

New Methods in Alkylidenecarbene Chemistry

A Mild Route to Cycloalkynes

By

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Dedicated to my family, Dimitrios, Ekaterini, Eleni, and Georgia Alexakos, and to Danielle Reusnow. Without their unwavering love and support, none of this would be possible.

“It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, we were all going direct to Heaven, we were all going direct the other way—in short, the period was so far like the present period, that some of its noisiest authorities insisted on its being received, for good or for evil, in the superlative degree of comparison only.”

-Charles Dickens, *A Tale of Two Cities*

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CONTRIBUTION OF AUTHORS

A benefit of research is the collaborative environment, where peers of all experience levels can contribute to the overall benefit of quality of life. Colleagues and collaborators assisted in improving the quality of projects presented in this dissertation. Chapter 1 provides a brief overview of cyclooctynes and our ideas of research.

Chapter 2 introduces various methods of 5-(1-hydroxyalkyl)tetrazoles preparation. A highly efficient, one-pot methodology is described therein, some of which are portions of previously published articles: N-Morpholinomethyl-5-lithiotetrazole: A Reagent for the One-Pot Synthesis of 5-(1-hydroxyalkyl)tetrazoles. Alexakos, P. D.; Wardrop, D. J. *J. Org. Chem.* **2019**, *84*, 12430-12436.

Chapter 3 describes prior syntheses of cyclooctynes and thereby utilizes the previous 5-(1-hydroxyalkyl)tetrazole methodology towards the efficient ring expansion preparation of cyclooctynes. The work performed in this chapter was with the assistance of Mariana Frojuello and Mario Noboa.

Chapter 4 studies the application of the preparation of cyclooctynes towards the synthesis of commercially available bioconjugation reagents. Extension and further utility of these reagents is also described. This project is currently ongoing.

Chapter 5 extends the developed ring expansion towards the preparation of cyclopentynes. This project is currently ongoing.

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Chapter 1. Introduction

1. Cyclooctynes

1.1 Importance of Cyclooctynes

Since the discovery of cyclooctyne's "explosive" reaction with phenyl azide,¹ cyclooctynes have been moved to the forefront of the click chemistry revolution as they represent a fine bridge between stability and reactivity for the strain-promoted azide-alkyne cycloaddition reaction (SPAAC) and its application in bioconjugation,² DNA tagging,³ and protein linking,⁴ amongst other applications. Their importance also extends beyond biological applications to the fields of material and surface science such as in nano rings⁵ and metal complexes.⁶ Pioneering studies by Bertozzi and other synthetic chemists have resparked interest in the preparation of these strained alkynes.

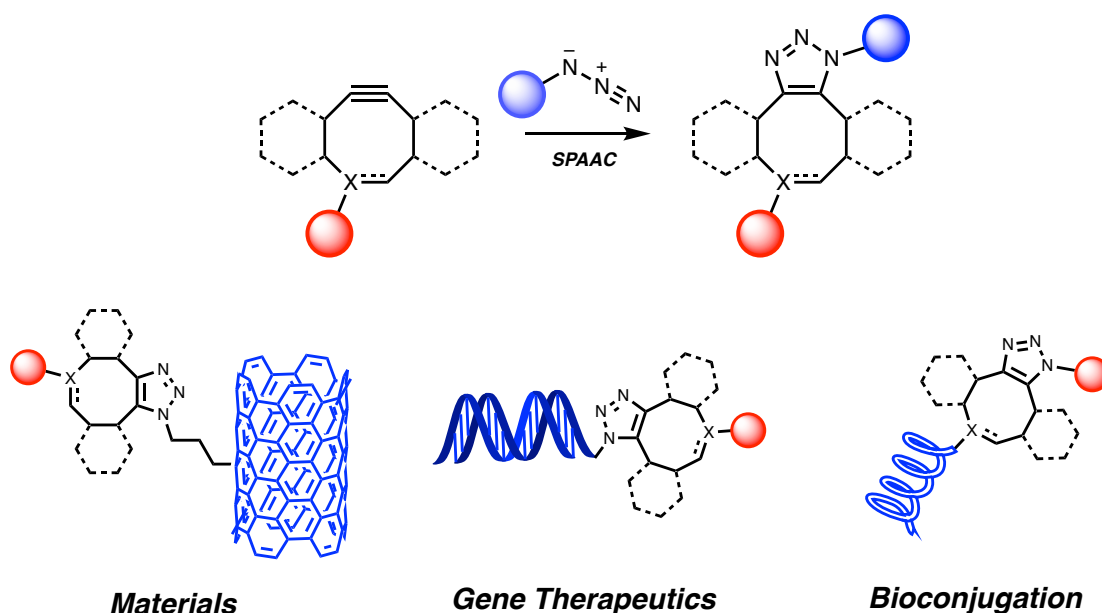


Figure 1. Importance of SPAAC

1.2 Classes of Cyclooctynes

The reactivity of cyclooctynes can generally be attributed to the two main components: angle strain and electronic activation (Figure 2). The model compound that has defined the angle strain

category is dibenzoannulated cyclooctyne (DIBO), synthesized by Ning.⁷ The presence of sp^2 -hybridized centers within the cyclooctyne core decreases the acetylene bond angle to 153° , thereby increasing the reactivity of the alkyne. The ring strain of cyclooctyne has been estimated to be ~ 18 kcal/mol, which is 6 kcal/mol more than cyclooctane.⁸ The addition of other sp^2 centers increases the reactivity of the cyclooctyne and thus its rate of cycloaddition, but compromises stability, and thus lifetime, of the cyclooctyne, such as the case with BARAC.⁹ An intermediate zone that exhibits high cycloaddition reactivity with benzyl azide, measured as k_2 , but also bench stability is found in ADIBO, where an additional handle can be placed for an *N*-linker. One disadvantage to this approach is the increase of lipophilicity, which can become problematic for applications in aqueous media. To overcome this issue, a different approach has been developed that utilizes electronic effects.

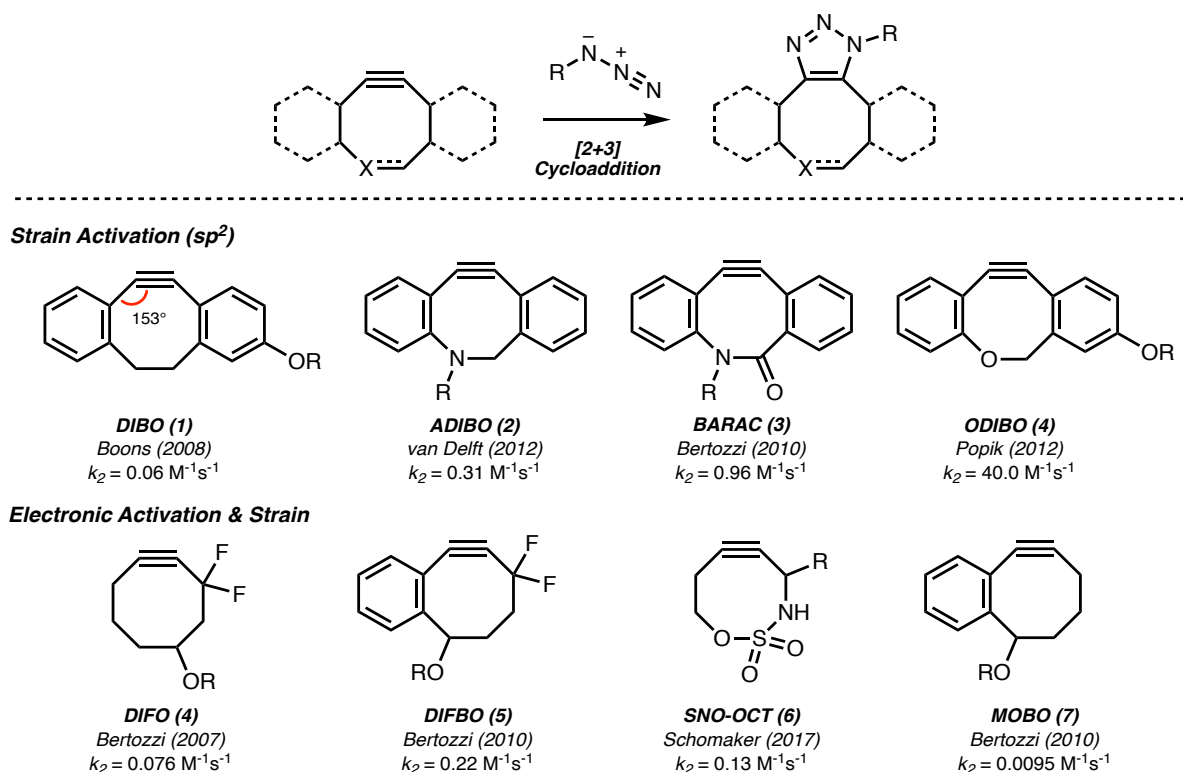


Figure 2. Representative examples of cyclooctyne reagents.

The electronic activation of cyclooctynes has been less explored approach to increasing strain but has also proved its importance. The addition of electron-withdrawing groups adjacent to the alkyne raises the distortion of the dipoles, increasing their interaction primarily due to charge-transfer interaction effects. Also, the LUMO is slightly depressed, while the HOMO is greatly elevated. Overall, the activation barrier of cycloaddition with DIFO (**4**) is dramatically lower by 2 kcal/mol compared to cyclooctyne.¹⁰

Due to the relative difficulty of fluorination, Alabugin inserted a heteroatom into the cyclooctyne ring to utilize electronic activation. This allows for hyperconjugative assistance due to the stabilization of the cycloaddition transition state.¹¹ Cyclononynes with propargyl heteroatoms have shown similar reactivity as DIFO (**4**).¹²

The increased activation of the angle strain by the addition of sp^2 centers is an appealing strategy; however, it also increases steric interactions, particularly $A^{1,3}$ -strain between the ortho hydrogens on the aryl groups and the alkyl group of the azide. This can be circumvented by removing one aryl group as in the case of MOBO. Not only does this reduce allylic strain but favors the formation of one triazole regioisomer.¹³ Upon cycloaddition of DIFO (**4**) with benzyl azide, the resulting triazole that was least sterically hindered was favored in a 2:1 ratio, supporting the theory of the ability to favor one regioisomer (Figure 3). Despite being benchtop stable, the cycloaddition of MOBO (**7**) and benzyl azide was slower ($0.0095\text{ M}^{-1}\text{s}^{-1}$) by about an order of magnitude compared to its counterparts.

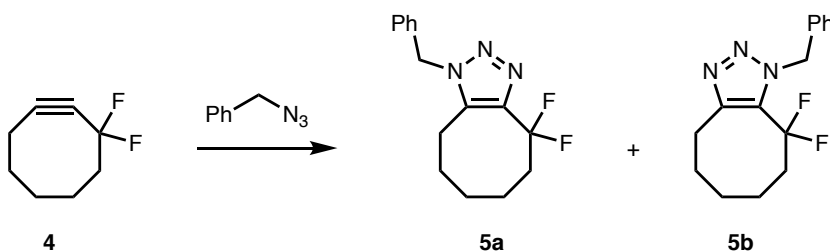


Figure 3. Cycloaddition of DIFO and benzyl azide

Bertozzi utilized both of angle strain and electronic activation, a combination of DIBO (**1**) and DIFO (**4**), to generate DIFBO (**5**), which shows significantly higher reactivity ($0.22\text{ M}^{-1}\text{s}^{-1}$) compared to both DIBO ($0.06\text{ M}^{-1}\text{s}^{-1}$) and DIFO ($0.076\text{ M}^{-1}\text{s}^{-1}$). Unfortunately, this cyclooctyne readily trimerized, compromising its practicality.¹⁴

1.3 Synthesis of Cyclooctynes

In light of the importance of cyclooctynes and a desire to introduce greater functionality and tune physical properties such as alkyne reactivity and solubility, there remains a demand for new synthetic methods (Figure 4). However, are relatively few approaches to cyclooctynes that employ mild conditions and show wide substrate scope. Indeed, most current methods require the construction of an 8-membered ring prior to introduction of the alkyne group, which often times has proven challenging. The basis of this research is to determine whether cyclooctynes can be synthesized via an alkylidenecarbene rearrangement, stemming from a cycloheptylidene intermediate. This would avoid the requirement of 8-membered ring construction.

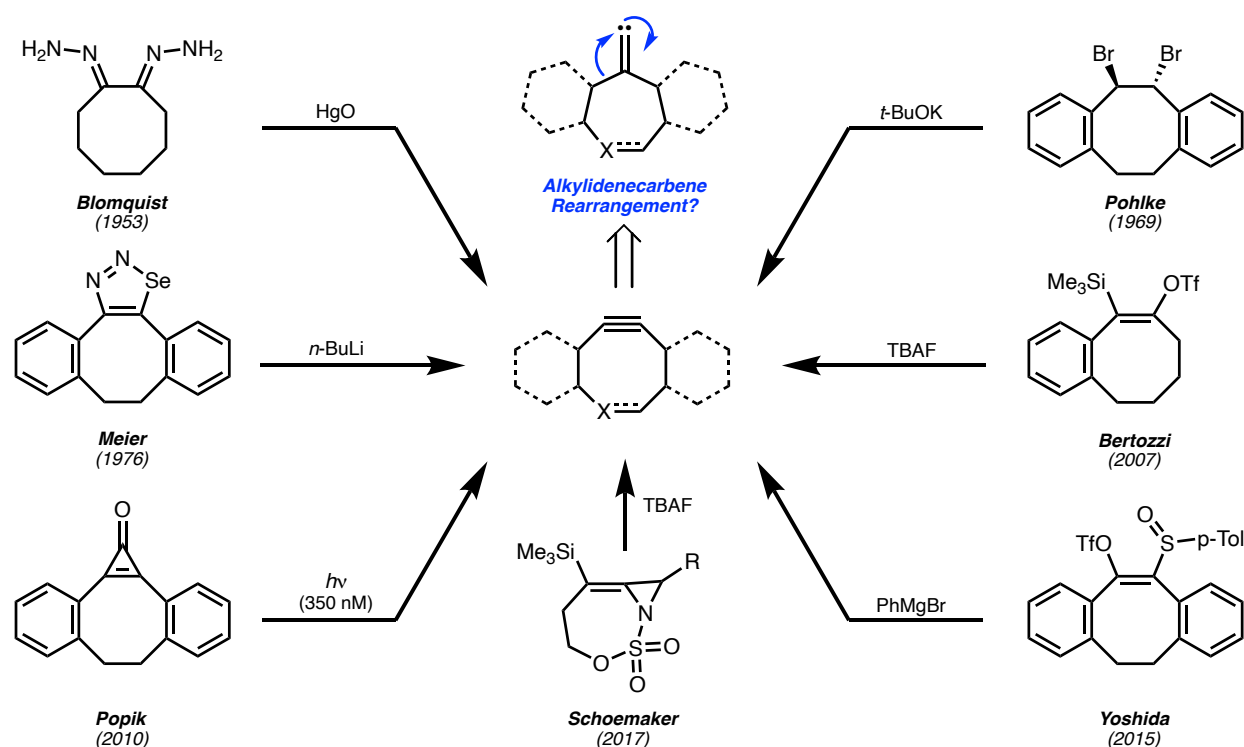


Figure 4. Summary of Cyclooctynes Synthesis.

2. Alkylidenecarbenes

Alkylidenecarbenes are very reactive intermediates in organic chemistry which have considerable untapped potential. Their high reactivity requires them to be generated in similar methods as with typical carbenes, but generation and trapping must be done in situ.^{15 16} Alkylidenecarbenes have a unique structure, which can potentially be in 3 distinct structures. In singlet state **8** (Figure 5), a lone pair of electrons is located on the sp non-bonding orbital (HOMO), and the p orbital (LUMO) is empty.¹⁷ Triplet state **9** is about 48 kcal/mol higher in energy and has a single electron in the sp and p orbitals.¹⁸ Free alkylidenecarbenes also occur as metal carbenoids **10**. Free **8** and encumbered **10** often share the same reactivity.

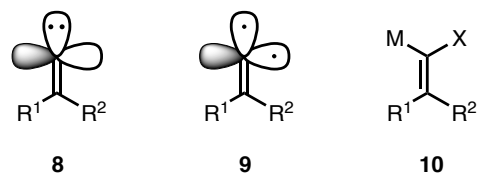


Figure 5. Singlet, triplet, and carbenoid states of alkylidenecarbenes.

Formation of unencumbered, singlet **8** is often accomplished via vinyldiazonium species through the release of dinitrogen, popular examples being the modified Horner-Wadsworth-Emmons reaction¹⁹ or Peterson olefination²⁰. Commonly employed reagents for alkylidenecarbene formation include diazomethylphosphaonate esters (DAMP), and trimethylsilyldiazomethane. Metal carbenoids **10** are achieved through metal/halogen exchange or deprotonation through the use of strong base or other harsh reaction conditions.¹⁵

These intermediates can undergo a number of transformations, (Figure 6) including heteroatom capture to form ylides or coordination complexes.²¹ In common with other carbenes, alkylidenecarbenes can be react with olefins to form methylenecyclopropenes.²² A common utilization of alkylidene carbenes is 1,5 C–H insertion.^{15 23} This process particularly favored at tertiary C–H positions due to the electron deficient nature of these divalent species. Relative rates of insertion between primary, secondary, and tertiary C–H bonds are 1:30:240, respectively, with increasing rates when the C–H bond in question is adjacent to a heteroatom.²⁴ Insertion into O–H and O–Si bonds are faster than C–H bond insertion.²⁵ Faster than 1,5-bond insertion is the formation of terminal and internal alkynes via the Fritsch-Buttenberg-Wiechell (FBW) rearrangement. One of the most common uses of FBW rearrangement is as key steps of the Corey-Fuchs reaction.²⁶ This methodology has been utilized in a variety of applications, notably the synthesis of polyynes and carbon allotropes, carbynes, by Tykwinski.^{27,28} Despite the focus on 1–5 insertion, the ability to convert carbonyl groups to alkynes is very powerful, particularly with the use of Ohira-Bestmann reagent. This reagent was utilized by Li in the synthesis of (±)-δ-

rubromycin.²⁹ This reagent was also used by Reddy during the synthesis of oplopandiol, oploxyne A, and (–)-oploxyne B.³⁰ In a previous work, Wardrop has employed the 1,2 rearrangement of an alkylidenecarbene, generated by dehydration of 1-(5-hydroxyalkyl)tetrazoles in the synthesis of combretastatin A4.³¹ Our hope was to utilize this reaction pathway to access cyclooctynes.

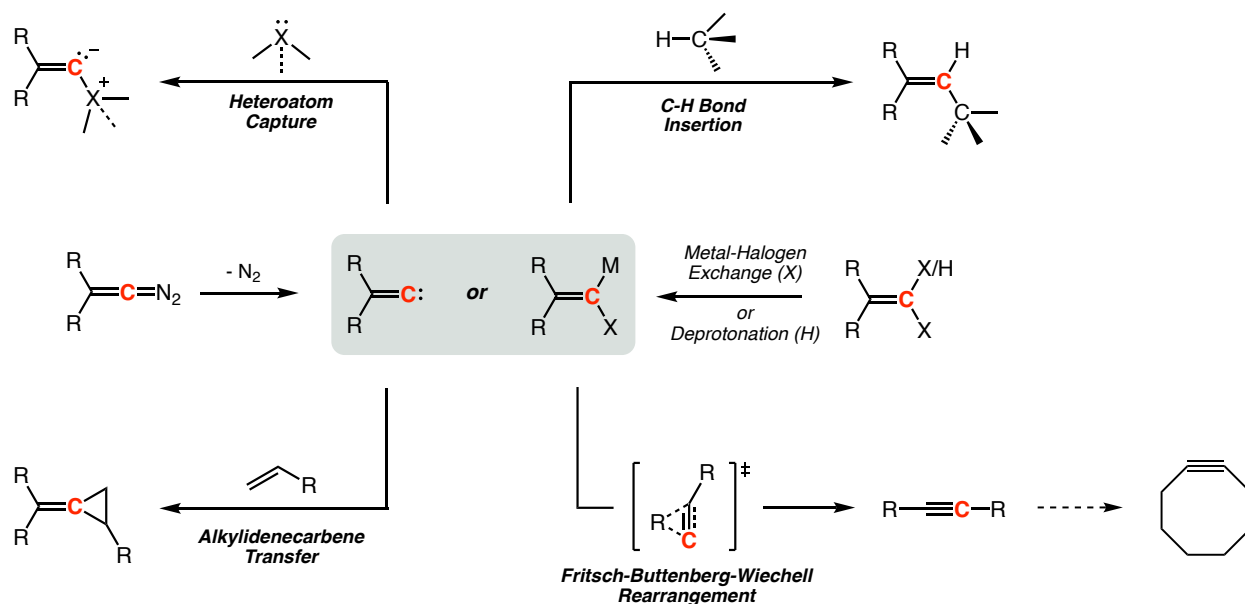


Figure 6. Transformations of alkylidenecarbenes.

FBW rearrangements are energetically favorable by as much as -45 kcal/mol (theory),³² -47.4 kcal/mol (observed)³³ with an activation barrier of about 1.5 kcal/mol, allowing for a lifetime of picoseconds.³⁴ The migratory aptitude of carbene substituents has been measured as $H \approx Ph > \text{alkyl}$.^{35,36} The migratory aptitude of alkyl chains has been explored by Walsh and show the trend tertiary > secondary > primary, suggesting more electron-donating group are more likely to migrate.³⁷

3. Literature Basis

Despite the powerful utility of converting carbonyl groups to alkynes, there has been little research into the synthesis of cyclooctynes using an alkylidenecarbene, leaving this area of

research ripe for exploration. In collaboration with Dr. Shahid Islam, DFT studies (Figure 7) shows that the overall transformation of alkylidenecarbene **11** to DIBO (**1**) is calculated to have a low activation barrier (5.8 kcal/mol), but more importantly, is exothermically favorable (-39.5 kcal/mol).

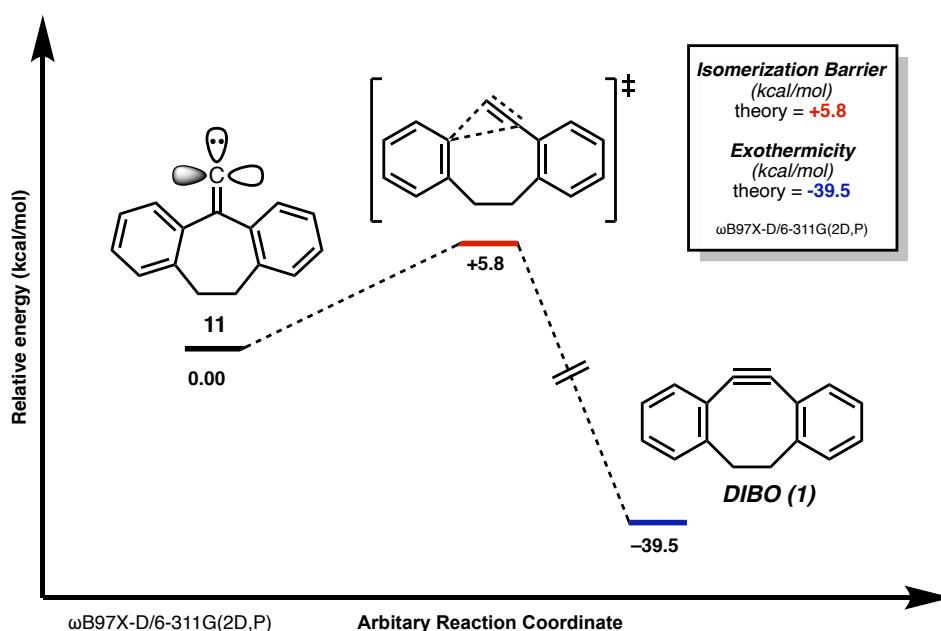


Figure 7. DFT energy diagram of alkylidenecarbene rearrangement

The formation of cyclooctynes by ring expansion via 1,2-shift was first reported in 1959 by Curtin (Figure 8).³⁸ While exploring the reactivity of phenyllithium with vinyl halides, he reacted diarylvinylchloride **12** with phenyllithium and isolated the ring expanded cyclooctene **15** in modest yield. He postulated that the deprotonation and ipso-elimination of vinyl chloride **12** gave rise to an alkylidenecarbene **13** which goes rearrangement to form dibenzoannulated cyclooctyne (DIBO). Due to its high reactivity from ring strain the cyclooctyne undergoes nucleophilic attack with excess phenyllithium to form vinylphenyl lithium **14**, which on protonation yields **15**.

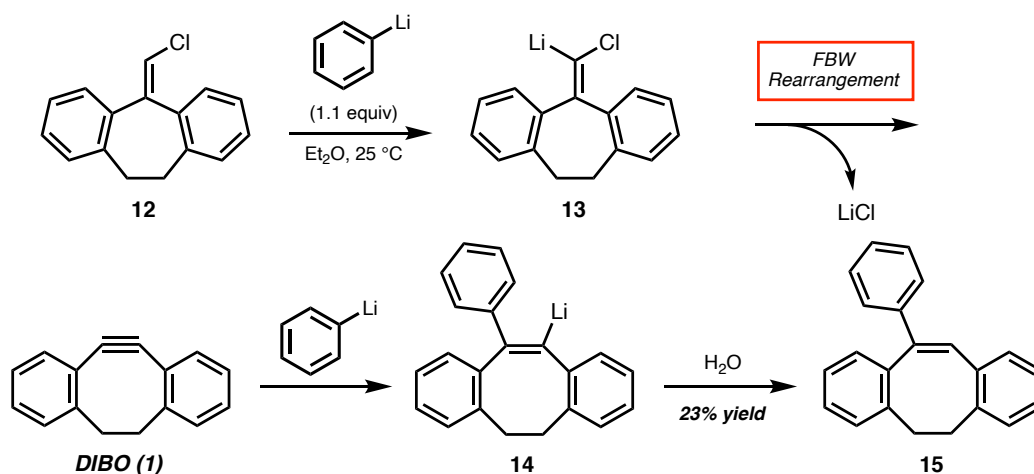


Figure 8. Treatment of diarylvinylchlorides with phenyllithium by Curtin.

Wanting to avoid cyclooctyne reactivity with harsh reaction conditions, we wanted to opt towards a method that would allow for latent alkylidenecarbene formation, which was reported by Behringer,³⁹ where he reported that the pyrolysis of various 1-(5-substitutedalkyl)tetrazoles resulted in formation of phenylacetylene **20**. He proposed tetraazafulvene intermediate **17** was generated after expulsion of the leaving group. He postulated that the fragmentation of **17** proceeded in two discrete steps; initial loss of the dinitrogen generates diazoalkane **18**, which undergoes a second nitrogen expulsion event to yield alkylidenecarbene intermediate **19**, followed by a 1,2-shift, rearranging into diphenylacetylene **20** (Figure 9).

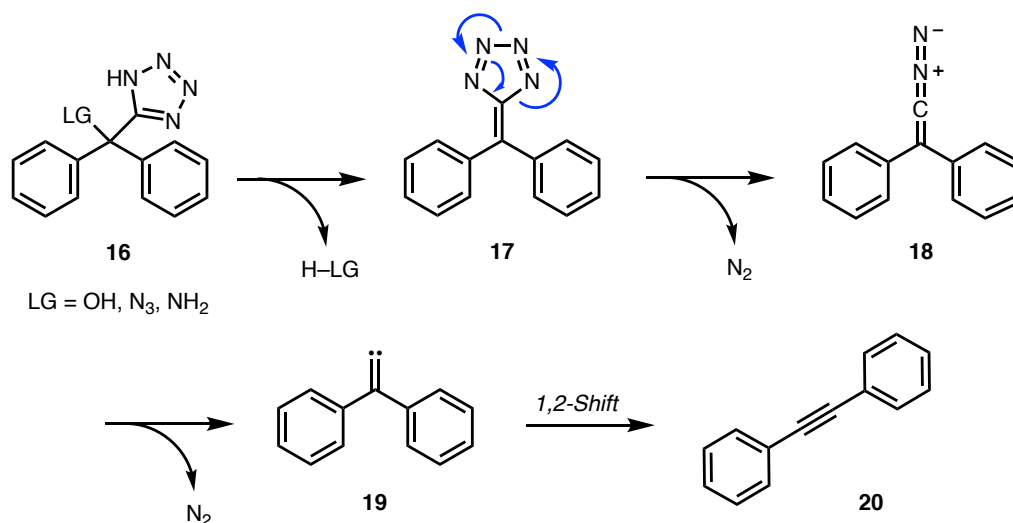


Figure 9. Proposed mechanism of the pyrolysis of 5-(1-Hydroxyalkyl)tetrazoles

4. Hypothesis

Our hypothesis was whether we would be able to apply this chemistry to the preparation of cyclooctynes from 5-(1-hydroxyalkyl)tetrazoles via a latent alkylidenecarbene in the presence of a dehydrating agent that can subsequently undergo rearrangement into the strained ring that can also be trapped in situ (Figure 10). This would allow formation of cyclooctynes under mild reaction conditions that can also be intercepted in situ, provide versatile scope, and more importantly, circumvent the need for preconstruction of an eight-membered ring core.

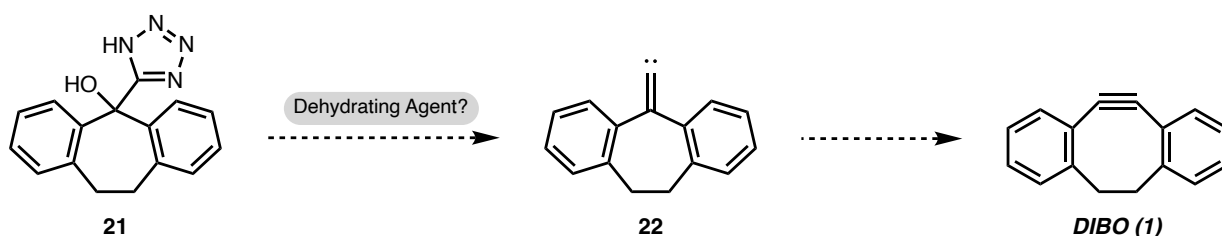


Figure 10. Our hypothesis towards the preparation of cyclooctynes.

5. Chapter Summary

Herein, the research conducted within my thesis begins with the development of an efficient, one-pot method towards the preparation of 5-(1-hydroxyalkyl)tetrazoles (Chapter 2), followed by utility of these precursors as latent alkylidenecarbenes towards the synthesis of cyclooctynes (Chapter 3). This 2-step methodology was then utilized towards the application of commercially cyclooctyne reagents and enhancing their practicality (Chapter 4) and extension of our method towards the synthesis of cyclopentynes (Chapter 5).

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Chapter 2. Tetrazoles

Previously published as Alexakos, P.; Wardrop, D. *N*-Morpholinomethyl-5-lithiotetrazole: A Reagent for the One-Pot Synthesis of 5-(1-Hydroxyalkyl)tetrazoles. *J. Org. Chem.* **2019**, *84*, 12430-12436.

1. Introduction

Since Bladin's preparation of tetrazole in 1892,¹ this nitrogen-rich heterocycle and its derivatives have found application in an array of disciplines. In medicinal chemistry, tetrazoles are deployed as metabolically-stable *cis*-constrained peptide bonds and carboxylic acid isosteres,² and are among the ten most common heterocycles in FDA-approved drugs.³ Tetrazoles have also found use as organocatalysts,⁴ potent anion binders,⁵ capping ligands for nanomaterials,⁶ *N*-donors in functionalized metal-organic materials⁷ and metal-coordinating peptides,⁸ as well as high-energy materials.⁹

Tetrazoles, particularly 5-(1-hydroxyalkyl)tetrazoles, continue to be of particular interest (Figure 1). Of particular note is the HIV-1 inhibitor **1**, which has been found to potently inhibit viral Gag-Pol Polyprotein.¹⁰ 5-(1-Hydroxyalkyl)tetrazole **2** was found to inhibit rapamycin (mTOR) and has potential as a cancer agent,¹¹ while **3** inhibits neuraminidase and, as such, is the interest in the treatment H1N1 swine flu,¹² and **4** was examined as an inhibitor of PDE7 to treat various inflammatory diseases.¹³ Other recently discovered pharmaceutically active hydroxyalkyltetrazoles include **5**, an oxerlin receptor antagonist,¹⁴ **6**, a metabotropic glutamate receptor 2 (mGluR2) allosteric modulator,¹⁵ **7**, a CD73 adenosine A2A receptor inhibitor,¹⁶ and **8**, a Histamine H1 and H4 antagonist.¹⁷ Even in cases where hydroxyalkyltetrazoles are linked as ligands yet prove to be inactive,¹⁸ their frequent appearance continue to be of high importance.

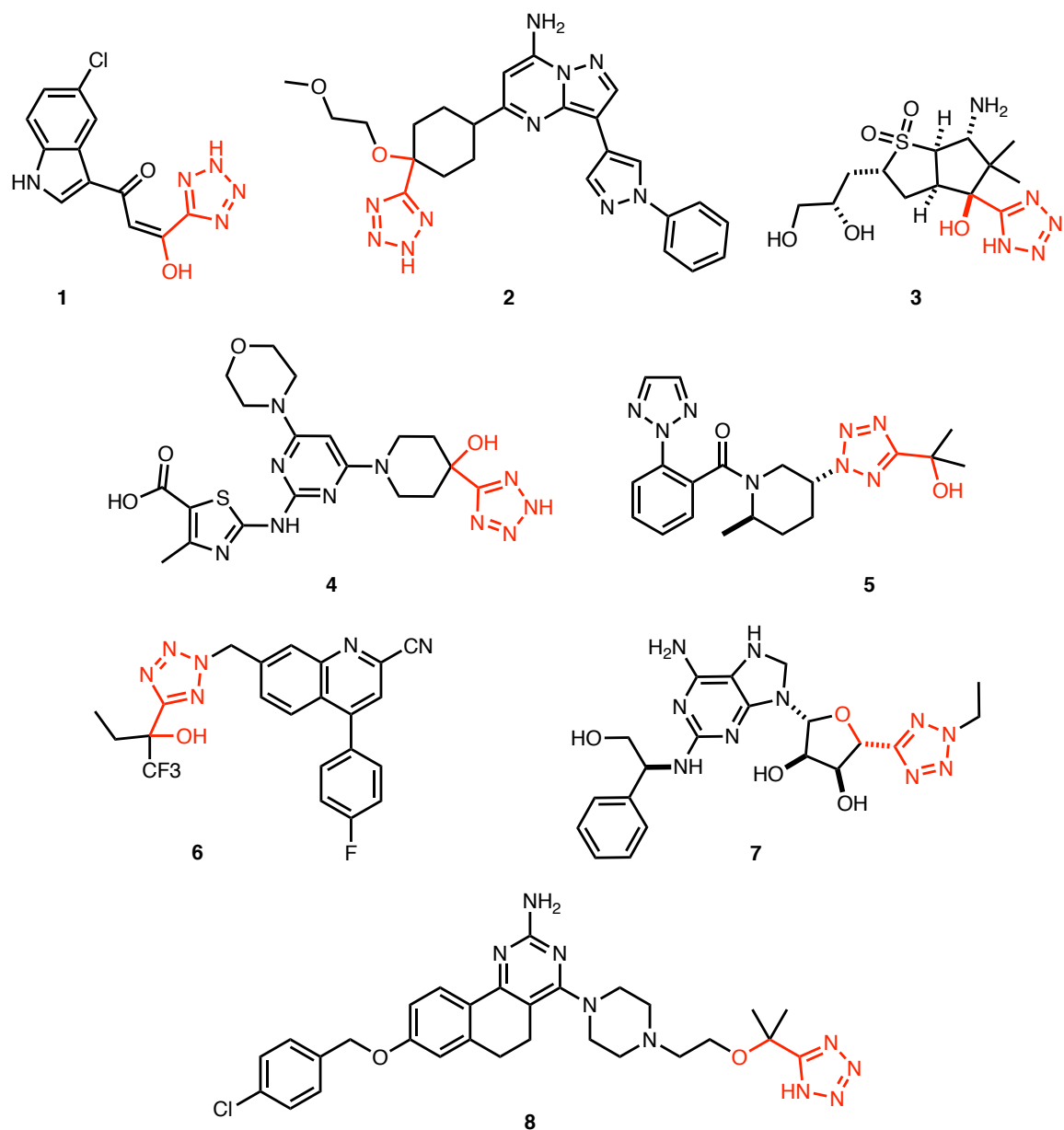


Figure 1. Pharmacologically active 5-(1-hydroxyalkyl)tetrazoles.

That the synthesis of tetrazoles remains a topic of intense interest after more than 125 years, reflects the enduring relevance of this ring system.^{19 20} While multiple methods of preparation have been reported, but they can be broadly categorized into three distinct categories: cyanohydrin-azide cycloaddition; multicomponent Passerini reactions; and addition of 5-metallotetrazole

species to carbonyl groups. Each provide unique advantages and disadvantages which will be discussed in overview.

2. Cyanohydrin–Azide Cycloaddition

The most common method to prepare 5-(1-hydroxyalkyl)tetrazoles is via formal [2+3] cycloaddition of cyanohydrins with azide and azide-based reagents. This method continues to be widely used preparation of tetrazoles with various advances in forming this special functional group. Herein, this category can be divided dependent on the use of a Bronsted or Lewis acid catalyst to accelerate the rate cycloaddition. The cycloaddition route has been explored allowing for wide substrate scope but is limited to steric hinderance of congested substrates as well as the use of harmful reagents such as hydrazoic acid.

2.1 Acid-Catalyzed Cycloaddition

The acid-catalyzed cycloaddition for the preparation of 5-(1-hydroxyalkyl)tetrazoles is one of the earliest methods of preparation of this nitrogen-rich ring system and has been extensively investigated. However, the use of harmful reagents, including cyanide and hydrazoic acid poses physical danger. Another disadvantage of this method is the insufficient orbital overlap of the LUMO of the nitrile without induction; thus requiring high temperatures, catalysts, or electron withdrawing groups.^{20, 21} Sharpless was the first to utilize acid catalysis for the cycloaddition of cyanides to azides. He proposed that this transformation proceeds via an eight-member transition state **10** wherein nitrile activation by an ammonium ion leads to formation of imidoyl azide **11** which subsequently undergoes cyclization (Figure 2).²²

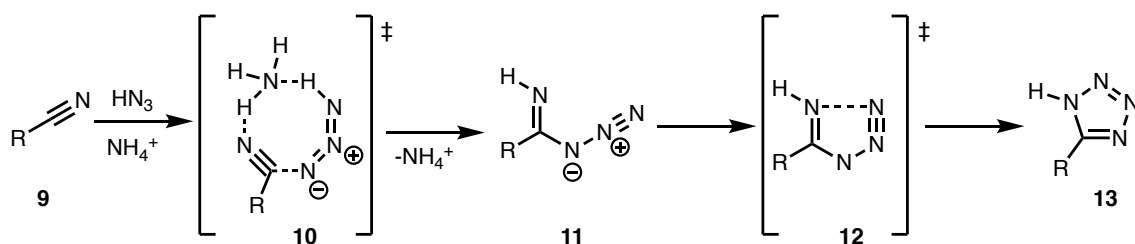


Figure 2. Sharpless' mechanistic proposal for the acid-catalyzed nitrile-azide cycloaddition reaction.

While the acid-catalyzed cycloaddition has shown to be efficient, it has several disadvantages, including cyanohydrin preparation which involves cyanide use. The cycloaddition of cyanohydrin and azide salts also must be carried out under carefully controlled conditions to prevent formation of hydrazoic acid, which can spontaneously detonate at high concentration. In addition to safety concerns, high temperatures are often required to promote this process.

Due to the crowded nature of the proposed mechanism, it is unsurprising that this transformation is highly susceptible to steric hindrance.²³ This can greatly prolong reaction times and, in some cases, require higher temperatures. An illustrative example of the effects of steric hindrance has been reported by Vasudevan, who prepared acyl tetrazoles as potential HDAC inhibitors (Figure 3).²⁴ In this case, a THP-protected cyanohydrin **14** was transformed to monosubstituted tetrazole **15**. The cycloaddition of azide and cyanohydrin proceeds with a modest yield, which was ascribed by the authors to steric hindrance unsung from the THP-protected alcohol.

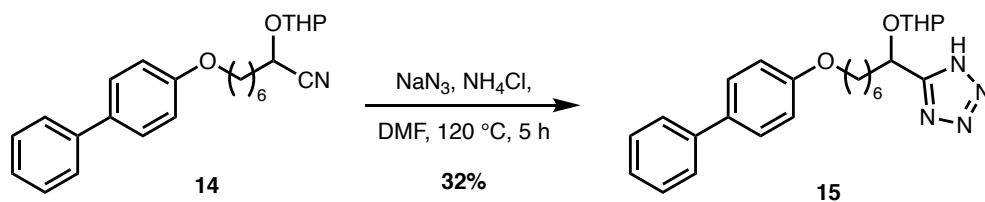


Figure 3. THP-protected tetrazole formation via cycloaddition.

2.2 Lewis Acid-Catalyzed Cycloaddition

So as to lower reaction temperatures, the use of Lewis acid catalysis has been extensively investigated. The use of such catalysis allows for less hydrazoic acid exposure, which was prevalent in acid-catalyzed cycloadditions. Beyond safety concerns, Lewis acid-catalyzed cycloadditions are of particular interest and preference because they facilitate the cyclization of imidoazide **17** through coordination of nitrile **16** (Figure 4). Zinc-catalyzed cycloadditions are favorable because they lower the activation barrier of cyclization up to 6 kcal/mol leading to a four-fold rate acceleration, allowing for shorter reaction times.²⁵

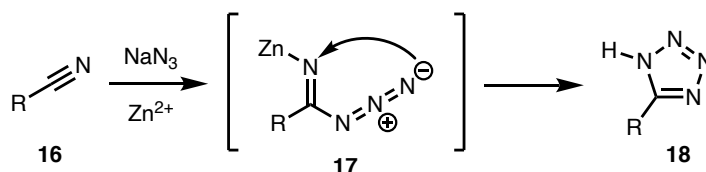


Figure 4. Zinc (II)-catalyzed azide-nitrile cycloaddition mechanism

Zinc (II) salts surprisingly also have some variability in catalysis ability. Sharpless compared zinc (II) chloride, bromide, triflate, and perchlorate, zinc bromide and analyzed the effectiveness for formation of 1-(5-hydroxyalkyl)tetrazoles. Zinc chloride was found to be inefficient due to slightly favorability above the others to hydrolyze the nitrile.²⁶ To date, zinc bromide has been found to be the preferred reagent for azide-nitrile cycloaddition.

The efficiency of ZnBr₂-catalyzed cycloaddition is slightly more favorable than the acid-catalyzed version, in that slightly lower reaction temperatures can be employed. For example. Takács and coworkers found that cyanohydrin **19** underwent Zn (II)-catalyzed cycloaddition to form 1-(5-hydroxyalkyl)tetrazole **20** in excellent yield (Figure 5, A).²⁷ There have been reports that the cycloaddition could be conducted in partially- and near fully- aqueous conditions (Figure 5, B & C).^{26, 28, 29}

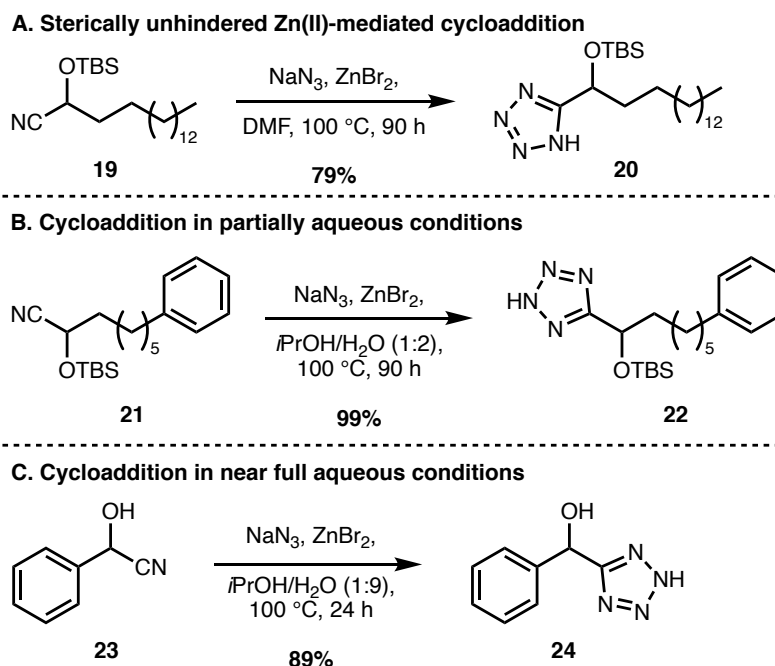


Figure 5. Scope of zinc-catalyzed cyanohydrin-azide cycloaddition under various conditions.

With zinc bromide being the most predominant reagent for Lewis Acid cycloaddition, avenues into other elements that could catalyze this reaction have been explored. Of note are organoaluminum azide,³⁰ boron trifluoride etherate,³¹ and dibutyltin oxide³². Each of these reagents offer a unique reagent for catalysis with comparable yield, yet they all possess similarities. Preparation of the starting materials involves exposure to toxic reagents, harsh conditions are often required, and dangerous byproducts, such as hydrazoic acid, are formed. More importantly, this cycloaddition is very susceptible to steric hindrance, demanding elevated temperatures and prolonged reaction times, inefficiently accessing 1-(5-hydroxyalkyl)tetrazoles.

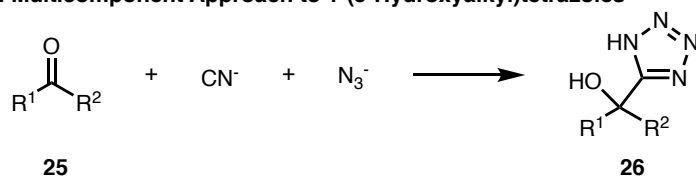
3. Multicomponent Reactions

Multicomponent reactions are a unique approach to organic synthesis by providing a multifaceted route within one reaction. A traditional approach to the preparation 1-(5-hydroxyalkyl)tetrazoles has been the condensation of cyano- and azide-reagents with a reactive

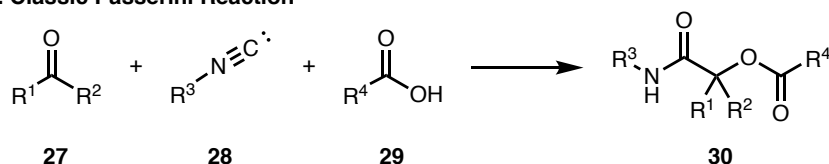
carbonyl group, which allows for *in-situ* preparation of the cyanohydrin, followed by immediate cycloaddition with azide. This offers direct access to 1-(5-hydroxyalkyl)tetrazoles **26** (Figure 6, A). Development of this approach has also allowed for the formation of 1-(5-hydroxyalkyl)tetrazoles under aqueous conditions.³³ Despite the use of cyanide and azide reagents, this approach minimizes exposure time to such dangerous and toxic chemicals, but often involves reaction times as long as 96 h.

The Passerini reaction, originally developed to provide α -cyloxyamides **30** (Figure 6, B) utilizes a three-component reaction between a reactive carbonyl compound **27**, isonitriles **28**, and carboxylic acids **29**. In 1961, Ugi and Meyr discovered that by substituting hydrazoic acid with the carboxylic acid, substituted 1-(5-hydroxyalkyl)tetrazoles **33** could be accessed (Figure 6, C).³⁴ TMS-azide was subsequently substituted as a safer azide source than hydrazoic acid by Nixey and Humle in their work to generate *cis*-constrained norstatines.³⁵

A. Multicomponent Approach to 1-(5-Hydroxyalkyl)tetrazoles



B. Classic Passerini Reaction



C. Passerini Modification to form N-substituted 1-(5-hydroxyalkyl)tetrazoles

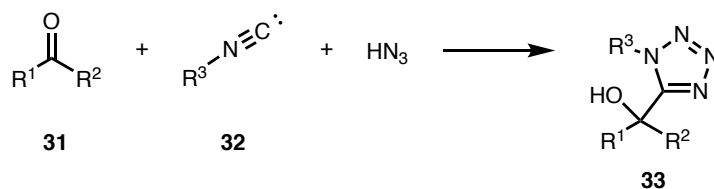


Figure 6. Multicomponent & Passerini modifications for the synthesis of 1-(5-hydroxylalkyl)tetrazoles).

This modification of the Passerini reaction has been extensively used in medicinal chemistry to prepare libraries for screening. Ding has utilized 2-azidobenzaldehydes to access 4-tetrazolyl-4*H*-3,1-benzoxazines via 1-(5-hydroxyalkyl)tetrazoles.³⁶ Another application of this multicomponent reaction is in the exploration of a potential X-linked inhibitor of apoptosis protein (XIAP).³⁷ In this work by Ding, dipeptide **34** was converted to tetrazole **35** to provide a separable 1:3 mixture of diastereomers in modest yield; upon acid deprotection, however, the diastereomers epimerized resulting in loss of stereocontrol (Figure 7).

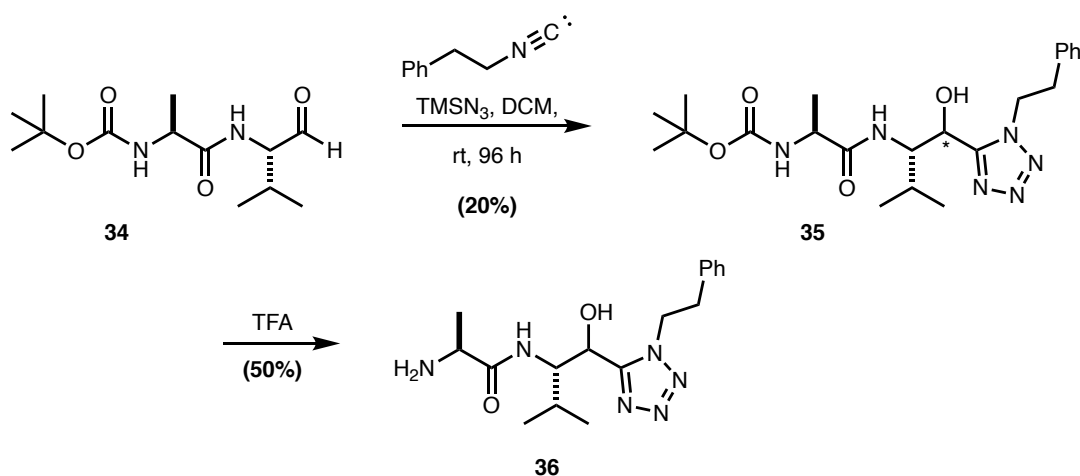


Figure 7. Application of Passerini multicomponent reaction for the synthesis of XIAP inhibitors.

To circumvent this loss of stereochemistry, a chiral catalyst was developed by Zhu, where a [(salen)Al^{III}Cl] complex was used to catalyze the Passerini-modified tetrazole formation in good to near quantitative yields with excellent enantioselectivity.³⁸ Despite its high efficiency and stereocontrol, the scope of this methodology is limited to aliphatic aldehydes and sterically uncongested isocyanides. Another notable disadvantage is the appreciable formation of an α -hydroxyamide byproduct stemming from the hydrolysis of the nitrilium intermediate.³⁹

To avoid the hydrolysis to α -hydroxyamide byproducts, Taguchi explored other Lewis acids, where he found notable success with In (III) salts. This method utilizes the dehydration of aldehyde **37** with an alcohol to provide carboxonium ion **38**. The isocyanide then adds to **38** to provide

nitrilium **39**. This then undergoes cyclization with azide to form the tetrazole ring (Figure 8). Here Tagushi found that by decreasing the catalyst loading of $\text{In}(\text{OTf})_3$, the 1-(5-hydroxyalkyl)tetrazole product was significantly favored over the α -hydroxyamide byproduct and significantly shortened reaction time. Tagushi explored various aliphatic and aromatic aldehydes with overall good yields.⁴⁰ Overall, however, the scope of the methodology is still limited to aldehydes due to A1,2 strain of the tetrazole substituents.

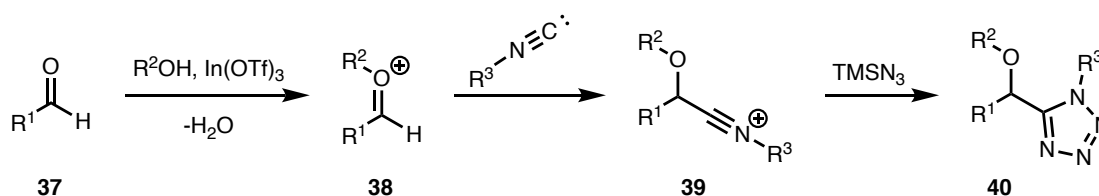


Figure 8. Indium-catalyzed cyclization of 5-(1-hydroxyalkyl)tetrazoles.

An alternate approach to overcome the steric hindrance issue of the multicomponent approach to 1-(5-hydroxyalkyl)tetrazoles was first explored by Dömling, by using sonication.⁴¹ Coupled with catalyst-free and aqueous conditions, this methodology allows for increased substrate scope and affords modest to excellent yields. The catalyst-free conditions expand substrate scope, allowing access to aryl halides and the sonication allows for reaction with ketones, yet only aliphatic ketones were displayed. This method is highly efficient with aliphatic aldehydes as with the previously mentioned methods, yet still exhibits comparable yields with aromatic aldehydes suggesting this method is still prone to steric hindrance.

To circumvent the steric hindrance posed by ketones, oxocarbenium ions stemming from ketals **41** were utilized by Voskressensky.⁴² This was formed using a zinc catalyst and the resulting oxocarbenium **43** was then used in the multicomponent cyclization (Figure 9). This approach allowed for broader substrate scope forming more sterically encumbered 1-(5-

hydroxyalkyl)tetrazoles. This approach does pose limitations in that when aromatic ketals were used, efficiency decreased; suggesting that this approach is still prone to steric hindrance.

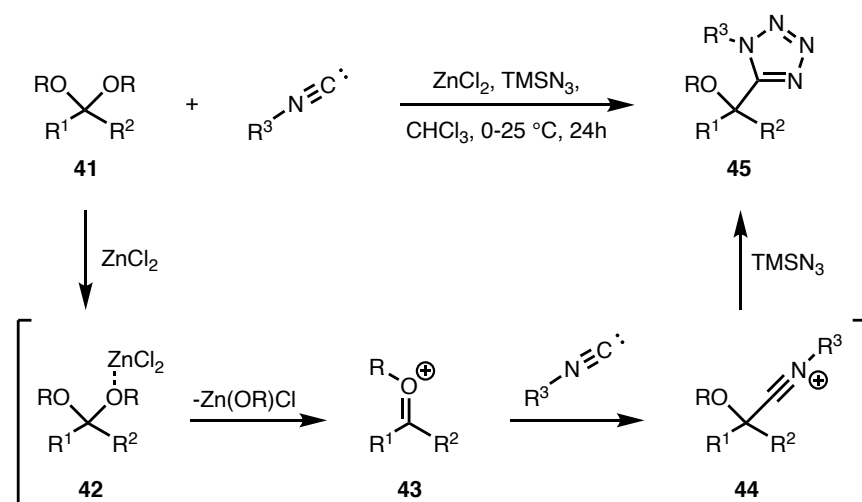


Figure 9. Preparation of 5-(1-hydroxyalkyl)tetrazoles via ketals.

The modified Passerini reaction is an efficient approach to the preparation of 1-(5-hydroxyalkyl)tetrazoles. Most reports to date aim to activate the carbonyl species through use of Lewis acid-catalysis or via the involvement of an oxocarbenium intermediate. These reactions exhibit lower reaction times compared to their cycloaddition counterparts, but variable reaction times of up to 96 h. The unpleasantness of isocyanides, coupled with azide reagents allow for potentially dangerous reaction conditions. From a synthetic standpoint, in order to access unprotected 1-(5-hydroxyalkyl)tetrazoles, a separate, unique deprotection step must be conducted to access to the 1*H*-tetrazole products. Another drawback to this strategy is the sensitivity to steric hindrance due to allylic strain of the *N*- and *C*-tetrazole substituents. Traditionally this method was only applicable to aliphatic aldehydes, but recent developments have allowed the use of aromatic aldehydes as well.

4. 5-Metallotetrazole Addition to Carbonyl Compounds

A less commonly used method in the preparation 1-(5-hydroxyalkyl)tetrazoles includes the addition of 5-substituted-1-metallotetrazoles to carbonyl compounds. This approach was first reported in 1971 by Raap, who generated 5-methyl-1-lithiotetrazole by deprotonation of 5-methyltetrazole with *n*-butyllithium. This species was then trapped with a wide range of electrophiles.⁴³ In this case, the 5-position proton on the tetrazole is the most acidic allowing for the formation of the resonance-stabilized anion.⁴⁴

This methodology was expanded by Satoh to provide access towards free 1*H*-tetrazoles^{45, 46, 47–49} through the use of *N*-benzyl- and *N*-PMB-protected tetrazoles.⁴⁵ This method was later applied by Siddiqui for the preparation of potential thrombin inhibitors⁵⁰ and assembly of Hepatitis C NS3/NS4A serine protease inhibitors prepared by Narjes.⁴⁹ Here, deprotonation of tetrazole precursor **46** at -95 °C with *n*-butyllithium formed tetrazolate anion **47** that undergoes addition to aldehydes and ketones to form protected 5-(1-hydroxyalkyl)tetrazoles **49** in good to excellent yield (Figure 10). Subsequent *N*-deprotection allowed for access to 1-(5-hydroxylalkyl)tetrazoles. Prior to the work herein, *N*-protecting group strategy of this preparation was limited to *N*-benzyl, *N*-PMB-,⁴⁵ and *N*-allyl- protected tetrazoles.⁵¹

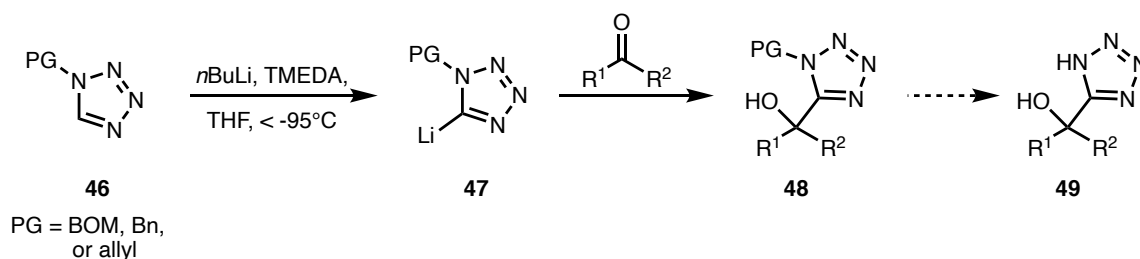


Figure 10. Addition of *N*-protected tetrazoles via 5-metallotetrazoles.

N-Deprotection of benzyl- and PMB-protected tetrazoles to access 1*H*-tetrazoles provided its own limitations, requiring forcing conditions depending on the protecting group (Figure 11). De-*N*-benzylation was performed using heterogenous hydrogenolysis conditions at high pressures and

stoichiometric Pd/C as reported by Satoh (A).⁴⁵ *N*-BOM deprotection could be achieved under various conditions such as heterogenous hydrogenolysis at elevated pressures, harsh acid hydrolysis, and oxidative conditions (B). In previous works by Wardrop and Komenda, de-*N*-allylation was done using Yamamoto conditions using catalytic nickel (C).⁵² Deprotection conditions showed overall good yields.

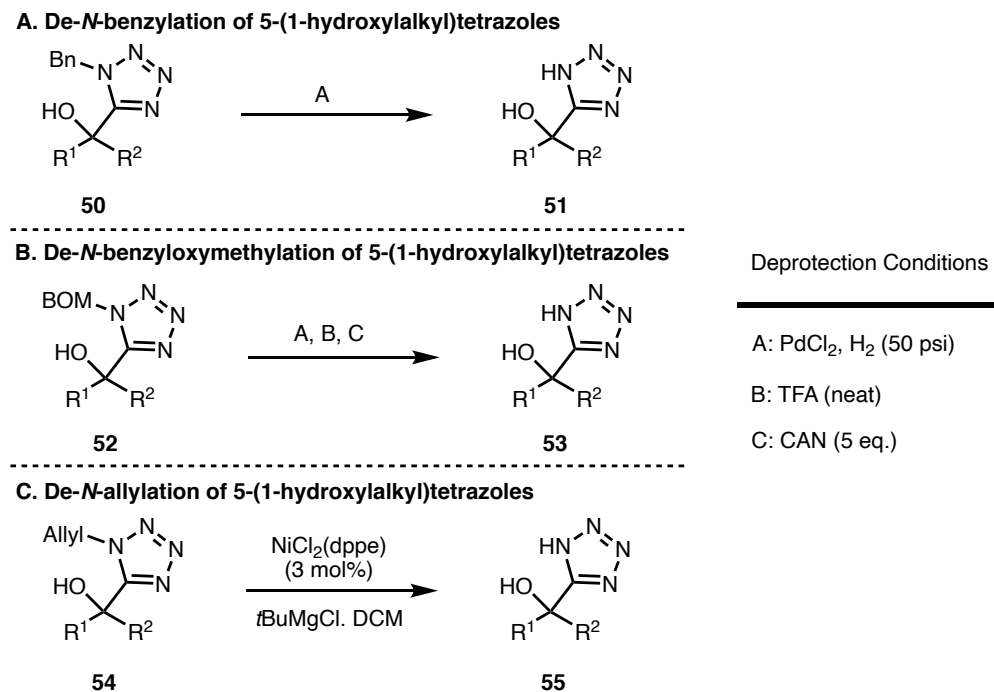


Figure 11. Methods for the deprotection of *N*-protected tetrazoles.

The fact that this method of preparation allows for addition to ketones is a distinct advantage compared to previous approaches allowing for access to more sterically hindered products. Despite its high efficiency, the need for a discrete deprotection step poses a significant limitation. Forcing deprotection conditions such as concentrated acid excludes the preparation of targets prone to decomposition. Heterogenous hydrogenolysis, the most preferred method of *N*-benzyl and *N*-PMB-deprotection, requires a full equivalent of Pd/C,⁴⁵ severely limiting the functional group tolerance of the reaction denying the use of halides and p-bonds. Additionally, this method is not highly efficient with enolizable ketones, as they favor enolate formation rather than 1,2-addition.

The most significant disadvantage to the use of 5-(1-hydroxyalkyl)tetrazoles via 5-metallotetrazoles addition is the thermal stability of these organometallic reagents. Cryogenic temperatures of below -95 °C must be maintained throughout the reaction to prevent the irreversible fragmentation of 5-lithiotetrazole **56** to form lithium cyanamide **57** and dinitrogen (Figure 12).⁴⁵

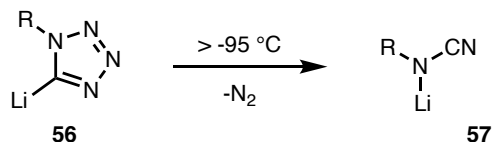


Figure 12. Fragmentation of 5-lithiotetrazoles.

More recently, attempts to increase the lifetime of 5-metallotetrazoles have been developed altering the metal cation other than lithium. Wiedemann has demonstrated that the magnesium and zinc derivatives of **58** display improved thermal stability via magnesium-halogen exchange with **59** (Figure 13).⁵³ The utility of the halogen-metal exchange through **59** allows for increased covalent character of **60**. A synthetic limitation of this methodology is the need to prepare *N*-benzyl-5-bromotetrazole (**59**) via bromination of **58**, prolonging the overall synthesis of 5-(1-hydroxyalkyl)tetrazoles. Additionally, reproducibility of this method has been unsuccessful and thus unreliable.

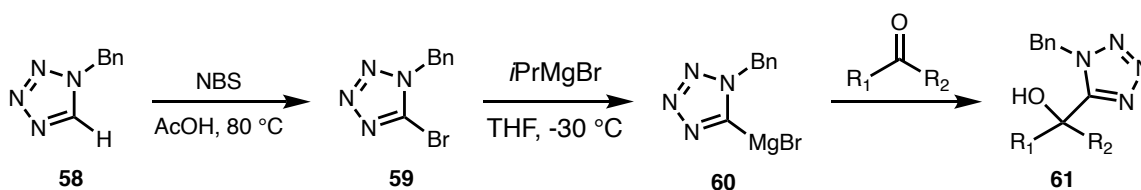


Figure 13. Formation of 5-magnesiometetrazoles via magnesium-halogen exchange.

To increase the thermal stability of 5-lithiotetrazoles and the harshness of the subsequent deprotection step, Satoh developed addition to carbonyls via the lithiation of 1-benzyloxymethyl (BOM) protected tetrazole **62**.⁴⁶ This method has been utilized in a range of applications including

the assembly of hydrodibenzofurans,⁴⁸ cis-amide bioisosteres,⁵⁴ and fatty acid amide hydrolase inhibitors.⁵⁵ This 5-lithiotetrazole was claimed to be stable at -78 °C, significantly greater than previous methods that required -100 °C. It was noted that the increased stability is partly due to the coordination of the BOM-protecting group with the lithium cation, however, this has not been empirically supported. In regard to the deprotection step, *N*-BOM deprotection was achieved using strongly acidic conditions but required slightly elevated temperatures. Also, hydrogenolysis conditions were now catalytic rather than stoichiometric palladium⁴⁵ (Figure 14); however, this method is without limitation.

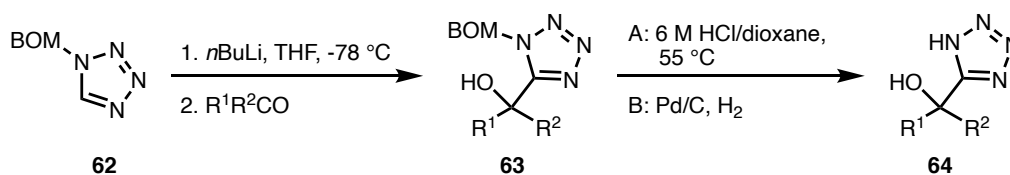


Figure 14. Preparation of 5-(1-hydroxyalkyl)tetrazoles via addition of *N*-BOM-protected tetrazoles

The preparation of the *N*-BOM protected tetrazole **62** is achieved through the alkylation of tetrazole **65** to yield a separable 1:1 mixture of N-1 isomer **66** and N-2 isomer **67** (Figure 15). Satoh utilized the N-2 isomer as an anion precursor for his preparation of 5-(1-hydroxyalkyl)tetrazoles. The use of only one isomer is a severe limitation as the overall efficiency of the reaction is halved.

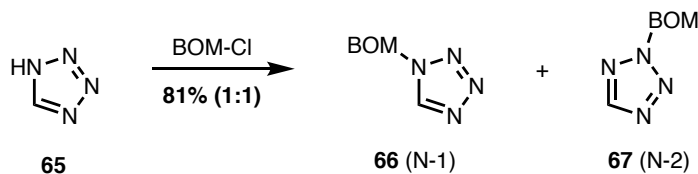


Figure 15. Preparation of *N*-BOM-protected tetrazole.

The increased stability between the 5-lithiotetrazole **58** Satoh claims is attributed to the lack of allylic A1,2 strain between the lithium and *N*-protecting group. A study by Bookser of the formation of stannane **69** for use on Stille reactions showed that the lithiation of each isomer

produced different results. Treatment of the N-2 isomer **67** with *n*-BuLi and TMEDA generated 5-lithiotetrazole **68**, which has an appreciable lifetime at -78 °C that subsequently undergoes reaction to form desired product **69** (Figure 16, A). The tetrazole anion **70**, derived from the N-1 isomer **66**, underwent rapid decomposition with gas evolution at -78 °C to produce cyanamide **71**, the product of ring fragmentation (Figure 16, B). The spontaneous gas evolution is similar to previous works by Satoh and others, but it is noted that electron-withdrawing groups such as benzyloxymethyl, appear to promote fragmentation, while electronically neutral groups such as benzyl and *p*-methoxybenzyl tend to stabilize the 5-lithiotetrazole.⁵⁶

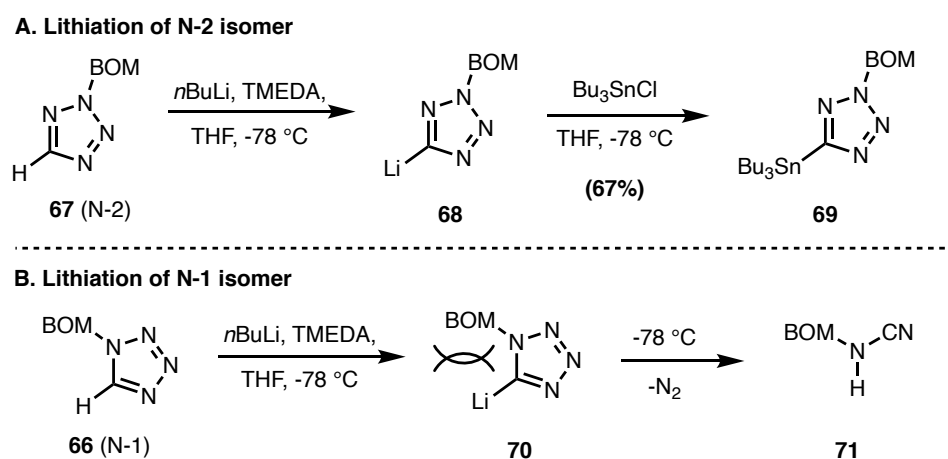


Figure 16. Relative stability of aryllithium species prepared from the lithiation of N-1 and N-5 BOM-protected tetrazoles.

The preparation of 5-(1-hydroxyalkyl)tetrazoles via the lithiation of *N*-BOM-protected tetrazoles showed increased stability of the lithiotetrazole and slightly milder deprotection conditions. Despite these advances, the need for a discrete deprotection step, such as hydrogenolysis or strongly acidic hydrolysis, hinders the overall scope of the transformation. Enolizable ketones are slightly more efficient using this methodology, but they still tend to favor enolization rather than addition, hindering their efficiency.

The formation of 1-(5-hydroxyalkyl)tetrazoles via addition of 5-metallotetrazoles to ketones and aldehydes is distinct from the cycloaddition and multicomponent approaches. It offers access to highly substituted products, alleviating the steric hindrance restriction common to the methods involving cycloaddition and multicomponent reactions. However, the stability of 5-metallotetrazoles is a severe limitation. Due to the tendency of these anions to fragment to form cyanamides, 5-metallotetrazoles must be prepared and handled at low temperatures, as low as -100 °C. Addition of 5-metallotetrazoles is also limited through the demand for a distinct deprotection step, typically including heterogenous hydrogenolysis or strongly acidic hydrolysis conditions, highly limiting substrate scope.

5. Hypothesis

Our interest in tetrazoles arises from the potential of 5-(1-hydroxyalkyl)tetrazoles **72** as latent alkylidenecarbenes. Previously, Komenda and Wardrop demonstrated that treatment of **72** with a carbodiimide triggers a sequence of dehydration and fragmentations to generate alkylidenecarbene **74**, and the products of their reactions under mild, non-basic conditions (Figure 17).^{51 57 58}

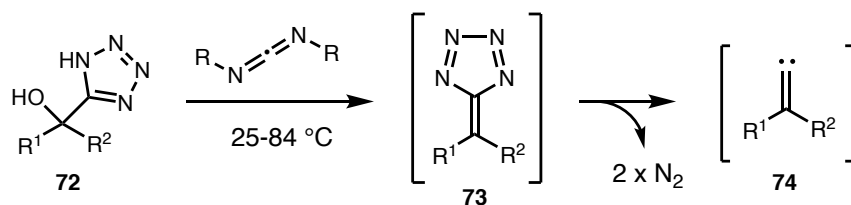


Figure 17. 5-(1-hydroxyalkyl)tetrazoles as latent alkylidenecarbenes.

In this study, a two-step procedure was developed to access substrates **77**, namely addition of 1-allyl-5-lithio-1*H*-tetrazole to ketones and aldehydes **75** and catalytic de-*N*-allylation of **76** (Figure 18) using the method reported by Wardrop.⁵²

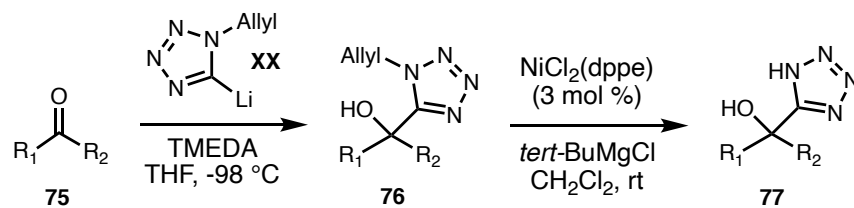


Figure 18. Previous work by Komenda and Wardrop utilizing 1-allyl-5-lithio-1H-tetrazoles.

Despite its high efficiency, this approach requires extremely low reaction temperatures, to prevent decomposition of **73** and a discrete *N*-deprotection step which involves use of a Grignard reagent. Wishing to avoid these drawbacks and thereby increase the practicality of our alkylidenecarbene methodology, we sought to develop a one-pot process for the preparation of 5-(1-hydroxyalkyl)tetrazoles **77**, employing a tractable, *N*-protected 5-metallotetrazole that would provide increased stability upon deprotonation, while also avoiding strong nucleophilic bases such as *n*-butyllithium. Upon addition to a carbonyl compounds, we envisioned the product to be unmasked during reaction workup following carbonyl addition (Figure 19).

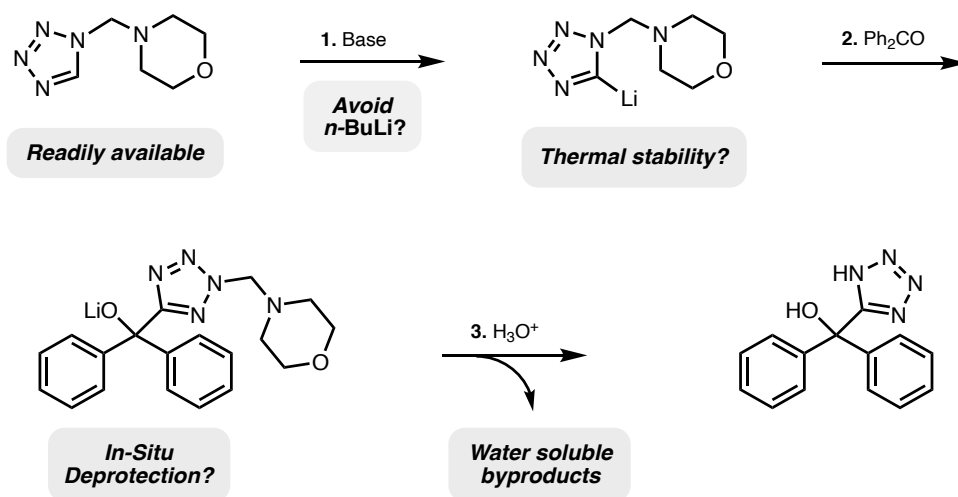


Figure 19. Proposed hypothesis for a one-pot preparation of 5-(1-hydroxyalkyl)tetrazoles.

6. Results and Discussion

Our search for an *N*-protected tetrazole anion precursor, which could be unmasked under mild hydrolytic conditions, led us to the work of Katritzky, who successfully utilized the *N*-pyrrolidinomethyl (aminal) group to facilitate C5-lithitation of 1,2,4-triazoles.⁵⁹ In light of its ready availability, through the reaction of morpholine with tetrazole and formaldehyde, and favorable physical properties, 4-(*N*-tetrazolylmethyl)morpholine (**78**) was selected as a candidate for evaluation and prepared in multi-gram quantities (**Figure 20**). In common with other *N*-(α -aminoalkyl)heterocycles, **78** displays fluxional behavior in solution, existing in *d*₈-THF as a 56:44 equilibrium mixture of N2 (**78a**) and N1 (**78b**) tautomers that interconvert rapidly at room temperature.⁶⁰

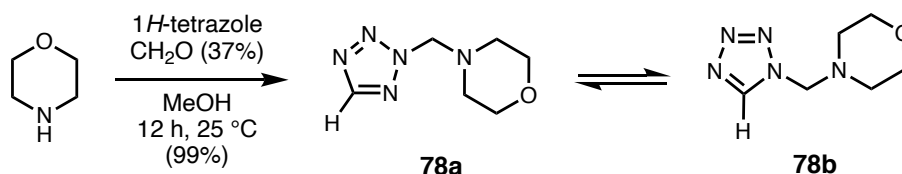
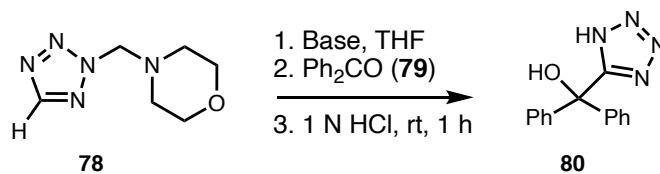


Figure 20. Preparation of 4-(*N*-tetrazolylmethyl)morpholine

Similar to previous works, we envisioned that carbonyl addition of **78**, the anion(s) generated from **78**, followed by acidic hydrolysis of the resulting adduct would offer direct access to 5-(1-hydroxyalkyl)tetrazoles **72**. Wary that deprotonation of **78** with alkyl lithium reagents might be competitive with aminal lithiation,⁶¹ we opted to evaluate an equally strong, but less nucleophilic base, specifically lithium hexamethyldisilazide (LiHMDS), using benzophenone as an electrophilic trap. The results of our optimization study are summarized in Table 1.



Entry	78 (equiv)	base	<i>t</i> (h) ^b	<i>T</i> (°C) ^c	yield (%) ^d
1	1.5	<i>n</i> BuLi	0.3	-78	0
2	1.1	LiHMDS	0.50	-78	73
3	1.5	LiHMDS	0.50	-78	92
4	2	KHMDS	0.50	-78	15
5	1.5	<i>t</i> BuMgCl	0.5	-78	0
6	1.5	BMDA	0.5	-78	0
7	1.5	LiHMDS	0.25	-78	85
8	1.5	LiHMDS	1.00	-78	26
9	2	LiHMDS	0.25	-78	95
10 ^e	2	LiHMDS	0.5	-78	88
11 ^f	2	LiHMDS	0.50	-78	97
12	2	LiHMDS	0.50	0	< 2
13 ^g	2	LiHMDS	-	-78	98

Table 1. ^aUnless otherwise noted, reactions were conducted in the following manner: i) **78** (1.1-2.0 mmol), LiHMDS (1.1-2.0 equiv), THF, -78 °C; ii) benzophenone (**79**) (1 mmol), -78 °C, 2 h→rt, 16 h; iii) 1 M HCl, rt 1 h. ^bAnion maturation time. ^cDeprotonation temperature. ^dIsolated yield of **80**, after purification by flash chromatography on silica gel. ^eAnhydrous DCM as solvent. ^f**Method A**: lithiation of **78**; addition of **79**. ^g**Method B**: lithiation of **78** in the presence of **79**.

When a solution of butyl lithium was used to form the anion and thus the adduct, no product formation was seen, thus concluding that alkyllithium bases compete with amination and being trapped by the tight ion pair (Entry 1).⁶¹ Treatment of a solution of **78** with LiHMDS (1.1 equiv) at -78 °C for 30 min, addition of benzophenone, and *in-situ* hydrolysis of the amination group with aqueous HCl (1 M) for 1 h, provided tertiary alcohol **80** in 73% yield (entry 2). Since the mass balance of benzophenone was recovered in this case, the number of molar equivalents of **78** was increased to 1.5 (Entry 3) and then 2.0 (Entry 11, Method A), leading to significant improvements in yield (92% and 97%, respectively). In light of Katritzky's observation that distribution of tetrazole tautomers **78** was influenced by solvent,⁵⁹ the reaction was conducted in anhydrous DCM. In this case, a small reduction in yield, compared to THF, was observed (Entry 10).

Although Wiedemann and Bio have demonstrated that 2-benzyl-5-potassio-1*H*-tetrazole (**82**) can be generated *in-situ* from **81** and behaves as a proficient nucleophile when used in molar excess (Figure 21),⁵³ our efforts to generate the potassium congener of **82** using KHMDS were largely unsuccessful (entry 4). Use of other bases, including *tert*-butylmagnesium bromide (Entry 5) and bromomagnesium diisopropylamide (Entry 6) proved unsuccessful in forming the tetrazole anion, as indicated by lack of product formation.

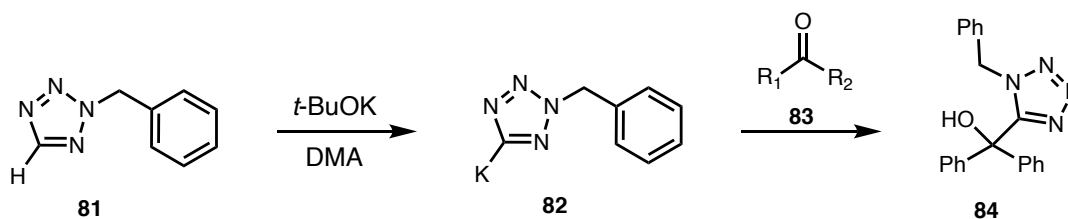


Figure 21. Wiedemann's preparation of hydroxyalkyltetrazoles via potassium congener **80**

In comparison to *N*-alkyl-protected 5-lithiotetrazoles, the anion generated from **78** displays improved thermal stability at -78 °C but, as anticipated, undergoes decomposition at higher temperatures (Entry 12) and after extended time periods (Entry 8). That decreasing anion

maturation time had little impact on overall efficiency, suggests that tetrazole metalation is rapid (Entries 7 and 9). Considering this observation, we evaluated the viability of *in-situ* carbanion generation and were most encouraged to find that deprotonation of **78** (2.0 equiv) in the presence of benzophenone, termed **Method B**, provided **80** in near quantitative yield (Entry 13)!

That the by-products of amination hydrolysis and tetrazole anion fragmentation are water soluble is a useful feature of the methodology as removal of *N*-alkyl cyanamide byproducts has proved problematic with tetrazole equivalents **67** and **73**.⁵³ Given the operational convenience and efficiency offered by *in-situ* metallotetrazole generation, we proceeded to explore the scope of **Method B** with a range of ketones and aldehydes.

In common with benzophenone, cyclic diarylketones underwent addition to provide tertiary alcohols **86a-d** in excellent yield (83-98%); as indicated in Figure 22. Importantly, **Method B** is amendable to scale up, with **86a** being prepared in quantitative yield on a 5.5 mmol (1 gram) scale, without need for purification following isolation. The efficiency, ease, and scalability of this transformation makes it a significant improvement on previously methods.

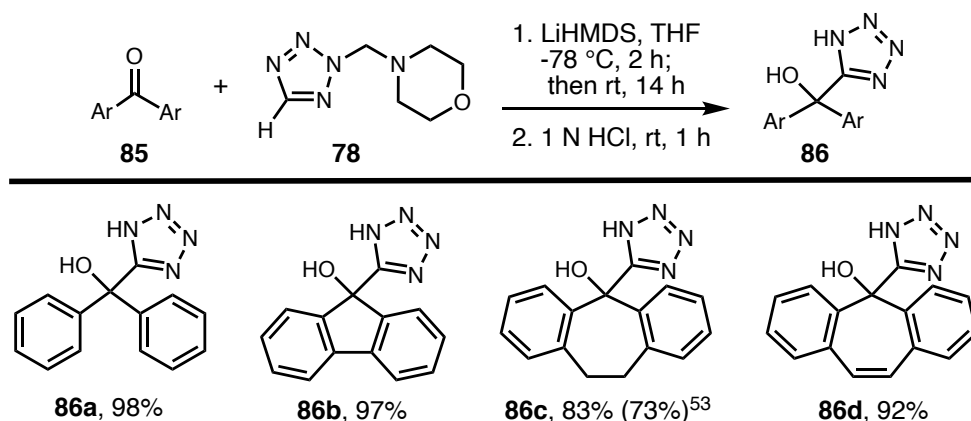


Figure 22. Substrate scope studies—Cyclic aryl ketones

Upon extending the protocol to cyclic ketones (Figure 23), we were delighted to find that despite their potential to undergo enolization, these substrates underwent efficient addition to yield the

desired products **88a-e** (78-99%). In this regard, the near quantitative formation of **88a** from cyclopentanone is particularly notable since the previously reported yield of this product was only 34%, over two steps.^{16b}

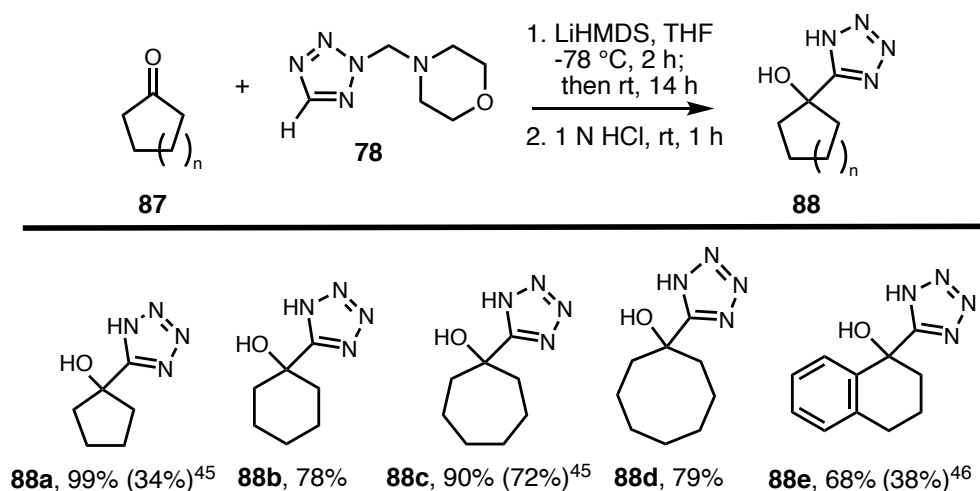


Figure 23. Substrate scope studies—cyclic ketones

The formation of **88a** in quantitative yield is most notable given that the yield reported for its preparation using cyclopentanone is only 34%. Cyclopentanone has a lower pKa (18.5) than other cyclic ketones and is prone to competitive enolization. Addition to 1-tetralone was less efficient than other substrates which, in addition to enolization competition, may also be attributable to the acid sensitivity of tertiary alcohol **88e**. The 5-(1-hydroxyalkyl)tetrazole derived from 1-tetralone, is prone to dehydration, extending the conjugation of the aryl system as previously been noted by Satoh to provide **90** (Figure 24).^{16b}

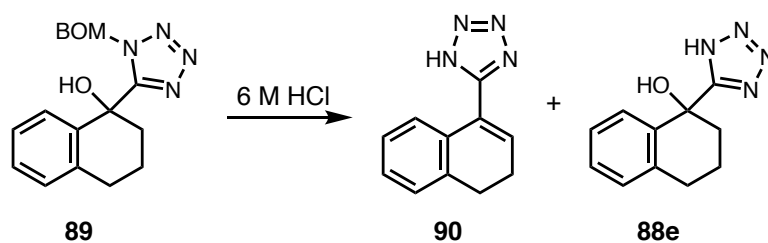


Figure 24. Dehydration of 1-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-ol.

(*R*)-(-)-Carvone underwent exclusive 1,2-addition with high diastereoselectivity to yield allylic alcohol **92a**. Our assignment of stereochemistry in this case was based on literature precedent as one face of the ketone is sterically blocked.⁶² The successful formation of piperidine **92b** and nortropinone derivative **92c** (Figure 25), which was isolated as a single diastereomer arising from *exo*-face addition,⁶³ indicate a tolerance for carbamate functionalities. Of particular note is the nortropinone derivative as it contains unique biological properties.

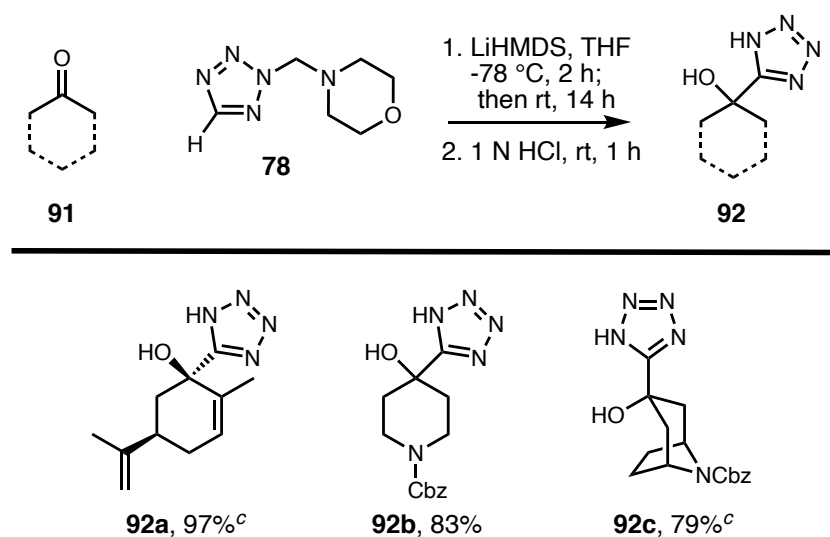


Figure 25. Substrate scope studies—other cyclic ketones

Extension of **Method B** to aromatic aldehydes (Figure 26), to provide benzylic alcohols **94a-d** and the α,β -unsaturated aldehyde citral, to yield **94e** also proved to be efficient. Since 5-(1-alkylhydroxy)tetrazoles can be utilized as precursors to form alkynes, the addition to citral can potentially offer access to enynes. Importantly, our method's tolerance for aryl bromides, alkynes, and alkenes is notable as these functional groups are largely incompatible with the *N*-deprotection methods employed with existing 5-metallotetrazole reagents. Typical *N*-deprotection methods include metal-mediated hydrogenolysis and de-allylation, or harsh acid hydrolytic conditions, all of which are severely limiting in scope.

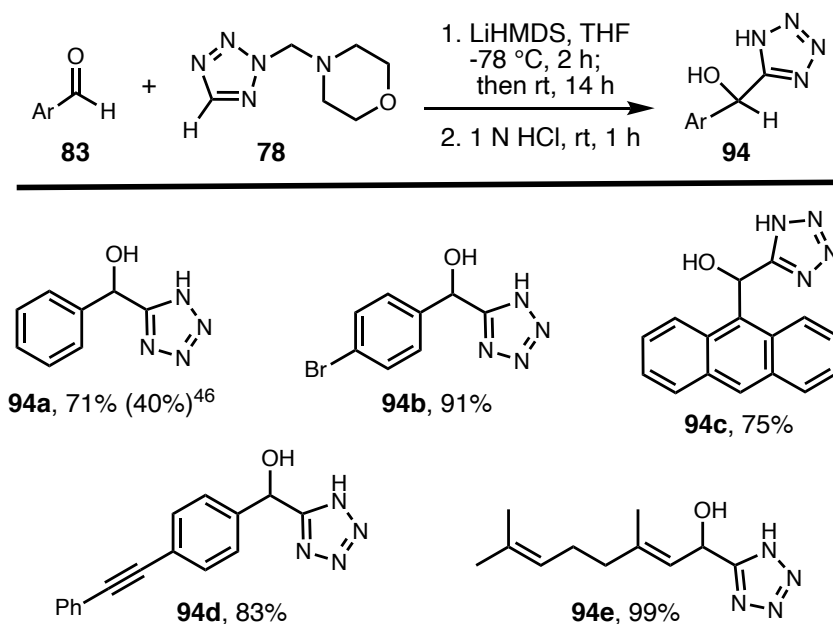


Figure 26. Substrate scope studies–aldehydes.

With ketones and aldehydes adequately explored, we turned our attention to less reactive carbonyl compounds to further explore the scope of our methodology. In this regard, methyl benzoate proved to be unreactive and the starting material was recovered in near quantitative yield. Addition of magnesium chloride was then used as an additive to promote addition, however this also proved to be unsuccessful.

Given our interest in accessing cyclooctynes through ring expansion of cycloheptylidene carbenes, we now evaluated our methodology with dibenzosuberones and other cycloheptanones. Gratifyingly, addition to these substrates proved to be overall efficient (Figure 27). The presence of electron donating groups as in the case of substrates **96l** and **96n** led to only moderate yields of the addition products. The presence of electropositive substituents, including the morpholino group of **96m**, seems to decrease the reactivity of the distant carbonyl group towards addition.

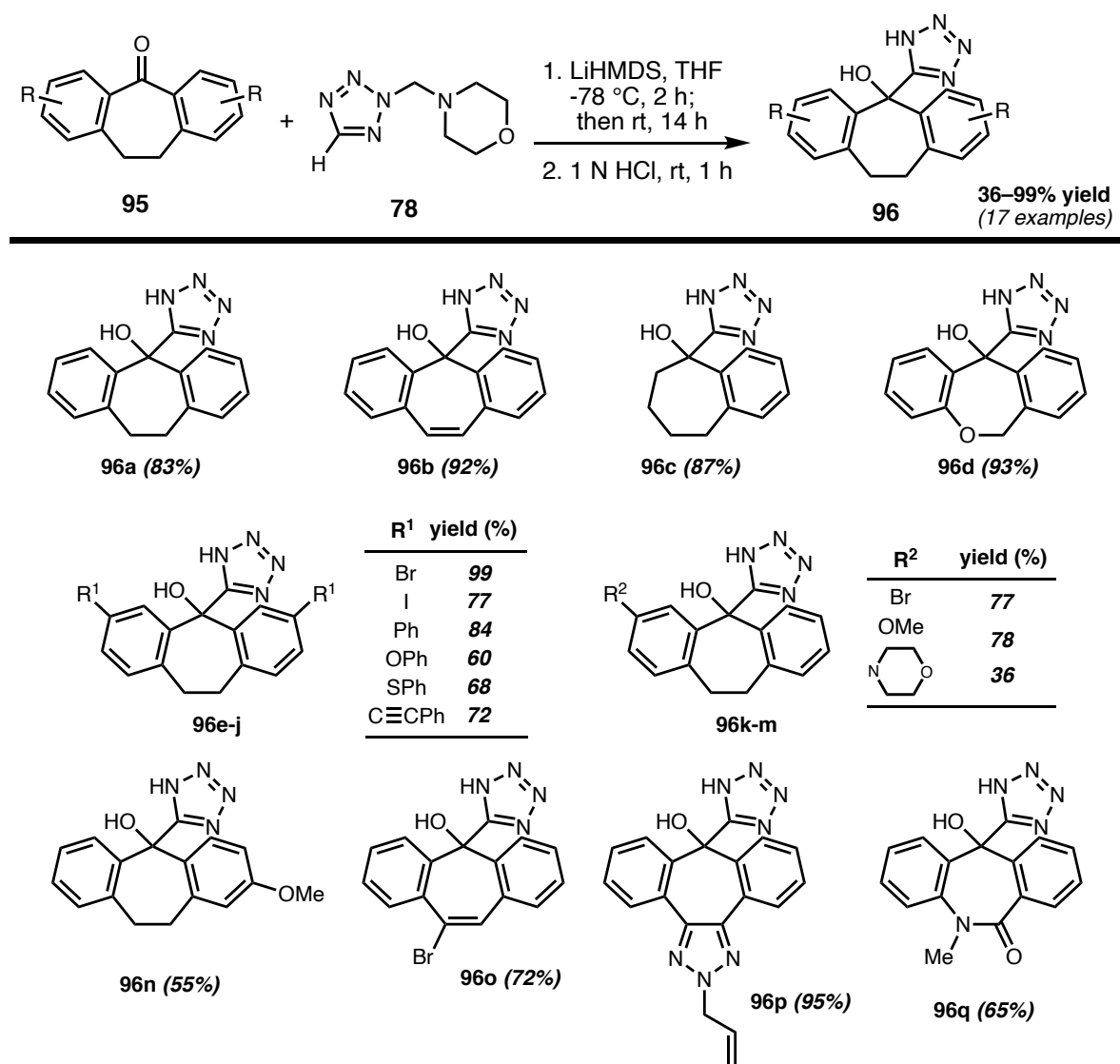


Figure 27. Substrate scope studies—dibenzosuberones and related substrates

Given the importance of biarylazacyclooctyne (BARAC) in the development of bioconjugation, which its precursor **96q** can be found in the figure above. We also examined the reaction of **97** in our efforts to synthesize aza-dibenzocyclooctyne (ADIBO), which will be discussed in greater detail in Chapter 3. ADIBO precursors **97** of various *N*-substitution were subject to tetrazole addition under our methodology (Figure 28). Electron neutral groups such as *N*-methyl- **98a** and *N*-sulfonamide-substituted **98b** did not undergo addition as the ketone was stabilized via induction through the amine. Upon substituted with a pivalamide, addition to the ketone was highly efficient,

allowing access to ADIBO. Retroactively analyzing the ^{13}C NMR of precursors **97a**, **97b**, and **97c**, it was found that the carbonyl signal for the substrates **97a** & **97b** that did not undergo addition were significantly shielded (185 ppm) compared to *N*-pivalamide **97c** (195 ppm).

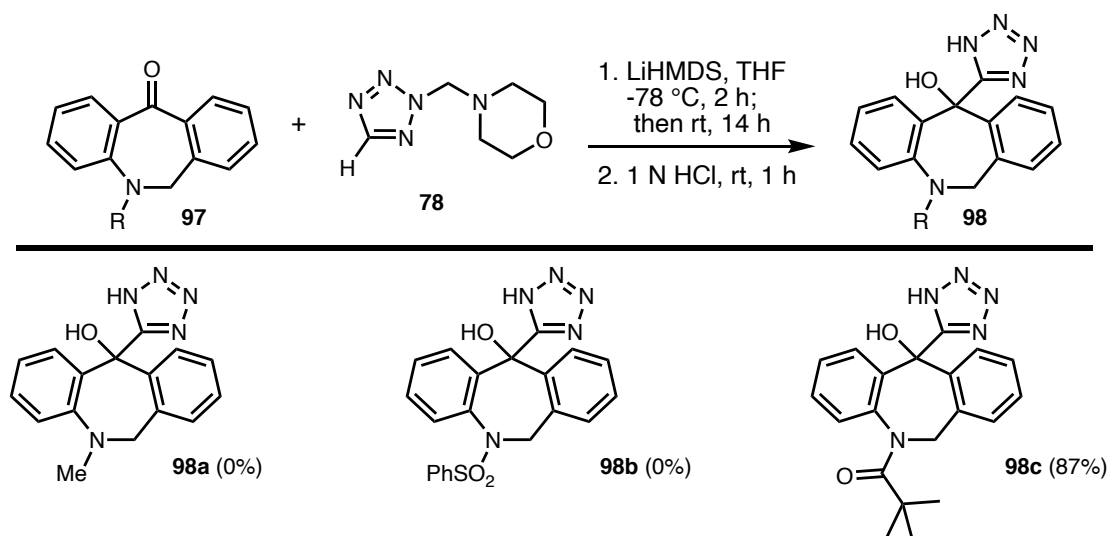


Figure 28. Substrate scope studies–ADIBO precursors

7. Conclusion

We have developed *N*-morpholinomethyl-5-lithiotetrazole as a readily accessible reagent for the one-pot preparation of 5-(1-hydroxyalkyl)tetrazoles **72** from both enolizable and non-enolizable ketones and aldehydes. Importantly, introduction of the 1*H*-tetrazole system can be made without recourse to azide salts and the attendant dangers of hydrazoic acid,⁶⁴ which has been detected during the preparation of 1-benzyl-1*H*-tetrazole (**58**).⁵³ In the cases where comparisons can be made, the current approach to 5-(1-hydroxyalkyl)tetrazole is more efficient than existing 5-metallotetrazole reagents, which require two discrete steps to access 1*H*-tetrazoles.

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Appendix A, Tetrazoles

1. General Comments

This work was previously published in Alexakos, P.; Wardrop, D. *N*-Morpholinomethyl-5-lithiotetrazole: A Reagent for the One-Pot Synthesis of 5-(1-Hydroxyalkyl)tetrazoles. *J. Org. Chem.* **2019**, *84*, 12430-12436. All permissions are permitted as by the authors, which are myself and my advisor.

1.1 General Methods

All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Visualization was accomplished by UV light (254 nm), potassium permanganate solution, or phosphomolybdic acid solution. Flash column chromatography was performed according to the method of Still¹ using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

1.2 Materials

Anhydrous tetrahydrofuran (THF) was passed through a solvent dispensing system under a dry argon atmosphere. All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

1.3 Instrumentation

All melting points were determined in unsealed Pyrex capillaries with a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide disks, or thin films on sodium chloride or zinc selenide plates using an ATI Mattson Genesis series FTIR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, ¹H, 100 MHz, ¹³C) or a Bruker Avance 500 (500 MHz, ¹H, 125 MHz, ¹³C) spectrometer. Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.26 ppm for ¹H; δ 78.0 ppm for ¹³C), methanol (δ 3.31 ppm for ¹H; δ 49.2 ppm for ¹³C), acetone (δ 2.05 ppm for ¹H; δ 29.9 ppm for ¹³C), and dimethyl sulfoxide (δ 2.50 ppm for ¹H; δ 39.5 ppm for ¹³C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), m (multiplet) and br (broad) app (apparent). The identification of ¹H and ¹³C signals was achieved using a combination of ¹H, ¹³C, DEPT, COSY, HMBC, HMQC and NOESY experiments. High-resolution electrospray ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass Q-ToF Ultima instrument at the University of Illinois Mass Spectrometry Laboratory. High-resolution electron ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass 70-VSE instrument at the University of Illinois Mass Spectrometry Laboratory.

1.4 Literature Preparations

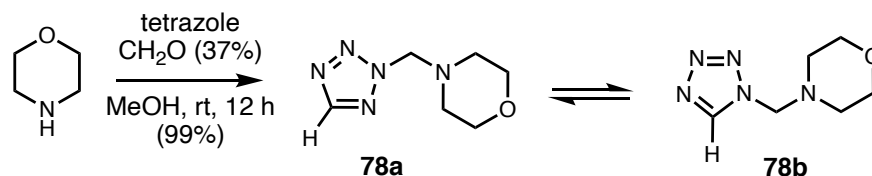
4-((*N*-Tetrazolyl)methyl)morpholine (**13**) was prepared using a modification of the method reported by Katritsky.²

1.5 Safety Precautions!

While all procedures involving tetrazoles were conducted without incident, it is advisable to take appropriate safety precautions, such as the use of shields in a fume hood and personal protection equipment, when undertaking work with these potentially energetic heterocycles.

2. Experimental Details

4-((*N*-Tetrazolyl)methyl)morpholine (**78**)²



Operation Conducted Behind Safety Screen!

To a cold (0 °C), stirred solution of tetrazole (2.00 g, 28.5 mmol) in methanol (20 mL) was added morpholine (2.74 mL, 31.4 mmol, 1.1 equiv) and the mixture stirred for 15 min. An aqueous solution of formaldehyde (2.8 mL, 37%, 34 mmol, 1.2 equiv) was added dropwise and the mixture stirred for 12 h at room temperature. The reaction mixture was then concentrated under reduced pressure to provide a residue which was recrystallized from a 1:2 mixture of hexanes and CH₂Cl₂ to give **78** (4.75 g, 28.1 mmol, 99%): white, crystalline solid; mp 81-82 °C [*lit.* 81-82 °C];² FTIR ν_{max} 3116, 2969, 2954, 2923, 2904, 2869, 2846, 1478, 1456, 1435, 1422, 1398, 1386, 1366, 1327, 1319, 1295, 1264, 1240, 1217, 1167, 1147, 1110, 1101, 1071, 1035, 1008, 963, 897, 859, 853, 775, 753, 717, 672, 652, 623 cm⁻¹; HMRS-ESI calcd for C₆H₁N₅O: 169.0964, found 169.0965.

N-Tautomers **78a/78b** (CDCl₃)

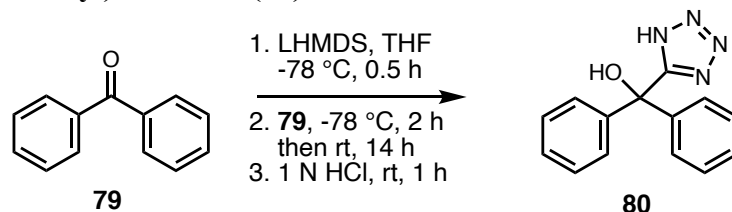
¹H NMR (400 MHz, CDCl₃) δ 8.70 (s, 0.2 H, **78b**), 8.52 (s, 0.8 H, **78a**), 5.49 (s, 1.6 H, **78a**), 5.29 (s, 0.4 H, **78b**), 3.67 (t, *J* = 4.4 Hz, 4.0 H, **78a/b**), 2.62 (t, *J* = 4.8 Hz, 3.2 H, **78a**), 2.58 (t, *J* = 4.4 Hz, 0.8 H, **78b**); ¹³C NMR (100 MHz, CDCl₃) δ 153.0 (**78a**), 143.2 (**78b**), 74.4 (**78b**), 70.2 (**78a**), 67.0 (**78b**), 66.8 (**78a**), 50.2 (**78a**) 50.1 (**78b**).

N-Tautomers **78a/78b** (*d*₈-THF)

¹H NMR (500 MHz, *d*₈-THF) δ 9.01 (s, 0.44H, **78b**), 8.63 (s, 0.56H, **78a**), 5.53 (s, 1.14H, **78a**), 5.35 (s, 0.86 H, **78b**), 3.58 (2, 4.0 H, **78a/b** + *d*₈-THF), 2.56-2.53 (m, 4.0 H, **78a/b**); ¹³C NMR (100 MHz, *d*₈-THF) δ 150.6 (**78a**), 141.5 (**78b**), 71.7 (**78a**), 67.1 (**78b**), 64.5 (**78a**), 64.5 (**78b**), 50.2 (**78b**) 47.9 (**78a**).

Representative Procedure (Method A, Preformation of Tetrazole Anion)

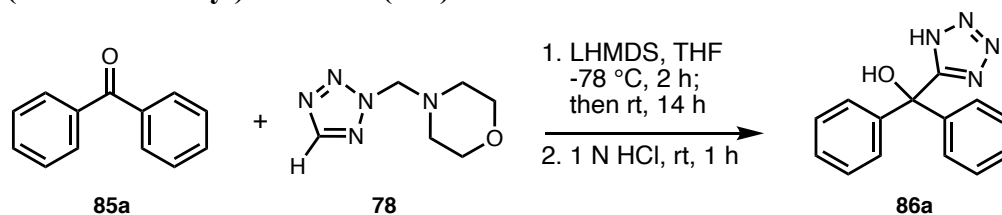
Diphenyl(1*H*-tetrazol-5-yl)methanol (**80**)³



To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**78**) (326 mg, 2 mmol, 2 equiv) in THF (4.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL), dropwise via syringe. After stirring for 30 min at -78 °C, a solution of benzophenone (**79**) (182 mg, 1 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 25 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 50 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), to provide **80** (244 mg, 97%): white, crystalline solid; mp 178-180 °C [*lit.* 173-175 °C]; FTIR ν_{max} 3303, 2852, 2739, 2678, 2597, 2298, 1558, 1491, 1448, 1382, 1271, 1172, 1130, 1064, 1052, 896, 768, 749, 716 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.43-7.40 (m, 4 H); 7.38-7.32 (m, 6 H); ¹³C NMR (100 MHz, CD₃OD) δ 162.6, 144.1, 128.31, 128.26, 127.3, 77.0. HRMS-ESI calcd for C₁₄H₁₁N₄O [M+H]⁺: 253.1089, found: 253.1087.

