 were unsuccessful because in comparison, the electronics in 24 provided an activating nature, whereas the electronics in 3 had a strong deactivating effect on the aromatic species due to the presence of the nitro groups. The presence of an activating substituent enabled the SN2 reaction to take place. A sulfur extrusion reaction was then performed to finally produce the diamino substrate 28 with a yield of 85%. The primary distinction used to determine the conversion of the nitro groups to the amino groups was the upfield shift of the aromatic protons due the additional shielding that was provided by the amino functional groups. This can be viewed in Figure 2.20.
The impressive success of reaction scheme #5 (Figure 2.18) provided the necessary diamino 28 for a dehydration reaction with 8 to generate the desired DCD-1 precursor. However, Scheme #5 (Figure 2.18), requires 8 synthetic steps to achieve 28, which is not very efficient. While experiments were being conducted using the strategy presented in reaction scheme #5 (Figure 2.18), an idea was developed that lead to the
successful synthesis of 28 using reaction scheme #4 (Figure 2.10), which requires only 4 synthetic steps to reach 28.

As previously mentioned, the bottleneck lying in reaction scheme #4 (Figure 2.10) was the challenge of reducing the nitro groups to amino groups, while keeping the double bonds present in the alkoxy chains. By further considering the mechanism
involved in the reduction of nitro compounds to amino compounds\textsuperscript{81} with the use of tin, acid, and a polar solvent, experiments were conducted to find the optimal point for sole reduction of the nitro groups. This innovative strategy was tested using tin powder and hydrochloric acid and can essentially be viewed as achieving the required reduction conditions \textit{in situ}.

![Figure 2.21: Nitro-reduction reaction using tin and hydrochloric acid.](image)

In order to discover the optimal reaction conditions to satisfy the hypothesis, it was decided to start with excessive amounts of hydrochloric acid and slowly decrease the equivalents of acid added, while keeping the equivalents of tin powder constant. The reaction conditions are displayed in Figure 2.21.

![Figure 2.22: Production of 28B using 30 eq of HCl and 12 eq of tin powder.](image)
The first experiment involved using 30 equivalents of hydrochloric acid and 12 equivalents of tin, which resulted in the reduction of 21 to 28B (Figure 2.22), indicating that both the nitro functional groups and alkenes were reduced. The equivalents of hydrochloric acid were continuously decreased until the optimum point of 10 equivalents of hydrochloric acid was reached, along with 12 equivalents of tin, and a large excess of methanol. This gave the reduction of 21 to 28 in quantitative yields and no reduction of the double bonds was observed in the $^1$H NMR spectrum, as displayed in Figure 2.20. None of the starting material 21 was present in the proton NMR spectrum either as the aromatic singlet had shifted upfield, as expected. The development of these optimized reaction conditions provided a simple experimental setup that could be used in the future to test the reduction capabilities on other substrates containing nitro and alkene functional groups.

Due to the shorter synthetic path in reaction scheme #4 (Figure 2.10), this was used to proceed to the synthesis of the DCD-1 precursor.
The same synthetic protocol was used for the dehydration reaction between 28 and 8 as was used for the synthesis of 27, which involves using a zirconium tetrachloride catalyst. The optimized yield obtained for the tautomeric mixture of 29 under these conditions was 38%. The low yield is due to the occurrence of a double dehydration reaction, resulting in a large amount of byproduct 29B shown in **Figure 2.25**. The purification of 29 was performed using column chromatography, which proved to be very challenging due to the similar R\textsubscript{i} values obtained for 29 and 29B. The observance of the labile proton from the imidazole moiety (N-H, 9.80 ppm) was very broad in the \textsuperscript{1}H NMR spectrum due to fast exchange with water in the NMR solvent, which can be observed in **Figure 2.24**.
Figure 2.24: $^1$H NMR spectrum of 29 in CDCl$_3$ (500MHz).
Figure 2.25: Byproduct obtained from the condensation reaction between 8 and 28.

For the majority of the benzimidazole based compounds synthesized in the Loeb group, the formation of additional byproducts such as 29B are not common due to the presence of “stopper” groups meta to the nitrogen atoms, which prevent the double dehydration reaction due to steric hindrance. There is a literature procedure for this; a series of benzimidazoles were synthesized using hypervalent iodine as an oxidant\(^{100}\) and starting materials similar to 28 with regards to the absence of functional groups ortho to the amino substituents. The mechanism is outlined in Figure 2.26.
Figure 2.26: Mechanism for the IBD condensation reaction.

These reaction conditions for the IBD condensation were used in an attempt to obtain higher yields of 29 and to simplify the purification procedure by obtaining less of 29B. Unfortunately, the reaction did not work even after numerous attempts of modifying solvents used and catalyst loading quantities. Therefore, the optimal synthesis of 29 was achieved using the zirconium tetrachloride catalyst, leaving 29 in position to prepare for the synthesis of a [c2]daisy-chain.
Figure 2.27: Retrosynthetic Scheme #1 for the synthesis of DCD-1 34.
With the successful synthesis of 29 confirmed, subsequent steps could be taken to functionalize 29 appropriately to serve as a template precursor for the proposed double ring closing metathesis reaction required to generate 34, or the [c2]daisy-chain DCD-1.

![Reaction Scheme for the synthesis of DCD-1](image)

**Figure 2.28**: Reaction Scheme for the synthesis of DCD-1 34.

As shown in Figure 2.28, the first synthetic step involved protonating 29 with a tetrafluoroboric acid diethyl ether complex to generate the salt 30. Purification of 30 was trivial and the purity of the product can be observed in the $^1$H NMR spectrum in Figure
2.29. The spectrum obtained of 30 was much sharper and symmetrical in comparison to 29 due to the fact that 30 does not contain a mixture of tautomers.

Figure 2.29: $^1$H NMR spectrum of 30 in CD$_3$CN (500MHz).

Compound 30 was submitted to a double ring closing metathesis reaction using Grubbs first generation catalyst. The conditions used in terms of concentration and catalyst loadings and concentration were based on previous [c2]daisy-chains synthesized.
by the Grubb’s research group. Following the completion of the reaction, the mixture was neutralized with sodium bicarbonate to allow for the purification of neutral species instead of charged products. The neutral mixture was first analyzed using thin layer chromatography, which indicated the presence of some starting material 29 (highest R\(_f\)) and two additional spots with lower R\(_f\) values. The initial thought was that spot with the 2\(^{nd}\) highest R\(_f\) value was the [c2]daisy-chain 33, followed by the daisy chain monomer 31 byproduct (lowest R\(_f\)) due to the fact that the protons from each imidazole in the dimer 33 would be shielded by the rings, therefore causing it to bind less to the silica. The monomer 31 would contain a free imidazole proton causing it to bind more strongly to the silica, hence giving it the lowest R\(_f\) value. The purification was undertaken, which was extremely challenging, typically requiring preparatory plate chromatography. The initial theoretical TLC analysis was incorrect following \(^1\)H NMR spectroscopy characterization, considering that the 2\(^{nd}\) TLC spot corresponded to the monomer 31, which was obtained in a much larger quantity (30% yield) in comparison to the dimer 33, with yields less than 5%.

Compounds 31 and 33 were both characterized using \(^1\)H NMR spectroscopy, as well as MALDI-MS. The proton NMR spectra obtained for 31 and 33 was very broad due to the presence of both tautomers and cis/trans isomers in each. The results from the MALDI-MS experiments resulted in the collection of very accurate [M+H]\(^+\) molecular ion peaks for both 31 and 33 (See Experimental). The MALDI-MS results indicated that either a [c2] or [a2]daisy-chain was formed.

The issue with the \(^1\)H NMR data obtained for 31 and 33 was that each has a mixture of tautomers and cis/trans isomers, which caused the peaks observed in the
spectra to be very broad. To eliminate the issue of the tautomers and invoke stronger interactions at the recognition sites, both 31 and 33 were protonated to give 32 and 34 respectively, which is shown in Figure 2.28.

The more symmetrical proton NMR data collected for 32 (monomer) and 34 (dimer) enabled the determination as to whether a [c2] or [a2] daisy-chain was formed. Figure 2.30 depicts stacked $^1$H NMR spectra of both 32 and 34 and the first noticeable difference observed in the chemical shifts of the protons labeled x and y. The Chemical shift of protons in y (34) (7.05 ppm) are more shielded than protons x (32) (7.25 ppm) due to the fact that y in (34) encounters shielding from the crown ether ring, whereas x in (32) is free and does not experience shielding. In addition the imidazolium protons in 34 (12.62 ppm) are more deshielded, potentially due to increased hydrogen bonding with the crown ether oxygen atoms, whereas the imidazolium protons in 32 (12.40 ppm) are not bound and experienced less hydrogen bonding making them more shielded. Compound 34 was confirmed to be a [c2] daisy-chain due to the presence of only one peak observed for y and the imidazolium protons. If an [a2] daisy-chain had been synthesized, and additional peak would have been observed for y and the imidazolium protons due to one recognition site being bound by a crown ether ring, and the other left unbound. This may have been more favoured if a larger crown ether moiety was used or a more flexible thread. The peaks observed in the spectra of 32 and 34 exhibit splitting due to the mixture of cis/trans isomers. The olefinic protons in 34 can be observed between 5.27 ppm - 5.14 ppm and the olefinic protons in 32 can be observed between 5.44 ppm - 5.39 ppm. Another interesting fact that was garnered from Figure 2.30 is that the Daisy Chain monomer 32 obtained is not self-complexed. If it was, the chemical shifts of x in 32 and y
in 34 would have been almost the same. This also theoretically makes sense due to the fact that self-complexation would more commonly be observed with a longer, flexible thread component\textsuperscript{42}, as opposed to the shorter more rigid thread exhibited in 32. This proved to be the first [c2]daisy-chain synthesized containing a benzimidazolium-crown ether based recognition site.

![Chemical structures](image)

**Figure 2.30:** \textsuperscript{1}H NMR spectra depicting 32 (Blue) (Bottom) in CD\textsubscript{3}CN (500MHz) and 34 (Red) (Top) in CD\textsubscript{3}CN (500MHz). Also shown in the labelled proton x in 32 and proton y in 34.

Other than purification, the largest issue with the synthesis was the yields of less than 5%, in which the dimer 31 was obtained. Attempts were made to try to improve the yield while maintaining the same template approach. Increased and decreased catalyst
loadings were pursued, but yields still remained under 5%. The concentration was increased and decreased with respect to previous reports\textsuperscript{51} of $10^{-3}$ M, but in both experiments, the monomer byproduct 31 was obtained in much larger proportions in comparison to the [c2]daisy-chain 33. Due to the extremely small quantities of material obtained, no further reactions using 33 were performed. If larger yields were obtained, this would have resulted in the Suzuki Coupling of pyridyl groups to the dimer to give 33B, followed by hydrogenation to reduce the double bonds to give 33C so that the dimer could potentially be used as pillar ligand for MOF synthesis. This is illustrated in Figure 2.31.

![Figure 2.31: Potential reaction scheme to synthesize desired pillared linker for MOF synthesis.](image)

One of the potential reasons as to why the yield of DCD-1 was so low is the template design. The thread portion of the daisy chain precursor may not have been electron poor enough, resulting in relatively weak interactions between the
benzimidazolium recognition site and the electron rich crown ether. This makes sense considering the much large quantities of the daisy chain monomer being obtained due to the ring simply closing and not templating around the recognition site. This initiated the development of a more electron deficient benzimidazole based thread to increase the strength of the non-covalent interactions\textsuperscript{101} during the ring closing metathesis, hence improving the template.
2.2.h. Discussion and Analysis of Synthetic strategy for DCD-2 precursor (37)

Figure 2.32: Retrosynthetic Scheme #1 for the synthesis of DCD-2 precursor 37.
The modification made in order to improve the template and make the thread portion of the precursor more electron poor was accomplished by changing the methyl stopper groups to ethyl esters. The addition of the diester groups provided a more acidic thread that should improve the overall template.

Figure 2.33: PCC Oxidation reaction for the synthesis of 36.

As shown in Figure 2.33, the new stopper 36 was synthesized by performing a PCC oxidation of the alcohol 35 to give the desired aldehyde 36. The product was characterized using $^1$H NMR spectroscopy and the obtained chemical shifts corresponded to literature values.\textsuperscript{102}
Using the previously prepared diamino substrate 28, a condensation reaction (Figure 2.34) with 36 was performed using a zirconium tetrachloride catalyst, with the exception of a slight modification that was made to minimize the formation of the double dehydration byproduct 37B (Figure 2.35). This was accomplished by decreasing the equivalents of the aldehyde 36 being used in comparison to the diamino 28, in a ratio of 0.7:1 respectively. After the reaction was complete, the product was challenging to purify, but was done so using column chromatography to produce 37 as a mixture of tautomers in 60% yield, a significant improvement in comparison to other attempts with similar substrates in this reaction. The improvement in yield can be attributed to the production of lower quantities of 37B.

