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Unprecedented Reactivity And Applications Of 1-Aza-2-Azoniaallene Salts

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UNPRECEDENTED REACTIVITY AND APPLICATIONS OF 1-AZA-2-
AZONIAALLENE SALTS

A Dissertation Presented

by

Ramya Srinivasan

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Chemistry

October, 2018

Defense Date: July 19, 2018
Dissertation Examination Committee:

Matthias Brewer, Ph.D., Advisor
Sayamwong Hammack, Ph.D., Chairperson
Christopher Landry, Ph.D.
Adam Whalley, Ph.D.
Cynthia J. Forehand, Ph.D., Dean of the Graduate College

ABSTRACT

1-Aza-2-azoniaallene salts, derived by oxidation of substituted hydrazones, are highly reactive cationic heteroallenes. These species participate in several mechanistically distinct reactions including: (1) intramolecular [3+2] cycloadditions, (2) polar [4 +2] cycloadditions, (3) stereospecific C-H aminations, (4) electrophilic aromatic substitutions, and (5) chloroamination reactions. We have shown that this versatile reactivity is governed by the length of the tether and nature of the π -system.

A novel intramolecular electrophilic aromatic substitution reaction is observed when the tether length separating the 1-aza-2-azoniaallene salt and a pendant aryl ring is three methylene units to generate alkylaryl azo products. Variations in the electronics and sterics of the heteroallenes greatly affects their reactivity. The azo product obtained from 5-phenyl-pentan-2-one undergoes spontaneous photochemical cleavage, exhibiting interesting applications to this class of compounds.

Heteroallenes derived from pent-5-ene-2-one scaffolds undergo a concerted polar [4+2] cycloaddition to give a 1,2,3,4-tetrahydrocinnoline product. These products are structural motifs found in biologically and pharmaceutically active compounds. This reaction can give the structurally complex tetracyclic iminium salt from a cyclohexene based heteroallene which serves as good precedence to the key step of our proposed synthesis of a terpene indole alkaloid, (+)-ibophyllidine.

DEDICATION

This work is dedicated to my four pillars of strength: Appa, Amma, Paati and

Lavanya.

“Ubuntu: I am because we are”

ACKNOWLEDGEMENTS

First and foremost, I would like to express my sincere gratitude to my advisor Prof. Matthias Brewer for his continuous support and guidance. He has set an example of excellence as a researcher and a mentor.

I would also like to thank my thesis committee: Prof. Christopher Landry, Prof. Adam Whalley, and Dr. Sayamwong Hammack, for their insightful comments and constant encouragement.

I thank my fellow Brewer groupmates for all their support in the last six years. They have celebrated my successful experiments and commiserated in the not-so-successful ones. In particular, I am grateful to Dr. Daniel Bercovici for training and teaching me several lab techniques and for always leading by example.

This work would not have been possible without the financial support from NSF Grant # 1362286.

My graduate school experience wouldn't have been as great if it were not for my fellow graduate students in the Chemistry Department who have been my support system these last six years. I am fortunate to not only have had great scientific discussions but also develop some life-long friendships.

Last but not the least, I would like to thank my family. Words cannot express how grateful I am to them for all the unconditional love, support and prayers for me that sustained me thus far.

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CHAPTER 1: AZONIAALLENE SALTS – PRECURSORS FOR THE SYNTHESIS OF N-HETEROCYCLES

1.1. Cationic Heteroallenes

Allenes, as defined by the International Union of Pure and Applied Chemistry, are hydrocarbons (and by extension, derivatives formed by substitution) having two double bonds from one carbon atom to two other carbons. Propadiene (**1**, Figure 1.1) is the simplest allene and serves as the parent compound to heteroallenes, a class of allene-based compounds produced by the replacement of one or more carbon atom with a heteroatom.

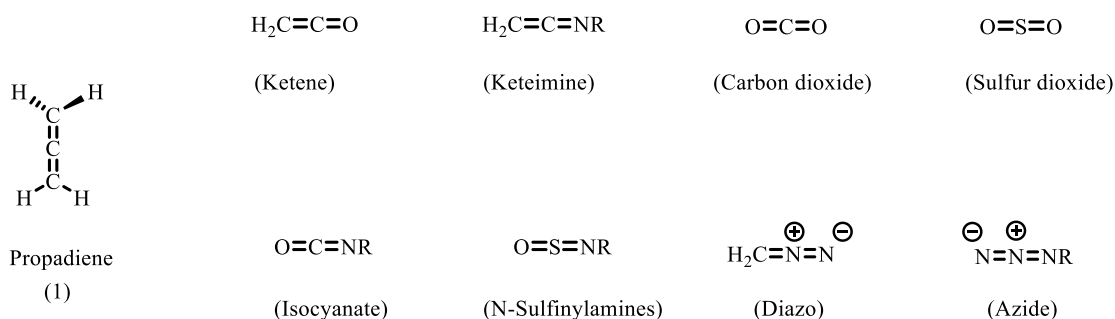


Figure 1.1: Examples of heteroallene salts

The 2-aza analogues of allenes, 2-azoniaallene salts (**2**, Figure 1.2), are cationic heteroallenes that serve as versatile synthetic building blocks for a series of open-chain and heterocyclic compounds. The 1-aza (**3**) and 1,3-diaza (**4**) substituted 2-azoniaallene

salts are strong electrophiles that undergo cyclization reactions to yield a wide range of nitrogen containing heterocyclic compounds. N-heterocycles are ubiquitous in biologically active compounds and natural products. Hence reactions leading to structurally complex heterocyclic products provide new methods to prepare interesting scaffolds that is pervasive in many areas of life sciences and technology.^{1,2}

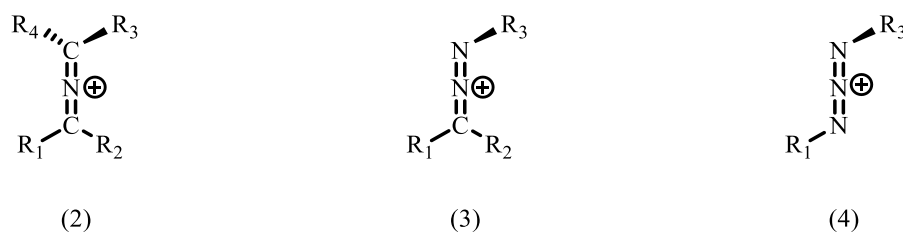


Figure 1.2: Cationic 2-aza analogues of heteroallenes

The investigation and development of the reactivity of 1-aza-2-azoniaallene salts (3) has been a primary focus in the Brewer group and serves as the basis of this thesis. In this chapter I will explore all the previous studies on the reactivity of 1-aza-2-azoniaallene salts, highlighting the Brewer group's contributions in this field. Under the subsequent chapters, I will discuss the development of methods for the preparation and synthetic applications of 1-aza-2-azoniaallene salts.

1.2. 1-Aza-2-azoniaallene salts: Background and reactivity

1-Aza-2-azoniaallene salts (**3**) are highly reactive species that can react through several mechanistically distinct pathways. These heteroallenes consist of a central nitrogen atom that is double bonded to a carbon atom on one side and a nitrogen atom on the other side. The versatile reactivity exhibited by these salts can be best explained by the multiple structures (Figure 1.3), all of which carry a formal charge of +1.

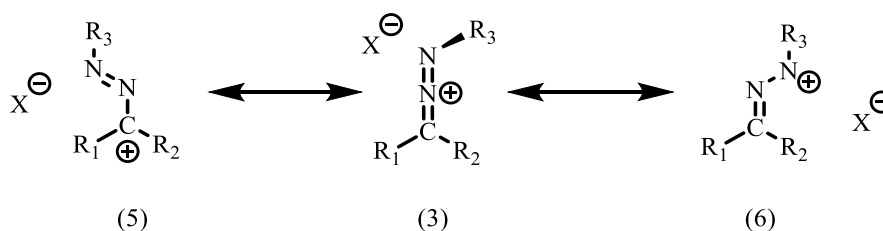
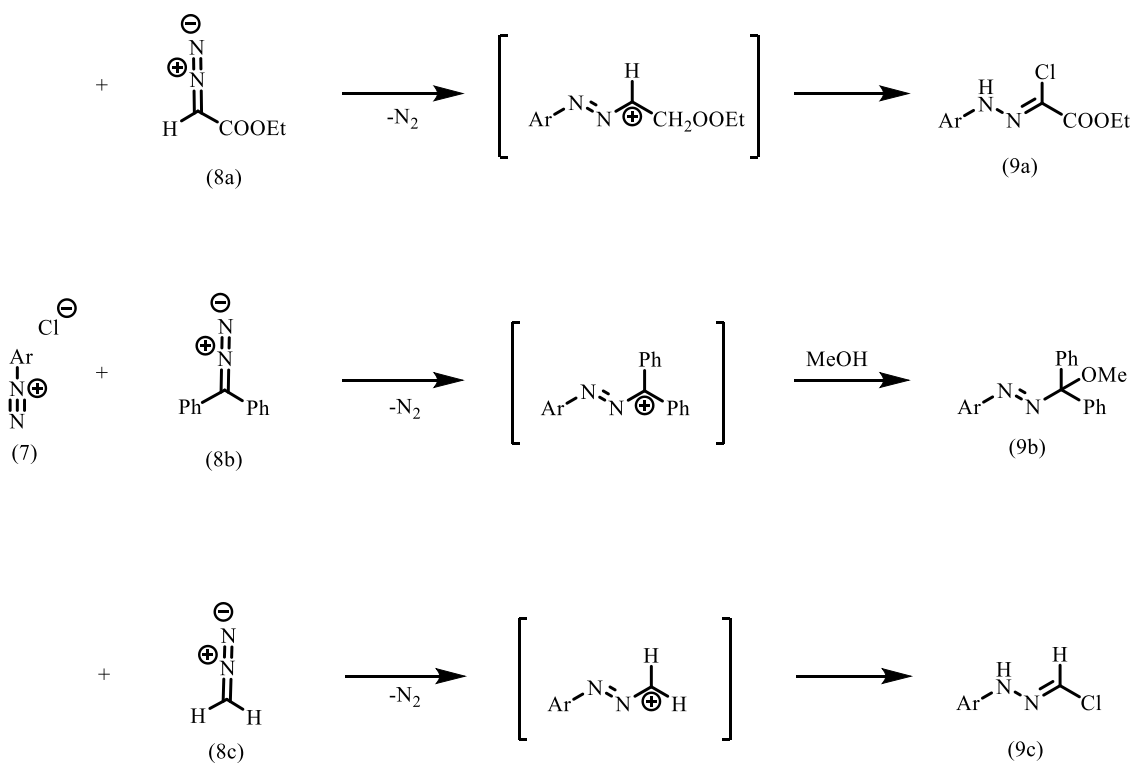


Figure 1.3: Resonance structures of 1-aza-2-azoniaallene salts

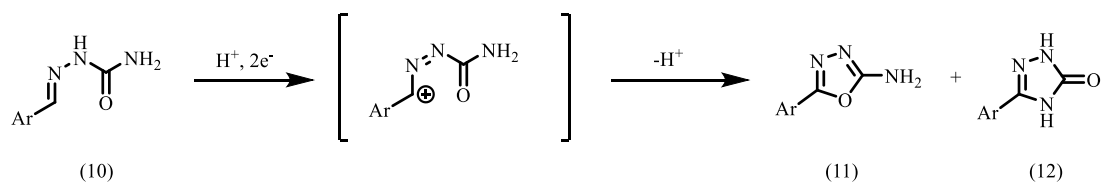
As seen in Figure 1.3, the positive charge can be accommodated either on the carbon atom (5) or one of the two nitrogen atoms (3 and 6) which can result in a wide range of reactivity.

The existence of 1-aza-2-azoniaallene salts was first postulated in 1955 by Huisgen and Koch.³ They proposed that diazo compounds (**8a-c**, Scheme 1.2) reacted with aryl diazonium salts (**7**) by extrusion of N₂ to generate a 1-aza-2-azoniaallene intermediate that subsequently trapped by either the chloride counterion or the solvent to yield chloro hydrazones and azo ether products (**9a-c**).



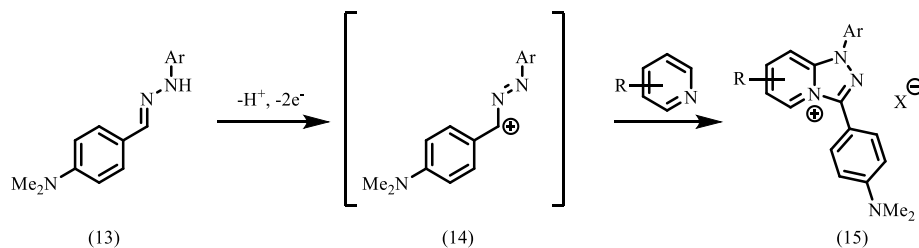
Scheme 1.2: Reaction of diazonium salts with diazo compounds via 1-aza-2-azoniaallene intermediates

After Huisgen and Koch's report, 1-aza-2-azoniaallene salts have been reported as intermediates in several oxidation processes of hydrazone derivatives resulting in the formation of azo products through a nucleophilic addition at the heterocumulene carbon center.⁴ Hammerich and Parker⁵ proposed the anodic oxidation of 1-arylmethylsemicarbazides (**10**) proceeded through a 1-aza-2-azoniaallene intermediate to provide oxadiazoles (**11**) and triazolinones (**12**).



Scheme 1.3: Anodic oxidation of 1-arylmethylsemicarbazides via 1-aza-2-azoniaallene intermediate

Tabakovic and coworkers⁶ showed that N-arylhydrazones like **13** (Scheme 1.4) generated an azoniaallene intermediate **14** that reacted with various substituted pyridines to furnish s-triazolo[4,3-a] pyridinium salts **15**. The [3+2] cycloaddition is believed to be stepwise initiated by initial nucleophilic attack of pyridine on the electrophilic carbon of the azoniaallene intermediate and a subsequent cyclization and oxidation to yield **15**.

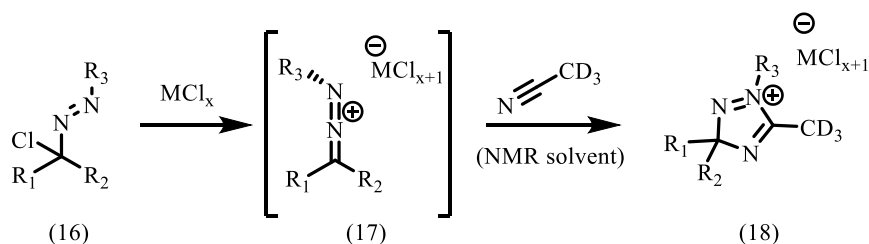


Scheme 1.4: Reaction of 1-aza-2-azoniaallene intermediates with substituted pyridines

The existence of 1-aza-2-azoniaallene salts was further supported by spectroscopic evidence. These species have a strong broad IR absorption at $\nu = 1899 \text{ cm}^{-1}$, which is consistent with the unsymmetrical vibration of other cumulenes.⁷⁻⁹

1.3. Polar [3⁺+2] cycloaddition of 1-aza-2-azoniaallene salts

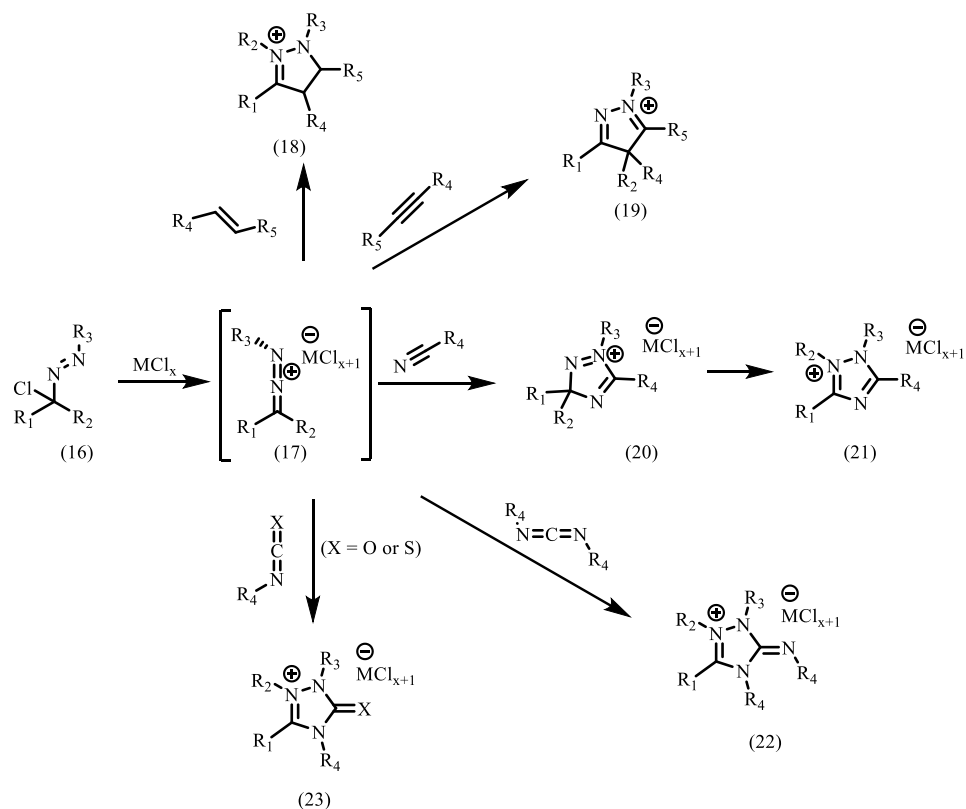
To isolate and characterize the first stable 1-aza-2-azoniaallene salt, Jochims and coworkers prepared 1-aza-2-azoniaallene intermediates via the treatment of α -chloroazo compounds with Lewis acids like antimony pentachloride (SbCl₅) and aluminum trichloride (AlCl₃) in deuterated acetonitrile (CD₃CN) at low temperatures. Subsequent NMR experiments revealed the formation of a 1,2,4 triazolium salt which they presumed formed by the polar [3⁺+2] cycloaddition reaction between the 1-aza-2-azoniaallene intermediate and the NMR solvent.¹⁰



Scheme 1.5: Polar [3+2] cycloaddition between 1-aza-2-azoniaallene salt and NMR solvent

To test this serendipitous discovery, Jochims and coworkers reacted an array of α -chloroazo compounds with a halophilic Lewis acid in the presence of several nitrile substrates and obtained substituted 1,2,4-triazolium salts (20), many of which rearranged to a thermodynamically more stable product (21). They further explored these heteroallene salts as cationic 1,3-dipoles in intermolecular reactions with several

dipolarophiles such as alkenes, alkynes, carbodiimides, isocyanates and isothiocyanates to provide a variety of heterocyclic products.¹¹⁻¹³



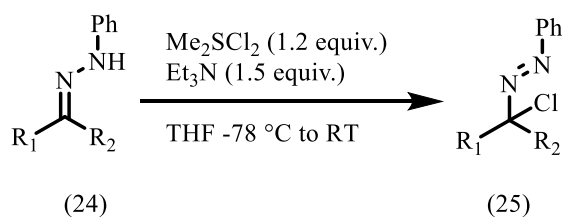
Scheme 1.6: Polar [3+2] cycloaddition between 1-aza-2-azoniaallene salts and common dipolarophiles

Jochim proposed that the cycloaddition reactions with alkenes and acetylenes are concerted,¹⁴ while the cycloaddition reactions with nitriles, isocyanates, isothiocyanates and carbodiimides occur via a two-step reaction through the formation of a nitrilium or acylium ion.¹²

1.4. Preparation of α -chloroazo compounds from aryl hydrazones

Among the few methods that existed for the preparation of α -chloroazo compounds, the most commonly used method was developed by Moon.¹⁵ In this method, hydrazones of ketones were treated with either chlorine gas or tert-butyl hypochlorite to obtain geminal substituted chloro azo compounds. The problem with this method is the use of highly reactive and harsh chlorinating reagents. Additionally, this method was limited to simple alkyl hydrazones. When aryl hydrazones were subjected to similar conditions, they often resulted in a complex mixture of chloro aryl products.

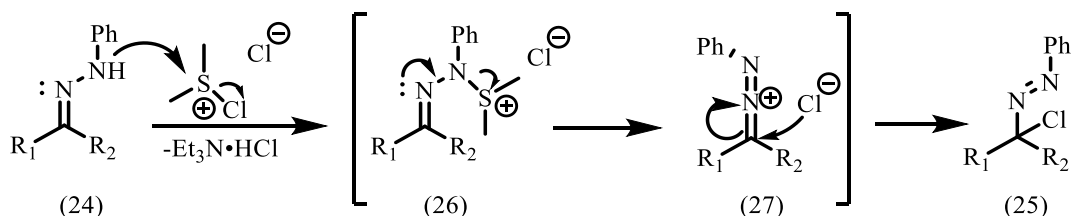
The Brewer group discovered that unsubstituted hydrazones react effectively with chlorodimethylsulfonium chloride (Me_2SCl_2 , also referred to as the Swern reagent) to generate diazo products.¹⁶⁻¹⁸ This work led to the subsequent discovery that aryl hydrazones react with chlorodimethylsulfonium chloride to yield α -chloroazo compounds.¹⁹



Scheme 1.7: Formation of α -chloroazo compounds using chlorodimethylsulfonium chloride

Our group's approach proved to be milder and more efficient compared to the previous reported methods and was well tolerated by a wide range of functional groups,

except for benzylic and allylic hydrazones. We postulated that the formation of the α -chloroazo compound occurs via the formation of an azoniaallene intermediate, as shown in Scheme 1.8. In the first step, the anilinic nitrogen of the hydrazone attacks the chlorodimethylsulfonium chloride, generated from oxalyl chloride and dimethylsulfoxide, to generate azosulphonium ion **26**. Next, the lone pair on the imine nitrogen of the hydrazone forms a double bond to the anilinic nitrogen resulting in the elimination of dimethyl sulfide, thereby generating a 1-aza-2-azoniaallene intermediate **27**. Lastly, the 1-aza-2-azoniaallene intermediate is trapped by the chloride counterion at the heteroallene carbon to give α -chloroazo compound **25**.

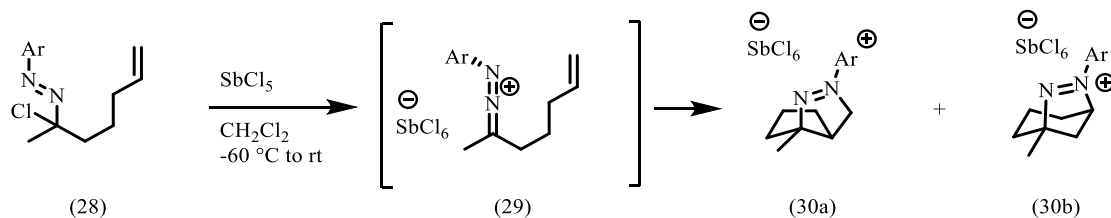


Scheme 1.8: Mechanism for the generation of α -chloroazo compounds from hydrazones and chlorodimethylsulfonium chloride

After developing a more efficient and functional group tolerant route to achieve α -chloroazo compounds, the Brewer group expanded Jochim's work on [3+2] polar cycloadditions and further investigated 1-aza-2-azoniaallene intermediates.

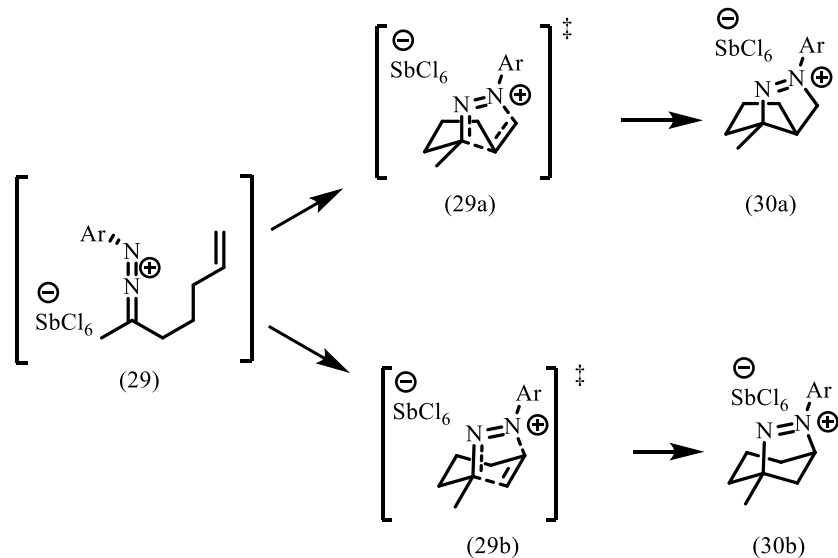
1.5. Intramolecular polar [3+2] cycloaddition reactions of 1-aza-2-azoniaallene salts with olefins

Jochims and coworkers reported that α -chloroazo compounds react with halophilic Lewis acids to generate 1-aza-2-azoniaallene salts that undergo polar [3+2] cycloaddition reactions with alkenes to yield diazenium salts (e.g. 19, Scheme 1.6). However, this report was only limited to simple diazenium salts prepared in an intermolecular fashion.¹¹ Tethering the reacting species together imposes conformational constraints to the molecule and thus increases its structural complexity. Due to the proximity of reacting species in an intramolecular reaction, high levels of regioselectivity and stereoselectivity can be attained in substrates. To investigate this Dr. Jodi Ogilvie and Dr. Muhammad Irfan reacted 1-aza-2-azoniaallene intermediates with tethered olefins, such as in **28** (Scheme 1.9) and observed a mixture of fused 5,5 and bridged 6,5 bicyclic diazenium salts through an intramolecular [3+2] cycloaddition reaction.¹⁷⁻¹⁸



Scheme 1.9: Intramolecular [3+2] cycloaddition of 1-aza-2-azoniaallene intermediate

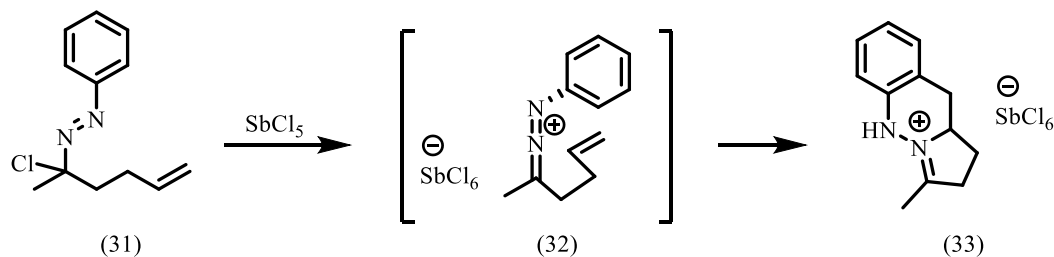
It was observed that when Ar was a phenyl ring, **30a** and **30b** were obtained in a 1:0.2 ratio with an overall yield of 87%. As expected, the products obtained in this reaction were more structurally complex than those obtained by Jochim. The group postulated that the carbon-carbon bond formation to the highly electrophilic carbon atom of the 1-aza-2-azoniaallene intermediate **29** is more advanced at the transition state compared to the carbon-nitrogen bond formation to the anilinic nitrogen of the heteroallene. This results in an accumulation of a partial positive charge on the carbon atom that forms a new bond with the nitrogen. Transition state **29a**, resulting in the formation of 5,5 fused product, would develop a partial positive charge at a primary carbon, whereas transition state **29b**, leading to 6,5 bridged product, would develop a partial positive charge at a secondary carbon. Since transition state **29a** is entropically favored the 5,5 fused product is predominantly obtained. It was determined that the electronics of the N-aryl ring had a great effect on the ratio of the fused to bridged products. Compounds with electron withdrawing groups on the N-aryl ring favored the formation of fused products as they tend to increase the partial positive charge developed in the transition state thereby delaying the carbon nitrogen bond formation. Mechanistically, this observation supports the existence of an asynchronous transition state at the [3+2] cycloaddition step.



Scheme 1.10: Formation of bridged and fused diazenium salts through an asynchronous pathway

1.6. Intramolecular polar [4+2] cycloaddition reactions of 1-aza-2-azoniaallene salts with olefins

Section 1.5 described the polar [3+2] cycloaddition reactions that 1-aza-2-azoniaallene salts undergo with tethered olefins three methylene units away. Dr. Ogilvie observed that by shortening the tether by one carbon as in **31** (Scheme 1.11), an entirely different product was isolated. Reacting α -chloroazo compound **31** with SbCl_5 generated 1-aza-2-azoniaallene intermediate **32** which subsequently formed a tricyclic protonated azomethine imine **33**.²⁰



Scheme 1.11: Intramolecular [4+2] cycloaddition of 1-aza-2-azoniaallene salts

Computational modeling in collaboration with the Houk group (UCLA), indicated that this reaction occurs by a [4+2] cycloaddition wherein the olefin tether behaves as the 2π dienophile and one of the π -bonds of the aryl ring along with the $N=N^+$ bond act as the 4π diene. The heterocyclic product obtained contains a 1,2,3,4-tetrahydrocinnoline which is prevalent in several biologically active compounds and pharmaceuticals.

The chemo- and regiochemical fate of the reaction between an aryl-1-aza-2-azoniaallene salt and an alkene is clearly dictated by the length of the tether between the two reacting sites. Computational studies were carried out to better understand the tether-controlled reaction selectivity. Brewer and Houk investigated the intramolecular cycloaddition between aryl-1-aza-2-azoniaallenes and alkenes with tether lengths varying from $n = 0-2$ (Figure 1.4).²¹ When $n = 0$, the energy barrier for the [3+2] cycloaddition is almost double than that for the [4+2] cycloaddition, supporting the experimental observations mentioned earlier in this section. When $n = 1$, two [3+2] regioisomeric transition states were observed along with one [4+2] transition state. In this case, the energy barrier for the [4+2] cycloaddition is much greater than that of the [3+2] cycloadditions in line with the experimental findings reported in section 1.5. Lastly when

$n = 2$, it was observed that the [3+2] cycloaddition was more favorable as the tether connecting the reacting partners is sufficiently long to exhibit chemo- and regioselectivities like that of intermolecular reactions.