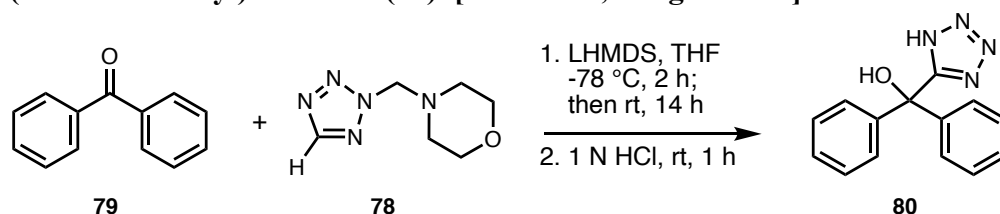
Representative Procedure (Method B, In-Situ Tetrazole Anion Generation)

Diphenyl(1*H*-tetrazol-5-yl)methanol (**86a**)^{Error! Bookmark not defined.}



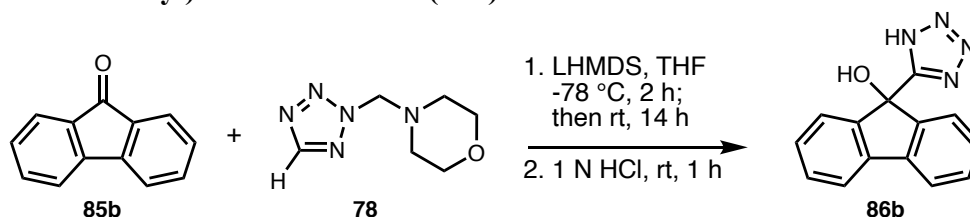
To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**78**) (338 mg, 2 mmol, 2 equiv) and benzophenone (**85a**) (182 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 25 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 50 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96) to provide **86a** (248 mg, 98%) as a white solid.

Diphenyl(1*H*-tetrazol-5-yl)methanol (**80**)³ [Method B, Larger Scale]



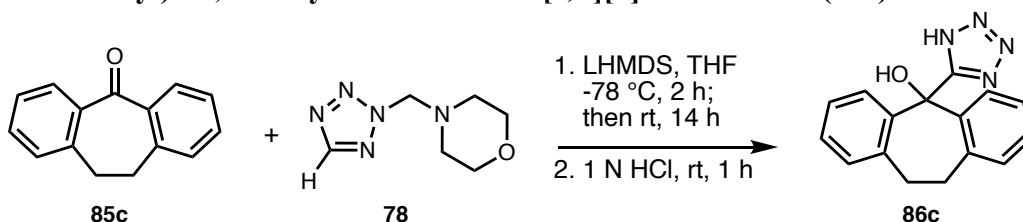
To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**78**) (1.86 g, 11 mmol, 2.0 equiv) and benzophenone (**79**) (1.00 g, 5.49 mmol, 1.0 equiv) in THF (27.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (1.93 g, 11.5 mmol, 2.1 equiv) in THF (11.5 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 100 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 150 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure to provide **80** (1.38 g, 99.6%) as a white solid, which required no further purification.

(±)-9-(1*H*-Tetrazol-5-yl)-9*H*-fluoren-9-ol (**86b**)⁴



Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 9-fluorenone (**85b**) (180 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **86b** (242 mg, 97%): yellow solid; mp 102-115 °C dec; FTIR ν_{max} 3314, 3064, 2852, 2736, 1651, 1606, 1587, 1539, 1450, 1286, 1198, 1103, 1033, 916, 770, 748, 729, 684 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.77 (d, *J* = 7.5 Hz, 2 H), 7.48-7.41 (m, 4 H), 7.33-7.29 (m, 2 H); ¹³C NMR (101 MHz, CD₃OD) δ 161.3, 147.2, 140.2, 130.0, 128.5, 124.8, 120.5, 78.5. HRMS-ESI calcd for C₁₄H₉N₄O⁺: 249.0776, found: 249.0766.

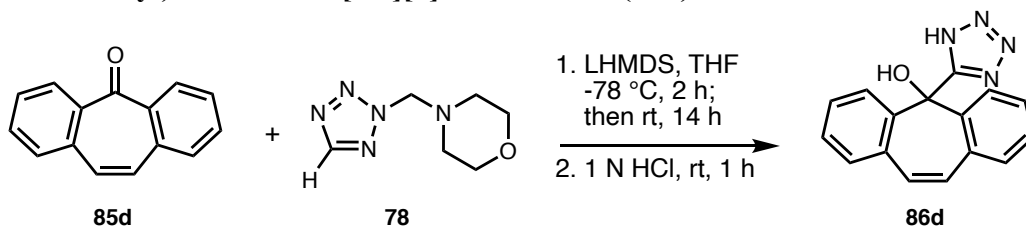
5-(1*H*-Tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**86c**)⁵



Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and dibenzosuberone (**85c**) (208 mg, 1 mmol, 1 equiv) in THF (5.0 mL) was treated with a solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **86c** (230 mg, 83%): white solid; mp 110-113 °C; FTIR ν_{max} 3306, 3177, 3062, 2946, 2192, 1651, 1644, 1563, 1482, 1292, 1161, 1106, 917, 869, 783, 660,

636, 596 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 8.04-8.01 (m, 2 H), 7.31-7.24 (m, 4 H), 7.15 (dd, $J = 7.1, 1.8$ Hz, 2 H), 2.83 (s, 4 H); ^{13}C NMR (100 MHz, CD_3OD) δ 162.5, 141.5, 138.3, 130.6, 128.4, 126.2, 125.6, 72.2, 32.5. HMRS-ESI calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}$ $[\text{M}+\text{Na}]^+$: 301.1065, found: 301.1064.

5-(1*H*-Tetrazol-5-yl)-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**86d**)

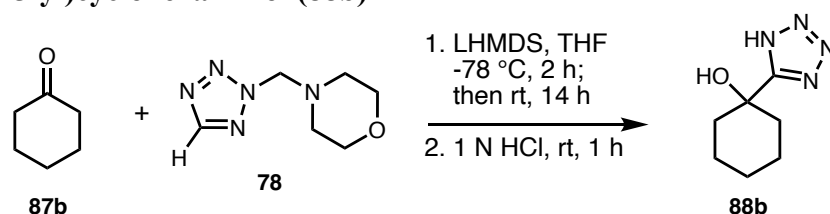


Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and dibenzosuberone (**85d**) (206 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78°C (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$, 4:96), **86d** (253 mg, 92%): yellow solid; mp $143\text{--}145^\circ\text{C}$ dec with gas evolution; FTIR ν_{max} 3310, 3063, 3021, 2358, 1668, 1621, 1599, 1484, 1436, 1322, 1302, 1282, 1221, 1158, 1032, 913, 798, 770, 744, 663 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 8.14-8.12 (m, 2 H), 7.53 (ddd, $J = 8.0, 5.3, 3.4$ Hz, 2 H), 7.38-7.37 (m, 4 H), 6.78 (s, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.8, 140.2, 133.3, 131.1, 128.8, 128.5, 127.4, 123.6, 71.4. HRMS-ESI calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 277.1089, found: 277.1078.

1-(1*H*-Tetrazol-5-yl)cyclopentan-1-ol (**88a**)

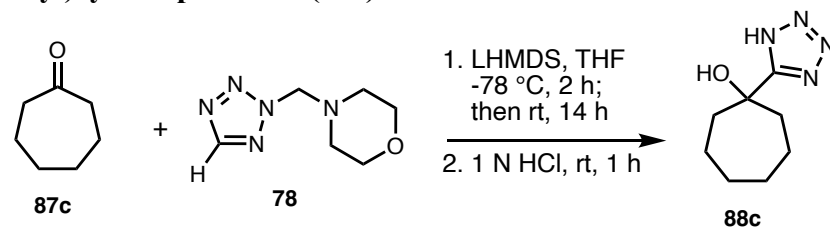
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and cyclopentanone (**87a**) (112 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78°C (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **88a** (154 mg, >99%): white solid; mp $112\text{--}115^\circ\text{C}$ [*lit.* $112\text{--}114^\circ\text{C}$]; FTIR ν_{max} 3373, 3298, 2966, 2871, 2703, 2605, 1866, 1662, 1598, 1564, 1444, 1398, 1323, 1252, 1212, 1144, 1070, 1040, 1012, 1002, 902, 883, 757, 719, 661 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 2.18-2.14 (m, 2 H), 2.12-2.08 (m, 2 H), 2.00 (m, 2 H), 1.92-1.89 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 162.7, 77.4, 41.1, 23.9. HRMS-ESI calcd for $\text{C}_6\text{H}_{10}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 155.0933, found: 155.0931.

1-(1*H*-Tetrazol-5-yl)cyclohexan-1-ol (**88b**)



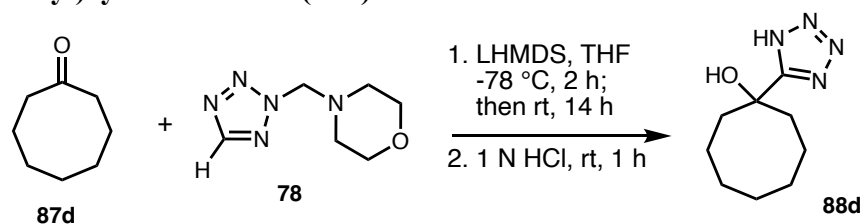
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and cyclohexanone (**87b**) (98 mg, 104 mL, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **88b** (132 mg, 78%): white solid; mp 120-127 °C dec with gas evolution; FTIR ν_{max} 3157, 3099, 2984, 2941, 2847, 2750, 2649, 1547, 1520, 1446, 1435, 1424, 1411, 1370, 1355, 1273, 1266, 1258, 1190, 1146, 1123, 1105, 1077, 997, 933, 901, 849, 761, 662 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.01 (m, 2 H), 1.92-1.84 (m, 2 H), 1.79 (ddd, J = 15.6, 8.9, 3.3 Hz, 2 H), 1.63 (m, 3 H), 1.48-1.38 (m, 1 H); ¹³C NMR (100 MHz, CD₃OD) δ 163.8, 69.0, 37.2, 25.2, 21.4. HRMS-ESI calcd for C₇H₁₂N₄O [M+H]⁺: 169.1089, found 169.1086.

1-(1*H*-Tetrazol-5-yl)cycloheptan-1-ol (**88c**)⁶



Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and cycloheptanone (**87c**) (112 mg, 118 mL, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **88c** (164 mg, 90%): white solid; mp 120-124 °C dec with gas evolution; FTIR ν_{max} 3097, 2952, 2861, 2365, 2255, 2197, 2117, 1538, 1448, 1357, 1275, 1247, 1199, 1088, 1038, 1012, 998, 914, 870, 914, 745, 648 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.18 (ddd, J = 14.6, 9.2, 1.3 Hz, 2 H), 2.03 (ddd, J = 14.6, 9.2, 1.3 Hz, 2 H), 1.83-1.58 (m, 8 H); ¹³C NMR (100 MHz, CD₃OD) δ 164.6, 72.9, 41.2, 29.5, 21.8. HRMS-ESI calcd for C₈H₁₄N₄O [M+H]⁺: 183.1246, found: 183.1244.

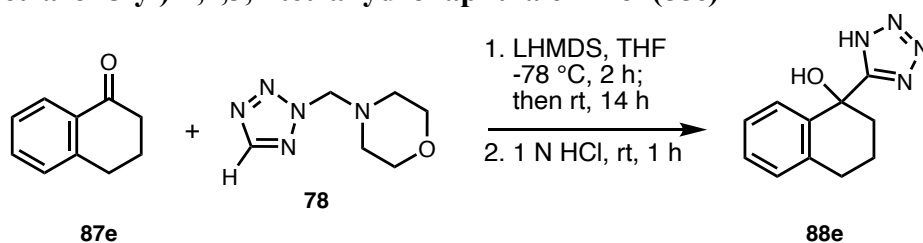
1-(1*H*-Tetrazol-5-yl)cyclooctan-1-ol (**16h**)



Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and cyclooctanone (**87d**) (126 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise

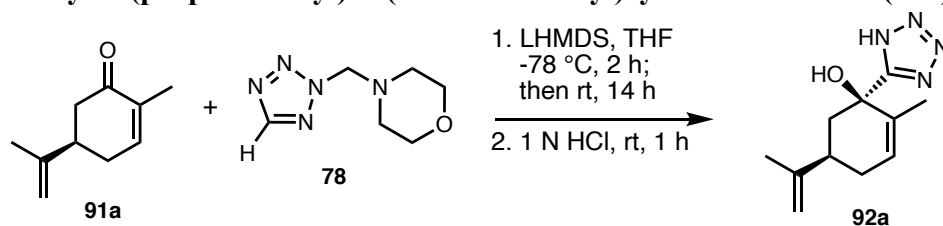
via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **88d** (154 mg, 79%): white solid; mp 121-127 °C dec with gas evolution; FTIR ν_{max} 3093, 3000, 2958, 2854, 2806, 2780, 2752, 2626, 2194, 1644, 1538, 1474, 1446, 1376, 1365, 1294, 1270, 1247, 1139, 1050, 1008, 903, 851, 736 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 2.23-2.09 (m, 4 H), 1.78-1.51 (m, 10 H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 163.3, 73.1, 36.4, 28.2, 24.8, 21.6. HRMS-ESI calcd for $\text{C}_9\text{H}_{16}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 197.1402, found: 197.1399.

(\pm)-1-(1*H*-Tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (88e**)⁷**



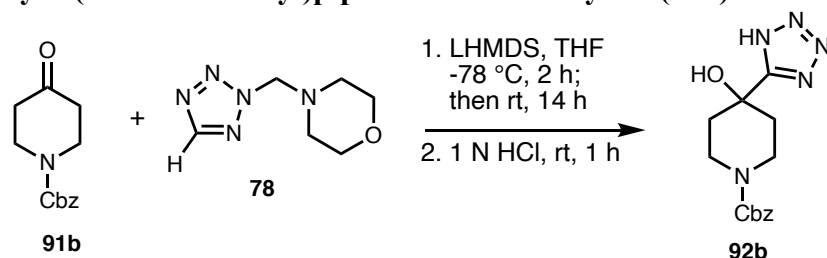
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and α -tetralone (**87e**) (146 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **88e** (146 mg, 68%): yellow oil; FTIR ν_{max} 3062, 3021, 2943, 2873, 2840, 2464, 2219, 2069, 1491, 1336, 1280, 1194, 1166, 1117, 971, 818, 746, 728 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 7.24-7.18 (m, 2 H), 7.13 (td, $J = 7.3, 1.9$ Hz, 1 H), 7.04 (dd, $J = 7.8, 0.7$ Hz, 1 H), 2.93 (t, $J = 6.4$ Hz, 2 H), 2.39 (ddd, $J = 13.4, 8.7, 3.2$ Hz, 1 H), 2.23 (ddd, $J = 13.4, 8.7, 3.2$ Hz, 1 H), 2.14-1.96 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.9, 138.2, 137.4, 129.3, 128.36, 128.29, 126.4, 70.6, 38.5, 29.3, 18.9. HRMS-ESI calcd for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 217.1089, found: 217.1080.

(1*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)-1-(1*H*-tetrazol-5-yl)cyclohex-2-en-1-ol (92a**)**



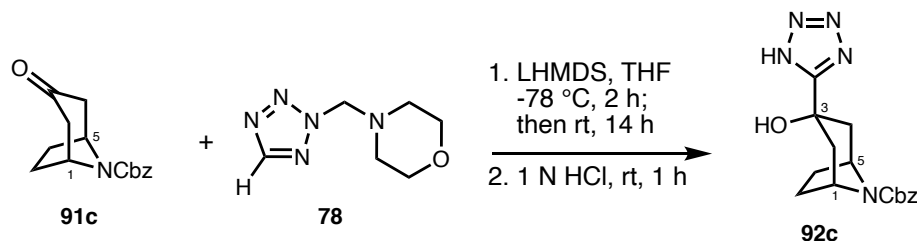
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and (*R*)-carvone (**91a**) (150 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **92a** (214 mg, 97%) as a single diastereomer: yellow solid; mp 107-115 °C dec; FTIR ν_{max} 3410, 3091, 2971, 2944, 2852, 2707, 2592, 2509, 2450, 1799, 1647, 1557, 1539, 1527, 1449, 1435, 1374, 1320, 1273, 1264, 1222, 1190, 1123, 1107, 1067, 1045, 1003, 981, 959, 895, 865, 822, 798, 771, 645 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 5.71 (m, 1 H), 4.71 (m, 2 H), 2.92-2.85 (m, 1 H), 2.28-2.21 (m, 2 H), 1.99 (m, 2 H), 1.70 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 161.4, 148.8, 135.1, 126.7, 109.0, 72.3, 43.4, 38.6, 31.2, 20.3, 17.1. HRMS-ESI calcd for $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 221.1402, found: 221.1401.

Benzyl 4-hydroxy-4-(1*H*-tetrazol-5-yl)piperidine-1-carboxylate (**92b**)



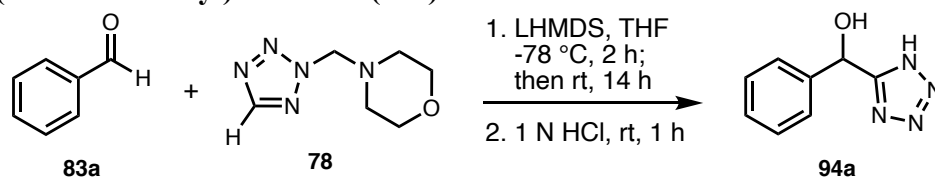
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and *N*-Cbz piperidone (**91b**) (233 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **92b** (253 mg, 83%): colorless oil; FTIR ν_{max} 3307, 3138, 3032, 2956, 2874, 1667, 1548, 1497, 1478, 1434, 1365, 1279, 1243, 1154, 1086, 1027, 1002, 978, 904, 860, 754, 736, 697, 660, 594 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.37-7.30 (m, 5 H), 5.15 (s, 2 H), 5.07 (s, 2 H), 3.96 (d, *J* = 13.5 Hz, 2 H), 2.11 (m, 2 H), 1.94 (m, 2 H); ¹³C NMR (100 MHz, CD₃OD) δ 163.1, 155.9, 137.1, 128.6, 128.1, 127.9, 67.4, 67.2, 39.7, 36.4. HRMS-ESI calcd for C₁₄H₁₇N₅O₃ [M+H]⁺: 304.1410, found: 304.1410.

Benzyl-(1*R*,3*r*,5*S*)-3-hydroxy-3-(1*H*-tetrazol-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (**92c**)



Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and *N*-Cbz nortropinone (**91c**) (259 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **92c** (259 mg, 79%) as a single diastereomer: white solid; mp 94-100 °C dec; FTIR ν_{max} 3322, 3031, 2953, 1661, 1497, 1417, 1356, 1325, 1223, 1175, 1092, 1041, 979, 928, 912, 882, 862, 836, 737, 696, 596 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 9.16 (s, 1 H), 7.39-7.29 (m, 5 H), 5.17 (s, 2 H), 5.07 (s, 2 H), 4.40 (s, 2 H), 2.42-2.35 (m, 4 H), 2.09-1.99 (m, 4 H); ¹³C NMR (100 MHz, CD₃OD) δ 164.4, 154.3, 137.2, 128.6, 128.1, 127.8, 68.7, 67.1, 53.4, 42.2, 41.5, 29.7, 28.1, 27.3. HRMS-ESI calcd for C₁₆H₁₉N₅O₃ [M+H]⁺: 330.1566, found 330.1560.

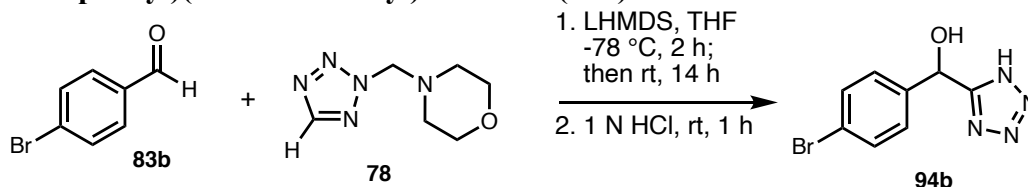
(±)-Phenyl(1*H*-tetrazol-5-yl)methanol (**94a**)⁷⁸



Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and benzaldehyde (**83a**) (106 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was

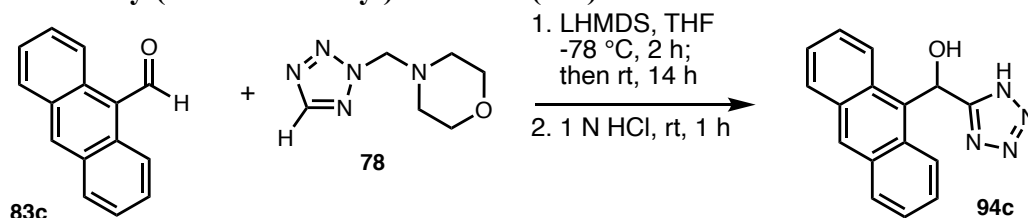
added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **94a** (125 mg, 71%): white solid; mp 129-132 °C dec with gas evolution [*lit.* 178-179 °C]; **Error! Bookmark not defined.** FTIR ν_{max} 3390, 3157, 3065, 2948, 2838, 2691, 2574, 2458, 1883, 1667, 1563, 1495, 1455, 1434, 1370, 1285, 1249, 1144, 1101, 958, 836, 823, 750, 695 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 9.20 (s, 1H), 7.47 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.30 (m, 1H), 6.19 (s, 1H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 159.4, 140.7, 128.5, 128.2, 126.4, 67.3. HRMS-ESI calcd for $\text{C}_8\text{H}_8\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 177.0776, found: 177.0770.

(±)-(4-Bromophenyl)(1H-tetrazol-5-yl)methanol (94b**)**



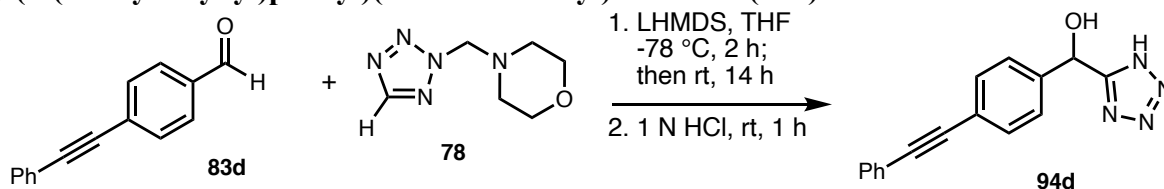
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and p-bromobenzaldehyde (**83b**) (185 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **94b** (233 mg, 91%): white solid; mp 178-180 °C dec with gas evolution; FTIR ν_{max} 3343, 2851, 2683, 2503, 2065, 2015, 1907, 1677, 1587, 1572, 1488, 1442, 1430, 1403, 1395, 1370, 1316, 1297, 1280, 1255, 1180, 1117, 1051, 1010, 937, 850, 834, 823, 793, 783, 759, 730, 712, 690, 647 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 7.54 (d, $J = 8.5$ Hz, 2H), 7.41 (d, $J = 8.3$ Hz, 2H), 6.16 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.6, 140.0, 131.8, 128.4, 122.3, 66.9. HRMS-ESI calcd for $\text{C}_8\text{H}_7\text{N}_4\text{OBr}$ $[\text{M}+\text{H}]^+$: 254.9881, found: 254.9882.

(±)-Anthracen-9-yl(1H-tetrazol-5-yl)methanol (94c**)**



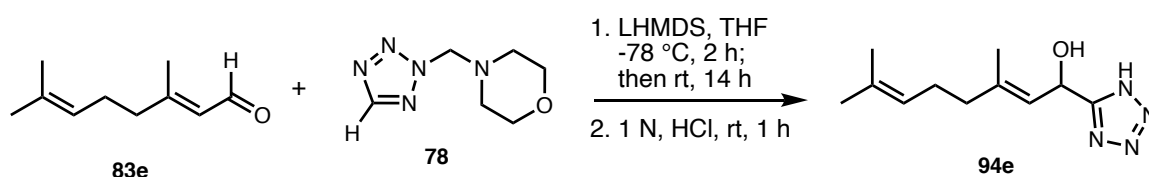
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 9-anthraldehyde (**83c**) (206 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **94c** (207 mg, 75%): brown solid; mp 208-214 °C dec; FTIR ν_{max} 3327, 3139, 2858, 2473, 1698, 1674, 1651, 1634, 1590, 1580, 1447, 1417, 1367, 1318, 1303, 1283, 1248, 1170, 1070, 934, 892, 870, 817, 808, 782, 758, 733, 693 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.63 (s, 1H), 8.54 (dd, $J = 6.5, 3.4$ Hz, 2H), 8.10 (dd, $J = 6.5, 3.4$ Hz, 2H), 7.83 (s, 1H), 7.49 (dd, $J = 6.5, 3.4$ Hz, 4H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 159.6, 130.7, 129.2, 128.7, 127.92, 127.80, 124.8, 123.4, 122.8, 61.8. HRMS-ESI calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 277.1089, found: 277.1078.

(±)-(4-(Phenylethynyl)phenyl)(1*H*-tetrazol-5-yl)methanol (94d**)**



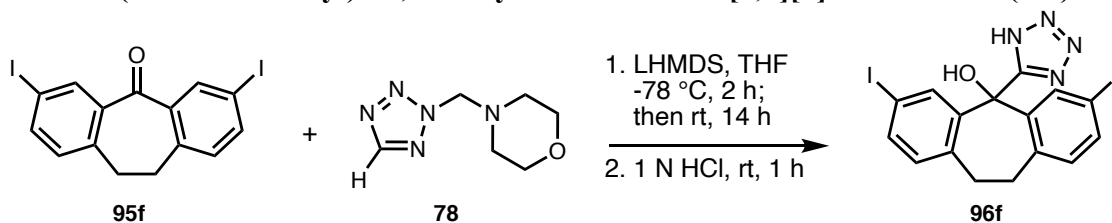
Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 4-(phenylethynyl)benzaldehyde (**83d**) (206 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:4), **94d** (228 mg, 83%): yellow solid; mp 165-170 °C dec; FTIR ν_{max} 3401, 3155, 2924, 2850, 2585, 2190, 1660, 1597, 1563, 1510, 1486, 1436, 1408, 1367, 1298, 1250, 1177, 1111, 1042, 955, 858, 846, 822, 801, 757, 726, 692, 595 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 9.24 (s, 1 H), 7.58-7.55 (m, 6 H), 7.42 (m, 3 H), 6.39 (s, 1 H); ¹³C NMR (100 MHz, (CD₃)₂CO) δ 159.3, 143.3, 141.4, 131.98, 131.89, 131.83, 129.0, 127.1, 123.4, 89.9, 89.2, 67.3. HMRS-ESI calcd for C₁₆H₁₁N₄O⁺: 275.0933, found 275.0935.

(±)-(E)-3,7-Dimethyl-1-(1*H*-tetrazol-5-yl)octa-2,6-dien-1-ol (94e**)**



Following Method B, a solution of **78** (338 mg, 2 mmol, 2 equiv) and geranial (**83e**) (152 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (acetone/hexanes, 1:5), **94e** (222 mg, 99%): yellow oil; FTIR ν_{max} 3339, 3138, 2965, 2917, 2855, 1667, 1621, 1563, 1489, 1447, 1376, 1282, 1245, 1160, 1096, 1019, 975, 872, 821, 746, 654 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.37 (m, 1H), 5.09 (m, 1 H), 4.80 (d, *J* = 8.4 Hz, 1 H), 1.82 (d, *J* = 1.4 Hz, 3 H), 1.69 (s, 3 H), 1.62 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.1, 132.4, 123.8, 119.9, 104.2, 79.8, 40.1, 26.5, 26.1, 18.14, 18.08. HRMS-ESI calcd for C₁₁H₁₈N₄O [M+H]⁺: 223.1559, found: 223.1555.

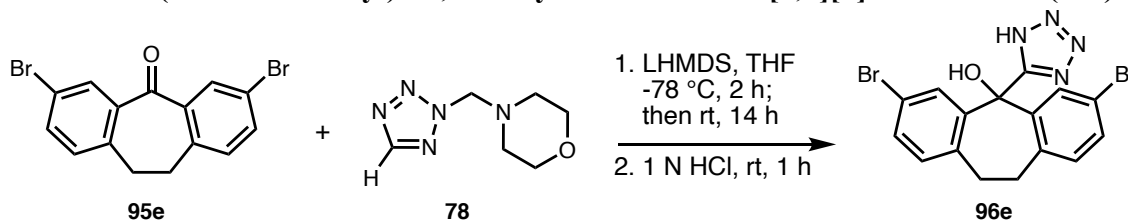
3,7-Diiodo-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (96f**)**



Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 3,7-diiodo-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95f**) (460 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to

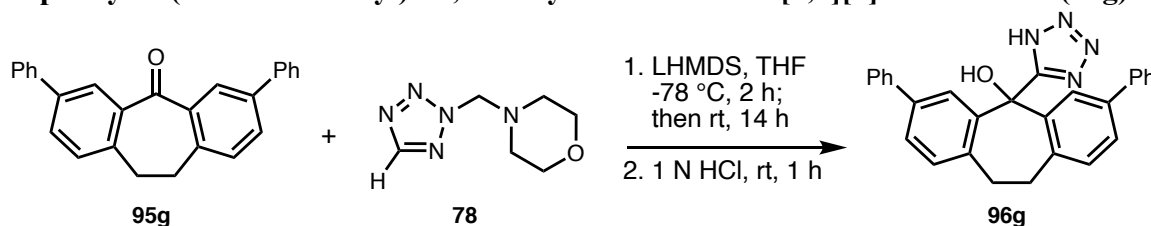
provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96f** (408 mg, 77%): white solid; mp 157-160 °C dec with gas evolution; FTIR ν_{max} 3043, 2941, 2921, 2851, 1887, 1739, 1585, 1557, 1537, 1519, 1504, 1463, 1434, 1412, 1397, 1384, 1326, 1274, 1195, 1119, 1091, 1067, 954, 946, 904, 875, 814, 783, 760, 733, 675, 665, 634, 615, 575, 567, 558 cm⁻¹; ¹H NMR (400 MHz; (CD₃)₂CO) δ 8.47—8.42 (m, 2H), 7.63 (dd, J = 7.9, 1.9 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 2.83—2.67 (m, 4H).; ¹³C NMR (101 MHz; CDCl₃) δ 162.08 (s, 1C), 143.47 (s, 2C), 138.02 (s, 2C), 137.78 (s, 2C), 134.70 (s, 2C), 133.30 (s, 2C), 91.39 (s, 2C), 71.42 (s, 1C), 31.55 (s, 2C). HRMS-ESI calcd for C₁₆H₁₃N₄OI₂ [M+H]⁺: 530.9179, found: 530.9184.

3,7-Dibromo-5-(1H-tetrazol-5-yl)-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-ol (**96e**)



Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 3,7-dibromo-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-one (**95e**) (366 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96e** (431 mg, 99%): white solid; mp 140-145 °C dec with gas evolution; FTIR ν_{max} 3175, 3106, 3022, 2948, 2896, 2834, 2747, 1693, 1682, 1660, 1651, 1622, 1587, 1573, 1557, 1537, 1475, 1424, 1393, 1355, 1297, 1275, 1253, 1231, 1177, 1169, 1127, 1117, 109, 1061, 1036, 986, 952, 930, 876, 826, 812, 789, 778, 739, 703, 640, 718, 596, 571, 555 cm⁻¹; ¹H NMR (400 MHz; (CD₃)₂CO) δ 8.24 (d, J = 2.2 Hz, 2H), 7.46 (dd, J = 8.1, 2.2 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 2.87—2.71 (m, 4H).; ¹³C NMR (101 MHz; (CD₃)₂CO) δ 162.02 (s, 1C), 143.52 (s, 1C), 137.46 (s, 1C), 133.16 (s, 1C), 131.65 (s, 1C), 128.79 (s, 1C), 119.92 (s, 1C), 71.63 (s, 1C), 31.40 (s, 1C). HRMS-ESI calcd for C₁₆H₁₃N₄OBr₂ [M+H]⁺: 434.9456, found: 434.9447.

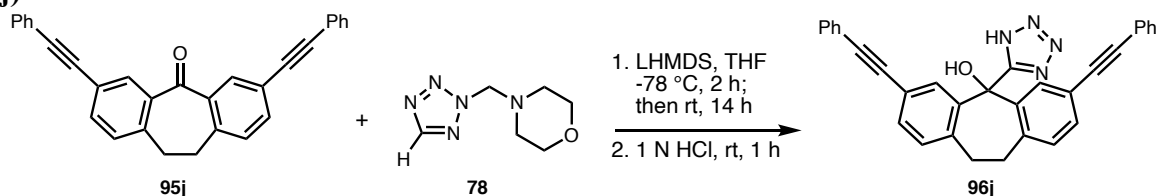
3,7-Diphenyl-5-(1H-tetrazol-5-yl)-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-ol (**96g**)



Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and dibenzosuberone **95g** (240 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96g** (240 mg, 84%): yellow solid; mp 137-141 °C dec with gas evolution; FTIR ν_{max} 3056, 3028, 2945, 1693, 1599, 1480, 1364, 1232, 1163, 1111, 1091, 1072, 1026, 918, 893, 842, 813, 761, 746, 699, 660, 630 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.46 (d, J = 1.8 Hz, 2H), 7.71 (dd, J = 8.1, 0.9 Hz, 4H), 7.59 (dd, J = 7.8,

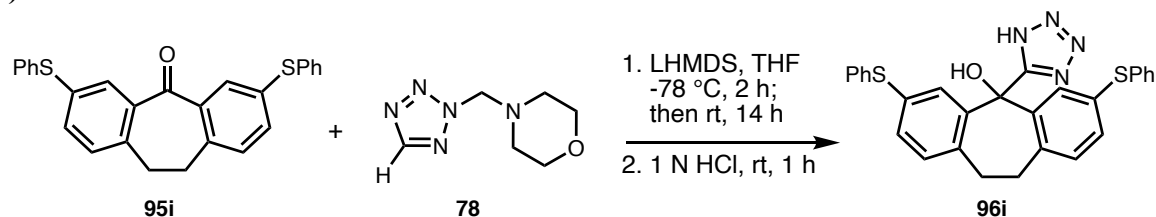
1.9 Hz, 2H), 7.48 (t, $J = 7.7$ Hz, 4H), 7.37 (t, $J = 7.4$ Hz, 2H), 7.30 (d, $J = 7.8$ Hz, 2H), 2.95 (s, 4H); ^{13}C NMR (126 MHz; CDCl_3) δ 167.23 (s, 1C), 141.67 (s, 1C), 140.90 (s, 1C), 138.62 (s, 1C), 137.33 (s, 1C), 131.37 (s, 1C), 128.81 (s, 1C), 127.17 (s, 1C), 126.71 (s, 1C), 126.51 (s, 1C), 124.15 (s, 1C), 72.32 (s, 1C), 31.74 (s, 1C). HRMS-ESI calcd for $\text{C}_{28}\text{H}_{22}\text{N}_4\text{ONa}$ $[\text{M}+\text{Na}]^+$: 453.1691, found: 453.1706.

3,7-Bis(phenylethynyl)-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (96j)



Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 3,7-bis(phenylethynyl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95j**) (409 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at $-78\text{ }^{\circ}\text{C}$ (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$, 4:96), **96j** (346 mg, 72%): yellow solid; mp $158\text{--}163\text{ }^{\circ}\text{C}$ dec with gas evolution; FTIR ν_{max} 3310, 3058, 2942, 2887, 2351, 2204, 2190, 2176, 2164, 1682, 1595, 1573, 1495, 1440, 1403, 1359, 1318, 1262, 1231, 1167, 1120, 1098, 1069, 1026, 999, 911, 855, 834, 753, 722, 688, 606 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 8.32 (d, $J = 1.6$ Hz, 2H), 7.61—7.56 (m, 4H), 7.48—7.40 (m, 9H), 7.23 (d, $J = 7.8$ Hz, 2H), 2.89—2.85 (m, 4H); ^{13}C NMR (101 MHz; CDCl_3) δ 162.01 (s, 1C), 141.83 (s, 1C), 139.09 (s, 1C), 131.81 (s, 1C), 131.57 (s, 1C), 129.18 (s, 1C), 129.04 (s, 1C), 129.00 (s, 1C), 128.87 (s, 1C), 123.58 (s, 1C), 121.26 (s, 1C), 89.72 (s, 1C), 89.28 (s, 1C), 72.07 (s, 1C), 32.15 (s, 1C). HRMS-ESI calcd for $\text{C}_{32}\text{H}_{23}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 479.1872, found: 479.1871.

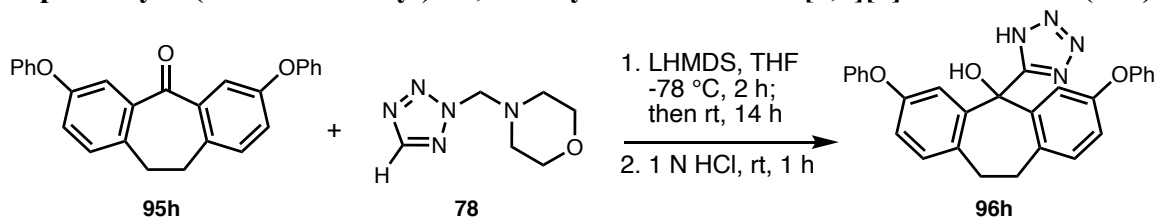
3,7-Bis(phenylthio)-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (96i)



Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 3,7-bis(phenylthio)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95i**) (355 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at $-78\text{ }^{\circ}\text{C}$ (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$, 4:96), **96i** (280 mg, 68%): golden solid; mp $132\text{--}135\text{ }^{\circ}\text{C}$ dec with gas evolution; FTIR ν_{max} 3309, 3053, 3005, 2948, 1694, 1581, 1474, 1438, 1391, 1360, 1303, 1265, 1229, 1175, 1108, 1083, 1067, 1023, 999, 938, 891, 829, 804, 783, 738, 689, 622 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 8.21 (dd, $J = 4.9, 1.9$ Hz, 3H), 7.40—7.30 (m, 12H), 7.29—7.22 (m, 5H), 7.17 (d, $J = 7.9$ Hz, 2H), 2.85—2.79 (m, 4H); ^{13}C NMR (126 MHz; CDCl_3) δ 161.92 (s, 1C), 142.27 (s, 1C), 137.62 (s, 1C), 136.04 (s, 1C), 132.48 (s, 1C), 131.98 (s, 1C), 131.34 (s, 1C), 130.20 (s, 1C),

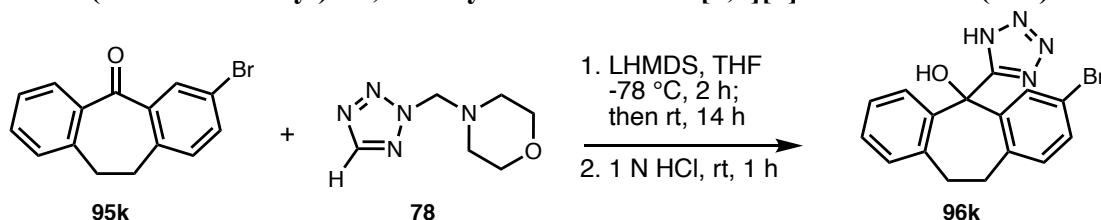
129.32 (s, 1C), 128.80 (s, 1C), 126.93 (s, 1C), 71.83 (s, 1C), 31.54 (s, 1C). HRMS-ESI calcd for $C_{28}H_{22}N_4OS_2Na$ $[M+Na]^+$: 517.1133, found: 517.1133.

3,7-Diphenoxy-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**96h**)



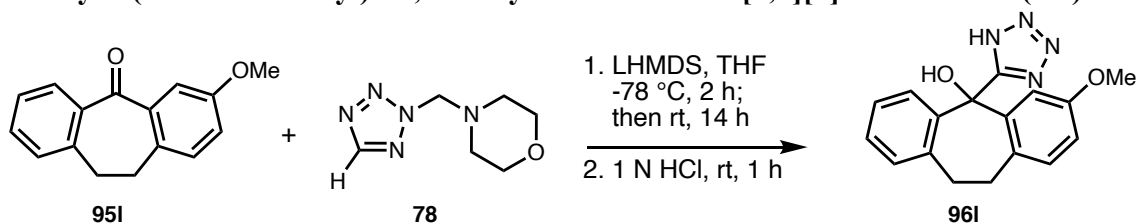
Following Representative Procedure 1, a solution of **78** (338 mg, 1 mmol, 2 equiv) and 3,7-diphenoxy-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95h**) (200 mg, 0.5 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at $-78\text{ }^{\circ}\text{C}$ (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/ CH_2Cl_2 , 4:96), **96h** (140 mg, 60%): white solid; mp $133\text{--}136\text{ }^{\circ}\text{C}$ dec with gas evolution; FTIR ν_{max} 3065, 2928, 2179, 1693, 1651, 1588, 1483, 1456, 1417, 1380, 1361, 1333, 1265, 1238, 1214, 1163, 1114, 1071, 1023, 939, 889, 854, 753, 691 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.80 (d, $J = 2.4$ Hz, 1H), 7.37—7.33 (m, 5H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.12—7.09 (m, 3H), 7.03—7.01 (m, 4H), 6.90 (dd, $J = 8.3, 2.4$ Hz, 2H), 2.83—2.76 (m, 4H); ^{13}C NMR (126 MHz; CDCl_3) δ 162.24 (s, 1C), 157.54 (s, 1C), 155.24 (s, 1C), 143.24 (s, 1C), 132.99 (s, 1C), 132.11 (s, 1C), 129.78 (s, 1C), 129.71 (s, 1C), 123.01 (s, 1C), 118.42 (s, 1C), 116.45 (s, 1C), 71.69 (s, 1C), 31.30 (s, 1C). HRMS-ESI calcd for $C_{28}H_{22}N_4O_3Na$ $[M+Na]^+$: 485.1590, found: 485.1610.

3-Bromo-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**96k**)



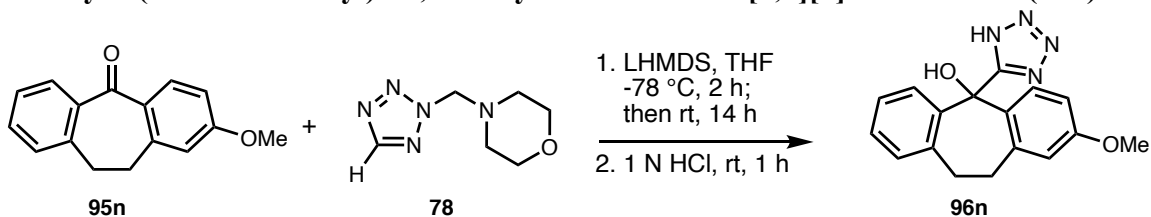
Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 3-bromo-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95k**) (287 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at $-78\text{ }^{\circ}\text{C}$ (acetone/ CO_2), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/ CH_2Cl_2 , 4:96), **96k** (276 mg, 77%): orange solid; mp $148\text{--}151\text{ }^{\circ}\text{C}$ dec with gas evolution; FTIR ν_{max} 3312, 3106, 3064, 2943, 1682, 1651, 1634, 1587, 1557, 1475, 1456, 1424, 1393, 1360 1333, 1288, 1266, 1164, 1111, 1090, 1030, 953, 923, 880 816, 752, 708, 666 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 8.13—8.03 (m, 1H), 7.87—7.75 (m, 1H), 7.28—7.23 (m, 1H), 7.19—7.08 (m, 2H), 7.07—7.00 (m, 1H), 6.95—6.83 (m, 1H), 2.78—2.43 (m, 4H); ^{13}C NMR (101 MHz; CDCl_3) δ 163.92 (s, 1C), 142.48 (s, 1C), 140.24 (s, 1C), 137.76 (s, 1C), 137.01 (s, 1C), 133.04 (s, 1C), 131.74 (s, 1C), 131.19 (s, 1C), 129.14 (s, 1C), 128.66 (s, 1C), 126.81 (s, 1C), 125.31 (s, 1C), 120.45 (s, 1C), 72.02 (s, 1C), 32.08 (s, 1C). HRMS-ESI calcd for $C_{16}H_{14}N_4OBr$ $[M+H]^+$: 357.0351, found: 357.0346.

3-Methoxy-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**96l**)



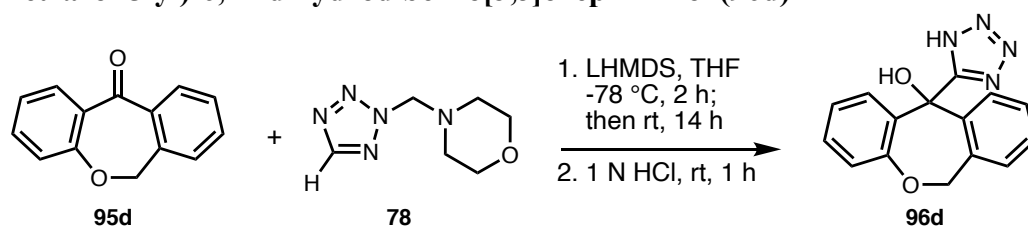
Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 3-methoxy-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95l**) (238 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96l** (241 mg, 78%): white solid; mp 115-118 °C dec with gas evolution; FTIR ν_{max} 3335, 2925, 2853, 1600, 1495, 1455, 1374, 1363, 1270, 1160, 1115, 1032, 913, 899, 856, 814, 756, 694, 650 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.08 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.71 (d, *J* = 2.7 Hz, 1H), 7.25 (ddd, *J* = 7.2, 5.1, 1.9 Hz, 2H), 7.14—7.13 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.79 (s, 3H), 2.81 (t, *J* = 6.5 Hz, 2H), 2.75 (dt, *J* = 6.2, 2.9 Hz, 2H); ¹³C NMR (126 MHz; CDCl₃) δ 162.42 (s, 1C), 158.03 (s, 1C), 142.71 (s, 1C), 141.37 (s, 1C), 138.09 (s, 1C), 131.64 (s, 1C), 130.57 (s, 1C), 129.70 (s, 1C), 128.11 (s, 1C), 125.81 (s, 1C), 125.33 (s, 1C), 113.17 (s, 1C), 111.46 (s, 1C), 72.01 (s, 1C), 54.65 (s, 1C), 32.30 (s, 1C), 31.07 (s, 1C). HRMS-ESI calcd for C₁₇H₁₇N₄O₂ [M+H]⁺: 309.1352, found: 309.1355.

2-Methoxy-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**96n**)



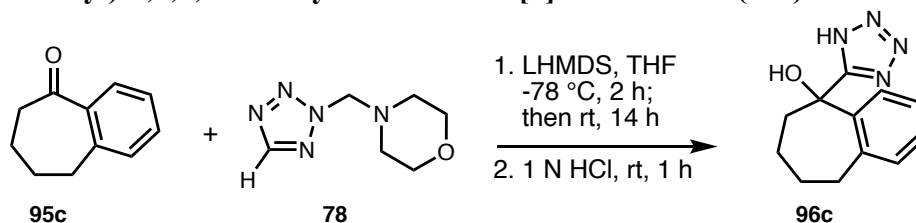
Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 2-methoxy-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95n**) (238 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96n** (170 mg, 55%): white solid; mp 116-120 °C dec with gas evolution; FTIR ν_{max} 3333, 2927, 2851, 1599, 1495, 1454, 1373, 1360, 1270, 1252, 1159, 1114, 1032, 913, 897, 854, 812, 755, 695, 649 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.09—8.06 (m, 1H), 8.00 (q, *J* = 8.3 Hz, 1H), 7.27—7.23 (m, 2H), 7.14 (d, *J* = 6.9 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 3.77 (s, 3H), 2.91—2.79 (m, 4H); ¹³C NMR (101 MHz; CDCl₃) δ 162.98 (s, 1C), 159.83 (s, 1C), 142.35 (s, 1C), 140.05 (s, 1C), 138.66 (s, 1C), 133.94 (s, 1C), 130.70 (s, 1C), 128.39 (s, 1C), 127.64 (s, 1C), 126.25 (s, 1C), 125.84 (s, 1C), 116.05 (s, 1C), 111.35 (s, 1C), 72.58 (s, 1C), 54.96 (s, 1C), 32.95 (s, 1C), 32.60 (s, 1C). HRMS-ESI calcd for C₁₇H₁₇N₄O₂ [M+H]⁺: 309.1352, found: 309.1359.

11-(1*H*-Tetrazol-5-yl)-6,11-dihydrodibenzo[*b,e*]oxepin-11-ol (**96d**)



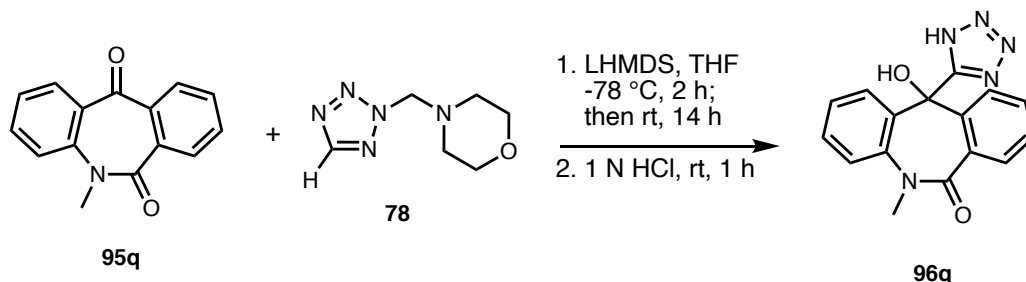
Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and dibenzo[*b,e*]oxepin-11(6*H*)-one (**95d**) (210 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96d** (261 mg, 93%): white solid; mp 125-128 °C dec with gas evolution; FTIR ν_{max} 3324, 3201, 3075, 1694, 1644, 1602, 1482, 1440, 1374, 1305, 1275, 1225, 1198, 1154, 1130, 1099, 1035, 1016, 954, 913, 867, 818, 800, 754, 739, 662 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 8.10 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.40—7.29 (m, 3H), 7.19—7.13 (m, 2H), 7.01 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.46 (d, *J* = 14.8 Hz, 1H), 4.98 (d, *J* = 14.8 Hz, 1H); ¹³C NMR (101 MHz; CDCl₃) δ 162.29 (s, 1C), 155.68 (s, 1C), 140.88 (s, 1C), 136.59 (s, 1C), 135.58 (s, 1C), 130.22 (s, 1C), 128.81 (s, 1C), 127.76 (s, 1C), 127.57 (s, 1C), 126.73 (s, 1C), 125.56 (s, 1C), 123.69 (s, 1C), 121.62 (s, 1C), 72.89 (s, 1C), 71.95 (s, 1C). HRMS-ESI calcd for C₁₅H₁₃N₄O₂ [M+H]⁺: 281.1039, found: 281.1046.

5-(1*H*-Tetrazol-5-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol (**96c**)



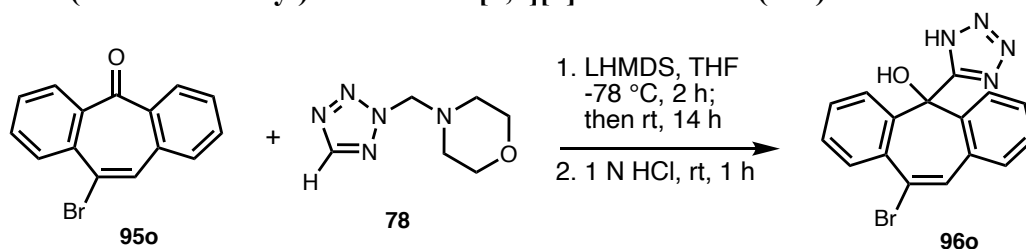
Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (**95c**) (160 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96c** (201 mg, 87%): white solid; mp 90-93 °C dec with gas evolution; FTIR ν_{max} 3304, 2927, 2854, 1667, 1615, 1531, 1484, 1445, 1366, 1222, 1156, 1099, 1027, 947, 923, 910, 855, 797, 746, 676, 648 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 7.52 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.23—7.13 (m, 3H), 2.88 (ddd, *J* = 14.4, 7.5, 2.0 Hz, 1H), 2.77 (dq, *J* = 11.8, 4.1 Hz, 1H), 2.68 (ddd, *J* = 14.1, 11.4, 2.5 Hz, 1H), 2.21 (ddd, *J* = 14.0, 8.9, 5.0 Hz, 1H), 2.07 (dt, *J* = 4.4, 2.2 Hz, 1H), 1.99 (td, *J* = 7.3, 3.8 Hz, 1H), 1.84—1.76 (m, 1H), 1.61—1.53 (m, 1H); ¹³C NMR (101 MHz; CDCl₃) δ 161.54 (s, 1C), 142.97 (s, 1C), 141.50 (s, 1C), 130.98 (s, 1C), 128.43 (s, 1C), 126.76 (s, 1C), 126.32 (s, 1C), 74.45 (s, 1C), 40.80 (s, 1C), 35.82 (s, 1C), 27.67 (s, 1C), 25.74 (s, 1C). HRMS-ESI calcd for C₁₂H₁₄N₄ONa [M+Na]⁺: 253.1065, found: 253.1077.

11-Hydroxy-5-methyl-11-(1*H*-tetrazol-5-yl)-5,11-dihydro-6*H*-dibenzo[*b,e*]azepin-6-one (96q)



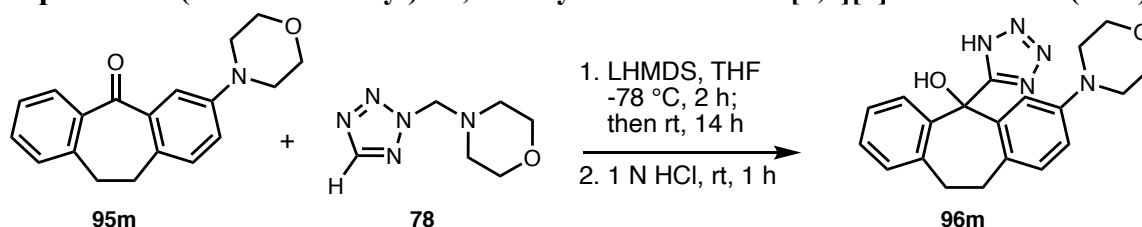
Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 5-methyl-5*H*-dibenzo[*b,e*]azepine-6,11-dione (**95q**) (237 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96q** (199 mg, 65%): yellow solid; mp 155-159 °C dec with gas evolution; FTIR ν_{max} 3074, 2814, 2736, 1615, 1595, 1568, 1504, 1472, 1422, 1377, 1307, 1263, 1198, 1163, 1142, 1122, 1088, 1043, 997, 915, 877, 711, 666, 657, 634, 592 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 8.03—8.00 (m, 2H), 7.66 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.54 (td, *J* = 7.7, 1.1 Hz, 1H), 7.37—7.25 (m, 4H), 3.03 (s, 3H); ¹³C NMR (101 MHz; CDCl₃) δ 169.02 (s, 1C), 168.78 (s, 1C), 142.97 (s, 1C), 139.27 (s, 1C), 131.23 (s, 1C), 130.69 (s, 1C), 130.01 (s, 1C), 127.91 (s, 1C), 127.30 (s, 1C), 126.58 (s, 1C), 125.96 (s, 1C), 123.73 (s, 1C), 123.62 (s, 1C), 122.18 (s, 1C), 71.64 (s, 1C), 36.45 (s, 1C). HRMS-ESI calcd for C₁₆H₁₄N₅O₂ [M+H]⁺: 308.1147, found: 308.1143.

10-Bromo-5-(1*H*-tetrazol-5-yl)-5*H*-dibenzo[*a,d*][7]annulen-5-ol (96o)



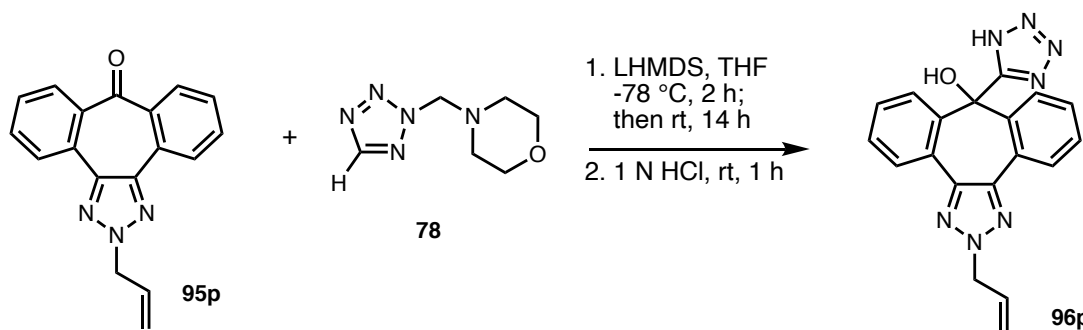
Following Representative Procedure 1, a solution of **78** (338 mg, 2 mmol, 2 equiv) and 10-bromo-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95o**) (285 mg, 1 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (351 mg, 2.1 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96o** (256 mg, 72%): brown solid; mp 135-138 °C dec with gas evolution; FTIR ν_{max} 3066, 2920, 2848, 1694, 1594, 1563, 1558, 1480, 1440, 1417, 1355, 1232, 1190, 1171, 1131, 1109, 1038, 958, 914, 903, 854, 821, 755, 743, 716, 667, 635 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 8.20—8.16 (m, 2H), 7.84 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.61—7.53 (m, 2H), 7.45 (td, *J* = 7.6, 1.0 Hz, 1H), 7.41—7.37 (m, 3H); ¹³C NMR (101 MHz; CDCl₃) δ 160.73 (s, 1C), 142.14 (s, 1C), 141.44 (s, 1C), 134.36 (s, 1C), 133.03 (s, 1C), 132.35 (s, 1C), 130.30 (s, 1C), 129.93 (s, 1C), 129.16 (s, 1C), 128.81 (s, 1C), 128.02 (s, 1C), 127.81 (s, 1C), 123.99 (s, 1C), 123.43 (s, 1C), 109.95 (s, 1C), 71.74 (s, 1C). HRMS-ESI calcd for C₁₆H₁₂N₄OBr [M+H]⁺: 355.0194, found: 355.0182.

3-morpholino-5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**96m**)



Following Representative Procedure 1, a solution of **78** (231 mg, 1.36 mmol, 2 equiv) and 3-morpholino-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95m**) (200 mg, 0.682 mmol, 1 equiv) in anhydrous THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (240 mg, 1.43 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 4:96), **96m** (90 mg, 36%): yellow solid; mp 125-129 °C dec with gas evolution; FTIR ν_{max} 3361, 3064, 3023, 2952, 2921, 2852, 2191, 1693, 1650, 1644, 1596, 1574, 1557, 1538, 1498, 1484, 1448, 1376, 1360, 1287, 1266, 1238, 1162, 1114, 1066, 1030, 993, 955, 909, 873, 819, 811, 753, 718, 698, 674, 634, 616, 593, 560, 553 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 8.07 (dd, *J* = 6.2, 2.9 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.26—7.23 (m, 2H), 7.16—7.13 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.79 (t, *J* = 4.7 Hz, 4H), 3.14 (t, *J* = 4.7 Hz, 4H), 2.82 (t, *J* = 6.9 Hz, 2H), 2.73 (dd, *J* = 10.0, 5.2 Hz, 2H); ¹³C NMR (101 MHz; CDCl₃) δ 162.39 (s, 1C), 150.15 (s, 1C), 142.02 (s, 1C), 141.75 (s, 1C), 138.58 (s, 1C), 131.75 (s, 1C), 130.96 (s, 1C), 129.19 (s, 1C), 128.49 (s, 1C), 126.18 (s, 1C), 125.69 (s, 1C), 115.71 (s, 1C), 113.31 (s, 1C), 72.52 (s, 1C), 66.94 (s, 1C), 49.78 (s, 1C), 32.77 (s, 1C), 31.47 (s, 1C). HRMS-ESI calcd for C₂₀H₂₂N₅O₂ [M+H]⁺: 364.1764, found: 364.1773.

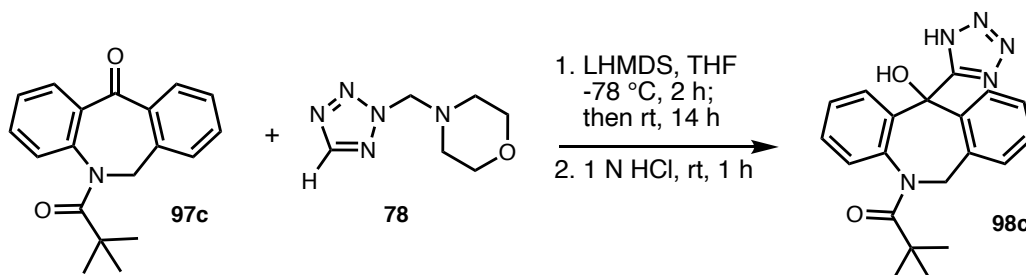
2-allyl-8-(1*H*-tetrazol-5-yl)-2,8-dihydrodibenzo[3,4:6,7]cyclohepta[1,2-*d*][1,2,3]triazol-8-ol (**96p**)



Following Representative Procedure 1, a solution of **78** (95 mg, 0.56 mmol, 2 equiv) and **95p** (80 mg, 0.28 mmol, 1 equiv) in THF (2.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (103 mg, 0.62 mmol, 2.2 equiv) in THF (1.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel (MeOH/CH₂Cl₂, 2:98), **96p** (95 mg, 0.27 mmol, 95%): white solid; mp >200 °C; FTIR ν_{max} 3348 (w), 3068 (w), 2834 (w), 2678 (w), 2508 (w), 1548 (w), 1428 (m), 1268 (m), 1187 (m), 1077 (w), 038 (m), 906 (s), 743 (s) cm⁻¹; ¹H NMR (500 MHz, CD₃OD): δ 8.23 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.82 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.63—7.55 (m, 2H), 7.50—7.45 (m, 2H), 6.00 (ddt, *J* = 17.0, 10.5, 5.4 Hz, 1H), 5.20 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.04 (d, *J* = 5.4 Hz, 2H), 4.84 (dd, *J* = 17.0, 1.0

Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD): δ 162.3, 145.7, 141.7, 133.0, 130.2, 129.3, 128.6, 128.0, 125.6, 118.6, 72.7, 58.1; HRMS-ESI calcd for $\text{C}_{19}\text{H}_{16}\text{N}_7\text{O}$ $[\text{M}+\text{H}]^+$: 358.1411, found: 358.1404.

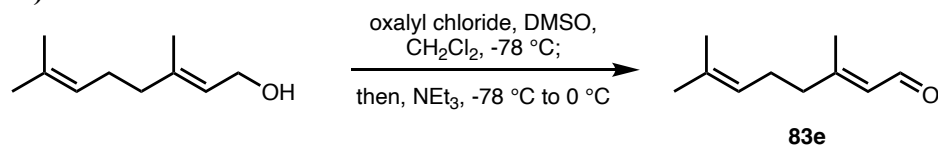
1-(11-hydroxy-11-(1*H*-tetrazol-5-yl)-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl)ethan-1-one (98c)



Following Representative Procedure 1, a solution of **78** (633 mg, 3.74 mmol, 2 equiv) and pivalamide **97c** (366 mg, 1.25 mmol, 1 equiv) in anhydrous THF (7.5 mL), under nitrogen at -78°C (acetone/ CO_2), was added a freshly prepared solution of LHMDS (66.8 mg, 4.00 mmol, 2.1 equiv) in THF (2.0 mL) dropwise via syringe over 5 min, to provide, after work up and purification by column chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$, 4:96), **98c** (394 mg, 87%) as a mixture of isomers: yellow solid; mp $105\text{--}108^\circ\text{C}$ dec with gas evolution; FTIR ν_{max} 3325, 3201, 3138, 2971, 2871, 1614, 1595, 1557, 1538, 1531, 1505, 1479, 1462, 1448, 1402, 1364, 1291, 1268, 1193, 1161, 1121, 1095, 1035, 983, 922, 871, 747, 712, 698, 663, 629, 603, 593, 581, 560 cm^{-1} ; ^1H -NMR (500 MHz; CDCl_3): δ 8.09 (dd, $J = 5.7, 3.6$ Hz, 6H), 7.47 (dd, $J = 6.0, 3.8$ Hz, 4H), 7.38–7.16 (m, 29H), 5.62 (d, $J = 2.8$ Hz, 4H), 5.26 (d, $J = 13.7$ Hz, 1H), 3.43 (d, $J = 13.6$ Hz, 1H), 2.11–2.07 (m, 4H), 0.84 (s, 9H); ^{13}C -NMR (126 MHz; CDCl_3): δ 177.90 (s, 1C), 176.20 (s, 1C), 161.96 (s, 1C), 161.02 (s, 1C), 153.05 (s, 1C), 149.06 (s, 1C), 143.21 (s, 1C), 134.62 (s, 1C), 133.37 (s, 1C), 132.95 (s, 1C), 132.54 (s, 1C), 132.45 (s, 1C), 130.87 (s, 1C), 129.68 (s, 1C), 129.11 (s, 1C), 129.05 (s, 1C), 128.67 (s, 1C), 128.62 (s, 1C), 128.46 (s, 1C), 128.42 (s, 1C), 128.35 (s, 1C), 128.27 (s, 1C), 128.11 (s, 1C), 127.92 (s, 1C), 127.84 (s, 1C), 127.64 (s, 1C), 127.55 (s, 1C), 127.47 (s, 1C), 127.45 (s, 1C), 126.74 (s, 1C), 126.66 (s, 1C), 125.48 (s, 1C), 125.44 (s, 1C), 125.32 (s, 1C), 123.27 (s, 1C), 115.27 (s, 1C), 108.61 (s, 1C), 71.60 (s, 1C), 56.93 (s, 1C), 53.08 (s, 1C), 40.96 (s, 1C), 27.09 (s, 1C), 26.64 (s, 1C). HRMS-ESI calcd for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_2$ $[\text{M}+\text{Na}]^+$: 386.1593, found: 386.1588.

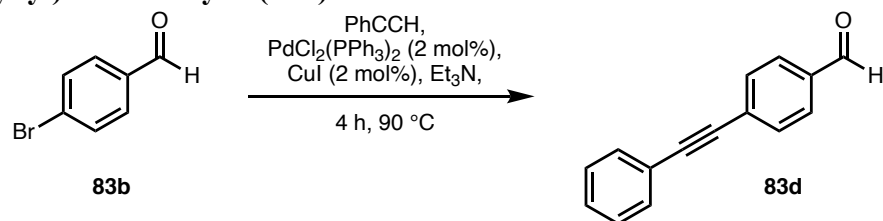
2.2 Substrate Preparation

Geranial (83e)⁹



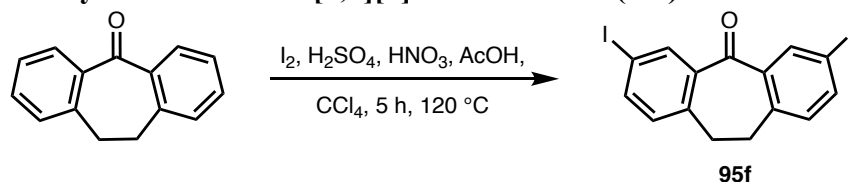
Geranial was prepared according to literature protocol and isolated in quantitative yield. ^1H and ^{13}C NMR matched previously reported procedures.

4-(phenylethynyl)benzaldehyde (**83d**)



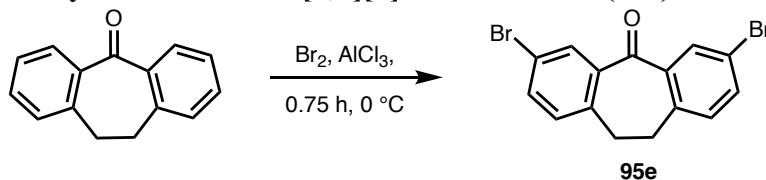
To an oven-dried vial was added *p*-bromobenzaldehyde (**83b**) (1g, 5.4 mmol, 1 equiv.), PdCl₂(PPh₃)₂ (75.9 mg, 0.108 mmol, 0.02 equiv.), and CuI (20.6 mg, 0.108 mmol, 0.02 equiv.). The vial was then sealed with a Teflon cap. It was then evacuated and backfilled with nitrogen thrice. Phenylacetylene (0.34 mL, 6.49 mmol, 1.2 equiv.) and anhydrous triethylamine (6mL) were added by syringe. The reaction was then heated at 90 °C for 4 hours. Upon completion, the reaction was passed through celite and filtrate was diluted with ethyl acetate. The solution was then washed sequentially with 1 M HCl and brine. It was then dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done via column chromatography (1:9 ethyl acetate/hexanes) to provide **83d** (930 mg, 83%); ¹H-NMR (500 MHz; CDCl₃): δ 10.04 (s, 1H), 10.04 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.59 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.59 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.40 (t, *J* = 3.1 Hz, 3H), 7.40 (t, *J* = 3.1 Hz, 3H); ¹³C-NMR (126 MHz; CDCl₃): δ 191.40 (s, 1C), 135.40 (s, 1C), 132.11 (s, 1C), 131.80 (s, 1C), 129.58 (s, 1C), 128.98 (s, 1C), 128.49 (s, 1C), 122.49 (s, 1C), 93.46 (s, 1C), 88.55 (s, 1C).

3,7-diiodo-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95f**)¹⁰



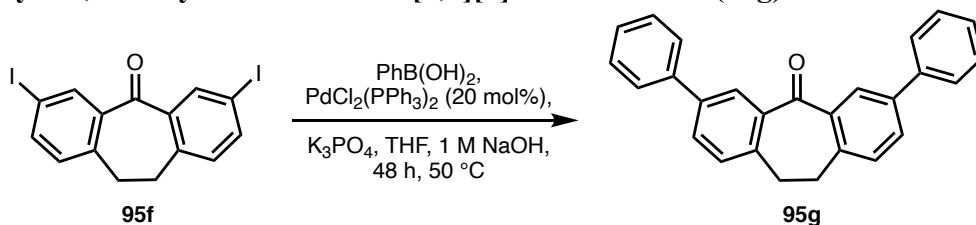
Diaryldioiodide **95f** was prepared according to literature protocol and isolated in 29% yield. ¹H-NMR (500 MHz; CDCl₃): δ 8.31 (d, *J* = 1.9 Hz, 2H), 7.77 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 3.15 (s, 4H); ¹³C-NMR (126 MHz; CDCl₃): δ 192.38 (s, 1C), 141.27 (s, 1C), 141.23 (s, 1C), 139.59 (s, 1C), 139.26 (s, 1C), 131.27 (s, 1C), 91.67 (s, 1C), 34.27 (s, 1C).

3,7-dibromo-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (**95e**)¹¹



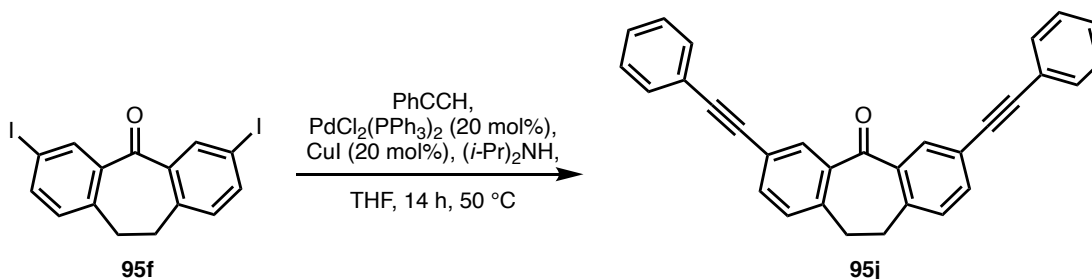
Diaryldibromide **95e** was prepared according to literature protocol and isolated in 13% yield. ¹H and ¹³C NMR matched previously reported procedures.

3,7-diphenyl-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-one (**95g**)¹²



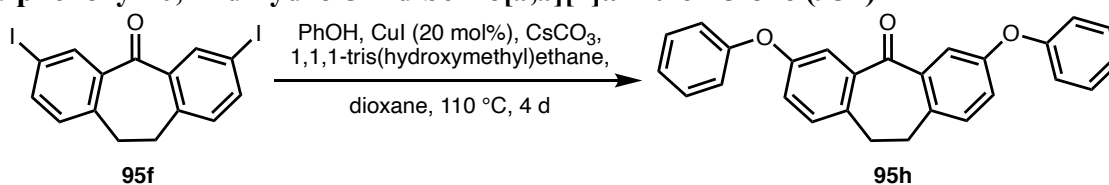
To an oven-dried vial was added diaryliodide **95f** (230 mg, 0.5 mmol, 1 equiv.), K_3PO_4 (371 mg, 1.75 mmol, 3.5 equiv.), and $\text{PdCl}_2(\text{PPh}_3)_2$ (66.4 mg, 0.1 mmol, 0.2 equiv.). The vial was sealed with a teflon cap and evacuated and backfilled with nitrogen thrice. THF (7.5 mL) and 1 M NaOH (1 mL) were added via syringe and the reaction was heated to 50 °C for 48 hours. Upon completion, the reaction was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The organics were then combined and washed with brine. They were then dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done through column chromatography on silica gel (1:9 hexanes/ethyl acetate) to provide **95g** (150 mg, 83%) as a white solid. ^1H and ^{13}C NMR matched previously reported procedures. HRMS-ESI calculated for $\text{C}_{27}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 361.1592, found 361.1587.

3,7-bis(phenylethynyl)-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-one (**95j**)



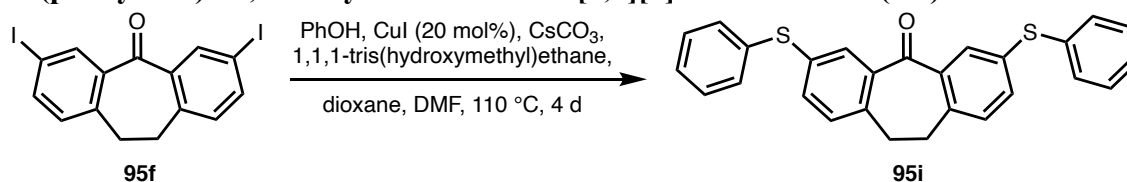
To an oven-dried vial was added diaryliodide **95f** (460 mg, 1 mmol, 1 equiv.), $\text{PdCl}_2(\text{PPh}_3)_2$ (140 mg, 0.2 mmol, 0.2 equiv.), and CuI (38.1 mg, 0.2 mmol, 0.2 equiv.). The vial was sealed with a teflon cap and evacuated and backfilled with nitrogen thrice. Using a syringe, phenylacetylene (0.329 mL, 3 mmol, 3 equiv.), diisopropylamine (0.423 mL, 3 mmol, 3 equiv.), and anhydrous THF (15 mL) was added to the sealed vial. The reaction was then heated to 50 °C for 14 hours. Upon completion, the reaction was cooled to room temperature and quenched with 1 M HCl. The solution was then extracted with ethyl acetate. The organics were then combined, washed with brine, dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done via column chromatography on silica gel (1:9 hexanes/ethyl acetate) to provide **95j**: (401 mg, 98%), black oil; ^1H -NMR (400 MHz; CDCl_3): δ 8.24 (d, J = 1.5 Hz, 2H), 7.62-7.57 (m, 6H), 7.39 (dd, J = 5.0, 1.5 Hz, 7H), 7.24 (d, J = 7.8 Hz, 2H), 3.23 (s, 4H); ^{13}C NMR (101 MHz; CDCl_3): δ 194.3, 142.2, 138.8, 135.5, 134.3, 132.1, 130.1, 128.84, 128.81, 123.5, 122.5, 90.5, 88.8, 35.2. HRMS-ESI calculated for $\text{C}_{31}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 409.1592, found 409.1592.

3,7-diphenoxy-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-one (95h)



This procedure was adapted from literature protocol.¹³ To an oven-dried vial was added diaryldiiodide **95f** (460 mg, 1 mmol, 1 equiv.), phenol (282 mg, 3 mmol, 3 equiv.), copper iodide (38.1 mg, 0.2 mmol, 0.2 equiv.), 1,1,1-tris(hydroxymethyl)ethane (24 mg, 0.2 mmol, 0.2 equiv.), and cesium carbonate (1.323 g, 4.06 mmol, 4.06 equiv.). The vial was then sealed with a teflon cap. It was then evacuated and refilled with nitrogen thrice. Using a syringe, anhydrous dioxane (5 mL) was added and the reaction was refluxed at 110 °C for 4 days with stirring. Upon completion, the reaction was passed through celite and the filter cake was washed with ethyl acetate. The filtrate was then partitioned between ethyl acetate and water. The layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The organics were then combined and sequentially washed with 10% NaOH and brine. The organic solution was then dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done via column chromatography on silica gel (1:4 hexanes/ethyl acetate) to provide **95h** (249 mg, 63%): white solid, ¹H-NMR (400 MHz; CDCl₃): δ 7.70-7.55 (m, 2H), 7.36 (quintet, *J* = 8.2 Hz, 5H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.15-7.09 (m, 4H), 7.06-6.92 (m, 4H), 3.25-3.18 (m, 4H); ¹³C-NMR (101 MHz; CDCl₃): δ 194.16 (s, 1C), 157.28 (s, 1C), 156.50 (s, 1C), 139.89 (s, 1C), 137.33 (s, 1C), 131.40 (s, 1C), 130.27 (s, 1C), 123.98 (s, 1C), 123.48 (s, 1C), 120.64 (s, 1C), 119.41 (s, 1C), 34.75 (s, 1C). HRMS-ESI calculated for C₂₇H₂₁O₃ [M+H]⁺: 393.1491, found 393.1490.

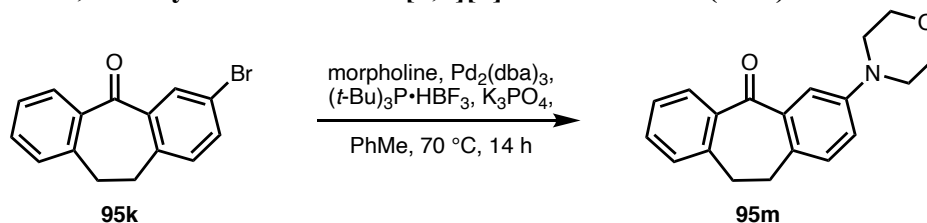
3,7-bis(phenylthio)-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-one (95i)



This procedure was adapted from literature protocol.¹³ To an oven-dried vial was added diaryldiiodide **95f** (460 mg, 1 mmol, 1 equiv.), copper iodide (38.1 mg, 0.2 mmol, 0.2 equiv.), 1,1,1-tris(hydroxymethyl)ethane (24 mg, 0.2 mmol, 0.2 equiv.), and cesium carbonate (1.323 g, 4.06 mmol, 4.06 equiv.). The vial was then sealed with a teflon cap. It was then evacuated and refilled with nitrogen thrice. Using a syringe, thiophenol (0.307 mL, 3 mmol, 3 equiv.), anhydrous dioxane (4 mL) and anhydrous DMF (0.5 mL) were added and the reaction was refluxed at 110 °C for 4 days with stirring. Upon completion, the reaction was passed through celite and the filter cake was washed with ethyl acetate. The filtrate was then partitioned between ethyl acetate and water. The layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The organics were then combined and sequentially washed with 10% NaOH and brine. The organic solution was then dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done via column chromatography on silica gel (1:4 hexanes/ethyl acetate) to provide **95i**: (433 mg, 99%); ¹H-NMR (400 MHz; CDCl₃): δ 8.02 (d, *J* = 2.1 Hz, 2H), 7.41-7.38 (m, 6H), 7.36-7.26 (m, 7H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.18 (s, 4H); ¹³C-NMR (101 MHz; CDCl₃): δ 194.33 (s, 1C), 141.10 (s, 1C), 139.45 (s, 1C), 135.55 (s, 1C), 135.16 (s, 1C), 135.11 (s, 1C), 133.22 (s, 1C), 131.74 (s, 1C), 130.86 (s, 1C), 129.75 (s,

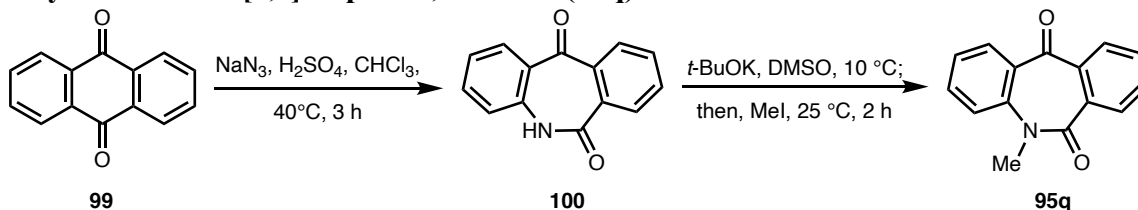
1C), 127.82 (s, 1C), 34.82 (s, 1C). HRMS-ESI calcd for C₂₇H₂₁OS₂ [M+H]⁺: 425.1034, found 425.1026.

3-morpholino-10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-one (95m)



In a glovebox, arylbromide **95k** (1 g, 3.48 mmol, 1 equiv.) Pd₂(dba)₃ (128 mg, 0.139 mmol, 0.04 equiv.), tri-*tert*-butylphosphonium tetrafluoroborate (78.4 mg, 0.289 mmol, 0.08 equiv.), and potassium phosphate tribasic (2.255 g, 10.6 mmol, 3.05 equiv.) were added to a vial. The vial was then sealed with a septum and taken out of the glovebox. Morpholine (0.8 mL, 9.26 mmol, 2.66 equiv.) and toluene (17 mL) was added to the vial by syringe. The reaction was then heated at 70 °C overnight. Upon completion, the reaction cooled to room temperature and filtered through a silica plug. The plug was eluted with DCM and the filtrate was concentrated in vacuo. Additional purification was done by column chromatography on silica gel (1:4 ethyl acetate/hexanes) to provide **95m** (350 mg, 34%); ¹H-NMR (400 MHz; CDCl₃): δ 7.98 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.60 (d, *J* = 2.7 Hz, 1H), 7.44 (td, *J* = 7.4, 1.4 Hz, 1H), 7.36-7.32 (m, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.89 (t, *J* = 4.7 Hz, 4H), 3.21 (t, *J* = 4.7 Hz, 4H), 3.17 (d, *J* = 4.1 Hz, 3H); ¹³C-NMR (101 MHz; CDCl₃): δ 196.21 (s, 1C), 150.25 (s, 1C), 142.32 (s, 1C), 139.30 (s, 1C), 139.16 (s, 1C), 134.19 (s, 1C), 132.64 (s, 1C), 130.90 (s, 1C), 130.87 (s, 1C), 129.53 (s, 1C), 126.98 (s, 1C), 120.64 (s, 1C), 117.25 (s, 1C), 67.26 (s, 1C), 49.74 (s, 1C), 35.50 (s, 1C), 34.55 (s, 1C).

5-methyl-5H-dibenzo[*b,e*]azepine-6,11-dione (95q)¹⁴

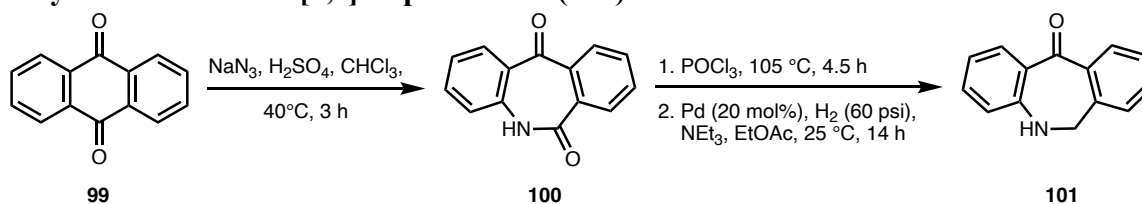


Anthraquinone (**99**) (20 g, 96.1 mmol, 1 equiv.) was suspended in concentrated sulfuric acid (250 mL) and chloroform (50 mL). The biphasic system was then rapidly stirred while sodium azide (7.81 g, 120 mmol, 1.25 equiv.) was added in parts at room temperature. The reaction was stirred at room temperature for 1 hour and then at 40 °C for 3 hours. Upon completion, the reaction was poured onto ice water (200 mL). The precipitate was then filtered and washed with water. The precipitate was then filtered with ether to remove excess water to provide **100** (21.3 g, 100%); ¹H-NMR (500 MHz; DMSO-*d*₆): δ 11.12 (d, *J* = 5.6 Hz, 1H), 8.20-8.19 (m, 1H), 7.84 (s, 3H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H); ¹³C-NMR (126 MHz; CDCl₃): δ 192.92 (s, 1C), 165.92 (s, 1C), 138.68 (s, 1C), 137.08 (s, 1C), 134.30 (s, 1C), 133.60 (s, 1C), 133.43 (s, 1C), 131.62 (s, 1C), 130.60 (s, 1C), 130.04 (s, 1C), 129.70 (s, 1C), 128.61 (s, 1C), 124.26 (s, 1C), 120.89 (s, 1C).

To a flame-dried flask was lactam **100** (750 mg, 3.36 mmol, 1 equiv.) dissolved in DMSO (13.5mL) under nitrogen at 10 °C. After addition of *tert*-butoxide (528 mg, 4.7 mmol, 1.4

equiv.), the reaction was stirred for 15 minutes. Methyl iodide (0.426 mL, 6.72 mmol, 2 equiv.) was added and the flask was brought to room temperature for 2 hours. The reaction was quenched with 1 M HCl (12 mL). The solution was then extracted with ethyl acetate. The organics were then combined and washed with water and brine, sequentially. Afterwards, it was dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done via column chromatography on silica gel (1:2 ethyl acetate/hexanes) to provide **95q** (413 mg, 52%): $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.20-8.17 (m, 1H), 7.71-7.67 (m, 2H), 7.65 (t, $J = 1.7$ Hz, 1H), 7.62 (td, $J = 6.3, 1.7$ Hz, 1H), 7.54 (ddd, $J = 8.2, 7.4, 1.7$ Hz, 1H), 7.34 (dd, $J = 8.2, 0.5$ Hz, 1H), 7.29-7.25 (m, 1H), 3.65 (s, 3H); $^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 195.64 (s, 1C), 166.88 (s, 1C), 140.71 (s, 1C), 136.84 (s, 1C), 133.18 (s, 1C), 132.87 (s, 1C), 132.76 (s, 1C), 132.71 (s, 1C), 132.45 (s, 1C), 131.26 (s, 1C), 128.51 (s, 1C), 126.76 (s, 1C), 125.94 (s, 1C), 122.67 (s, 1C), 39.18 (s, 1C).

5,6-dihydro-11H-dibenzo[b,e]azepin-11-one (**101**)



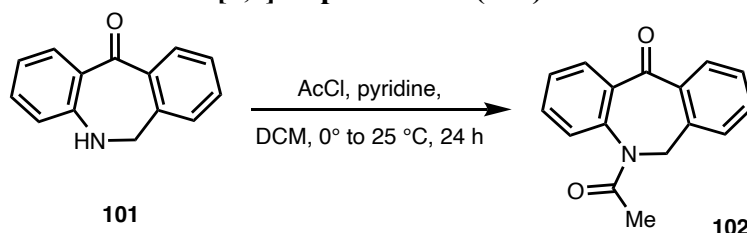
Anthraquinone (**99**) (20 g, 96.1 mmol, 1 equiv.) was suspended in concentrated sulfuric acid (250 mL) and chloroform (50 mL). The biphasic system was then rapidly stirred while sodium azide (7.81 g, 120 mmol, 1.25 equiv.) was added in parts at room temperature. The reaction was stirred at room temperature for 1 hour and then at 40 °C for 3 hours. Upon completion, the reaction was poured onto ice water (200 mL). The precipitate was then filtered and washed with water. The precipitate was then filtered with ether to remove excess water to provide **100** (21.3 g, 100%): $^1\text{H-NMR}$ (500 MHz; $\text{DMSO-}d_6$): δ 11.12 (d, $J = 5.6$ Hz, 1H), 8.20-8.19 (m, 1H), 7.84 (s, 3H), 7.74 (d, $J = 7.4$ Hz, 1H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.25 (t, $J = 7.4$ Hz, 1H); $^{13}\text{C-NMR}$ (126 MHz; CDCl_3): δ 192.92 (s, 1C), 165.92 (s, 1C), 138.68 (s, 1C), 137.08 (s, 1C), 134.30 (s, 1C), 133.60 (s, 1C), 133.43 (s, 1C), 131.62 (s, 1C), 130.60 (s, 1C), 130.04 (s, 1C), 129.70 (s, 1C), 128.61 (s, 1C), 124.26 (s, 1C), 120.89 (s, 1C).

In a flame-dried flask, lactam **100** (3 g, 13.4 mmol, 1 equiv.) was dissolved in phosphorus oxychloride (20.2 mL, 216 mmol, 16.1 equiv.). The solution was then refluxed for 4.5 hours under nitrogen. The reaction was then cooled and concentrated in vacuo. Ice water was then added to the residue and transferred to a separatory funnel. The aqueous was then extracted with DCM. The organics were then combined and washed with half-saturated NaHCO_3 . After drying with sodium sulfate, the solution was filtered and concentrated in vacuo. The residue was then dissolved in toluene and filtered through neutral alumina. The plug was eluted with additional toluene. The filtrate was then concentrated in vacuo to provide an unstable chloroimine that was immediately taken to the next step as it is unstable under ambient conditions.

In a Parr hydrogenation flask, the previously synthesized imidoil chloride (1.08 g, 4.48 mmol, 1 equiv.) was dissolved in ethyl acetate (20 mL). Triethylamine (0.887 mL, 6.36 mmol, 1.42 equiv.) and 5% Pd/C (0.09 g, 0.811 mmol, 0.18 equiv.) was added and the flask was equipped to the Parr hydrogenator. The reaction was evacuated and filled with hydrogen thrice. The reaction was then shaken at 60 psi overnight. The reaction was then filtered through celite and eluted with

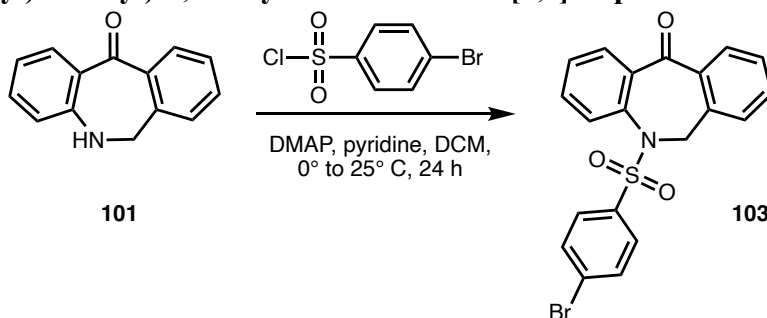
ethyl acetate. The filtrate was then sequentially washed with water, saturated NaHCO₃, and brine. The organics were then dried with sodium sulfate, decanted, and concentrated in vacuo to provide **101** (937 mg, 100%). The product of this reaction was used directly to the next step without purification. Tan solid; ¹H-NMR (500 MHz; CDCl₃): δ 8.24 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.49 (td, *J* = 7.5, 1.3 Hz, 1H), 7.37 (td, *J* = 7.5, 1.1 Hz, 1H), 7.30 (ddd, *J* = 8.2, 6.8, 1.6 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 6.86 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 (dd, *J* = 8.3, 0.6 Hz, 1H), 5.58 (s, 1H), 4.19 (d, *J* = 4.6 Hz, 2H); ¹³C-NMR (126 MHz; CDCl₃): δ 194.39 (s, 1C), 150.71 (s, 1C), 137.67 (s, 1C), 134.24 (s, 1C), 132.33 (s, 1C), 131.67 (s, 1C), 129.11 (s, 1C), 128.87 (s, 1C), 127.96 (s, 1C), 126.39 (s, 1C), 121.64 (s, 1C), 118.57 (s, 1C), 118.01 (s, 1C), 49.43 (s, 1C).

5-acetyl-5,6-dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (**102**)



To a flask was added vinylagous amide **101** (2.50 g, 11.9 mmol, 1 equiv.) and dissolved in DCM (12 mL). The flask was cooled to 0 °C. Pyridine (3.85 mL, 47.8 mmol, 4 equiv.), and acyl chloride (1.28 g, 17.9 mmol, 1.5 equiv.) were added to the solution and stirred for 24 hours. The solution as allowed to reach room temperature during this time. Upon completion, the solution was diluted with water and acidified. The aqueous phase was extracted with DCM. The combined organics were sequentially washed with saturated NaHCO₃ and brine, dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done via column chromatography on silica gel (1:3 ethyl acetate/hexanes) to provide **102** (2.68 g, 89%): white solid, ¹H-NMR (500 MHz; CDCl₃): δ 8.26 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.59-7.55 (m, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.40 (td, *J* = 16.2, 7.2 Hz, 3H), 7.28 (d, *J* = 6.6 Hz, 1H), 4.96 (s, 1H), 1.94 (s, 3H); ¹³C-NMR (126 MHz; CDCl₃): δ 189.97 (s, 1C), 169.01 (s, 1C), 141.94 (s, 1C), 140.60 (s, 1C), 135.78 (s, 1C), 135.14 (s, 1C), 133.52 (s, 1C), 133.33 (s, 1C), 132.09 (s, 1C), 131.81 (s, 1C), 128.98 (s, 1C), 127.95 (s, 1C), 127.85 (s, 1C), 126.74 (s, 1C), 51.69 (s, 1C), 22.36 (s, 1C).

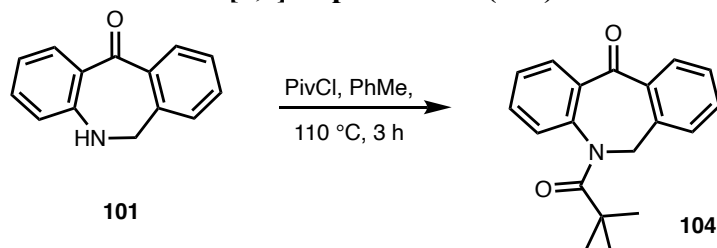
5-((4-Bromophenyl)sulfonyl)-5,6-dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (**103**)



To a flask was added vinylagous amide **101** (2.20 g, 10.5 mmol, 1.05 equiv.) and dissolved in DCM (10.5 mL). The flask was cooled to 0 °C. DMAP (61.2 mg, 0.501 mmol, 0.05 equiv.), pyridine (1.61 mL, 20 mmol, 2 equiv.), and brosyl chloride (2.56 g, 10 mmol, 1 equiv.) were

added to the solution and stirred for 24 hours. The solution as allowed to reach room temperature during this time. Upon completion, the solution was diluted with water and acidified. The aqueous phase was extracted with DCM. The combined organics were sequentially washed with saturated NaHCO_3 and brine, dried with sodium sulfate, decanted, and concentrated in vacuo. Additional purification was done via column chromatography on silica gel (1:4 ethyl acetate/hexanes) to provide **103** (4.29 g, 100%): white solid, ^1H -NMR (500 MHz; CDCl_3): δ 8.27 (ddd, $J = 6.9, 2.3$ Hz, 1H), 7.85-7.81 (m, 2H), 7.69-7.66 (m, 1H), 7.56-7.48 (m, 2H), 7.37 (dd, $J = 14.5, 7.3$ Hz, 2H), 7.10 (d, $J = 8.6$ Hz, 2H), 6.72 (d, $J = 8.6$ Hz, 2H), 5.09 (s, 2H); ^{13}C -NMR (126 MHz; CDCl_3): δ 187.57 (s, 1C), 139.77 (s, 1C), 137.45 (s, 1C), 136.46 (s, 1C), 135.84 (s, 1C), 134.82 (s, 1C), 134.12 (s, 1C), 133.99 (s, 1C), 133.23 (s, 1C), 132.74 (s, 1C), 131.69 (s, 1C), 131.64 (s, 1C), 129.79 (s, 1C), 128.99 (s, 1C), 128.36 (s, 1C), 128.27 (s, 1C), 127.98 (s, 1C), 127.36 (s, 1C), 127.21 (s, 1C), 55.87 (s, 1C).

5-pivaloyl-5,6-dihydro-11H-dibenzo[*b,e*]azepin-11-one (**104**)



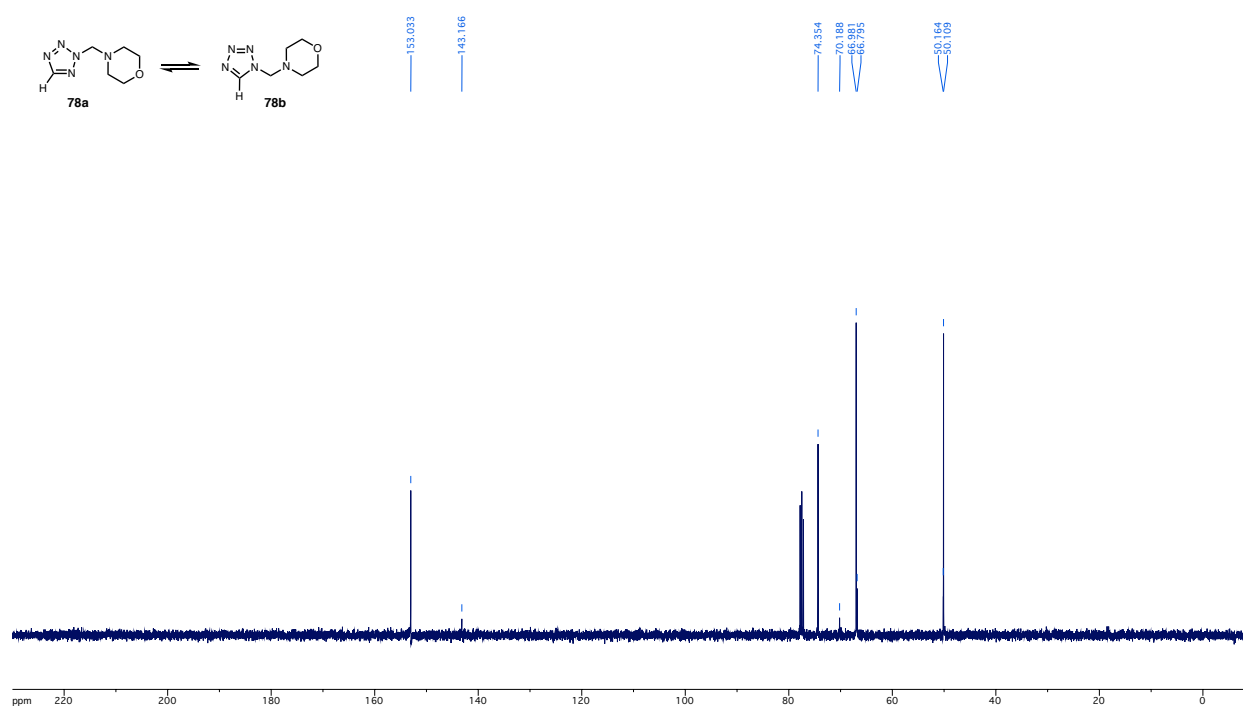
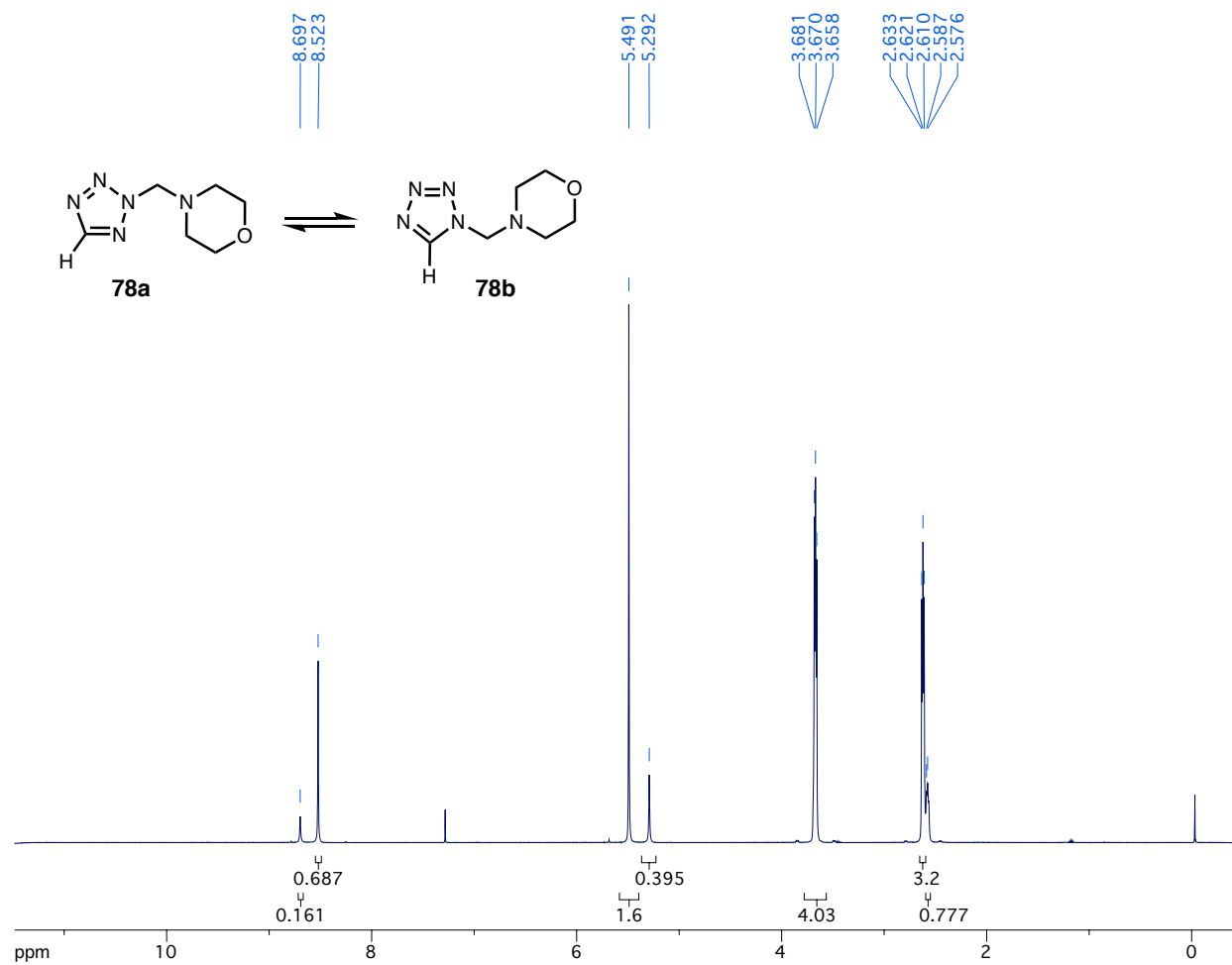
In a flask under nitrogen, the vinylagous amide **101** was dissolved in toluene and neat pivaloyl chloride (2.48 mL, 20.2 mmol, 1.5 equiv.) was added by syringe. The reaction was refluxed for 3 hours. Upon completion, the reaction was cooled and quenched with water. The biphasic system was rapidly stirred for about 20 minutes. It was then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with ethyl acetate. The organics were then combined, washed with brine, dried with sulfate, decanted and concentrated in vacuo to provide **104** (3.61 g, 91%): white solid, ^1H -NMR (400 MHz; CDCl_3): δ 8.29 (d, $J = 7.8$ Hz, 1H), 7.91 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.59-7.55 (m, 1H), 7.53-7.45 (m, 2H), 7.39 (dd, $J = 12.4, 7.5$ Hz, 3H), 5.07 (s, 2H), 0.99 (s, 9H); ^{13}C -NMR (101 MHz; CDCl_3): δ 192.40 (s, 1C), 177.22 (s, 1C), 142.75 (s, 1C), 142.40 (s, 1C), 139.42 (s, 1C), 134.58 (s, 1C), 133.91 (s, 1C), 132.94 (s, 1C), 131.86 (s, 1C), 131.30 (s, 1C), 129.32 (s, 1C), 128.89 (s, 1C), 128.05 (s, 1C), 127.99 (s, 1C), 55.09 (s, 1C), 41.43 (s, 1C), 29.46 (s, 1C).

