Progress toward Studying the Intramolecular Cyclization of a Carbene

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A carbene is a carbon bonded to only two other atoms and has two unshared electrons. Carbenes are neutral molecules, with a formal charge of zero.[1,2] Carbenes are short-lived, highly reactive species[3] and most, in fact, are only stable in frozen matrices of solid argon at 77 K.[2]

Methylene, the simplest carbene (CH_2), is the model for the theoretical chemistry of carbenes and therefore is used to describe characteristics of the molecules. There are two possible electronic states for methylene, a singlet state and a triplet state. The two states have different energies, reactivities, and lifetimes, under different conditions.[1]

Singlet states have nonbonding electrons with their spins paired.[1] They are located in a single orbital so the second orbital is vacant (Figure 1). These two qualities allow singlet state carbenes to have a carbon atom that resembles both a carbocation (a positively charged carbon with three substituents for a total of six electrons in its valence shell[3]) and a carbanion (a negatively charged carbon with three substituents and an unshared pair of electrons for a total of eight valence electrons in its valence shell[3]).[2] Triplet states on the other hand, have the two electrons in separate non-bonded orbitals with unpaired spins (Figure 1). Triplet states represent diradicals.[2]

Figure 1[1,2]

Singlet State **Triplet State**

It has been determined that for methylene, the lowest energy state is the triplet and the singlet state has a higher energy state.[1] The triplet state is more stable than the singlet state in methylene because of Hund's Rule[2] which explains that a greater total

spin state usually makes the resulting atom more stable, because it forces the unpaired electrons to reside in different special orbitals.[3] The energy difference between a singlet and triplet state for a carbene is called the singlet-triplet gap.[2]

While generally hydrocarbon carbenes are the most stable in triplet states, substituents on singlet state carbenes can make them more stable. For example, single state carbenes with electron-donating or electron-withdrawing substituents can be notably more stable than triplet state forms.[2]

The structures of singlet and triplet carbenes also vary. Singlet carbenes have close to 90° angles with unshared electrons located in an orbital with strong *s*-character. The triplet carbenes have close to linear arrangements, having 137° angles (Figure 2).[2]

Figure 2[2]

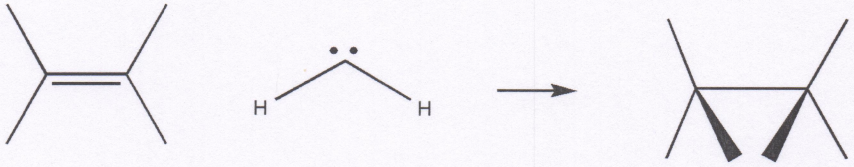
~90° angle **~137° angle**

As stated before methylene is a paradigm for carbenes. The same principles apply to other carbenes, but with some additional considerations.[1]

There are important differences in reactions of singlet and triplet carbenes. As previously stated, singlet states have an empty *p*-orbital (like a carbocation) and a non-bonding pair of electrons (like a carbanion) and therefore have carbocation and carbanion characteristics. Triplets have diradical character.

One major reaction carbenes undergo is cycloaddition with double bonds (Figure 3). This procedure is extremely useful to form polycyclic molecules, as they are quite difficult to synthesize otherwise.[2]

Figure 3[1]



Singlet carbenes add stereospecifically; a *cis*-alkene will give only a *cis*-cyclopropane and likewise a *trans*-alkene will only give a *trans*-cyclopropane.[1] In other words, the cyclopropanes retain the geometries of the alkenes (Figure 4a). Furthermore, a singlet can add in one step (Figure 4b).[1]

Figure 4a[1]

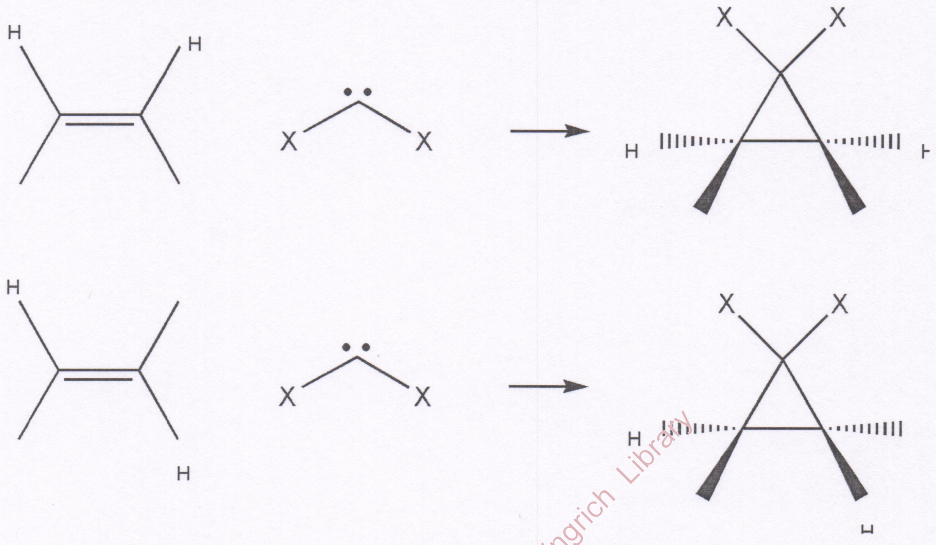
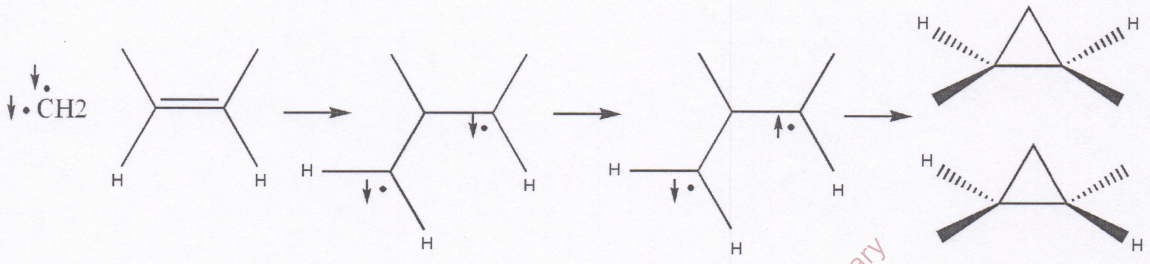


