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Aldehydic C-H Amination Reactions via Co(II)-Based Metalloradical Catalysis and Construction of Novel Chiral meso-Amidoporphyrin Ligands

Christopher Lee Lizardi
University of South Florida, clizardi@mail.usf.edu

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Aldehydic C–H Amination Reactions via Co(II)-Based Metalloradical Catalysis and Construction of Novel Chiral meso-Amidoporphyrin Ligands

by

Christopher Lee Lizardi

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science
Department of Chemistry
College of Arts and Sciences
University of South Florida

Major Professor: X. Peter Zhang, Ph.D.
Jon Antilla, Ph.D.
Edward Turos, Ph.D.
Shengqian Ma, Ph.D.

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Dedication

I dedicate this thesis to my family and friends, who unknowingly, with their love and support throughout the years gave me the remarkable and audacious courage I needed to complete this grand undertaking. Thank you all for the amazing parts you each have played in my life.
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I want to give thanks to my major advisor and great mentor, Professor X. Peter Zhang. During the arduous process of graduate study Peter was always there to help encourage me and motivate me to pursue my love of chemistry. His passion and support in the field made me unafraid to ask exciting questions and probe new mysteries no matter how improbable they may have seemed.

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Abstract

Medium-sized organic ring synthesis poses a seemingly insurmountable challenge, and because of this it is a field under immense investigation. Heterocyclic containing medium-sized rings are common structural motifs in nature, which has caused researchers to investigate their potential biological activity and properties as materials. This research focused on the grand challenge of medium-sized heterocyclic ring synthesis, providing the synthesis community with new tools to generate these highly evasive products, while elucidating energetic and geometric properties of one of Nature’s least understood organic ring systems.

Cobalt(II)-Amidoporphyrins, [Co(D$_2$-Por)], are an emerging class of metalloradical catalysts (MRC) which can facilitate a wide range of atom and group transfer reactions. A strategy was employed using [Co(D$_2$-Por)] to carry out an intramolecular C–H amination reaction using sulfamoyl azides as the radical nitrene source to aminate the highly reactive aldehydic C–H bond. This newfound reaction allowed for the generation of previously unobtainable medium-sized heterocycles, which surprisingly provided a racemic mixture of chiral medium-sized rings.

A wide array of chiral amidoporphyrins including meso-heteroatom containing porphyrins were synthesized as well during the course of research to probe their potential as new chiral ligands for the emerging field of cobalt(II)-amidoporphyrin catalyzed MRC system. A practical synthetic scheme was discovered employing the highly selective Zn(II)-bromoporphyrin synthon to generate a new library of chiral amidoporphyrin ligands for the MRC system through well-established cross-coupling methodologies.
1.1 Introduction

In modern organic synthesis there lies a desire to utilize all reactive sites on a molecule, giving chemists complete control over the construction of new organic materials. For single bond formation and transformation on a substrate carbon atom, it would be ideal for chemists to employ radical chemistry. Radical reactions involve a 1 electron (e⁻) process where bonds are homolytically cleaved and subsequently formed by the union of two radical species.¹ In the case of organic radicals these species tend to occupy high energy and un-stable $p_{z,x,y,1}$ orbitals where they are found to be short-lived, highly reactive intermediates in most reactions. To precisely conduct the formation of new bonds onto a carbon skeleton researchers have searched for methods of controlling radical reactivity and generating “free” radicals *in situ*, these are commonly termed *persistent free radicals*.² Indeed many traditional methods have already been developed for performing radical reactions, such as the famous halogenation reactions involving $N$-halosuccinimides and radical-sensitive substrates.³ Not solely used for halogenations, radical chemistry has many notable applications such as dehalogenation, radical cyclization, and fragmentation amongst others.⁴

Unfortunately radical chemistry suffers many drawbacks associated with its high reactivity. With free radicals being as reactive as they are, stereo- and regio-selectivity is often sacrificed, and multiple side reactions can lead to reaction systems with many by-products. An example of this is the radical cyclization to synthesize pyranosides using azidoisobutyronitrile (AIBN) as a radical initiation source and tri-butyltin hydride as a hydrogen (TBTH) atom source.⁵ **Scheme 1.1**
outlines this typical lack of stereo-selective control in a radical cyclization reaction and the formation of multiple by-products.

**Scheme 1.1 Stereo-selectivity Issues in Radical Cyclization**

![Scheme 1.1](image)

Due to the abundance of stereo-chemical complexity in natural products and complex organic molecules, the chemist will ultimately choose reactions in his toolbox which give reliable results in terms of stereo-control. Thus it remains a worthy area of research to produce radical reagents which can provide researchers with the tools they need to synthesize complex molecular architectures. In response to this Zhang group has begun an immense research program of developing metal catalysts for stereo-selective transformations of ubiquitous organic feedstock molecules. From these research efforts a new class of metalloradical catalysts were discovered, cobalt(II)-amidoporphyrin catalysts.

### 1.2 Cobalt(II)-Amidoporphyrins and the Metalloradical Catalysis (MRC) System

Cobalt(II)-porphyrins ([Co(II)(Por)]) are an emerging class of metalloradical catalysts which have recently been used to catalyze a wide array of organic reactions, most notably those involving an atom or group transfer reaction. In these catalyst systems the cobalt center exists as an open shell d⁷ metal, giving it radical character in its unpaired d_z² orbital. Through chelation with the porphyrin ring, a square pyramidal molecular geometry is adopted by the catalyst. This geometry forces the radical in the d_z² orbital of the catalyst to be positioned perpendicular to the
porphyrin ring. This in turn leads the $d_{z^2}$ orbital as an exposed metalloradical, granting [Co(II)(Por)] catalysts the ability to react with suitable substrates which enter the pocket of the porphyrin macrocycle. Radical transformations by [Co(II)(Por)] proceed via a step-wise fashion, which allows for unique reactivity and stereo-selectivity on a substrates’ reactive sites. The porphyrin ligand also serves to enhance the reactivity of these catalytic systems by providing auxiliary steric and electronic control parameters, such as electron donating/withdrawing groups or chiral inducing moieties strategically positioned on the porphyrin ring. Indeed these unique building parameters have been exploited by workers in the Zhang group, and led to the development of a large porphyrin-based catalyst toolbox. Figure 1.1 shows a general description of the [Co(II)(Por)] catalyst system and key design features for developing stereo- and regio-selective catalysts.

**Figure 1.1** Cobalt(II) Catalysts with Porphyrin Ligand Promoted Stereo- and Regio-Control

As stated previously, one of the prime features of [Co(II)(Por)] catalysts is the metalloradical nature of the Co(II) center. Porphyrins as tetradeutate macrocyclic ligands are known to readily generate stable Co(II) species by reaction of the four nitrogen atoms binding the metal in Co(II) salts. The electron configuration of this $d^7$ cobalt species is $(d_{xy})^2(d_{xz}, d_{yz})^4(d_{z^2})^1$, leaving the unpaired electron exposed, and opposite the coordination environment of the porphyrin ligand. This unique geometry promotes the accessibility of reactive organic species to
the metalloradical. To illustrate this, a detailed diagram of the ligand field splitting of the [Co(II)(Por)] system is provided in **Scheme 1.2** outlining the electronics of the system.

**Scheme 1.2** Electron Pairing of [Co(II)(Por)] Catalysts

![Diagram showing electron pairing of [Co(II)(Por)]](image)

This type of radical chemistry seen in cobalt porphyrin catalysts is converse to the common ionic metal chemistry that is typically employed in catalytic atom and group transfer reactions. Most 2 electron (e⁻) closed shell systems react with substrates in a concerted mechanism, in contrast [Co(II)(Por)] react in a step-wise fashion. Shown in **Scheme 1.3** is a representative catalytic cycle of both a closed shell 2 e⁻ process and an open shell 1 e⁻ process catalyzed by [Co(II)(Por)] illustrating their differences in reactivity.

**Scheme 1.3** Cyclopropanation by Closed Shell and Open Shell Catalysts

![Diagram showing cyclopropanation catalysis](image)
The catalytic cycle for closed shell systems begin with an ionic electrophilic addition of the carbene precursor to the metal center, decomposing the diazo group releasing nitrogen gas. This type of carbene formation is known as a Fischer-type carbene. In Fischer carbenes the carbon atom exists in the singlet state as a pair of electrons occupies an $sp^2$ orbital and no electron-electron splitting occurs between this orbital and a neighboring $p$ orbital. Then as the olefin substrate approaches the active site of the catalyst, a strong coordination bond is formed, bringing the olefin in close proximity to the highly reactive metal-carbene. As shown above, closed shell catalysts have a final concerted step where cyclization occurs via a 3-coordinate 4-electron process.

In the case of [Co(II)(Por)] in open shell catalysis, the reaction begins similarly with decomposition of the diazo group releasing nitrogen gas and forming a persistent carbon radical, Figure 1.2 shows the formation of a carbene radical in conjunction with a classical metal-carbene. As the olefin substrate approaches it undergoes radical addition with the newly formed organic radical on the cobalt center. Within each of these steps a persistent organic radical is formed, allowing the potential for a wide array of transformative possibilities, owing as well the possibility of cascade reactions. In the last step of the Co(II)-based MRC there exists a short-lived $\gamma$-alkyl radical, being positioned on a freely rotatable $\sigma$-bond. This free rotation allowed in substrates in the MRC system grants the opportunity for the porphyrin ligand to impart chirality on the substrate via intramolecular interactions.

![Figure 1.2 Co(II)-Carbene Radical and Fischer Carbene](image-url)
Taking this detailed mechanistic explanation into account, it clear to see that the chemistry found in [Co(II)(Por)] based MRC is not equivalent to the typical ionic metal-carbene chemistry seen so often in Rh(II) and Cu(I) based systems. By imparting the radical character from the Co(II) metal center to a suitable organic substrate, the advantages of radical chemistry and catalysis can be joined in the [Co(II)(Por)] system. In addition to this, modifications of the porphyrin ligand play a role in modifying the reactivity and stereo-selectivity on a given substrate, and the intricate relationship of the porphyrin ligand and the organic substrate has become a fertile research topic in itself.

1.3 The Porphyrin Ring and Amidoporphyrins as Ligands for Co(II)-MRC

Porphyrins are a class of heterocyclic organic macrocycles that are pervasive in nature, and have attracted the interest of researchers since their first synthesis by Fischer and Halbig in 1926. Porphyrins have an extensive \( \pi \) system of 26 e\(^{-}\) delocalized throughout the ring. Following Hückel’s rule for aromaticity where \( 4n+2 \) is calculated to with \( n \) as a positive integer, we see that porphyrins are aromatic with \( n = 6 \). This makes porphyrins relatively stable molecules, yet still able to undergo traditional chemistries, which can be exploited by the chemist to functionalize the porphyrin ring further. Indeed, because of their unique electronic system and modifiable architecture, porphyrins have seen application in fields as diverse as solar energy conversion, functional dyes, organic electronics, photodynamic therapy, catalysis, metal-organic materials and many others.

Porphyrins have definitive reactive sites positioned throughout the macrocycle which make it possible for researchers to tailor and construct diverse porphyrin molecules. These sites are present on both the periphery of porphyrin ring, the meso- and \( \beta \)-positions, and within the cavity with two weakly acidic N–H pyrrole units. By transformation of these localities, porphyrins may be functionalized through diverse chemistries. First are the meso-positions, which are located on the -5, 10, 15, and 20 positions of the porphyrin ring. These meso-positions are
comprised of \( sp^2 \) carbons which bridge the four pyrroline units together to close the macrocycle. 

*Meso*-carbons exhibit marked aromatic chemistry and are among the most common positions that research groups choose to functionalize. The \( \beta \)-positions of the porphyrin ring are the -2, 3, 7, 8, 12, 13, 17, 18, 22, and 23 positions, which correspond to the \( \beta \)-positions of the pyrrole ring (C3 and C4 on a pyrrole cycle). As is the case with the pyrrole motif, the porphyrin \( \beta \)-positions show diminished reactivity through aromatic substitutions (Electrophilic aromatic substitutions, \( S_{N,Ar} \)), and instead portray the traditional olefin chemistry of electrophilic addition reactions (bromination, hydration, etc.). Finally are the pyrrole N–H units themselves, while being weak acids (\( pK_a = 15 - 16 \), \( pK_a = 13 - 16 \)) are still reactive to Brønsted-Lowry acid-base reactions, causing them to be fully deprotonated in the presence of such strong bases as hydroxides, alkoxides, and highly-basic tertiary amines. For an overview of this diverse porphyrin chemistry, **Figure 1.3** demonstrates the structure and generic reactivity of the porphyrin macrocycle.

