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The development of novel reactions is a crucial facet of organic synthesis. Cyclopropanes are a difficult moiety to produce in organic syntheses due to their large ring strain yet can be found in many natural products and are a common moiety in pharmaceuticals, making their accessibility valuable. The use of hypervalent iodonium alkynyl triflates (HIATs) to generate cyanocarbenes *in situ* provides a novel way of synthesizing cyano-substituted cyclopropanes. A number of novel reactions were carried out by reacting a variety of electron-rich olefins with phenylcyanocarbene to further expand the substrate scope.

The cyclopropanation products that were obtained from those reactions were then tested as potential donor-acceptor cyclopropane reagents in a 1,3-dipolar cycloaddition reaction. While several unsuccessful attempts at the reaction were carried out using the vinyl acetate cyclopropanation product, current work in progress on the *n*-butyl vinyl ether derivative shows promise. Additionally, the ring-opening necessary for a potential dipolar cycloaddition has been shown through the conversion of the vinyl acetate cyclopropane product to ß-cyano-ß-phenylpropanal, expanding upon the very limited synthetic approaches currently available to it and similarly substituted compounds.

USE OF CYANOCARBENES FOR THE SYNTHESIS OF DONOR-ACCEPTOR CYCLOPROPANES

by

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Approved by

Dr. Mitchell P. Croatt
Committee Chair

DEDICATION

To my lurve, my amazing wife who I would be completely lost without. There is no possible way to ever fully thank you for the years you spent supporting me that allowed me to see this through, but I'm looking forward to spending the rest of our years together trying to do so. Also to my family and friends who supported me over the past several years, even when it was hard to find time together, and to the amazing faculty at UNCG who have always been such a source of inspiration: thank you from the bottom of my heart.

APPROVAL PAGE

This thesis written by David John von Dohlen has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

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CHAPTER I: INTRODUCTION

Development of New Reactions in Organic Synthesis

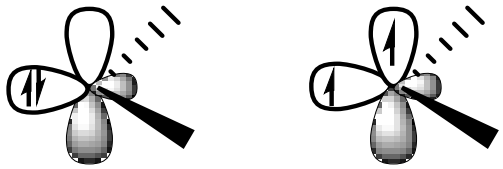
At the heart of organic chemistry research lies carbon chemistry; after all, it is what the field is named after. Thus, it may not be surprising that among the most desirable reactions in organic synthesis are those capable of creating carbon-carbon bonds. The stability of carbon-carbon bonds that allows it to function as the backbone of nearly all biologically relevant macromolecules inherently makes the cleavage or formation of such bonds a challenge. Biologically, enzymatic environments can provide spontaneity to such reactions that are simply not feasible *in situ*, leaving organic chemists with the challenge of finding alternative pathways. The difficulty and importance of developing such reactions can be evidenced by the vast number of Nobel prizes awarded for such work over the years. Regardless of whether novel reactions are prize worthy, versatile or niche, the result is the invaluable expansion of the collective reaction toolbox available to organic chemists.

Carbenes

While the typical carbon atom in a molecule contains four covalent bonds and is electronically neutral, carbenes represent a more unique arrangement consisting of a divalent carbon atom with two additional non-bonding electrons. The result of such a configuration is that while electrically neutral, an incomplete octet and two valence electrons available for bonding make carbenes a highly reactive species. The reactivity of carbenes is in part dictated by the hybridization of the two non-bonding electrons, which can adopt either a singlet or triplet state configuration. Typically, in the singlet state the electrons are spin-paired and occupy the same orbital, leaving an empty p-orbital and overall adopting an sp^2 hybridization; in the triplet state, the electrons occupy separate orbitals and can adopt either an sp or sp^2 hybridization.[1] In terms of

reactivity, the presence of an electron pair and an empty p-orbital gives the singlet state carbene properties of both a carbanion and carbocation, respectively, while triplet state carbenes behave more as a diradical species. **Figure 1** highlights the differences between these configurations (note that both are drawn in an sp^2 configuration for simplicity).

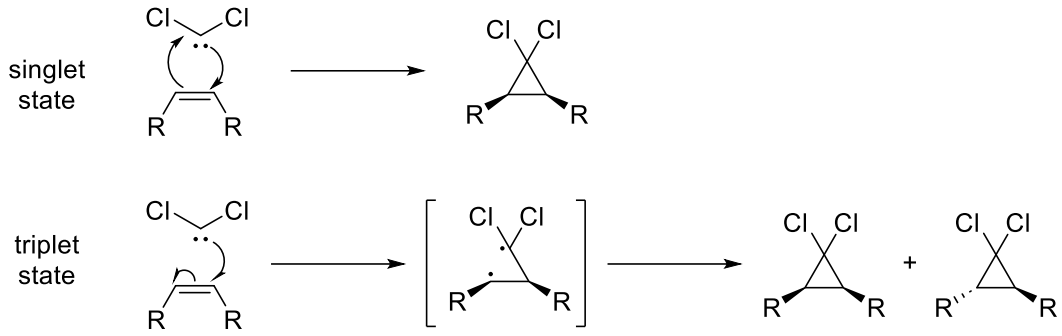
Figure 1. Singlet and Triplet State Carbenes



Reactivity of Carbenes

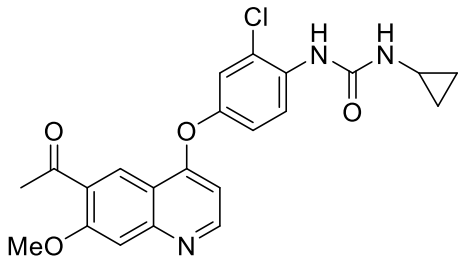
While carbene formation was speculated on in the early 1900s,[2] it would not be until halfway through the 20th century that the most convincing paper to date of carbene formation and use would be reported by Doering and Hoffman,[3] where chloroform and bromoform were used as carbene precursors in the preparation of cyclopropane derivatives of olefins. Their hypothesis that carbenes could be useful for the preparation of cyclopropanes has since been well established and remains one of the primary uses of carbene chemistry.[4] The mechanism for cyclopropane formation from alkenes is shown in **Figure 2**. In the case of singlet state carbenes (top), the cyclopropanation reaction is a concerted one and the alkene stereochemistry is conserved. For triplet carbenes (bottom), the radical intermediate allows for bond rotation and a scrambling of stereochemistry can be observed.[5]

Figure 2. Mechanism of Carbene Cyclopropanation

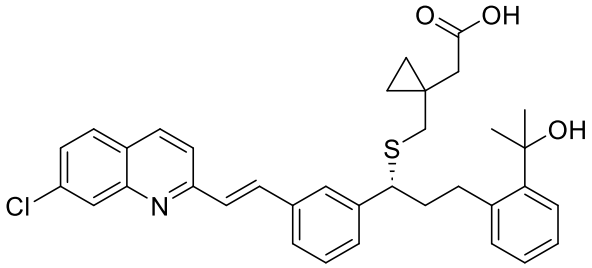


Cyclopropanation of alkenes and bond insertion reactions are the most common applications of carbene chemistry in organic synthesis, both of which are synthetically challenging reactions.[6] Cyclopropanes are an important moiety in pharmaceuticals, serving varied roles in a multitude of medications;[7] in 2014, it was reported as the 10th most common ring system present in drugs listed in the FDA Orange Book,[8] a couple of which are shown in **Figure 3**. However, the ring strain of cyclopropane (27.5 kcal/mol)[9] is a significant barrier to its formation, which can be exacerbated by the number and/or size of substituents present. The energetic and electronic properties of carbenes allows cyclopropanation formation from alkenes to be spontaneous, fast, and even chemoselective. Bond insertion reactions also take advantage of these properties to facilitate exergonic reactions of relatively inert bonds, being particularly useful for C-H bond insertion, which otherwise often requires the use of metal or photoredox catalysts.[10]

Figure 3. Cyclopropane Moiety in Drug Molecules



Lenvima
(lenvatinib)

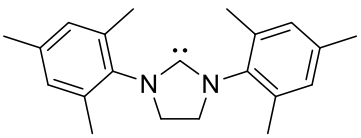


Singulair
(montelukast)

Classes of Carbenes

Challenges of carbene chemistry are typically centered around their highly reactive nature. A non-stabilized carbene often has a lifetime on the order of nanoseconds,[11] not allowing them to be isolated and limiting their use to *in situ* formation. Development since the initial works on carbene research has primarily been focused on incorporating electron-donating heteroatoms as a means to stabilize the empty p-orbital of singlet carbenes, leading to an isolable class of carbenes known as persistent carbenes.[12] Among this class, N-heterocyclic carbenes (NHCs) have emerged as the predominant form of carbenes for both synthetic utility and as an area of research.[13] The stability granted by the adjacent nitrogen atoms and conjugation from substituents result in precursor NHCs that are shelf stable and can be sold as reagents, typically as protonated salts. A representative NHC is pictured in **Figure 4**, shown in its active carbene form.