The $^1$H NMR data obtained for 37 is presented in Figure 2.36. The peak corresponding to the imidazole proton at 10.23 ppm is very broad due to the fast exchange with water in the NMR solvent. With the successful preparation of 37, this enabled the functionalization of 37 to a suitable precursor for a double ring closing metathesis reaction to generate the desired [c2]daisy-chain.
Figure 2.36: $^1$H NMR spectrum of 37 in CDCl$_3$ (500MHz).
2.2.i. Discussion and Analysis of Synthetic strategy for DCD2-TA and MOF synthesis

Figure 2.37: Retrosynthetic Reaction scheme#1 for the synthesis of DCD2-TA 45.
Following the successful dehydration reaction, 37 was protonated (Figure 2.38) with HBF$_4$ to generate the final precursor 38 necessary for a double ring closing metathesis reaction using Grubb’s I catalyst. The $^1$H NMR spectrum obtained for 38 is displayed in Figure 2.39. The spectrum produced is very symmetrical due to the elimination of the tautomers, however, the imidazolium protons could not be observed due to the fast exchange with water in the NMR solvent, leaving the peak very broad.

![Figure 2.38: Protonation of 37.](image-url)
Figure 2.39: $^1$H NMR spectrum of 38 CD$_3$CN (500MHz).
Figure 2.40: Reaction Scheme #1 for the synthesis of DCD-2 42.

Similar in fashion to the synthesis of DCD-1(33), a mixture of the daisy chain monomer 40 and the dimer 42 were obtained following the work-up of the reaction. The
monomeric and dimeric species (40 and 42) were separated and purified using column chromatography. The monomer 40 was collected in 3% yield and the dimer 42 was obtained in 16% yield. The low yields obtained were due to the identification of leftover starting material following the reaction, as well as mixed fractions containing both 40 and 42 due to the challenging purification procedure and the strong binding of both 40 and 42 to the silica stationary phase. 40 and 42 were characterized using MALDI-MS, which resulted in collection of accurate [M+H]^+ molecular ion peaks for both monomeric and dimeric species (See experimental).

The $^1$H NMR spectra obtained for 40 and 42 resulted in broad spectral peaks due to the presence of tautomeric mixtures, as well as cis/trans isomers. In order to observe a symmetrical proton NMR spectrum and eliminate the mixture of tautomers, 40 and 42 were protonated with HBF$_4$ to produce 39 and 41. By looking at the stacked $^1$H NMR spectra of 39 and 41 presented in Figure 2.41, several differences can be noted. Firstly, proton y in 41 (7.01 ppm) appears more shielded in comparison to proton x in 39 (7.28 ppm), which was expected due to the shielding provided by the crown ether ring bound around the benzimidazolium site. In addition, the imidazolium protons in 41 are present as a “triplet like peak” (12.93 ppm) located further downfield in comparison to the imidazolium protons in 39 (12.69 ppm) due to hydrogen bonding. The “triplet like peak” observed in 41 was an interesting characteristic because it may have presented the mixture of cis/cis, trans/trans, and cis/trans isomers present due to the two olefins present. In turn, it was also identified that 41 is a [c2]daisy-chain because only one chemical shift was displayed for the protons in environment y and only one peak is observed for the imidazolium protons in 41. The chemical shift presenting the olefinic protons in 41 can be
observed between 5.23 ppm -5.05 ppm and for 39, they can be observed between 5.45 ppm - 5.39 ppm.

Figure 2.41: $^1$H NMR spectra of 39 (Blue) and 41 (Red) in CD$_3$CN (500MHz).

By performing a hydrogenation reaction on 42 to reduce the olefins, 43 was collected in 42% yield. By increasing the reaction scale and improving purification methods, higher yields of 43 can be obtained. The $^1$H NMR spectrum of 43 was also useful for concluding the successful synthesis of a [c2]daisy-chain over an [a2]daisy-chain, because once again, the spectrum was symmetrical and only one peak was
observed for the imidazolium protons (12.88 ppm), as well as proton d in 43 (6.97 ppm), which only consisted of one peak in the spectrum. The $^1$H NMR spectrum of 43 can be observed in Figure 2.43.

In order to obtain a suitable sample for MALDI-MS, 43 was neutralized with triethylamine to give 44 in quantitative yield. The MALDI-MS results of 44 confirmed the successful synthesis of the hydrogenated Daisy Chain Dimer, which resulted in the display of an accurate [M+H]$^+$ molecular ion peak (See experimental).
Figure 2.42: Retrosynthetic Scheme #2 for the hydrogenation and hydrolysis to produce DCD2-TA 45.
Figure 2.43: $^1$H NMR spectrum of 43 in CD$_3$CN (500MHz).
Compound 43 was submitted to a hydrolysis reaction to generate product 45 in 98% yield. The purity of the tetra-acid 45 was confirmed through proton NMR (Figure 2.44) and MALDI-MS studies (See experimental). The proton NMR spectra (Figure 2.44) indicated that the esters were completely hydrolyzed, which was evident from the disappearance of the quartet (4.52 ppm) and the triplet (1.49 ppm), which were present in the $^1$H NMR spectrum of 43 (Figure 2.43). Attempts were made to grow single crystals of 45 by diffusing methanol into a solution of 45 in DMSO, but all trials were unsuccessful due to solubility issues with 45.

The synthesis of ligand 45 provided a suitable linker to be used in the synthesis of metal-organic frameworks with copper nodes. Several trials were conducted using solvent conditions reported by the Loeb research group$^{56}$, but unfortunately the ligand consistently precipitated from solution due to poor solubility and no MOF was synthesized.
Figure 2.44: $^1$H NMR spectrum of 45 in DMSO-$d_6$ (500MHz).

The adjustments that were made to make the thread more acidic by substituting the methyl stoppers for isophthalic groups indeed improved the template, which can be
supported by the higher yields obtained following the double ring closing metathesis to produce 41. Although the improved yield obtained was still low, further adjustments can be made in the future to increase the yield. In terms of improving MOF conditions, the ligand 45 will have to be decorated in an alternative way to enhance solubility.

2.3. Experimental Data

General Comments

All starting materials were purchased from Aldrich and used as received. Deuterated solvents were obtained from Cambridge Isotope Laboratories and used as received. Solvents were dried using an Innovative Technologies Solvent Purification System. Thin layer chromatography (TLC) was performed using Teledyne Silica gel 60 F254 plates and viewed under UV light. Column chromatography was performed using Silicycle Ultra Pure Silica Gel (230 – 400 mesh). Flash column chromatography was performed using Teledyne Ultra Pure Silica/RP-C18 Silica Gel (230 – 400 mesh) on a Teledyne Isco Combiflash-Rf instrument. $^1$H and $^{13}$C NMR solution experiments were performed on a Brüker Avance 500 instrument, with working frequencies of 500.1 MHz for $^1$H nuclei and 125.7 MHz for $^{13}$C. Chemical shifts are quoted in ppm relative to tetramethylsilane using the residual solvent peak as a reference standard. Matrix Assisted Laser Ionization/Desorption Mass Spectrometry was used for analytical characterization with accuracy within 5ppm. Elemental Analysis data was collected using a PerkinElmer 2400 combustion CHN analyser. All IR spectra were collected using a Bruker-Equinox-Infrared microscopy and mapping instrument.

Experimental Data and Results
2.3.a. Synthesis of 6

To a 500mL, 3-neck round bottom flask at 0°C was added 3,5-dimethylaniline 5 (10 g, 82.52 mmol, 1 eq) in 83mL of distilled acetonitrile. After 10 minutes of stirring, a solution of n-bromosuccinimide (14.69 g, 82.52 mmol, 1 eq) in distilled acetonitrile (83 mL) was added drop wise over an hour via an addition funnel. The reaction mixture was allowed to come to room temperature and stirred for an additional 72 hour period. The reaction was quenched by slow addition of distilled water. Acetonitrile was removed under reduced pressure, followed by an extraction with ethyl acetate (3 x 150 mL). The remaining organic phase was isolated, dried with magnesium sulfate and filtered. Ethyl acetate was removed under reduced pressure. The crude orange solid was recrystallized from 600 mL of boiling hexanes to give 6 (13.21 g, 80% yield), as a white solid. An alternative purification method is subjecting the crude product to column chromatography (SiO₂: Hexanes: Ethyl acetate, 5:1). \(^1\)H NMR (500MHz, CDCl₃): δ(ppm) = 6.44 (s, 2H), 3.53 (br s, 2H), 2.31 (s, 6H). Values obtained are in correlation with reported literature values.
Table 2.1: $^1H$ NMR data for 6 in CDCl$_3$ (500MHz).

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<td>s</td>
<td>2.31</td>
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2.3.b. Synthesis of 7

To a mixture of 4-bromo-3,5-dimethylaniline 6 (6 g, 29.9 mmol, 1 eq) in 120 mL of distilled water at 0°C was added 10mL of concentrated sulfuric acid dropwise. The mixture was kept at 0°C and stirred for an additional 30 minutes upon which 60 mL of acetone was added to the mixture, followed by 15 additional minutes of stirring. Still maintaining a reaction temperature of 0°C, a solution of sodium nitrite (6.20 g, 89.9 mmol, 3 eq) in 50 mL of distilled water was added to the mixture dropwise, followed by an additional 60 minutes of stirring. A solution of potassium iodide (24.89 g, 149.9 mmol, 5 eq) in 50 mL of distilled water was added to the mixture dropwise. The reaction was allowed to warm to room temperature and stirred overnight. Following completion of the reaction, an extraction with ethyl acetate was performed (3 x 150ml). The resulting organic layer was isolated and washed with a 5% solution of hydrochloric acid to remove
any excess starting material. 100 mL of a 20% solution of sodium bisulfite was added to the organic material and stirred for a period of 45 minutes, after which the organic phase was separated. This process was repeated once more. The organic phase was then dried with sodium sulfate, filtered and the ethyl acetate was removed under reduced pressure to give a sample of orange oil. The resulting oil was purified using column chromatography (SiO$_2$: Hexanes), which gave 7 (8.51 g, 91% yield). $^1$H NMR (500MHz, CDCl$_3$): $\delta$(ppm) = 7.432 (s, 2H), 2.387 (s, 6H). Values obtained are in correlation with reported literature values.$^{79}$

![Chemical Structure](image)

**Table 2.2:** $^1$H NMR data for 7 in CDCl$_3$ (500MHz).

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2.3.c. Synthesis of 8

A 250mL flame-dried schlenk flask containing 7 (3 g, 9.6 mmol, 1 eq) was evacuated and backfilled with nitrogen. Approximately 125mL of distilled THF was added to the schlenk flask, which was subsequently cooled to -78°C. A 2.5 M solution of n-butyllithium (3.86 mL, 9.7 mmol, 1.01 eq) was added dropwise to the solution, followed by stirring for a period of 1 hour. While maintaining a temperature of -78°C, Dimethylformamide (2.31 mL, 29.9 mmol, 3.1 eq) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. 25mL of a 5% solution of hydrochloric acid was added to neutralize the reaction mixture. The contents were transferred to a separatory funnel and the organic layer was isolated. The remaining aqueous layer was extracted with diethyl ether (2 x 50mL). The organic fractions were combined and dried with sodium sulfate, filtered, and the solvents were removed under reduced pressure to give a yellow solid. The crude product was purified via column chromatography (SiO2: Hexanes: Ethyl Acetate, 10:1), which gave 8 (1.21 g, 59% yield).

\[
\begin{align*}
\text{Br} & \quad \text{1. nBuLi, THF, -78^\circ C} \\
\text{7} & \quad \text{2. DMF, -78^\circ C to rt (59\%)} \\
\text{Br} & \quad \text{CHO} \\
\end{align*}
\]

\(^1\)H NMR (500MHz, CDCl\textsubscript{3}): δ (ppm) = 9.928 (s, 1H), 7.566 (s, 2H), 2.501 (s, 6H). Values obtained are in correlation with reported literature values.\textsuperscript{80}
Table 2.3: $^1H$ NMR data for 8 in CDCl$_3$ (500MHz).