![Porphyrrin Reactive Sites](image)

**Figure 1.3** Functional Positions of the Porphyrin Ring

Zhang and co-workers had early on saw the potential of using porphyrins and their derivatives to make ligands for catalytic atom and group transfer reactions. Commercially available porphyrins or symmetric porphyrin ligands were initially used for diastereo-selective and enantio-selective cyclopropanations reactions, such as in the work done in 2003 using ethyl diazoacetate (EDA) with styrene derivatives to generate *trans* predominant cyclopropanes. Indeed, Zhang and co-workers found that *trans:cis* selectivity’s as high as 92:8 using [Co(TPP)] (TPP = *meso*-tetraphenylporphyrin) as the catalyst with a catalyst loading of 2 mol % and *N*
methylimidazole as an additive to improve diastereo-selectivity, presumably due to coordination at the –z axial position on the Co(II) center.\textsuperscript{10} The effect of chiral porphyrin ligands on the enantio-control was also studied in this work. It was discovered that use of the chiral porphyrin catalyst [Co(II)(P1)] with a chiral lactam on the 2,6-position of the phenyl ring on the meso-positions of the porphyrin ligand could influence enantio-selectivity and provided a 77% ee for the predominant trans isomer.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{chiral_catalyst.png}
\caption{Chiral Co(II)-Porphyrin Catalyst for Preliminary Stereo-selective Cyclopropanation}
\end{figure}

With these promising preliminary results the Zhang group continued pursuit of utilizing chiral porphyrin ligands for stereo-selective transformations. This in turn led to their seminal work, published in 2004, using chiral porphyrin ligands specifically tailored for stereo-selective cyclopropanation reactions.\textsuperscript{11} The porphyrin ligands used in this work represented a new generation of porphyrins that are synthesized from what has been termed by Zhang and co-workers as bromoporphyrin synthons (1). Synthesis of bromoporphyrins are carried out using Lindsey conditions for porphyrin condensation, whereby a MacDonald [2+2] cyclization occurs between two moles of meso-(2,6-dibromophenyl)dipyrrromethane and two moles of user defined aldehyde with the desired R substituent. The reaction produces a 5,15-bis(2',6'-dibromophenyl)porphyrin (1) with the R functionalities present on the meso-10, 20-positions from the parent aldehyde. Employing well-established Buchwald-Hartwig C–N cross-coupling
methodologies, chiral amide groups can then be coupled on the bromoporphyrin synthon of choice generating a chiral amidoporphyrin (2). The cross-coupling reactions are practical and afford high yielding products, these quadruple amidations produce products in up to 88% yield, which equates to ～97% yield per single amidation reaction. This type of synthetic scheme allows for the modular and divergent synthesis of a large “toolbox” (Figure 1.5) of chiral porphyrin ligands, with diverse functional groups strategically arranged on the porphyrin periphery (Scheme 1.4).

**Scheme 1.4 Modular and Divergent Synthesis of Chiral Amidoporphyrin Ligands**

To generate a [Co(II)(Por)] catalyst (3), a metallation reaction is carried out, causing metallation of the two pyrrole N–H groups with a Co^{2+} salt, typically CoCl\(_2\). Due to the strong chelation of the Co\(^{2+}\) ion by the tetradentate porphyrin, dissociation of the Co\(^{2+}\) into the free ion does not occur even under high temperatures, as the newly formed catalyst is thermodynamically stable. In addition to this, these [Co(II)(Por)] catalysts are resilient to air and moisture.
decomposition, and can be used in simple reaction protocols, including open air reactions. Indeed their stability allows the catalysts to be stored almost indefinitely without the need of a glove-box or other specialized equipment, thus granting researchers the propensity to store and compile large libraries of [Co(II)(Por)] catalysts for future investigations.

Figure 1.5 A Catalyst “Toolbox” of Chiral Co(II)-Amidoporphyrins

1.4 Intramolecular C–H Amination by Co(II)-based MRC

In this thesis Co(II)-based MRC was studied for an intramolecular C–H amination of sulfamoyl azides, inserting a long-lived nitrogen radical into highly reactive aldehydic C–H bonds. In order to adequately discuss this chemistry under research, a synopsis of intramolecular C–H amination by Co(II)-MRC shall be discussed. Indeed, [Co(II)(Por)] have not been used for C=C cyclopropanation reactions alone as previously discussed, but have found application in a myriad of atom and group transfer reactions (Figure 1.6).6
Figure 1.6 Co(II)-Metalloradical Catalysis of Atom and Group Transfer Reactions

Of these reactions intramolecular C–H amination finds great interest among researchers in the chemical sciences due to its practical synthesis of chiral, and complex nitrogen-based heterocycles. In nature and technology, nitrogen-based heterocycles play a commanding role in biologically active molecules, natural products, medicines, and organic materials. In lieu of traditional amine syntheses, it would be paramount for chemical workers to utilize ubiquitous C–H bonds for the synthesis of highly desirable amines on a carbon skeleton.

The traditional method for carrying out C–H amination reactions has focused on nitrene generation in situ with an external oxidant, followed by subsequent reaction with a metal catalyst and the substrate. Common nitrene sources include hypervalent iodine reagents, and haloamine-T reagents, which have highly documented success in the literature (Figure 1.7). However, several disadvantages occur in using these methods, such as the undesirable ArI byproducts in the reaction with hypervalent iodine, or in both cases the need of an external oxidant/nitrene source in addition to the substrate. Also, oxidative or basic reaction conditions can readily decompose these reagents, limiting their versatility. It is in response to this that the Zhang group pursued a different class of nitrene precursors for intramolecular C–H amination.
Organic azides are an important class of highly reactive molecules as evidenced by their application in traditional chemistries such as; the Staudinger ligation, the Schmidt reaction, and the Curtius rearrangement. Azides are prepared by facile synthetic routes with wide functional group tolerance and substrate scope, making them ideal candidates for synthesizing substrate intermediates. Moreover, many organoazides have already been made commercially available, further bolstering their practicality to the synthetic chemist. In regards to C–H amination, organoazides are of paramount significance due to their parallel structure and reactivity as of diazo reagents (Figure 1.8). Diazao reagents have already been shown to decompose to highly reactive metal-carbene or carbon radical species via closed shell (2 e\(^{-}\)) and open shell (1 e\(^{-}\)) catalysis respectively. Seeing the potential for azides to react in a manner similar to diazo reagents, the Zhang group was then prompted to investigate azides’ decomposition into persistent nitrogen radicals by reaction of the Co(II)-MRC system.

**Figure 1.7** Traditional Nitrene Sources for C–H Amination Reactions

**Figure 1.8** Parallels of Organic Azides and Diazo Reagents
The preliminary study on intramolecular C–H amination using azides by the Zhang group was carried out in 2007, where it was found that indeed [Co(II)(Por)] could decompose arylsulfonyl azides and bring about an intramolecular C–H amination. Upon generation of the nitrogen radical, a radical hydrogen atom abstraction (HAA) occurs on the highly reactive benzylic C–H bond (~90 kcal/mol). This newly formed benzylic radical can then close in a 5-exo-tet cyclization forming the desired product. Using the commercially available [Co(TPP)] as the catalyst with a loading of 2 mol %, a wide range of benzosultam derivatives were synthesized from 1°, 2°, and 3° benzylic C–H bonds in excellent yields (> 99%, Scheme 1.5).

**Scheme 1.5 Intramolecular C–H Amination by [Co(TPP)] with Arylsulfonyl Azides**

Intrigued with these preliminary results, Zhang and co-workers set out to explore further Co(II)-based intramolecular C–H amination reactions. In 2010 they published their work on C–H amination using phosphoryl azides as the nitrene radical source (1). The [Co(II)(Por)] catalyzed system was found to catalyze 1°, 2°, and 3° C–H bonds, and not solely at the highly reactive benzylic carbons (1b). Interestingly, when the position for a 1,6-C–H nitrene insertion was blocked as in 1b, the 1,7-C–H amination occurred, affording 7-membered cyclophosphoramidates (2b). However, the most remarkable find of this work was the ligand accelerated catalysis brought on by hydrogen bonding between the substrate and the amido groups on the porphyrin periphery (Scheme 1.6).
Scheme 1.6 Phosphoramidation by [Co(II)(Por)] and Ligand Accelerated Catalysis

Using the commercially available [Co(TPP)] ([Co(II)(P1)]) no noticeable reaction was observed, however, upon screening the newly synthesized 3,5-di-t-Bu-IbuPhyrin ([Co(II)(P2)]) almost quantitative yields (>99% yield) could be obtained with a broad substrate scope. The rationale behind this marked increase in reactivity is that during the key nitrogen radical formation step, the highly reactive radical intermediate can be stabilized via hydrogen bonding with the amide moieties on the porphyrin ring. The postulated hydrogen bonding intermediate is surmised in Figure 1.9, showing the (N5) N–H---O=P (O5) hydrogen bond with a calculated distance measured at 2.327 Å.
The discovery of the dramatic role that porphyrin ligands play in Co(II)-MRC has become a hallmark in intramolecular C–H amination reactions pioneered by the Zhang group. Indeed, the strategic use of hydrogen bond donating ligands has become a central motif in Co(II)(-MRC, owing to many successful future works pursued by the Zhang group. In their following work, this strategy was employed in intramolecular C–H amination of sulfamoyl azides (3). As was found in the previous phosphoramidation system, no reaction occurred using [Co(TPP)], however once conducted with an amidoporphyrin, a yield of 95% was achieved in the reaction. Using Co(II)-3,5-di-t-Bu-IbuPhyrin again as the catalyst ([Co(II)(P1)], reaction parameter screening was conducted, finding that the optimal aminations occurred in trifluorotoluene as a solvent, at 40 °C with MS 4A as a water scavenger over the course of 20 h. The crux of this work was the demonstration of aliphatic C–H bond amination of 1°, 2°, and 3° C–H bonds. Juxtaposed to the
previous amination with phosphoryl azides, which forced C–H amination at an aliphatic carbon due to blocking the benzylic carbon with two Me groups, the insertion into aliphatic C–H bonds was achieved on ordinary aliphatic substrates (3, Scheme 1.7).

Scheme 1.7 Intramolecular C–H Amination with Sulfamoyl Azides

\[
\begin{align*}
\text{3} & \quad \xrightarrow{[\text{Co(II)}(\text{P2})](2 \text{ mol } \%) } \quad \text{4} \\
\text{PhCF}_3, 4\text{Å MS, 40 °C, 20 h} & \quad \text{15 examples up to 99\% yield}
\end{align*}
\]

With the growth of intramolecular C–H amination, it was inquired whether or not this highly reactive system could be used for chemo-selectivity testing in the presence of other well-known atom/group transfer pathways. Nitrene chemistry has a long standing history with successful aziridination reactions, and it was clear from early on that substrates with the olefin functionality present may have chemo-selectivity issues that would need to be addressed. Seeing this challenge as a grand opportunity to put intramolecular C–H amination chemistry to the test, Zhang and co-workers explored in their 2011 work the chemo-selective allylic C–H amination over the C=C aziridination pathway. Remarkably, using 5a as a model substrate, the ratio of C–H amination (6a) product to C=C aziridination (7a) was found to be >99:1. With a broad substrate scope, excellent yields and mild conditions, the Co(II)-MRC chemo-selective allylic C–H amination with sulfamoyl azides proved unequivocally the high reactivity and selectivity of metalloradical chemistry.
Following some of the examples shown in Scheme 1.8, the high level of chemo-selectivity by Co(II)-MRC can be seen. The substrates 6a and 6b demonstrate C–H amination even in the presence of C–H bonds of differing reactivity. However one may attempt to argue that the C=C aziridination is unfavorable in these reactions due to the formation of the thermodynamically less favored 7-membered ring (7). In response to this substrates 6c and 6e were synthesized and still exhibited the preferential C–H amination over C=C aziridination. Interestingly substrate 6f showed a chemo-selective reaction as well, that is the insertion into an allylic C–H bond over an aliphatic
C–H bond. This is presumably due to the much lower homolytic B.D.E. for allylic C–H (~89 kcal/mol) bonds in comparison with aliphatic C–H (~101 kcal/mol) bonds.20

Inspired by the high chemo-selectivity observed in allylic C–H amination, Zhang and co-workers next studied the amination of propargylic C–H bonds.21 Propargyl amines had until recently been considered difficult to access, yet highly valuable synthetic intermediates due to the proximity of reactive sites on these molecules.22 Traditionally, difficult to handle metal alkynylides would be employed to undergo a C=N addition on imines to generate the highly sought after propargyl amines.23 Despite the high yields obtained, the system remains impractical in terms of starting material synthesis and handling. Rh₂-based nitrene insertions were found to fare no better, as the electrophilic rhodium center would undergo addition with the reactive π orbital of the C≡C bond and lead to moderate yields with undesirable by-product formation.24

Once tested, the Co(II)-MRC system had no difficulty in affording propargyl amines in excellent yields, just as in the allylic C–H amination reaction. Using 2 mol % of [Co(II)(P2)] to catalyze the intramolecular C–H amination of sulfamoyl azides (8), a diverse substrate scope was explored (9, 19 examples in up to 99% yield). Due to the high degree of functional group tolerance, this system would provide synthetic chemists with a practical system for the preparation of structurally diverse molecules containing the sensitive propargyl amine group (9). Scheme 1.9 outlines the general procedure for synthesizing these functionalized propargyl amines by Co(II)-based intramolecular propargylic C–H amination.
Of the C–H amination reactions explored thus far, all experience high reactivity and excellent chemo-selectivity due to the benefit of insertion into C–H bonds that are greatly susceptible to homolytic cleavage. To demonstrate the utility of Co(II)-MRC, nitrene radical insertion into a un-reactive, yet still omnipresent C–H bonds would be highly attractive. This in turn prompted the Zhang group to investigate the intramolecular C–H amination of electron-deficient C–H bonds. If a successful C–H amination could be achieved with electron-deficient C–H bonds this could lead to a new method of synthesizing α-amino acid derivatives.