Figure 4b[1]

Singlet carbenes prefer to add to alkenes substituted with electron-donating groups.[2]

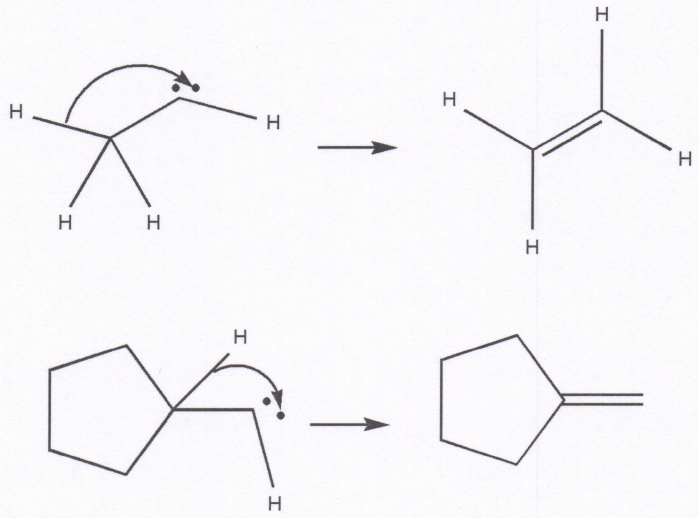
Triplet carbenes do not add stereospecifically to alkenes; the products are a mixture of isomers.[1] Unlike singlet carbenes, triplet carbenes cannot add to alkenes in one step. If there was only one step, there would be a very high energy state of a σ bond due to the two unpaired electrons in the single σ bond. Triplet state carbenes instead add first to form a diradical. Intersystem crossing between the singlet and triplet forms often occurs quicker than other reactions of triplets when there is a small singlet-triplet gap. The diradicals undergo this intersystem crossing to singlets, the electron spins pair up, and finally close to form cyclopropanes (Figure 5). In time, there may be rotation around the single bonds to give a mixture of isomers.[1,2]

Figure 5[1,2]



Another common reaction of carbenes is a 1,2-hydrogen migration to form alkenes (Figure 6). This reaction is frequent in singlet carbenes (The activation energy for hydrogen shifts is approximately 1 kcal/mol), but practically unknown in triplet carbenes because they do not have an empty *p*-orbital.[2]

Figure 6[2]

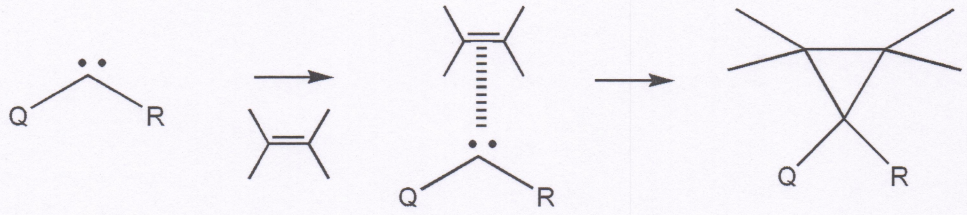


The extent of the reactions depends on the structure and electronic state of the carbene. Alkyl and dialkyl carbenes undergo such rapid *intra*molecular reactions that *inter*molecular reactions often cannot compete with the rearrangements to alkenes.[1,2]

The detailed mechanism of obtaining the three products, cyclopropanes, *cis*-alkenes and *trans*-alkenes, is highly debated. The idea debated is whether or not there are intermediates involved in the reactions. These mechanistic studies involve bimolecular reactions starting with the diazirine and an alkene trap. These reactions are said to be either stepwise, which involve an intermediate, or concerted. In the case of the 1,2-hydrogen migration reaction, it can also proceed stepwise with a carbine intermediate or concerted with the loss of nitrogen from the diazirine. Much effort and research has been made to look at the bimolecular cycloaddition. With halocarbenes, not much has been done with intramolecular cycloaddition.

In the cycloaddition reaction, it is suggested that a carbene-olefin complex is the intermediate to the cyclopropane product (Figure 7).

