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The design and development of novel reactions are long-standing goals within the synthetic community. Specifically, reactions that can give molecularly complex products through the manipulation of readily available starting materials are of considerable interest. In pursuit of this goal, phenyl hypervalent iodonium alkynyl triflate (PhHIAT) is used as a precursor for the *in situ* generation of a reactive cyanocarbene intermediate.

The reactive cyanocarbene was investigated as a potential gateway for synthesizing molecules of greater complexity. Specifically, novel reactions between cyanocarbenes and various symmetrical and unsymmetrical dienes were explored as a method for performing [2+1] cycloadditions. Preliminary reactions performed using a simple diene substrate showed promising results and further reactions allowed for the construction of an optimized procedure which was used on a variety of diene substrates. These reactions were studied for their potential viability as a method for accessing complex molecular moieties and to elucidate their mechanisms. The discovery of novel reactions adds to the tools that are at the disposal of the synthetic community and thus investigation into various synthetic methodologies can prove to be invaluable in achieving previously inaccessible or complex products in the most efficient way.

DESIGN AND DEVELOPMENT OF NOVEL REACTIONS UTILIZING DIENES AND CARBENE INTERMEDIATES

by

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Approved by

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Committee Chair

To Muhammad and Asma

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TABLE OF CONTENTS

Page

CHAPTER I

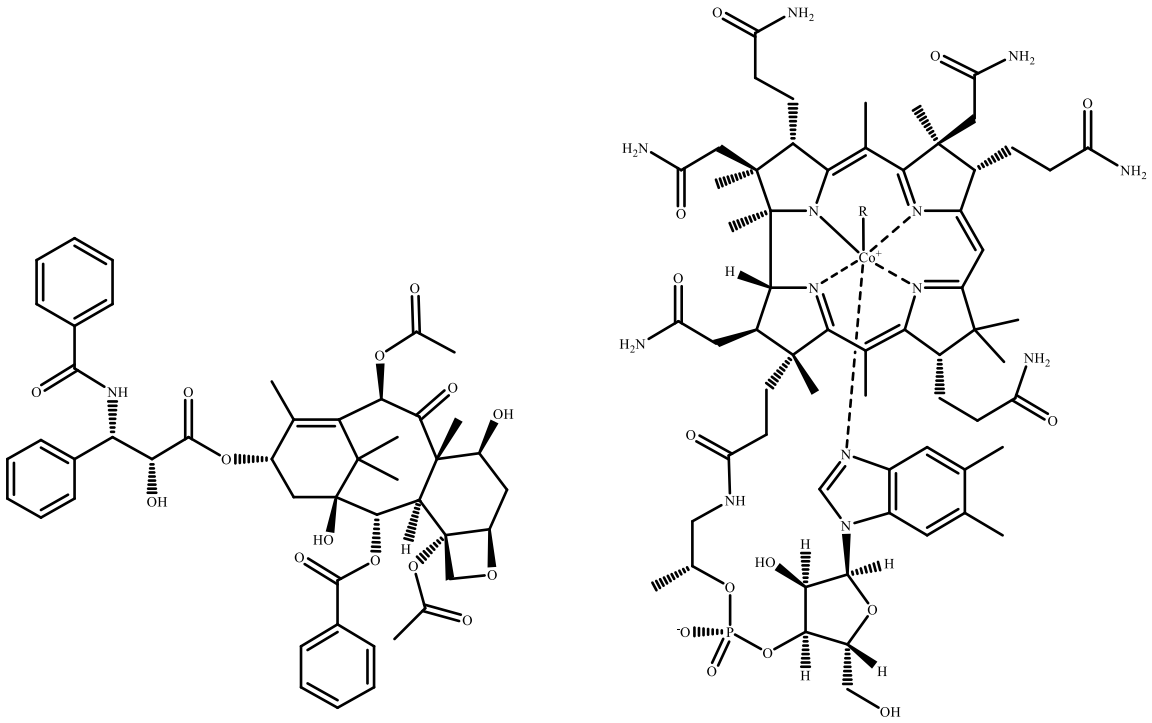
INTRODUCTION

Utility of Synthetic Methodology

A recurrent theme within the field of organic synthesis is the development of novel reactions and methods to construct complex molecules from simple, readily accessible starting materials. Such methodologies would be of great value, and would have vast scientific, economic, and ecological impacts.[1] The success of researchers in pursuit of this goal has led to the synthesis of molecules that have been instrumental in more specialized applications such as in medicine, engineering, and materials science. The strides made in these fields can be partially attributed to the fundamental research that is done to expand the resources available to the scientific community and understand the mechanisms with which the natural world operates. As such, research done towards advancing fundamental knowledge can have significant impact and is of great value.

To this end, effort has been put towards discovering methods that would be instrumental in accessing motifs that would be otherwise difficult to synthesize.[2] Such work has led to the successful total synthesis of molecules with high complexity that were previously only available through biological processes.[3] The total syntheses of natural products such as the widely used chemotherapeutic Taxol **(Figure 1a)**, Vitamin B_{12} **(Figure 1b)**, and the antimalarial agents Quinine **(Figure 1c)** and Artemisinin

(Figure 1d) are only few examples of the results that were achieved thanks in part to the synthetic methodologies available to the researchers at the time. [4,5,6,7]



1a **1b**

1c **1d**

Figure 1: Taxol, Vitamin B12, Quinine, Artemisinin

The complex moieties featured in these molecules, and molecules of similar value, are often difficult to access. With the advent of new synthetic strategies, such

problems would prove to be negligible.[8] It is for this reason that advancement in synthetic methods is paramount. To improve the ways in which synthetic chemistry approaches modern challenges in an efficient manner, novel methods must be discovered. To this extent, research towards expanding the field of organic methodology was conducted. Described herein is a method in which a reactive phenylcarbene intermediate is generated from phenyl hypervalent iodonium alkynyl triflate (PhHIAT) **(Figure 2)** and is used in tandem with readily available dienes to give complex cyclic products.

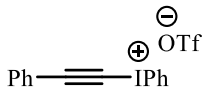
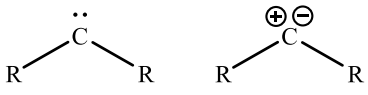


Figure 2: PhHIAT

Introduction to Carbenes

Carbenes are any molecules containing at least one neutral, divalent carbon atom with a six-electron valence shell **(Figure 3)**. The molecular and electronic configurations of these often short lived and transient molecules are considered by many to be of great interest and have shown to be a source of fascinating reactivity.

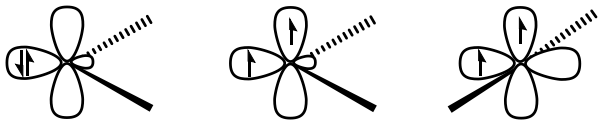


3a **3b**

Figure 3: Carbene

This unique configuration and its resulting reactivity can be attributed to the unshared electrons and the influence of the surrounding R-groups, if any, upon them.

Depending on the carbene species, the unshared electrons may or may not be spin paired. This distinction in states is formalized as the singlet **(Figure 4a)** or triplet states **(Figure 4b)**, respectively.[9,10] Furthermore, the notation for each state is representative of the hybridization they adopt and the reactivity that they present.[11] Singlet carbenes, displayed as zwitterionic species and being sp^2 **(Figure 4a)** hybridized, react in a manner traditional of the two-electron nucleophilic and electrophilic concerted processes while triplet carbenes behave as diradical species reacting in a multistep pathway, that may adopt an sp^2 **(Figure 4b)** or sp **(Figure 4c)** hybridization.[12]



4a **4b** **4c**

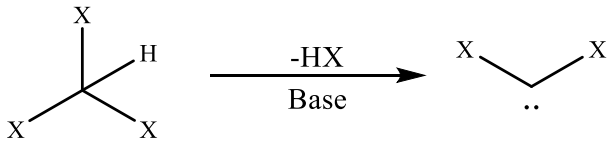
Figure 4: Singlet sp^2, Triplet sp and Triplet sp^2 Hybridization

Knowledge of the existence of carbenes can be traced back as far as 1903 when Buchner and Feldmann first hypothesized the existence of a carbene species while studying the cyclopropanation of ethyl diazoacetate in the presence of toluene.[13] This was followed by further evidence for the existence of carbenes by Staudinger in 1912 while studying the reactivity of diazomethane.[14] By the mid 1900's work towards discovering new carbene intermediates and studying their reactivity was well underway.

Common Carbene Species

As the century went on, studies were done in an attempt at finding new carbene species and uncovering the possible part that they played in already well-known

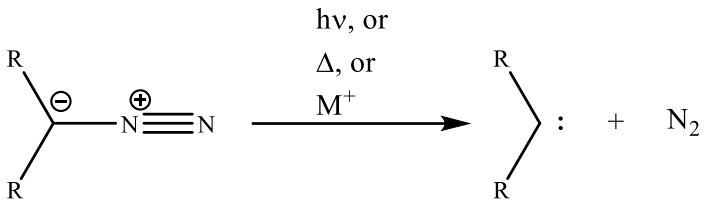
reactions. An early set of studies was presented by Doering confirming the existence of dichlorocarbene and dibromocarbene intermediates during the processes of cyclohexene dehydration.[15] Doering asserts that the generation of the dihalocarbenes is as an intermediate step that transpires when a haloform, such as chloroform or bromoform, is deprotonated by a base yielding a dihalocarbene **(Scheme 1)**. Doering states that this allows for the mechanistic explanation of the observed cyclopropanations and resultant dihalogen products during reactions between dihalocarbenes and various substrates.[15] As research continued, significant strides were made in identifying carbenes and the precursors from which they are generated.



X= Halogen

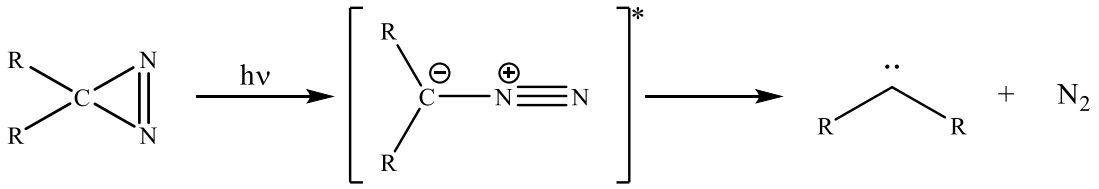
Scheme 1: Dihalocarbene Generation

One of the most ubiquitous forms of carbene generation, and by proxy, one of the most ubiquitous forms of carbenes spawn from diazoalkanes. Research towards this goal has led to the confirmation and development of methods in which diazoalkanes were used to generate carbenes. This process involves the generation of a carbene by exposing a precursor to heat, light, or a metal catalyst.[16] The generation occurs through the lysis of the diazo bond by an initiating component thus leading to the generation of the carbene and evolution of nitrogen gas **(Scheme 2)**.