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2.3.d. Synthesis of 2

A 250 mL round bottom flask was charged with veratrole 1 (17.8 mL, 140 mmol, 1 eq) and glacial acetic acid (19 mL). The mixture was cooled to 0°C, followed by the addition of 90% fuming nitric acid (53 mL) via a dropping funnel. Following the completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solution was slowly poured into 500 mL of cold distilled water, which caused the precipitation of a yellow solid. The solid was filtered and then recrystallized from 700 mL of ethanol to produced 2 as yellow needles (26.8 g,
84% yield). $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 6.40 (s, 2H), 3.80 (s, 6H). Values obtained are in correlation with reported literature values.\textsuperscript{81}

![Chemical Structure]

**Table 2.4: $^1$H NMR data for 2 in CDCl$_3$ (500MHz).**

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**2.3.e. Synthesis of 3**

![Chemical Reaction]

A 250 mL round bottom flask was charged with 2 (1.25 g, 5.5 mmol, 1 eq) and 100 mL of 40% hydrobromic acid. The mixture was refluxed for 2 days. The mixture was cooled to room temperature and poured into cold water. An extraction was performed with ethyl acetate (2 x 100 mL). The organic phase was isolated and dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure to afford 3 (0.45 g, 41% yield) as a brown solid. The material was used with further purification. $^1$H NMR
(500MHz, DMSO-d₆): δ (ppm) = 11.00 (br, s, 1H), 7.45 (s, 2H). Values obtained are in
correlation with reported literature values.⁸¹

![Image of chemical structure]

**Table 2.5: **¹H NMR data for 3 in DMSO-d₆ (500MHz).

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2.3.f. Synthesis of 3

A 250 mL oven dried Schlenk flask was charged with 2 (1 g, 4.38 mmol, 1 eq)
and 100 mL of dry dichloromethane. The flask was evacuated and backfilled with
nitrogen, cooled to -78°C, followed by the dropwise addition of 1 M solution of BBr₃ in
DCM (22 mL, 21.9 mmol, 5 eq). The reaction was then allowed to warm to room
temperature and stirred overnight. The reaction was quenched by slow addition of 30 mL
of cold distilled water and subsequent stirring for 30 minutes. The mixture was then
placed in a separatory funnel, the organic phase was drained off and washed twice with an
additional 50mL of distilled water. The organic phase was dried with magnesium sulfate,
filtered, and the solvent was removed under reduced pressure to give 3 as a brown solid (0.552 g, 63% yield). The material was used with further purification. \(^1\)H NMR (500MHz, DMSO-\(d_6\)): \(\delta\) (ppm) = 11.00 (br, s, 1H), 7.45 (s, 2H). Values obtained are in correlation with reported literature values.\(^{82}\)

![Chemical Structure](image)

**Table 2.6:** \(^1\)H NMR data for 3 in DMSO-\(d_6\) (500MHz).

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**2.3.g. Synthesis of 18**

![Chemical Reaction](image)

An oven dried 250 mL 3-neck round bottom flask was charged with 3 (0.4 g, 2 mmol, 1 eq), \(K_2CO_3\) (0.774 g, 5.60 mmol, 2.8 eq) and equipped with a reflux condenser. The system was sealed, evacuated, and backfilled with nitrogen. A solution of 4 (0.697 g, 5.60 mmol, 2.8 eq) in 110 mL of dry DMF was cannulated into the 3-neck round bottom
flask under a nitrogen atmosphere. The mixture was then heated to 120°C and stirred for 3 days. Over the 3 day period, the reaction was monitored using proton NMR and TLC, neither of which provided indication that the reaction took place.

2.3.h. Synthesis of 11

![Reaction Diagram]

A 500 mL round bottom flask equipped with a stir bar and reflux condenser was charged with diethylene glycol 10 (142.41 g, 1.342 moles, 20 eq) and 5-bromo-1-pentene 9 (10 g, 0.0671 moles, 1 eq). A solution of sodium hydroxide and water (13.42 g NaOH, 0.336 moles, 5 eq; 13.5 mL of Water) was added dropwise over a period of 45 minutes. The reaction was heated to 80°C and stirred for one day, followed by cooling to room temperature. The mixture was transferred to a separatory funnel, along with 250 mL of DCM and 250 mL of distilled water. The organic layer was drawn off and the aqueous layer was extracted three times using DCM (3 x 100 mL). The combined organic fractions were washed twice with a solution of brine (2 x 100 mL), dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure to give a red oil. The resulting oil was purified using column chromatography (SiO₂: gradient from 2:1 hexanes to ethyl acetate to 1:1 hexanes to ethyl acetate) which resulted in a light yellow oil (9g, 77% yield). ¹H NMR (500MHz, CDCl₃): δ (ppm) = 5.81 (m, 1H), 5.05-4.94 (m, 2H), 3.75-3.72 (m, 2H), 3.69-3.66 (m, 2H), 3.64-3.61 (m, 2H), 3.61-3.58 (m, 2H), 3.48 (t, J = 6.7Hz, 2H), 2.42 (t, J = 6.1Hz, 1H), 2.14-2.09 (m, 2H), 1.70 (qt, J = 7.1Hz, 2H). Values obtained are in correlation with reported literature values.⁵¹
Table 2.7: $^1\text{H NMR data for 11 in CDCl}_3(500\text{MHz})$.

<table>
<thead>
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<th>Multiplicity</th>
<th>$\delta$ (ppm)</th>
<th># of Protons</th>
<th>J(Hz)</th>
</tr>
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<td>b</td>
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<td>3.48</td>
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<tr>
<td>h</td>
<td>t</td>
<td>2.42</td>
<td>1</td>
<td>6.1</td>
</tr>
<tr>
<td>i</td>
<td>m</td>
<td>2.14-2.09</td>
<td>2</td>
<td>-</td>
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<tr>
<td>j</td>
<td>qt</td>
<td>1.70</td>
<td>2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

2.3.i. Synthesis of 12

An oven dried 250 mL Schlenk flask was equipped with a stir bar, and charged with 11 (4 g, 0.023 moles, 1 eq). The flask was sealed, evacuated, and backfilled with
nitrogen, followed by the cannulation of 125 mL of dry DCM. The flask was cooled to 0°C and methanesulfonyl chloride (2.7 mL, 0.0345 moles, 1.5 eq) and triethylamine (5.62 mL, 0.0403 moles, 1.5 eq) were added in alternate increments. After the additions were complete, the reaction was warmed to room temperature and stirred overnight. When the reaction was complete, the mixture was transferred into a separatory funnel, along with 200 mL of distilled water. The organic phase was drained off, followed by two subsequent extractions of the aqueous layer with DCM (2 x 100 mL). The combined organic fractions were washed with brine (2 x 100 mL), dried with magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure to give a dark orange oil. The resulting crude product was purified using column chromatography (SiO$_2$: 3:2 hexanes to ethyl acetate to give 12 (5.27 g, 91% yield) as a light yellow oil. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 5.80 (m, 1 H), 5.04-4.94 (m, 2H), 4.39-4.37 (m, 2H), 3.78-3.75 (m, 2H), 3.67-3.64 (m, 2H), 3.59-3.56 (m, 2H), 3.45 (t, $J = 6.6$Hz, 2H), 3.06 (s, 3H), 2.17-2.07 (m, 2H), 1.67 (qt, $J = 7.1$Hz, 2H). Values obtained are in correlation with reported literature values.$^{51}$
Table 2.8: $^1H$ NMR data for 12 in CDCl$_3$ (500MHz).

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<th>$\delta$ (ppm)</th>
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<th>J(Hz)</th>
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<td>m</td>
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<tr>
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<td>s</td>
<td>3.06</td>
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<td>-</td>
</tr>
<tr>
<td>i</td>
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<tr>
<td>j</td>
<td>qt</td>
<td>1.67</td>
<td>2</td>
<td>7.1</td>
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2.3.j. Synthesis of 21

An oven dried 250 mL 3-neck round bottom flask was charged with 3 (0.3 g, 1.5 mmol, 1.5 eq), K$_2$CO$_3$ (0.622 g, 4.5 mmol, 3 eq) and equipped with a reflux condenser.
The system was sealed, evacuated, and backfilled with nitrogen. A solution of \textbf{12} (1.134 g, 4.5 mmol, 3 eq) in 110 mL of dry DMF was cannulated into the 3-neck round bottom flask under a nitrogen atmosphere. The mixture was then heated to 120\(^\circ\)C and stirred for 3 days. Over the 3 day period, the reaction was monitored using proton NMR and TLC, neither of which provided indication that the reaction took place.

\textbf{2.3.k. Synthesis of 14}

\[ \text{ClCH}_2\text{CH}_2\text{OH} + \text{CO}_2\text{H} \xrightarrow{24\text{h}} \text{ClCH}_2\text{CH}_2\text{OAc} \]

A 250 mL oven dried Schlenk flask was equipped with a stir bar and charged with diethylene glycol monochlorohydrin \textbf{4} (5 g, 0.040 moles, 1 eq). The flask was evacuated and backfilled with nitrogen, followed by the addition of acetic anhydride \textbf{13} (4.51 g, 0.0442 moles, 1.1 eq) via syringe and the reaction was stirred for 24 hours. The resulting viscous oil was dissolved in 125 mL of DCM, washed with 100 mL of water, 100 mL of an aqueous solution of sodium bicarbonate, and finally an additional 100 mL of water. The organic was dried using sodium sulfate, filtered, and the solvent was removed under reduced pressure to give \textbf{14} (6.15 g, 92\% yield) as a clear oil. The product was used without further purification. \(^1\)H NMR (500MHz, CDCl\(_3\)): \(\delta\) (ppm) = 4.26 (t, \(J = 4.7\)Hz, 2H), 3.79 (t, \(J = 6.3\)Hz, 2H), 3.74 (t, \(J = 4.7\)Hz, 2H), 3.65 (t, \(J = 5.9\)Hz, 2H), 2.11 (s, 3H). Values obtained are in correlation with reported literature values.\(^{83}\)
Table 2.9: $^1H$ NMR data for 14 in CDCl$_3$ (500MHz).

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<th>J(Hz)</th>
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<td>e</td>
<td>s</td>
<td>2.11</td>
<td>3</td>
<td>-</td>
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</tbody>
</table>

2.3.1. Synthesis of 16

An oven dried 250 mL 3-neck round bottom flask was charged with 15 (1.5 g, 0.0136 moles, 1 eq), K$_2$CO$_3$ (5.65 g, 0.0409 moles, 3 eq) and equipped with a reflux condenser. The system was sealed, evacuated, and backfilled with nitrogen. A solution of 14 (6.13 g, 0.0368 mol, 2.7 eq) in 110 mL of dry DMF was cannulated into the 3-neck round bottom flask under a nitrogen atmosphere. The mixture was then heated to 110°C and stirred for 2 days. The reaction was cooled to room temperature, filtered to remove
excess potassium carbonate, and the DMF was removed under reduced pressure. The resulting residue was dissolved in ethyl acetate, extracted with water (3 x 75 mL) and washed with brine (2 x 50 mL). The resulting organic fraction was dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure leaving a dark red oil in the flask. The crude product was purified using column chromatography (SiO<sub>2</sub>: 2:1 Hexanes to ethyl acetate) to afford 16 (3.1g, 61% yield) as a light yellow oil. <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>): δ (ppm) = 6.93-6.89 (m, 4H), 4.22-4.18 (m, 4H), 4.14-4.08 (m, 4H), 3.84-3.80 (m, 4H), 3.77-3.73 (m, 4H), 2.02 (s, 6H).<sup>84</sup>

![Chemical Structure](image)

**Table 2.10**: <sup>1</sup>H NMR data for 16 in CDCl<sub>3</sub> (500MHz).

<table>
<thead>
<tr>
<th>Proton</th>
<th>Multiplicity</th>
<th>δ (ppm)</th>
<th># of Protons</th>
<th>J(Hz)</th>
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<tbody>
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<td>-</td>
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<td>c</td>
<td>m</td>
<td>4.22-4.18</td>
<td>4</td>
<td>-</td>
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<tr>
<td>d</td>
<td>m</td>
<td>4.14-4.08</td>
<td>4</td>
<td>-</td>
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<td>e</td>
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<td>f</td>
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<tr>
<td>g</td>
<td>s</td>
<td>2.02</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>
2.3.m. Synthesis of 17

16 (5 g, 13.5 mmol) was added to a 250 mL oven-dried Schlenk flask, along with 100 mL of dry dichloromethane. The mixture was evacuated and purged with nitrogen and cooled on ice. Nitric acid (9 mL) and concentrated sulfuric acid (4.5 mL) were transferred to the mixture slowly while maintaining a constant stream of nitrogen in the flask. Following the completion of the transfer, the reaction was allowed to warm to room temperature and stirred for an additional 2 days. The reaction was quenched by adding 50 mL of cold distilled water and stirred for an additional 30 minutes. The mixture was then transferred to a separatory funnel where the organic fraction was isolated and washed with a solution of sodium bicarbonate (5%, 75 mL). The remaining organic solution was then washed with water (2 x 75 mL), then dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to give a dark orange oil. The crude product was purified using column chromatography (SiO₂: 2:1 to 1:1 Hexanes to ethyl acetate) to afford 16 (3.42 g, 55% yield) as a light yellow oil. ¹H NMR (500MHz, CDCl₃): δ (ppm) = 7.45 (s, 2H), 4.32-4.28 (m, 4H), 4.25-4.21 (m, 4H), 3.93-3.89 (m, 4H), 3.78-3.74 (m, 4H), 2.07 (s, 6H).
Table 2.11: $^1H$ NMR data for 17 in CDCl$_3$ (500MHz).

<table>
<thead>
<tr>
<th>Proton</th>
<th>Multiplicity</th>
<th>$\delta$ (ppm)</th>
<th># of Protons</th>
<th>J(Hz)</th>
</tr>
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<td>b</td>
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<tr>
<td>e</td>
<td>m</td>
<td>3.78-3.74</td>
<td>4</td>
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</tr>
<tr>
<td>f</td>
<td>s</td>
<td>2.07</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

2.3.n. Synthesis of 18

18 (1 g, 2.17 mmol, 1 eq) was added to a 100 mL round bottom flask and dissolved in 50 mL of methanol. With constant stirring, K$_2$CO$_3$ (0.63 g, 4.56 mmol, 2.1 eq) was added to the flask and the reaction was stirred for an additional 30 minutes, and
monitored using thin layer chromatography (1:1 Hexanes: Ethyl acetate) until the starting material 17 was no longer visible on the TLC paper. The solution was filtered to remove any excess potassium carbonate. The filtrate was transferred to a separatory funnel, along with 75 mL of dichloromethane and 50 mL of water. The Organic layer was removed and subsequently washed with water (3 x 30 mL). The organic filtrate was dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure at room temperature. This resulted in the collection of a fine yellow solid (0.654 g, 80% yield) of 18. The yellow solid obtained was used without further purification. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 7.38 (s, 2H), 4.31-4.27 (m, 4H), 3.97-3.94 (m, 4H), 3.76-3.71 (m, 4H), 3.70-3.67 (m, 4H), 3.18 (s (br), 2H).