Figure 4. 1,3-Bis(2,4,6-Trimethylphenyl)-4,5-Dihydroimidazol-2-ylidene



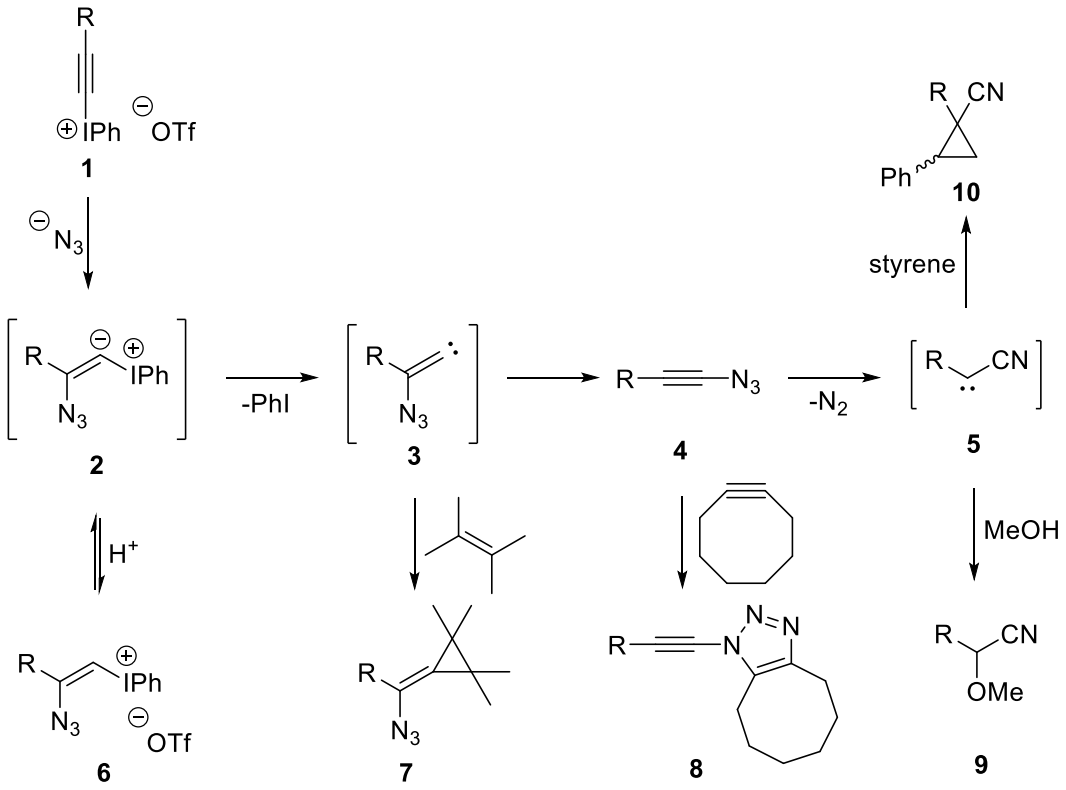
Despite the advantages afforded to NHCs, they do have restrictions in terms of their synthetic utility relative to other carbenes. The stability granted by electron-donation from the nitrogen atoms requires an empty p-orbital, and combined with strong σ-bonding to the metal center in metal carbenoids, most NHCs react as singlet carbenes exclusively. Thermodynamic studies show that the energy barrier for triplet to singlet conversion for NHCs can be in the 70-90 kcal/mol range.[14] While this is useful in cyclopropanation reactions as singlet carbenes typically add to alkenes in a concerted mechanism, a triplet-state carbene presents opportunities for bond rotation[15] (as shown in **Figure 2**) or potentially other reactions to occur.[16] Triplet state additions result in a short-lived di-radical species,[17] requiring a spin-flip in one of the electrons before the addition can be completed. Although the inability to access the triplet state can be a boon for NHCs in terms of controlling and predicting reactivity, it is nevertheless still a limitation of the carbene class. Additionally, expensive transition metals such as rhodium, iridium, and palladium are often used which can present economic issues.[18-19] However, they are frequently able to be used in catalytic amounts, greatly reducing the overall cost.

CHAPTER II: PHENYL HYPERVALENT IODONIUM ALKYNYL TRIFLATE

Introduction and Development

In 2012, the Croatt group published their preliminary work on the *in situ* generation of cyanocarbenes (**5**) formed from reacting hypervalent iodonium alkynyl triflates (HIATs, **1**) with azides.[20] The proposed pathway in **Figure 5** was published by the Croatt group in 2017 and highlights some of the relevant products from trapped intermediates (**6-9**) that lend support to the proposed pathway.[20] Previous work by Banert et al. in 2010[23] had demonstrated the proof-of-concept for their previously theorized formation of cyanocarbenes from alkynyl azides driven by the liberation of dinitrogen, but utilized chloroalkynes that suffered from poorer yields and much longer reaction conditions in comparison to the hypervalent iodonium salts that would be reported on by both groups in 2012.[24]

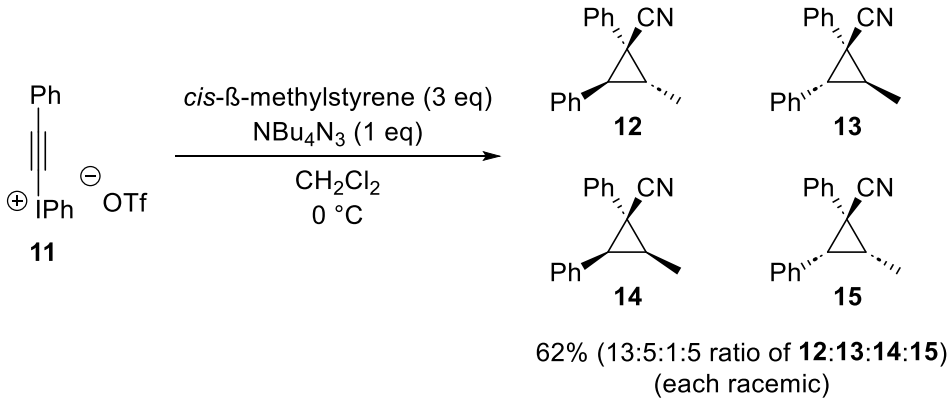
Figure 5. Generation of Cyanocarbenes from HIATs and Key Products



While the initial work on HIATs focused primarily on method optimization and demonstrated the potential utility through varied reactions, the following work of the Croatt group greatly expanded substrate scope for cyanocarbene reactions. A number of both electron-rich and electron-deficient carbocyclic and heterocyclic aromatic compounds were screened, with results that included C-H and O-H bond insertion, cyclopropanation, and subsequent rearrangements such as ring-opening. An important result was that for phenylcyanocarbene (**5**, R = phenyl) the triplet state was preferred based on experimental data regarding chemoselectivity and scrambling of alkene stereochemistry. **Scheme 1**, as published by the Croatt group, shows this result as the *cis*-ß-methylstyrene starting material produces a mix of all possible diastereomers, when only products **14** and **15** would be produced given singlet state reactivity.[21] However, singlet reactivity was also observed, primarily based on observed O-H bond insertion

when phenylcyanocarbene was reacted with methanol; the significant homolytic O-H bond strength makes it unlikely for concerted insertion to occur. It was instead hypothesized that a stepwise process of nucleophilic addition of the oxygen to the carbene followed by proton transfer occurs, a process more aligned with singlet carbene reactivity. The presence of both singlet and triplet reactivity for phenylcyanocarbene gives evidence that the barrier for the conversion between the two states is relatively small. Similar access to both states has been reported for phenylcarbene,[21] but unlike phenylcyanocarbene, it required elevated temperatures (130 °C) and demonstrated a significant preference for the singlet state.

Scheme 1. Reation of Phenylcyanocarbene with *cis*-ß-Methylstyrene



Previous work had determined that the conversion between vinylidene intermediate **3** and the alkynyl azide **4** was more efficient for aryl HIATs than for alkyl HIATs, and had less explosive potential. Thus, research since that time has been focused on using aryl HIATs as the starting material, in particular phenyl HIAT (**11**), which was used exclusively for all further experiments herein.

Phenyl-HIAT Synthesis Optimization

Although a standard operating procedure for phenyl-HIAT synthesis had been established by the Croatt group, including a video published in 2013,[25] the reproducibility of the experiment

had been inconsistent at best and became an immediate roadblock for this thesis's research for several months. Many attempts early on at synthesizing phenyl-HIAT consistently yielded a yellow oil during the work-up (instead of the expected white solid precipitate), which was not able to be carried through for further experiments. At the core of the precipitation issue was the qualitative nature of the SOP instructions that simply say to use diethyl ether and hexane to force precipitation of the product, with no specification given to the ratio or amounts of each solvent.

At the time the research for this thesis had begun, there were three people in the Croatt group who had firsthand experience of the synthesis of phenyl HIAT and were asked to assist with the synthesis. Not only were the attempts to precipitate the phenyl HIAT frequently unsuccessful between all three, but it was noted that each person had their own approach to doing so, highlighting the flaw of the inherently irreproducible procedure. While attempts to produce a quantitative work-up procedure were unfortunately unsuccessful, an alternative qualitative work-up procedure was established that has yielded consistent results. The key additions are the descriptions of physical changes to the solution when adding the solvents, which provides a point of consistency not only between runs but for differing reaction scales. The use of a glass stir rod to scrape the flask and use of chilled hexanes are modifications that have been observed to improve consistency as well. Overall yields saw an improvement as well and ranged between 63-75%, compared to the 11-50% yields (average = 22%) of the few successful attempts that had been achieved prior. The steps before the work-up remain the same as previously reported.