On first consideration it would be presumed that electron-deficient C–H amination would be unfeasible. Indeed it had previously been hypothesized that electron deficient C–H amination would be incompatible with the electrophilic C–H amination systems of the more commonly used ionic nitrene insertion catalysts, and thus this reaction remained mostly un-explored to researchers using Rh$_2$ and other closed shell metal catalytic systems except for a few sole references in the literature. For the Co(II)-MRC based system, one may argue that due to the unfavorable resonance stabilization of the intermediate organic radical after hydrogen atom abstraction intramolecular C–H amination of the α-C–H bond would be improbable. However, upon screening the reaction for activity, it was found that Co(II)-based MRC could in fact bring about an amination into electron-deficient C–H bonds. Surprisingly, even the commercially
available [Co(TPP)] could bring about a reaction, albeit at relatively high catalyst loadings for Co(II)-MRC. To explain this remarkable reactivity one need only look at the bond dissociation energy for a typical electron-deficient substrate (B.D.E.-e−-det. ~ 92 kcal/mol). Even though these type of bonds may be unreactive in the presence of electrophilic catalysts, due to the ease of homolysis of the α-C–H bond, metalloradical catalysis can indeed still proceed.

**Scheme 1.10** Electron-Deficient C–H Amination Using [Co(II)(Por)]

![Scheme 1.10](image)

Using the $D_{2h}$-symmetric Co(II)-3,5-di-t-Bu-lbuPhyrin ([Co(II)(P2)]) as the catalyst, efficient α-C–H amination of electron-deficient C–H bonds was carried out (**Scheme 1.10**). A high
functional group tolerance was observed in this system, as insertion into the $\alpha$-C–H bond of an ester (11a), amide (11b), ketone (11c), and nitrile (11d) were all supported. Interestingly, a high diastereo-selectivity was observed in the presence of substrates (11e, 11f, 11g, and 11h), showing that a regio-selective C–H amination could be realized. This regio-selectivity was unobtainable in the Rh$_2$ based amination. This electron-deficient C–H amination reaction system highlighted the uniqueness of Co(II)-based MRC, and opened many avenues in Co(II)-MRC research. Looking at the results of this work, we are able to see that there was no mention of insertion into the C–H bond $\alpha$ to an aldehyde. There is good reason for this, as the discoveries made from using aldehyde containing substrates led to the work that will herein be described in this thesis.

To further comprehend Co(II)-catalyzed intramolecular C–H amination it is imperative to understand the mechanistic path by which the reaction proceeds. Bas de Bruin and co-workers reported in 2011 their findings for intermolecular C–H amination catalyzed by Co(II) porphyrins. The evidence found to elucidate the mechanism was based on density functional theory (DFT) calculations and solution electron paramagnetic resonance (EPR) spectroscopy. Although this study was for the intermolecular variant, key parallels in terms of reactivity and the intermediates formed can be imposed on the intramolecular reaction.

The catalytic cycle begins with coordination of the organic azide to the Co(II)-center (A) in the porphyrin ring. In the model system used by de Bruin and workers (methyl azidoformate as the azide, ethylbenzene as the substrate and [Co(TPP)] as the catalyst), the activation energy for this first step was found to be exothermic at $\sim$ -1.8 kcal/mol. The Co(II)-azide complex (B) then undergoes azide decomposition, forming a new nitrene radical ligand on a Co(III)-complex (C), and releasing nitrogen gas as the by-product. The activation enthalpy ($\Delta H^\ddagger$) for this previous step is on the order of +12.3 kcal/mol which is in line with the experimentally determined optimal conditions for temperature ($\sim$40 °C). Once the substrate approaches the newly formed nitrogen
radical a facile hydrogen atom abstraction can occur bringing about the Co(III) complex (D) and a “free” short-lived organic radical from the substrate. From here, a close-contact pair of the organic radical and Co(III)-ammine complex occur within the solvent shell of the system. The “free” radical can then “back attack” the nitrogen atom of this Co(III)-ammine complex, releasing the desired amine product and regenerating the active catalyst (A).

**Scheme 1.11** Mechanism of Intermolecular Co(II)-Catalyzed C–H Amination

Intramolecular C–H amination shares the first two elementary steps as intermolecular C–H amination, with coordination to Co(II) followed by subsequent nitrene radical formation. However instead of a hydrogen atom abstraction on a separate substrate molecule, the intramolecular variant causes hydrogen atom abstraction on a reactive C–H bond on itself. Finally, a radical cyclization can occur affording the C–H amination product as seen experimentally.
1.5 Summation of Co(II)-Based Metalloradical Catalysis

In summary, we have shown that Co(II)-amidoporphyrins are an emerging class of highly selective catalysts which interact through an unique radical pathway. By special design of the porphyrin ligand, it is possible to accelerate the reaction to favorable yields and to influence stereo-selectivity through the use of intramolecular interactions between the metal-bound substrate and ligand. Finally, organic azides were chosen as the nitrene radical precursors applied in this Co(II)-MRC system for their ease of synthesis, high reactivity and generation of the benign by-product, N₂ gas.

1.6 References


Chapter 2. Divergent Synthesis of a New Generation of Chiral Amidoporphyrin Ligands for Cobalt(II)-Porphyrin Based Metalloradical Catalysis

2.1 Background on Porphyrins in Co(II)-MRC and the New Generation Porphyrin Ligands

Porphyrins and amidoporphyrin derivatives have been shown to be suitable ligands for Co(II)-based metalloradical catalysis.\(^1\) By utilizing the unique chemistry of the porphyrin ring, porphyrin ligands can be tailored and synthesized to meet a specific end-use. Moreover, porphyrin ligands are able to promote the reactivity of Co(II)-MRC through ligand accelerated catalysis. **Scheme 2.1** provides a brief look at the enhanced reactivity achievable in the aziridination of styrene derivatives (12) with N-fluoroaryl azides (13) through proper porphyrin ligand design.\(^2\)

**Scheme 2.1** The Dramatic Ligand Effect of Chiral \(D_{2h}\)-Symmetric Amidoporphyrins

\[
\begin{align*}
&\text{styrene} + \text{N-fluoroaryl azide} \\
&\xrightarrow{[\text{Co}(\text{III})\text{Por}](1 \text{ mol} \%) \text{, 4AMS, rt. } \text{C}_{6} \text{H}_{6}} \\
&\text{aziridine}
\end{align*}
\]
Currently amidoporphyrin ligands are synthesized through the method described in Chapter 1.3, whereby a bromoporphyrin synthon is synthesized via condensation of an aldehyde with dipyrromethane using Lindsey’s conditions. This bromoporphyrin synthon can then be derivatized with cross-coupling reactions to produce an expansive library of chiral porphyrin ligands. It is desirable to have access to a large catalyst library for screening stereo-selective transformations, and thus this has prompted the search for methods of generating new chiral porphyrins. As the status quo are amidoporphyrins which are A₂B₂ porphyrins possessing chirality in solely one plane of the porphyrin ring (A₂-segment, HNCOR*). To further increase the control over chirality and diastereo-selectivity in stereo-selective reactions, the synthesis of porphyrin ligands with chirality in both the A₂B₂ segments would be highly desirable.

In addition to this, porphyrin ligand diversity can be further expanded by the addition of meso-heteroatoms on the porphyrin ring. It is hypothesized that with meso-heteroatoms there will be an influence on the electronics of the Co(II)-metal center, as the resonance of metallo-porphyrins shows delocalization primarily through the meso positions. The current synthetic scheme to generate chiral amidoporphyrin ligands does not allow for the construction meso-heteroatom substitution, due to the reaction of the parent aldehyde and dipyrromethane (Scheme 1.4).

It is clear that in order to synthesize chiral meso-heteroatom functionalized porphyrins for Co(II)-MRC that an alternate bromoporphyrin synthon will be required. This in turn, is the crux of the work described in this chapter, the development of a new generation bromoporphyrin synthon and its application towards divergent porphyrin functionalization through well-developed cross-coupling reactions. Through examination on the limitations of the previous generation of bromoporphyrin synthons, insight is given into the design of this theoretical next generation bromoporphyrin synthon (Figure 2.1). Specifically, the work contributed to this project in this thesis is that of the C–O and Suzuki-Miyaura cross-coupling reactions.
To synthesize the proposed (Figure 2.1) porphyrin ligand, an inverse approach must be taken to the current method of synthesizing porphyrins (Scheme 1.4). Cross-coupling installation of the amide groups must be carried out first with 5,15-bis(2,6-dibromophenyl)porphyrin (15), this in turn allows for meso-bromination at the open 10,20-positions. This bromination reaction forms the bromoporphyrin synthon (16), which can be tested with the common C–Z (heteroatom and carbon based) cross-coupling methodologies to synthesize newly proposed porphyrin ligands (Figure 2.2). What’s more, this synthetic scheme not only will allow for the synthesis of new chiral porphyrin ligands, but is also inclusive of the previous chiral porphyrin pool.

Figure 2.1 Proposal to Expand the Chiral Porphyrin Library

2.2 Next Generation Bromoporphyrin Synthon Synthesis
Bromination at the 10,20-\textit{meso} positions (17) is the key step in this synthetic scheme, but when first explored gave unsatisfactory results (Scheme 2.2). Using 2.1 equivalents of NBS (N-bromosuccinimide) in a chloroform:pyridine solvent system led to a complex mixture of \textit{meso}-bromination and \(\beta\)-bromination porphyrin products. This was examined by \(^1\)H NMR and indeed showed multiple signals in the -2 to -2.5 ppm range (TMS standard, 400 MHz, CDCl\(_3\) solvent) which is a diagnostic signal of porphyrins, showing the highly shielded two N–H protons in the cavity. Although possible that bromoporphyrin synthon 18 was synthesized, it was clear that this methodology is unsuitable for large scale and efficient synthesis of chiral porphyrin ligands.

Scheme 2.2 Preliminary Results for \textit{meso}-Bromination
To overcome this synthetic barrier, metallation of the porphyrin ring was explored. It is well documented that metallation of the porphyrin ring affects the electronics of the system, and indeed can lead to different reactivity’s on the meso- and β-positions. The breakthrough for this porphyrin synthesis was found with zincation of the amidoporphyrin 19, which produces the highly meso-activating Zn(II)-amidoporphyrin (20). This is because the Zn(II)-amidoporphyrin’s resonance has more aromatic character in the meso-positions, leaving the β-positions to react solely by olefinic chemistries.

Zn(II)-porphyrins can be formed in quantitative yields by a simple mettallation reaction, which can be conducted in open air and proceeds to completion in as little as 1 hour. Gratifyingly, the Zn(II)-ion can be easily removed from the porphyrin ring by a simple procedure of acidifying with concentrated HCl in a solution of DCM, protonating the two porphyrin pyrrole nitrogens and generating ZnCl₂ as the by-product which is readily removed by an aqueous wash. This de-metallation occurs in quantitative yield, and provides researchers with the opportunity to metallate the porphyrin ring again further on in the synthesis with the desired metal ion, such as Co(II) for the Co(II)-MRC system. After metallation the porphyrin is brominated with 2.1 equivalents of NBS to give a Zn(II)-5,15-bis(2,6-amidophenyl)-10,20-dibromoporphyrin (21). The chemo-selective meso-bromination is clean, facile and reliable, unlike the previous bromination attempted with the free-base porphyrin (Scheme 2.2). Analyzing (21) by ¹H NMR, no noticeable peaks are observed in the 10-9 ppm region owing to the complete meso-bromination. De-metallation occurs as described previously as the final step, giving form to the new generation bromoporphyrin synthon (22). Proton NMR analysis at this step shows a single peak in the -2 ppm range, signifying the presence of one pure porphyrin product. The newly formed bromoporphyrin synthon can then be used for cross-coupling reactions to generate the targeted chiral porphyrin ligands (23). A synthetic roadmap of this procedure is outlined in Scheme 2.3, which also shows the yields of each step and scales of reaction tested.
Scheme 2.3 Synthetic Route for New Generation Bromoporphyrin Synthon Synthesis

2.3 Buchwald-Hartwig C–N Bond Formation on the Porphyrin Ring

Carbon-Nitrogen bond formation on the meso-position of the porphyrin ring remains one of the most intriguing reactions for the synthesis of meso-heteroatom functionalized porphyrins. With the addition of a nitrogen atom on the meso-position it is possible to add a new element of chirality on the B2-plane of the porphyrin ring and to influence the electronics of both the porphyrin, and if applicable, a chelated metal center. This compelling chemistry has previously been explored and reported in the literature. The majority of the reactions involve the coupling of an amide to the meso-position of the porphyrin ring. Examples in the literature also include cross-coupling of chiral amides, however the opposing meso-positions are generally carbon based.
phenyl groups, with little to no diversity or other functional groups. So far no reports have been
given of using cross-coupling to install a new chiral amide group on an already chiral
amidoporphyrin, or other highly functionalized porphyrin. **Scheme 2.4** shows a few selected
test examples of N-meso substituted porphyrins made through these current methods.