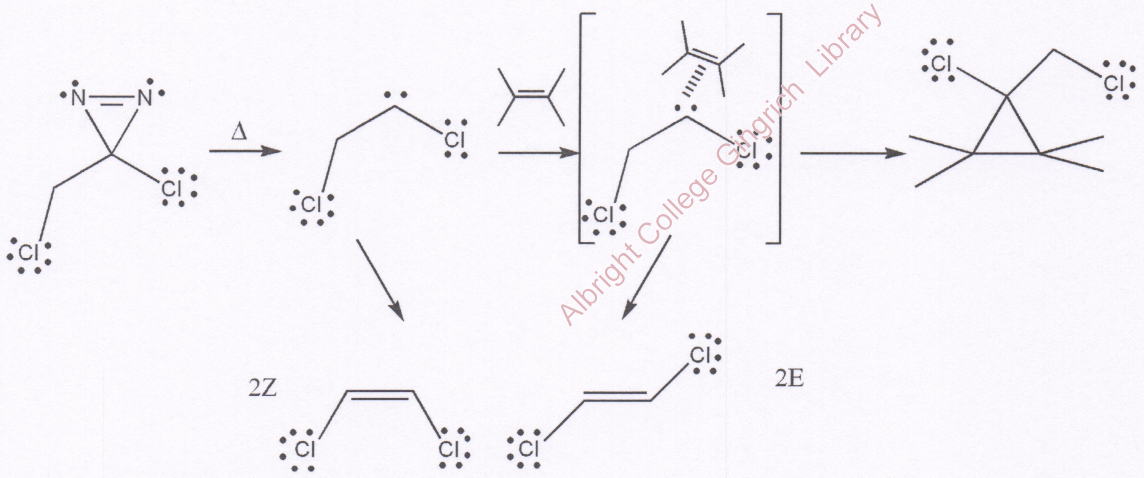
Figure 7[4]



From Figure 7 above, you can see that the generated carbene was trapped with tetramethylethylene (TME) to form the cyclopropane product.[4] This trapping process, however, does not proceed alone. This process competes with the 1,2-hydrogen shift to form Z and E alkene products.[4]

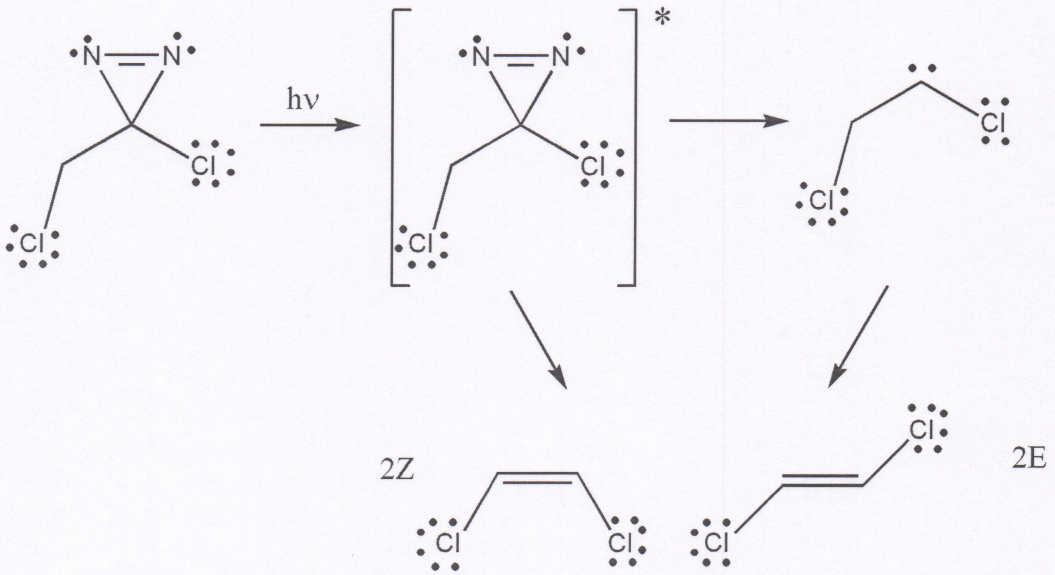
The Z:E ratio of the alkene products is dependent upon the presence of the TME trap.[5] It has been found that the selectivity of the reaction (producing the Z and E alkene) decreases when TME is in excess. Because the amount of trap affects the Z:E alkene ratio, the following reaction pathway is suggested (Figure 8). There is still much debate on these mechanisms; it is hoped our work here will help verify which one is occurring.

Figure 8[5]



The excited state of the diazirine from the photochemical reaction can account for another pathway with a rearrangement of products (Figure 9).[5] This step shows the stepwise and concerted paths from the diazirine.

Figure 9[5]

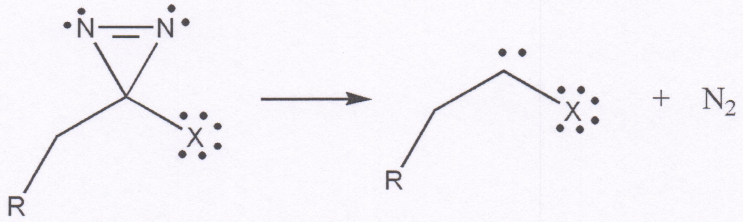


I hope to determine how a bromocarbene will react by intramolecular reactions. This will be found from studying the ratio of hydrogen migration products, *cis*- and *trans*-bromoalkenes, relative to cyclopropane products. A bromodiazirine has been chosen because it is different than a chlorodiazirine, and comparative results can later be studied to determine the differences due to the different halogens. It is not yet clear how substituents (chloro- vs. bromo-) will determine the ratio of products, nor how geometry (cyclohexene vs. a chain alkene) will affect the ratio (Syntheses A and B).