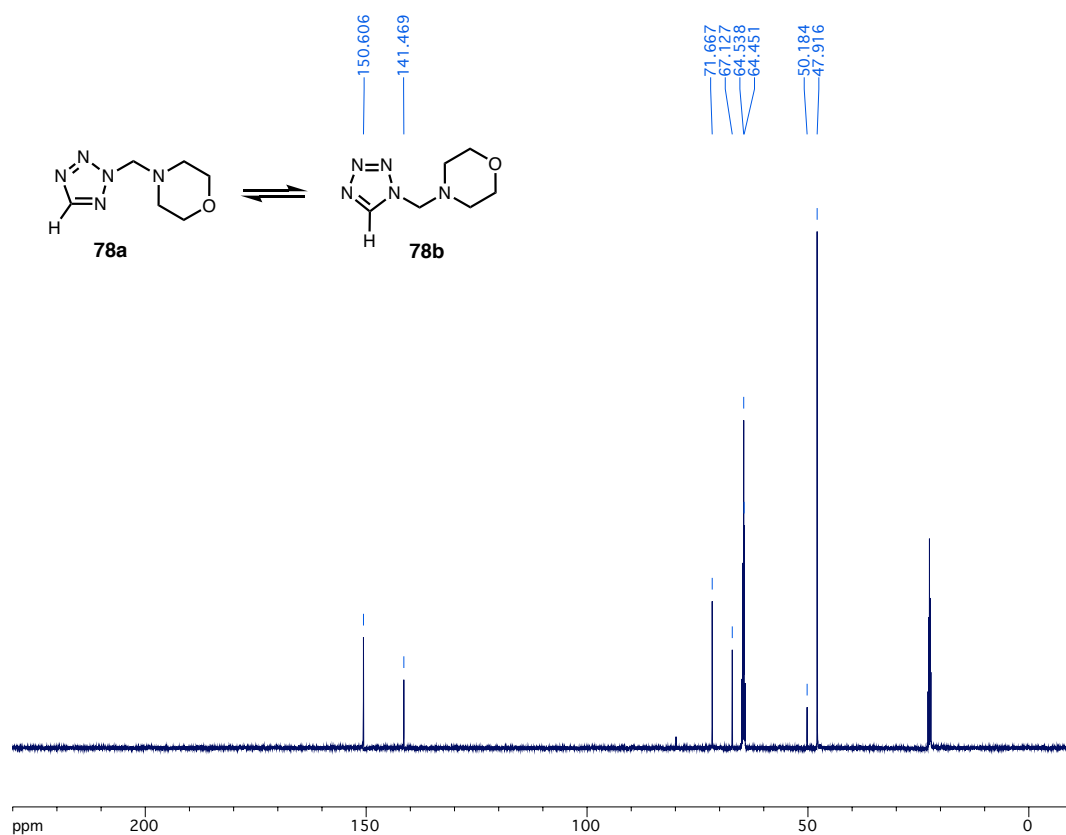
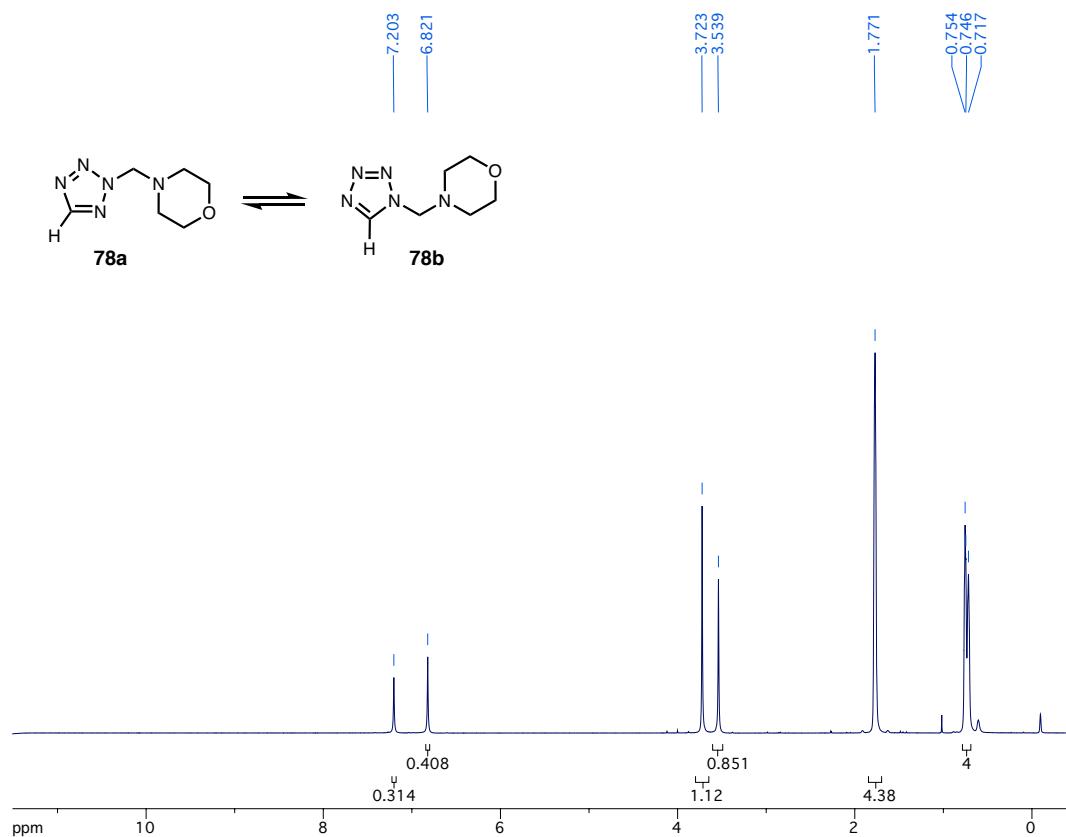
3. References

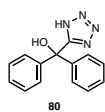
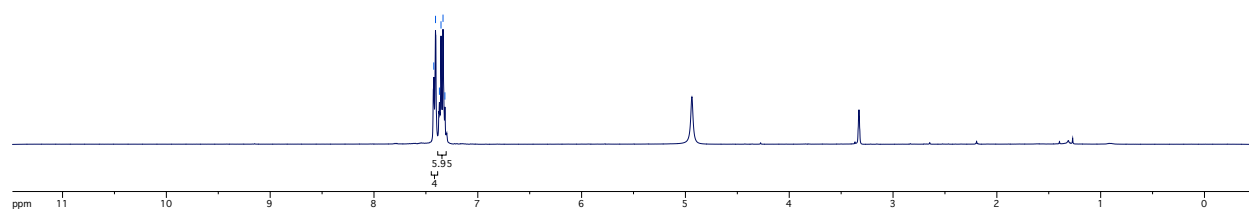
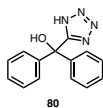
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Appendix B, Tetrazoles





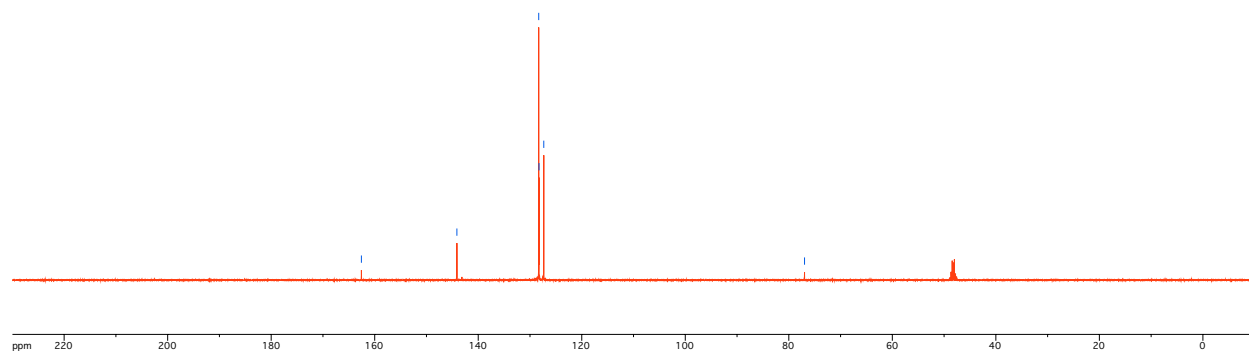


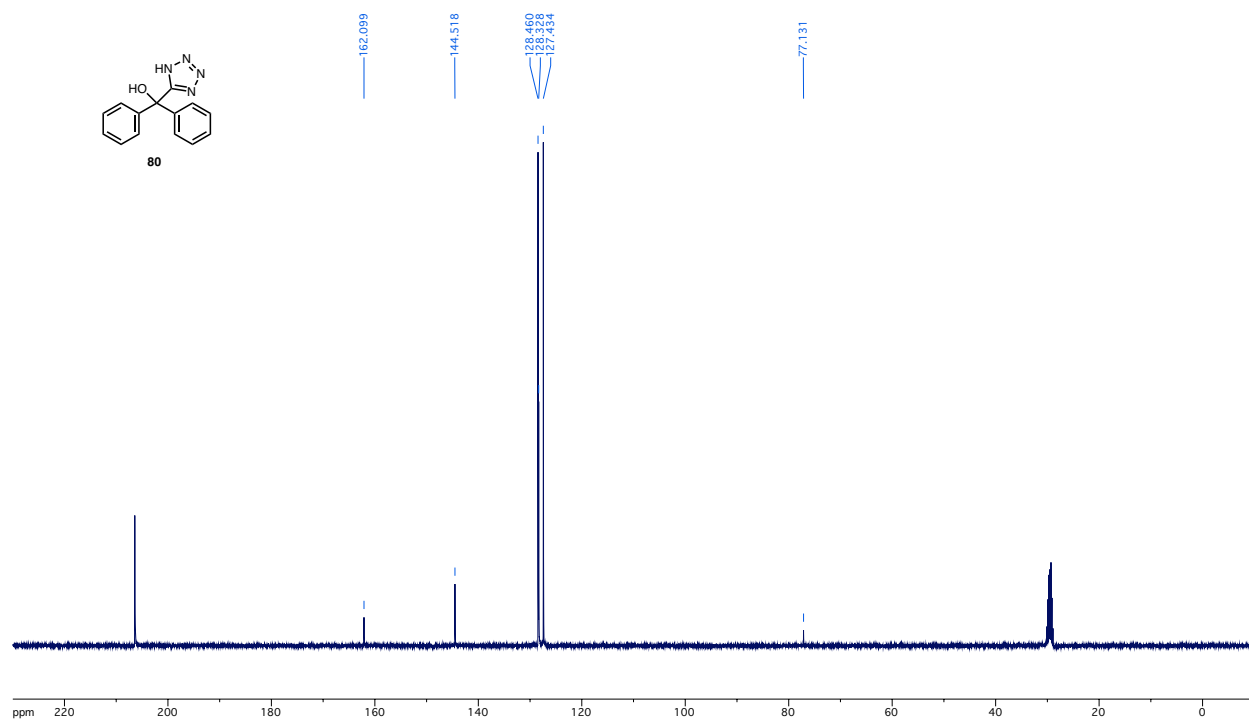
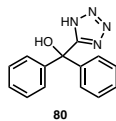
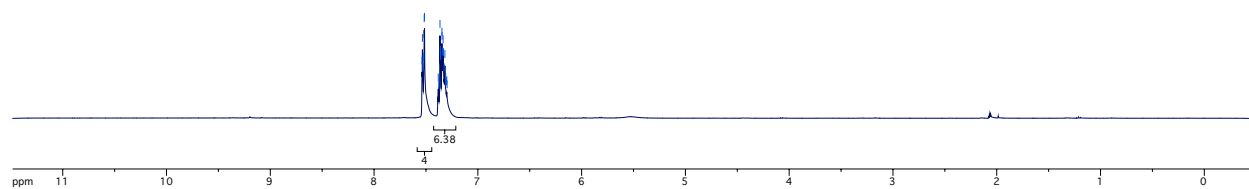
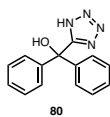
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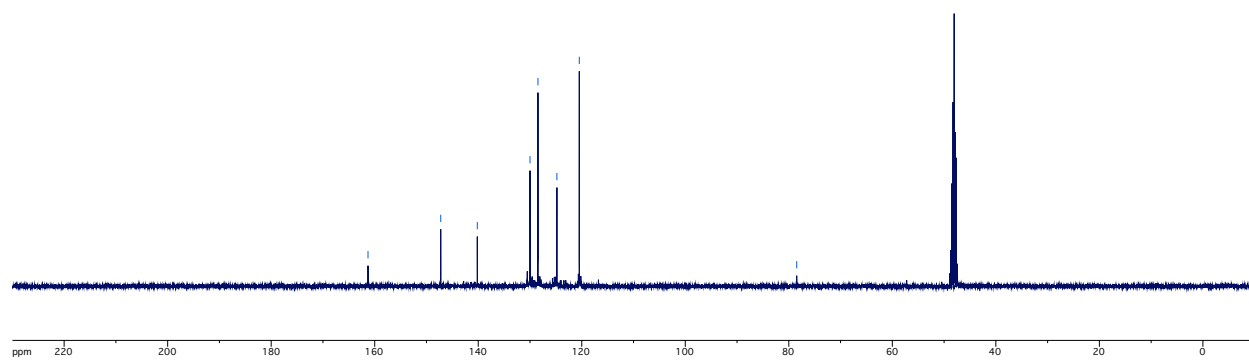
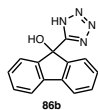
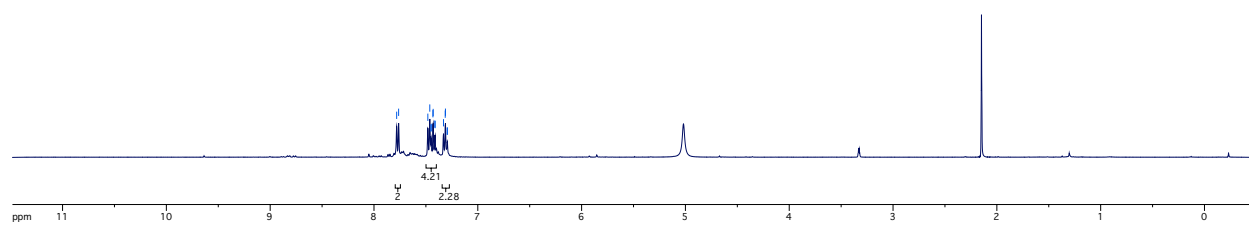
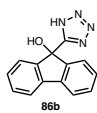
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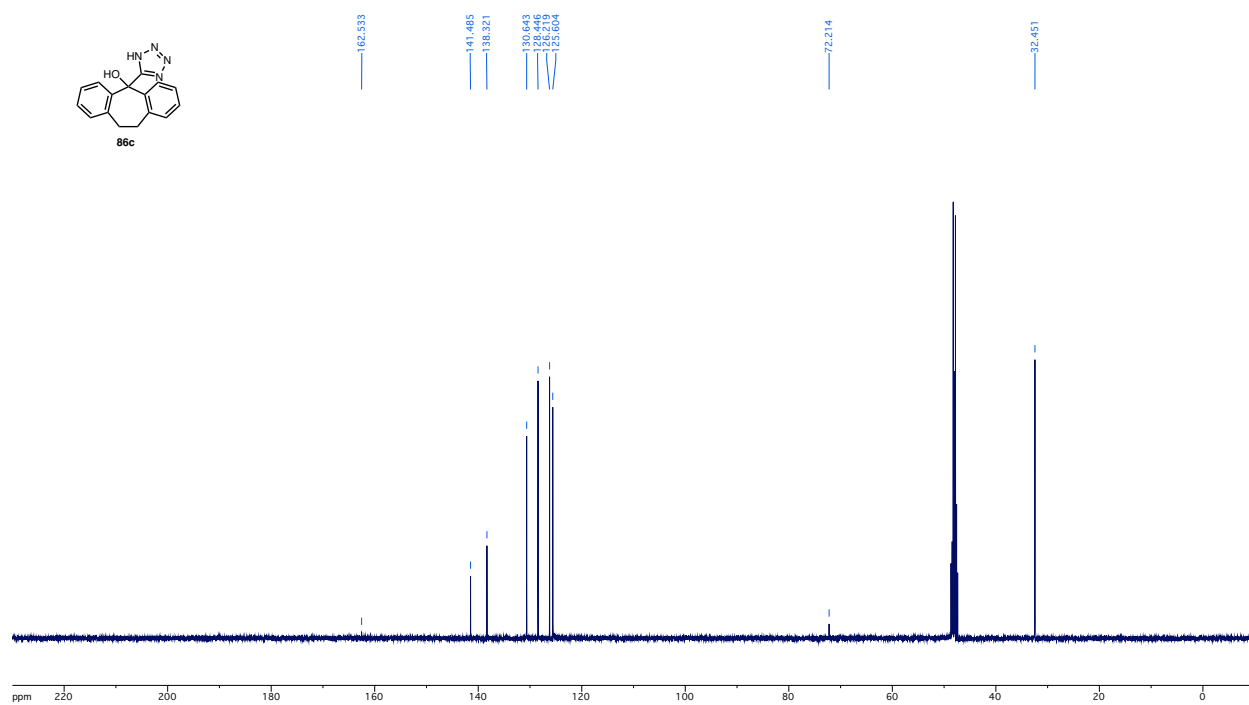
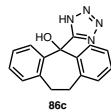
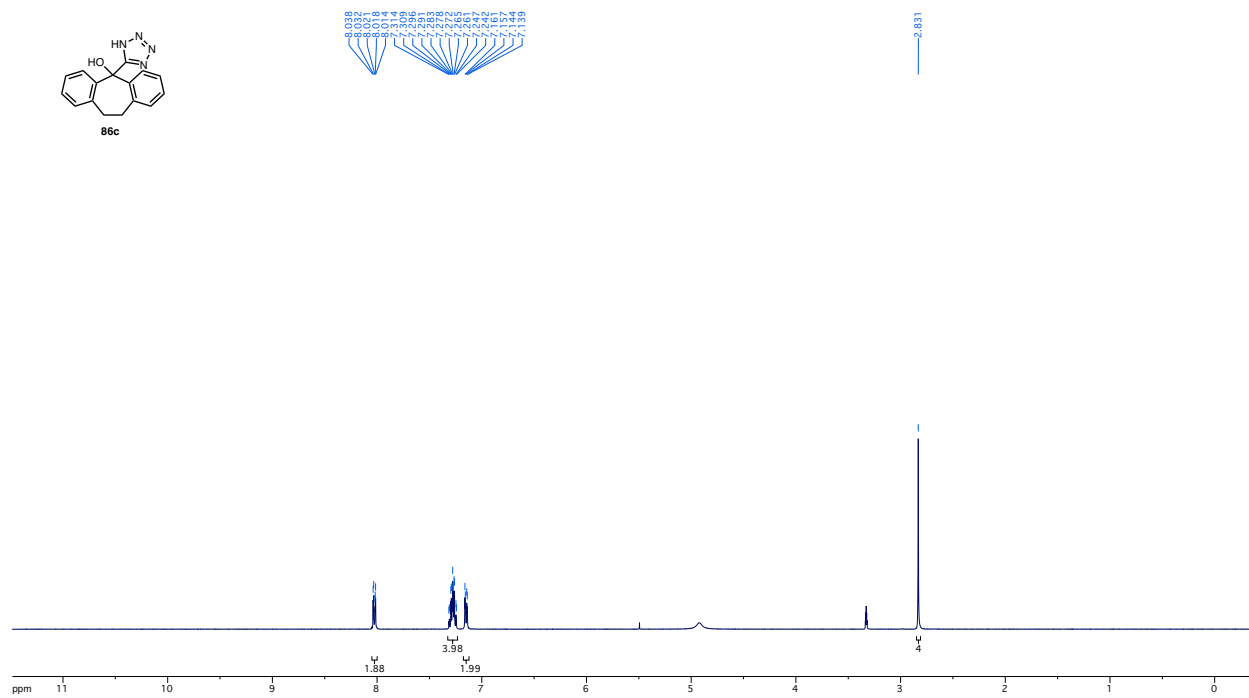
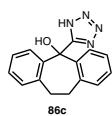
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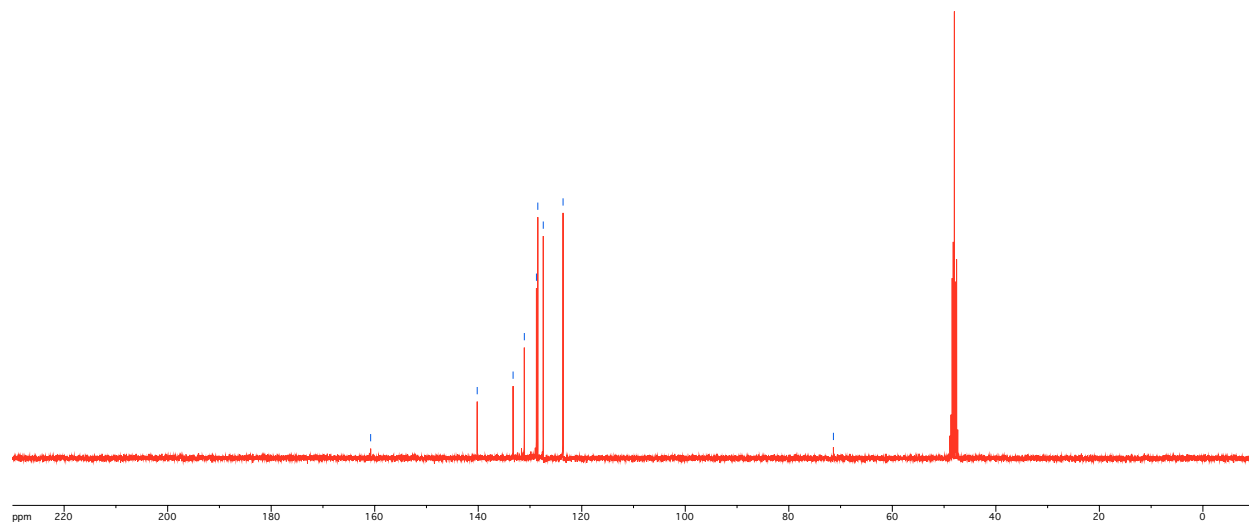
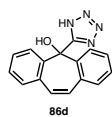
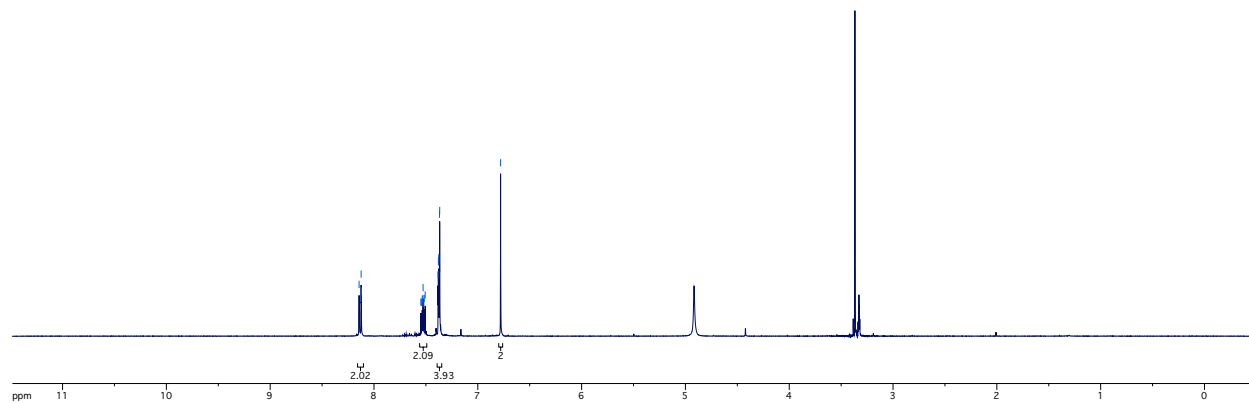
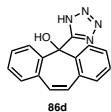
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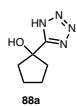
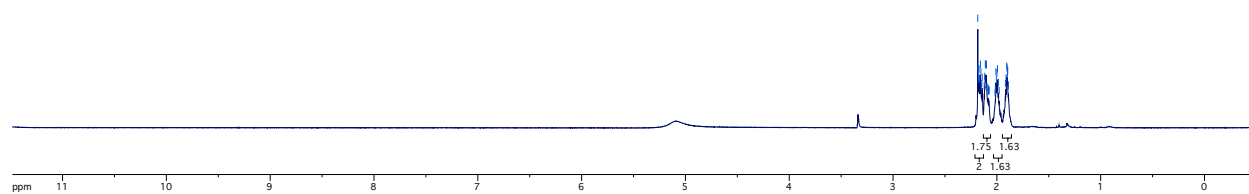
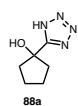










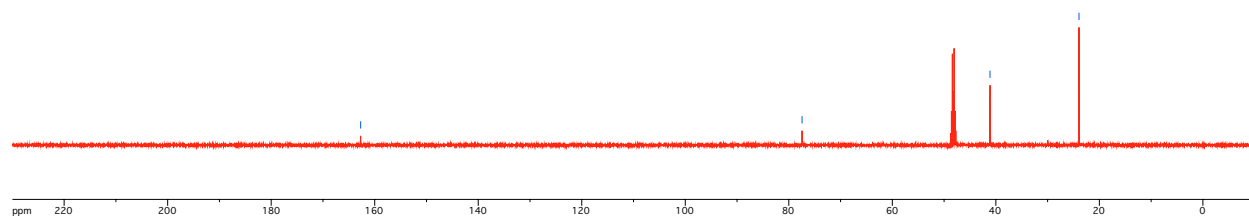


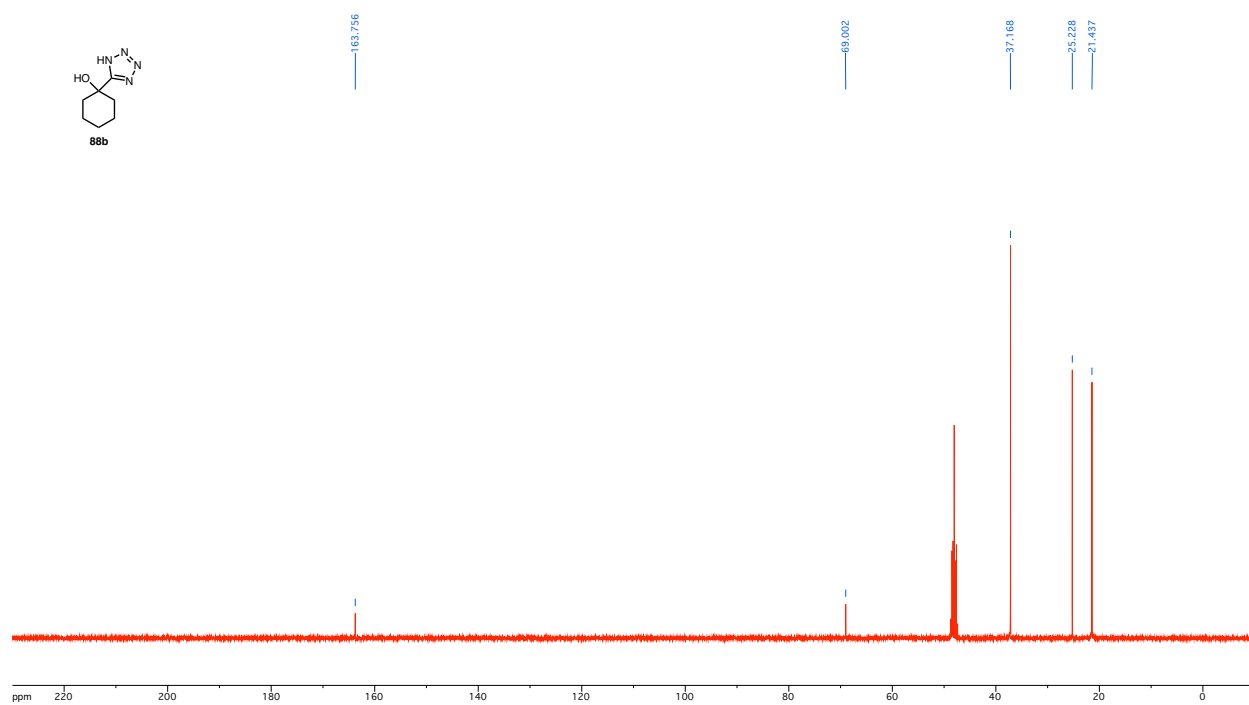
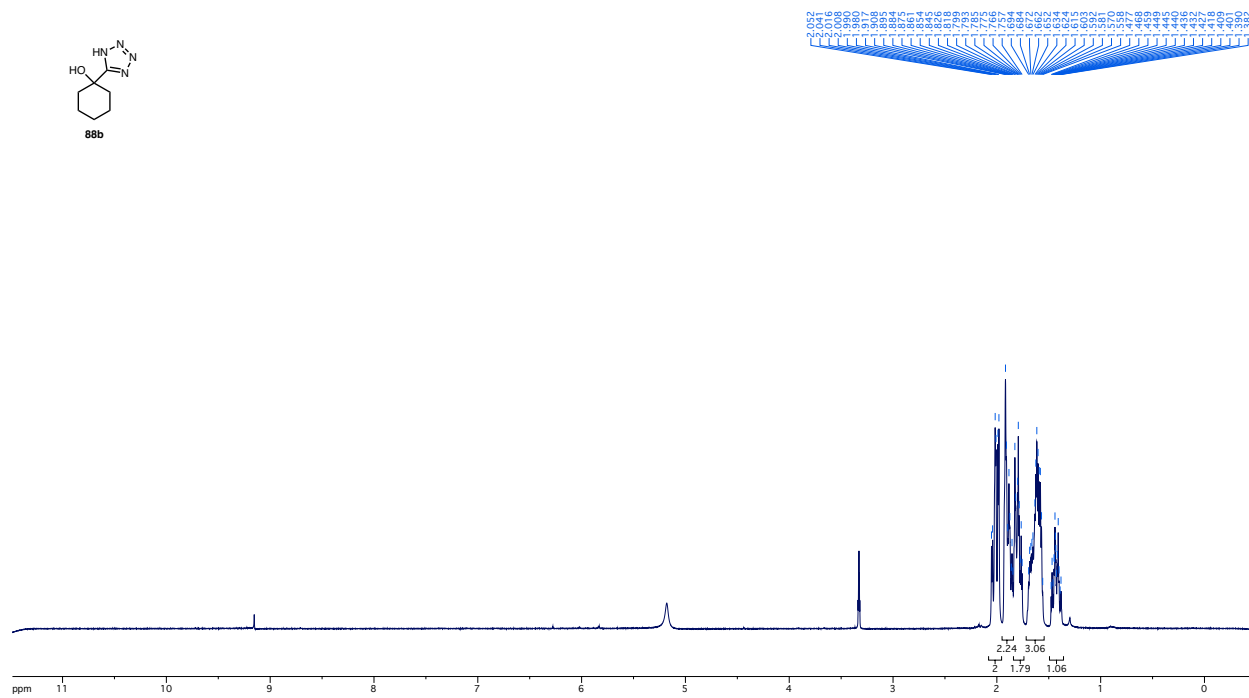
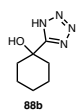
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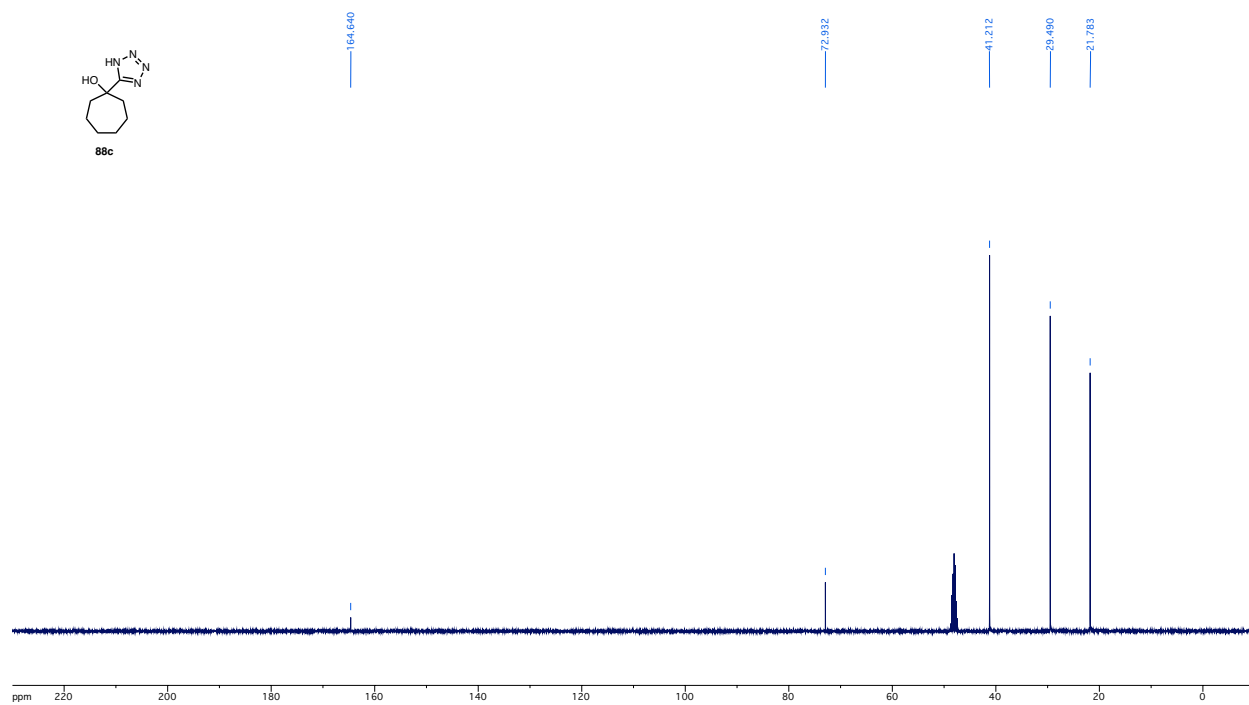
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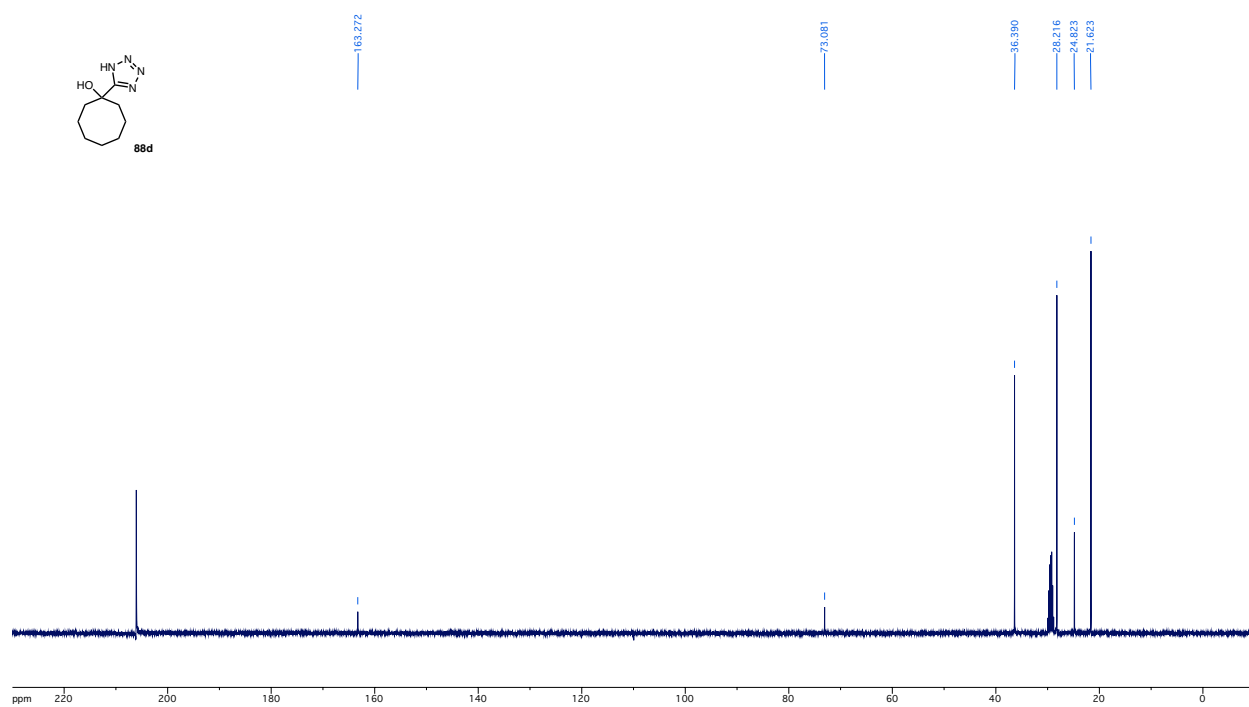
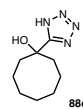
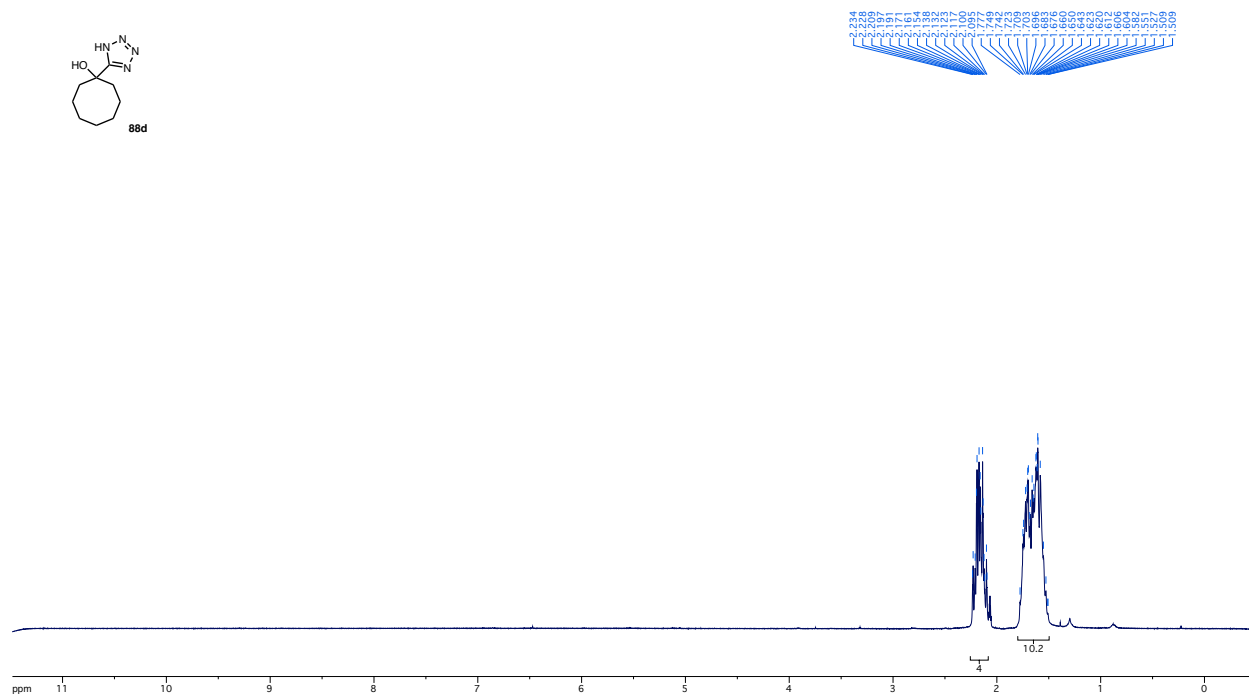
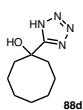
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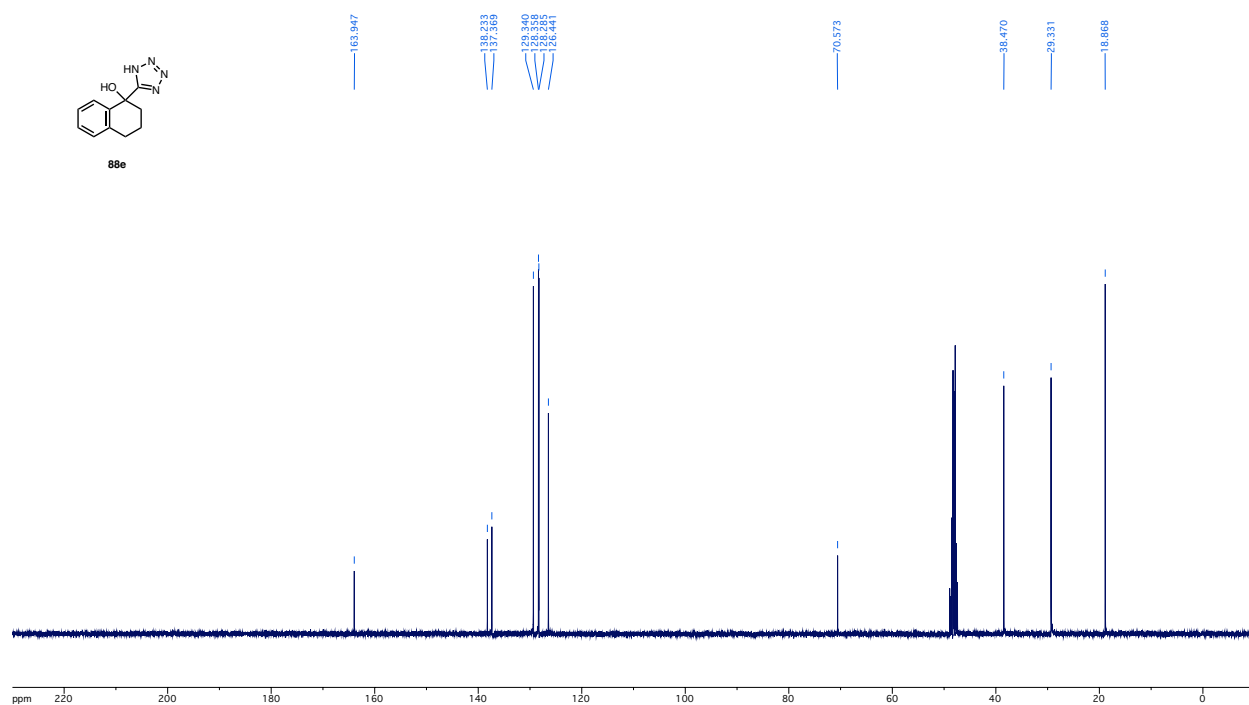
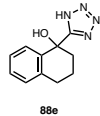
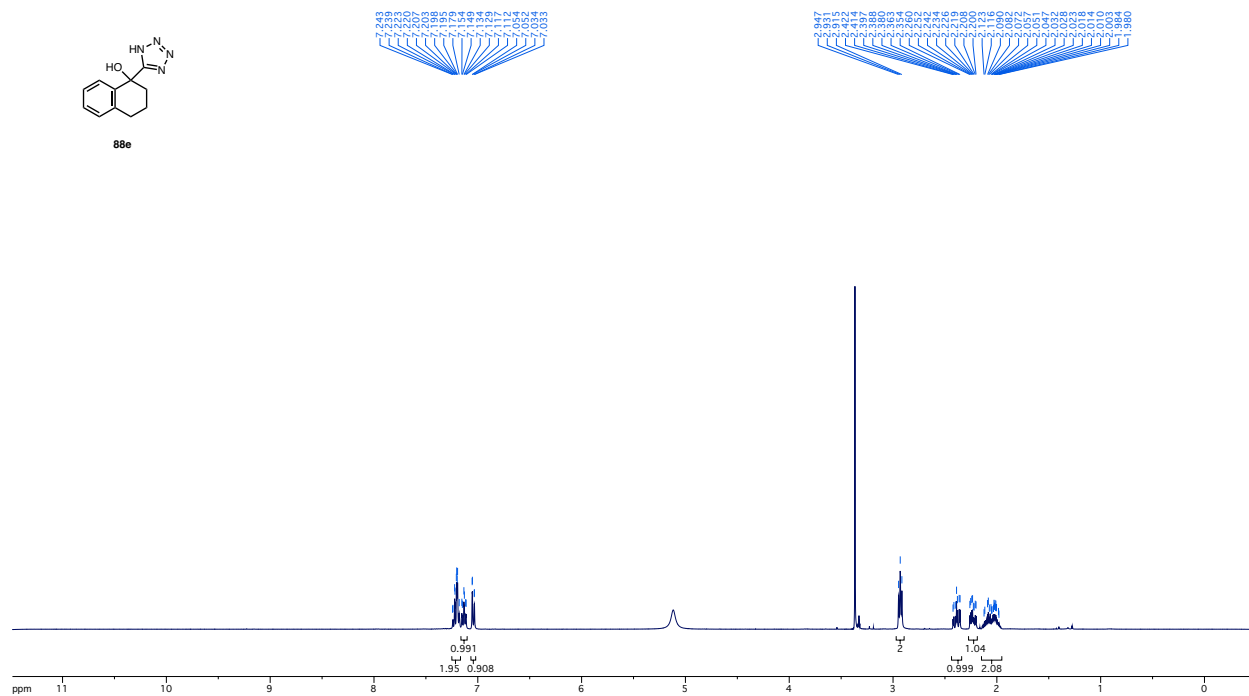
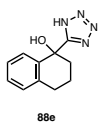
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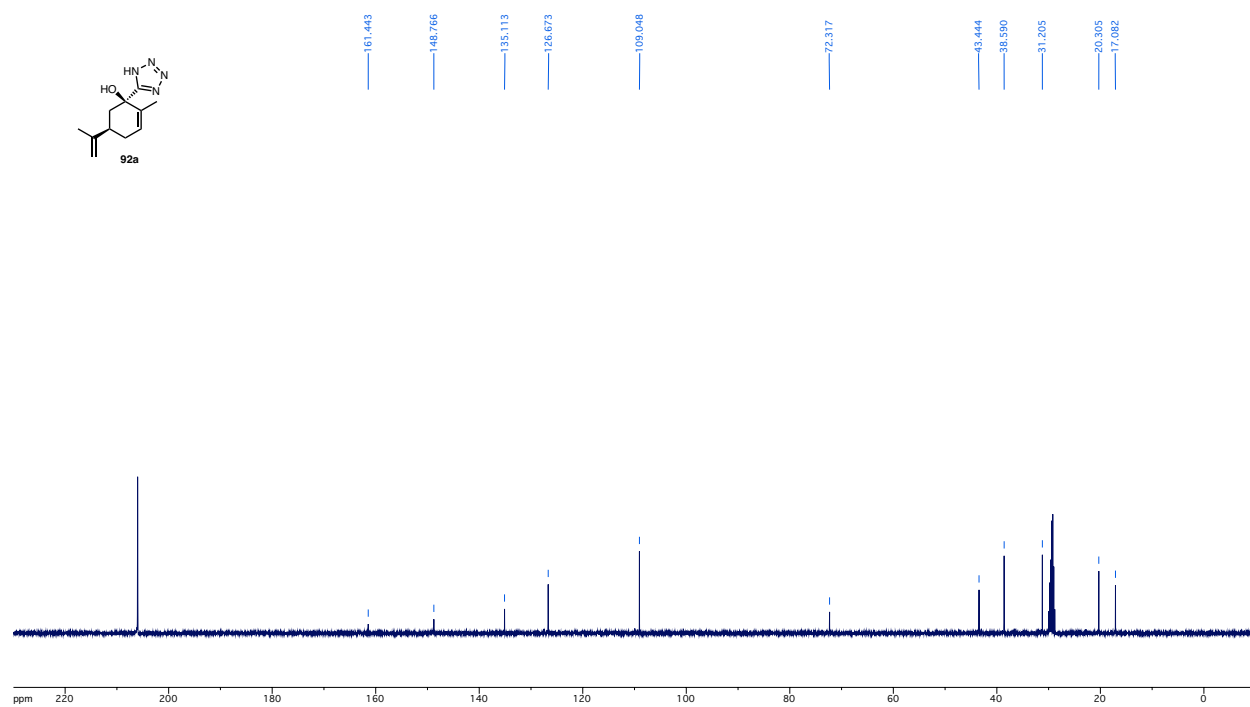
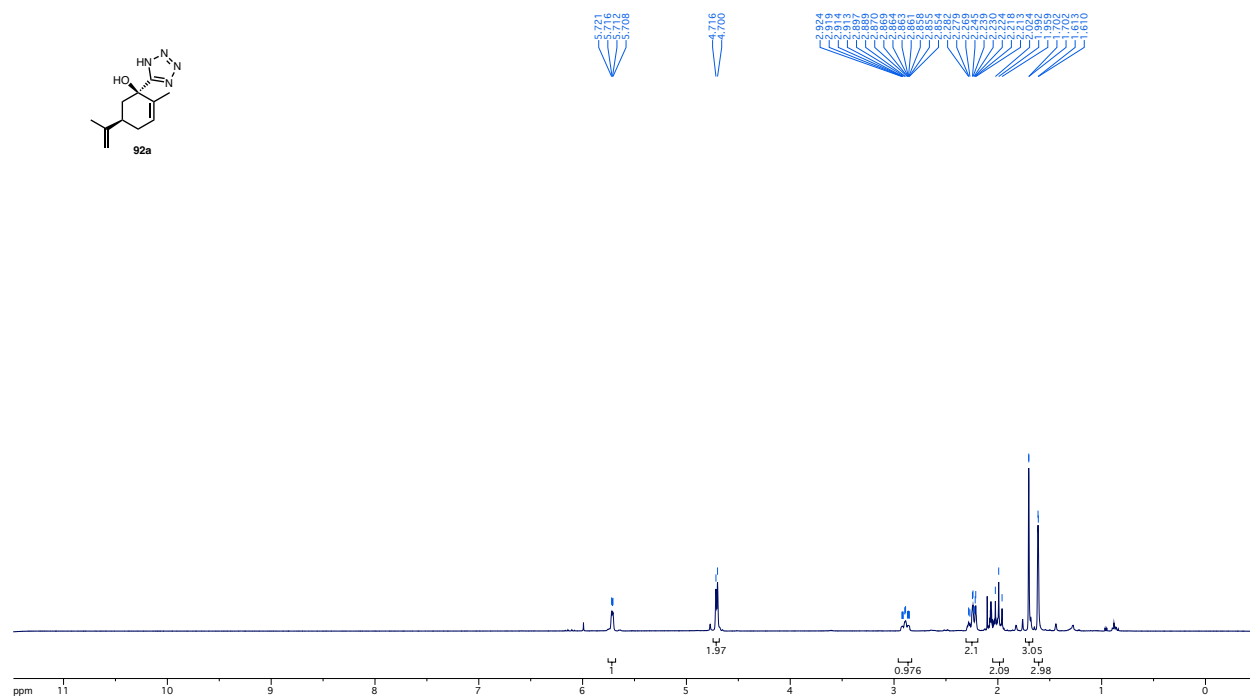


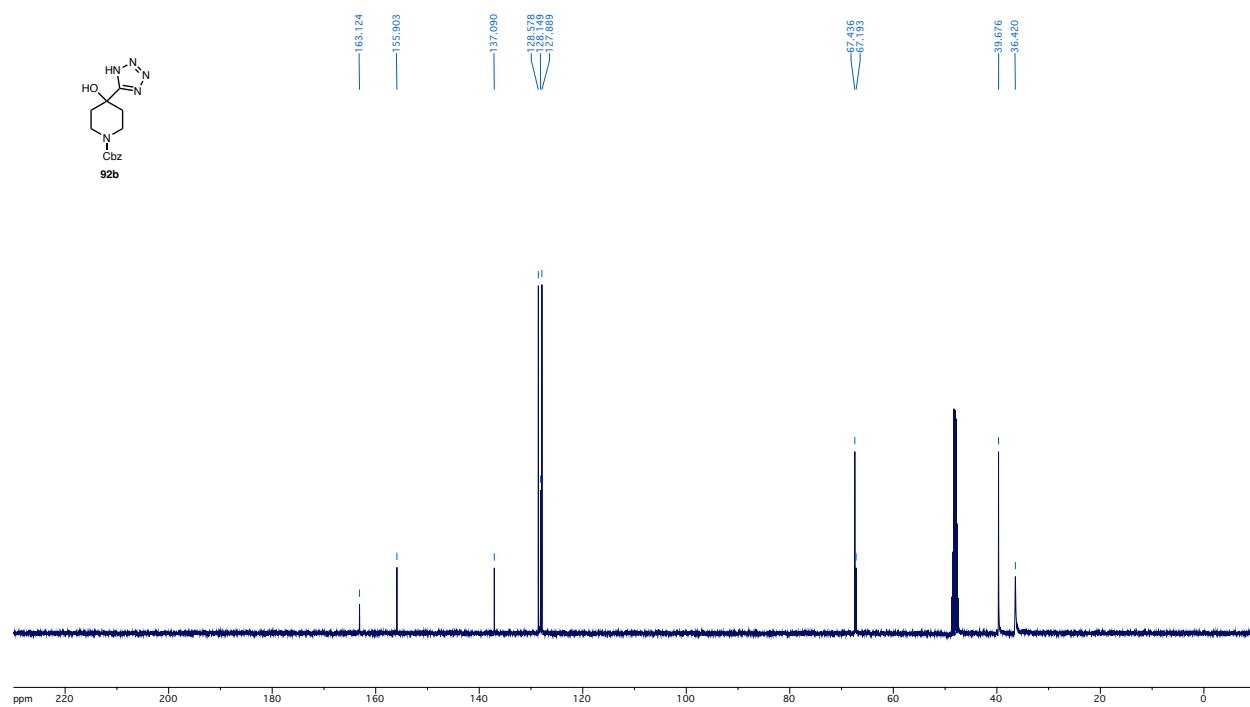
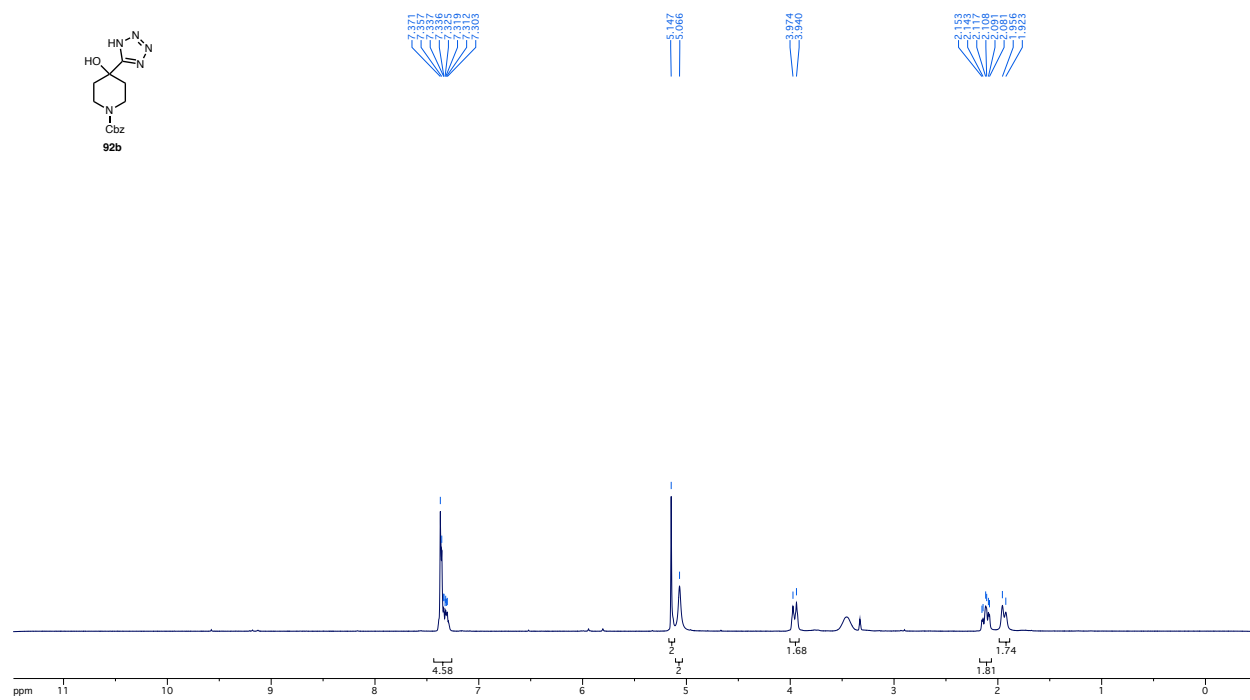


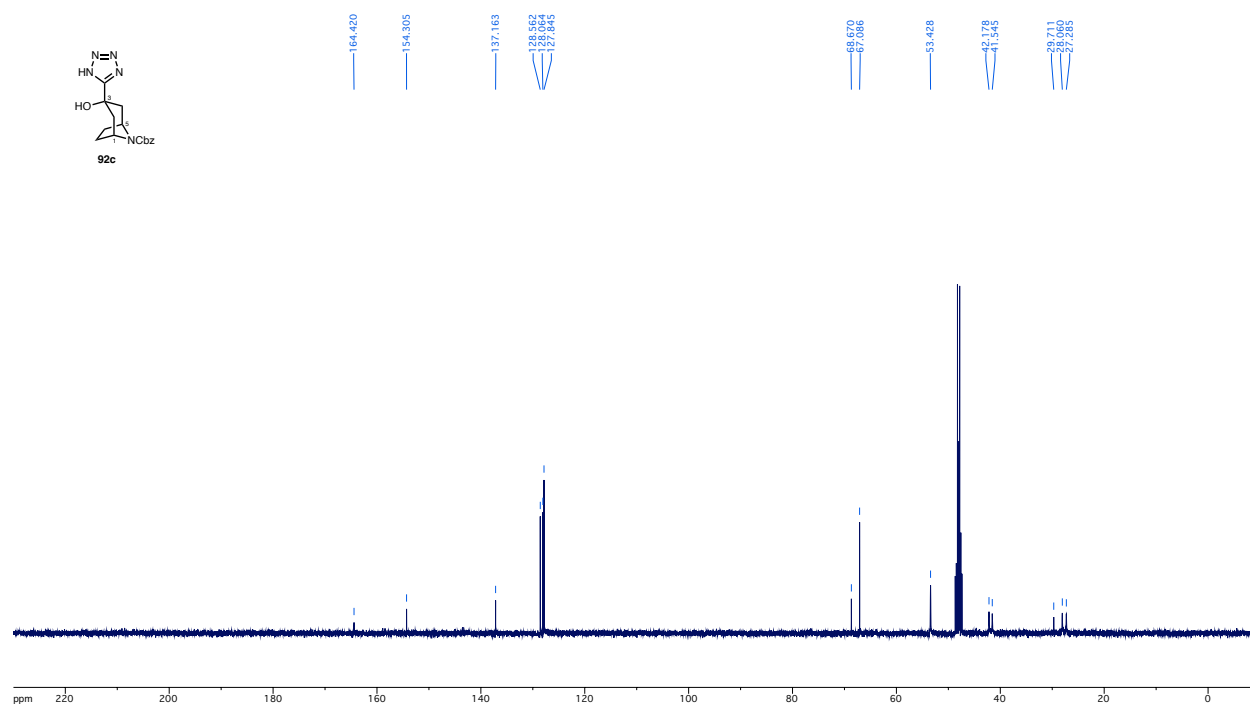
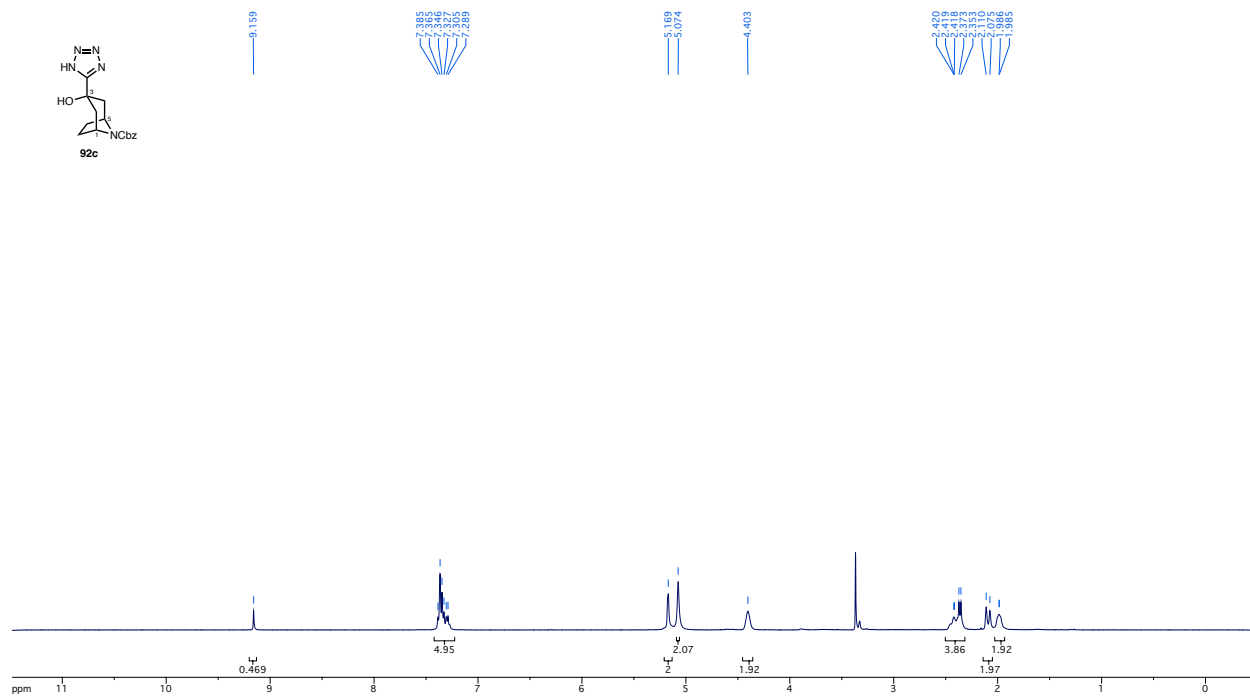


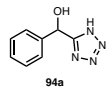


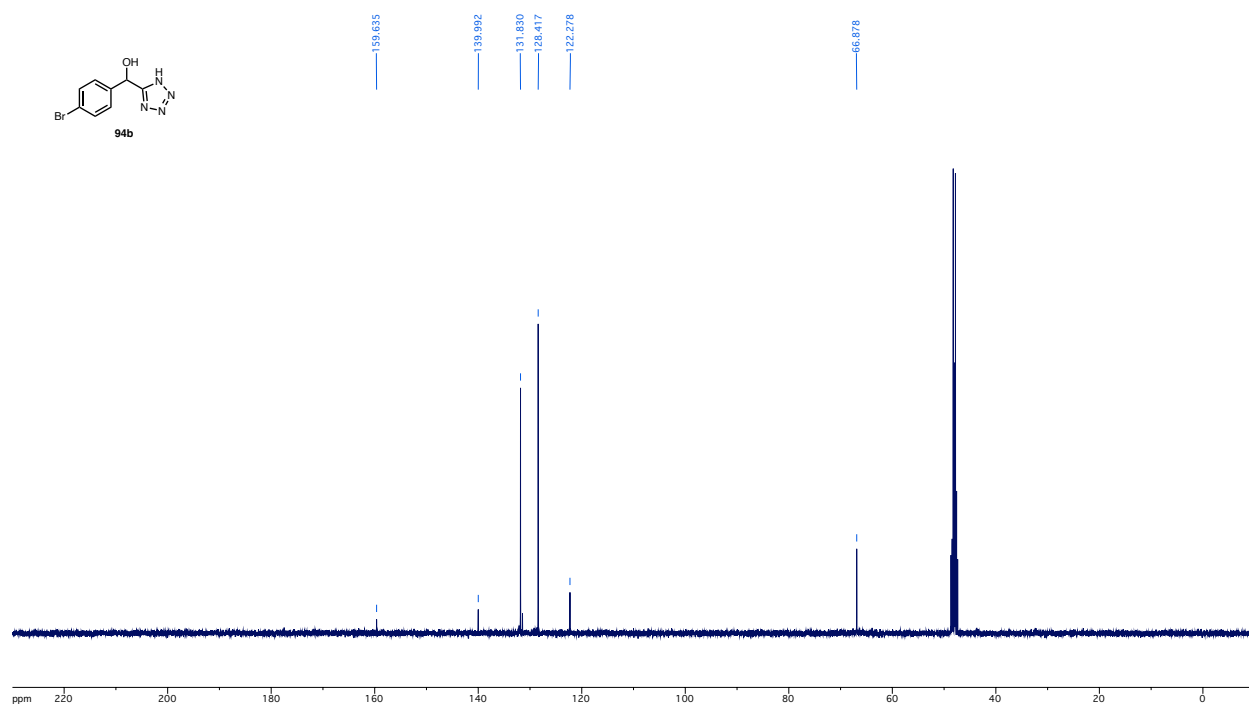
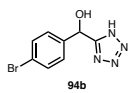
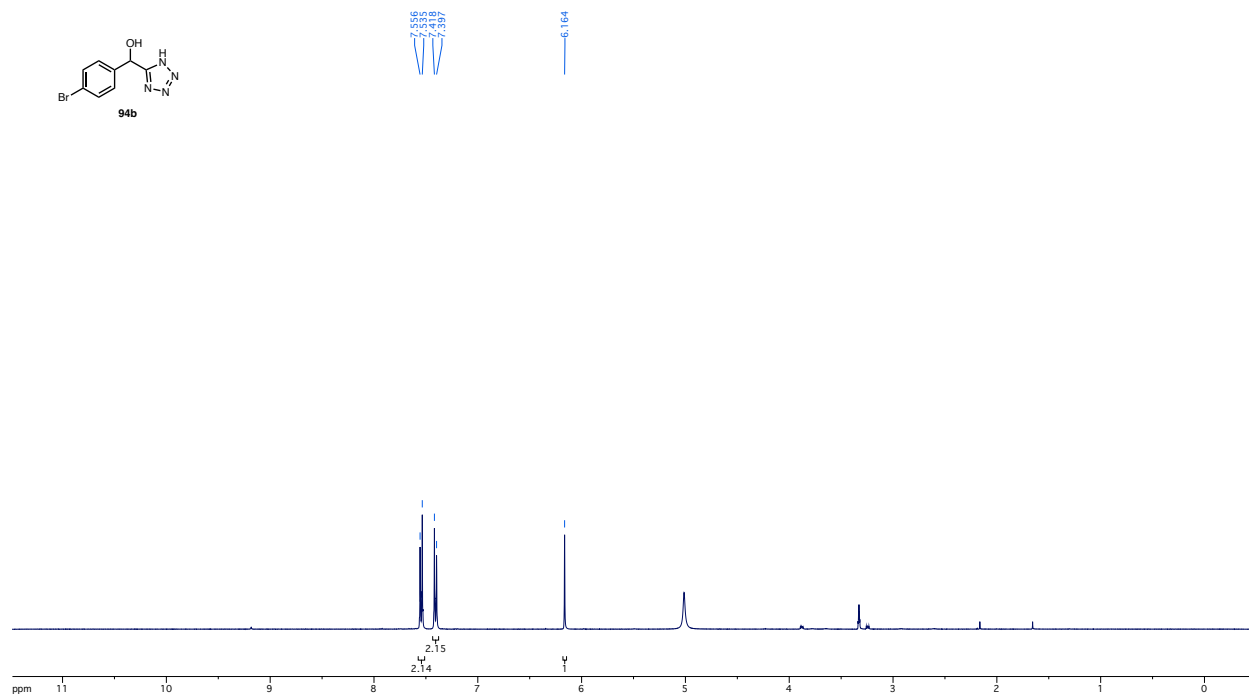
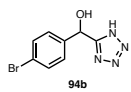


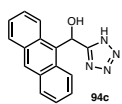
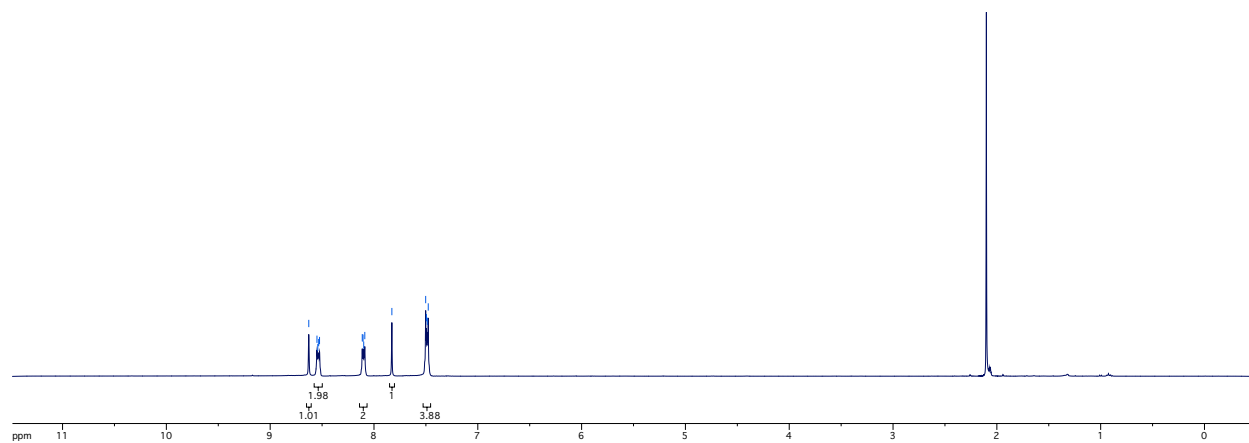
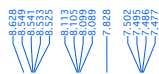
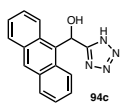








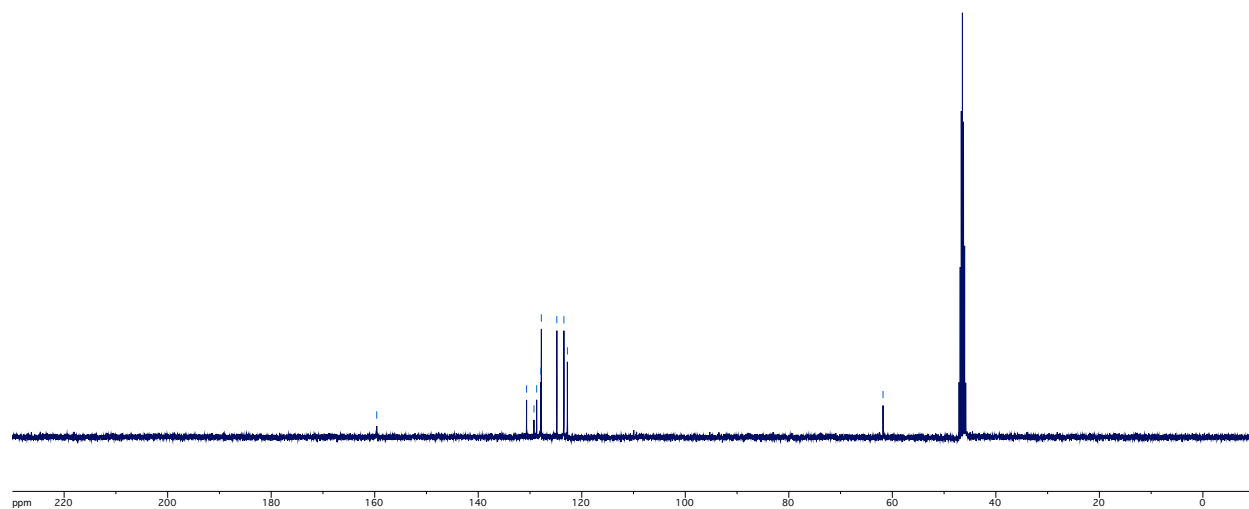


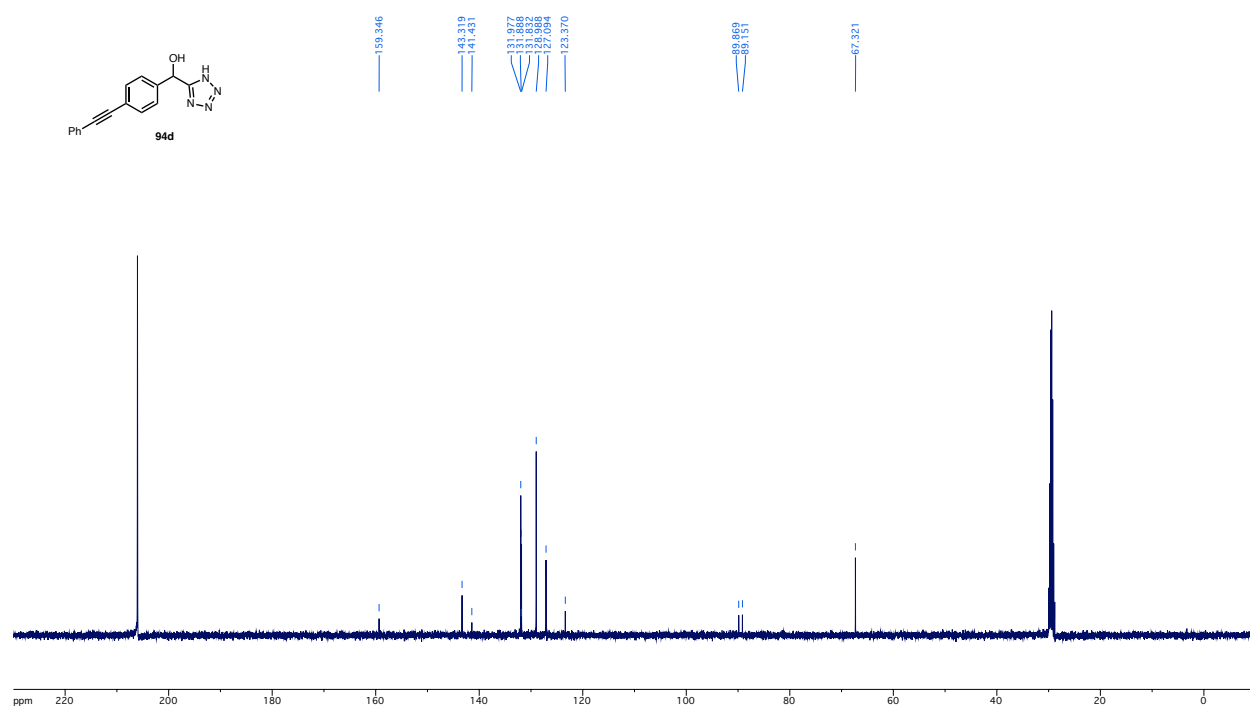
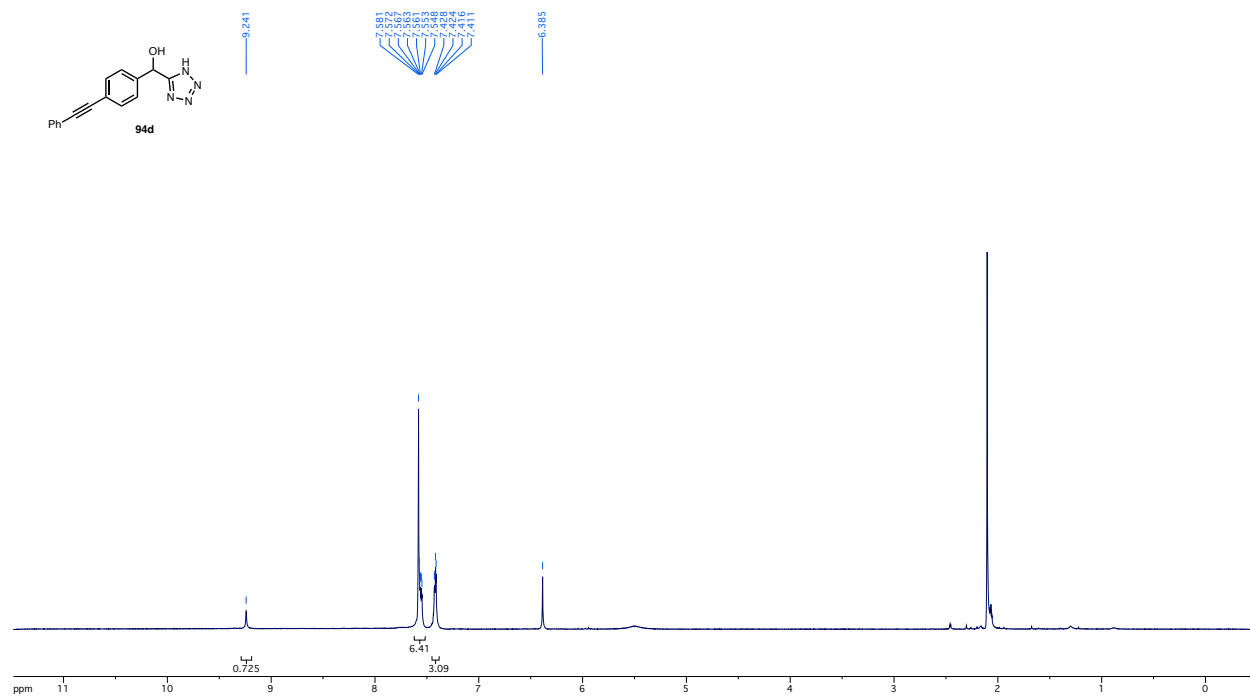


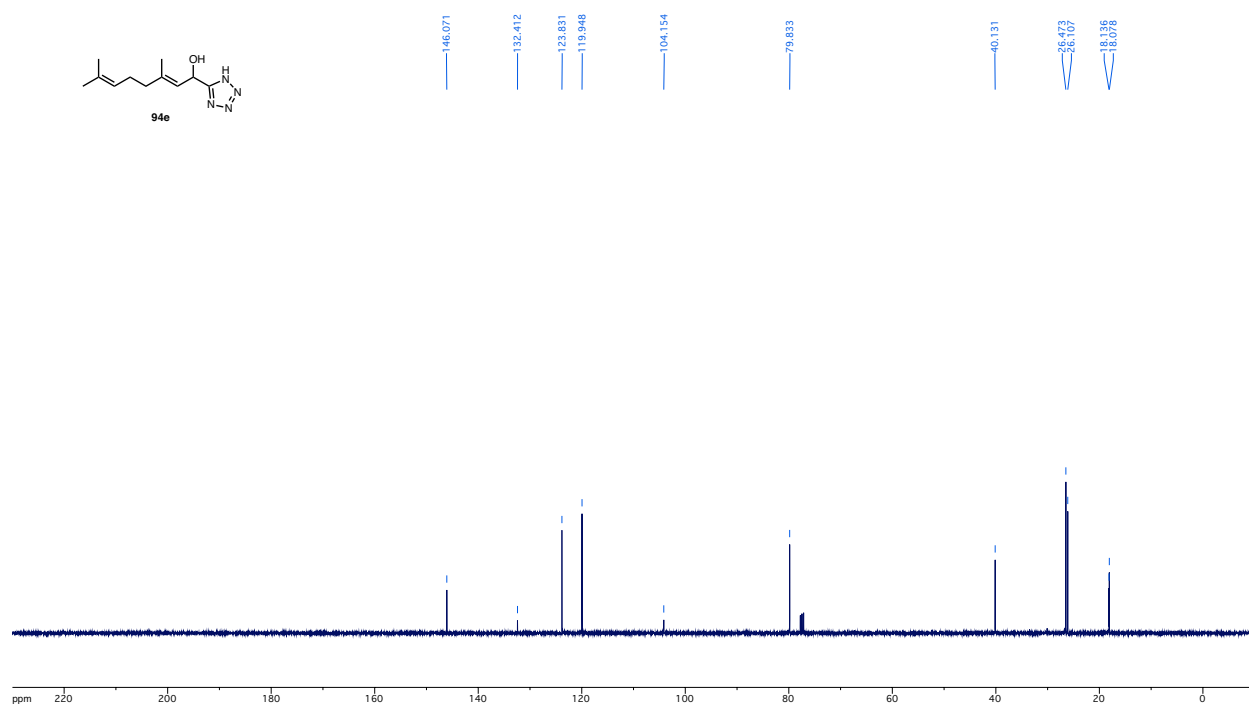
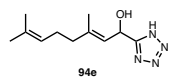
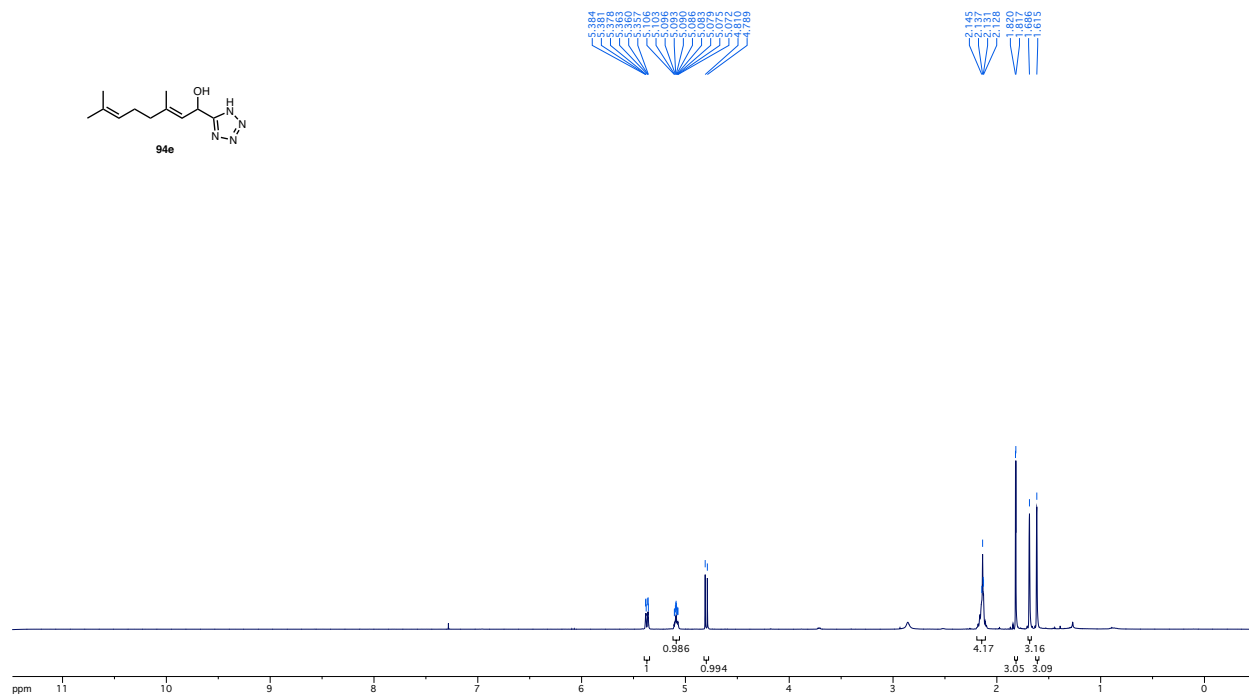
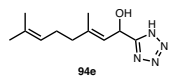
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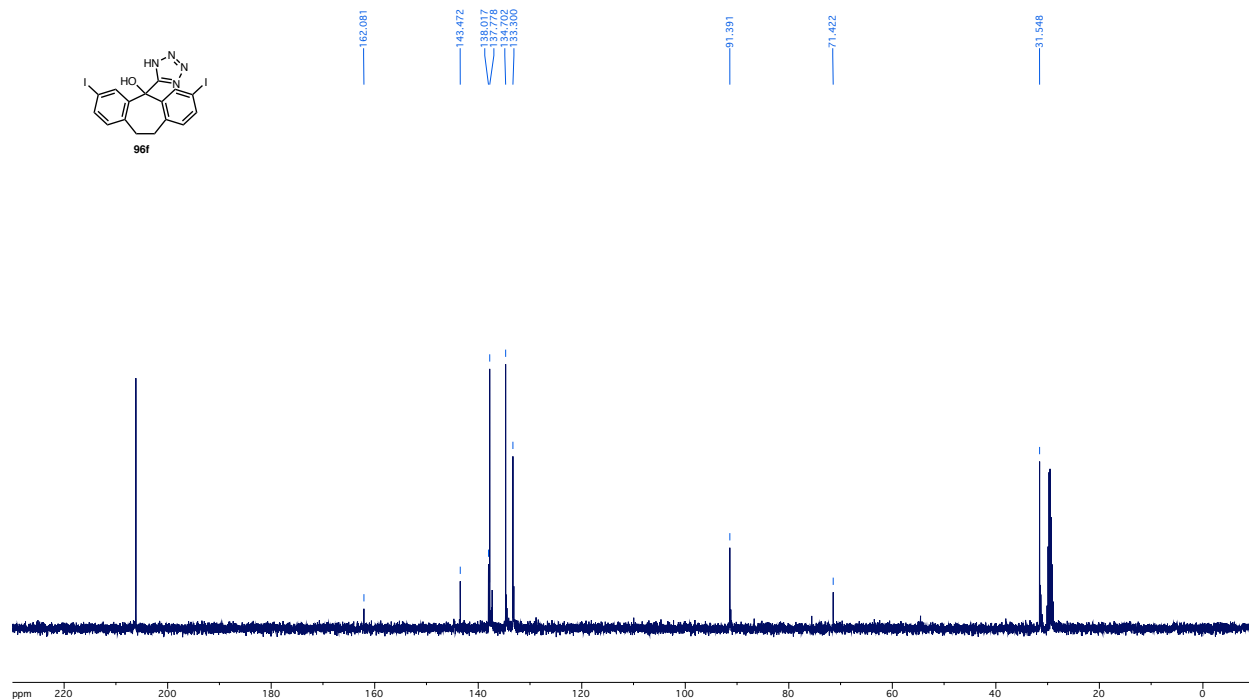
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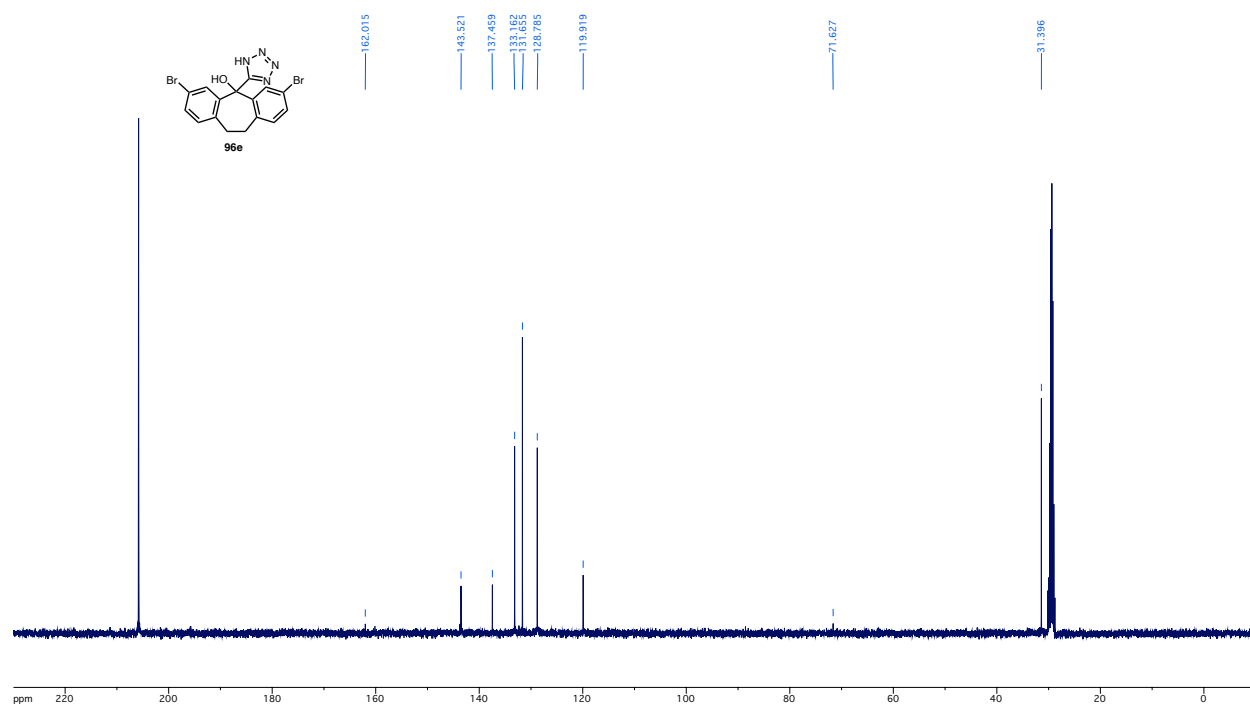
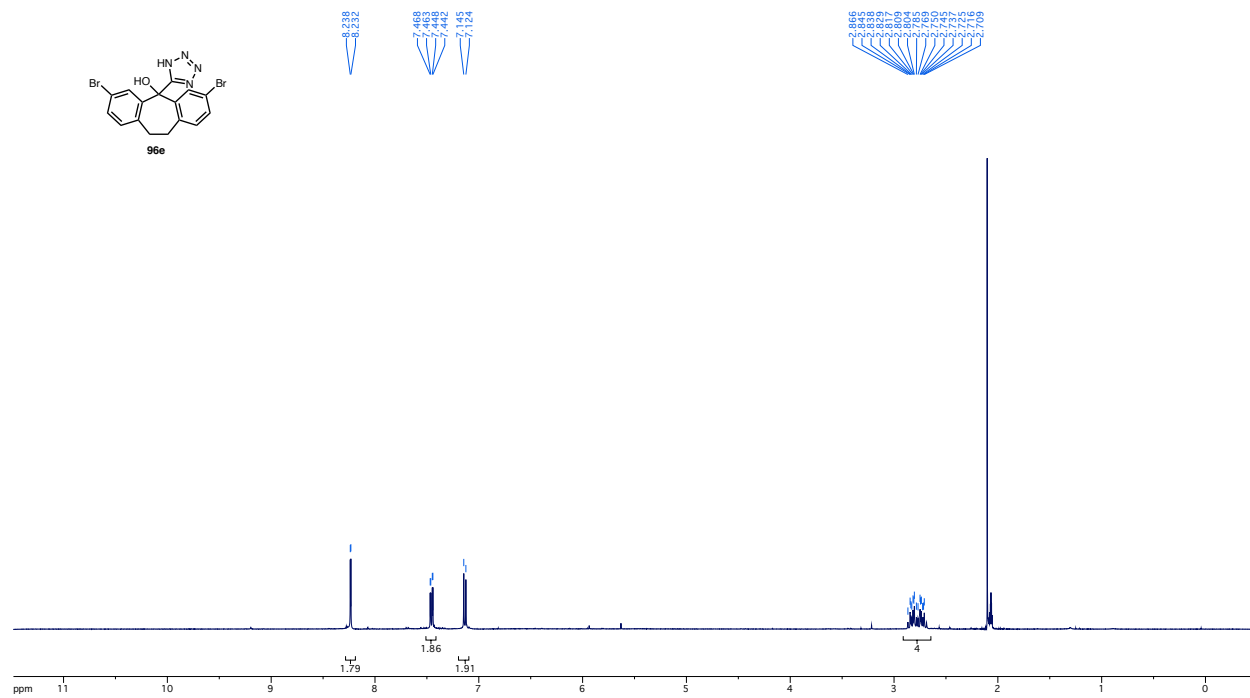
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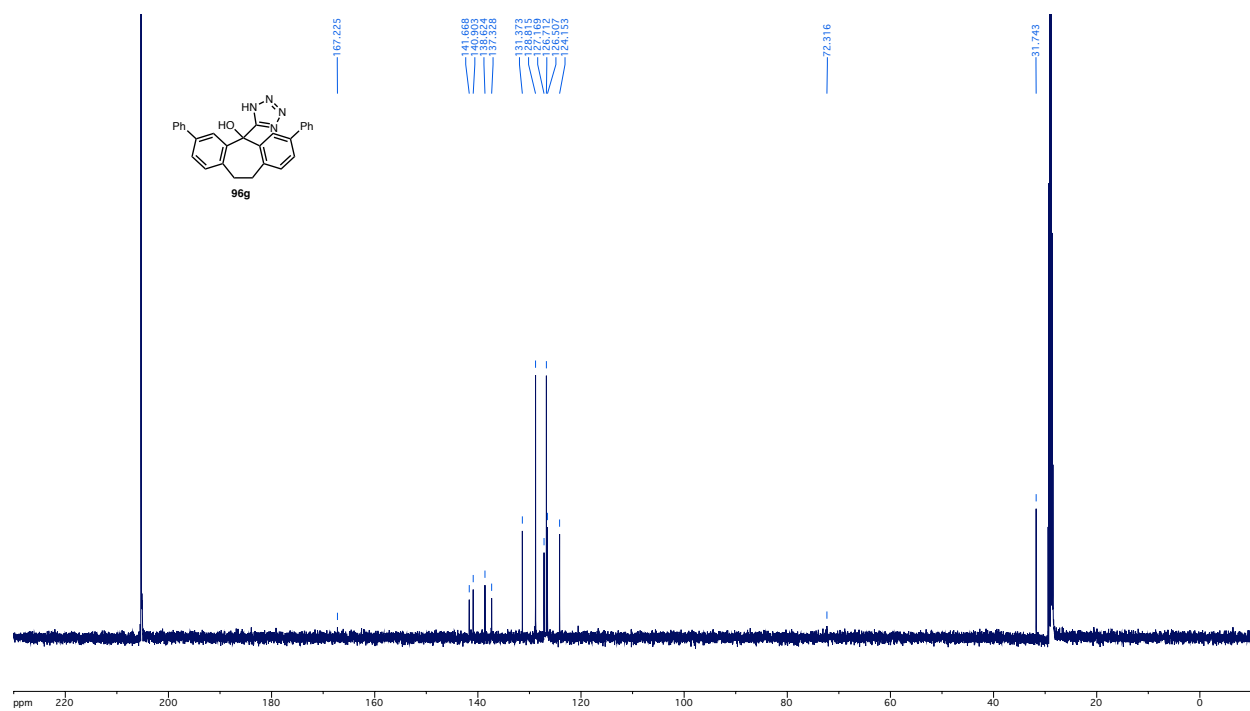
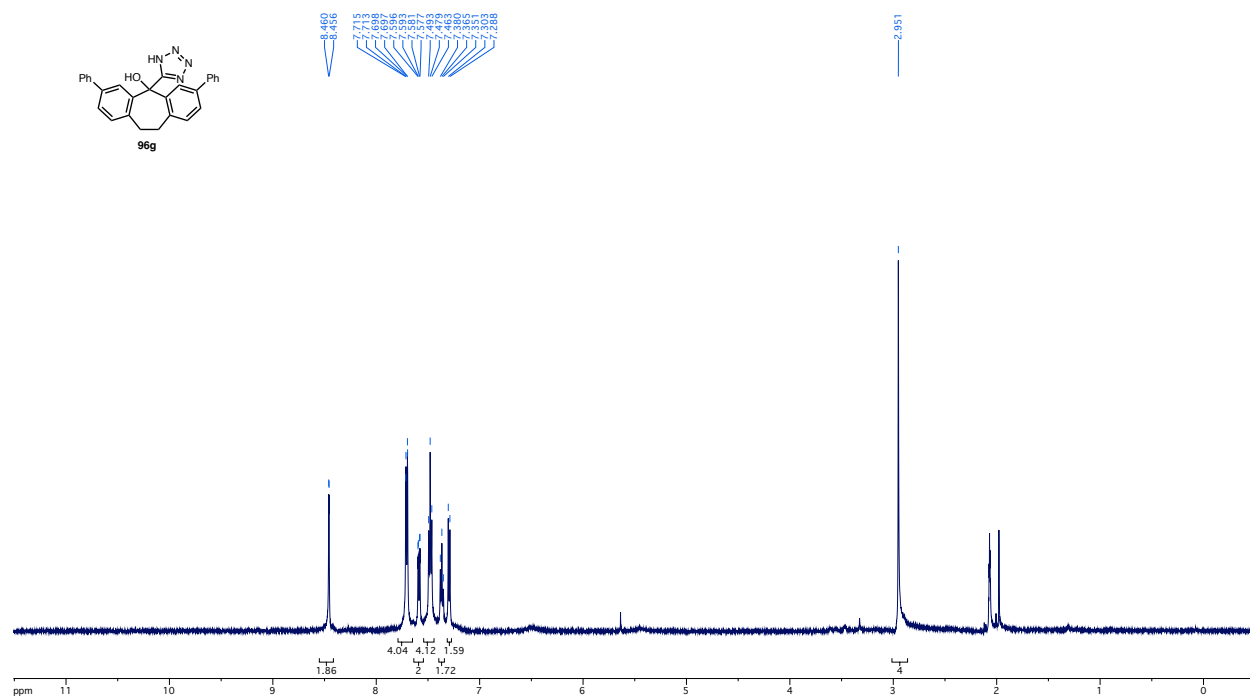


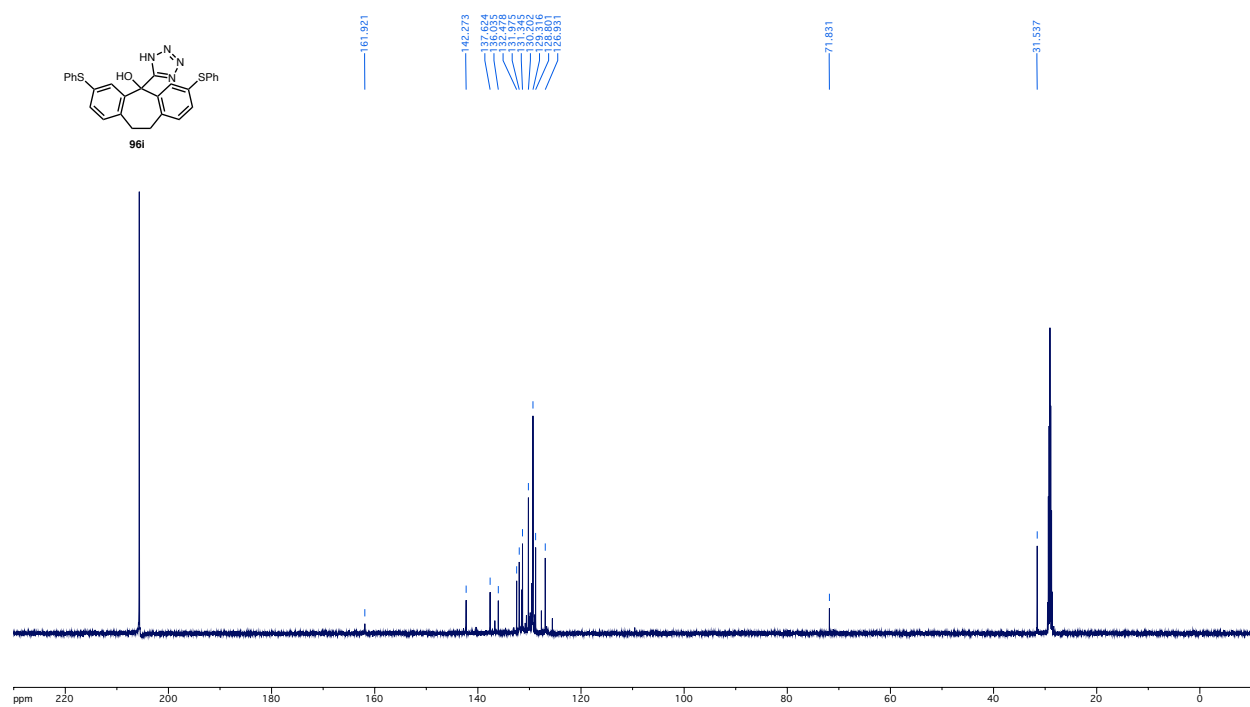
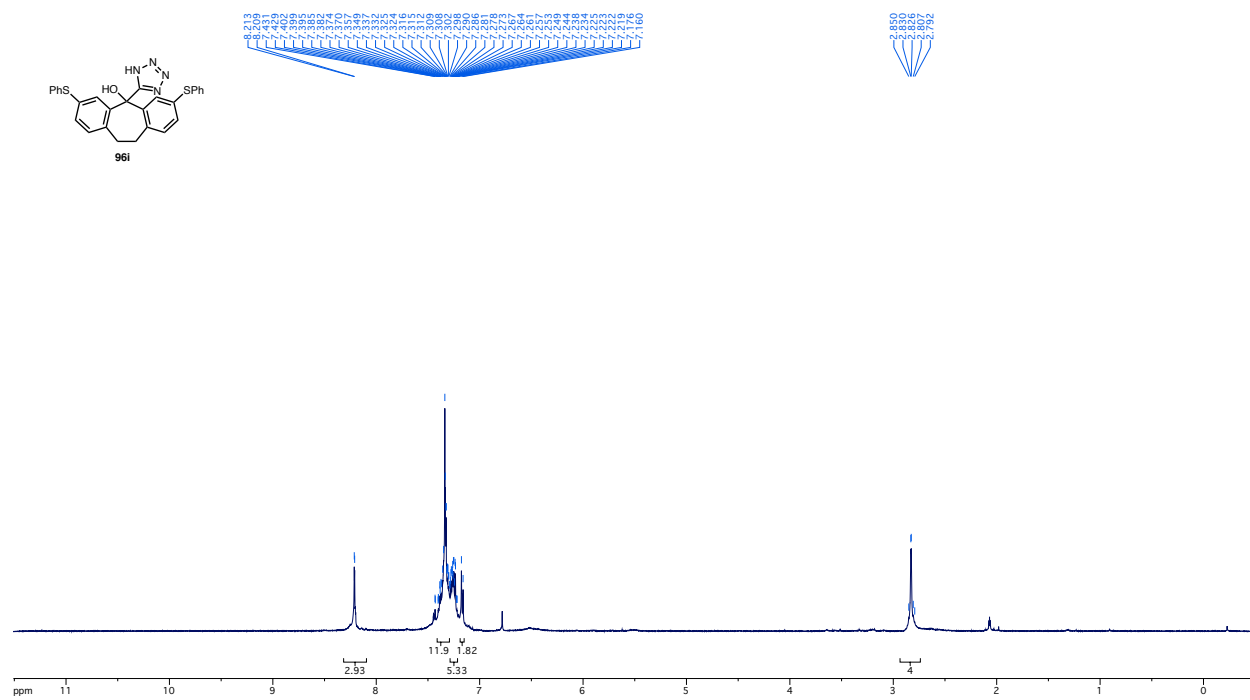


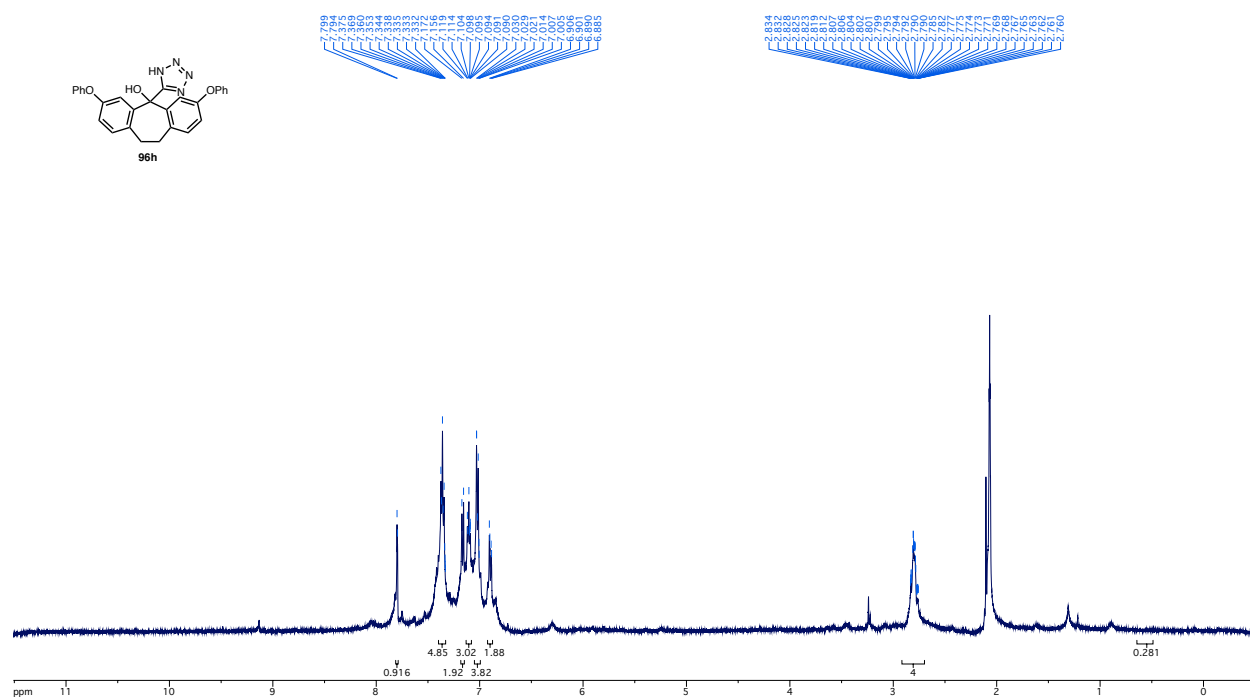
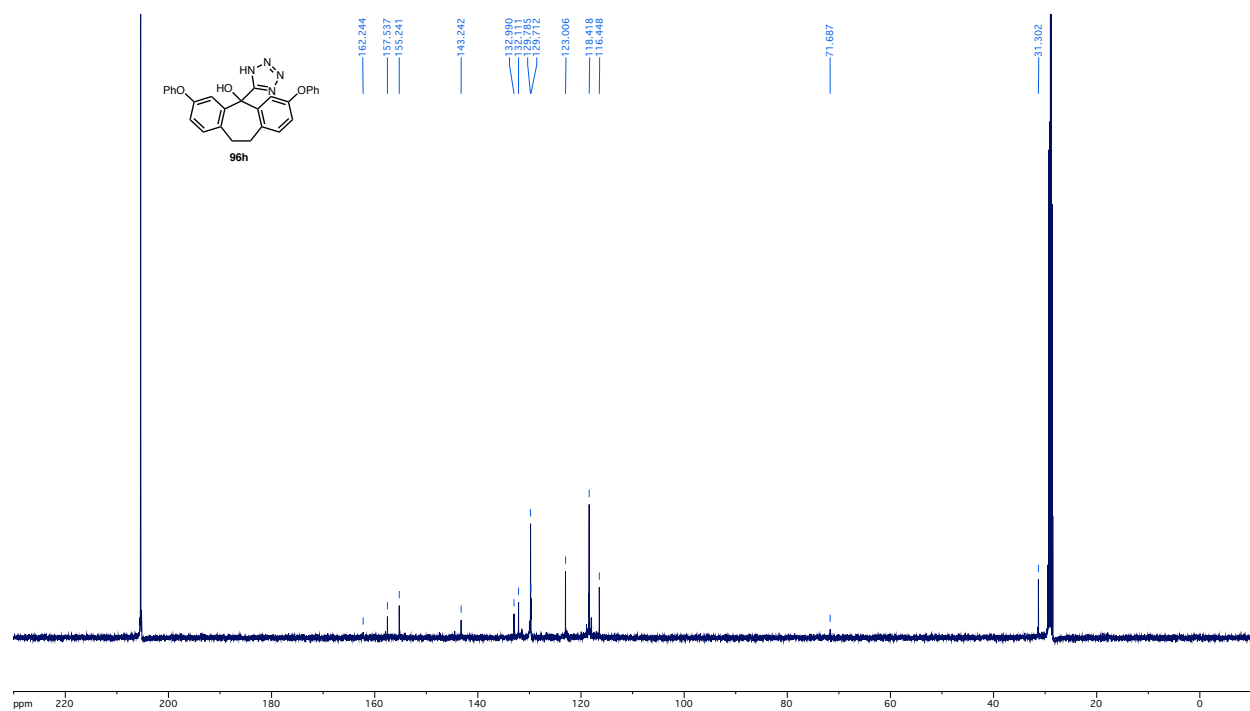


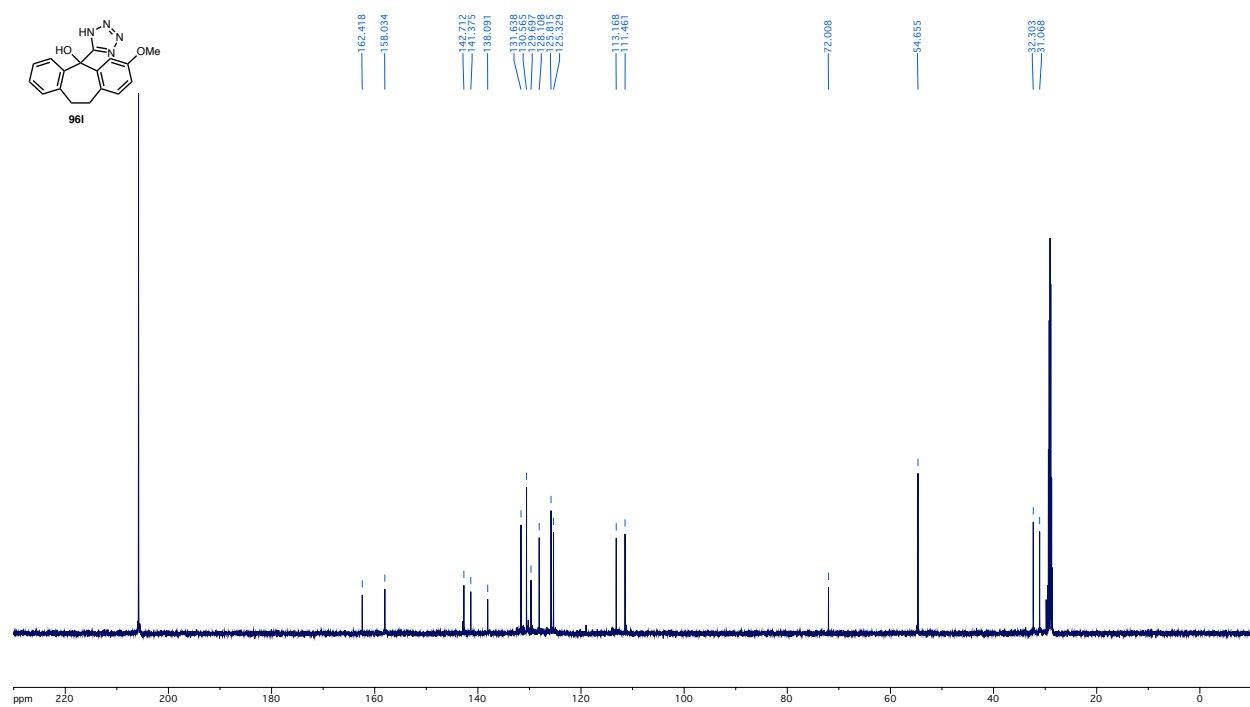
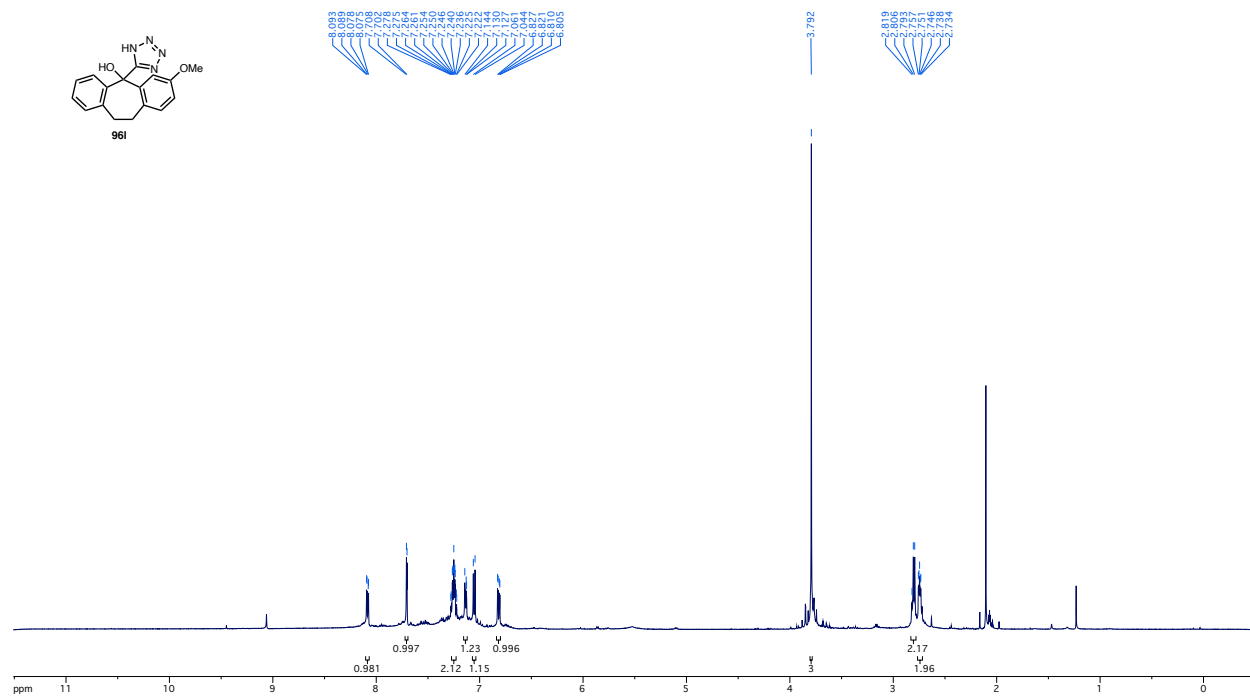