**Scheme 2.4** Nitrogen-*meso* Substituted Porphyrins

Testing of the new generation of bromoporphyrin synthons with Buchwald-Hartwig cross-
coupling showed that these synthons were highly amenable to C–N functionalization, regardless
of the increased steric hindrance of the 5,15-bis(2,6-substituted) chiral amides. A broad substrate
scope was explored with the cross-coupling of amides (26, 27), aniline derivatives (23, 24, 28)
and even imine 25. Interestingly the cross-coupling of amines and amides with electron-deficient
substituents proceeded smoothly in good yields (24, 27). In cross-coupling reactions, the soft
nucleophile is generally required to be basic to accommodate the deprotonation, transmetallation
and reductive elimination steps of the reaction. Also noteworthy are the paralleled reaction
conditions with initial cross-coupling of the chiral amide group, using the Pd(OAc)$_2$/XantPhos pair
as a practical catalyst for Buchwald-Hartwig C–N cross couplings of porphyrins.
Scheme 2.5 C–N Cross-Coupling Functionalized Chiral Amidoporphyrin Ligands

2.4 C–O and C–S Bond Formation on the Porphyrin Ring

Cross-coupling of oxygen and sulfur containing molecules on porphyrins gives rise to flexible A₂B₂ porphyrins, which exhibit free rotation about the σ-bond of the O/S atom and sp² carbon of the meso-position, due the large size and bent molecular geometry of these atoms. Additionally the electronics of the porphyrin ring can be influenced by the highly electron-donating oxygen atom in C–O cross-coupling reactions.

Reports of C–O⁵b, ⁵d, ⁶ and C–S⁷ cross-coupling on porphyrins exists throughout the literature with Zhang and co-workers at the fore of this research. For example in their 2003 work done on C–O cross-coupling, mono and di-etherations were carried out in up to 93% yield, albeit
these porphyrins had to be complexed with a Zn metal center to increase the reactivity. In Chen’s work which was previously described for Buchwald-Hartwig C–N cross-coupling (Section 2.3), C–O cross-coupling was also supported with the Ni(II)-activated metalloporphyrin, producing the meso-aryloxy substituted metalloporphyrins in moderate yields for di-etheration, and up to 98% yield for mono-etheration. Carbon-sulfur cross-coupling was described in 2004 by Zhang, generating the thio-etherated porphyrins in excellent yields.

**Scheme 2.6** Oxygen and Sulfur-meso Substituted Porphyrins

Scheme 2.7 lists the results from the C–O cross-coupling reactions on bromoporphyrin synthon 22. A wide functional group tolerance was observed, coupling electron-rich (30) and electron-deficient substrates (31), sterically hindered substrates (34, 35, and 36), and aliphatic alcohols (37, 38, and 39). Access to chiral A2B2 porphyrins was possible by the coupling of chiral alcohols (38, 39). The yields measured are moderate to good, and the procedure is operationally similar to C–N cross-coupling with sole replacement of the catalyst as Pd2(dba)3 (dba = dibenzylideneacetone). Certain attempts were made to increase the yield, such as higher catalyst loading and alcohol equivalency, with no substantial increases. Through examination by 1H NMR it was found that the yield suffers due to competing dehalogenation reactions of the bromoporphyrin synthon.6
Scheme 2.7 C–O Cross-Coupling Functionalized Chiral Amidoporphyrin Ligands

Scheme 2.7

**Chemical Structures and Yields**

- **29**: 69% yield
- **30**: 87% yield
- **31**: 77% yield
- **32**: 75% yield
- **33**: 48% yield
- **34**: 31% yield
- **35**: 44% yield
- **36**: 35% yield
- **37**: 79% yield
- **38**: 33% yield
- **39**: 22% yield
- **40**: 65% yield
Coupling with thiols proceeded in excellent yields, presumably due to the stronger nucleophilicity of the sulfur atom. Two examples were explored using similar reaction conditions as in the C–O cross-coupling system, whereby only the ligand was replaced with DPEPhos (DPEPhos = Bis-[2-(diphenylphosphino)phenyl]ether), (41, 42). **Scheme 2.8** lists the results of the C–S thio-etheration reactions.

**Scheme 2.8** C–S Cross-Coupling Functionalized Chiral Amidoporphyrin Ligands

2.5 Suzuki-Miyaura and Sonogashira Carbon Bond Formation on the Porphyrin Ring

Suzuki-Miyaura cross-coupling is a potent method for forming new C–C bonds and thus was employed for the synthesis of carbon based meso-substitution. With the application of successful Suzuki-Miyaura couplings, the previous generation of amidoporphyrin ligands could be potentially included in the new synthetic route. Several boronic acids were studied for the synthesis of previously established amidoporphyrins (Scheme 2.9). Common porphyrin ligands in the Co(II)-MRC system such as 44 were synthesized amongst others in excellent yields. Gratifyingly, the Suzuki-Miyaura coupling did not require metal aided reactivity as can be the case
with cross-coupling reactions of porphyrins. Substrates 45, 47, and 46, 48 had the same excellent yields regardless of the presence or absence of Zn in the porphyrin ring.

**Scheme 2.9** C–C Cross-Coupling Functionalized Chiral Amidoporphyrin Ligands

\[
\text{HN} \quad \text{O} \quad *R \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{HN} \\
\text{O} \quad *R \\
\text{OH} \quad \text{OH} \\
\text{Pd(PPh}_3\text{)}_4 \quad (10 \text{ mol} \%) \\
8 \text{ equiv. } \text{K}_3\text{PO}_4, \quad 20:1 \text{ Toluene}:\text{H}_2\text{O}, \quad 100 \degree \text{C}, \text{overnight} \\
\]

\[ \begin{align*}
43 & \quad 99\% \text{ yield} \\
44 & \quad 89\% \text{ yield} \\
45 & \quad 99\% \text{ yield} \\
46 & \quad 99\% \text{ yield} \\
47 & \quad 94\% \text{ yield} \\
48 & \quad 99\% \text{ yield}
\end{align*} \]

Sonogashira coupling was explored with the intent of studying porphyrin ligands with rigid 10,20-\textit{meso}-substitution. Presumably in Co(II)-porphyrin based catalysis, the alkynyl group may promote substrate approach due to \(\pi-\pi\) interactions. Converse of the Suzuki coupling, the Sonogashira coupling only gave satisfying results when the Zn(II)-metallated porphyrin was used (21) to increase reactivity (**Scheme 2.10**).
**Scheme 2.10** Sonogashira Cross-Coupling Functionalized Chiral Amidoporphyrin Ligands

A new generation of bromoporphyrin synthons was synthesized and provided a successful route (Scheme 2.3) for accessing meso-heteroatom substituted chiral amidoporphyrins and A2*B2* chiral porphyrins (38, 39). This methodology was applied to carry out successful C–C, C–N, C–O, C–S and C≡C bond formations in moderate to excellent yields. With this powerful new methodology, an expanded chiral porphyrin ligand library can now be synthesized and explored for their potential in ligand accelerated catalysis in the Co(II)-MRC system. Work is currently under way in the Zhang group investigating the potential of some of these ligands for novel atom/group transfer reactions. The experimental results of this works’ focus on C–O and Suzuki-Miyaura C–C cross-coupling is discussed in the following section.
2.7 Experimental Section

General Considerations

Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F254), visualizing with UV-light 254 nm or 365 nm fluorescence quenching. Flash column chromatography was performed with silica gel (60 Å, 230-400 mesh, 32-63 μm). Proton nuclear magnetic resonance ('H NMR) spectra and carbon nuclear magnetic resonance ('C NMR) spectra were recorded on a Varian 400-MHz instrument. Chemical shifts for protons are reported in ppm downfield from tetramethylsilane (TMS) and are referenced to residual protium in the NMR solvent (CHCl₃ = 7.26 ppm). Chemical shifts for carbon are reported in ppm downfield from TMS and are referenced to the carbon resonances of the solvent residual peak (CDCl₃ = 77.00 ppm). ('F) spectra were recorded on a Varian 400 spectrometer (376 MHz), using CFCl₃ (δ=0) as internal standard.

5,15-bis(2,6-dibromophenyl)porphyrin

To a clean, oven-dried flask was added activated molecular sieves 4 Å (2 g), chloroform (700 mL), aldehyde 1 (7 mmol, 1.85 g) and dipyrrromethane 2 (7 mmol 1.02 g) equipped with a magnetic stir bar set to stirring. Nitrogen was sparged through the solution over the duration of ~15 min, and after filling with a nitrogen atmosphere the flask was fitted with a N₂ balloon to maintain the pressure. The flask was then shielded from light by the use of aluminium foil, at which point the catalyst, BF₃·Et₂O (60 mol %, 0.760 mL), was added drop-wise over the course of several minutes. The reaction was then allowed to stir under N₂, shielded from light for 20 h. Once
the 20 h was complete the mixture was charged with DDQ (2,3-dichloro-5,6-dicyano-1,4-
benzoquinone, 9.1 mmol, 2.06 g) and allowed to stir for an additional 3 h. After 3 h triethylamine
(3x catalyst, 3.00 mL) was added to quench the reaction and promote efficient separation in
column chromatography. The resulting slurry was then heated with sonication to agitate the
conglomerates formed from the poorly soluble porphyrin 3 and MS 4Å. After this the slurry was
directly poured over a column packed with hexanes, the solvent from the reaction and DCM
(dichloromethane) were used to elute the desired product as a dark red-purple band. The
collected fractions were pooled, and the solvent removed under reduced pressure. Once dried
the resulting purple-brown powder was washed several times with MeOH (~250 mL), dried under
the high vacuum, and then characterized. A bright purple powder was obtained (560 mg, 20%
yield). $^1$H NMR (400 MHz, CDCl₃) δ ppm, 10.26 (s, 2H), 9.36 (d, $J = 4.8$ Hz, 4H), 8.84 (d, $J = 4.8$
Hz, 4H), 8.01 (d, $J = 8.1$ Hz), 7.57 (t, $J = 8.1$ Hz, 2H), -3.07 (s, 2H).

**meso-H-ChenPhyrin**

![Diagram](image-url)

To a clean, oven-dried Schlenk tube equipped with a Teflon® coated magnetic stir bar, all
solid reagents were added: porphyrin 3 (0.52 mmol, 404 mg), Chen amide 4 (8.26 mmol, 1.07 g),
Pd(OAc)$_2$ (40 mol %, 47.0 mg), XantPhos (80 mol %, 232 mg), and Cs$_2$CO$_3$ (8.26 mmol, 2.70 g).
The Schlenk tube was then capped with a Teflon® screw-cap and set to the high vacuum for ~ 1
h at 30 mtorr. The tube was then backfilled with N$_2$ and put back to the vacuum, alternating 3x
then set under N$_2$ at which point the Teflon® screw-cap was replaced with a rubber septum.
Freshly refluxed and de-gassed solvent was added (Dioxane:H₂O 20:1, 25:1.5 mL) to the Schlenk tube which was subsequently re-fitted with the Teflon® screw-cap and set to stir at the desired temperature (100 °C) for 3 days. Once the reaction was complete, it was allowed to cool to rt, after which time the solution was withdrawn and filtered through a plug of Celite®. The Celite® plugged was washed with a little EtOAc (~2 mL), then all the organic fractions pooled and reduced in vacuo on a RotaVap® R-210. The residue was then purified via column chromatography (eluent 4:1 Hexanes:EtOAc) to give the title compound as a purple-red powder (400 mg, 85% yield, 1:1 Hexanes:EtOAc, $R_f = .51$). $^1$H NMR (400 MHz, CDCl₃) δ ppm, 10.45 (s, 2H), 9.51 (d, $J = 4.8$ Hz, 4H) 9.09 (d, $J = 4.8$ Hz, 4H), 8.50 (broad s, 4H), 7.88 (t, $J = 8.4$ Hz, 2H), 6.48 (broad s, 4H), 0.89 (s, 12H), 0.68 (broad s, 4H), 0.13 (broad s, 16H), -0.14 (broad s, 4H), -3.05 (broad s, 2H).