When carbenes are immediately formed, they are in the singlet state, and bromocarbenes are expected to be in the singlet state. There are several ways to generate carbenes. In the end, the main idea is to eliminate two bonds from a tetravalent carbon

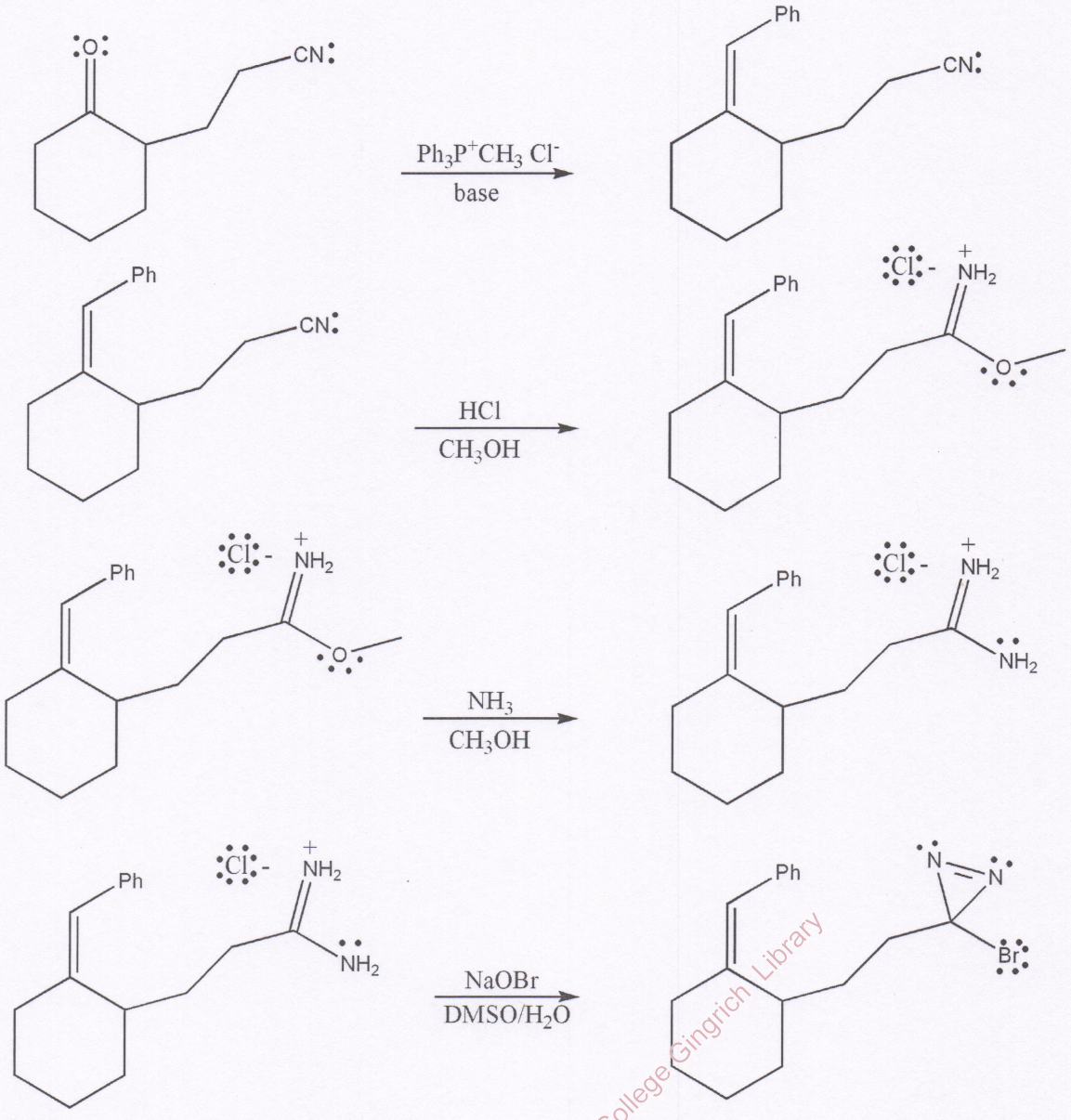
atom. Reactive carbenes can be formed from diazarines, when the diazirine loses N_2 [10] (Figure 10).

