Studies Toward the Synthesis of a Novel Diastereomerically Pure Cyclopropyl N-Heterocyclic Carbene Ligand for Asymmetric Catalysis

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Studies Toward the Synthesis of a Novel Diastereomerically Pure Cyclopropyl N-Heterocyclic Carbene Ligand for Asymmetric Catalysis

Brandon T. Milliken

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

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COLLEGE OF SCIENCE
ROCHESTER INSTITUTE OF TECHNOLOGY
ROCHESTER, NY
December, 2014
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Dr. Joseph Hornak (Program Director)
ABSTRACT

This M.S. Thesis research objective is designed towards the racemic synthesis of a novel diastereoselectively pure, sterically bulky, cyclopropyl-containing, N-heterocyclic carbene (NHC) ligand. It is hypothesized that introduction of the sterically bulky cyclopropyl moiety at the N-substituent position of the imidazolium backbone will cause the self-assembly to develop a well defined C$_2$-symmetric N-heterocyclic ligand, thereby limiting the free rotation about the C–N bond and creating a well-defined chiral pocket. It was discovered through utilizing classic synthetic methods that a diastereomeric imidazolium salt product was yielded, which can be attributed to the racemic synthesis of a diastereomeric cyclopropane starting material.
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In conclusion, I owe everything to my mother and father who have been there for me my entire life with the utmost support and belief in me, and to whom I dedicate my success too.

TABLE OF CONTENTS
\(^1\text{H NMR}\) Proton NMR

\(^{13}\text{C NMR}\) Carbon NMR

\(\text{aq.}\) Aqueous

\text{BINAP} 1,1-dinaphthyl

\text{CuI} copper iodide

\text{DBU} 1,8-diazabicycloundec-7-ene

\text{DCM} dichloromethane

\text{DFT} Density Functional Theory

\text{DI} Deionized Water

\text{DPPA} diphenylphosphoryl azide

\text{dr} Diastereometric Ratio

\text{ee} Enantiomeric Excess

\text{Et}_2\text{O} diethyl ether

\text{EtOAc} ethyl acetate

\text{HCl} hydrochloric acid

\text{HRMS} High Resolution Mass Spectrometer

\text{IAd} 1,3-di-l-adamantylimidazol-2-ylidene

\text{IR} Infrared Spectroscopy

\text{LiOH} lithium hydroxide

\text{LRMS} Low Resolution Mass Spectrometer

\text{M} Molarity

\text{MeI} methyl iodide

\text{MeOH} methanol

\text{N} Normality

\text{NaN}_3 sodium azide

\text{NHC} Nucleophilic Heterocyclic Carbene

\text{NMR} Nuclear Magnetic Resonance
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**THESIS OVERVIEW**
**N-Heterocyclic carbenes (NHCs)** are a new class of persistent carbenes that have elicited increasing attention by the chemical community (Figure 1).\(^1\) The field of NHCs was revolutionized with Arduengo’s isolation of the first persistent free carbene \(^2\) and Herrmann’s demonstration of the catalytic potential of NHCs in organometallic transformations.\(^3, 4\) The number of NHC-related publications has grown exponentially to reflect the vast degree of newly discovered catalytic applications of NHC systems (Figure 1A). In spite of their wide range of effectiveness in catalytic organometallic transformations, the development of chiral NHCs for catalytic asymmetric transformations has lagged significantly behind (Figure 1B). The promise of this research moving forward after this optimization study is to explore a new stereo-directing cyclopropyl moiety for catalytic asymmetric transformations.

![NHC Publications](image1.png)  ![Chiral NHC Publications](image2.png)

**Figure 1**: NHC and Chiral NHC Publications from 1975-May 2014

Asymmetric catalysis is a chemical reaction where an element of chirality is introduced into the product via a stereodirecting catalytic agent. Since enantiomers and diastereomers often exhibit different biological activity in living organisms, asymmetric catalysis is an extremely important tool in the fine chemical industry and natural product synthesis to selectively synthesize a single stereoisomer. The development of novel asymmetric catalytic methods is one of the single most researched areas in organic chemistry, natural product synthesis, and organometallic chemistry. The synthesis of chiral natural products and pharmaceuticals in an economically efficient and enantiomerically pure process is the driving force behind the field of catalytic asymmetric synthesis. However, the utility of these ligands is continuously outpaced by the multitude of new discoveries in optically active natural products and active
pharmaceutical ingredients. To date, only a select few ‘privileged ligands’ have exhibited a high degree of stereoselectivity in catalytic asymmetric transformations. A stereodirecting catalytic agent that exhibits a high degree of stereoselectivity in a wide range of organometallic transformations is an ideal green alternative to the racemic synthesis, purification, and waste disposal of undesired stereoisomeric mixtures at both the milli- to kilogram scale.

Traditionally, these privileged ligands be categorized by two main structural characteristics (Figure 2).

Privileged ligands in asymmetric syntheses possess a rigid chiral pocket, are easy to modify with stereocenters located near the coordination site, and bind strongly to a metal center. It has also been well established that a vast majority of privileged ligands possess C$_2$-symmetry, as it plays a crucial role in stereoselectivity by reducing the possible diastereomeric transition states in the reaction pathway.$^{[5]}$

In the past decade, chiral NHCs have been employed with moderate success in a variety of catalytic asymmetric transformations.$^{[6,7]}$ Presently, the families of chiral NHCs are limited in their structural diversity, and few reports exist where they can be employed over multiple catalytic transformations with high activity and stereoselectivity. It is proposed that the introduction of a rigid cyclopropyl moiety with sterically bulky substituents for the NHC ligand design will cause a self-assembly into a C$_2$-symmetric geometry that will hinder rotation of the N-substituent and produce a well-defined chiral pocket as illustrated in Figure 3.
The cyclopropyl moiety consists of a planar framework with eclipsed substituents that exist in a well-defined geometric orientation, and via known catalytic asymmetric methodologies the substituents can be readily constructed into a obtaining a well-defined rigid chiral pocket.\[8,9,10,11\] The diastereomerically pure cyclopropyl NHC ligand (1) proposed in this study is rationally designed with these key elements in mind.

CARBENE CHEMISTRY

As NHCs are a carbene species, it is important to understand the chemistry of the carbene and carbenoid moiety. A free carbene or carbenoid (metal-bound carbene) consists of a neutral, divalent carbon center with six valence electrons, two of which are in non-bonding orbitals. Depending on the electronic structure of the carbene (Figure 4), these non-bonding electrons exist in either a singlet or triplet state.
In the singlet state, the carbene’s unshared electrons are paired and the carbon center takes on an $sp^2$ hybridization, while in the triplet state, the carbene’s electrons are unshared and adopt either an $sp$ or $sp^2$ hybridization with linear or bent geometry, respectively.\cite{12} Because most carbenoid species are known to have short lifetimes, Skell and Woodworth developed a straightforward experiment to characterize the electronic state of carbene species \textit{in situ}.\cite{13} The result is that when the cycloaddition of the singlet state carbene to \textit{cis}-2-butene is concerted, the product is \textit{cis}-1,2-dimethylcyclopropane. On the other hand, the cycloaddition of the triplet state carbene to \textit{cis}-2-butene yields both the \textit{cis}- and \textit{trans}-1,2,3-dimethylcyclopropanes (Scheme 1).

Generally, the triplet state (ground state) carbene is at lower energy compared to the singlet state (excited state), but substituents can assist in stabilizing the singlet state by through the donation of electron density.\cite{12} NHCs are primarily singlet state carbenes that are stabilized by the adjacent nitrogen atoms through resonance and induction. Furthermore, these singlet-state NHCs form strong $\sigma$-bonds to the metal center and decreases the need for $\pi$-backbonding to stabilize the carbene-metal ‘carbenoid’ complex.

Fischer was the first to report the synthesis of a complex containing a C=M double bond in 1964.\cite{14} They bind to late transition metals through $\sigma$-donation of a lone pair of electrons from the
carbene carbon, and are typically weak π-backbonding acceptors from the d_x^* orbitals of the metal center. This characteristic makes Fischer carbenes electrophilic in nature because the empty π-type orbital of the carbene is only partially stabilized by the d_x orbitals of the metal. The bonding characteristics of a Fischer carbene can be best summarized as a three-centered four-electron bond with the majority of the electron density located at either the d_x^* orbital of the metal or the p orbitals of the carbene substituents (Figure 5).