![Chemical Structure of 18](image.png)

Table 2.12: $^1$H NMR data for 18 in CDCl$_3$ (500MHz).

<table>
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<th>Proton</th>
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<tr>
<td>e</td>
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<td>3.70-3.67</td>
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<td>-</td>
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</tbody>
</table>
2.3.o. Synthesis of 21

A solution of 18 (500 mg, 1.33 mmol, 1 eq) in 30 mL of dry DMF was added slowly to a 250 mL, oven dried Schlenk flask containing a suspension of sodium hydride (60% in oil, 0.133 g, 3.33 mmol, 2.5 eq) in 40 mL of DMF. The mixture was stirred for an hour, after which 9 (0.5 g, 3.3 mmol, 2.5 eq) in 30 mL of DMF was added to the mixture slowly. The reaction was monitored over a 3 day period resulting in no indication of product formation from both proton NMR and TLC studies.

2.3.p. Synthesis of 20

A 500 mL, 2-neck round bottom flask equipped with a stir bar and reflux condenser was placed in an ice bath and cooled to approximately 0°C. 19 (12.6 g, 110 mmol) was added into the flask, followed by careful addition of 40mL of concentrated sulfuric acid via a dropping funnel. The flask was kept at 0°C and 100 mL of fuming
nitric acid was added was added using a dropping funnel. The mixture was allowed to warm to room temperature and stirred for an additional 2 hours. The flask was then placed in an oil bath and slowly heated to 100°C over a 2 hour period. Once 100°C was reached, the reaction was stirred for an additional 12 hours and then cooled to room temperature. The contents of the flask were then poured slowly into a 1000mL Erlenmeyer flask containing 500 mL of crushed ice under constant stirring. A white solid precipitated out of the solution and was collected using vacuum filtration. The white solid was washed with 500 mL of distilled water, and then transferred to a flask containing 200 mL of diethyl ether. The diethyl ether was removed under reduced pressure in order to reduce the drying time. This resulted in the collection of 20 (8.4 g, 35% yield) as a white solid. The material was used without further purification. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 7.84 (t, 9.5Hz).$^{87}$

![Image of compound 20]

**Table 2.13: $^1$H NMR data for 20 in CDCl$_3$ (500MHz).**

<table>
<thead>
<tr>
<th>Proton</th>
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<th>$\delta$ (ppm)</th>
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<td>9.5</td>
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</table>
2.3.q. Synthesis of 21

An oven dried, 500 mL round bottom flask equipped with a gas adapter, stir bar, and two septa was charged with 11 (18.44 g, 0.106 moles, 2.7 eq). The flask was evacuated and backfilled with nitrogen, followed by the addition of 250 mL of DME. While maintaining a positive flow of nitrogen, Sodium hydride (4.23 g, 0.106 moles, 2.7 eq) was added slowly to the solution. Following the completion of the addition of sodium hydride, the mixture was stirred for 1 hour until H$_2$ gas evolution was no longer observed. At this point, while maintaining a positive nitrogen flow, 20 (8 g, 0.039 moles, 1 eq) was added to the flask in portions over a 30 minute period. The mixture was left to stir for 2 days and was then place in an ice bath and quenched by slow addition of 7 mL of cold distilled water. The solution was stirred for an additional 30 minutes and then filtered through a 1 cm plug of celite, and washed with 100 mL of dichloromethane. The solvents were removed under reduced pressure, which resulted in the collection of a dark red oil. The crude product was purified using column chromatography (SiO$_2$: 2:1 to 1:1 Hexanes to ethyl acetate) to afford 21 (8 g, 40% yield) as a light orange oil. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 7.50 (s, 2H), 5.85-5.80 (m, 2H), 5.06-4.97 (m, 4H), 4.33 (t, 5 Hz, 4H), 3.94 (t, 5 Hz, 4H), 3.73 (t, 4.5 Hz, 4H), 3.61 (t, 4.5 Hz, 4H), 3.49 (t, 6.5 Hz, 4H), 2.14-2.11 (m, 4H), 1.72-1.67 (m, 4H). $^{13}$C NMR (125.7MHz, CDCl$_3$): $\delta$ (ppm) = 158.78, 138.32,
136.79, 114.89, 109.33, 71.21, 70.95, 70.28, 70.01, 69.59, 30.33, 28.86. IR (ATR) (ν/cm	extsuperscript{-1}) = 3067, 2915, 2865, 1640, 1589, 1531, 1450, 1414, 1351, 1335, 1282, 1220, 1108, 1049, 994, 946, 863, 809, 799, 751, 720, 659, 635. EA (CHN) (%): Calculated: C = 56.24, H = 7.08, N = 5.47; Experimental: C = 56.59, H = 7.25, N = 5.22.

![Chemical Structure](image)

**Table 2.14**: \textsuperscript{1}H NMR data for 21 in CDCl\textsubscript{3}(500MHz).

<table>
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</table>
2.3.r. Synthesis of 28

A 100 mL Schlenk flask was charged with 21 (300 mg, 0.59 mmol), and 50 mL of ethyl acetate. The flask was then equipped with a reflux condenser and Tin(II) chloride dehydrate (1.32 g, 5.9 mmol, 10 eq) was added. The mixture was stirred and heated to 70°C for 24 hours. The reaction was cooled to room temperature and a concentrated solution of sodium hydroxide was added (20 mL) to neutralize the reaction. The organic layer was isolated and washed with water (2 x 40 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure and resulted in the recovery of starting material.

2.3.s. Synthesis of 28

A 100 mL Schlenk flask was charged with 21 (300 mg, 0.59 mmol), and 50 mL of methanol. The flask was then equipped with a reflux condenser and Tin(II) chloride
dehydrate (1.32 g, 5.9 mmol, 10 eq) was added. The mixture was stirred and heated to 70°C for 24 hours. The reaction was cooled to room temperature and a concentrated solution of sodium hydroxide was added (20 mL) to neutralize the reaction. The mixture was transferred to a separatory funnel with 100 mL of dichloromethane. The organic layer was removed and washed with water (2 x 40 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure, which resulted in the collection of primarily starting material.

2.3.t. Synthesis of 28

A 100 mL Schlenk flask was charged with 21 (300 mg, 0.59 mmol), and 50 mL of methanol. The flask was then equipped with a reflux condenser and Sodium sulfide nonahydrate (1.41 g, 5.9 mmol, 10 eq) was added. The mixture was stirred and heated to 70°C for 24 hours. The reaction was cooled to room temperature and a concentrated solution of sodium hydroxide was added (20 mL) to neutralize the reaction. The mixture was transferred to a separatory funnel with 100 mL of dichloromethane. The organic layer was removed and washed with water (2 x 40 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure, which resulted in the collection of primarily starting material.
2.3.u. Synthesis of 28

A 100 mL Schlenk flask was charged with 21 (300 mg, 0.59 mmol), and 50 mL of methanol. The flask was then equipped with a reflux condenser and activated zinc (0.383 g, 5.9 mmol, 10 eq) was added. The mixture was stirred and heated to 70°C for 24 hours. The reaction was cooled to room temperature and a concentrated solution of sodium hydroxide was added (20 mL) to neutralize the reaction. The mixture was transferred to a separatory funnel with 100 mL of dichloromethane. The organic layer was removed and washed with water (2 x 40 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure, which resulted in the collection of primarily starting material.

2.3.v. Synthesis of 28
A 100 mL Schlenk flask was charged with 21 (300 mg, 0.59 mmol), and 50 mL of methanol. The flask was then equipped with a reflux condenser and activated zinc (0.383 g, 5.9 mmol, 10 eq) was added. The mixture was stirred and heated to 70°C for 24 hours. The reaction was cooled to room temperature and a concentrated solution of sodium hydroxide was added (20 mL) to neutralize the reaction. The mixture was transferred to a separatory funnel with 100 mL of dichloromethane. The organic layer was removed and washed with water (2 x 40 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure, which resulted in the collection of primarily starting material.

2.3.w. Synthesis of 28B

An oven dried, 3-neck round bottom flask was equipped with a stir bar and charged with 21 (200 mg, 0.39 mmol, 1 eq) and 10 % Palladium on Carbon (39 mg, 9mol%, 0.035 mmol). The flask was then equipped with two septa, a reflux condenser, evacuated, and backfilled with nitrogen. A separate solution of 35 mL of anhydrous ethanol was cannulated into the 3-neck flask and hydrazine monohydrate (0.137 g, 2.7 mmol, 7 eq) was slowly added to the mixture. The solution was then heated to reflux and continuously stirred overnight. The reaction was cooled to room temperature, filtered to remove excess palladium on carbon, and the remaining ethanol was removed under
reduced pressure. The remaining contents were dissolved in dichloromethane, washed with water (2 x 20 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure to give a clear oil (0.175 g, quantitative yield). $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 6.33 (s, 2H), 4.10-4.08 (m, 4H), 3.82-3.80 (m, 4H), 3.74-3.72 (m, 4H), 3.64-3.61 (m, 4H), 3.50 (t, 6.5Hz, 4H), 3.20, (s (br), 4H), 1.73-1.31 (m, 14H), 1.19-1.05 (m, 4H).

Table 2.15: $^1$H NMR data for 28B in CDCl$_3$ (500MHz).

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<td>m</td>
<td>3.64-3.61</td>
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<tr>
<td>f</td>
<td>t</td>
<td>3.50</td>
<td>4</td>
<td>6.5</td>
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<tr>
<td>g</td>
<td>s (br)</td>
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<td>k</td>
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<td>1.19-1.05</td>
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2.3.x. Synthesis of 22

![Chemical Reaction Diagram]

An oven dried, 3-neck round bottom flask was equipped with a stir bar and charged with 2 (5 g, 21.9 mmol, 1 eq) and 10 % Palladium on Carbon (2.17 g, 9 mol%, 1.97 mmol). The flask was then equipped with two septa, a reflux condenser, evacuated, and backfilled with nitrogen. A separate solution of 35 mL of anhydrous ethanol was cannulated into the 3-neck flask and hydrazine monohydrate (7.68 g, 153.5 mmol, 7 eq) was slowly added to the mixture. The solution was then heated to reflux and continuously stirred overnight. The reaction was cooled to room temperature, filtered to remove excess palladium on carbon, and the remaining ethanol was removed under reduced pressure. The remaining contents were dissolved in dichloromethane, washed with water (2 x 20 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure to give a light yellow solid (3.68 g, quantitative yield). $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 6.37 (s, 2H), 3.79 (s, 6H), 3.19 (s (br), 4H).
Table 2.16: $^1H$ NMR data for 22 in CDCl$_3$ (500MHz).

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<th>J(Hz)</th>
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<td>b</td>
<td>s</td>
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<td>6</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td>s (br)</td>
<td>3.19</td>
<td>4</td>
<td>-</td>
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</table>

2.3.y. Synthesis of 23

A 250 mL oven dried round bottom flask was equipped with a reflux condenser and charged with 22 (2.5 g, 14.9 mmol, 1 eq). The flask was then sealed, evacuated, and backfilled with nitrogen. A mixture of 120 mL of dry dichloromethane and triethylamine (3.2 mL, 22.3 mmol, 1.5 eq) was cannulated into the flask. The contents were stirred and thionyl chloride (2.40 mL, 32.7 mmol, 2.2 eq) was added slowly using a dropping funnel while maintaining a positive nitrogen atmosphere. The reaction was refluxed overnight and then cooled to room temperature. The contents were filtered to remove the triethylamine hydrochloride salt produced and the remaining solvent was removed under reduced pressure. The contents left in the flask were dissolved in 100 mL of dichloromethane and transferred to a separatory funnel. The organic phase was isolated, washed with 25 mL of a 2 M hydrochloric acid solution and with water (2 x 50 mL). The organic solution was dried with sodium sulfate, filtered, and the solvent was removed.
under reduced pressure to give a reddish-brown solid (2.19 g, 75% yield). The product was used without further purification. $^1$H NMR (500MHz, CD$_3$OD): $\delta$ (ppm) = 7.25 (s, 2H), 3.96 (s, 6H). The proton NMR data correlated with the reported literature values.$^{97}$

![Chemical Structure](image)

**Table 2.17:** $^1$H NMR data for 23 in CDCl$_3$ (500MHz).

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<tr>
<th>Proton</th>
<th>Multiplicity</th>
<th>$\delta$ (ppm)</th>
<th># of Protons</th>
<th>J(Hz)</th>
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<tr>
<td>b</td>
<td>s</td>
<td>3.96</td>
<td>6</td>
<td>-</td>
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</tbody>
</table>