Figure 10

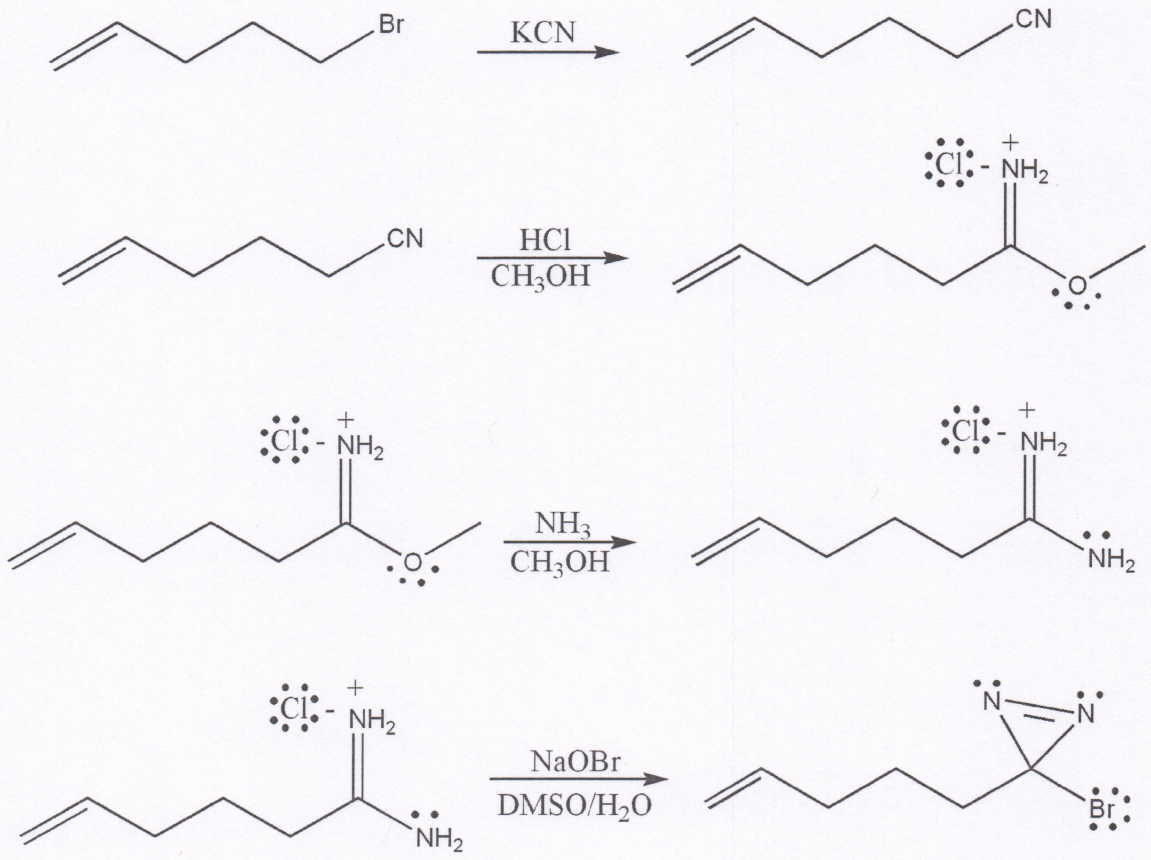


I chose two, four step synthesis pathways to create a diazirine. Synthesis A starts with a Wittig reaction and Synthesis B starts with a substitution reaction. The second, third, and forth steps are the same for both pathways.

Synthesis A



Synthesis B



From the final product of a diazirine, a carbene will be synthesized and studied. The reaction involving the carbene will produce a mixture of products, a *cis*- and *trans*-alkene from hydrogen-migration and a bicyclic ring, from cycloaddition. Figures 11A and 11B below show the steps of the diazirine to a carbene and then into the mixture of products.

Figure 11A

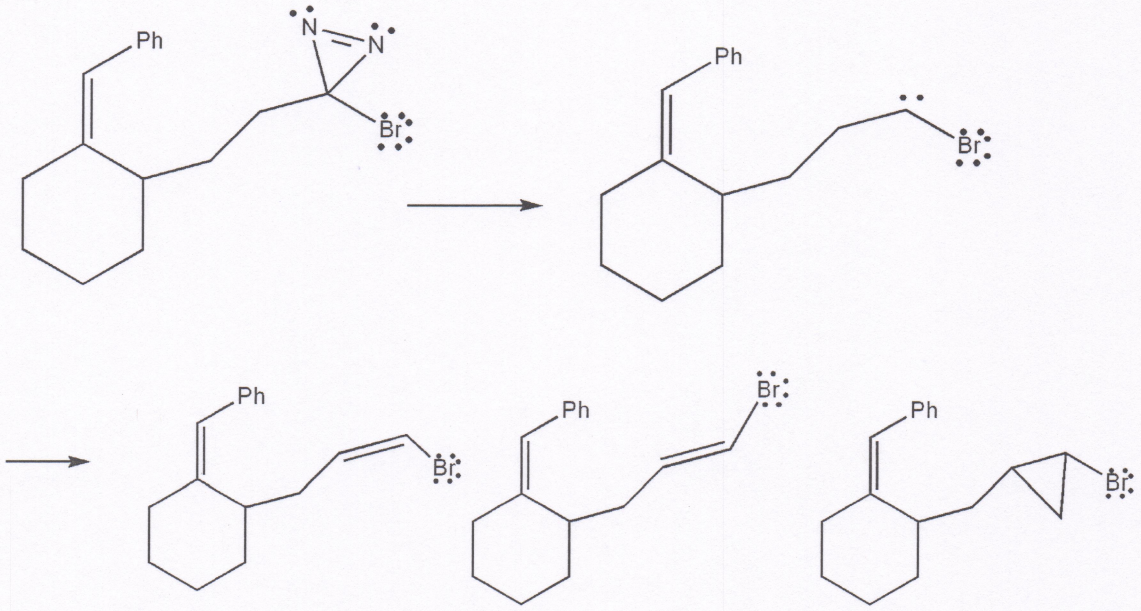
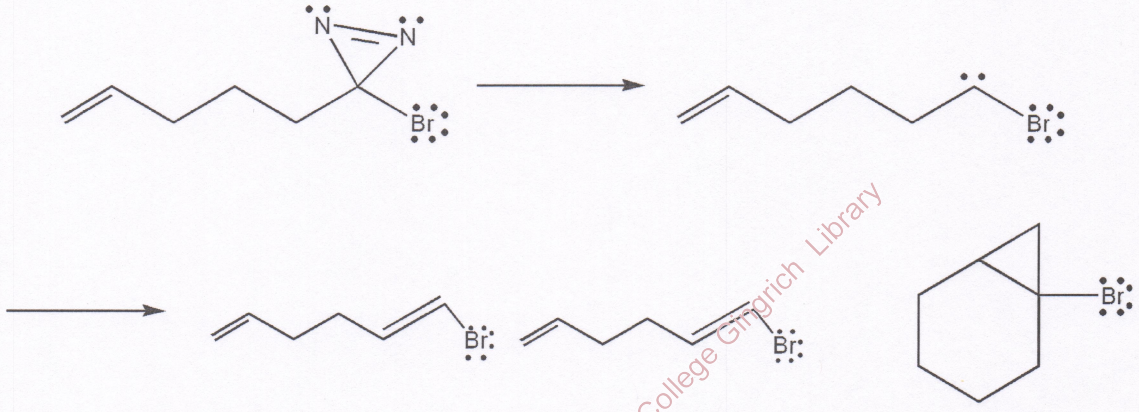