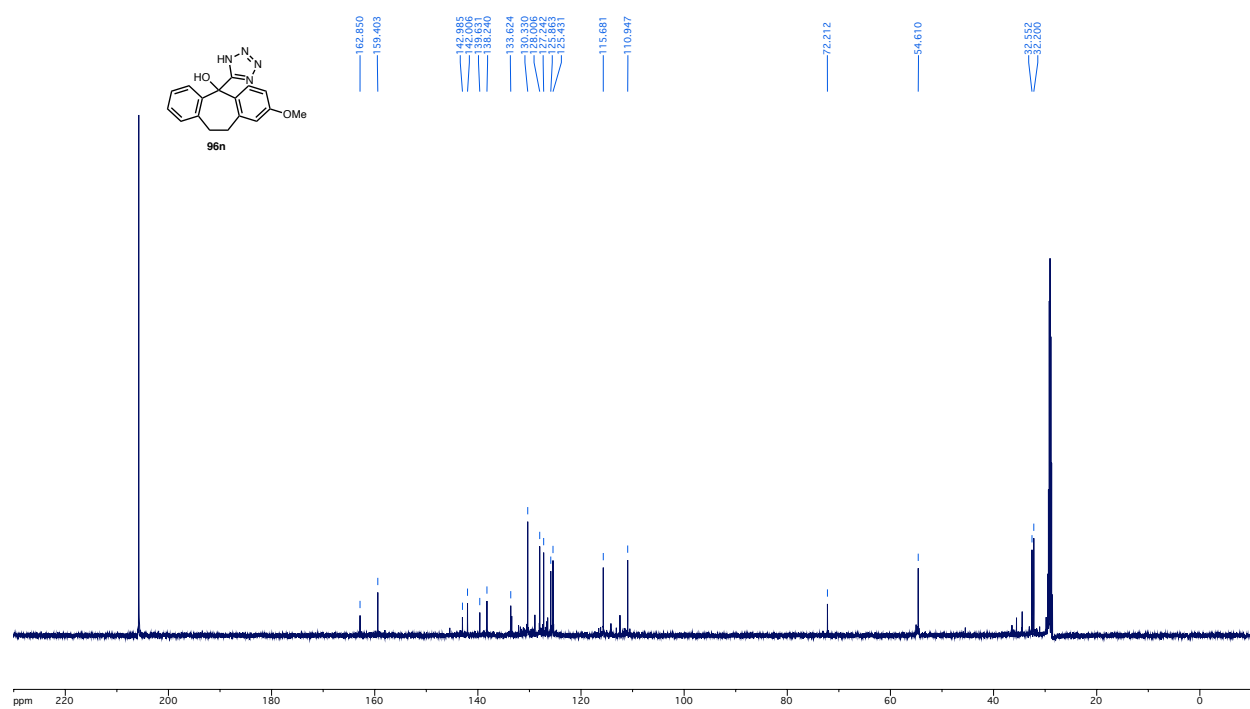
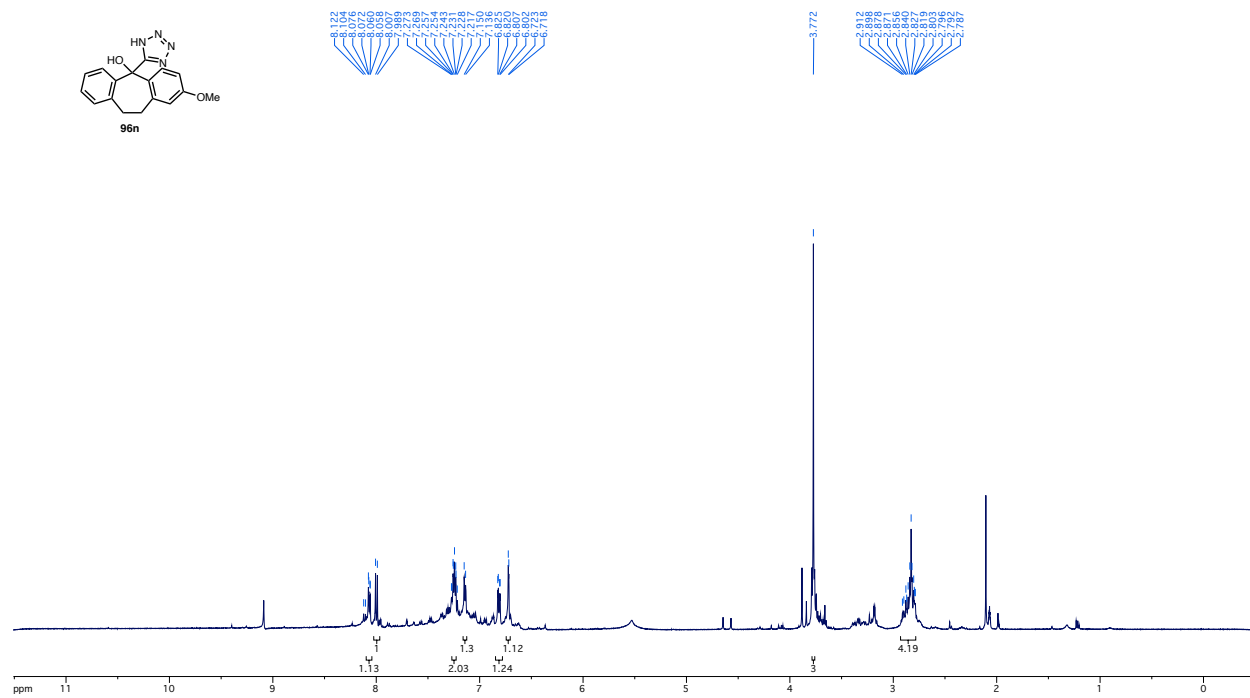


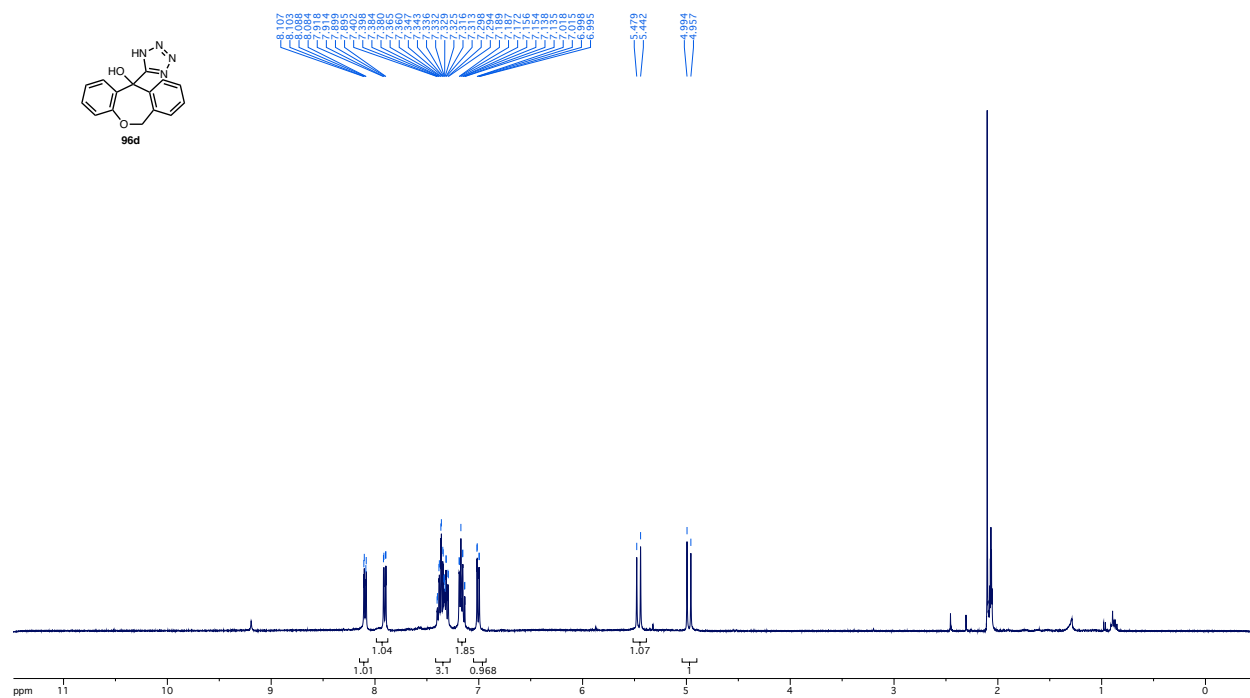


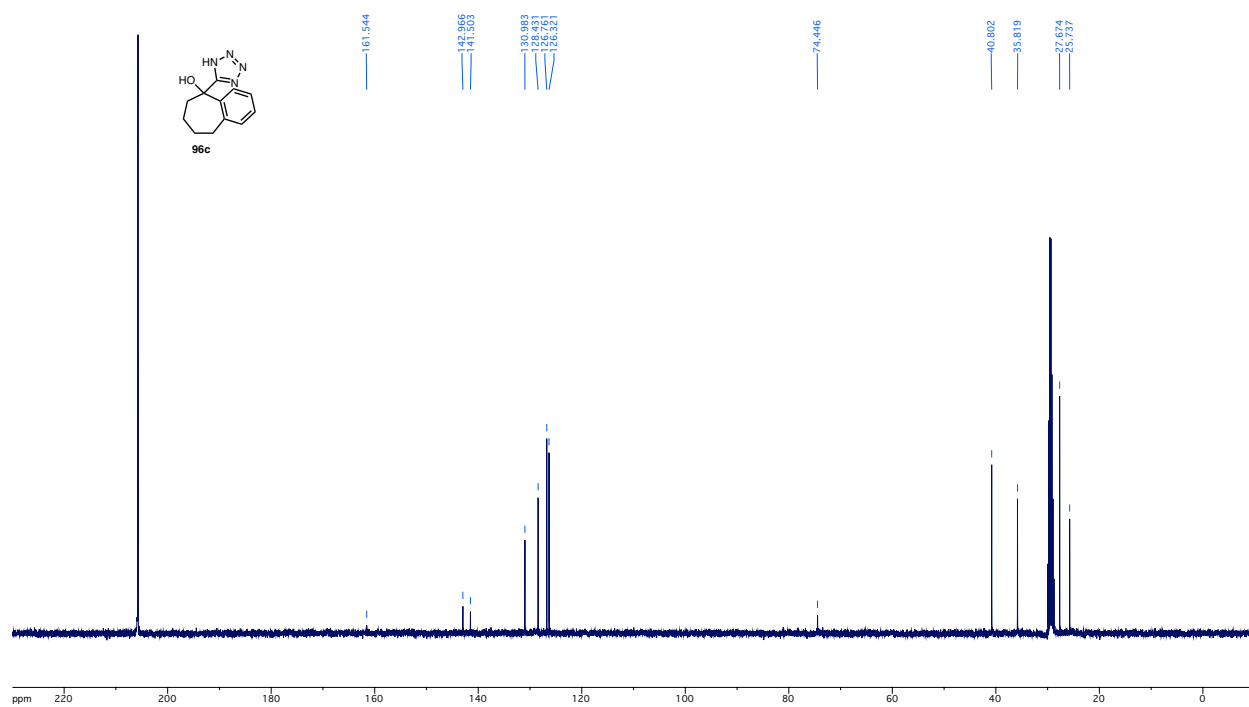
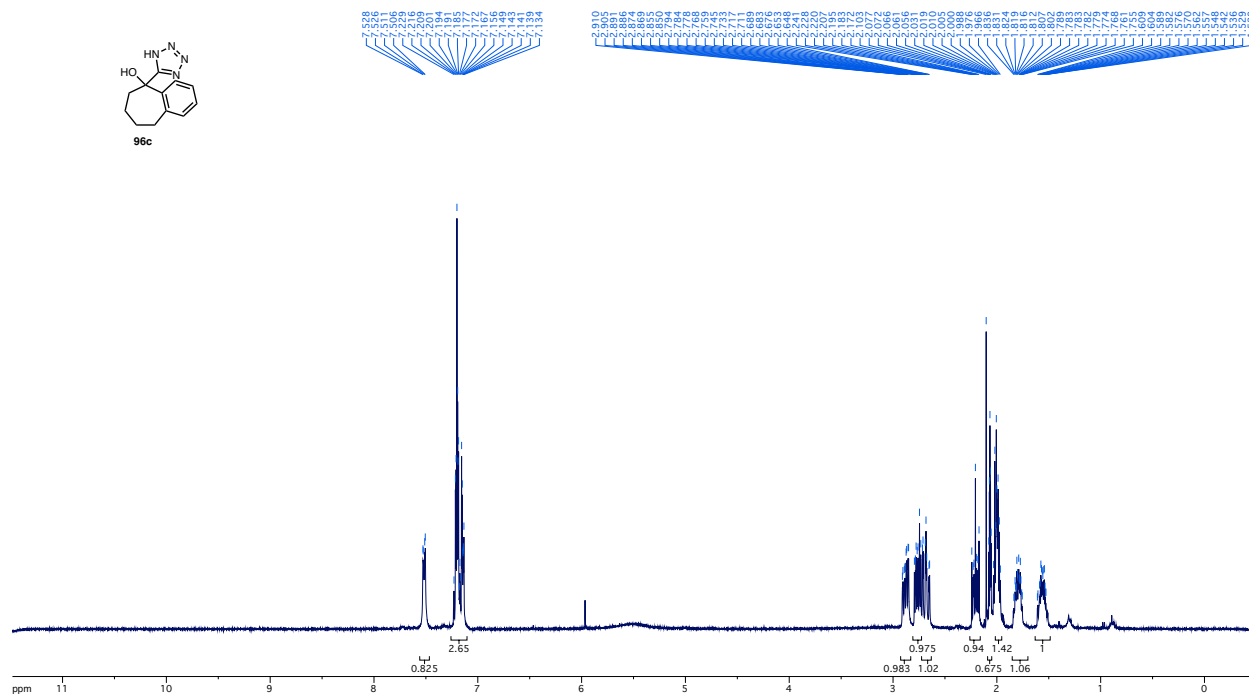
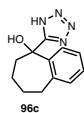


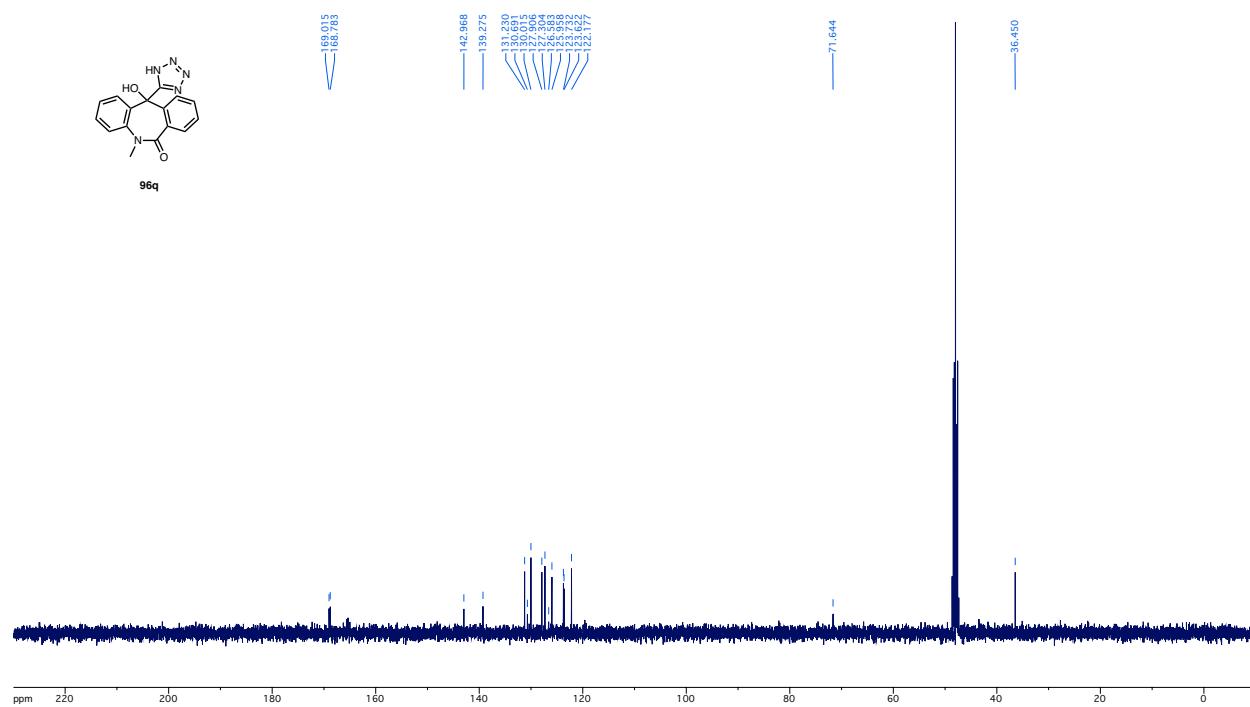
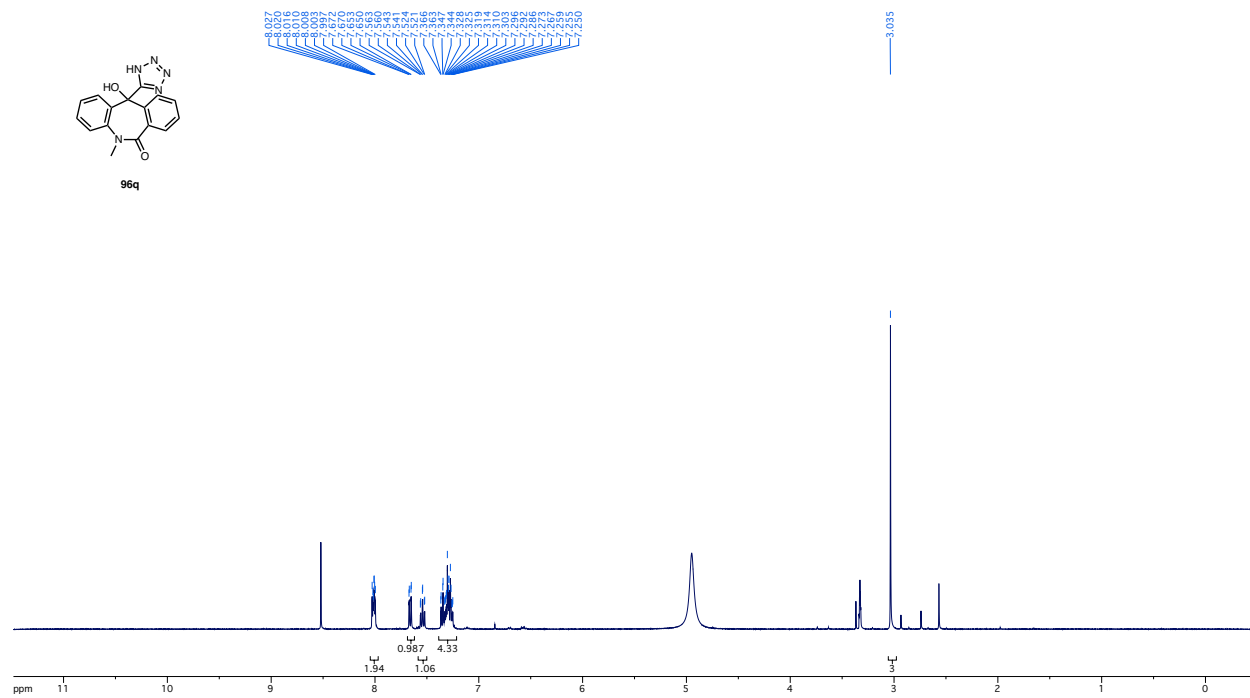


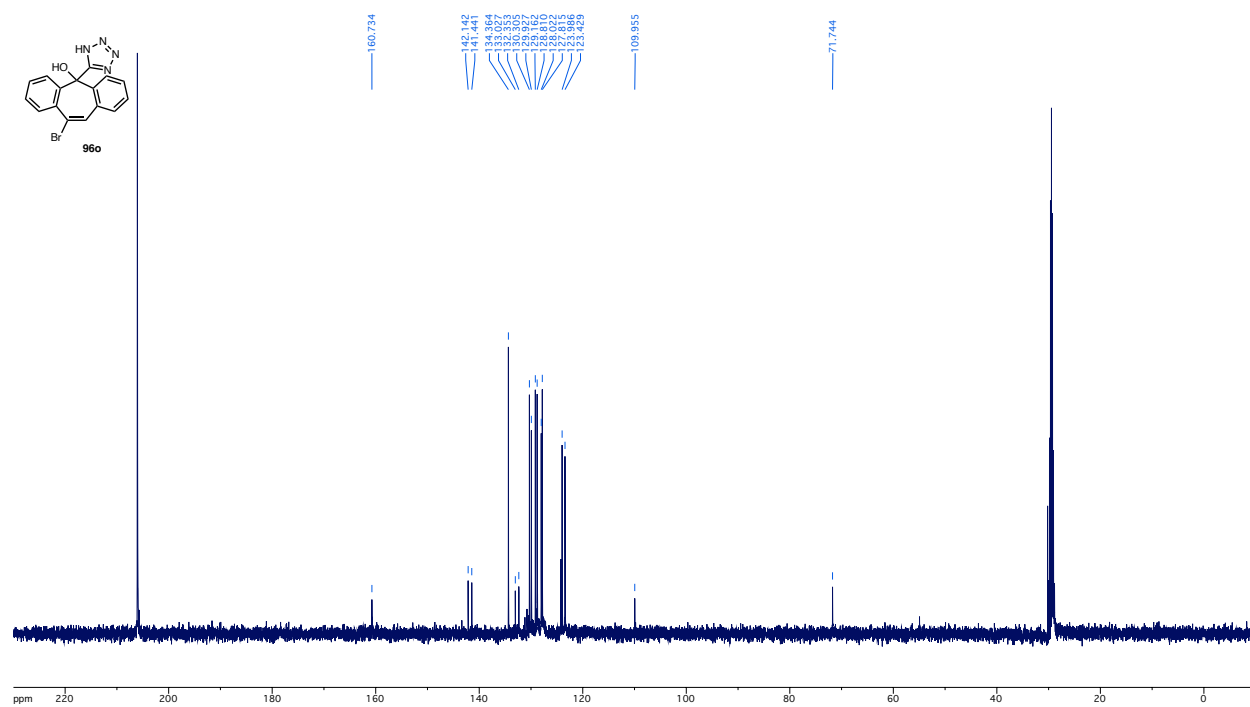
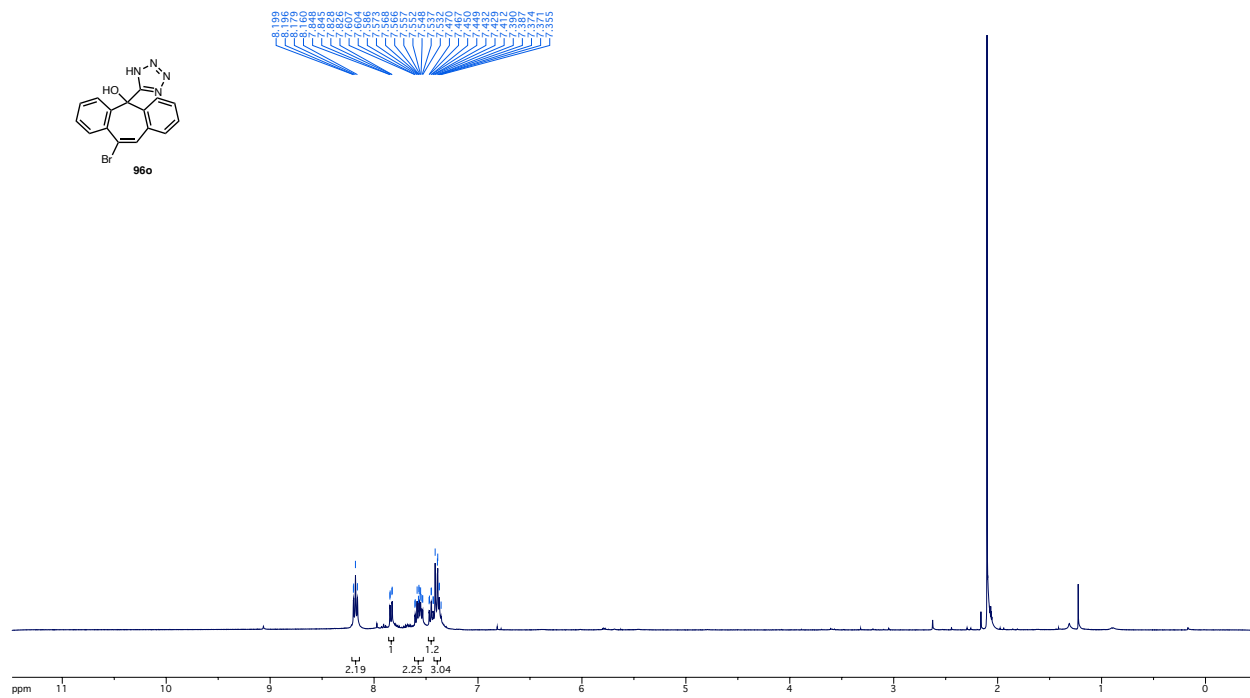


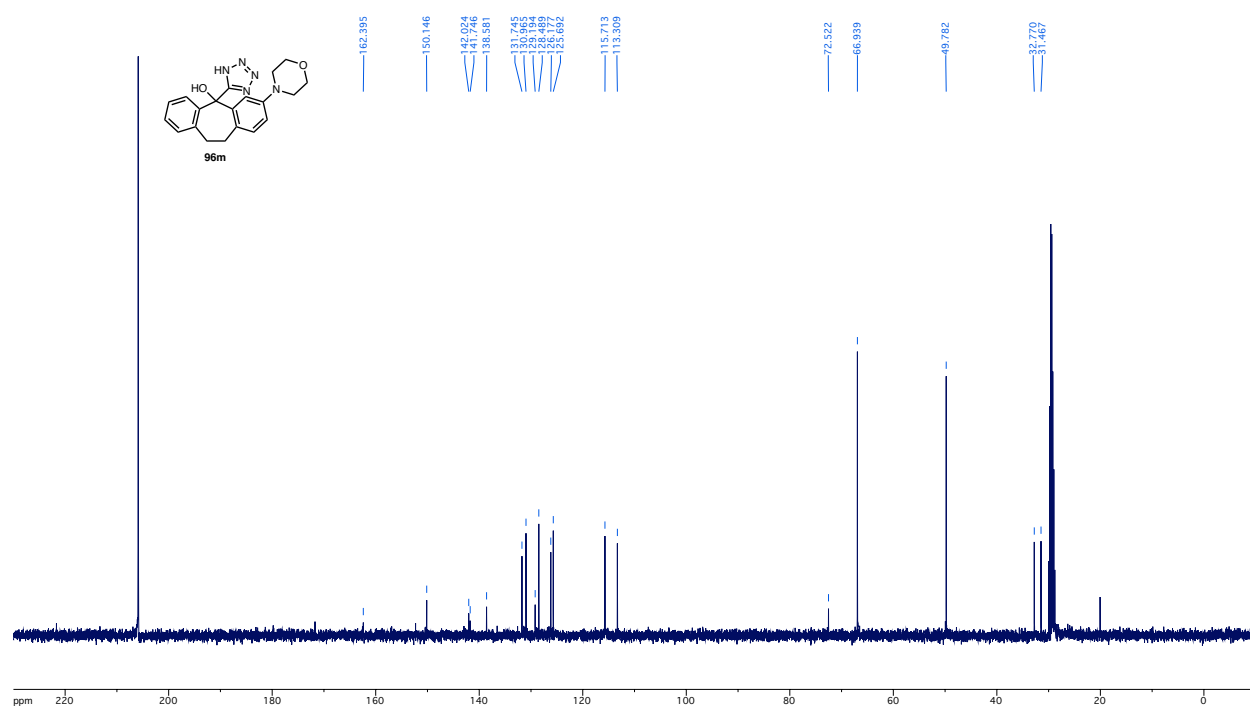
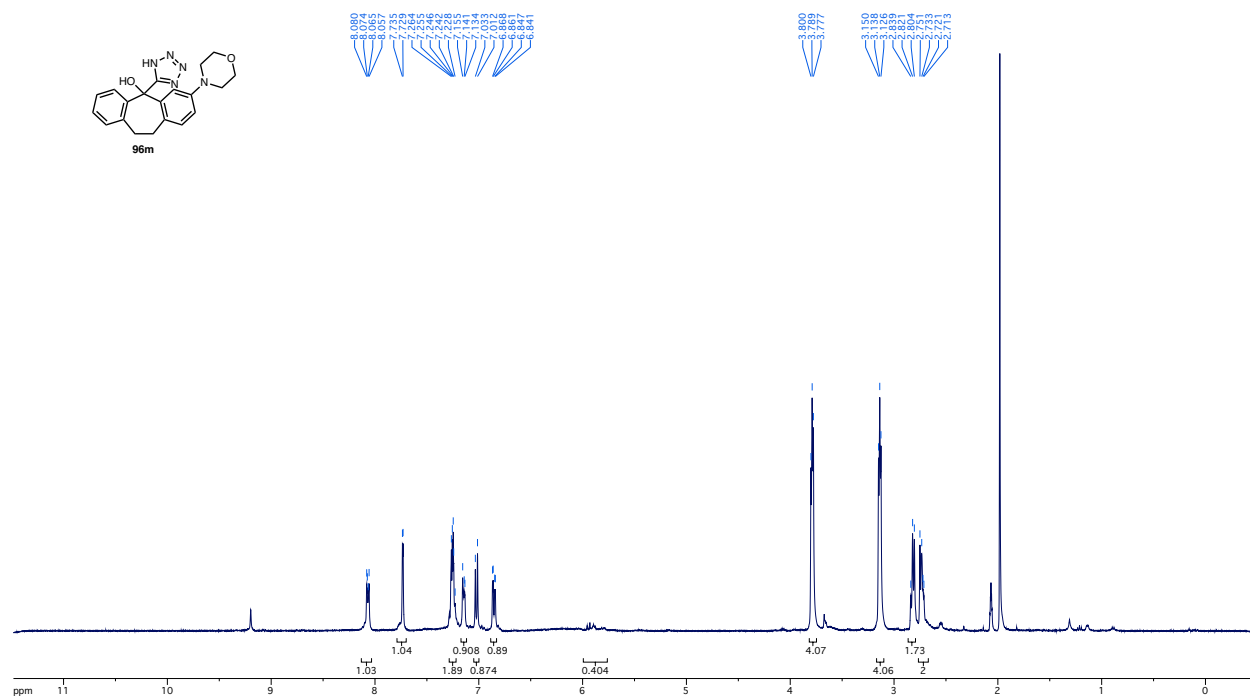


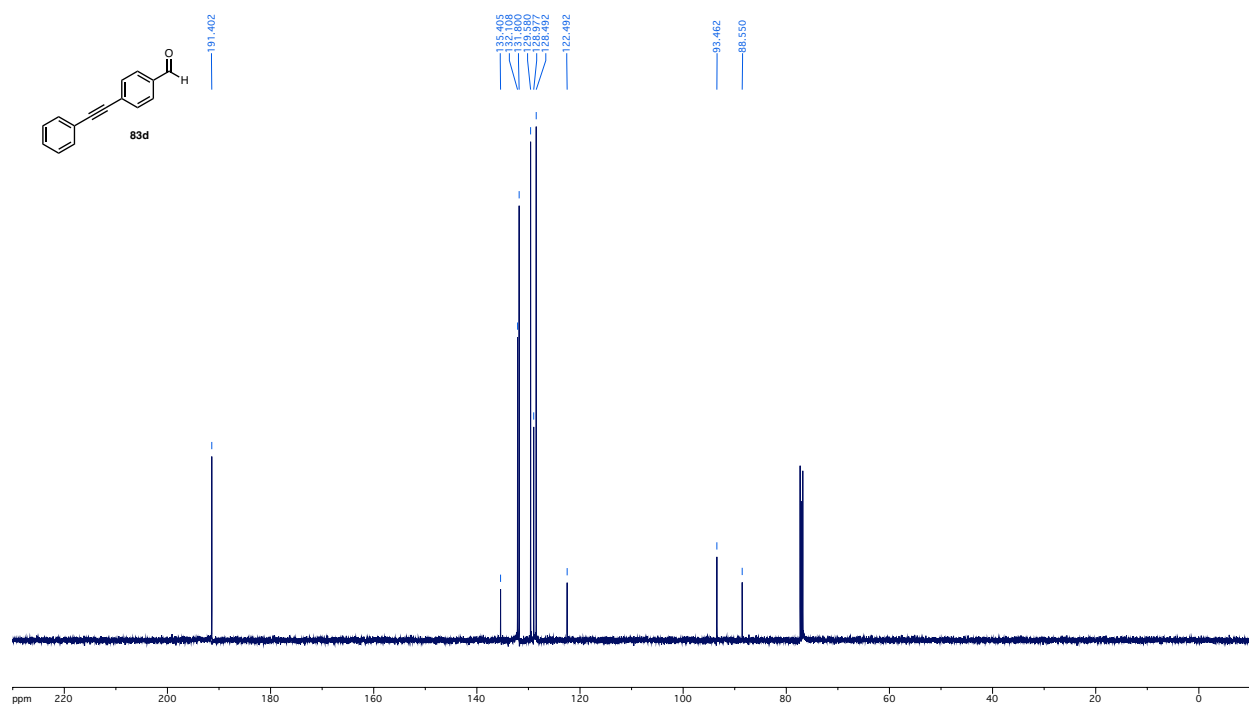
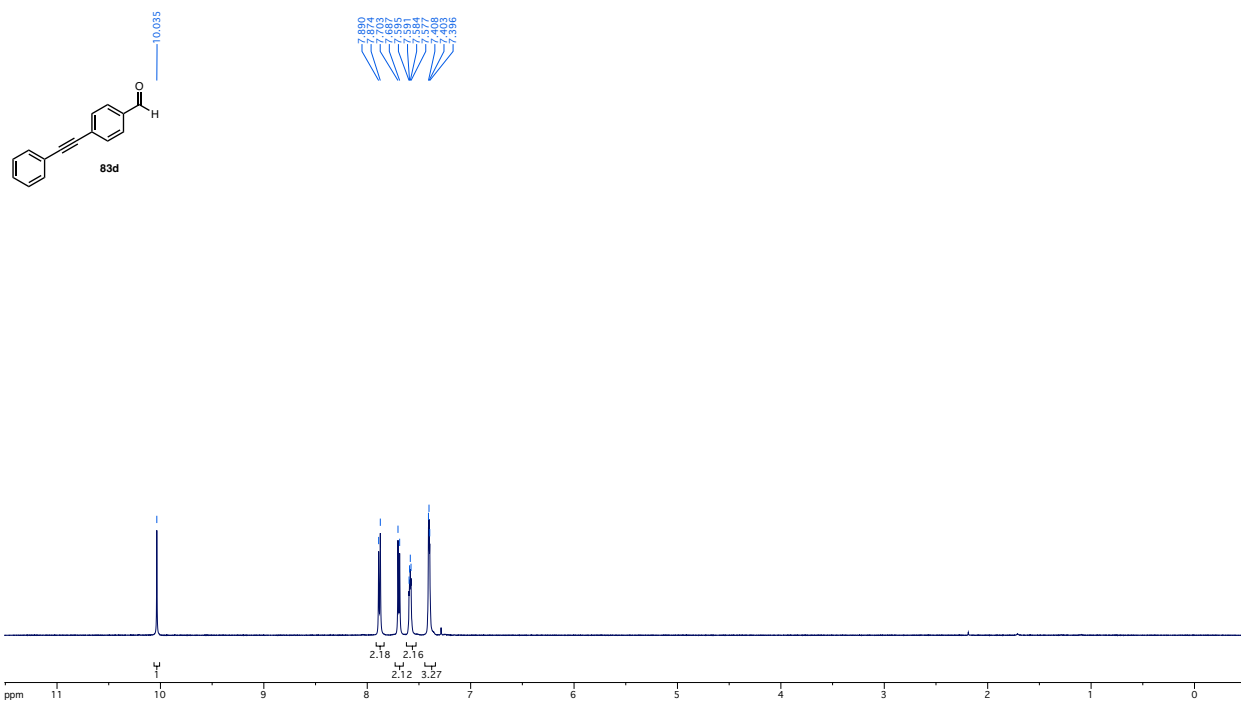


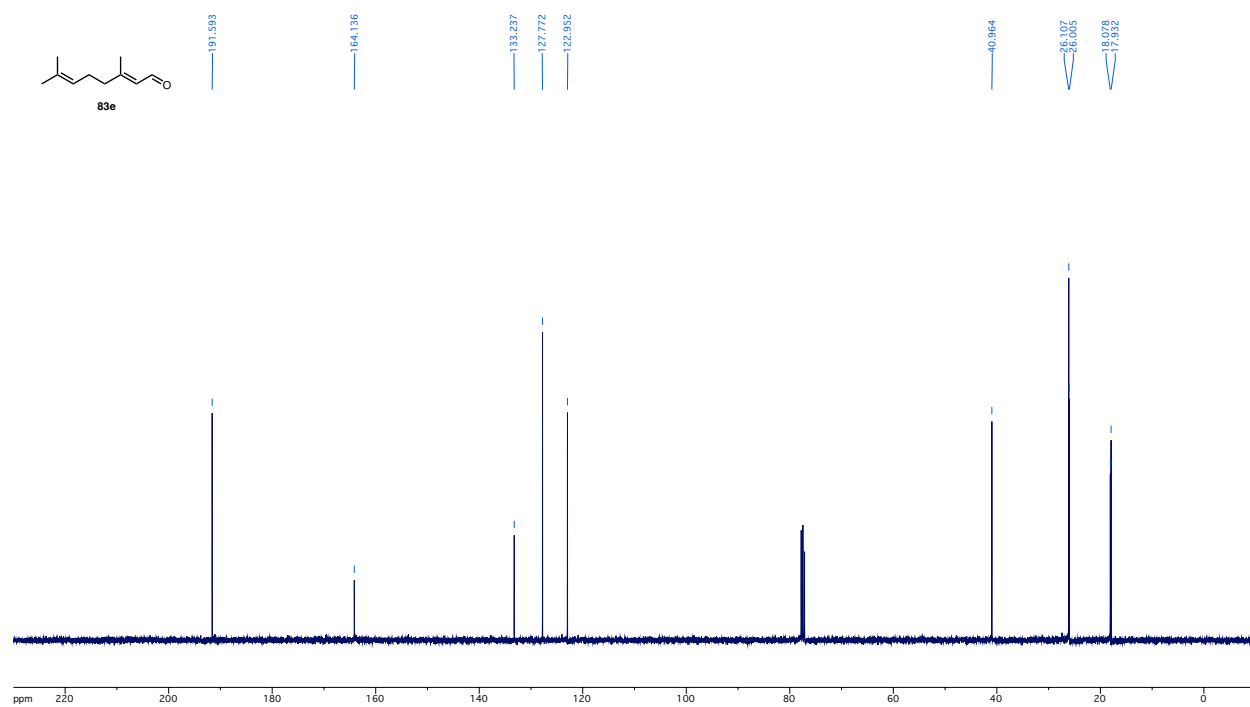
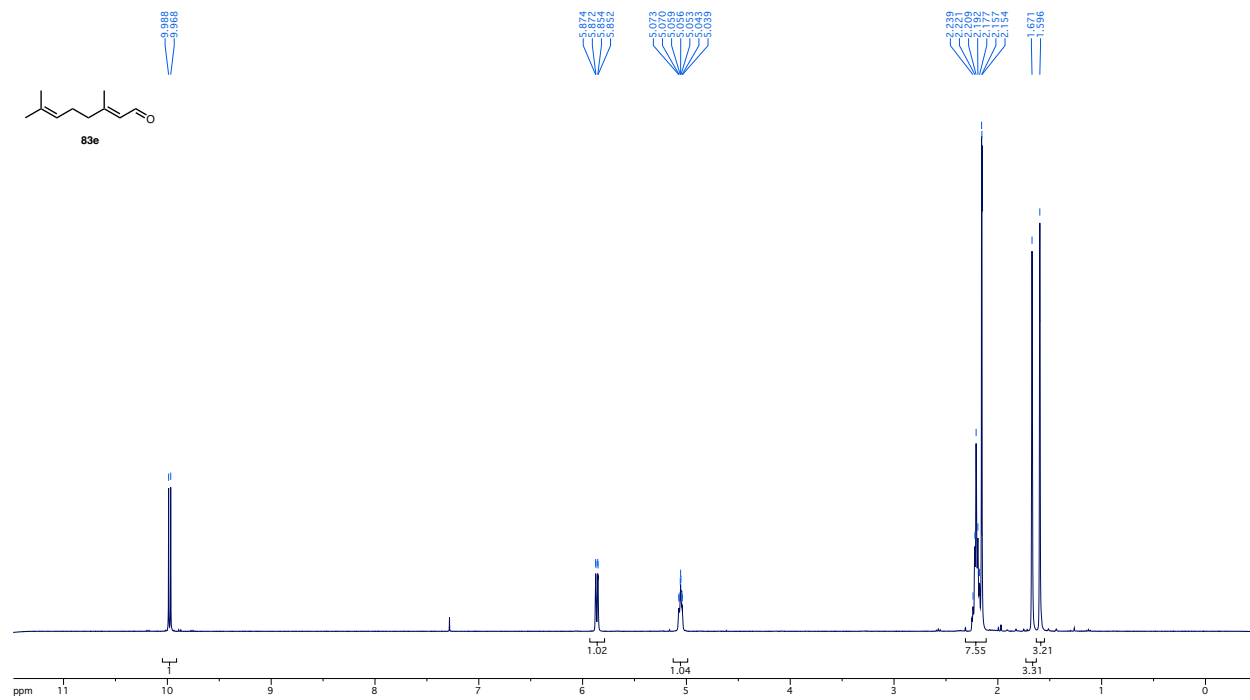


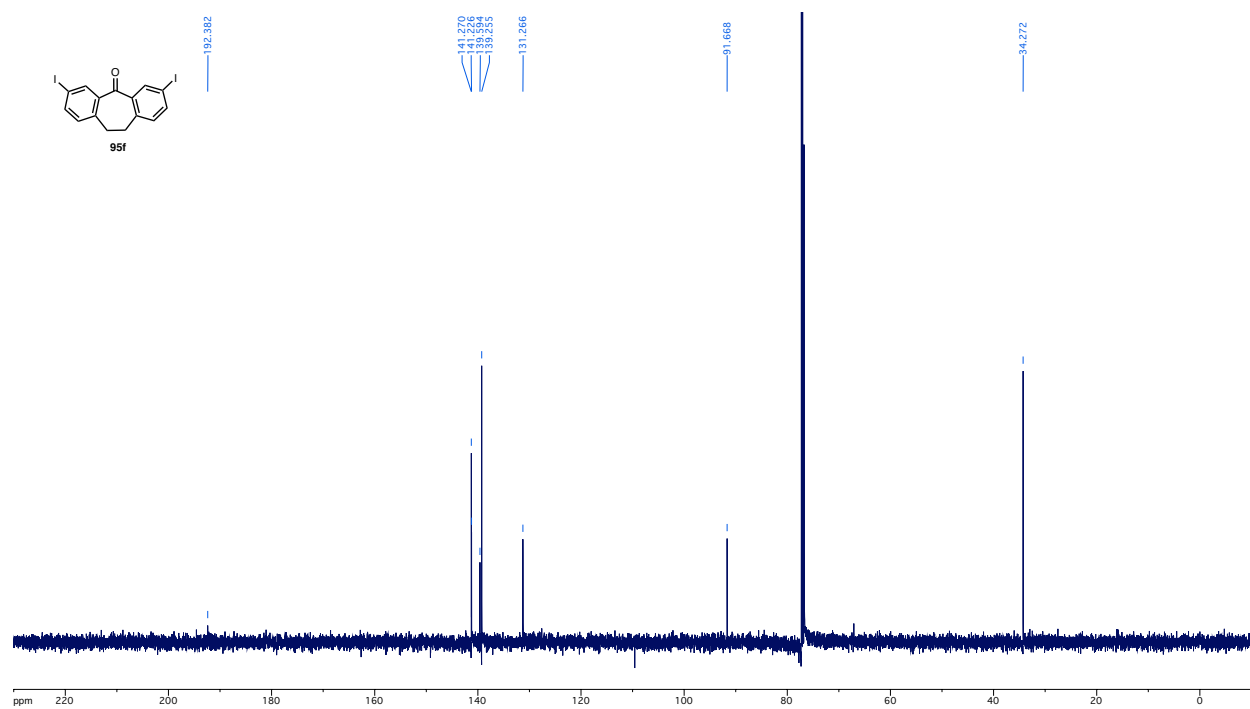
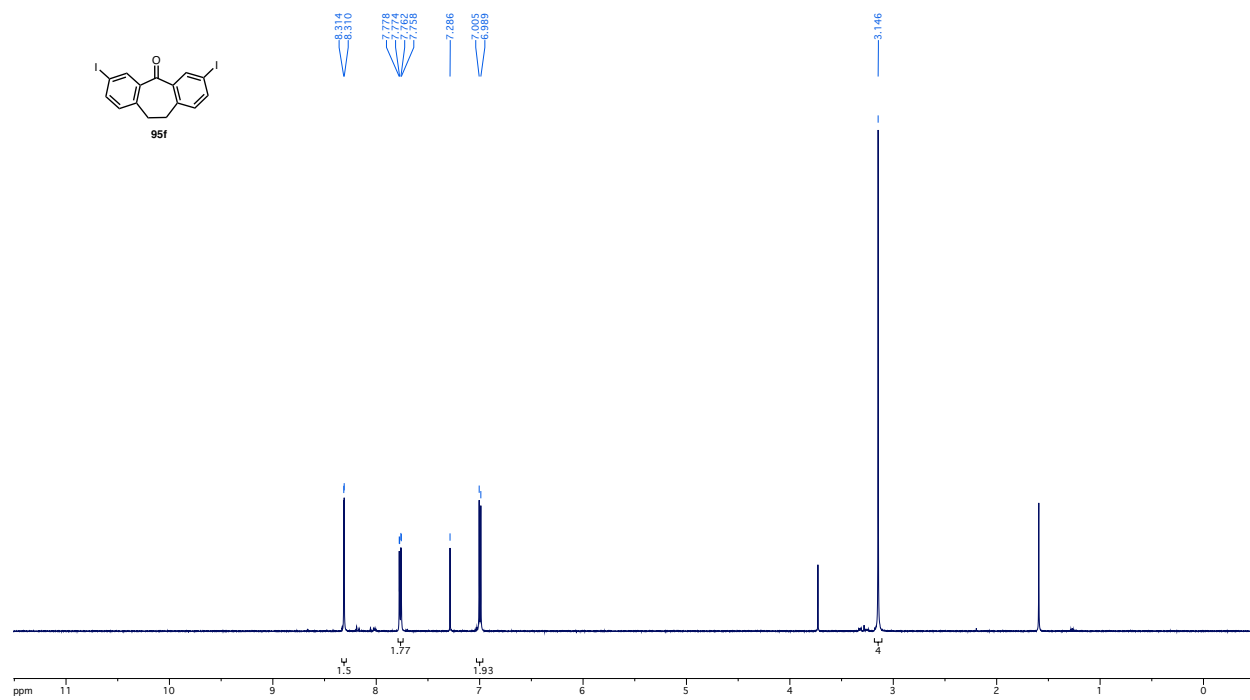


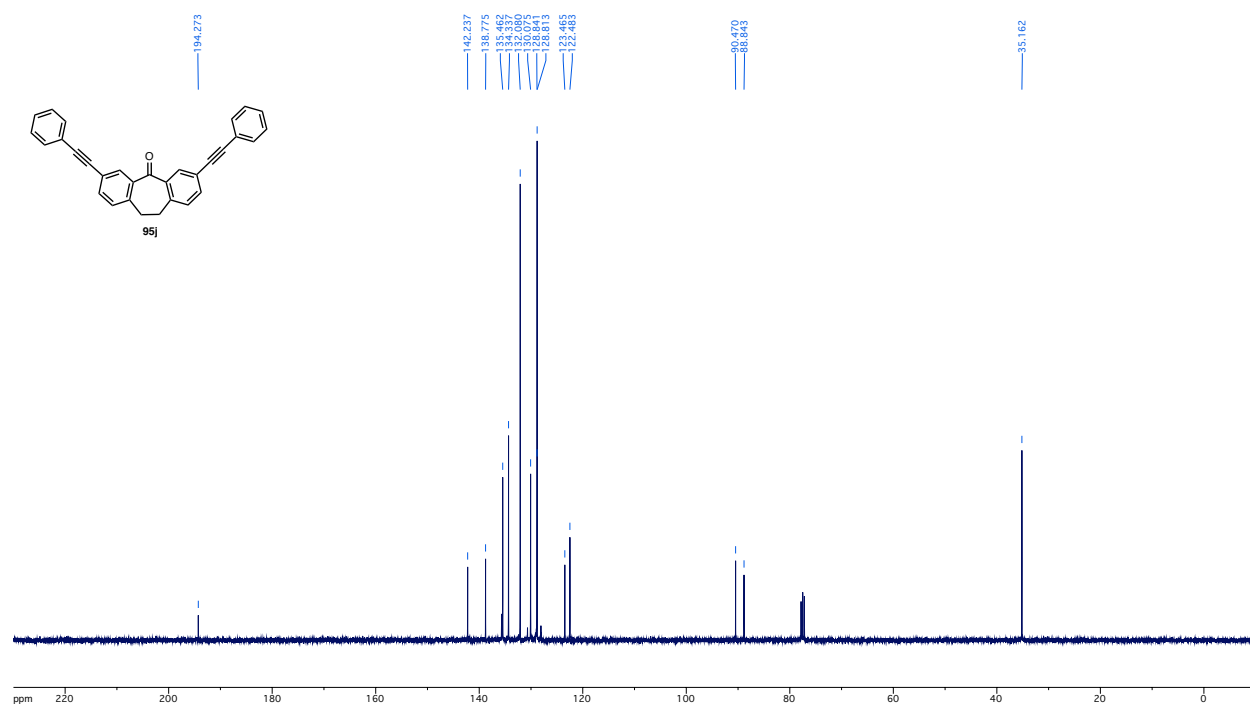
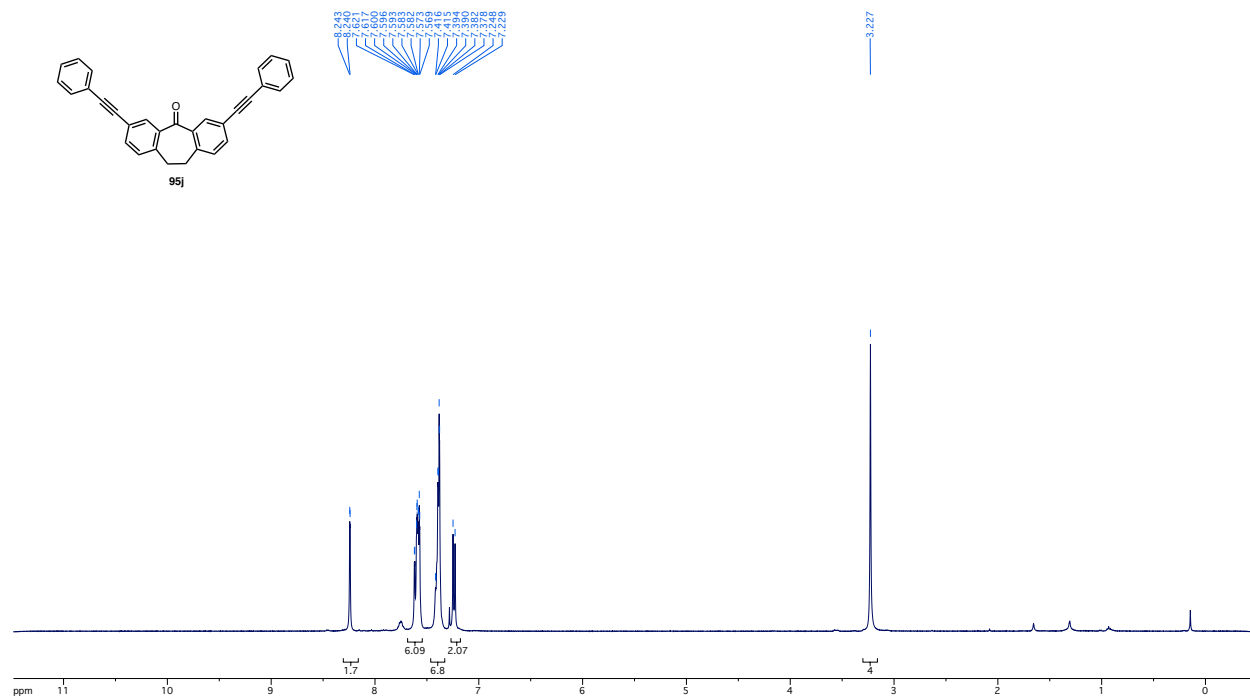


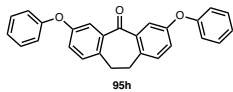
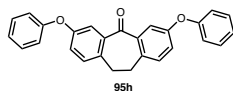


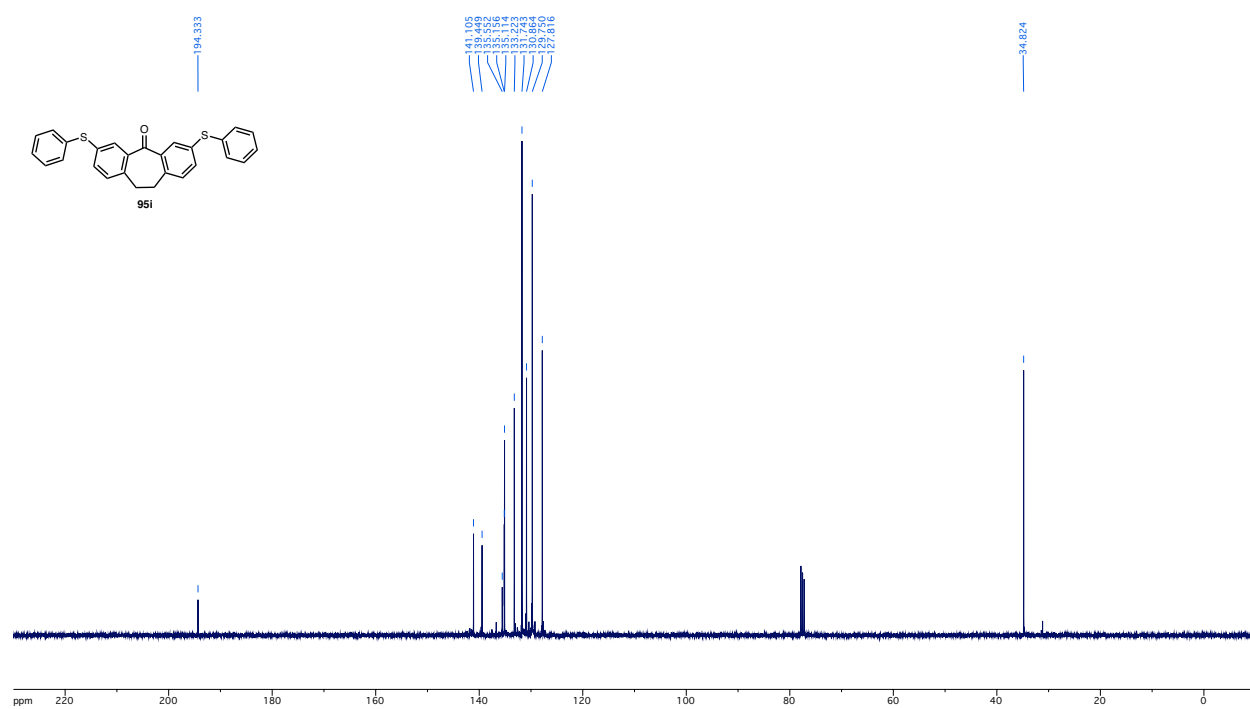
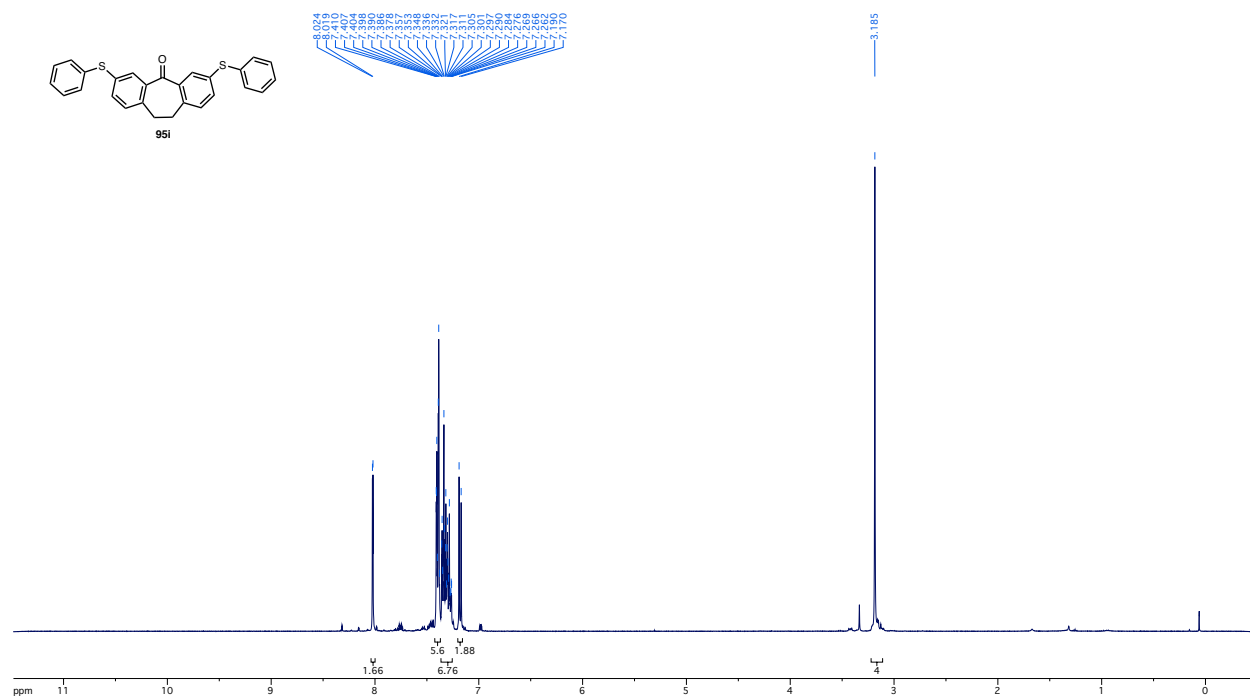


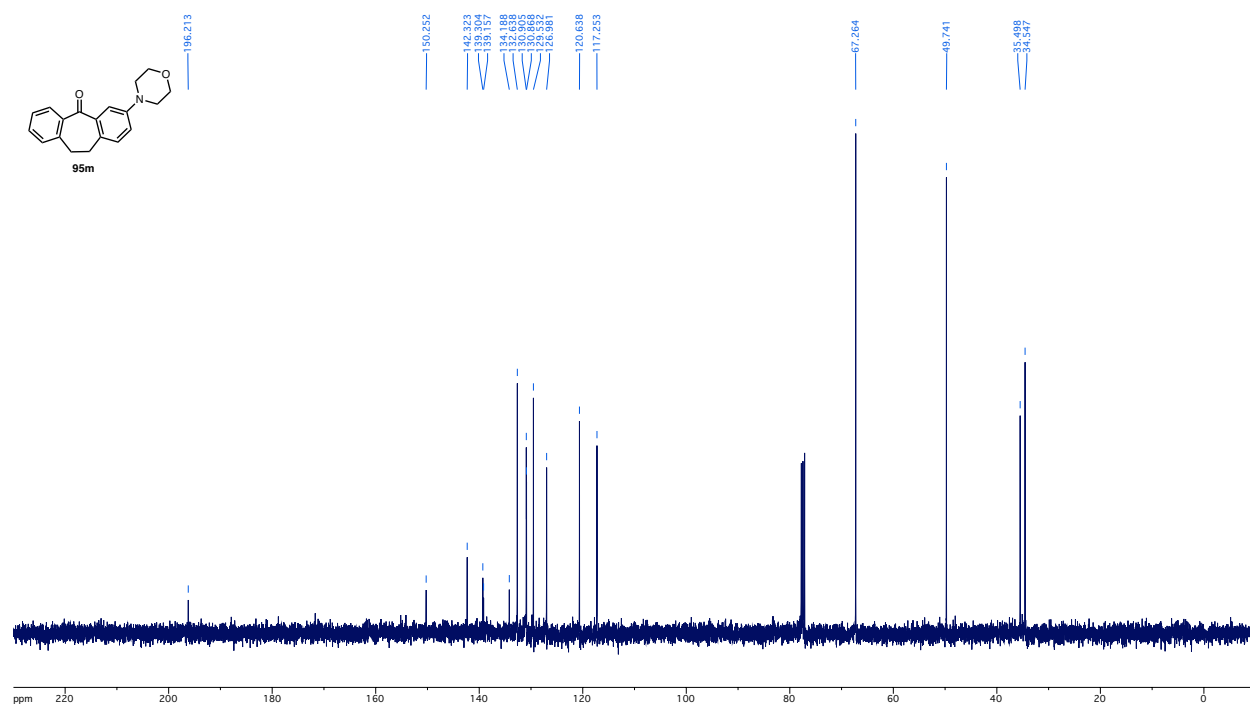
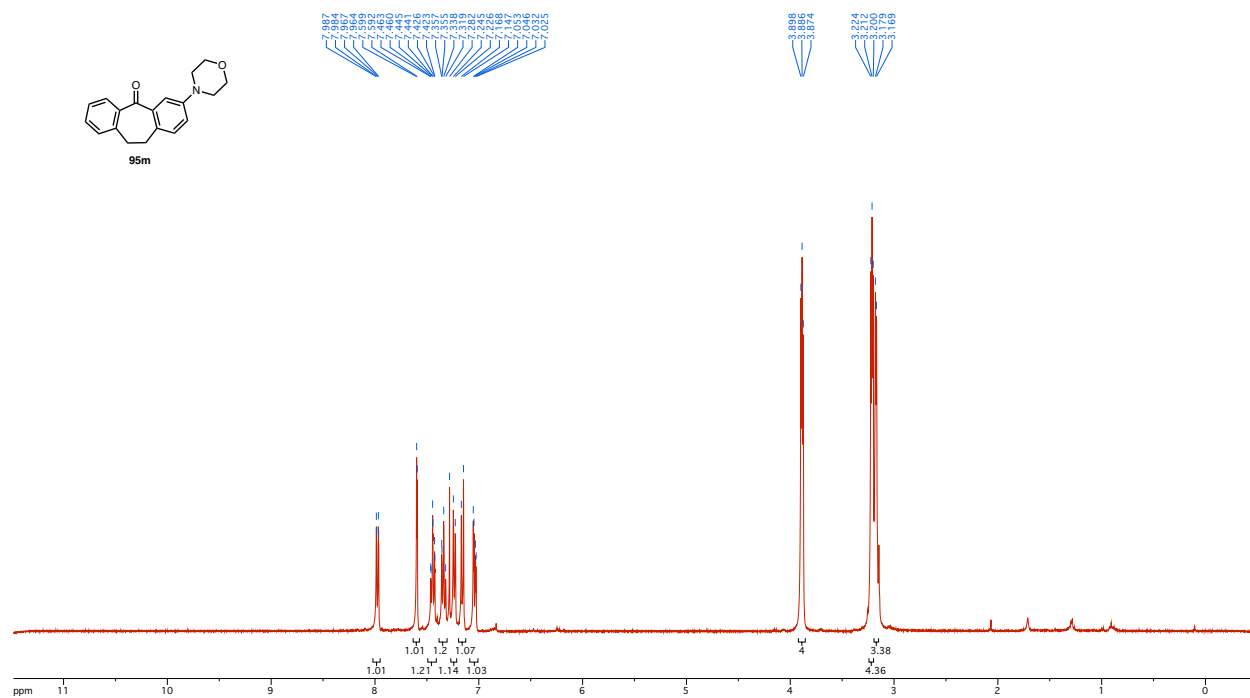


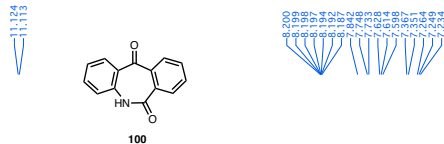


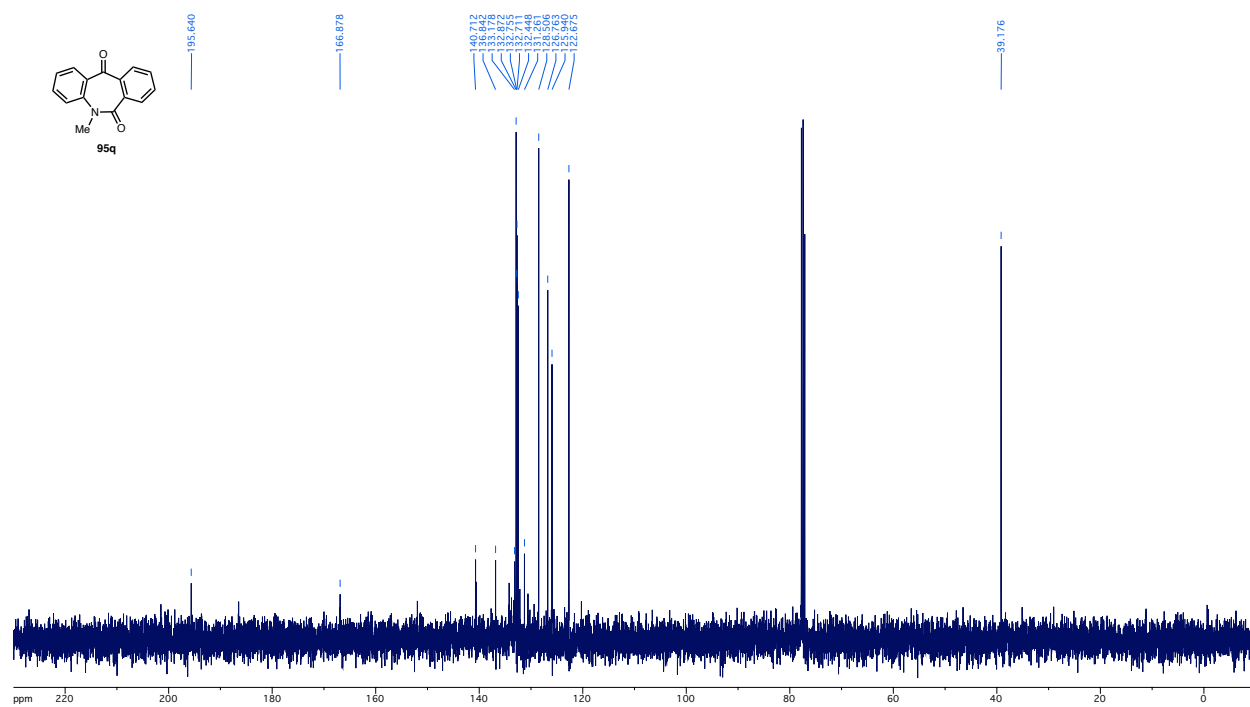
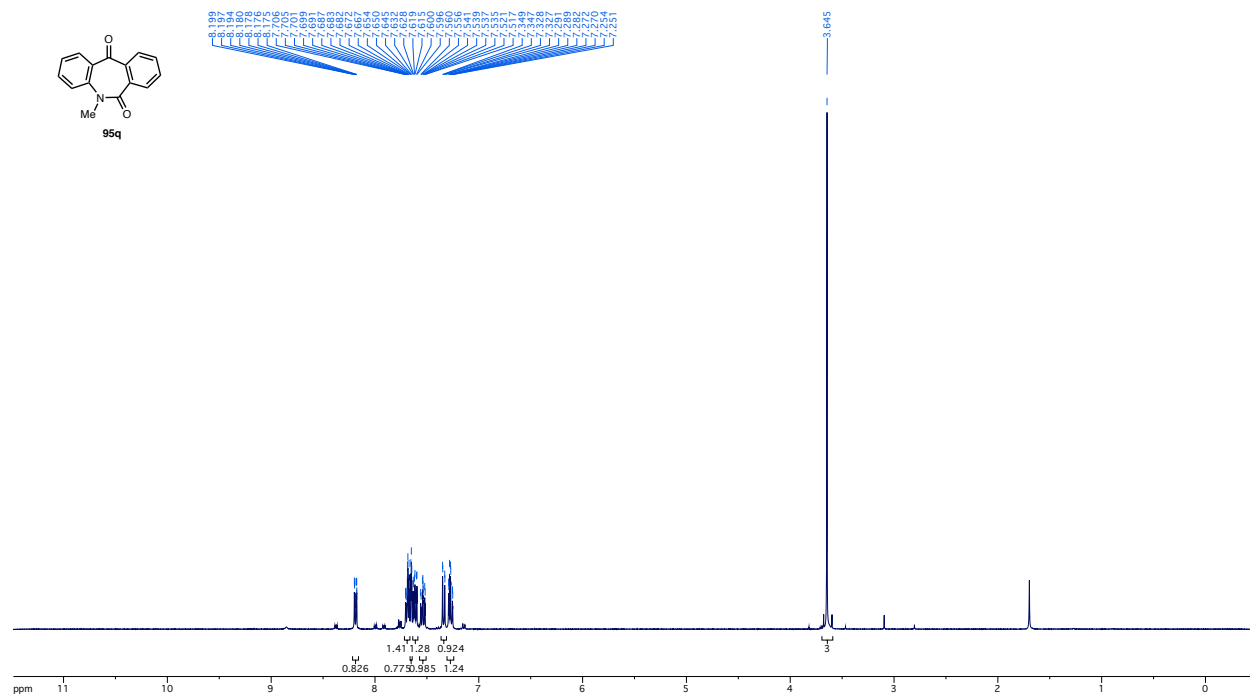


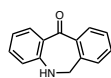




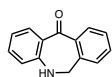
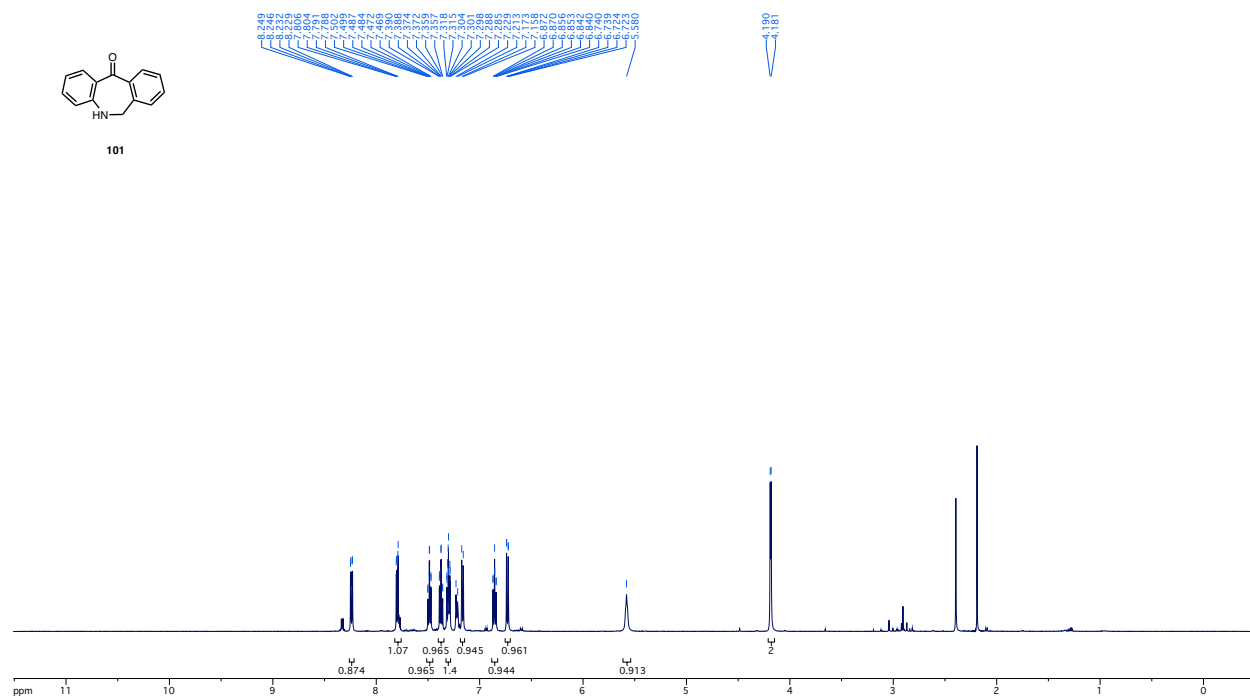




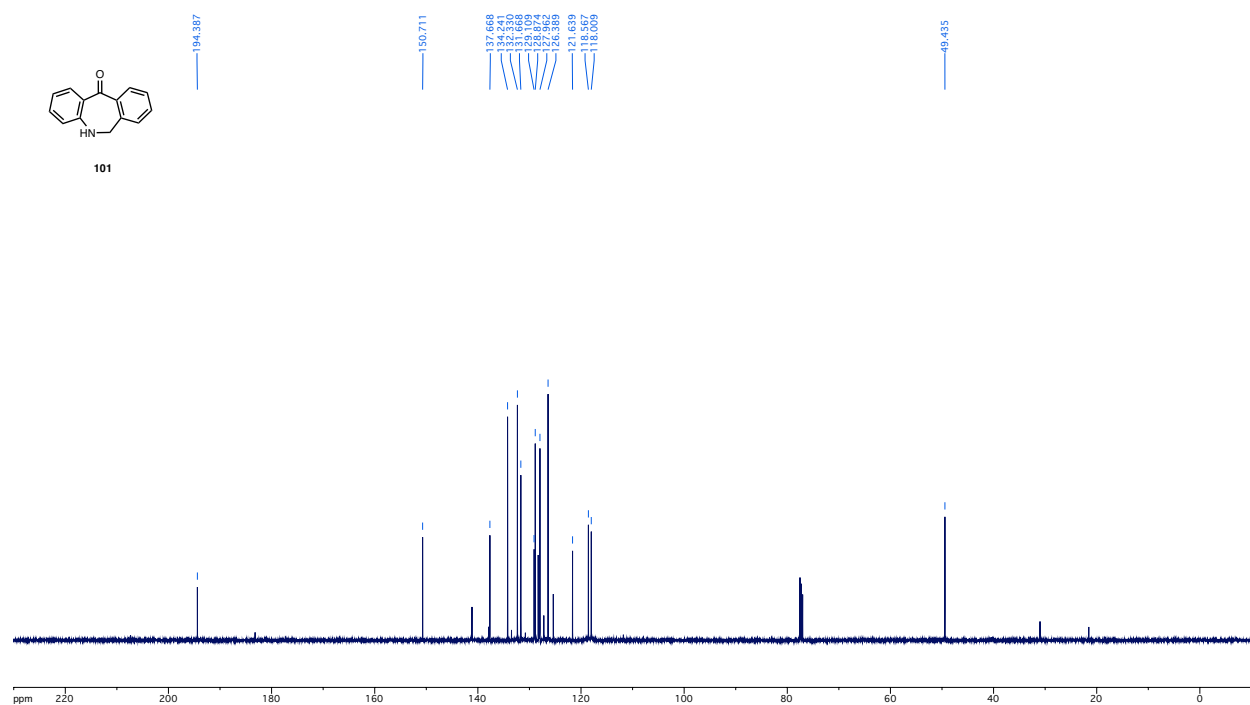


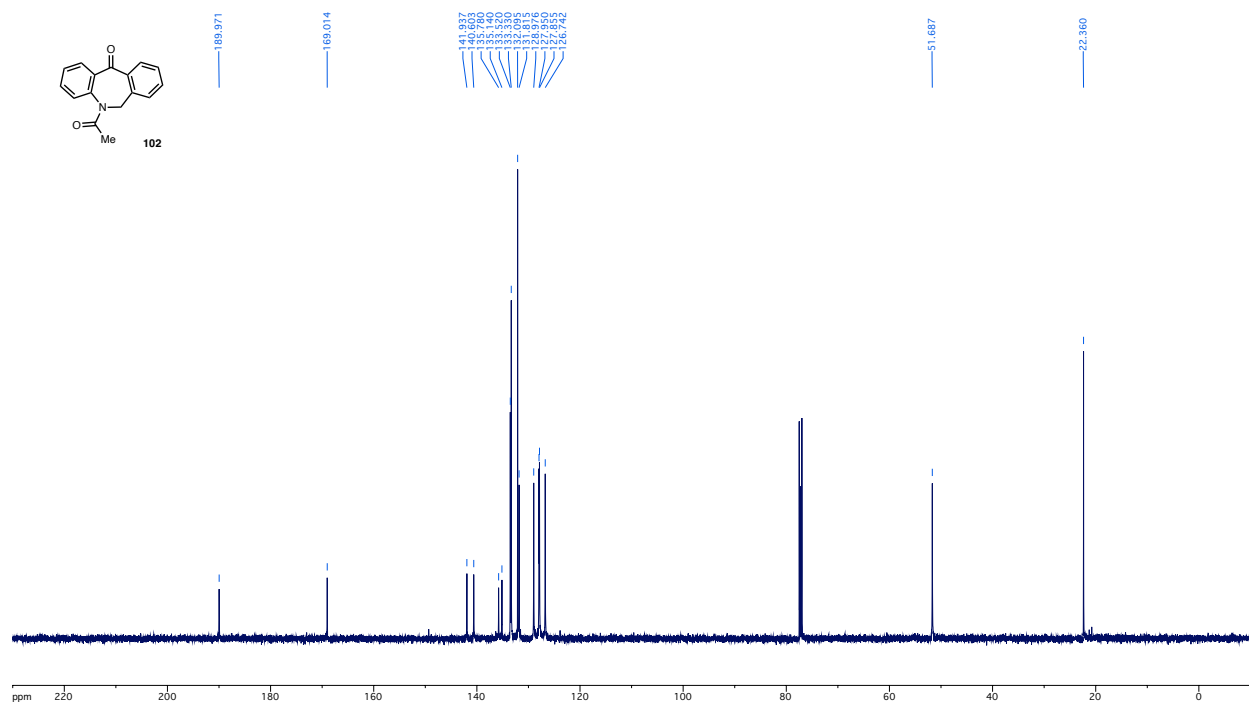
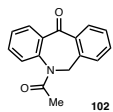
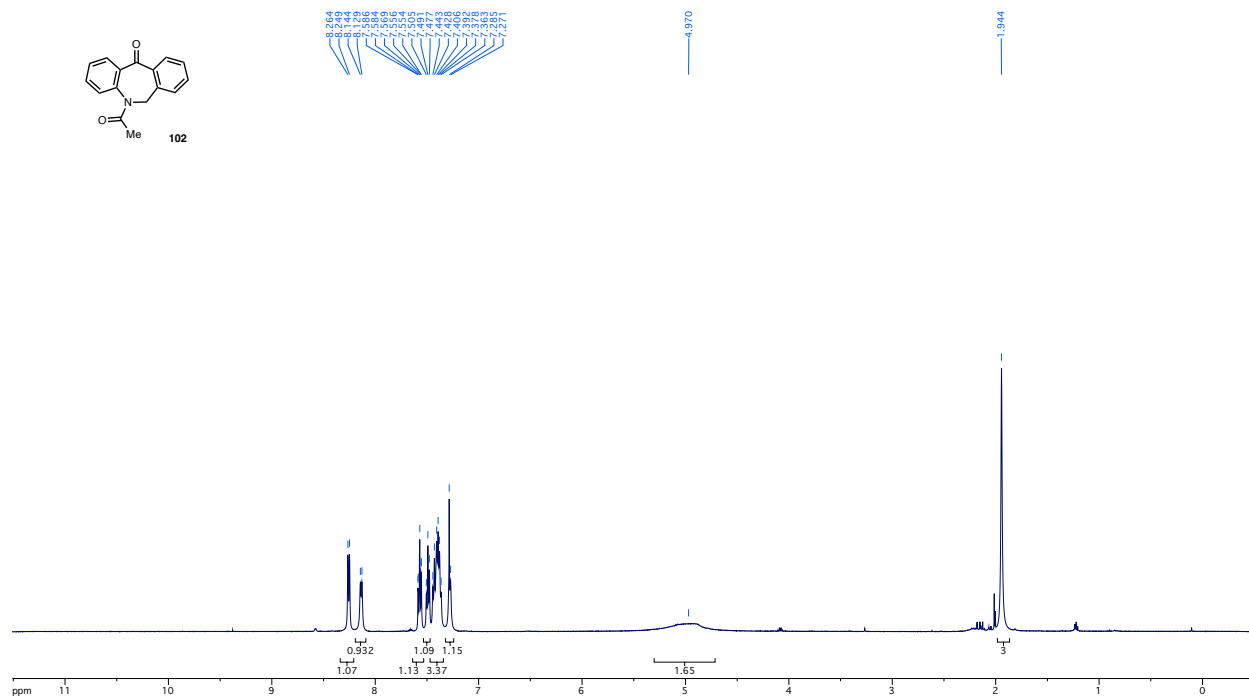
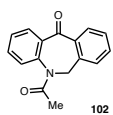


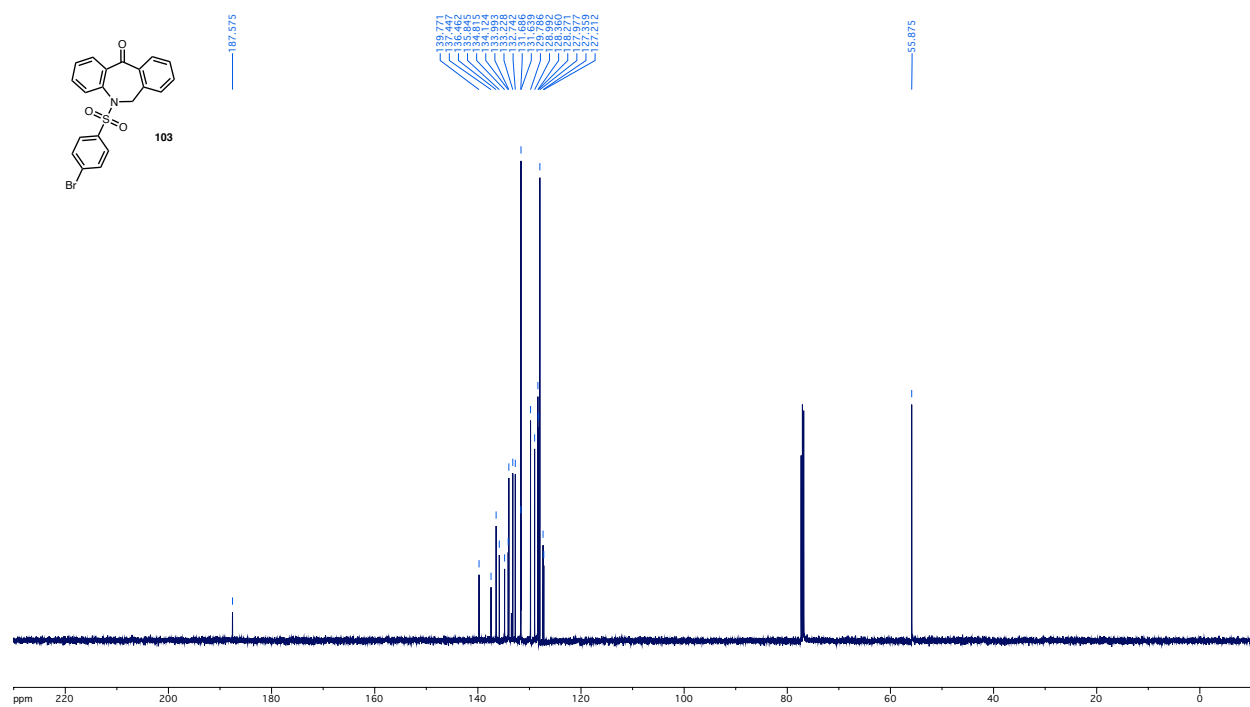
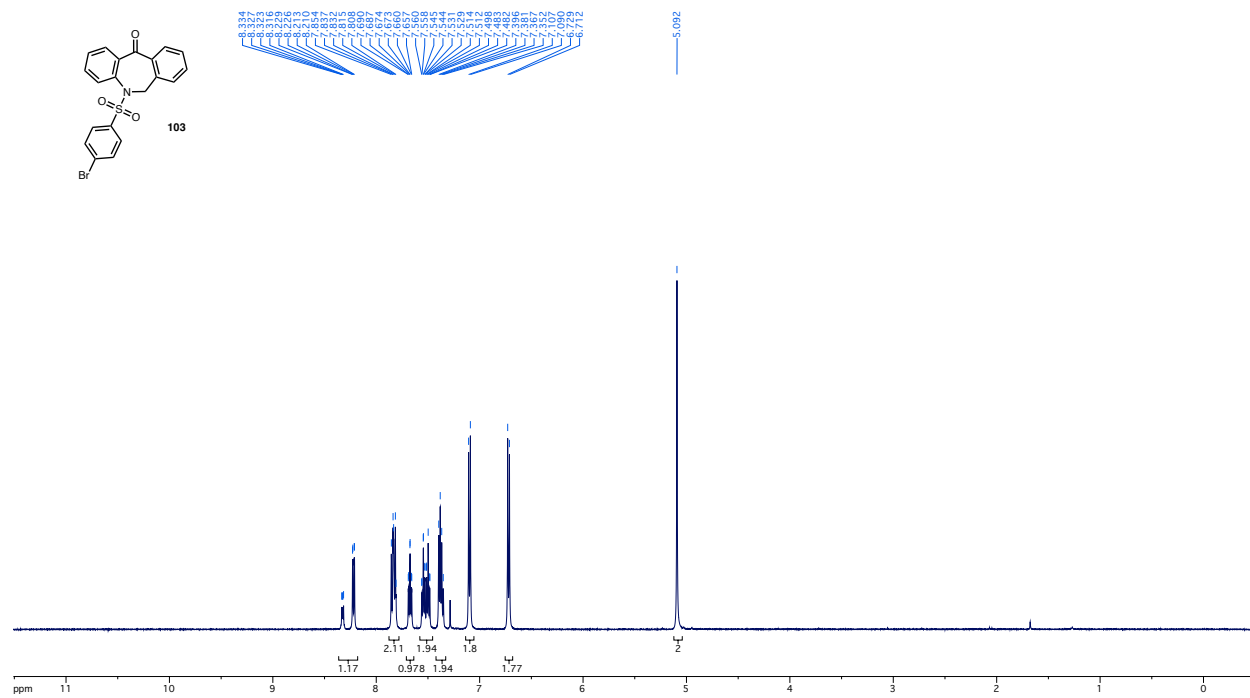
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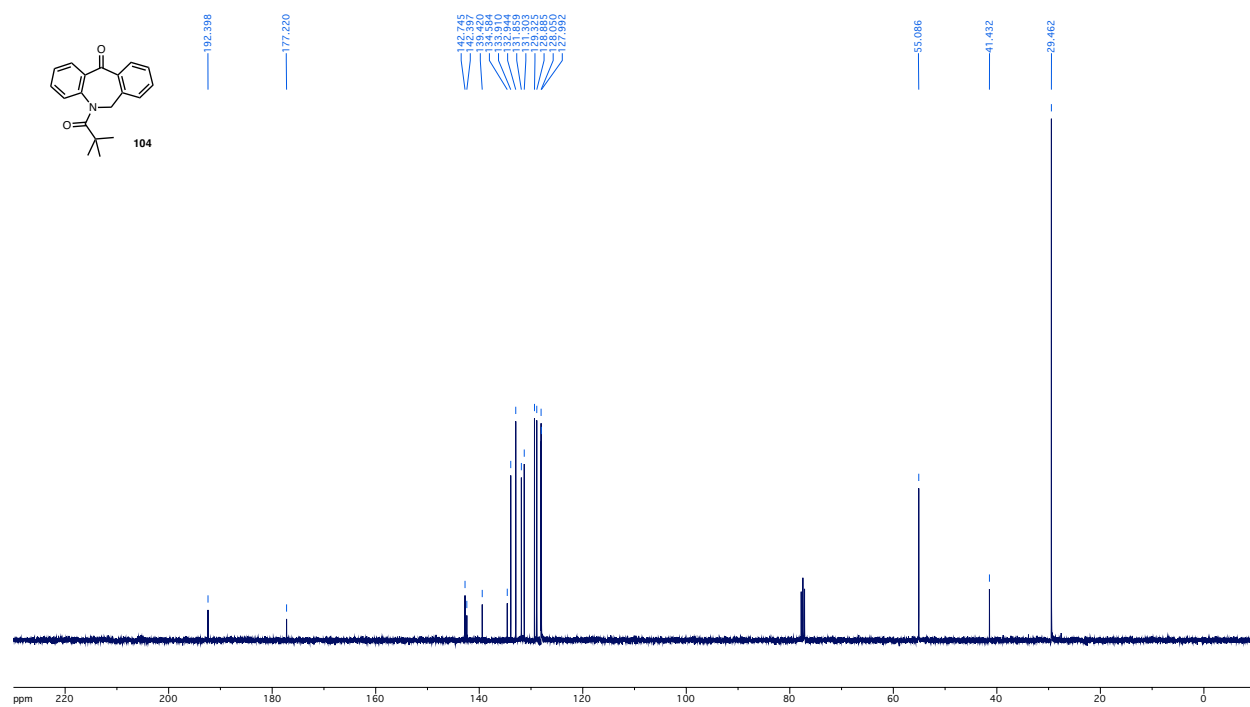
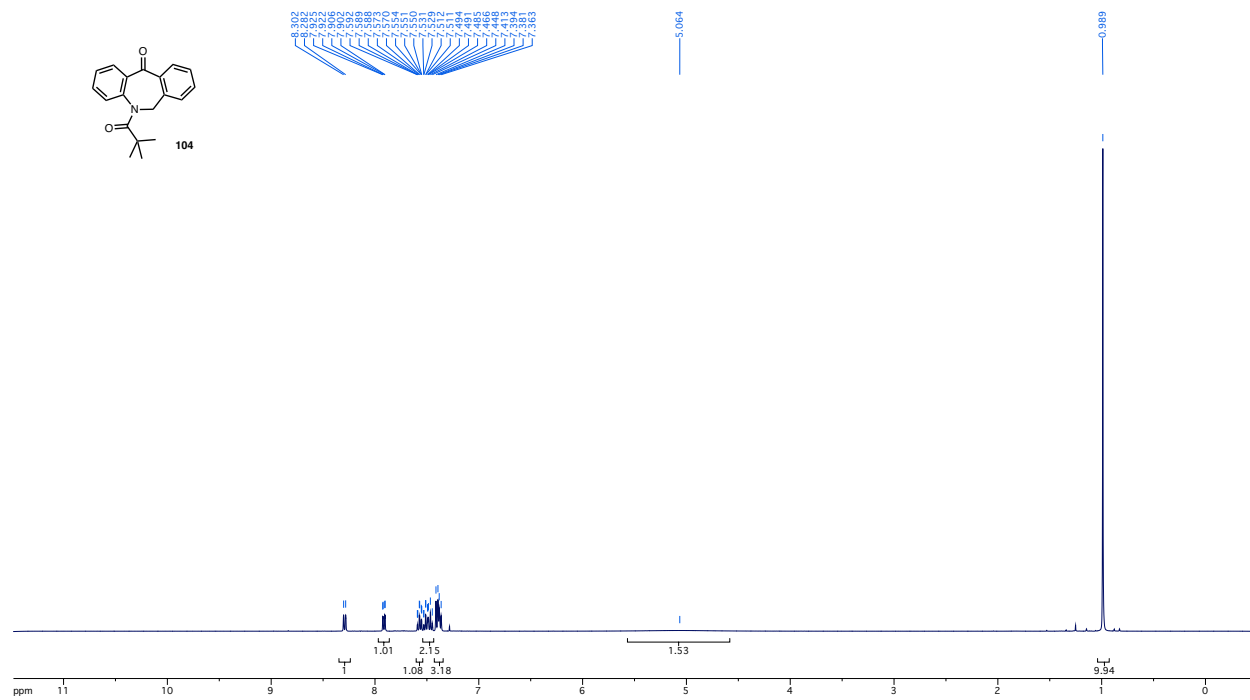


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Chapter 3. Cyclooctynes

1. Cyclooctynes

1.1 Importance of Cyclooctynes

Since the discovery of cyclooctyne's "explosive" reaction with phenyl azide,¹ cyclooctynes have been moved to the forefront of the click chemistry revolution as they represent a fine bridge between stability and reactivity for the strain-promoted azide-alkyne cycloaddition reaction (SPAAC) and its application in bioconjugation,² DNA tagging,³ and protein linking,⁴ amongst other applications. Their importance also extends beyond biological applications to the fields of material and surface science such as in nano rings⁵ and metal complexes⁶ Pioneering studies by Bertozzi and other synthetic chemists have resparked interest in the preparation of these strained alkynes.

1.2 Classes of Cyclooctynes

The reactivity of cyclooctynes can generally be attributed to the two main components: angle strain and electronic activation (Figure 1). The model compound that has defined the angle strain category is dibenzoannulated cyclooctyne (DIBO), synthesized by Ning.⁷ The presence of sp^2 -hybridized centers within the cyclooctyne core decreases the acetylene bond angle to 153° , thereby increasing the reactivity of the alkyne. The ring strain of cyclooctyne has been estimated to be ~ 18 kcal/mol, which is 6 kcal/mol more than cyclooctane.⁸ The addition of other sp^2 centers increases the reactivity the cyclooctyne and thus its rate of cycloaddition, but compromises stability, and thus lifetime, of the cyclooctyne, such as the case with BARAC.⁹ An intermediate zone that exhibits high cycloaddition reactivity with benzyl azide, measured as k_2 , but also bench stability is found in ADIBO, where an additional handle can be placed for an *N*-linker. One disadvantage to this approach is the increase of lipophilicity, which can become problematic for applications in

aqueous media. To overcome this issue, a different approach has been developed that utilizes electronic effects.

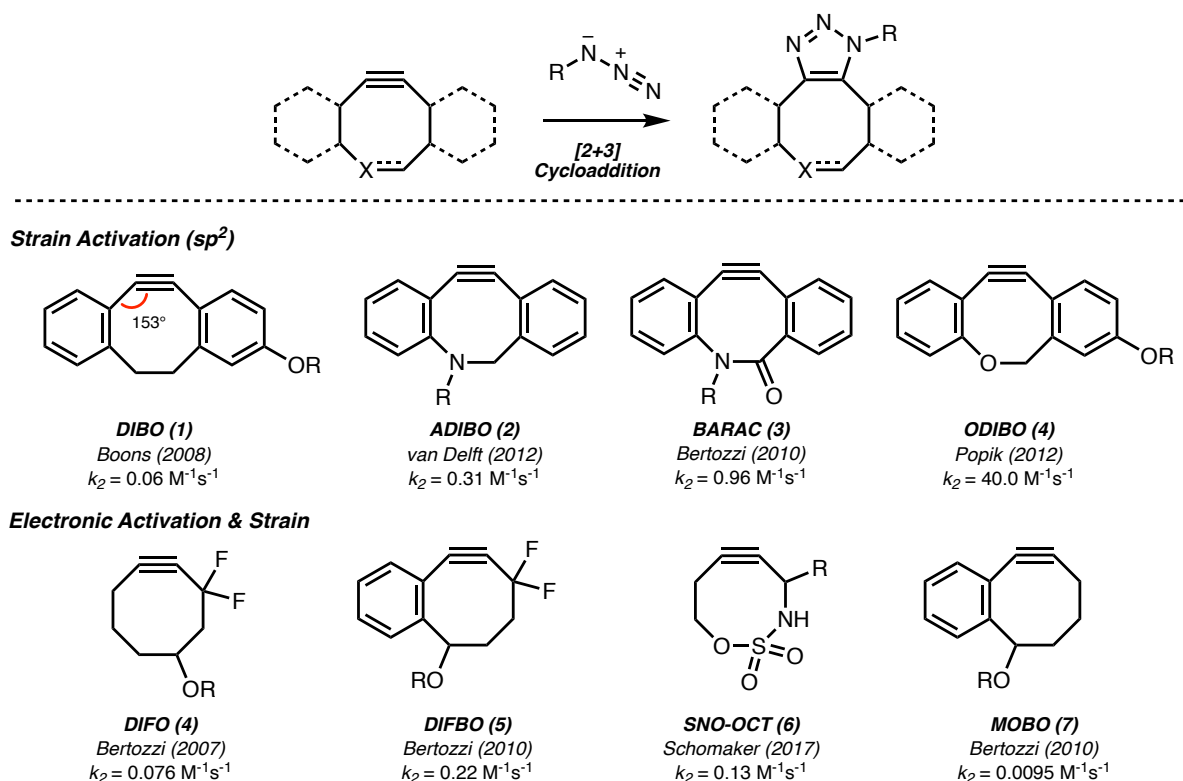


Figure 1. Representative examples of cyclooctyne reagents.

The electronic activation of cyclooctynes has been less explored approach to increasing strain but has also proved its importance. The addition of electron-withdrawing groups adjacent to the alkyne raises the distortion of the dipoles, increasing their interaction primarily due to charge-transfer interaction effects. Also, the LUMO is slightly depressed, while the HOMO is greatly elevated. Overall, the activation barrier of cycloaddition with DIFO (**4**) is dramatically lower by 2 kcal/mol compared to cyclooctyne.¹⁰

Due to the relative difficulty of fluorination, Alabugin inserted a heteroatom into the cyclooctyne ring to utilize electronic activation. This allows for hyperconjugative assistance due to the stabilization of the cycloaddition transition state.¹¹ Cyclononynes with propargyl heteroatoms have shown similar reactivity as DIFO (**4**).¹²

The increased activation of the angle strain by the addition of sp^2 centers is an appealing strategy; however, it also increases steric interactions, particularly $A^{1,3}$ -strain between the ortho hydrogens on the aryl groups and the alkyl group of the azide. This can be circumvented by removing one aryl group as in the case of MOBO. Not only does this reduce allylic strain but favors the formation of one triazole regioisomer.¹³ Upon cycloaddition of DIFO (**4**) with benzyl azide, the resulting triazole that was least sterically hindered was favored in a 2:1 ratio, supporting the theory of the ability to favor one regioisomer (Figure 2). Despite being benchtop stable, the cycloaddition of MOBO (**7**) and benzyl azide was slower ($0.0095\text{ M}^{-1}\text{s}^{-1}$) by about an order of magnitude compared to its counterparts.

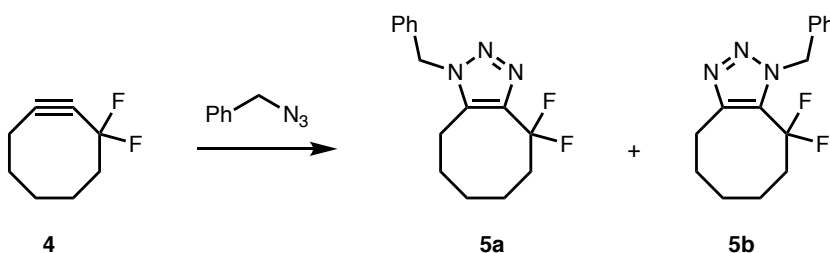


Figure 2. Cycloaddition of DIFO and benzyl azide

Bertozzi utilized both of angle strain and electronic activation, a combination of DIBO (**1**) and DIFO (**4**), to generate DIFBO (**5**), which shows significantly higher reactivity ($0.22\text{ M}^{-1}\text{s}^{-1}$) compared to both DIBO ($0.06\text{ M}^{-1}\text{s}^{-1}$) and DIFO ($0.076\text{ M}^{-1}\text{s}^{-1}$). Unfortunately, this cyclooctyne readily trimerized, compromising its practicality.¹⁴

1.3 Alkynophiles

In addition to the development of various cyclooctyne reagents, numerous traps have been developed to intercept cycloalkynes. This not only allows for avenue to study cyclooctynes, but to also diversify their scope and capability towards further functionalization. These traps can be categorized in their reactivity mechanism as either $[3+2]$ or $[4+2]$ cycloadditions.

The most common method to trapping reactive cyclooctynes is via [3+2] cycloaddition with 1,3-dipoles. Azides are the most prevalent member of this category due to their general high reactivity with alkynes and functionalization in biological scaffolds.¹⁵ Various functionalized azido titanocenes have been trapped by cyclooctynes displaying their inactivity and compatibility with metals.¹⁶ These reactions have been well studied with computational and experimental studies revealing correlations of second-order kinetics, allowing for activation energy prediction of other cyclooctyne derivatives.¹⁷ Remarkably, even in sterically congested environments, cycloaddition of cyclooctynes and azides occur efficiently such as with the synthesis of dual cycloaddition to form bis(triazoles)¹⁸ and even tris(triazoles) via triazides¹⁹ Other traps that are not as common include diazoalkanes,²⁰ azomethine ylides,²¹ nitrile oxides,²² and nitrous oxide.²³ Atypical traps include β -(ethylsulfanyl)propionyl fluoride•BF₃ complex²⁴ and carbon diselenide;²⁵ despite the former not being a formal 1,3-dipole, this heteroallene cycloadducts with cyclooctynes in a similar fashion as azides.

Diels–Alder reactions, or [4+2] cycloadditions are another common trapping mechanism with cyclooctynes. Depending on the electronics of the alkynophile, trapping proceeds through the typical HOMO_{diene}–LUMO_{alkynophile} or an inverse electron demand Diels–Alder, also known as IEDDA. This process proceeds through the overlap of the HOMO_{alkynophile}–LUMO_{diene}. Following the initial cycloaddition, often times expulsion of an inert gas such as dinitrogen or carbon dioxide takes place in a reverse Diels–Alder upon reaction. One of the first extensive reports was by Meier and co-workers, where electron-rich systems such as tetraphenylcyclopentadienone and electron-poor 4 π systems such as 3,6-diphenyl-1,2,4,5-tetrazine and 2-pyrone were used.²⁶ Other common 4 π alkynophile systems include 1,3,4-oxadiazoles and thiodiazoles,²⁷ 1,2-thiaphospholes,²⁸ and tetrazines.²⁹ The latter has recently become further explore to develop faster cycloadditions by

using a pyridine-functionalized tetrazine.³⁰ Other notable mentions are 1,3,5-triphosphabenezes to yield phosphorous-carbon cages.³¹ The reaction of cyclooctynes with thiocyanate-substituted buta-1,3-dienes yield thiocyanate precursors that can be utilized for further functionalization.³² Additionally, sterically congested thiophenes react with cyclooctynes to provide hexasubstituted benzene derivatives in excellent yields; this method however requires elevated temperatures.³³

Recent research has allowed for the discovery of cyclooctynes to be trapped with the assistance of metals forging. Cyclooctynes have formed metallocycles and complex with molybdenum,³⁴ tungsten,³⁵ gold,³⁶ copper,³⁷ tin,³⁸ cobalt,³⁹ and manganese.⁴⁰ The unique nature of cyclooctynes has forged unique and novel reactions in the presence of metals. Trimerization, despite not being a highly sought product has been previously occurred under thermal conditions, but can be facilitated with aluminum,⁴¹ iron,⁴² and platinum⁴³ salts. Palladium catalyzed C-H activation of benzamides in the presence of strained cycloalkynes, developing a novel annulation reaction.⁴⁴ Titanocene oxide complexes have been known to react with cyclooctyne in a [2+2] fashion to forge oxametallacyclobutene.⁴⁵ Another notable example is the intermolecular macrocyclization using organometallic reagent with cyclooctyne.⁴⁶

2. Synthesis of Cyclooctynes

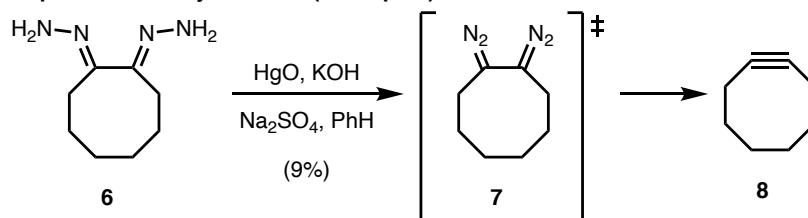
In light of the importance of cyclooctynes and a desire to introduce greater functionality and tune physical properties such as alkyne reactivity and solubility, there remains a demand for new synthetic methods. However, are relatively few approaches to cyclooctynes that employ mild conditions and show wide substrate scope. Indeed, most current methods require the construction of an 8-membered ring prior to introduction of the alkyne group.