**2.3.z. Synthesis of 23**

A 250 mL oven dried round bottom flask was equipped with a reflux condenser and charged with 22 (2.5 g, 14.9 mmol, 1 eq). The flask was then sealed, evacuated, and backfilled with nitrogen. A mixture of 120 mL of dry dichloromethane and pyridine (2.0 mL, 25.3 mmol, 1.7 eq) was cannulated into the flask. The contents were stirred and thionyl chloride (2.40 mL, 32.7 mmol, 2.2 eq) was added slowly using a dropping funnel while maintaining a positive nitrogen atmosphere. The reaction was refluxed overnight and then cooled to room temperature. The contents were filtered and the remaining
solvent was removed under reduced pressure. The contents left in the flask were dissolved in 100mL of dichloromethane and transferred to a separatory funnel. The organic phase was isolated, washed with 25 mL of a 2 M hydrochloric acid solution and with water (2 x 50mL). The organic solution was dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure to give a reddish-brown solid (1.52 g, 52% yield). The product was used without further purification. \(^1\)H NMR (500MHz, CD\(_3\)OD): \(\delta\) (ppm) = 7.25 (s, 2H), 3.96 (s, 6H). The proton NMR data correlated with the reported literature values.\(^97\)

\[
\text{Table 2.18: } ^1\text{H NMR data for 23 in CD}_{3}\text{OD (500MHz).}
\]

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<th>J(Hz)</th>
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<tr>
<td>b</td>
<td>s</td>
<td>3.96</td>
<td>6</td>
<td>-</td>
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</table>

2.3.aa. Synthesis of 24

A 250 mL round bottom flask was charged with 23 (250 mg, 1.28 mmol, 1eq), and 100 mL of 48% Hydrobromic acid. The flask was equipped with a reflux condenser.
and the mixture was stirred and heated to a temperature exceeding 150°C for 6 hours. The reaction was then cooled to room temperature, diluted with 50 mL of water and the solvents were removed under reduced pressure. The remaining residue was washed with a small amount of water (15 mL) and the solids were filtered off. The solids were then suspended in diethyl ether and the diethyl ether was subsequently removed under reduced pressure resulting in a dark brown solid (0.111 g, 52% yield). The product was used without further purification. $^1$H NMR (500MHz, CD$_3$OD): $\delta$ (ppm) = 7.09 (s, 2H), 9.02 (s (br), 2H). The proton NMR data correlated with the reported literature values.$^{97}$

![Chemical Structure](image)

**Table 2.19:** $^1$H NMR data for 24 in CD$_3$OD (500MHz).

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<td>b</td>
<td>s (br)</td>
<td>9.02</td>
<td>2</td>
<td>-</td>
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</table>

**2.3.bb. Synthesis of 25**

![Chemical Structure](image)

To a dry 250 mL Schlenk flask equipped with a stir bar was added TsCl (5.69 g, 29.8 mmol, 1.3 eq), and 4-DMAP (0.28 g, 2.3 mmol, 0.1 eq). The flask was then
evacuated, backfilled with nitrogen and triethylamine (5.76 mL, 41.3 mmol, 1.8 eq) in dry dichloromethane (50 mL) was cannulated into the 250 mL Schlenk flask. The mixture was cooled to 0°C using and ice bath, followed by the addition of 11 (4 g, 22.95 mmol, 1 eq) in 60 mL of dry dichloromethane was added slowly to the flask via a syringe. The reaction was allowed to come to room temperature and stirred overnight. The reaction was quenched by adding 25 mL of cold distilled water and the contents were then transferred into a separatory funnel. The organic phase was collected, washed with a solution of ammonium chloride, followed by a solution of brine. The remaining organic layer was washed with water (2 x 50 mL), dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure, which left a dark red oil remaining in the flask. The crude product was purified using column chromatography (SiO₂: 2:1 Ethyl acetate to Hexanes) to afford 25 (7.5 g, 98% yield) as a light yellow oil. \(^1\)H NMR (500MHz, CDCl\(_3\)): δ (ppm) = 7.58 (d, 7.8Hz, 2H), 7.30 (d, 8.4Hz, 2H), 5.80-5.71 (m, 1H), 5.00-4.88 (m, 2H), 3.66-3.63 (m, 2H), 3.54-3.52 (m, 2H), 3.51-3.46 (m, 2H), 3.46-3.44 (m, 2H), 3.39 (t, 6.6Hz, 2H), 2.40, (s, 3H), 2.08-2.01 (m, 2H), 1.64-1.59 (m, 2H).
Table 2.20: \(^1H\) NMR data for 25 in CDCl\(_3\) (500MHz).

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2.3.cc. Synthesis of 26

An oven dried 100 mL, 3-neck round bottom flask was equipped with a stir bar, reflux condenser and charged with 24 (100 mg, 0.6 mmol, 1 eq), and K\(_2\)CO\(_3\) (0.246 g,
1.79 mmol, 3 eq). The flask was sealed, evacuated, backfilled with nitrogen, and 25 (0.586 g, 1.79 mmol, 3 eq) in 55 mL of dry MeCN was cannulated into the 3-neck round bottom flask. The mixture was heated to 100°C for 2 days, and then cooled to room temperature. The solution was filtered to remove excess potassium carbonate and the MeCN was removed under reduced pressure. The proton NMR of the crude product, as well as TLC measurements indicated only the presence of starting material.

2.3.dd. Synthesis of 26

An oven dried 100 mL, 3-neck round bottom flask was equipped with a stir bar, reflux condenser and charged with 24 (100 mg, 0.6 mmol, 1 eq), and K₂CO₃ (0.246 g, 1.79 mmol, 3 eq). The flask was sealed, evacuated, backfilled with nitrogen, and 25 (0.586 g, 1.79 mmol, 3 eq) in 55 mL of dry DMF was cannulated into the 3-neck round bottom flask. The mixture was heated to 100°C for 2 days, and then cooled to room temperature. The solution was filtered to remove excess potassium carbonate and the DMF was removed under reduced pressure. The residue remaining was dissolved in 75 mL of ethyl acetate and washed with brine (2 x 50 mL) and water (2 x 50 mL). The resulting organic layer was dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure leaving a dark red oil. The crude product was purified using column chromatography (SiO₂: 2:1 to 1:1: Hexanes to Ethyl acetate) to afford 26 (0.162 g, 56% yield) as a yellow oil. ¹H NMR (500MHz, CDCl₃): δ (ppm) = 7.20 (s, 2H), 5.85-5.78 (m,
2H), 5.06-4.96 (m, 4H), 4.29 (t, 4.5Hz, 4H), 4.01 (t, 4.5Hz, 4H), 3.81-3.79 (m, 4H), 3.65-3.63 (m, 4H), 3.51 (t, 6.5Hz, 4H), 2.16-2.11 (m, 4H), 1.74-1.69 (m, 4H). $^{13}$C (125.7MHz, CDCl$_3$): $\delta$ (ppm) = 152.80, 151.41, 138.35, 114.87, 99.02, 71.22, 70.92, 70.35, 69.30, 68.85, 30.35, 28.87. IR (ATR) (v/cm$^{-1}$) = 3075, 2018, 2863, 1702, 1640, 1614, 1527, 1490, 1449, 1399, 1351, 1299, 1199, 1111, 1054, 949, 910, 848, 816, 769, 659, 631, 553, 535, 520, 513, 502, 493. EA (CHN) (%): Calculated: C = 59.98, H = 7.55, N = 5.83; Experimental: C = 59.59, H = 7.64, N = 5.67.

![Diagram of molecule 26]

Table 2.21: $^1$H NMR data for 26 in CDCl$_3$(500MHz).

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### 2.3.ee. Synthesis of 28

A 100 mL round bottom flask was equipped with a stir bar, reflux condenser, and charged with 26 (100 mg, 0.21 mmol, 1 eq) and a 1:3 mixture of THF: Ethanol (10 mL: 30 mL). Once the starting material was dissolved, sodium borohydride (80 mg, 2.08 mmol, 10 eq) was added in two portions over a 20 minute time interval. Cobalt chloride hexahydrate (5 mg, 10 mol%) was added and the mixture was heated to reflux overnight. The reaction was cooled to room temperature, filtered to remove the excess cobalt chloride hexahydrate, and the solvents were removed under reduced pressure. The remaining residue was dissolved in DCM (60 mL) and washed with water (2 x 50 mL). The remaining organic content was dried with sodium sulfate, and filtered. The solvent was removed under reduced pressure and a dark yellow oil was recovered (80 mg, 85% yield). The product was used without further purification. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 6.45 (s, 2H), 5.88-5.80 (m, 2H), 5.07-4.97 (m, 4H), 4.10 (t, 5Hz, 4H), 3.82 (t, 5Hz, 4H), 3.74-3.72 (m, 4H), 3.64-3.61 (m, 4H), 3.51 (t, 6.5Hz, 4H), 3.22 (s (br), 4H), 2.16-2.12 (m, 4H), 1.75-1.71 (m, 4H). $^{13}$C (125.7MHz, CDCl$_3$): $\delta$ (ppm) = 143.14, 135.43,
129.11, 114.85, 107.57, 70.88, 70.83, 70.30, 70.11, 69.80. IR (ATR) (v/cm$^{-1}$) = 3077, 2919, 2864, 1640, 1508, 1492, 1415, 1351, 1093, 1017, 956, 909, 865, 796, 659, 497, 444. EA (CHN) (%): Calculated: C = 63.69, H = 8.91, N = 6.19; Experimental: C = 54.24, H = 8.13, N = 3.85.

Table 2.22: $^1$H NMR data for 28 in CDCl$_3$ (500MHz).

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2.3.ff. Synthesis of 27

![Chemical reaction image]

A 100 mL round bottom flask was equipped with a stir bar and charged with 8 (200 mg, 0.93 mmol, 1 eq) and 50 mL of chloroform. Zirconium tetrachloride (22 mg, 10 mol%) was added and the mixture was stirred for 10 minutes. 22 (158 mg, 0.93 mmol, 1 eq) was then added to the mixture and it was left to stir overnight. The solution was filtered to remove excess zirconium tetrachloride and the chloroform was removed under reduced pressure. The crude product was purified using column chromatography (SiO2: 1:2 to 1:5: Hexanes to Ethyl acetate) to afford 27 (142 mg, 42% yield). $^1$H NMR (500MHz, CDCl$_3$): δ (ppm) = 10.12 (s (br), 1H), 7.96 (s, 2H), 6.88 (s, 2H), 3.80 (s, 6H), 2.50 (s, 6H).
Table 2.23: $^1H$ NMR data for 27 in CDCl$_3$ (500MHz).

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<th># of Protons</th>
<th>J(Hz)</th>
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<td>2</td>
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<td>d</td>
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<td>e</td>
<td>s</td>
<td>2.50</td>
<td>6</td>
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</table>

2.3.gg. Synthesis of 27

To a solution of 22 (100 mg, 0.59 mmol, 1 eq) and 8 (127 mg, 0.59 mmol, 1 eq) in dioxane (20 mL) was added iodobenzene diacetate (IBDA) (287 mg, 0.89 mmol, 1.5 eq). The mixture was stirred over a 24 hours period and monitored using both TLC and proton NMR spectroscopy. No reaction was observed and both monitoring techniques indicated the presence of starting material.
2.3.hh. Synthesis of 46

An oven dried 100 mL Schlenk flask was charged with 27 (100 mg, 0.27 mmol, 1 eq), evacuated, and backfilled with nitrogen. 50 mL of dry dichloromethane was cannulated into the flask and the mixture was cooled to -78°C. Prior to the addition of BBr₃, the starting material 27 began to crash out of solution due to poor solubility at this low temperature.

2.3.ii. Synthesis of 46

An oven dried 100 mL Schlenk flask was charged with 27 (100 mg, 0.27 mmol, 1 eq), evacuated, and backfilled with nitrogen. 50 mL of dry THF was cannulated into the flask and the mixture was cooled to 0°C. Prior to the addition of BBr₃, the starting material 27 began to crash out of solution due to poor solubility at this low temperature.
2.3.jj. Synthesis of 28B

A 100 mL round bottom flask was equipped with a stir bar and charged with 21 (200 mg, 0.39 mmol, 1 eq) and 40 mL of methanol. Concentrated hydrochloric acid (12 M) (1 mL, 11.7 mmol, 30 eq) was added slowly, followed by tin powder (0.556 g, 4.7 mmol, 12 eq). The round bottom was equipped with a reflux condenser and placed under a positive stream of nitrogen. The mixture was refluxed overnight and then cooled to room temperature. A solution of sodium hydroxide was added to neutralize the mixture (30 mL) and stirred for an additional 30 minutes. The excess tin was filtered off and the filtrate was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 50 mL) and all of the organic fractions were combined. The organic phase was washed with water (2 x 50 mL), dried with sodium sulfate, and filtered. The DCM was removed under reduced pressure to give a light yellow oil 28B (178 mg, 100% yield). $^1$H NMR (500MHz, CDCl$_3$): δ (ppm) = 6.33 (s, 2H), 4.10-4.08 (m, 4H), 3.82-3.80 (m, 4H), 3.74-3.72 (m, 4H), 3.64-3.61 (m, 4H), 3.50 (t, 6.5Hz, 4H), 3.20, (s (br), 4H), 1.73-1.31 (m, 14H), 1.19-1.05 (m, 4H).
Table 2.24: $^1H$ NMR data for 28B in CDCl$_3$ (500MHz).