Scheme 2: Diazoalkane Carbene Generation

Similar to the previous method of exploiting dinitrogen containing compounds to generate carbenes, the photolysis of diazirines is known to form them as well. [17,18] The strained ring system of diazirines is also known to form carbenes and nitrogen gas. More specifically, photolysis is believed to initiate the process by producing an excited state diazonium ion that further decomposes to a carbene **(Scheme 3)**. [19,20] However, these intermediates are often found only in the gas and solution phases due to their high reactivity and instability.[21] As such, the carbenes generated through this method are often flanked by R-groups that electronically promote and help stabilize the intermediate.



Scheme 3: Diazirine Carbene Generation

The difference in reactivity between the singlet and triplet states makes carbenes an attractive proposition for synthetic schemes that seek to exploit these properties. Likewise, one electronic state may be more favorable in some circumstances compared to others. Fortunately, the small difference in energy between some carbenes allows for the

equilibration between the triplet and singlet states.[22] As well, certain methods make it possible to stabilize carbenes in one state over another.

These aptly named stable carbenes, sometimes referred to as persistent carbenes and postulated to exist as early as the mid 1900's by Breslow, [23] are not as transient as their unstable carbene counterparts and allow for enhanced utility and ease of use. Often, these persistent carbenes may not degrade as fast as other carbenes and in some cases may be isolable. This enhanced stability is largely due to the groups flanking the carbene carbon and may not require stabilization through metal coordination.[24] Some common stable carbenes include but are not limited to N-heterocyclic carbenes (NHC's), and the silicon-phosphorus stabilized Bertrands carbenes. Interestingly, most forms of stable carbenes are found in their singlet state, although relatively stable triplet carbenes have also been reported. [25]

Beginning with the largest class of stable carbenes by far; N-heterocyclic carbenes are heterocyclic molecules containing a carbene carbon and one or more nitrogen atoms within the ring (**Figure 5)**.[26] Indeed, the early hypotheses by Breslow described the prevalence of an NHC intermediate in the catalytic cycle of thiamine. However, despite this prediction it would be years before an NHC would be isolated and stabilized due to the prevailing belief that carbenes were far too unstable. Such beliefs thwarted many efforts to further investigate the possibility of stable carbenes.

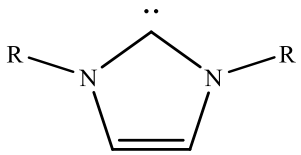


Figure 5: N-Heterocyclic Carbenes

Not long after Breslows predictions, Wanzlick and colleagues postulated the existence of stable carbenes sharing moieties similar to dihydroimidazol-2-ylidene.[27] This was further supported by Hoffman's research hypothesizing that the aromaticity of these analogues would promote stability.[28] Despite Wanzlicks belief that a stable carbene derivative of dihydroimidazol-2-ylidene may exist, the researchers were unable to isolate a free NHC of that character. Instead Wanzlick and coworkers isolated and characterized the mercury coordinated compound **(Figure 6)**.[29]

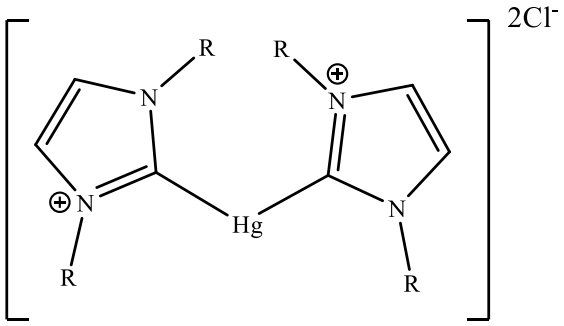
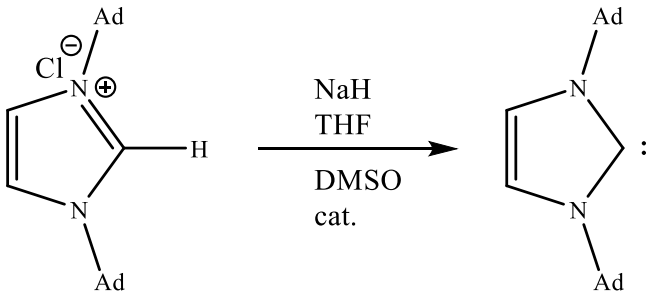


Figure 6: Hg-NHC Coordination Complex

However, despite the Wanzlick groups best efforts, the first stable, isolable, free NHC would not be reported until 1991 when the Arduengo group synthesized 1,3-di-l-adamantylimidazol-2-ylidene **(Scheme 4)**, through the deprotonation of the imidazolium

chloride salt, in what is now considered to be a seminal work in the field of stable carbenes.[30]



Ad = Adamantyl

Scheme 4: Formation of 1,3-di-l-adamantylimidazol-2-ylidene

Inspired by the work of Wanzlick, Arduengo and colleagues aimed to synthesize a NHC like the hypothetical free carbenes first postulated more than two decades earlier. This discovery was groundbreaking due partly to the unusually high stability and "storability" of this electron rich NHC. As such, both experimental and theoretical research within the field grew very quickly in an effort to find more NHC's and to explain their unusual stability. Further research would explain the latter. The NHC discovered by Arduengo is affected by both electronic and steric stabilization.[31] The electronic stabilization is attributed to the orbital overlap across the N-C-C-N system that allows for a negative inductive effect, caused by the higher electronegativity of the nitrogen atoms, and a positive mesomeric effect, caused by the π-donation of the nitrogen lone pairs into the carbenes p-orbital, thus creating an electronic push-pull effect and stabilizing the carbene.[32] Continued interest within the subfield of NHC chemistry has grown considerably and research in this field has proven to be fruitful. However, despite

NHCs being the most ubiquitous form of stable carbenes, they are not the first carbenes to be first isolated.

The first carbene to be isolated was by Bertrand and coworkers during their seminal work in 1988.[33] At the time of discovery there was doubt as to whether these push-pull carbenes stabilized by their flanking phosphorus and silicon groups could truly be considered stabilized carbenes **(Figure 7)**. Despite this, the work done by Bertrand and colleagues set the stage for further discoveries in stable carbene chemistry by proving that such a species was isolable.

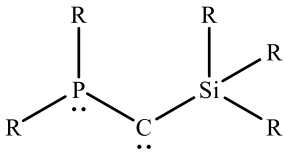


Figure 7: Bertrands Carbene

Within the same vein of carbenes, a more esoteric class of "carbene like" molecules, often referred to as carbenoids do exist. Before the advent of isolable stable carbenes, the formation of carbenoids to access the carbene moiety and trap them indirectly was, and continues to be, very popular.[34] As for their formation, the methods often include the trapping of a carbene with a metal. [35] The trapping of free carbenes with metals is a common practice as seen by the prevalence of Fischer and carbenes Schrock. [36,37] The advent of a metal bound carbenoid was first proven to be possible by the former during the synthesis of the first Fischer carbene in 1964. Schrock and colleagues would eventually synthesize carbenoids of their own and two camps of

divergent reactivity and characteristics would emerge. [38,39] Fischer carbenes are trapped in the singlet state using low oxidation state metals such as W(0) or Cr(0). Conversely, Shrock carbenes are trapped in their triplet state with high oxidation state metals such as Ti(IV) or Ta(V). These carbene-metal bonds add a layer of stability that allows for better ease of use and access to the carbene moiety.

As well, some methods take inspiration from the other methods used to form carbenes. For example, by exploiting the theme of strained ring systems to generate carbenes, such as in the use of diazirines, it is known that certain epoxides will undergo carbenoid formation when lithiated at the α position. [40,41] The metallation of the oxirane allows for the establishment of an equilibrium between the alkyl chain carbenoid species and the α-metal oxirane. [42] The former shows further reactivity similar to a carbene.

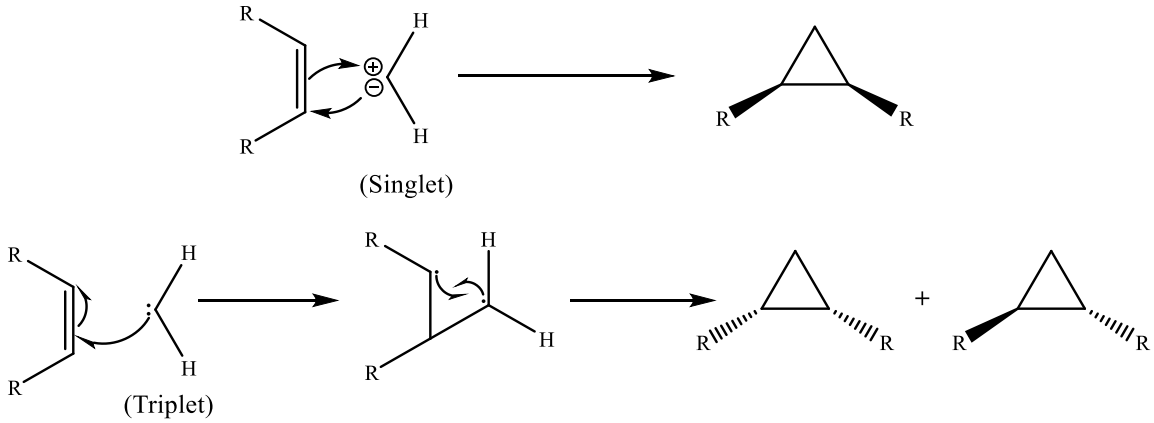
Although not a complete review of the state of current or past carbenes, the aforementioned species contribute significantly to the field. Just as important as the carbenes themselves is the reactivity that they present.

Known Carbene Reactivity

Free carbenes, whether stable or otherwise are known to perform a variety of reactions. This reactivity makes their use attractive to certain researchers looking to access specific moieties. As such, research elucidating the potential reactions that can be performed by carbenes, and the mechanisms by which they proceed, is highly valuable. Notably, carbenes are capable of cyclopropanation of olefins, bond insertion, and dimerization. Likewise, some stable carbenes, such as NHCs, can be used to tune the reactivity of metals which can go on to perform catalytic activities. It should be noted that

the type of carbene, whether singlet or triplet, can influence reactivity and the mechanisms by which they occur.