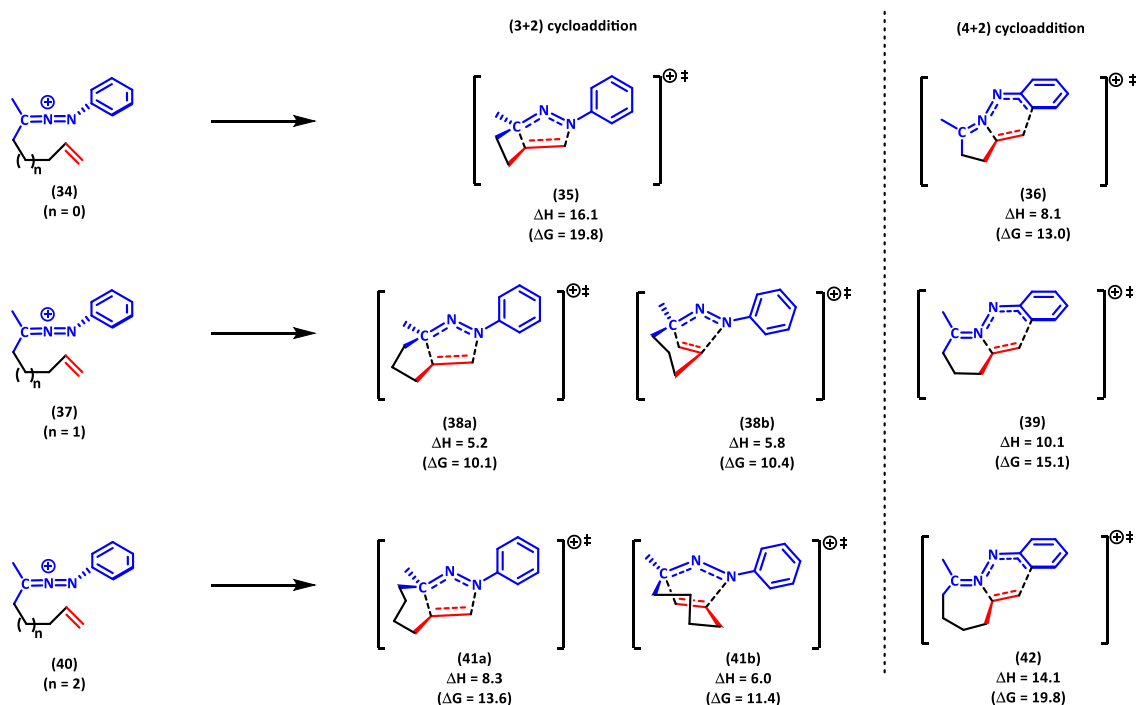


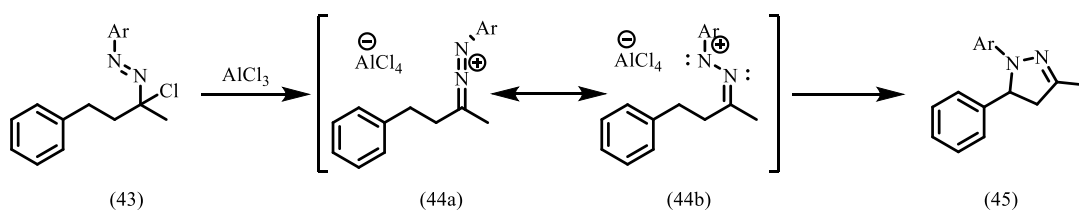
Figure 1.4: DFT computed activation enthalpies and free energies (in kcal/mol) for intramolecular [3+2] and [4+2] cycloaddition reactions of 1-aza-2-azoniaallene salts with tethered alkenes with varying lengths

After the initial discovery of this unprecedented reactivity by Dr. Ogilvie, Dr. Daniel Bercovici further explored this reaction and provided a solid understanding to the mechanism and insights to the electronic limitations of this reaction, which I will discuss in detail in Chapter 3 of this thesis. Dr. Ram Dhakal further expanded the substrate scope reported by Dr. Bercovici of this reaction and provided a cleaner and more efficient

route to generate these products using α -OTFA compounds.^{22,23} As will be described in Chapter 3 of this thesis, these products contain a tetrahydrocinnoline core and a protonated azomethine motif and serve as a potential progenitor of the terpene alkaloid (+)-ibophyllidine.

1.7. Intramolecular stereospecific C-H amination reactions of 1-aza-2-azoniaallene salts

While attempting to study the 1,3 dipolar reactions of 1-aza-2-azoniaallene intermediates in the absence of olefins, Dr. Daniel Bercovici replaced the pendant alkene with a benzene ring. The products isolated from this reaction were pyrazoline **45** and trace amounts of the corresponding pyrazole. Optimization investigations of this reaction revealed that by switching the halophilic Lewis acid from SbCl_5 to AlCl_3 yielded exclusively the pyrazoline product.²⁴



Scheme 1.12: Intramolecular C-H amination of 1-aza-2-azoniaallene salts

Mechanistic studies revealed the reaction proceeds through a nitrenium ion like pathway²⁵ (Figure 1.5). Substrate scope analysis of these compounds revealed their dependence on the electronic nature of the pendant ring. Electron donating groups

facilitated the C-H insertion whereas electron withdrawing groups (such as nitro) diminished the overall yield of the reaction. Successful insertion products of 1-aza-2-azoniaallene salts were achieved at non-benzylic sites including tertiary carbons, ethereal carbons and cyclopentenyl systems as well. This work is significant because pyrazolines motifs are widely present in biologically active compounds.

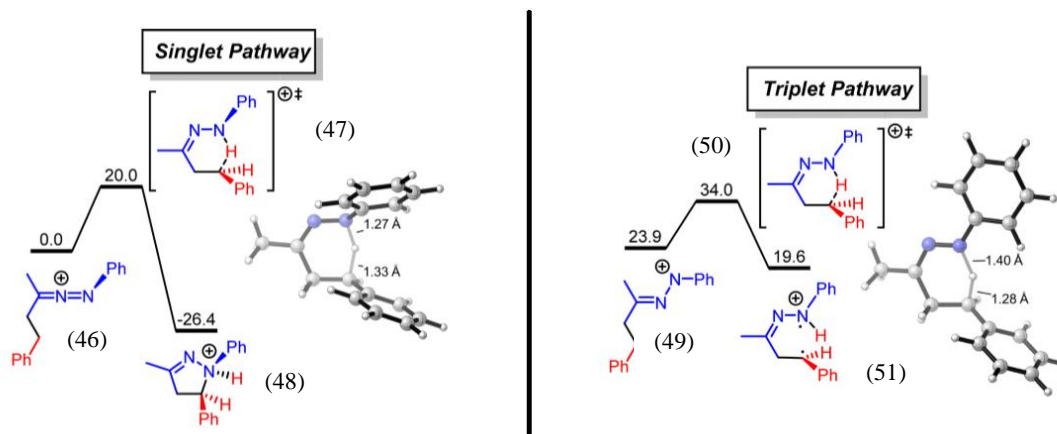
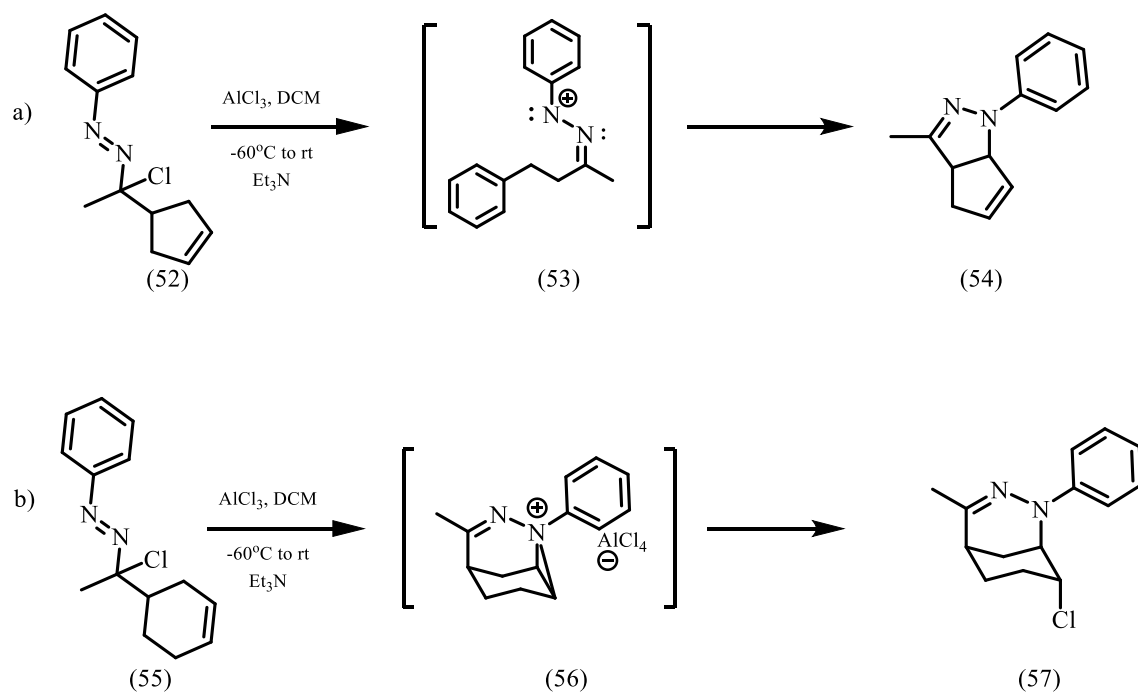


Figure 1.5: Transition state and Free energy changes (in kcal/mol) of singlet and triplet C-H insertion pathways of 1-aza-2-azoniaallene salts

1.8. Intramolecular [2+1] cycloaddition reactions of 1-aza-2-azoniaallene salts

As mentioned in the previous section, C-H insertion reaction occurred at the allylic position of cyclopentenyl system ($52 \rightarrow 54$, Scheme 1.13). However, this reactivity is not general for all constrained allylic systems. In fact, increasing the cyclic olefin system by one carbon, i.e. a cyclohexenyl system, resulted in a bridged heterocycle through a chloroamination reaction ($55 \rightarrow 57$).



Scheme 1.13: C-H amination versus [2+1] cycloaddition of 1-aza-2-azoniaallene salts with constrained cyclic alkenes

Dr. Nezar Al-Bataineh proposed that the chloroamination²⁶ occurs via aziridinium ion intermediate **56** formation that is opened by the chloride ion. Computational analysis revealed that in the cyclohexene-based system, the [2+1] cycloaddition is a more favorable process and is 4.0 kcal/mol more favorable than the C-H insertion reaction, thereby, supporting the experimental findings.

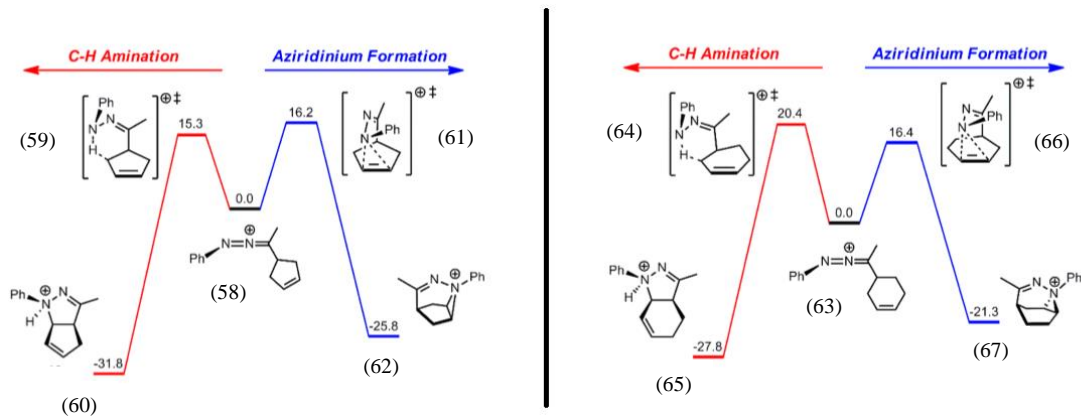
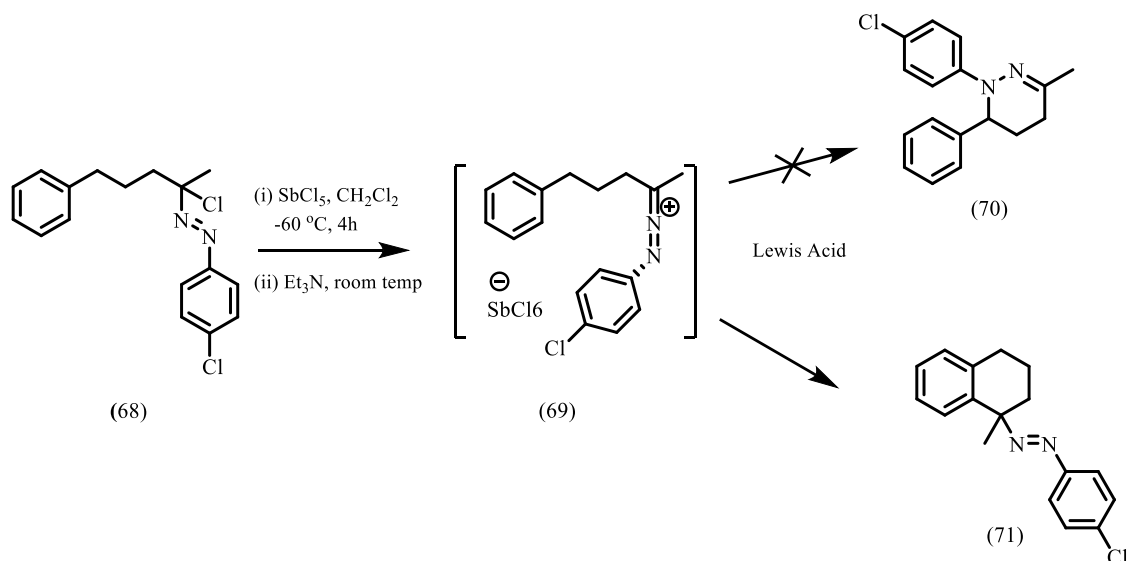


Figure 1.6: DFT- computed Gibbs free energy (in kcal/mol) comparing C-H amination and aziridinium formation of heteroallenes of constrained cyclic alkenes

1.9. Intramolecular electrophilic aromatic substitution of 1-aza-2-azoniaallene salts

An electrophilic aromatic substitution reaction involving the heteroallene salt was first observed by Dr. Daniel Bercovici while studying C-H amination reactions (discussed in section 1.7) of 1-aza-2-azoniaallene salts bearing pendant aryl rings. Dr. Bercovici observed that by increasing the tether length between the 1-aza-2-azoniaallene intermediate and the pendant aromatic ring by one methylene unit, an azo product **71** was observed rather than the expected insertion product **70**.²⁸



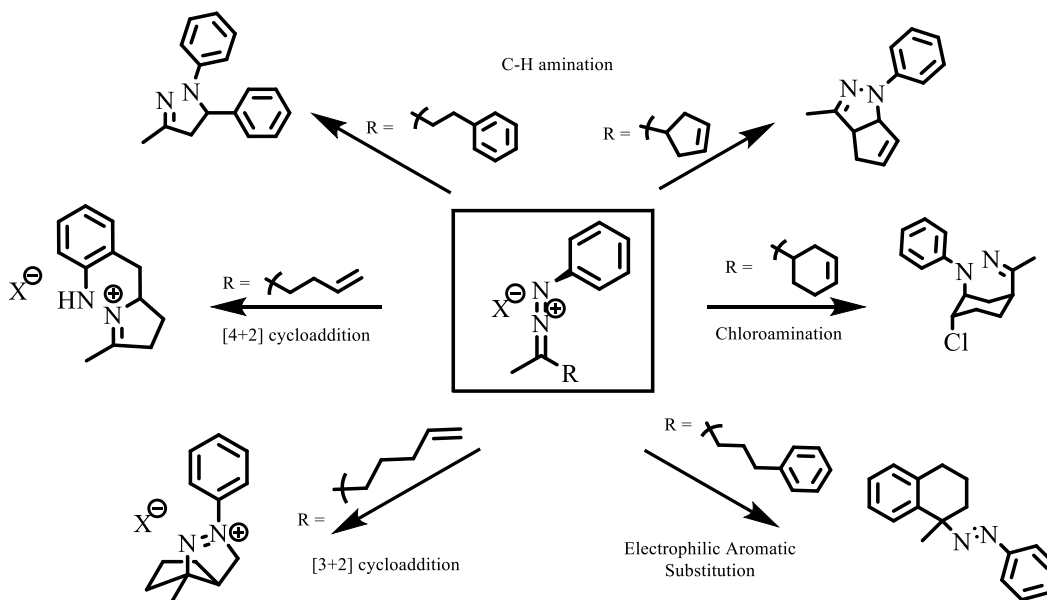
Scheme 1.14: Intramolecular electrophilic aromatic substitution of 1-aza-2-azoniaallene salts

Unlike the previous reported products generated by 1-aza-2-azoniaallene salts, electrophilic aromatic substitution reactions do not provide heterocyclic compounds. However, this reaction is still of interest and served as the basis of my first project in the Brewer group and I have detailed my studies in the following chapter of this thesis.

1.10. Conclusions

1-aza-2-azoniaallene salts are versatile reactive intermediates for the preparation of a wide range of heterocyclic compound. The Brewer group has contributed greatly in the generation of these heteroallenes and in the study of their varied reaction pathways with several π -systems, namely; (1) intramolecular [3+2] cycloaddition reactions, (2) polar [4 +2] cycloadditions, (3) stereospecific C-H amination reactions, (4) electrophilic

aromatic substitution reactions, and (5) chloroamination reactions. It was found that this unique and versatile chemistry was governed by the length of the tether length and nature of the π -system.



Scheme 1.15: Intramolecular reactions of 1-aza-2-azoniaallene salts with π -systems by the Brewer group

My study of the reactivity and applications of 1-aza-2-azoniaallene salts is the focus of this thesis and in the chapters to follow I will first discuss the involvement of these heteroallene salts in electrophilic aromatic substitution reactions. In the latter part of this thesis, I will discuss the Brewer group's prior work in the polar [4+2] cycloaddition of 1-aza-2-azoniaallene salts and their synthetic utility in the total synthesis of a natural product.

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CHAPTER 2: INTRAMOLECULAR ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS OF 1-AZA-2-AZONIAALLENE SALTS

2.1. Quantification of nucleophilicity and electrophilicity

The early 1930's saw the introduction of terms associated with electron-deficient (electrophile) and electron-rich (nucleophile) species.¹⁻³ Since then, several attempts have been made to classify organic molecules within empirical scales of electrophilicity and nucleophilicity. Swain and Scott were the first to quantify nucleophilic reactivity through a linear free energy relationship:

$$\log(k/k_0) = sn \quad (2.1)$$

where k is the rate constant for bimolecular nucleophilic substitution reactions (S_N2) of a substrate with a nucleophile at 25°C, k_0 is the corresponding rate constant with a standard nucleophile (water), n is the intrinsic nucleophilicity for a nucleophile, and s represents the sensitivity parameter (usually < 1), that measures the sensitivity of the substrate to variations in the nucleophile system.⁴

Since then several similar equations were proposed with attempts to incorporate several factors of a nucleophile, such as its basicity, polarizability, solvation et cetera, however they all lacked wide application.⁵⁻⁹ While observing the reactions of carbocations and diazonium ions, Ritchie postulated that a nucleophile can be characterized by one constant parameter, N_+ , which is independent of the nature of the electrophile.¹⁰

$$\log(k/k_0) = N_+ \quad (2.2)$$

This relationship was referred to as the “constant selectivity relationship” where the selectivity of a nucleophile, determined by their relative reaction rates, does not depend on the reactivity of the electrophile. Conversely, the relative reaction rate of electrophiles is independent of the strength of the nucleophile.¹¹⁻¹⁵

The validity of this relationship was further broadened in the areas of organic and organometallic chemistry by Sweigart and Kane-Maguire.^{16,17} In the early 1990’s, Mayr and coworkers postulated a new linear free energy relationship to quantify the reaction rates of a variety of electrophile-nucleophile combinations, namely,

$$\log k = s(N+E) \quad (2.3)$$

where s is a nucleophile specific sensitivity parameter and N and E are the nucleophilicity and electrophilicity parameters, respectively.¹⁸⁻²²

For qualitative analyses, the sensitivity factor s can be neglected, and as a rule of thumb one can expect the electrophile-nucleophile combinations to take place at room temperature if the value of $(N+E) > -5$. Since the diffusion limit is generally reached around $k = 10^9 - 10^{10} \text{ M}^{-1}\text{s}^{-1}$, regio-, chemo- and stereoselectivity often break down when the value of $(N+ E) > 10$. As a result, most synthetically used reactions, such as Michael additions, cross coupling reactions and electrophilic aromatic substitution reactions among others occur when the value of k lies between $10^{-6} - 10^{10} \text{ L mol}^{-1} \text{ s}^{-1}$.²³

2.2. Electrophilic aromatic substitution reactions

Electrophilic aromatic substitutions reactions are among the most fundamental transformations in organic chemistry where one atom or group on an aromatic ring, usually hydrogen, is replaced by an incoming electrophile. The driving force of this reaction is the capability of a carbon on the aromatic ring to donate electrons to the incoming electrophile. The reactivity and regioselectivity of these reactions is greatly influenced by any substituent group already present on the aromatic ring. If the six carbons in the benzene ring differ in their nucleophilicity (i.e. electron-donating property) then the attacking electrophile would preferentially attack the carbon with largest nucleophilicity.

2.2.1. Reactivity quantification of electrophilic aromatic substitution reaction with Hirshfeld charges

It is well known that the reactivity and regioselectivity of electrophilic aromatic substitution reactions is governed by the existing substituents on the aromatic ring. Electron donating groups (alkyl, amino, aryl, ether, halogen, hydroxyl) make the aromatic ring more nucleophilic and “activate” the *ortho* and *para* positions for substitution to occur. Electron withdrawing groups (aldehyde, ketone, cyano, carboxylic acid, nitro, nitroso, sulfonate) on the other hand, “deactivate” the ring towards substitution and direct the incoming electrophile to the *meta* position. Resonance and inductive effects are often used to justify the substitution pattern.

In 2015, Liu proposed a novel quantitative explanation for the regioselectivity of electrophilic aromatic substitution reactions which stated that the nucleophilicity of the substituted aromatic ring is inversely proportional to the Hirshfeld charge at the substituted site.²⁴ Hirshfeld charges are defined relative to the deformation density and is the difference between the molecular and unrelaxed atomic charge densities.²⁵ Liu and coworkers studied 18 substitution groups and established that Hirshfeld charges are accurate descriptors of reactivity and regioselectivity for electrophilic aromatic substitutions. The more negative Hirshfeld charge indicates the preferred reaction site on the aromatic ring.²⁴

Table 2.1: HOMO energy, Hirshfeld charges for meta and para positions, and barrier heights of EAS with monosubstituted benzene derivatives

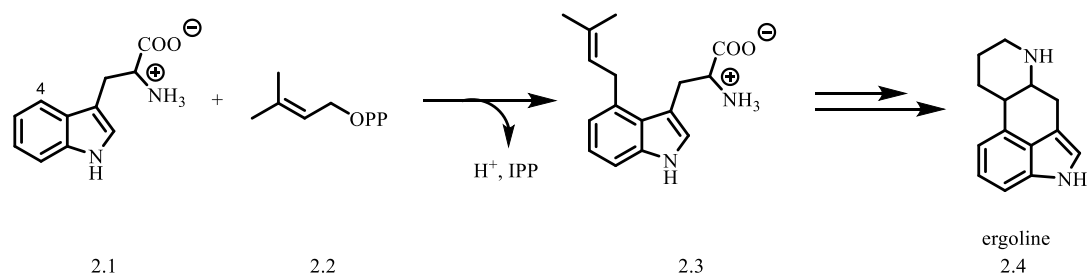
Entry	-R	HOMO	Hirshfeld charge		Barrier height	
			<i>meta</i>	<i>para</i>	<i>meta</i>	<i>para</i>
1	-H	-0.3080	-0.0498	-0.0498	28.41	28.41
2	-Cl	-0.3039	-0.0414	-0.0488	31.57	27.35
3	-Et	-0.2947	-0.0506	-0.0554	27.79	25.23
4	-F	-0.3069	-0.0419	-0.0560	31.64	25.38
5	-Me	-0.2947	-0.0506	-0.0558	28.45	24.59
6	-NH ₂	-0.2595	-0.0501	-0.0717	30.29	11.09
7	-NMe ₂	-0.2430	-0.0525	-0.0748	29.83	12.18
8	-OH	-0.2430	-0.0474	-0.0658	29.56	16.69
9	-Pr	-0.2939	-0.0508	-0.0554	28.49	24.69
10	- <i>t</i> Bu	-0.2945	-0.0514	-0.0554	27.63	25.34
11	-CCl ₃	-0.3206	-0.0417	-0.0387	31.10	31.89
12	-CF ₃	-0.3293	-0.0399	-0.0368	32.23	33.16
13	-CHO	-0.3234	-0.0449	-0.0337	31.16	32.96
14	-CN	-0.3273	-0.0380	-0.0326	33.47	33.94
15	-COF	-0.3329	-0.0408	-0.0292	33.00	34.90
16	-NH ₃ ⁺	-0.4752	-0.0082	-0.0048	53.02	54.92
17	-NO ₂	-0.3392	-0.0365	-0.0296	34.29	35.37
18	-NO	-0.3032	-0.0420	-0.0298	31.85	34.08
19	-SO ₃ H	-0.3394	-0.0356	-0.0296	33.68	35.33

Liu and coworkers found that *ortho/para* directing groups (entries **2 -10**) had the largest negative charges on the *ortho/para* positions, whereas the *meta* directing groups (entries **11 -19**) had the largest negative charge on the *meta* position.

Importantly, they established that the electron donating or withdrawing effect of the substituent group is irrelevant to the phenomenon of *ortho/para* and *meta* directing.

2.2.2. Examples of Electrophilic Aromatic Substitutions in common reactions

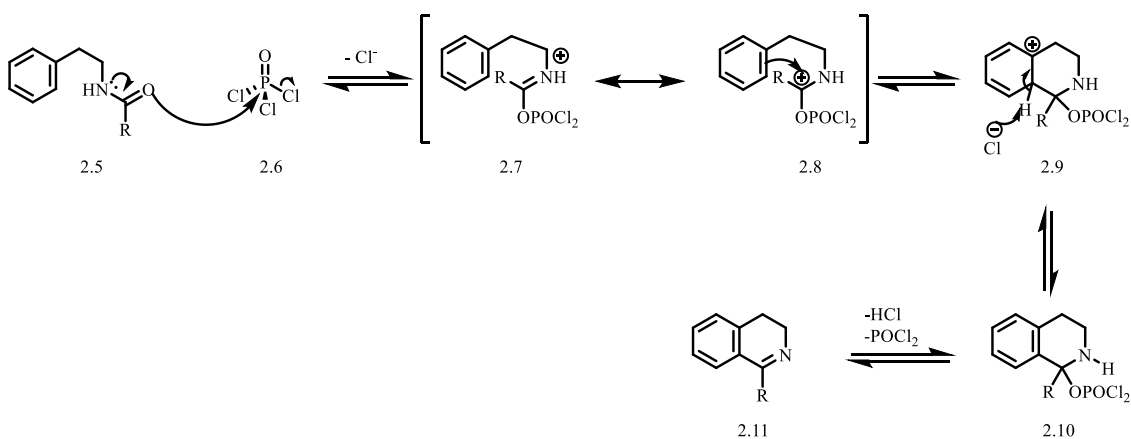
Prominent examples of electrophilic aromatic substitution reactions include nitration, halogenation, sulfonation, and Friedel-Crafts acylation and alkylation reactions. In 1992, Gebler, Woodside and Poulter reported a dimethylallyltryptophan (DMAT) synthase catalyzed alkylation of L-tryptophan (2.1) at the C4 site by dimethylallyl diphosphate (DMAPP) highlighting the utility of electrophilic aromatic substitution reaction in the biosynthesis of ergot alkaloids (2.4).²⁶



Scheme 2.2: Intermolecular electrophilic aromatic substitution in the biosynthesis of ergot alkaloids

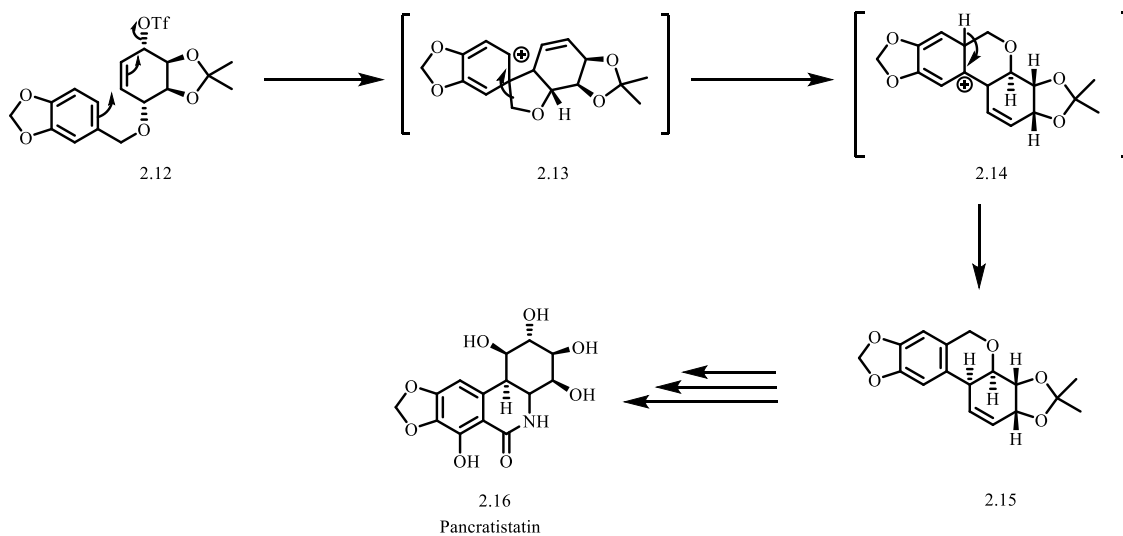
The intramolecular variants of electrophilic aromatic substitutions tend to impose conformational constraints on the overall reaction, thereby introducing chemo- and regioselectivity to the molecule. The Bischler-Napieralski reaction is one such example of intramolecular electrophilic aromatic substitutions used for the synthesis of

dihydroisoquinolines (which subsequently oxidize to isoquinolines) from the cyclization of β -aryl ethyl amides or β -aryl ethyl carbamates.²⁷ There are two proposed mechanisms for this transformation reported in the literature: the reaction proceeds either through an imine-ester intermediate, as shown below in Scheme 2.2, or via a nitrilium ion intermediate. However, both pathways postulate the formation of the quinoline structure (2.9, Scheme 2.2) through an intramolecular electrophilic aromatic substitution reaction.



Scheme 2.3: Mechanism for Bischler-Napieralski reaction via an imine-ester intermediate

In 1997, Haseltine reported a convergent formal synthesis of the natural product (+)-Pancratistatin²⁸ that took advantage of an intramolecular electrophilic aromatic substitution reaction to establish the carbon skeleton (2.12 \rightarrow 2.15, Scheme 2.3).