On the other hand, Schrock was the first to introduce carbenes to organometallic chemistry as a nucleophilic species. Schrock introduced a series of carbene complexes that involved early to middle transition metal complexes. The metals in Schrock carbenes are typically of high oxidation state, which produces strongly anionic ligands. Unlike the Fischer carbenes, the Schrock carbenes have strong π-backbonding to the metal, and these carbene complexes can be viewed as an ylide in a sense where the metal is the electrophile and the carbon is the nucleophile (Figure 6). Schrock’s carbene research has played a key role in olefin metathesis and he along with others were awarded the Nobel Prize in 2005.

N-HETEROCYCLIC CARBENE CHEMISTRY
The reactivity of NHC-transition metal complexes is strikingly different from traditional Fisher and Schrock carbenes.\textsuperscript{[14,15]} Even though all formalisms utilize a ‘carbene ligand’, NHCs possess properties and reactivity unlike the Fischer and Schrock transition metal carbene complexes. The strong σ-bond between the carbene carbon of the NHC and the transition metal center is represented by a single bond, in contrast with Fischer and Schrock carbenes that are typically presented with a double bond between the carbene carbon and metal center. Furthermore, the free carbene species of the NHCs have been isolated and deemed ‘persistent carbenes’ unlike the carbene species utilized in Fischer and Schrock’s carbene-metal complexes.

In 1991, Arduengo\textsuperscript{[2]} revolutionized NHCs with the ability to synthesize the first stable NHC that could also be isolated as a free carbene. The carbene, 1,3-di-l-adamantylimidazol-2-ylidene (IAd), is a colorless crystal that is thermodynamically and kinetically stable in the presence of air and does not decompose upon melting at 240-241 °C (Scheme 2).

![Scheme 2: First Isolated NHC by Arduengo](image)

Arduengo attributed the stability of IAd to a combination of electronic and steric effects.\textsuperscript{[2]} With regard to its unique electronic character, the singlet-state carbene possesses a lone pair of electrons in the $sp^2$ orbital that is involved in σ-bonding, and a vacant $p$ orbital that is available for π-backbonding. The lone pair electrons of nitrogen at the 1 and 3 positions of the imidazol-2-ylidene delocalize into the empty $p$ orbital of the carbene center (Scheme 3). As a result, this greatly increases its stability and reduces π-backbonding from the metal center. Additionally, the steric bulkiness of the adamantyl substituents
increases its stability through shielding and that hinders the decomposition pathways of the free carbonic species.

Scheme 3: NHC Electronic Stability by Resonance

NHCs have been synthesized with a variety of N-substituents without affecting the electronic properties of the active carbene center.[14, 15] In this study, the N-substituted cyclopropyl moiety is predicted to possess an analogous electronic and steric effect on the NHC backbone as compared to previous bulky N-substituents throughout the literature.[15]

N-HETEROCYCLIC CARBENE CATALYTIC ADVANCEMENT

In 1995, Herrmann[3] reported the first catalytic activity of NHC-metal complexes in a series of Heck coupling reactions with aryl halides and methyl acrylate derivatives. Historically, the Heck reaction predominantly utilized phosphine ligands, even though they have several inherent disadvantages. Phosphine ligands were known to decompose throughout the course of the reaction and required excess ligand loading, which is not amenable for large scale applications of the Heck reaction. Herrmann discovered that at extremely low loadings (0.4 mmol%) the NHC-palladium catalyst afforded nearly quantitative yield of the trans-alkene product (Scheme 4).

![Scheme 4: Heck Reaction with NHC-Palladium Catalyst](image-url)
Herrmann attributed the high yield and high catalytic activity to the strong σ-bond between the NHC carbenic carbon and the palladium metal center, which increased the thermal stability, hydrolytic, and oxidative-stability of the NHC–metal catalyst, as compared to traditional phosphine ligand additives. This seminal discovery initiated the evaluation of NHC-metal complexes for other catalytic organometallic transformations.

After the initial discovery of the utility of NHC-palladium complexes, the synthesis and application of a wide range of structurally and electronically diverse NHC-transition metal complexes in catalytic organometallic transformations exploded. In fact, NHC ligands are known to bind to both low and high oxidation state transition metals giving access to a wide range of robust complexes and organometallic transformations outside the scope of traditional phosphine ligands. This phenomenon is attributed to the lack of π-backbonding in the NHC–metal complex, which allows for greater electron density at the metal center. An increase in electron density at the metal center leads to higher Lewis basicity producing a robust and catalytically active NHC–metal complex. Nolan concluded from a series of DFT studies that NHCs are soft ligands and are able to form stronger bonds to transition metals as compared to phosphine ligands.

In addition to their higher catalytic activities, NHCs are structurally different than their phosphine counterparts. NHC–metal complexes are structurally shaped like an umbrella protecting the catalytic metal center, while the phosphine ligands are cone-shaped (Figure 7).

Figure 7: Metal Center Shielding of NHCs vs. Phosphines
The umbrella shape allows for the $N$-substituents to generate a rigid well-defined pocket, whereas the substituents of the phosphine ligands are direct away from the metal center which limits their effect on defining a pocket about the metal center. Leveraging the unique shape of NHC-transition metal complexes as a sterically directing group, it was postulated that chiral NHCs could be useful ligands in catalytic asymmetric synthesis of optically active organic compounds.\(^{[17]}\) Towards that end, Herrmann was the first to report the synthesis and applications of a novel chiral NHC ligand for asymmetric organometallic catalysis.\(^{[17]}\) Chiral NHC-rhodium complex 14 was evaluated in the hydrosilylation of acetophenone to generate a secondary chiral alcohol. Although Herrmann’s NHC displayed good activity with 90% yield, it was fraught with poor (32% $ee$) stereoselectivity (Scheme 5).

![Scheme 5: First Chiral NHC Ligand Employed in Asymmetric Catalysis by Herrmann](image)

The lack of stereoselectivity can be attributed to the inability of the chiral $N$-substituents to effectively restrict the rotation about the C–N bond, resulting in an ill-defined chiral pocket. Since Herrmann’s first chiral NHC, the field of catalytic asymmetric synthesis has had varying degrees of success developing novel chiral NHC-transition metal complexes for stereoselective transformations.

Nevertheless, four predominant classes of chiral NHCs have emerged during the past decade.\(^{[6]}\) These classes include:

1. NHC ligands that contain $N$-substituents with centers of chirality ($\alpha$-chirality) is of interest in this current work.
2. Chirality is also introduced into NHC ligands by containing chiral elements within the N-heterocyclic ring at the 4 and 5 position of the imidazolium backbone.

3. NHC ligands also achieve chirality by utilizing elements of axial or planar chirality as substituents to the imidazolium core.

4. Introduction of an oxazoline unit to form a bidentate oxazoline-NHC ligand system is another effective means of developing chiral NHC ligand.

To rationalize the research objective of this MS Thesis, a brief discussion will follow with respect to the development of C\textsubscript{2}-symmetric NHC ligands with N-substituents containing alpha asymmetric carbon centers.

**BRIEF OVERVIEW OF C\textsubscript{2}-SYMMETRIC NHCs**

NHC ligands containing chiral elements within the N-heterocyclic ring use sterically bulky aromatic substituents at positions 4 and 5 of the imidazol-2-ylidene core which have been demonstrated to indirectly force a C\textsubscript{2}-symmetric chiral pocket. Grubbs performed a series of catalytic asymmetric ring-closing metathesis reactions (15) which achieved yields >90% and ee >80% (Scheme 6).\textsuperscript{[18]}

![Scheme 6: NHC Ligand Containing Chiral Elements within the N-Heterocyclic Ring by Grubbs](image)

Analogous to the axial chirality exhibited by the 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) moiety, the NHC-BINAP ligand contains an element of axial chirality which is designed to
reduce the atropisomerization that arises from the free rotation about the C–N bond (Figure 5). The NHC-BINAP bridging moiety results in the self-assembly of a C2-symmetric catalyst (16). Shi reported the catalytic asymmetric hydrosilylations on various ketones with NHC-BINAP 16 followed by hydrolysis to afford optically active secondary alcohols with good yields (>85%) and excellent enantiomeric purity (>90% ee) (Scheme 7).[19]

![Scheme 7: NHC Ligand with Axial Chirality used in Hydrolysis by Shi](image)

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<th>R</th>
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NHC ligands with N-substituents that contain α-chiral centers have dominated the field with varying measures of activity and selectivity. In 2003, Chung synthesized a series of chiral ferrocenyl imidazolium iridium catalysts for asymmetric transfer hydrogenation reactions with extremely low catalyst loadings (0.2 mol%) (Scheme 8).[20] It was found that chiral NHC catalyst 17 achieved nearly quantitative yields but displayed poor enantioselectivity (<22.1% ee).
Roland and Alexakis performed an extensive analysis of chiral NHC ligands with N-substituents containing α-centers of chirality in a series of copper-catalyzed 1,4-conjugate addition reactions (Scheme 9). These chiral imidazolium salts were complexed to copper in-situ which makes this an extremely attractive feature for screening catalytic asymmetric transformations as a library of transition metals and ligand partners. In all, these chiral ligands showed good activity with yields exceeding 85% and modest enantioselectivity peaking at 54% ee (Scheme 9).
In particular, the 2-naphthyl imidazolium salt 18 showed excellent activity (>85%) with moderate selectivity (37-51% ee). This example of the 2-naphthyl substituent supports the notion that the sterically bulky groups can reduce atropism and act as a powerful stereodirecting group at the \( \alpha \)-carbon position.