Zn(II)-meso-H-ChenPhyrin

To a clean, oven-dried flask equipped with a Teflon® coated magnetic stir bar, Zn(OAc)_2 (0.94 mmol, 206 mg), and as little MeOH (3 mL) as needed to dissolve the Zn(OAc)_2 with stirring was added. To this stirring solution was added 10x the volume in DCM (30 mL), and porphyrin 5 (.19 mmol, 169 mg), and the solution was left to stir under a N₂ balloon for 1 h when the reaction was complete. The mixture was then washed 3x with H₂O (15 mL), dried with Na₂SO₄, and then poured over a bed of silica packed in a vacuum filtration funnel. A vacuum was generated through an aspirator with a trap for security and the DCM layer pulled off the silica and discarded. After
the DCM was eluted, the silica gel was washed with EtOAc (~20 mL) to obtain the product as a slow moving bright pink band in the silica gel. The collected pools of EtOAc were evaporated in vacuo, giving brilliant pink crystals (184 mg, >99% yield). TLC; 1:1 Hexanes:EtOAc, \( R_f = 0.47 \). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \), 10.28 (broad s, 2H), 9.44 (broad s, 4H), 8.99 (broad s, 3H), 8.49 (broad s, 1H), 7.85 (broad s, 2H), 6.56 (broad s, 4H), 5.17 (broad s, 2H), 3.54 (broad s, 2H), 0.86 (broad s, 12H), 0.63 (broad s, 4H), 0.25 (broad s, 4H), 0.042 (broad s, 4H), -0.24 (broad s, 4H).

Zn(II)-*meso*-Br-ChenPhyrin

To a clean, oven-dried flask was added 10:1 CHCl\(_3\):Pyridine (7.5 mL: 0.75 mL), Zn(II)-porphyrin 6 (0.12 mmol, 120 mg) and a Teflon\(^\circledR\) coated magnetic stir bar. The flask was set to stir @ 0 °C in an ice-water slurry, then NBS (0.26 mmol, 46.8 mg) was added portion-wise to the stirring solution, at which point the color changed from a deep pink to a green-brown. The flask was fitted with a N\(_2\) balloon and allowed to cool to rt over the course of ~ 5 min, at which time the reaction was considered complete by TLC. The residual NBS was quenched by the addition of acetone (~ 1 mL), then the mixture was reduced in vacuo on a Rotavap\(^\circledR\) R-210. The residue was purified by column chromatography (1:1 Hexanes:EtOAc, \( R_f = .53 \)) and the resulting purple-green crystals isolated were the title compound (135 mg, >99% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \), 9.73 (broad s, 4H), 8.45 (broad s, 3H), 8.12 (broad s, 1H), 7.82 (t, \( J = 7.0 \text{ Hz} \), 2H), 6.61 (broad s,
4H), 0.93 (broad s, 12H), 0.59 (broad s, 2H), 0.099 (broad s, 12H), -0.056 (broad s, 4H), -0.503 (broad s, 2H).

**meso-Br-ChenPhyrin**

In a clean, oven-dried flask was added Zn(II)-porphyrin 7 (0.1 mmol, 120 mg), DCM (20 mL), excess, conc. HCl (1 mL), and a Teflon® coated magnetic stir bar. The flask was set to stir and fitted under a N2 balloon, the stirring was continued over 30 min. Once stirring was completed the solution was transferred to a separatory funnel (60 mL) and washed 3x with DI H2O (~7 mL). The organic layer was then poured over a plug of silica packed in a vacuum filtration funnel attached to a vacuum filtration flask hooked up to an aspirator and trap. A vacuum was pulled, eluting the DCM layer from the silica gel, which was subsequently discarded. The plug was then washed with EtOAc (~10 mL) to obtain the product as a brown-purple band in the silica gel. The collected pools of EtOAc were reduced in vacuo to afford the title product as a dull purple powder (107 mg, >99% yield). ¹H NMR (400 MHz, CDCl₃) δ, 9.71 (d, J = 4.8 Hz, 4H), 8.88 (d, J = 4.8 Hz, 4H), 8.42 (broad s, 4H), 7.85 (t, J = 8.4 Hz, 2H), 6.38 (s, 4H), 0.87 (s, 12H), 0.70 (broad s, 4H), 0.23 (broad s, 12H), 0.13 (broad s, 4H), -0.046 (broad s, 4H).
C–O Cross-Coupling Reaction Procedure and Results

To a clean, oven-dried Schlenk tube equipped with a Teflon® coated magnetic stir bar, all solid reagents were added: porphyrin 9 (0.03 mmol, 31.0 mg), alcohol (0.24 mmol), Pd$_2$(dba)$_3$ (10 mol %, 6.30 mg), XantPhos (80 mol %, 9.30 mg), and Cs$_2$CO$_3$ (0.12 mmol, 41.3 mg). The Schlenk tube was then capped with a Teflon® screw-cap and set to the high vacuum for ~ 1 h at 30 mtorr. The tube was then backfilled with N$_2$ and put back to the vacuum, alternating 3x then set under N$_2$ at which point the Teflon® screw-cap was replaced with a rubber septum. Freshly refluxed solvent, which was dried of H$_2$O and stripped of O$_2$ by Na/benzophenone co-distillation, was added (Toluene, 3 mL) to the Schlenk tube which was subsequently re-fitted with the Teflon® screw-cap and set to stir at the desired temperature (80 °C) for overnight (~12 h). Once the reaction was complete, it was allowed to cool to rt, after which time the solution was withdrawn and filtered through a plug of Celite®. The Celite® plugged was washed with a little EtOAc (~1 mL), then all the organic fractions were pooled and evaporated *in vacuo* on a RotaVap® R-210. The residue was then purified via column chromatography to give the desired compounds.
meso-(4-MeO)PhO-ChenPhyrin was synthesized according to the general procedure as a purple-red solid (87% yield, 1:1 Hexanes:EtOAc $R_f = 0.38$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 9.39 (d, $J = 4.8$ Hz, 4H), 8.78 (d, $J = 4.8$ Hz, 4H), 8.41 (broad s, 4H), 7.81 (t, $J = 8.4$ Hz, 2H), 7.03 (d, $J = 9.2$ Hz, 4H), 6.81 (d, $J = 9.2$ Hz, 4H), 6.46 (broad s, 4H), 3.76 (s, 6H), 0.84 (broad s, 12H), 0.69 (broad s, 4H), 0.24 (broad s, 12H), 0.12 (broad s, 4H), 0.009 (broad s, 4H), -2.33 (broad s, 2H).

meso-PhO-ChenPhyrin was synthesized according to the general procedure as a purple-red solid (69% yield, 1:1 Hexanes:EtOAc $R_f = 0.61$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 9.38 (d, $J = 4.8$ Hz, 4H), 8.80 (d, $J = 4.8$ Hz, 4H), 8.40 (broad s, 4H), 7.82 (t, $J = 8.4$ Hz, 2H), 7.30 (t, $J = 8.4$ Hz, 4H), 7.097 (m, 6H), 6.47 (broad s, 4H), 0.83 (broad s, 12H), 0.68 (broad s, 4H), 0.24 (broad s, 12H), 0.12 (broad s, 4H), 0.017 (broad s, 4H), -2.34 (broad s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$,
meso-(3,5-di-Me)PhO-ChenPhyrin was synthesized according to the general procedure as a purple-red solid (48% yield, 1:1 Hexanes:EtOAc \(R_f = 0.69\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\), 9.41 (d, \(J = 4.8\) Hz, 4H), 8.81 (d, \(J = 4.8\) Hz, 4H), 8.44 (broad s, 4H), 7.82 (t, \(J = 8.4\) Hz, 2H), 6.74 (broad s, 2H), 6.71 (broad s, 4H), 6.50 (broad s, 4H), 2.16 (s, 12H), 0.87 (broad s, 12H), 0.70 (broad s, 4H), 0.28 (broad s, 12H), 0.13 (broad s, 4H), 0.015 (broad s, 4H), -2.33 (broad s, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\), 169.65, 165.91, 139.74, 139.10, 132.95, 130.69, 130.49, 129.97, 124.18, 117.98, 114.59, 109.22, 29.68, 29.01, 26.41, 22.49, 21.31, 30.51, 18.21.
meso-(2-Ph)PhO-ChenPhyrin was synthesized according to the general procedure as a purple-red solid (44% yield, 1:1 Hexanes:EtOAc \( R_f = 0.69 \)). \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \), 9.27 (d, \( J = 4.8 \) Hz, 4H), 8.76 (d, \( J = 4.8 \) Hz, 4H), 8.38 (broad s, 4H), 8.24 (d, \( J = 7.6 \) Hz, 4H) 7.80 (t, \( J = 8.4 \) Hz, 2H) 7.73 (d, \( J = 8.0 \) Hz, 2H), 7.65 (t, \( J = 7.6 \) Hz, 4H), 7.51 (t, \( J = 7.6 \) Hz, 2H), 7.17 (t, \( J = 7.6 \) Hz, 2H), 6.91 (t, \( J = 7.6 \) Hz, 2H), 6.44 (broad s, 4H), 6.39 (d, \( J = 8.4 \) Hz, 2H), 0.84 (broad s, 12H), 0.68 (broad s, 4H), 0.24 (broad s, 12H), 0.13 (broad s, 4H), -0.005 (broad s, 4H), -2.35 (broad s, 2H). \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \), 169.59, 162.62, 139.05, 138.02, 133.23, 131.56, 130.86, 130.61, 130.47, 129.83, 128.59, 127.8, 122.69, 118.07, 117.45, 109.31, 29.69, 29.01, 26.35, 22.46, 20.48, 18.22.

meso-(4-F)PhO-ChenPhyrin was synthesized according to the general procedure as a purple-red solid (77% yield, 1:1 Hexanes:EtOAc \( R_f = 0.55 \)). \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \), 9.38 (d, \( J = 8.6 \) Hz, 4H), 8.54 (d, \( J = 8.6 \) Hz, 4H), 8.38 (broad s, 4H), 8.24 (d, \( J = 7.6 \) Hz, 4H) 7.80 (t, \( J = 8.4 \) Hz, 2H) 7.73 (d, \( J = 8.0 \) Hz, 2H), 7.65 (t, \( J = 7.6 \) Hz, 4H), 7.51 (t, \( J = 7.6 \) Hz, 2H), 7.17 (t, \( J = 7.6 \) Hz, 2H), 6.91 (t, \( J = 7.6 \) Hz, 2H), 6.44 (broad s, 4H), 6.39 (d, \( J = 8.4 \) Hz, 2H), 0.84 (broad s, 12H), 0.68 (broad s, 4H), 0.24 (broad s, 12H), 0.13 (broad s, 4H), -0.005 (broad s, 4H), -2.35 (broad s, 2H). \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \), 169.59, 162.62, 139.05, 138.02, 133.23, 131.56, 130.86, 130.61, 130.47, 129.83, 128.59, 127.8, 122.69, 118.07, 117.45, 109.31, 29.69, 29.01, 26.35, 22.46, 20.48, 18.22.
4.8 Hz, 4H), 8.83 (d, J = 4.8 Hz, 4H), 8.40 (broad s, 4H), 7.82 (t, J = 8.4 Hz, 4H) 7.05 (m, 4H)
6.99 (m, 4H), 6.47 (broad s, 4H), 0.85 (broad s, 12H), 0.71 (broad s, 4H), 0.26 (broad s, 12H),
0.14 (broad s, 4H), 0.033 (broad s, 4H), -2.36 (broad s, 2H). ^13^C NMR (100 MHz, CDCl 3 ) δ, 169.60,
161.80, 159.20, 156.80, 146.71, 144.33, 139.13, 132.78, 131.04, 130.59, 129.77, 118.98, 118.31,
MHz, CDCl 3 ) δ, -12.