Figure 11B

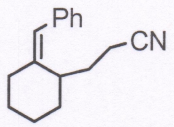


Experimental Section

Reagents were obtained from commercial sources. Chemicals were used as received. Methanol was dried and used for the synthesis of methyl 5-hexeneimidate hydrochloride. To dry methanol, magnesium turnings (2.0 g) and iodine (0.2 g) were added to a 250 mL round-bottom flask. Methanol (25 mL, 0.618 mol) was added and the mixture was heated under reflux until the iodine color disappeared and the magnesium

was converted to magnesium methoxide (a white powder). Methanol (25 mL, 0.618 mol) was added again once the methoxide started to form. Iodine (0.2 g) was added to initiate the reaction.[6] ^{1}H-NMR and IR spectra were used to study the starting material of the complete synthesis, and to characterize the products of each step. The IR used was a Perkin-Elmer Spectrum One FT-IR spectrophotometer and the NMR used was a Varian Unity Inova 300 MHz.

Attempt at the synthesis of 2-(β-cyanoethyl)-benzylidenecyclohexane[7]



Sodium hydroxide (5.044 g, 0.126 mol) was added to deionized water (5 mL) in a small beaker. Dichloromethane (10 mL) was added to a 50-mL round-bottom flask. 2-(β-Cyanoethyl)-cyclohexanone (1 mL, 9.76 mmol) and benzyltriphenylphosphonium chloride (3.804 g, 9.78 mmol) was added to the 50-mL round-bottom flask with a stir bar. The mixture heated until it refluxed gently. The prepared sodium hydroxide solution was added dropwise while stirring. Mixture stirred under gentle reflux for 30 min. TLC in 1:1 v:v hexanes:ethyl acetate was preformed.

The reaction mixture was cooled to room temperature and transferred to a separatory funnel. The round-bottom flask was rinsed with dichloromethane (5 mL) and transferred to the funnel. The organic layer was washed with deionized water (10 mL). Saturated aqueous sodium bisulfite was prepared by adding excessive sodium bisulfite to deionized water (15 mL) and stirring for 10 min to ensure saturation. The organic layer was washed with the saturated aqueous sodium bisulfite. The organic layer was washed with water (10 mL) until the solution tested neutral with pH paper. The organic solution

was dried over several spatula tips of anhydrous sodium sulfate and stirred for 10 min. The solution was rotary evaporated for 10 min and the solid white powder that remained was transferred into a vial. The neat IR (3100, 1707, 1591, 1484, 1437, 1189, 1115, 1072, 996, 753, 718, 694 cm^{-1}) indicated that a carbonyl was still present.

5-Hexenenitrile[4]

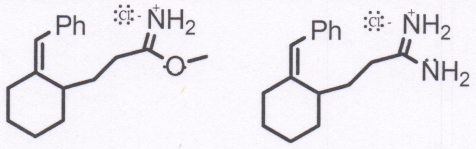
Potassium cyanide (1.346 g, 0.0207 mol) was dissolved in water (5.6 mL, 0.311 mol). The mixture was heated to 60 °C. 5-Bromo-1-pentene (2.57 g, 0.0172 mol) was added to methanol (2.9 mL, 0.0717 mol). This solution was added to the KCN solution. The reaction refluxed over heat overnight.

TLC in 3:1 v:v hexanes:ethyl acetate was preformed. The plate was stained with a solution of $KMnO_4$ (2 g), K_2CO_3 (1 g) and water (100 mL) to visualize the compound on the TLC plate after charring.

The solution was cooled to room temperature and was diluted with water (80 mL). The mixture was washed three times with methylene chloride. The methylene chloride layers were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. The methylene chloride was removed by simple distillation: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.77 (m, 2H), 2.22 (m, 2H), 2.34 (t, J = 6.1 Hz, 2H), 5.12 (t, J = 7 Hz, 2H), 5.74 (m, 1H) ppm.

The synthesis of 5-hexenenitrile was repeated using 2.578 g and 10.46 g 5-bromo-1-pentene. Product yield was 1.61 g (97.9%) and 6.26 g (93. %) respectively. In the repeated syntheses TLC analysis was not performed.