Beginning with one of the most common uses of carbenes; cyclopropanation of olefins **(Scheme 5)** can be performed by singlet and triplet carbenes alike.[43]

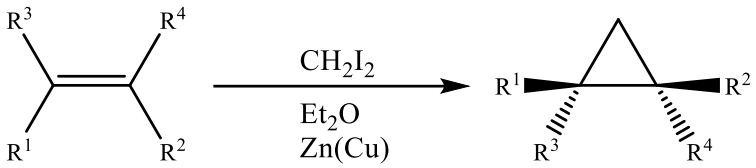


Scheme 5: Cyclopropanation of Olefins using Carbenes

However, the mechanism differs between the two. As expected, singlet carbenes act in the traditional two electron concerted process and as such the process is stereoretentive. Conversely, a triplet carbene would cyclopropanate through a diradical process, thus the potential for scrambling of the stereochemistry. [44,45]

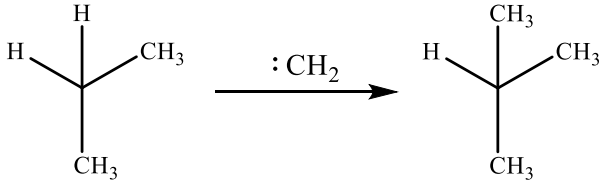
A canonical example of this is the Simmons-Smith reaction which utilizes an organozinc carbenoid to perform a two electron cyclopropanation **(Scheme 6)**.[46] However, the Simmons-Smith is not without its limitations. The reaction can produce uncontrolled side products despite being very tolerant to a wide variety of functional groups. These unwanted reactions often include undesired methylations and, in the case

of thioethers, the formation of sulfur ylides. [47,48] This rogue reactivity can usually be attributed to the lewis acidity of ZnI, a byproduct of the reaction.



Scheme 6: Simmons-Smith Cyclopropanation

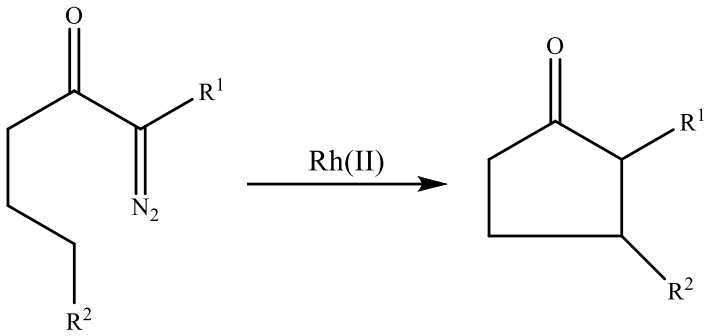
Continuing with the theme of carbene reactivity, bond insertion is a common reaction performed by carbenes as well. Often, the carbene inserts into C-H bond. This can result in the formation of a new C-C bond **(Scheme 7)**, thus making carbene bond insertion an attractive reaction. First reported by Doering and colleagues in 1956, the group found that the simplest methylene carbene was nonselective in its insertions into aliphatic bonds.[49]However, due to the lack of regioselectivity of C-H insertion, these reactions were primarily seen as laboratory oddities or undesired reactions.[50]



Scheme 7: C-H Bond Insertion

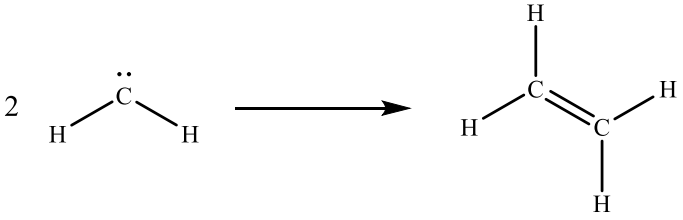
It would not be until Teyssie and colleagues devised a more regioselective method of carbene bond insertion using metal catalysts such as dirhodium(II) tetraacetate **(Scheme 8)** that the reactivity would be seen as an applicable synthetic

methodology.[51,52] The discovery of a regioselective carbene bond insertion influenced many other researchers to seek out more interesting reactivity for carbenes.



Scheme 8: Rhodium(II) Catalyzed Carbene Bond Insertion

One such set of reaction process stems from an unlikely source. It is known that carbenes have a disposition for dimerization **(Scheme 9)**.[53] Such reactivity is inevitable and is often seen as an undesired consequence of carbene formation.



Scheme 9: Carbene Dimerization

Thus, dimerization of carbenes is sometimes considered a behavior without synthetic applicability. However, the process has seen some appreciation through its use in certain synthetic schemes such as in the synthesis of polyalkynylethenes.[54]

The aforementioned reactivities are only a small swathe of the synthetic possibilities of carbenes. They represent some of the most common uses within the field

and complex variations exist for each. However, the descriptions are not exhaustive and continued research is being done to elucidate further reactivity. To this end, the Croatt group has made efforts to synthesize a novel carbene precursor and probe its behavior.

CHAPTER II

PHENYL HYPERVALENT IODONIUM ALKYNYL TRIFLATE

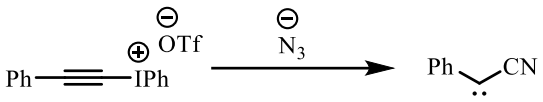
Introduction to PhHIAT

Phenyl hypervalent iodonium triflate (PhHIAT) was initially discovered by the Croatt group in 2012 in an attempt to find a facile method that would allow access to reactive cyanocarbenes.[55] Previous work on cyanocarbenes had been done by the Banert group and despite successfully trapping cyanocarbene products, the reaction conditions and yields were not ideal.[56] As such, the Croatt group has sought to obtain cyanocarbene intermediates *in situ* and react them with a slew of substrates. Croatt and colleagues reported the synthesis of PhHIAT through the reaction of tributlystannyl alykynes and cyanophenyliodonium triflate. The resulting PhHIAT was treated with azide to form the carbene intermediate **(Scheme 10)**. Further work was done by the group to elucidate the mechanism of carbene formation and to test reactivity.

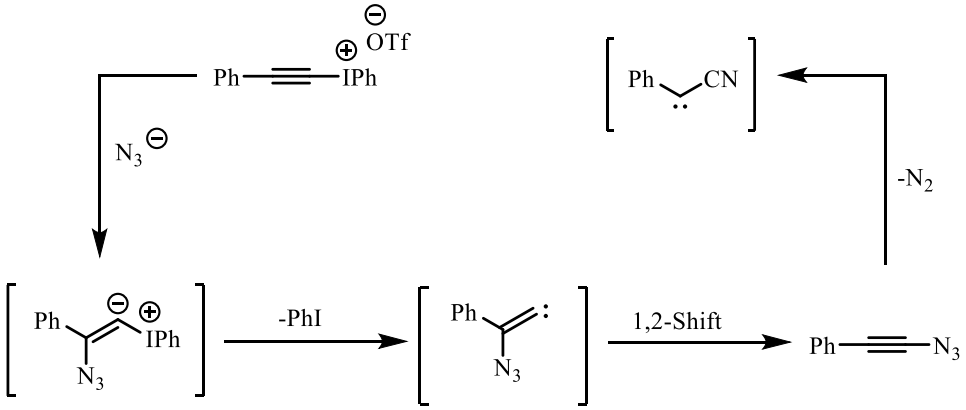
Mechanism of Formation

Through the Croatt group's initial studies of PhHIAT, the researchers were able to propose a mechanism for the formation of a cyanocarbene **(Scheme 11)**. Croatt and collegues proposed a mechanism by which nucleophilic attack of the azide to the beta carbon of the alkyne leads to the formation of a transient iodoylide which readily decomposes to form iodobenzene and a vinylidene.

The resulting vinylidene undergoes a 1,2-shift to form phenylalkynyl azide which undergoes further decomposition resulting in the formation of phenylcyanocarbene and the evolution of nitrogen gas.[57]



Scheme 10: Cyanocarbene Formation from PhHIAT

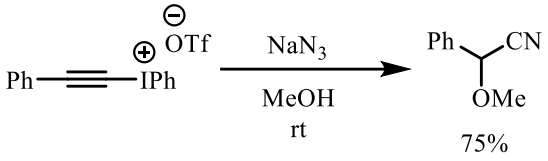


Scheme 11: Mechanism of Cyanocarbene Formation

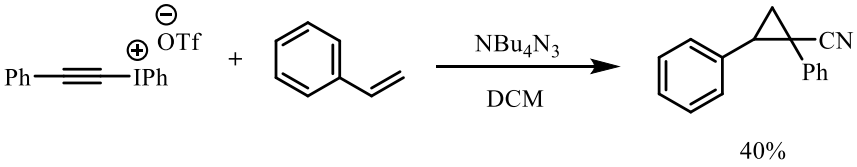
Known Reactivity of PhHIAT

Having synthesized a novel carbene precursor and successfully isolated it; the Croatt group sought to probe the reactivity of PhHIAT thus determining its synthetic utility and elucidating its mechanism of reaction with varied substrates. Similar to the reactivity of many other carbenes, PhHIAT can undergo bond insertions and cyclopropanations. In reactions with methanol, the Croatt group discovered that the phenylcyanocarbene performs O-H bond insertions at room temperature **(Scheme 12)**. In

reactions with styrene the phenyl carbene was found to cyclopropanate the olefin **(Scheme 13)**.

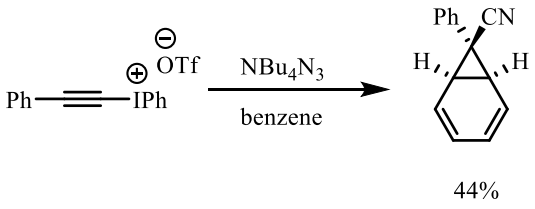


Scheme 12: O-H Insertion

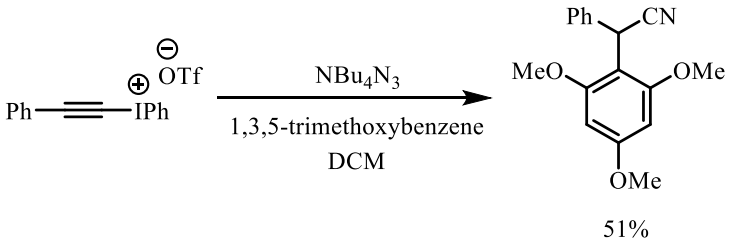


Scheme 13: Cyclopropanation of Styrene

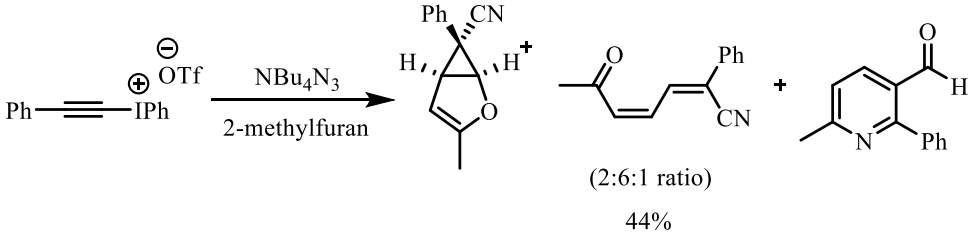
Having successfully performed the canonical carbene reactions using PhHIAT, the Croatt group aimed to increase the library of molecules reacted with the cyanocarbene intermediate. As such, attention was turned to aromatic substrates.[58] The group experimented with a variety of substrates some of which included benzene **(Scheme 14)**, 1,3,5-trimethoxybenzene **(Scheme 15)** and 2-methylfuran **(Scheme 16)**.