Alternative Work-up Procedure for the Synthesis of Phenyl HIAT SOP

After 2 hours, remove the flask from the -40 °C bath. After 5 minutes, add a small amount of cold hexane to the flask while stirring, just enough for the solution to turn a cloudy

grey and for the cloudiness to persist. The amount of hexane required to achieve this varies between attempts and again is one of the reasons why a quantitative approach proved difficult. Afterwards, a small aliquot (~0.3 mL) of Et_2O should be added; visible changes to turbidity may or may not be observed upon addition. Cold hexane (again a variable amount) should then be added to the solution until there is a large amount of white cloudiness present. The stirring can then be stopped, and the flask scraped with a glass stirring rod until a large amount of visible white precipitate forms. Collect the precipitate via vacuum filtration and wash with Et_2O to yield the product as a white solid.

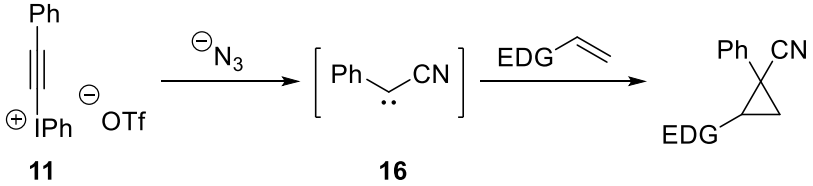
If precipitate does not form upon scraping with the glass stir rod, the product should be allowed to continue stirring in the -40 °C bath if a yellow oil has formed and is still present, or allowed to rest without stirring in the -40 °C bath otherwise. After a couple of minutes, remove the flask from the bath and try to induce precipitation via scraping with a glass stirring rod if needed. Repeat this process as necessary. If after multiple attempts there is still no visible white precipitate formation, then the reaction mixture may be added to a -78 °C flask containing about 125 mL dry hexane, from which a yellow precipitate will form that can be collected via vacuum filtration. No impurities besides solvent were observed by ^1H NMR for the yellow solid, nor has it been observed to significantly affect the reactivity of previously established procedures that use phenyl-HIAT thus far. However, more data is needed to draw definitive conclusions regarding potential differences between the two.

CHAPTER III: EXPANDING THE CYANOCARBENE SUBSTRATE SCOPE TOWARDS THE SYNTHESIS OF DONOR-ACCEPTOR CYCLOPROPANES

Expansion of Substrate Scope

Towards the development of new reactions in organic synthesis, an important step is to probe the reactivity of newly discovered reagents or methods in order to gain insight into the applicability and limitations of such previously untested reactions. As mentioned previously, the development of using HIATs for in the *in situ* generation of cyanocarbenes was a novel discovery and presented the opportunity for several classes of substrates to be screened as new reactions. In previous work on the reactions of phenylcyanocarbene (**16**) with aromatic systems, it was observed that electron-deficient aromatic substrates were not successful substrates, with only dimerization of the phenylcyanocarbene observed as products.[21] Thus, it was determined that more nucleophilic or electron-rich systems were needed. Focused upon in this work were a number of electron-rich alkenes as potential substrates in the reaction with phenylcyanocarbene, partially directed by those previous results. Specifically, it was hypothesized that the cyclopropanation of such reagents would give rise to an array of donor-acceptor cyclopropanes that could be carried forward as potential reagents for a dipolar cycloaddition reaction, which will be expanded upon in Chapter IV. **Figure 6** shows a generic scheme for the reactions carried out in this chapter.

Figure 6. Cyclopropanation Reaction of Phenylcyanocarbenes with Electron-Rich Alkenes

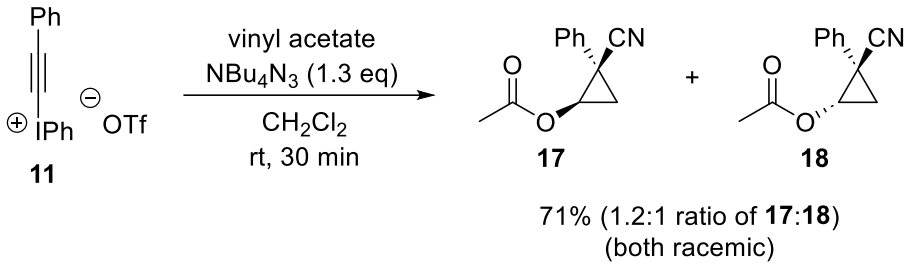


11 **16**

Successful Cyclopropanation Reactions

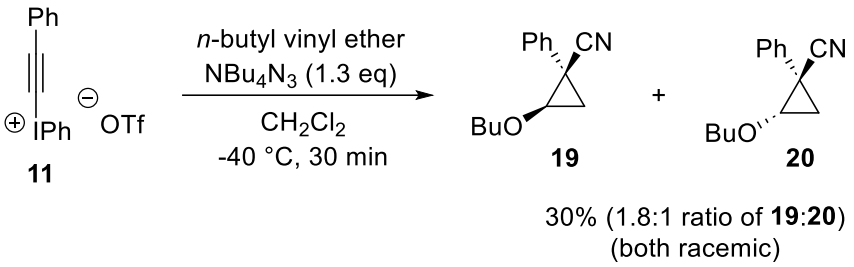
Of the compounds tested, three reagents underwent cyclopropanation reactions when treated with HIAT and an azide source. For all reactions, phenyl HIAT (**11**) and tetrabutylammonium azide would be used based on optimizations done in previous work. The most efficient reaction in terms of cyclopropanation yield was carried out using vinyl acetate, as shown in **Scheme 2**.

Scheme 2. Cyclopropanation of Vinyl Acetate



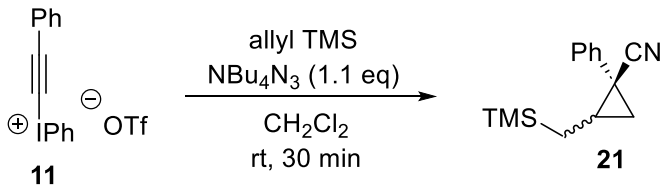
Cyclopropanation products **17** and **18** were formed in similar amounts with **17** formed as the slight major product. It is presumed that **17** is likely favored as the kinetic product due to the steric interaction between the acetoxy and phenyl substituents. The reaction as reported in **Scheme 2** was run on a 0.1 mmol scale but has been carried out at a 0.5 mmol scale. While the overall yield in that instance dropped to 42%, the obtained mixture of isomers was observed to remain consistent. The products for the reaction were verified by ^{1}H and ^{13}C NMR spectrometry, and the obtained spectral data agrees with the previously published data. While a small amount of product **17** has been isolated from **18** and characterized on its own, further experiments using the vinyl acetate cyclopropanation product would use the obtained mixture of isomers.

Scheme 3. Cyclopropanation of *n*-Butyl Vinyl Ether



The reaction in **Scheme 3** of *n*-butyl vinyl ether with phenylcyanocarbene gave the cyclopropanated products **19** and **20** as a mixture of isomers. Initial attempts at carrying out the reaction resulted in highly exothermic decomposition, which was observed to take place immediately upon addition of the phenyl HIAT to *n*-butyl vinyl ether (no azide present). Optimization of the reaction including alterations to the order of addition, ether concentration, and temperature of the reaction were carried out and ultimately resulted in successful yield of the products. Again, the (*R*,*S*) configuration of **19** was observed as the major product just as the (*R*,*S*) product **17** was in the vinyl acetate reaction, but the diastereomeric ratio between the two potential products was slightly larger in the case of the *n*-butyl vinyl ether reaction. It is suspected that the more electronic rich alkene of the vinyl ether resulted in a greater propensity towards undesired side reactions, decreasing the overall yield, however the exact cause of the differences in diastereoselectivity and yield require further study for definitive answers.

Scheme 4. Cyclopropanation of Allyl TMS

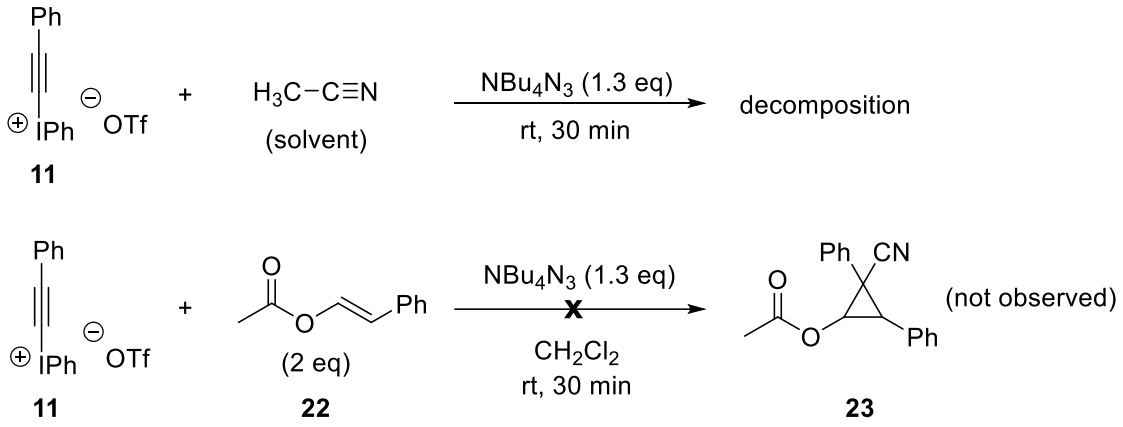


The reaction of allyl TMS and phenylcyanocarbene has been carried out as according to **Scheme 4**. The cyclopropanated product **21** has been proposed to have been formed via the data obtained from ^{1}H NMR analysis, however further work is needed for a full characterization of the product.