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<td>d</td>
<td>m</td>
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<tr>
<td>e</td>
<td>m</td>
<td>3.64-3.61</td>
<td>4</td>
<td>-</td>
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<tr>
<td>f</td>
<td>t</td>
<td>3.50</td>
<td>4</td>
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<tr>
<td>h</td>
<td>m</td>
<td>1.73-1.31</td>
<td>14</td>
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<tr>
<td>i</td>
<td>m</td>
<td>1.19-1.05</td>
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</table>
A 100 mL round bottom flask was equipped with a stir bar and charged with 21 (1 g, 1.95 mmol, 1 eq) and 50 mL of methanol. Concentrated hydrochloric acid (12 M) (1.63 mL, 19.5 mmol, 10 eq) was added slowly, followed by tin powder (2.77 g, 23.4 mmol, 12 eq). The round bottom was equipped with a reflux condenser and placed under a positive stream of nitrogen. The mixture was refluxed overnight and then cooled to room temperature. A solution of sodium hydroxide was added to neutralize the mixture (30 mL) and stirred for an additional 30 minutes. The excess tin was filtered off and the filtrate was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 75 mL) and all of the organic fractions were combined. The organic phase was washed with water (2 x 50 mL), dried with sodium sulfate, and filtered. The DCM was removed under reduced pressure to give a light yellow oil 28 (0.883 g, 100% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) = 6.45 (s, 2H), 5.88-5.80 (m, 2H), 5.07-4.97 (m, 4H), 4.10 (t, 5Hz, 4H), 3.82 (t, 5Hz, 4H), 3.74-3.72 (m, 4H), 3.64-3.61 (m, 4H), 3.51 (t, 6.5Hz, 4H), 3.22 (s (br), 4H), 2.16-2.12 (m, 4H), 1.75-1.71 (m, 4H).

$^{13}$C (125.7 MHz, CDCl$_3$): $\delta$ (ppm) = 143.14, 135.43, 129.11, 114.85, 107.57, 70.88, 70.83, 70.30, 70.11, 69.80.

IR (ATR) (v/cm$^{-1}$) = 3077, 2919, 2864, 1640, 1508, 1492, 1449, 1415, 1351, 1359, 1093, 1017, 956,
909, 865, 796, 659, 497, 444. EA (CHN) (%): Calculated: C = 63.69, H = 8.91, N = 6.19;
Experimental: C = 54.24, H = 8.13, N = 3.85.

Table 2.25: $^1H$ NMR data for 28 in CDCl$_3$ (500MHz).

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2.3.II. Synthesis of 29

8 (400 mg, 1.88 mmol, 1 eq) was added to a 100 mL round bottom flask containing 50 mL of chloroform. Zirconium tetrachloride (44 mg, 10 mol%) was added and the mixture was stirred for 10 minutes until the solution became turbid. 28 (850 mg, 1.88 mmol, 1 eq) was dissolved in 10 mL of chloroform and added to the solution containing 8. The reaction was stirred overnight and the contents were filtered to remove excess zirconium tetrachloride. The solvent was removed under reduced pressure to give a dark red residue. The crude product was purified using column chromatography (SiO₂: 1:2 to 1:5: Hexanes to Ethyl acetate) to afford 29 (0.364 g, 30% yield) as a light brown oil. **¹H NMR (500MHz, CDCl₃):** δ (ppm) = 11.51 (s (br), 1H), 7.75 (s, 2H), 7.02 (s (br), 2H), 5.86-5.78 (m, 2H), 5.05-4.96 (m, 4H), 4.19-4.17 (m, 4H), 3.90-3.88 (m, 4H), 3.76-3.74 (m, 4H), 3.65-3.62 (m, 4H), 3.50 (t, 6.5Hz, 4H), 2.49 (s, 6H), 2.14-2.10 (m, 4H), 1.73-1.68 (m, 4H). **¹³C NMR (125.7MHz, CDCl₃):** δ (ppm) = 150.39, 146.78, 139.00, 138.21, 129.01, 128.46, 125.96, 114.93, 114.59, 101.19, 70.80, 70.56, 70.28, 70.21,
69.72, 69.21, 30.27, 28.77, 23.92. IR (ATR) (v/cm⁻¹) = 3076, 2919, 2864, 1640, 1593, 1483, 1448, 1403, 1377, 1348, 1295, 1240, 1181, 1123, 1061, 1027, 993, 909, 832, 754, 721, 644, 634, 556. EA (CHN) (%): Calculated: C = 60.29, H = 6.69, N = 4.54;
Experimental: C = 50.15, H = 6.41, N = 3.35.

Table 2.26: ¹H NMR data for 29 in CDCl₃ (500MHz).

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2.3.mm. Synthesis of 30

To a 100 mL round bottom flask was added 29 (300 mg, 0.46 mmol, 1 eq) and a 1:1 mixture of Hexanes/Diethyl ether (50 mL). Upon stirring, HBF₄·Et₂O (67 µL, 0.49 mmol, 1.05 eq) was added slowly. After an additional 20 minutes of stirring, a precipitate crashed out of solution and was collected via vacuum filtration. After washing with diethyl ether, a white solid was recovered 30 (0.262 g, 77% yield). The product was used with further purification. ¹H NMR (500MHz, CD₃CN): δ (ppm) = 12.38 (s, 2H), 7.71 (s, 2H), 7.14 (s, 2H), 5.84-5.78 (m, 2H), 4.98-4.92 (m, 4H), 4.17 (t, 4.5Hz, 4H), 3.84 (t, 4.5Hz, 4H), 3.74-3.71 (m, 4H), 3.62-3.60 (m 4H), 3.46 (t, 6.5Hz, 4H), 2.55 (s, 6H), 2.10-2.02 (m, 4H), 1.62-1.57 (m, 4H). ¹³C NMR (125.7MHz, CD₃CN): δ (ppm) = 149.60, 146.10, 140.63, 138.51, 132.84, 126.54, 125.13, 120.93, 114.26, 96.89, 70.60, 70.30, 69.95, 69.33, 69.17, 65.43, 30.03, 28.68, 23.36. IR (ATR) (v/cm⁻¹) = 3217, 2934, 2861, 1637, 1483, 1469, 1452, 1437, 1406, 1381, 1352, 1292, 1245, 1217, 1195, 1173, 1129, 1106, 1084, 1029, 977, 950, 909, 884, 831, 786, 765, 750, 717, 563, 525, 430. EA (CHN) (%): Calculated: C = 54.04, H = 6.32, N = 3.83; Experimental: C = 53.18, H = 6.13, N = 3.79.
Table 2.27: $^1H$ NMR data for 30 in CD$_3$CN (500MHz).

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<td>-</td>
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</table>
2.3.nn. Synthesis of 34

A cooled, oven-dried Schlenk flask was equipped with a stir bar, reflux condenser, and septum was charged, under nitrogen with 30 (200 mg, 0.27 mmol, 1 eq) and dry DCM (41 mL, 0.01 M). After 30 had dissolved, Grubb’s I catalyst (13.5 mg, 6 mol %) was added to the solution while maintaining a positive flow of nitrogen. The mixture was stirred and heated at 44°C for 24 hours after which another 6 mol% of Grubb’s I catalyst
was added to the flask. The reaction was stirred for an additional 24, and a third portion of 6 mol% Grubb’s I catalyst was added to the flask. After stirring for an additional 18 hours, 0.5 mL of ethyl vinyl ether was added and the mixture was stirred for 25 minutes. The solution was then cooled, and the solvents were removed under reduced pressure. The remaining residues was dissolved DCM and washed with a solution of sodium bicarbonate to neutralize the contents in solution. The phases were separated, the organic fraction was collected, and the solvent was removed under reduced pressure. The remaining black residue was purified using column chromatography (SiO₂: 3:1 DCM to Acetone). 31 and 33 were collected and acidified using HBF₄ to yield 32 (58 mg, 30% yield) as a white solid and 34 (15 mg, 4% yield) as a white solid.

**Characterization Data for 32**

Mp = 142⁰C. \(^{1}H\) NMR (500MHz, CD₃CN): \(\delta\) (ppm) = 12.88 (s, 2H), 7.73 (s, 2H), 7.29 (s, 2H), 5.43 (t, 4Hz, 1H), 5.39 (t, 4.5Hz, 1H), 4.29-4.26 (m, 4H), 3.92-3.89 (m, 4H), 3.75-3.71 (m, 4H), 3.59-3.57 (m, 4H), 3.45 (t, 7Hz, 4H), 2.59 (s, 6H), 2.08-2.00 (m, 8H). \(^{13}\)C NMR (125.7MHz, CD₃CN): \(\delta\) (ppm) = 148.90, 146.61, 140.63, 132.96, 126.43, 125.37, 97.23, 83.94, 71.01, 70.63, 69.81, 69.28, 68.65, 31.49, 29.89, 27.59. IR (ATR) (v/cm\(^{-1}\)) = 3555, 2947, 2891, 1689, 1636, 1546, 1492, 1465, 1392, 1352, 1295, 1243, 1026, 950, 904, 766, 715, 516.
**Table 2.28:** $^1\text{H NMR data for 32 in CD}_3\text{CN (500MHz).}$

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Characterization Data for 34

Mp = >300°C. $^1$H NMR (500MHz, CD$_3$CN): $\delta$ (ppm) = 12.62 (s (split), 4H), 7.72 (s (split), 4H), 7.05 (s (split), 4H), 5.27 (t, broad, 2H), 5.14 (t, broad, 4H), 4.13-4.09 (m, 8H), 3.81-3.60 (m, 24H), 3.58 (t, 6.5Hz, 8H), 2.57 (s, 12H), 2.00-1.93 (m, 16H). IR (ATR) ($\nu$/cm$^{-1}$) = 3198, 2260, 1500, 1468, 1458, 1407, 1287, 1222, 1191, 1149, 812, 768, 751, 733, 714, 700, 676, 632, 602, 593, 562, 549, 540, 525, 496, 483.

Table 2.29: $^1$H NMR data for 34 in CD$_3$CN (500MHz).

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<th>$\delta$ (ppm)</th>
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<td>m</td>
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<td>m</td>
<td>3.81-3.60</td>
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<td>t</td>
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<td>i</td>
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<td>j</td>
<td>m</td>
<td>2.00-1.93</td>
<td>16</td>
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</tbody>
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2.3.00. Synthesis of 31

A flask was charged with 34 (15 mg, 0.011 mmol) and 5 mL of DCM. An excess of Na₂CO₃ in water was added and stirred for 30 minutes. The layers were separated and
the DCM was removed under reduced pressure. The remaining residue was washed with hexanes (2 x 10 mL) and dried to give 33 (13 mg, Quantitative) as a light orange solid.

**Characterization Data for 31**

Mp = 69°C. \(^1\)H NMR (500MHz, CD\(_3\)CN): \(\delta\) (ppm) = 10.77 (s, (broad), 1H), 7.83 (s, 2H), 7.16 (s, 2H), 5.46-5.39 (m, 2H), 4.21-4.18 (m, 4H), 3.89-3.85 (m, 4H), 3.73-3.68 (m, 4H), 3.59-3.56 (m, 4H), 3.46 (t, 6.5Hz, 4H), 2.52 (s, 6H), 2.10-2.05 (m, 4H), 1.80-1.72 (m, 4H). \(^{13}\)C NMR (125.7MHz, CD\(_3\)CN): \(\delta\) (ppm) = 147.14, 139.19, 130.43, 129.89, 129.35, 128.48, 125.91, 125.63, 104.04, 70.95, 70.75, 70.39, 70.21, 69.65. IR (ATR) (v/cm\(^{-1}\)) = 2943, 2862, 1719, 1639, 1491, 1462, 1438, 1404, 1381, 1353, 1295, 1243, 1178, 1093, 1049, 1026, 947, 905, 890, 828, 760, 719, 711. MALDI-MS: Calculated for [M + H]\(^+\) [C\(_{31}\)H\(_{42}\)BrN\(_2\)O\(_6\)]\(^+\) m/z = 617.2226; found m/z = 617.2242

![Chemical structure of 31](image)

Table 2.30: \(^1\)H NMR data for 31 in CDCl\(_3\) (500MHz).
<table>
<thead>
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<th>Proton</th>
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<th>J(Hz)</th>
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<td>c</td>
<td>s</td>
<td>7.16</td>
<td>2</td>
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<td>d</td>
<td>m</td>
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<td>t</td>
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<td>4</td>
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<tr>
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<td>1.80-1.72</td>
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</tbody>
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2.3.pp. Synthesis of 33

![Synthesis Diagram](image-url)
A flask was charged with 34 (15 mg, 0.011 mmol) and 5 mL of DCM. An excess of Na$_2$CO$_3$ was added and stirred for 30 minutes. The organic layer was isolated and the DCM was removed under reduced pressure. The remaining residue was washed with hexanes (2 x 10 mL) and dried to give 33 (13 mg, Quantitative) as a light orange solid.

**Characterization Data for 33**

Mp = 180°C. $^1$H NMR (500MHz, CDCl$_3$): δ (ppm) = 10.22 (s (br), 2H), 7.83 (s, 4H), 6.99 (s (br), 4H), 5.23 (m, 4H), 4.03-3.40 (m, 40H), 2.45 (s, 12H), 1.97-1.90 (m, 8H), 1.56-1.52 (m, 8H). IR (ATR) (v/cm$^{-1}$) = 2923, 2850, 1720, 1640, 1492, 1444, 1351, 1297, 1259, 1215, 1158, 1093, 1020, 886, 857, 849, 796, 760, 747, 710, 660, 546, 532, 502, 479, 469, 443, 410. MALDI-MS: Calculated for [M + H]$^+$ [C$_{62}$H$_{83}$Br$_2$N$_4$O$_{12}$]$^+$ m/z = 1233.4374; found m/z = 1233.4359
Table 2.31: $^1$H NMR data for 33 in CDCl$_3$ (500MHz).