2.1 Blomquist

One of the earlier reported syntheses of cyclooctynes was made by Blomquist in 1953. In this case, oxidative decomposition of 1,2-cyclooctanedione dihydrazone **6**, via didiazonium **7** (Figure 3, A) generated **8** in 9% yield.⁴⁷ Despite its use of harsh oxidative reagents such as mercury and extremely low yields, this was one of the first novel approaches towards the synthesis and isolation of cyclooctynes. A silver oxide method that forms diazirines with subsequent photolysis has also been recently discovered.⁴⁸ However, formation of cyclooctynes via diazirines, in this case is inefficient.

Dihydrazone **6** proved to be rather difficult (Figure 3, B). It began with a long synthesis of suberoin **10**, in low yield.⁴⁹ The suberoin was then inefficiently oxidized, followed the condensation with hydrazine to yield dihydrazone **6** in excellent yield. Overall, the synthesis of the starting material proved to be fairly long and inefficient.

A. Oxidative Decomposition of Dihydrazones (Blomquist)



B. Synthesis of Dihydrazones

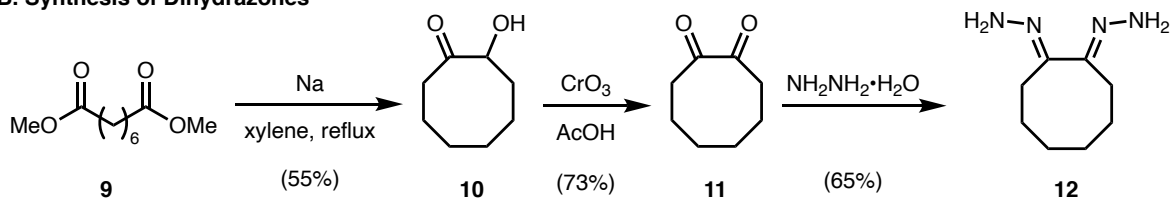


Figure 3. Blomquist's synthesis of cyclooctyne.

2.2 Meier

Meier's synthesis of cyclooctynes proceeds via the pyrolysis of cycloalkeno-1,2,3-selenadiazole **13**, prepared from cycloalkanone-semicarbazone **18** (Figure 4, A).⁵⁰ Cyclooctyne generated in this process was then trapped in situ with tetraphenyl cyclopentadienone providing low yields of **15**. Although this method avoids the use of the harsh oxidative conditions used in Blomquist's synthesis, it still requires temperatures up to 220 °C. A notable byproduct in this reaction is bis-cycloalkeno-1,4-diselenine **16** and elemental selenium. The necessity for high temperatures is incompatible with cyclooctyne, thus mandating a trap in-situ trapping of this strained alkyne. Despite the formation of various of byproducts under high reaction temperatures, this method showed the efficient trapping of cycloalkynes with alkynophiles *in situ*.

The synthesis of selenadiazole **13** follows Blomquist's preparation of dihydrazone **12** (Figure 4, B). Using the same preparation to make suberoin **17**,⁴⁹ the ketone is then oxidized and condensed with a semicarbazide to give semicarbizone **18**. This was then oxidized with arsenous acid to provide cycloalkeno-1,2,3-selenadiazole **18**, in an overall modest yield.

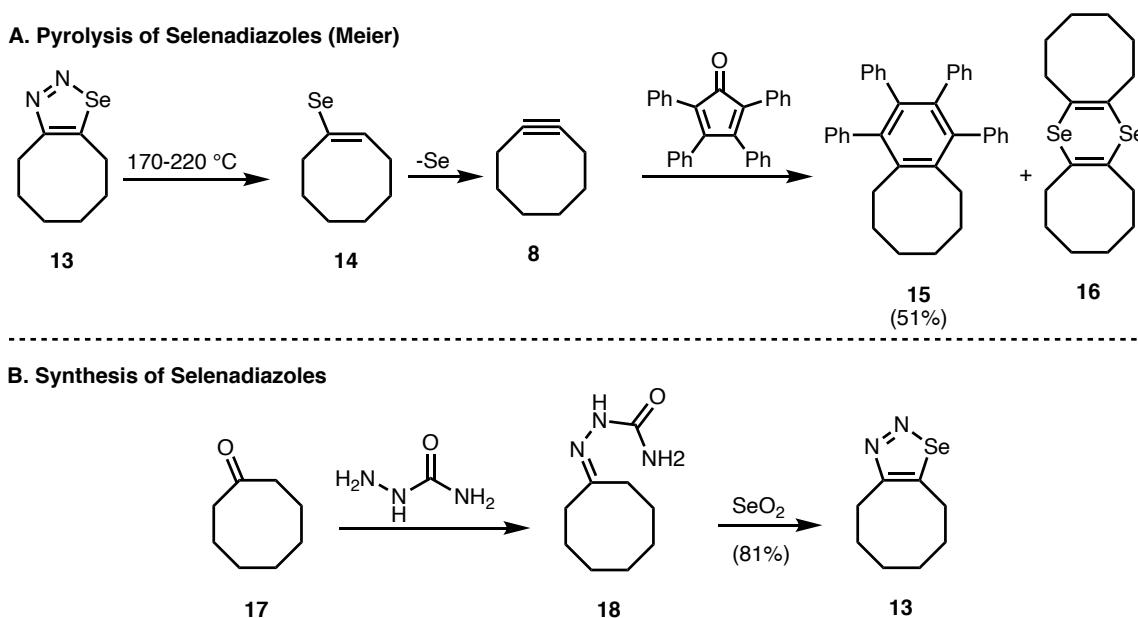
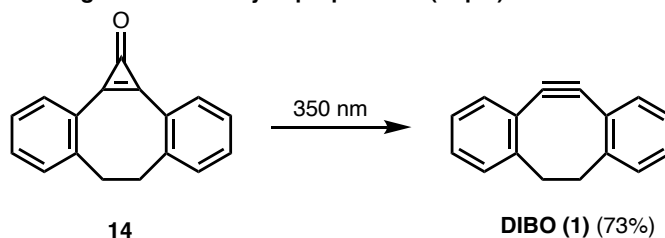


Figure 4. Meier Synthesis of Cyclooctyne.

2.3 Popik

A less common approach to cyclooctynes, but one that is becoming increasingly popular, is the photolysis of cyclopropenones. Initially discovered by Trost,⁵¹ and later applied by Chapman to the preparation cyclopentynes,⁵² and most recently by Popik to access cyclooctynes. In this case, cyclopropenones **14** undergo extrusion of carbon monoxide upon radiation with UV light (Figure 5, A).⁵³ Despite the overall efficiency of this method, it is not suitable for the in-situ trapping of cyclooctynes, which is a major limitation since reactive alkynes cannot be intercepted. The use of cyclopropenone **14** also proved a limitation, as its preparation through the Friedel-Crafts reaction of tetrachlorocyclopropene (**16**) and diarylethane (**15**) is highly inefficient (Figure 5, B).

A. Photochemical Fragmentation of Cyclopropenones (Popik)



B. Synthesis of Cyclopropenones

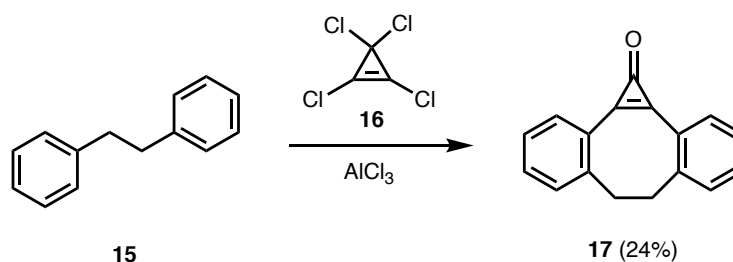


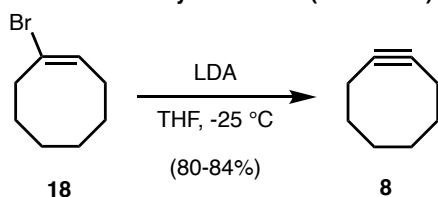
Figure 5. Popik Synthesis of Cyclooctynes.

2.4 Brandsma and Boons

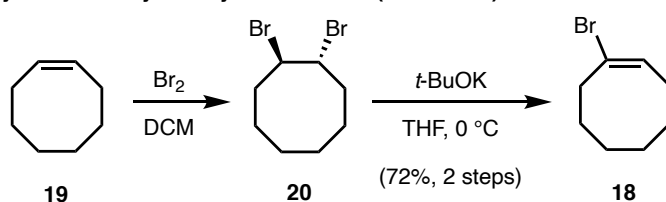
The most common approach to the preparation of cyclooctynes utilizes classical β -eliminations to form the strained alkyne. Brandsma employed this approach in the preparation of **8** via the elimination of bromide **18** using LDA (Figure 6, A).⁵⁴ This method's advantage is that high

reaction temperatures or oxidative conditions are not required and is overall efficient. While the use of strong base is of concern, this method has been utilized numerous times in the preparation of other cyclooctynes such as DIBO.⁵⁵ The synthesis of dibromide **20** is simple and efficient (Figure 6, B). Brandsma's synthesis of **18** begins with the bromination of cyclooctene (**19**), followed by elimination to provide vinyl bromide **18**. The bromide is then eliminated under stronger basic conditions to provide cyclooctyne (**8**) in good overall yield. If one wishes to expand on the scope of this reaction to other targets, the synthesis of an eight-membered rings is non-trivial hurdle to overcome. A popular solution to this problem is the ring expansion of seven-membered ring substrates accomplished from dibenzosuberone (**21**) using diazomethane to provide cyclooctenone **22** in good yield (Figure 6, C).⁵⁵ Cyclooctenone **22** was then reduced and brominated to provide dibromide **24** in fair yield. This dibromide then underwent elimination with LDA to provide DIBO in reasonable yield. The need for harshly basic conditions, coupled with multiple transformations reduces the in overall efficiency of this approach and greatly limits substrate scope using β -elimination.

A. Elimination of Vinyl Bromides (Brandsma)



B. Synthesis of Cyclooctyne Precursor (Brandsma)



C. Synthesis of DIBO (Boons)

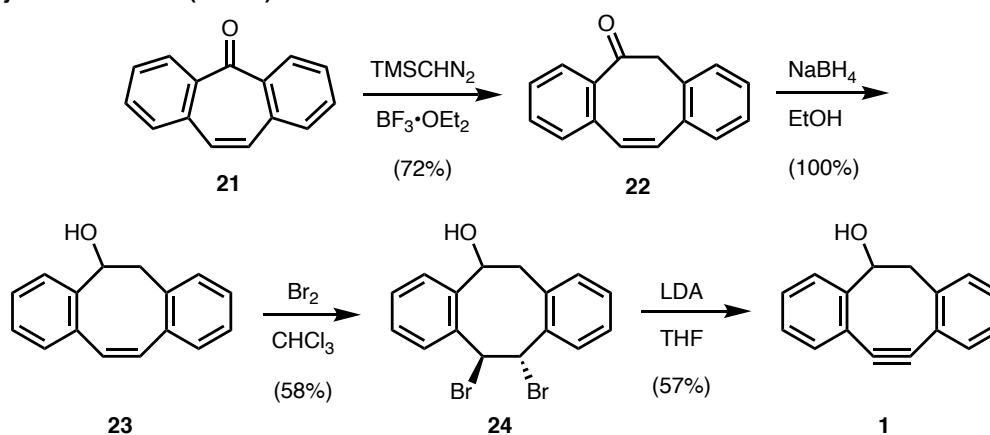


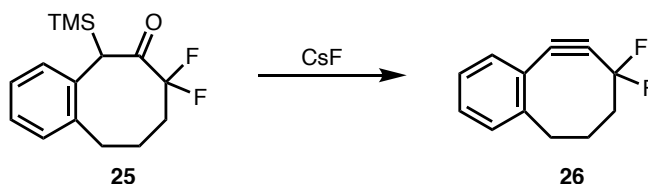
Figure 6. Synthesis of Cyclooctyne via β -eliminations (Brandsma & Boons)

2.5 Bertozzi

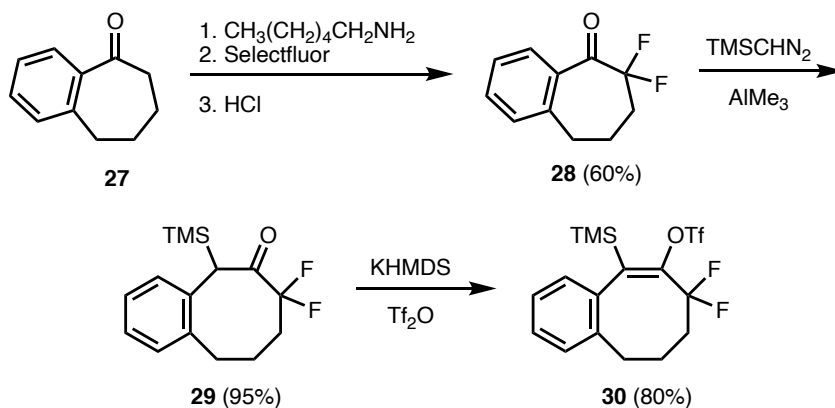
In order to circumvent the need for strong basic conditions, Bertozzi developed an approach to cycloalkyne DIFBO (**5**) using fluoride-induced elimination of silyl enol triflate precursor **25** (Figure 7, A).¹⁴ This strategy drew inspiration from similar eliminations of trimethylsilyl triflates⁵⁶ and has subsequently been used in the synthesis of smaller cycloalkynes.⁵⁷ Due to the absence of harsh conditions and opportunity to trap transient alkynes have emerged as one of the most versatile methods for the synthesis of cycloalkynes (Figure 7, C).

Analogous to Boon's synthesis of DIBO, the Bertozzi route begins with fluorination of 7-membered ring ketone **27** to yield **28**. Ring expansion using trimethylsilyl diazomethane, catalyzed by trimethylaluminum, installing a trimethylsilyl group α to the carbonyl group provided **29**. Enol triflate generated with triflic anhydride completed the synthesis of the elimination substrate **30** (Figure 7, B). While the synthesis of precursor **30** was accomplished with good efficiency, over 6 steps, the alkyne synthesis proved rather difficult. Upon fluoride-induced elimination, the alkyne product spontaneously trimerized and could only be trapped in β -cyclodextrin. Trapping with benzyl azide *in situ* proceeded near quantitative efficiency to provide regioisomers, **31a** and **31b** (Figure 7, C). The long process of synthesizing silyl enol triflate precursors is challenging and inefficient, primarily due to the difficulty of installing a silyl group α to the carbonyl group. Silyl enol formation is much more favorable.⁵⁸

A. Fluoride-Induced Elimination of Silyl Enol Triflate (Bertozzi)



B. Synthesis of Cyclooctyne Precursor



C. *In Situ* Trapping of DIFBO

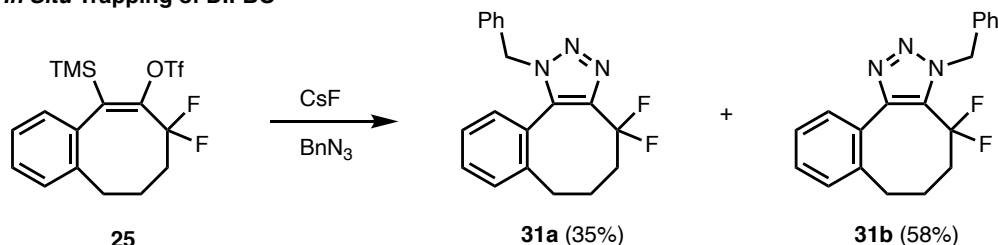


Figure 7. Bertozzi Synthesis of DIFBO.

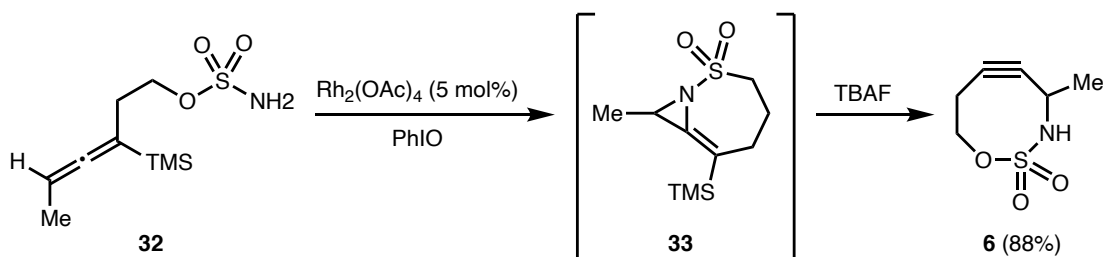
2.6 Schomaker

Similar to Bertozzi's approach to the synthesis of cyclooctynes, Schomaker applied this method, but introduced functionality into the ring in which she utilized a sulfamate ring to promote ring expansion.⁵⁹ This allowed for sulfur, nitrogen, and oxygen-containing cyclooctynes (SNO-OCT) to be further modified for polymerization or increasing rate of reactivity and stability (Figure 8, A).⁶⁰ Using homoallenic sulfamate **32** as a precursor, the eight-membered ring was formed using

rhodium catalyzed aziridination and quenching with TBAF to promote ring expansion. Schomaker demonstrated that alkyne formation is highly efficient, but in situ trapping was not reported.

One major limitation of Schomaker's method is the synthesis of the requisite homoallenic sulfamates (Figure 8, B) as this route has shown to be rather long, and at points, inefficient starting from homoallenic alcohol **37**.⁶¹ The synthesis began with propargyl alcohol **34** which was silylated at the terminal alkyne to form **35**. This silane was then transformed into the homoallenic ester **36** using trimethylorthoacetate and acid. Reduction with lithium aluminum hydride provided **37**, which was then subjected to sulfamate formation to form homoallenic sulfamate **38**,⁶² in moderate yield. Despite the high efficiency of the cyclooctyne synthesis, the inability to allow for trapping restricts the scope of this method.

A. Synthesis of NSO-OCT via homoallenic sulfamates (Schomaker)



B. Synthesis of homoallenic sulfamates

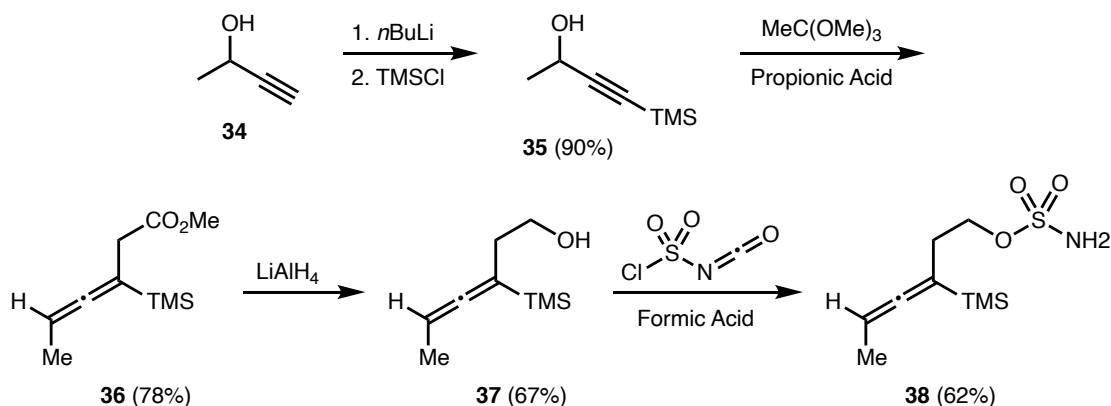
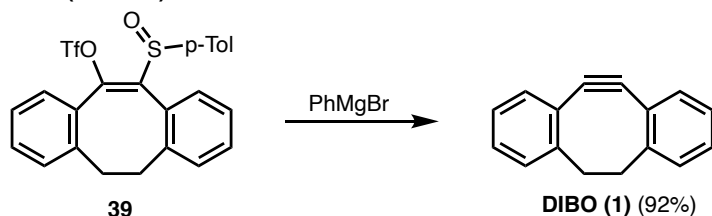


Figure 8. Schomaker's Synthesis of Cyclooctyne (SNO-OCT)

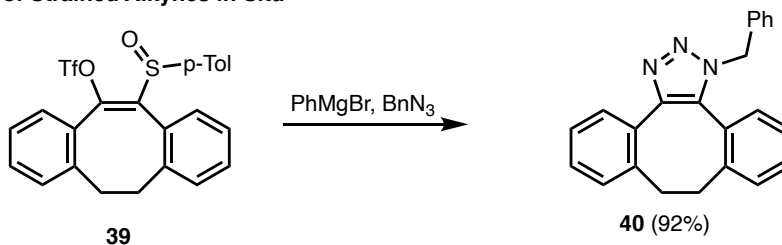
2.7 Yoshida

Following a similar theme to the classical elimination method for the synthesis of cyclooctynes, Yoshida employed sulfoxide-magnesium exchange to induce alkyne formation. Due to the difficulty of installing a silyl group α to a carbonyl group, Yoshida chose to install a sulfonyl group in its place.⁶³ This method was not only applied to the preparation of cyclooctynes, but to smaller rings, including cycloheptynes. Upon treatment of phenylmagnesium bromide, 2-sulfinylcycloalkenyl triflate **39** readily provided DIBO (**1**) in excellent yield (Figure 9, A). Additionally, strained alkynes could be trapped in situ with no loss in yield (Figure 9, B). Unlike Bertozzi's method, one distinct disadvantage is the use of harsh basic and nucleophilic Grignard reagents, limiting this methodology. Another disadvantage of Yoshida's method, is the long synthetic route towards sulfinylcycloalkenyl triflates **39** (Figure 9, C). The synthesis of DIBO begins with the hydrogenation of diarylcycloalkenone **41**, followed by alkylation with *S-p-tolyl p*-toluenethiosulfonate to form **42**. Enolate trapping with phenyl triflimide generated enol triflate **44**, which was then oxidized with *m*CPBA to form the corresponding sulfoxide and thus sulfinylcycloalkenyl triflate **39**. The long synthetic route towards the cycloalkyne precursor is a major disadvantage due to its overall inefficiency (16%), again illustrating the need for new routes towards cyclooctyne synthesis with greater yield.

A. Synthesis of DIBO (Yoshida)



B. Trapping of Strained Alkynes *in Situ*



C. Synthesis of 2-Sulfinylalkenyl Triflate Precursor

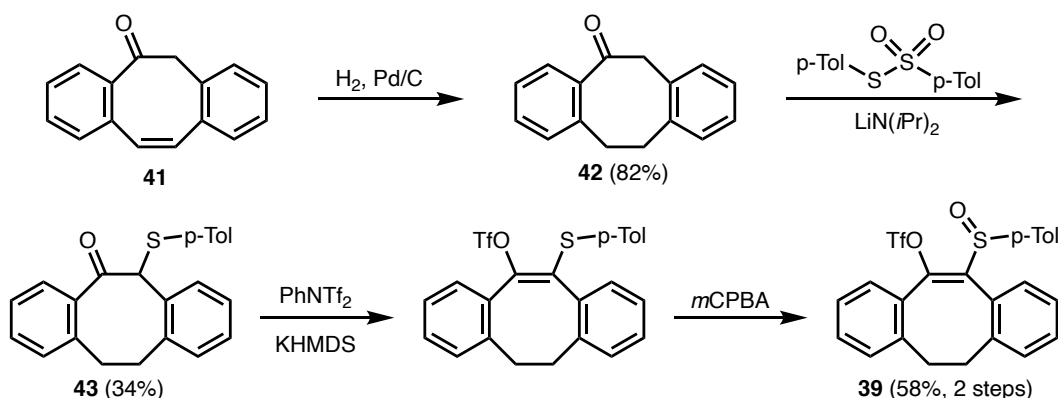


Figure 9. Synthesis of Cyclooctynes via 2-Sulfinylcycloalkenyl Triflates (Yoshida)

2.8 Summary and Initial Idea

The primary approach towards cyclooctynes is a classical elimination approach, either with the use of strong base, fluoride-induced, or via sulfur magnesium exchange. Other methods include oxidative decomposition of dihydrazones and pyrolysis of selenodiazoles. Despite various approaches and methods towards the synthesis of cyclooctynes, each possess similar disadvantages. Most methods require harsh reaction conditions such as strong bases, oxidative conditions, or high reaction temperatures, compromising stability of transient cyclooctynes. Each

involves the non-trivial formation of the eight-membered ring. Thus, there remains a demand for a method that relies on mild and versatile reaction conditions which will offer access to reactive cycloalkynes, while employing a short, efficient route of the requisite precursor formation. Thus, we were inclined to develop a method that would form cyclooctynes utilizing ring expansion from a seven-membered alkylidenecarbene intermediate that would avoid difficult installation of functional groups. (Figure 10).

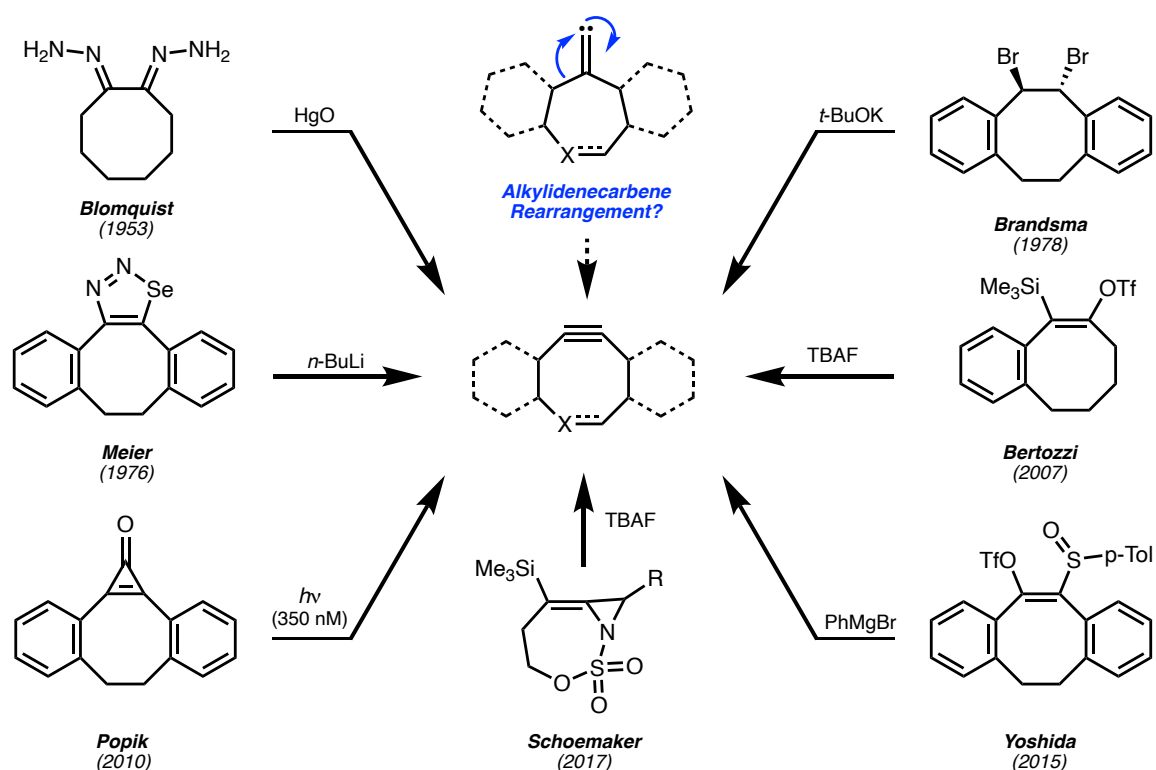


Figure 10. Summary of Cyclooctynes.

3. Alkylidenecarbenes

Alkylidenecarbenes are very reactive intermediates in organic chemistry which have considerable untapped potential. Their high reactivity requires them to be generated in similar methods as with typical carbenes, but generation and trapping must be done in situ.^{64 65} Alkylidenecarbenes have a unique structure, which can potentially be in 3 distinct structures. In single state **44** (Figure 11), a

lone pair of electrons is located on the sp non-bonding orbital (HOMO), and the p orbital (LUMO) is empty.⁶⁶ Triplet state **45** is about 48 kcal/mol higher in energy and have a single electron in the sp and p orbitals.⁶⁷ Free alkylidenecarbenes also occur as metal carbenoids **46**. Free **44** and encumbered **46** often share the same reactivity.

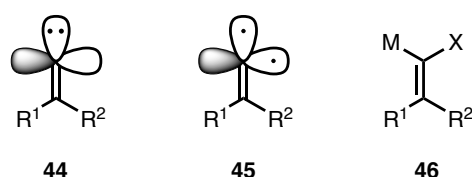


Figure 11. Singlet, triplet, and carbenoid states of alkylidenecarbenes.

Formation of unencumbered, singlet **44** is often accomplished via vinyldiazonium species through the release of dinitrogen, popular examples being the modified Horner-Wadsworth-Emmons reaction⁶⁸ or Peterson olefination⁶⁹. Commonly employed reagents for alkylidenecarbene formation include diazomethylphosphonate esters (DAMP), and trimethylsilyldiazomethane. Metal carbenoids **46** are achieved through metal/halogen exchange or deprotonation through the use of strong base or other harsh reaction conditions.⁶⁴

These intermediates can undergo a number of transformations, (Figure 12) including heteroatom capture to form ylides or coordination complexes.⁷⁰ In common with other carbenes, alkylidenecarbenes can be react with olefins to form methylenecyclopropenes.⁷¹ A common utilization of alkylidene carbenes is 1,5 C–H insertion.^{64 72} This process particularly favored at tertiary C–H positions due to the electron deficient nature of these divalent species. Relative rates of insertion between primary, secondary, and tertiary C–H bonds are 1:30:240, respectively, with increasing rates when the C–H bond in question is adjacent to a heteroatom.⁷³ Insertion into O–H and O–Si bonds are faster than C–H bond insertion.⁷⁴ Faster than 1,5-bond insertion is the formation of terminal and internal alkynes via the Fritsch-Buttenberg-Wiechell (FBW) rearrangement.

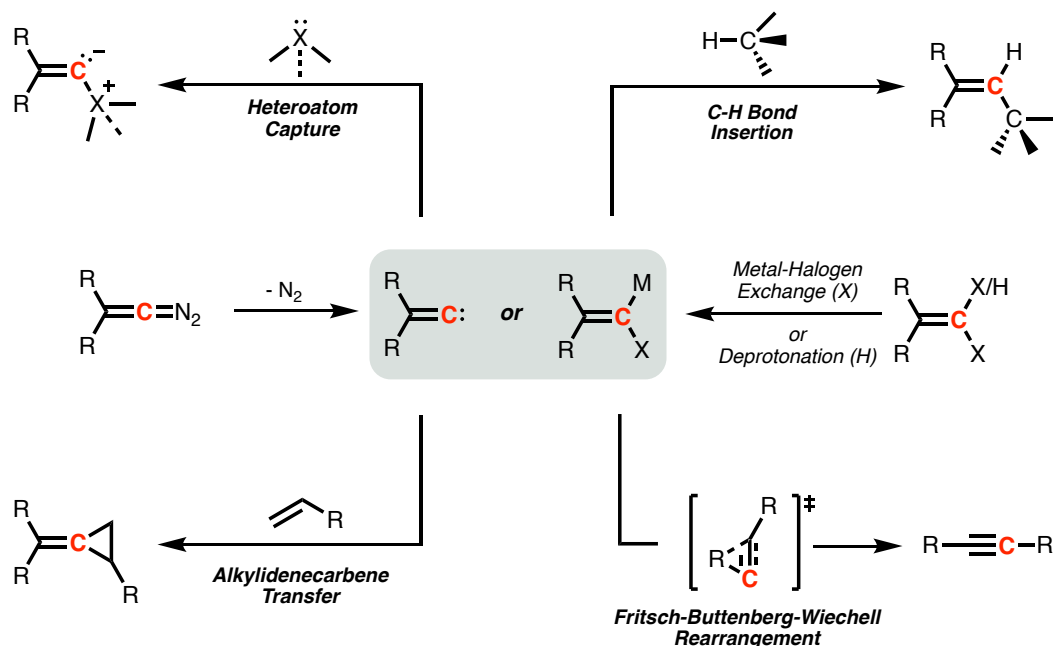


Figure 12. Transformations of alkylidenecarbenes.

The FBW rearrangement was first reported in 1894 and named after its discoverers, Fritsch, Buttenberg, and Wiechell. This transformation involves the preparation of diarylacetylenes from 2,2-diaryl-1-halogenoalkenes in the presence of sodium ethoxide in ethanol, at high temperatures (Figure 13).⁷⁵

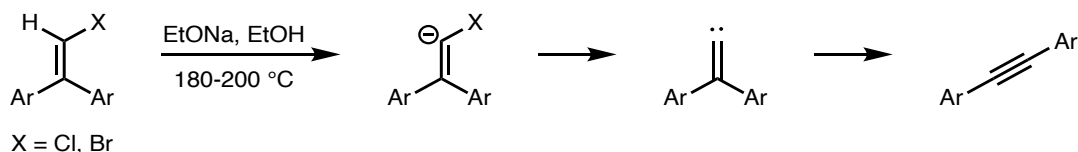


Figure 13. Original Fritsch-Buttenberg-Wiechell rearrangement

FBW rearrangements are energetically favorable by as much as -45 kcal/mol (theory),⁷⁶ -47.4 kcal/mol (observed)⁷⁷ with an activation barrier of about 1.5 kcal/mol, allowing for a lifetime of picoseconds.⁷⁸ The migratory aptitude of carbene substituents has been measured as $\text{H} \approx \text{Ph} > \text{alkyl}$.^{79,80} The migratory aptitude of alkyl chains has been explored by Walsh and show the trend tertiary > secondary > primary, suggesting more electron-donating group are more likely to migrate.⁸¹

One of the most common uses of FBW rearrangement is as key steps of the Corey-Fuchs reaction.⁸² This methodology has been utilized in a variety of applications, notably the synthesis of polyynes and carbon allotropes, carbynes, by Tykwinski.^{83,84} Despite the focus on 1–5 insertion, the ability to convert carbonyl groups to alkynes is very powerful, particularly with the use of Ohira-Bestmann reagent. This reagent was utilized by Li in the synthesis of (±)- δ -rubromycin.⁸⁵ This reagent was also used by Reddy during the synthesis of oplopandiol, oploxyne A, and (–)-oploxyne B.⁸⁶ In a previous work, Wardrop has employed the 1,2 rearrangement of an alkylidenecarbene, generated by dehydration of 1-(5-hydroxyalkyl)tetrazoles in the synthesis of combretastatin A4.⁸⁷

4. Hypothesis and Preliminary Results

Despite the powerful utility of converting carbonyl groups to alkynes, there has been little research into the synthesis of cyclooctynes using an alkylidenecarbene, leaving this area of research ripe for exploration. In collaboration with Dr. Shahid Islam, DFT studies (Figure 14) shows that the overall transformation of alkylidenecarbene **47** to DIBO is calculated to have a low activation barrier (5.8 kcal/mol), but more importantly, is exothermically favorable (-39.5 kcal/mol).

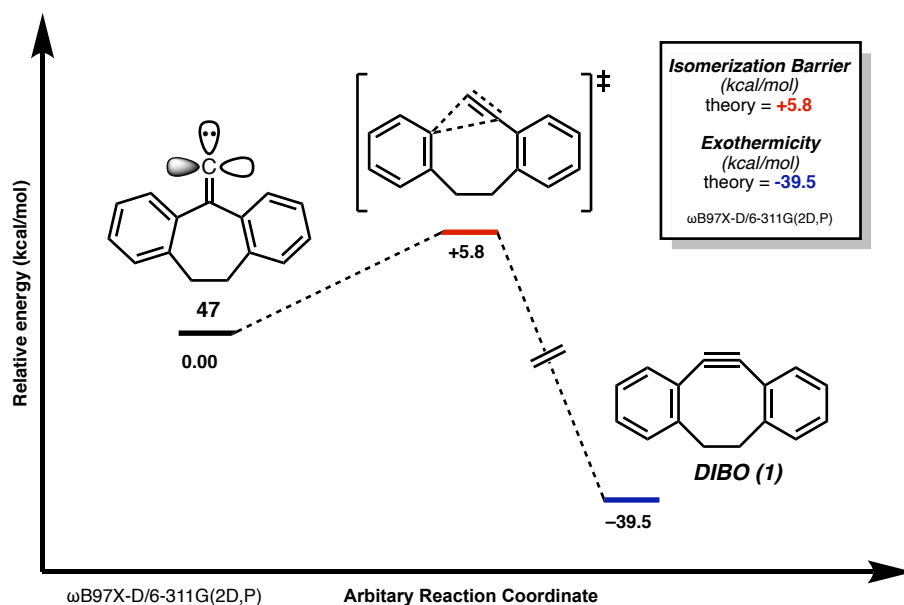


Figure 14. DFT energy diagram of alkylidenecarbene rearrangement

The formation of cyclooctynes by ring expansion via 1,2-shift was first reported in 1959 by Curtin (Figure 15).⁸⁸ While exploring the reactivity of phenyllithium with vinyl halides, he reacted diarylvinylchloride **48** with phenyllithium and isolated the ring expanded cyclooctene **51** in modest yield. He postulated that the deprotonation and ipso-elimination of vinyl chloride **48** gave rise to an alkylidenecarbene **49** which goes rearrangement to form dibenzoannulated cyclooctyne (DIBO). Due to its high reactivity from ring strain the cyclooctyne undergoes nucleophilic attack with excess phenyllithium to form vinylphenyl lithium **50**, which on protonation yields **51**.

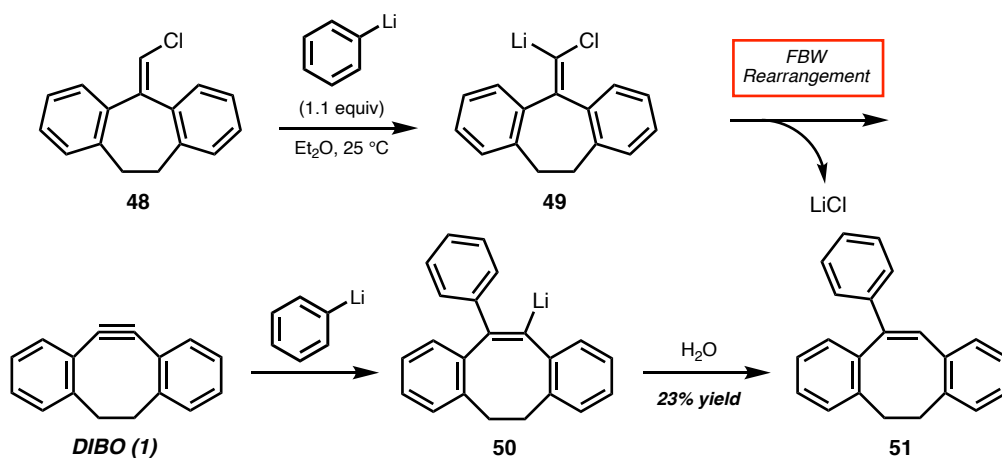


Figure 15. Treatment of diarylvinylchlorides with phenyllithium by Curtin.

Wanting to avoid cyclooctyne reactivity with harsh reaction conditions, we opted towards a method that allow for latent alkylidenecarbene formation, which was reported by Behringer,⁸⁹ where he reported that the pyrolysis of various 1-(5-substitutedalkyl)tetrazoles resulted in formation of phenylacetylene **56**. He proposed tetraazafulvene intermediate **53** was generated after expulsion of the leaving group. He postulated that the fragmentation of **53** proceeded in two discrete steps; initial loss of the dinitrogen generates diazoalkane **54**, which undergoes a second nitrogen expulsion event to yield alkylidenecarbene intermediate **55**, followed by a 1,2-shift, rearranging into diphenylacetylene **56** (Figure 16).

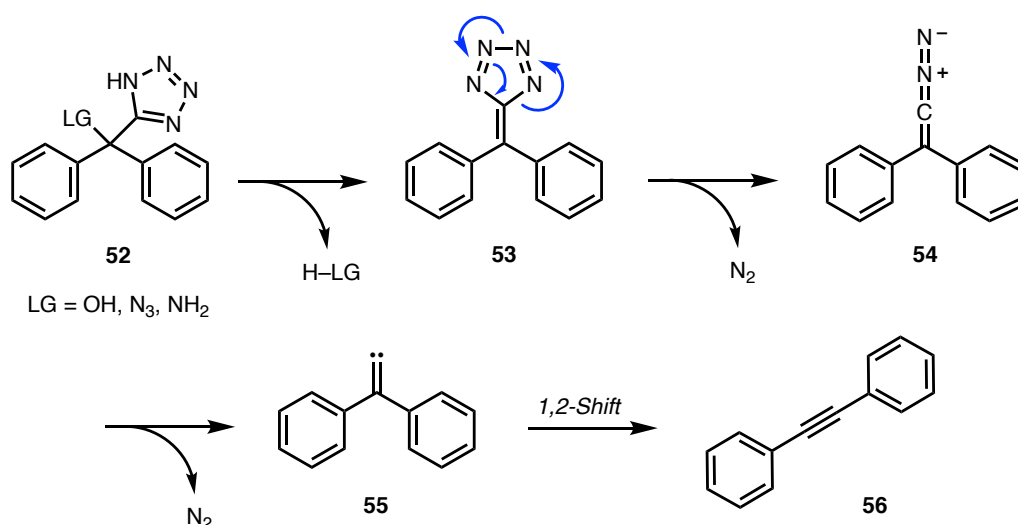


Figure 16. Proposed Mechanism of the Pyrolysis of 5-(1-Hydroxyalkyl)tetrazoles

With an efficient method for the preparation of 5-(1-hydroxyalkyl)tetrazoles secured, we questioned whether we would be able to apply this chemistry to the preparation of cyclooctynes from 5-(1-hydroxyalkyl)tetrazoles via a latent alkylidenecarbene in the presence of a dehydrating agent that can subsequently undergo rearrangement into the strained ring that can also be trapped in situ (Figure 17). This would allow formation of cyclooctynes under mild reaction conditions

that can also be intercepted in situ, provide versatile scope, and more importantly, circumvent the need for preconstruction of an eight-membered ring core.

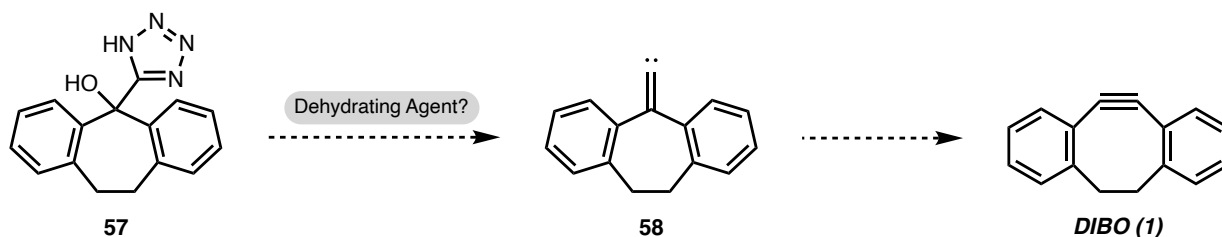


Figure 17. Our hypothesis towards the preparation of cyclooctynes.

We first opted to see if pyrolysis of **57** would result in the substituted alkyne DIBO upon reflux in toluene (Figure 18). We were delighted to be able to isolate the cyclooctyne in moderately low yield with the remaining reaction mixture recovered as starting material. This supported our hypothesis that 5-(1-hydroxyalkyl)tetrazoles could be used as alkyne precursors.

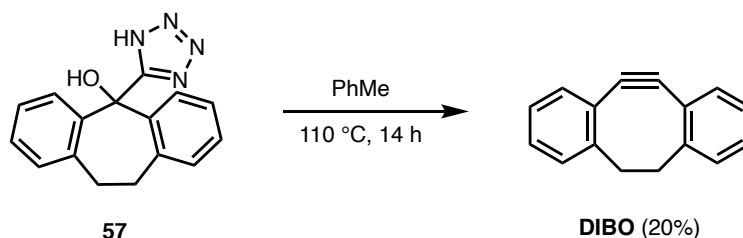


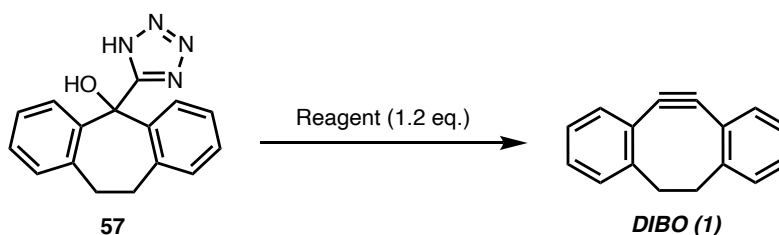
Figure 18. Pyrolysis of 5-(1*H*-tetrazol-5-yl)-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (**57**)

5. Results and Discussion

5.1 Optimization of Ring Expansion

With our preliminary synthesis of DIBO achieved, we sought to optimize the conditions to the efficiency of ring expansion. Since the byproducts of the reactions are dinitrogen and water, we postulated that a dehydrating agent would be suitable to promote the fragmentation. We chose to limit our search mild dehydration reagents, to avoid harsh reaction conditions. We also sought to use reagents that would preferentially lead to *O*-activation, rather than *N*-activation and, thereby

maximizing the scope of our methodology, catalyzing the dehydration. A range of solvents were also examined, including aqueous conditions as water-solubility is an important consideration in the development of bioconjugation reactions. A summary of the results is below (Figure 19).



Entry	Dehydrating Agent	Solvent	T (°C)	Yield (%)
1	-	PhMe	110	20
2	DIC	DCM	40	74
3	EDC	DCM	40	88
4	DAST	DCM	40	80
5	POP	DCM	25	78 ^a
6	EDC	PhMe	110	98
7	EDC	THF/H ₂ O (1:1)	65	66
8	EDC	MeOH	65	34
9	EDC	H ₂ O	100	50

^a yield of dibenzosuberone

Figure 19. Optimization Studies—Fragmentation and Rearrangement

Dehydration reagents that would undergo rearrangement under mild reaction conditions were preferred; as used in a previous methodology to synthesize linear alkynes,⁸⁷ a range of carbodiimides were initially screened. DIC (Entry 2) and EDC (Entry 3) were equally high yielding, but EDC was preferred due to its higher efficiency and ease of use. DCC was also evaluated, but an accurate yield could not be determined due the difficulty in isolating the product from dicyclohexylurea. We also found that increasing the reagent equivalents did not have an effect on yield of the reaction.

Other dehydration reagents including such the fluorinating agent diethylaminosulfur trifluoride (DAST) was also evaluated and provided DIBO in excellent yield (Entry 4); however, due to the abundance of fluoride in the reaction, we questioned whether this would be a viable reagent for synthesis of more reactive cyclooctynes. Triphenylphosphonium anhydride trifluoromethane sulfonate (Hendrickson ‘POP’) reagent was screened as well but produced an interest result (Entry 5). Our attempt to synthesize DIBO through the use of Hendrickson reagent did not provide the desired alkyne (Entry 8), but it provided dibenzosuberone in good yield, which was the starting material for making the 5-(1-hydroxyalkyl)tetrazole. We believe this is due to *N*-activation of the tetrazole instead of *O*-activation as was our intention (Figure 20).

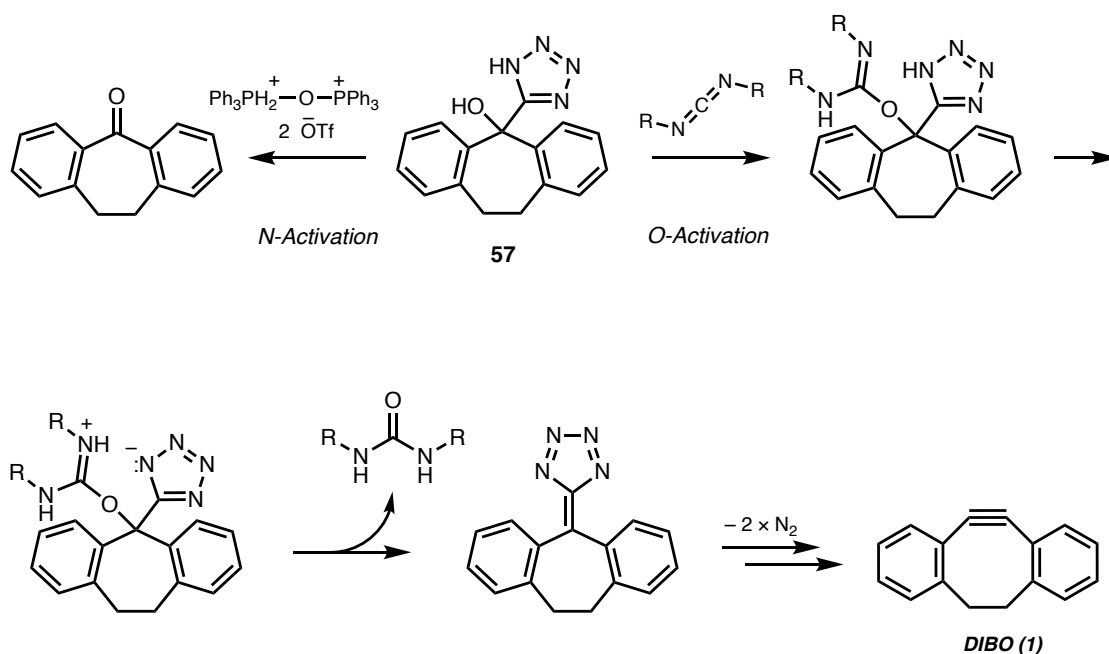


Figure 20. *N*-Activation vs *O*-Activation Mechanistic Pathways.

Due to its high yield and mildness, EDC was chosen as the dehydration reagent of choice. Solvents were also screened. It was noted that no reaction took place when the reaction was stirred at room temperature, thus requiring elevated temperatures. Undergoing the reaction in refluxing DCM provided excellent yields with EDC (Entry 3). Toluene (Entry 6) was also evaluated and

provided near quantitative yields; however, we were cautious whether synthesis of transient alkynes would be stable in refluxing toluene thus opting for lower temperatures.

The use of more polar solvents, resulted in decreased yields, possibly due to reaction of the alkylidenecarbene; there have been reports of oxonium ylide formation with alkylidenecarbenes (Figure 21, A) in THF, which resulted moderate yield (Entry 7).⁹⁰ Conducting the reaction in methanol (Entry 8) yielded low efficiency due to methanol insertion of the alkylidenecarbene (Figure 21, B), which was noted upon GCMS analysis. Despite the decreased yield, the ability to conduct the reaction in water (Entry 9) is truly remarkable and potentially has important consequences for the application of this to biological assays and protein tagging in situ.

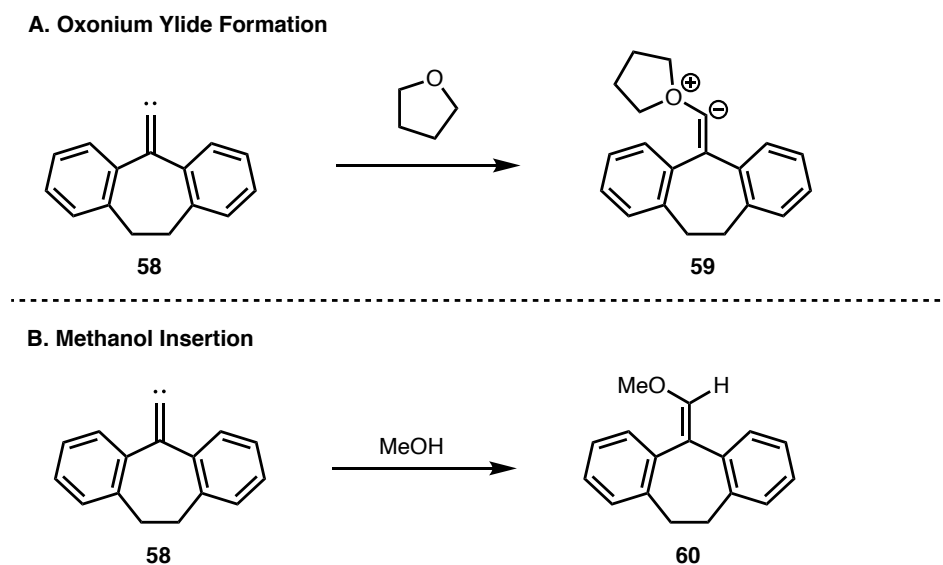


Figure 21. Alkylidenecarbene reactivity in THF and methanol.

5.2 Substrate Scope Studies—Generation of Isolable Cyclooctynes

With our optimized conditions, we analyzed the substrate scope of this methodology. In this regard, we targeted substrates that were readily prepared from dibenzosuberone that would provide ample functional group tolerance, as well as the possibility for further functionalization. We extended the scope towards monosubstituted dibenzosuberone derivatives as this could be a

potentially attractive as a capping ligator. In addition to showing the tolerance and scope to new substrates, we synthesized known alkynes so as to directly compare the efficiency of our method with that of others. The substrates were prepared utilizing the methodology in Chapter 1.⁹¹ The results are summarized herein.

Disubstituted DIBO derivatives showed overall excellent yield with good functional group tolerance. Aryl halides (**62a**, **62b**) are tolerable with high efficiency under this methodology and can be further functionalized if necessary. Thioethers and linear alkynes are also tolerated. Arylether **62f** was formed in lower yield possibly due to stabilization of the tetrazafulvene intermediate proposed by Behringer (Figure 23).⁸⁹ The added stability prevents decomposition towards the alkylidenecarbene, allowing the tetrazafulvene to become susceptible to other reactions.

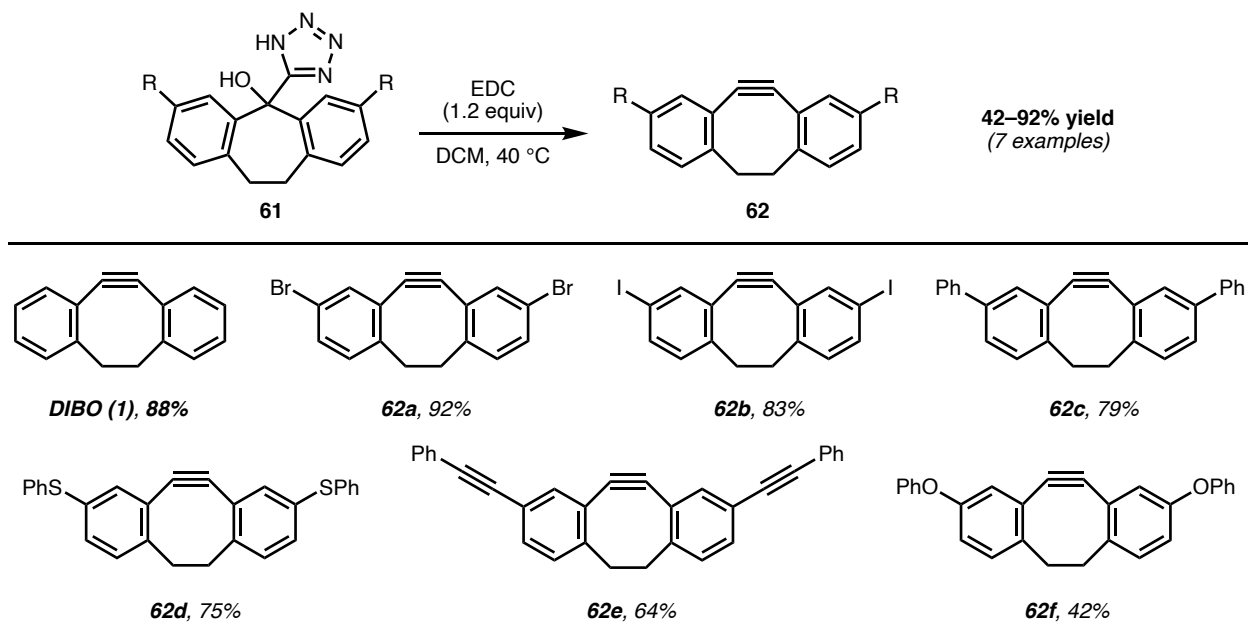


Figure 22. Substrate Scope Studies–Disubstituted DIBO Derivatives

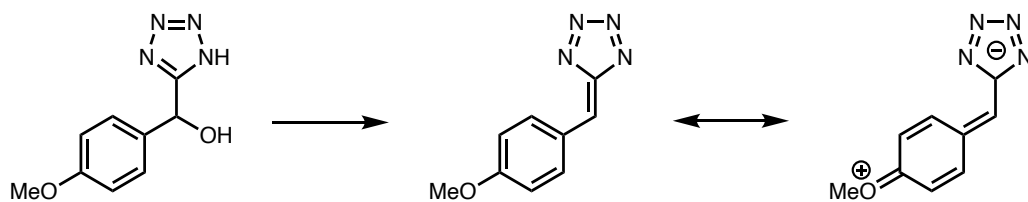


Figure 23. Stabilization of tetrazafulvene intermediate

Monosubstituted DIBO derivatives were also accessed in good yields (Figure 21). Aryl bromide **64a** was formed in high yield, while methoxy-substituted DIBO **64b** and **64c** were only moderately efficient (Figure 23).⁸⁹ Aniline-derivative **64d** was also prepared with good efficiency, potentially allowing for peptide conjugation.

The synthesis of known cyclooctynes provided mixed results, primarily due to their inherent reactivity (Figure 24). ODIBO was synthesized with excellent efficiency, while BARAC was isolated in low yield. This was primarily due to its high reactivity of the additional sp^2 centers on the eight-member ring. To add further evidence of this, when attempting to synthesize the unsaturated versions of DIBO, **64e** and **64f**, these readily decomposed and were unisolatable. **64e** have been isolated by Sondheimer as “golden yellow crystals, which proved to be very unstable. Thus, it decomposed after being allowed to stand for a few minutes at room temperature with protection from light or air.”⁹² Monobenzocyclooctyne (MOBO) proved to be volatile at room temperature, and thus difficult to isolate.

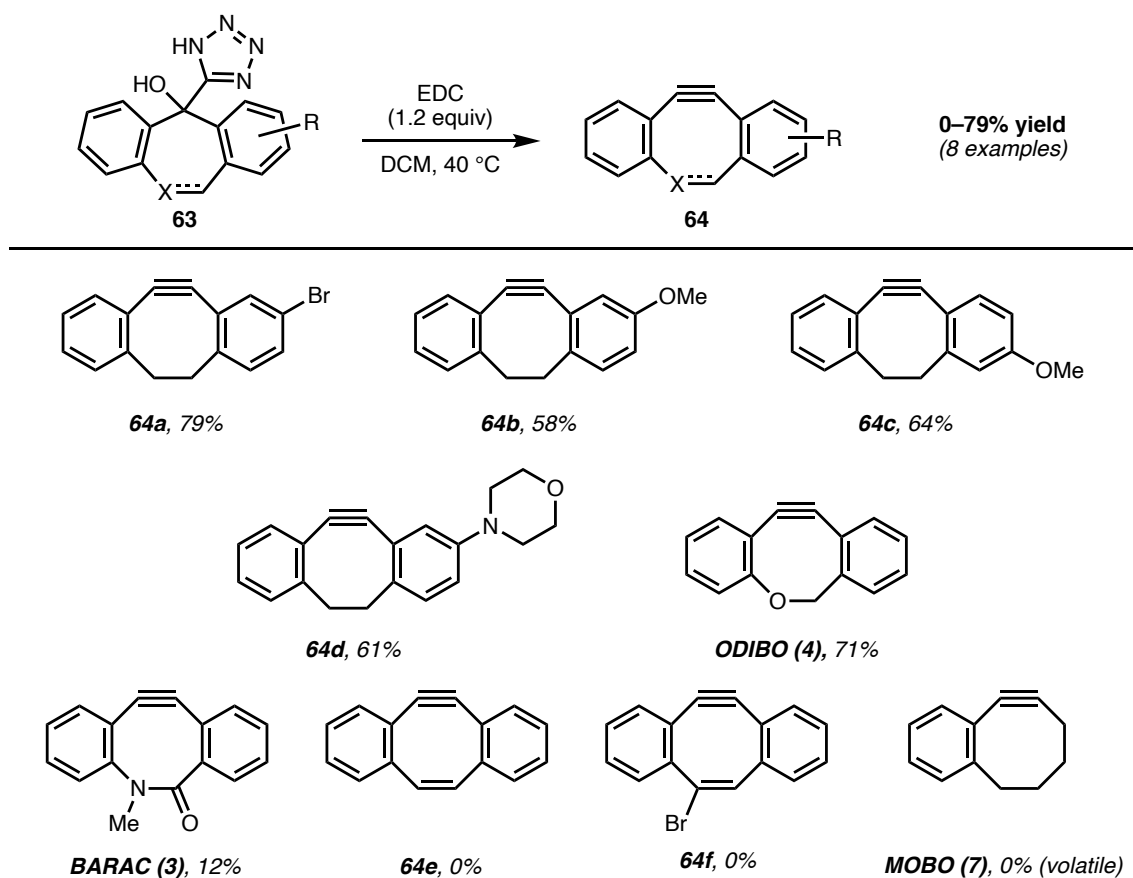


Figure 25. Substrate Scope Studies–Monosubstituted DIBO Derivatives

Ultimately, this method has shown good efficiency of cyclooctynes with a simpler synthetic route than previous methods. Most starting cycloheptanones are either commercially available, such as dibenzosuberone and dibenzosuberone, or can be functionalized through either halogenation or cross-coupling. The ease of synthesizing the precursors allows this method to be more attractive and more efficient when compared to previous methods. Also, this method does not utilize harsh reaction conditions such as strong bases, allowing for milder conditions. Additionally, the ability for cyclooctynes preparation to be done in aqueous conditions, coupled with the urea byproduct, allows our method to potentially be used *in vivo*.

5.3. Substrate Scope Studies–Intercepting Transient Cyclooctynes

Due to the inability to isolate more unstable alkynes, we questioned whether trapping these cyclooctynes in situ might be possible using our methodology. We decided to employ the same reaction conditions, a 5-(1-hydroxyalkyl)tetrazole treated with EDC in refluxing DCM, but in the presence of an ynophile. The alkyne trap of choice was benzyl azide, as it is the trademark for many bioconjugations. The cautionary note was whether the transient alkynes would be trapped in situ, which has been a limiting factor for previous methodologies. Our results are summarized in Figures 26 and 27.

Our 5-(1-hydroxyalkyl)tetrazoles were treated with EDC in DCM with 5 equivalents of benzyl azide. Unsurprisingly, the disubstituted DIBO analogs were successfully trapped in situ in the presence of benzyl azide to form the resulting triazoles (Figure 26). In the monosubstituted substrates, regioisomers were formed and the resultant ratios were measured by ¹H NMR spectroscopy, most being 1:1, with the exception of when larger groups such as bromine **66h** and morpholine **66k**, allowing the possibility of selectivity control between regioisomers. We attributed this selectivity due to the steric hindrance of the larger groups on the aromatic rings. We speculated that substitution on the peri-position of the aromatic rings would allow further selectivity, but we became wary of hindering the formation of the cyclooctyne with carbodiimide.

yield and interestingly good selectivity, due to the absence of one aromatic ring allowing for less steric hindrance on that side.

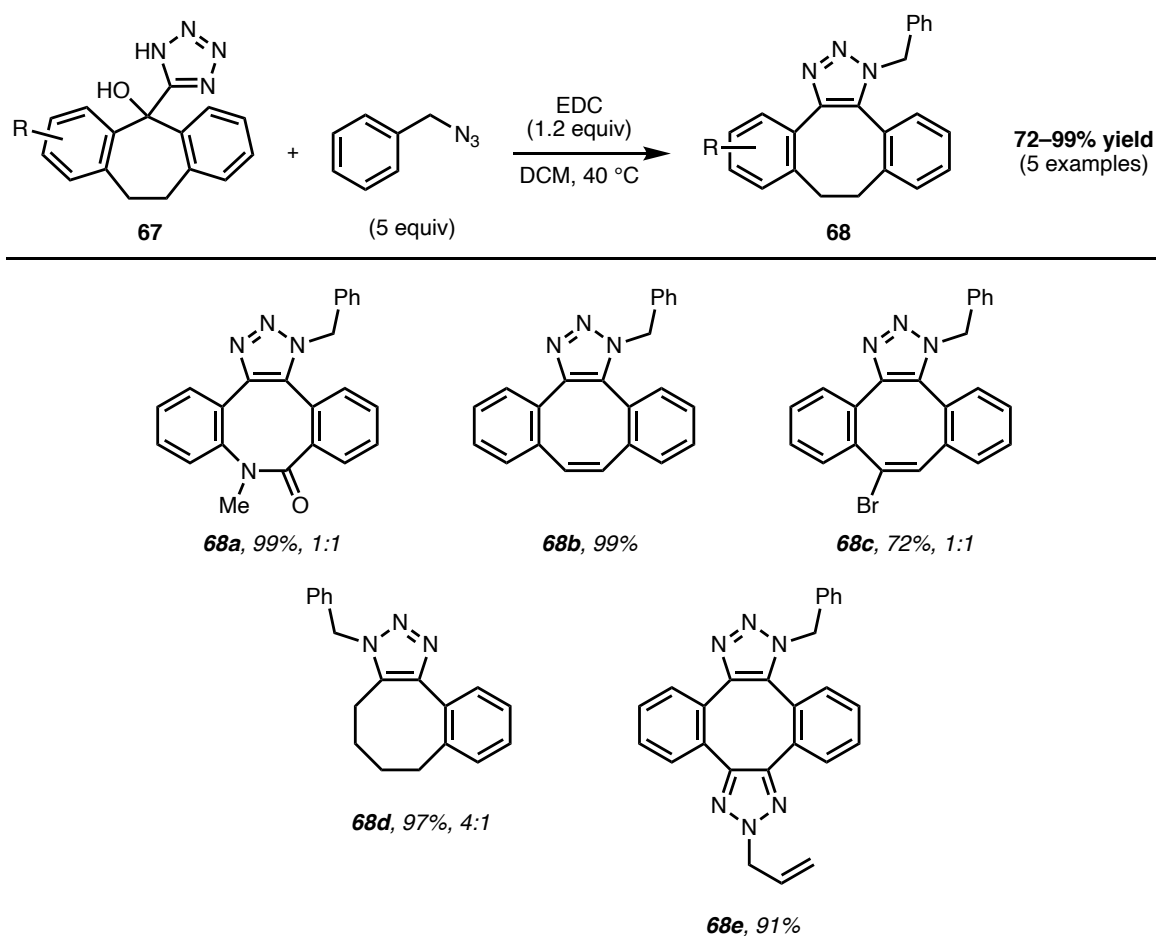


Figure 27. Substrate Scope Studies–Interception of Transient Cyclooctynes with Benzyl Azide

With this method, we displayed the ability to trap stable and transient cyclooctynes in situ with benzyl azide. This allows access for reactive cyclooctynes to be used as potential intermediates, as well as the possibility to allow access towards smaller ring cycloalkynes. Additionally, for unsymmetric cyclooctynes, selectivity was displayed due to steric hindrance with meta substitution on the aromatic ring. This allows avenue towards selectivity control for formation of one regioisomer over the other, where it could become favorable in biological application. With these

two methods displayed, we turned our attention to diversify the ynophiles to analyze the trapping efficacy of 1,3-dipoles towards transient cyclooctynes.

5.4 Substrate Scope Studies—Other Ynophiles

Despite benzyl azide being the standard trap for cyclooctyne, we sought to diversify the scope of our methodology by applying to various trapping agents. We hoped to provide some insight in the trapping affinity of these various reagents. Also, this would allow our methodology to be more attractive due to its diversity to easily accessible heterocycles such as indolizines and pyrazoles.

We examined several reagents that would cycloadduct with a strained cyclooctyne in a [3+2] and [4+2] fashion. We did not experiment with metal complexes, so this could provide another avenue of research. The strained cyclooctyne we chose was the one that would stem from dibenzosuberone, or unsaturated DIBO, due to its simpleness of NMR analysis. As previous stated, the additional sp^2 centers allow for increased strain and thus Sondheimer's cyclooctyne (**70**) is unstable at room temperature. The results are summarized in Figure 24.

The traps that undergo [3+2] cycloaddition with cyclooctyne exhibited overall good efficiency with yields ranging from moderate to near quantitative (Figure 28). Benzyl azide (**72**) proved to be the “industry standard” as the trap of choice, displaying near quantitative yield to provide access to triazoles. Pyridine ylide,⁹³ **76** and **80**, allowed access to indolizine cores in good yields, while also providing handle for further functionalization. Both diazo compounds⁹⁴ and syndones⁹⁵ allow access to pyrazoles of various substitution. Syndone **74** have recently come to the forefront of cycloalkyne trapping as they display high rates of reactivity and excellent efficiency, while allowing access to *N*-substituted pyrazoles. Diazo compounds, in this case ethyl diazoacetate (**78**), trapped cyclooctyne in moderate yields, while also allowing access to 3-substituted pyrazoles.

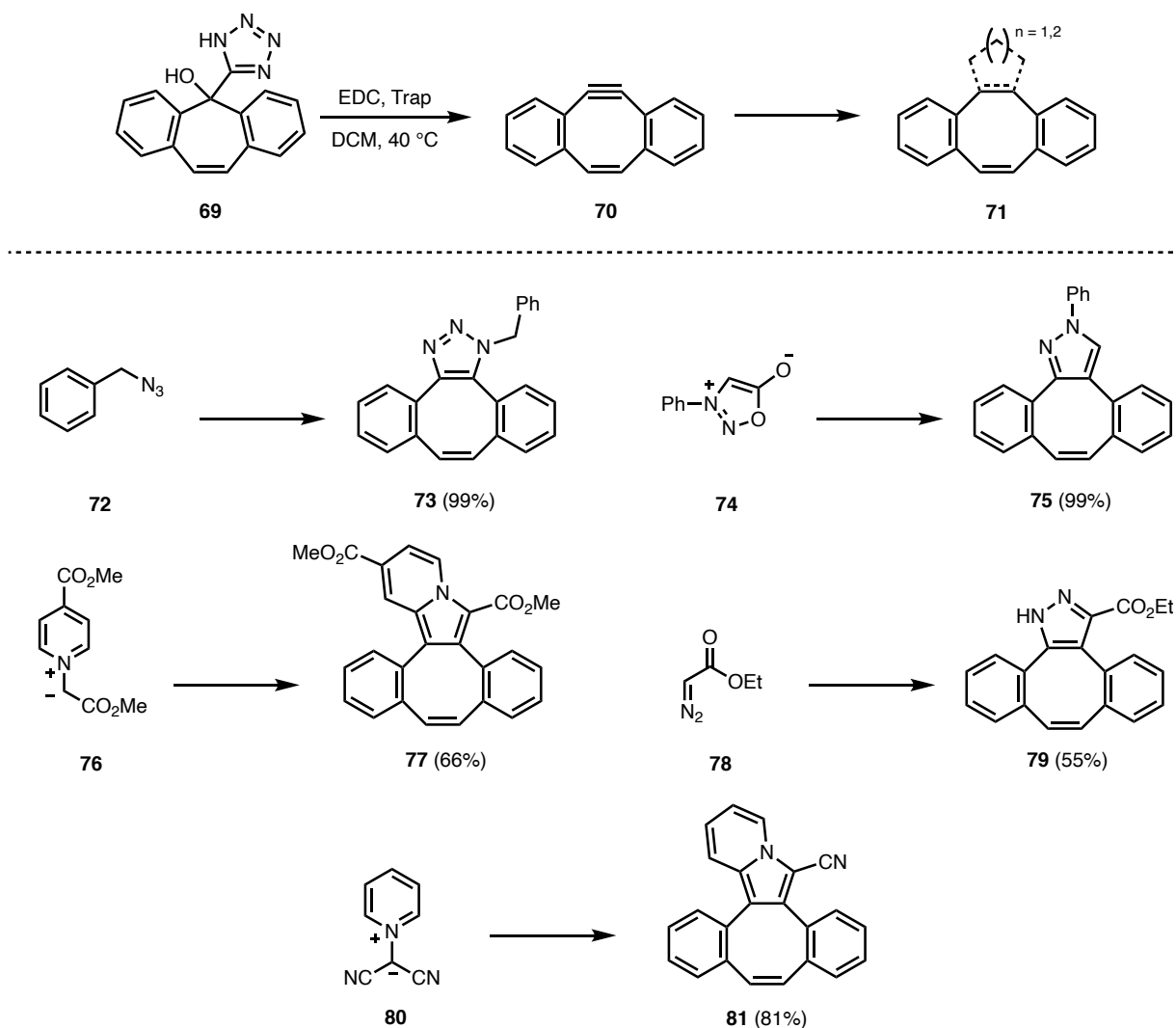


Figure 28. Substrate Scope Studies–Interception with 1,3-Dipoles.

The second group of trapping reagents reacted with cyclooctyne **70** in a [4+2] cycloaddition. Pyrones⁹⁶ were found to trap cyclooctyne in good yields, while also providing an additional aromatic ring which can often times be difficult to synthesize in natural products. Also, the substitution of the pyrone can allow for further functionalization, such as an ester in this case. Trapping with tetrazine^{30 97} allowed access to pyridazine derivatives in good yield. Cycloaddition to the in situ formed pyridazine, also known as “double addition”, was not observed in appreciable amount, however this route could be explored with equivalent manipulation of the alkyne and tetrazine trap. Cyclooctyne has been reported to react with oxadiazole and thiodiazole in moderate

yield in dioxane at about 60 °C in dioxane.²⁷ We predicted that by using a more reactive alkyne, would allow trapping at lower temperatures. Interestingly, no trapping product observed, despite the cyclooctyne's elevated ground state.

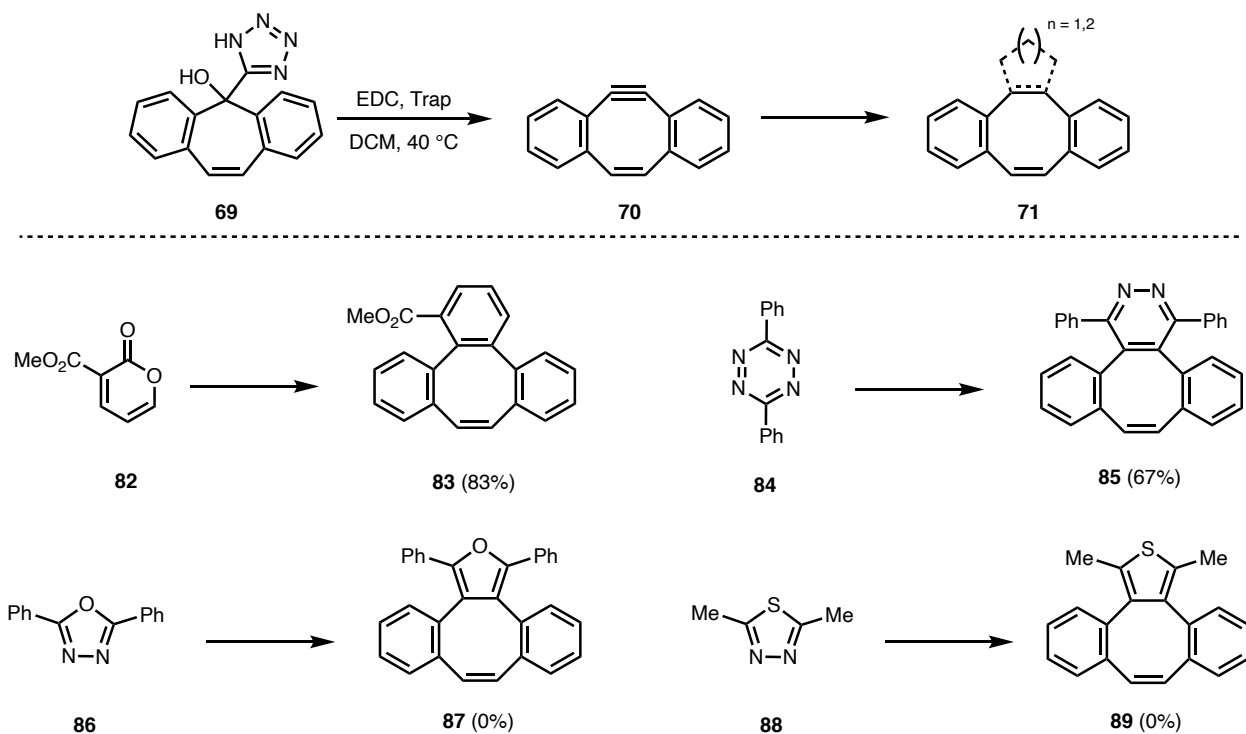


Figure 29. Substrate Scope Studies–Interception with 1,4-Dipoles.

5.5 Mass Spec

The mechanism of our methodology was also explored serendipitously. Our proposal (Figure 30) was similar to Behringer's postulated mechanism, where dehydration of **90** with carbodiimide would condense water in the form of urea **96** resulting in tetrazafulvene **91**. This would then undergo one event of nitrogen expulsion, forming diazo compound **92**. A second extrusion of dinitrogen resulted in alkylidenecarbene **93**, which would undergo a 1,2-shift forming diphenylacetylene (**94**).

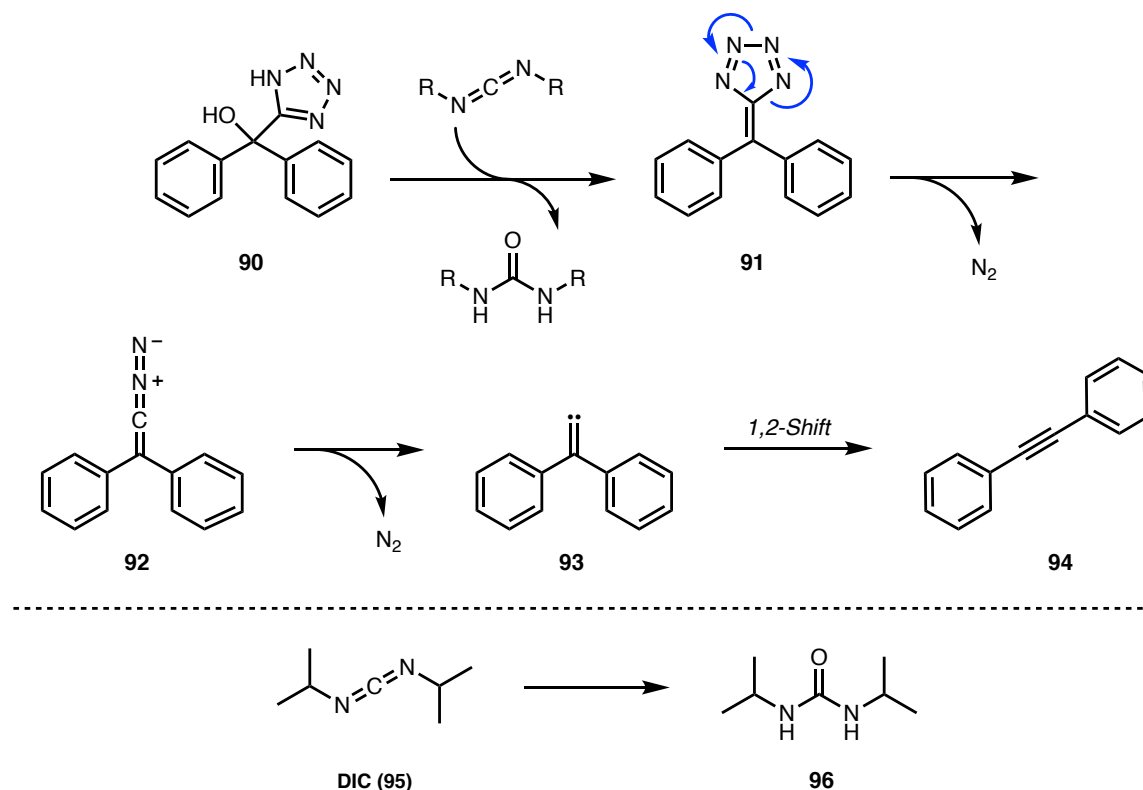


Figure 30. Proposed Mechanism of our Methodology.

Analysis of the MS spectrum of **90** identified each intermediate in our proposed mechanism, essentially confirming our proposal (Figure 31). In collaboration with Professor Cologna, we are currently deciphering whether this process takes place thermally or is acid catalyzed. If the transformation is thermal, the reaction would happen within the electrospray droplet emitter tip. The acid catalyzed pathway would take place within the microdroplets that have been known to accelerate reactions.⁹⁸

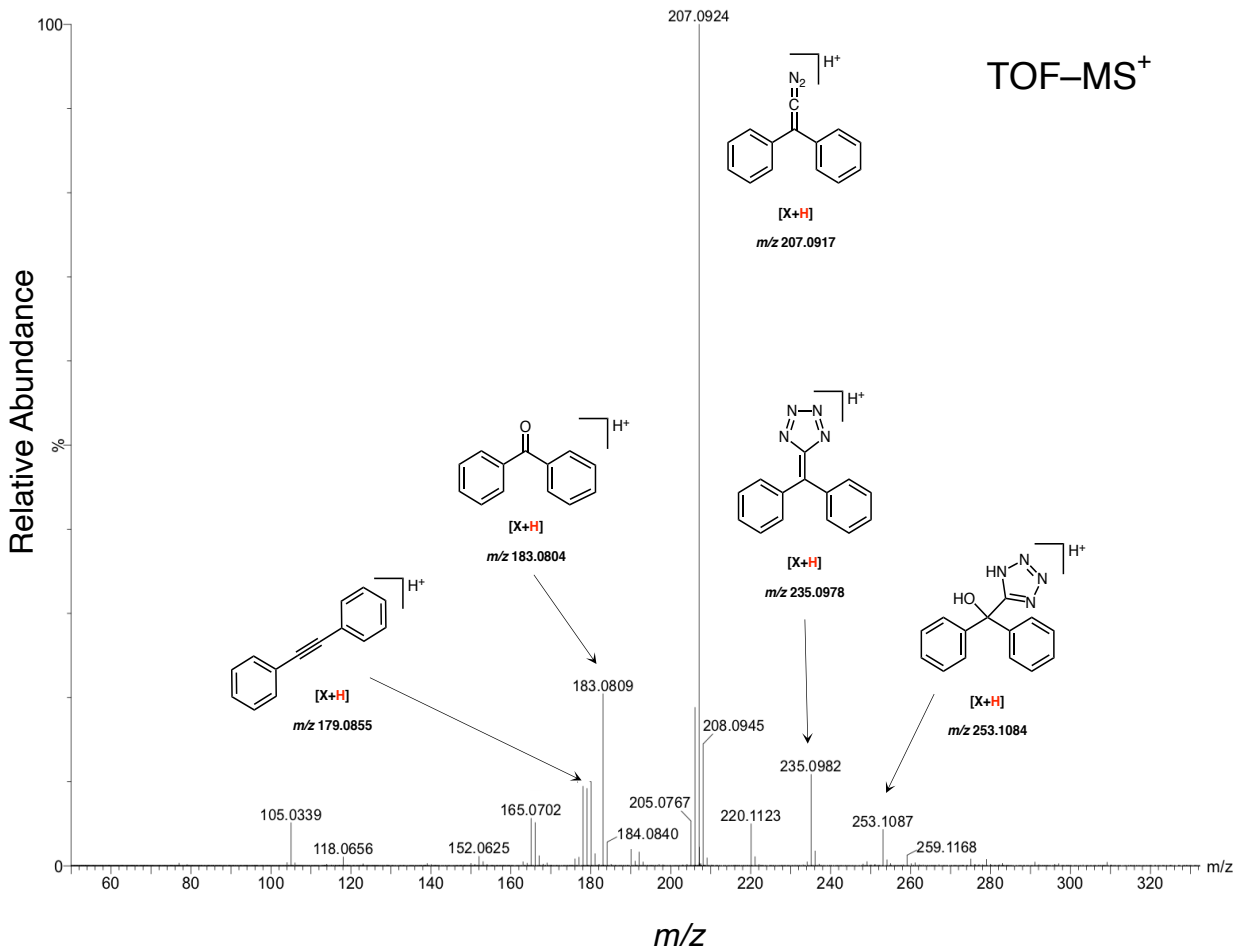


Figure 30. Mass Spec of Diphenyl(1*H*-tetrazol-5-yl)methanol

6. Conclusion

Cyclooctynes has been of great importance in numerous fields, primarily in bioconjugation. Development of these transient species has advanced over many years, yet their overall efficiency is still depleted. Recent discoveries have allowed their reactivity to be accelerated by additional angle strain via addition of sp² carbons on the eight-member ring. Advances have allowed for in-situ trapping of transient alkynes, while also allowing isolation of stable cyclooctynes. Despite recent advances for the formation of cyclooctynes becoming more and more efficient, their synthesis suffers from the use of harsh reaction conditions, such as strong bases or high

temperatures, or require lengthy synthetic routes towards their precursors, which often times can become inefficient overall.

We have developed a method that utilizes the dehydrative fragmentation of 5-(1-hydroxyalkyl)tetrazoles as latent alkylidenecarbenes that will undergo FBW rearrangement with ring expansion to form the cyclooctyne efficiently under mild reaction conditions. The synthesis of the precursors is easily accessible, stemming from either commercially available cycloheptanones or straightforward modification, providing optimal access towards cyclooctynes, when compared to previous methods (Figure 25). Additionally, transient cyclooctynes can be trapped in situ by a variety of alkynophiles, providing access to a variety of heterocycles that could be utilized for further synthesis.

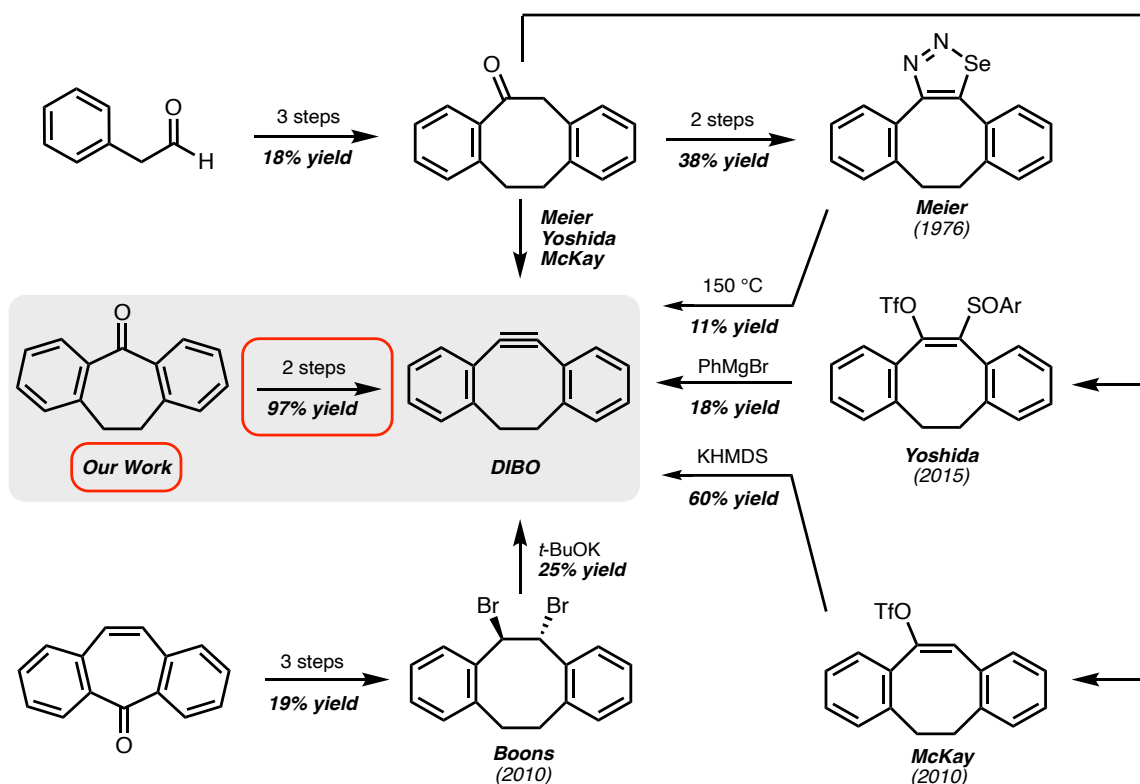


Figure 31. Comparison of our methodology with previous methods.

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Appendix A, Cyclooctynes

1. General Comments

1.1 General Methods

All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Visualization was accomplished by UV light (254 nm), potassium permanganate solution, or phosphomolybdic acid solution. Flash column chromatography was performed according to the method of Still¹ using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

1.2 Materials

Anhydrous tetrahydrofuran (THF) was passed through a solvent dispensing system under a dry argon atmosphere. All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

1.3 Instrumentation

All melting points were determined in unsealed Pyrex capillaries with a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide disks, or thin films on sodium chloride or zinc selenide plates using an ATI Mattson Genesis series FTIR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, ¹H, 100 MHz, ¹³C) or a Bruker Avance 500 (500 MHz, ¹H, 125 MHz, ¹³C) spectrometer. Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.26 ppm for ¹H; δ 78.0 ppm for ¹³C), methanol (δ 3.31 ppm for ¹H; δ 49.2 ppm for ¹³C), acetone (δ 2.05 ppm for ¹H; δ 29.9 ppm for ¹³C), and dimethyl sulfoxide (δ 2.50 ppm for ¹H; δ 39.5 ppm for ¹³C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), m (multiplet) and br (broad) app (apparent). The identification of ¹H and ¹³C signals was achieved using a combination of ¹H, ¹³C, DEPT, COSY, HMBC, HMQC and NOESY experiments. High-resolution electrospray ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass Q-ToF Ultima instrument at the University of Illinois Mass Spectrometry Laboratory. High-resolution electron ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass 70-VSE instrument at the University of Illinois Mass Spectrometry Laboratory.

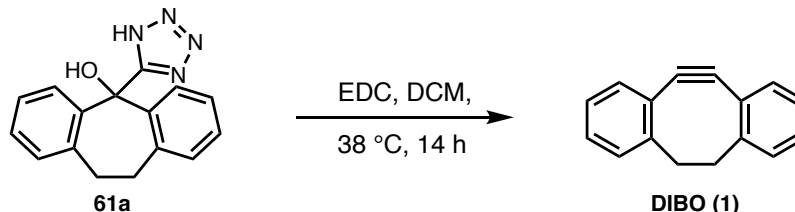
1.4 Safety Precautions!

While all procedures involving tetrazoles were conducted without incident, it is advisable to take appropriate safety precautions, such as the use of shields in a fume hood and personal protection equipment, when undertaking work with these potentially energetic heterocycles.

2. Experimental Details

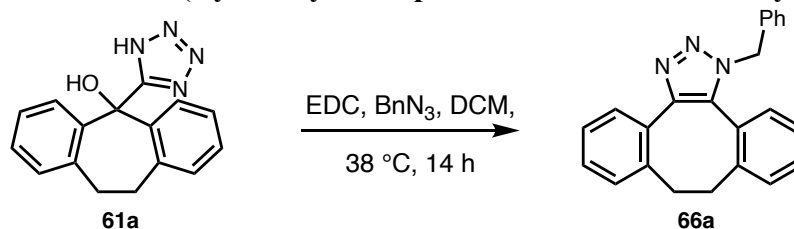
2.1 Representative Procedures

Representative Procedure 1 (Cyclooctyne Preparation without Trapping)



To an oven-dried vial equipped with a stir bar was added **61a** (55.7 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv). The vial was flushed with nitrogen and anhydrous DCM (2 mL) was added. The reaction was heated to 38 °C over 14 hours. The reaction was then transferred to a column of silica to which the final product was purified by flash column chromatography on silica gel (hexanes) to provide **1** (35.8 mg, 88%).

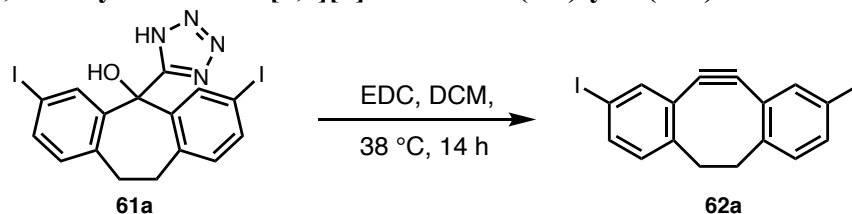
Representative Procedures 2 (Cyclooctyne Preparation with Various Alkynohiles)



To an oven-dried vial equipped with a stir bar was added **61a** (55.7 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv). The vial was flushed with nitrogen and anhydrous DCM (2 mL) and benzyl azide (125 μ L, 1 mmol, 5 equiv) was added. The reaction was heated to 38 °C over 14 hours. The reaction was then transferred to a column of silica to which the final product was purified by flash column chromatography on silica gel (EtOAc/Hexanes 1:3) to provide **66a** (61.8 mg, 92%).

2.2 Cycloalkyne Formation without Trapping

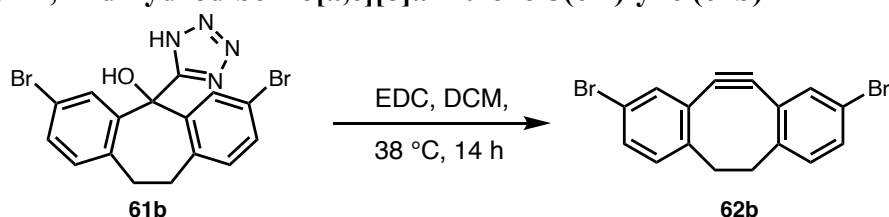
3, 8-Diiodo-11,12-dihydrodibenzo[a,e][8]annulene-5(6H)-yne (**62a**)²

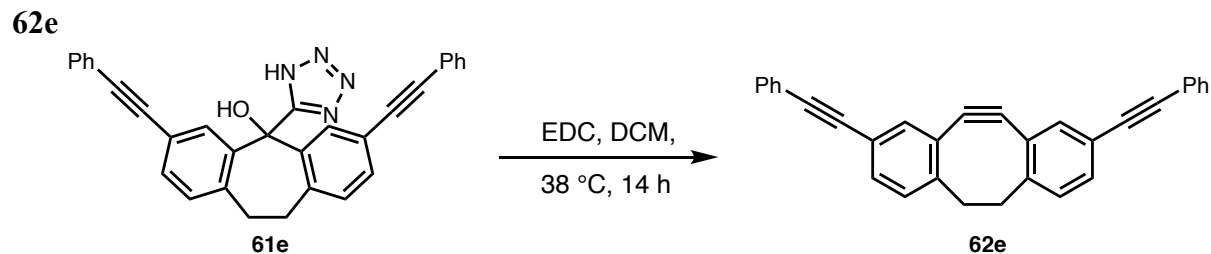


Following Representative Procedure 1, a solution of **61a** (106 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **62a** (75 mg, 83 %): white solid; mp 160-163 °C; FTIR ν_{max} 3043, 2942, 2922, 2844, 2144, 1888, 1741,

1585, 1537, 1467, 1463, 1434, 1413, 1398, 1384, 1327, 1292, 1273, 1261, 1155, 1092, 1067, 954, 946, 904, 876, 814, 760, 876, 615, 576, 558 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.66 (d, J = 1.1 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 3.30—3.21 (m, 2H), 2.35—2.25 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 153.19 (s, 1C), 137.26 (s, 1C), 135.23 (s, 1C), 131.39 (s, 1C), 126.09 (s, 1C), 111.45 (s, 1C), 91.52 (s, 1C), 36.17 (s, 1C). HRMS-EI $^+$ calcd for $\text{C}_{16}\text{H}_{10}\text{I}_2$ $[\text{M}]^+$: 455.8872, found: 455.8874.

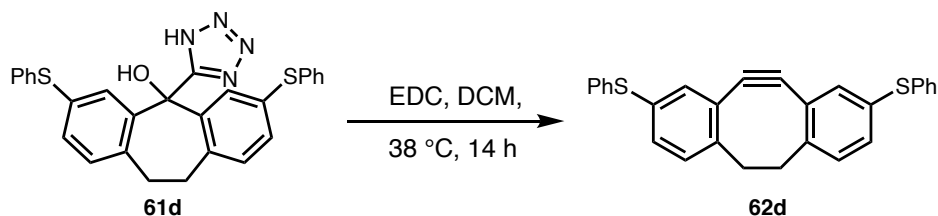
3, 8-Dibromo-11,12-dihydrodibenzo[a,e][8]annulene-5(6H)-yne (62b)





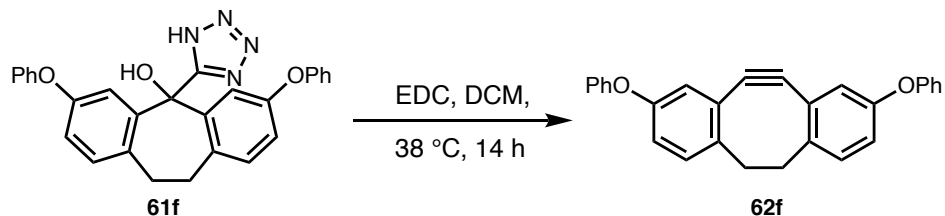
Following Representative Procedure 1, a solution of **61e** (96 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **62e** (52 mg, 64 %): tan solid; mp 169–171 °C; FTIR ν_{max} 3049, 2917, 2850, 2209, 2152, 1946, 1606, 1569, 1544, 1490, 1470, 1455, 1440, 1397, 1318, 1294, 1277, 1260, 1246, 1216, 1174, 1158, 1128, 1069, 978, 908, 894, 881, 833, 797, 750, 686, 668, 614, 592 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.59–7.56 (m, 4H), 7.54–7.50 (m, 2H), 7.47 (d, J = 1.7 Hz, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.42–7.35 (m, 6H), 7.32 (s, 1H), 7.30 (s, 1H), 3.39–3.29 (m, 2H), 2.50–2.41 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 153.85 (s, 1C), 132.05 (s, 1C), 131.35 (s, 1C), 129.90 (s, 1C), 129.47 (s, 1C), 128.78 (s, 1C), 124.48 (s, 1C), 123.52 (s, 1C), 122.20 (s, 1C), 111.69 (s, 1C), 109.96 (s, 1C), 90.12 (s, 1C), 89.08 (s, 1C), 36.64 (s, 1C). HRMS-EI⁺ calcd for $\text{C}_{32}\text{H}_{20}$ $[\text{M}]^+$: 404.1565, found: 404.1566.

62d



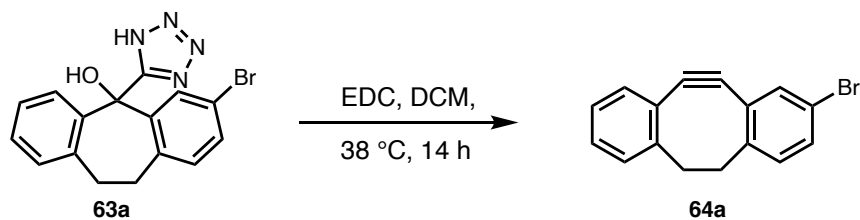
Following Representative Procedure 1, a solution of **61d** (99 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **62d** (63 mg, 75 %): brown solid; mp 95–98 °C; FTIR ν_{max} 3072, 3055, 3019, 2954, 2921, 2848, 2160, 1593, 1581, 1540, 1478, 1472, 1438, 1412, 1385, 1335, 1328, 129, 1267, 1195, 1181, 1163, 1125, 1107, 1080, 1068, 1022, 999, 978, 956, 903, 892, 864, 821, 810, 790, 747, 732, 706, 684, 666, 647, 615, 599, 582, 576 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.44 (dd, J = 7.7, 1.2 Hz, 1H), 7.40 (d, J = 0.5 Hz, 1H), 7.38 (s, 2H), 7.36 (s, 1H), 7.33 (s, 1H), 7.31 (s, 3H), 7.28 (s, 1H), 7.24 (t, J = 3.9 Hz, 1H), 3.35–3.25 (m, 2H), 2.44–2.35 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 152.68 (s, 1C), 134.67 (s, 1C), 131.66 (s, 1C), 130.70 (s, 1C), 130.47 (s, 1C), 129.79 (s, 1C), 129.71 (s, 1C), 128.77 (s, 1C), 127.71 (s, 1C), 125.14 (s, 1C), 111.88 (s, 1C), 36.34 (s, 1C). HRMS-EI⁺ calcd for $\text{C}_{28}\text{H}_{20}\text{S}_2$ $[\text{M}]^+$: 420.10065, found: 420.10047.

3, 8-Diphenoxy-11,12-dihydrodibenzo[a,e][8]annulene-5(6H)-yne (62f)



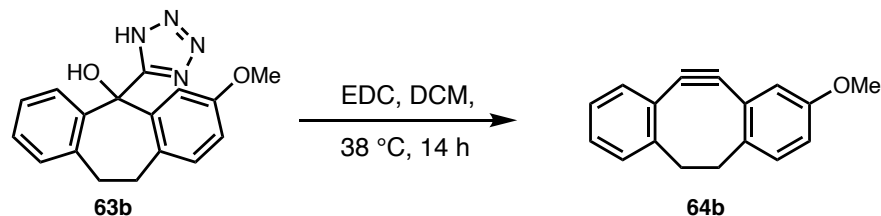
Following Representative Procedure 1, a solution of **61f** (46 mg, 0.1 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **62f** (16 mg, 42 %): white solid; mp 93-97 °C; FTIR ν_{max} 3061, 3037, 2910, 2847, 2165, 2034, 1941, 1612, 1588, 1560, 1487, 1469, 1454, 1417, 1337, 1295, 1273, 1228, 1180, 1165, 1135, 1116, 1068, 1020, 984, 943, 898, 876, 833, 820, 768, 712, 689, 631, 599, 578, 566, 552 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.37 (d, J = 15.9 Hz, 4H), 7.30—7.27 (m, 3H), 7.14 (td, J = 7.4, 3.6 Hz, 2H), 7.06—7.02 (m, 3H), 6.99—6.97 (m, 2H), 6.96—6.93 (m, 2H), 3.37—3.27 (m, 2H), 2.46—2.36 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 157.49 (s, 1C), 156.22 (s, 1C), 148.94 (s, 1C), 130.70 (s, 1C), 130.20 (s, 1C), 125.24 (s, 1C), 123.82 (s, 1C), 119.29 (s, 1C), 118.62 (s, 1C), 116.91 (s, 1C), 111.74 (s, 1C), 36.31 (s, 1C). HRMS-EI⁺ calcd for $\text{C}_{28}\text{H}_{20}\text{O}_2$ $[\text{M}]^+$: 388.14633, found: 388.14704.

3-Bromo-11,12-dihydrodibenzo[a,e][8]annulene-5(6H)-yne (64a)



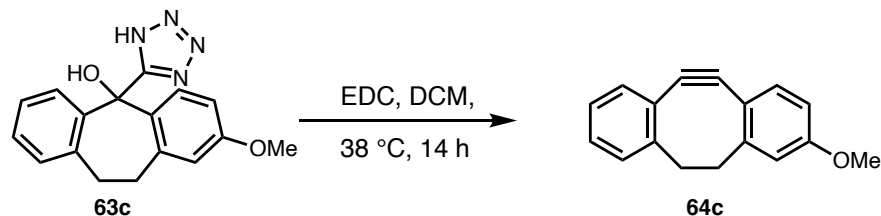
Following Representative Procedure 1, a solution of **63a** (71 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **64a** (45 mg, 79 %): tan solid; mp 95-99 °C; FTIR ν_{max} 3067, 3012, 2951, 2917, 2851, 2152, 1953, 1916, 1846, 1842, 1783, 1627, 1600, 1584, 1563, 1543, 1505, 1460, 1451, 1440, 1402, 1336, 1300, 1259, 1248, 1197, 1170, 1159, 1116, 1086, 1069, 1034, 978, 958, 939, 903, 872, 813, 798, 756, 719, 665, 633, 577 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.48 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.2, 2.1 Hz, 1H), 7.39—7.28 (m, 4H), 7.19 (d, J = 8.1 Hz, 1H), 3.36—3.26 (m, 2H), 2.44—2.35 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 153.97 (s, 1C), 152.64 (s, 1C), 131.04 (s, 1C), 130.88 (s, 1C), 129.90 (s, 1C), 129.28 (s, 1C), 128.51 (s, 1C), 127.05 (s, 1C), 126.66 (s, 1C), 126.42 (s, 1C), 123.79 (s, 1C), 120.36 (s, 1C), 113.50 (s, 1C), 110.26 (s, 1C), 36.61 (s, 1C), 36.39 (s, 1C). HRMS-EI⁺ calcd for $\text{C}_{16}\text{H}_{11}\text{Br}$ $[\text{M}]^+$: 282.0044, found: 282.0046.

3-Methoxy-11,12-dihydrodibenzo[a,e][8]annulene-5(6H)-yne (64b)



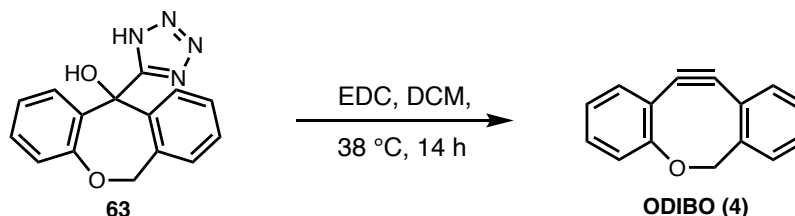
Following Representative Procedure 1, a solution of **63b** (62 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **64b** (27 mg, 58 %): white solid; mp 87-90 °C; FTIR ν_{max} 3057, 3012, 2956, 2934, 2836, 2160, 2148, 1950, 1878, 1610, 1595, 1560, 1480, 1463, 1450, 1435, 1422, 1333, 1320, 1298, 1273, 1254, 1240, 1192, 1168, 1151, 1111, 1086, 1036, 974, 949, 943, 932, 884, 870, 861, 815, 772, 754, 726, 713, 674, 634, 604, 595, 574, 564 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.34—7.25 (m, 5H), 6.93 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.4, 2.5 Hz, 1H), 3.86 (s, 3H), 3.29 (qd, J = 11.2, 7.3 Hz, 2H), 2.50—2.44 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 159.80 (s, 1C), 155.79 (s, 1C), 153.52 (s, 1C), 129.72 (s, 1C), 127.66 (s, 1C), 127.46 (s, 1C), 126.91 (s, 1C), 126.19 (s, 1C), 124.77 (s, 1C), 116.58 (s, 1C), 116.23 (s, 1C), 112.08 (s, 1C), 111.74 (s, 1C), 110.79 (s, 1C), 55.78 (s, 1C), 37.19 (s, 1C), 36.76 (s, 1C). HRMS-EI⁺ calcd for $\text{C}_{17}\text{H}_{14}\text{O}$ $[\text{M}]^+$: 234.1045, found: 234.1044.