Scheme 14: PhHIAT and Benzene



Scheme 15: PhHIAT and Trimethoxybenzene



Scheme 16: PhHIAT and 2-methylfuran

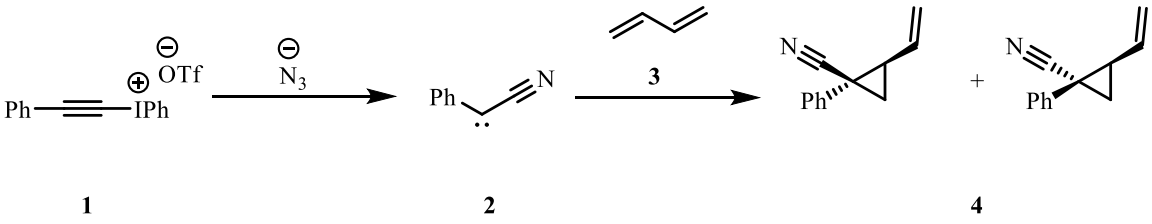
The reactions performed using benzene and trimethoxybenzene showed classic carbene reactivity with cyclopropanation and C-H insertion products, respectively. However, the reaction performed with 2-methylfuran yielded ring opening and ring expansion products along with cyclopropanation. At the time of publication, the mechanism for the latter product was unclear. With the reactivity of PhHIAT and aromatic substrates explored, the Croatt group now looks to expand the library of known reactivity of PhHIAT with more molecular motifs.

CHAPTER III

PhHIAT and DIENES

Proposed Methodology

Using knowledge of the previously established reactivity of PhHIAT, the Croatt group has sought to further test the behavior of cyanocarbenes. Specifically, recent interest has shifted toward substrates containing dienes. It has been established that PhHIAT performs the canonical cyclopropanations of olefins. As well, aromatic systems containing conjugated π-systems have also been investigated. However, an expanded substrate scope containing systems in which the diene motif is nonaromatic have yet to be tested. As such, this work proposes a method in which PhHIAT, **1**, is reacted with an azide source to form an *in situ* cyanocarbene intermediate, **2**, which performs [2+1] cycloadditions, **4**, on readily available diene, **3**, substrates **(Scheme 17)**.

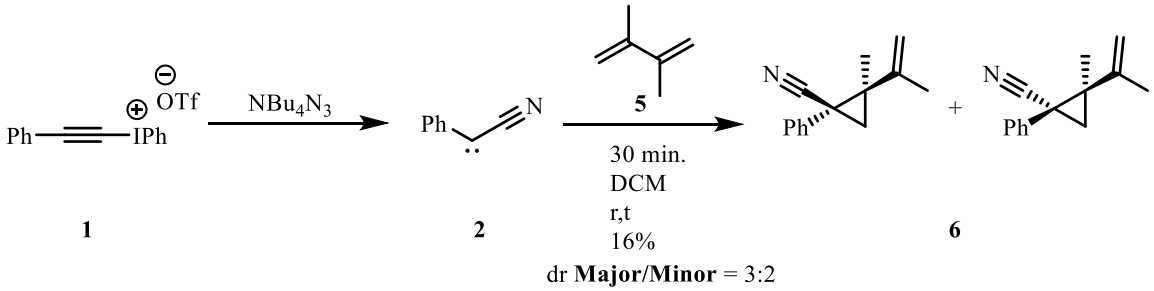


Scheme 17: Proposed [2+1] Cycloaddition

Initial Findings

As an initial investigation into the viability of the hypothesized procedure, the simplest readily available diene was required to carry out a preliminary test. 2,3-

dimethyl-1,3-butadiene, **5**, was chosen as the initial substrate for reactivity probing. The substrate was chosen due to its molecular simplicity, commercial availability, and ease of use. An unoptimized method was carried out **(Scheme 18)**. However, further optimizations were later performed.



Scheme 18: 2,3-dimethyl-1,3-butadiene and PhHIAT

The initial experiment was achieved in a dried and purged 50 ml round bottom flask to which 2,3-dimethyl-1,3-butadiene (0.150 g) was added followed by tetrabutylammonium azide (0.052 g) and PhHIAT (0.083 g), each independently dissolved in 0.5 ml of DCM and added simultaneously. The reaction was left to stir at room temperature for 30 minutes at which point the solvent and excess reagents were evaporated under reduced pressure. The crude mixture was then purified through column chromatography to yield a yellow oil (0.059 g, 16% yield) **6**, as a mixture of major and minor diastereomers.

As expected, when **2** is formed *in situ* and allowed to react with **5**, cyclopropanation of a singular olefin occurs. Not only is there a [2+1] cycloaddition, but the method offers a leap in molecular complexity by forming 2 C-C bonds, thus resulting in two quaternary stereogenic centers. Product formation was confirmed through proton

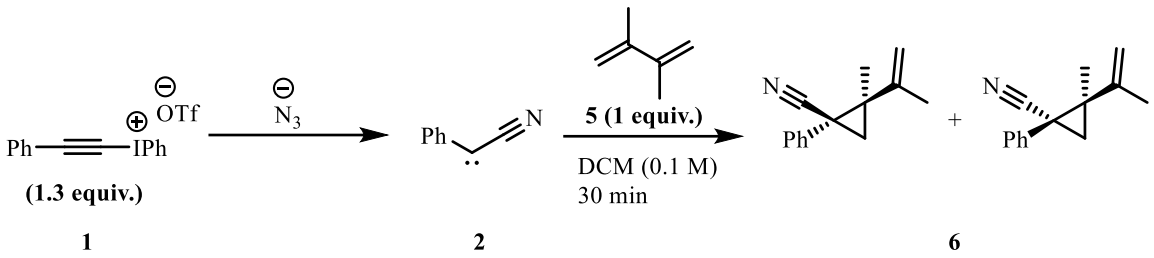
and carbon NMR as well as HRMS analysis giving a $[M+H]^+$ of 198.127. With the confirmation of cyclopropanation in hand, optimizations were performed.

Method Optimization

Once initial experiments confirmed the reactivity of PhHIAT with dienes, focus was shifted toward optimizing the [2+1] cycloaddition method. Primarily, attention was given towards the source of azide and the amounts of both azide and PhHIAT. The source of azide was varied between tetrabutylammonium azide **(Table 1)** and sodium azide. It was found that the former gave the best results.

As well, it was found that having equal molar equivalents of azide and PhHIAT gave the best results. Specifically, having 1.3 molar equivalents of each were chosen for the substrate scope.

Through thin layer chromatography, it was determined that 30 minutes was the shortest appropriate reaction time frame. Finally, temperature was varied for the last entry to better test thermodynamic control of the reaction. However, the yields were not severely affected. With the optimization of the method completed, work was begun to test a set of readily available dienes. All yields were isolated.



Entry	NBu_4N_3 (equiv.)	NaN_3 (equiv.)	Temp.	Yield
1	1.3	----	r.t	14%
2	1.3	----	r.t	28%
3	1.3	----	r.t	30%
4	1.3	----	r.t	62%
5	1.3	----	r.t	29%
6	1.3	----	r.t	33%
7	1.3	----	r.t	36%
8	----	0.3	r.t	25%
9	----	0.5	r.t	19%
10	----	1	r.t	26%
11	----	1.3	r.t	19%
12	----	1.5	r.t	38%
13	----	2	r.t	43%
14	1.3	----	0 °C.	61%

Table 1: Method Optimization

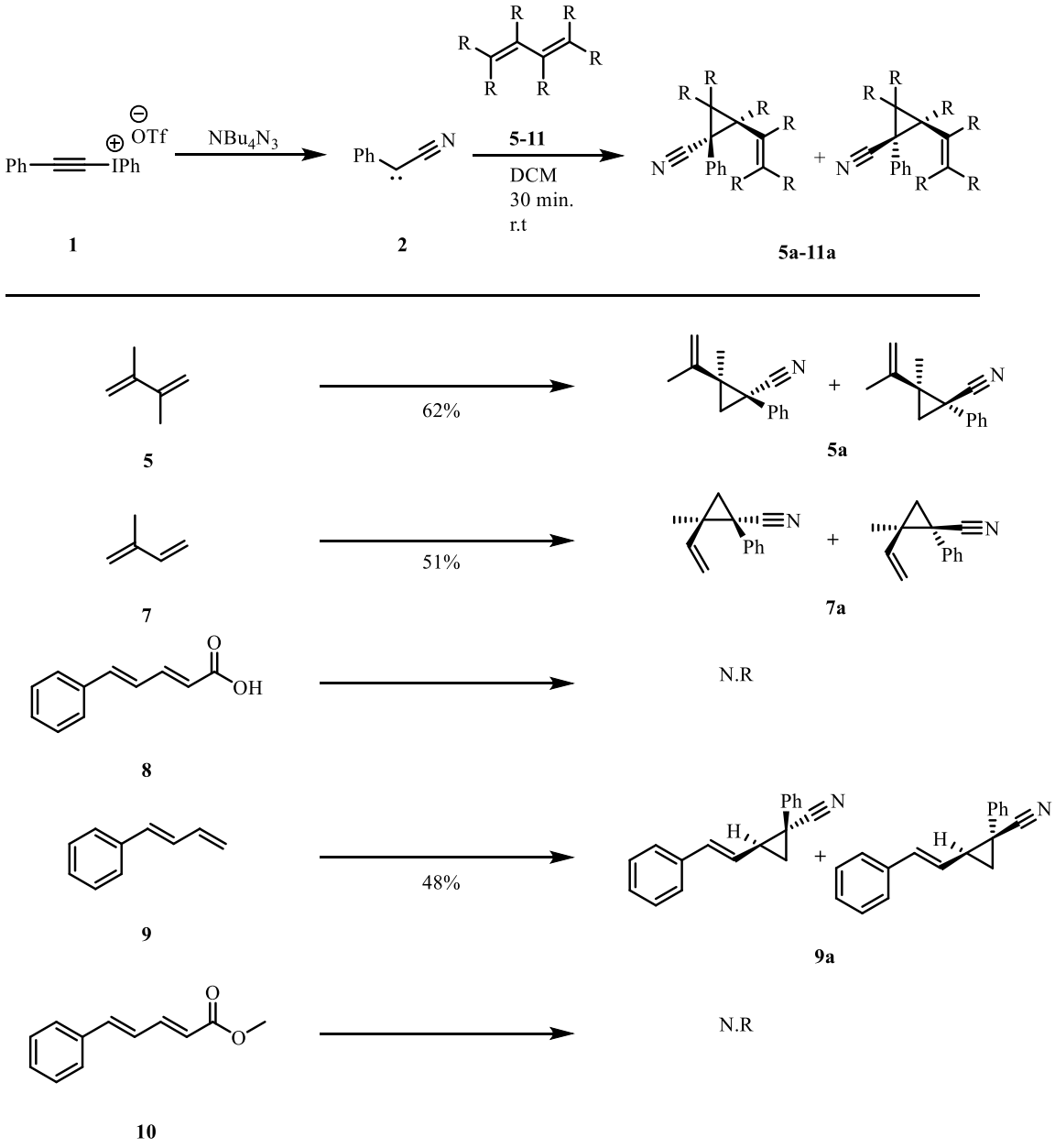
Substrate Scope

Using the optimized method for the [2+1] cycloaddition, a set of readily available substrates were purchased and prepared for testing. Substrates include the aliphatically substituted dienes, dienoic acids and esters, unsaturated aryl dienes and allylic alcohols **(Figure 8)**. Substrates **5**, **7** and **8** were purchased while **9** and **10** were prepared. Diene **9**

was prepared from by palladium catalyzed protodecarboxylation of (2*E*,4*E*)-5-phenylpenta-2,4-dienoic acid.[59] Substrate **10** was prepared by Fischer esterification and reduction of acid **8**.[60]