Sato performed a series of three-component coupling reactions involving various 1,3-dienes, aldehydes, and triethylsilane to form functionally and sterically complex protected allylic alcohols catalyzed by nickel and imidazolium salts (Scheme 10).\textsuperscript{[22]}
The \textit{in situ} active catalyst formation procedure afforded good yields, as well as, impressive regio-, enantio-, and diastereoselectivity. Sato’s concluding remarks stated that the high degree of selectivity observed is “rare”, but his results “...pave the way for extension of the utilization of NHCs as chiral ligands.”

In 2006, Ayoama published the catalytic stereoselective intramolecular $\alpha$-arylation of \textit{ortho}-substituted \textit{N}-acetyl amides to form optically active oxindoles using two different families of chiral NHC Pd complexes.\textsuperscript{[23]} The enantioselectivity of the palladium catalyst with the chiral NHC ligand (19) that contains elements of chirality at the 4 and 5 positions of the \textit{N}-heterocyclic core was modest. A year later

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Scheme 10: NHC Ligand with Alpha Chirality in a Three Component Coupling by Sato
Kündig made a breakthrough in the same intramolecular α-arylation reaction using a chiral NHC ligand (20) that contains α-centers of chirality (Scheme 11).[24]

This reaction independently conducted by different research organizations underscores the necessity for developing structurally diverse chiral NHC families and the need to screen them in a wide range of catalytic asymmetric transformations.

Later, Kündig evaluated a series of structurally similar chiral NHCs containing α-centers for the methoxycyclization of (8-methyl-1-phenylnon-7-en-1-yne-5,5-diyldisulfonyl)dibenzene (Scheme 12).[25]
Kündig’s chiral NHC ligands (21–26) displayed excellent catalytic activity with yields >85%, but a wide range of enantioselectivity from 7-72% ee.

CYCLOPROPYL MOIETY AS STERICALLY BULKY DIRECTING GROUPS

The field of chiral NHC-transition metal asymmetric catalysis suggests that there is a need to develop sterically bulky N-substituents. The goal of this current work is to optimize the synthetic pathway in order to incorporate the cyclopropyl moiety as a sterically-bulky substituent resulting in a C$_2$-symmetric NHC ligand design strategy. The cyclopropyl moiety has been utilized as a conformationally restricted mechanistic probe [26] and as a directing group in asymmetric catalysis.[27,28] For example, Zhang published a series of chiral cyclopropyl-containing cobalt porphyrin D$_2$-symmetric catalysts that were used in the catalytic asymmetric cyclopropanation of styrene (Scheme 13).[27]

Scheme 13: Cyclopropyl-Containing Cobalt Catalyst by Zhang

Zhang’s cyclopropyl-containing cobalt catalyst (27) achieved good yields (>84%) of the cyclopropane product and moderate to excellent stereoselectivity (31–98% ee). Additionally, catalyst 27 imparted high trans:cis ratios from 83:13 to >99:1, which is an especially important advancement in the field of cyclopropanation reactions.
In 2011, Davies synthesized and evaluated the catalytic performance of a D$_2$-symmetric Rh$_2$(_R-
BTPCP)_4 catalyst (28), which incorporated the cyclopropyl moiety as a stereodirecting group for the
cyclopropanation reactions of styrene (Scheme 14). [28]

```

Scheme 14: Davies’ Cyclopropyl-Containing Rh$_2$(R-BTPCP)$_4$ Catalyst

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>23</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>2.0</td>
<td>0</td>
<td>72</td>
<td>92</td>
</tr>
<tr>
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<td>-78</td>
<td>71</td>
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</tr>
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</tr>
<tr>
<td>60</td>
<td>23</td>
<td>46</td>
<td>92</td>
</tr>
</tbody>
</table>
```

Catalyst 28 it displayed good activity (46-86% yields), excellent enantioselectivities (91-92% ee), and
consistently high trans:cis diastereomeric ratios for a wide variety of reaction conditions. Today, the
Rh$_2$(R-BTPCP)$_4$ catalyst (28) is sold by Strem Chemicals, USA and is marketed for the asymmetric
synthesis of bicyclo[1,1,0]butane rings and 2,5-dihydroisooxazoles compounds.

These previous studies by Zhang[27] and Davies[28] suggest that the design of the chiral
cyclopropyl-containing NHC ligand in the current work is a promising design element for an asymmetric
catalyst. Potentially, a cyclopropyl-containing NHC ligand could be used in future catalytic asymmetric
cyclopropanation reactions, and this could be an intriguing feature where a continuous closed-loop of
catalyst 1 regenerating optically active cyclopropyl starting materials necessary to make analogous chiral
cyclopropyl-containing NHC transition metal catalysts.

SYNTHETIC METHODOLOGY
It was envisioned that the synthetic methodology for the cyclopropyl-containing NHC ligand (1) would utilize classic and modern synthetic reactions as shown in the retrosynthesis (Scheme 15).

Scheme 15: Retrosynthesis 1,3-bis(1-(naphthalen-2-yl)-2-phenylcyclopropyl)-1H-imidazol-3-ium chloride (1)

NHC (1) will be synthesized from the free amine 10 in a one-pot reaction that is analogous to the first NHC synthesis in 1925 by Wallach. The imidazolium ring closure reaction has since advanced through several synthetic modifications. The free base amine 10 will arise from the amine salt 9 precursor due its likelihood of higher stability and shelf life. The one-pot Curtius degradation of the carboxylic acid 6 can afford the amine salt 9 as a classic and general reaction procedure. This ‘home-run’ approach has several synthetic challenges. As an alternative, a multistep amination can be achieved from acid 6, through an acyl azide 7 intermediate, followed by anhydrous heating to afford the isocyanate 8.

An acid-catalyzed decarboxylation of compound 8 will afford the amine salt 9. The synthetic versatility of the ‘one-pot’ versus the ‘multi-step’ Curtius degradation is an important attribute to this retrosynthetic strategy. The cyclopropane carboxylic acid 6 will be produced via a saponification of the cyclopropane
ester 5. The saponification is preceded by a [2+1] cyclopropanation reaction of commercially available styrene and the diazoacetate 4. Although, the diazoacetate 4 is not commercially available, it will be easily synthesized via a known diazo transfer reaction on the acetate 3. A simple esterification reaction from the commercially available carboxylic acid starting material 2 will serve as the starting point.

RESULTS AND DISCUSSION

It was reasoned that prior to synthesizing the enantiomerically pure 1, a model study using a diastereomerically pure racemic cyclopropane (5) was an excellent start. The results from this current work will be utilized in future research towards the enantiomerically and diastereometrically-pure chiral synthesis of 1.

This current study began with the esterification of 2-naphthylacetic acid (2) purchased from Sigma Aldrich (Scheme 16).

![Scheme 16: Synthesis of methyl 2-(naphthalene-2-yl)acetate (3)](image)

The first attempt at the esterification of 2 was successful with an isolated yield of 3 at 70%. Higher yields (89%) were achieved by slower addition of the electrophilic reagent MeI, and performing excess washes during extraction of the product (3). A \(^1\)H NMR spectrum (Appendix 1) verified that 3 was successfully synthesized in high purity by comparing the results to previously published spectral data.\(^{[30]}\)

After esterification, the acetate (3) was converted to the diazoacetate (4). Diazo transfer reactions are a classic synthetic method in the formation of diazoacetate compounds.\(^{[31, 32]}\) This diazo transfer
reaction is analogous to the synthesis of previous diazoacetate species reported in the literature (Scheme 17).[^31]

![Scheme 17: Synthesis of methyl 2-diazo-2-(naphthalene-2-yl)acetate (4)](image)

The non-nucleophilic base, DBU, was added dropwise to deprotonate the methylene protons (3) in a manner that would favor the resulting carbanionic species to perform a nucleophilic attack on the azide of p-ABSA in an effort to reduce the Claisen condensation reaction pathway. Purification by flash column chromatography eluted the product 4 as a brilliantly shiny orange band. A crystalline product (4) was isolated in good yields (73-81%) comparable to a reported yield of 75%^[^32]. A ^1^H NMR spectrum (Appendix 2) verified the highly pure diazoacetate product (4) as compared with previously reported spectral data[^32].