4-Methoxy -11,12-dihydrodibenzo[a,e][8]annulene-5(6H)-yne (64c)



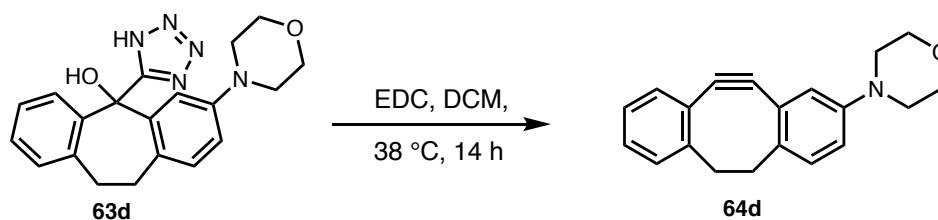
Following Representative Procedure 1, a solution of **63c** (62 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **64c** (30 mg, 64 %): oil; FTIR ν_{max} 3056, 3030, 3011, 2956, 2935, 2917, 2835, 2160, 1591, 1877, 1732, 1610, 1595, 1560, 1480, 1463, 1449, 1434, 1422, 1333, 1298, 1273, 1254, 1239, 1192, 1167, 1151, 1111, 1086, 1036, 975, 949, 943, 932, 884, 870, 861, 815, 772, 753, 726, 713, 674, 634, 594, 574, 565 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.33 (ddd, J = 6.5, 4.6, 2.3 Hz, 2H), 7.30—7.28 (m, 2H), 7.27—7.25 (m, 1H), 6.94 (d, J = 2.6 Hz, 1H), 6.82 (dd, J = 8.4, 2.6 Hz, 1H), 3.86 (s, 3H), 3.29 (dq, J = 11.1, 5.5 Hz, 2H), 2.50—2.44 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 159.81 (s, 1C), 155.80 (s, 1C), 153.52 (s, 1C), 129.74 (s, 1C), 127.65 (s, 1C), 127.46 (s, 1C), 126.91 (s, 1C), 126.19 (s, 1C), 124.77 (s, 1C), 116.58 (s, 1C), 116.23 (s, 1C), 112.08 (s, 1C), 111.76 (s, 1C), 110.79 (s, 1C), 55.78 (s, 1C), 37.20 (s, 1C), 36.77 (s, 1C). HRMS-ESI calcd for $\text{C}_{17}\text{H}_{15}\text{O}$ $[\text{M}+\text{H}]^+$: 235.1123, found: 235.1115.

Oxadibenzocyclooctyne (ODIBO, **4**)³



Following Representative Procedure 1, a solution of **63** (56 mg, 0.2 mmol, 1 equiv) and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **4** (29 mg, 71 %): white solid; mp 126-128 °C; FTIR ν_{max} 3061, 3027, 2923, 2921, 2852, 2249, 2161, 1940, 1721, 1698, 1682, 1651, 1598, 1573, 1483, 1454, 1444, 1402, 1375, 1350, 1265, 1207, 1159, 1106, 1036, 984, 947, 906, 837, 798, 755, 727, 647, 638, 606 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.47—7.40 (m, 2H), 7.38—7.34 (m, 2H), 7.32—7.31 (m, 1H), 7.30—7.28 (m, 1H), 7.24 (dd, $J = 7.9, 0.7$ Hz, 1H), 7.16—7.13 (m, 1H), 5.34—5.31 (m, 1H), 4.60 (d, $J = 12.1$ Hz, 1H); ^{13}C NMR (126 MHz; CDCl_3) δ 169.79 (s, 1C), 147.11 (s, 1C), 130.14 (s, 1C), 129.27 (s, 1C), 128.92 (s, 1C), 127.91 (s, 1C), 126.90 (s, 1C), 126.29 (s, 1C), 125.76 (s, 1C), 123.88 (s, 1C), 122.02 (s, 1C), 117.88 (s, 1C), 114.18 (s, 1C), 111.61 (s, 1C), 77.86 (s, 1C). HRMS-ESI calcd for $\text{C}_{15}\text{H}_{10}\text{O}$ $[\text{M}]^+$: 206.07317, found: 206.07304.

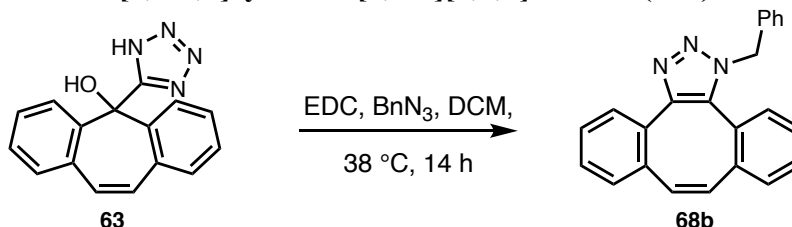
3-Morpholino-11,12-dihydrodibenzo[a,e][8]annulene-5(6H)-yne (**64d**)



Following Representative Procedure 1, a solution of **63d** (6 mg, 0.0165 mmol, 1 equiv) and EDC (4 mg, 0.0198 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (hexanes) **64d** (3 mg, 61 %): white solid; mp 136-138 °C; FTIR ν_{max} 3050, 2952, 2919, 2852, 2162, 1738, 1651, 1604, 1548, 1480, 1449, 1432, 1377, 1340, 1300, 1278, 1263, 1231, 1213, 1188, 1174, 1159, 1125, 1078, 1048, 1028, 1003, 970, 933, 911, 887, 853, 845, 813, 748, 737, 721, 701, 667, 633, 617, 592, 572 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.35—7.21 (m, 6H), 6.94—6.84 (m, 2H), 3.91—3.89 (m, 4H), 3.34—3.25 (m, 2H), 3.22—3.15 (m, 4H), 2.46—2.35 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 154.09 (s, 1C), 130.32 (s, 1C), 130.24 (s, 1C), 129.80 (s, 1C), 128.10 (s, 1C), 126.83 (s, 1C), 126.49 (s, 1C), 125.02 (s, 1C), 124.25 (s, 1C), 115.53 (s, 1C), 114.02 (s, 1C), 111.86 (s, 1C), 108.99 (s, 1C), 104.17 (s, 1C), 94.59 (s, 1C), 67.24 (s, 1C), 49.98 (s, 1C), 37.15 (s, 1C), 35.92 (s, 1C). HRMS-ESI calcd for $\text{C}_{20}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 290.1545, found: 290.1534.

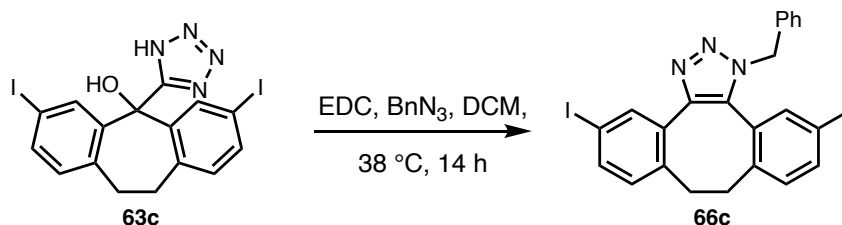
2.2 Cycloalkyne Formation with Azide Trapping

(*Z*)-1-Benzyl-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**68b**)



Following Representative Procedure 2, a solution of **63** (56 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **68b** (67 mg, 99 %): white solid; mp 139-141 °C; FTIR ν_{max} 3060, 3030, 3007, 2953, 2921, 2851, 1948, 1732, 1693, 1673, 1644, 1604, 1574, 1505, 1496, 1482, 1454, 1425, 1398, 1351, 1331, 1313, 1301, 1278, 1243, 1208, 1159, 1126, 1111, 1094, 1075, 1044, 1024, 101, 985, 952, 909, 879, 861, 818, 791, 773, 755, 743, 722, 692, 651, 623, 590, 555 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.61—7.59 (m, 1H), 7.37—7.31 (m, 3H), 7.29—7.25 (m, 4H), 7.19—7.15 (m, 2H), 7.09—7.05 (m, 3H), 6.66 (d, J = 12.4 Hz, 1H), 6.51 (d, J = 12.4 Hz, 1H), 5.55 (d, J = 2.3 Hz, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 147.39 (s, 1C), 139.28 (s, 1C), 137.55 (s, 1C), 135.74 (s, 1C), 134.17 (s, 1C), 131.63 (s, 1C), 130.83 (s, 1C), 130.72 (s, 1C), 130.22 (s, 1C), 130.21 (s, 1C), 130.06 (s, 1C), 129.71 (s, 1C), 129.63 (s, 1C), 129.06 (s, 1C), 128.75 (s, 1C), 128.46 (s, 1C), 128.08 (s, 1C), 127.83 (s, 1C), 127.68 (s, 1C), 126.40 (s, 1C), 52.48 (s, 1C). HRMS-ESI calcd for $\text{C}_{23}\text{H}_{18}\text{N}_3$ $[\text{M}+\text{H}]^+$: 336.1501, found: 336.1501.

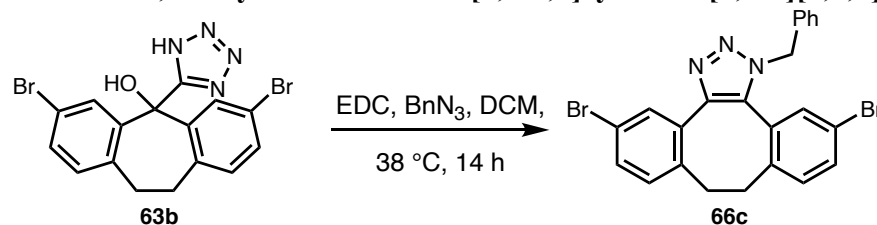
1-Benzyl-5,12-diiodo-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**66c**)



Following Representative Procedure 2, a solution of **63c** (106 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **66c** (93 mg, 79 %): white solid; mp 207-209 °C; FTIR ν_{max} 3062, 2936, 1616, 1589, 1568, 1495, 1479, 1452, 1424, 1378, 1360, 1336, 1309, 1278, 1241, 1207, 1167, 1133, 1122, 1104, 1083, 1038, 997, 974, 964, 952, 914, 905, 890, 881, 841, 822, 796, 778, 763, 744, 729, 712, 705, 691, 683, 666, 631, 613, 604, 595 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.70 (d, J = 2.2 Hz, 1H), 7.47—7.44 (m, 1H), 7.31 (ddq, J = 11.7, 5.9, 2.9 Hz, 4H), 7.19 (d, J = 2.0 Hz, 1H), 7.16—7.10 (m, 3H), 7.02—7.00 (m, 1H), 5.64—5.53 (m, 2H), 3.26—3.19 (m, 1H), 3.01—2.92 (m, 1H), 2.80—2.68 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 140.56 (s, 1C), 136.74 (s, 1C), 135.35 (s, 1C), 134.62 (s, 1C), 133.41 (s, 1C), 133.33 (s, 1C), 132.89 (s, 1C), 132.20 (s, 1C), 132.01 (s, 1C), 131.86 (s, 1C), 131.69 (s, 1C), 129.27 (s, 1C), 128.84 (s, 1C), 128.51 (s, 1C), 128.03 (s, 1C), 120.32 (s, 1C), 120.27 (s, 1C), 109.96 (s, 1C), 53.08

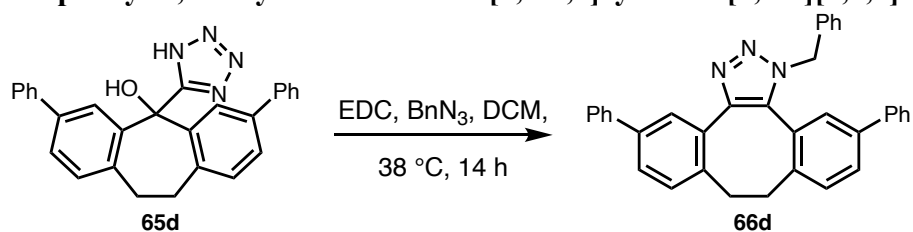
(s, 1C), 36.11 (s, 1C), 32.49 (s, 1C). HRMS-ESI calcd for $C_{23}H_{18}N_3I_2$ $[M+H]^+$: 589.9590, found: 589.9598.

1-benzyl-5,12-dibromo-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (66b)



Following Representative Procedure 2, a solution of **63b** (87 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **66b** (90 mg, 91 %): white solid; mp 178–181 °C; FTIR ν_{\max} 3030, 2944, 2930, 2888, 2869, 2851, 1581, 1556, 1494, 1475, 1456, 1422, 1397, 1374, 1355, 1331, 1301, 1272, 1239, 1210, 1204, 1173, 1157, 1133, 1119, 1101, 1072, 1035, 1001, 992, 969, 959, 950, 909, 894, 824, 811, 790, 774, 763, 748, 725, 708, 693, 683, 660, 650, 628, 614, 605, 596, 575, 565 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.70 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.2, 2.1 Hz, 1H), 7.33–7.27 (m, 4H), 7.18 (d, J = 2.0 Hz, 1H), 7.15–7.10 (m, 3H), 7.00 (d, J = 8.3 Hz, 1H), 5.64–5.52 (m, 2H), 3.21 (dt, J = 10.9, 5.4 Hz, 1H), 3.01–2.93 (m, 1H), 2.72 (dtd, J = 15.4, 10.1, 5.2 Hz, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 146.44 (s, 1C), 140.58 (s, 1C), 136.77 (s, 1C), 135.35 (s, 1C), 134.61 (s, 1C), 133.41 (s, 1C), 133.34 (s, 1C), 132.93 (s, 1C), 132.18 (s, 1C), 132.02 (s, 1C), 131.85 (s, 1C), 131.68 (s, 1C), 129.27 (s, 1C), 128.86 (s, 1C), 128.47 (s, 1C), 128.04 (s, 1C), 120.30 (s, 1C), 120.27 (s, 1C), 53.08 (s, 1C), 36.14 (s, 1C), 32.48 (s, 1C). HRMS-ESI calcd for $C_{23}H_{18}N_3Br_2$ $[M+H]^+$: 493.9867, found: 493.9871.

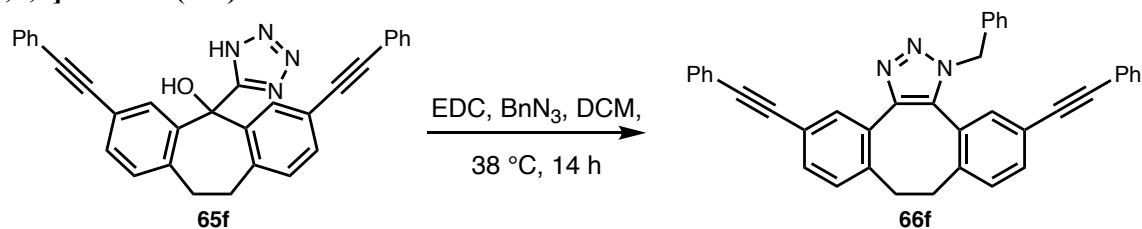
1-Benzyl-5,12-diphenyl-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (66d)



Following Representative Procedure 2, a solution of **65d** (86 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **66d** (80 mg, 81 %): white solid; mp 181–186 °C; FTIR ν_{\max} 3056, 3027, 2923, 2852, 1601, 1547, 1487, 1450, 1425, 1377, 1364, 1318, 1301, 1272, 1256, 1243, 1216, 1170, 1154, 1123, 1103, 1074, 1028, 1018, 1000, 967, 953, 924, 907, 896, 889, 836, 827, 782, 757, 746, 732, 720, 700, 693, 677, 666, 639, 626, 612, 597, 582 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.89 (d, J = 1.9 Hz, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.59 (dd, J = 8.0, 1.8 Hz, 1H), 7.49 (dd, J = 8.0, 1.9 Hz, 1H), 7.44–7.38 (m, 7H), 7.36–7.33 (m, 2H), 7.31–7.29 (m, 5H), 7.15–7.14 (m, 2H), 5.67 (dd, J = 82.8, 15.2 Hz, 2H), 3.44–3.39 (m, 1H), 3.19–3.13 (m, 1H), 3.04–2.98 (m, 1H), 2.90–2.85 (m, 1H); ^{13}C NMR (126 MHz; CDCl_3) δ 147.08 (s, 1C), 140.45 (s, 1C), 140.31 (s, 1C), 139.53 (s, 1C), 139.15 (s, 1C), 138.96 (s, 1C), 136.83 (s, 1C), 135.72 (s, 1C), 134.23 (s, 1C), 131.49 (s, 1C), 130.61 (s, 1C), 130.36 (s, 1C), 130.26 (s, 1C), 128.82 (s, 1C),

128.67 (s, 1C), 128.28 (s, 1C), 128.16 (s, 1C), 127.76 (s, 1C), 127.59 (s, 1C), 127.34 (s, 1C), 127.21 (s, 1C), 127.02 (s, 1C), 126.79 (s, 1C), 126.74 (s, 1C), 52.46 (s, 1C), 36.14 (s, 1C), 32.57 (s, 1C). HRMS-ESI calcd for $C_{35}H_{28}N_3$ $[M+H]^+$: 490.2283, found: 490.2272.

1-Benzyl-5,12-bis(phenylethynyl)-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (66f)



Following Representative Procedure 2, a solution of **65f** (96 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **66f** (99 mg, 92 %): white solid; mp 99-103 °C; FTIR ν_{max} 3058, 3030, 2929, 2884, 2206, 2186, 1732, 1597, 1470, 1557, 1548, 1496, 1454, 1441, 1424, 1406, 1378, 1361, 1344, 1329, 1310, 1271, 1240, 1211, 1176, 1157, 1128, 1114, 1095, 1069, 1040, 1027, 1000, 967, 902, 878, 834, 821, 752, 731, 713, 706, 688, 666, 623, 611, 585, 575 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.79 (d, J = 1.7 Hz, 1H), 7.51 (ddd, J = 10.1, 7.6, 2.7 Hz, 5H), 7.40—7.33 (m, 7H), 7.31—7.25 (m, 5H), 7.15—7.13 (m, 3H), 5.68—5.59 (m, 2H), 3.35—3.28 (m, 1H), 3.09—3.01 (m, 1H), 2.85 (td, J = 12.4, 5.1 Hz, 1H), 2.78—2.72 (m, 1H); ^{13}C NMR (101 MHz; CDCl_3) δ 146.93 (s, 1C), 141.88 (s, 1C), 138.25 (s, 1C), 135.64 (s, 1C), 135.26 (s, 1C), 133.84 (s, 1C), 133.09 (s, 1C), 132.58 (s, 1C), 131.99 (s, 1C), 131.45 (s, 1C), 131.40 (s, 1C), 130.61 (s, 1C), 130.38 (s, 1C), 129.18 (s, 1C), 128.93 (s, 1C), 128.83 (s, 1C), 128.71 (s, 1C), 128.56 (s, 1C), 128.12 (s, 1C), 127.04 (s, 1C), 127.02 (s, 1C), 123.74 (s, 1C), 123.27 (s, 1C), 122.09 (s, 1C), 121.75 (s, 1C), 109.96 (s, 1C), 90.65 (s, 1C), 90.00 (s, 1C), 89.27 (s, 1C), 88.56 (s, 1C), 53.02 (s, 1C), 36.67 (s, 1C), 33.05 (s, 1C). HRMS-ESI calcd for $C_{39}H_{28}N_3$ $[M+H]^+$: 538.2283, found: 538.2286.

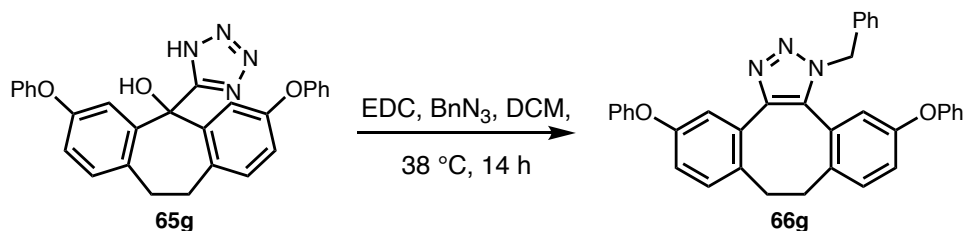
1-Benzyl-5,12-bis(phenylthio)-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (66e)



Following Representative Procedure 2, a solution of **65e** (50 mg, 0.1 mmol, 1 equiv), benzyl azide (0.06 mL, 0.5 mmol, 5 equiv), and EDC (23 mg, 0.12 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **66e** (47 mg, 85 %): white solid; mp 80-83 °C; FTIR ν_{max} 3055, 3029, 2925, 2884, 1948, 1666, 1580, 1557, 1538, 1495, 1475, 1454, 1438, 1397, 1374, 1358, 1336, 1302, 1271, 1241, 1210, 1173, 1156, 1111, 1082, 1067, 1037, 1023, 1000, 966, 886, 828, 811, 781, 731, 688, 666, 593, 560 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.58 (dd, J = 26.6, 1.7 Hz, 1H), 7.44—7.33 (m, 6H), 7.31 (t, J = 1.4 Hz, 1H), 7.29—7.22 (m, 7H), 7.18 (dt, J =

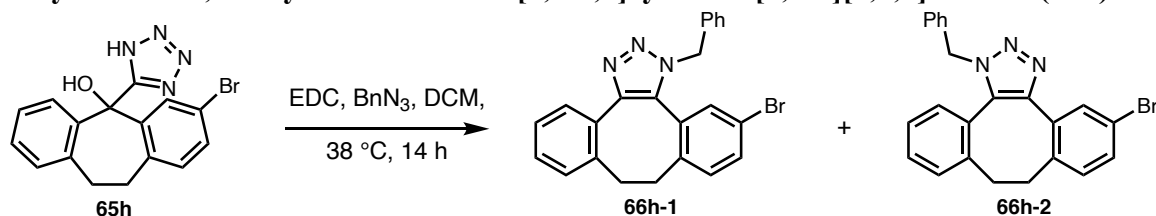
7.6, 3.5 Hz, 2H), 7.09—7.03 (m, 2H), 7.01—6.96 (m, 2H), 5.53—5.33 (m, 2H), 3.29—3.21 (m, 1H), 3.04—2.95 (m, 1H), 2.83—2.66 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 140.37 (s, 1C), 137.15 (s, 1C), 135.43 (s, 1C), 135.15 (s, 1C), 134.52 (s, 1C), 133.85 (s, 1C), 133.74 (s, 1C), 132.45 (s, 1C), 132.30 (s, 1C), 132.18 (s, 1C), 132.12 (s, 1C), 131.36 (s, 1C), 131.30 (s, 1C), 131.26 (s, 1C), 131.15 (s, 1C), 130.85 (s, 1C), 129.82 (s, 1C), 129.54 (s, 1C), 129.12 (s, 1C), 128.64 (s, 1C), 128.18 (s, 1C), 127.88 (s, 1C), 127.71 (s, 1C), 127.69 (s, 1C), 127.37 (s, 1C), 52.83 (s, 1C), 36.33 (s, 1C), 32.73 (s, 1C). HRMS-ESI calcd for $\text{C}_{35}\text{H}_{28}\text{N}_3\text{S}_2$ $[\text{M}+\text{H}]^+$: 554.1725, found: 554.1732.

1-Benzyl-5,12-diphenoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (66g)



Following Representative Procedure 2, a solution of **65g** (20 mg, 0.0432 mmol, 1 equiv), benzyl azide (0.027 mL, 0.216 mmol, 5 equiv), and EDC (10 mg, 0.0519 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **66g** (12 mg, 53 %): white solid; mp 78-82 °C; FTIR ν_{max} 3054, 2984, 2992, 2929, 2889, 1733, 1589, 1487, 1455, 1435, 1419, 1394, 1363, 1343, 1311, 1264, 1251, 1228, 1180, 1163, 1131, 1114, 1071, 1037, 1023, 1003, 954, 916, 894, 833, 734, 701, 668, 624, 617, 603, 592, 584, 576, 559, 553 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.39—7.31 (m, 4H), 7.29—7.26 (m, 1H), 7.22 (ddd, J = 9.4, 4.8, 2.2 Hz, 4H), 7.17—7.07 (m, 3H), 7.05—6.99 (m, 6H), 6.91 (dd, J = 8.5, 2.7 Hz, 1H), 6.77 (d, J = 2.5 Hz, 1H), 5.57—5.47 (m, 2H), 3.27—3.21 (m, 1H), 3.06—2.98 (m, 1H), 2.84—2.71 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 156.17 (s, 1C), 155.73 (s, 1C), 146.91 (s, 1C), 136.43 (s, 1C), 135.50 (s, 1C), 134.25 (s, 1C), 134.08 (s, 1C), 133.47 (s, 1C), 132.94 (s, 1C), 132.61 (s, 1C), 131.86 (s, 1C), 131.58 (s, 1C), 130.31 (s, 1C), 130.10 (s, 1C), 129.09 (s, 1C), 128.59 (s, 1C), 127.83 (s, 1C), 124.20 (s, 1C), 123.63 (s, 1C), 121.77 (s, 1C), 120.56 (s, 1C), 119.52 (s, 1C), 119.39 (s, 1C), 119.29 (s, 1C), 119.14 (s, 1C), 109.96 (s, 1C), 52.75 (s, 1C), 36.10 (s, 1C), 32.57 (s, 1C). HRMS-ESI calcd for $\text{C}_{35}\text{H}_{28}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 522.2182, found: 522.2179.

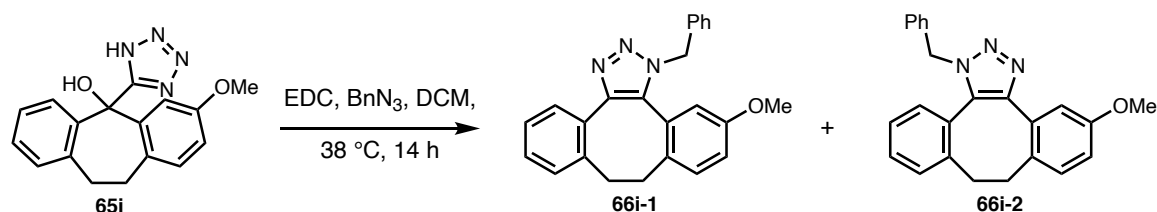
1-Benzyl-bromo-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (66h)



Following Representative Procedure 2, a solution of **65h** (71 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a mixture of inseparable triazoles **66h-1** and **66h-2** (61 mg, 73 %): white solid; mp 129-131 °C; FTIR ν_{max} 3089, 3029, 2945, 2930, 2888, 2870,

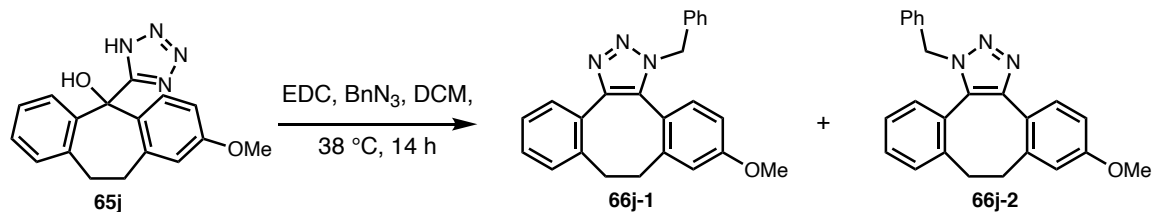
2824, 1582, 1554, 1495, 1475, 1456, 1433, 1420, 1398, 1375, 1356, 1333, 1316, 1303, 1273, 1241, 1231, 1213, 1174, 1161, 1134, 1120, 1102, 1072, 1035, 1002, 993, 960, 959, 950, 908, 894, 825, 810, 790, 774, 763, 748, 733, 726, 709, 694, 683, 661, 627, 605, 592, 575, 269, 558, 553 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.72 (d, J = 2.2 Hz, 1H), 7.57—7.54 (m, 1H), 7.44—7.42 (m, 1H), 7.36—7.19 (m, 13H), 7.15—7.06 (m, 7H), 7.02—7.00 (m, 1H), 5.63—5.54 (m, 4H), 3.30—3.22 (m, 2H), 3.04—2.97 (m, 2H), 2.87—2.70 (m, 4H); ^{13}C NMR (126 MHz; CDCl_3) δ 147.26 (s, 1C), 145.82 (s, 1C), 141.27 (s, 1C), 140.48 (s, 1C), 137.44 (s, 1C), 136.70 (s, 1C), 135.27 (s, 1C), 135.11 (s, 1C), 134.29 (s, 1C), 134.21 (s, 1C), 132.78 (s, 1C), 132.70 (s, 1C), 132.55 (s, 1C), 131.80 (s, 1C), 131.67 (s, 1C), 131.63 (s, 1C), 131.04 (s, 1C), 130.82 (s, 1C), 130.02 (s, 1C), 130.00 (s, 1C), 129.55 (s, 1C), 128.96 (s, 1C), 128.82 (s, 1C), 128.73 (s, 1C), 128.36 (s, 1C), 128.33 (s, 1C), 128.23 (s, 1C), 127.65 (s, 1C), 127.45 (s, 1C), 126.49 (s, 1C), 126.23 (s, 1C), 126.04 (s, 1C), 119.68 (s, 1C), 119.66 (s, 1C), 52.62 (s, 1C), 52.33 (s, 1C), 36.11 (s, 1C), 36.04 (s, 1C), 32.45 (s, 1C). HRMS-ESI calcd for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{Br}$ $[\text{M}+\text{H}]^+$: 416.0762, found: 416.0760.

1-Benzyl-methoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**66i**)



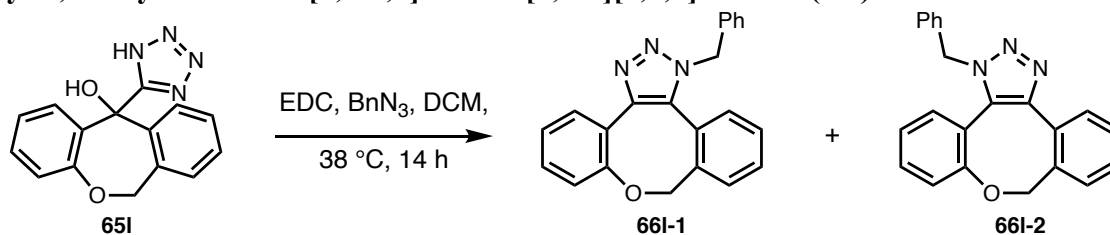
Following Representative Procedure 2, a solution of **65i** (62 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a mixture of inseparable triazoles **66i-1** and **66i-2** (46 mg, 62 %): oil; FTIR ν_{max} 3061, 3029, 3004, 2931, 2848, 2833, 1606, 1574, 1508, 1494, 1454, 1428, 1362, 1346, 1313, 1289, 1280, 1247, 1230, 1209, 1202, 1176, 1109, 1074, 1030, 995, 968, 952, 909, 872, 862, 817, 769, 754, 730, 717, 703, 693, 664, 625, 587, 554 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.57 (dd, J = 6.8, 1.8 Hz, 1H), 7.35—7.19 (m, 12H), 7.17—7.04 (m, 7H), 6.83 (ddd, J = 45.1, 8.5, 2.6 Hz, 2H), 6.57 (d, J = 2.4 Hz, 1H), 5.70—5.51 (m, 4H), 3.79 (s, 3H), 3.60 (s, 2H), 3.31—3.20 (m, 2H), 3.06—2.96 (m, 2H), 2.88—2.71 (m, 4H); ^{13}C NMR (126 MHz; CDCl_3) δ 157.73 (s, 1C), 157.59 (s, 1C), 146.99 (s, 1C), 141.68 (s, 1C), 137.95 (s, 1C), 135.73 (s, 1C), 135.40 (s, 1C), 134.12 (s, 1C), 133.56 (s, 1C), 131.98 (s, 1C), 131.67 (s, 1C), 131.10 (s, 1C), 130.87 (s, 1C), 130.67 (s, 1C), 130.06 (s, 1C), 129.83 (s, 1C), 129.77 (s, 1C), 129.02 (s, 1C), 128.76 (s, 1C), 128.68 (s, 1C), 128.14 (s, 1C), 127.49 (s, 1C), 127.30 (s, 1C), 127.02 (s, 1C), 126.31 (s, 1C), 126.23 (s, 1C), 125.98 (s, 1C), 116.18 (s, 1C), 115.42 (s, 1C), 115.20 (s, 1C), 113.68 (s, 1C), 55.33 (s, 1C), 55.15 (s, 1C), 52.26 (s, 1C), 36.54 (s, 1C), 35.55 (s, 1C), 32.92 (s, 1C), 31.96 (s, 1C). HRMS-ESI calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 368.1763, found: 368.1757.

1-Benzyl-11-methoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**66j**)



Following Representative Procedure 2, a solution of **65j** (62 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a mixture of inseparable triazoles **66j-1** and **66j-2** (49 mg, 67 %): oil; FTIR ν_{max} 3062, 3030, 3003, 2927, 2870, 2852, 2836, 1731, 1707, 1573, 1510, 1496, 1485, 1454, 1426, 1362, 1344, 1309, 1280, 1252, 1236, 1208, 1158, 1117, 1103, 1075, 1044, 1022, 1003, 984, 951, 917, 871, 850, 820, 770, 750, 731, 717, 707, 692, 665, 613, 594, 564, 552 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.58—7.55 (m, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.27 (ddd, J = 8.3, 4.0, 2.5 Hz, 8H), 7.23—7.20 (m, 2H), 7.17—7.06 (m, 7H), 7.00 (d, J = 8.5 Hz, 1H), 6.82—6.74 (m, 3H), 6.67 (d, J = 2.3 Hz, 1H), 5.56 (d, J = 12.4 Hz, 4H), 3.81 (s, 3H), 3.76 (s, 3H), 3.33—3.26 (m, 2H), 3.06—2.99 (m, 2H), 2.90—2.81 (m, 2H), 2.76—2.71 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 160.87 (s, 1C), 159.55 (s, 1C), 147.32 (s, 1C), 147.26 (s, 1C), 143.64 (s, 1C), 141.99 (s, 1C), 139.57 (s, 1C), 138.17 (s, 1C), 138.13 (s, 1C), 136.02 (s, 1C), 135.89 (s, 1C), 134.42 (s, 1C), 134.10 (s, 1C), 133.47 (s, 1C), 132.68 (s, 1C), 131.96 (s, 1C), 131.14 (s, 1C), 130.79 (s, 1C), 130.43 (s, 1C), 130.34 (s, 1C), 130.10 (s, 1C), 129.30 (s, 1C), 129.06 (s, 1C), 128.51 (s, 1C), 128.43 (s, 1C), 127.86 (s, 1C), 127.83 (s, 1C), 126.90 (s, 1C), 126.69 (s, 1C), 126.43 (s, 1C), 122.87 (s, 1C), 118.82 (s, 1C), 116.24 (s, 1C), 115.55 (s, 1C), 112.50 (s, 1C), 112.26 (s, 1C), 55.67 (s, 1C), 55.53 (s, 1C), 52.65 (s, 1C), 52.54 (s, 1C), 37.18 (s, 1C), 36.62 (s, 1C), 33.61 (s, 1C), 32.93 (s, 1C). HRMS-ESI calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 368.1763, found: 368.1759.

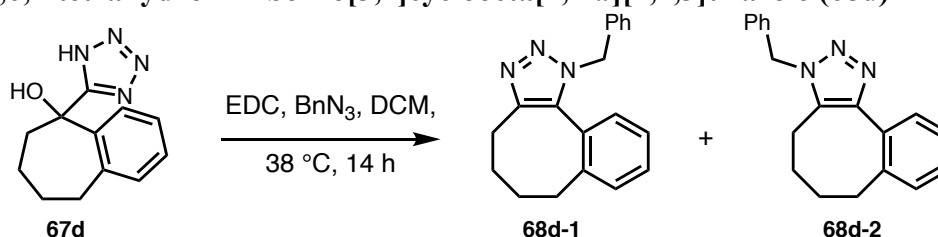
Benzyl-3,9-dihydrodibenzo[2,3:6,7]oxocino[4,5-*d*][1,2,3]triazole (**66l**)³



Following Representative Procedure 2, a solution of **65l** (56 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a mixture of inseparable triazoles **66l-1** and **66l-2** (67 mg, 98 %): white solid; m.p. 186–188 °C; FTIR ν_{max} 3053, 3026, 3005, 2954, 2921, 2851, 1738, 1732, 1613, 1605, 1567, 1502, 1494, 1481, 1467, 1455, 1430, 1367, 1319, 1291, 1282, 1275, 1248, 1220, 1208, 1194, 1159, 1144, 126, 1118, 1098, 1074, 1054, 1027, 1001, 958, 939, 909, 886, 863, 832, 824, 799, 789, 765, 747, 740, 731, 715, 696, 675, 666, 650, 620, 610, 573, 562 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.78—7.71 (m, 2H), 7.54—7.52 (m, 1H), 7.48—7.40 (m, 4H), 7.35—7.32 (m, 4H), 7.31—7.29 (m, 2H), 7.27 (d, J = 1.9 Hz, 1H), 7.21—7.12 (m, 4H), 7.10 (td, J = 4.8, 3.4 Hz, 3H), 7.03—6.98 (m, 3H), 6.93 (dd, J = 8.3, 1.1 Hz, 1H), 5.64 (s, 2H), 5.61—5.56

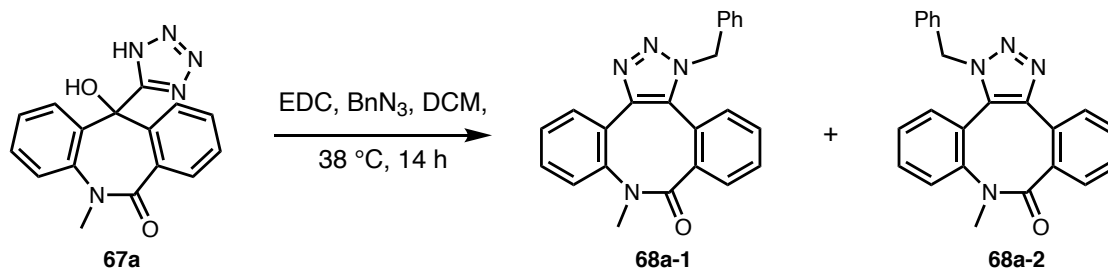
(m, 2H), 5.24 (s, 2H), 5.15—5.05 (m, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 156.46 (s, 1C), 156.46 (s, 1C), 154.85 (s, 1C), 154.85 (s, 1C), 145.78 (s, 1C), 145.78 (s, 1C), 145.56 (s, 1C), 145.56 (s, 1C), 136.82 (s, 1C), 136.82 (s, 1C), 135.87 (s, 1C), 135.87 (s, 1C), 135.48 (s, 1C), 135.48 (s, 1C), 133.67 (s, 1C), 133.67 (s, 1C), 133.54 (s, 1C), 133.54 (s, 1C), 132.65 (s, 1C), 132.65 (s, 1C), 131.57 (s, 1C), 131.57 (s, 1C), 131.51 (s, 1C), 131.51 (s, 1C), 131.02 (s, 1C), 131.02 (s, 1C), 130.88 (s, 1C), 130.88 (s, 1C), 130.56 (s, 1C), 130.56 (s, 1C), 130.10 (s, 1C), 130.10 (s, 1C), 129.52 (s, 1C), 129.52 (s, 1C), 129.34 (s, 1C), 129.34 (s, 1C), 129.27 (s, 1C), 129.27 (s, 1C), 129.06 (s, 1C), 129.06 (s, 1C), 128.99 (s, 1C), 128.99 (s, 1C), 128.93 (s, 1C), 128.93 (s, 1C), 128.62 (s, 1C), 128.62 (s, 1C), 127.92 (s, 1C), 127.92 (s, 1C), 127.73 (s, 1C), 127.73 (s, 1C), 123.02 (s, 1C), 123.02 (s, 1C), 122.28 (s, 1C), 122.28 (s, 1C), 121.85 (s, 1C), 121.85 (s, 1C), 120.75 (s, 1C), 120.75 (s, 1C), 117.44 (s, 1C), 117.44 (s, 1C), 117.21 (s, 1C), 117.21 (s, 1C), 73.94 (s, 1C), 73.94 (s, 1C), 69.58 (s, 1C), 69.58 (s, 1C), 52.82 (s, 1C), 52.82 (s, 1C), 52.69 (s, 1C), 52.69 (s, 1C). HRMS-ESI calcd for $\text{C}_{22}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 340.1450, found: 340.1441.

Benzyl-4,5,6,7-tetrahydro-1H-benzo[3,4]cycloocta[1,2-d][1,2,3]triazole (68d)⁵



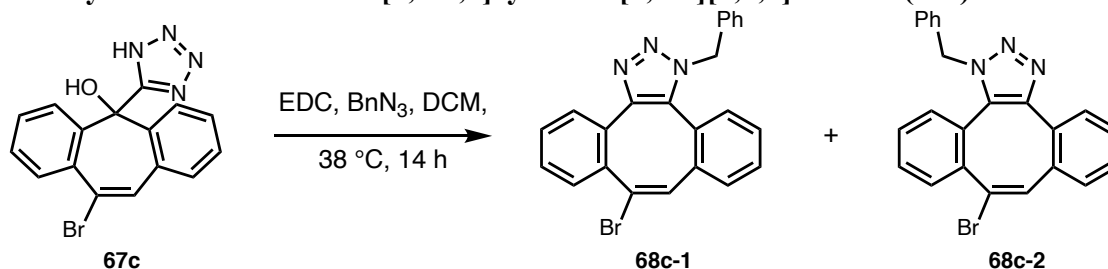
Following Representative Procedure 2, a solution of **67d** (46 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a (1:3) mixture of inseparable triazoles **68d-1** and **68d-2** (56 mg, 97 %): m.p. 105-109 °C; FTIR ν_{max} 3061, 3048, 3034, 2941, 2927, 2863, 2850, 1681, 1594, 1560, 1545, 1491, 1452, 1445, 143, 1424, 1389, 1353, 1341, 1307, 1291, 1272, 1254, 1239, 1217, 1182, 1174, 1159, 1142, 1105, 1090, 1074, 1058, 1027, 1012, 1001, 990, 970, 950, 900, 890, 873, 840, 817, 789, 769, 764, 757, 730, 722, 696, 665, 747, 725, 593, 578, 564, 556 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.82—7.80 (m, 1H), 7.82—7.80 (m, 1H), 7.41—7.32 (m, 4H), 7.41—7.32 (m, 4H), 7.26—7.20 (m, 3H), 7.26—7.20 (m, 3H), 7.20—7.16 (m, 1H), 7.20—7.16 (m, 1H), 7.01—6.99 (m, 1H), 7.01—6.99 (m, 1H), 5.54 (s, 2H), 5.54 (s, 2H), 5.42 (d, J = 15.3 Hz,), 5.42 (d, J = 15.3 Hz,), 3.07 (dddd, J = 16.3, 10.7, 1.5, 0.5 Hz,), 3.07 (dddd, J = 16.3, 10.7, 1.5, 0.5 Hz,), 2.81—2.75 (m,), 2.81—2.75 (m,), 2.67 (td, J = 10.9, 4.7 Hz, 4H), 2.67 (td, J = 10.9, 4.7 Hz, 4H), 2.28—2.22 (m,), 2.28—2.22 (m,), 2.02—1.96 (m,), 2.02—1.96 (m,), 1.81—1.76 (m, 2H), 1.81—1.76 (m, 2H), 1.68 (dt, J = 11.2, 5.7 Hz, 2H), 1.68 (dt, J = 11.2, 5.7 Hz, 2H), 1.61—1.51 (m, 1H), 1.61—1.51 (m, 1H), 1.28 (d, J = 0.3 Hz,), 1.28 (d, J = 0.3 Hz,); ^{13}C NMR (126 MHz; CDCl_3) δ 146.92 (s, 1C), 143.83 (s, 1C), 138.34 (s, 1C), 135.83 (s, 1C), 134.79 (s, 1C), 134.12 (s, 1C), 131.95 (s, 1C), 129.84 (s, 1C), 129.80 (s, 1C), 129.06 (s, 1C), 129.02 (s, 1C), 128.65 (s, 1C), 128.60 (s, 1C), 128.49 (s, 1C), 128.27 (s, 1C), 127.90 (s, 1C), 127.15 (s, 1C), 127.11 (s, 1C), 126.45 (s, 1C), 126.01 (s, 1C), 51.85 (s, 1C), 51.82 (s, 1C), 32.01 (s, 1C), 31.34 (s, 1C), 30.74 (s, 1C), 30.39 (s, 1C), 26.18 (s, 1C), 24.04 (s, 1C), 20.15 (s, 1C). HRMS-ESI calcd for $\text{C}_{19}\text{H}_{20}\text{N}_3$ $[\text{M}+\text{H}]^+$: 290.1657, found: 290.1659.

(1-Benzyl-1,9-dihydro-8H-dibenzo[*b,f*][1,2,3]triazolo[4,5-*d*]azocin-8-yl)ethan-1-one (68a)⁶



Following Representative Procedure 2, a solution of **67a** (62 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a mixture of inseparable triazoles **68a-1** and **68a-2** (61 mg, 83 %): white solid; mp 133-136 °C; FTIR ν_{max} 3063, 3031, 3003, 2923, 2851, 1632, 1602, 1567, 1537, 1513, 1496, 1483, 1454, 1418, 1379, 1357, 1331, 1316, 1301, 1287, 1276, 1240, 1210, 1181, 1160, 1127, 1108, 1086, 1049, 1039, 1028, 1008, 984, 952, 904, 881, 848, 807, 781, 774, 762, 750, 743, 725, 699, 691, 674, 663, 586, 574 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 7.60—7.55 (m, 2H), 7.50 (dd, J = 7.4, 1.9 Hz, 2H), 7.44—7.31 (m, 11H), 7.26 (dt, J = 6.8, 3.3 Hz, 5H), 7.04 (dd, J = 6.3, 2.7 Hz, 2H), 6.89 (d, J = 7.7 Hz, 1H), 5.83 (dd, J = 41.9, 15.2 Hz, 2H), 5.51 (dd, J = 50.3, 15.2 Hz, 2H), 3.26 (s, 3H), 2.73 (s, 2H); ^{13}C NMR (101 MHz; CDCl_3) δ 170.36 (s, 1C), 169.66 (s, 1C), 147.70 (s, 1C), 144.11 (s, 1C), 143.54 (s, 1C), 142.80 (s, 1C), 139.32 (s, 1C), 137.65 (s, 1C), 135.59 (s, 1C), 135.46 (s, 1C), 135.09 (s, 1C), 132.24 (s, 1C), 131.44 (s, 1C), 131.11 (s, 1C), 130.51 (s, 1C), 130.41 (s, 1C), 130.03 (s, 1C), 129.71 (s, 1C), 129.62 (s, 1C), 129.43 (s, 1C), 129.32 (s, 1C), 129.19 (s, 1C), 129.09 (s, 1C), 129.00 (s, 1C), 128.93 (s, 1C), 128.88 (s, 1C), 128.86 (s, 1C), 128.28 (s, 1C), 128.23 (s, 1C), 128.17 (s, 1C), 128.11 (s, 1C), 127.79 (s, 1C), 127.68 (s, 1C), 127.28 (s, 1C), 125.41 (s, 1C), 123.39 (s, 1C), 53.10 (s, 1C), 52.84 (s, 1C), 39.54 (s, 1C), 38.71 (s, 1C). HRMS-ESI calcd for $\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 367.1555, found: 367.15559.

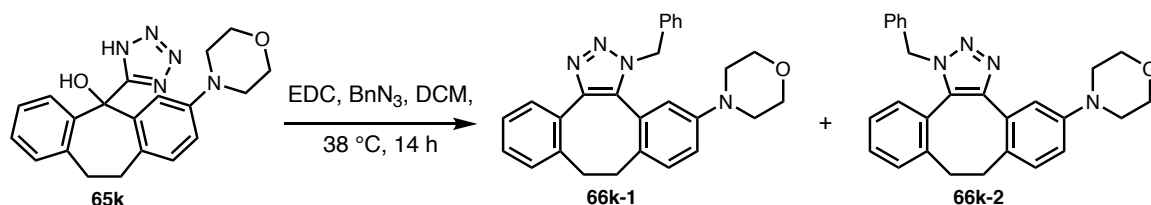
(E)-1-Benzyl-bromo-1H-dibenzo[3,4:7,8]cycloocta[1,2-d][1,2,3]triazole (68c)



Following Representative Procedure 2, a solution of **67c** (71 mg, 0.2 mmol, 1 equiv), benzyl azide (0.125 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a mixture of inseparable triazoles **66c-1** and **66c-2** (60 mg, 72 %): white solid; mp 94-97 °C; FTIR ν_{max} 3060, 3029, 2922, 2851, 1731, 1638, 1606, 1569, 1505, 1496, 1479, 1454, 1427, 1351, 1314, 1301, 1285, 1240, 1211, 1159, 1126, 1112, 1096, 1074, 1044, 1026, 1002, 985, 952, 905, 870, 849, 815, 772, 756, 745, 723, 702, 675, 666, 653, 592, 581, 564, 551 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.59 (dd, J = 8.2, 4.8 Hz, 2H), 7.54 (dd, J = 6.6, 2.4 Hz, 2H), 7.43 (td, J = 7.7, 1.1 Hz, 1H), 7.39—7.34 (m, 6H), 7.32—7.29 (m, 6H), 7.22—7.18 (m, 3H), 7.15—7.14 (m, 2H), 7.10—7.05 (m, 5H), 5.69—5.61 (m, 2H), 5.56 (q, J = 15.2 Hz, 2H); ^{13}C NMR (126 MHz; CDCl_3) δ 147.00 (s, 1C), 146.15 (s, 1C), 140.18 (s, 1C),

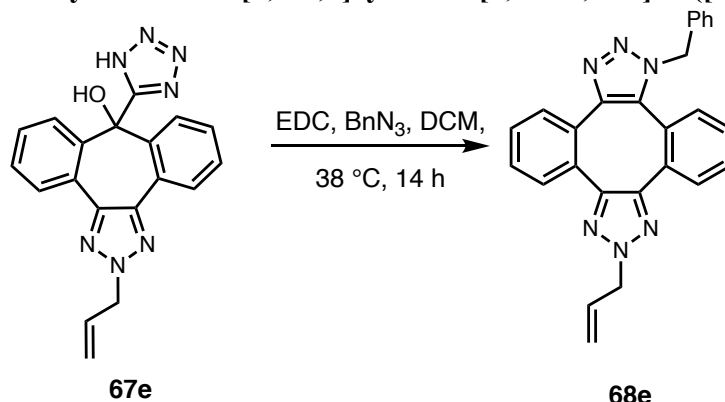
138.62 (s, 1C), 137.71 (s, 1C), 136.17 (s, 1C), 135.44 (s, 1C), 135.34 (s, 1C), 135.21 (s, 1C), 134.90 (s, 1C), 134.21 (s, 1C), 133.09 (s, 1C), 131.37 (s, 1C), 130.64 (s, 1C), 130.36 (s, 1C), 130.05 (s, 1C), 129.98 (s, 1C), 129.79 (s, 1C), 129.64 (s, 1C), 129.52 (s, 1C), 129.18 (s, 1C), 129.09 (s, 1C), 129.02 (s, 1C), 128.74 (s, 1C), 128.57 (s, 1C), 128.51 (s, 1C), 128.27 (s, 1C), 128.20 (s, 1C), 128.14 (s, 1C), 127.90 (s, 1C), 127.46 (s, 1C), 127.25 (s, 1C), 125.76 (s, 1C), 125.59 (s, 1C), 123.99 (s, 1C), 121.10 (s, 1C), 52.30 (s, 1C), 52.23 (s, 1C). HRMS-ESI calcd for $C_{23}H_{17}N_3Br$ $[M+H]^+$: 414.0606, found: 414.0602.

4-(1-Benzyl-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazolyl)morpholine (66k)



Following Representative Procedure 2, a solution of **65k** (15 mg, 0.04 mmol, 1 equiv), benzyl azide (0.026 mL, 1 mmol, 5 equiv), and EDC (10 mg, 0.045 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) a mixture of inseparable triazoles **66k-1** and **66k-2** (15 mg, 84 %): white solid; mp 145-148 °C; FTIR ν_{max} 3061, 3031, 3007, 2954, 2926, 2888, 2854, 2830, 1725, 1676, 1605, 1573, 1512, 1495, 1450, 1428, 1379, 1362, 1301, 1287, 1263, 1244, 1211, 1201, 1174, 1121, 1068, 1052, 1029, 998, 940, 911, 862, 818, 790, 774, 756, 731, 716, 696, 640, 620, 605, 591, 585 cm^{-1} ; ^1H NMR (500 MHz; CDCl_3) δ 7.59—7.57 (m, 1H), 7.34—7.26 (m, 9H), 7.23—7.22 (m, 3H), 7.19—7.15 (m, 4H), 7.11—7.07 (m, 2H), 7.04 (d, J = 8.6 Hz, 1H), 6.86—6.78 (m, 1H), 6.43 (d, J = 2.3 Hz, 1H), 5.78—5.75 (m, 1H), 5.61—5.53 (m, 1H), 5.43 (d, J = 15.4 Hz, 1H), 3.83 (dd, J = 6.1, 3.1 Hz, 3H), 3.73 (dd, J = 6.3, 3.2 Hz, 4H), 3.31—3.18 (m, 3H), 3.15—3.12 (m, 2H), 3.06—2.93 (m, 4H), 2.88—2.86 (m, 2H), 2.83—2.79 (m, 3H); ^{13}C NMR (126 MHz; CDCl_3) δ 149.20 (s, 1C), 149.17 (s, 1C), 138.24 (s, 1C), 136.29 (s, 1C), 134.73 (s, 1C), 132.36 (s, 1C), 131.77 (s, 1C), 131.50 (s, 1C), 130.93 (s, 1C), 130.74 (s, 1C), 130.01 (s, 1C), 129.93 (s, 1C), 129.74 (s, 1C), 128.95 (s, 1C), 128.92 (s, 1C), 128.82 (s, 1C), 128.67 (s, 1C), 128.11 (s, 1C), 127.96 (s, 1C), 127.48 (s, 1C), 127.02 (s, 1C), 126.65 (s, 1C), 126.18 (s, 1C), 125.96 (s, 1C), 118.36 (s, 1C), 117.02 (s, 1C), 115.91 (s, 1C), 66.91 (s, 1C), 66.67 (s, 1C), 52.23 (s, 1C), 52.18 (s, 1C), 49.24 (s, 1C), 48.68 (s, 1C), 36.23 (s, 1C), 35.73 (s, 1C), 32.76 (s, 1C), 32.23 (s, 1C). HRMS-ESI calcd for $C_{27}H_{27}N_4O$ $[M+H]^+$: 423.2185, found: 423.2179.

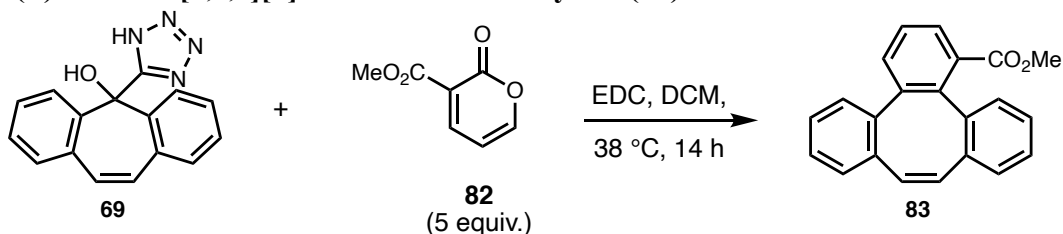
9-Allyl-1-benzyl-1,9-dihydrodibenzo[3,4:7,8]cycloocta[1,2-*d*:5,6-*d'*][1,2,3]triazole (**68e**)



Following Representative Procedure 2, a solution of **67e** (95 mg, 0.27 mmol, 1 equiv), benzyl azide (0.166 mL, 1.33 mmol, 5 equiv), and EDC (61 mg, 0.32 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (CH₂Cl₂/MeOH, 99:1), **68e** (103 mg, 0.25 mmol, 91%): white solid; mp 80–82 °C; FTIR ν_{max} 3062 (w), 2932 (w), 1644 (w), 1517 (m), 1420 (m), 1348 (m), 1256 (w), 1207 (w), 1010 (m), 984 (s), 971 (m), 783 (s), 704 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.72–7.69 (m, 1H), 7.54–7.45 (m, 4H), 7.45–7.37 (m, 2H), 7.28–7.23 (m, 3H), 7.15 (d, *J* = 7.6, 1H), 7.04–6.99 (m, 2H), 6.10 (ddt, *J* = 16.5, 10.2, 6.1 Hz, 1H), 5.53 (d, *J* = 15.3 Hz, 1H), 5.37 (d, *J* = 15.3 Hz, 1H), 5.34–5.26 (m, 2H), 5.05 (d, *J* = 6.1 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 146.2, 145.6, 145.2, 135.3, 134.4, 132.5, 131.5, 131.3, 130.8, 130.7, 130.5, 130.2, 130.1, 129.4, 129.0, 129.0, 128.9, 128.3, 127.4, 126.8, 119.8, 57.7, 52.3; HRMS-ESI calcd for C₂₆H₂₁N₆ [M+H]⁺: 417.1822, found: 417.1825.

2.3 Transient Cycloalkyne Formation with Various Alkynophiles

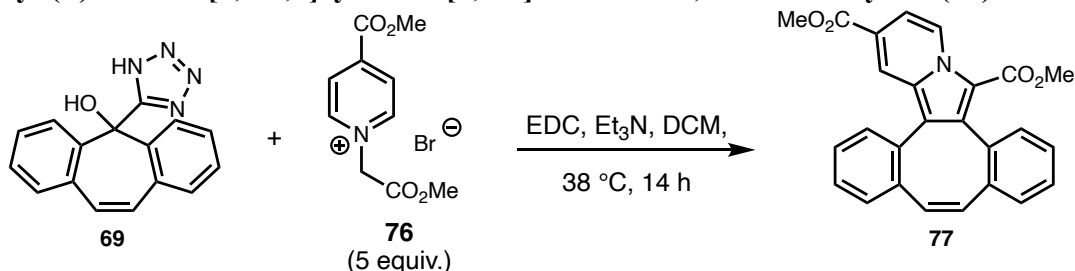
Methyl (*Z*)-tribenzo[*a,c,e*][8]annulene-1-carboxylate (**83**)⁷



Following Representative Procedure 2, a solution of **69** (56 mg, 0.2 mmol, 1 equiv), methyl 2-oxo-2H-pyran-3-carboxylate (**82**) (55 mg, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **83** (52 mg, 83 %): yellow oil; FTIR ν_{max} 3060, 3057, 3012, 2948, 2869, 1721, 1641, 1589, 1489, 1458, 1429, 1423, 1390, 1360, 1309, 1288, 1272, 1244, 1220, 1197, 1142, 1108, 1058, 1037, 1004, 966, 932, 887, 861, 808, 792, 771, 749, 729, 712, 678, 647, 630, 572 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 8.26–8.24 (m, 1H), 7.81–7.79 (m, 1H), 7.68–7.64 (m, 1H), 7.60–7.56 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.28 (m, 2H), 7.17–7.11 (m, 4H), 6.97–6.94 (m, 2H), 6.77 (t, *J* = 10.7 Hz, 1H), 3.48 (s, 3H). ¹³C NMR (126 MHz; CDCl₃) δ 169.61 (s, 1C), 143.80 (s, 1C), 141.54 (s, 1C), 141.35 (s, 1C), 140.08 (s, 1C), 137.75 (s, 1C), 137.49 (s, 1C), 133.60 (s, 1C), 133.14 (s, 1C), 132.69 (s, 1C), 132.34 (s, 1C), 132.05 (s, 1C), 131.14 (s, 1C), 130.57 (s, 1C), 129.92 (s, 1C), 129.32 (s, 1C), 129.24 (s, 1C),

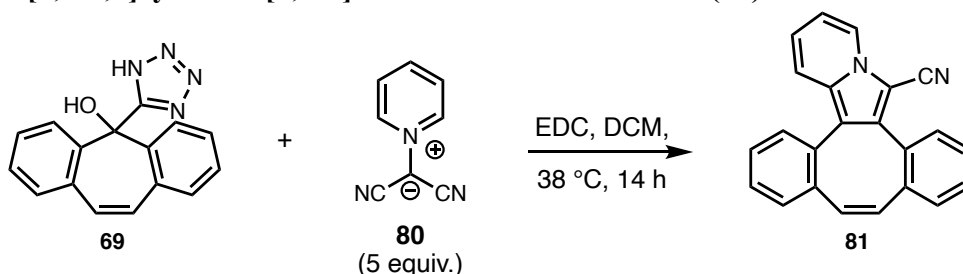
128.76 (s, 1C), 127.86 (s, 1C), 127.58 (s, 1C), 127.50 (s, 1C), 127.42 (s, 1C), 127.39 (s, 1C), 126.92 (s, 1C), 52.31 (s, 1C). HRMS-ESI calcd for C₂₂H₁₇O₂ [M+H]⁺: 313.1229, found: 313.1223.

Dimethyl (Z)-dibenzo[3,4:7,8]cycloocta[1,2-*a*]indolizine-3,15-dicarboxylate (77**)**



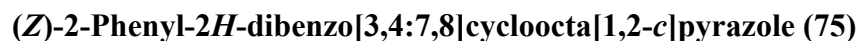
Following Representative Procedure 2, a solution of **69** (56 mg, 0.2 mmol, 1 equiv), 1-(2-methoxy-2-oxoethyl)-4-(methoxycarbonyl)pyridin-1-ium bromide (**76**) (290 mg, 1 mmol, 5 equiv), triethylamine (0.14 mL 1.02 mmol, 5.1 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **77** (54 mg, 66 %): yellow oil; FTIR ν_{max} 2982, 2953, 1717, 1684, 1628, 1443, 1415, 1378, 1301, 1263, 1235, 1205, 1148, 1118, 1096, 1047, 809, 756, 730, 691, 635, 572 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ 9.54 (d, *J* = 7.4 Hz, 1H), 8.13 (s, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.33—7.31 (m, 4H), 7.25—7.19 (m, 5H), 6.84 (d, *J* = 11.9 Hz, 1H), 6.72 (d, *J* = 11.9 Hz, 1H), 3.92 (s, 3H), 3.65 (s, 3H); ¹³C NMR (126 MHz; CDCl₃) δ 166.24 (s, 1C), 162.57 (s, 1C), 139.42 (s, 1C), 137.71 (s, 1C), 134.29 (s, 1C), 133.79 (s, 1C), 133.46 (s, 1C), 133.08 (s, 1C), 133.00 (s, 1C), 132.63 (s, 1C), 132.45 (s, 1C), 132.33 (s, 1C), 131.13 (s, 1C), 130.57 (s, 1C), 129.35 (s, 1C), 129.23 (s, 1C), 128.33 (s, 1C), 127.74 (s, 1C), 127.62 (s, 1C), 127.60 (s, 1C), 127.37 (s, 1C), 126.25 (s, 1C), 120.99 (s, 1C), 112.26 (s, 1C), 52.71 (s, 1C), 51.33 (s, 1C). HRMS-ESI calcd for C₂₆H₂₀NO₄ [M+H]⁺: 410.1392, found: 410.1384.

(Z)-Dibenzo[3,4:7,8]cycloocta[1,2-*a*]indolizine-15-carbonitrile (81**)**



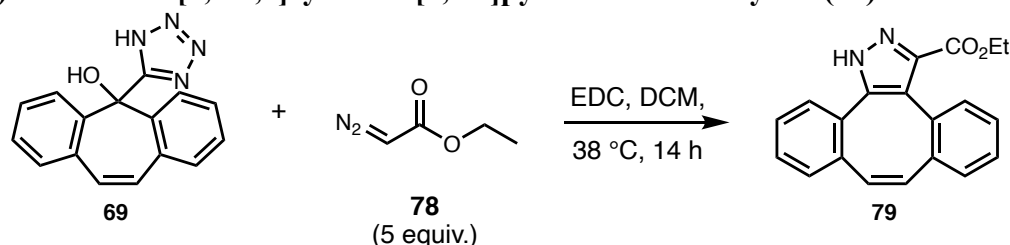
Following Representative Procedure 2, a solution of **69** (56 mg, 0.2 mmol, 1 equiv), dicyano(pyridin-1-ium-1-yl)methanide (**80**) (143 mg, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **81** (51 mg, 81 %): yellow oil; FTIR ν_{max} 3060, 3029, 2922, 2851, 2195, 1717, 1640, 1587, 1533, 1482, 1473, 1419, 1380, 1319, 1300, 1243, 1208, 1149, 1114, 1090, 1040, 1010, 959, 932, 885, 860, 802, 786, 766, 756, 725, 702, 684, 659, 629, 606, 590 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 8.33 (d, *J* = 6.6 Hz, 1H), 8.33 (d, *J* = 6.6 Hz, 1H), 7.68—7.56 (m, 1H), 7.68—7.56 (m, 1H), 7.46 (t, *J* = 6.8 Hz, 2H), 7.46 (t, *J* = 6.8 Hz, 2H), 7.34—7.33 (m, 3H), 7.34—7.33 (m, 3H), 7.28—7.25 (m, 3H), 7.28—7.25 (m, 3H), 7.03 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 6.7 Hz, 1H), 6.87 (t, *J* = 6.7 Hz, 1H), 6.80—6.73 (m, 2H), 6.80—6.73 (m, 2H); ¹³C NMR (101 MHz; CDCl₃) δ 139.08 (s, 1C), 138.49 (s, 1C), 134.32 (s, 1C), 133.35 (s, 1C), 133.25 (s, 1C), 132.49 (s, 1C), 132.34 (s,

(Z)-1,4-Diphenyldibenzo[3,4:7,8]cycloocta[1,2-*d*]pyridazine (85)



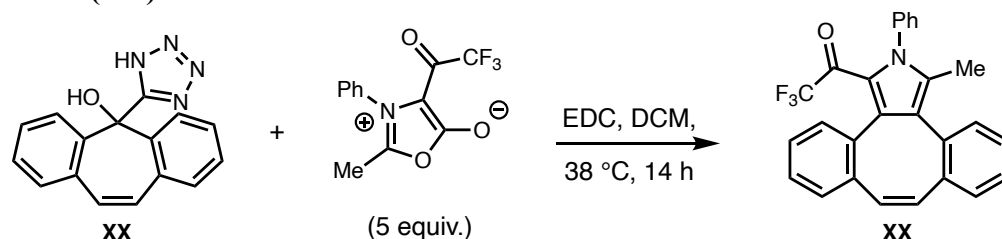
127.74 (s, 1C), 126.82 (s, 1C), 125.88 (s, 1C), 119.29 (s, 1C). HRMS-ESI calcd for C₂₃H₁₇N₂ [M+H]⁺: 321.1392, found: 321.1377.

Ethyl (Z)-1H-dibenzo[3,4:7,8]cycloocta[1,2-c]pyrazole-3-carboxylate (79)



Following Representative Procedure 2, a solution of **69** (56 mg, 0.2 mmol, 1 equiv), ethyl diazoacetate (**78**) (0.11 mL, 1 mmol, 5 equiv), and EDC (46 mg, 0.24 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **79** (33 mg, 52 %): yellow oil; FTIR ν_{max} 3061, 2982, 2933, 1720, 1444, 1403, 1382, 1302, 1262, 1205, 1191, 1125, 1111, 1084, 1039, 1022, 999 972, 908, 859, 843, 793, 772, 755, 732, 684, 668, 648 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 7.35—7.16 (m, 8H), 6.80 (d, J = 12.2 Hz, 1H), 6.69 (d, J = 12.2 Hz, 1H), 4.33 (dq, J = 10.8, 7.1 Hz, 1H), 4.26—4.20 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz; CDCl₃) δ 161.18 (s, 1C), 138.55 (s, 1C), 137.75 (s, 1C), 133.78 (s, 1C), 132.81 (s, 1C), 132.21 (s, 1C), 130.79 (s, 1C), 130.57 (s, 1C), 130.11 (s, 1C), 129.56 (s, 1C), 129.13 (s, 1C), 128.90 (s, 1C), 127.82 (s, 1C), 127.73 (s, 1C), 126.79 (s, 1C), 124.81 (s, 1C), 61.40 (s, 1C), 14.40 (s, 1C). HRMS-ESI calcd for C₂₀H₁₇N₂O₂ [M+H]⁺: 317.1290, found: 317.1282.

(Z)-2,2,2-Trifluoro-1-(3-methyl-2-phenyl-2H-dibenzo[3,4:7,8]cycloocta[1,2-c]pyrrol-1-yl)ethan-1-one (XX)



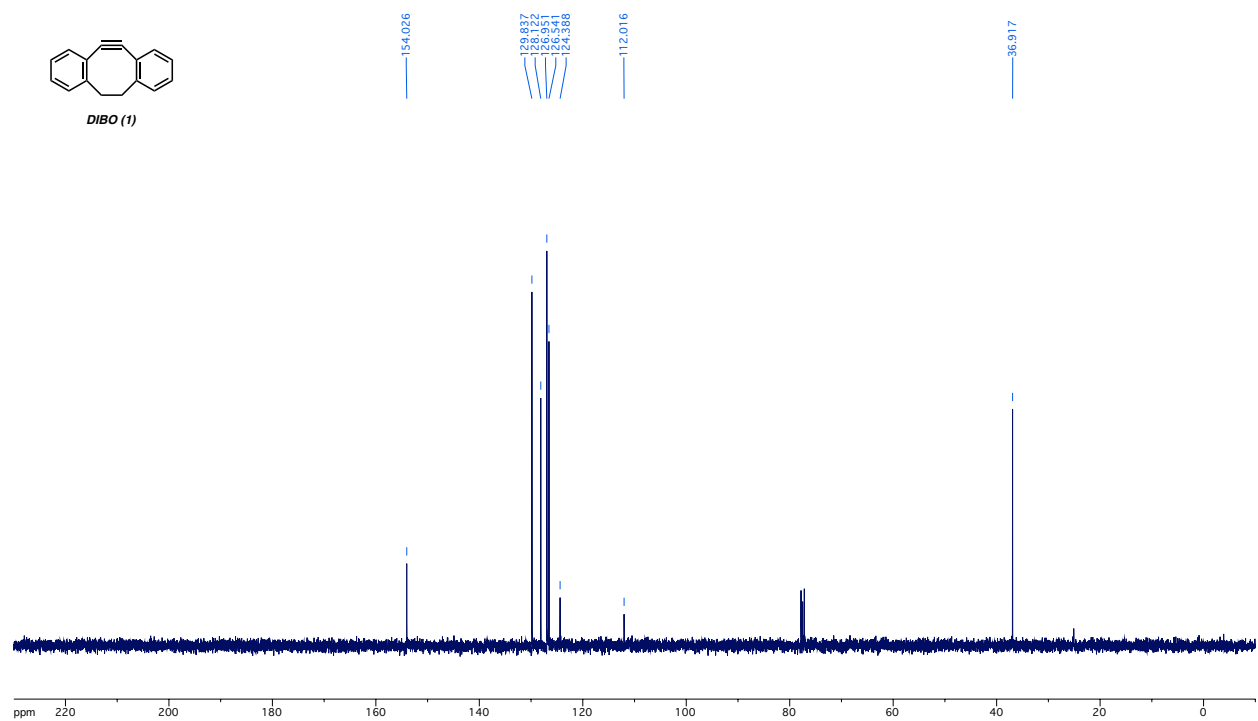
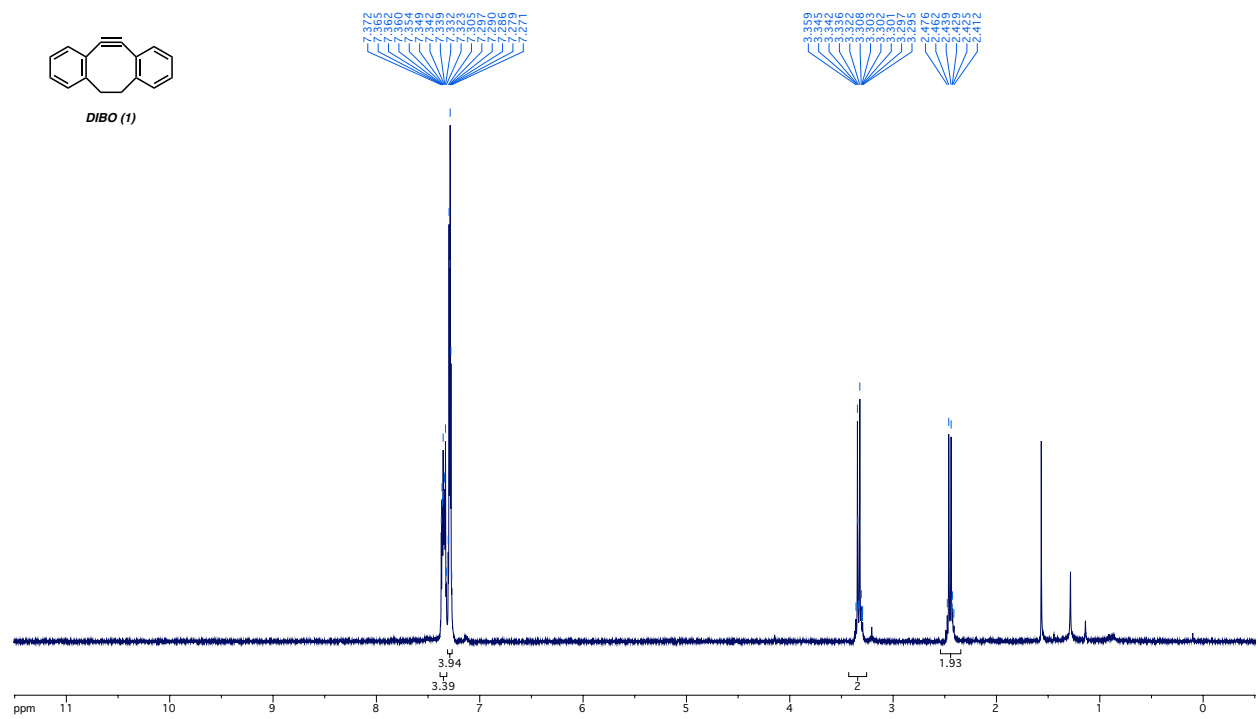
Following Representative Procedure 2, a solution of **69** (27.6 mg, 0.1 mmol, 1 equiv), 2-methyl-3-phenyl-4-(2,2,2-trifluoroacetyl)oxazol-3-ium-5-olate (136 mg, 0.5 mmol, 5 equiv), and EDC (23 mg, 0.12 mmol, 1.2 equiv) in anhydrous DCM, under nitrogen was refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (DCM:Hex 1:4) **XX** (19 mg, 44 %): white powder; ¹H-NMR (500 MHz; CDCl₃): δ 7.60-7.56 (m, 2H), 7.50-7.45 (m, 2H), 7.31-7.09 (m, 9H), 6.94 (d, J = 11.8 Hz, 1H), 6.82 (d, J = 11.8 Hz, 1H), 2.03 (s, 3H); ¹³C NMR (125 MHz; CDCl₃): δ 173.5 (q, J = 37 Hz), 173.4, 173.1, 139.34, 139.14, 138.6, 138.2,

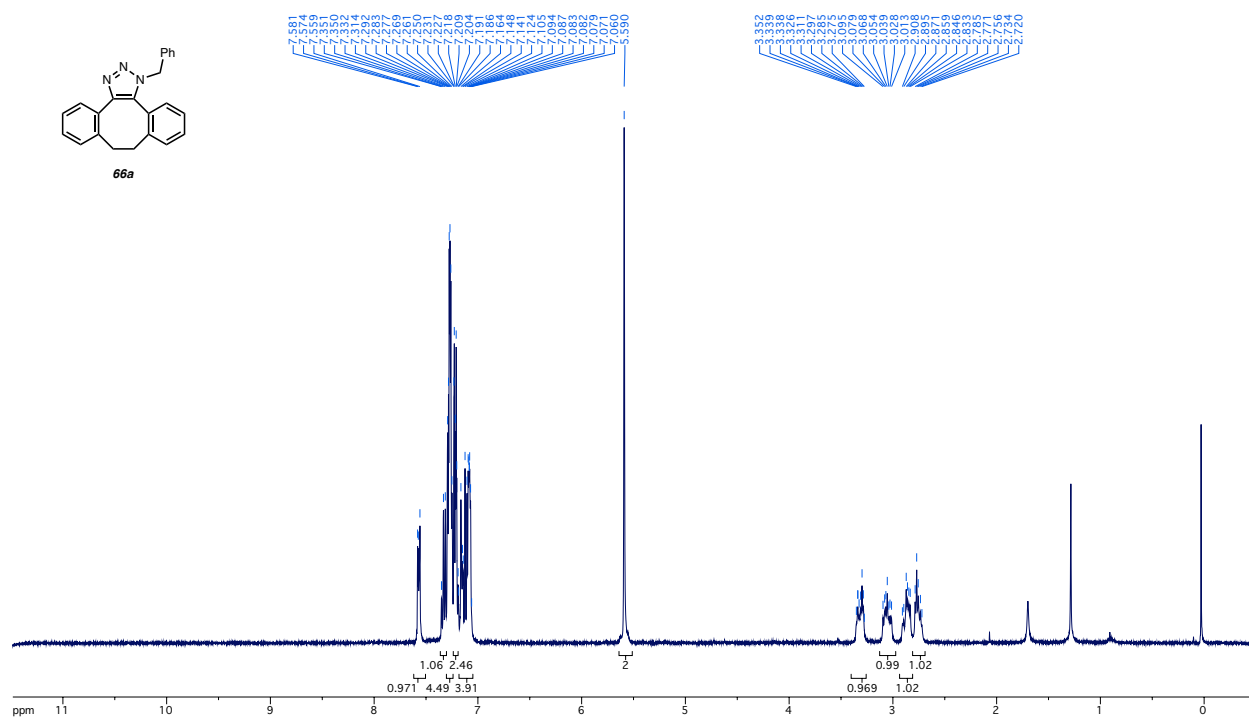
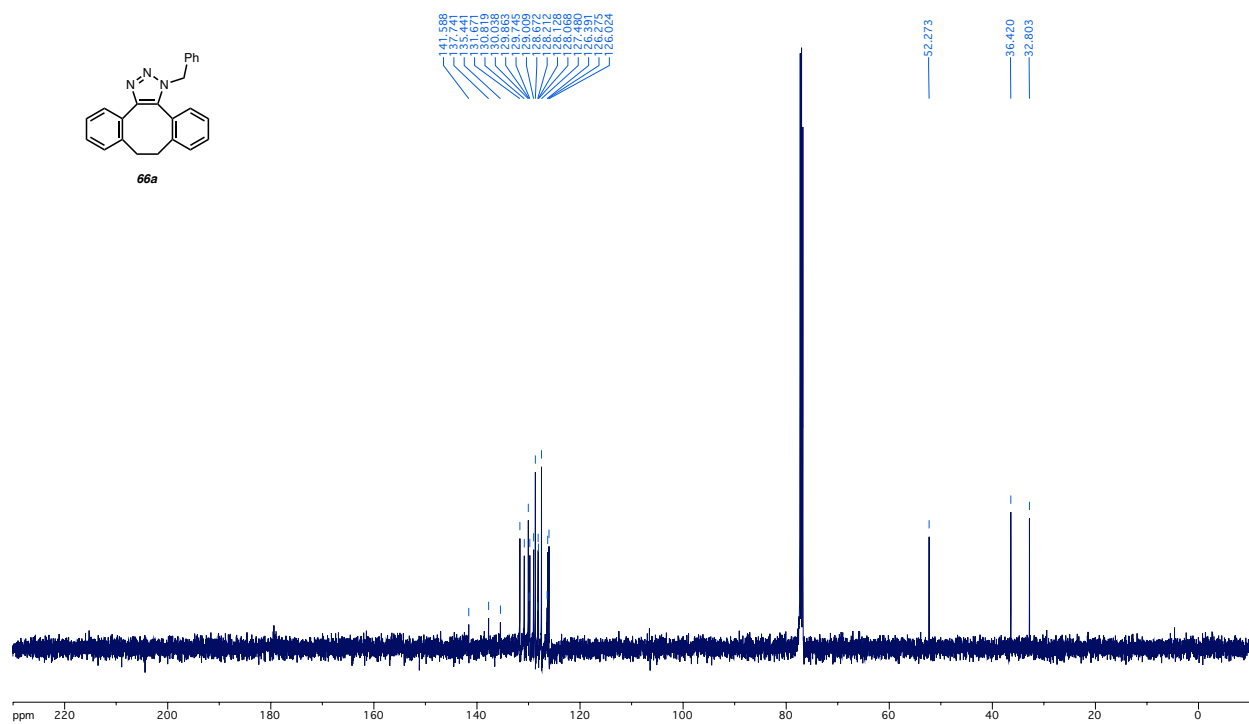
137.5, 133.78, 133.68, 133.11, 133.05, 132.0, 131.1, 129.7, 129.5, 129.2, 128.9, 128.45, 128.37, 128.2, 127.5, 127.3, 126.96, 126.77, 125.0, 119.9, 117.6, 116.4 (q, $J = 288$ Hz), 12.4. HRMS-ESI⁺ calculated for C₂₇H₁₉NOF₃ [M+H]⁺: 430.1417, found: 430.1419.

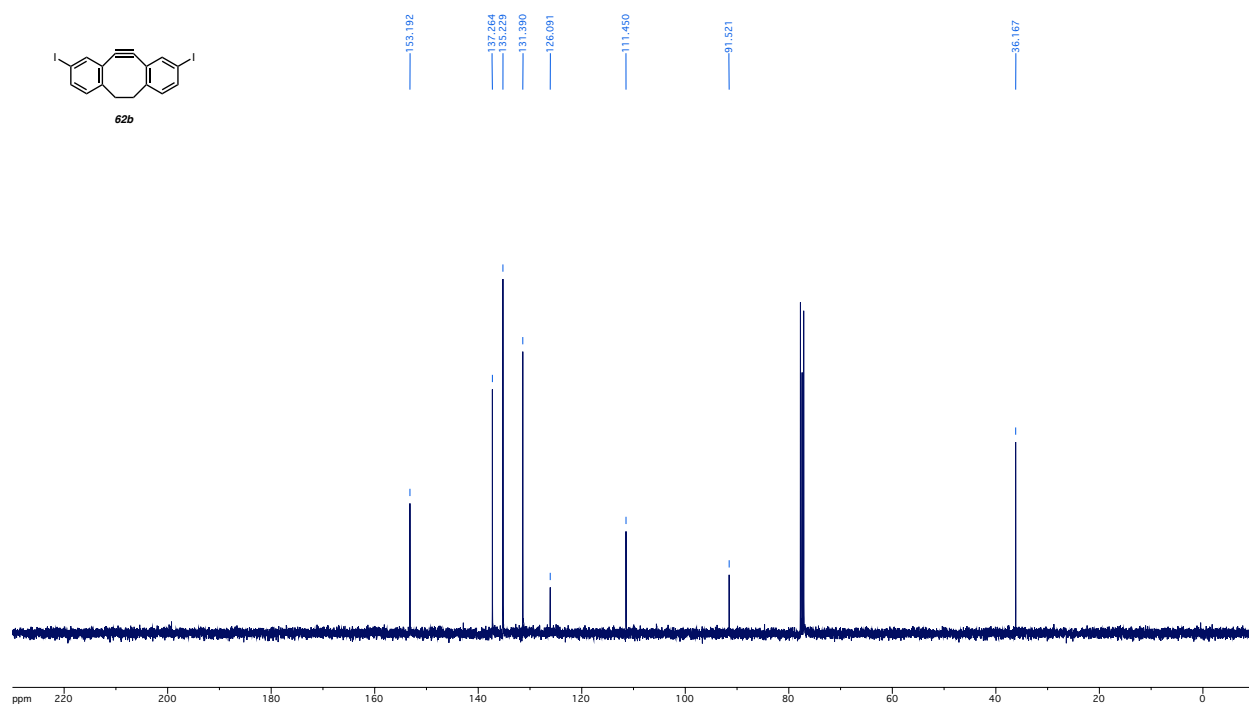
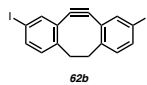
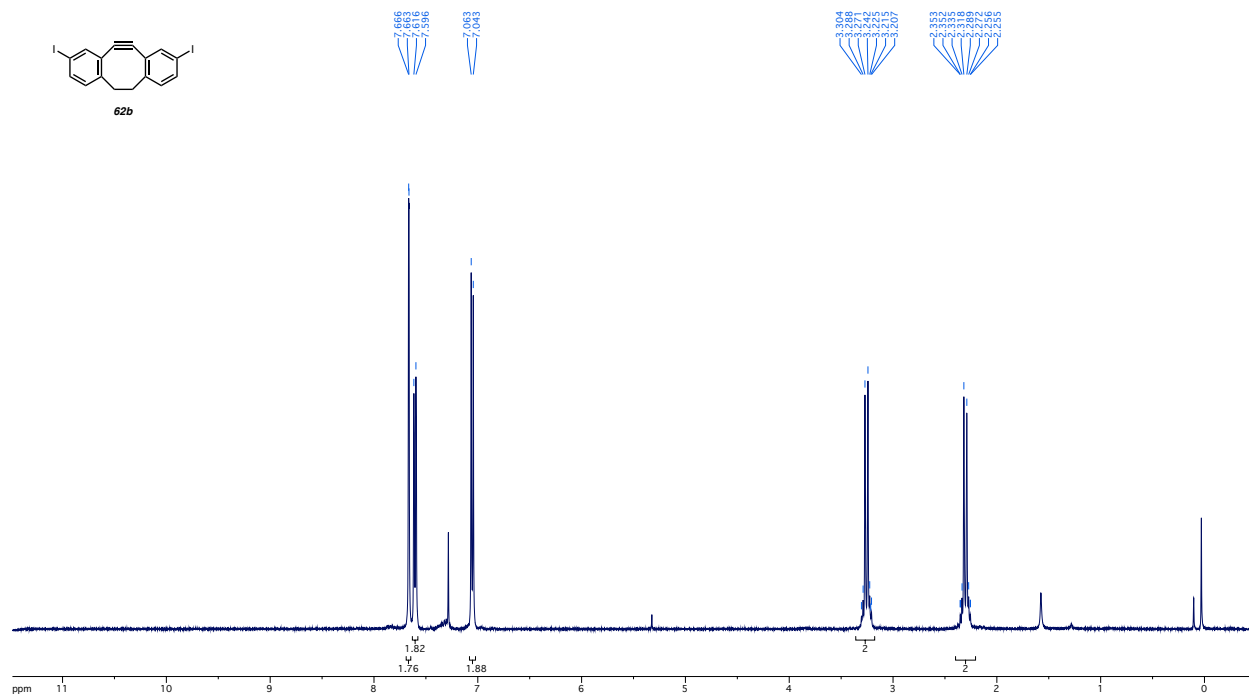
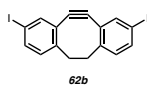
4. References

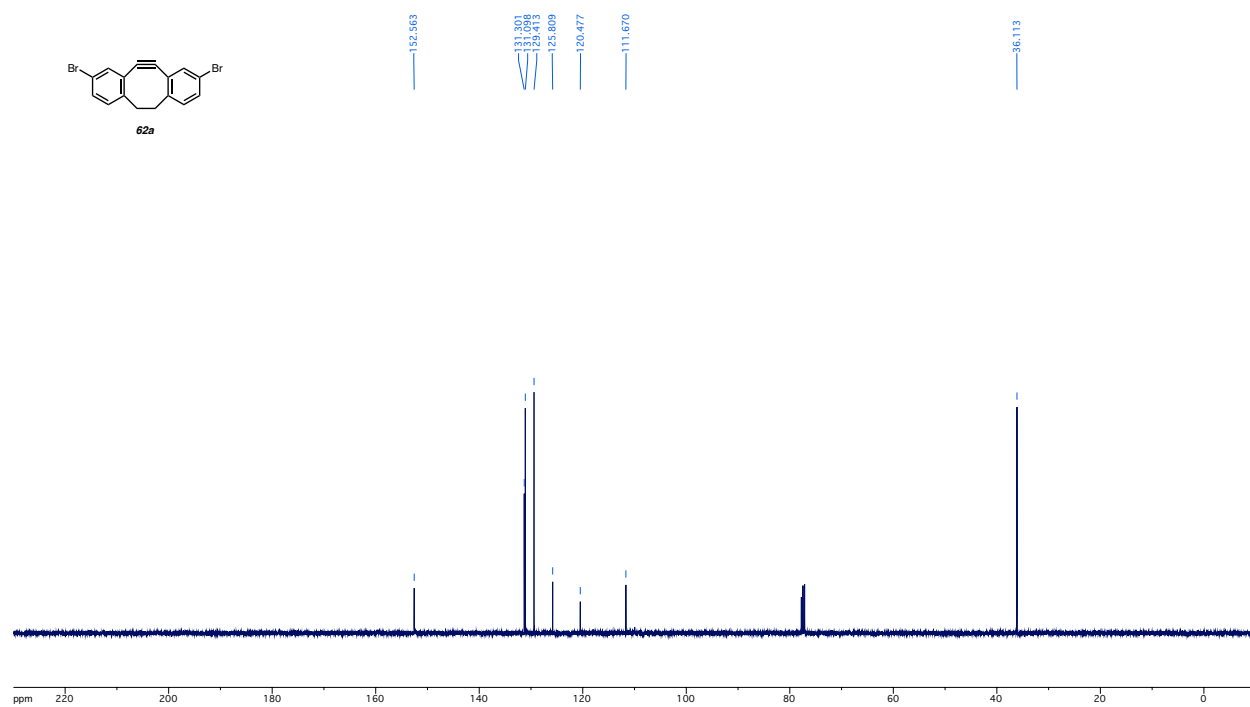
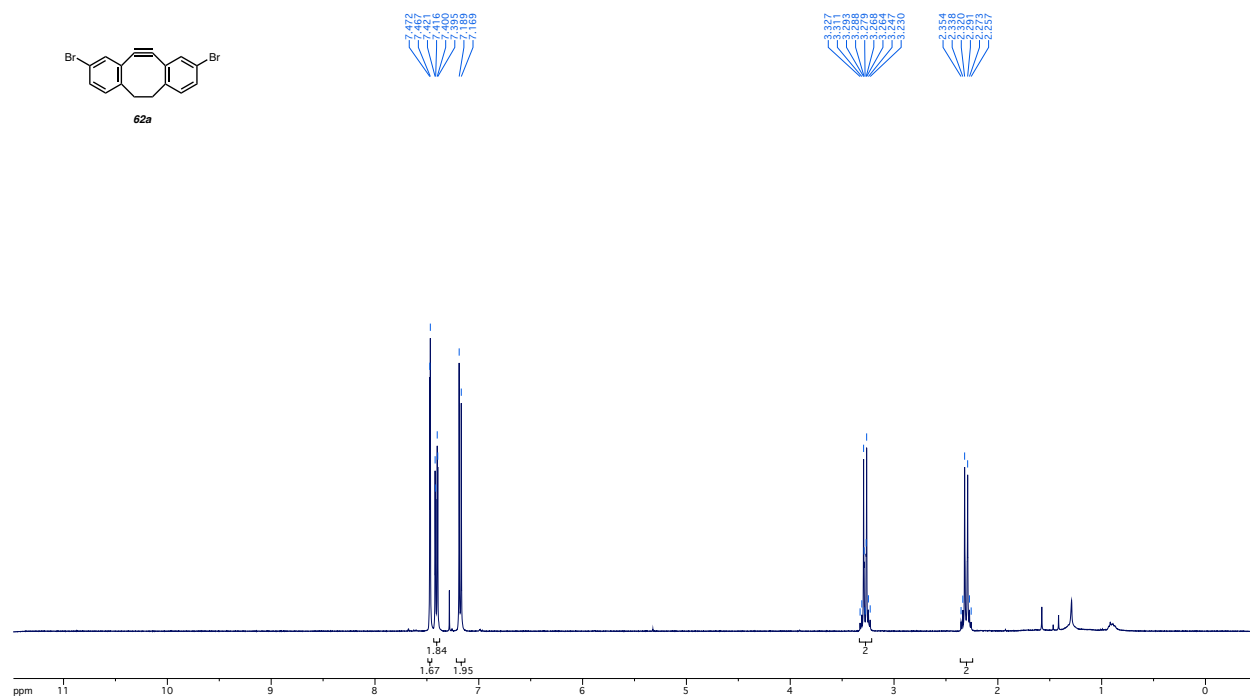
- (1) Rapid Chromatographic Technique for Preparative Separations With Moderate Resolution Still, W. C.; Kahn, M.; Mitra, A. *The Journal of Organic Chemistry* 1978, 43, 2923-2925.
- (2) Preparation and Properties of a Hydrolytically Stable Cyclooctyne-Containing Polymer Li, K.; McNelles, S. A.; Adronov, A. *Synlett* 2018, 29, 2535-2541.
- (3) Photochemical Generation of Oxa-Dibenzocyclooctyne (Odibo) for Metal-Free Click Ligations. McNitt, C. D.; Popik, V. V. *Org. Biomol. Chem.* 2012, 10, 8200-8202.
- (4) Strain-Promoted Azide-Alkyne Cycloaddition With Ruthenium(ii)-Azido Complexes. Cruchter, T.; Harms, K.; Meggers, E. *Chemistry* 2013, 19, 16682-16689.
- (5) Difluorobenzocyclooctyne: Synthesis, Reactivity, and Stabilization By Beta-Cyclodextrin. Sletten, E. M.; Nakamura, H.; Jewett, J. C.; Bertozzi, C. R. *J. Am. Chem. Soc.* 2010, 132, 11799-11805.
- (6) Discovery of New Mutually Orthogonal Bioorthogonal Cycloaddition Pairs Through Computational Screening. Narayanam, M. K.; Liang, Y.; Houk, K. N.; Murphy, J. M. *Chem. Sci.* 2016, 7, 1257-1261.
- (7) 1-Substituted and 1, 4-Disubstituted Tribenzo [a, c] Cyclooctenes Wong, H.; Hou, X. L. *Synthesis (Stuttgart)* 1985, 1111-1115.