As expected, **5** and **7** gave [2+1] cycloaddition products. However, contrary to expectation, **7** resulted in cyclopropanation of the sterically hindered olefin. This is contrasted by the cycloaddition product of **9**, which interestingly resulted in cyclopropanation of the terminal, less sterically hindered alkene.

Ester **10** and acid **8** gave complex mixtures with no discernible reaction products as monitored by TLC and crude ^{1}H NMR. This is likely due to the electron withdrawing nature of the carboxylic acid and ester. The resonance delocalization of the, usually electron rich dienes, on to the carbonyl oxygens of both **10** and **8** leave the olefins with less electron density. Naturally, this makes them more electrophilic and thus less likely to participate in the [2+1] cycloaddition.

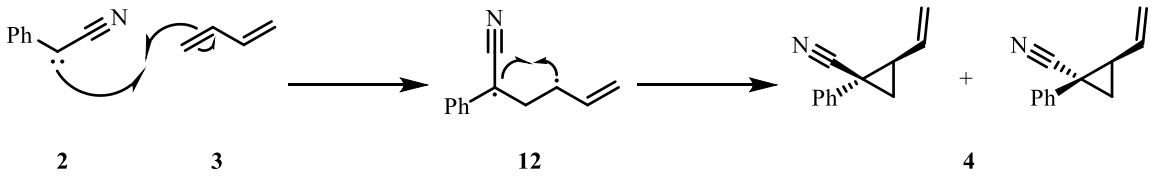


Scheme 19: Substrate Scope

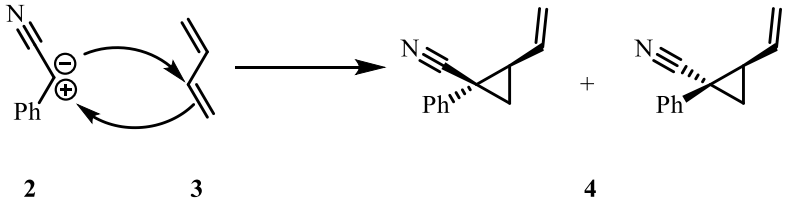
Proposed Mechanism

Now with an understanding of the reactivity that PhHIAT presents, a mechanism can be proposed. It was initially believed that, in the presence of electron rich dienes, the

cyanocarbene intermediate, **2**, behaved in the triplet state (**Scheme 20)**. This would allow for a multistep reaction in which a π bond of the olefin is lysed through a radical process. This leads to the relatively stable benzyl radical intermediate **12**. In the final step, radical recombination would yield the product **4** as a mixture of diastereomers. However, the mixture would be present in both singlet and triplet mechanisms. Interestingly, no [4+1] ring formation is observed and no further reactivity past cyclopropanation is observed. As such a singlet state mechanism was proposed to better accommodate the findings **(Scheme 21)**.



Scheme 20: Triplet Mechanism of Cyclopropanation



Scheme 21: Singlet Mechanism of Cyclopropanation

Within the singlet state mechanism, it is hypothesized that carbene **2** interacts with **3** through a concerted two electron process. This one step mechanism yields a diastereomeric mixture of **4** but does not produce any [4+1] reaction products.

In summation, the process described herein is a novel method for [2+1] cycloadditions using a unique carbene precursor, and unique *in situ* carbene. The potentially singlet carbene lends itself well to such reactions with modest yields, mild conditions, and short time spans. The method allows for a leap in molecular complexity from simple readily available starting materials as shown by its ability to construct new quaternary C-C bonds in modest yields. Further studies with an expanded substrate scope and varied functional groups will be needed and further mechanistic studies would be prudent. Specifically, dienes with cis substituents are needed to further confirm the possibility of a singlet state mechanism. As well, fully substituted or sterically hindered dienes are needed to test the steric components of the reaction. Furthermore, aryl dienes with electron withdrawing and electron donating ring substitutions are attractive candidates for testing the electron limitations of the procedure and potential functional group intolerance.

CHAPTER IV

CONCLUSIONS AND FUTURE WORK

The purpose of this work was to demonstrate the synthetic opportunities that carbenes present and to explore one such method in which [2+1] cycloadditions of dienes were accomplished in a mild, one step reaction using readily available starting materials and an *in situ* cyanocarbene intermediate.

More specifically, a novel carbene precursor discovered by the Croatt group in 2012 has allowed for access to cyanocarbenes, a highly reactive functional group that has shown to be useful in the canonical synthetic carbene reactions. The precursor easily synthesized through reactions between alkynyltin reagents and cyanophenyl iodonium triflate salts has shown to be able to cyclopropanate aromatic groups, insert into O-H bonds, and perform ring expansions. As such it has been an attractive candidate for further study by Croatt and colleagues. To this end, this work seeks to test the reactivity of PhHIAT with dienes and elucidate the mechanism with which it reacts. Using PhHIAT and tetrabutylammonium azide in DCM has shown that the cyanocarbene intermediate is able to cyclopropanate dienes through a potentially singlet process in modest yields.

Future work with PhHIAT is needed to further confirm the singlet state mechanism and test the electronic and steric tolerance of the method. As well, an expanded substrate scope testing a variety of other dienes is an attractive goal

Specifically, cis substituted dienes, sterically hindered dienes, and dienes with varying electron withdrawing and donating groups are attractive candidates.

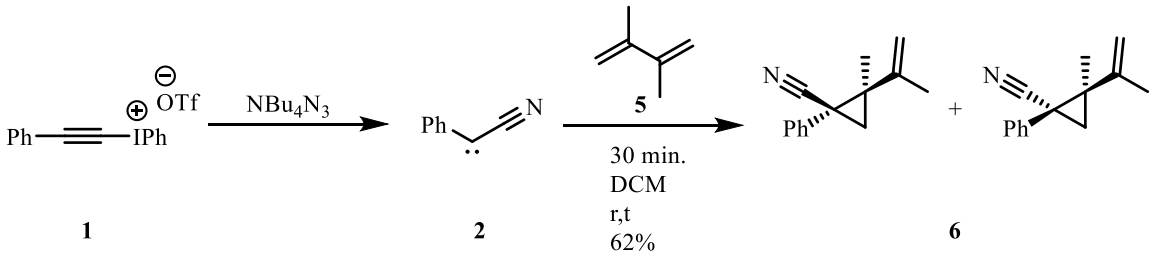
CHAPTER V

EXPERIMENTAL DATA

General Information

All reactions were run in oven dried glassware and under a nitrogen atmosphere. Solvents and reagents were acquired from commercial sources unless otherwise noted and used as received. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL instrument. Coupling constants, *J*, are reported in hertz (Hz) and multiplicities are listed as singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd) and multiplet (m). High Resolution Mass Spectrometry data was acquired on a Thermo Fisher Scientific LTQ Orbitrap XL.