Unsuccessful Cyclopropanation Reactions

Two substrates that have been tested have been confirmed to not yield the desired cyclopropanation products when reacted with phenylcyanocarbene. The attempted reactions are detailed in **Scheme 5** below.

Scheme 5. Unsuccessful Cyclopropanation Reactions of Acetonitrile and Phenyl Vinyl Acetate



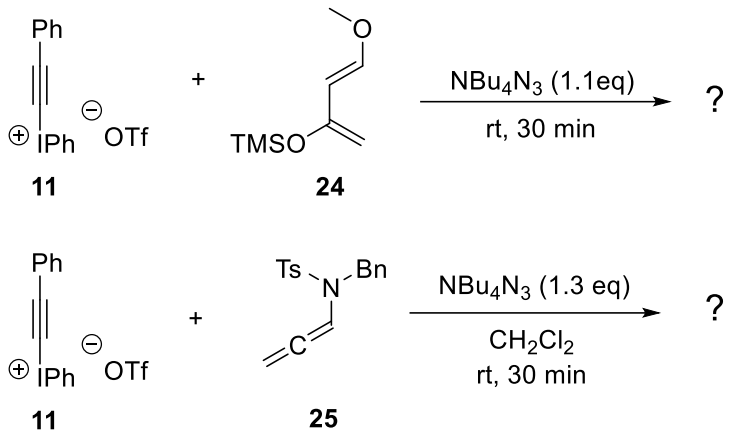
In experiments with acetonitrile, only decomposition was ever observed, and no products were able to be identified from the resultant black tar generated in the reaction. In the case of phenyl vinyl acetate (**22**), the cyclopropanation product **23** was expected to be obtained in even less yield (if at all) than the vinyl acetate products **17**+**18** due to the significant increase in bulk provided by the extra phenyl ring. Indeed, none of **23** could be identified in the product, while a significant amount of unreacted **22** was still present, consistent with expectations. Unlike in the

case of acetonitrile where decomposition was observed, or electron-deficient aromatic systems where only dimerization was observed, obtained spectral data does appear to indicate that some amount of non-cyclopropanated product was formed from the reaction. Further analysis of the data is needed and may be carried out in future work.

Undetermined Cyclopropanation Reactions

Lastly, two substrates have been reacted with phenylcyanocarbene as shown in **Scheme 6**, but no determination has been able to made on what products were formed from the reaction, cyclopropanation or otherwise.

Scheme 6. Undetermined Cyclopropanation Reactions



In both cases, the reactions for Danishefsky's diene (**24**) and allenamide **25** have yielded products that are not representative of either decomposition or dimerization. For Danishefsky's diene, a complex mix of products appears to have been generated that, as of yet, have not successfully been able to be separated cleanly enough for identification. Fractions obtained from the column chromatography purification of the allenamide **25** reaction are much more pure overall than the diene reaction, but due to time constraints have not been further characterized.

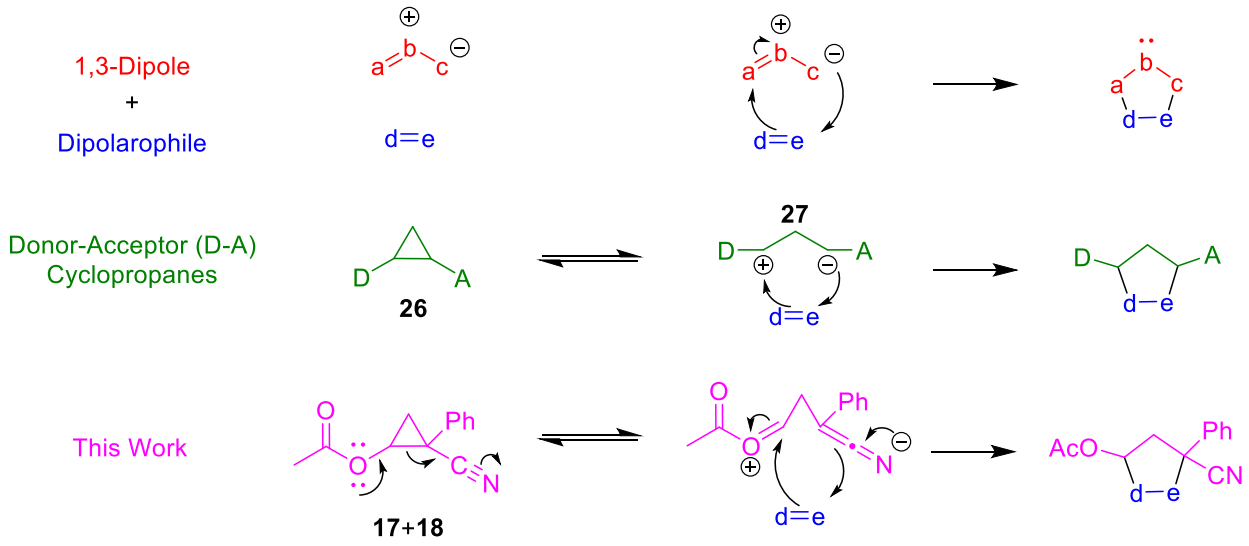
CHAPTER IV: PROGRESS TOWARDS NOVEL DIPOLAR CYCLOADDITION REACTIONS

Background Theory and Donor-Acceptor Cyclopropanes

While the ring strain of cyclopropane can often act as a barrier towards the synthesis of such moieties, once formed it may also be utilized as leverage to enable subsequent ring-opening or ring-expansion reactions. In particular, the use of donor-acceptor cyclopropanes (D-A cyclopropanes), cyclopropanes containing both an electron-donating (donor) and electron-withdrawing (acceptor) substituent, has emerged as a widely studied and valuable tool in organic synthesis.[26] Despite the degree of ring-strain, an unsubstituted cyclopropane is more kinetically inert than it may seem,[27] with only select systems such as vinylcyclopropane derivatives readily undergoing rearrangement processes without activating substituents.[28] Earlier works utilizing acceptor groups had been reported,[29] but it wasn't until the 1980s that the donor-acceptor term would be coined following the works of Wenkert and Reissig.[30-31]

Figure 7 illustrates the advantage D-A cyclopropanes have when it comes to their reactivity. For vicinal D-A cyclopropanes (**26**), the push-pull relationship of the donor and acceptor substituents helps to polarize the C-C bond in the cyclopropane, pushing it towards a ring-opening reaction, and crucially stabilizing the zwitterionic intermediate (**27**) formed after such an opening. As a result, D-A cyclopropanes such as **26** are functionally similar to 1,3-dipole reagents, and have been shown to react as such in dipolar cycloaddition reactions.[26] Ring-opening and rearrangement reactions are also common,[26c] however the focus of this work was on cycloaddition reactions.

Figure 7. Proposed Use of Generated Donor-Acceptor Cyclopropanes Towards Dipolar Cycloaddition



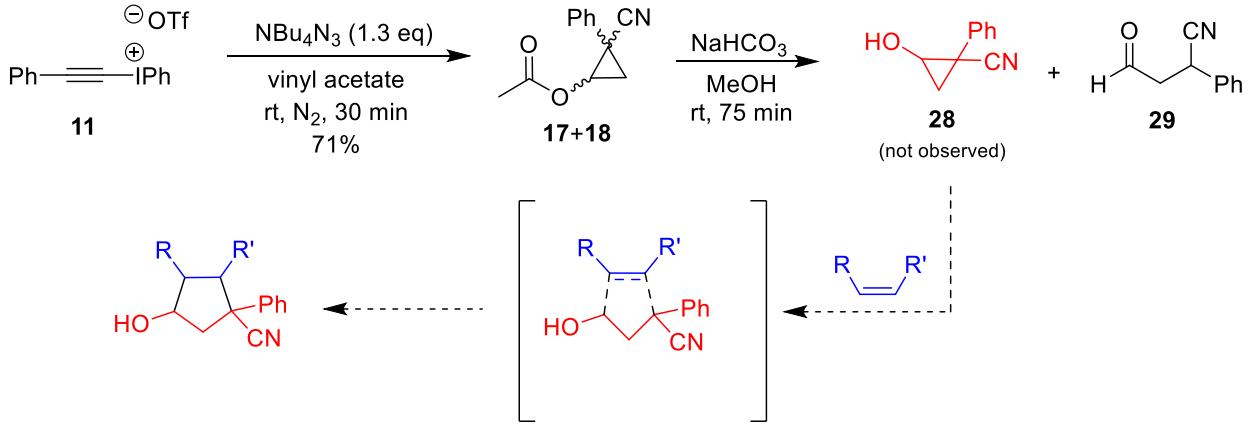
The use of phenylcyanocarbene to generate cyclopropanated products seemed promising towards the goal of generating D-A cyclopropanes as it inherently establishes the acceptor group via the cyano substituent. By using alkenes with vinyl electron-donating groups as substrates, the aim of the research in Chapter III, D-A cyclopropanes such as **17** and **18** could be readily generated and subsequently used as reagents in dipolar cycloaddition reactions (**Figure 7**).