Methyl-5- hexeneimidate hydrochloride[8]
Attempt at the synthesis of 5-Hexeneamidinium hydrochloride[8]



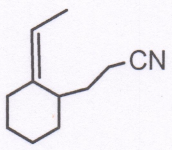
Dried methanol (~30 mL, 0.741 mol) was distilled. 5-Hexenenitrile (prepared 10/11/05-10/20/05) was added and the mixture was cooled with ice. Sulfuric acid was added in portions to sodium chloride to generate hydrogen chloride gas that was bubbled through the solution. When the bubbling stopped, more sulfuric acid was added over the course of 30 min. The mixture was stirred for one hour with a drying tube. The methanol was rotary evaporated off to form the crude, unstable methyl-5-hexeneimidate hydrochloride. Ammonia in methanol (2 M, 1 eq, 8.5 mL) was added to form 5-hexeneamidinium hydrochloride.

The product mixture containing, 5-hexeneamidinim hydrochloride, was rotary evaporated to remove the remaining methanol.

The product was re-dissolved in methanol and rotary evaporated again. Ether (3 mL) was added and warmed. Methanol was added until the solid just dissolved in attempt to recrystalize the product.

The synthesis of methyl 5-hexeneimidate hydrochloride and 5-hexeneamidinium hydrochloride was repeated using 5-hexenenitrile. There was not an attempt to recrystalize the final product.

Attempt at the synthesis of 2-(β-cyanoethyl)-methylenecyclohexene[9]



A 100-mL three-necked round bottom flask was fitted with a N_2 balloon, a mechanical stirrer, and two rubber stoppers. The flask was set up over ice. Ether (10 mL, 0.0962 mol) was added followed by *n*-butyllithium (1.9 mL, 1.6M, 0.0202 mol) in hexanes via syringe while the solution was stirred. Methyltriphenylphosphonium chloride (0.940 g, 2.42 mmol) was added in three portions over five min. The solution was stirred for 1 h. The N_2 balloon was replaced with an active nitrogen tank. 2-β-(Cyanoethyl)-cyclohexanone (0.506 g, 9.76 mmol) was added via syringe. The mixture was heated under reflux overnight.

The mixture was removed from heat and cooled to room temperature. The precipitate was removed by vacuum filtration. The precipitate and round bottom flask were washed with ether and the filtrates were washed with water until neutral to pH paper. The solution was dried over magnesium sulfate. The solution was rotary evaporated to remove the ether. It appeared the remaining product was still wet so it was redissolved in ether and dried again over magnesium sulfate. The ether was rotary evaporated off.

Analysis

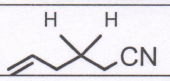
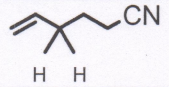
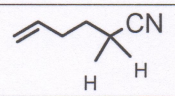
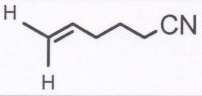
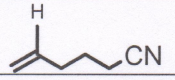
I have not yet completed an entire synthesis of a diazarine; however, there are several things to analyze from the partial synthesis. This first step in Synthesis A was the Wittig reaction, which prepares an alkene from a carbonyl functional group. This method of the Wittig reaction used sodium hydroxide and benzyltriphenylphosphonium chloride.[7] The attempt at the synthesis of 2-(β-cyanoethyl)benzylidenecyclohexane was unsuccessful. Because there was a carbonyl peak (1707 cm^{-1}) in the IR spectra of the product, the reaction did not completely form an alkene. The ^{1}H-NMR of the starting

material, 2-(β-cyanoethyl)cyclohexanone and the unknown product contained clusters of peaks that were indistinguishable. However, there was a transformation from the starting material to a product, as in the ^{1}H-NMR of the starting material there was only a cluster from 1.2 ppm to 2.4 ppm, but in the product, there was the same beginning cluster, but also a second group from 7.2 ppm to 7.8 ppm.

A second Wittig reaction was run as the first step of Synthesis A. This Wittig reaction used *n*-butyllithium and methyltriphenylphosphonium chloride in replace of sodium hydroxide and benzyltriphenylphosphonium chloride. The synthesis of 2-(β-cyanothethyl)methylenecyclohexene by this reaction was unsuccessful. The reaction was done under constant nitrogen. The ^{1}H-NMR of the product of this Wittig was similar to the product ^{1}H-NMR of the first Wittig reaction, with a cluster of messy peaks from 1 ppm to 2.6 ppm and a second cluster from 7.2 ppm to 7.8 ppm. A ^{13}C-NMR was also taken of the product which indicated a partial reaction in the mixture. Future separation of the reaction mixture could be attempted.

The synthesis of 5-hexenenitrile is an S_N2 reaction of bromide with cyanide. Both the organic substrate and the anionic nucleophile are both soluble in methanol, so the reaction is done in methanol. It was refluxed overnight to ensure the reaction reached completion. This synthesis was successful every time and produced high yields (97.9%, 93.7%). The yield from the first trial was not determined. The ^{1}H-NMR of the nitrile product each trial was comparable. While the peaks were small from the first ^{1}H-NMR of the 5-hexenenitrile product, it is the neatest spectra and gives the following clear data.

^{1}H-NMR 5-hexenenitrile (in $CDCl_3$)

δ, ppm	splitting	H ratio	H illustrated
1.77	multiplet	2	
2.22	multiplet	2	
2.34	triplet	2	
5.12	multiplet	2	
5.74	multiplet	1	

In the remaining two ^{1}H-NMR spectra of 5-hexenenitrile, the same chemical shift values are present, but the splitting is not defined and there are additional peaks in the spectra. One additional peak in all three spectra is at 5.3 ppm. This chemical shift value corresponds to methylene chloride. This peak shows that the methylene chloride was not completely distilled off. The peak in all three spectra at 7.3 ppm corresponds to the chloroform.