<table>
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<th>J(Hz)</th>
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<td>b</td>
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<td>-</td>
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<tr>
<td>c</td>
<td>s (br)</td>
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<td>-</td>
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<td>d</td>
<td>m</td>
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<td>-</td>
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<td>e-i</td>
<td>m</td>
<td>4.03-3.40</td>
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<td>-</td>
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<tr>
<td>j</td>
<td>s</td>
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<td>-</td>
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<td>k</td>
<td>m</td>
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<td>-</td>
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<td>l</td>
<td>m</td>
<td>1.56-1.52</td>
<td>8</td>
<td>-</td>
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</tbody>
</table>

2.3.qq. Synthesis of 36

![Chemical Reaction](image)

35 (5 g, 19.8 mmol, 1 eq) was placed into a 250 mL round bottom flask and dissolved in dichloromethane (150 mL). PCC (4.5 g, 20.8 mmol, 1.05 eq) was added to the flask and the mixture was stirred for 24 hours. Stirring was halted and the DCM was removed under reduced pressure. The residue was dissolved in a mixture of diethyl ether and water (200 mL: 150 mL) and placed into a separatory funnel. The organic layer was collected and the remaining aqueous fraction was extracted with diethyl ether (2 x 100 mL). All of the organic fractions were combined and washed with water (2 x 100 mL).
The organic content was dried with magnesium sulfate, filtered, and the diethyl ether was removed under reduced pressure. Left in the flask was a white solid 36 (3.77 g, 76% yield). The product was used without further purification. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 10.17 (s, 1H), 8.92 (t, 6Hz, 1H), 8.74 (d, 4Hz, 2H), 4.45 (qt, 7Hz, 2H), 1.45 (t, 6.5Hz, 3H).

![Chemical Structure of 36](image)

**Table 2.32: $^1$H NMR data for 36 in CDCl$_3$ (500MHz).**

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<th>J(Hz)</th>
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<td>b</td>
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<td>e</td>
<td>t</td>
<td>1.45</td>
<td>3</td>
<td>6.5</td>
</tr>
</tbody>
</table>
2.3.rr. Synthesis of 37

36 (387 mg, 1.55 mmol, 0.7 eq) was added to a 100mL round bottom flask containing 50 mL of chloroform. Zirconium tetrachloride (40 mg, 10 mol%) was added and the mixture was stirred for 10 minutes until the solution became turbid. 28 (1 g, 2.21 mmol, 1 eq) was dissolved in 10 mL of chloroform and added to the solution containing 8. The reaction was stirred overnight and the contents were filtered to remove excess zirconium tetrachloride. The solvent was removed under reduced pressure to give a dark red residue. The crude product was purified using column chromatography (SiO$_2$: 1:2 to 1:5: Hexanes to Ethyl acetate) to afford 37 (0.644 g, 61% yield) as a red oil. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ (ppm) = 10.23 (s (br), 1H), 8.90 (s, 2H), 8.75 (s, 1H), 7.17 (s (br), 2H), 5.86-5.77 (m, 2H), 5.04-4.96 (m, 4H), 4.47 (qt, 7.0Hz, 4H), 4.18-4.16 (m, 4H), 3.91-3.89 (m, 4H), 3.78-3.76 (m, 4H), 3.66-3.64 (m, 4H), 3.51 (t, 6.5Hz, 4H), 2.14-2.10 (m, 4H), 1.72 (t, 3.5Hz, 6H), 1.62-1.55 (m, 4H). $^{13}$C NMR (125.7MHz, CDCl$_3$) = 165.32, 146.99, 138.09, 131.59, 131.27, 130.99, 130.75, 114.77, 70.95, 70.41, 69.65, 69.07,
69.01, 61.55, 30.18, 28.09, 15.07. IR (ATR) (v/cm$^{-1}$) = 3078, 2977, 2934, 2867, 1721,
1640, 1606, 1534, 1452, 1432, 1395, 1369, 1351, 1303, 1236, 1105, 1058, 1023, 996,
911, 865, 762, 730, 646, 553. EA (CHN) (%): Calculated: C = 65.08, H = 7.38, N = 4.10;
Experimental: C = 64.20, H = 7.78, N = 3.56

![Chemical structure](image)

**Table 2.33:** $^1$H NMR data for 37 in CDCl$_3$ (500MHz).

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<th>J(Hz)</th>
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<td>1</td>
<td>-</td>
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<td>b</td>
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<td>-</td>
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<td>c</td>
<td>s</td>
<td>8.75</td>
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<td>-</td>
</tr>
<tr>
<td>d</td>
<td>s (br)</td>
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<td>-</td>
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<td>m</td>
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<td>f</td>
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<td>i</td>
<td>m</td>
<td>3.91-3.89</td>
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To a 100 mL round bottom flask was added 27 (500 mg, 0.73 mmol, 1 eq) and a 1:1 mixture of Hexanes/Diethyl ether (50mL). Upon stirring, HBF$_4$.Et$_2$O (105 µL, 0.77 mmol, 1.05 eq) was added slowly. After an additional 20 minutes of stirring, a precipitate crashed out of solution and was collected via vacuum filtration. After washing with diethyl ether, a white solid was recovered 30 (0.446 g, 79% yield). The product was used with further purification. Mp = 167ºC. $^1$H NMR (500MHz, CD$_3$CN): δ (ppm) = 12.80 (s (br), 2H), 8.85 (s, 2H), 8.82 (s, 1H), 7.20 (s, 2H), 5.87-5.79 (m, 2H), 4.99-4.91 (m, 4H), 4.50 (qt, 7.0Hz, 4H), 4.21 (t, 4.5Hz, 4H), 3.85 (t, 4.5Hz, 4H), 3.74-3.72, (m, 4H), 3.64-3.62 (m, 4H), 3.46 (t, 6.5Hz, 4H), 2.05-2.02 (m, 4H), 1.58 (t, 7.5Hz, 6H), 1.49-1.46 (m, 4H). $^{13}$C NMR (125.7MHz, CD$_3$CN): δ (ppm) = 164.30, 150.07, 138.56, 132.95, 131.99, 125.56, 114.23, 97.13, 70.62, 70.26, 69.98, 69.53, 69.22, 62.22, 30.06, 28.84, 13.66. IR
(ATR) (v/cm$^{-1}$) = 3171, 3081, 3073, 2919, 2874, 1719, 1641, 1610, 1567, 1493, 1462, 1445, 1420, 1364, 1347, 1310, 1280, 1248, 1204, 1166, 1146, 1122, 1098, 1056, 1041, 1024, 959, 939, 920.29, 902.42, 853.18, 841.93, 829.43, 807.77, 758.65, 720.61, 708.99, 674.14, 641.85, 627.65, 598.79, 556.68, 530.53, 519.14, 504.65, 487.91, 481.26, 469.25, 463.18. EA (CHN) (%): Calculated: C = 57.67, H = 6.67, N = 3.64;
Experimental: C = 55.99, H = 6.64, N = 3.57.

Table 2.34: $^1$H NMR data for 38 in CD$_3$CN (500MHz).

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<td>g</td>
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<td>1.49-1.46</td>
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</table>
A cooled, oven-dried Schlenk flask was equipped with a stir bar, reflux condenser, and septum was charged, under nitrogen with 38 (450 mg, 0.58 mmol, 1 eq) and dry DCM (58 mL 0.01 M). After 30 had dissolved, Grubbs’s I catalyst (29 mg, 6 mol%) was added to the solution while maintaining a positive flow of nitrogen. The mixture was
stirred and heated at 44°C for 24 hours after which another 6 mol% of Grubb’s I catalyst was added to the flask. The reaction was stirred for an additional 24, and a third portion of 6 mol% Grubb’s I catalyst was added to the flask. After stirring for an additional 18 hours, 0.5 mL of ethyl vinyl ether was added and the mixture was stirred for 25 minutes. The solution was then cooled, and the solvents were removed under reduced pressure. The remaining residue was dissolved DCM and washed with a solution of sodium bicarbonate to neutralize the contents in solution. The phases were separated, the organic fraction was collected, and the solvent was removed under reduced pressure. The remaining black residue was purified using column chromatography (SiO$_2$: 3:1 DCM to Acetone). 40 (12 mg, 3% yield) as a white solid and 42 (120 mg, 16% yield) as a light brown solid.

**Characterization Data for 41:**

Mp = 171°C. $^1$H NMR (500MHz, CD$_3$CN) = 12.93 (s (split), 4H), 8.86 (s, 4H), 8.83 (s, 2H), 7.01 (s, 4H), 5.23-5.07 (m, 4H), 4.50 (qt, J = 7.0Hz, 8H), 4.05-3.37 (m, 40H), 1.75 (t, J = 7.5Hz, 12H), 1.42-1.29 (m, 16H). $^{13}$C NMR (125.7MHz, CD$_3$CN) = 164.21, 149.30, 144.69, 132.86, 131.97, 131.82, 129.74, 124.99, 123.70, 96.69, 83.91, 70.55, 70.19, 70.09, 69.65, 69.07, 65.61, 62.21, 28.85, 28.42, 14.47, 14.44. IR (ATR), (v/cm$^{-1}$) = 3233, 2937, 2882, 1725, 1699, 1640, 1610, 1544, 1492, 1455, 1369, 1355, 1312, 1257, 1195, 1088, 1049, 1022, 952, 905, 849, 760, 721, 708, 574, 524.
Table 2.35: \textit{\textsuperscript{1}H NMR data for 41 in CD\textsubscript{3}CN (500MHz).}

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<td>d</td>
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</table>
Characterization Data for 39:

Mp = 121°C. $^1$H NMR (500MHz, CD$_3$CN) = 12.69 (s, 2H), 8.85 (s, 2H), 8.81 (s, 1H), 7.28 (s, 2H), 5.43 (m, 2H), 4.46 (qt, J = 7.0Hz, 4H), 4.06-3.40 (m, 20H), 1.91 (t, J = 7.5Hz, 6H), 1.56-1.41 (m, 8H). $^{13}$C NMR (125.7MHz, CD$_3$CN) = 164.04, 149.77, 144.55, 133.25, 132.82, 131.41, 125.31, 125.14, 123.41, 96.91, 83.91, 70.38, 69.83, 69.08, 68.99, 66.90, 62.21, 53.74, 31.92, 28.50, 14.06. IR (ATR) (v/cm$^{-1}$) = 3525, 2936, 2872, 1725, 1640, 1545, 1492, 1452, 1417, 1368, 1310, 1253, 1198, 1016, 953, 849, 759, 707, 558, 522.

Table 2.36: $^1$H NMR data for 39 in CD$_3$CN (500MHz).

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<th>J(Hz)</th>
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<td>s (split)</td>
<td>8.81</td>
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2.3. uu. Synthesis of 40

\[
\begin{align*}
\text{EtOOC} & \quad \text{COOEt} \\
\text{BF}_4^- & \\
\text{HN} & \quad \text{HN} \\
\text{39} & \quad \text{40}
\end{align*}
\]

40 (12 mg, 0.018 mmol, 1 eq) was dissolved in 5 mL of DCM and an excess of Na$_2$CO$_3$ was added and stirred for 30 minutes. The organic layer was isolated and the DCM was remove under reduced pressure. The residue remaining was washed with Hexanes (2 x 5 mL). The white solid was dried to give 39 (13.5 mg, quantitative yield).
Characterization Data for 40:

Mp = 99°C. $^1$H NMR (500MHz, CDCl$_3$) = 10.55 (s, 1H), 8.85 (s, 2H), 8.65 (s, 1H), 7.10 (s, 2H), 5.39-5.24 (m, 2H), 4.40 (qt, J = 7.0, 4H), 4.12-3.46 (m, 20H), 2.06-1.58 (m, 8H), 1.36 (t, J = 7.5Hz, 6H). $^{13}$C NMR (125.7MHz, CDCl$_3$) = 165.46, 147.33, 138.18, 131.80, 131.04, 130.55, 130.00, 114.89, 71.08, 70.84, 70.57, 70.35, 70.21, 69.94, 69.68, 61.78, 30.25, 29.45, 14.40. IR (ATR) (v/cm$^{-1}$) = 2981, 2920, 2867, 1720, 1636, 1606, 1453, 1397, 1369, 1303, 1236, 1160, 1105, 1058, 1023, 998, 916, 862, 845, 761, 728, 648, 561, 544. MALDI-MS: Calculated for [M + H]$^+$ [C$_{35}$H$_{47}$N$_2$O$_{10}$]$^+$ m/z = 655.3231; found m/z = 617.3236

![Chemical Structure of 40](image)

Table 2.37: $^1$H NMR data for 40 in CDCl$_3$ (500MHz).