Experiments with Vinyl Acetate Derivative

The majority of experiments attempting to achieve a dipolar cycloaddition utilized the cyclopropanated derivative of vinyl acetate (**17**+**18**) as the base substrate due to the efficiency of the reaction (**Scheme 2**). The combination of relatively good yield and ease of purification for the cyclopropanation reaction allowed for a consistent source of starting material to carry forward, especially as optimizations for the *n*-butyl vinyl ether derivative had not yet been established. However, it has been reported that D-A cyclopropanes containing an acetoxy group as the donor substituent show significantly more stability than ether substituted cyclopropanes,

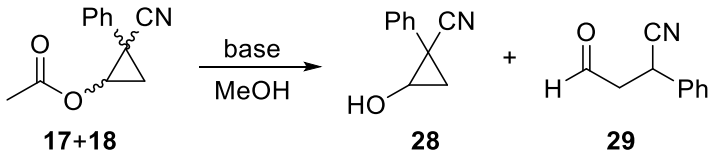
where rearrangement was not observed even when a variety of Lewis acids were employed.[32] Due to the seemingly significant presence of a stronger electron-donating substituent, attempts were carried out to convert vinyl acetate products **17**+**18** to alcohol derivative **28** (as shown in **Scheme 7**) in a preemptive effort to increase the reactivity towards a dipolar cycloaddition.

Scheme 7. Proposed Synthetic Pathway Towards Dipolar Cycloaddtion



In theory, the conversion to alcohol **28** would proceed readily under simple basic conditions via nucleophilic addition to the ester and subsequent elimination of an alkoxide intermediate, which would yield the desired product following work-up. A variety of conditions were screened for the reaction (**Table 1**), yet the expected product was never observed. Instead, aldehyde **29** was consistently formed via a subsequent ring-opening reaction upon formation of the alkoxide intermediate.

Table 1. Attempted Conversion of Vinyl Acetate Product to Alcohol 28

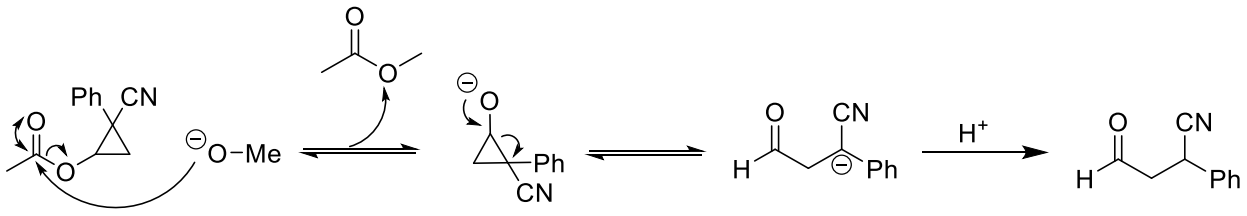


17+18 28 29

Entry	Base (1 eq)	Temperature (°C)	Time (h)	Yield (28)	Formation of 29
1	K_2CO_3	60	1.5	-	Yes
2	K_2CO_3	rt	24	-	Trace
3	K_2CO_3	rt	1	-	Yes
4	$NaHCO_3$	rt	1.25	-	Yes

The proposed mechanism for aldehyde formation is shown in **Figure 8**, and it was ultimately determined based on experimental data that the intramolecular ring-opening was spontaneously proceeding due to the much greater electron-donating effect of the alkoxide intermediate and anionic stability provided by the nitrile, happening before the alcohol could form and be isolated. While this type of reactivity for the phenylcyanocarbene cyclopropane products currently has no literature precedent (in terms of the compound itself), similar ring-opening reactions have been reported upon desilylation of trimethylsilyl ether cyclopropanes that provides support for the proposed mechanism.[33]

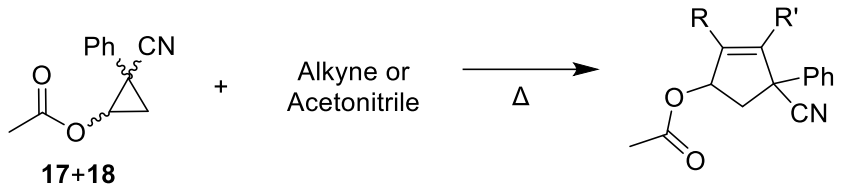
Figure 8. Proposed Mechanism for Ring Opening Aldehyde Formation

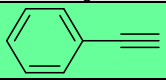
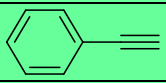
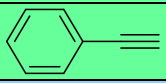
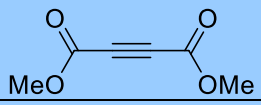
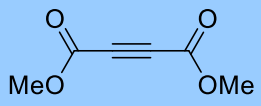


Although the attempts to stop the reaction before the ring-opening occurred were unsuccessful, the propensity towards ring-opening was still a promising result for phenylcyanocarbene cyclopropanated products as potential substrates for dipolar cycloaddition reactions. Furthermore, the obtained ß-cyano-ß-phenylpropanal product (**29**) is a molecule with very few methods for synthesis currently reported, but it has been synthesized and used as an intermediate in the synthesis of CCR5 antagonists for the treatment of HIV-1[34] and in the construction of tri- and tetra-substituted ethenes,[35] with the highest net yield between the two at 38%. It is unknown whether the lack of research involving aldehyde **29** is a result of its poor synthetic utility or relative absence of facile synthesis, but the latter is suspected due to the versatility of its functional groups. Regardless, the approach given by **Figure 8** provides a novel approach towards the synthesis of ß-cyano-ß-phenylpropanal via the ring-opening of cyclopropanes **17**+**18**, and may even provide a more efficient synthesis when optimized.

With the unsuccessful synthesis attempts at alcohol **28** and demonstrated potential for ring-opening, the initial vinyl acetate products **17**+**18** were carried forward for use as the 1,3-dipole equivalent. **Table 2** lists the reaction conditions that were carried out, which utilized alkynes or acetonitrile as the dipolarophile. Alkynes and nitriles are well-studied as dipolarophiles in cycloaddition reactions[36] and were in part chosen to try and compensate for the weaker acetoxy electron-donating group.[37] No significant reaction appeared to have taken place in any of the entries, evidenced by the consistent recovery of starting material from the reactions.

Table 2. Reaction Conditions for Dipolar Cycloaddtion of Vinyl Acetate Product

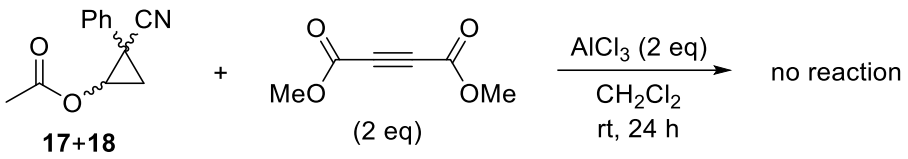


Alkyne	Temperature (°C)	Time	Yield
	50	1 h	-
	75	1 h	-
	100	1 h	-
	50	4 h	-
 **(10 eq)**	150	2 h	-
MeCN	40	1 h	-
MeCN	50	1 h	-
MeCN	50	4 h	-
MeCN	100	1 h	-
MeCN	150	2 h	-
MeCN	200	2 h	-

The observed stability of the acetoxy-substituted cyclopropane seems to reinforce the findings mentioned previously.[32] A final attempt was made using a Lewis acid catalyst, shown in **Scheme 8**. Lewis catalysts are frequently used in dipolar cycloadditions of D-A cyclopropanes,[26] however they are frequently used to activate common electron-withdrawing acetyl groups and similar derivatives. In the case of **17**+**18**, coordination of the Lewis acid to the acetoxy substituent would have the opposite effect as desired, hindering its electron-donating effect. Dimethyl acetylenedicarboxylate (DMAD) was chosen as the dipolarophile with the idea that

coordination of the Lewis acid to DMAD could potentially occur instead, and in the process further activate the alkyne.

Scheme 8. Lewis Catalyzed Dipolar Cycloaddition

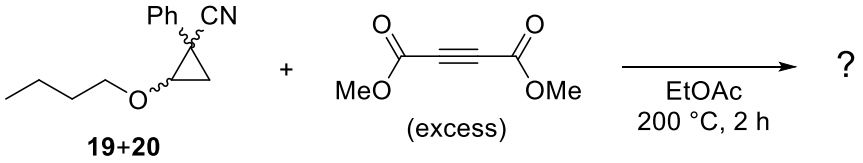


Recovery of the starting material was again observed for **Scheme 8**, which was the last reaction to be carried out using the vinyl acetate product. At this point, attention was returned to the reaction of *n*-butyl vinyl ether with phenylcyanocarbene.

Experiments with n-Butyl Vinyl Ether Derivative

The observed lack of reactivity of the vinyl acetate derivative prompted a revisit to the reaction of phenylcyanocarbene and *n*-butyl vinyl ether (**Scheme 3**), which had been previously dismissed as a possibility due to the violently exothermic decomposition. The product of the reaction was particularly appealing, as not only are ether D-A cyclopropanes a common substrate in dipolar cycloadditions,[26] but the ether product would also function as a nice intermediate in terms of its electron-donating properties between the non-reactive acetoxy cyclopropane and the too-reactive alkoxide derivative that yielded aldehyde **29**. Optimization of the reaction led to successful synthesis of the desired cyclopropane derivatives **19**+**20**, which was isolated and used in the most recent reaction that has been carried out, shown in **Scheme 9**.