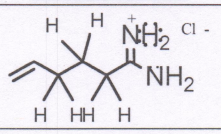
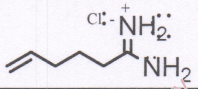
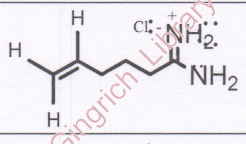
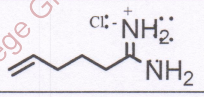
The second step to produce methyl-5-hexeneimidate hydrochloride is a Pinner synthesis. The Pinner synthesis involves the addition of an alcohol over a carbon-nitrogen triple bond. The methyl-5-hexeneimidate hydrochloride is formed by bubbling HCl through a solution of the cyano compound and dry methanol. The result is an imidate, as you can see in the name of the salt product, where the nitrogen is protonated. The third step to produce 5-hexeneamidinium hydrochloride involves the formation of an amidine from the substitution of the methoxy group by nucleophilic attack. The synthesis of the two salts, methyl 5-hexeneimidate hydrochloride and 5-hexeneamidinium hydrochloride, was difficult because as you continue through the steps of a multi-step synthesis, product is lost each time. By the time the product of the third step was

complete, there was not enough to continue. The second product was not analyzed under normal circumstances because it was immediately used for the third step because of its low stability; the imidate hydrolyzes slowly in air to form an ester. In one case, however, the reaction was not completed, and the product of the second step was analyzed by ^{1}H-NMR to determine if it could still be used. ^{1}H-NMRs were taken of the product of the third reaction. The salt was not soluble in $CDCl_3$, so the ^{1}H-NMRs were taken in DMSO.

In the case where the second product was analyzed by ^{1}H-NMR, it was determined that the product mixture was impure.

The ^{1}H-NMR of the third step concluded that the product most likely was **5-hexeneamidinium hydrochloride.**

^{1}H-NMR 5-hexeneamidinium hydrochloride (in DMSO)

δ, ppm	Description	H illustrated
1.6, 2.1, 2.4	alkane CH_2	
3.0	broad NH_2	
5.0, 5.8	alkene	
8.7, 9.1	$=NH_2^+$	

Both ^{1}H-NMRs were consistent but the peaks from the second have a much weaker intensity. The product was used up in the analysis and could not be used to continue to the final synthesis step.

When the total synthesis is complete, the diazirine will be used to study the 1,2-hydrogen shift and the cycloaddition reactions. By exposing the diazarine to heat, I

theoretically will get two products from the 1,2-hydrogen shift, and a third product from the cycloaddition. These products will be studied and the results will be analyzed through various analytical techniques.

Conclusion

The several step syntheses of two molecules was attempted. In Synthesis A, two forms of the Wittig reaction were studied. In the method involving sodium hydroxide and benzyltriphenylphosphonium chloride, the reaction was unsuccessful. The method involving *n*-butyllithium and methyltriphenylphosphonium chloride was also unsuccessful; however the reaction mixtures were not separated.

Synthesis B was partially complete, but by the third step, the yield was too low to continue. Future work will include scaling up the reactions to get more material so that the product can be better studied.

When the total synthesis is complete, the diazirine will be used to study the 1,2-hydrogen shift and the cycloaddition reactions. By exposing the diazarine to heat, I theoretically will get two products from the 1,2-hydrogen shift, and a third product from the cycloaddition. These products will be studied and the results will be analyzed through various analytical techniques.

References

[1] Carroll, Felix A. Reactive Intermediates. *Perspectives on Structure and Mechanism in Organic Chemistry*, Brooks/Cole Publishing: Pacific Grove, 1998; 275-282.

[2] Miller, Bernard. Carbenes, Carbenoids, and Nitrenes. *Advanced Organic Chemistry: Reactions and Mechanisms*, 3nd Ed; Prentice Hall: Upper Saddle River, 2004, 257-276.

[3] Eğe, Seyhan. *Organic Chemistry: Structure and Reactivity,* 4th Ed; Houghton Mifflin Company: Boston, 1999.

[4] Dr. Rhile's Research Plans.

[5] Keating, Amy E.; Garcia-Garibay, Miguel A.; Houk, K.N. Origins of Stereoselective Carbene 1,2-Shifts and Cycloadditions of 1,2-Dichloroethylidene: A Theoretical Model Based on CBS-Q and B3LYP Calculations. *J. Am. Chem. Soc* **1997,** *119*, 10805-10809.

[6] Perrin, D. D., Armarego, W. L. F., Perrin, Dawn R. Purification of Individual Organic Chemicals. *Purification of Laboratory Chemicals,* 2nd Ed; Pergamon Press: Oxford, 1980; 320.

[7] Gilbert, John C.; Martin, Stephen F. Reactions of Carbonyl Compounds. *Experimental Organic Chemistry: A Miniscale and Microscale Approach*, 3rd Ed; Harcourt College Publishers: Forth Worth, 2002, 556-569.

[8] Roger, R.; Neilson, G.G. *Chem. Rev.* **1961,** *87*, 439604397.

[9] Wittig, George; Schoellkoph, U. In *Organic Syntheses*, Rabjohn, Norman, Editor-in-Chief; John Wiley & Sons, Inc.: New York, 1973, Vol. 4, 751-754.

[10]Moss, R. A. *Acc. Chem. Res*. **2006**, *39*, 262-272.