For the purpose of this model study, commercially available and inexpensive CuI catalyst was used to carry out the cyclopropanation of styrene in the presence of the diazoacetate 4 (Scheme 18).

![Scheme 18: Synthesis of methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate (+/-)-5](image)

Despite the fact that the achiral catalyst CuI cannot elicit enantioselectivity, it did diastereoselectively favor the cis-aryl (5) stereoisomer in high purity (10:1 dr). The dr was determined by the integration
ratios of the cyclopropyl-proton peaks that were evident in the crude $^1$H NMR spectra of diastereomers 5 and 11 (Figure 8).

![Figure 8: $^1$H NMR Spectrum of the Crude Product from the [2+1] Cycloaddition Reaction](image)

Previous reports have suggested that the cis-aryl orientation about the cyclopropane ring was favored due to the preferred approach of styrene to the strong electron-withdrawing acetate substituent side of the Cu-carbenoid complex.\cite{33} Subsequently, the lone pairs of electrons of the acetate are thought to assist in stabilizing the positive charge that develops on the most substituted carbon of the olefin as the [2+1] cycloaddition ensues.\cite{33} In fact, the thermally induced cyclopropanation of styrene and other donor-acceptor diazoacetates such as 4 also have reportedly high diastereoselectivity.

![Figure 9: Favorable Geometric Confirmation for the [2+1] Cycloaddition](image)

Purification of the diastereomeric cyclopropane crude product was difficult as the diastereomers had comparable $R_f$ values (Figure 7).
After several unsuccessful purification attempts via flash column chromatography, an ideal separation was achieved using a dry-mounted crude product on silica where the crude product was dissolved in a minimal amount of chloroform followed by the addition of silica gel to yield a slushy mixture. Removal of the chloroform to concentrate via rotary evaporator and vacuum pump yielded a tan powder with the crude product absorbed onto the silica gel. The column was packed with a hexane-silica gel slurry prior to dry-mounting the crude product. A slow gradient fashion (1-5% EtOAc in hexanes) gravity-assisted column chromatography was performed to achieve an ample separation and isolated yields of 5 up to 84%. A $^1$H NMR spectrum (Appendix 3) confirmed the isolation of the diastereomerically pure cyclopropane carboxylate (5) by comparison to known spectral data.$^{[34]}$ $^{13}$C NMR (Appendix 4) and IR spectra (Appendix 5) confirmed the identity of the product 5.

Again, since the goal of the current work was to test the synthetic feasibility and optimize the total synthesis (1), a known stereoselective catalyst such as Rh$_2$(S-biTISP)$_2$ was not employed in this [2+1] cycloaddition reaction due to economic efficiency. Davies reported an analogous cyclopropanation reaction to Scheme 18 employing his chiral catalyst, Rh$_2$(S-biTISP)$_2$, which showed excellent activity and selectivity with yields of 5 at 86% and 94% ee.$^{[34]}$ In future work, the use of chiral rhodium catalyst will be investigated to afford 1 in high yields with enantio- and diastereoselectivity.

With (+/-)-5 in hand, a saponification reaction produced carboxylic acid (6) using an aq. solution of KOH in the presence of a phase-transfer catalyst, TBAB (Scheme 19).
TBAB works by facilitating in the migration of the hydroxide anion from the aqueous phase to the organic phase (toluene) so hydroxide can perform its nucleophilic attack on the ester (+/−)-5, which is abundant only in the organic phase. In the workup, the aqueous solution was collected and acidified with 3.3 M HCl and the product (+/−)-6 was extracted with chloroform in isolated yields from 80 to 94%. The carboxylic acid (+/−)-6 was characterized by ¹H NMR (Appendix 6), ¹³C NMR (Appendix 7), and IR spectra (Appendix 8).[34]

Next the Curtius reaction was used to convert the carboxylic acid (+/−)-6 to the corresponding amine (+/−)-10. This thermal decomposition is known as the Curtius rearrangement (Scheme 20), first reported by Theodor Thomas in 1890.[35] Mechanistically, the Curtius rearrangement occurs with an alkyl shift of the R group from the carbonyl carbon to the nearest nitrogen after the loss of N₂ gas. For this reaction, the conversion of (+/−)-6 to (+/−)-10 proceeds via an acyl azide intermediate (Scheme 20).

This acyl azide species then thermally decomposes to yield an isocyanate intermediate, which is then converted to the desired amine in a decarboxylation reaction by the addition of an aqueous basic or acidic solution.
The one-pot Curtius study was monitored via $^1$H NMR and IR spectroscopy of the crude reaction mixture to determine the efficiency of the transformations. The cyclopropyl proton peaks were followed by $^1$H NMR spectroscopy to note any changes in the chemical shifts for the cyclopropyl proton peaks as evidence of a chemical reaction had occurred. IR spectroscopy was also used to observe the appearance of acyl azide ($2160–2120$ cm$^{-1}$), isocyanate ($2276–2240$ cm$^{-1}$), and amine (primary aliphatic $3400-3380$ and $3345-3325$ cm$^{-1}$; salt $3000–2800$ cm$^{-1}$) bands that were indicative of intermediates or product formation. [36]

The one-pot Curtius reactions that were initially attempted are analogous to others reported in the literature. [37,38] In particular, numerous reactions throughout the literature use diphenylphosphoryl azide (DPPA) as an azide source, Et$_3$N, and non-polar solvents such as benzene or toluene. The one-pot DPPA Curtius reaction is known to aminate sterically-demanding substrates successfully. [37]

The reaction proceeded by dissolving cyclopropanecarboxylic acid ($+/-$)-6 in benzene and treating it with DPPA and Et$_3$N over a seven-hour reflux. The reaction vessel was cooled to room temperature and concentrated via rotary evaporator. The crude residue was then dissolved in THF and stirred for 1h at room temperature in a 4 N LiOH aq. solution. The reaction mixture was diluted with DI H$_2$O and the crude product was extracted with EtOAc (Scheme 21).

The one-pot Curtius reactions that were initially attempted are analogous to others reported in the literature. [37,38] In particular, numerous reactions throughout the literature use diphenylphosphoryl azide (DPPA) as an azide source, Et$_3$N, and non-polar solvents such as benzene or toluene. The one-pot DPPA Curtius reaction is known to aminate sterically-demanding substrates successfully. [37]

The Carda reaction procedure followed preceded by dissolving cyclopropanecarboxylic acid ($+/-$)-6 in benzene and treating it with DPPA and Et$_3$N over a seven-hour reflux. The reaction vessel was cooled to room temperature and concentrated via rotary evaporator. The crude residue was then dissolved
in THF and stirred for 1h at room temperature in a 4 N LiOH \textit{aq.} solution. The reaction mixture was diluted with DI H$_2$O and the crude product was extracted with EtOAc (Scheme 21).

Carda \textit{et al.} reported the isolation of their amine product upon extraction, but in the current work the $^1$H NMR indicated a complex mixture.$^{[37]}$

No distinctive cyclopropyl proton peaks were identified in the alkyl region of the $^1$H NMR spectrum to suggest the presence of the cyclopropyl moiety (Figure 8). Furthermore, the IR spectrum did not suggest that product (+/-)-10 was formed. TLC analysis and flash column chromatography with 2.5% EtOAc in hexanes did not reveal any promising isolated fractions by $^1$H NMR. A second one-pot synthetic approach to the Curtius reaction was attempted via an acid chloride intermediate in the formation of the acyl azide (Scheme 22).
This classic reaction pathway is still used today and it presented yet another intriguing one-pot technique. The starting acid (+/-)-6 was dissolved in acetonitrile, treated with thionyl chloride, and refluxed for two-hours. The reaction vessel was cooled to room temperature and Et$_3$N and NaN$_3$ were added. The reaction mixture was heated at reflux for seven hours. Next, a 4 M LiOH _aq_ solution was added to the reaction vessel and reflux for an additional twelve hours. Then reaction mixture was cooled to room temperature diluted with DI H$_2$O, and the crude product was extracted with EtOAc.