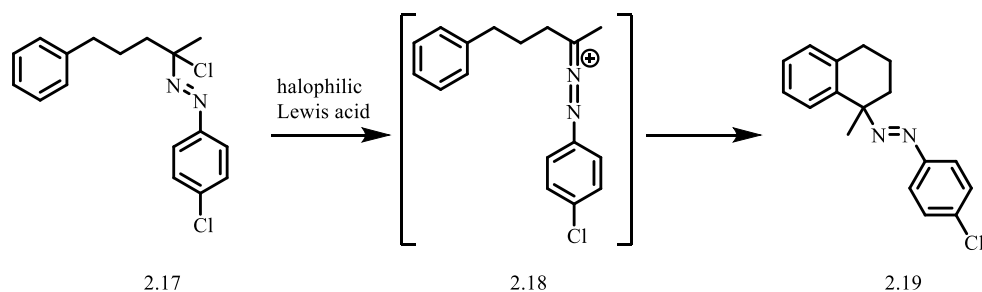


Scheme 2.4: Formation of Pancratistatin core through intramolecular electrophilic aromatic substitution

The highly electrophilic nature of heteroallenes make them viable candidates for electrophilic aromatic substitution reactions. In view of this, we sought to explore the reactivity of 1-aza-2-azoniaallene salts in this field.

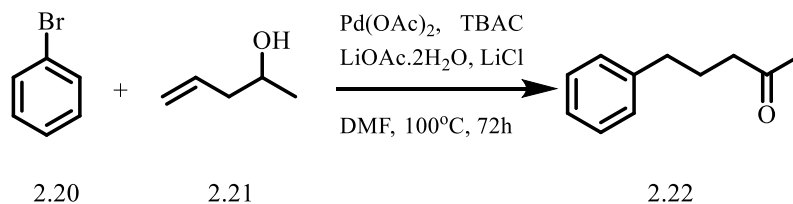
2.3. Intramolecular electrophilic aromatic substitution reaction of 1-aza-2-azoniaallene salts

As introduced in section 1.9, the participation of 1-aza-2-azoniaallene intermediates in electrophilic aromatic substitution reactions was first observed by Dr. Daniel Bercovici. It was observed that 1-aza-2-azoniaallene intermediates reacted with a pendant aromatic ring tethered three methylene units away (**2.17** → **2.19**, Scheme 2.4)



Scheme 2.5: Intramolecular electrophilic aromatic substitution of 1-aza-2-azoniaallene salts

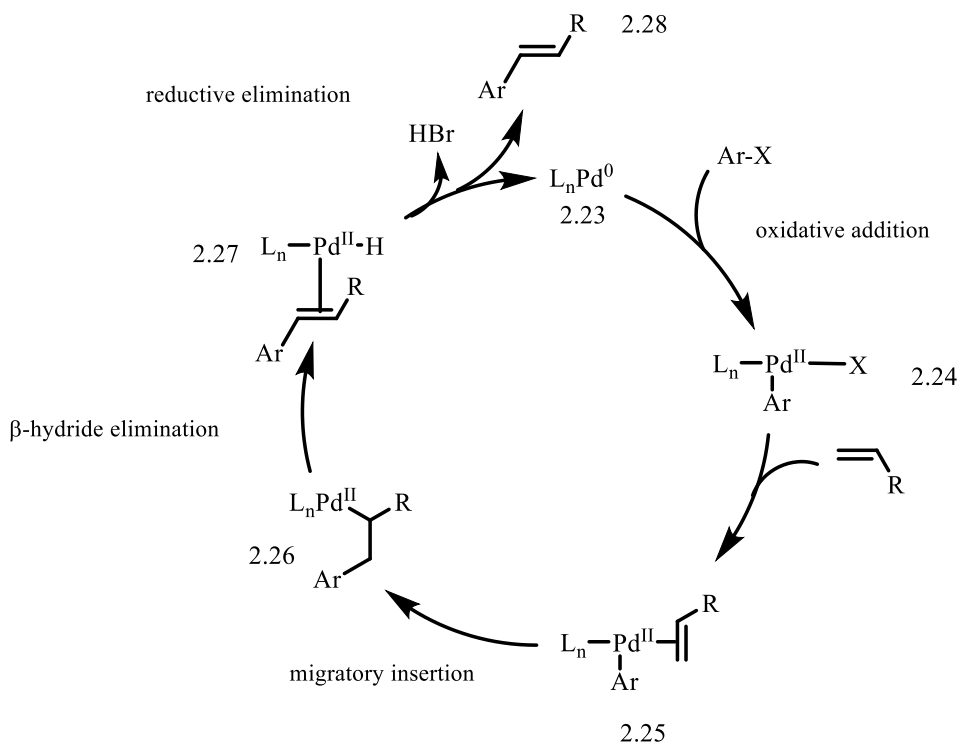
5-phenyl-pentan-2-one, the ketone precursor of the requisite α -chloroazo, was previously prepared via a Grignard reaction of hydrocinnamyl magnesium bromide with acetyl chloride. However, this synthetic route resulted in an inseparable impurity which fortunately did not interfere with the formation of the α -chloroazo and other subsequent reactions. To obtain a pure α -chloroazo substrate, I synthesized the precursor ketone via a Heck coupling between 4-hydroxy-pent-1-ene and bromobenzene (Scheme 2.5).



Scheme 2.6: Synthesis of 5-phenyl-pentan-2-one via Heck coupling

Since its discovery in 1968, the Heck reaction has proven to be a powerful tool for the functionalization of alkenes with aryl groups. The catalytic cycle involves the

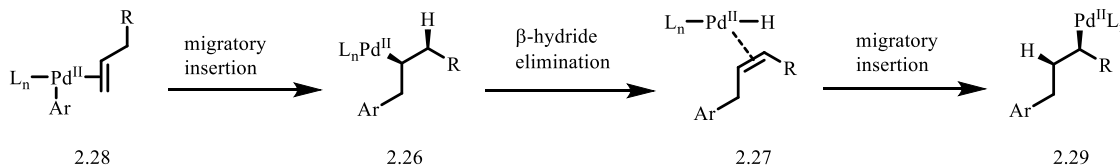
insertion of palladium (0) into the Ar-X bond, coordination of the alkene to palladium, a *syn* migratory insertion of the alkene into the Ar-Pd bond and a *syn* β -hydride elimination to give a new palladium-alkene π -complex **2.27**. The palladium (0) compound is finally regenerated by a reductive elimination that also gives new alkene **2.28**.²⁹



Scheme 2.7: Catalytic cycle of Heck reaction

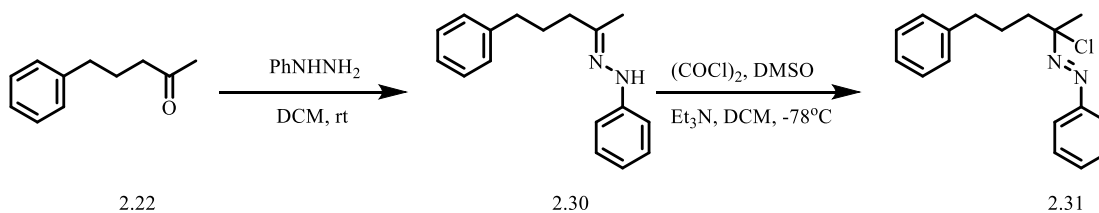
In some cases, isomerization of the new carbon-carbon bond may occur by a *syn* readdition of HPdX in the reverse direction, positioning the Pd catalyst one carbon down the alkyl chain like **2.29** (Scheme 2.7). This is called a “relay” or “chain walking” and

produces alkene isomers.^{30,31} Sigman and coworkers established a redox relay reaction, where the relay by palladium is controlled by a thermodynamic sink (an alcohol) to form aldehydes or ketones,^{32,33} like the synthesis of 5-phenyl-pentan-2-one (**2.22**, Scheme 2.5).



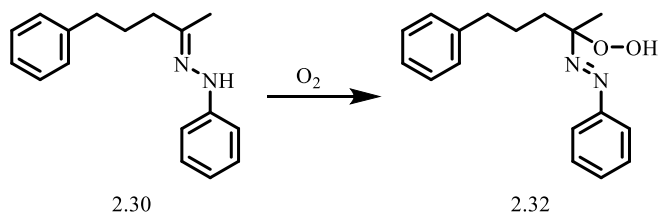
Scheme 2.8: Palladium catalyzed “chain walking”

The ketone synthesized was then converted to the corresponding α -chloroazo by methods previously reported in the group. This involves the initial condensation reaction between ketone and phenyl hydrazine to form the phenylhydrazone **2.30**, which is later subjected to oxidation with dimethylsulfonium chloride (prepared from DMSO and oxalyl chloride) to liberate the corresponding α -chloroazo compound **2.31**.



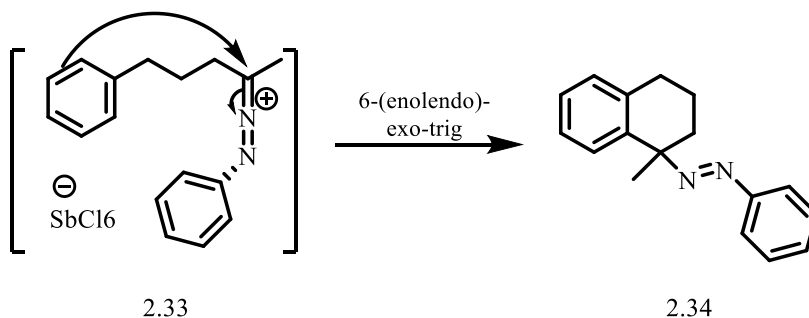
Scheme 2.9: Formation of α -chloro azo compound

A frequent problem faced in this synthetic route is the susceptibility of phenylhydrazones to undergo spontaneous oxidation as shown below in scheme 2.9. Hence conscious efforts were made to handle the substrate under inert conditions (nitrogen) and limit its exposure to atmospheric oxygen.



Scheme 2.10: Auto-oxidation of phenylhydrazones

The subsequent electrophilic aromatic substitution reaction closely resembles a Friedel-Crafts acylation reaction where the halophilic Lewis acid abstracts the chloride to generate a reactive electrophile which when attacked by the nucleophilic pendant aromatic ring provides a fused bicyclic azo product. Ring formation is a Baldwin favored ring closure similar to a 6-(enolendo)-exo-trig cyclization).³⁴⁻³⁶



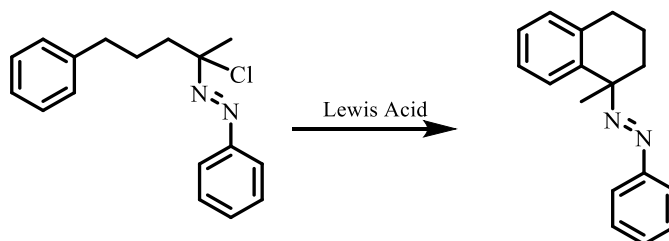
Scheme 2.11: Electrophilic aromatic substitution of 1-aza-2-azoniaallene salts

2.4. Optimization of reaction conditions for intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts

2.4.1. Optimization of halophilic Lewis acid

With a cleaner and efficient route to prepare the starting ketone, I investigated the electrophilic aromatic substitution reaction using other halophilic Lewis acids, such as AlCl_3 , TMSOTf and AgOTf, that had been instrumental in the generation of 1-aza-2-azoniaallene salts for polar $[4^++2]$ cycloadditions. I observed that by changing the Lewis Acid to AlCl_3 (entry 2) the yield improved over the initial SbCl_5 result by 14%. Both TMSOTf (entry 3) and AgOTf (entry 4) exhibited comparable yields to that of AlCl_3 . Since TMSOTf was easier to store and handle, is more cost efficient, and involves simpler reaction conditions, it was chosen as the best Lewis acid to pursue the substrate scope.

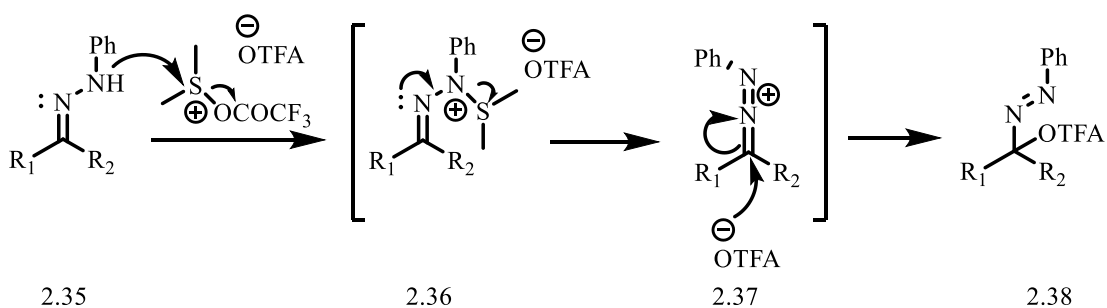
Table 2.2: Screening halophilic Lewis acids



Entry	Lewis Acid	Time (h)	Temperature (°C)	Yield (%)
1	SbCl_5	3	-60	55
2	AlCl_3	4	-60	69
3	TMSOTf	4	Room temperature	71
4	AgOTf	2	Room temperature	68

2.4.2. Comparison of α -OTFA vs α -Cl variants of azo compounds

As mentioned in section 1.6, Dr. Ram Dhakal reported the use of α -trifluoroacetoxy azo compounds as alternate progenitors of 1-aza-2-azoniaallene salts. He was able to achieve high yields of products even with sterically hindered systems. This requires activation of DMSO with trifluoroacetic anhydride to generate trifluoroacetoxy dimethylsulfonium trifluoroacetate which is attacked by the anilinic nitrogen of the hydrazone **2.35**. The lone pair on the imine nitrogen then forms a double bond with the adjacent nitrogen leading to the elimination of dimethylsulfide to generate a 1-aza-2-azoniaallene intermediate **2.37**. This intermediate then traps a trifluoroacetoxy counterion to form the α -trifluoroacetoxy azo compound **2.38**.

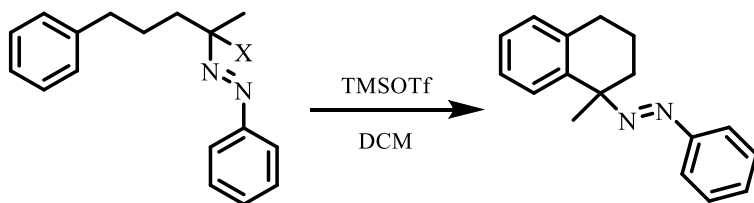


Scheme 2.12: Mechanism for the generation of α -OTFA compounds from hydrazone and trifluoroacetoxy dimethylsulfonium trifluoroacetate

Dr. Dhakal observed that the formation of chloro and trifluoroacetoxy analogues of α -substituted azo compounds are comparable with respect to yields and reaction time. However, the higher reaction temperature used for α -trifluoroacetoxy compounds opens the potential to carry out the desired transformation on sterically hindered systems. These

observations were found to be consistent when ketone **2.22** successfully underwent an intramolecular electrophilic aromatic substitution in the presence TMSOTf. The yields of the obtained azo product **2.34** is comparable to that obtained with the α -chloroazo analogue.

Table 2.3: α -Cl versus α -OTFA in electrophilic aromatic substitution of 1-aza-2-azoniaallene salts



X	Time (h)	Temperature (°C)	Yield (%)
Cl	4	Room temperature	71
OTFA	4	40	69

In the upcoming sections, all 1-aza-2-azoniaallene salts will be generated from α -OTFA precursors and will be treated with TMSOTf to study the intramolecular electrophilic aromatic substitution reactions.

2.5. Electronic effects on intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts

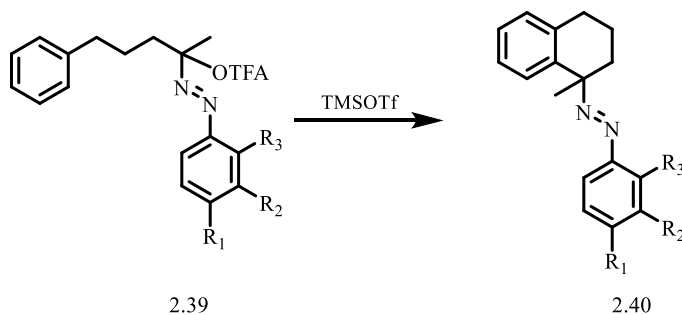
Having optimized the reaction conditions for the model substrate **2.34**, I began to investigate how the electronics of the system would impact the reactivity of 1-aza-2-

azoniaallene salts. I hypothesize that varying the electronics on both aryl rings would influence the efficiency of the electrophilic aromatic substitution. The results provided in this section support this hypothesis.

2.5.1. Effect on N-aryl ring electronics on intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts

The effects of the electronics of the N- aryl ring was studied on substrates containing either an electron withdrawing or donating group around the N-aryl ring. These substrates were prepared by treating 5-phenyl pentan-2-one with different phenylhydrazines containing various electron withdrawing and electron releasing groups along the aryl ring (Table 2.4). The 4-chlorophenyl derivative gave a product yield 14% less than the unsubstituted variant, whereas, the electron rich 4-methoxy analogue gives comparable yields. The electron deficient 3-nitrophenyl derivative did not participate in the reaction and thus no electrophilic aromatic substitution product was observed.

Table 2.4: Effect on N-aryl ring electronics on intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts



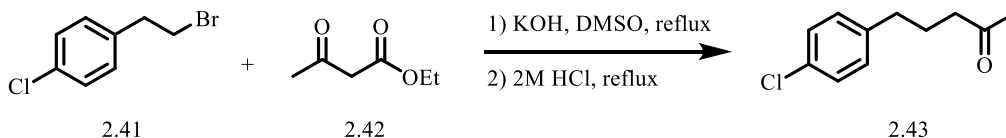
α -OTFA	R ₁	R ₂	R ₃	Yield (%)
2.23a	H	H	H	69
2.23b	Cl	H	H	52
2.23c	OMe	H	H	71
2.23d	H	NO ₂	H	0

From the above table we observe that electron rich N-aryl rings have less impact on the TMSOTf mediated electrophilic aromatic substitution and generate azo products **2.40b-c** in comparable yields. However, the presence of electron withdrawing groups potentially diminish the electrophilicity of the heteroallene carbon and hence impedes the electrophilic aromatic substitution reaction.

2.5.2 Effect of pendant aryl ring electronics on intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts

The effects of the electronics of the pendant aryl ring were studied by preparing substrates containing various electron withdrawing and electron releasing groups along the pendant aryl ring (Table 2.5).

The preparation of the 4-methoxy, 4-nitro and 2,5-dimethoxy ketones (precursors to entries 1,2 and 4 respectively) were accomplished by Heck coupling as mentioned earlier.³⁷ The 4-chloro analogue was prepared by the alkylation of ethyl acetoacetate with *p*-(2-bromoethyl)-chlorobenzene (2.25) followed by decarboxylation.³⁸

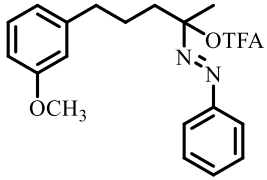
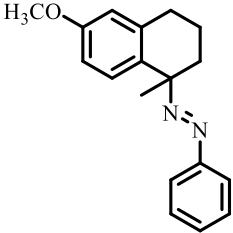
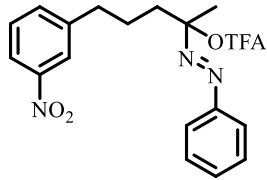
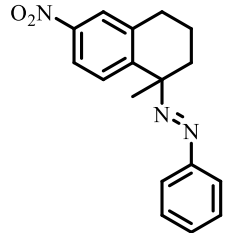
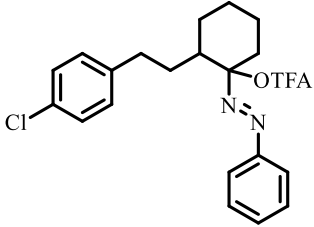
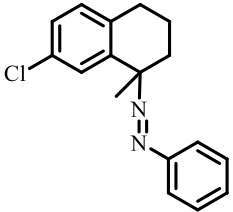
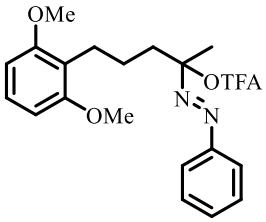
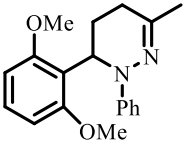


Scheme 2.13: Preparation of 4-chloroanalogue from ethyl acetoacetate and *p*-(2-bromoethyl)-chlorobenzene

The variation of the electronics on the pendant aryl ring have a large influence on the outcome of the electrophilic aromatic substitution reactions, yielding lower to no yield of the desired products. The strongly electron donating methoxy group **2.44a** (Table 2.5) has two potential sites available for substitution. However, due to steric hinderance, the substitution product *para* to the methoxy group **2.45a** is only observed. The 4-chloroaryl derivative **2.44c** gave a diminished overall yield of 34%. Interestingly, the introduction

of an electron withdrawing group (nitro) deactivates the pendent aryl ring greatly and inhibits the occurrence of electrophilic aromatic substitution and returns the starting ketone. We speculated that by substituting both *ortho* positions of the pendent aryl ring **2.44d** the system might undergo a C-H insertion reaction (as discussed in section 1.7) as the electrophilic aromatic substitution sites are blocked. Surprisingly, no insertion product was observed, and the starting ketone was returned almost entirely.

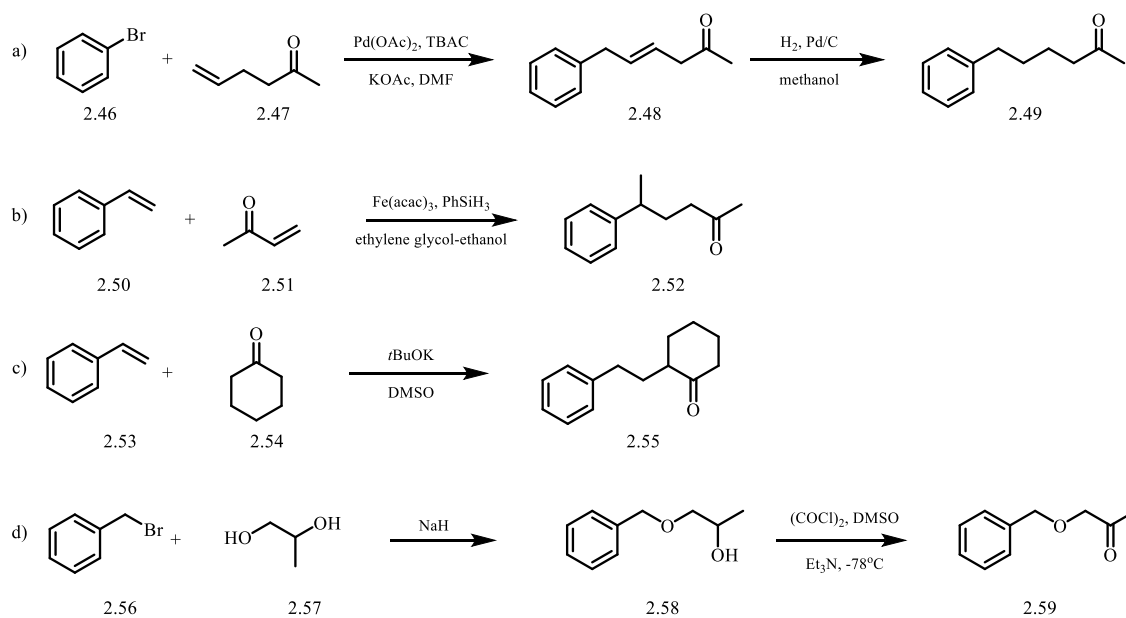
Table 2.5: Effect of pendant aryl ring electronics on intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts

α -OTFA compound	Expected EAS product	Yield (%)
 <p>2.44a</p>	 <p>2.45a</p>	56
 <p>2.44b</p>	 <p>2.45b</p>	0
 <p>2.44c</p>	 <p>2.45c</p>	34
 <p>2.44d</p>	 <p>(Expected insertion product)</p> <p>2.45d</p>	0

2.6. How variations along the carbon tether effect intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts

Several substrates were designed with substituents along the carbon tether to examine the effects of sterics on the electrophilic aromatic substitution of 1-aza-2-azoniaallene intermediates. All the ketone precursors were not commercially available and thus needed to be synthesized.

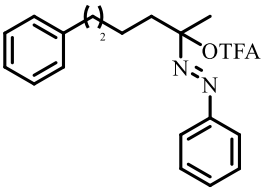
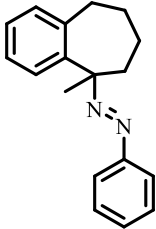
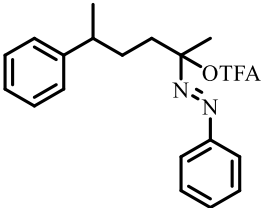
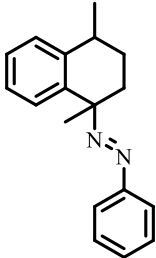
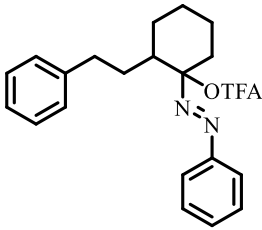
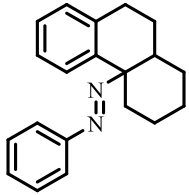
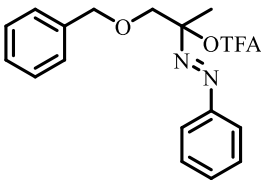
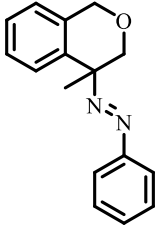
The ketone precursor with a longer tether by one methylene unit **2.49** was prepared by Heck coupling followed a hydrogenation reaction.³⁷ Ketones substituted at the benzylic (**2.36**) and *alpha* positions (**2.39**) were prepared by reaction of styrene with methyl vinyl ketone⁶⁵ and cyclohexanone⁴⁰ respectively. Finally, a ketone containing a heteroatom within the backbone chain (**2.43**) was synthesized by Williamson synthesis of benzyl bromide and 1,2-propanediol, followed by a Swern oxidation.⁴¹



Scheme 2.14: Preparation of ketone precursors

As shown in Table 2.6, increasing the tether by one carbon unit did not yield the desired 7-membered azo product **2.61a**. The substitution of the benzylic position with a methyl groups introduces a chiral center and provides the ring closed product in 54% yield as a 1:1 mixture of the diastereomers of **2.61b**. Surprisingly, substitutions *alpha* to the heteroallene carbon did not negatively impact the reaction. Cyclohexane derivative **2.60c** provided the fused tricyclic system **2.61c** in 79% yield. Finally, ether derivative **2.60d** gave the electrophilic aromatic substitution product **2.61d** exclusively in 82% yield. Insertion at the doubly activated benzylic position was not observed.