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<td>b</td>
<td>s</td>
<td>8.85</td>
<td>2</td>
<td>-</td>
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2.3. vv. Synthesis of 42

\[ \text{42 (15 mg, 0.011 mmol, 1 eq) was dissolved in 5 mL of DCM and an excess of Na}_2\text{CO}_3 \text{ was added and stirred for 30 minutes. The organic layer was isolated and the DCM was removed under reduced pressure. The residue remaining was washed with Hexanes (2 x 5 mL). The white solid was dried to give 41 (17 mg, quantitative yield).} \]
Characterization Data for 42:

Mp = 160°C. $^1$H NMR (500MHz, CDCl$_3$) = 11.67 (s, 2H), 8.86 (s, 4H), 8.84 (s, 2H), 6.88 (s, 4H), 5.25-5.09 (m, 4H), 4.50 (qt, J = 7.5Hz, 8H), 4.28-3.47 (m, 40H), 1.95-1.47 (m, 16H), 1.48 (t, J = 7.5Hz, 12H). $^{13}$C NMR (125.7MHz, CDCl$_3$) = 165.57, 148.80, 146.50, 131.76, 131.73, 130.98, 130.88, 130.81, 130.24, 129.95, 129.77, 129.54, 129.21, 104.15, 96.76, 70.96, 70.83, 70.61, 70.36, 70.24, 70.04, 69.82, 69.66, 69.34, 69.15, 68.86, 68.74, 61.61, 29.45, 28.99, 26.97, 26.33, 14.43, 14.40. IR (ATR) (v/cm$^{-1}$) = 3230, 2935, 2880, 1722, 1690, 1638, 1611, 1542, 1495, 1455, 1370, 1361, 1312, 1259, 1195, 1088, 1053, 1017, 953, 907, 851, 765, 723, 577. MALDI-MS: Calculated for [M + H]$^+$

[C$_{70}$H$_{93}$N$_4$O$_{20}$]$^+$ m/z = 1309.6383; found m/z = 1309.6403
Table 2.38: $^1H$ NMR data for 42 in CDCl$_3$ (500MHz).

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<td>m</td>
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<td>7.5</td>
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2.3.ww. Synthesis of 43

1. Pd/c, H$_2$, MeOH/THF, 24h
2. HBF$_4$.Et$_2$O, MeCN

(39%)
A 100 mL, oven-dried Schlenk flask was charged with Pd/C 10 wt% (17 mg, 20 mol%) and 42 (100 mg, 0.76 mmol, 1 eq) in a mixture of Methanol/THF (20 mL:5 mL). The flask was evacuated, backfilled with nitrogen, and evacuated once more. The reaction vessel was flushed with H₂, which was introduced via a balloon, and the mixture was stirred overnight at room temperature. The mixture was filtered through a filter paper and the filtrate was played aside. The remaining contents on the filter paper were washed with a concentrated solution of HBF₄ in MeCN (2 x 20 mL). The solvent from the filtrate collected was removed under reduced pressure. The remaining solid was recrystallized from ethyl acetate and then washed with diethyl ether to give 43 (44 mg, 39% yield) as a yellow solid. Mp = 151°C. ¹H NMR (500MHz, CD₃CN): δ (ppm) = 12.88 (s, 4H), 8.89 (t, 1.5Hz, 4H), 8.84 (d, 1.5Hz 2H), 6.97 (s, 4H), 4.51 (qt, 7Hz, 8H), 4.10–4.08 (m, 8H), 3.77–3.75 (m, 8H), 3.63–3.61 (m, 16H), 3.36 (t, 6.5Hz, 8H), 1.48 (t, 7Hz, 12H), 1.30–1.27 (m, 8H), 1.26–1.23 (m, 8H), 1.04–1.00 (m, 8H). ¹³C NMR (125.7MHz, CD₃CN): δ (ppm) = 164.24, 149.44, 133.40, 132.89, 132.1, 96.55, 70.70, 70.62, 69.71, 69.58, 69.10, 62.23, 29.20, 28.96, 25.70, 13.64. IR (ATR) (v/cm⁻¹) = 2927, 2855, 1726, 1635, 1607, 1494, 1456, 1367, 1308, 1245, 1107, 1051, 1019, 951, 916, 863, 755, 726, 704, 569, 564.
Table 2.39: $^1H$ NMR data for 43 in CD$_3$CN (500MHz).

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2.3.xx. Synthesis of 44

43 (5 mg, 0.0033 mmol, 1 eq) was dissolved in DCM (5 mL) and an excess of triethylamine (1 mL). The solvents were removed under reduced pressure and the remaining residue was recrystallized from anhydrous ethanol to give 44 (4.40 mg) in quantitative yield.

Characterization Data for 44:

Mp= 77°C. $^1$H NMR (500MHz, CDCl$_3$): δ (ppm) = 11.62 (s (br), 1H), 11.31 (s (br), 1H), 9.02 (m, 4H), 8.74 (s, 2H), 6.88 (s, 4H), 4.46 (qt, J = 7.0Hz, 8H), 4.22-3.25 (m, 40H), 1.49 (t, J = 7.5Hz, 12H), 1.63-1.27 (m, 24H). $^{13}$C NMR (125.7MHz, CDCl$_3$): δ (ppm) = 165.62, 147.35, 146.37, 138.07, 131.74, 131.01, 130.78, 103.97, 96.31, 71.20, 71.02,
70.75, 70.18, 70.02, 69.67, 69.14, 68.96, 68.59, 61.60, 29.26, 26.23, 14.43. IR (ATR) 
(v/cm\(^{-1}\)) = 2926, 2858, 1719, 1633, 1534, 1581, 1393, 1369, 1303, 1234, 1165, 
1113, 1055, 1022, 983, 929, 917, 861, 846, 820, 814, 761, 727, 715, 682. MALDI-MS: Calculated for [M + H]\(^+\) [C\(_{70}\)H\(_{97}\)N\(_4\)O\(_{20}\)]\(^+\) m/z = 1313.6696; found m/z = 1313.6685

Table 2.40: \(^1\)H NMR data for 44 in CDCl\(_3\) (500MHz).

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2.3. yy. Synthesis of 45

43 (40 mg, 0.027 mmol, 1 eq) was dissolved in anhydrous ethanol (5 mL) to which a solution of 1 M NaOH (5 mL) was added. The solution was heated at 75°C for 24 hours, after which the anhydrous ethanol was removed under reduced pressure. A small amount of water (1 mL) was added to the remaining solution and the solution was slowly acidified using a 1 M solution of HCl until the solution had a pH = 7. A solid crashed out, which was filtered, and washed with water (2 x 1 mL) and diethyl ether (2 x 5 mL). This resulted in the collection of an orange solid 45 (31.8 mg, 98% yield). The product was used with further purification. Mp = >300°C. \(^1\)H NMR (500MHz, DMSO-d\(_6\)): \(\delta (ppm) = 13.17 (s (br), 6H), 8.93 (s, 4H), 8.54 (s, 2H), 7.19 (s (br), 4H), 4.17 (m, 8H), 3.81-3.48 (m, 32H), 1.46 (m, 8H), 1.22 (m, 16H). \(^13\)C NMR (125.7MHz, CD\(_3\)CN): \(\delta (ppm) =

\[
\begin{array}{|c|c|c|c|c|}
\hline
k & t & 1.49 & 12 & 7.5 \\
\hline
j, l, m & m & 1.63 - 1.27 & 24 & - \\
\hline
\end{array}
\]
166.62, 147.68, 132.74, 131.11, 130.05, 116.83, 100.32, 70.83, 70.76, 70.09, 69.60, 69.51, 29.70, 29.39, 26.11, IR (ATR) (v/cm\(^{-1}\)) = 2928, 2853, 1702, 1698, 1660, 1633, 1615, 1569, 1490, 1455, 1402, 1360, 1346, 1323, 1296, 1270, 1214, 1165, 1118, 1103, 1057, 993, 947, 911, 886, 827, 818, 797, 770, 706, 686, 671, 666, 628, 613, 576, 564.

MALDI-MS: Calculated for \([M + H]^+\) [C\(_{62}\)H\(_{81}\)N\(_4\)O\(_{20}\)]\(^+\) m/z = 1201.5444; found m/z = 1201.5432

![Chemical structure](image)

**Table 2.41: \(^1\)H NMR data for 45 in DMSO-d\(_6\) (500MHz).**

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<td>f</td>
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</table>
2.3.zz. MOF Synthesis

45 (6 mg, 0.005 mmol, 1 eq) and Cu(NO₃)₂·3H₂O (2.4 mg, 0.01 mmol) were dissolved in a solution of DMF/EtOH/H₂O (2.67 mL 3:3:2 v/v/v), to which 2 drops of HNO₃ was added. The solution was then injected through a 13 mm syringe filter (0.2 µm PTFE membrane) into a 20 mL borosilicate scintillation vial, which was rinsed with deionized water and dried at 100°C prior to use. The vial was then placed in a programmable heating oven at a constant heating rate of 1°C min⁻¹ to 65°C and kept at this temperature for 48 hours. The vial was then cooled to room temperature at a constant cooling rate of 0.1°C min⁻¹. A green powder crashed out of solution, which was not the desired MOF product.
Chapter 3: Summary and Future Work

3.1. Summary

As described in Chapter 2, two [2]daisy-chains were synthesized and characterized. DCD-1 (34) was synthesized over 10 steps, but was unfortunately obtained in very low yields (4%) after multiple modifications to the experimental procedure, which included varying the concentration of the reaction, as well as the temperature and catalyst loadings. The purification of the material proved to be extremely challenging, particularly in separating the daisy chain monomer 32 and DCD-1 (34), which attributed to the low isolated yield and absolute amount of DCD-1 (34) that was obtained.

In an attempt to improve the yields of the ring-closing metathesis reaction, a new Daisy Chain with an improved template was developed, which involved exchanging the methyl stopper groups in DCD-1 (34) with ethyl ester groups and the removal of Bromine for the synthesis of DCD2-TA (45). This was proposed in order to make the thread portion of the daisy chain precursor more acidic, thereby increasing the interaction strength between the crown ether wheel and the benzimidazolium recognition site. DCD-2 (41) was successfully synthesized in higher yields (16%) compared to DCD-1 (4%), but still proved to be extremely challenging to purify and ultimately separate DCD-2 (41) and the monomer byproduct (39). An adequate amount of DCD-2 was obtained and it was further functionalized following a reduction reaction and hydrolysis reaction to produce the DCD2-TA. DCD2-TA provided a suitable structure to serve as a linker for MOF synthesis. After conducting several trials using similar conditions reported to synthesize UWDM-156, no MOF was produced due to poor ligand solubility.
In turn, even though a MOF was not generated, the synthetic procedure pioneered to generate DCD-1 and DCD2-TA provides a range of future uses for similar materials if the yields from the ring-closing metathesis reaction can be optimized and the cyclic dimers can be produced on a larger scale.

3.2. Future Work

There are several approaches that can be taken to improve the yields of the [c2]daisy-chains. Firstly, for DCD-1, by taking note of the fact that higher yields were obtained for DCD-2 by improving the template and increasing the acidity of the thread, an interesting suggestion would be to use CF₃ groups as stoppers instead of methyl groups in DCD-1. This will not only promote a more electron poor thread, but also enable a very similar pillared linker to be used for MOF synthesis.
The only challenge arising from this idea is the potential steric hindrance brought about by the CF$_3$ groups, which may give rise to a challenging Suzuki coupling reaction (Scheme 3.1) to incorporate a pyridyl moiety and hence a coordination site. The soft, yet rigid nature of the neutral Daisy Chain would be an excellent choice as a flexible linker as a pillar in a layered Zn$^{II}$ MOF. Typically, pillared MOF’s are sensitive to the amount of solvent in the layers and they tend to collapse upon drying.$^{103}$ This opens up the potential to control the spacing between layers in the MOF, similar to the breathable porous coordination polymers described by Kitagawa.$^{66}$
Scheme 3.1: Suzuki Coupling reaction and hydrogenation of the CF$_3$ based DCD-1.

A more complex design would be to increase the length of each thread in the daisy chain by incorporating an additional recognition site. This will allow for control of both the rigidity and length of the daisy chain linker, which could be accomplished by altering the concentration of Li$^+$ ions (Figure 3.2). This would be quite intriguing, especially if the change in length of the crystal itself can be observed, similar to the recent reports in *Nature Chemistry.*$^{104}$
Figure 3.1: Observance of a nickel complex exhibiting reversible shape change upon thermal changes at room temperature. The crystalline shape change depicted between the high temperature (HT) and low temperature (LT) forms is induced by a $90^\circ$ rotation of uniaxially aligned oxalate molecules. Reproduced from Ref. 104.
**Figure 3.2:** Changes in linker length and rigidity that would be observed upon changes in Li\(^+\) ion concentration.

Some of the improvements that can be made for the synthesis of **DCD-2** include decreasing the size of the crown ether ring from 24C6 to 22C6 to see if this increases the binding strength of the ring to the recognition site. By also decorating the crown, solubility can be enhanced, which would thereby provide a better opportunity to at least form a MOF consisting entirely of daisy chain linkers to give a reasonable structure outlook.
References


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100. L-H. Du, Y-G. Wang, Synthesis., 2007, 5, 675-678


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Hi Joe.
I acknowledge that you have appropriately acknowledged my contributions to your research in your MSc thesis.
Steve

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Kelong Zhu

to sbroccaj

I, Dr. Kelong Zhu, give Joseph Sbrocca permission to use the results and ideas presented in the thesis entitled “Daisy Chain Ligands for the Control of Layering in Pillared Metal-Organic Frameworks”.

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