Analysis of the crude product by $^1$H NMR spectroscopy was promising despite fact that the reaction mixture went dry. Once noticed, additional acetonitrile was added to the reaction vessel, the leak was fixed, and the procedure was continued accordingly. Upon extraction of the crude product, $^1$H NMR (Figure 9) and IR (Figure 10) spectra were obtained to evaluate the efficiency of the second attempt at the one-pot Curtius reaction.
The $^1$H NMR spectrum (Figure 9) showed two possible sets of cyclopropyl proton peaks that were at chemical shifts not yet observed by isolated cyclopropyl-containing compounds in this study. Furthermore, the IR spectrum (Figure 10) revealed peaks at 3387 and 3325 cm$^{-1}$ that are indicative of primary aliphatic amines.

![Figure 13: Crude Product IR Spectrum from Scheme 22 Reaction](image)

Despite the promising results afforded both NMR and IR spectroscopic data, purification by flash column chromatography did not yield any peaks of corresponding to molecule of interest. After flushing the column with polar solvents, MeOH and DCM separately, to remove any remaining polar compounds no peaks of interests were found by $^1$H NMR. Amines are highly polar and possess a high affinity for the silica-gel, but using deactivated silica-gel in the column chromatography process is a way to avoid this interaction. So this one-pot approach (Scheme 22) was further studied in hope the reaction was reproducible and the deactivated silica-gel purification technique would be successful. Repeating this reaction did not yield the crude product and was not reproducible. Numerous attempts at the reaction, some with slight variations, failed to produce a crude product resembling the first attempt by $^1$H NMR. The evaporation of solvent under reflux in the first reaction yielded reaction conditions that were not reproducible.
After two failed one-pot synthetic approaches to the Curtius reaction, a multi-step synthetic approach was pursued (Scheme 23).

Scheme 23: Multi-Step Approach to the Curtius Reaction

Firstly, the conversion of cyclopropanecarboxylic acid (+/-)-6 to cyclopropanecarbonyl azide (+/-)-7 was considered. If the acyl azide (+/-)-7 is isolable, then the thermal decomposition to the isocyanate (+/-)-8 in high yield and avoid undesirable side-reactions. Isocyanate (+/-)-8 is then decarboxylated under alkaline conditions to form amine (+/-)-10. Although this route is not as ideal as a one-pot synthesis, it creates an opportunity to study the nucleophilic acyl substitution from the carboxylic acid (+/-)-6 to the amine (+/-)-10 with characterizable intermediates in this Curtius reaction. The multi-step Curtius approach began with the conversion of acid (+/-)-6 to the acyl azide (+/-)-7. Formation of the acyl azide (+/-)-7 proceeded via an acid anhydride intermediate, followed by treatment of aq. NaN₃ (Scheme 24).

Scheme 24: Synthesis of cyclopropanecarbonyl azide (+/-)-7

The crude reaction mixture revealed two interesting features by ¹H NMR and IR spectra. The peaks had the same chemical shift as the starting material (+/-)-6 which indicated one of two things. Either there was still unreacted starting material present or the acid anhydride intermediate reverted to the carboxylic acid (+/-)-6. Also, evident in the ¹H NMR spectrum is the appearance of a new set of cyclopropyl-proton peaks in close proximity to those of the starting material. However, the most intriguing result from this
crude sample came from the IR spectrum (Figure 11). The band at 2137 cm\(^{-1}\) was a strong indication of the acyl azide (+/-)-7 formation as the band can be indicative of the acyl azide functionality (2160–2120 cm\(^{-1}\)) \(^{36}\), and purification of the crude product was subsequently performed.

![Crude Product IR Spectrum from First Acyl Azide Reaction](image)

Purification was performed by flash column chromatography using a 10% EtOAc in hexane eluent that resulted in a 67% isolated yield of acyl azide 7. Acyl azide 7 was characterized by \(^{1}\)H NMR (Appendix 9), \(^{13}\)C NMR (Appendix 10), and IR spectra (Appendix 11). Low Resolution Mass Spectroscopy (LRMS) was attempted but a molecular ion peak was not observed, possibly due to the reactivity of the acyl azide or the ionization source of the instrument.

A TGA was performed in order to evaluate the exothermic behavior and subsequent thermal stability of the acyl azide (Figure 12). The TGA revealed that the acyl azide began to thermally decompose at approximately 60 °C. \(^{1}\)H NMR spectral analysis of the product recovered from the TGA later indicated that one of the two products formed in the TGA analysis was the isocyanate (+/-)-8. The additional product formed was not identified, but the TGA results indicated that the Curtius rearrangement and formation of the isocyanate (+/-)-8 took place between 60–95 °C, and upon further heating to a temperature exceeding 105 °C an additional decomposition occurred.
After the acyl azide (+/-)-7 was isolated and characterized, various attempts were made to optimize the isolated yield. Initially, longer reaction times were pursued but produced similar yields as the first reaction. A $^1$H NMR analysis of Et$_3$N and THF indicated that water had contaminated both starting materials. In the presence of water, the reaction cannot go to completion due to competing reaction pathways that result in the regeneration of the starting material. Consequently, both the solvents were distilled and stored in a desiccators with 4 Å molecular sieves prevent water absorption for the open atmosphere. Consequently, higher yields (96%) of the acyl azide (+/-)-7 were achieved using freshly distilled anhydrous solvents and reagents. In fact, the reactions produced such clean products that no further purification was needed. Simply decanting the solvents from the reaction vessel, washing the vessel and solid residue with EtOAc, and concentrating the collected solutions via rotary evaporator yielded a clean acyl azide (+/-)-7 product in high yields (>90%).

Next, the multi-step Curtius reaction required the thermal decomposition of azide (+/-)-7 to the isocyanate (+/-)-8. Both 1,4-dioxane and toluene were evaluated as solvents in the thermal decomposition but neither generated any comprehensive results. Analysis was performed by $^1$H NMR
and IR spectra but both resulted in a disarray of peaks. Meanwhile, it was observed that the NMR tube containing (+/-)-7 in CDCl₃ had underwent the slight conversation to the isocyanate (+/−)-8 (Figure 13).

![Figure 16: ¹H NMR Spectrum of the Acyl Azide NMR Sample after Prolonged Exposure to Light](image)

The presence of an additional new set of cyclopropyl-proton peaks was thought to correspond to formation of the isocyanate (+/−)-8. The results from the TGA indicated that heating the mixture might result in complete decomposition to the isocyanate (8) at approximately 60°C. To confirm this hypothesis, the NMR tube heated at 65 °C for two hours in a water bath. Upon completion, the ¹H NMR spectrum revealed nearly full conversion. Once again, the IR spectrum was very informative with a strong band at 2249 cm⁻¹ (Figure 17).

![Figure 17: IR Spectrum of Acyl Azide (7) Conversion to Isocyanate (8) in NMR Tube](image)
This band is indicative of the isocyanate functionality (2276–2240 cm\(^{-1}\))\(^{36}\), so the Curtius rearrangement was further investigated with chloroform as the solvent moving forward.

The preliminary reaction employing stock chloroform for the Curtius rearrangement resulted in a crude mixture that yielded the desired isocyanate product (+/-)-8 and likely the corresponding urea. Using freshly distilled anhydrous chloroform resulted in quantitative conversion of (+/-)-7 to the isocyanate (+/-)-8 (Scheme 25).

Scheme 25: Synthesis of 2-(1-isocyanato-2-phenylcyclopropyl)naphthalene (+/-)-8

No further purification was required and isocyanate (+/-)-8 was characterized by \(^1\)H NMR (Appendix 12), \(^13\)C NMR (Appendix 13), IR spectra (Appendix 14), and HRMS (Appendix 15).

The final reaction in the multi-step approach was the formation of the amine (+/-)-10 from the isolated isocyanate (+/-)-8. There are numerous examples in the literature that displayed successful transformation to the free amine from the isocyanate by treatment with \(a.q.\) 4 N LiOH in THF. This process was initially attempted by dissolving the isocyanate (+/-)-8 into THF and treating it with \(a.q.\) 4 N LiOH. The reaction was unsuccessful in that the extracted crude product did not yield any spectral data that supported free amine (+/-)-10 formation, so it was determined that formation of the amine salt (+/-)-9 would be more viable from an acidic decarboxylation strategy. Although the free amine (+/-)-10 is used for the NHC ring-closure reaction, the salt (+/-)-9 should be easier to isolate as a solid precipitate, and can be stored more readily as the amine salt is more stable under ambient conditions. Furthermore the amine salt (+/-)-9 should readily convert to the free amine (+/-)-10 in a standard acid-base reaction.
The first attempt at forming the amine salt (+/-)-9 was successful by treating the isocyanate (+/-)-8 with 8 M HCl. The salt product (+/-)-9 crashed out of aqueous solution as a yellow precipitate that formed hard clumps that adhered to the reaction vessel (Scheme 26).