Table 2.6: Effect on intramolecular electrophilic aromatic substitution reactions of 1-aza-2-azoniaallene salts by variations along the carbon tether

α -OTFA compound	Expected EAS product	Yield (%)
 <p>2.60a</p>	 <p>2.61a</p>	0
 <p>2.60b</p>	 <p>2.61b</p>	54
 <p>2.60c</p>	 <p>2.61c</p>	79
 <p>2.60d</p>	 <p>2.61d</p>	82

2.7. Reactivity and applications of azo compounds

Azo compounds are a class of compounds with the general formula $R-N=N-R'$, where R and R' can be either an alkyl or an aryl group. Diaryl azo compounds, where R and R' are both aryl groups, are generally stable and crystalline species. They tend to be colored compounds, due to the delocalization of charges, and have found a wide use as dyes.^{42,43}

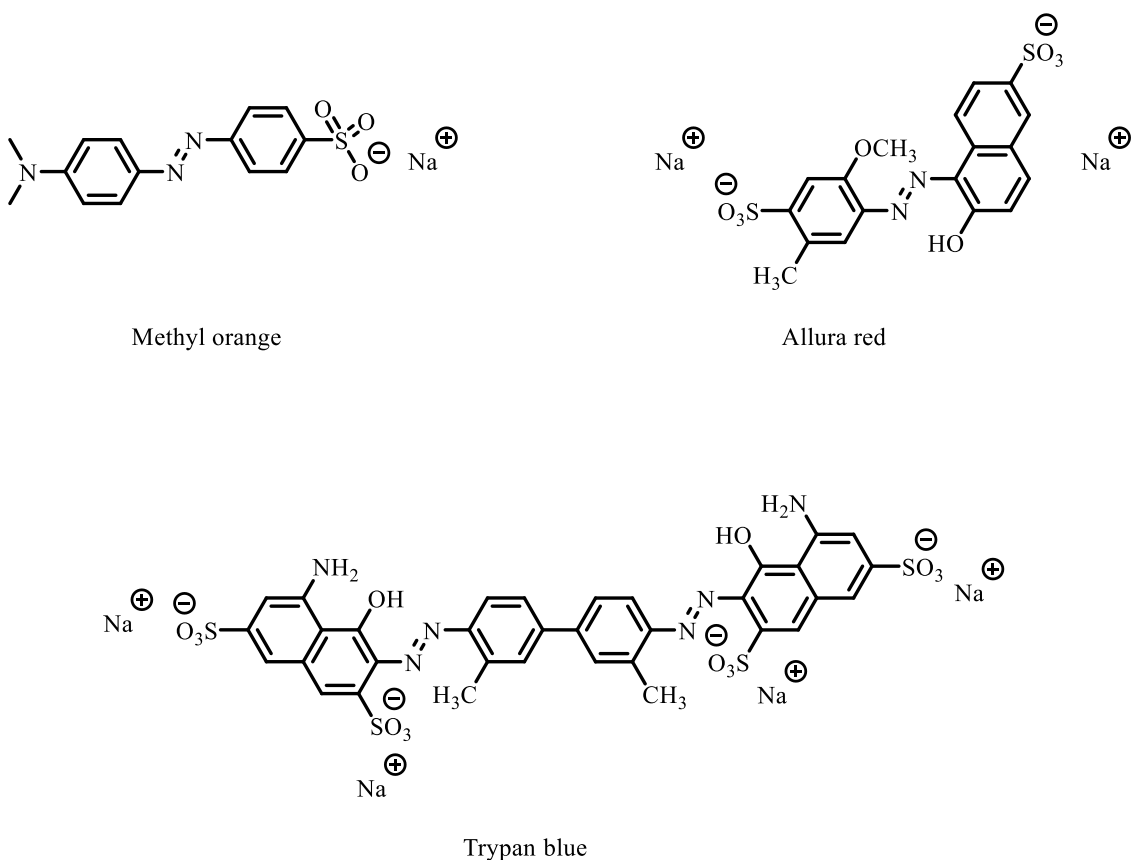


Figure 2.6: Few examples of azo dyes

Dialkyl azo compounds, where R and R' are both alkyl groups, are less commonly encountered than their aryl counterparts. Most available dialkyldiazines are symmetrical and are widely used as initiators to many radical-induced reactions. They can achieve initiation by decomposition, followed by elimination of N₂ molecule to generate a radical (2.62 → 2.63, Figure 2.5). The alkyl groups are generally tertiary with functionality to stabilize the initial radical (e.g. cyano in 2.62, ester in 2.67, or phenyl in 2.68). The most commonly encountered are the azonitriles, these include AIBN (2.46) and water-soluble initiator **2.68**.^{44,45}

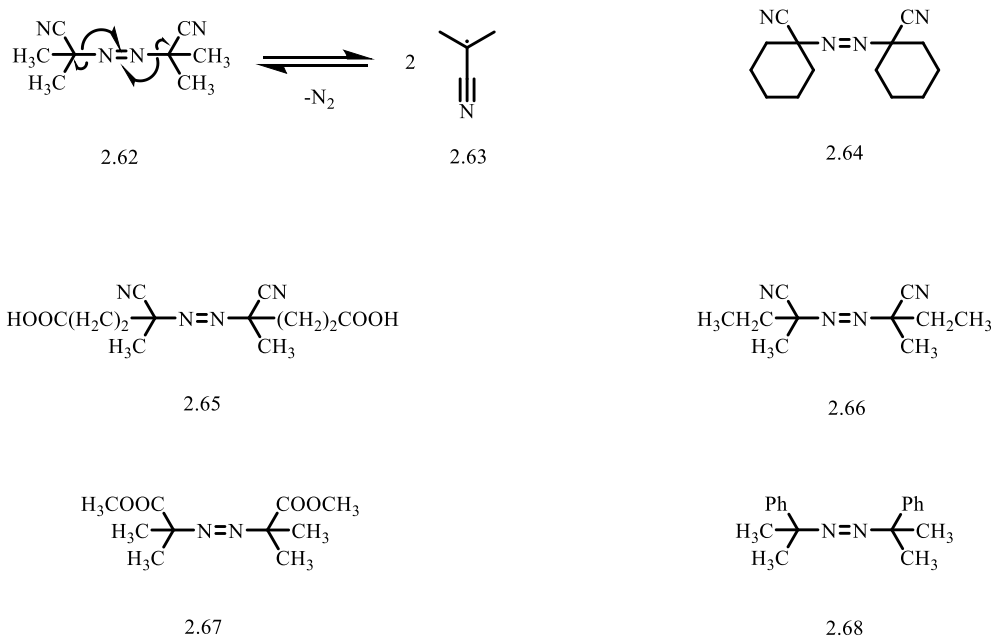
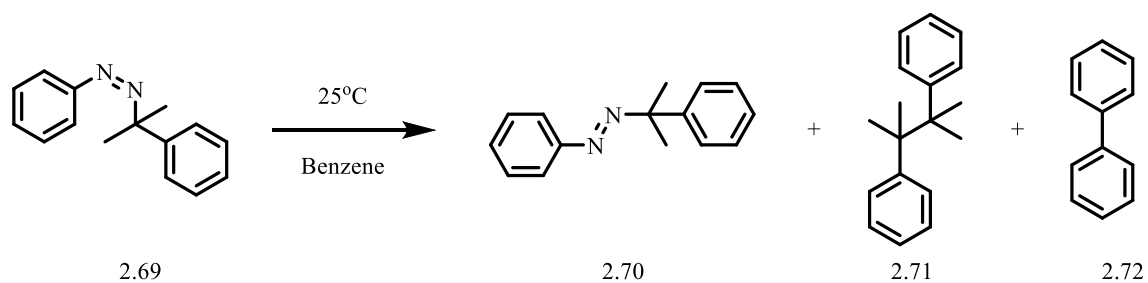


Figure 2.7: Some examples of dialkyl azo compounds

There are limited reports of unsymmetrical alkyl aryl azo compounds. Porter and Marnett synthesized the azo compound N-phenyl-N'-(2-phenyl-2-propyl) diazene by

unsymmetric urea oxidation method and studied its decomposition. They observed that the *cis* isomer thus formed (**2.69**, Scheme 2.14) is stable at temperatures up to 0°C but isomerize and decomposes in benzene at room temperature to give the corresponding *trans* isomer (**2.70**), dicumyl (**2.71**) and biphenyl (**2.72**) along with other volatile products.⁴⁶



Scheme 2.15: Decomposition of alkyl azo compound

2.7.1. Decomposition of azo products obtained by the intramolecular electrophilic aromatic substitution of 1-aza-2-azoniaallene salts

The azo products obtained from the electrophilic aromatic substitution of 1-aza-2-azoniaallene intermediates with pendent aryl rings fall under the category of alkyl aryl azo compounds and could potentially exhibit thermal and/or photochemical decomposition. During the substrate scope analysis of the electrophilic aromatic substitution reaction of 1-aza-2-azoniaallene salts, I observed that the NMR sample of product **2.34** in CDCl₃ underwent a color change from bright yellow to deep purple when left on the lab bench overnight at room temperature. Reexamination of the NMR spectrum revealed the emergence of new peaks (indicated with asterisks in Figure 2.6), a sharp

singlet at 7.36 ppm and an alkene peak at 5.88 - 5.84 ppm among others, indicating some level of decomposition. I allowed the sample to stand for a week at room temperature and then reanalyzed the sample by NMR, which showed a 1:2 ratio of azo compound **2.34** and a new product. Closer examination of the ^1H and ^{13}C NMR spectra revealed the formation of benzene (singlet at 7.36 ppm) and 4-methyl-1,2-dihydronaphthalene, (**2.78**, Scheme 2.15) which was confirmed by exact mass and comparison to reported spectra.⁴⁷ It is of interest to note that alkylaryl azo compounds generated by the intramolecular electrophilic aromatic substitution of 1-aza-2-azoniaallene salts vaguely resembles decomposition patterns observed by dialkyl compounds.

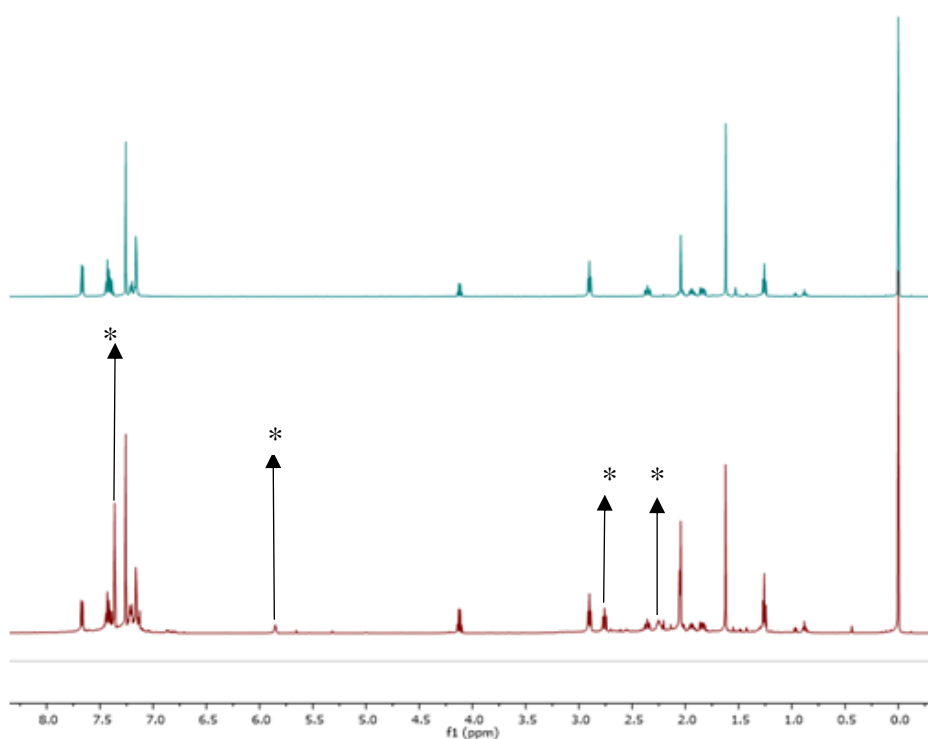
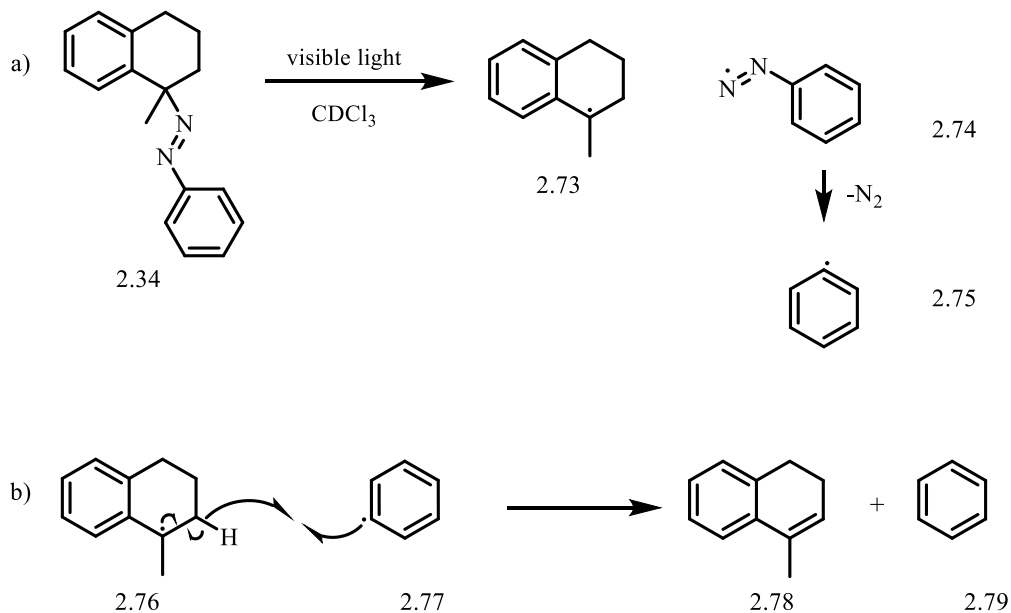


Figure 2.8: ^1H - NMR comparison of azo compound **2.18** before (top, teal color) and after standing at room temperature (bottom, red color). Observable new peaks are indicated with asterisks

2.7.2. Proposed mechanism for thermal decomposition

Based on the observed color change of the compounds and the confirmed characterization of the obtained products, I propose that the azo product **2.34** undergoes spontaneous cleavage of the C-N bond to generate a stable tertiary radical **2.73** and a phenylazo radical **2.74**. The phenylazo radical subsequently forms a benzene radical with the extrusion of nitrogen gas. Lastly, the benzene radical abstracts a proton *beta* to the tertiary radical resulting in the formation of benzene and 4-methyl-1,2-dihydronaphthalene **2.78** as observed in the NMR (Figure 2.6).



Scheme 2.16: Proposed mechanism for the decomposition of azo product **2.34**

2.8. Conclusions

As described in the sections above, 1-aza-2-azoniaallene intermediates undergo electrophilic aromatic substitution reactions with tethered pendent aryl rings three methylene units away to give alkyl aryl azo compounds. This reactivity is however inhibited under certain cases, namely when: (1) strong electron withdrawing groups are present on either aryl ring, (2) the tether is increased beyond three methylene units and (3) the positions *ortho* to the tether are blocked. These alkyl aryl azo compounds undergo a spontaneous decomposition under visible light at room temperature. It is worth examining these compounds in a photoreactor to determine the exact wavelength of visible light that causes this decomposition and applying it to the other azo compounds obtained in this chapter.

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CHAPTER 3: TOTAL SYNTHESIS OF (+)-IBOPHYLLIDINE BY THE [4+2] CYCLOADDITION OF 1-AZA-2-AZONIAALLENE SALTS

The unprecedented polar [4+2] cycloaddition between 1-aza-2-azoniaallene salts and olefins tethered three methylene units away (discussed in section 1.6) was originally established by Dr. Jodi Ogilvie. This reactivity was further studied by Dr. Daniel Bercovici and Dr. Ram Dhakal. In this chapter, I will discuss their experimental observations and the application of the polar [4+2] cycloaddition as the key step in the proposed total synthesis of a natural product, (+)-ibophyllidine.

3.1. Cycloaddition reactions

Cycloaddition reactions are a class of pericyclic reactions involving two or more unsaturated systems (within the same molecule or different molecules) that combine to form a cyclic adduct. They are among the most important types of reactions in organic chemistry since these reactions are one of the most efficient ways to make rings and are vital in the synthesis of natural products and biologically active substances.¹⁻⁹ The Woodward-Hoffman notation for describing cycloadditions uses square brackets indicating the number of electrons involved in the formation of the cycloadduct. For example, Stevenson and coworkers reported the synthesis of **3.2**, precursor compound of pterosin, by an intramolecular [2+2+2] cycloaddition of three alkyne groups in **3.1** (Figure 3.1).¹⁰

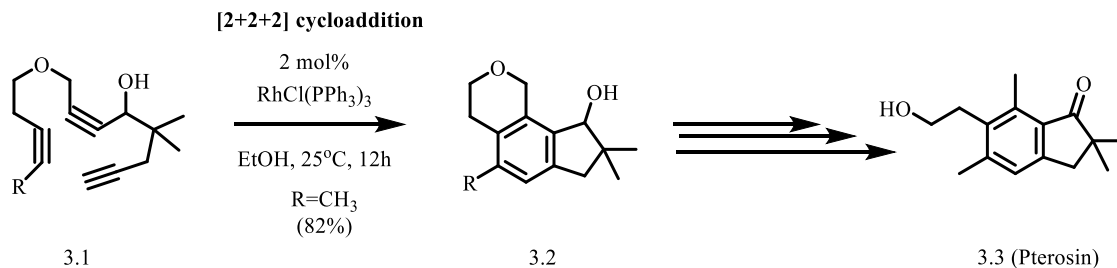


Figure 3.1: Example of an intramolecular [2+2+2] cycloaddition reaction

3.1.1. [4+2] cycloaddition reactions

The Diels-Alder reaction is the most commonly used cycloaddition reaction and several variants have been developed for the construction of cyclohexenes and heterocyclic compounds.¹¹⁻¹⁵ The reaction was first described in 1928 by Otto Diels and his student Kurt Alder while analyzing the products (**3.6** and **3.7**) formed from the reaction of cyclopentadiene with quinone, for which they later shared the Nobel prize in 1950.¹⁶

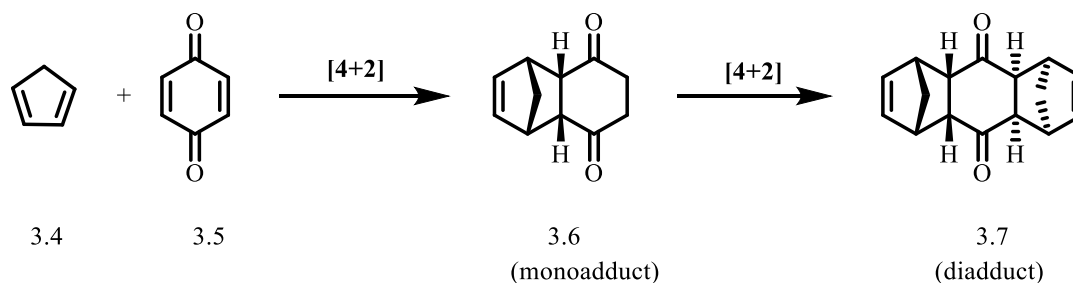


Figure 3.2: The discovery of the Diels-Alder reaction in 1928

Woodward and coworkers were one of the first to implement the Diels-Alder reactions to solve challenging synthetic hurdles during their total synthesis of steroids like cortisone and cholesterol¹⁷ and other biologically significant molecules like reserpine (Figure 3.3).¹⁸⁻²⁰

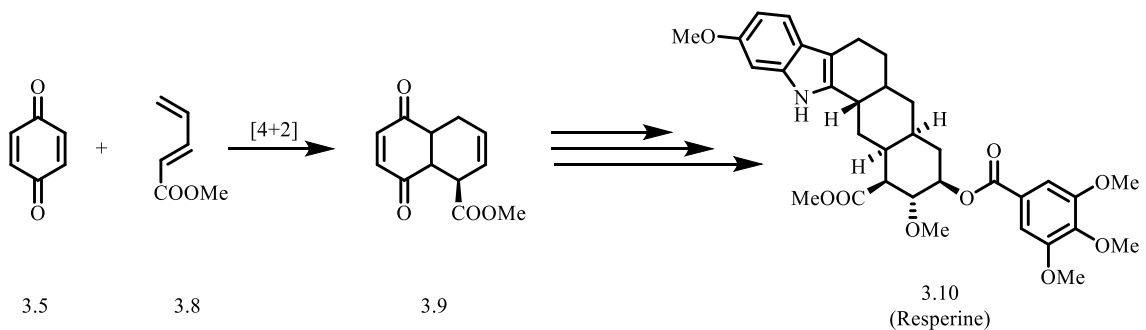


Figure 3.3: Use of Diels-Alder reaction by Woodward and coworkers in the total synthesis of reserpine

3.1.2. Polar [4+2] cycloaddition reactions

Most of the reports of [4+2] cycloaddition reactions involve uncharged species, like the Diels-Alder reaction. There is an inadequacy of examples involving charged atoms involved in cycloaddition reactions. Schmidt described that several variations of polar [4+2] cycloadditions can occur based on the structure of the 4 π system.²¹ The variations can be broadly divided into two classes; (1) positive charge is fixed on one of the atoms (**3.11a-d**, Figure 3.4) and (2) the positive charge can be delocalized over two or more atoms (**3.12a-e**, Figure 3.4).

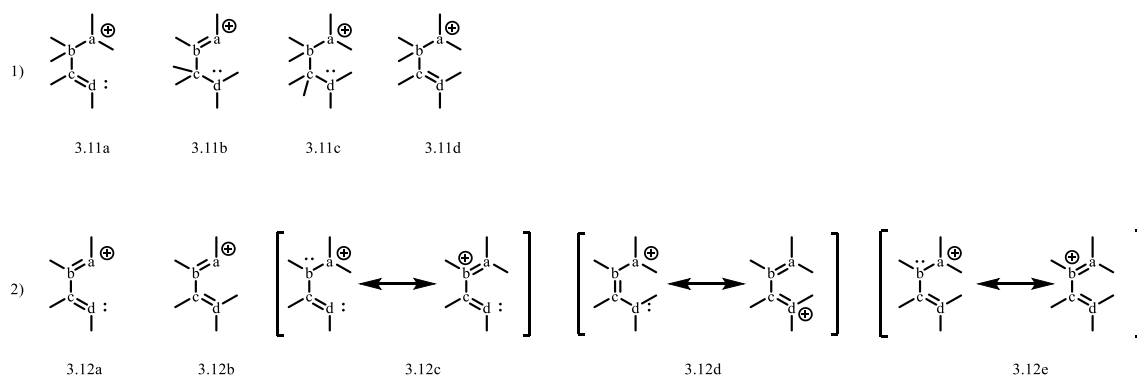


Figure 3.4: Cationic 4 π systems for cycloaddition according to Schmidt

The 4 π structure involved in the polar [4+2] cycloaddition of 1-aza-2-azoniaallene salts is structurally most like **3.12d**, as shown below in Figure 3.5.

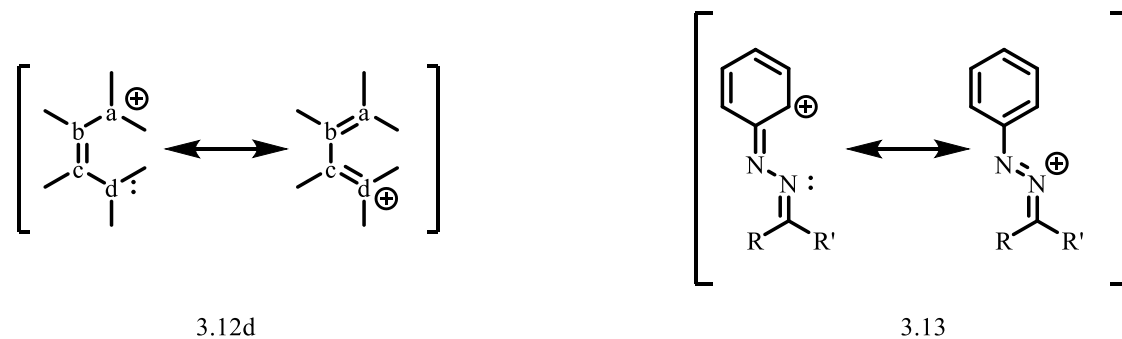


Figure 3.5: 4 π system of 1-aza-2-azoniaallene salts

3.2. Products derived from polar [4+2] cycloaddition of 1-aza-2-azoniaallene salts

The heterocyclic product obtained from the [4+2] cycloaddition of the olefin tether (behaving as the 2 π dienophile) and one of the π -bonds of the aryl ring along with the N=N⁺ bond (behaving as the 4 π diene) contains a 1,2,3,4-tetrahydrocinnoline

(Scheme 3.6) which is prevalent in several biologically active compounds and pharmaceuticals.²²⁻²⁴ In the following section, I will discuss the previous work done in the Brewer group to determine what effects substituents along on aryl ring and on the tether chain have on the intramolecular [4+2] cycloaddition.

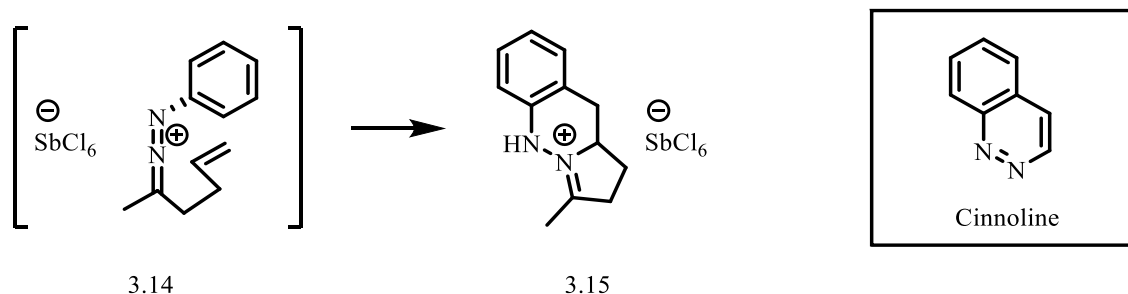
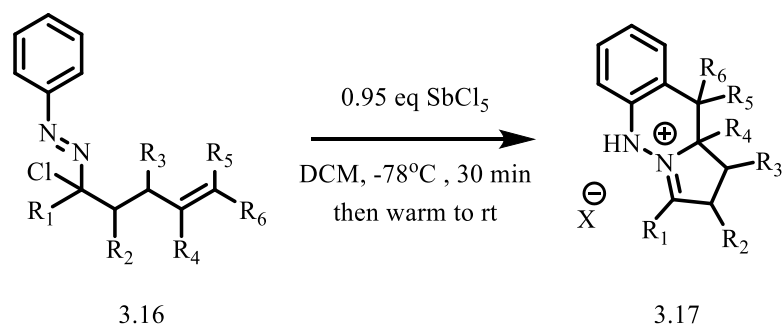


Figure 3.6: Intramolecular [4+2] cycloaddition of 1-aza-2-azoniaallene salts and olefins to form 1,2,3,4-tetrahydrocinnoline

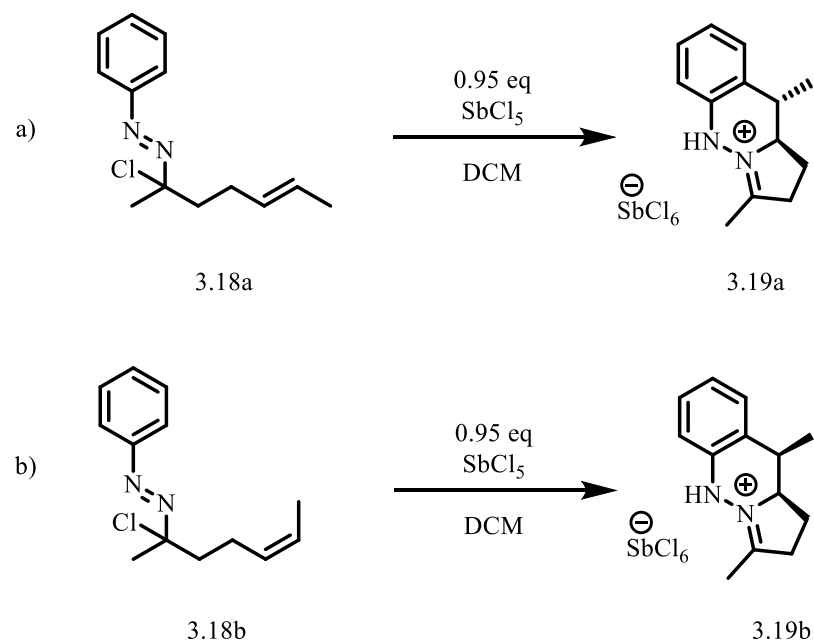
3.2.1. How variations along the carbon tether effect intramolecular polar [4+2] cycloaddition reactions of 1-aza-2-azoniaallene salts by

Dr. Daniel Bercovici discovered that adding 0.95 eq of SbCl_5 to a solution of **3.16** (Scheme 3.1) in DCM at $-78\text{ }^\circ\text{C}$ with subsequent warming to room temperature were optimal conditions to obtain the protonated azomethine imine products **3.17**. This reaction shows high tolerance for alkene substitution and steric substitutions on the tether as well giving most products in high yields (Scheme 3.1)



Scheme 3.1: Effect of variation of the substituents along the carbon tether on [4+2] cycloaddition of 1-aza-2-azoniaallene salts

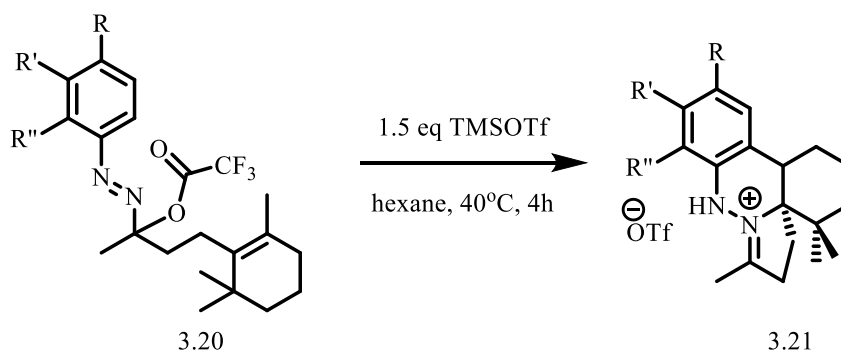
To provide a better understanding of the concerted nature of the bond-forming events, Dr. Bercovici subjected the α -chloroazo compounds of *trans* and *cis* alkenes **3.18a** and **3.18b** to cycloaddition conditions. He observed that each substrate provided a unique diastereomer of the product and is hence stereospecific implying that the cycloaddition reaction proceeds in a concerted manner.



Scheme 3.2: Evidence of a concerted mechanism for the polar [4+2] cycloaddition of 1-aza-2-azoniaallene salts

3.2.2. Effect of N-aryl ring electronics on intramolecular polar [4+2] cycloaddition reactions of 1-aza-2-azoniaallene salts

Dr. Ram Dhakal developed an improved reaction sequence for the synthesis of tri- and tetra-cyclic protonated azomethine imine products using α -OTFA azo compounds as an alternate 1-aza-2-azoniaallene precursor. He discovered that adding 1.5 eq of TMSOTf to a solution of **3.20** (Scheme 3.3) in hexanes at 40°C were optimal conditions and provided sterically hindered products (e.g. **3.21**) in high yields. This reaction was well tolerated by all substrates with varying substitutions along the aryl ring (with electron withdrawing and electron donating groups).



Scheme 3.317: Effect of variation of N-aryl electronics on [4+2] cycloaddition of 1-aza-2-azoniaallene salts

3.2.3. Substrate scope of intramolecular polar [4+2] cycloaddition of 1-aza-2-azoniaallene salts

The substrate scope analysis of the polar [4+2] cycloaddition of 1-aza-2-azoniaallene salts showed that the reaction is well tolerated to alkene substitution, steric variations along the tether, and electronic substitutions on the N-aryl ring. The generation of the structurally complex tetracyclic iminium salt **3.22d**, formed from a cyclohexene based 1-aza-2-azoniaallene salt, is good precedence for the key step of our proposed synthesis of terpene indole alkaloid (+)-ibophyllidine.

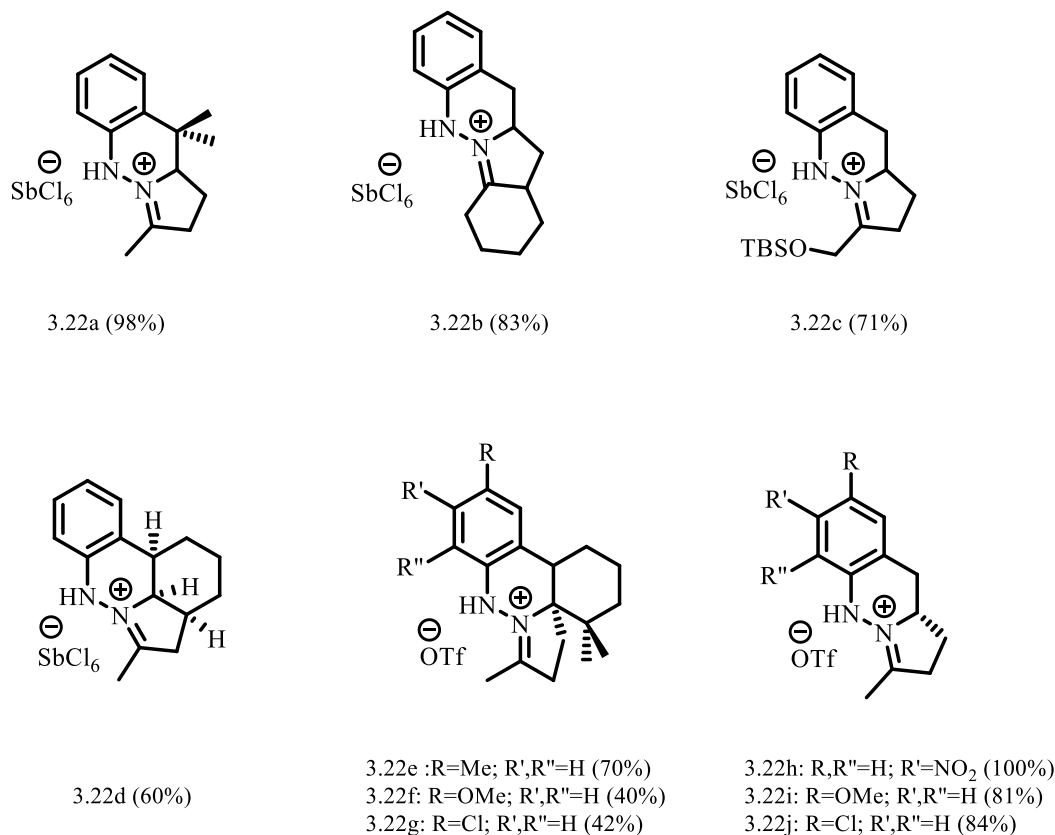


Figure 3.7: Example of protonated azomethine imine salts formed by the intramolecular [4+2] cycloaddition of 1-aza-2-azoniaallene salts

3.3. (+)-Ibophyllidine

Ibophyllidines, are a small family of terpene indole alkaloid that contain a fused pentacyclic skeleton but differ in the substitution and stereochemistry pattern at C20 (Figure 3.8).^{25,26} Ibophyllidine, along with other alkaloids, was isolated in 1976 from the iboga plant (*Tabernanthe iboga*) found in west-central Africa.^{27,28} Many African tribes in Gabon, Cameroon and the Republic of Congo use the alkaloid-containing roots of this

plant in several traditional ceremonies. Over the years several reports have claimed that the iboga plant has the potential ability to reverse addiction to recreational drugs such as alcohol and opiates.