Scheme 9. Reaction of *n*-Butyl Vinyl Ether Derivative with DMAD



The reaction in **Scheme 9** has been carried out but has not been fully characterized thus far. Spectral data of the crude product indicates an absence of the starting cyclopropanes **19**+**20**, which is promising in comparison to the lack of reactivity and recovery of starting material observed for the vinyl acetate derivative. Time constraints have prevented further analysis of the reaction, but the utilization of the ether starting material for probing potential reaction conditions for dipolar cycloadditions is the current priority for future work.

CHAPTER V: CONCLUSIONS AND FUTURE WORK

This work sought to explore novel reactions of phenylcyanocarbene with electron-rich substrates, and to investigate the donor-acceptor cyclopropanes that would be generated from such reactions for their potential as 1,3-dipoles in dipolar cycloaddition reactions. The work towards those goals was severely hampered by the inability to consistently synthesize the phenyl HIAT starting material, an issue that would be likely to affect future research into phenylcyanocarbenes as well. Attempts to remedy this issue have resulted in an updated SOP, which while not quantitatively consistent, qualitatively details a procedure that has led to consistent and reproducible synthesis of phenyl HIAT.

A variety of electron-rich substrates have been reacted with phenylcyanocarbene, expanding the known substrate scope. In particular, the reactions with vinyl acetate and *n*-butyl vinyl ether (after optimization of reaction conditions) have yielded cyclopropanated products that were able to be isolated and characterized, which had only been done once previously.[38] Other substrates were tested and resulted in decomposition, a lack of the desired cyclopropanated products, or as of yet unknown products. Analysis towards these reactions is ongoing and a focus of future research.

Finally, the obtained cyclopropanated products of vinyl acetate and *n*-butyl vinyl ether were tested as compatible donor-acceptor cyclopropanes towards dipolar cycloaddition reactions. A significant effort was made using the vinyl acetate derivative, but despite a multitude of reaction conditions and dipolarophiles, it remained inert. In the attempt to convert the vinyl acetate product into a more reactive alcohol derivative, a ring-opening reaction was observed that resulted in the synthesis of ß-cyano-ß-phenylpropanal, a molecule with very limited research towards its synthesis currently published. The efficacy of the ring-opening is particularly notable

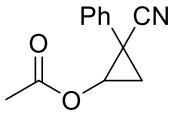
given that efforts were only made to inhibit its production, and likely warrants further investigation. Although the cyclopropanated ether product was not obtained early enough to have conducted significant research towards a potential cycloaddition, the preliminary data shows promise with observed reactivity, unlike the vinyl acetate product. Future work should focus on optimizing the conditions for the ether substrate, and potentially explore alkenes that would yield cyclopropanes containing electron-donating substituents with similar properties.

CHAPTER VI: EXPERIMENTAL DATA

General Information

All reactions were carried out using oven dried glassware and under a nitrogen atmosphere. Solvents and reagents were acquired from commercial sources unless otherwise noted and used without further purification. All column chromatography was performed as a normal phase flash column using silica gel (60 Å, 32-63 μm) as the stationary phase and gradient elution (EtOAc in hexanes). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ using a JEOL ECA 400 spectrometer with chemical shifts reported in parts per million (ppm) relative to TMS. Coupling constants, *J*, are reported in hertz (Hz) and multiplicities are listed as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), or multiplet (m).

Synthesis of 2-acetyloxy-1-phenylcyclopropanecarbonitrile (17 and 18).



To an oven-dried round bottom flask with stir bar and purged with N_2 was injected phenyl HIAT (**11**, 53.2 mg, 0.12 mmol) that had been dissolved in 1.0 mL of dry DCM. To this solution, vinyl acetate (1.0 mL, 11 mmol) was injected, after which NBu_4N_3 (36.3 mg, 0.13 mmol) which had been dissolved in 0.8 mL of dry DCM was also injected. Upon addition of the azide, the solution immediately turned a clear orange-yellow color, and was allowed to stir at room temperature under N_2 for 30 min. The solution was then concentrated under vacuum resulting in a dark-brown oil for the crude product. The mixture was then redissolved in minimal DCM and isolated after column chromatography. The product was dried overnight under high

vacuum to yield products **17**+**18** as a dark brown oil (16.7 mg, 71%) and mixture of isomers. Obtained spectral data is consistent with previously reported data.[38]

(R,S + en) Major product, 39% yield. **^{1}H NMR** (400 MHz, CDCl3, ppm): δ 7.38-7.30 (m, 5H), 4.4 (dd, *J* = 4.9, 7.0 Hz, 1H), 2.2 (s, 3H), 2.0 (dd, *J* = 4.7, 7.2 Hz, 1H), 1.8 (t, *J* = 7.0 Hz, 1H). **^{13}C NMR** (100 MHz, CDCl3, ppm): δ 171.0, 133.4, 129.3 (2C), 128.6, 127.3 (2C), 118.8, 57.8, 21.3, 21.2, 20.8.

(*R*,*R* + en) Minor product, 32% yield. **^{1}H NMR** (400 MHz, $CDCl_3$, ppm): δ 7.38-7.30 (m, 5H), 4.7 (t, *J* = 6.2 Hz, 1H), 1.95 (d, *J* = 6.1 Hz, 2H), 1.78 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, ppm): δ 170.3, 129.9, 128.8 (4C), 128.6, 120.7, 56.5, 20.2, 19.8, 17.8.

Figure 9. ^{1}H NMR of Vinyl Acetate Cyclopropanation Products

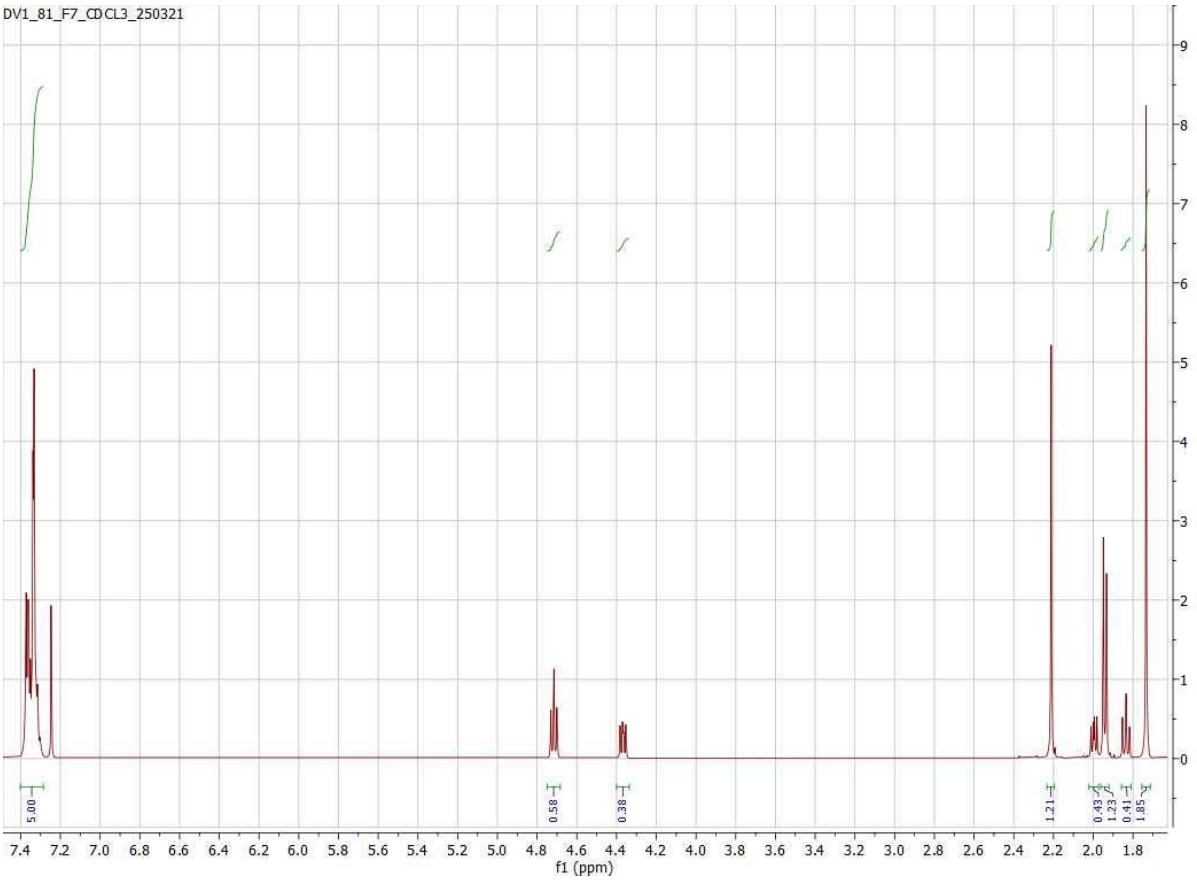
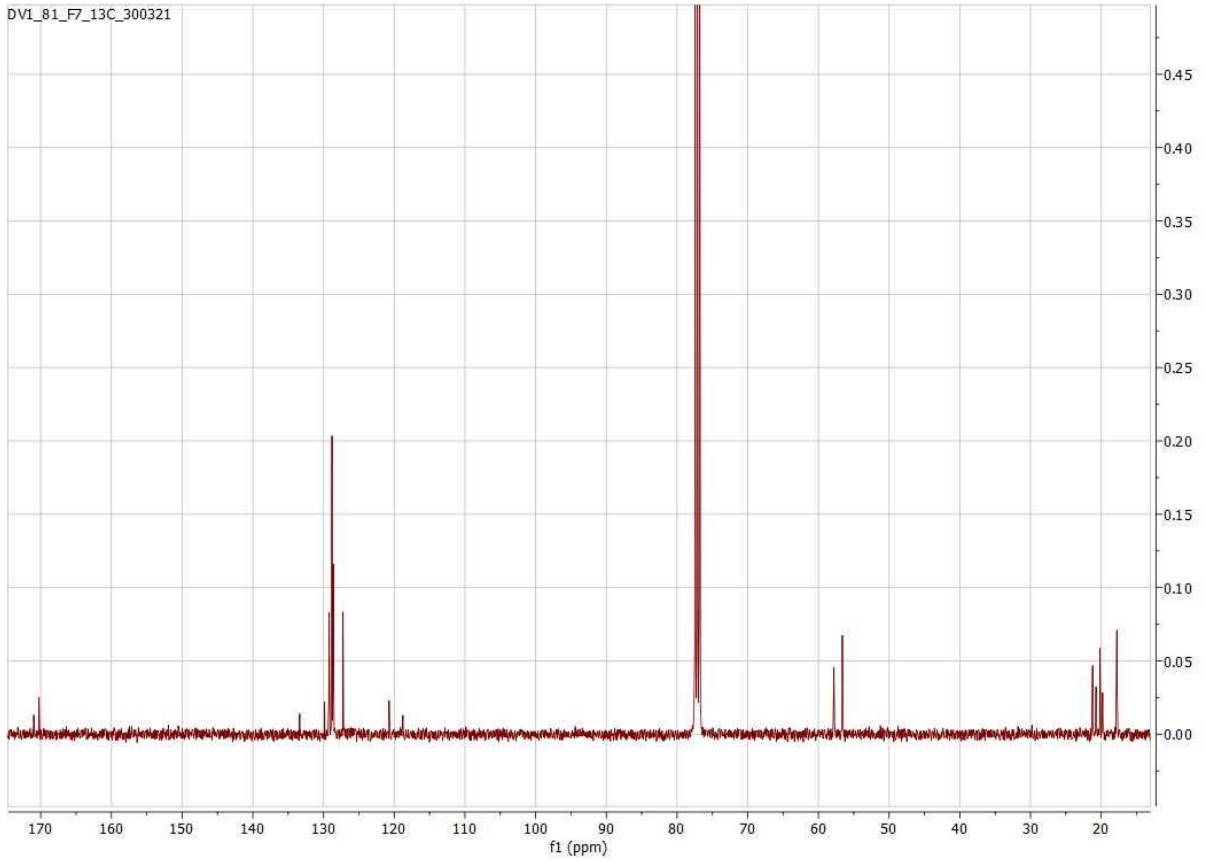
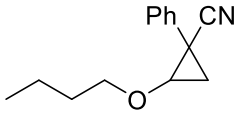