Upon vacuum filtration the yellow amine salt (+/-)-9 was isolated at 91% yield. The aqueous solution from the reaction was neutralized with 1 M NaOH to a pH >10 and extracted with Et₂O. The ¹H NMR spectrum of the extract revealed no evidence of the cyclopropyl moiety and an IR spectrum did not display any primary aliphatic amine stretches which indicated that all of the amine salt (+/-)-9 precipitated out of solution. Generally, the reaction was reproducible in high isolated yields of the amine salt (+/-)-9 from 90–96%. The amine salt (+/-)-9 was characterized by ¹H NMR (Appendix 16), ¹³C NMR (Appendix 17), IR spectra (Appendix 18), and HRMS (Appendix 19).

The free amine (+/-)-10 could be formed by using a straightforward acid-base reaction (Scheme 27).

The amine salt (+/-)-9 was dissolved in warm aqueous solution of saturated sodium bicarbonate. 1M NaOH was then added until the reaction maintained a steady pH >10. The free amine (+/-)-10 appeared
as a thin film on top of the solution and was extracted from the basic aqueous media with Et₂O. Upon extraction, the free amine (+/-)-10 was isolated in 85% yield and identified by ¹H NMR spectrum (Appendix 20).

With the isolation of the free amine (+/-)-10, the imidazolium salt ring-closure reaction was initiated. Several known synthetic routes to construct imidazolium salts have been reported starting from primary amines. Prior to performing the final ring-closure reaction, a model imidazolium salt ring-closure was performed with a chiral amine S-12 (Scheme 28). More importantly, imidazolium salt ring-closure reactions can be challenging in both procedure and work-up, so it seemed advantageous to have a practice run with a model reaction before carrying the free amine (+/-)-10 forward. Herrmann’s one-pot synthetic approach utilized in the first chiral NHC synthesis was employed in the model reaction.[39]

The one-pot model reaction used the chiral free amine S-12, paraformaldehyde, 40% aq. glyoxal, and 3.3 M HCl in formation of the chiral NHC salt S,S-13 (Scheme 28). The enantiomerically pure chiral amine S-12 was purchased from Sigma Aldrich. After completing the model reaction procedure[40] on the chiral amine S-12, a ¹H NMR spectrum indicated further purification was required.

Recrystallization by supersaturating the crude product in DCM and diluting the mixture with an excess volume of Et₂O resulted in the precipitation of a tan solid. Upon isolation by vacuum filtration, the tan solid was confirmed by known ¹H NMR (Appendix 20), ¹³C NMR spectra (Appendix 21), and HRMS (Appendix 22).
Following procedure by Herrmann, the synthesis of the NHC (+/-)-1 containing the cyclopropyl moiety was successful starting from diastereomerically pure cyclopropane amine (+/-)-10 (Scheme 29).

Purification was attempted with DCM/hexane and a light brown precipitate formed. Upon vacuum filtration the light brown solid was collected and identified by $^1$H NMR (Appendix 23) and $^{13}$C NMR spectra (Appendix 24) as the imidazolium salt (+/-)-1.

Interestingly, it was established by Herrmann that use of racemic amines will result in the formation of the *meso* forms of the imidazolium salt product due to the nature of the self-assembly in the imidazolium salt synthesis.$^{[18]}$ A result of this occurrence leads to the appearance of two sets of peaks in the NMR spectrum for the imidazolium salt (+/-)-1 (Figure 18b), as opposed to employing the enantiomerically pure imidazolium salt $S,S$-13 and obtaining one set of signals on the NMR spectra (Figure 18a).

Figure 18: $^1$H NMR Spectrum of the Imidazolium Proton Peaks of 13 (a) and 1 (b)
In this study, it was known from the synthesis of the cyclopropyl carboxylate (+/-)-5 that a racemic mixture of the cyclopropyl-containing free amine (+/-)-10 would be utilized in the NHC synthesis (Scheme 29). It was evident by the NMR spectra for the NHC (1) product (Appendices 24 and 25) that the meso forms of the compound were obtained with the two sets of signals that were present in both the $^1$H and $^{13}$C NMR spectra.

CONCLUSION AND FUTURE WORK

The formation and isolation of the meso forms of the imidazolium salt (+/-)-1 concluded the model study toward the synthesis of a novel cyclopropyl-containing imidazolium salt ligand. Complete optimizations of the reactions prior to the imidazolium salt ring-closure reaction have been achieved with yields in each transformation exceeding 80%. A total isolated yield from acid (+/-)-2 to free amine (+/-)-10 was achieved in 44% yield over the eight synthetic steps. These optimized results will assist in the high yielding synthesis of the chiral imidazolium salts synthesis in future studies.

The next step in this research is the synthesis of the chiral NHC ligand 1 using the synthetic pathway designed in this work by employing a chiral rhodium catalyst to yield an enantiomerically pure cyclopropyl-containing ester 5. The enantiomerically pure cyclopropyl-containing material will be carried forward in the synthesis of the C$_2$-symmetric chiral NHC 1, and X-ray structural, catalytic activities and selectivities will be evaluated in due course by the Coleman research group.

EXPERIMENTAL PROCEDURES
CHEMICALS AND INSTRUMENTATION

All chemicals were obtained from Sigma-Aldrich or Stream and proper storage and handling were followed when not in use. Bulk chemicals were obtained from the Chemical Stockroom of the College of Science at RIT. All chemicals and solvents were used from the storage vessel as is, unless otherwise indicated. All reactions were conducted under dry argon gas in over-dried glassware. Infrared spectroscopic data were performed neat on a Shimadzu IRPrestige-21 Fourier Transform Infrared Spectrometer. Samples for liquid chromatography mass spectroscopic data were dissolved in a solution of 1% acetic acid in methanol then filtered prior to injection. LCMS analyses were performed on an Applied Biosystems MDS SCIEX 3200 Q Trap LC/MS/MS System. High resolution mass spectral (HRMS) samples (< 1mg) were dissolved in methanol and sent for analysis on the Thermo Finnigan MAT 95XL Mass Spectrometer at State University of Buffalo’s Mass Spectrometry Facility which was made available thanks to NSF Grant CHE0091977. All NMR data was collected on RIT’s Bruker Avance DRX-300 MHz or Bruker Avance III 500 MHz NMR spectrometer. All samples were dissolved in CDCl₃ with a TMS internal standard prior to analysis.

EXPERIMENTAL PROCEDURE

**Methyl 2-(naphthalen-2-yl)acetate (+/-)-3:** To a solution of acetone (100 mL) 2-(naphthalen-2-yl)acetic acid (5.468 g, 29.26 mmol) and cesium carbonate (6.546 g, 20.09 mmol) were added, followed by the addition of methyl iodide (3.86 mL, 62.07 mmol) via syringe over five minutes while stirring. Then the reaction mixture was heated and refluxed at 60 °C for 24 hours. The mixture was cooled to room temperature and extracted with ethyl ether (2 x 100 mL). The organic extracts were combined and
washed with brine (2 x 100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated via rotary evaporator and vacuum pump. The product (+/-)-3 was isolated as pale yellow oil without further purification (4.143 g, 20.69 mmol, 70% yield). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.81 (m, 3H), 7.73 (s, 1H), 7.45 (m, 3H), 3.80 (s, 2H), 3.71 (s, 3H) [30]

**Methyl 2-diazo-2-(naphthalen-2-yl)acetate (+/-)-4:** Methyl 2-(naphthalen-2-yl)acetate (+/-)-3 (3.807 g, 19.01 mmol) and p-acetamidobenzenesulfonylazide (5.482 g, 22.82 mmol) was dissolved in acetonitrile (50 mL) at 0°C. 1,8-diazabicycloundec-7-ene (3.98 mL, 26.62 mmol) was added dropwise at a rate of 0.1 mL/min to the reaction vessel. The mixture was concentrated via rotary evaporator, dissolved into ethyl ether (50 mL), and washed with deionized water (3 x 25 mL). The organic extract was collected, dried over anhydrous magnesium sulfate, filtered, and concentrated via rotary evaporator. The product was purified on silica and eluted with a solution of 5% ethyl ether in hexane (300 mL) followed by 10% ethyl ether in hexanes until all product was off the column. The fractions collected were concentrated via rotary evaporator and reduced pressure yielding a shiny flaky orange solid (3.15 g, 13.92 mmol, 73% yield). $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.02 (s, 1H), 7.83 (m, 3H), 7.5 (m, 3H), 3.9 (s, 3H) [32]

**Methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate (+/-)-5:** Styrene (1.15 mL, 10 mmol) and copper(I) iodide (19 mg, 0.1 mmol) were added to trifluorotoluene (10 mL), followed by the treatment of diazo (+/-)-4 (0.452 g, 2 mmol) dissolved in trifluorotoluene (20 mL) at 1 mL/hour while the reaction vessel stirred and refluxed at 100 °C. The mixture was cooled to room temperature and concentrated via rotary evaporator. A Kugelrohr short-path vacuum distillation was performed (120 °C, <1 mm Hg) to remove unreacted styrene starting material. The product was further purified via a dry-mount on silica and eluted in gradient fashion with 1-5% ethyl ether in hexanes. The product obtained was a white solid (0.514 g, 1.7 mmol, 85% yield). $^1$H NMR (CDCl$_3$, 125 MHz): δ 7.72 (m, 2H), 7.62 (m, 1H), 7.54 (d, $J = 8.5$ Hz, 1H), 7.41 (m, 2H), 7.04 (dd, $J = 8.5$, 1.7 MHz, 1H), 7.02 (m, 3H), 6.81 (m, 2H), 3.66 (s, 3H), 3.20 (dd, $J = 9.3$, 7.3 Hz, 1H), 2.23 (dd, $J = 9.3$, 4.9 Hz, 1H), 2.03 (dd, $J = 7.3$, 4.9 Hz, 1H);
$^{13}$C (CDCl$_3$, 300 MHz): δ 174.4 (C), 136.3 (C), 133.0 (C), 132.6 (C), 132.4 (C), 130.5 (CH), 130.1 (CH), 128.0 (CH), 127.6 (CH), 127.0 (CH), 126.3 (CH), 125.8 (C), 125.7 (C), 52.7 (CH), 37.5 (CH), 33.2 (CH), 20.7 (CH$_3$) [34]; IR (neat): 1711 cm$^{-1}$

1-(naphthalen-2-yl)-2-phenylcyclopanecarboxylic acid (+/−)-6: Potassium hydroxide pellets (2.128 g, 37.9 mmol) and tetrabutylammonium bromide (203.1 mg, 0.65 mmol) were added to stirring deionized water (4 mL). To the reaction vessel cyclopanecarboxylate (+/−)-5 (382.3 mg, 1.26 mmol) was dissolved in toluene (4 mL) and added via a glass syringe. The reaction was then brought to a reflux at 100 °C for 16 hours. The reaction mixture was cooled to room temperature and extracted with water and acidified with 3.3 M HCl to a pH < 3. The acidic solution was washed with chloroform (3x 25 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated via rotary evaporator. The cyclopanecarboxylic acid (+/−)-6 was a tan powder (289.3 mg, 1.00 mmol, 80% yield). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.71 (dt, $J$ = 6.1, 2.9x(2) Hz, 2H), 7.63 (s, 1H), 7.55 (d, $J$ = 8.5 Hz, 1H), 7.41 (m, 2H), 7.06 (dd, $J$ = 8.5, 1.7 Hz, 1H), 7.02 (m, 2H), 6.82 (m, 1H), 3.24 (t, $J$ = 9.3, 7.3 Hz, 1H), 2.29 (dd, $J$ = 9.4, 4.9 Hz, 1H), 2.02 (dd, $J$ = 7.3, 4.9 Hz, 1H); $^{13}$C (CDCl$_3$, 125 MHz): δ 179.2 (C), 135.7 (CH), 132.9 (CH), 132.5 (CH), 131.8 (CH), 130.6 (CH), 129.8 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 126.6 (CH), 126.0 (C), 125.8 (C), 37.2 (CH), 34.0 (CH), 20.9 (CH); IR (neat): 1682 cm$^{-1}$

1-(naphthalen-2-yl)-2-phenylcyclopanecarbonyl azide (+/−)-7: To a solution of distilled THF (10 mL) cyclopanecarboxylic acid (+/−)-7 (577.2 mg, 2.00 mmol) and distilled triethylamine (0.56 mL, 4.0 mmol) were added, chilled to 0°C, and stirred for 20 minutes. Methyl chloroformate (0.16 mL, 2.00 mmol) was added via a glass syringe to the reaction vessel and stirred for 30 minutes at 0 °C. A 4 M sodium azide (130.6 mg, 2.00 mmol) solution in water was added to the reaction mixture and allowed to stir for 15 minutes at 0 °C, then brought to room temperature and stirred for 2 hours. The mixture was diluted with 15 mL of DI H$_2$O and the product was extracted with EtOAc (3x 10 mL), dried over MgSO$_4$, filtered, and concentrated via rotary evaporator. The product was purified on silica and eluted with 5%
ethyl ether in hexanes to yield a thick viscous yellowish tan oil (+/-)-7 (599 mg, 1.91 mmol, 96% yield).

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.71 (td, $J = 6.6, 3.4$ Hz, 2H), 7.59 (s, 1H), 7.56 (d, $J = 8.5$ Hz, 1H), 7.42 (m, 2H), 7.01 (m, 4H), 6.81 (m, 2H), 3.28 (dd, $J = 9.3, 7.6$ Hz, 1H), 2.33 (dd, $J = 9.4, 4.9$ Hz, 1H), 2.12 (dd, $J = 7.7, 4.9$ Hz, 1H); $^{13}$C (CDCl$_3$, 75 MHz): $\delta$ 180.8 (C), 135.5 (C), 132.9 (C), 132.6 (C), 131.6 (C), 131.0 (CH), 129.80 (CH), 128.1 (CH), 127.9 2x(CH), 127.8 (CH), 127.6 (CH), 127.3 (CH), 126.7 (CH), 126.1 (CH), 126.0 (CH), 40.1 (CH), 35.4 (CH$_2$), 22.4 (C); IR (cm$^{-1}$): 3055, 3026, 2133, 1686, 1231; IR (neat): 2133, 1686  cm$^{-1}$

2-(1-isocyanato-2-phenylcyclopropyl)naphthalene (+/-)-8: cyclopropanecarbonyl azide (+/-)-7 (560 mg, 1.79 mmol) was dissolved in distilled chloroform and refluxed at 70 °C for 12 hours. Upon completion, the reaction vessel was cooled to room temperature and concentrated via rotary evaporator to yield the product, a light tan viscous oil (+/-)-8 (466.4 mg, 1.63 mmol, 91% yield). $^1$H – (CDCl$_3$, 500 MHz) $\delta$ 7.72 (m, 3H), 7.62 (d, $J = 8.5$ Hz, 1H), 7.42 (m, 1H), 7.24 (m, 1H), 7.20 (dd, $J = 8.5, 1.7$ Hz, 1H), 7.01 (m, 3H), 6.87 (m, 2H), 2.83 (dd, $J = 9.9, 7.7$ Hz, 1H), 1.98 (t, $J = 7.0$ Hz, 1H), 1.80 (dd, $J = 10.0, 6.4$ Hz, 1H); $^{13}$C - (CDCl$_3$, 125 MHz) $\delta$ 136.0 (C), 134.4 (C), 132.9 (C), 132.7 (C), 128.3 (CH), 128.0 2x(CH), 127.96 (CH), 127.94 2x(CH), 127.59 (CH), 127.55 (CH), 126.3 (CH), 126.24 2x(CH), 126.18 (CH), 123.4 (C), 45.2 (C), 32.8 (CH$_2$), 19.0 (CH); IR (neat): 2249 cm$^{-1}$; HRMS: Calcd for C$_{20}$H$_{15}$O$_1$N$_1$ 285.1148: found 285.1152.