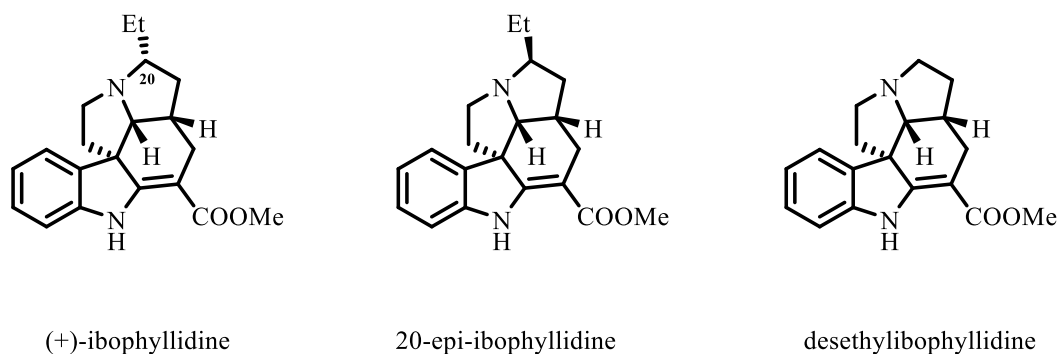


Figure 3.8: Representative ibophyllidines

Most indole and dihydroindole alkaloids are biosynthetically derived from tryptamine and the iridoid terpene secologanin and tend to maintain all the carbons of their biosynthetic precursors.²⁹ (+)-Ibophyllidine and 20-epi-ibophyllidine were found to be structurally like the C20 epimers of Ψ -vincadifformines (**3.23a-b**, Figure 3.9) and pandolines (**3.24a-b**) with a loss of the C21 carbon, probably through an oxidative cleavage process. The presence of a five-membered pyrrolidine ring in place of the more common six-membered piperidine ring, found in aspidospermine and pseudoaspidospermidine alkaloids, brings up synthetic challenges. The all-*syn*-pyrrolidine framework of ibophyllidine pushes the C20 ethyl group into the highly congested concave face of the cupped structure, thus making it the synthetically most demanding structure in the family.

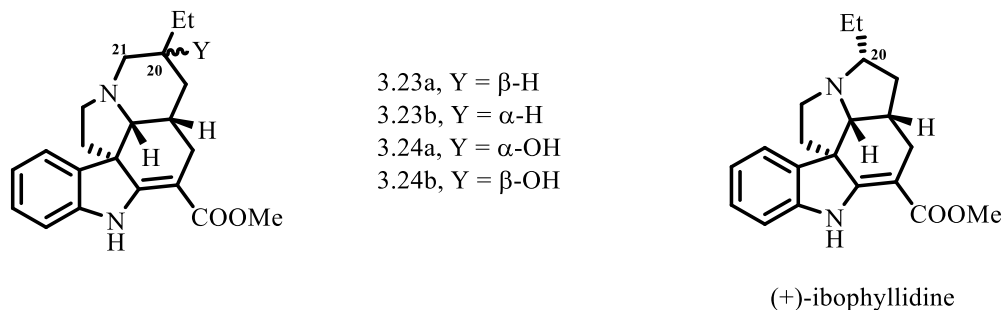


Figure 3.9: Structural similarity of (+)-ibophyllidine to aspidospermine and psuedoaspidospermidine

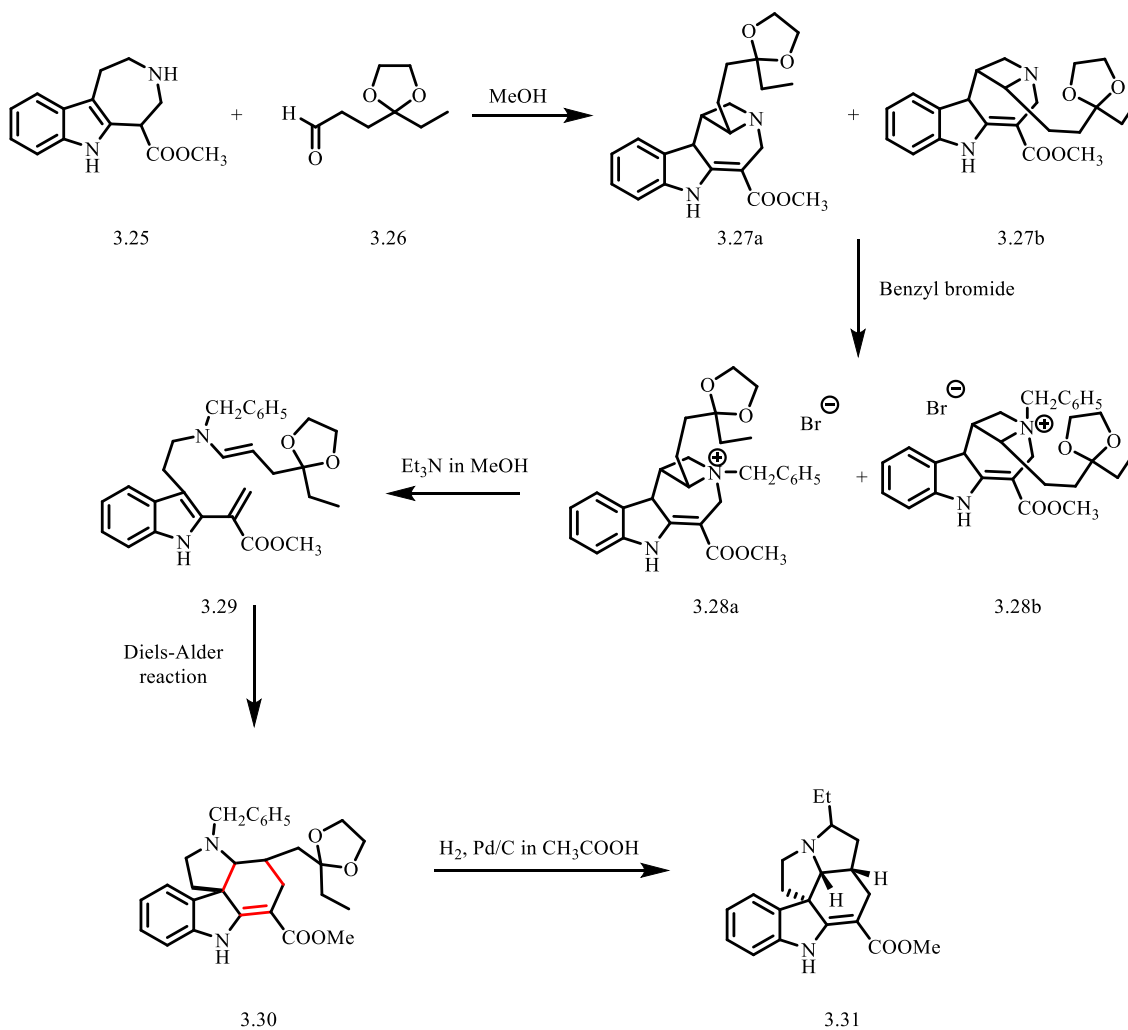
3.4. Previous syntheses of (+)-ibophyllidine

Despite a unique carbon skeleton, (+)-ibophyllidine has received less attention compared to its higher-carbon homologues. There are only two successful strategies reported for the construction of the (+)-ibophyllidine structure, which I will be discussing in this section.

3.4.1. Kuehne's Diels-Alder approach

The first approach to the total synthesis of (+)-ibophyllidine was implemented by Kuehne and Bohnert in 1981 involving a biomimetically inspired Diels-Alder reaction of an *in situ* generated secodine analogue.³⁰ Their approach involved the synthesis of bridged azepines **3.27a** and **3.27b** (Scheme 3.4), from the condensation of indoloazepine **3.25** with the ethylene ketal of 4-oxohexanal (**3.26**). Both azepine epimers were alkylated

with benzyl bromide and the subsequent quaternary salts generated were reacted with Et₃N in methanol to yield a single amino ketal **3.29**. The key Diels-Alder cyclization generated the A-B-C-E ring system. Hydrogenolysis of the N-benzyl substituent of the amino ketal, full epimerization of C3 and C7 and cyclization in acetic acid followed by hydrogenation gave ibophyllidine (**3.31**).



Scheme 3.4: Kuehne's biomimetic synthesis of ibophyllidine

Kuehne's strategy is one of the most successful ways to synthesize ibophyllidine, and several other research groups have used this approach as a blueprint to prepare ibophyllidine.³¹⁻³³ Kuehne and coworkers modified their original synthesis in 1998 to prepare optically active (+)-ibophyllidine using a bulky ferrocenyl chiral auxiliary³⁴ to control the stereochemistry of the Diels-Alder reaction. This was the first reported non-racemic synthesis of (+)-ibophyllidine.

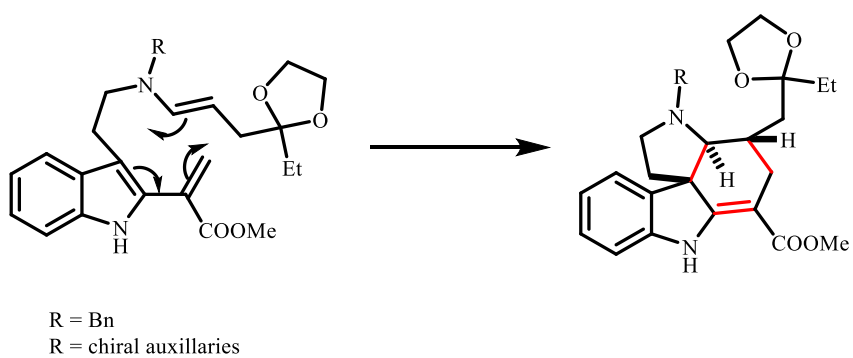


Figure 3.10: Kuehne's Diels-Alder approach to synthesize (+)-ibophyllidine

3.4.2. Andrews and Kwon's asymmetric phosphine-catalyzed [3+2] annulation approach to (+)-ibophyllidine

While investigating the reactivity of electron deficient π -systems in nucleophilic phosphine catalyzed reactions, Andrews and Kwon established a method to generate 1,2,3,5-tetrasubstituted pyrroline rings.³⁵⁻³⁷ This scaffold is present in ibophyllidine and they successfully developed an asymmetric (3+2) using chiral phosphine **3.37** and applied it to the successful total synthesis of (+)-ibophyllidine in 2012.³⁸

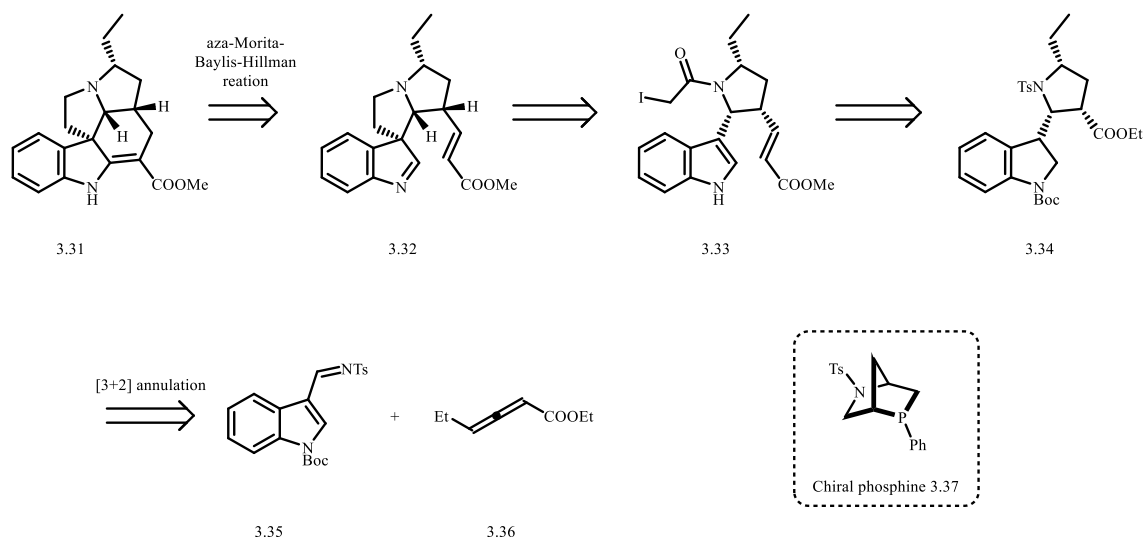
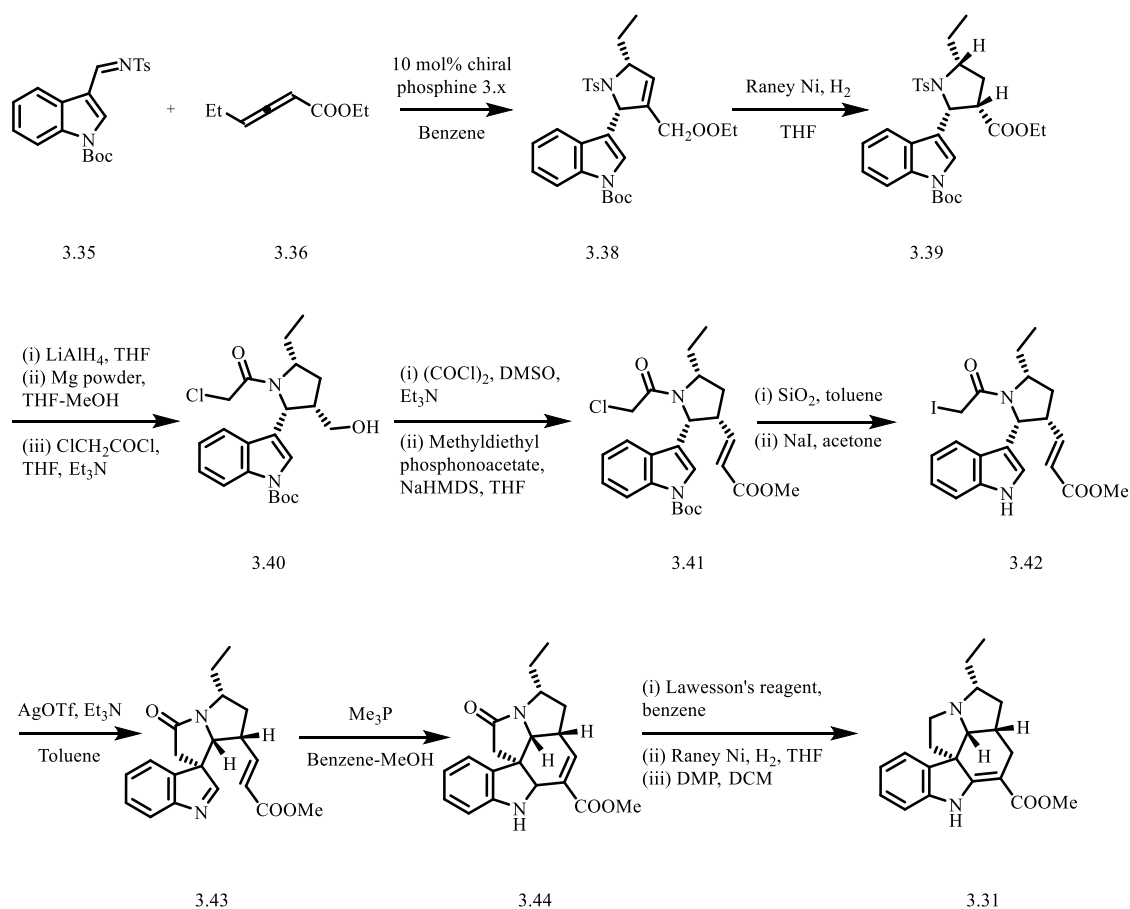


Figure 3.11: Andrews and Kwon's retrosynthetic approach to the total synthesis of (+)-ibophyllidine

Andrews and Kwon carried out the key (3+2) annulation between commercially available allenoate **3.36** and N-tosyl amine **3.35** to obtain the corresponding pyrroline followed by a diastereoselective hydrogenation which gave **3.39** and established the congested arrangement of ring D in (+)-ibophyllidine (Scheme 3.5). This step established an all *syn*-pyrrolidine ring with three out of four desired stereocenters found in ibophyllidine with a high level of diastereo- and enantio-selectivity. The ester group in **3.39** was reduced followed by the reductive cleavage of the tosyl group to generate an amino alcohol that was condensed with chloroacetyl chloride to give **3.40**. Swern oxidation of the primary alcohol to an aldehyde followed by a Horner-Wardsworth-Emmons olefination generated α,β -unsaturated ester **3.41**. The Boc group removal gave

the free indole, and Finkelstein conditions were used to convert the chloride to an iodide. In the presence of AgOTf, the iodide **3.42** was activated and gave spiro compound **3.43** that underwent an aza Morita-Baylis-Hillman³⁹⁻⁴¹ reaction to form the pentacyclic skeleton of ibophyllidine. Subsequent deoxygenation of the lactam and a final oxidation with Dess-Martin periodinane gave the desired alkaloid, establishing the first enantioselective total synthesis of (+)-ibophyllidine in 15 steps and 13% overall yield.



Scheme 3.5: Andrews and Kwon's enantioselective total synthesis of (+)-ibophyllidine via an asymmetric phosphine-catalyzed [3+2] annulation

3.5. Brewer groups proposed retrosynthesis via [4+2] cycloadduct of 1-aza-2-azoniaallene salts

Tetracyclic iminium salts **3.22d** (Figure 3.7) contains a key portion of the ibophyllidine framework. We proposed that the ethyl analogue of **3.22d** could serve as a precursor in a proposed synthesis of (+)-ibophyllidine. In the retrosynthetic sense, we envisioned (+)-ibophyllidine as being derived from amino alcohol **3.45** (Figure 3.12). The diamine could in turn be generated by the diastereoselective reduction and nitrogen-nitrogen bond cleavage of protonated azomethine **3.46**. We planned for this key intermediate to be accessible by the intramolecular polar [4+2] cycloaddition of the 1-aza-2-azoniaallene intermediate derived from ketone **3.48**.

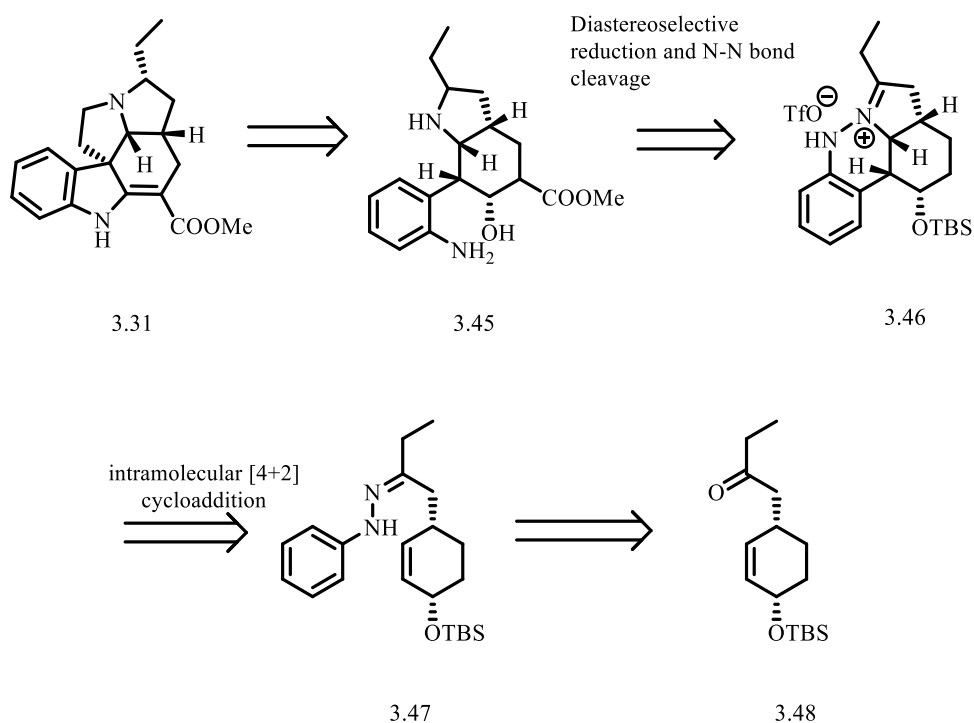


Figure 3.12: Brewer groups proposed retrosynthesis to (+)-ibophyllidine via a [4+2] cycloadduct of 1-aza-2-azoniaallene salt

3.6. Preparation of protonated azomethine imine salt 3.47

Our synthetic route started with a palladium catalyzed 1,4 dibenzoyloxylation of 1,3 cyclohexadiene. The palladium catalyzed 1,4 functionalization of conjugated dienes was developed in depth by Backvall and coworkers in depth.⁴²⁻⁴⁵ In these reactions two nucleophiles (X^- and Y^-) are introduced at the 1- and 4- positions of a diene. These 1,4-additions involve an intermediate (π -allyl) palladium complex (3.50, Figure 3.13) that directs the introduction of the second nucleophile (Y^-) to the 4-position relative to the first nucleophile (X^-). An external *trans* attack by Y^- (pathway a) would result in an overall *cis* addition across the diene whereas an intramolecular *cis* migration (pathway b) would lead to an overall *trans* addition.

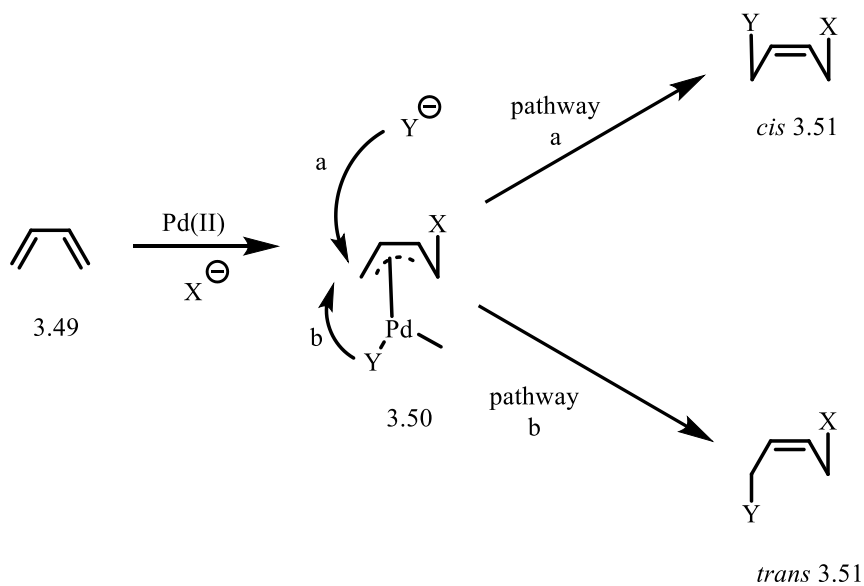
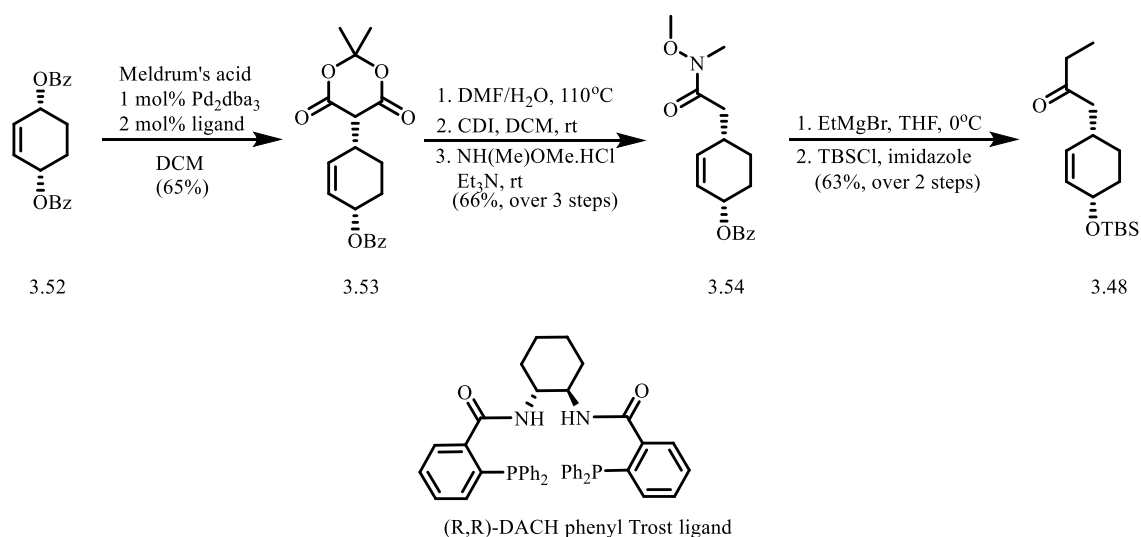


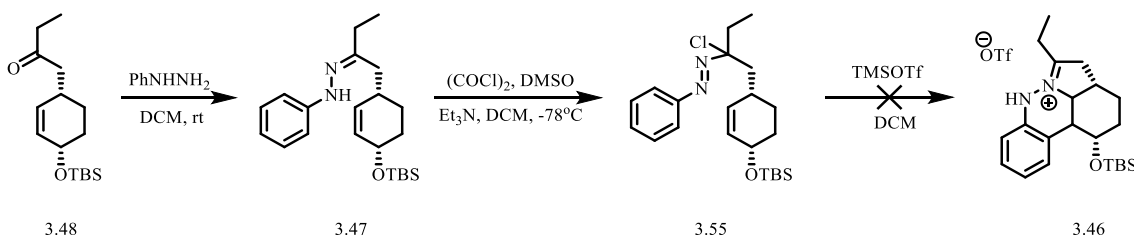
Figure 3.93: Palladium catalyzed 1,4-addition to conjugated dienes via a (π -allyl) palladium intermediate

The reaction of 1,3-cyclohexadiene with benzoic acid in the presence of Pd(OAc)₂ and p-benzoquinone in acetone yields *cis* **3.52** (Scheme 3.6) in 85% yield.¹¹⁷ p-Benzoquinone not only behaves like an oxidant but also acts as a ligand that coordinates to palladium (II) in the (π-allyl) palladium complex. The reaction of **3.52** with Meldrum's acid in the presence of 1 mol% Pd₂dba₃ and 2 mol% of (R,R)-DACH phenyl Trost ligand with NaH as base at 0°C in DCM resulted in the monoalkylated product **3.53**, as reported by Trost.⁴⁶ Heating **3.53** in a 9:1 mixture of DMF and water at 110°C liberated carbon dioxide gas and acetone to generate the free carboxylic acid group. The acid was converted to Weinreb amide **3.54** by activation with 1,1'-carbonyldiimidazole with N,O-dimethylhydroxylamine hydrochloride and Et₃N.⁴⁷ Amide **3.54** was treated with commercially available ethyl magnesium bromide to form the ethyl ketone variant with a free alcohol, which was immediately protected by the reaction with TBSCl and imidazole to generate **3.48**.^{48,49}



Scheme 3.6: Preparation of ethyl ketone 3.48

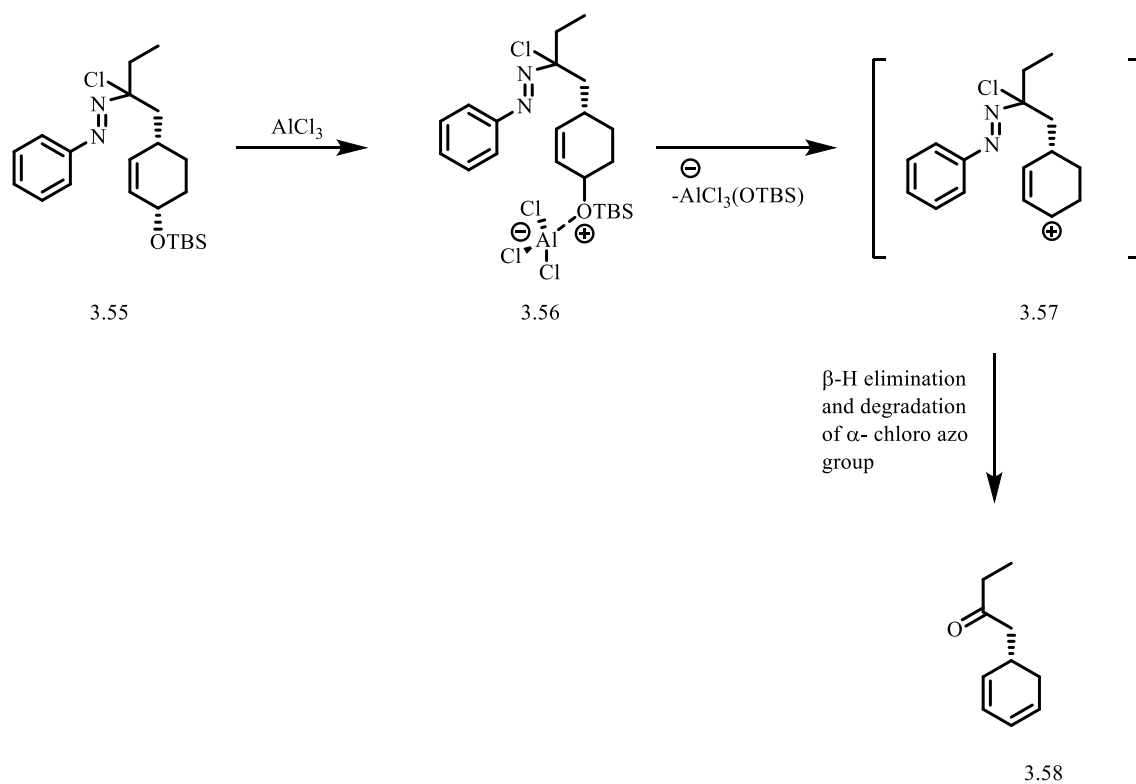
Having successfully synthesized the precursor ketone **3.48** we were almost able to attempt the key [4+2] cycloaddition. To achieve this, we converted the ketone into the corresponding α -chloroazo by methods previously reported in the group. This involved reacting ketone **3.48** with phenyl hydrazine to form the phenylhydrazone **3.47**, which was then oxidized with chloro dimethylsulfonium chloride at -78°C (prepared from DMSO and oxalyl chloride) to liberate the corresponding α -chloroazo compound **3.55**. Adding TMSOTf to a solution of **3.55** in DCM and heating it to 40°C did not yield the desired protonated azomethine imine **3.46** (Scheme 3.22).