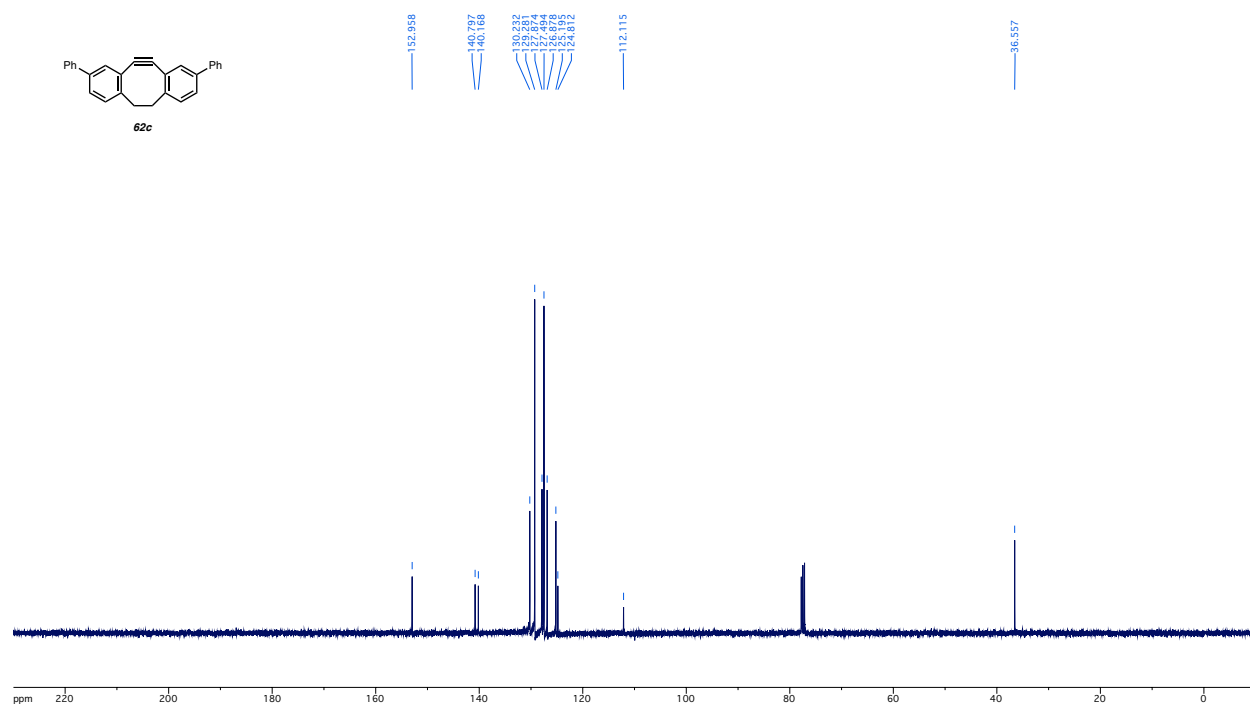
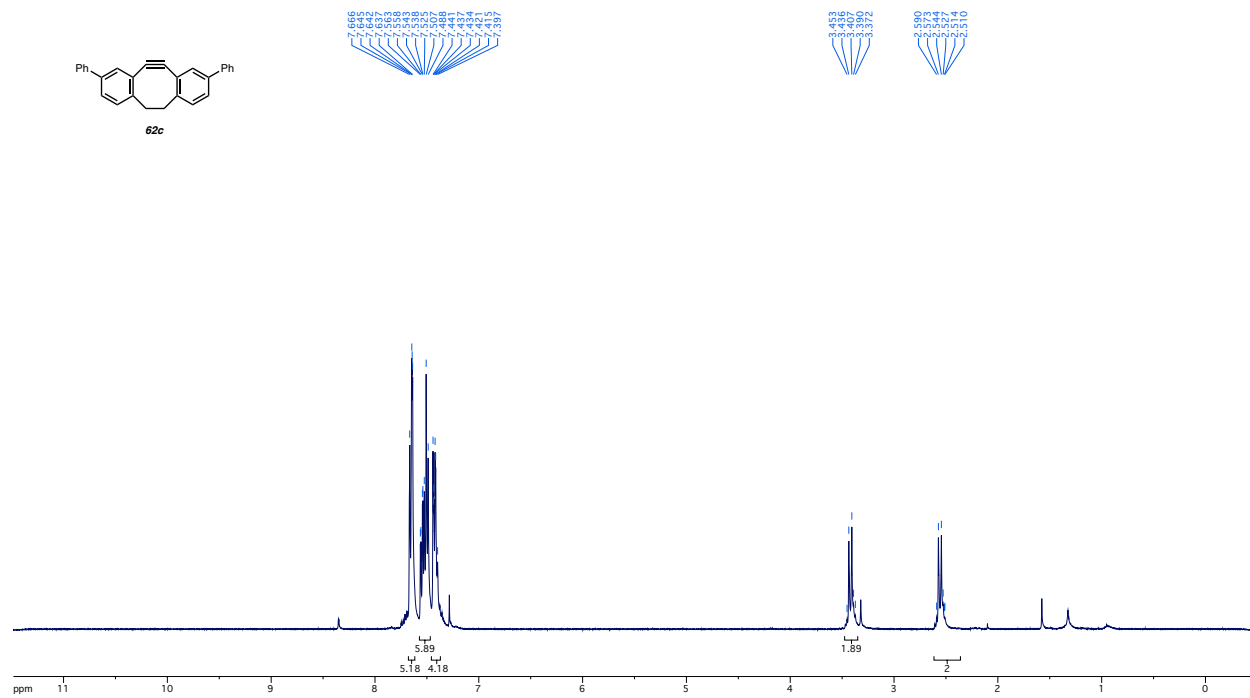
Appendix B, Cyclooctynes

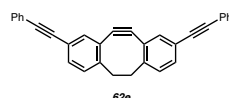
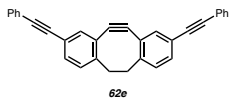


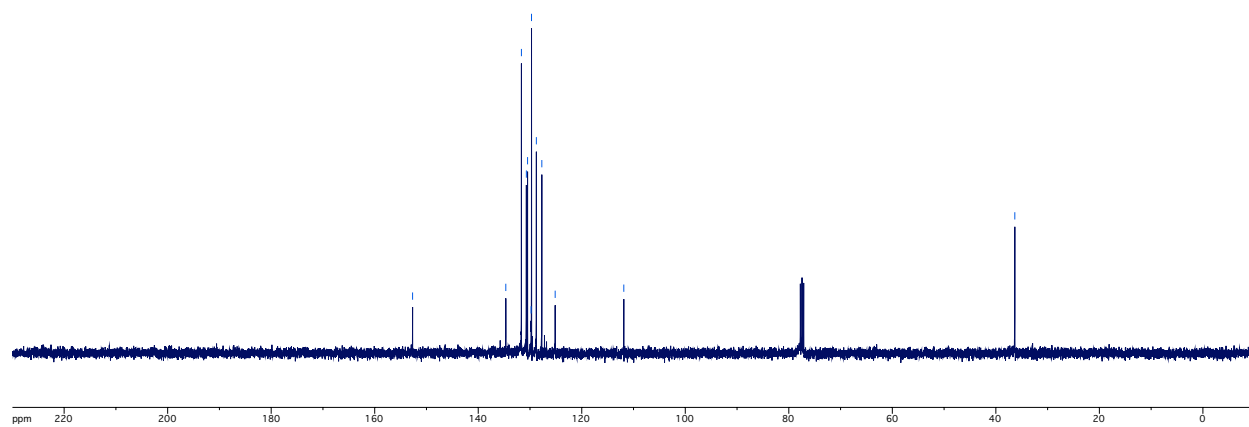
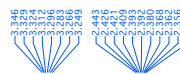


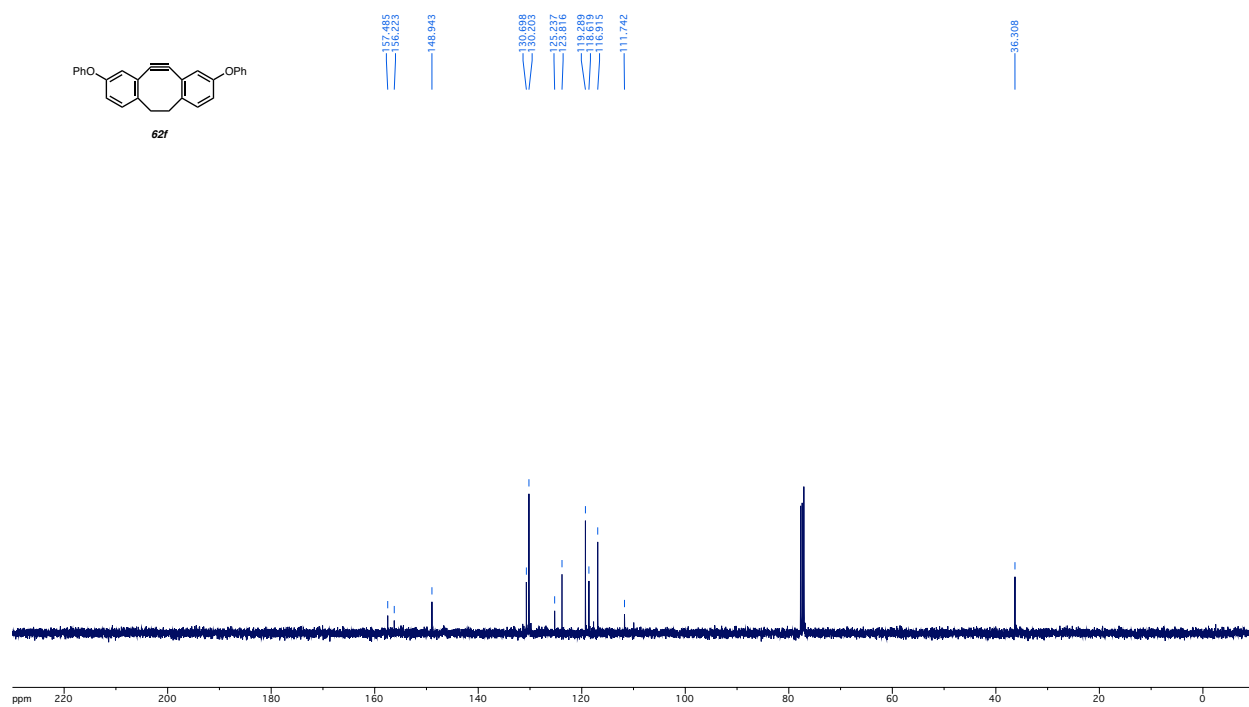
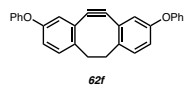
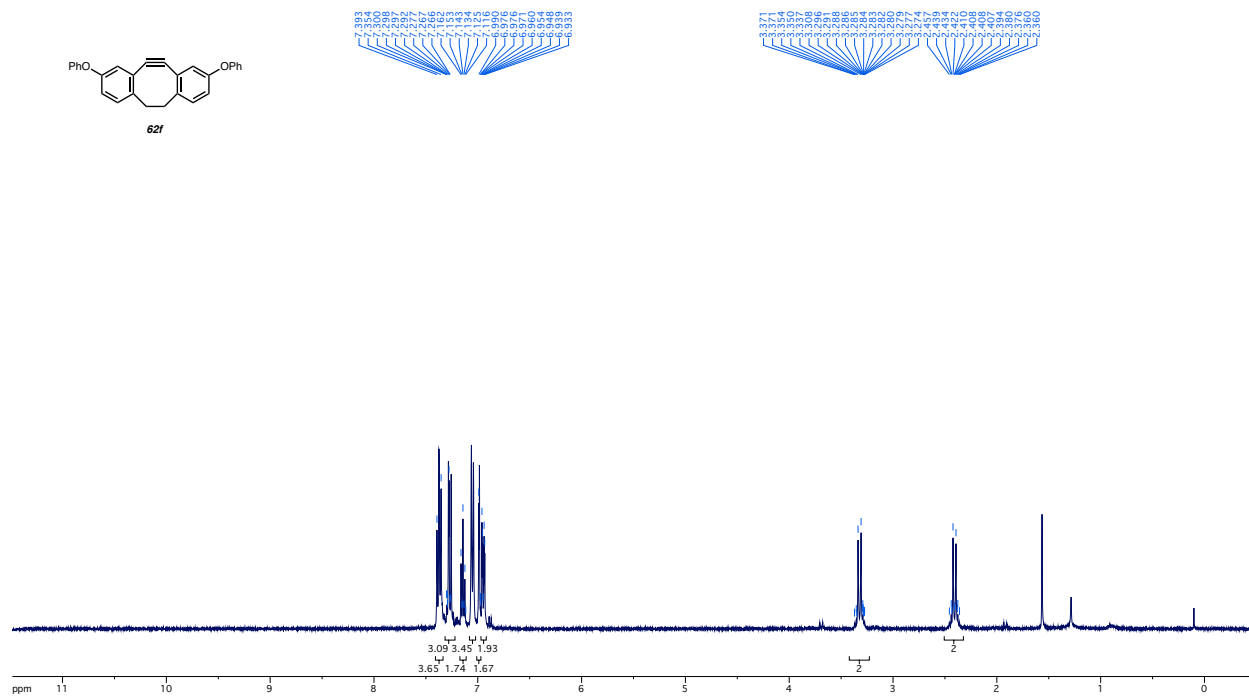
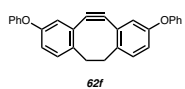


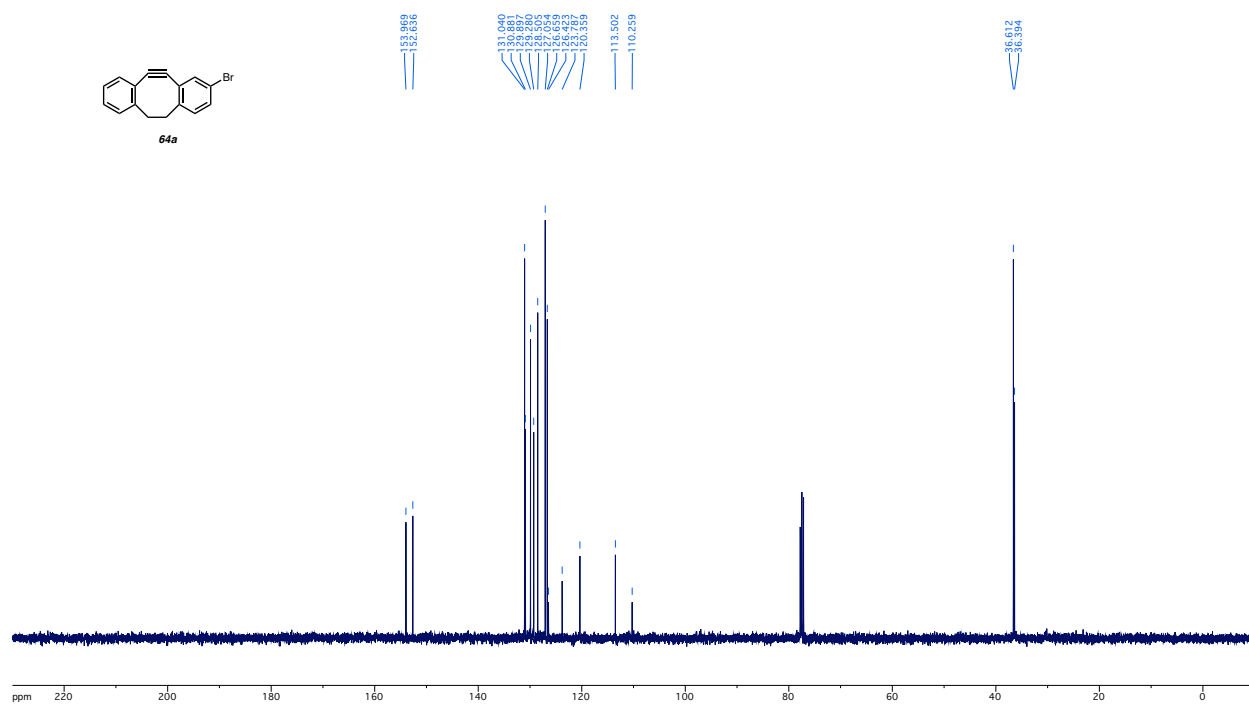
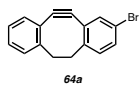
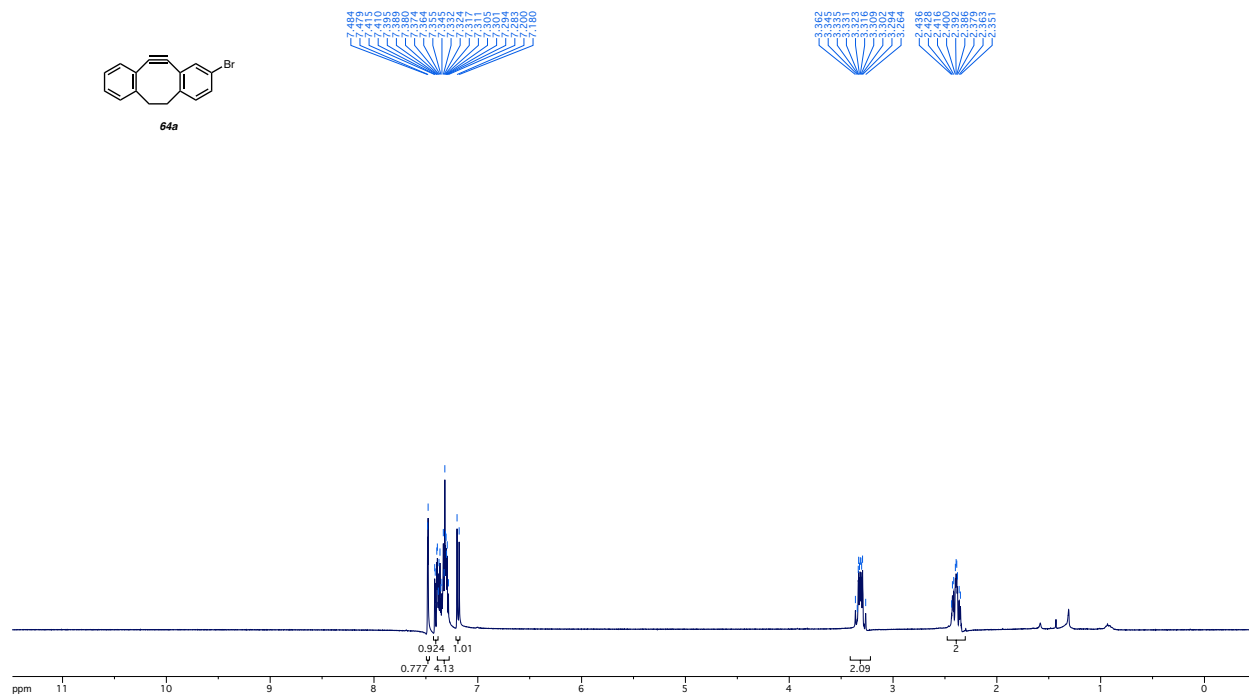
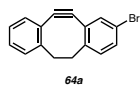


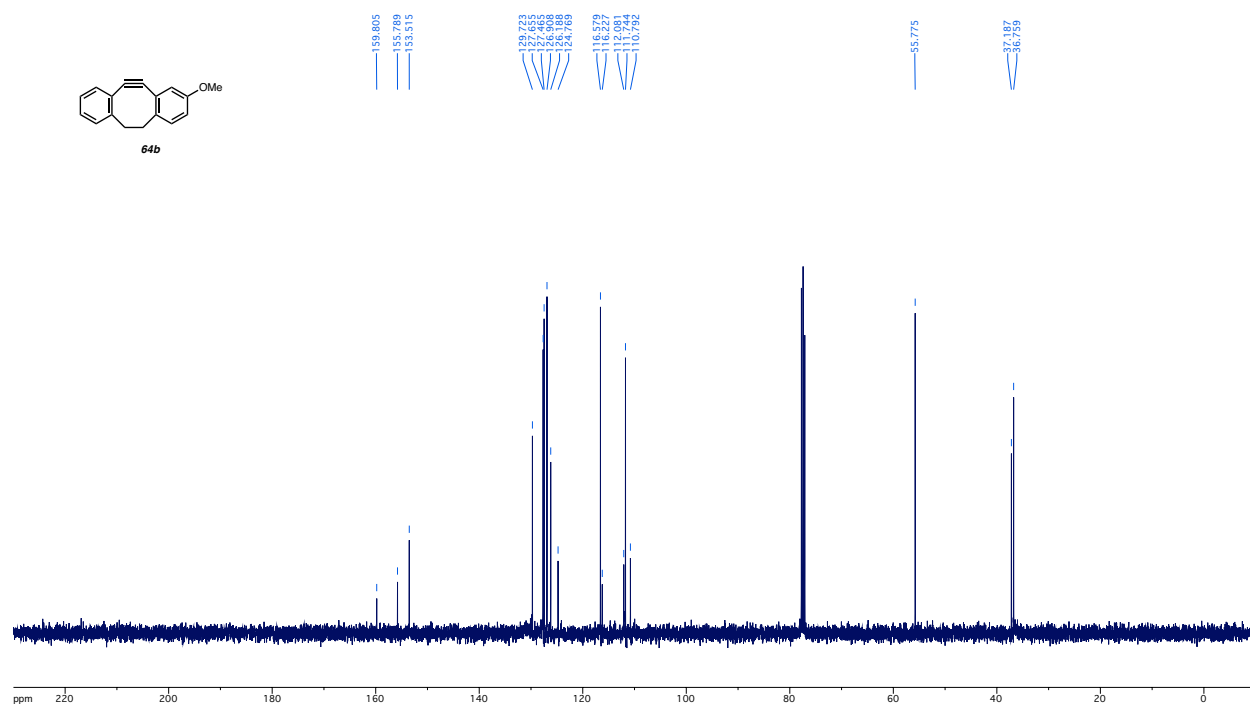
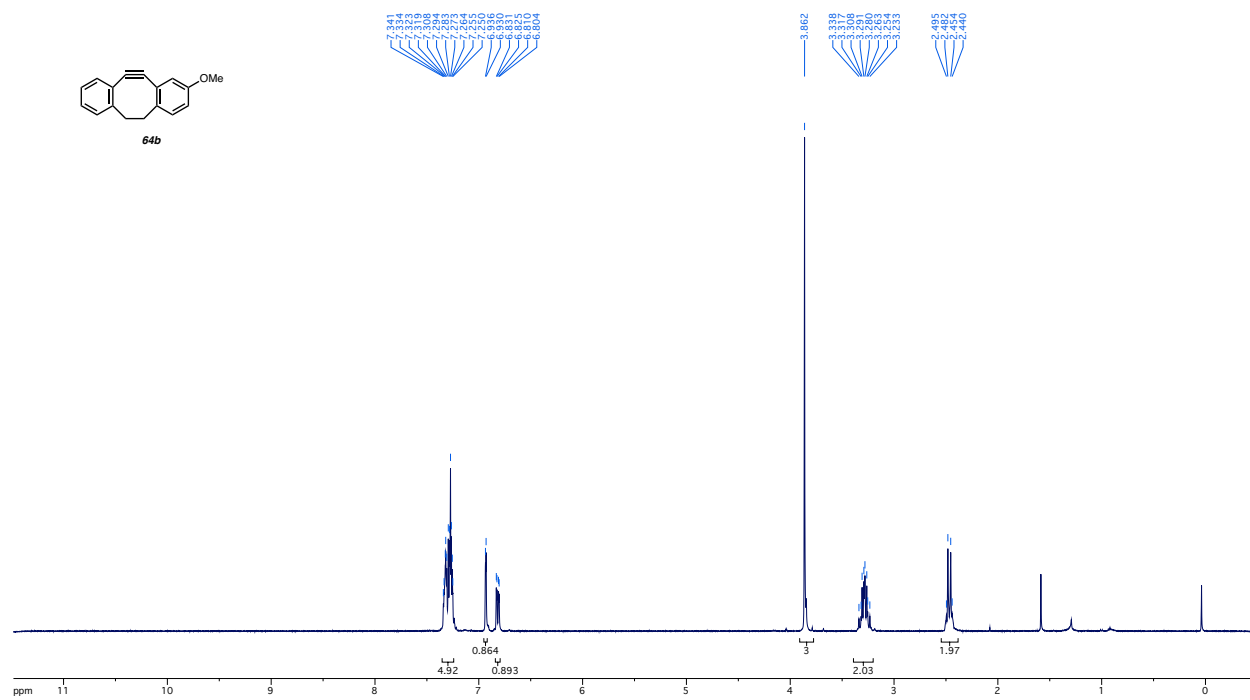


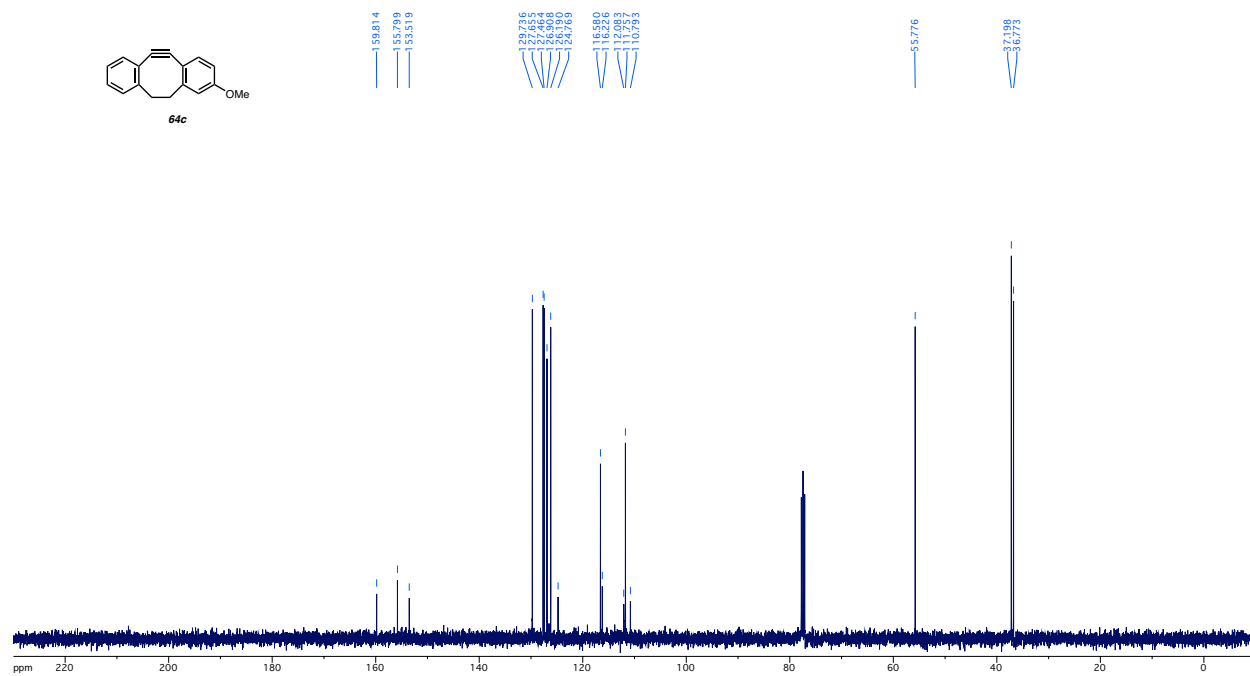
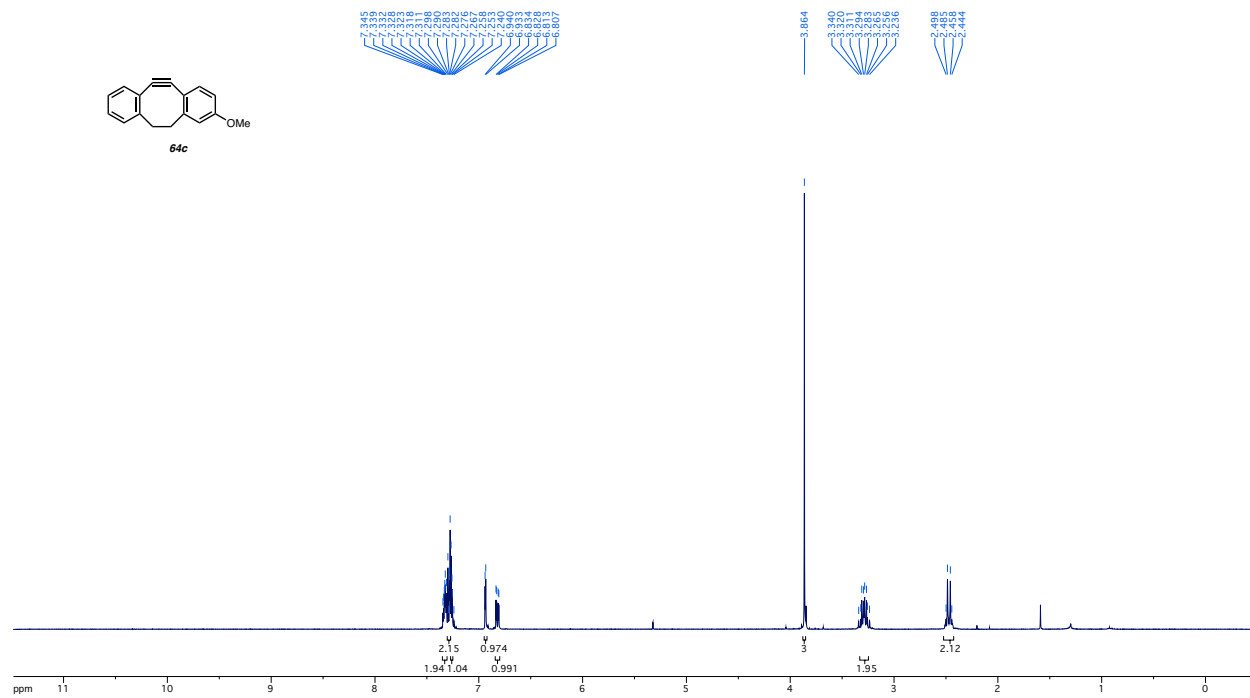


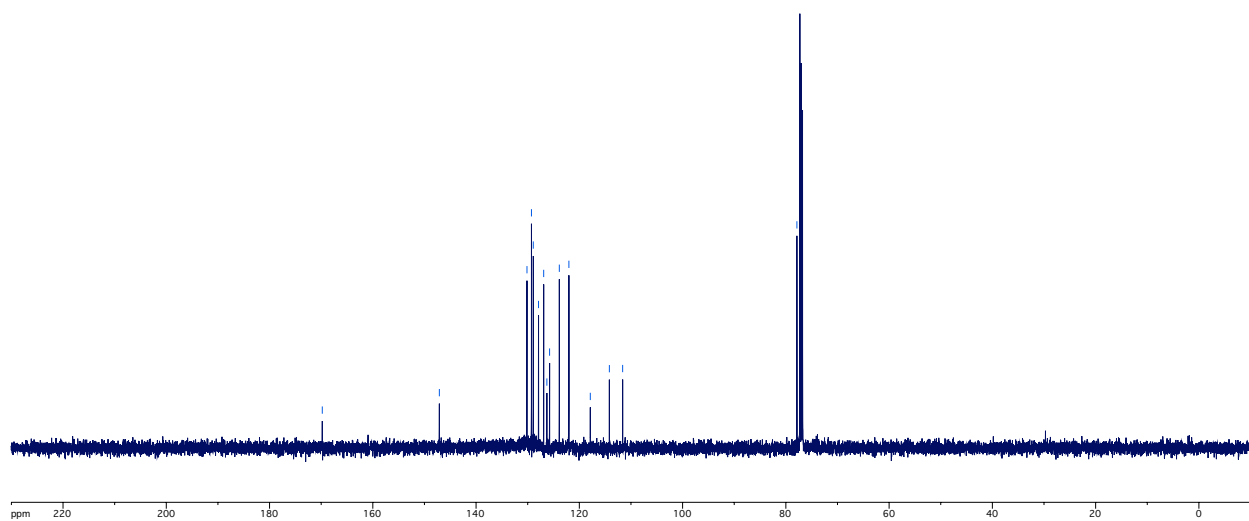
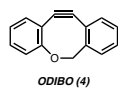
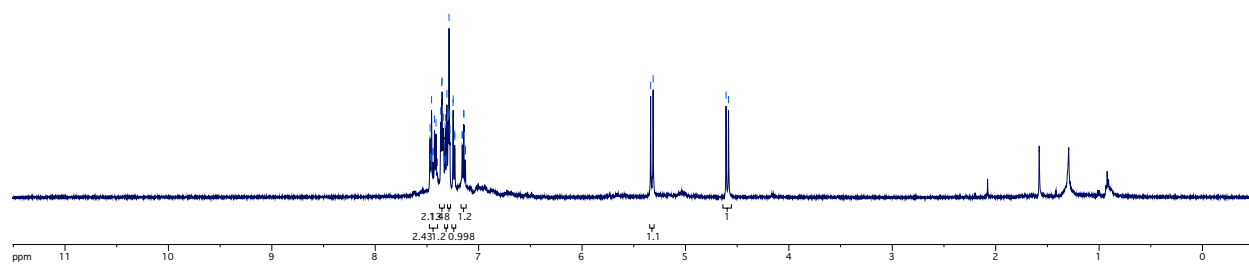
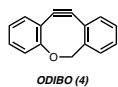


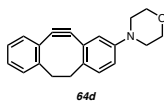
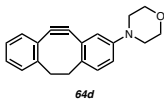


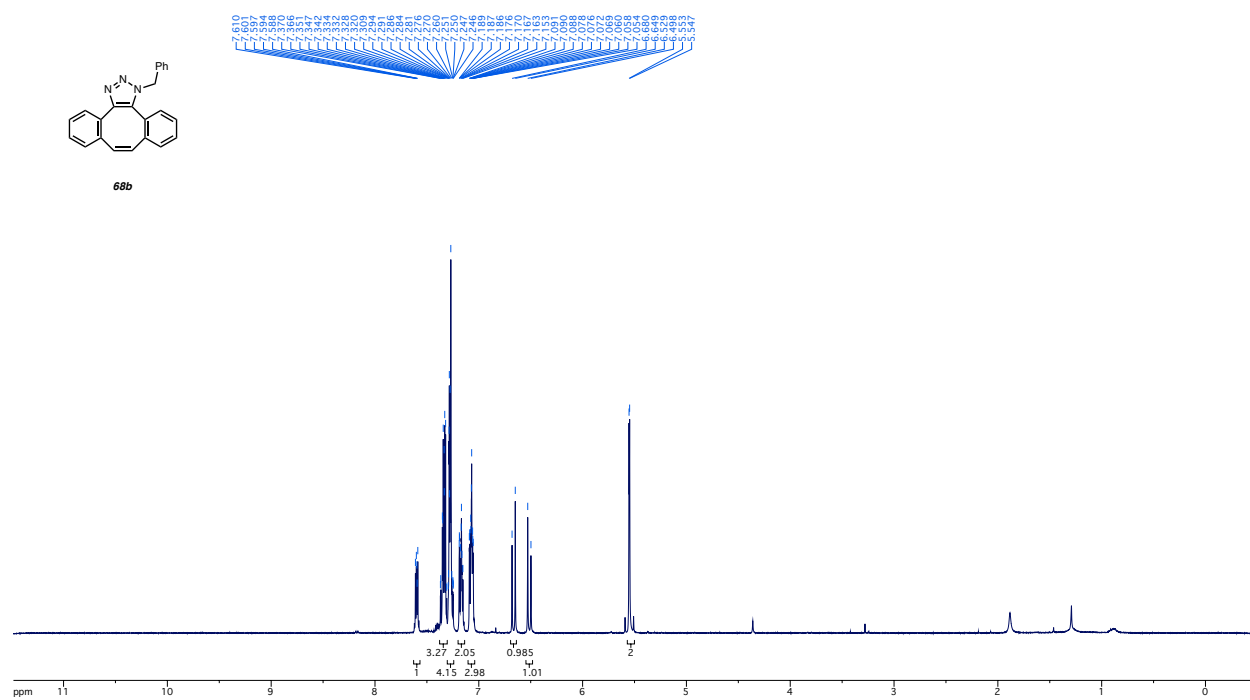
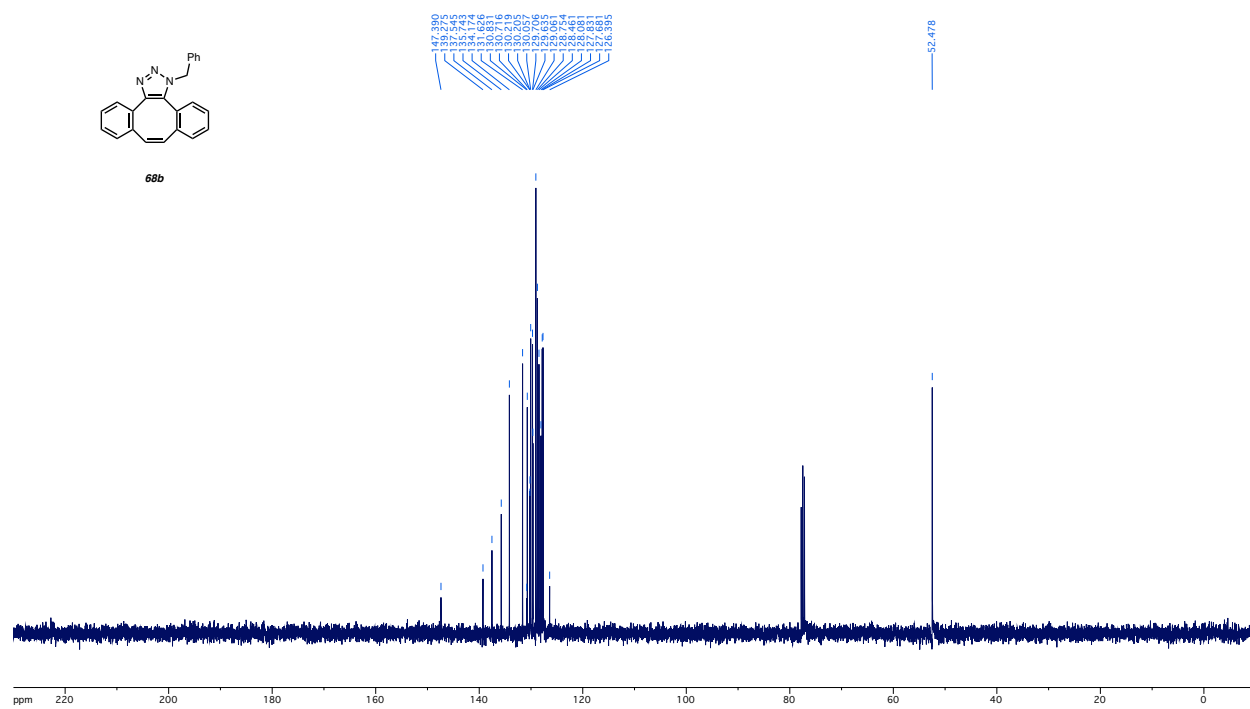


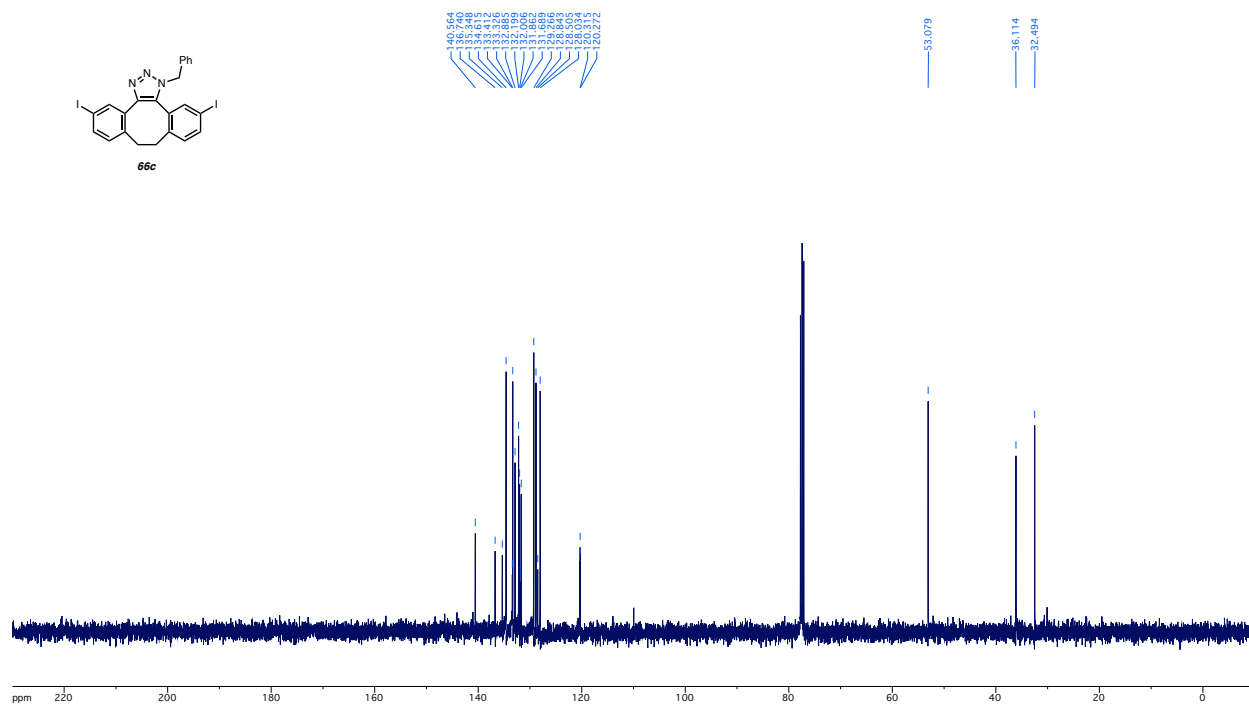
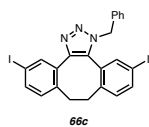
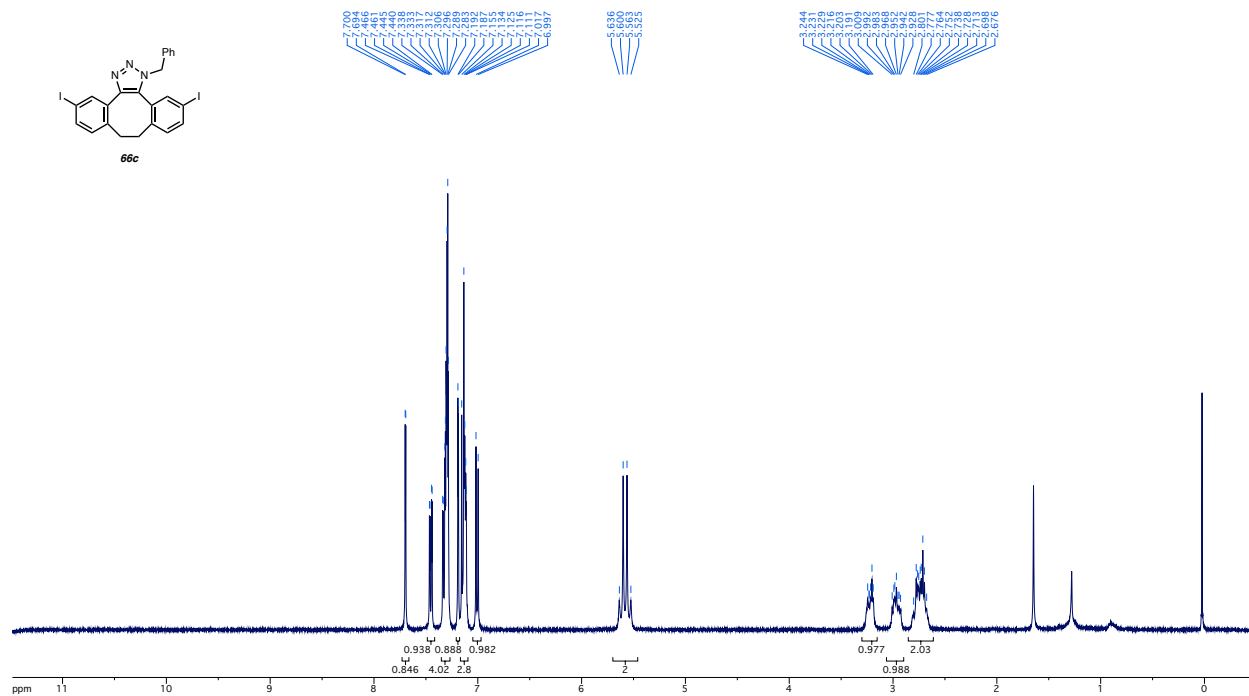
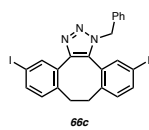


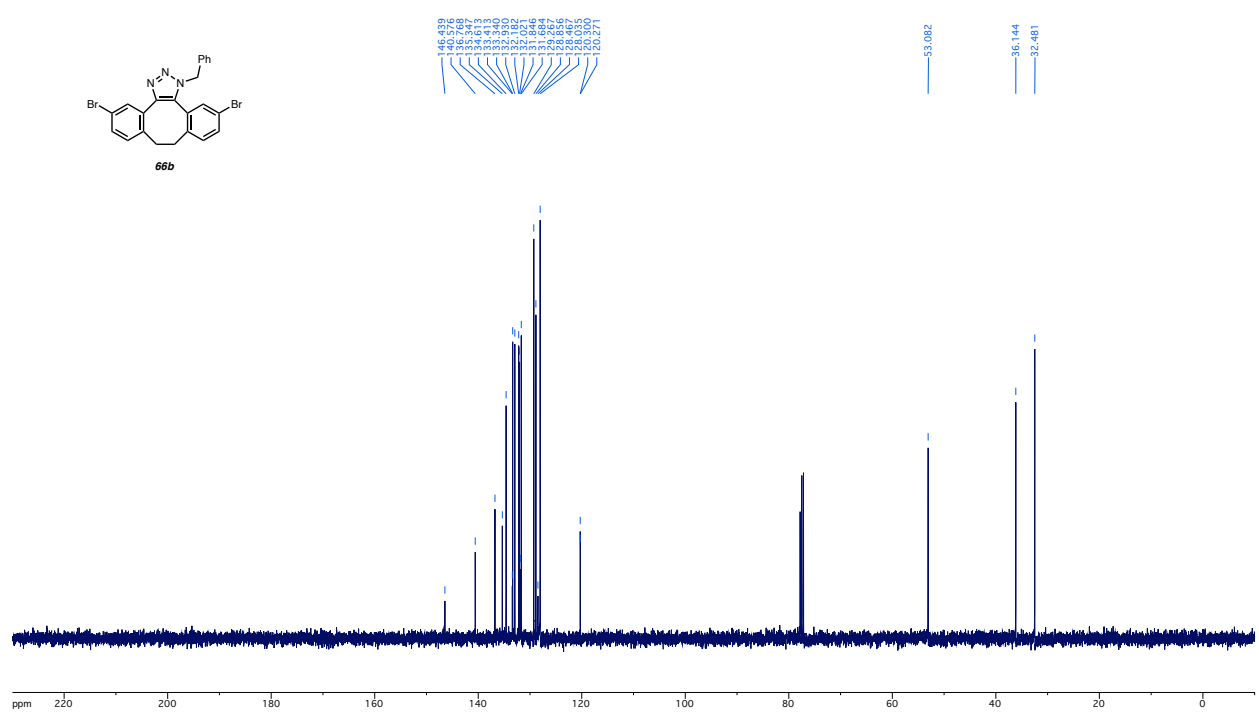
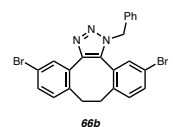
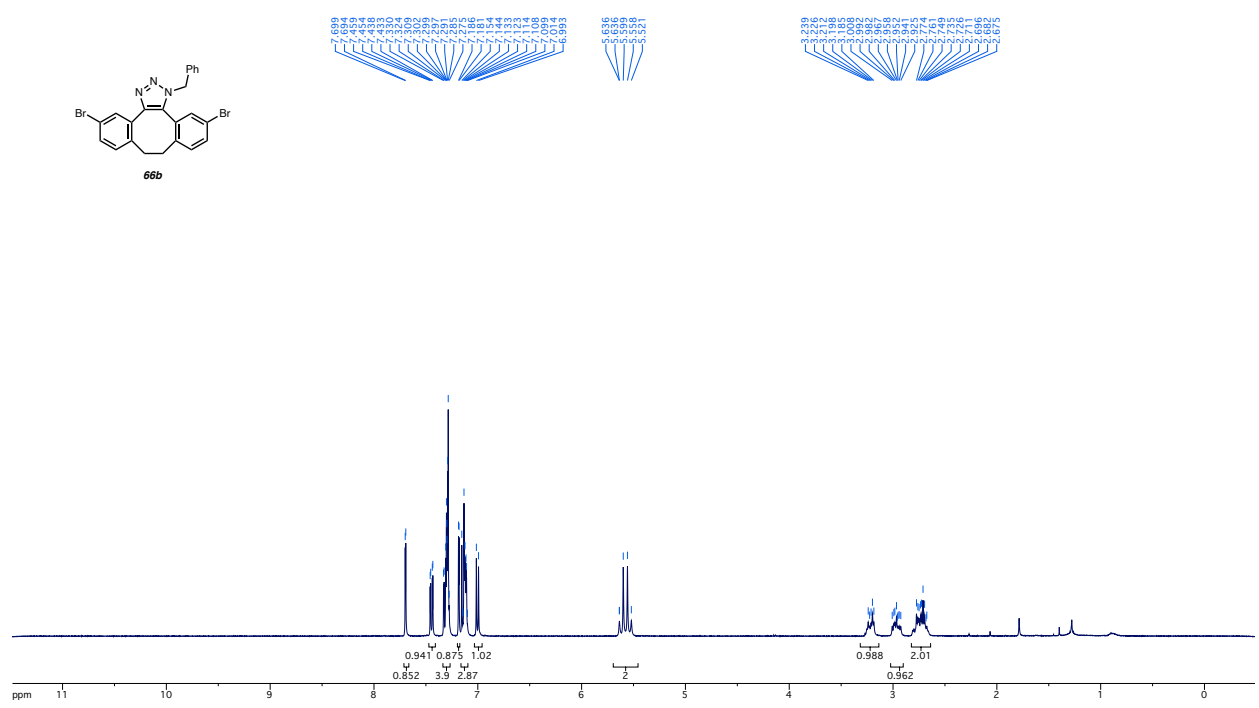
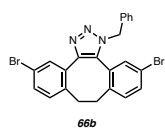


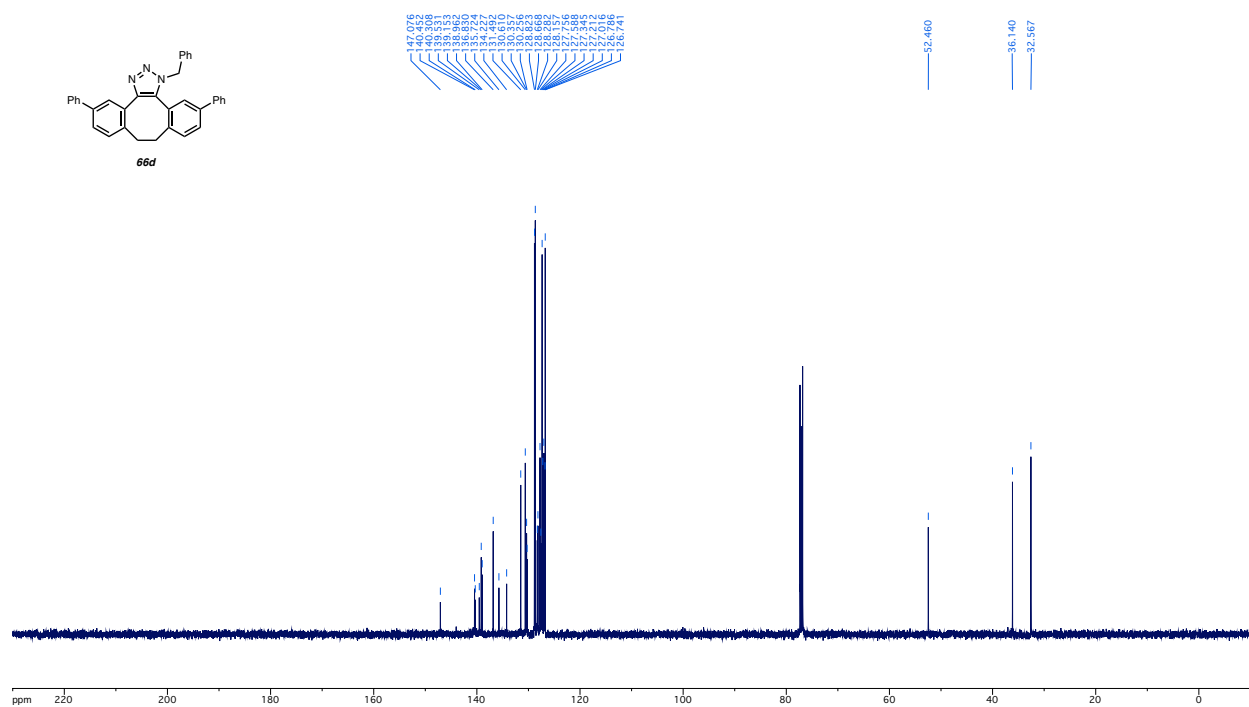
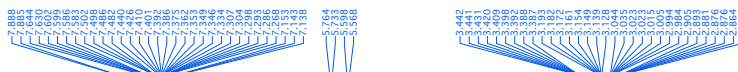


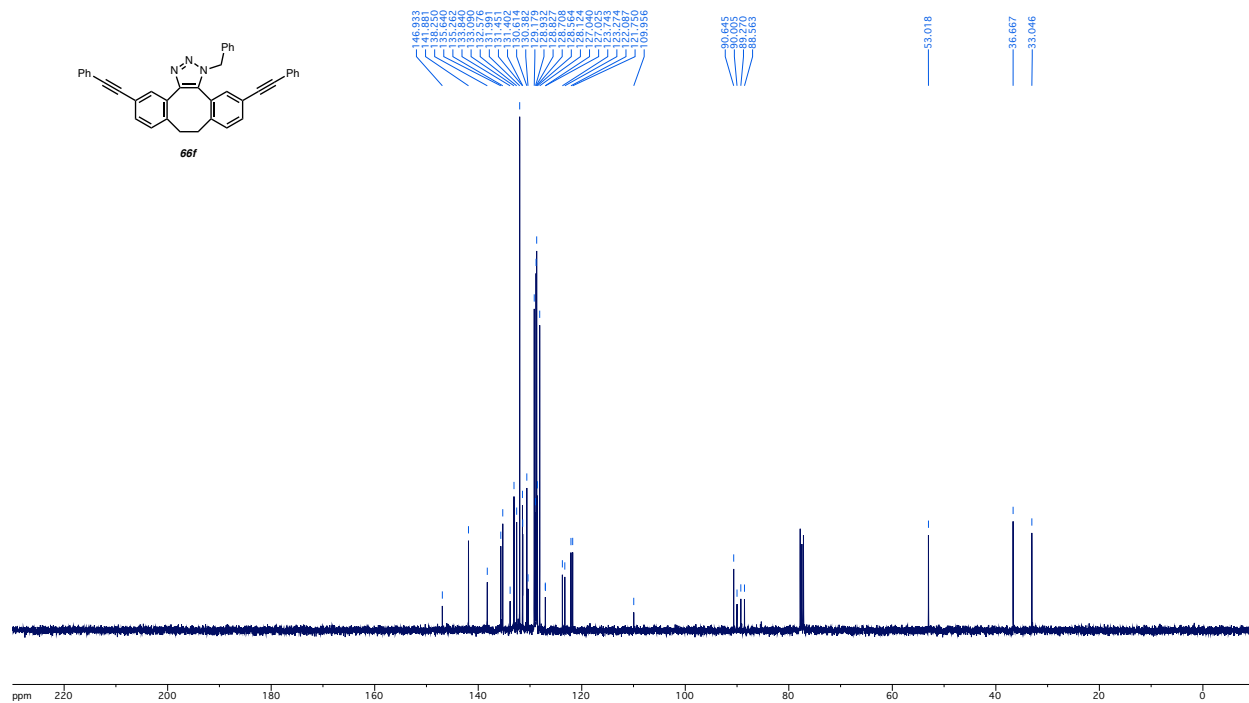


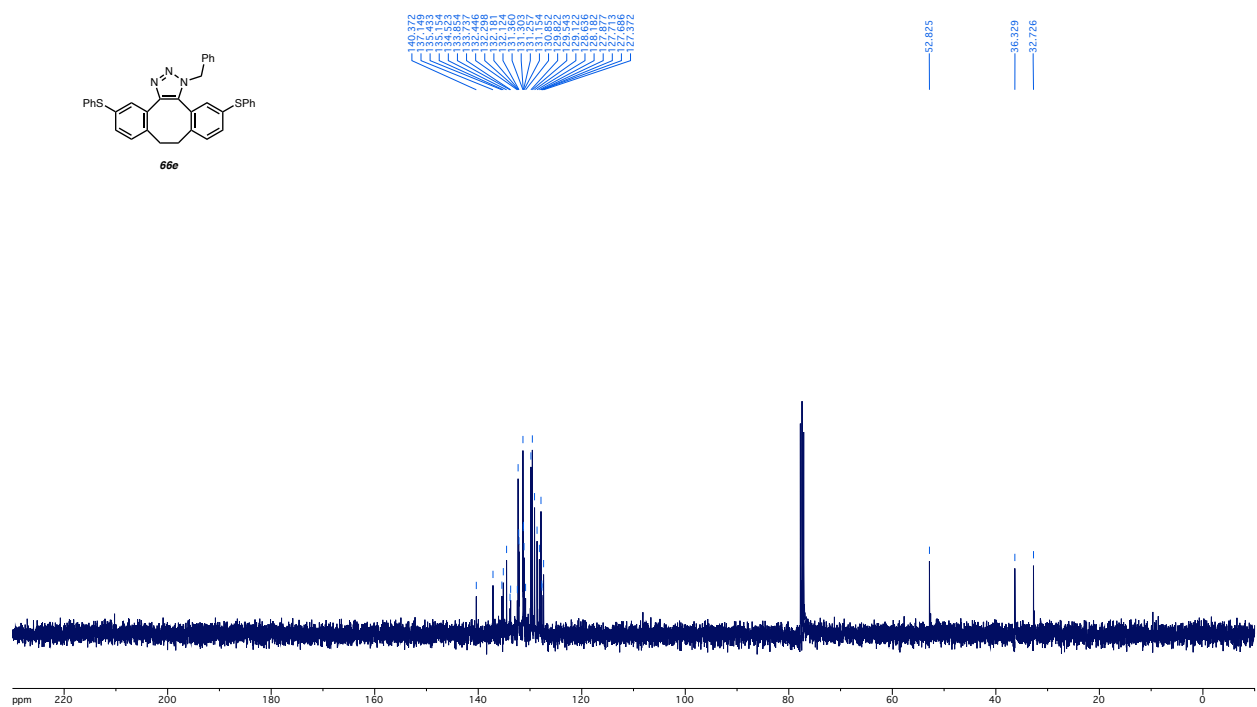
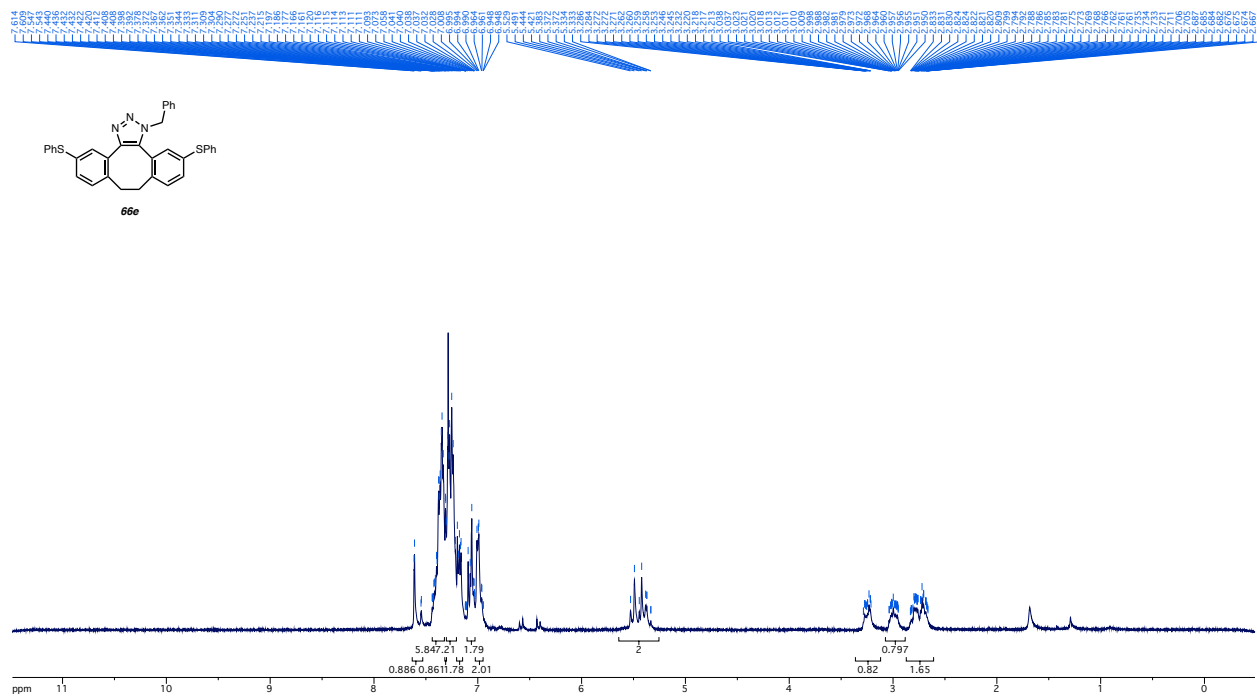


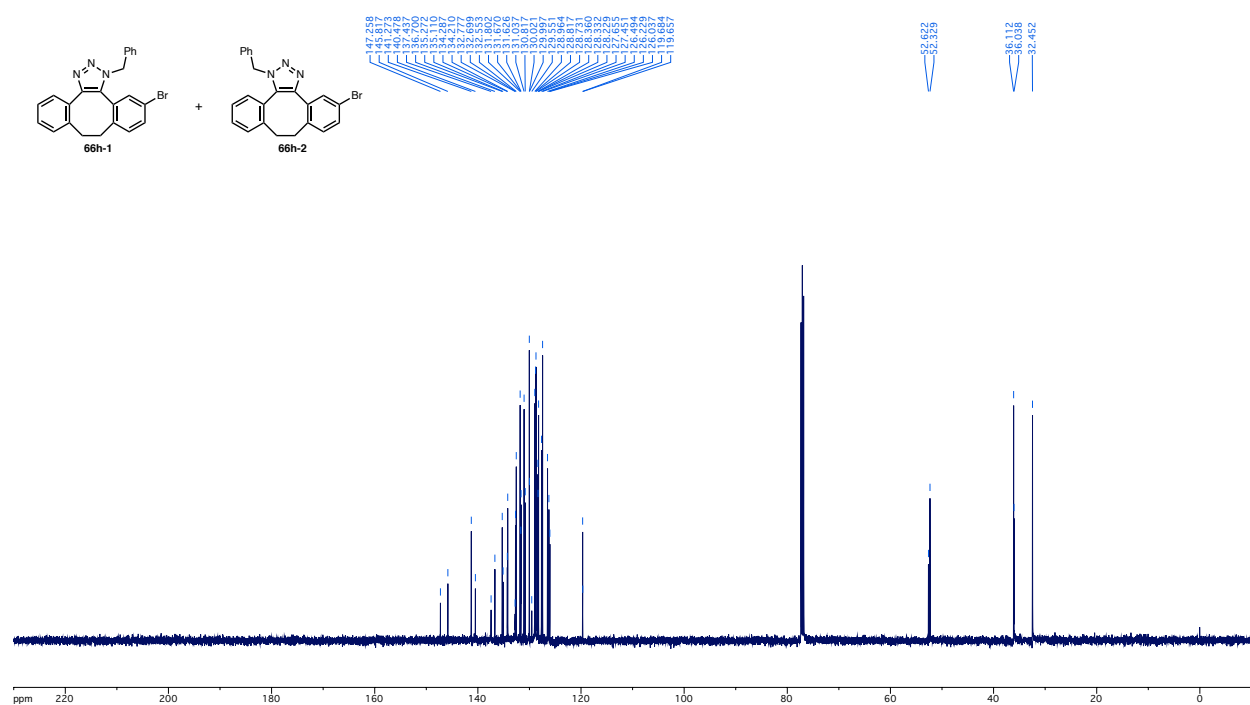


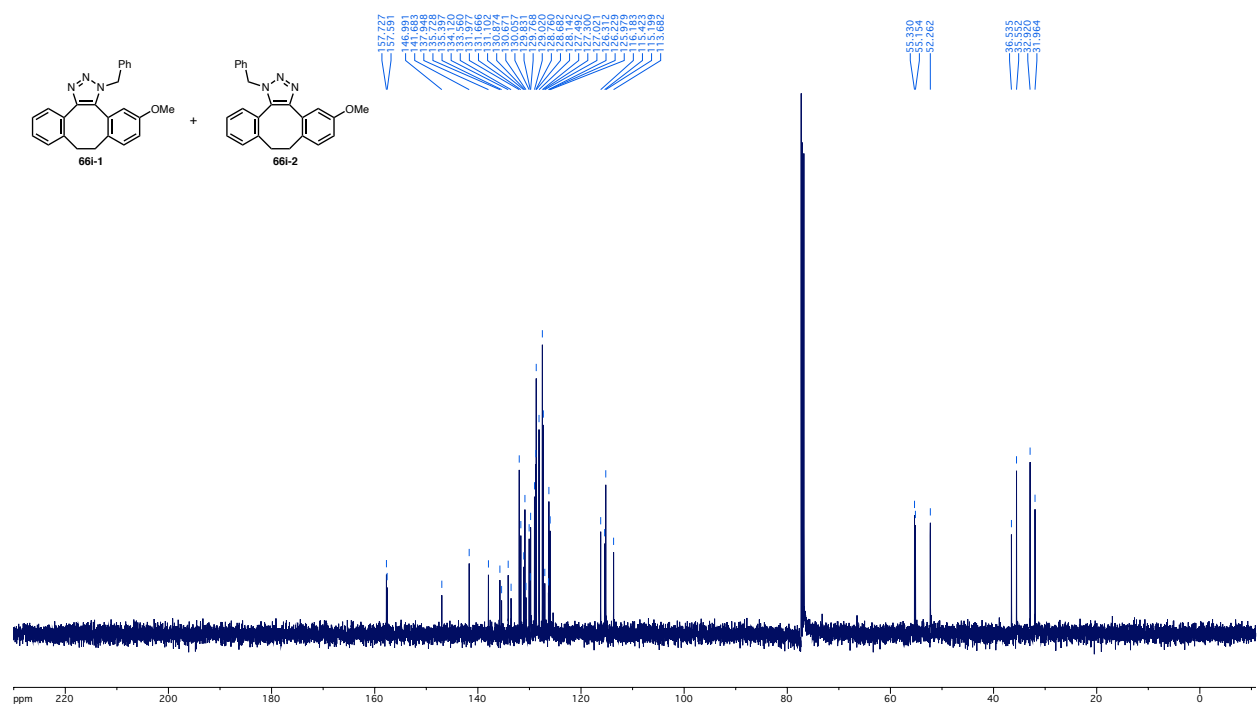


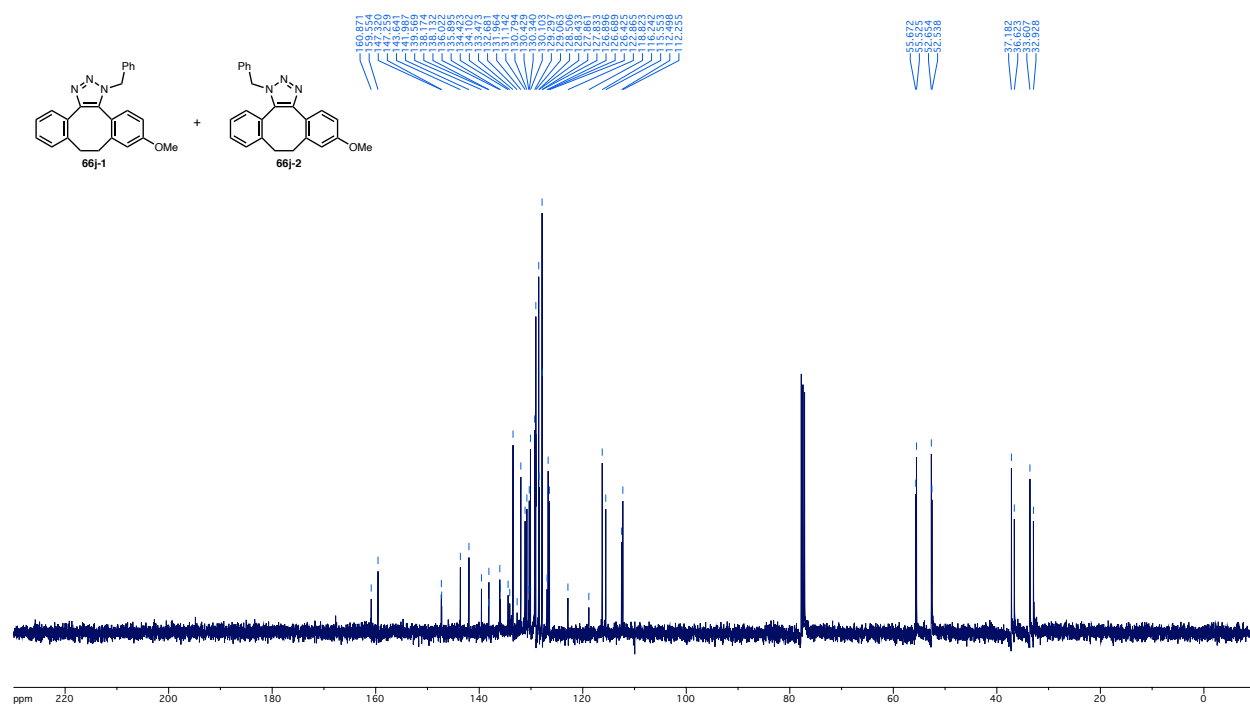
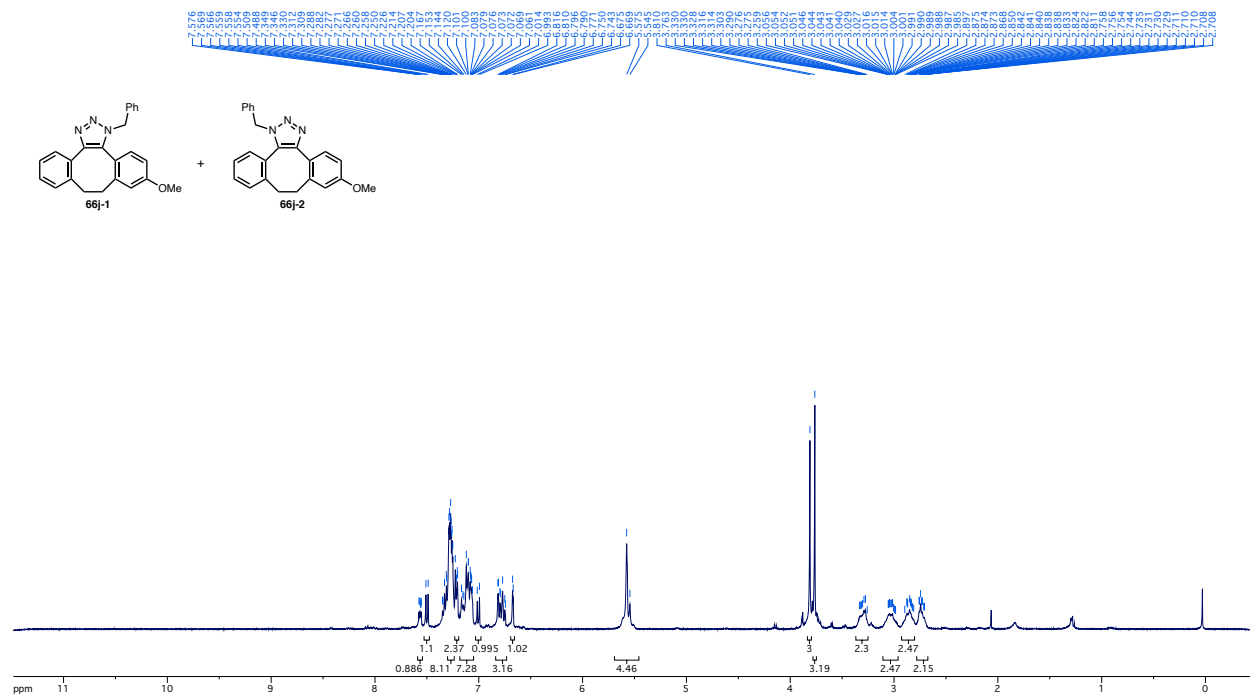


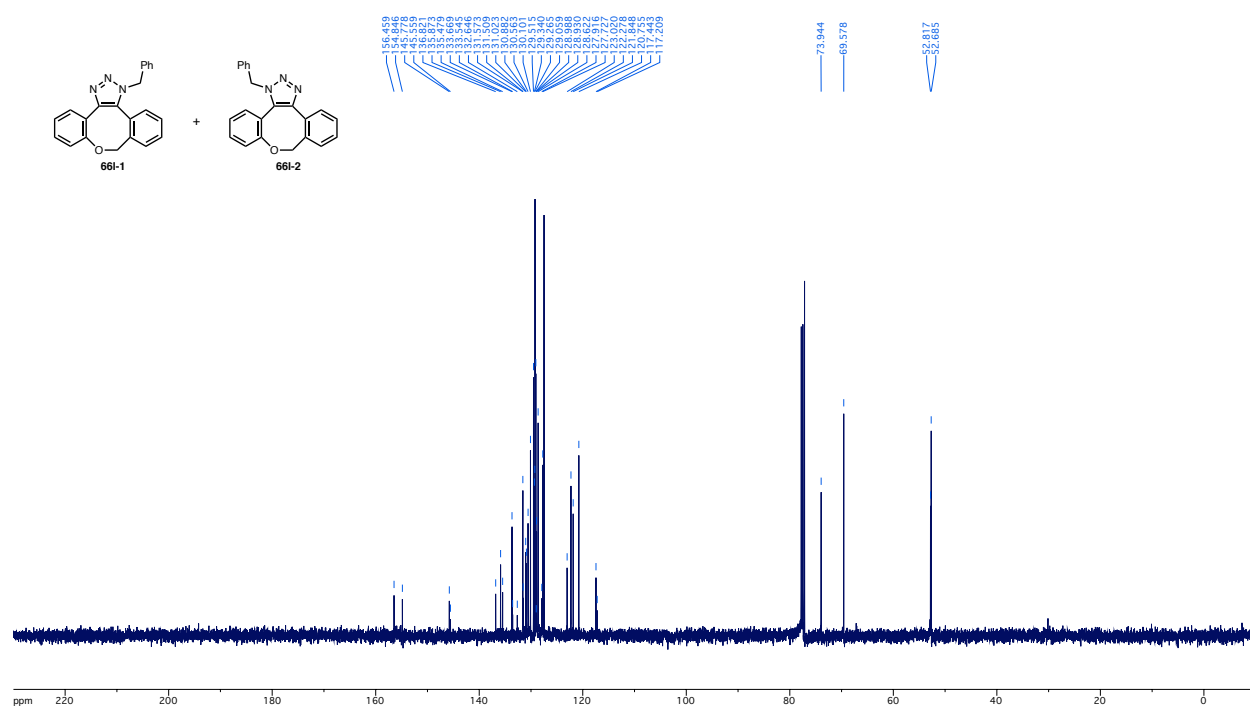
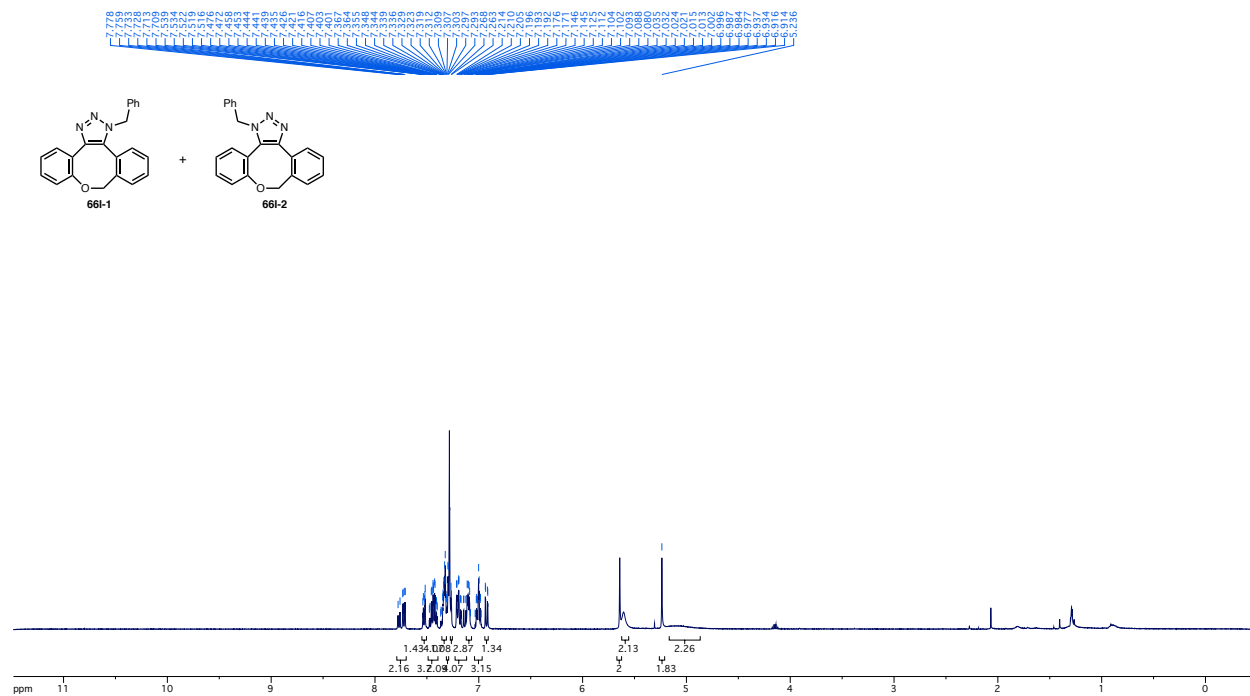


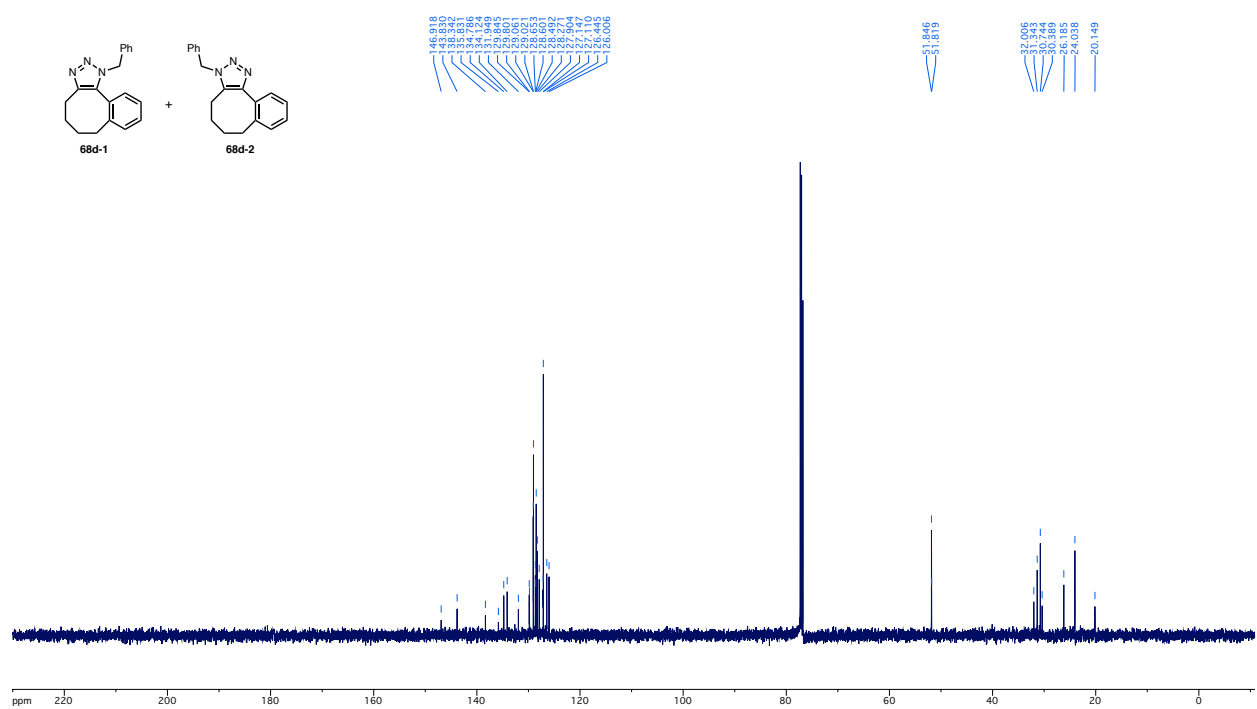
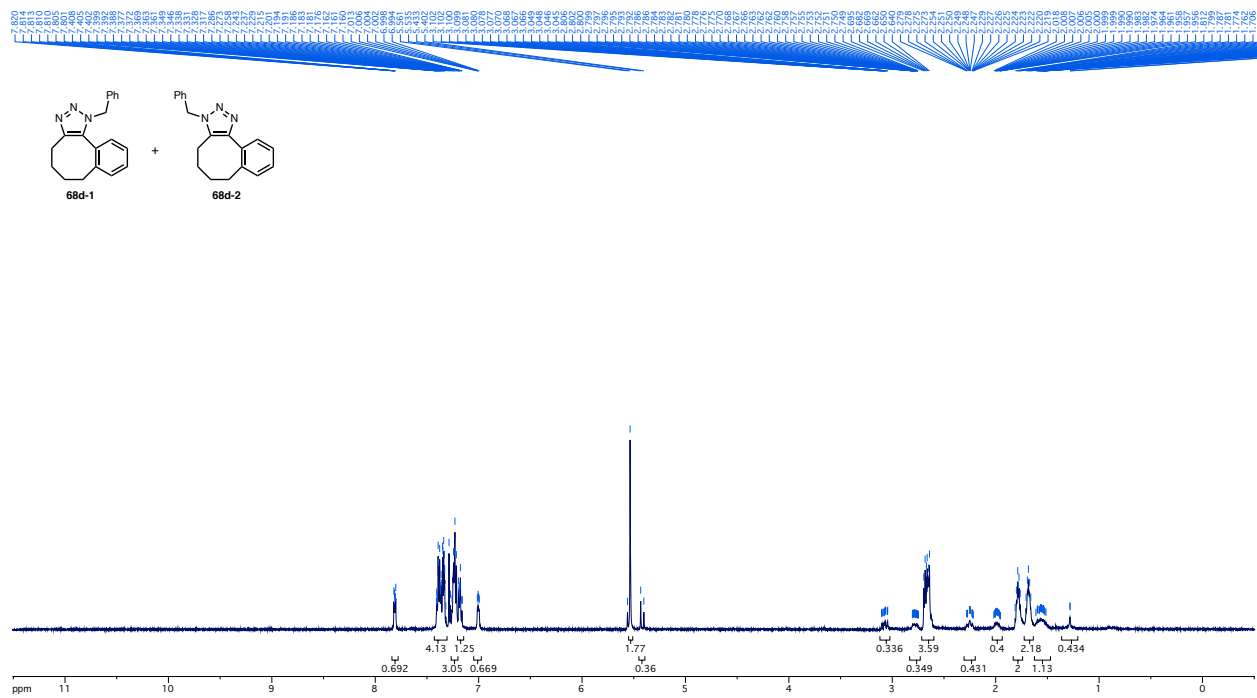


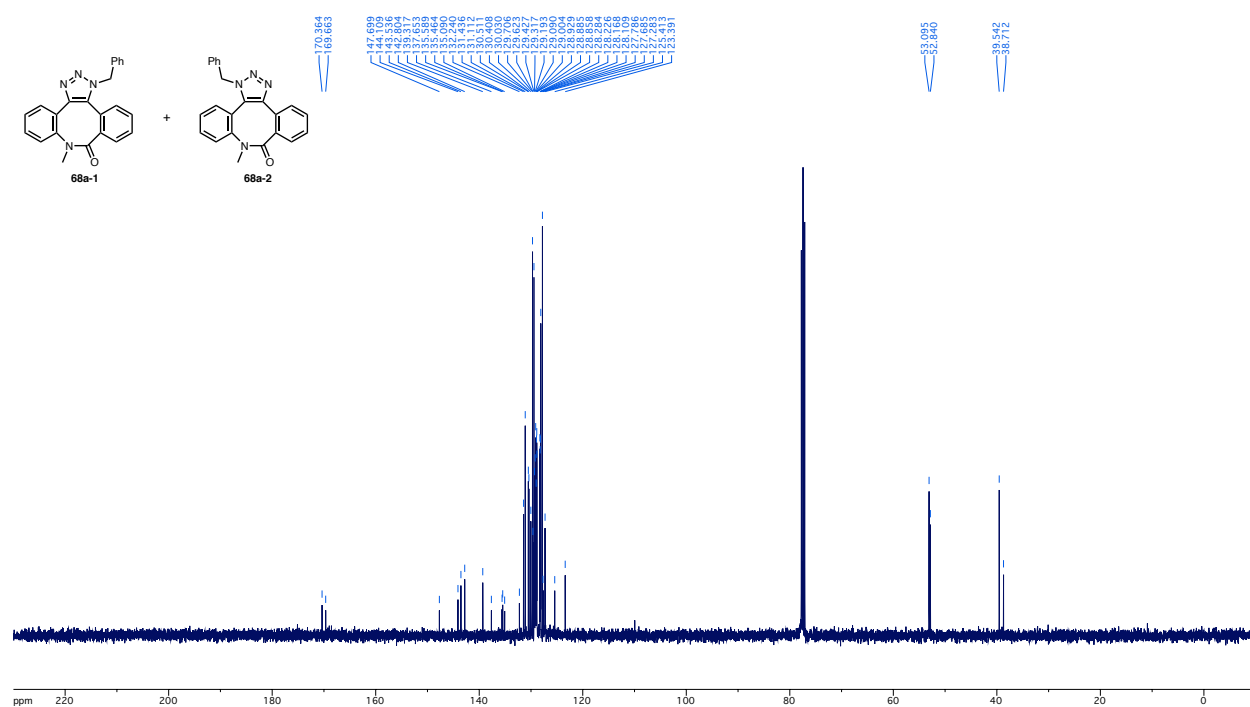
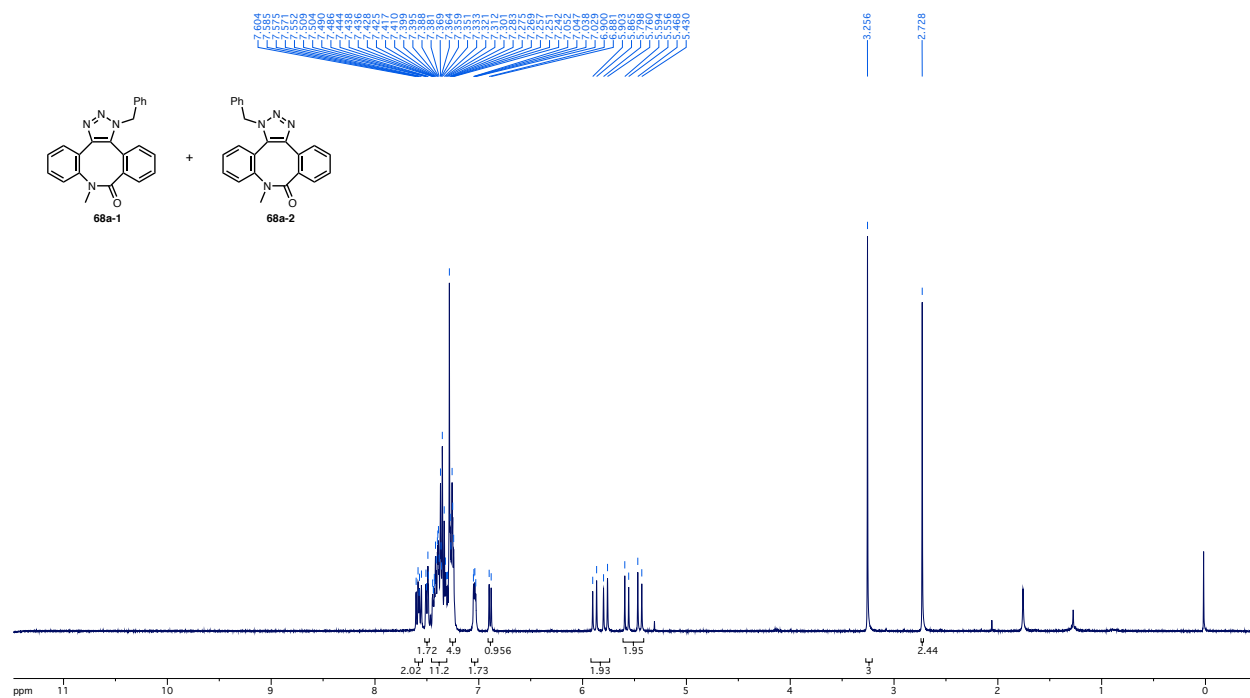


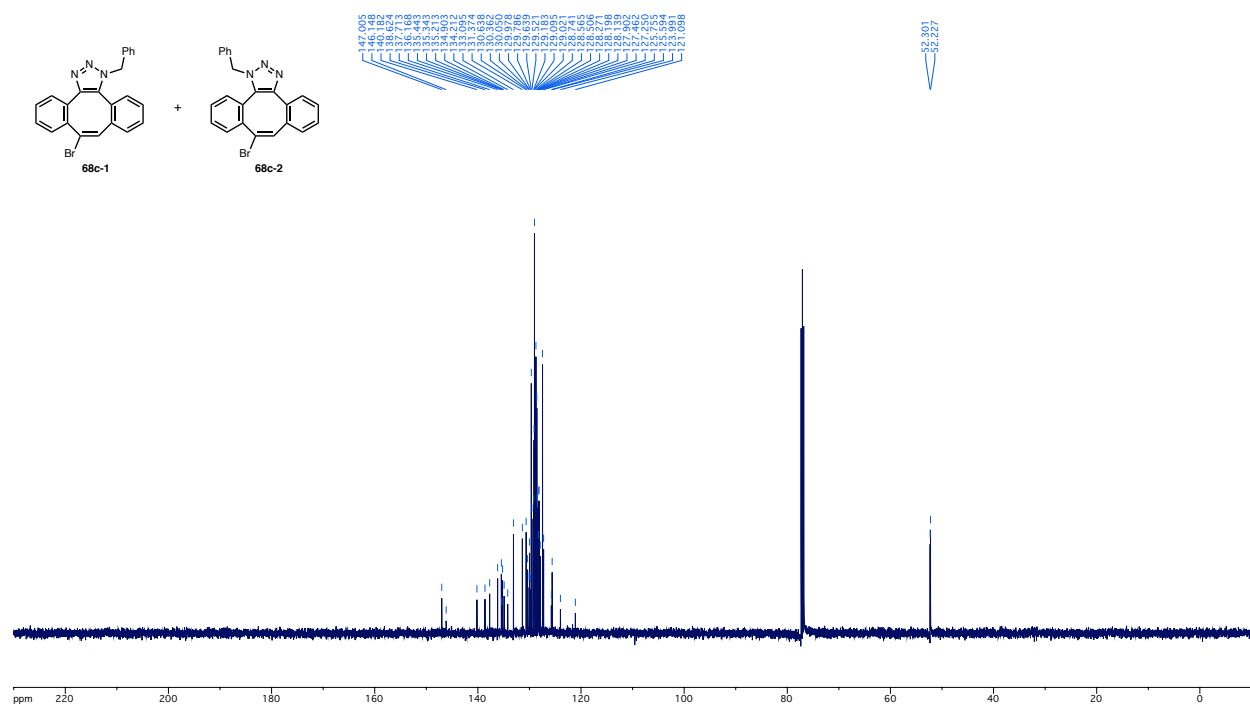
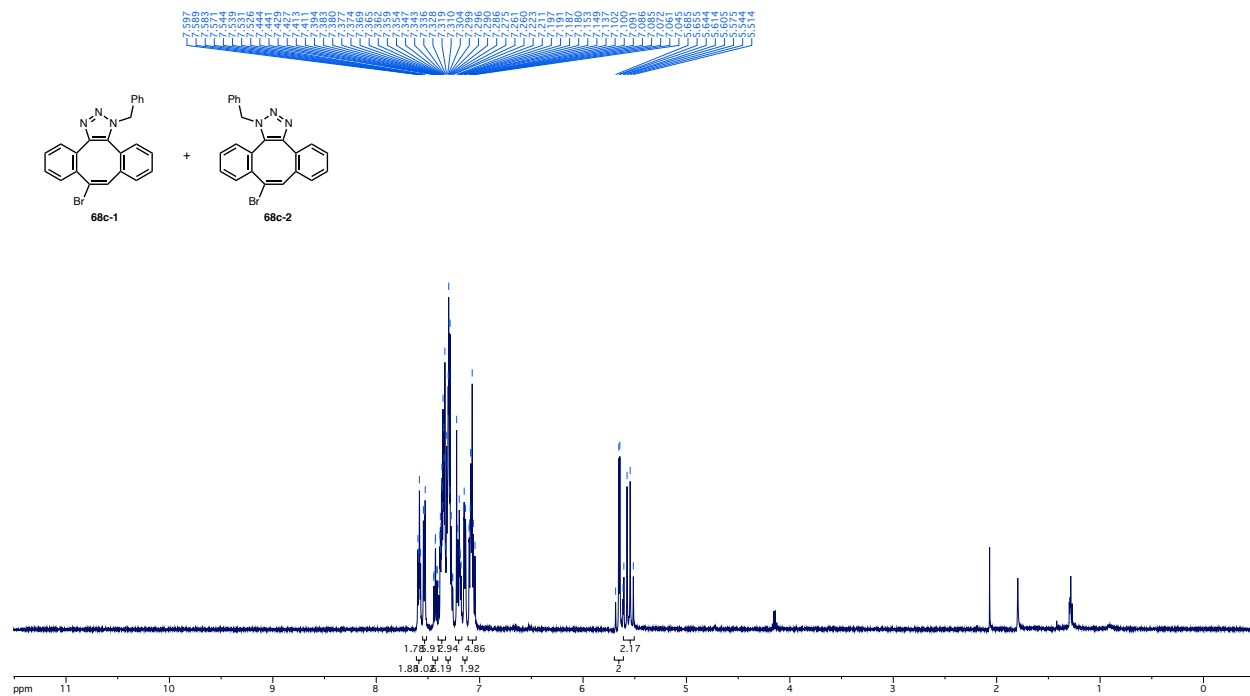


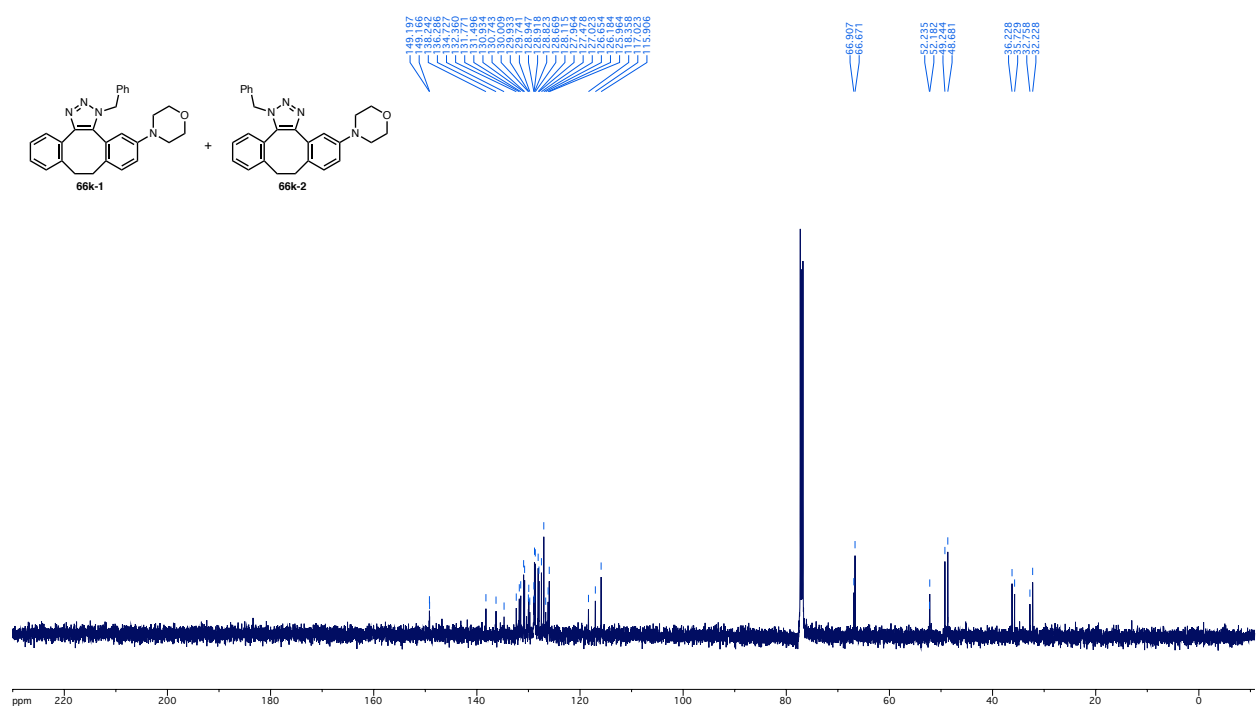


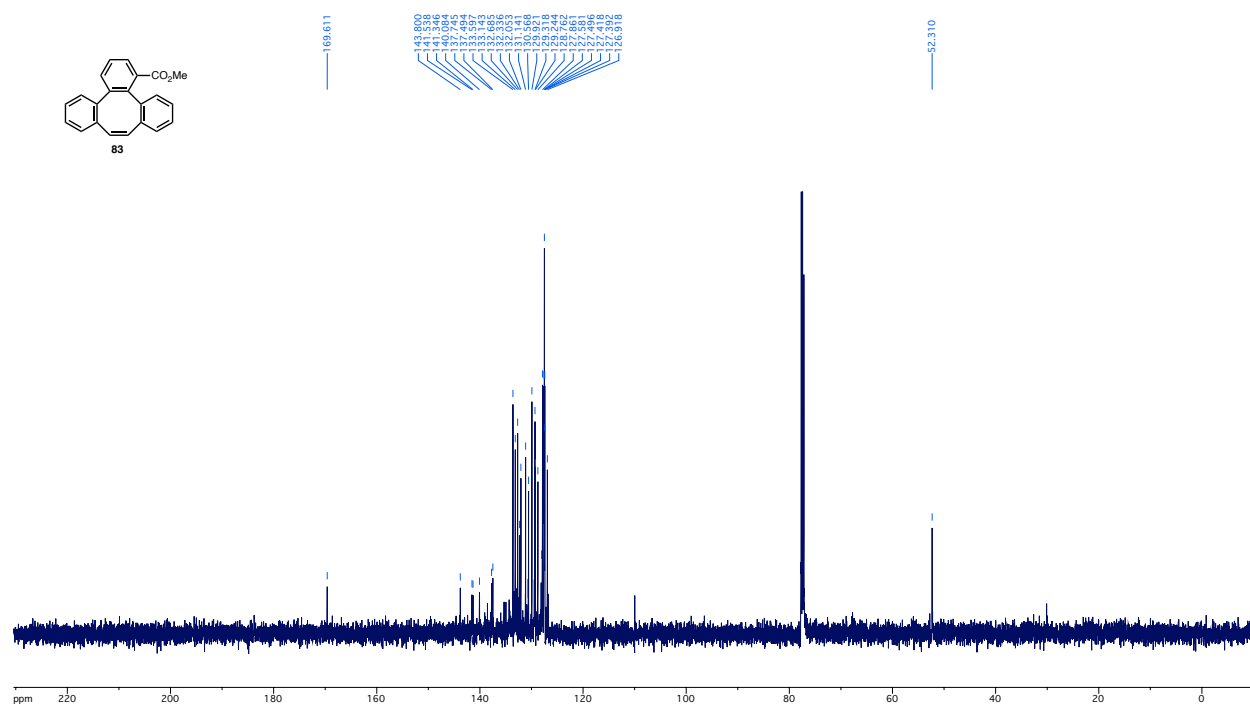
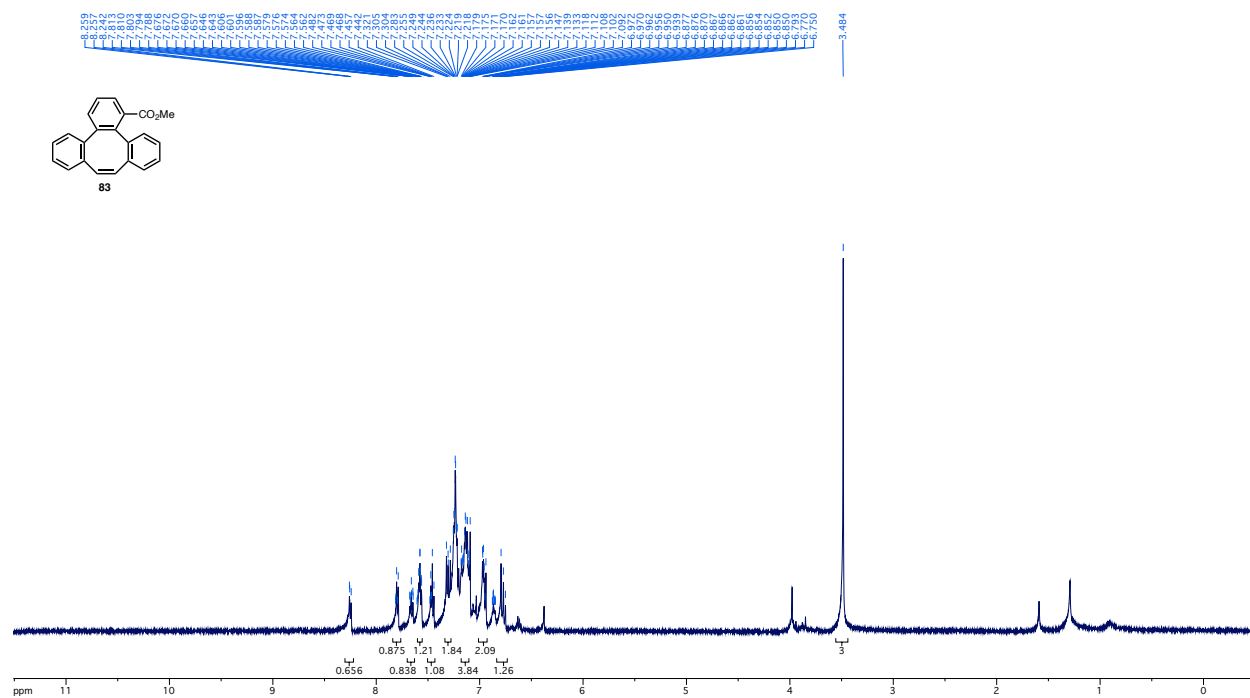


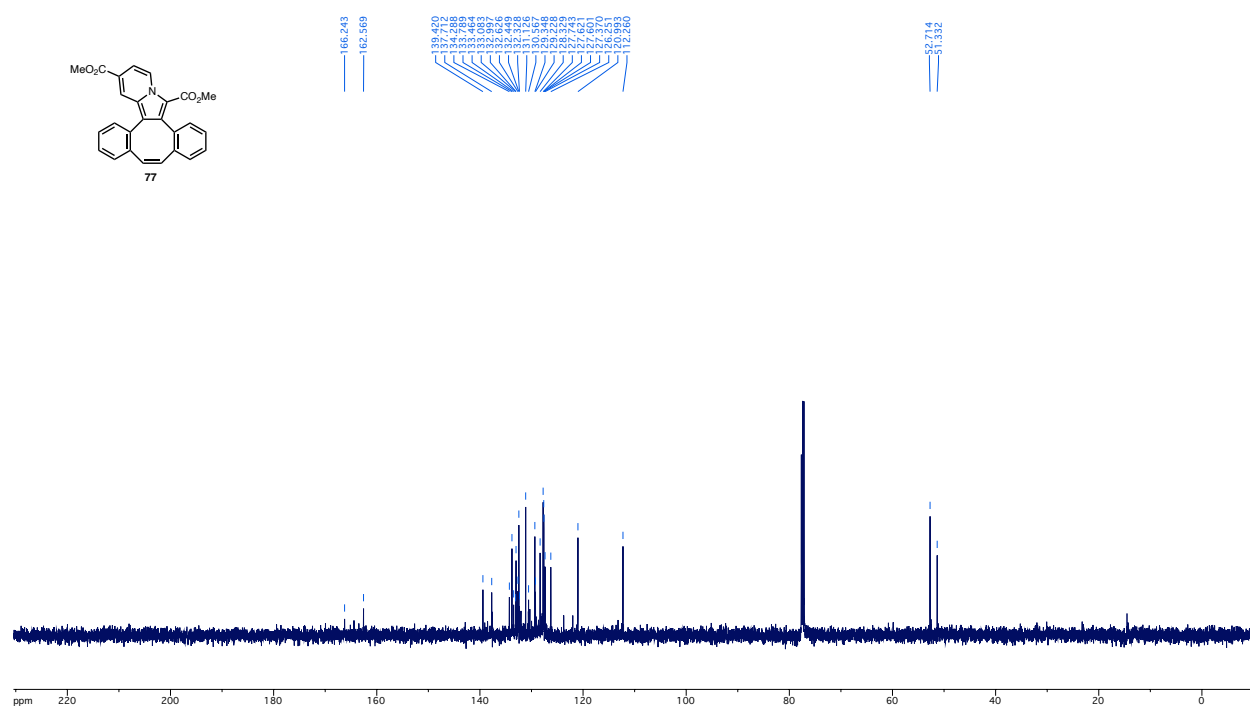
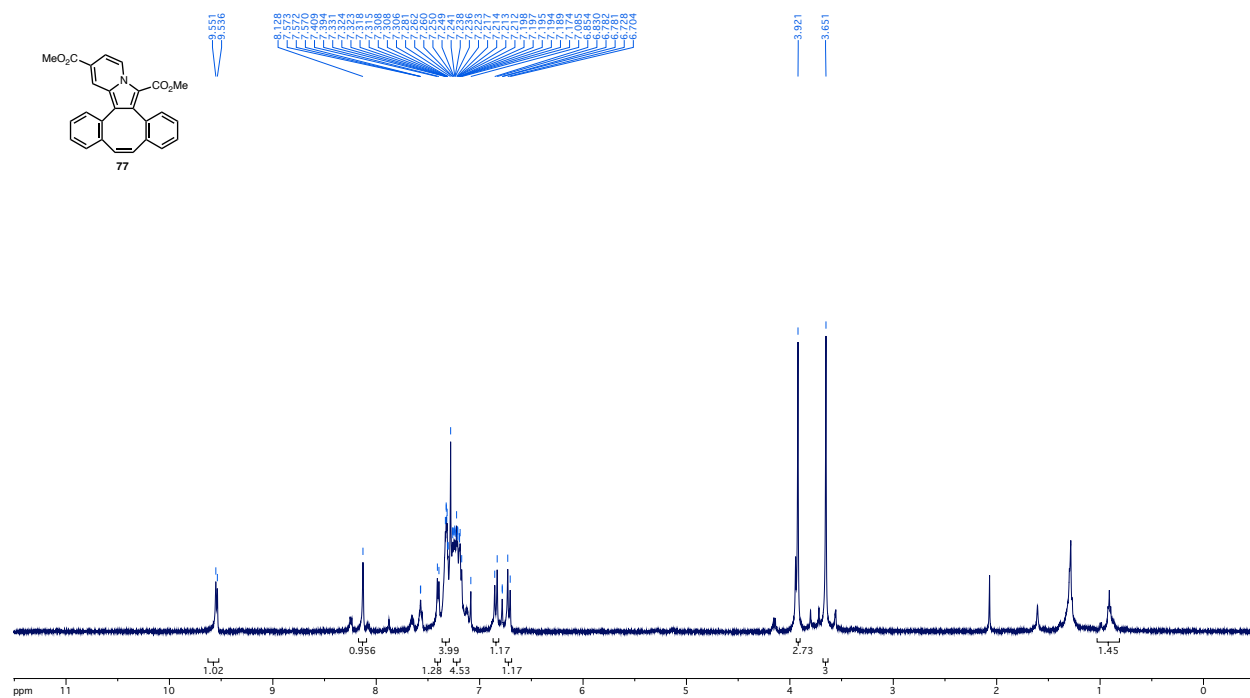


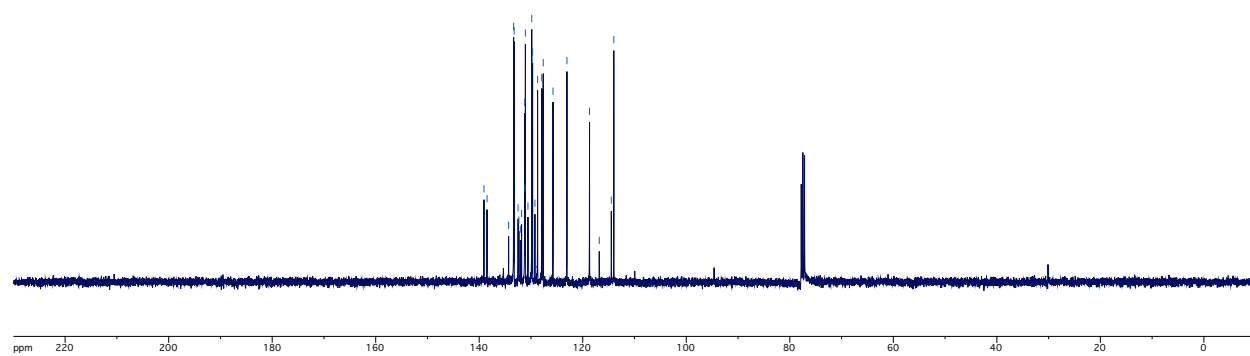
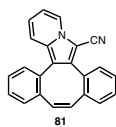
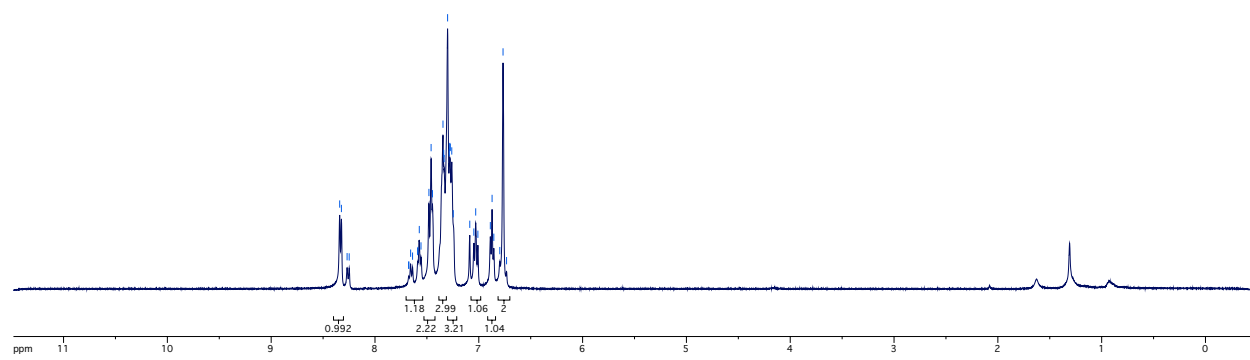
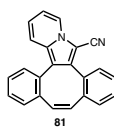


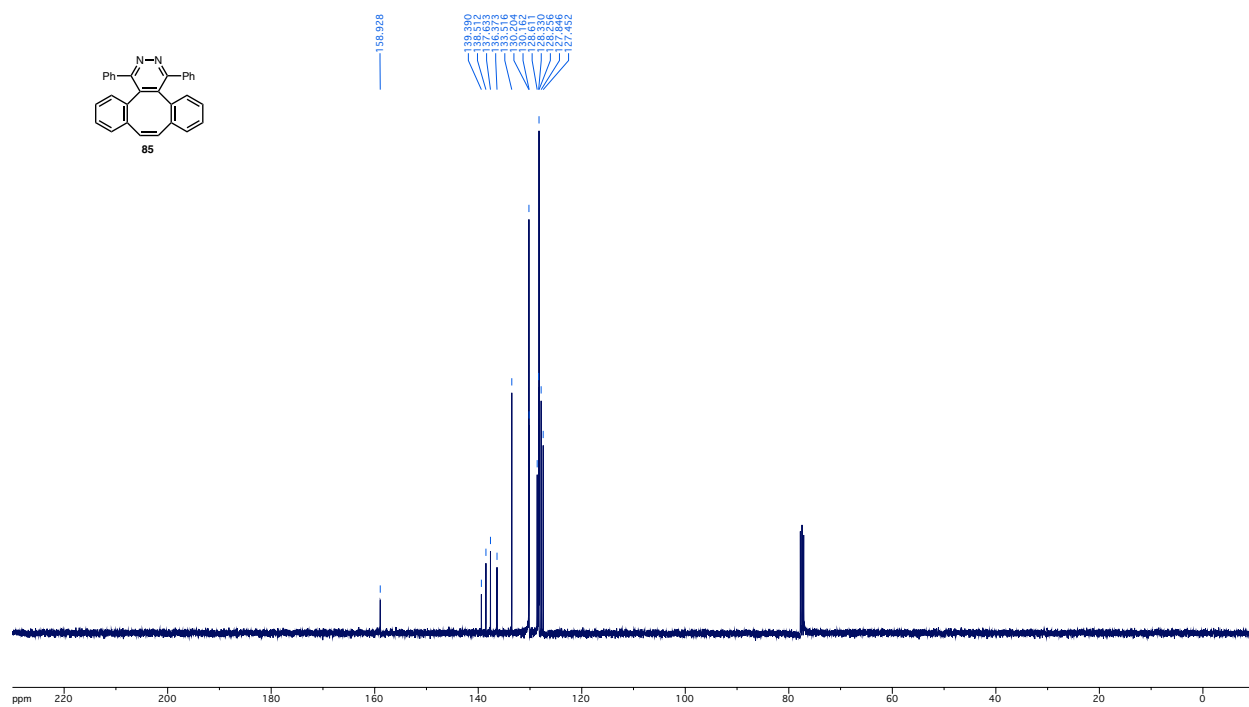
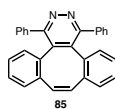
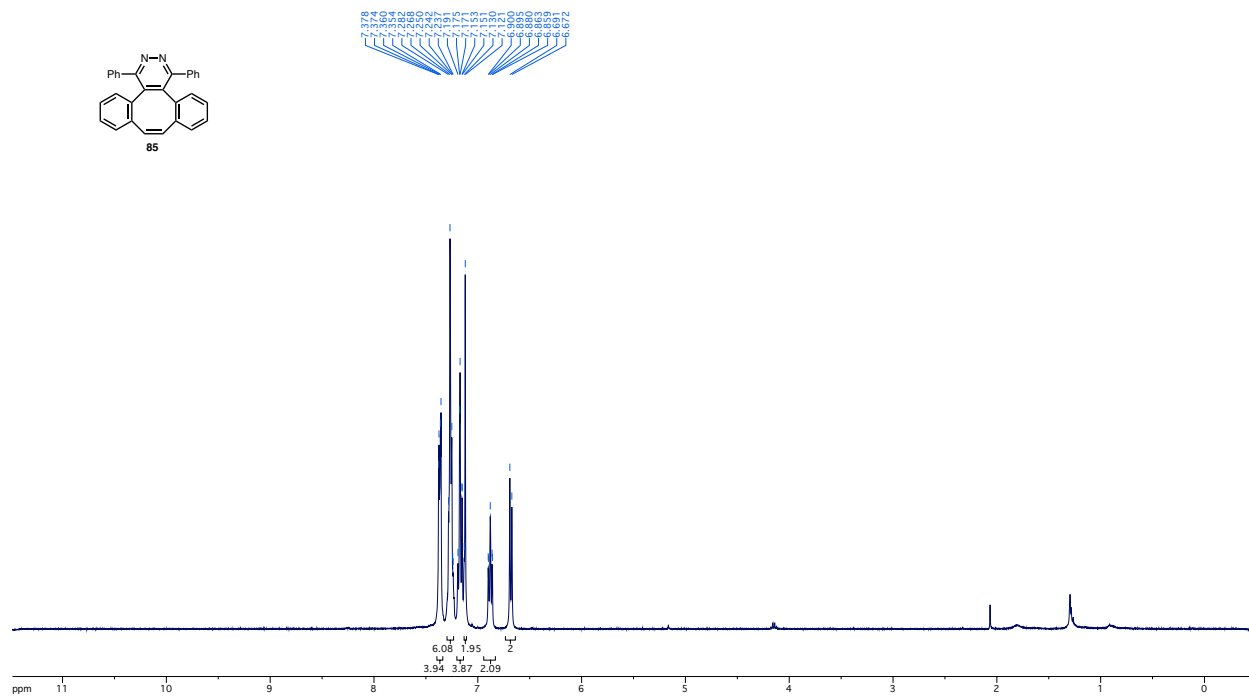
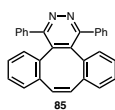


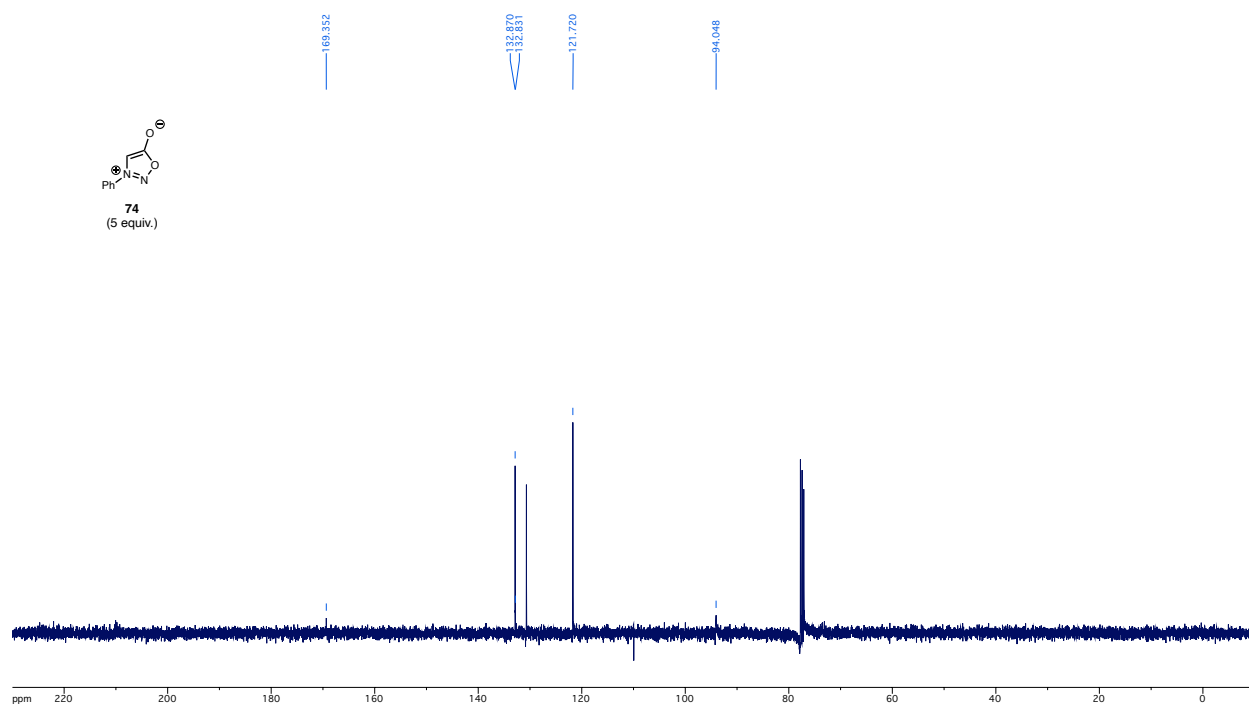
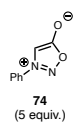
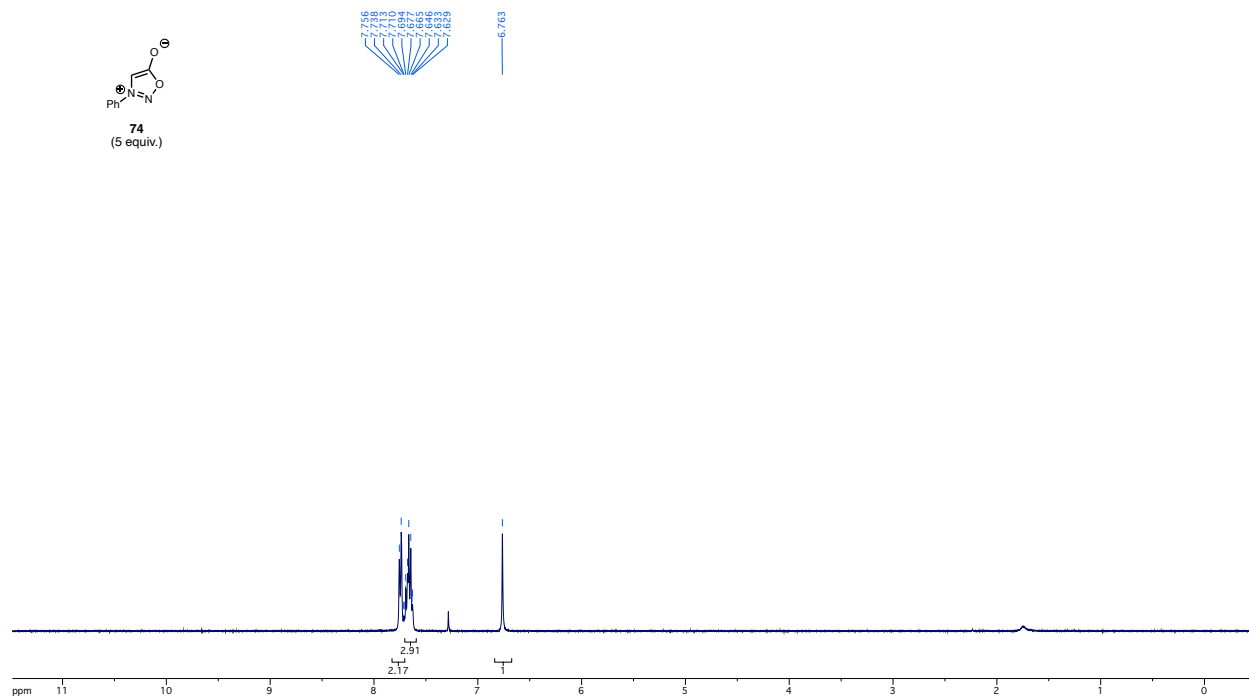
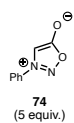