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_meso-(2-iPr)PhO-ChenPhyrin_ was synthesized according to the general procedure as a purple-
red solid (31% yield, 1:1 Hexanes:EtOAc _Rf_ = 0.61). ^1^H NMR (400 MHz, CDCl 3 ) δ, 9.28 (d, J =
4.8 Hz, 4H), 8.78 (d, J = 4.8 Hz, 4H), 8.40 (broad s, 4H), 7.81 (t, J = 8.4 Hz, 2H) 7.61 (d, J = 8.4
Hz, 2H) 7.05 (t, J = 7.6 Hz, 2H), 6.73 (t, J = 7.6 Hz, 2H), 6.47 (broad s, 4H), 6.1 (d, J = 8.0 Hz,
2H), 4.33 (septet, 2H), 1.80 (d, J = 6.8 Hz, 12H), 0.83 (broad s, 12H), 0.68 (broad s, 4H), 0.26
(broad s, 12H), 0.12 (broad s, 4H), 0.013 (broad s, 4H), -2.27 (broad s, 2H).
**meso-(4-Ph)PhO-ChenPhyrin** was synthesized according to the general procedure as a purple-red solid (65% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 9.43 (d, $J = 4.8$ Hz, 4H), 8.83 (d, $J = 4.8$ Hz, 4H), 8.40 (broad s, 4H), 7.82 (t, $J = 8.4$ Hz, 2H) 7.52 (m, 12H) 7.46, (d, $J = 8.8$ Hz, 4H), 7.41 (m, 8H), 7.31 (m, 4H), 7.16 (d, $J = 8.8$ Hz, 4H), 6.8 (d, $J = 8.8$ Hz, 4H), 6.5 (broad s, 4H), 0.84 (broad s, 12H), 0.70 (broad s, 4H), 0.26 (broad s, 12H), 0.14 (broad s, 4H), 0.043 (broad s, 4H), -2.30 (broad s, 2H).

**Suzuki-Miyaura C–C Cross-Coupling Reaction Procedure and Results**

To a clean, oven-dried Schlenk tube equipped with a Teflon® coated magnetic stir bar, all solid reagents were added: porphyrin 9 (0.03 mmol, 31.0 mg), boronic acid (0.15 mmol), Pd(PPh$_3$)$_4$ (10 mol %, 5.70 mg), and K$_3$PO$_4$ (0.24 mmol, 51.0 mg). The Schlenk tube was then
capped with a Teflon® screw-cap and set to the high vacuum for ~ 1 h at 30 mtorr. The tube was then backfilled with N₂ and put back to the vacuum, alternating 3x then set under N₂ at which point the Teflon® screw-cap was replaced with a rubber septum. Freshly refluxed solvent, which was dried of H₂O and stripped of O₂ by Na/benzophenone co-distillation, was added (20:1 Toluene:H₂O, 3 mL: 0.3 mL) to the Schlenk tube which was subsequently re-fitted with the Teflon® screw-cap and set to stir at the desired temperature (100 °C) for overnight (~12 h). Once the reaction was complete, it was allowed to cool to rt, after which time the solution was withdrawn and filtered through a plug of Celite®. The Celite® plugged was washed with a little EtOAc (~1 mL), then all the organic fractions pooled and reduced in vacuo on a RotaVap® R-210. The residue was then purified via column chromatography to give the desired compounds.

**meso-(4-CF₃)-ChenPhyrin** was synthesized according to the general procedure as a purple-red solid (>99% yield, 1:1 Hexanes:EtOAc *Rf* = 0.71). ¹H NMR (400 MHz, CDCl₃) δ, 8.92 (broad s, 8H), 8.45 (broad s, 4H), 8.35 (d, *J* = 7.6 Hz, 4H), 8.11 (d, *J* = 8.0 Hz, 4H) 7.86 (t, *J* = 8.4 Hz, 2H) 6.50 (broad s, 4H), 0.88 (broad s, 12H), 0.72 (broad s, 4H), 0.23 (broad s, 10H), 0.13 (broad s, 2H), -0.033 (broad s, 4H), -2.63 (broad s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ, 169.64, 144.39, 139.25, 134.44, 133.02, 131.05, 130.72, 130.53, 125.64, 124.18, 122.93, 119.61, 118.17, 109.73, 29.68, 28.91, 26.32, 22.45, 20.43, 18.22.
**meso-(3,5-di-CF₃)-ChenPhyrin** was synthesized according to the general procedure as a purple-red solid (>99% yield, 1:1 Hexanes:EtOAc *Rf* = 0.74). ¹H NMR (400 MHz, CDCl₃) δ, 8.99 (broad d, *J* = 2.8 Hz, 4H), 8.83 (broad d, *J* = 4 Hz, 4H), 8.66 (broad s, 4H), 8.43 (s, 2H) 8.375 (s, 2H) 7.86 (t, *J* = 8.0 Hz, 2H) 6.50 (broad s, 4H), 0.88 (broad s, 12H), 0.75 (broad s, 4H), 0.22 (broad s, 12H), 0.014 (broad s, 4H), -2.64 (broad s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ, 169.76, 142.85, 139.15, 134.08, 133.47, 132.54, 132.04, 131.10, 130.70, 127.38, 124.67, 122.66, 118.95, 117.57, 115.60, 110.62, 29.70, 29.22, 28.92, 26.30, 22.55, 20.46, 18.18. ¹⁹F NMR (376 MHz, CDCl₃) δ, -63.29 (t, *J* = 148.52, 3F).

## 2.8 References


Chapter 3. Chemo-selective Medium-Sized Ring Formation via Cobalt(II)-Catalyzed Intramolecular C–H Amination of Aldehydic C(sp²)–H Bonds

3.1 Medium-Sized Organic Ring Formation

In Nature, medium-sized organic rings represent a unique class of structures which pose great challenge for synthesis.¹ Consisting of 7 to 11 atoms in size, construction of these rings suffer from entropic and enthalpic effects in their formation and stabilization.²,³ Examples of these issues include the closing of many carbon tethered chains, which is discouraged by entropy, and transannular strain in the ring which reduces thermodynamic payoff when the ring product is formed (Scheme 3.1).

Scheme 3.1 Entropic and Enthalpic Effect Hindering Medium-Sized Ring Formation

Most ring structures have unfavorable interactions in their conformation due to the change from the ideal bond angles and bond lengths of sp³ carbons. In small-sized rings this is seen as angular strain, which are constraints forced on the bond angles that bring the sp³ carbons to adopt bond angles more aligned with sp² trigonal planar geometry (120° vs 109.5°). This strain can cause an energy demand as high as 27.5 kcal/mol in terms of 3-membered rings. Common-sized
organic rings are 5-6 atoms in constitution and most commonly suffer from torsional strain, which itself is caused by substituted groups eclipsing each other or unfavorable orbital alignment. This type of strain is the traditionally described strain in most organic chemistry texts, with one famous example being the 1,3-diaxial flagstaff interactions of a 1,3-substituted cyclohexane ring. But what makes the medium-sized organic rings unique and most difficult to conceive, is the presence of transannular strain, which is the strain of eclipsing groups inside the ring (Scheme 3.1). Take into account as well that transannular strain can be a large energy increase, as most 8-membered rings suffer a strain of ~9.8 kcal/mol, and 9-membered rings, often considered the most difficult ring size to synthesize, typically have a transannular strain of ~12.3 kcal/mol. Notwithstanding, medium-sized rings still suffer from angular and torsional strain, and all three de-stabilizing interactions dramatically increase the energy of medium-sized rings, thus causing their formation to be unfavorable. From here it is clear to see the challenge that comprises medium-sized ring synthesis.

Figure 3.1 Medium-Sized Ring Structures in Nature

Regardless of these synthetic hurdles, Nature has made routine use of medium-sized rings, as evidenced by their abundance in natural products. In order to study the effects of these medium-sized rings in pharmacologically active products it would be imperative that the synthetic
chemist have access to synthesizing these complex structures. Unfortunately, the exhibition of medium-sized rings in pharmaceuticals and other biologically active materials are minimal due to the still maturing field of medium-sized ring synthesis. Figure 3.1 shows some the motif of medium-sized rings in natural products, giving inspiration for developing synthetic schemes to synthesize derivatives of these evasive compounds.

3.2 Literature Background on Medium-Sized Sulfonamide and Sulfonylurea Synthesis

Of the methods used to synthesize medium-sized rings, Grubbs olefin metathesis remains a staple synthetic method in this field. For sulfamoyl and sulfonyl containing medium-sized rings Grubbs olefin metathesis works best with the second generation catalyst and at high catalyst loadings between 10 and 20 mol%. Liskamp\(^6\) reported in 2004 a yield of 47-60% for 3 nine-membered ring substrates, however, this method requires an electron withdrawing group on an aromatic ring attached that is attached to one of the nitrogens of the sulfamoyl group. In addition to this, the system loses efficiency if \(\alpha,\alpha\)-dichlorotoluene is not used as the solvent, presumably used to prevent catalyst degradation for second generation Grubbs catalysts. Leit\(^7\) published a paper in *J. Am. Chem. Soc.* that showed Grubbs olefin metathesis could be applied to making an 8-membered ring in 53% yield, and bridged 8 and 9-membered rings *via* electrocyclization. The yields of these two products were 69% and 37% yield, respectively (Scheme 3.2).

**Scheme 3.2** Medium-Sized Ring Synthesis through Grubbs Olefin Metathesis-Electrocyclization

Palladium catalyzed methods have also been developed to build medium-sized containing sulfones and sulfonamides.\(^8\) Evans and workers reported in the literature an intramolecular Heck
olefination which produced two products in up to 39% yield.⁸a This method suffered from slow metallacycle formation and led to a mixture of dehalogenated product and desired product.

In addition to the synthesis of sulfone and sulfonamide containing medium-sized rings, palladium catalyzed methods have also shown promise in generating functionalized medium-sized rings through C–H activation methods. Although these systems do not generate the same final product as through intramolecular C–H amination of sulfamoyl azides with [Co(II)(Por)], they are nonetheless of great importance as C–H activation continues to lead the foray of desired methodologies in synthesis. Greaney and Pintori published their intriguing work on biaryls synthesis via Pd-catalyzed oxidative C–H activation, where they showed the synthesis of fused indole biaryls with formation of 7 and 8-membered rings.⁸b The work focused on seven membered ring synthesis, with an interesting substrate scope demonstrated, however only four 8-membered ring products were shown in 51 to 62% yield. This work also required the use of an electron withdrawing group adjacent to the reactive C–H bond for activation (for practicality they chose to use 3-indolecarboxaldehydes). Use of electron withdrawing groups on the opposing aromatic ring (52 vs. 53) greatly increased yield as well (Scheme 3.3).

**Scheme 3.3** Pd-Catalyzed Intramolecular C–H Oxidative Coupling
Zhu and workers reported the synthesis of fused medium-sized rings via a Pd-catalyzed domino reaction, which involved a key C–H activation step. Intriguingly they were able to synthesize many 8-11 atom containing rings, and even more so was the report that the 8-membered ring synthesis was the lowest yielding product. Unfortunately this system requires high temperatures, 120°C, and high dilution conditions, .02M to .001M, but other than that it provides an elegant domino reaction to generate complex molecular scaffolds.

**Scheme 3.4 Pd-Catalyzed Cascade Synthesis of Medium-Sized Lactams**

Rh-catalyzed C–H insertion reactions abound in the literature, and have also been applied to medium-sized ring sulfone and sulfonamide synthesis. The cationic Rh(I)-catalyzed ([Rh(dppe)ClO₄]) intramolecular hydroacylation (insertion into an aldehyde C–H bond) to produce cyclooctenones was described by Shair in 2000. The paper described the optimization of a known system that generated cyclopentenones, however upon application with vinyl cyclopropane the strained ring could be fragmented by the Rh(III) metallacycle and produce a larger sized ring product. Unfortunately high catalyst loading of 20 mol % was needed for good yields and an ethylene atmosphere was required to prohibit decarbonylation after insertion of the Rh(I)-catalyst into the aldehydic C–H bond. Two years later Tiley’s research group at Lycoming College reported the use of directing group assisted medium-sized ring formation. In their *Tetrahedron Letters* paper they used the sulfur of thioether substrates to chelate with the Rh(III) intermediate and bring about a more facile ring closure. Two examples of 8-membered rings in 62 and 86% yield were obtained. It is of interest to mention that Tiley and workers attempted the
synthesis of the nine-membered ring with no product obtained, and without the use of sulfur also obtained no product for the seven and eight membered rings. Inspired by Shair’s pioneering work and Tiley’s practical addition, Dong and workers expanded the Rh(I)-based hydroacylation system and its application towards generating medium ring sized compounds. First they reported in J. Am. Chem. Soc. in 2009 the use of sulfur, oxygen and sulfoxide (S=O) directing groups to produce seven and eight membered rings in an enantio-selective fashion. None of their examples with oxygen included the synthesis of an eight membered ring, however two sulfur and one sulfoxide bearing substrate were given with high yields and enantio-selectivities (86-91% yield, 93% ee). They also noted that when no heteroatom was used to direct the catalyst no reaction occurred, and attempts at synthesizing the nine-membered ring lead to no reaction. Later they observed in that the use of nitrogen as a directing group greatly improved the activity of the system. It was hypothesized that the stronger Lewis basicity of the amine nitrogen caused this increase in reactivity. In addition to this, insertion into a ketone was carried out producing a lactone ring instead of the traditional olefin insertion (Scheme 3.5). With as little as 1-5 mol% of their Rh(I) catalyst ([Rh(DTBM-SEGPHOS)BF₄] they were able to get excellent yields (84-99%) and enantio-selectivities (88-99%) for several examples. Although this was an outstanding piece of work, all of their substrates had little variation. Each substrate contained an N-methylated amine for the directing group, and a fused benzaldehyde, thus only the R groups on the ketone provided a route for functionalization.