Scheme 3.7: Attempt to generate cycloadduct 3.46 via an intramolecular [4+2] cycloaddition in the presence of a halophilic Lewis acid

Screening other halophilic Lewis acids previously used in the group (SbCl_5 , AlCl_3 and AgOTf) gave similar results as TMSOTf and generated a new product. With the aid of NMR and mass spectrometry experiments, I discovered that the new product obtained upon reacting α -chloro azo compound with halophilic Lewis acids was the diene analogue of ketone **3.48**. This can be explained by the fact that the Lewis acids used in the reaction have an affinity for oxygen as well as for halogens and thus the alcoholic

group creates a competitive coordination site. The Lewis acids preferentially coordinate to the OTBS group in **3.55** (Scheme 3.8) due to the formation of a stable allylic cation **3.57** that undergoes a β -hydride elimination to regenerate the Lewis acid along with a cyclohexadiene product. The inability of α -chloro azo compound **3.55** to generate the corresponding 1-aza-2-azoniaallene intermediate lead to its potential degradation back to a ketone, overall resulting in the formation of ethyl ketone diene **3.58** which was consistent with the characterization data.



Scheme 3.8: Formation of cyclohexadiene ethyl ketone 3.58 via allylic cationic intermediate

Efforts of increasing the equivalence of the previously mentioned array of halophilic Lewis acids up to 5 eq as well as making the alcoholic group less accessible by a bulkier protecting group such as TBDPS were rendered futile. Aforementioned results indicate that 1-aza-2-azoniaallene intermediates containing allylic alcohols are unable to undergo an intramolecular polar [4+2] cycloaddition with reaction conditions established in the Brewer group (Section 3.2) and thus poses as a limitation to the substrate scope of this reaction.

3.7. Alternate route to (+)-ibophyllidine

The discovery that 1-aza-2-azoniaallene salts derived from cyclic ketones containing allylic alcohols would not undergo polar [4+2] cycloaddition reactions was a major setback in my research. To circumvent this roadblock, I attempted to construct analogues of ketone **3.48** that would lead to protonated azomethine imine analogues of **3.46**, that could be alternative intermediates. For this purpose, three cycloadducts were considered (**3.59-3.61**, Figure 3.14), as possible candidates.

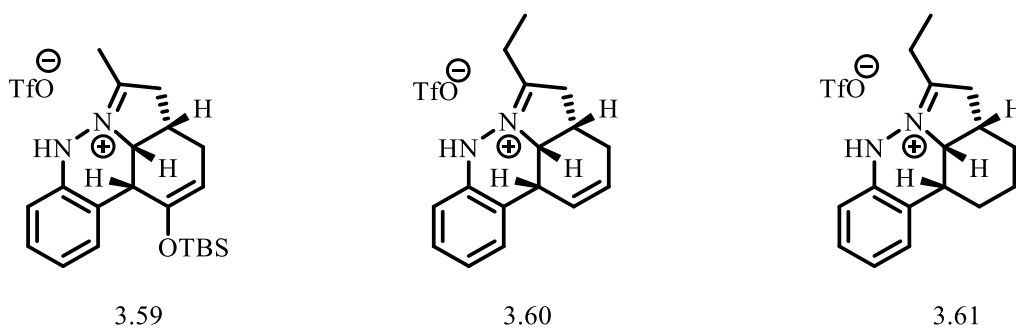


Figure 3.14: Potential precursors to (+)-ibophyllidine

Of these, **3.61** stood out as the best choice since a close analogue (**3.22d**) had been made in the group. Additionally, Glorius' work on palladium catalyzed intramolecular amidation reaction of unactivated C(sp³)-H bonds in anilines⁸⁴ to form numerous indolines in good yields serves as good literature precedence for subsequent reactions in the proposed synthetic route (**3.63** → **3.62**, Figure 3.15).

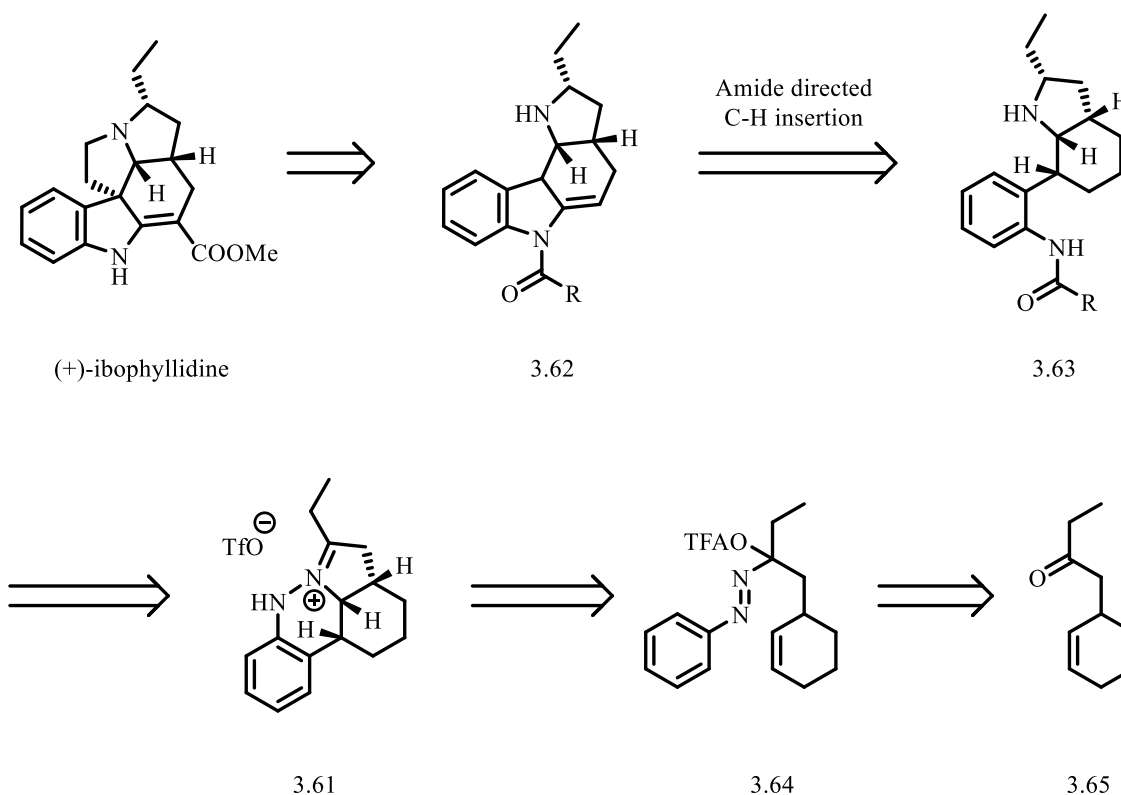
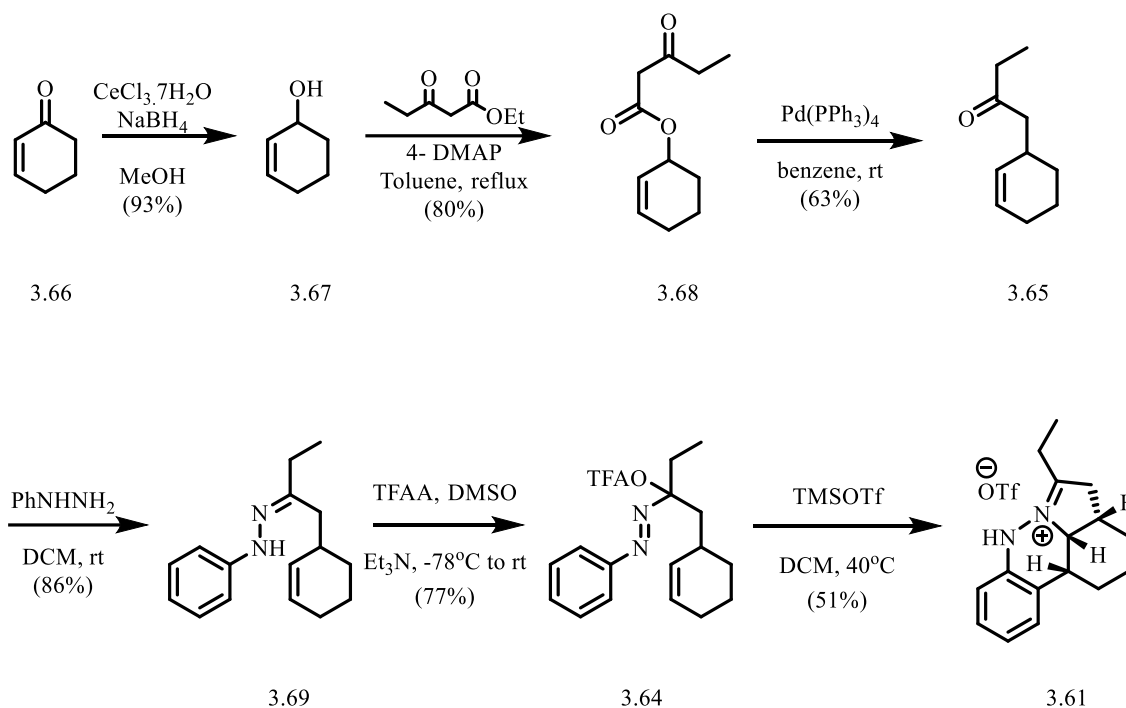


Figure 3.15: New proposed retrosynthetic approach towards (+)-ibophyllidine

The ketone (**3.66**, Scheme 3.8) leading to cycloadduct **3.61** (Scheme 3.8) was prepared by a palladium catalyzed Carroll rearrangement of oxo-ester **3.61**, that was prepared by a 4- dimethylaminopyridine (DMAP) catalyzed transesterification of ethyl propionylacetate with cyclohexanol.^{50,51} Ketone **3.62** was converted to the corresponding

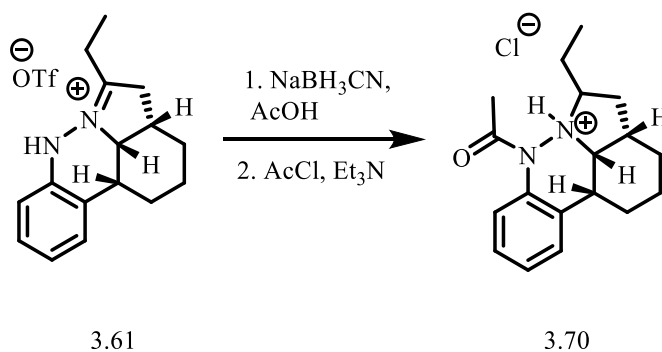
α -OTFA azo compound (**3.64**) by subjecting its corresponding phenyl hydrazone **3.63** to the oxidation with trifluoroacetoxy dimethylsulfonium trifluoroacetate at -78°C (prepared from DMSO and TFAA). Adding TMSOTf to a solution of **3.64** in DCM and heating it to 40°C gave the desired protonated azomethine imine **3.58** in an unoptimized 51% yield.



Scheme 3.9: Successful synthesis of (+)-ibophyllidine precursor

With a successful route to generate the key intermediate to our new proposed synthesis to the natural product, my next task was to establish conditions to cleave the N-N bond in **3.61**. There are several examples of the nitrogen-nitrogen bond cleavage of hydrazines,⁵²⁻⁶⁸ hence it was essential to reduce the iminium group in **3.61** first to explore reduction reactions. Protonated azomethine iminium salt **3.61** is bowl-shaped and hence the hydride reduction should occur from the convex face thereby setting the ethyl side

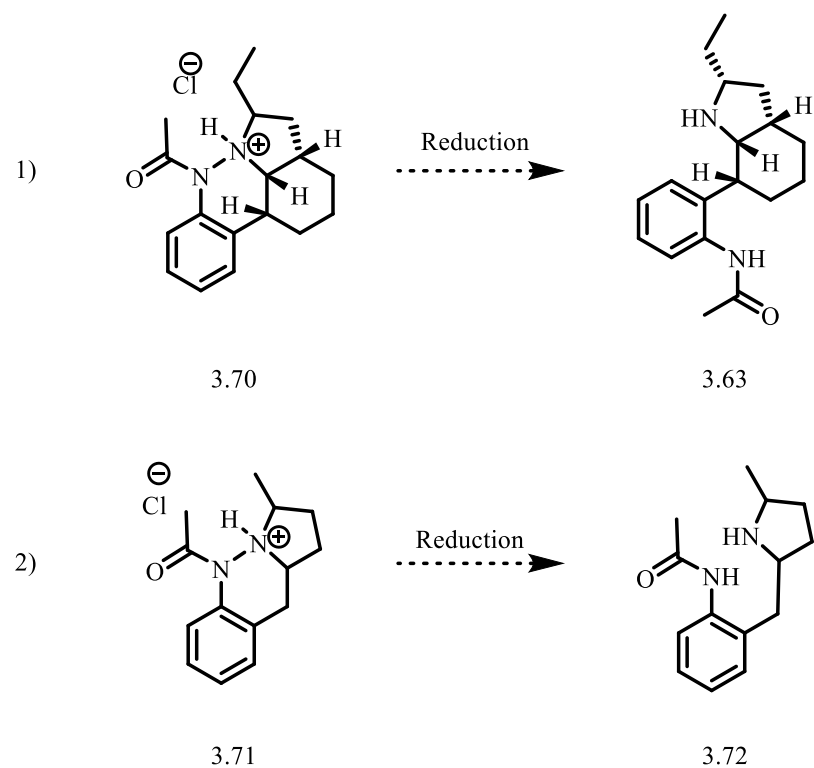
chain in the correct stereochemistry as (+)- ibophyllidine. The iminium ion was reduced under Borch conditions (NaBH_3CN , acetic acid) followed by the N-acylation of the anilinic nitrogen in the presence acetyl chloride to obtain protonated hydrazine **3.70**.



Scheme 3.10: Diastereoselective reduction and N-acylation of 3.61

3.8. Nitrogen-nitrogen bond cleavage

To determine the optimal conditions to carry out reductive cleavage of **3.70**, I performed all reactions on a model substrate **3.71** (Scheme 3.11) that was easily accessible and mimics **3.70** to a large extent.



Scheme 3.11: N-N bond cleavage of protonated azomethine salts

3.8.1. Previous reports of N-N bond cleavage

Nitrogen-nitrogen bond cleavage of hydrazines is widely used in the preparation of amines and thus is significant in organic synthesis. The most widely used methods for N-N bond cleavage are: (1) Zn/H^+ reduction under acidic conditions,⁵² (2) catalytic hydrogenolysis by Raney Nickel,⁵³⁻⁵⁶ PtO_2 (Adam's catalyst)⁵⁷ and palladium catalysts,⁵⁸⁻⁶² (3) metal reductions such as sodium or lithium in ammonia,^{63,64} (4) hydroboration using B_2H_6 or $\text{BH}_3\cdot\text{THF}$,⁶⁵ (5) reduction with samarium (II) iodide^{66,67} and (5) refluxing in aqueous titanium (III) chloride.⁶⁸ Even though the above-mentioned methods are frequently used, there are several limitations related to harsh acidic or basic conditions,

incompatible functional and protecting groups and sometimes lack of reactivity of the substrate.

Our model substrate was subjected to several of these reduction conditions such as hydrogenolysis by Raney Nickel, reflux in TiCl_3 and subjection to reaction with zinc in acetic acid,^{53,68} however in all cases hydrazine **3.71** was recovered thus hinting towards the lack of reactivity of this nitrogen-nitrogen bond. Among all the reported reduction conditions, substrates subjected to N-N bond cleavage using samarium (II) iodide are the closest to our model substrate, as they all require an activating acyl group on one of the nitrogens (in some cases both) of the hydrazine to promote the reaction. For example, in Figure 3.16, the reduction of (S)-1-amino-2-methoxymethyl pyrrolidine (SAMP) and (R)-1-amino-2-methoxymethyl pyrrolidine (RAMP) hydrazines⁶⁹ (**3.75a** \rightarrow **3.75b**) and the reduction of activated N–N bonds in adducts resulting from asymmetric allylation⁷⁰(**3.73a**) and organocatalytic α -amination⁷¹ (**3.74a**).

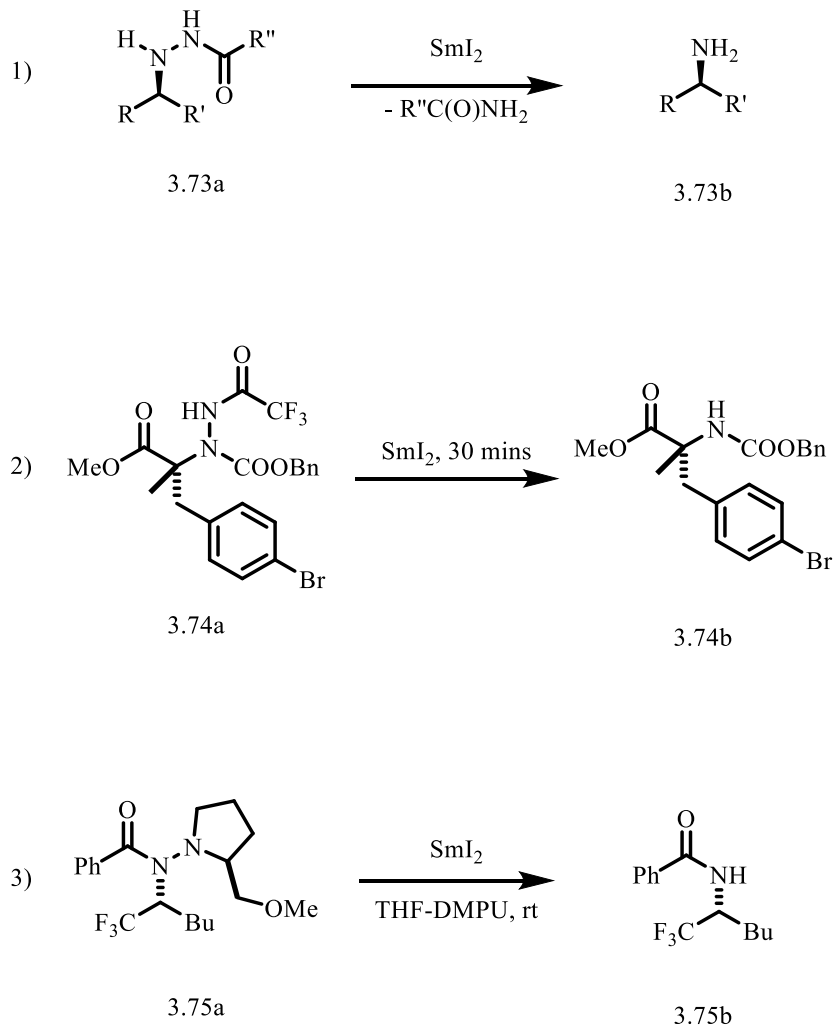


Figure 3.16: Examples of samarium(II) iodide mediated N-N bond cleavage

3.8.2. N-N bond cleavage with SmI₂

Although SmI₂ is commercially available as a 0.1 M solution in THF from a range of suppliers, it is straightforward to prepare. The two most convenient procedures involve addition of either 1,2-diiodoethane or iodine to a slight excess of samarium metal in THF.^{72,73} One of the unique features of SmI₂ is the use of cosolvents or additives to control reactions. Additives commonly utilized to alter reactions of SmI₂ can be classified

into three major classes: 1) Lewis bases – HMPA⁷⁴ and other electron donor ligands, chelating ethers; 2) Proton donors⁷⁵⁻⁷⁷ - predominantly alcohols, glycols, and water; 3) Transition-metal salts - NiI₂, FeCl₃.⁷⁸

Previous SmI₂ mediated N-N bond cleavage reactions use 2 - 5 equiv of SmI₂ at 0°C and obtained the corresponding amines in 30 minutes to 1 hour. Subjecting our model substrate **3.71** to similar conditions gave no desired product. Experiments were then carried out in a combination of varying the equivalence of samarium (II) iodide ranging from 1 - 50 equiv, altering the temperature conditions from -78°C to 35°C as well as introducing additives such as water, methanol (proton donor) and DMPU (Lewis base) in DCM; all of which were unsuccessful in carrying out the desired reduction. In attempts to quantify the lack of reactivity of the hydrazine in model substrate **3.71** towards SmI₂ as a reducing agent, I sought the collaboration with the Geiger group at UVM to analyze the reduction potential of **3.71** and to obtain insights into potential reduction conditions for this system.

3.8.3 Cyclic Voltammetry

Cyclic voltammetry is the most widely used technique for acquiring qualitative information about electrochemical reactions. It offers a rapid location of redox potentials of the electroactive species. A cyclic voltammogram is obtained by applying a linear potential sweep (that is, a potential that increases or decreases linearly with time) to the working electrode. As the potential is swept back and forth past the formal potential, E^o, of an analyte, a current flow through the electrode that either oxidizes or reduces the

analyte. The important parameters of a cyclic voltammogram are the magnitudes of anodic peak current (i_{pa}), the cathodic peak current (i_{pc}), the anodic peak potential (E_{pa}) and cathodic peak potential (E_{pc}). The ideal shape of the current versus potential response for a reversible reaction in a cyclic voltammetry experiment is shown below (Figure 3.17).^{79,80}

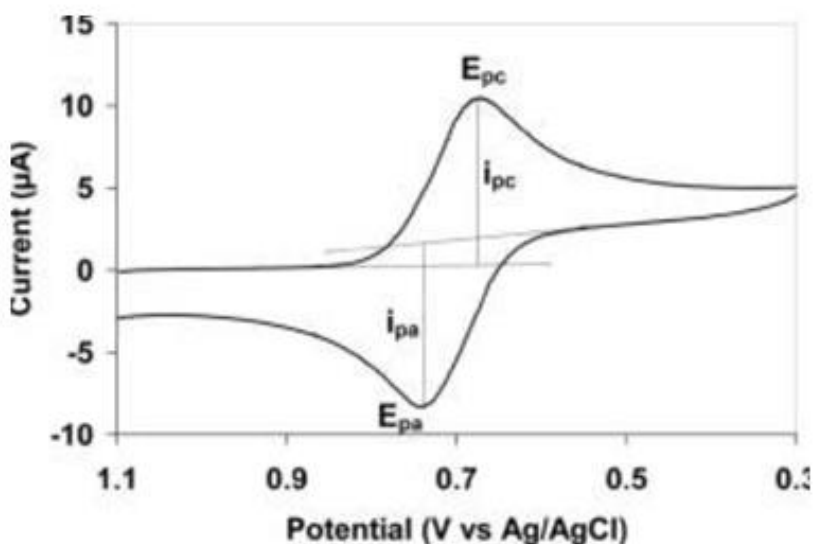


Figure 3.17: Ideal shape of current versus potential response for a reversible reaction in cyclic voltammetry (Image by Nicholson, R.)⁸⁰

For model substrate **3.71**, Dr. Rajan Kumar in the Geiger group observed an irreversible oxidation peak near 0.953 V vs FcH (Figure 3.18a) and no reduction peak (Figure 3.18b). However, after oxidizing compound **3.71**, he got a reduction peak near -0.645 V vs FcH (Figure 3.18c). This implies that there no possibility of reduction of the

compound without prior oxidation, confirmed by the absent reduction peak in voltammogram **3.18d**.

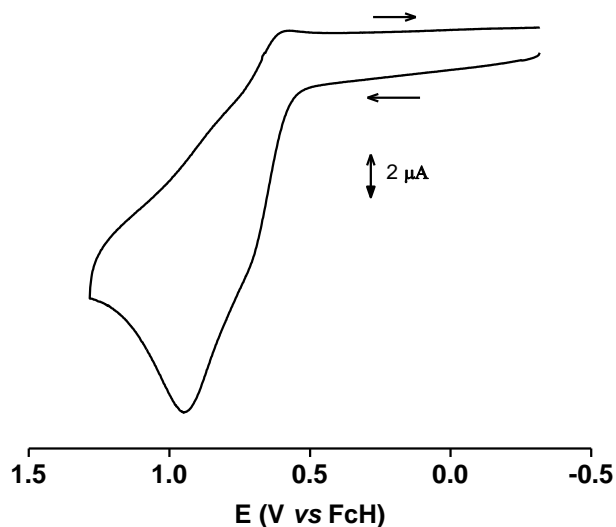


Figure 3.18a: CV of sample (1 mM) with switching potentials of 0 V then 1.6 V. (0.1 M [NBu₄][PF₆]/DCM solution). Scan rate = 200 mv/s, glassy carbon working electrode.

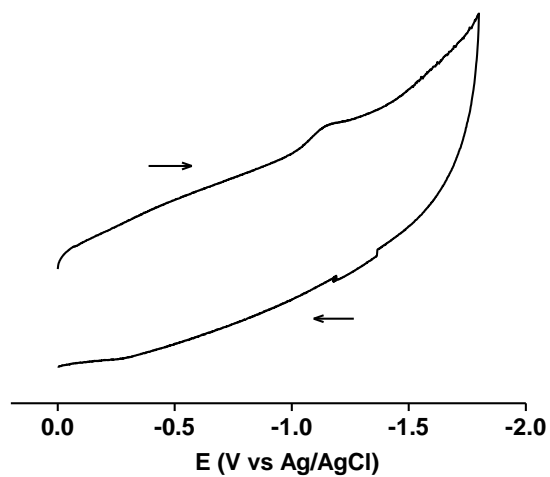


Figure 3.18b: CV of sample (1 mM) with switching potentials of 0 V then -1.8 V. (0.1 M [NBu₄][PF₆]/DCM solution). Scan rate = 200 mv/s, glassy carbon working electrode.

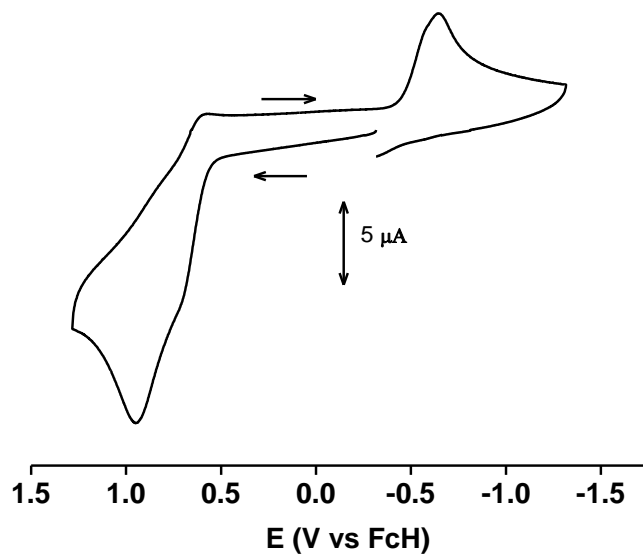


Figure 3.18c: CV of sample (1 mM) with switching potentials of 1.6 V then -1.0 V. (0.1 M $[\text{NBu}_4][\text{PF}_6]$ / DCM solution). Scan rate = 200 mv/s, glassy carbon working electrode.

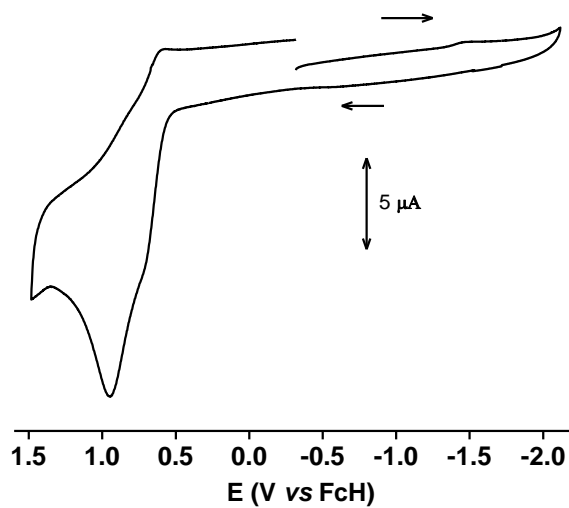


Figure 3.18d: CV of sample (1 mM) with switching potentials of -1.8 V then 1.6 V. (0.1 M $[\text{NBu}_4][\text{PF}_6]$ / DCM solution). Scan rate = 200 mv/s, glassy carbon working electrode.

We can conclude that the anodic wave is a composite of two irreversible waves wherein **3.71** undergoes one or more irreversible, probably multi-electron processes between about 0.7 V and 0.9 V vs ferrocene. The reduction potential of SmI₂ has been established using linear sweep and cyclic voltammetry and was found to be approximately -1.41 V, determined for a solution of SmI₂ in tetrahydrofuran (THF).¹⁵⁴ It will be worthwhile to determine the multi-electron processes of **3.71** and **3.61** in THF rather than DCM, to confirm the inability of samarium (II) iodide to reduce the nitrogen-nitrogen bond.

3.8.4. Other reduction conditions for N-N bond cleavage

While investigating an efficient route to synthesize functionalized lactams from fused tetrahydropyridazines, Gilchrist and coworkers were successful at cleaving the N-N bond in **3.76** (Figure 3.19). The N-acetylation followed by reaction with sodium in liquid ammonia gave the corresponding pyrrolidones **3.77** in an overall good yield. However, they found that it was necessary for both the nitrogen atoms to be activated via acylation for the reaction to proceed efficiently.⁸² This may be problematic in our substrates **3.70** and **3.71**, as the second nitrogen atom is sterically inaccessible for acylation to take place.

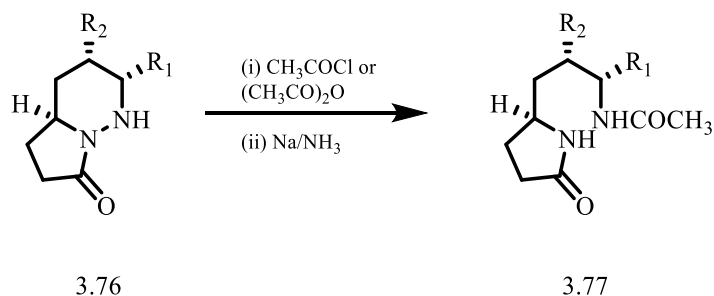


Figure 3.19: Gilchrist's N-N bond cleavage using sodium in ammonia

The potential inability of reduction with sodium in ammonia due to the absence of a second acyl group can be addressed by hydrogenolysis using Adam's catalyst (PtO_2). Carrier and coworkers⁸³ were able to carry out a ring opening of N-acyl pyrazolines (**3.76**, Figure 3.20) under high pressure conditions. It is possible that the stubborn nitrogen-nitrogen bond of **3.70** and **3.71** requires harsh pressure and/or temperature conditions to allow for its cleavage.