Figure 10. ^{13}C NMR of Vinyl Acetate Cyclopropanation Products



Synthesis of 2-butoxy-1-phenylcyclopropanecarbonitrile (19 and 20).



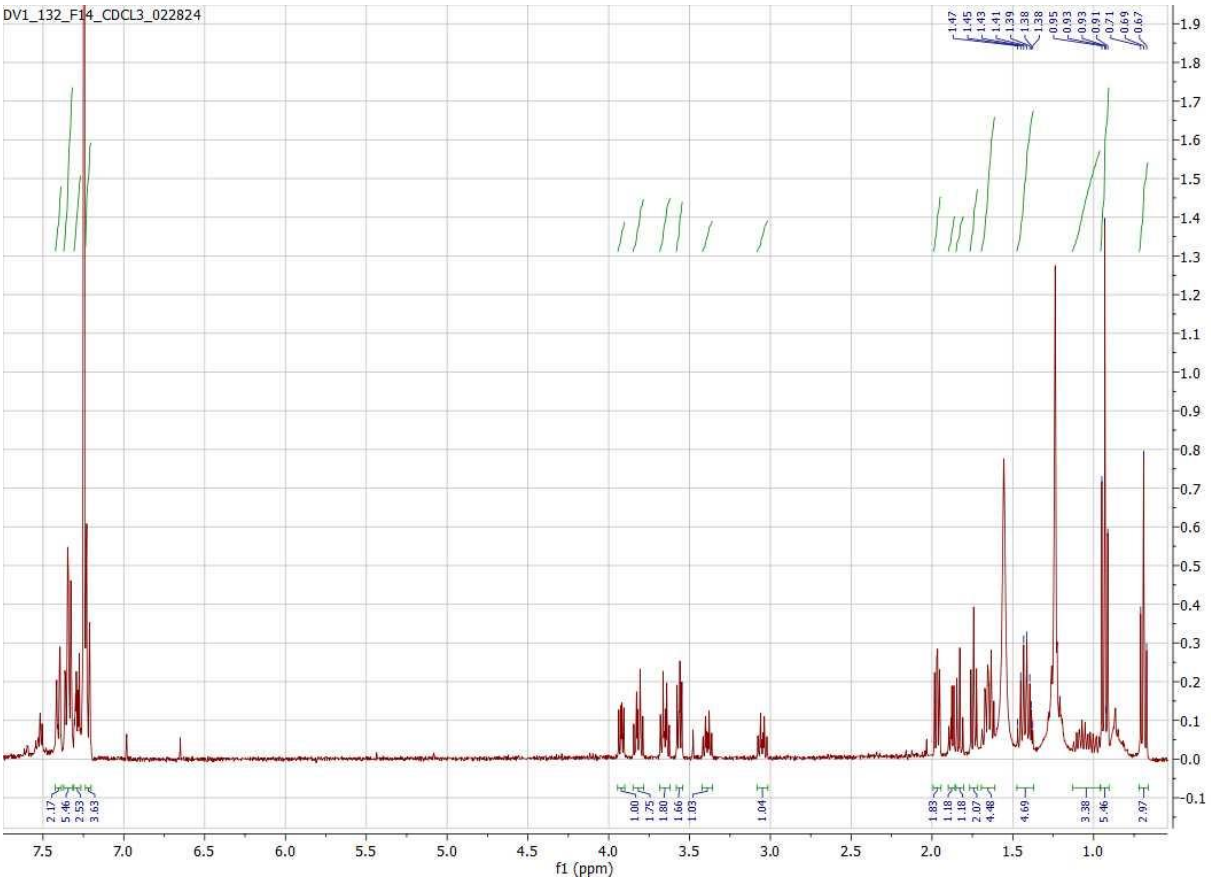
To an oven dried round bottom flask equipped with a stir bar and under a nitrogen atmosphere was added NBu_4N_3 (36.0 mg, 0.13 mmol) dissolved in 1 mL of dry DCM. To the solution was added an additional 3 mL dry DCM and *n*-butyl vinyl ether (14 µL, 0.11 mmol), after which the solution was cooled in a -40 °C bath. Once cooled, a solution of phenyl HIAT (**11**, 53.4 mg, 0.12 mmol) in 1 mL dry DCM was injected into the flask after which the reaction solution turned a dark yellow/light brown color. After stirring for 30 minutes, the reaction mixture was concentrated under vacuum and isolated after column chromatography (0-10%

EtOAc:hexanes) as a slight yellow oil (7.1 mg, 30%) and mixture of isomers. NOTE: the order of addition is extremely important for this reaction, as the phenyl HIAT had previously reacted violently with the *n*-butyl vinyl ether before the addition of azide. Obtained spectral data is consistent with previously reported data.[38]

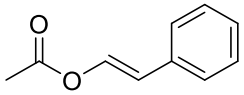
(R,S + en) Major product, 19% yield. **^{1}H NMR** (400 MHz, CDCl3, ppm): δ 7.42-7.20 (m, 5H), 3.85-3.79 (dt, *J* = 8.9, 6.8 Hz, 1H), 3.68-3.62 (dt, *J* = 9.0, 6.4 Hz, 1H), 3.58-3.54 (dd, *J* = 6.9, 5.0 Hz, 1H), 1.99-1.95 (dd, *J* = 7.3, 5.0 Hz, 1H), 1.76-1.72 (t, *J* = 6.8 Hz, 1H), 1.69-1.61 (m, 2H), 1.47-1.38 (m, 2H), 0.95-0.91 (t, *J* = 7.3 Hz, 3H).

(R,R + en) Minor product, 11% yield. **^{1}H NMR** (400 MHz, CDCl3, ppm): δ 7.42-7.20 (m, 5H), 3.95-3.92 (dd, *J* = 7.3, 5.0 Hz, 1H), 3.43-3.38 (dt, *J* = 9.2, 6.1 Hz, 1H), 3.09-3.04 (dt, *J* = 9.2, 6.8 Hz, 1H), 1.91-1.88 (dd, *J* = 7.3, 5.2 Hz, 1H), 1.86-1.82 (t, *J* = 7.3 Hz, 1H), 1.28-1.21 (m, 2H), 1.13-0.98 (m, 2H), 0.71-0.67 (t, *J* = 7.3 Hz, 3H).

Figure 11. ^{1}H NMR of *n*-Butyl Vinyl Ether Cyclopropanation Products

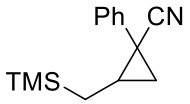


Synthesis of (*E*)-styryl acetate (22).