[2+1] Cycloaddition of 2,3-dimethyl-1,3-butadiene

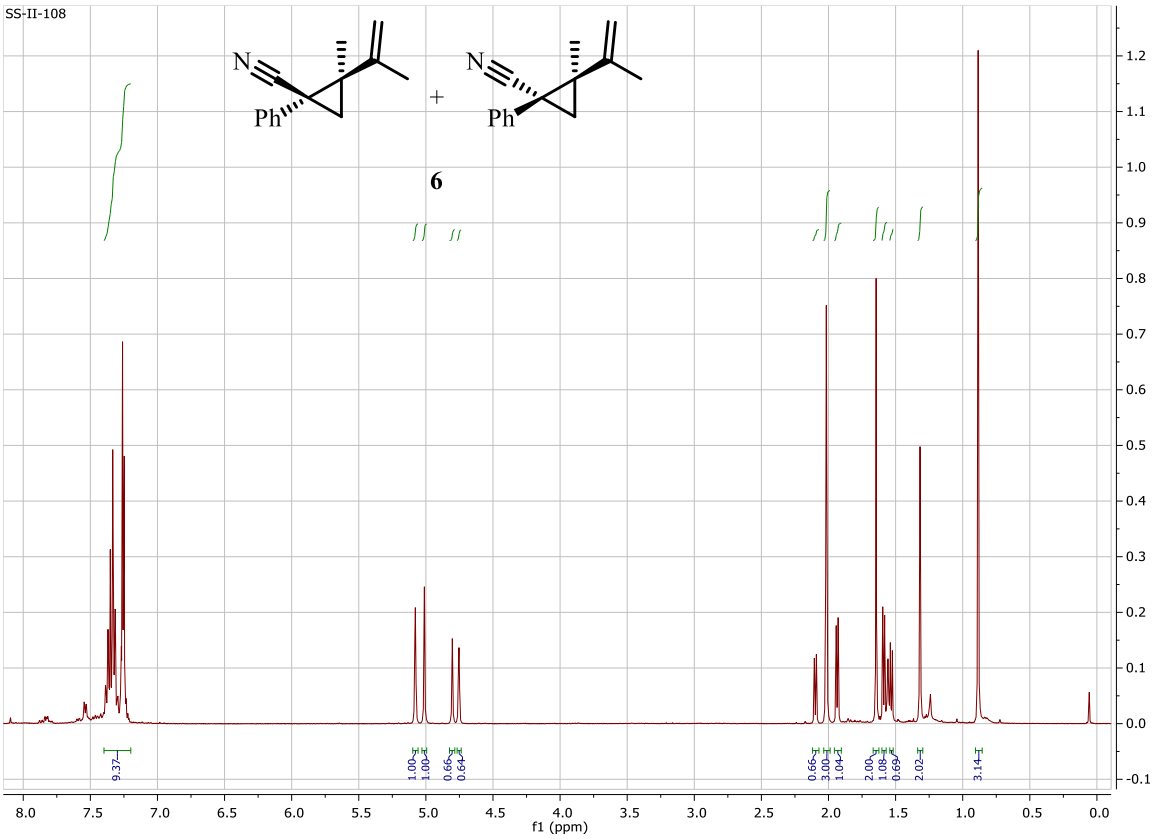


1 **2** **6**

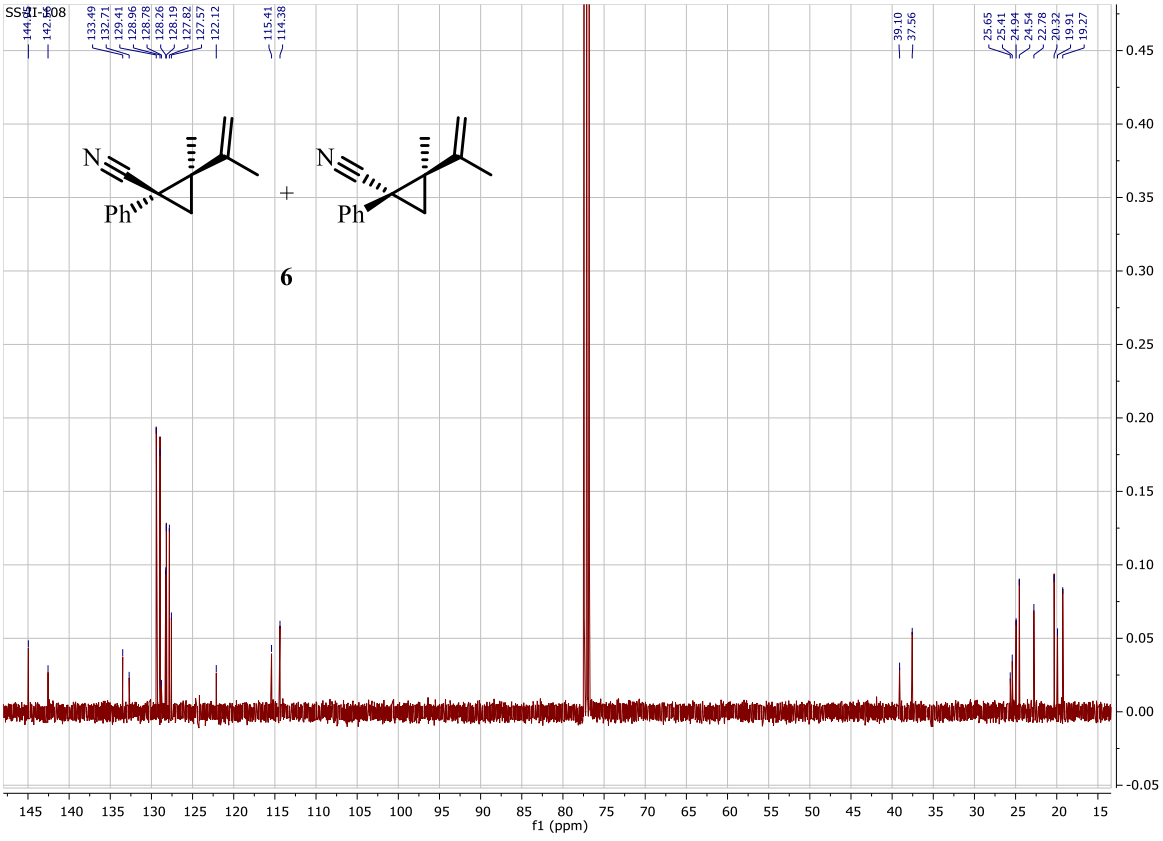
In a microwave vial 2,3-dimethyl-1,3-butadiene (0.050 g, 0.60 mmol) was added followed by tetrabutylammonium azide (0.225 g, 0.79 mmol) and PhHIAT (0.359 g, 0.79 mmol), each independently dissolved in a total of 6 ml of DCM and added simultaneously. The reaction was left to stir at room temperature for 30 minutes at which point the solvent and excess reagents were evaporated under reduced pressure. The crude mixture was then purified through column chromatography to yield a yellow oil (0.074 g, 62% yield, dr = 3:2) **6**, as a mixture of major and minor diastereomers. Integrations of minor compound peaks reported on spectra are relative to the major diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 - 7.23 (m, 10H, major and minor), 5.07 (s, 1H, major), 5.01 (s, 1H, major), 4.80 (s, 1H, minor), 4.75 (s, 1H, minor), 2.10 (d, *J* = 5.7 Hz, 1H, minor), 2.02 (s, 3H, major), 1.93 (d, *J* = 5.7 Hz, 1H, major), 1.64 (s, 3H, minor), 1.59 (d, *J* = 5.7 Hz, 1H, major), 1.53 (d, *J* = 6.0 Hz, 1H, minor), 1.31 (s, 3H, minor), 0.88 (s, 3H, major). **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 144.9 (1C), 142.7 (1C), 133.5 (1C), 132.7 (1C), 129.4 (1C), 128.9 (1C), 128.2 (2C), 128.1 (2C), 127.8 (1C), 127.5 (1C), 115.4 (1C), 114.3 (1C), 39.1 (1C), 37.5 (1C), 25.6 (1C), 25.4 (1C), 24.9 (1C), 24.4 (1C), 22.7 (1C), 20.2 (1C), 19.9 (1C), 19.2 (1C).

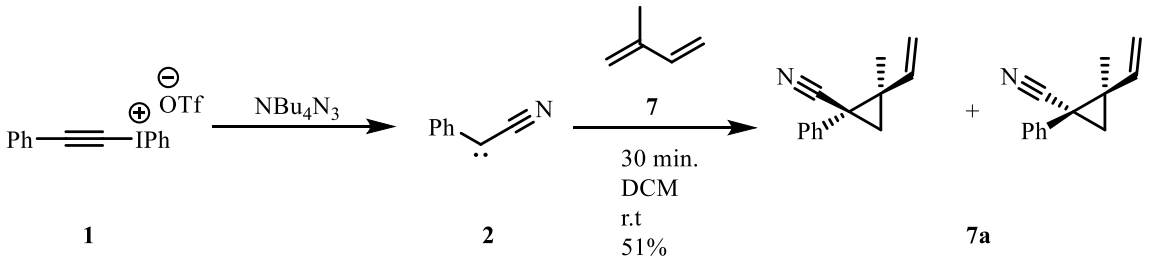
^{1}H NMR for the [2+1] Cycloaddition of 2,3-Dimethyl-1,3-butadiene