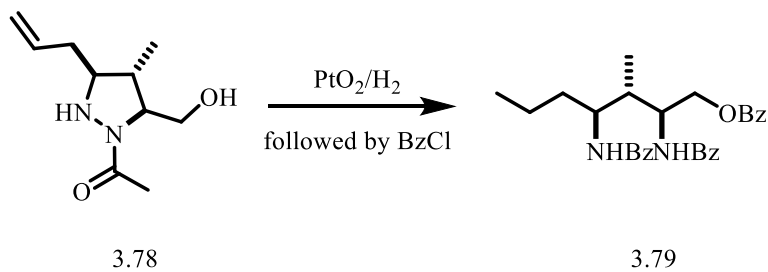
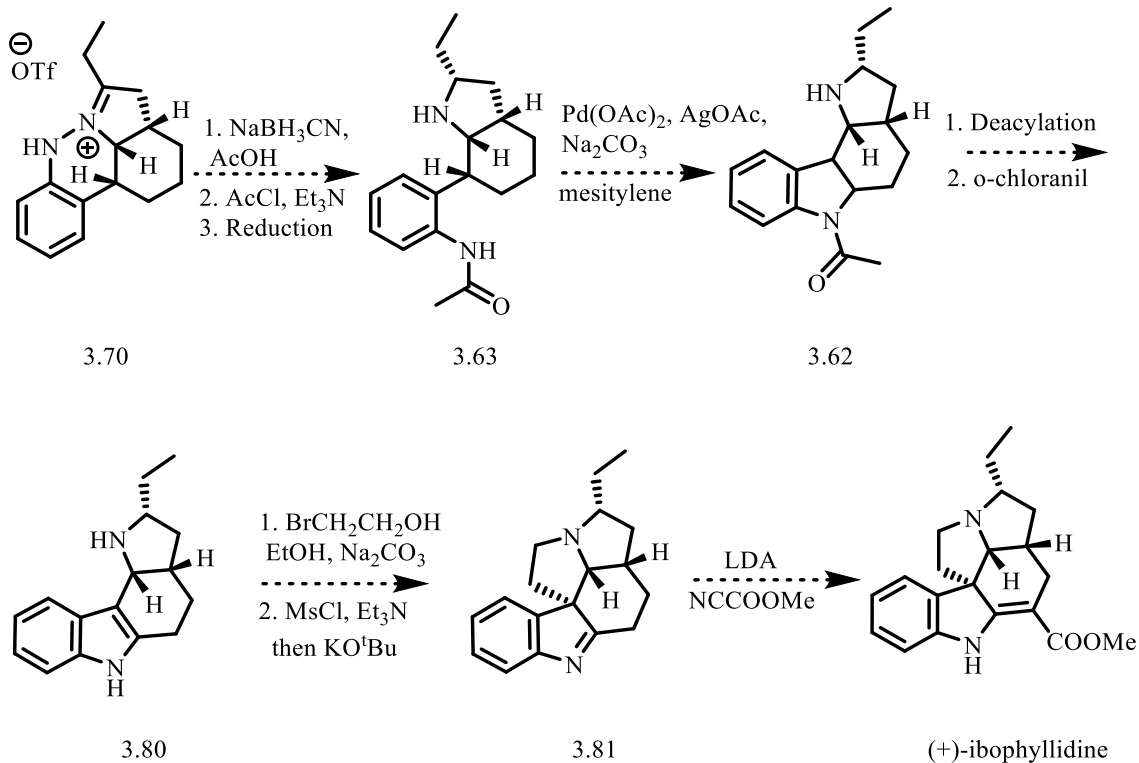


Figure 3.20: Carrier's N-N bond cleavage using Adam's catalyst

3.9. End game strategy

In this section I will discuss our proposed synthetic strategy succeeding the optimistic N-N bond cleavage of **3.70**. We would first start with the conversion of the amide **3.63** to indoline **3.62** by a palladium catalyzed amidation of the unactivated C(sp³)-H bond, as reported by Glorius and coworkers.⁸⁴ If the indoline formation step is successful, then a subsequent diacylation followed by an oxidation should yield indole **3.80**. Taking inspiration from Rawal and coworkers,⁸⁵ **3.80** will be subjected to an intramolecular S_N2 alkylation with bromoethanol followed by the treatment with methanesulfonyl chloride in triethyl amine and the final addition of *t*-BuOK will give **3.81**. Finally, reaction with Manders reagent to incorporate the carbomethoxy group should yield our target molecule, (+)-ibophyllidine.



3.10. Conclusions

The unprecedented reactivity of 1-aza-2-azoniaallene salts with pendant olefins through an intramolecular polar [4+2] cycloaddition furnishes a 1,2,3,4-tetrahydrocinnoline core. This reaction proceeds efficiently with di- and tri-substituted olefins thereby exhibiting high tolerance to sterics and electronic variations in the heteroallene system. The limitations to this [4+2] cycloaddition is: (1) competing reaction site in the presence of an allylic alcohol (protected or unprotected) and (2) the formation of products exclusively with an iminium π -bond contained in a five membered ring.

Additionally, the protonated azomethine iminium salt obtained by the intramolecular polar [4+2] cycloaddition of the 1-aza-2-azoniaallene intermediate derived from ketone

3.65 serves as a key intermediate in our proposed total synthesis of (+)-ibophyllidine. However, the N-N bond of **3.70** seems unreactive to standard reduction conditions and probably requires specialized harsh conditions for this bond cleavage.

In summary, 1-aza-2-azoniaallene intermediates have depicted an impressive array of reactivity in the preparation of diverse heterocyclic and carbocyclic compounds. Owing to their high reactivity and useful products they have potential applications in the synthesis of several structurally complex and biologically relevant products.

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CHAPTER 4: EXPERIMENTAL INFORMATION

The following section describes the experimental methods utilized to prepare requisite substrates to study and investigate the reactivity of 1-aza-2-azoniaallene salts in electrophilic aromatic substitution reactions. The procedures to synthesize the various compounds used in the total synthesis of (+)-ibophyllidine attempt are also included here. Lastly, all spectral data for previously unreported compounds are listed in this section as well.

4.1. General experimental information

All reactions were performed under an inert atmosphere of nitrogen in flamedried glassware. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF) and acetonitrile (CH_3CN) were dried via the solvent dispensing system, unless otherwise indicated. Subsequently, all solvents were removed *in vacuo* with a rotary evaporator and further dried under reduced high pressure in a high vacuum line. Oxalyl chloride, trifluoroacetic anhydride (TFAA) and trimethylsilyl trifluoromethane sulfonate (99%, TMSOTf) were purchased from Acros Organics and freshly distilled before use. Triethylamine (Et_3N) was freshly distilled over CaH_2 prior to every use. Extra dry dimethylsulfoxide (DMSO) stored over molecular sieves was purchased from Acros Organics and was used as received.

All hydrazones were freshly prepared from their corresponding ketones as these phenyl hydrazones underwent facile aerial oxidation and hence could not be stored.

Molecular sieves (4 Å) used during hydrazone formation were activated by overnight heating at 120°C in a vacuum oven. Reactions were cooled to -78°C using dry-ice acetone baths. Silica gel flash column chromatography was performed using silica gel (230 – 400 mesh) and TLC analysis was carried out using silica on glass plates. Visualization of TLC plates were done using ultraviolet light and ceric ammonium molybdate stain.

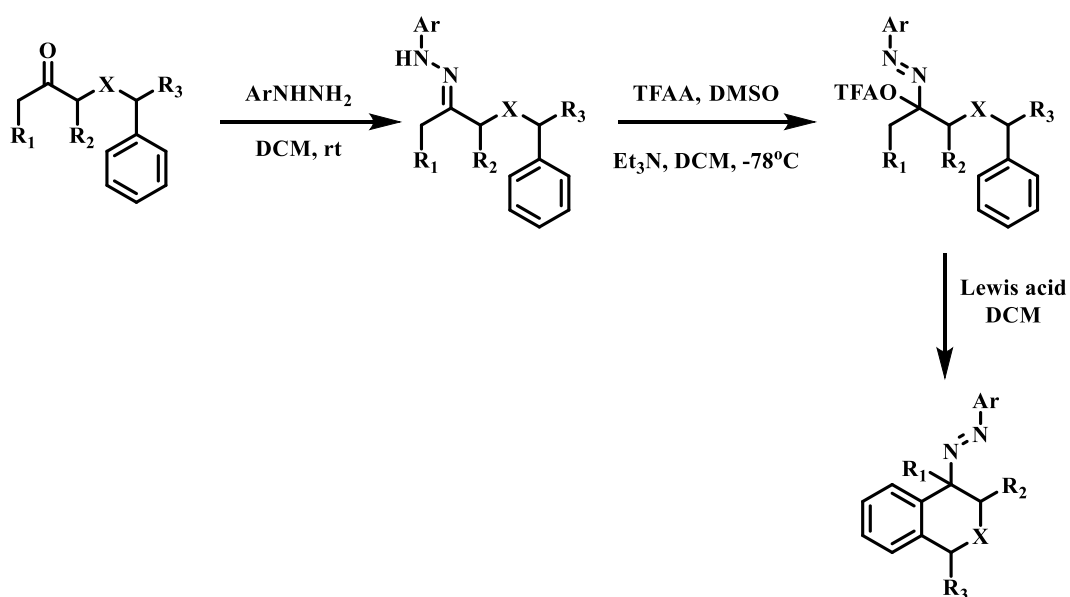
¹H and ¹³C NMR data was collected at room temperature on a 500 MHz Bruker spectrometer in deuterated chloroform (CDCl₃), unless otherwise indicated. The chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane (TMS). Exact mass data was acquired in ESI mode using Waters Xevo G2-XS LCMS-QTOF.

During the investigation of the reactivity of 1-aza-2-azoniaallene salts, a common synthetic sequence of reactions is maintained. First, an aryl hydrazone is generated by the condensation reaction of a ketone substrate and an aryl hydrazine. The aryl hydrazones are then reacted with chloro- or trifluoroacetoxy- dimethylsulfonium chloride, to prepare the corresponding α-chloro- or α-trifluoroacetoxy- azo compound. These substrates were subsequently reacted with halophilic Lewis acids to generate the 1-aza-2-azoniaallene intermediate, which then proceeded to intramolecularly react with the pendant π-functionality of the substrate.

In the first part of the following sections, I will describe the experimental procedures I followed in this synthetic sequence to understand the reactivity of 1-aza2-azoniaallene salts in electrophilic aromatic substitutions and will provide the characterization data for all previously unreported compounds. Subsequently in the

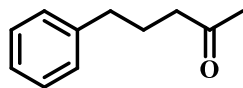
second part, I will provide all novel methods used in the preparation the chemical reagents used in the total synthesis of (+)-ibophyllidine along with their characterization data.

4.2. Experimental information for intramolecular electrophilic aromatic substitution of 1-aza-2-azoniaallene salts



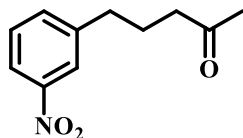
4.2.1. Methods of preparation and characterization data for ketones used in the scope of intramolecular electrophilic aromatic substitutions of 1-aza-2azoniaallene salts

Representative procedure for preparation of aryl ketones by Heck coupling



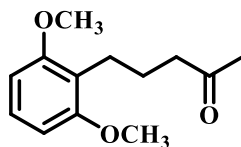
5-phenylpentan-2-one (**2.22**): Bromobenzene (200 mg, 1.27 mmol), 4-penten-2-ol (165 mg, 1.91 mmol), palladium (II) acetate (129 mg, 0.57 mmol), tetra-*n*-butylammonium chloride (708 mg, 2.55 mmol), lithium chloride (54 mg, 1.27 mmol) and lithium acetate dihydrate (325 mg, 3.19 mmol) were suspended in DMF (4 mL) and the mixture was stirred at 100°C for 72 h. After cooling to room temperature, brine (25 mL) was added and the product was extracted with diethyl ether (2 x 50 mL). The combined organic layers were dried with Na₂SO₄, filtered and concentrated under reduced pressure to afford a brownish-red liquid which was purified by column chromatography to give 137 mg (67% yield) of 5-phenylpentan-2-one as a colorless liquid (*R*_f = 0.54, eluent 4:1 Hexanes: EtOAc). Spectroscopic data matched previously reported values.

Ketones leading to α -OTFA compounds **2.44a-b,d** and **2.49** were prepared by a similar Heck coupling and the ketones of **2.28a** and **2.33** matched their reported spectra.^{37,38}



Ketone leading to **2.44b**: Yield = 82%; *R*_f = 0.31 (1:4 EtOAc:Hexanes); ¹H-NMR (CDCl₃, 500MHz): 8.07-8.05 (m, 2H), 7.51 (d, 1H, *J* = 8 Hz), 7.44-7.47 (t, 1H, *J* = 7.7

Hz), 2.72-2.75 (t, 2H, J = 7.7 Hz), 2.47-2.50 (t, 2H, J = 7.2 Hz), 2.15 (s, 3H), 1.92 (m, 2H); ^{13}C -NMR (CDCl_3 , 125MHz): 208.1, 149.4, 136.7, 133.0, 131.9, 127.2, 124.7, 42.9, 32.0, 29.9, 24.6; Exact mass: Calculated [$\text{C}_{11}\text{H}_{13}\text{NO}_3\text{Na}$] 230.08, found 230.0787.

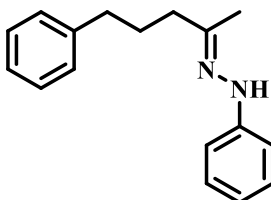


Ketone leading to **2.44d**: Yield = 45%; R_f = 0.60 (3:7 EtOAc:Hexanes); ^1H -NMR (CDCl_3 , 500MHz): 7.11-7.14 (t, 1H, J = 7.59 Hz), 6.52-6.54 (d, 2H, J = 8 Hz), 3.80 (s, 6H), 2.64-2.67 (t, 2H, J = 8.11 Hz), 2.39-2.42 (t, 2H, J = 8.11 Hz), 2.11 (s, 3H), 1.76 -1.82 (m, 2H); ^{13}C -NMR (CDCl_3 , 125MHz): 209.7, 158.4, 126.9, 118.1, 103.6, 55.6, 43.4, 29.6, 23.3, 21.9; Exact mass: Calculated [$\text{C}_{13}\text{H}_{18}\text{O}_3\text{Na}$] 245.12, found 245.1147.

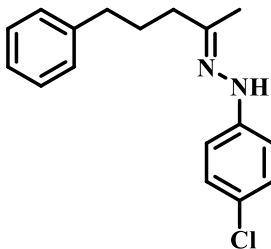
The ketones leading to **2.44b-c** were prepared by the conjugate addition of styrene to methyl vinyl ketone (MVK) and cyclohexanone respectively and matched the reported spectra.^{39,40} The ketone leading to **2.45d** was prepared by a Williamson ether synthesis directly followed by a Swern oxidation and matched its literature data.⁴¹

4.2.2. Methods of preparation and characterization data for hydrazones used in the scope of intramolecular electrophilic aromatic substitutions of 1-azoniaallene salts

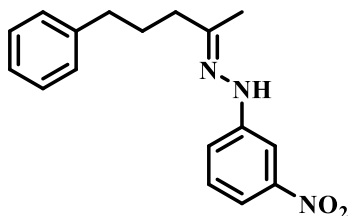
Representative procedure for aryl hydrazone formation



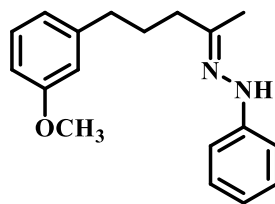
1-phenyl-2-(5-phenylpentan-2-ylidene) hydrazine (2.30): Phenyl hydrazine (394 mg, 3.64 mmol) was added to a solution of 5-phenylpentan-2-one (590 mg, 3.64 mmol) in CH₂Cl₂ (1 mL), which contained 4Å molecular sieves, under a nitrogen atmosphere. After 2 h the reaction mixture was passed through a plug of basic alumina and concentrated in vacuo to provide 891 mg (97% yield) of the title hydrazone as a dark red oil: ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.20 (m, 7H), 7.08-7.04 (m, 2H), 6.86-6.76 (m, 2H), 2.68 (t, J = 7.45 Hz, 2H), 2.35 (t, J = 7.45 Hz, 2H), 1.97-1.89 (m, 2H), 1.83 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 146.3, 142.3, 129.2, 129.1, 128.5, 128.3, 125.7, 119.6, 113.0, 38.4, 35.4, 28.3, 14.4; MS: Calculated [C₁₇H₂₁N₂]⁺ : 253.1699, found: 253.1694.



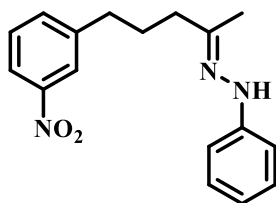
Phenyl hydrazone compound, **precursor to 2.39b**: $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.28-7.30 (m, 3H), 7.16-7.25 (m, 4H), 6.97-6.99 (d, 1H), 6.83-6.85 (d, 1H), 2.61-2.64 (m, 2H), 2.42-2.45 (t, 2H), 2.11 (s, 3H), 1.88-1.94 (m, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 208.7, 141.6, 129.0, 128.5, 128.5, 128.4, 128.3, 126.0, 114.1, 42.8, 35.0, 30.0, 25.2; Exact mass: Calculated $[\text{C}_{17}\text{H}_{20}\text{ClN}_2]^+$ 287.1315, found 287.1318.



Phenyl hydrazone compound, **precursor to 2.39d**: Yield = quantitative; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.90 (s, 1H), 7.63-7.65 (d, 1H), 7.22-7.30 (m, 4H), 7.18-7.21 (m, 3H), 7.10 (brs, 1H), 2.68-2.71 (t, 2H, $J = 7.5$ Hz), 2.36-2.39 (t, 2H, $J = 7.1$ Hz), 1.89-1.98 (m, 2H), 1.86 (s, 3H); ($^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 148.6, 146.8, 129.8, 129.3, 128.6, 128.4, 125.9, 118.5, 114.0, 107.5, 38.3, 35.4, 28.1, 14.6; Exact mass: Calculated $[\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}_2]^+$ 298.1556, found 298.1559.

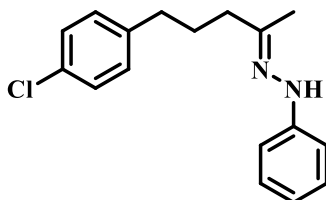


Phenyl hydrazone compound, **precursor to 2.44a**: Yield = 97%; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.19-7.25 (m, 4H), 7.04-7.06 (d, 1H), 6.82-6.84 (m, 2H), 6.73-6.76 (m, 2H), 3.80 (s, 3H), 2.66 (t, 2H), 2.35 (t, 2H), 1.90-1.94 (m, 2H), 1.84 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 159.6, 145.9, 143.9, 129.2, 129.2, 129.1, 120.9, 119.6, 114.3, 112.9, 111.1, 55.1, 38.3, 35.5, 28.1, 14.5; Exact mass: Calculated $[\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}]^+$ 283.1810, found 283.1804.

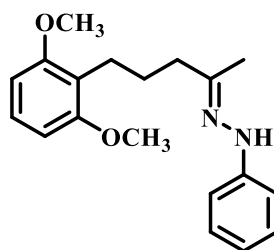


Phenyl hydrazone compound, **precursor to 2.44b**: Yield = 77%; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 8.09 (s, 1H), 8.05-8.07 (d, 1H), 7.53-7.55 (d, 1H), 7.43-7.46 (t, 1H), 7.24-7.26 (m, ~2H), 7.05-7.06 (d, 2H), 6.82-6.89 (m, 2H), 2.78-2.81 (t, 2H), 2.34-2.37 (t, 2H), 1.95 – 2.01 (m, 2H), 1.86 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 145.8, 145.3, 144.3, 134.9,

129.2, 129.2, 129.2, 123.4, 121.1, 119.7, 112.9, 37.9, 34.9, 27.7, 14.6; Exact mass:
Calculated $[C_{17}H_{20}N_3O_2]^+$ 298.1556, found 298.1550.

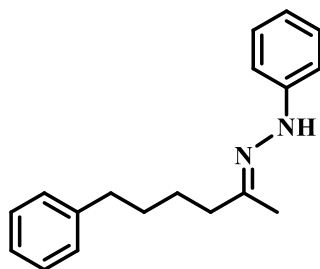


Phenyl hydrazone compound, **precursor to 2.44c**: Yield = 94%; 1H -NMR ($CDCl_3$, 500MHz): 7.24-7.25 (m, 3H), 7.12-7.14 (d, 2H), 7.04-7.05 (d, 2H), 6.81-6.86 (m, 2H), 2.65 (t, 2H), 2.32 (t, 2H), 1.89-1.92 (m, 2H), 1.83 (s, 3H); ^{13}C -NMR ($CDCl_3$, 125MHz): 145.9, 145.8, 140.7, 131.4, 129.9, 129.2, 128.4, 119.6, 112.9, 38.1, 34.7, 28.1, 14.5; Exact mass: Calculated $[C_{17}H_{20}ClN_2]^+$ 287.1315, found 287.1306.

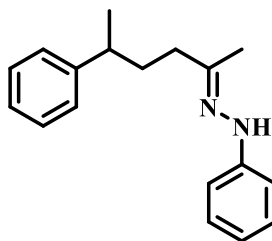


Phenyl hydrazone compound, **precursor to 2.44d**: Yield = 84%; 1H -NMR ($CDCl_3$, 500MHz): 7.20-7.24 (m, 2H), 7.11-7.14 (t, 1H), 7.04-7.06 (d, 2H), 6.82-6.54 (t, 1H), 6.52-6.54 (d, 2H), 3.80 (s, 6H), 2.68-2.71 (t, 2H), 2.35-2.38 (t, 2H), 1.84 (s, 3H), 1.75-

1.77 (m, 2H); ^{13}C -NMR (CDCl_3 , 125MHz): 158.3, 146.1, 129.1, 126.6, 119.4, 112.9, 103.7, 103.6, 55.7, 39.1, 26.1, 22.6, 14.2; Exact mass: Calculated $[\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2]^+$ 313.1916, found 313.1924.

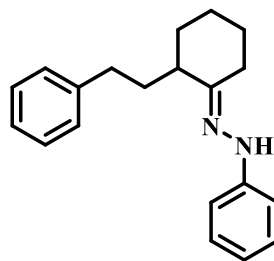


Phenyl hydrazone compound, **precursor to 2.60a**: Yield = 94%; ^1H -NMR (CDCl_3 , 500MHz): 7.177.28 (m, 4H), 6.98-7.03 (m, 3H), 6.81-6.83 (m, 3H), 2.65 (t, 2H, $J = 7.7$ Hz), 2.35 (t, 2H, $J = 7.3$ Hz), 1.83 (s, 3H), 1.63-1.69 (m, 4H); ^{13}C -NMR (CDCl_3 , 125MHz): 146.7, 145.9, 142.54, 129.2, 128.4, 128.3, 125.7, 119.5, 112.9, 38.7, 35.8, 31.0, 26.2, 14.3; Exact mass: Calculated $[\text{C}_{18}\text{H}_{23}\text{N}_2]^+$ 267.1861, found 267.1865.

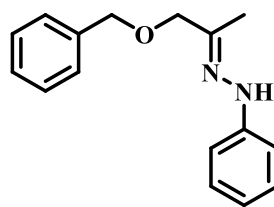


Phenyl hydrazone compound, **precursor to 2.60b**: Yield = 66%; ^1H -NMR (CDCl_3 , 500MHz): 7.35-7.38 (t, 1H), 7.19-7.31 (m, ~4H), 7.03-7.05 (d, 2H, $J = 7$ Hz), 6.80-6.88 (m, 2H), 2.73-2.78 (m, 1H), 2.15-2.30 (m, 2H), 1.86-1.90 (m, 2H), 1.78 (s, 3H), 1.29-

1.30 (d, 3H); ^{13}C -NMR (CDCl_3 , 125MHz): 147.3, 146.6, 145.9, 129.2, 129.2, 128.3, 127.1, 125.9, 119.5, 112.9, 112.1, 39.6, 37.1, 34.9, 22.3, 14.5; Exact mass: Calculated $[\text{C}_{18}\text{H}_{23}\text{N}_2]^+$ 267.1861, found 267.1864.



Phenyl hydrazone compound, **precursor to 2.60c**: ^1H -NMR (CDCl_3 , 500MHz): 7.23-7.35 (m, 8H), 6.81-6.85 (d, 1H), 6.77-6.80 (m, 1H), 1.42-2.77 (m, 13H); Exact mass: Calculated $[\text{C}_{20}\text{H}_{25}\text{N}_2]^+$ 293.2018, found 293.2020.

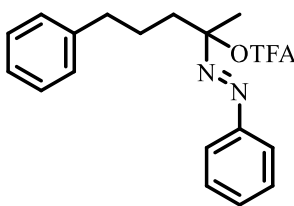


Phenyl hydrazone compound, **precursor to 2.60d**: Yield = Quantitative; ^1H -NMR (CDCl_3 , 500MHz): 7.35-7.37 (m, 4H), 7.24-7.30 (m, 2H), 6.84-6.87 (t, 1H, $J = 7.34$ Hz), 4.51(s, 2H), 4.17 (s, 2H), 1.93 (s, 3H); ^{13}C -NMR (CDCl_3 , 125MHz): 145.1, 142.7, 138.1,

129.2, 128.4, 127.9, 127.7, 120.1, 113.1, 74.5, 72.0, 12.0; Calculated $[C_{16}H_{19}N_2O]^+$ 255.1492, found 255.1492.

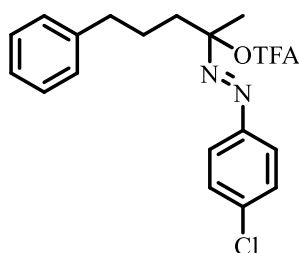
4.2.3. Methods of preparation and characterization data for *α -OTFA azo compounds* used in the scope of intramolecular electrophilic aromatic substitutions of 1-aza-2-azoniaallene salts

Representative procedure for α -OTFA azo formation

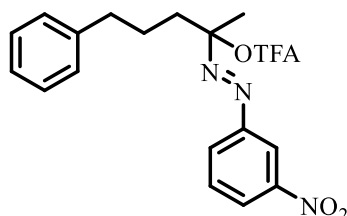


Compound 2.23a: Trifluoroacetic anhydride (414 mg, 3.26 mmol) was added dropwise to a solution of DMSO (319 mg, 4.08 mmol) in THF (20 mL) that was maintained between $-55\text{ }^{\circ}\text{C}$ to $-65\text{ }^{\circ}\text{C}$ and the resulting solution was stirred until the formation of bubbles ceased (typically 30 min). The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of the phenyl hydrazone of 5-phenylpentan-2-one (685 mg, 2.72 mmol) and Et_3N (413 mg, 4.08 mmol) in THF (10 mL) was added. After 30 min the cold bath was removed. Upon reaching room temperature the mixture was filtered and the filtrate was concentrated. The oily residue was dissolved in pentane to give an orange solution that was filtered to remove a dark red insoluble residue. The pentane was removed in vacuo

give 584 mg (75% yield) of α -OTFA azo **2.33a** as an orange-red liquid: ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.70 (m, 2H), 7.44-7.46 (m, 3H), 7.21-7.28 (m, ~2H), 7.14-7.16 (m, 3H), 2.62-2.64 (t, $J = 7.7$ Hz, 2H), 2.09-2.14 (m, 2H), 1.86 (s, 3H), 1.84-1.87 (m, 1H), 1.68-1.70 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 150.6, 141.4, 131.6, 129.1, 128.4, 128.3, 126.9, 126.0, 122.8, 107.4, 37.9, 35.6, 24.4, 22.0.

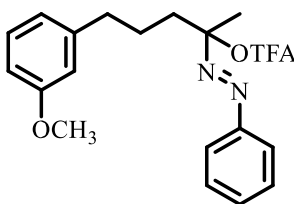


Compound 2.39b: ^1H -NMR (CDCl_3 , 500MHz): 7.63-7.64 (d, 1H), 7.43-7.44 (d, 1H), 7.25-7.30 (m, ~2H), 7.14-7.20 (m, 5H), 2.60-2.62 (t, 2H), 2.42-2.45 (t, 2H), 2.11 (s, 3H), 1.88-1.94 (m, 2H); ^{13}C -NMR (CDCl_3 , 125MHz): 148.9, 141.6, 137.7, 129.4, 128.5, 128.4, 128.3, 126.0, 124.2, 42.9, 35.0, 30.0, 25.2.

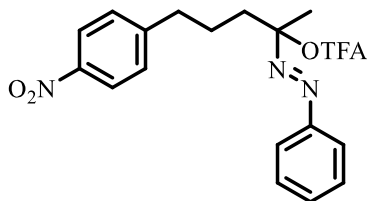


Compound 2.39d: Yield = quantitative; ^1H -NMR (CDCl_3 , 500MHz): 8.51 (s, 1H), 8.33-8.35 (d, 1H), 8.02-8.03 (d, 1H), 7.66-7.69 (t, 1H), 7.26-7.30 (m, 2H), 7.16-7.21 (m, 3H);

2.64-2.67 (t, 2H), 2.13-2.15 (t, 2H), 1.90-1.93 (m, 4H), 1.70-1.74 (m, 1H); ^{13}C -NMR (CDCl_3 , 125MHz): 250.9, 148.9, 141.1, 130.2, 129.1, 128.5, 128.3, 126.1, 125.8, 117.3, 107.3, 37.8, 35.5, 24.3, 22.0.

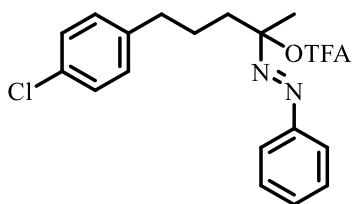


Compound 2.44a: Yield = quantitative; ^1H -NMR (CDCl_3 , 500MHz): 7.67-7.68 (d, 2H), 7.46-7.48 (m, 3H), 7.18 (t, 1H), 6.74-6.76 (m, 2H), 6.69 (s, 1H), 3.78 (s, 3H), 2.61-2.63 (m, 4H), 2.12 (t, 2H), 1.87 (s, 3H); ^{13}C -NMR (CDCl_3 , 125MHz): 159.7, 150.6, 143.0, 131.6, 129.4, 129.1, 122.8, 120.7, 114.1, 111.3, 107.4, 55.1, 37.9, 35.6, 24.3, 22.0.