Looking at this discussion on the literature so far we can see four major drawbacks in medium-sized ring synthesis of sulfonyl and sulfamoyl containing substrates, and synthetic methods based on C–H functionalization. These four major drawbacks are: 1) moderate to good yields for many sulfonyl and sulfamoyl containing substrates, 2) Limited and relatively little variation in the substrate scope, 3) Complete reliance on pre-functionalization of the substrate molecule and directing groups in substrates, 4) Examples mostly limited to the synthesis of 7-8
membered rings. With this in mind we envisioned that our chemistry can rise to meet several of these challenges, and thus set forth to study [Co(II)(Por)] catalyzed intramolecular C–H amination of aldehydic C–H bonds with sulfamoyl azides.

**Scheme 3.5 Rh(I)-Catalyzed Intramolecular C–H Hydroacylation**

3.3 Chemo-selective Medium-Sized Ring Synthesis via Intramolecular C–H Amination of Aldehyde C(sp²)–H Bonds with Sulfamoyl Azides by Co(II)-Based MRC

During the course of studying the electron-deficient intramolecular C–H amination reaction system by Co(II)-porphyrins a strange discovery was found when using aldehyde 54 as the substrate (Scheme 3.6). Instead of generating the α-carbonyl C–H amination 6-membered ring (56), 7-membered ring (55) formation was observed in a moderate 68% yield as the major product. At first glance, it may be puzzling as to why the highly unfavorable medium-sized ring was formed, but the results are justified when taking into account the metalloradical chemistry of [Co(II)(Por)]. The bond dissociation energy for homolytic bond cleavage of aliphatic aldehyde C–H bonds is generally ~89 kcal/mol. Comparatively to other common C–H bonds this is a relatively weak bond, and in fact the α-carbonyl C–H bond has a B.D.E. of ~92 kcal/mol. Quizzical as to the potential with [Co(II)(Por)], the medium-sized ring formation using aldehydes was explored.
A catalyst screen was done to determine which [Co(II)(Por)] catalyst would promote the intramolecular C–H amination the greatest (Table 3.1). The reaction was tried with the commercially available [Co(TPP)] ([Co(P1)]), but gave un-satisfactory results. [Co(II)(Por)] which had little steric hindrance in the 10,20-positions were screened hypothesizing that a wide porphyrin cavity would be needed to accommodate the larger ring-like transition state of the medium-sized rings ([Co(P3)], [Co(P4)], [Co(P5)], [Co(P11)]), and although a trend of increased reactivity could be slightly noticed, none of these catalysts matched the activity of [Co(P2)]. Sterically hindered catalysts were screened with the idea that a forced conformation could be brought about in the ring-like transition state, increasing the yield, especially since the more sterically demanding [Co(P2)] had superior results to less sterically demanding ligands. However upon examination, the sterically demanding Co(II)-porphyrins gave poor results ([Co(P6)], [Co(P9)], [Co(P10)]).

After these results, the theory was re-formulated with the notion that a porphyrin cavity “sweet-spot” had to be designed which would provide enough conformational rigidity to force medium-sized ring synthesis, yet be open enough to physically fit the medium-sized ring products. The distance between the outlier atoms in the 8-membered ring product of this system has a distance of 5.804 Å, seeing how [Co(P2)] has its two outlier distances from the inmost atoms on the ligand at 8.594 and 8.492 Å, we see that plenty of space must be allowed to prohibit van der
Scheme 3.7 Catalyst Screening for Intramolecular C–H Amination into Aldehyde C–H Bonds

\[ \text{[Co(II)](P)} \text{ (2 mol %) } \rightarrow \text{[Co(H)](P)} \]

54 \[ \rightarrow \]

58\text{a}

[Co(P1)]: Mostly s<sub>m</sub> remains
[Co(P2)]: 68% yield
[Co(P3)]: 31% yield

[Co(P4)]: 27% yield
[Co(P5)]: 15% yield
[Co(P6)]: 4% yield

[Co(P7)]: 81% yield
[Co(P8)]: All s<sub>m</sub> remains
[Co(P9)]: 2% yield

[Co(P10)]: All s<sub>m</sub> remains
[Co(P11)]: All s<sub>m</sub> remains
[Co(P12)]: 69% yield

\( \text{a) All yields reported are } ^{1} \text{H NMR yields (1.0mM ethylbenzene as a standard).} \)
Waals interactions, yet still have steric influence (Figure 3.2). When catalyst ([Co(P7)]) was tested, it was found to give the highest yields yet obtained, with 81% yields both from $^1$H NMR and later isolated. It is presumed that this catalyst has a cavity which supports the medium-sized ring formation according to the hypothesis previously ordained, however detailed mechanistic studies have not yet justified this.

Figure 3.2 Proposed Cavity Requirements of Porphyrin Ligand for Intramolecular Medium-sized Ring Synthesis

After the ideal catalyst was found, reaction parameters were optimization was carried out through several experiments. Table 3.2 provides an overview of the reaction conditions screened for when performing the 7-membered ring synthesis. Several catalysts were screened, mostly aromatic catalysts that are believed to provide a good radical cage for the intermediate organic radicals formed in metalloradical catalysis. Of these it was found that $\alpha,\alpha,\alpha$-trifluorotoluene and fluorobenzene performed the best by $^1$H NMR yields (7, 11). Changing the reaction temperature also proved promising, with higher reaction temperatures supplying higher yields (6, 12).
Unfortunately due to technical difficulties in the work-up, the highest yields obtained for this product was still only 88% yield.

**Table 3.2 Reaction Condition Screening for 7-Membered Ring Synthesis**

![Diagram](54.png) $[\text{Co(II)}(\text{P7})] \ (2 \text{ mol} \%)$ $\xrightarrow{X} \text{55}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Benzene</td>
<td>40° C</td>
<td>20 h</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>40° C</td>
<td>20 h</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Toluene</td>
<td>40° C</td>
<td>20 h</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Chlorobenzene</td>
<td>40° C</td>
<td>20 h</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>rt</td>
<td>20 h</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>60° C</td>
<td>20 h</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>40° C</td>
<td>30 h</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>40° C</td>
<td>10 h</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>40° C</td>
<td>5 h</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>40° C</td>
<td>1 h</td>
<td>N.R.</td>
</tr>
<tr>
<td>11</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Fluorobenzene</td>
<td>60° C</td>
<td>20 h</td>
<td>&gt;99</td>
</tr>
<tr>
<td>12</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>80° C</td>
<td>20 h</td>
<td>95</td>
</tr>
<tr>
<td>13</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Acetonitrile</td>
<td>60° C</td>
<td>20 h</td>
<td>11</td>
</tr>
<tr>
<td>14</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Hexafluorobenzene</td>
<td>60° C</td>
<td>20 h</td>
<td>91</td>
</tr>
<tr>
<td>15</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Methyl tert butyl ether</td>
<td>60° C</td>
<td>20 h</td>
<td>36</td>
</tr>
</tbody>
</table>

$^a$ All yields reported are $^1$H NMR yields (0.1mM ethylbenzene as a standard).

When performing reaction optimization for the 8-membered ring substrate it was found that temperature a made dramatic difference in the yield. Observing **Table 3.3** in **Entry 5** and **6**
the yield climbs by over 30% from the next highest reported yield (1, 31% yield). For the 9-membered ring no in-depth reaction parameter screening was carried out that led to viable conclusions.

**Table 3.3** Reaction Condition Screening for 8-Membered Ring Synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>60°C</td>
<td>31% yield</td>
</tr>
<tr>
<td>2</td>
<td>Co(4-MeO-ChenPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>60°C</td>
<td>8% yield</td>
</tr>
<tr>
<td>3</td>
<td>Co(meso-(4-MeO)Ph0-IbuPhyrin)</td>
<td>Trifluoromethylbenzene</td>
<td>60°C</td>
<td>11% yield</td>
</tr>
<tr>
<td>4b</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Hexafluorisopropanol</td>
<td>60°C</td>
<td>N.R.</td>
</tr>
<tr>
<td>5b</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Fluorobenzene</td>
<td>80°C</td>
<td>63% yield</td>
</tr>
<tr>
<td>6b</td>
<td>Co(4-MeO-IbuPhyrin)</td>
<td>Fluorobenzene</td>
<td>100°C</td>
<td>61% yield</td>
</tr>
</tbody>
</table>

a) All yields reported are ¹H NMR yields (0.1mM ethylbenzene as a standard) b) 5 mol % catalyst used

With these optimized reaction conditions in hand, a series of substrates were tested to examine the versatility of the Co(II)-based intramolecular C–H amination of sulfamoyl azides into aldehydic C–H bonds. Gratifyingly the 7,-8,- and 9-membered rings were synthesized (55, 57, 58) were synthesized in moderate to excellent yields; 88% yield, 63% yield, and 21% yield for 7,8,-8,- and 9-membered rings respectively. Substrates with electron-donating groups, 59, and 60 were tested and gave moderate results. These substrates were of paramount importance as the previous Pd-catalyzed and Rh-catalyzed systems required electron-deficient groups to activate their substrates. Sterically hindered substrates 62 and 63 were explored as well in the attempt to further understand the effect of steric on product formation and catalyst selectivity. Intriguingly, these substrates gave good yields, similar to the model substrate 55, with 65% yield for the tert-
butyl substituted substrate and 70% for the trimethylsilyl containing substrate. Substrate 61 was synthesized and examined to further study the chemo-selectivity of this reaction. Two positions are present on this molecule for 6-membered ring formation, both into a α-carbonyl C–H bond and a benzylic C–H bond. Surprisingly, even in the presence of these two reactive sites the 7-membered ring formation was still favored as the major product.

Scheme 3.8 Substrate Scope for Intramolecular C–H Amination of Aldehydic C(sp²)–H Bonds

With the surprising results obtained from this work, it was more than unprecedented when the Co(II)-MRC system provided one final surprise in the arrangement of these structures. Single crystals for XRD (X-Ray Diffraction) analysis were grown and submitted for identification for substrates 55, 57, and 59. Upon receiving the crystal structures of all three substrates it was realized that the 8,- and 9-membered ring substrates exhibited an unprecedented form of planar...
chirality. Although planar chirality was mentioned before in the work done by Leit in their Grubbs olefin metathesis reaction to synthesize bicyclic sultams\(^7\), this was expected as the tertiary nitrogen found in those substrates would have been locked in conformation. What was found with substrates 55, 57, and 59 was planar chirality across the bonds of the tertiary N–S–N–H. Although not determined as to why this has happened experimentally, we postulate that the rigid conformation of the medium-sized rings forces the lone pair \(p_z\) of the N–H nitrogen into a position so that it can form a pseudo \(\pi\)-bond by overlapping the empty \(d_{z^2}\) orbitals of the sulfur atom. This, in conjunction with the rigid sulfone and tertiary nitrogen would make a plane of chirality along the molecule which can be detected by XRD analysis. Unfortunately, since this work focused solely on medium-sized ring synthesis, little work had been done to examine the enantio-selective version of this reaction, and therefore these substrates were both synthesized in racemic mixtures. Figure 3.3 shows the crystal structures of the 7,-8- and 9-membered rings, including the two enantiomers for both the 8- and 9-membered rings.

![Figure 3.3 Crystal Structures for Medium-Sized Sulfamoyl Rings](image)

The proposed mechanism for the Co(II)-porphyrin catalyzed intramolecular C–H amination of sulfamoyl azides into aldehydic C(\(sp^2\))–H is similar to that of previously explored intramolecular C–H amination reactions in the Zhang group.\(^{12}\) The [Co(II)(Por)] catalyst (I) coordinates with the azide substrate 54, which causes a radical attack on the azide, generating a Co–N bond, giving rise to a [Co(III)(Por)] and nitrene radical complex. The newly formed nitrene
radical can then abstract a reactive hydrogen atom by homolytic cleavage (II), which generates a new carbon radical on the chain. This species (III) then undergoes 7-exo-tet radical cyclization to close on itself releasing both the desired product (55) and regenerating the [Co(II)(Por)] catalyst.