^{13}C NMR for the [2+1] Cycloaddition of 2,3-Dimethyl-1,3-butadiene

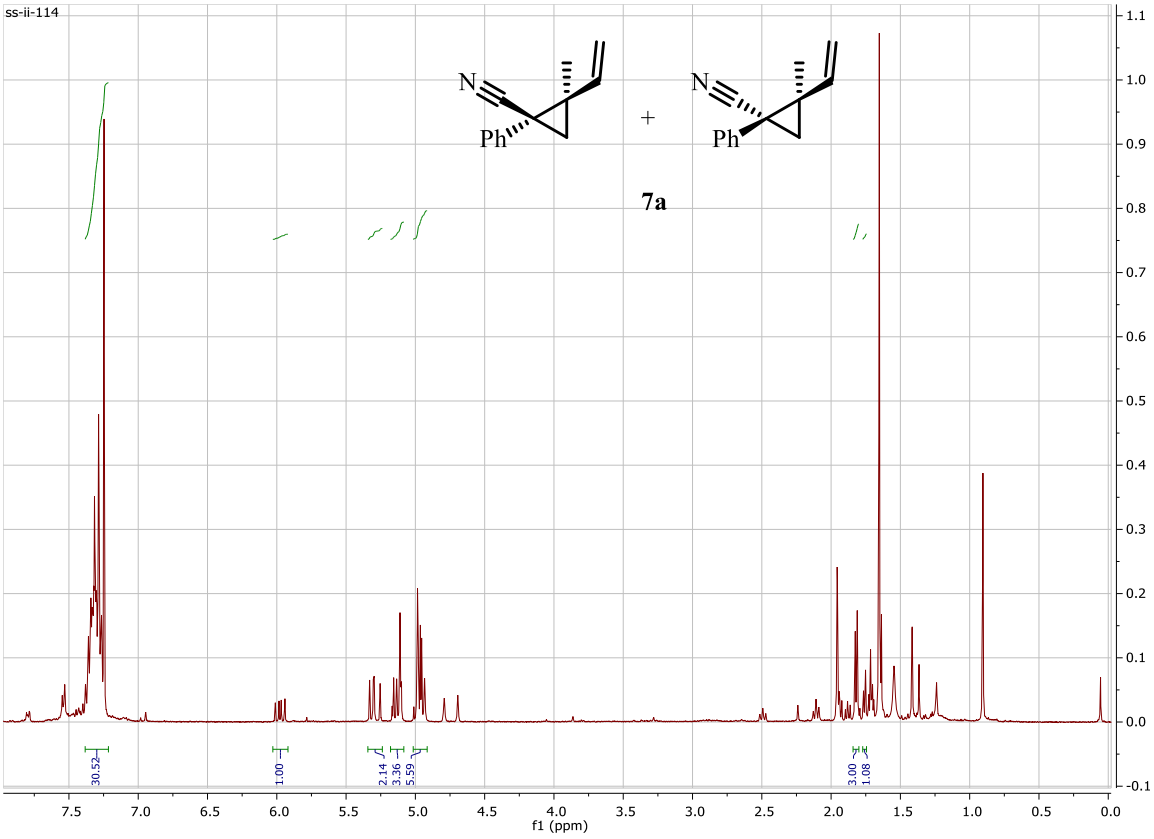


[2+1] Cycloaddition of Isoprene

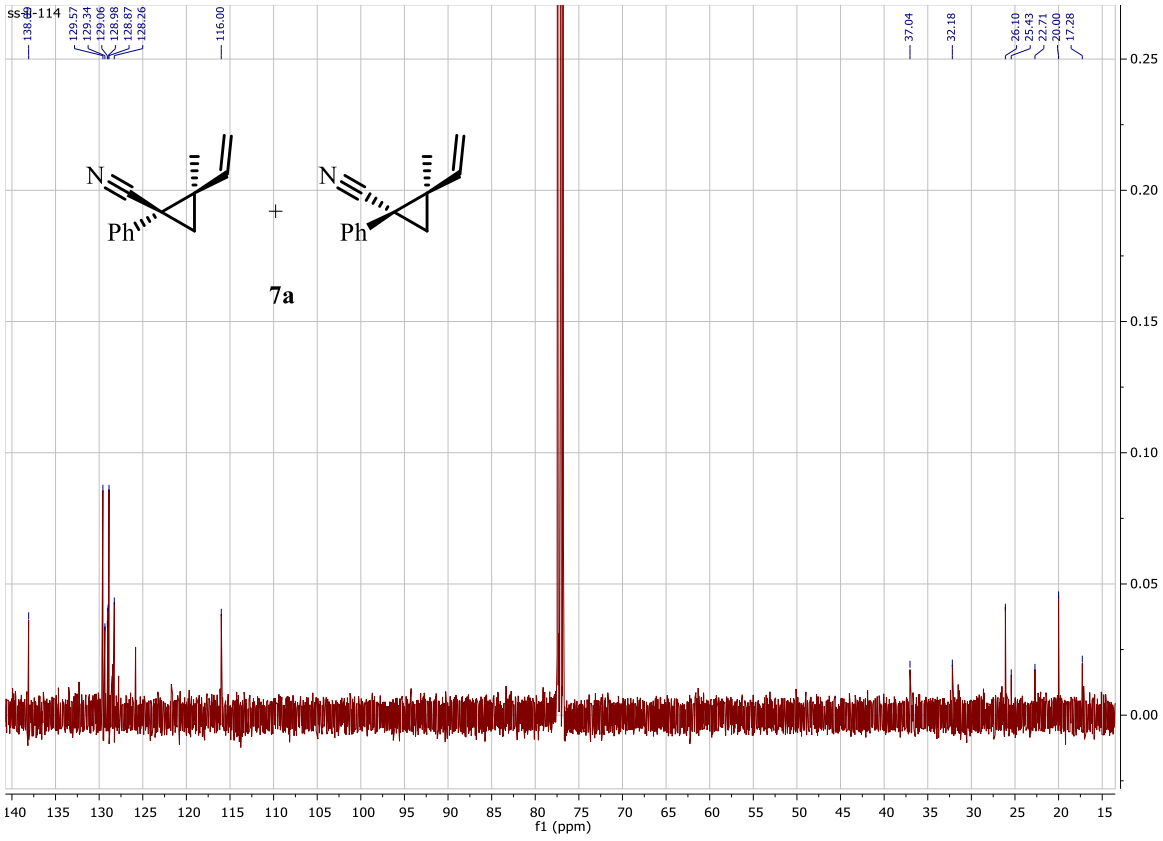


In a microwave vial isoprene (0.025 g, 0.36 mmol) was added followed by tetrabutylammonium azide (0.135 g, 0.47 mmol) and PhHIAT (0.217 g, 0.47 mmol), each independently dissolved in a total of 4 ml of DCM and added simultaneously. The reaction was left to stir at room temperature for 30 minutes at which point the solvent and excess reagents were evaporated under reduced pressure. The crude mixture was then purified through column chromatography to yield a yellow oil (0.034 g, 51% yield, dr = 2:1) **7a**, as a mixture of major and minor diastereomers. NMR spectra of the product mixture was inconclusive and further purification and characterization is required. .**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.40 - 7.23 (m, 10H, major and minor), 5.98 (dd, *J* = 10.6, 17 Hz, 1H, minor), 5.29 (dd, *J* = 10.6, 13.2 Hz, 1H, major), 5.17 – 5.10 (m, 2H), 5.01 – 4.93 (m, 2H), 1.82 (d, *J* = 5.7 Hz, 1H, major), 1.76 (d, *J* = 5.7 Hz, 1H, minor) 1.65 (s, 3H, major), 0.90 (s, 3H, minor). **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 138 (1C), 129.5 (2C), 129.3 (2C), 129.0 (2C), 128.9 (2C), 128.8 (1C), 128.2 (1C), 115.9 (1C), 37.0 (1C), 32.1 (1C), 26.1 (1C), 25.2 (1C), 22.7 (1C), 20.0 (1C), 17.2 (1C).

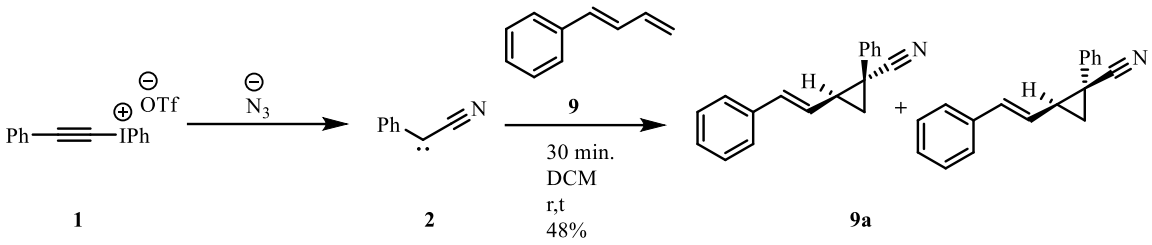
^{1}H NMR for the [2+1] Cycloaddition of Isoprene



^{13}C NMR for the [2+1] Cycloaddition of Isoprene



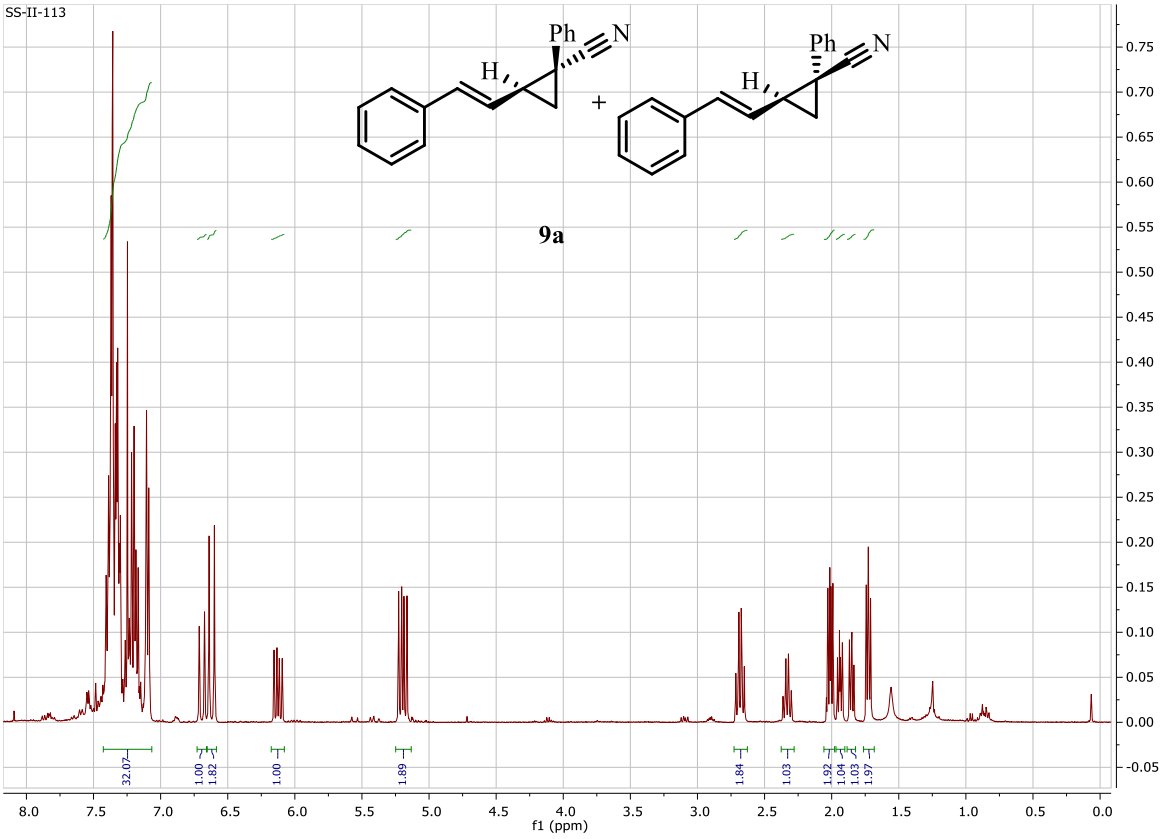
[2+1] Cycloaddition of (*E*)-1-Phenyl-1,3-butadiene