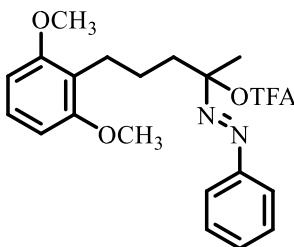


Compound 2.44b: Yield = 88%; ^1H -NMR (CDCl_3 , 500MHz): 8.06-8.02 (m, 2H), 7.68-7.70 (m, 2H), 7.44-7.48 (m, 5H), 2.73-2.77 (t, 2H), 2.14-2.17 (t, 2H), 1.88 (s, 3H), 1.88-

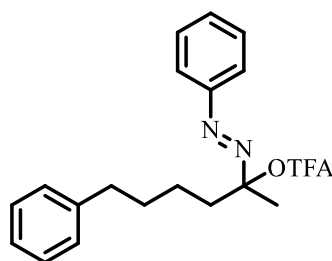
1.91 (m, 1H), 1.74-1.76 (m, 1H); ^{13}C -NMR (CDCl_3 , 125MHz): 150.5, 143.3, 134.6, 131.8, 1, 129.4, 129.1, 123.2, 122.9, 121.3, 107.1, 37.7, 35.2, 24.1, 22.1, 14.1.



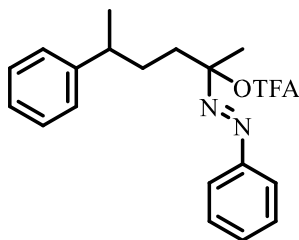
Compound 2.44c: Yield = 85%; ^1H -NMR (CDCl_3 , 500MHz): 7.67-7.69 (m, 2H), 7.46-7.48 (m, 3H), 7.22-7.25 (m, 2H), 7.06 (d, 2H), 2.58-2.62 (m, 2H), 2.07-2.12 (m, 2H), 1.86 (s, 3H), 1.81-1.86 (m, 1H), 1.65-1.70 (m, 1H); ^{13}C -NMR (CDCl_3 , 125MHz): 155.7, 150.6, 139.8, 131.8, 129.7, 129.1, 128.5, 123.1, 107.3, 37.8, 34.9, 24.3, 22.1.



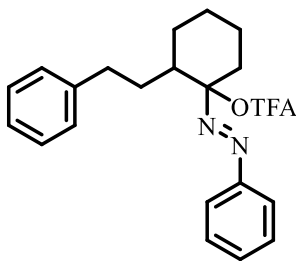
Compound 2.44d: Yield = 80%; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.67-7.68 (m, 2H), 7.45-7.46 (m, 3H), 7.10-7.14 (t, 1H), 6.51-6.53 (d, 2H), 3.76 (s, 6H), 2.65-2.68 (t, 2H), 2.11-2.14 (m, 2H), 1.84 (s, 3H), 1.68-1.72 (m, 1H), 1.56-1.58 (m, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 158.3, 146.7, 131.3, 129.0, 126.9, 122.8, 118.2, 107.8, 103.6, 72.7, 55.6, 37.9, 22.7, 22.2, 21.9, 15.6.



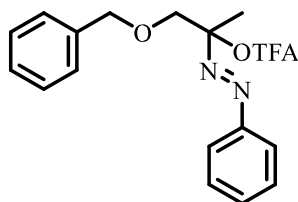
Compound 2.60a: Yield = 85%; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.68-7.70 (m, 2H), 7.46-7.48 (m, 4H), 7.16-7.20 (m, 4H), 2.59-2.62 (t, 2H), 2.09-2.15 (m, 2H), 1.86 (s, 3H), 1.78-1.81 (m, 1H), 1.64-1.67 (m, 2H), 1.41-1.42 (m, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 150.7, 142.1, 131.5, 129.1, 128.3, 128.3, 125.8, 122.8, 107.5, 38.1, 35.5, 31.3, 22.3, 22.0.



Compound 2.60b: Obtained 1:1 mixture of diastereomers, Yield = 87%; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.65-7.68 (m, 2H), 7.46-7.47 (m, 3H), 7.27-7.31 (m, ~2H), 7.12-7.21 (m, 3H), 2.53-2.55(m, 1H), 2.01-2.03 (m, ~2H), 1.83 – 1.84 (d, 6H), 1.64-1.68 (m, 1H), 1.24-1.28 (d, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 150.6, 146.4, 146.3, 131.5, 129.1, 128.5, 128.5, 127.0, 126.9, 126.9, 126.2, 122.8, 107.5, 107.4, 39.9, 39.9, 36.6, 36.6, 30.8, 30.7, 22.6, 22.5, 22.3, 22.0, 21.9, 14.1.



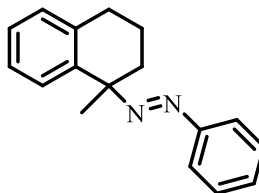
Compound 2.60c: $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.69-7.75 (m, 2H), 7.45-7.47 (m, 3H), 7.16-7.29 (m, ~5H), 7.06-7.08 (m, 1H), 2.37-2.77 (m, 3H), 1.99-2.30 (m, 7H), 1.42-1.88 (m, 7H- contains H_2O).



Compound 2.60d: Yield = 81%; $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.70-7.72 (m, 2H), 7.47-7.48 (m, 3H), 7.29-7.35 (m, 5H), 4.58-4.64 (m, 2H), 3.93-4.01 (dd, 2H), 1.90 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz): 150.6, 137.5, 131.8, 129.1, 128.5, 127.9, 127.7, 123.0, 115.7, 113.4, 106.2, 73.8, 71.9, 20.3.

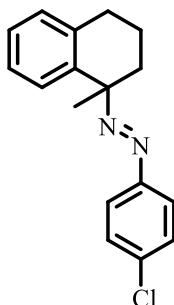
4.2.4. Methods of preparation and characterization data for azo compounds formed during intramolecular electrophilic aromatic substitutions of 1-azoniaallene salts

Representative procedure for azo product formation

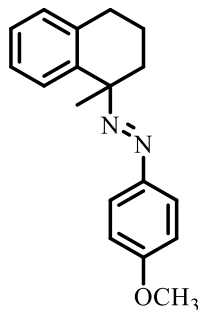


Compound 2.34: To a solution of α -OTFA **2.33a** (281 mg, 0.98 mmol) in CH_2Cl_2 (3 mL) a solution of TMSOTf (144 mg, 1.08 mmol) in CH_2Cl_2 (3 mL) was added and stirred for

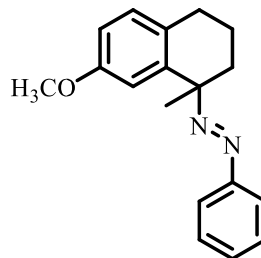
4 hours at room temperature. The reaction was diluted with CH₂Cl₂ (25 mL) and washed three times with saturated aq. NaHCO₃ solution (25 mL). The organic portion was dried over Na₂SO₄, filtered and concentrated in vacuo, to give an orange-brown liquid that was purified by column chromatography to give 215 mg of **2.34** (71% yield) as a yellow liquid: ¹H NMR (500 MHz, CDCl₃) δ 7.68-7.65 (m, 2H), 7.45-7.37 (m, 3H), 7.227.12 (m, 4H), 2.90 (t, J = 6.5 Hz, 2H), 2.39- 2.32 (m, 1H), 2.08-2.02 (m, 1H), 1.97-1.89 (m, 1H), 1.84 (ddd, J = 13.4, 8.4, 2.9 Hz, 1H), 1.62 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.3, 139.4, 137.4, 130.1, 129.1, 128.8, 128.4, 126.7, 125.9, 122.2, 71.9, 35.1, 30.2, 27.3, 19.8; MS (ESI): Calculated [C₁₇H₁₉N₂]⁺: 251.1543, found: 251.1547.



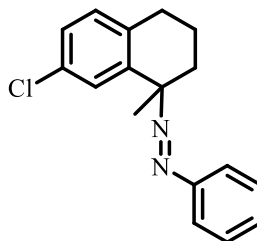
Azo product 2.40b: Yield = 52%; ¹H NMR (500 MHz, CDCl₃):7.61-7.63 (d, 2H), 7.39-7.40 (d, 2H), 7.16-7.18 (m, 4H), 2.89-2.91 (t, 2H), 2.31-2.35 (t, 1H), 2.03-2.09 (m, 1H), 1.90-2.00 (m, 1H), 1.81-1.86 (m, 1H), 1.61 (s, 3H); ¹³C-NMR (CDCl₃, 125MHz): 150.5, 139.2, 137.4, 136.0, 129.2, 129.0, 128.4, 126.8, 126.0, 123.6, 72.1, 35.1, 30.1, 27.2, 19.7; Exact mass: Calculated [C₁₇H₁₈ClN₂]⁺ 287.1129, found 287.1103.



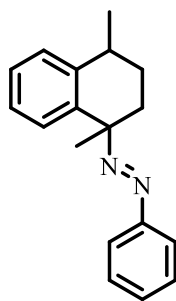
Azo product 2.40c: Yield = 71%; $^1\text{H NMR}$ (500 MHz, CDCl_3): 7.66-7.67 (d, 2H), 7.20 (m, 1h), 7.15-7.20 (m, 3H), 6.92-6.94 (d, 2H), 3.84 (s, 3H), 2.88-3.00 (t, 2H), 2.31-2.33 (m, 1H), 1.95-2.05 (m, 2H), 1.83-1.92 (m, 1H), 1.60 (s, 3H); Exact mass: Calculated $[\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}]^+$: 281.1654, found: 281.1636.



Azo product 2.45a: Yield = 56 %; $^1\text{H NMR}$ (500 MHz, CDCl_3): 7.97 (d, 1H), 7.44-7.46 (m, 3H), 7.11 (d, 1H), 6.70 (d, 1H), 6.60 (s, 1H), 4.06 (m, 1H), 3.75 (s, 3H), 2.98-3.09 (m, 2H), 2.35-2.38 (m, 2H), 1.54 (s, 3H). MS (ESI): Calculated $[\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}]^+$: 281.1654, found: 281.1639.

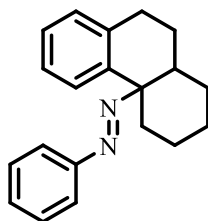


Azo product 2.45c: Yield = 34%; ^1H NMR (500 MHz, CDCl_3): 7.66-7.68 (d, 2H), 7.39-7.44 (m, 3H), 7.23 (s, 1H), 7.11-7.13 (dd, 2H), 2.80-2.83 (t, 2H), 2.30-2.33 (m, 1H), 1.84-1.99 (m, 2H), 1.79-1.80 (m, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): 152.1, 141.4, 135.7, 131.4, 130.4, 130.3, 128.9, 128.3, 126.9, 122.2, 71.6, 34.7, 29.6, 27.3, 19.5; ; Exact mass: Calculated $[\text{C}_{17}\text{H}_{18}\text{ClN}_2]^+$ 287.1129, found 287.1116.

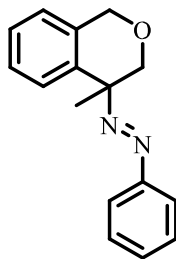


Azo product 2.61b: Yield = 54%; ^1H NMR (500 MHz, CDCl_3): 7.65-7.69 (m, 4H), 7.29-7.45 (m, 6H), 7.28-7.29 (m, 1H), 7.14-7.22 (m, 6H), 2.99-3.06 (m, 2H), 2.43-2.48

(m, 1H), 2.27-2.31 (m, 1H), 2.09-2.18 (m, 2H), 1.70-2.15 (m, 2H), 1.60-1.63 (d, 6H), 1.351.37 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3): 152.3, 142.3, 139.1, 130.1, 128.8, 128.4, 128.3, 127.9, 126.9, 126.8, 125.9, 125.8, 122.2, 72.2, 71.9, 33.0, 32.9, 32.3, 31.5, 27.8, 27.4, 27.4, 27.2, 23.0, 22.5. Exact mass: Calculated $[\text{C}_{18}\text{H}_{21}\text{N}_2]^+$ 265.1705, found 265.1698.

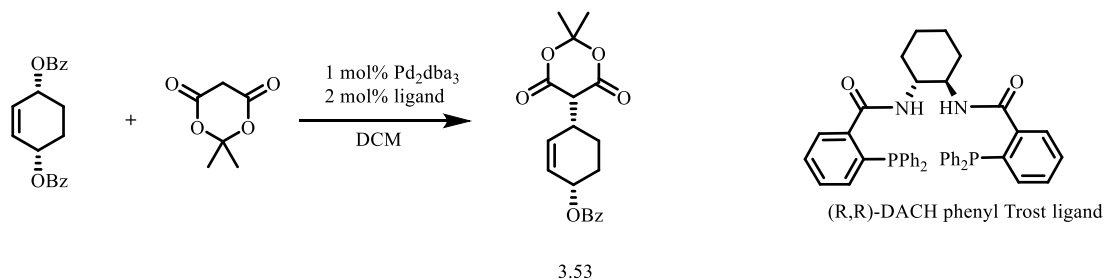


Azo product 2.61c: Yield = 79%; ^1H NMR (500 MHz, CDCl_3): 7.59-6.63 (m, 2H), 7.37-7.43 (m, 3H), 7.09-7.20 (m, 3H), 2.87-3.13 (m, 3H), 2.06 (m, 1H), 1.27-2.15 (m, 15H). Exact mass: Calculated $[\text{C}_{20}\text{H}_{22}\text{N}_2]^+$ 291.1861, found 291.1851.



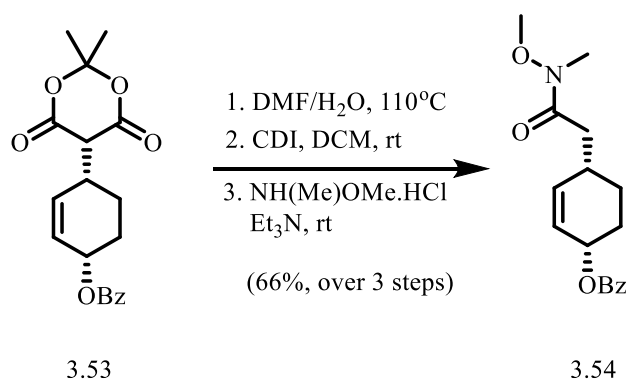
Azo product 2.61d: Yield = 82%; ^1H NMR (500 MHz, CDCl_3): 7.67-7.69 (d, 2H), 7.35-7.43 (m, 4H), 7.24-7.26 (m, 2H), 7.05-7.07 (m, 1H), 4.89 (s, 2H), 4.42-4.44 (d, 1H), 3.88-3.90 (d, 1H), 1.63 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): 152.0, 136.6, 134.5, 130.5, 128.9, 127.8, 127.1, 126.9, 124.1, 122.3, 73.0, 69.9, 68.8, 23.9; Exact mass: Calculated $[\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}]^+$ 253.1341, found 253.1348.

4.3. Experimental information for total synthesis of (+)-ibophyllidine by the [4+2] cycloaddition of 1-aza-2-azoniaallene salts



Compound 3.53: Meldrum's acid (0.049g, 0.34 mmol) was added to a solution of DBU (0.0566g, 0.372 mmol) in 5mL of DCM. The resultant mixture was cannulated into a solution of dibenzoate **3.52**, prepared by Backvall's method,¹¹⁷ Pd_2dba_3 (0.0028g, .0031 mmol) and (R,R)-DACH phenyl Trost ligand (0.0043g, 0.0062 mmol) in 10mL DCM at 0°C. After 3 hours, the reaction was warm to room temperature, washed with water three times (25mL). The CH_2Cl_2 layer was dried over Na_2SO_4 , filtered and concentrated in vacuo, to give an orange-brown liquid that was purified by column

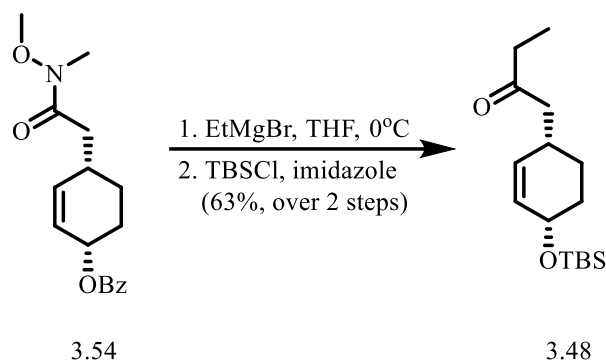
chromatography to give 65% yield of **3.53** as a white solid: $^1\text{H-NMR}$ (500 MHz, CDCl_3): 8.08-8.07 (d, 2H), 7.52-7.54 (m, 1H), 7.41-7.44 (m, 2H), 6.03 (m, 1H), 5.91 (d, 1H), 5.48 (m, 1H), 3.63 (d, 1H), 3.28 (m, 1H), 2.05-2.16 (m, 2H), 1.90-1.92 (m, 1H), 1.80-1.81 (d, 6H), 1.78-1.81 (m, 1H); $^{13}\text{C-NMR}$ (125, CDCl_3): 166.1, 164.3, 164.1, 134.0, 132.8, 129.7, 128.3, 126.0, 65.5, 50.0, 36.4, 28.3, 28.2, 27.4, 20.8.



Compound 3.54: Benzoate **3.53** (0.1211g, 0.352 mmol) was dissolved in 5 mL of DMF and 0.5 mL of water, and the solution was stirred at 115°C for 2 hours. Reaction mixture was diluted with 1:1 mixture of NH_4Cl solution and water (50 mL) and extracted with 30 mL diethyl ether, dried over MgSO_4 and concentrated *in vacuo* to obtain a brownish-orange liquid (A) that was utilized as is for the next step. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 8.03-8.04 (d, 2H), 7.54-7.56 (t, 1H), 7.42-7.45 (t, 2H), 5.93 (s, 2H), 5.47 (m, 1H), 2.64 (m, 1H), 2.40-2.63 (m, 2H), 2.02-2.03 (m, 1H), 1.88-1.99 (m, 2H), 1.56-1.63 (m, 1H);

^{13}C -NMR (125 MHz, CDCl_3): 176.6, 166.1, 135.8, 132.9, 130.6, 129.6, 128.3, 126.1, 67.1, 39.4, 32.2, 27.2, 24.5.

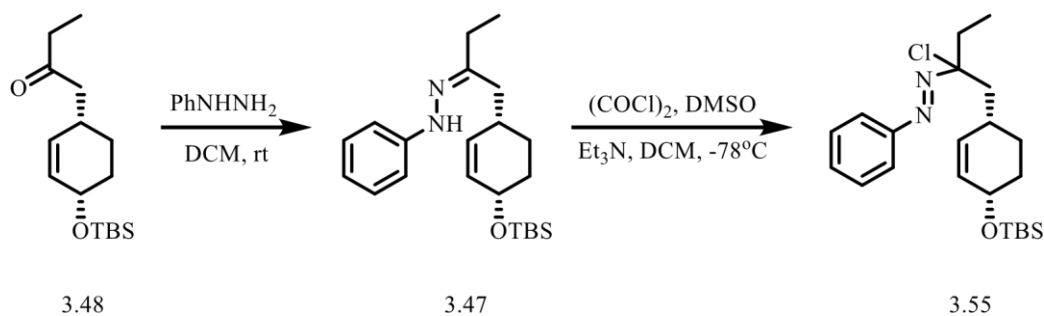
Carboxylic acid **A** (0.0997g, 0.383 mmol) was dissolved in 4 mL of DCM. To this heterogeneous solution, carbonyldiimidazole (0.0683g, 0.421 mmol) was added and stirred at room temperature for 45 minutes. At this time, *N,O*-dimethylhydroxylamine hydrochloride (0.0411g, 0.421 mmol) was added with a few drops of triethylamine and stirred at room temperature for 6 hours. The reaction mixture was then quenched with 25 mL of 1M HCl and stirred vigorously for 10 minutes. After separating out the layers, the aqueous layer was extracted with DCM twice (50 mL). The combined organic layers were washed with 1M HCl (50 mL), water (50 mL) and a 1:1 mixture of brine and a saturated NaHCO_3 (100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford Weinreb amide **3.54** (Yield = 66%, over 3 steps): ^1H -NMR (500 MHz, CDCl_3): 8.04-8.06 (d, 2H), 7.53-7.56 (t, 1H), 7.42-7.45 (t, 2H), 5.89-5.95 (m, 2H), 5.455.46 (m, 1H), 3.70 (s, 3H), 3.21 (s, 3H), 2.70-2.74 (m, 1H), 2.50-2.51 (m, 2H), 1.86-1.98 (m, 3H), 1.55 (m, 3H); ^{13}C -NMR (125 MHz, CDCl_3): 168.1, 166.1, 137.0, 135.1, 132.8, 130.7, 129.6, 128.3, 126.9, 125.5, 67.6, 66.9, 61.3, 40.6, 37.3, 31.9, 31.6, 27.3, 27.1, 24.8.



Compound 3.48: N-methoxy-N-methyl amide **3.54** (0.1319g, 0.4347 mmol) was dissolved in 5 mL of THF and cooled down to 0°C for 10 minutes. To this solution, commercially bought ethyl magnesium bromide (0.2899 g, 2.1735 mmol; 2.75M solution in THF) was added slowly and stirred and monitored by TLC. After 3 hours, the reaction mixture was quenched with aqueous 5% HCl (25 mL) at 0°C. The reaction mixture was washed with 25 mL and extracted with 50 mL. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to obtain pale yellow liquid (**B**): ¹H-NMR (500 MHz, CDCl₃): 5.78-5.80 (m, 1H), 5.67-5.69 (m, 1H), 4.16 (m, 1H), 2.61-2.63 (m, 1H), 2.43-2.46 (m, 4H), 1.71-1.78 (m, 3H), 1.35-1.70 (m, 2H), 1.05-1.06 (t, 3H); ¹³C-NMR (125 MHz, CDCl₃): 210.4, 134.5, 129.5, 62.3, 47.6, 36.7, 31.2, 30.1, 24.1, 7.8.

Ethyl ketone **B** (0.0618g, 0.3673 mmol), TBSCl (0.0664g, 0.4407 mmol) and imidazole (0.0625g, 0.9183 mmol) were dissolved in 5 mL of DMF and stirred overnight at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with 25 mL DCM. The organic layer was further treated with 0.1M HCl (20 mL), aqueous sodium bicarbonate (20 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give **3.48** as a pale-yellow liquid (Yield = 63%, over 2 steps): ¹H-NMR (500 MHz, CDCl₃): 5.78-5.80 (m,

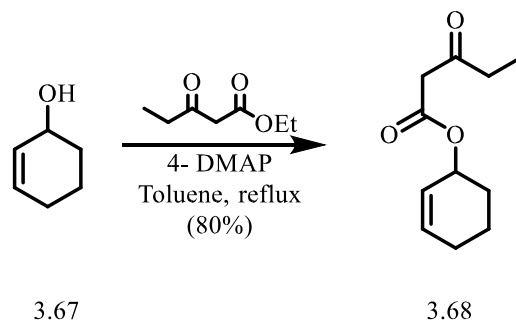
1H), 5.67-5.69 (m, 1H), 4.16-4.17 (m, 1H), 2.62 (m, 1H), 2.42-2.46 (m, 4H), 1.69-1.77 (m, 4H), 1.05-1.08 (t, 3H), 0.92 (s, 9H), 0.10 (s, 6H).



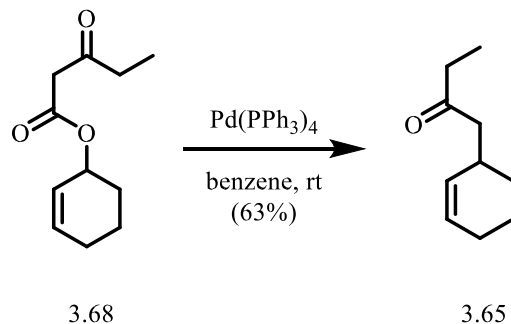
The hydrazone and α -Cl azo compounds were prepared with the same method used to prepare similar compounds in Chapter 2.

Compound 3.47: $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 7.23-7.21 (m, ~1H), 7.02-7.11 (m, 3H), 6.81-6.85 (m, 2H), 5.59-5.87 (m, 2H), 4.18 (br s, 1H), 2.25-2.56 (m, 4H), 1.68-1.72 (m, 3H), 1.13-1.17 (m, 2H), 0.90 (d, 9H), 0.08 (d, 6H).

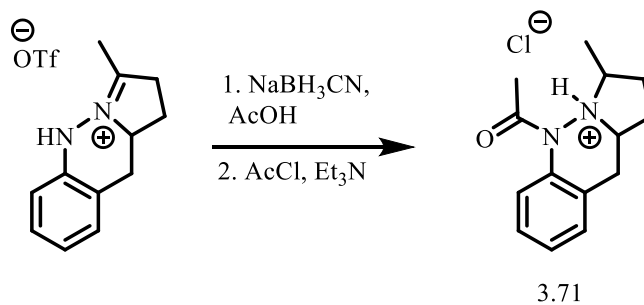
Compound 3.58 (Product obtained upon reaction of **3.55** with halophilic Lewis acids): $^1\text{H-NMR}$ (CDCl_3 , 500MHz): 5.65-5.89 (m, 2H), 2.82(m, 1H), 2.37-2.48 (m, 3H), 1.02-1.05 (t, 2H), 0.83-0.86 (m, 3H). GC-MS: m/z Calculated 150.10, found 150.7



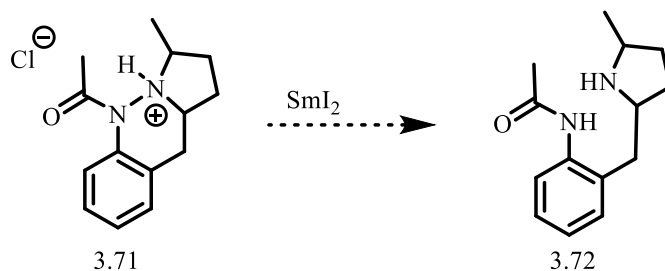
Compound 3.68: To a solution of ethyl propionyl acetate (1.937g, 13.438 mmol) and 2-cyclohexen-1-ol (0.4396g, 4.479 mmol) in 10 mL of toluene, N,N-dimethylaminopyridine (4-DMAP, 0.164 g, 1.344 mmol) was added and the reaction mixture was refluxed and monitored by TLC. After 24 hours of reflux, the reaction mixture was cooled to 0°C and quenched with saturated ammonium chloride solution (30 mL) and extracted with diethyl ether twice (30 mL). The organic layer was then washed with brine, dried over MgSO₄ and concentrated *in vacuo* to yield a bright orange liquid that was purified by column chromatography to give 0.6959 (80% yield) of compound **3.68** as a yellow liquid: ¹H-NMR (500 MHz, CDCl₃): 12.15 (br s, 10% enol OH), 5.96-5.97 (m, 1H), 5.70-5.72 (m, 1H), 5.32 (br s, 1H), 4.99 (s, 10% enol CH), 3.44 (s, 2H), 2.54-2.59 (m, 2H), 2.11-2.09 (m, 1H), 2.08-2.06 (m, 1H), 1.87-1.89 (m, 1H), 1.74-1.85 (m, 3H), 1.09-1.11 (t, 3H); ¹³C-NMR (125 MHz, CDCl₃): 203.3, 167.0, 133.2, 125.1, 88.5, 69.2, 49.3, 36.3, 29.7, 24.9, 18.8.



Compound 3.65: To a solution of $\text{Pd(PPh}_3)_4$ (0.4098g, 0.3546 mmol) in 12 mL of benzene was added the β -ketoester (0.6959g, 3.546 mmol). The solution was stirred for 3 days and monitored by TLC. The mixture was concentrated in vacuo and purified by flash chromatography (hexanes/ Et_2O 95:5) to yield ethyl ketone **3.65** (0.3402g, 63% yield). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 5.68-5.70 (m, 1H), 5.48-5.50 (m, 1H), 2.64 (m, 1H), 2.37-2.44 (m, 3H), 1.97 (m, 2H), 1.77-1.80 (m, 1H), 1.66-1.69 (m, 1H), 1.19-1.30 (m, 3H), 1.04-1.07 (t, 3H).



Compound 3.71: Protonated azomethine iminium salt **3.61** (0.1541g, 0.458 mmol) was dissolved in 3mL acetic acid. Addition of sodium cyanoborohydride (0.0432g, 0.687 mmol) to the solution resulted in color change from deep purple to orange accompanied by brisk effervescence. The reaction mixture was stirred at room temperature for 3 hours after which it was azeotroped with toluene three times (20 mL) and concentrated *in vacuo* to give a sticky brown oil. This reduced product was dissolved in 5 mL of acetonitrile along with acetyl chloride (0.0964g, 1.228 mmol) and to the reaction mixture, triethylamine (0.1863g, 1.8414 mmol) was added and stirred at room temperature for 1 hour. The reaction mixture was diluted in diethyl ether (25 mL), washed with water (20 mL) and brine 20 mL). the organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to give a yellow oil: ¹H-NMR (500 MHz, CDCl₃): 7.51-7.53 (d, 1H), 7.18-7.22 (m, ~1H), 7.14-7.16 (m, 1H), 4.04 (m, 1H), 2.65-2.73 (m, 2H), 2.51-2.53 (d, 1H), 2.36 (s, 3H), 1.98-1.99 (m, 0.90H), 1.74-1.77 (m, 1H), 1.38-1.40 (m, 2H), 1.11-1.12 (d, 3H); ¹³C-NMR (125 MHz, CDCl₃): 128.9, 128.6, 126.1, 126.0, 125.8, 124.3, 101.1, 60.1, 58.1, 31.0, 30.3, 30.1, 29.6, 22.0, 18.8.



General Procedure of reduction of **3.71**: A THF solution of SmI₂ (0.1 M THF solution) was added dropwise to a DCM/THF solution (2 mL) of **3.71** and additive (5% of SmI₂ used) at room temperature under argon. After 30 min at room temperature, the reaction mixture was quenched with a mixture of a diluted NaHCO₃ solution (50 mL) and DCM (20 mL), extracted with DCM (30 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*.

SmI₂	Temperature (°C)	Time (h)	Additive	Solvent
2.0	Room temperature	0.5	-	DCM
2.0	Room temperature	0.5	MeOH	DCM
5.0	-78	1	MeOH	DCM
5.0	35	24	MeOH	DCM
2.0	Room temperature	24	DMPU	THF
5.0	Room temperature	24	DMPU	THF
25.0*	Room temperature	24	MeOH	DCM
50.0*	60	24	MeOH	THF

(*) When large excess of SmI₂ was used an insoluble white solid crashed out that is not NMR active

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APPENDIX: ^1H AND ^{13}C NMR SPECTRA