1-(naphthalen-2-yl)-2-phenylcyclopropanaminonium chloride (+/-)-9: - isocyanate (+/-)-8 (466.4 mg, 1.63 mmol) was dissolved in 8 M HCl at room temperature. The mixture was slowly heated over 15 minutes and then refluxed at 70 °C for 90 minutes. Upon completion, the reaction was cooled to room temperature and the acid was decanted, followed by a wash with DI H$_2$O. The amine salt product was placed on a high vacuum pump for drying to yield a pale yellow solid (+/-)-9 (453.2 mg, 1.53 mmol, 94% yield). $^1$H – (CDCl$_3$, 500 MHz) $\delta$ 9.18 (s, 3H), 7.95 (s, 1H), 7.81 (m, 2H), 7.74 (dd, $J = 8.5, 4.4$ Hz, 1H), 7.48 (td, $J = 8.9, 3.9$ Hz, 3H), 7.02 (m, 5H), 2.99 (m, 1H), 2.24 (m, 1H), 1.96 (m, 1H); $^{13}$C – (CDCl$_3$, 125 MHz) $\delta$ 135.4 (C), 132.4 (C), 132.2 (C), 131.1 (C), 129.2 (CH), 128.1 CH), 127.83 (CH), 127.78
1-(naphthalen-2-yl)-2-phenylcyclopropanamine (+/-)-10: Finely ground cyclopropanaminium chloride (+/-)-9 (200 mg, 0.676 mmol) was added to a 50 mL beaker, followed by the 25 mL addition of saturated sodium bicarbonate. The beaker was then placed on a heating apparatus to dissolve the remaining solid granules. Once fully dissolved, the heat was held constant and 1 M NaOH was added dropwise until a pH >10 was maintained. After 10 minutes of stirring at a steady pH, the beaker was cooled to room temperature and the product was extracted with Et$_2$O (3x 8 mL). The extract was dried over potassium hydroxide, concentrated via rotary evaporator and vacuum pump to yield a grayish translucent viscous oil (+/-)-10 (149 mg, 0.575 mmol, 85% yield).

1,3-bis((S)-1-(naphthalen-2-yl)ethyl)-1H-imidazol-3-ium chloride (S,S)-13: Paraformaldehyde (160 mg, 3.4 mmol) and S(-)-1-(2-naphtyl)ethyamine S-12 (1.16 g, 3.4 mmol) were added to toluene (6.5 mL) and stirred vigorously for 15 minutes at room temperature. The reaction vessel was cooled to 0 °C and a second equivalent of S-12 (1.16 g, 3.4 mmol) dissolved in 3.3 M HCl (1.1 mL, 3.4 mmol) was added dropwise and stirred vigorously for 15 minutes. Then the reaction vessel was brought to room temperature and 40% aq. glyoxal (0.5 mL, 3.4 mmol) was added, heated to 40 °C, and stirred vigorously for 12 hours. Upon completion, the reaction was brought to room temperature, diluted with saturated sodium carbonate (8 mL), and the product was extracted with DCM (3 x 8 mL). The organic phases were combined, dried with anhydrous magnesium sulfate. The extract was then concentrated via rotary evaporator, supersaturated in DCM (1 mL), diluted with Et$_2$O (25 mL), and heated to reduce the total volume to ~10 mL. The precipitate was collected by vacuum filtration and dried on the high vacuum pump to yield a tan amorphous solid S,S-13 (335 mg, 0.81 mmol, 24% yield). $^1$H – (CDCl$_3$, 500 MHz) δ 11.8 (s, 1H), 7.94 (s, 2H), 7.89 – 7.83 (m, 6H), 7.55 – 7.51 (m, 6H), 6.98 (s, 2H), 6.25 (q, J = 6.9 Hz, 2H), 2.16 (d, J = 6.9 Hz, 6H); $^{13}$C – (CDCl$_3$, 125 MHz) δ 137.8 (CH), 135.0 (CH), 133.5 (CH), 133.1 (CH),
129.7 (CH), 127.8 (CH), 127.2 (CH), 127.0 (CH), 126.6 (CH), 124.2 (CH), 119.8 (CH), 60.1 (CH), 21.2 (CH); HRMS: Calcd for C_{27}H_{25}N_3 377.2012: found 377.2010.

1,3-bis(1-(naphthalen-2-yl)-2-phenylcyclopropyl)-1H-imidazol-3-ium chloride (+/-)-1:
Paraformaldehyde (14 mg, 0.278 mmol) and a solution of (+/-)-10 (122.2 mg, 0.278 mmol) in toluene (1 mL) was added to the reaction vessel and stirred vigorously for 15 minutes at room temperature. The reaction vessel was then cooled in an ice bath, followed by the addition of a second equivalent of (+/-)-10 (122.2 mg, 0.278 mmol) with 3.3 M HCl (0.2 mL, 0.278 mmol) and toluene (0.25 mL). The reaction mixture was stirred for 10 minutes in the ice bath and then brought to room temperature. At room temperature, 40% aq. glyoxal (0.04 mL, 0.278 mmol) was added to the reaction vessel, which was then placed in an oil bath, and the reaction mixture was refluxed at 40 °C for 12 hours. After 12 hours, the reaction was brought to room temperature, diluted with saturated sodium carbonate (4 mL), and the product was extracted with DCM (3x 5 mL), dried with anhydrous magnesium sulfate, and filtered. The extract was then supersaturated in DCM (0.25 mL), diluted with hexanes (10 mL), and heated to reduce the total volume to ~2.5 mL. The precipitate was then collected via vacuum filtration and dried on the high vacuum pump to yield a light brown amorphous solid (+/-)-1 (34.4 mg, 0.058 mmol, 21% yield). $^1$H – (CDCl$_3$, 500 MHz) $\delta$ 11.8 (s, 1H), 11.7 (s, 1H), 7.9 (s, 2H), 7.88 (s, 2H), 7.73 (m, 5H), 7.69-7.66 (dd, $J$ = 9.2, 4.3 Hz, 5H), 7.6-7.57 (m, 6H), 7.43-7.42 (d, $J$ = 4.6 Hz, 8H), 7.39-7.36 (m, 4H), 7.16 (s, 4H), 7.13 (s, 4H), 7.05 (m, 14H), 3.84 (s, 2H), 3.8 (s, 2H), 2.87 (s, 2H), 2.76 (s, 2H), 1.84 (s, 4H); $^{13}$C – (CDCl$_3$, 125 MHz) $\delta$ 134.4, 133.13, 133.12, 132.9, 131.33, 131.3, 130.4, 130.3, 129.0, 128.99, 128.5, 128.49, 128.3, 128.2, 128.1, 127.6, 127.1, 127.06, 126.9, 126.6, 126.59, 122.6, 51.45, 51.4, 31.06, 30.0, 19.53
APPENDIX
Appendix 1: $^1$H NMR Spectrum of methyl 2-(naphthalen-2-yl)acetate (3)
Appendix 2: $^1$H NMR Spectrum of methyl 2-diazo-2-(naphthalen-2-yl)acetate (4)
Appendix 3: $^1$H NMR Spectrum of methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate (±5)
Appendix 4: $^{13}$C NMR Spectrum of methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate (±)-5
Appendix 5: IR Spectrum of methyl 1-(naphthen-2-yl)-2-phenylcyclopropane-1-carboxylate (±/−)5
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Appendix 7: $^{13}$C NMR Spectrum of 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylic acid (+/-)-6
Appendix 8: IR Spectrum of 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylic acid (+/-)-6
Appendix 9: $^1$H NMR Spectrum of 1-(naphthalen-2-yl)-2-phenylcyclopropanecarbonyl azide (+/-)-7
Appendix 10: $^{13}$C NMR Spectrum of 1-(naphthalen-2-yl)-2-phenylcyclopropanecarbonyl azide ($\pm$-)·7
Appendix 11: IR Spectrum of 1-(naphthalen-2-yl)-2-phenylcyclopropanecarbonyl azide (+/-)-7
Appendix 12: $^1$H NMR Spectrum of 2-[(1-isocyanato-2-phenylcyclopropyl)naphthalene (+/-)-8
Appendix 13: $^{13}$C NMR Spectrum of 2-(1-isocyanato-2-phenylcyclopropyl)naphthalene (+/-)-8
Appendix 17: $^{13}$C NMR Spectrum of 1-(naphthalen-2-yl)-2-phenylcyclopropanium chloride (+/-)-9
Appendix 18: IR Spectrum of 1-(naphthalen-2-yl)-2-phenylcyclopropanaminium chloride (+/-)-9
Appendix 22: HRMS Spectrum of 1,3-bis((S)-1-(naphthalen-2-yl)ethyl)-1H-imidazol-3-ium chloride S,S-13
Appendix 24: $^1H$ NMR Spectrum of 1,3-bis(1-(naphthalen-2-yl)-2-phenylcyclopropyl)-1H-imidazol-3-ium chloride (1)
Appendix 25: $^{13}$C NMR Spectrum of 1,3-bis(1-(naphthalen-2-yl)-2-phenylcyclopropyl)-1H-imidazol-3-ium chloride (1)
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