**Scheme 3.9 Co(II)-MRC Proposed Mechanism**

3.4 Conclusions and Future Outlook

A new catalyst system using [Co(II)(Por)] as highly reactive metalloradical catalysts was developed which allowed for the synthesis of medium-sized rings via chemo-selective intramolecular C–H amination of sulfamoyl azides into aldehydic C(sp²)–H bonds. The system uses relatively benign conditions, and was used to synthesize an excellent preliminary substrate scope, containing the 7-, 8- and 9-membered rings in moderate to excellent yields. Also, the system has shone light on the potential for Co(II)-porphyrins to catalyze the stereo-selective construction of molecules which exhibit planar chirality. Future work in the Zhang group is
currently underway to publish the findings and pursue the potential for higher yields, an expanded substrate scope, synthesis of the remaining medium-sized rings (10 and 11) and further exploration into the intriguing planar chirality exhibited by these molecular scaffolds.

3.5 Experimental Section

\[
\text{Synthesis of Substrates 4–10}
\]

Sulfamoyl azides 4–10 were synthesized according to the literature procedure. First a commercially available alcohol was tosylated as reported in the literature to afford the tosyl derivative 1.\footnote{12} Next amination was carried out as reported before in the presence of excess amine under reflux conditions to afford the amine 2.\footnote{13} Bis(azido)sulfone which has been previously synthesized by the Zhang group, was used in a 0.15M DCM solution as a substrate for an $S_N2$ reaction producing the sulfamoyl azide 3.\footnote{14} Finally, Lemieux-Johnson oxidation with
osmium(VIII)tetroxide was used to oxidatively cleave the double bond on 3 and give rise to the desired aldehydes for intramolecular C–H amination.\textsuperscript{15}

**Lemieux-Johnson Oxidative Cleavage**

To a clean, oven-dried flask equipped with a Teflon\textsuperscript{®} coated magnetic stir bar was charged sulfamoyl azide 3 (4.8 mmol, 1.4 g), solvent (3:1 dioxane:H\textsubscript{2}O, 33 mL:11 mL) and 2,6-lutidine (9.5 mmol, 1.1 mL) and set to stir in an ice-water slurry bath. A 4wt% soln. of OsO\textsubscript{4} in H\textsubscript{2}O (2 mol %, 0.75 mL) was added drop-wise, then allowed to stir for an additional 2 minutes once the addition was complete. NaIO\textsubscript{4} (19.2 mmol, 4.12 g) was then added portion-wise to the stirring solution, at which point precipitates of NaIO\textsubscript{3} and other IO\textsubscript{x+y} were formed as a white-pink clumpy mass. The reaction mixture is then allowed to stir for 12 h while slowly warming to rt. Once the reaction is complete, 10% v/v NaHSO\textsubscript{3} (~2-5 mL) is slowly added to quench the OsO\textsubscript{4}, then the solution was poured into a separatory funnel (150 mL) washing the residual solid with DCM (~10 mL). The aqueous layer was extracted 3x with DCM (10 mL), the organic extracts were pooled then dried over Na\textsubscript{2}SO\textsubscript{4}. For some substrates which have a \textit{Rf} \approx 2,6-lutidine it is necessary to do an acid-base extraction (1M HCl: 1M NaOH: DCM) to remove the tertiary amine and promote facile purification of the desired product. The compound was then purified by column chromatography, then characterized.

\[
\begin{align*}
\text{(((azidosulfonyl)(4-oxobutyl)amino)methyl)benzene} \quad &\text{was synthesized according to the general procedure as an opaque viscous oil (72% yield, 1:1 Hexanes:EtOAc} \quad \text{Rf} = 0.68). \quad \text{\textsuperscript{1}H NMR (400}
\end{align*}
\]
MHz, CDCl₃) δ, 9.66 (d, J = 0.4 Hz, 1H), 7.37 (m, 5H), 4.45 (s, 2H), 3.25 (t, J = 7.2 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.84 (p, J = 7.2 Hz, 2H).

(2-((azidosulfonyl)(4-oxobutyl)amino)ethyl)benzene was synthesized according to the general procedure as an opaque viscous oil (25% yield, 1:1 Hexanes:EtOAc Rf = 0.59). ¹H NMR (400 MHz, CDCl₃) δ, 9.78 (d, J = 0.8 Hz, 1H), 7.26 (m, 5H), 3.28 (m, 4H), 2.67 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 6.6 Hz, 2H), 2.00 (p, J = 7.6 Hz, 2H), 1.90 (p, J = 7.2 Hz, 2H).

1-((azidosulfonyl)((tert-butyl)amino)-4-oxobutane was synthesized according to the general procedure as an opaque viscous oil (38% yield). ¹H NMR (400 MHz, CDCl₃) δ, 9.77 (s, 1H), 3.31 (t, J = 8 Hz, 2H), 2.52 (t, J = 6.8 Hz, 2H), 1.96 (p, J = 7.4 Hz, 2H), 1.47 (s, 9H). ¹³C (100 MHz, CDCl₃) δ, 200.91, 61.01, 47.07, 40.81, 29.45, 23.91.

(((azidosulfonyl)(4-oxobutyl)amino)methyl)trimethylsilane was synthesized according to the general procedure as an opaque viscous oil (49% yield, 2:1 Hexanes:EtOAc Rf = 0.65). ¹H NMR
(400 MHz, CDCl₃) δ, 9.79 (s, 1H), 3.26 (t, J = 7.6 Hz, 2H), 2.53 (t, J = 7 Hz, 2H), 1.95 (p, J = 7.4 Hz, 2H), 0.15 (s, 9H).

(((azidosulfonyl)(5-oxopentyl)amino)methyl)benzene was synthesized according to the general procedure as an opaque viscous oil (83% yield, 1:1 Hexanes:EtOAc Rf = 0.68). ¹H NMR (400 MHz, CDCl₃) δ, 9.68 (t, J = 1.4 Hz, 1H), 7.35 (m, 5H), 4.44 (s, 2H), 3.22 (t, J = 7 Hz, 2H), 2.37 (t, J = 6 Hz, 2H), 1.54 (m, 4H). ¹³C (100 MHz, CDCl₃) δ, 201.49, 134.45, 128.82, 128.46, 128.43, 52.57, 48.24, 42.91, 26.63, 18.70.

1-(((azidosulfonyl)(5-oxopentyl)amino)methyl)4-methoxybenzene was synthesized according to the general procedure as an opaque viscous oil (60% yield, 2:1 Hexanes:EtOAc Rf = 0.50). ¹H NMR (400 MHz, CDCl₃) δ, 9.71 (s, 1H), 7.26 (d, J = 7.2 Hz, 2H) 6.9 (d, J = 6.8 Hz, 2H), 4.38 (s, 2H), 3.81 (s, 3H), 3.19 (t, J = 5.6 Hz, 2H), 2.39 (t, J = 5.6 Hz, 2H), 1.54 (p, J = 2.8 Hz, 4H).
((azidosulfonyl)(6-oxohexyl)amino)methyl)benzene was synthesized according to the general procedure as an opaque viscous oil (48% yield, 2:1 Hexanes:EtOAc Rf = 0.50). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\), 9.71 (t, \(J = 1.2\) Hz, 1H), 7.38 (m, 5H) 4.44 (s, 2H), 3.21 (t, \(J = 6.2\) Hz, 2H), 2.37 (dt, 2H), 1.54 (m, 4H), 1.23 (m, 2H). \(^{13}\)C (100 MHz, CDCl\(_3\)) \(\delta\), 202.05, 134.61, 128.85, 128.48, 128.45, 52.64, 48.50, 43.40, 27.12, 25.86, 21.35.

**Medium-Sized Ring Synthesis by Intramolecular C–H Amination with Co(II)-Amidoporphyrins**

![Chemical structure](image)

To a clean, oven-dried Schlenk tube equipped with a Teflon\(^\circledR\) coated magnetic stir bar was added activated MS 4Å (~25 mg), and catalyst ([Co(P7]), 2 mol %, 2.8 mg). The Schlenk tube was then capped with a Teflon\(^\circledR\) screw-cap and set to the high vacuum for ~1 h at 30 mtorr. The tube was then backfilled with N\(_2\) and put back to the vacuum, alternating 3x then set under N\(_2\) at which point the Teflon\(^\circledR\) screw-cap was replaced with a rubber septum. The substrate was then added (4–10), (0.1 mmol), followed by anhydrous solvent (PhF, 1 mL) to rinse all the substrate into the Schlenk tube, which was then re-fitted with the Teflon\(^\circledR\) screw-cap and set to stir at the desired temperature (80 °C) for overnight (~12 h). Once the reaction was complete, it was allowed to cool to rt, after which time the solution was withdrawn and filtered through a plug of Celite\(^\circledR\). The Celite\(^\circledR\) plugged was washed with a little EtOAc (~1 mL), then all the organic fractions pooled and
reduced *in vacuo* on a RotaVap® R-210. The residue was then purified *via* column chromatography to give the desired compounds.

7-benzyl-1,2,7-thiadiazepan-3-one 1,1-dioxide was synthesized according to the general procedure as clear tan crystals (88% yield, 1:1 Hexanes:EtOAc *Rf* = 0.50). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 7.35 (m, 5H), 4.33 (broad s, 2H), 3.48 (broad s, 2H), 2.97 (d, $J$ = 4.4 Hz, 2H), 1.90 (t, $J$ = 4.8 Hz, 2H). X-Ray crystal structure solved, see Chapter 4.

7-(3-phenylpropyl)-1,2,7-thiadiazepan-3-one 1,1-dioxide was synthesized according to the general procedure as clear tan crystals (60% yield, DCM *Rf* = 0.19). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 8.37 (broad s, 1H), 7.17 (m, 5H), 3.58 (broad s, 2H), 3.13 (broad s, 2H), 2.89 (broad s, 2H) 2.64 (t, $J$ = 7.6 Hz, 2H), 1.91 (t, $J$ = 7.6 Hz, 2H), 1.83 (broad s, 2H). $^{13}$C (100 MHz, CDCl$_3$) $\delta$, 172.32, 140.74, 128.50, 128.30, 126.16, 49.08, 46.72, 35.89, 32.55, 29.66, 19.59.
7-(tert-butyl)-1,2,7-thiadiazepan-3-one 1,1-dioxide was synthesized according to the general procedure as clear tan crystals (65% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 8.60 (broad s, 1H), 3.84 (d, $J = 4.4$ Hz, 2H), 2.96 (d, $J = 3.6$ Hz, 2H), 1.85 (broad s, 2H), 1.48 (broad s, 9H).

![Image 14]

7-((trimethylsilyl)methyl)-1,2,7-thiadiazepan-3-one 1,1-dioxide was synthesized according to the general procedure as clear tan crystals (70% yield, 2:1 Hexanes:EtOAc $R_f = 0.25$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 8.32 (broad s, 1H), 3.60 (broad s, 2H), 2.91 (broad s, 2H), 2.64 (broad s, 2H), 1.89 (broad s, 2H), -0.13 (broad s, 9H). $^{13}$C (100 MHz, CDCl$_3$) $\delta$, 172.68, 51.30, 37.43, 35.86, 18.28, -2.04.

![Image 15]

8-benzyl-1,2,8-thiadiazocan-3-one 1,1-dioxide was synthesized according to the general procedure as clear tan crystals (63% yield, 2:1 Hexanes:EtOAc $R_f = 0.25$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, 7.35 (m, 5H), 3.41 (t, $J = 8.4$ Hz, 2H), 2.97 (t, $J = 10.6$ Hz, 2H), 1.96 (p, $J = 10$ Hz, 2H), 1.80 (m, 2H). X-Ray crystal structure solved, see Chapter 4.

![Image 16]
8-(4-methoxybenzyl)-1,2,8-thiadiazocan-3-one 1,1-dioxide was synthesized according to the general procedure as clear tan crystals (33% yield, 2:1 Hexanes:EtOAc *R*$_f$ = 0.23). $^1$H NMR (400 MHz, CDCl$_3$) δ, 8.54 (broad s, 1H), 7.24 (d, $J$ = 6.8 Hz, 2H), 6.88 (d, $J$ = 6.8 Hz, 2H), 4.30 (broad s, 2H), 3.80 (broad s, 3H), 3.38 (t, $J$ = 4.2 Hz, 2H), 2.96 (t, $J$ = 5.4 Hz, 2H), 1.94 (p, $J$ = 5.6 Hz, 2H), 1.79 (p, $J$ = 4.2 Hz, 2H). $^{13}$C (100 MHz, CDCl$_3$) δ, 174.73, 159.58, 129.85, 126.19, 141.17, 55.27, 49.72, 43.87, 30.54, 24.55, 22.39.

\[ \text{9-benzy-1,2,9-thiadiazonan-3-one 1,1-dioxide} \]

was synthesized according to the general procedure as clear tan crystals (21% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ, 7.35 (m, 5H), 4.42 (s, 2H), 3.50 (t, $J$ = 10 Hz, 2H), 2.87 (t, $J$ = 10.8 Hz, 2H), 1.89 (broad m, 2H), 1.68 (broad m, 2H), 1.57 (broad m, 2H). X-Ray crystal structure solved, see Chapter 4.

3.6 References


Chapter 4. Spectra

See Supplementary Information