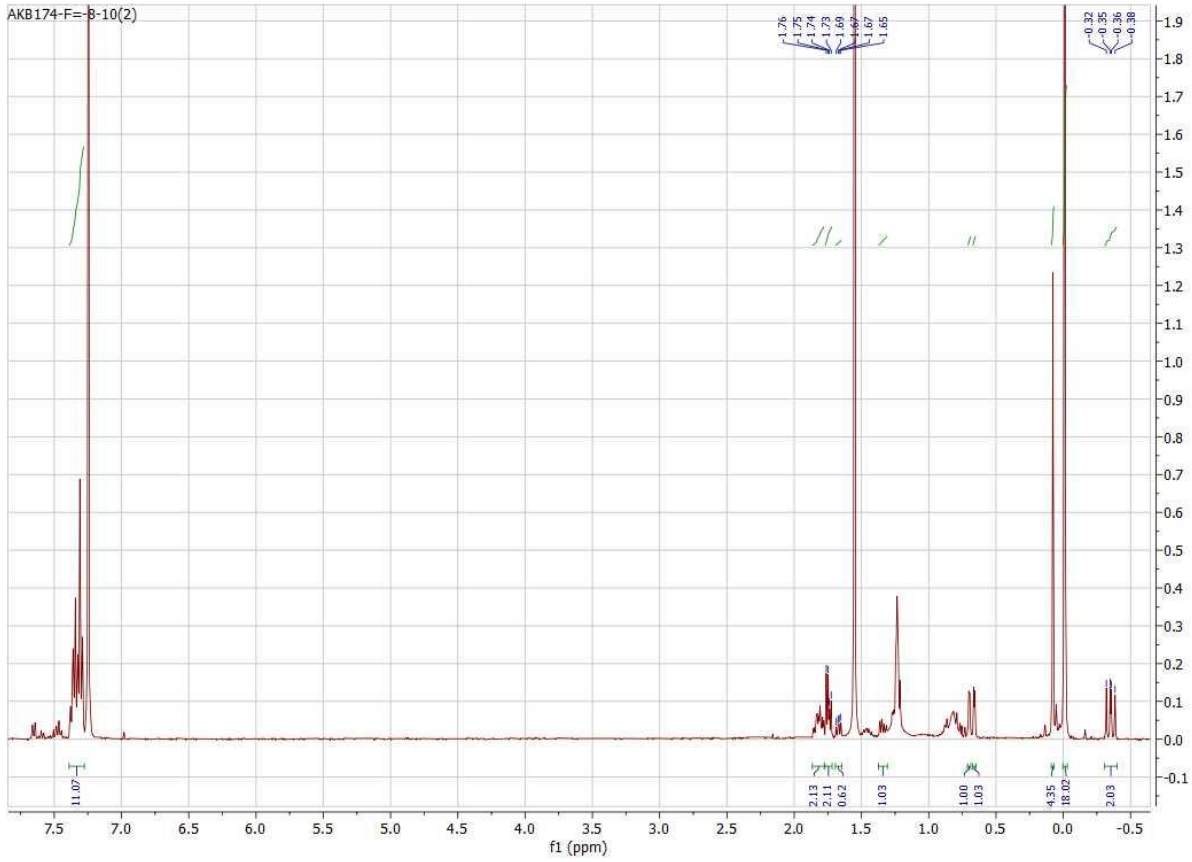
Compound was prepared and characterized based on literature procedure.[39] To an oven dried 50-mL round bottom flask equipped with stir bar was added 4-phenyl-3-buten-2-one (740 mg, 5.1 mmol) and 10.0 mL DMF. To this solution was added oxone (3.1 g, 10 mmol), which stirred at room temperature for 25 hours. The reaction mixture was added to a separatory funnel of H_2O/hexanes and extracted with hexanes (3 x 20 mL). The combined organic layer was then concentrated under vacuum and the product was obtained as a clear-yellow crystal (750 mg, 91% yield). Spectral data matched the previously reported data.[39]

Synthesis of 1-phenyl-2-((trimethylsilyl)methyl)cyclopropane-1-carbonitrile (21).

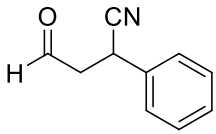


To an oven dried round bottom flask equipped with stir bar and purged with N_2 was added allyl TMS (0.5 mL, 3 mmol), followed by a solution of phenyl-HIAT (**11**, 46 mg, 0.10 mmol) dissolved in 0.5 mL of dry DCM. A solution of NBu_4N_3 (32.0 mg, 0.11 mmol) in 0.5 mL dry DCM was then injected into the flask and the solution was allowed to stir at room temperature for 30 minutes. The crude mixture was concentrated under vacuum and purified with column chromatography (0-50% EtOAc:hexanes). The reaction was carried out by an undergrad who worked with me on the project for a time. Overall yield information was not recorded and further data analysis is needed on the NMR spectra, although product appears present.

Figure 12. ^{1}H NMR of Allyl TMS Cyclopropanation Products

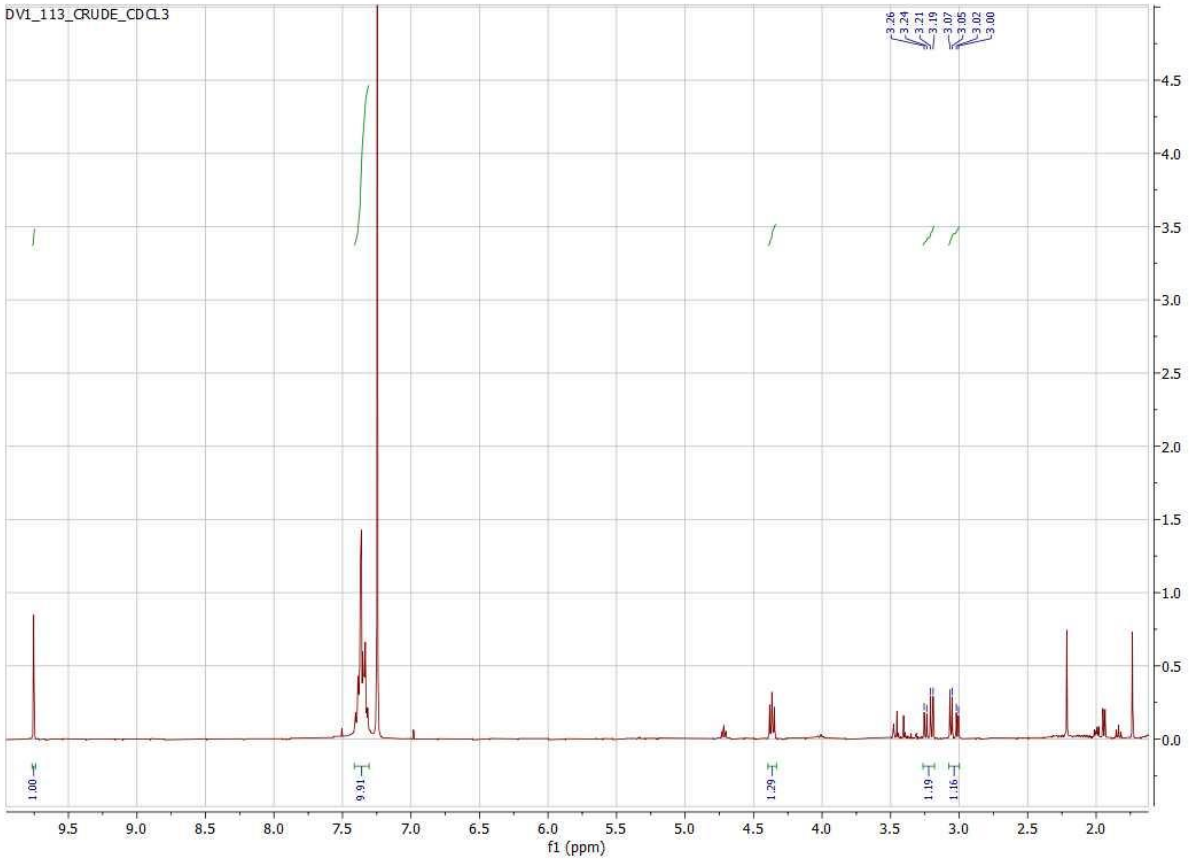


Synthesis of 4-oxo-2-phenylbutanenitrile (29).



To a solution of 2-butoxy-1-phenylcyclopropanecarbonitrile (12.4 mg, 0.06 mmol) in 5 mL MeOH was added $NaHCO_3$ (8.4 mg, 0.1 mmol), which was allowed to stir at room temperature for 75 minutes. The solution was then quenched with NH_4Cl, extracted with DCM (3 x 7 mL) and dried with Na_2SO_4. The decanted liquid was concentrated under vacuum. Product was obtained as a mixture with starting material, and overall yield was not determined. **^{1}H NMR** (400 MHz, CDCl3, ppm): δ 9.75 (s, 1H), 7.41-7.31 (m, 5H), 4.39-4.35 (dd, *J* = 7.6, 6.3 Hz, 1H), 3.26-3.18 (dd, *J* = 18.6, 7.6 Hz, 1H), 3.08-3.00 (dd, *J* = 18.6, 6.3 Hz, 1H).

Figure 13. ^{1}H NMR of Aldehyde Product



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