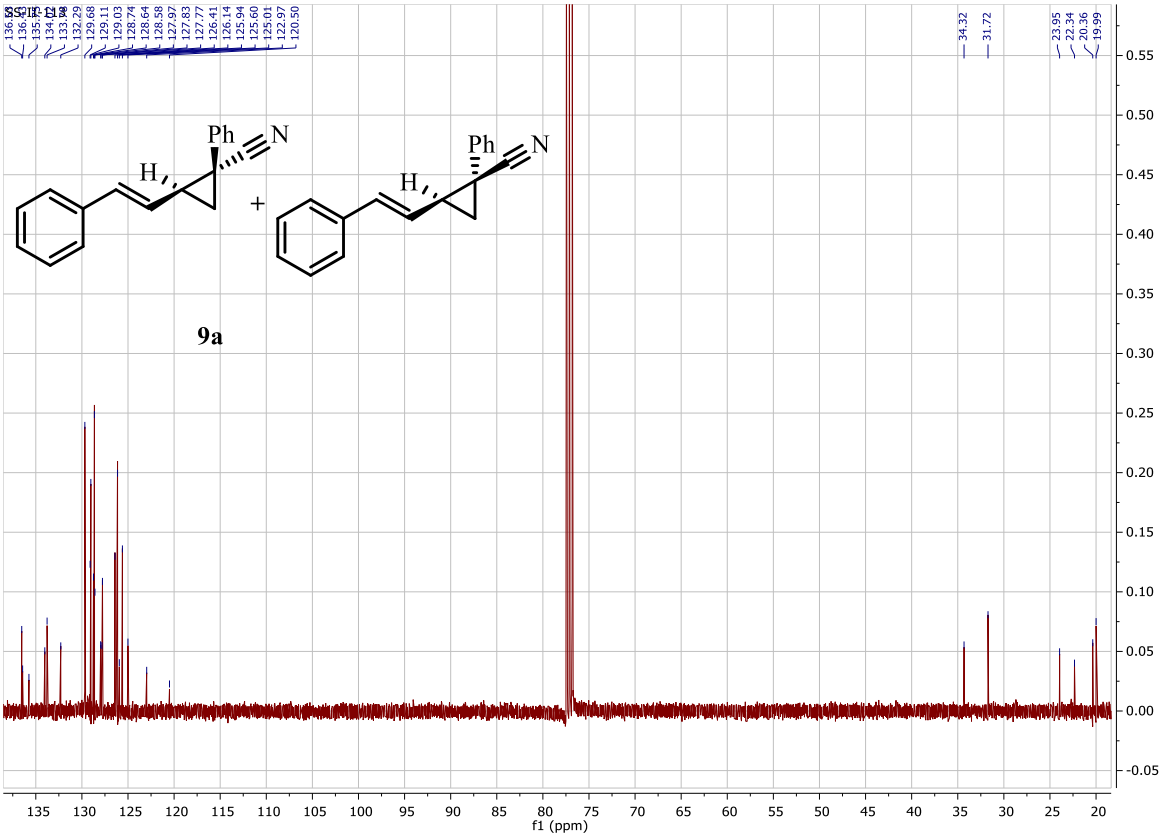
1 2 9a

In a microwave vial (*E*)-1-phenyl-1,3-butadiene (0.032 g, 0.25 mmol) was added followed by tetrabutylammonium azide (0.092 g, 0.32 mmol) and PhHIAT (0.146 g, 0.32 mmol), each independently dissolved in a total of 3 ml of DCM and added simultaneously. The reaction was left to stir at room temperature for 30 minutes at which point the solvent and excess reagents were evaporated under reduced pressure. The crude mixture was then purified through column chromatography to yield a yellow oil (0.029 g, 48% yield, dr = 9:5) **9a**, as a mixture of major and minor diastereomers.**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.43 - 7.08 (m, 20H, major and minor), 6.69 (d, *J* = 15.5 Hz, 1H, minor), 6.62 (d, *J* = 15.8 Hz, 1H, major), 6.12 (dd, *J* = 8.7, 15.7 Hz, 1H, minor), 5.18 (dd, *J* = 9.0, 15.8 Hz, 1H, major), 2.69 (ddd, *J* = 7.0, 9.1, 16.1 Hz, 1H, major), 2.33 (ddd, *J* = 8.4, 16.2 Hz, 1H, minor), 2.01 (dd, *J* = 5.8, 9.1 Hz, 1H, major), 1.94 (dd, *J* = 5.9, 8.6 Hz, 1H, minor), 1.85 (dd, *J* = 6.1, 7.3 Hz, 1H, minor), 1.72 (dd, *J* = 6.1, 6.7 Hz, 1H, major). **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 136.5 (1C), 136.4 (1C), 135.7 (1C), 133.9 (1C), 133.7 (2C), 132.2 (2C), 129.6 (2C), 129.1 (2C), 129.0 (2C), 128.7 (2C), 128.6 (1C), 128.5 (1C), 127.9 (1C), 127.8 (1C), 127.7 (1C), 126.3 (1C), 126.1 (2C), 125.9 (2C), 125.5 (1C), 125.0 (1C), 122.9 (1C), 120.5 (1C), 34.3 (1C), 31.7 (1C), 23.9 (1C), 22.3 (1C), 20.3 (1C), 19.9 (1C).

^{1}H NMR for the [2+1] Cycloaddition of (*E*)-1-Phenyl-1,3-butadiene



^{13}C NMR for the [2+1] Cycloaddition of (*E*)-1-Phenyl-1,3-butadiene



REFERENCES

1. Trost, B. M.; Li, C. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *36*, 13197-13202.

2. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res*. **2008**, *41*, 40-49.

3. Nicolaou, K. C.; Hale, C. R. H.; Nilewski, C.; Ioannidou, H. A. *Chem. Soc. Rev.* **2012**, *41*, 5185-5238.

4. Nicolaou, K. C.; Yang, Z.; Liu, J.; Ueno, H.; Nantermet, P.; Guy, R.; Claiborne, C.; Renaud, J.; Couladouros, E.; Paulvannan, K.; Sorensen, E. *Nature*. **1994**, *367*, 630-634.

5. Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*. VCH: 1996. 655-672.

6. Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc*. **1944**, *66*, 849-849.

7. Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc*. **1983,** *105*, 624-625.

8. Nicolaou, K. C. *Isr. J. Chem.* **2018**, *58*, 104-113.

9. Levitt, M, *J. Magn. Reason.* **2019**, *306*, 69-74.

10. Turro, N. *J. Chem. Educ.* **1969**, *46*, 2-6.

11. Skell, P.; Woodworth, R. *J. Am. Chem. Soc.* **1956**, *78*, 4496-4497.

12. Gilchrist, T. L.; Capon, B.; Rees, C. W.; In *Organic Reaction Mechanisms Series*. Wiley: 1973. 369-388.

13. Buchner, E.; Feldmann, L. *Ber. Dtsch. Chem. Ges*. **1903**, *36*, 3509-3517.

14. Staudinger, H.; Kupfer, O. *Ber. Dtsch. Chem. Ges*. **1912**, *45*, 501-509.

15. Doering, W. E.; Hoffman, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162-6165.

16. Bradley, J. N.; Cowell, G. W.; Ledwith, A. *J. Chem. Soc.* **1964**, 353-357.

17. Liu, M.; Chishiti, N.; Tencer, M.; Tomioka, H.; Izawa, I. *Tetrahedron*. **1984**, *40*, 887-892.

18. Akasaka, T.; Liu, Y.; Niino, Y.; Maeda, T.; Wakahara, M.; Okamura, K.; Nagase, S. *J. Am. Chem. Soc.* **2000**, *122*, 7134-7135.

19. Bradley, G.; Brian, W.; Evnas, L.; Stevens, I. *J. Chem. Soc*. **1977**, *2*, 1214-1220.

20. Liu, M. *Chem. Soc. Rev.* **1982**, *11*, 127-140.

21. Liu, M.; Elson, C. *J. Chem. Soc.* **1982**, *7*, 415-416.

22. Grasse, P.; Brauer, B.; Zupancic, J.; Kaufmann, K.; Schuster, G. *J. Am. Chem. Soc.* **1983**, *105*, 6833-6845.

23. Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726.

24. Bertrand, G.; Gabbai, F.; Guerret, O.; Bourissou, D. *Chem. Rev*. **2000**, *100*, 39-92.

25. Tomioka, H.; Itoh, T.; Nakata, Y.; Hirai, K. *J. Am. Chem. Soc.* **2006**, *128*, 957-967.

26. Glorius, F.; Hopkinson, M.; Richter, C.; Schedler, M. *Nature*. **2014**, *510*, 485-496.

27. Wanzlick, H. *Angew. Chem. Int. Ed*. **1962**, *1*, 75-80.

28. Hoffman, R.; Gleiter, R. *J. Am. Chem. Soc*. **1968**, *90*, 5457-5460.

29. Wanzlick, H.; Schonherr, H. *Liebigs Ann. Chem*. **1970**, *731*, 176-179.

30. Arduengo, A.; Harlow, R.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361-363.

31. Huynh, H. In *The Organometallic Chemistry of N-heterocyclic Carbenes*. Wiley: 2017. 17-51

32. Boehme, C; Frenking, G. *J. Am. Chem. Soc.* **1996**, *118*, 2039-2046.

33. Bertrand, G.; Igau, A.; Grutzmacher, A. *J. Am. Chem. Soc.* **1988**, *110*, 6463-6466.

34. Caballero, A.; Perez, P. *Chem. Eur. J.* **2017**, *23*, 14389-14393.

35. Moss, G. P.; Smith, P.; Tavernier, D. *Pure Appl. Chem*. **1995**, *67*, 1307-1375.

36. Fischer, E.; Maasbol, A. *Angew. Chem. Int. Ed*., **1964**, *3*, 580.-581.

37. Schrock, R. *J. Amer. Chem. Soc*. **1975**, *97*, 6578-6579.

38. Wulff, W. *Metal-Carbene Cycloadditions' in Comprehensive Organic Synthesis*, Wiley-Interscience:New York, 1988. 951-997.

39. Charette, A. *J. Am. Chem. Soc*. **2001**, *123*, 11829-11830.

40. Hodgson, D.: Chung, Y.; Paris, J. *J. Am. Chem. Soc*. **2004**, *126*, 8664-8665.

41. Dechouxa, L.; Agamia, C.; Dorisb, E.; Mioskowski, C. *Tetrahedron.* **2003**, *59*, 9701-9706.

42. Hodgson, D.; Gras, E. *Synthesis* **2002**, *12*, 1625-1642.

43. Fedoryński, M. *Chem. Rev*. **2003**, *103*, 1099-1132.

44. Skell, P.; Garner, A. *J. Am. Chem. Soc*. **1956**, *78*, 3409-3411.

45. Brookhart, M.; Studabaker, W. *Chem. Rev*. **1987**, *87*, 411-432.

46. Simmons, H.; Smith, R. *J. Am. Chem. Soc*. **1959**, *81*, 4256-4264.

47. Takakis, I.; Rhoades, Y. *J. Org. Chem.* **1978**, *43*, 3496-3500.

48. Cohen, T.; Kosarych, Z. *J. Org. Chem.* **1982**, *47*, 4005-4008.

49. Doering, W. E.; Buttery, R. G.; Laughlin, R. G.; Chaudhuri, N. *J. Am. Chem. Soc.* **1956**, *78*, 3224-3227.

50. Doyle, M.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev*. **2010**, *110*, 704-724.

51. Demonceau, A.; Noels, A.; Hubert, A.; Teyssié, P. *J. Chem. Soc*. **1981**, *14*, 688-689.

52. Doyle, M.; Westrum, L,; Wolthius, W.; See, M.; Boone, W.; Bagheri, V.; Pearson, M. *J. Am. Chem. Soc*. **1993**, *115*, 958-964.

53. Grundmann, C. *Liebigs Ann. Chem*. **1938**, *536*, 29-36.

54. Barluenga, J.; Sáa, D.; Gómez, A.; Ballesteros, A.; Santamaría, J.; Prado, A.; Tomás, M.; Suárez-Sobrino, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 6321-6324.

55. Banert, K.; Hagedorn, M; Wutke, J.; Ecorchard, P.; Schaarschmidt, D.; Lang, H. *Chem. Commun*, **2010**, *46*, 4058-4060.

56. Hyatt, I. F. D.; Croatt, M. P. *Angew. Chem. Int. Ed.* **2012**, *124*, 7629-7632.

57. Hyatt, I. F. D.; Nasrallah, D. J.; Maxwell, M. A.; Hairston, A. C. F.; Abdalhameed, M. M.; Croatt, M. P. *Chem. Commun*. **2015**, *51*, 5287–5289.

58. Al-Huniti, M. H.; Sullivan, Z. B.; Stanley, J. L.; Carson, J. A.; Hyatt, I. F. D.; Hairston, A. C.; Croatt, M. P. *J. Org. Chem*. **2017**, *82*, 11772-11780.

59. Al-Huniti, M. H.; Perez, M. A.; Garr, M. K.; Croatt, M. P. *Org. Lett*. **2018**, *20*, 7375-7379.

60. Huang, Y.; Fananas-Mastral, M.; Minaard, A.; Feringa, B. *Chem. Commun.* **2013,** *49*, 3309-3311.