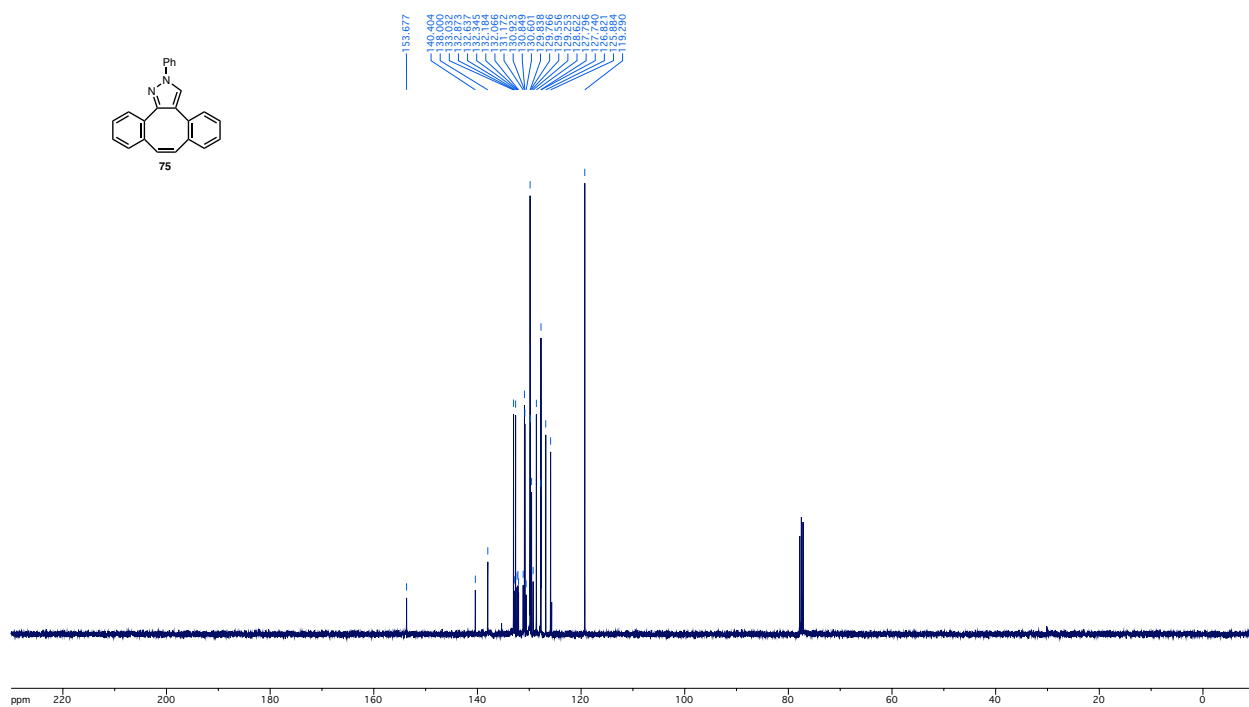
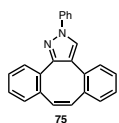
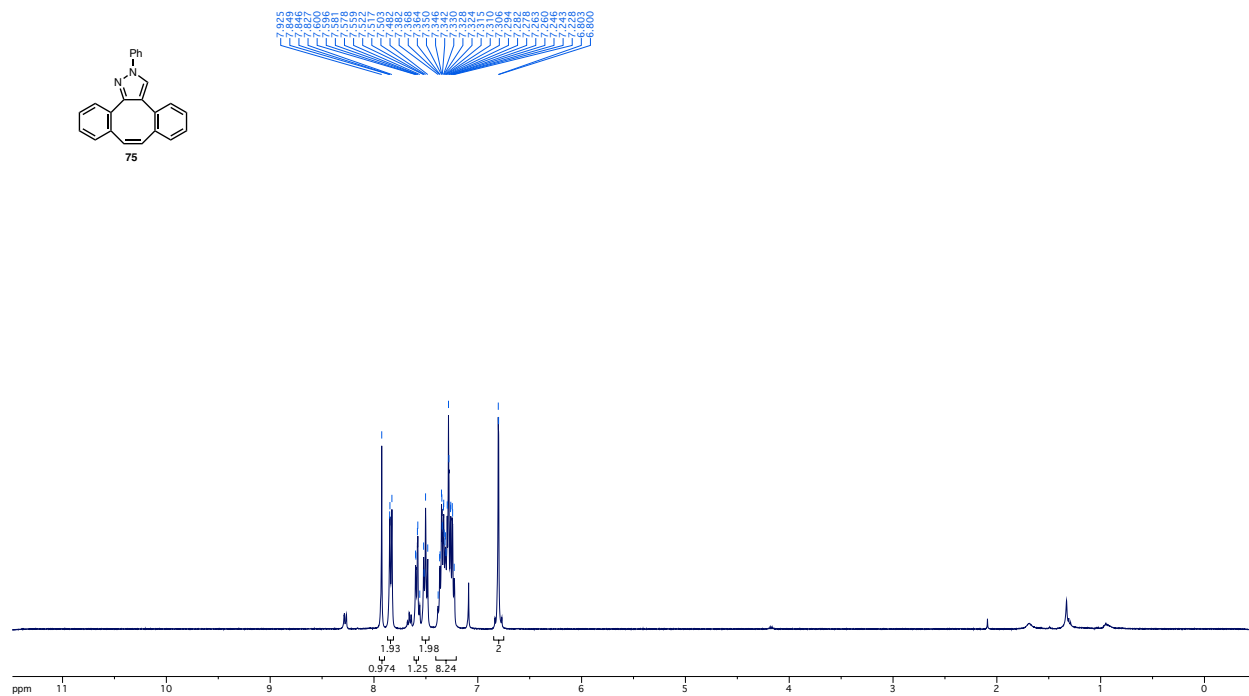
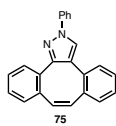


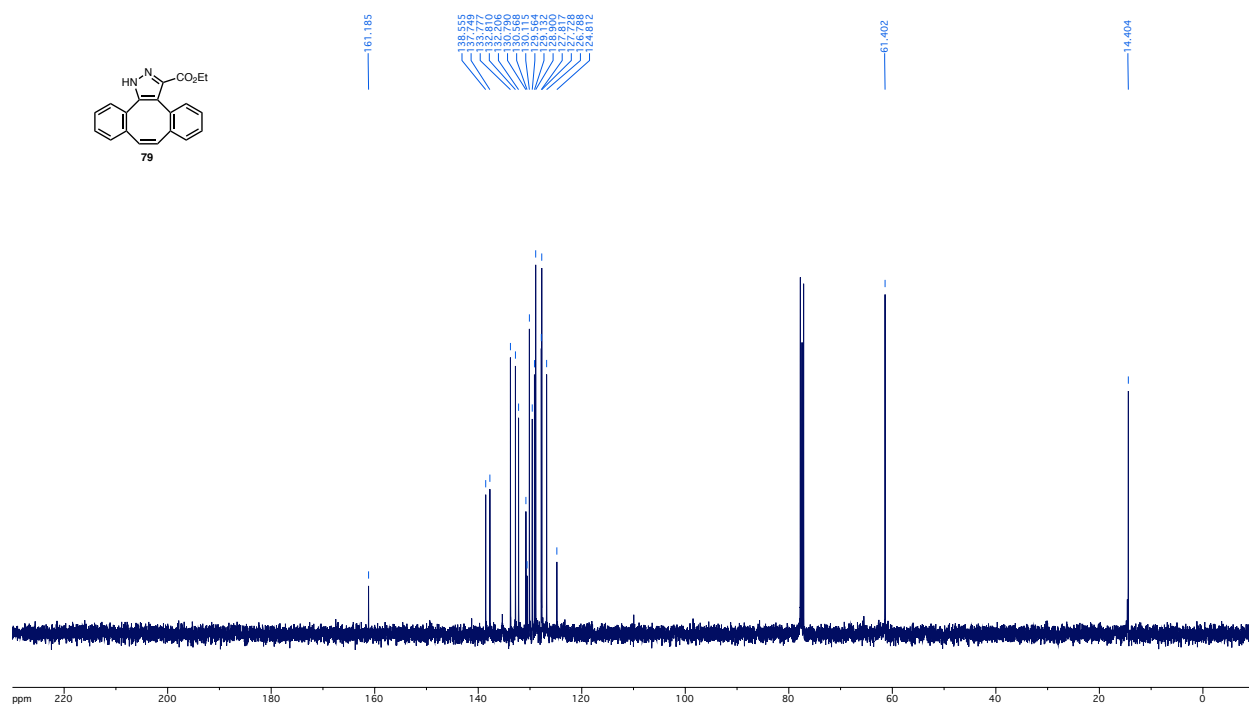
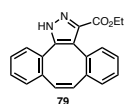
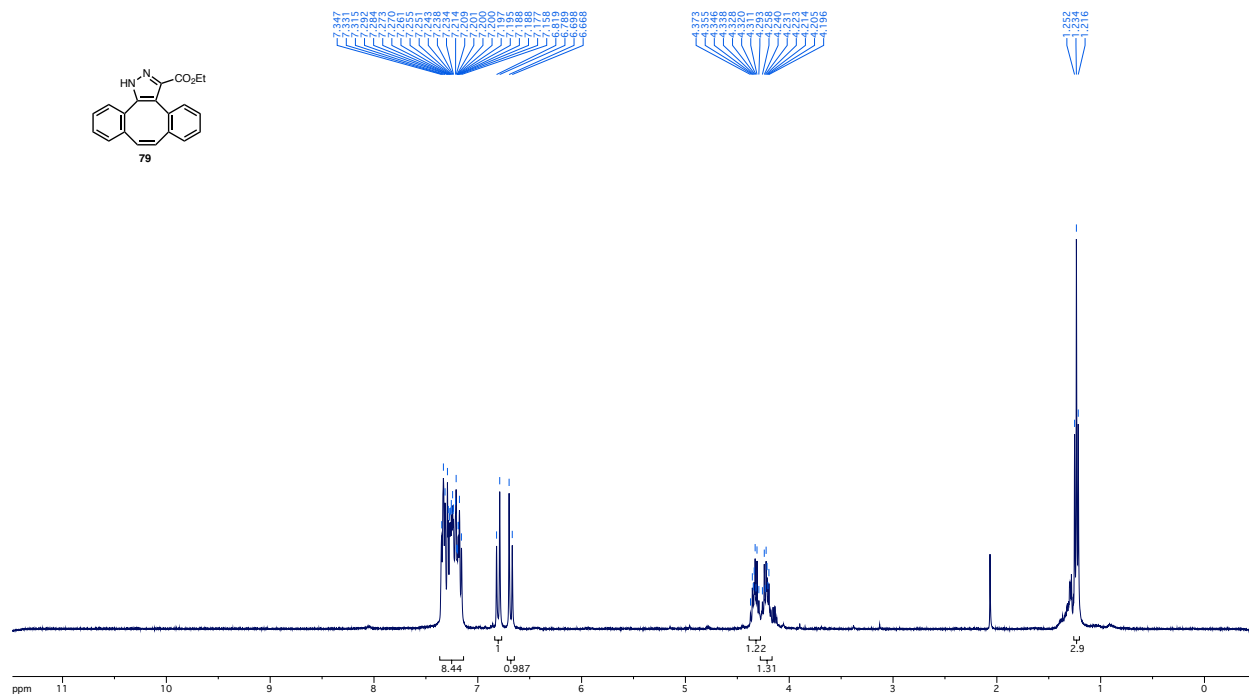
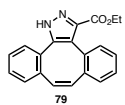












Chapter 4. ADIBO and its Analogs

1. Applications of ADIBO

Since the discovery of cyclooctyne's "explosive" reaction with phenyl azide,¹ this group of strained molecules have moved to the forefront of the click chemistry revolution as they pose as the fine bridge between stability and reactivity for strain-promoted azide-alkyne cycloaddition reactions (SPAAC), while their application has been inclined toward bioconjugation² including as DNA tagging³ and protein linking,⁴ their importance extends beyond biological applications to the fields of material and surface science.⁵

As discussed in the Chapter 2, strained cyclooctyne reagents can be activated via 2 possible pathways, electronic and angle strain (Figure 1). Electronic activation has been less explored but due to the addition of electron-withdrawing groups such as fluorine adjacent to the cyclooctyne, a distortion of the dipoles due to charge-transfer interaction is caused. This lowers the LUMO, while raising the HOMO of the cyclooctyne, lowering the activation barrier of cycloaddition by about 2 kcal/mol.⁶ Insertion of heteroatoms into the ring allows for hyperconjugative assistance of the cycloadduct transition state.⁷

The model reagent of angle strain cyclooctynes is derived from dibenzoannulated cyclooctyne (DIBO).⁸ Addition of sp^2 centers on the cyclooctyne ring increases angle strain by narrowing the acetylene bond angle to about 153° , and thus increasing its reactivity. By increasing the ground state energy of the cyclooctyne, its reactivity is also dramatically increased, but the overall stability of the alkyne can become compromised and prone to rapid decomposition such as in the case of BARAC.^{9 10}

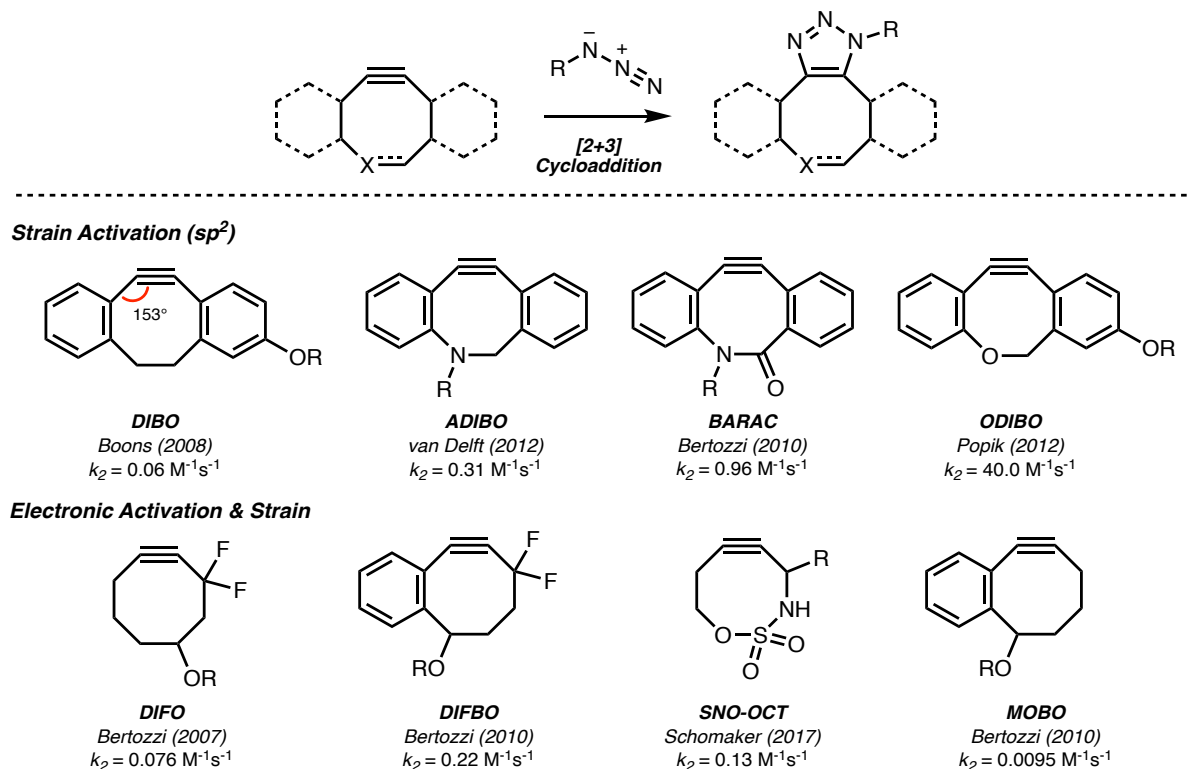


Figure 1. Examples of cyclooctyne reagents used for SPAAC-mediated bioconjugation

The addition of phenyl rings to promote angle strain of the alkyne poses a particular drawback under physiological conditions. The increased lipophilicity can lead to solubility issues in aqueous media. To circumvent this, van Delft developed the cyclooctyne reagent dubbed ADIBO (**1**), or DIBAC, which exhibits high cycloaddition reactivity ($0.31 \text{ M}^{-1}\text{s}^{-1}$),¹¹ but also provides benchtop stability, which was major drawback of its predecessor, BARAC. The addition of a nitrogen in the cyclooctyne ring is also appealing due to its mediation of increased solubility and more importantly, the provision of a ligation site that can be used for tethering (Figure 2).

ADIBO has found many applications in a range of fields. Notable applications biochemical application are such as biomolecule functionalization^{12 13} and delivery.¹⁴ Bioconjugation is also of outmost recent importance in the tagging of biomolecules¹⁵ such as glycoconjugates,⁸ lipids,¹⁶ micelles,¹⁷ and proteins.¹⁸ ADIBO has also been utilized in material sciences,¹⁹ finding use in surfaces,²⁰ nanobody tethering,²¹ and polymers.²²

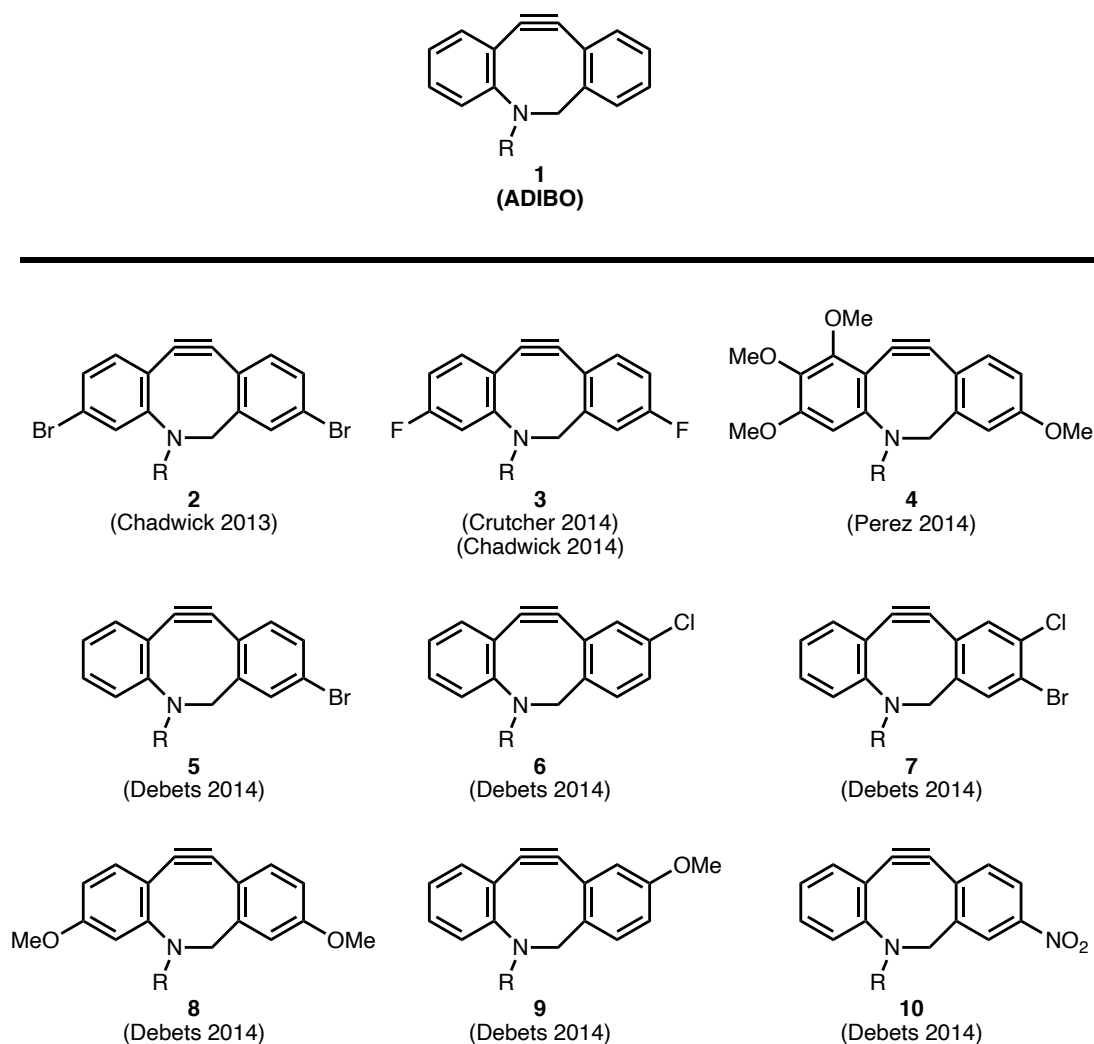


Figure 2. ADIBO and its various analogs.

2. Synthesis of ADIBO

Despite the growing popularity and importance of ADIBO as a cyclooctyne reagent of choice, the synthesis of ADIBO and its various analogs is somewhat limited. To date, only three synthetic pathways for the preparation of DIBAC have been reported. The two primary syntheses of ADIBO, van Delft's and Popik's, converge towards the same cyclooctyne precursor, which the target alkyne is formed from elimination.²³ A later synthesis, by Adranov, improved the overall synthesis of ADIBO without altering the synthetic pathway first reported by Popik.

2.1 van Delft Synthesis (2010)¹²

ADIBO was developed as a hybrid model between the dibenzocyclooctyne derivative (DIBC) and aza-dimethoxycyclooctyne (DIMAC) reported by Boons⁸ and Bertozzi,²⁴ respectively (Figure 3). DIBAC was initially sought to combine favorable kinetics and increased hydrophilicity to be utilized for the use in the PEGylation of proteins.¹²

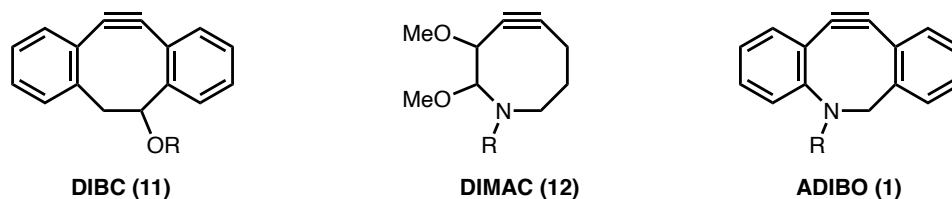


Figure 3. Structures of DIBC, DIMAC, and ADIBO.

Preparation of the key intermediate in the synthesis of ADIBO (Figure 4) begins with the Sonigashira cross-coupling of aryl iodide **13** and alkyne **14**. Under standard, inert conditions, the product of the Glaser coupling was formed. Performing the reaction under an atmosphere of N₂ and H₂, negated the unwanted Glaser coupling to provided **15** in quantitative yield.²⁵ Subsequent *N*-Boc protection gave **16**, which underwent hydrogenation in the presence of Lindlar catalyst to give *Z*-alkene **17**. Oxidation of the primary alcohol with Dess-Martin periodinane led to aldehyde **18**. Boc-deprotection under acidic conditions led to the spontaneous formation of the corresponding cyclic imine, which was immediately reduced with NaBH₄, generating secondary amine **19** in high yield. The synthesis of intermediate **19** was accomplished in 6 steps with an overall yield of 70%.

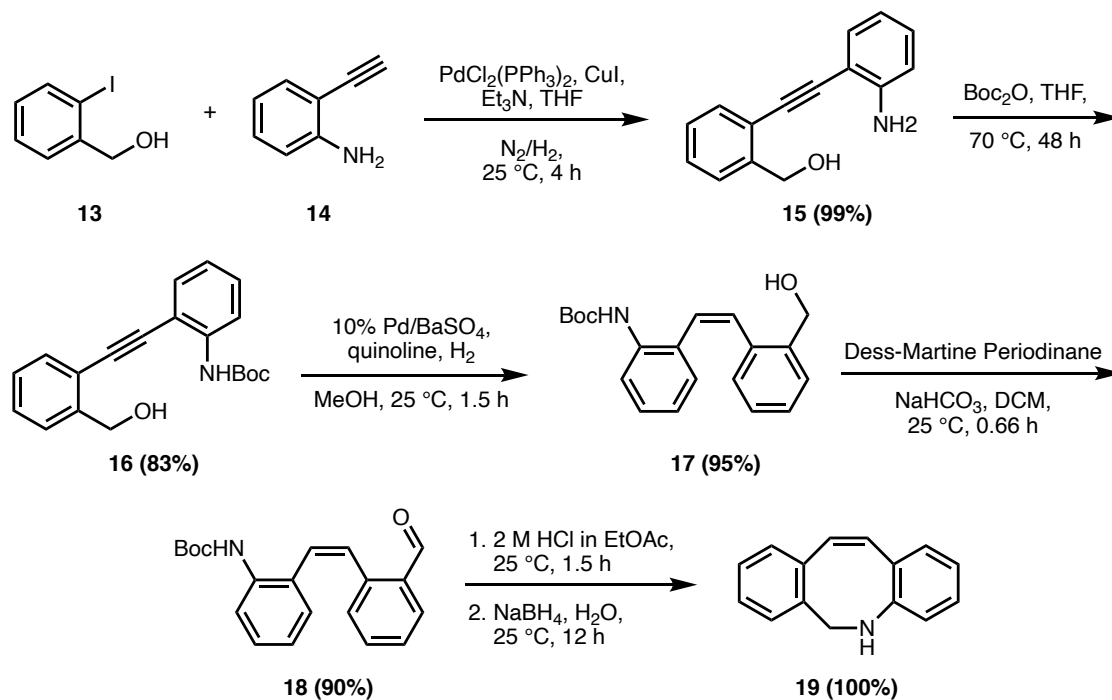


Figure 4. Synthesis of intermediate **19** (van Delft).

From compound **19**, the synthesis of ADIBO (Figure 5) is largely analogous to Boons' cyclooctyne synthesis.⁸ Direct bromination of alkene **20** resulted in intramolecular substitution of a bromide group providing an unwanted indoline, thus warranting protection of the free amine. Cbz-protection, addition of bromine, and elimination lead to in Cbz-protected ADIBO **22** in good yield. Elimination was achieved through the use of *t*-BuOK, while other bases including LDA, *n*-BuLi, and NaOH (6 or 12 M), were unsuccessful. Following the formation of ADIBO, van Delft turned his attention towards the functionalization of the *N*-linker.

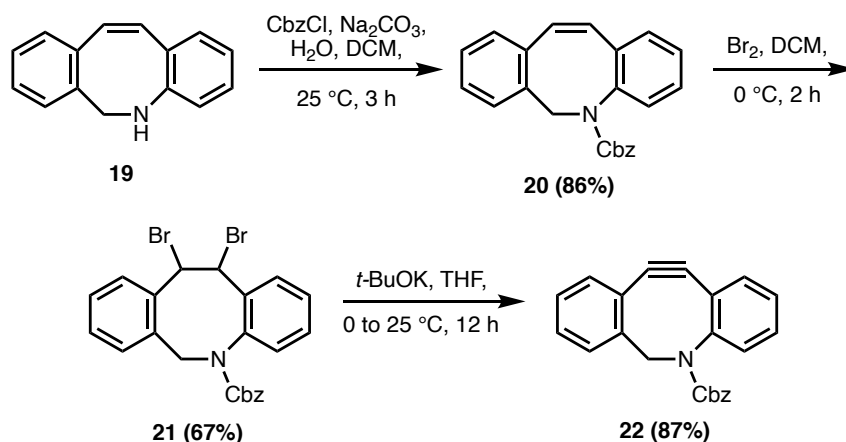


Figure 5. ADIBO synthesis (van Delft)

The preparation of unprotected ADIBO (**1**), *N*-functionalization was not as straightforward as anticipated. Cbz-deprotection of **22** under acidic or basic conditions failed to yield **1**, but rather generated 6*H*-isoindolo[2,1-*a*]indole (**23**) formed via 5-*endo-dig* alkyne hydroamination promoted by ring strain (Figure 6).

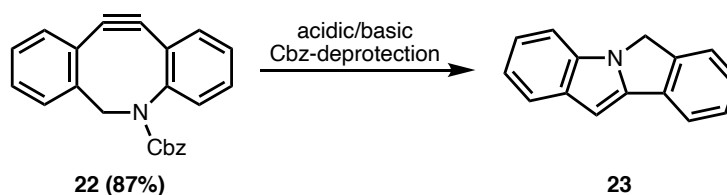


Figure 6. Deprotection of Cbz-protected ADIBO (van Delft)

Due to the unexpected reactivity of alkyne **22** displayed during deprotection, it was necessary to carry out *N*-functionalization prior to formation of the alkyne. To circumvent this limitation, functionalized linker **24** was used. This carboxylic acid linker was coupled to amine **19**, to provide **25** in excellent yields. This was followed by bromination of the alkene to provide 1,2-dibromide **26** in good efficiency. Elimination resulted in the alkyne in good yield, with subsequent hydrolysis or provide a functionalizable cyclooctyne **28** in an overall 41% yield over 10 steps (Figure 7).

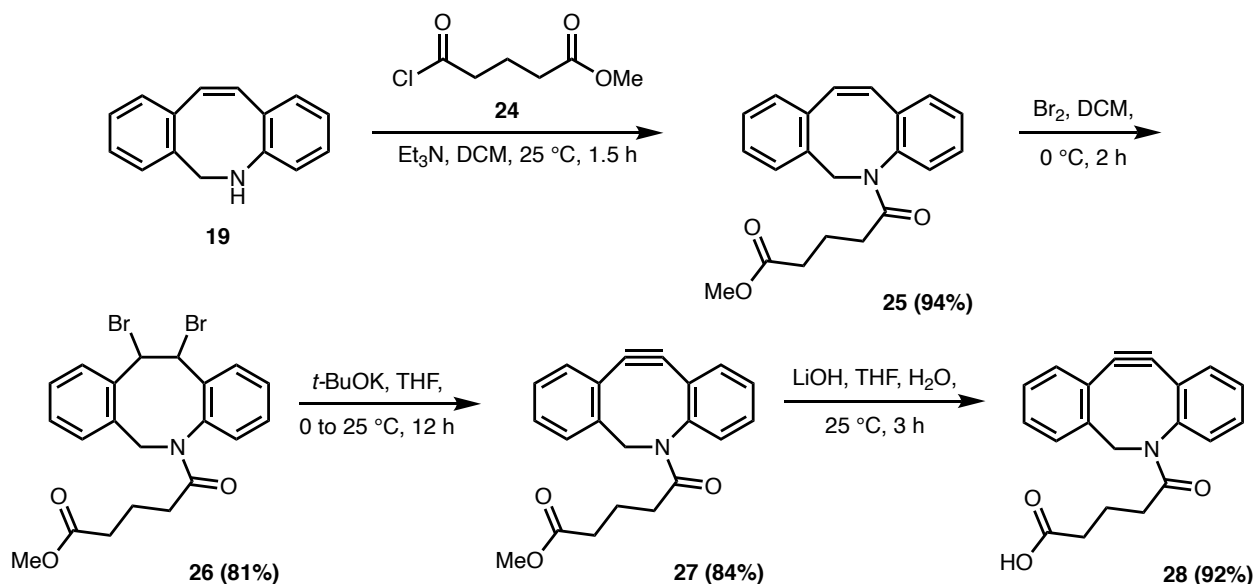


Figure 7. Synthesis of ADIBO (van Delft)

In summary, the first synthesis of ADIBO was completed in 9 steps from **13** with an overall yield of 41%. The major advantage of van Delft's route is the high yields that were obtained during the beginning of the synthesis, especially preparation of cyclooctyne precursor, where **19** was synthesized in 5 steps in 70% yield. Moreover, each additional step displayed high yields, but over numerous reactions.

2.2 Popik Synthesis (2010)

Popik's synthesis of ADIBO and derivatives also utilizes the same elimination strategy employed by van Delft towards the installation of the alkyne in ADIBO but involves a shorter route towards **19** (Figure 8).²⁰ Synthesis of this key intermediate began with the condensation of dibenzosuberone (**29**) with hydroxyamine to form oxime **30** in moderate yield. The subsequent Beckman Rearrangement with polyphosphoric acid provided amide **31** with good efficiency. Reduction of the lactam with LiAlH_4 provided amine **19**, in moderate yield.

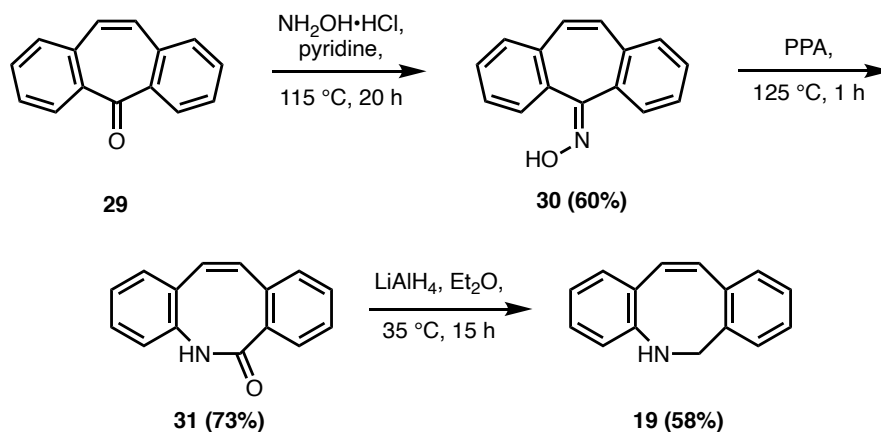


Figure 8. Synthesis of intermediate **19** (Popik)

Avoiding the pitfall faced by van Delft, Popik choose to install the *N*-linker prior to alkyne formation (Figure 9). Acylation of **19** using **32** allowed for formation of amide **33** in high yield. Addition of bromine and β -elimination allowed for generation of ADIBO **35** efficiently. Finally, methanolysis of the *N*-trifluoroacetamide under alkaline conditions provided **36**.

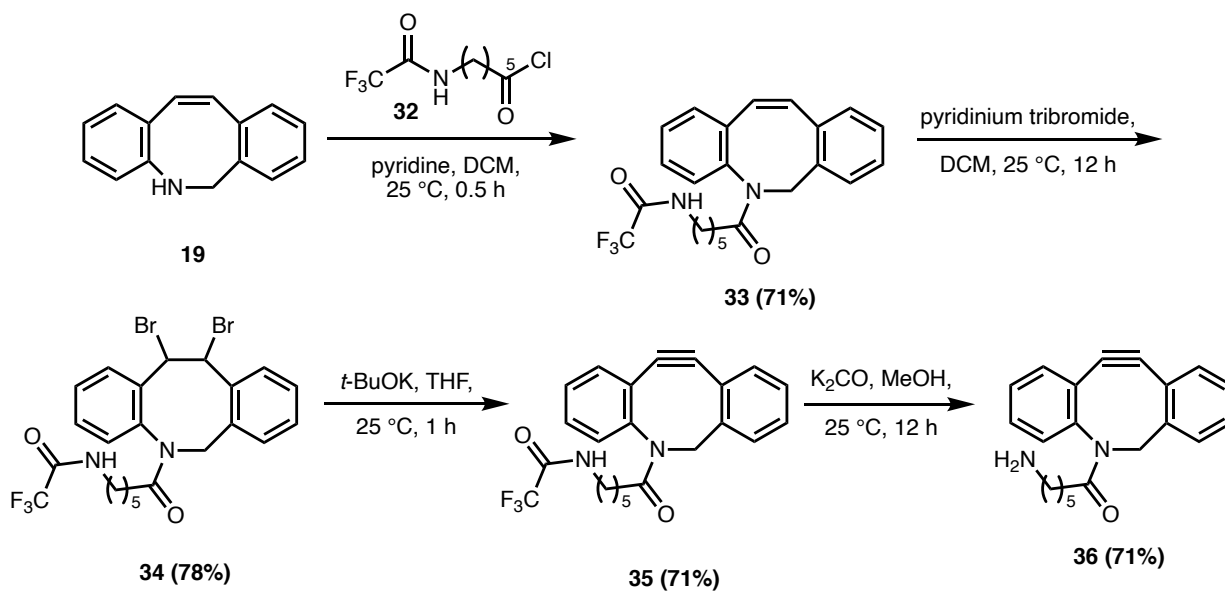


Figure 9. Synthesis of ADIBO (Popik).

Popik's synthesis of ADIBO derivative was accomplished in 7 steps with an overall 7% yield from dibenzosuberone (**29**). The preparation of intermediate **19** was accomplished in fewer steps

proved to be inefficient (40%, 3 steps), compared to van Delfts (70%, 5 steps), but was accomplished fewer steps.

2.3 Adranov's Synthesis (2014)

Adranov's synthesis of ADIBO was reported in 2014 and represents a significant improvement of Popik's method, as it displays the fewer steps, but more importantly, can be scaled up (Figure 10).⁹ Adranov's synthesis began with dibenzosuberone (**29**), which underwent condensation with hydroxylamine to form oxime **30**.²⁶ Popik's method used polyphosphoric acid to mediate Beckman Rearrangement, with Kim reporting increased results under identical conditions.²⁷ Feringa has also performed Beckmann rearrangements, but used trichlorotriazine, which resulted in a lower yield.²⁸ Adranov suggested that the inconsistent yields arose as a result of poor solubility. Use of Eaton's reagent²⁹ provided substrate conversion of **30** to **31** in near quantitative yield, without the need for purification. This reaction was carried out on scales of up to 50 grams with no change in efficiency. Reduction of amide **31** with LiAlH_4 provided **19** in high yield. In comparison to previous methods, Adranov's improved synthesis allowed for direct access to **19** the key intermediate for alkyne installation, in 87% yield over 3 steps on a multigram scale, the shortest and most efficient of the three, between van Delft, Popik, and Adranov.

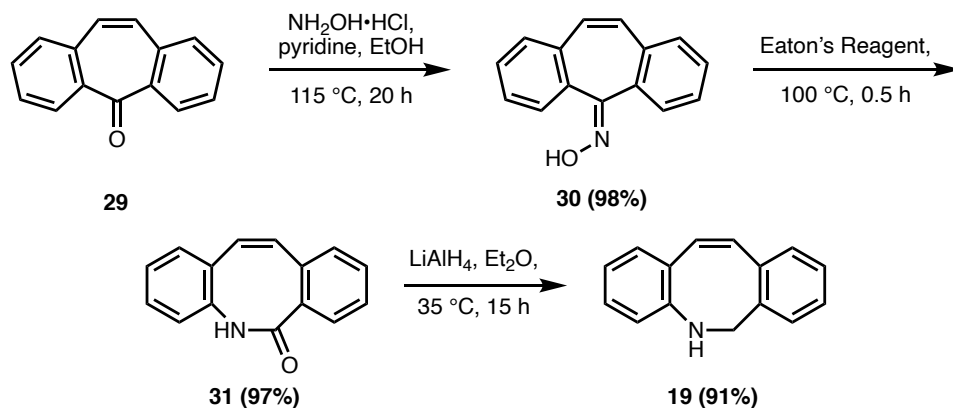


Figure 10. Synthesis of intermediate **19** (Adranov).

Acylation of amine **19** installed the necessary *N*-linker for further functionalization following saponification to reveal **39** (Figure 11). Bromination and elimination were straightforward and high yielding, providing ADIBO **41** in very high yields. In contrast to previous syntheses, unmasking of the *N*-linker sidechain was accomplished after alkyne formation, but this synthesis reveals it after acylation. Adranov noted that elimination with potassium *tert*-butoxide can be problematic with an ester protecting group as noted by van Delft;¹² however, should the protecting group be removed, the overall efficiency of the alkyne formation is high.

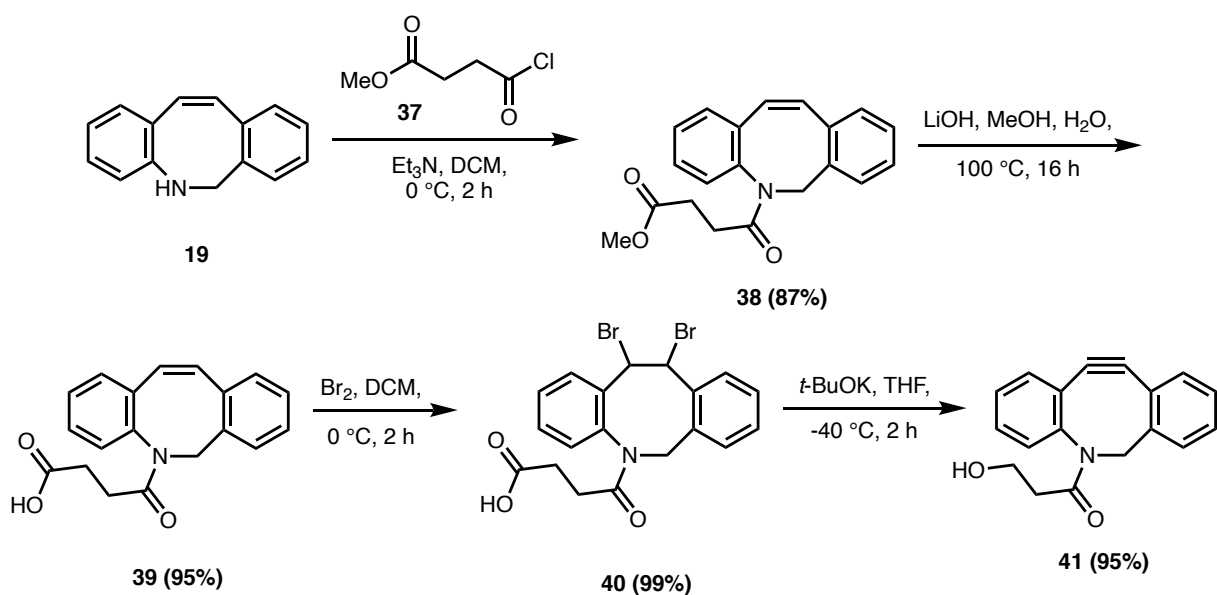


Figure 11. Synthesis of ADIBO (Adranov).

With this improved synthetic pathway of Popik's, Adranov increased the overall yield of ADIBO to 67% over 7 steps. This synthetic route benefits from the elimination of purification during the preparation of amine **19** and its amenability to scale up this reaction to multi-gram levels.

3. Hypothesis

Having established methodologies for the preparation of 5-(1-hydroxyalkyl)tetrazoles and ring expansion to form cyclooctynes, we were positioned to investigate the synthesis of ADIBO (**1**) and derivatives (Figure 12). Given the scope of our methodology, we due to previous preparation steps such as the use of strong bases or transition metals. We also aimed to be able to functionalize ADIBO without the use of an *N*-linker to promote the formation of ‘free’ ADIBO.

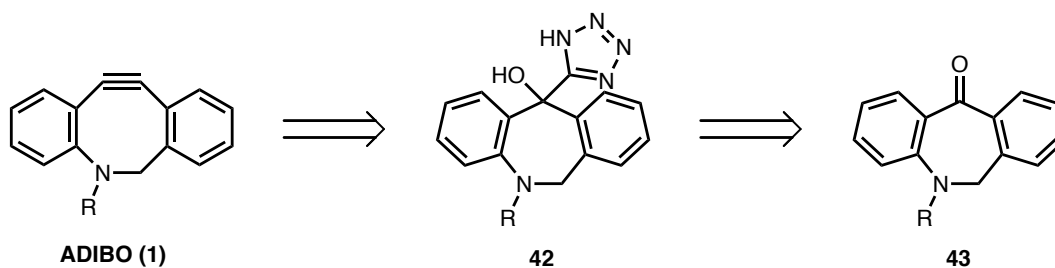


Figure 12. Retrosynthetic analysis of ADIBO.

Together with the synthesis of ADIBO, our initial goal was to develop analogs,³⁰ not necessarily for linkage, but for unique functionality, dependent on the applications at hand. We also wished to prepare to develop analogs of ADIBO, which would sterically bias one position of the alkyne, and thereby favor the formation of one regioisomer upon SPAAC. We envisioned this selectivity would be displayed with sterically hindered substituents such as phenyl and *tert*-butyl at the 4-position of ADIBO. We also envisioned substitution with a bromine at the same position as above. This would allow for a mass spec tag that can be used for mass spec based proteomics utilized which has been utilized in the past but can become a more attractive conjugation reagent, which has been utilized in numerous fields.³¹ The ADIBO analogs we envisioned are summarized in Figure 13.

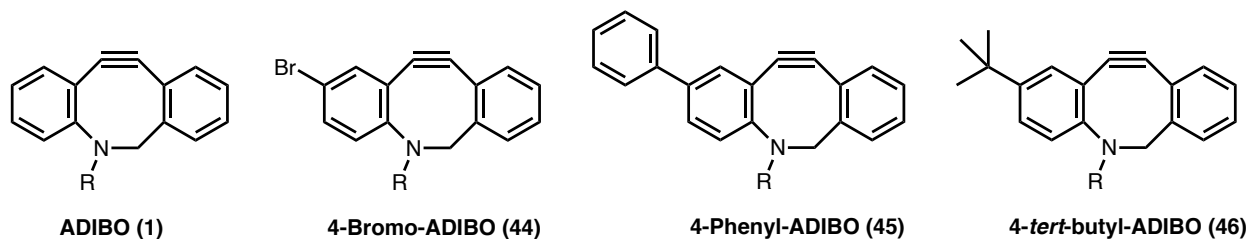


Figure 13. ADIBO and synthetic targets.

4. Results and Discussion

The synthesis of ADIBO and its analogs stem from a common intermediary ketone. Herein, I will describe our work towards this common intermediate and then discuss the preparation of each ADIBO analog in turn. A summary can be seen in Figure 14.

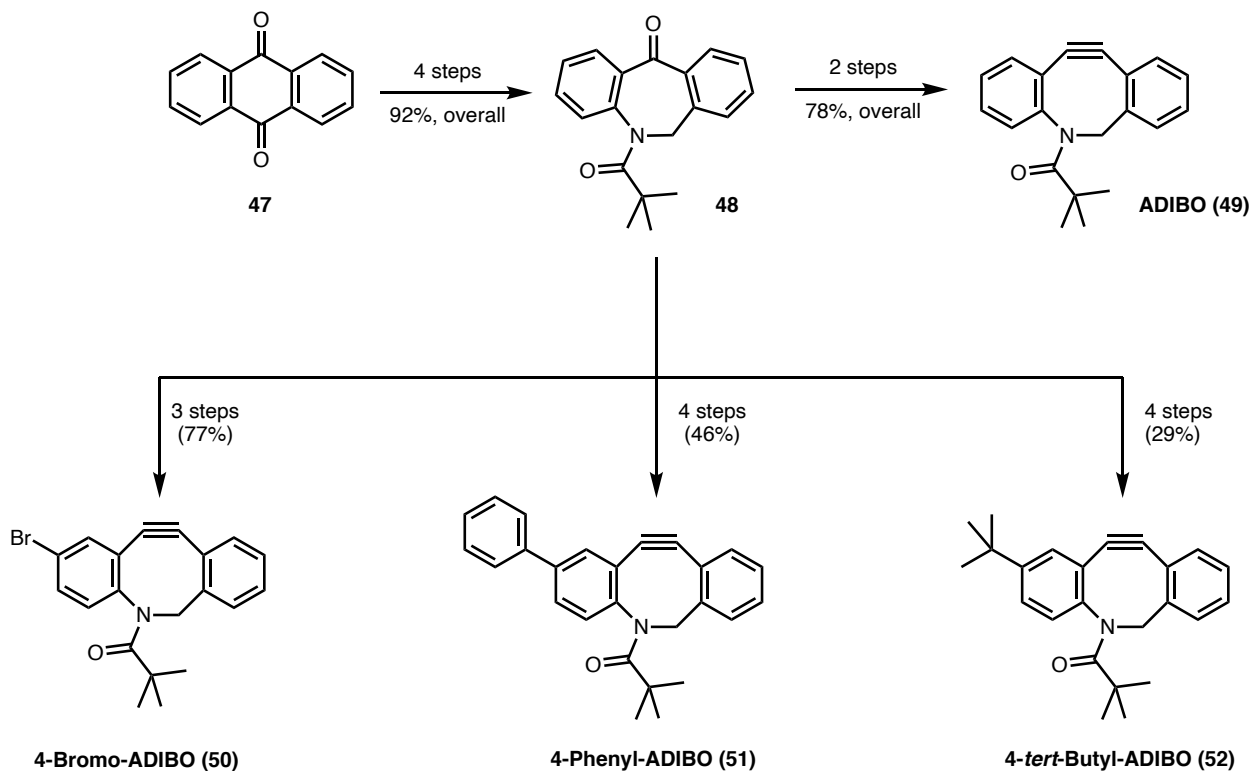


Figure 14. Synthetic scheme of ADIBO and analogs.

4.1 5-Pivaloyl-5,6-dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (48)

Compound **48** was prepared according to the method reported by Irurre (Figure 15).³² Schmidt rearrangement of anthraquinone (**47**) using sodium azide in sulfuric acid and chloroform provided **53** in near quantitative yield on scales of up to 20 grams. It should be noted that all safety precautions (safety screen, heavy gloves, fire shield) must be used during the preparation of lactam **53**. Lactam **53** was then treated with oxyphosphoryl chloride to generate chloroimine **54**. This intermediate was not stable under ambient conditions and was immediately hydrogenated under high pressure in the presence of triethylamine, to give amine **55** in high yields. This was then seamlessly *N*-acylated with pivaloyl chloride to provide addition substrate **48** in high yield.

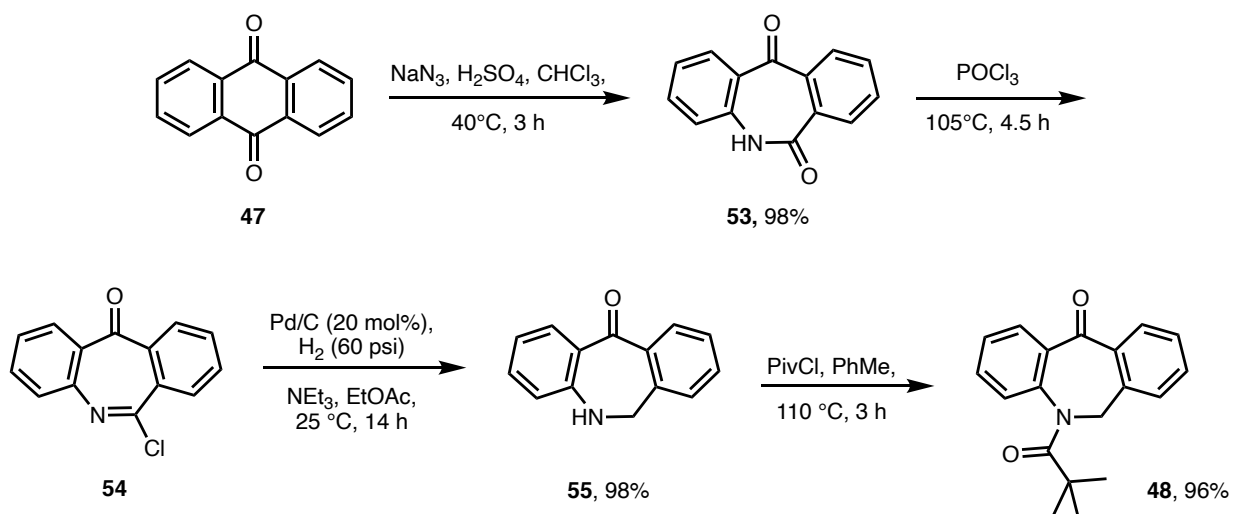


Figure 15. Preparation of addition substrate **48**.

Chlorination of **48** was not amenable to scale up beyond 1 gram; increasing the scale further resulted in drastically diminished yields. Other chlorinating reagents were assessed but proved widely unsuccessful. Use of phosphorus trichloride and pentachloride resulted in overchlorination, while thionyl chloride was also equally unsuccessful. It should be noted that work-up of this transformation can also be problematic. The chlorination of the lactam with oxyphosphoryl chloride should be generally worked up quickly with washing with cold bicarbonate to avoid

decomposition of the chloroimine. Additionally, purification by filtration through alumina plug is important as the phosphorous byproducts of this reaction inhibits the subsequent hydrogenation step. With the hydrogenation, elevated pressures are required as the reaction does not proceed under ambient pressures.

The synthesis of pivalamide **48** was accomplished in 92% yield over 4 steps. This is significantly more efficient than Adranov's synthesis of alkene precursor **29** and requires fewer steps. A caveat of our synthesis is the inability to scale up the chlorination of lactam **53**, which was possible in Adranov's route; however, the remaining steps could be scaled up, and the chlorination process carried batch-wise.

4.2 ADIBO

Utilizing our previously mentioned 5-(1-hydroxyalkyl)tetrazole methodology and employed it towards **1** (Figure 16). Treatment of pivalamide **48** with **56** with LiHMDS, formed **57** in good yield.

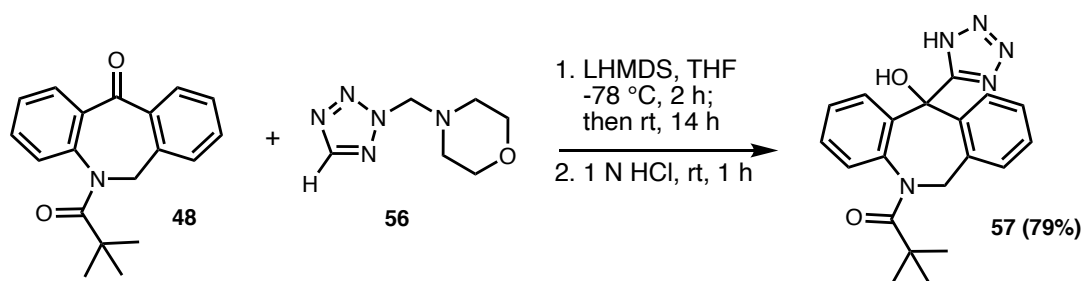


Figure 16. Tetrazole addition of **48**

To our delight, ring expansion of **57** proceeded in near quantitative yield, providing **49** (Figure 17). To our surprise, we also were able to remove the *N*-pivaloyl group under strongly acidic conditions to provide unprotected ADIBO **1** in very high yield. That this deprotection step is possible, appears to be possible because of unfavorable hard-soft theory between hydronium ions

and the soft alkyne. This is an important observation because it allows *N*-linkage *after* alkyne formation, which was a limitation in prior syntheses.

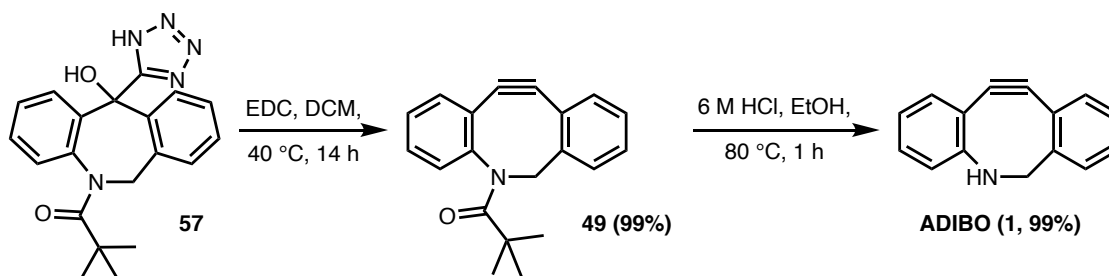


Figure 17. Preparation of ADIBO.

In summary, ADIBO (**1**) was synthesized with an overall yield of 71%, over 7 steps from commercially available anthraquinone. Most steps were amenable to scale up and telescoping and required little more purification than filtration through an alumina plug. In comparison with previous syntheses, our route provides higher efficiency in the same amount of steps, but without recourse to harsh reductive reagents such as LiAlH_4 .

When benzyl azide was added to the rearrangement of **57** in a parallel study, ADIBO was trapped in situ in near quantitative yield (99%) to provide a *separable* mixture of regioisomers **58a** and **58b** (Figure 18). Interestingly, separation of ADIBO-derived triazoles has not been previously reported. Additionally, previous regioisomers were formed in a near racemic ratio, but the triazoles of ADIBO provided a 1.6:1 ratio, where the benzyl azide would cycloadduct away from the pivalamide as the structure of these dibenzocyclooctynes appear to be boat-like, affecting selectivity.³³

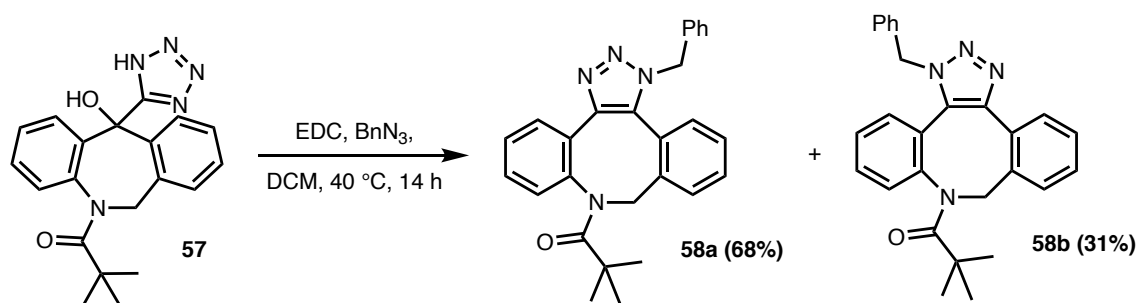


Figure 18. In-situ trapping of ADIBO with benzyl azide.

Having successfully synthesized ADIBO, we turned our attention to the preparation of its analogs. We focused on increasing the overall functionality of the ADIBO system and then later increasing the selectivity of regioisomers by addition of sterically bulky substituents on the aromatic rings of the ADIBO core.

4.3 4-Bromo-ADIBO

To show the ease and application of our methodologies, we set to increase the functionality of ADIBO. We sought to achieve this by incorporating a bromine tag on one of the aromatic rings. This would allow this analog, now dubbed 4-Bromo-ADIBO (**50**), to be an attractive reagent for MS-based proteomics as it can be easily identified due to bromine's 1:1 isotopic ratio. Synthesis of 4-Bromo-ADIBO began with pivalamide **48**, where bromination in acetic acid gave **59** as a single isomer in quantitative yield. Addition of the lithium tetrazole generated from **56** to ketone **59** provided **60**, the precursor of 4-bromo-ADIBO in high yield (Figure 19).

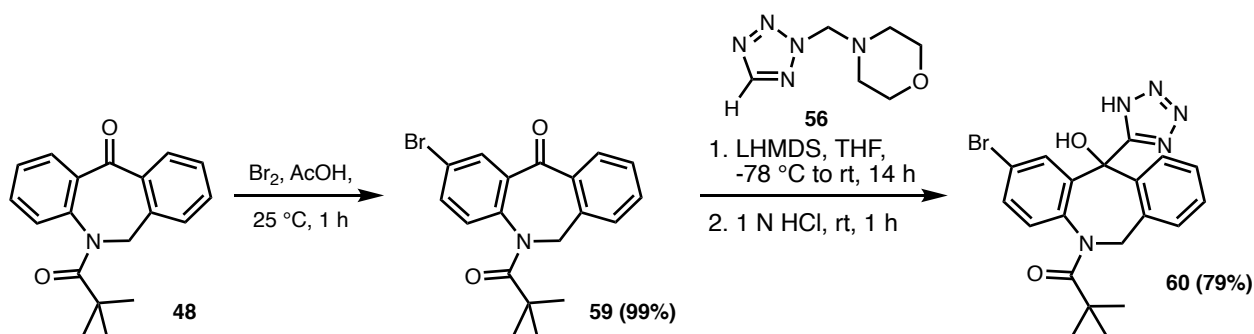


Figure 19. Synthesis of 4-Bromo-ADIBO precursor.

Using established protocol, the rearrangement of **60** provided 4-Bromo-ADIBO (**50**) in high yield (Figure 20). The overall efficiency of alkyne installation is more attractive than previous syntheses, which utilizes elimination of dibromides and can lead to unwanted side reactions and diminished yields.

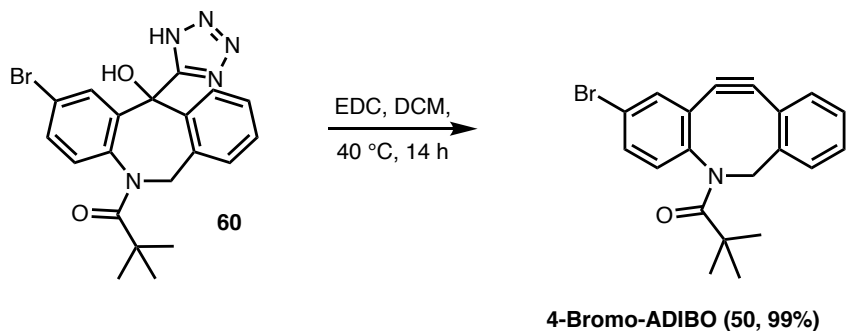


Figure 20. Synthesis of 4-Bromo-ADIBO (**50**).

In-situ trapping of 4-Bromo-ADIBO (**50**) with benzyl azide provided an *inseparable* mixture of regioisomers **61a** and **61b** in a near quantitative overall yield with a regioisomeric ratio of 1.6:1 (Figure 21). In this case, the major regioisomer was **61a**, which is the less sterically encumbered, inferred from the distribution of ADIBO triazoles.

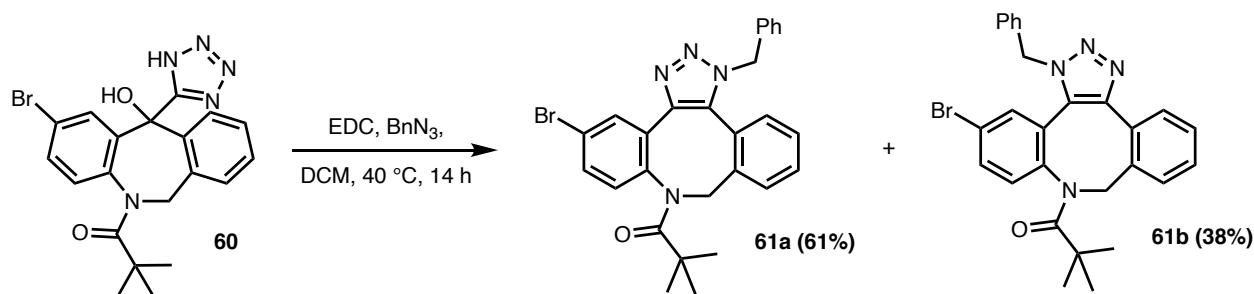


Figure 21. In-situ trapping of 4-Bromo-ADIBO with benzyl azide.

The isomer ratio observed during this reaction made us curious as to whether we could design ADIBO analogs that would selectively favor one regioisomer over the other. This would allow attraction to studies such as protein folding or other fields where specific selectivity is required. In this context, we opted to examine analogs with a high degree of steric bias.

4.4 4-Phenyl-ADIBO

4-Phenyl-ADIBO (**51**) was prepared from the bromination of pivalamide **48** to provide **59** in quantitative yield. Sonigashira coupling of **59** with phenylboronic acid gave biphenyl ketone **62** in high yield. Tetrazole addition to **62** provided the precursor **63** for 4-phenyl-ADIBO in excellent yield (Figure 22).

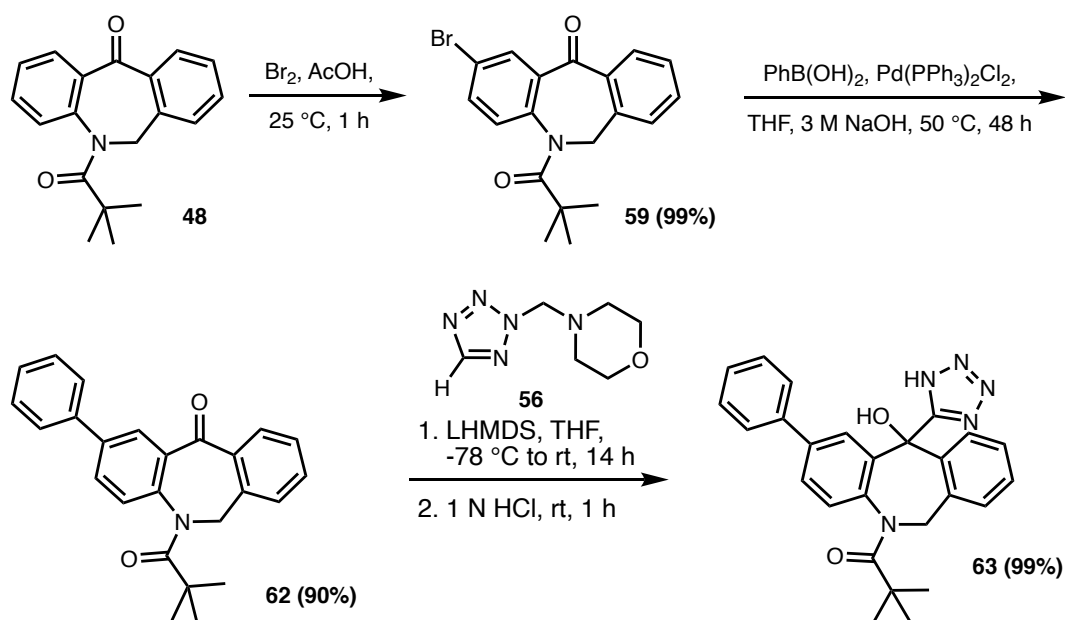


Figure 22. Synthesis of 4-Phenyl-ADIBO precursor

The dehydrative fragmentation of **63** led to formation of 4-phenyl-ADIBO (**51**) in moderate yield (Figure 23). The lowered efficiency of this transformation could be attributed to the increased steric hindrance around the reaction center due to the phenyl ring.

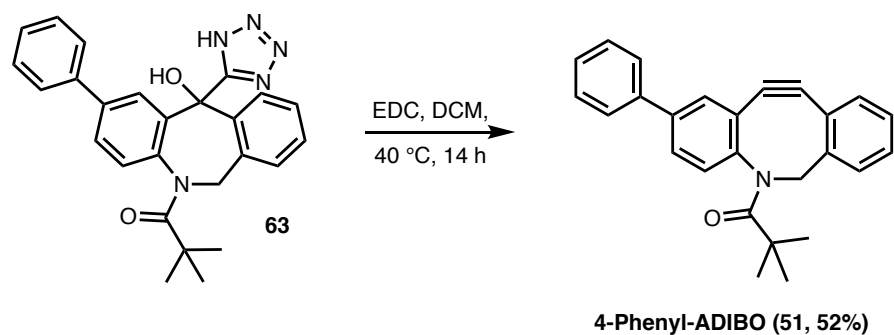


Figure 23. Preparation of 4-Phenyl-ADIBO

In-situ trapping of 4-phenyl-ADIBO (**52**) with benzyl azide generated a 3:1 *inseparable* mixture of regioisomers **64a** and **64b** with the favored regioisomer being **64a** in good yield (Figure 24). The selectivity of cycloaddition is a direct reflection of the steric bias of the phenyl system on the ADIBO ring. Additionally, the fact that trapping the cyclooctyne resulted in a slightly better yield could potentially allude to the overall stability of 4-phenyl-ADIBO.

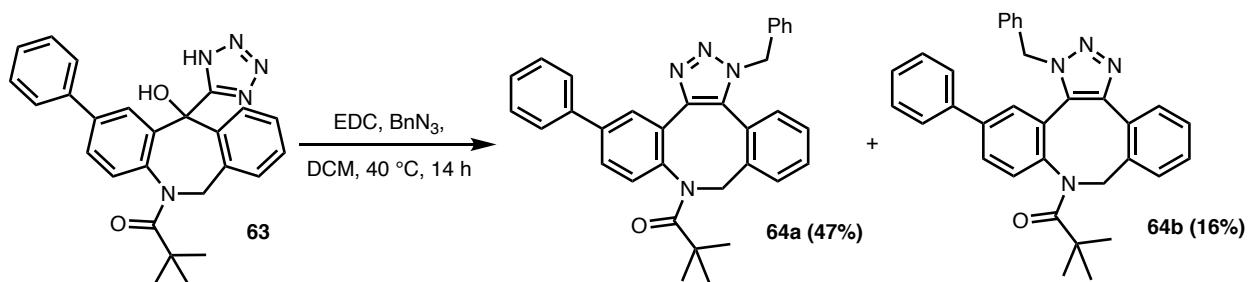


Figure 24. In-Situ trapping of 4-Phenyl-ADIBO with benzyl azide.

4.5 4-*tert*-Butyl-ADIBO

In the phenyl analog of ADIBO, the regioselectivity between triazoles was 1:3, but we opted to see if it was possible to increase selectivity. Therefore, we aimed to synthesize a *tert*-butyl ADIBO analog in the hope that it would provide more steric hindrance on one side of the cyclooctyne system. Starting from common ADIBO precursor **48**, we attempted a Friedel-Crafts alkylation, but was unsuccessful (Figure 25); however, it was noted that the starting material, particularly the pivalamide was consumed in the reaction.

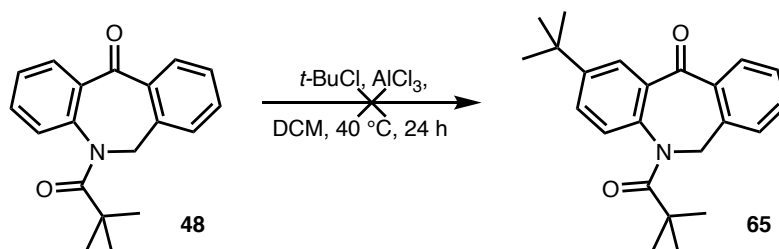


Figure 25. Attempted Friedel-Crafts Alkylation of **48**.

Having seen that the pivalamide is unstable to Friedel-Crafts alkylation, we decided to attempt the alkylation to amine **55**, the precursor of **48** (Figure 26). With this, we were able to successfully undergo a Friedel-Crafts alkylation in good yield. Subsequent acylation with pivalyl chloride allowed for the preparation of pivalamide **67** in high yield. Subsequent tetrazole addition

proceeded in overall good yield to provide **68**; comparable to past tetrazole additions, this was not the highest, potentially due to the added steric hindrance of the *tert*-butyl group.

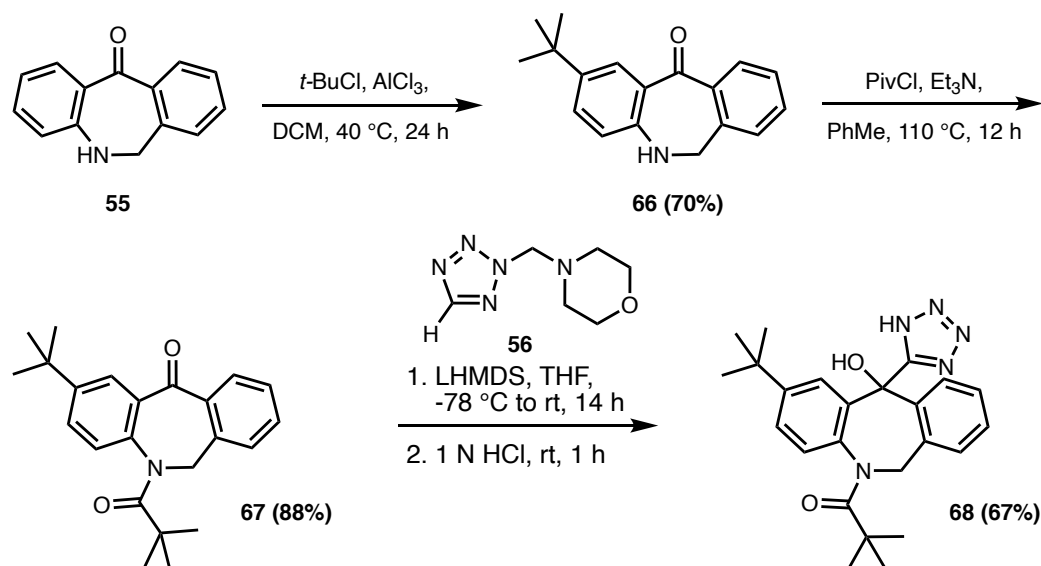


Figure 26. Synthesis of 4-*tert*-butyl-ADIBO precursor.

Having successfully synthesized the precursor **68**, the rearrangement towards 4-*tert*-butyl-ADIBO (**52**) proceeded in overall good yield (Figure 27). Compared to the phenyl ADIBO analog, the formation of this cyclooctyne was more efficient, hinting that 4-phenyl-ADIBO (**51**) may be slightly unstable as a result of the biphenyl system.

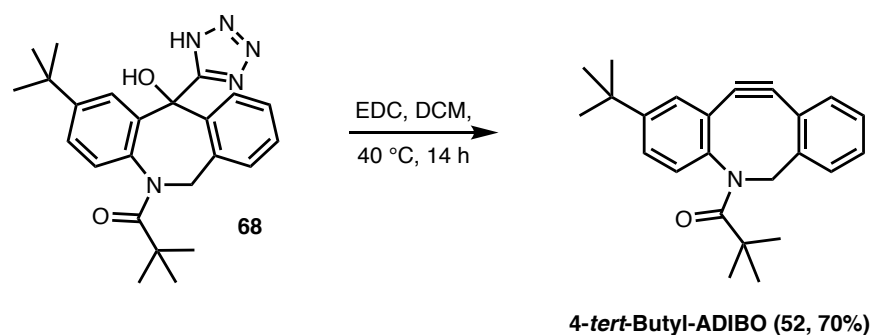


Figure 27. Preparation of 4-*tert*-butyl-ADIBO (**52**).

In-situ trapping of 4-*tert*-butyl-ADIBO (**52**) with benzyl azide gave an *inseparable* mixture of regioisomers **69a** and **69b** in an overall good yield (73%) with a regioisomeric ratio of 4:1 (Figure

28). The favored regioisomer, as per previous examples, was the less sterically encumbered triazole **69a**.

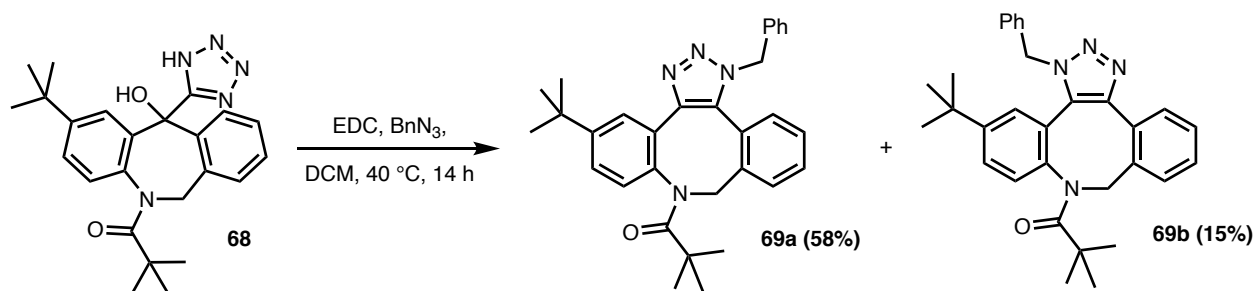


Figure 28. In-situ trapping of 4-*tert*-butyl-ADIBO.

5. Conclusion

We successfully employed both our tetrazole and rearrangement methodologies towards the synthesis of ADIBO, the cyclooctyne reagent of choice. The most recent synthesis of **1** by Adranov, provides ADIBO in 67% overall yield over 7 steps. This route utilizes harsh reductive reagents such as LiAlH₄ and is limited by the requirement that an *N*-linker be in place prior to alkyne formation. Additionally, while Adranov's synthesis of ADIBO is amenable to scale up, purification at each step is required. Our synthesis offers access to ADIBO in 71% overall yield over 7 steps. Our route avoids the use of harsh reagents, all but one step is amenable to scale up, and purification is generally minimal as byproducts are removed by filtration through an alumina plug. Additionally, the need for the *N*-linker to be installed prior to alkyne formation is avoided in our synthetic route, provided unique advantage than prior syntheses. Three novel analogs of ADIBO were also prepared. In particular, the addition of a bromine to the aromatic ring of this cyclooctyne provides an attractive functional utility. 4-Bromo-ADIBO (**50**) has potential as conjugation reagent for mass spectroscopy-based proteomics. 4-Phenyl (**51**) and 4-*tert*-butyl ADIBO (**52**) were also prepared. These compounds were developed to enable regioselective

SPAAC. Both the phenyl and *tert*-butyl analogs displayed reasonable regioselectivity of 1:3 and 1:4 in their respected reactions with benzyl azide.³⁰

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Appendix A, ADIBO and its Analogs

1. General Comments

1.1 General Methods

All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Visualization was accomplished by UV light (254 nm), potassium permanganate solution, or phosphomolybdic acid solution. Flash column chromatography was performed according to the method of Still¹ using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

1.2 Materials

Anhydrous tetrahydrofuran (THF) was passed through a solvent dispensing system under a dry argon atmosphere. All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

1.3 Instrumentation

All melting points were determined in unsealed Pyrex capillaries with a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide disks, or thin films on sodium chloride or zinc selenide plates using an ATI Mattson Genesis series FTIR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, ¹H, 100 MHz, ¹³C) or a Bruker Avance 500 (500 MHz, ¹H, 125 MHz, ¹³C) spectrometer. Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.26 ppm for ¹H; δ 78.0 ppm for ¹³C), methanol (δ 3.31 ppm for ¹H; δ 49.2 ppm for ¹³C), acetone (δ 2.05 ppm for ¹H; δ 29.9 ppm for ¹³C), and dimethyl sulfoxide (δ 2.50 ppm for ¹H; δ 39.5 ppm for ¹³C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), m (multiplet) and br (broad) app (apparent). The identification of ¹H and ¹³C signals was achieved using a combination of ¹H, ¹³C, DEPT, COSY, HMBC, HMQC and NOESY experiments. High-resolution electrospray ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass Q-ToF Ultima instrument at the University of Illinois Mass Spectrometry Laboratory. High-resolution electron ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass 70-VSE instrument at the University of Illinois Mass Spectrometry Laboratory.

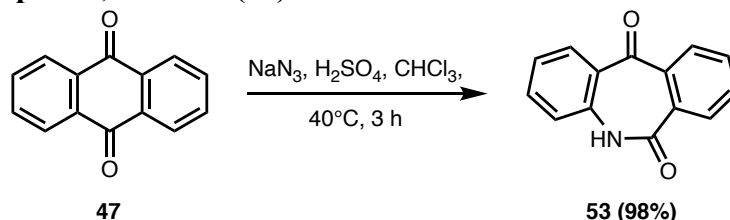
1.4 Safety Precautions!

While all procedures involving tetrazoles were conducted without incident, it is advisable to take appropriate safety precautions, such as the use of shields in a fume hood and personal protection equipment, when undertaking work with these potentially energetic heterocycles.

2. Experimental Details

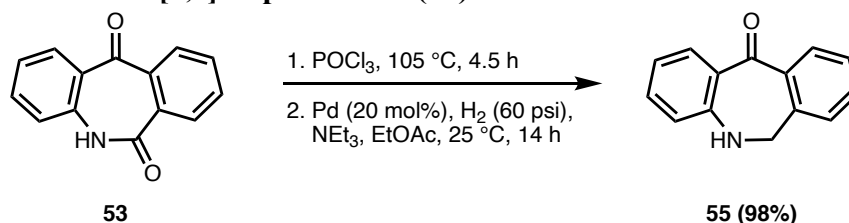
2.1 5-Pivaloyl-5,6-dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (48)

5*H*-Dibenzo[*b,e*]azepine-6,11-dione (53)



Warning: This reaction must be done behind a blast shield and all proper safety precautions must be taken! Antraquinone (**47**) (20 g, 96.1 mmol, 1 equiv) was suspended in chloroform (250 mL) and concentrated sulfuric acid (50 mL). The biphasic system was rapidly stirred while sodium azide was added in small portions at room temperature. The mixture was then stirred at room temperature for 1 hour and then at 40 °C for 3 h using a water bath. After addition of ice water (200 mL), the precipitate was then filtered and washed with additional water and ether (optional) to provide **53** (21.4 g, 98%): tan solid, ¹H-NMR (500 MHz; CDCl₃): δ 11.12 (s, 1H), 8.20-8.19 (m, 1H), 7.84 (d, *J* = 10.9 Hz, 3H), 7.75-7.73 (m, 1H), 7.63-7.60 (m, 1H), 7.37-7.35 (m, 1H), 7.26-7.23 (m, 1H). ¹³C-NMR (126 MHz; CDCl₃): δ 192.92 (s, 1C), 165.92 (s, 1C), 138.68 (s, 1C), 137.08 (s, 1C), 134.30 (s, 1C), 133.60 (s, 1C), 133.43 (s, 1C), 131.62 (s, 1C), 130.60 (s, 1C), 130.04 (s, 1C), 129.70 (s, 1C), 128.61 (s, 1C), 124.26 (s, 1C), 120.89 (s, 1C).

5,6-Dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (55)

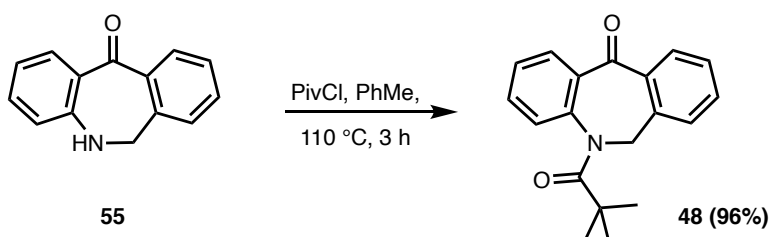


The reaction was done following literature protocol.² To a flame-dried flask under nitrogen was added lactam **53** (1g, 4.48 g, 1 equiv.), *N,N*-dimethyl aniline (0.34 mL, 2.69 mmol, 0.6 equiv) and oxyphosphoryl chloride (6.72 mL, 72.1 mmol, 16.1 equiv). The solution was refluxed for 4.5 hours. The reaction was then cooled and concentrated under vacuum. Ice water was then added to the residue and extracted with DCM. The organic phase was washed with 0.4 M HCl, water, cold 0.2 N Na₂CO₃, and water sequentially. The organics were then dried in sodium sulfate, decanted, and concentrated in vacuo. The residue was then dissolved in toluene and filtered through a neutral alumina plug. The plug was eluted with additional toluene (until the yellow came out). The filtrate was then concentrated in vacuo and immediately put to the next step as the product is unstable overnight.

To a Parr flask was added the previous product, Pd/C (0.1 g, 0.8 mmol, 0.18 equiv.), triethylamine (0.89 mL, 6.36 mmol, 1.42 equiv.), and dissolved in ethyl acetate (19 mL). The flask attached to a Parr hydrogenator and then evacuated and charged with hydrogen. The flask was shaken overnight under 60 psi of hydrogen at room temperature. Upon completion, the reaction was then filtered

through celite and washed with toluene. The filtrate was then washed with water and the organic layer was then concentrated in vacuo to provide **55** (917 mg, 98%): yellow oil, $^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 8.24 (dd, $J = 8.2, 1.5$ Hz, 1H), 8.24 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.80 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.80 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.49 (td, $J = 7.5, 1.3$ Hz, 1H), 7.49 (td, $J = 7.5, 1.3$ Hz, 1H), 7.37 (td, $J = 7.6, 1.1$ Hz, 1H), 7.37 (td, $J = 7.6, 1.1$ Hz, 1H), 7.30 (ddd, $J = 8.3, 6.8, 1.6$ Hz, 1H), 7.30 (ddd, $J = 8.3, 6.8, 1.6$ Hz, 1H), 7.17 (d, $J = 7.4$ Hz, 1H), 7.17 (d, $J = 7.4$ Hz, 1H), 6.86 (td, $J = 7.5, 1.0$ Hz, 1H), 6.86 (td, $J = 7.5, 1.0$ Hz, 1H), 6.73 (dd, $J = 8.3, 0.6$ Hz, 1H), 6.73 (dd, $J = 8.3, 0.6$ Hz, 1H), 5.58 (s, 1H), 5.58 (s, 1H), 4.19 (d, $J = 4.6$ Hz, 2H), 4.19 (d, $J = 4.6$ Hz, 2H). $^{13}\text{C-NMR}$ (126 MHz; CDCl_3): δ 194.39 (s, 1C), 194.39 (s, 1C), 150.71 (s, 1C), 150.71 (s, 1C), 137.67 (s, 1C), 137.67 (s, 1C), 134.24 (s, 1C), 134.24 (s, 1C), 132.33 (s, 1C), 132.33 (s, 1C), 131.67 (s, 1C), 131.67 (s, 1C), 129.11 (s, 1C), 129.11 (s, 1C), 128.87 (s, 1C), 128.87 (s, 1C), 127.96 (s, 1C), 127.96 (s, 1C), 126.39 (s, 1C), 126.39 (s, 1C), 121.64 (s, 1C), 121.64 (s, 1C), 118.57 (s, 1C), 118.57 (s, 1C), 118.01 (s, 1C), 118.01 (s, 1C), 49.43 (s, 1C), 49.43 (s, 1C).

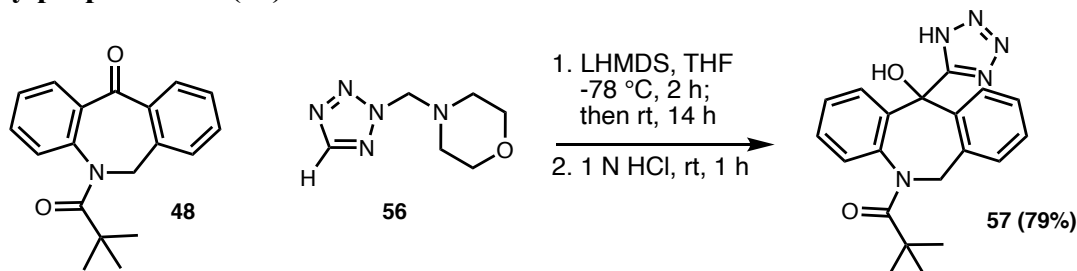
5-Pivaloyl-5,6-dihydro-11H-dibenzo[*b,e*]azepin-11-one (**48**)



To a flame-dried flask under nitrogen was added amine **55** (917 mg, 4.47 mmol, 1 equiv.), pivalyl chloride (0.83 mL, 6.73 mmol, 1.5 equiv.), and toluene (20 mL). The reaction was then refluxed for 3 hours. Upon completion, the reaction was cooled and quenched with water. The biphasic system was then rapidly stirred for 20 minutes before being transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were then combined and washed with saturated NaHCO_3 , brine, dried with sulfate, decanted, and concentrated in vacuo. The product was obtained after purification by column chromatography on silica gel (1:3 EtOAc:hexanes) to provide **48** (1.258 g, 96%): white solid, $\text{FTIR}_{\text{vmax}}$ 3061, 3033, 2972, 2958, 2930, 2867, 1645, 1631, 1589, 1508, 1477, 1445, 1428, 1395, 1360, 1297, 1283, 1271, 1237, 1217, 1196, 1185, 1150, 1106, 1099, 1049, 1037, 1006, 977, 976, 967, 926, 889, 828, 809, 784, 765, 748, 731, 711, 696, 668, 634, 625, 580, 524, 512, 495, 479, 455, 437, 417, 406 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.29 (d, $J = 7.9$ Hz, 1H), 7.91 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.59-7.45 (m, 3H), 7.39 (dd, $J = 12.4, 7.5$ Hz, 3H), 5.06 (s, 1H), 0.99 (s, 9H). $^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 192.40 (s, 1C), 177.22 (s, 1C), 142.75 (s, 1C), 142.40 (s, 1C), 139.42 (s, 1C), 134.58 (s, 1C), 133.91 (s, 1C), 132.94 (s, 1C), 131.86 (s, 1C), 131.30 (s, 1C), 129.32 (s, 1C), 128.89 (s, 1C), 128.05 (s, 1C), 127.99 (s, 1C), 55.09 (s, 1C), 41.43 (s, 1C), 29.46 (s, 1C).

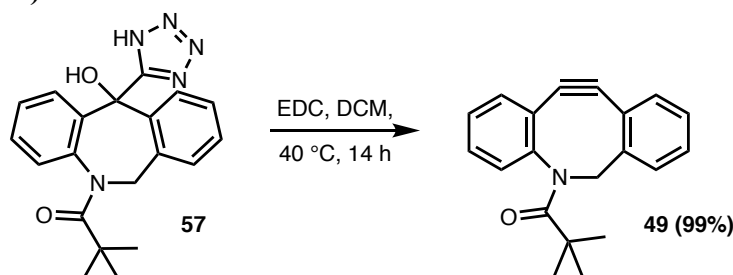
2.2 ADIBO (1)

1-(11-Hydroxy-11-(1*H*-tetrazol-5-yl)-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl)-2,2-dimethylpropan-1-one (57)



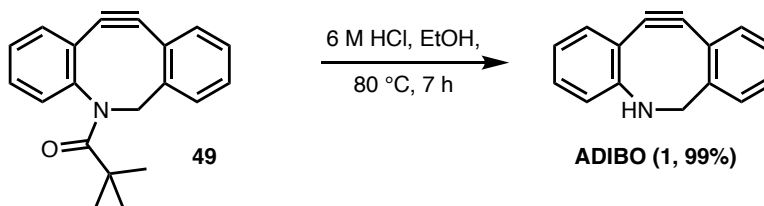
To a flame dried flask under nitrogen, the pivalamide **48** (366 mg, 1.25 mmol, 1 equiv.) and morpholinotetrazole **56** (633 mg, 3.74 mmol, 3 equiv.) were added and dissolved in anhydrous THF (18 mL). The solution was cooled to -78 °C (CO₂:acetone). A freshly prepared solution of LiHMDS (668 mg, 3.99 mmol, 3.2 equiv.) in THF (4 mL) was added dropwise slowly with continuous stirring. The reaction was then kept at -78 °C for 2 hours before being allowed to slowly reach room temperature overnight. Upon completion, the reaction was then concentrated, and the residue dissolved in 1 M HCl. The solution was then stirred for an hour before being transferred to a separatory funnel. The acidic layer was then extracted with ethyl acetate. The organics were then dried with sodium sulfate, decanted, and concentrated in vacuo. The product was purified by column chromatography on silica gel (1:1 acetone:hexanes) to provide **57** as a mixture of diastereomers (394 mg, 87%): white solid, FTIR_{max} 3272, 3198, 3133, 3062, 2969, 2929, 2868, 1735, 1718, 1654, 1617, 1597, 1508, 1479, 1448, 1398, 1364, 1293, 1267, 1228, 1216, 1196, 1116, 1097, 1025, 982, 929, 890, 868, 751, 734, 697, 662, 634, 612, 585, 572, 527, 514, 502, 486, 469, 454, 446, 440, 425, 413, 405 cm⁻¹; ¹H-NMR (500 MHz; CDCl₃): δ 8.09 (dd, *J* = 5.7, 3.6 Hz, 6H), 8.09 (dd, *J* = 5.7, 3.6 Hz, 6H), 7.47 (dd, *J* = 6.0, 3.8 Hz, 4H), 7.47 (dd, *J* = 6.0, 3.8 Hz, 4H), 7.38-7.16 (m, 29H), 7.38-7.16 (m, 29H), 5.62 (d, *J* = 2.8 Hz, 4H), 5.62 (d, *J* = 2.8 Hz, 4H), 5.26 (d, *J* = 13.7 Hz, 1H), 5.26 (d, *J* = 13.7 Hz, 1H), 3.43 (d, *J* = 13.6 Hz, 1H), 3.43 (d, *J* = 13.6 Hz, 1H), 2.11-2.07 (m, 4H), 2.11-2.07 (m, 4H), 0.84 (s, 9H), 0.84 (s, 9H). ¹³C-NMR (126 MHz; CDCl₃): δ 177.90 (s, 1C), 177.90 (s, 1C), 176.20 (s, 1C), 176.20 (s, 1C), 161.96 (s, 1C), 161.96 (s, 1C), 161.02 (s, 1C), 161.02 (s, 1C), 153.05 (s, 1C), 153.05 (s, 1C), 149.06 (s, 1C), 149.06 (s, 1C), 143.21 (s, 1C), 143.21 (s, 1C), 134.62 (s, 1C), 134.62 (s, 1C), 133.37 (s, 1C), 133.37 (s, 1C), 132.95 (s, 1C), 132.95 (s, 1C), 132.54 (s, 1C), 132.54 (s, 1C), 132.45 (s, 1C), 132.45 (s, 1C), 130.87 (s, 1C), 130.87 (s, 1C), 129.68 (s, 1C), 129.68 (s, 1C), 129.11 (s, 1C), 129.11 (s, 1C), 129.05 (s, 1C), 129.05 (s, 1C), 128.67 (s, 1C), 128.67 (s, 1C), 128.62 (s, 1C), 128.62 (s, 1C), 128.46 (s, 1C), 128.46 (s, 1C), 128.42 (s, 1C), 128.42 (s, 1C), 128.35 (s, 1C), 128.35 (s, 1C), 128.27 (s, 1C), 128.27 (s, 1C), 128.11 (s, 1C), 128.11 (s, 1C), 127.92 (s, 1C), 127.92 (s, 1C), 127.84 (s, 1C), 127.84 (s, 1C), 127.64 (s, 1C), 127.64 (s, 1C), 127.55 (s, 1C), 127.55 (s, 1C), 127.47 (s, 1C), 127.47 (s, 1C), 127.45 (s, 1C), 127.45 (s, 1C), 126.74 (s, 1C), 126.74 (s, 1C), 126.66 (s, 1C), 126.66 (s, 1C), 125.48 (s, 1C), 125.48 (s, 1C), 125.44 (s, 1C), 125.44 (s, 1C), 125.32 (s, 1C), 125.32 (s, 1C), 123.27 (s, 1C), 123.27 (s, 1C), 115.27 (s, 1C), 115.27 (s, 1C), 108.61 (s, 1C), 108.61 (s, 1C), 71.60 (s, 1C), 71.60 (s, 1C), 56.93 (s, 1C), 56.93 (s, 1C), 53.08 (s, 1C), 53.08 (s, 1C), 40.96 (s, 1C), 40.96 (s, 1C), 27.09 (s, 1C), 27.09 (s, 1C), 26.64 (s, 1C), 26.64 (s, 1C). HRMS-ESI⁺ calculated for C₂₀H₂₁N₅O₂Na [M+Na]⁺: 386.1593, found 386.1588.

N-Pivoyl-ADIBO (49)

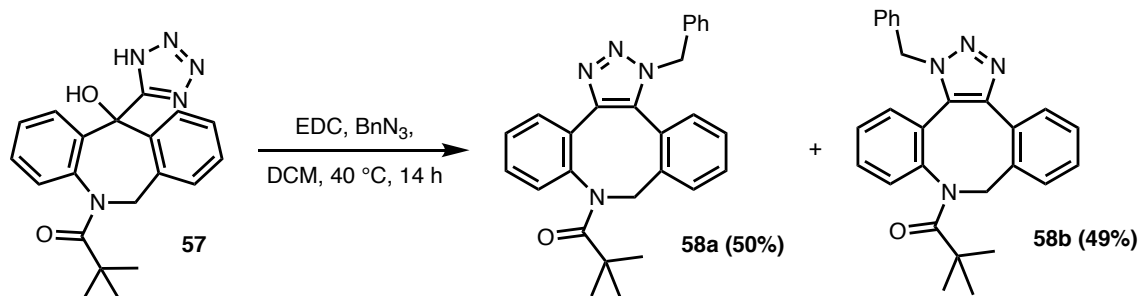


To an oven-dried vial was added the hydroxytetrazole **57** (14.5 mg, 0.04 mmol, 1 equiv.) and EDC (9.2 mg, 0.048 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where it was transferred to a column for purification by column chromatography on silica gel (1:4 hexanes:EtOAc) to provide **49** (11.5 mg, 99%): oil, FTIR_{vmax} 2980, 2869, 2358, 2342, 2331, 2239, 2195, 2188, 2183, 2161, 2137, 2128, 2049, 2042, 2034, 2025, 2018, 2003, 1996, 1978, 1978, 1972, 1932, 1867, 1733, 1715, 1558, 1540, 1508, 1373, 1140, 720, 678, 668, 650, 633, 616, 604, 591, 569, 563, 538, 531, 521, 500, 491, 483, 472, 458, 450, 442, 417, 410 cm⁻¹; ¹H-NMR (400 MHz; CDCl₃): δ 7.68 (d, *J* = 7.4 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.41-7.28 (m, 7H), 7.41-7.28 (m, 7H), 5.29 (d, *J* = 13.6 Hz, 1H), 5.29 (d, *J* = 13.6 Hz, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 0.88 (s, 9H), 0.88 (s, 9H). ¹³C-NMR (101 MHz; CDCl₃): δ 179.36 (s, 1C), 153.27 (s, 1C), 149.18 (s, 1C), 132.70 (s, 1C), 129.82 (s, 1C), 128.56 (s, 1C), 128.46 (s, 1C), 128.18 (s, 1C), 127.93 (s, 1C), 127.27 (s, 1C), 125.93 (s, 1C), 123.89 (s, 1C), 123.60 (s, 1C), 116.68 (s, 1C), 108.78 (s, 1C), 57.66 (s, 1C), 41.74 (s, 1C), 29.62 (s, 1C). HRMS-ESI⁺ calculated for C₂₀H₂₀NO [M+H]⁺: 290.1545, found 290.1541.

ADIBO (1)



To a vial, pivalamide-protected ADIBO **49** (11.5 mg, 0.04 mmol, 1 equiv.) was dissolved in ethanol (7 mL) and to it, 6 M HCl (1 mL) was added. The vial was then flushed with nitrogen and refluxed for 7 hours. The product was then cooled and evaporated. The product was isolated by purification via column chromatography on silica gel (1:3 ethyl acetate:hexanes) to provide **1** (8 mg, 98%): oil; ¹H-NMR (400 MHz; CDCl₃): δ 7.72 (dd, *J* = 20.1, 7.7 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.45-7.32 (m, 3H), 7.24-7.21 (m, 1H), 7.15-7.11 (m, 1H), 6.66 (s, 1H), 5.10 (s, 2H). ¹³C-NMR (101 MHz; CDCl₃): δ 142.10 (s, 1C), 133.47 (s, 1C), 133.18 (s, 1C), 128.54 (s, 1C), 127.42 (s, 1C), 123.92 (s, 1C), 122.08 (s, 1C), 121.88 (s, 1C), 121.31 (s, 1C), 120.01 (s, 1C), 109.96 (s, 1C), 109.61 (s, 1C), 91.66 (s, 1C), 48.80 (s, 1C). HRMS-ESI⁺ calculated for C₁₅H₁₂N [M+H]⁺: 206.0970, found 206.0970.



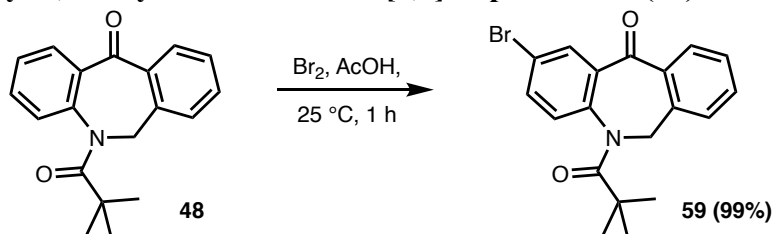
To an oven-dried vial was added the hydroxytetrazole **57** (36.3 mg, 0.1 mmol, 1 equiv.), benzyl azide (0.06 mL, 0.5 mmol, 5 equiv.) and EDC (23 mg, 0.12 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where it was transferred to a column for purification by column chromatography on silica gel (1:2 hexanes:EtOAc) to provide a separable mixture of regioisomers:

58a (10.5 mg, 50%): oil, FTIR_{vmax} 3058, 3031, 2956, 2929, 2868, 1634, 1508, 1496, 1480, 1453, 1397, 1374, 1357, 1284, 1239, 1195, 1131, 1076, 1050, 1028, 1003, 980, 904, 829, 775, 758, 727, 695, 644, 611, 581, 567, 541, 487, 459, 434, 423, 414, 408, 402 cm⁻¹; ¹H-NMR (400 MHz; CDCl₃): δ 7.69-7.66 (m, 1H), 7.45-7.41 (m, 2H), 7.39-7.35 (m, 2H), 7.33 (td, *J* = 5.3, 1.5 Hz, 2H), 7.31-7.26 (m, 2H), 7.23-7.21 (m, 2H), 7.19-7.15 (m, 2H), 7.00-6.98 (m, 1H), 5.83 (d, *J* = 16.7 Hz, 1H), 5.66 (q, *J* = 16.3 Hz, 2H), 4.42-4.38 (m, 1H), 0.83 (s, 9H). ¹³C-NMR (101 MHz; CDCl₃): δ 178.53 (s, 1C), 143.87 (s, 1C), 142.11 (s, 1C), 136.54 (s, 1C), 135.70 (s, 1C), 135.63 (s, 1C), 133.19 (s, 1C), 131.52 (s, 1C), 130.41 (s, 1C), 130.19 (s, 1C), 130.10 (s, 1C), 129.72 (s, 1C), 129.37 (s, 1C), 129.31 (s, 1C), 128.61 (s, 1C), 127.68 (s, 1C), 127.32 (s, 1C), 124.97 (s, 1C), 56.21 (s, 1C), 53.11 (s, 1C), 41.89 (s, 1C), 29.58 (s, 1C). HRMS-ESI⁺ calculated for C₂₇H₂₇N₄O [M+H]⁺: 423.2185, found 423.2188.

58b (10.3 mg, 49%): oil, FTIR_{vmax} 3061, 3031, 2959, 2867, 1735, 1634, 1508, 1496, 1478, 1454, 1432, 1398, 1361, 1315, 1286, 1260, 1240, 1197, 1122, 1094, 1077, 1053, 1029, 1003, 994, 980, 949, 906, 855, 828, 799, 760, 725, 704, 659, 645, 611, 594, 579, 542, 513, 485, 455, 427, 411 cm⁻¹; ¹H-NMR (400 MHz; CDCl₃): δ 7.74 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.52 (td, *J* = 7.7, 1.4 Hz, 1H), 7.44-7.34 (m, 6H), 7.33-7.24 (m, 4H), 7.15-7.13 (m, 1H), 6.95 (dd, *J* = 7.6, 1.1 Hz, 1H), 5.93-5.89 (m, 1H), 5.76 (d, *J* = 15.6 Hz, 1H), 5.21-5.17 (m, 1H), 4.89 (d, *J* = 17.7 Hz, 1H), 1.10 (s, 9H). ¹³C-NMR (101 MHz; CDCl₃): δ 177.54 (s, 1C), 144.27 (s, 1C), 136.56 (s, 1C), 134.21 (s, 1C), 133.53 (s, 1C), 132.62 (s, 1C), 131.87 (s, 1C), 129.60 (s, 1C), 129.58 (s, 1C), 129.32 (s, 1C), 129.24 (s, 1C), 128.76 (s, 1C), 128.75 (s, 1C), 128.56 (s, 1C), 128.16 (s, 1C), 128.04 (s, 1C), 127.95 (s, 1C), 127.83 (s, 1C), 127.64 (s, 1C), 56.74 (s, 1C), 52.25 (s, 1C), 39.88 (s, 1C), 28.65 (s, 1C). HRMS-ESI⁺ calculated for C₂₇H₂₇N₄O [M+H]⁺: 423.2185, found 423.2185.

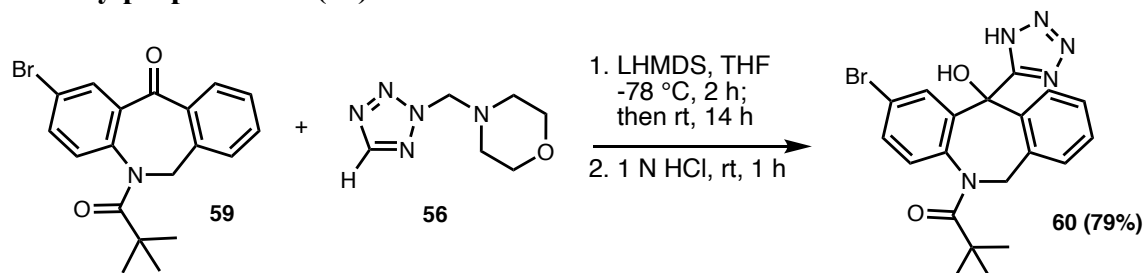
2.3 4-Bromo-ADIBO (50)

2-Bromo-5-pivaloyl-5,6-dihydro-11H-dibenzo[*b,e*]azepin-11-one (59)



Pivalamide **48** (1 g, 3.41 mmol, 1 equiv.) was dissolved in acetic acid (6mL). Elemental bromine (1.26g, 7.84 mmol, 2.3 equiv.) was added dropwise. The reaction was then stirred at room temperature in the dark for an hour before quenching with sodium thiosulfate. The solution was then diluted with water and extracted with ethyl acetate. The organics were then combined and sequentially washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, decanted, and concentrated in vacuo to provide **59** (1.26 g, 99%): $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.27-8.25 (m, 1H), 8.03 (d, $J = 2.3$ Hz, 1H), 7.68 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.52 (td, $J = 7.4, 1.1$ Hz, 1H), 7.39 (dd, $J = 15.7, 7.7$ Hz, 2H), 7.30-7.27 (m, 1H), 5.05 (s, 2H), 0.99 (s, 9H). $^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 190.79 (s, 1C), 177.40 (s, 1C), 142.16 (s, 1C), 141.69 (s, 1C), 140.62 (s, 1C), 135.83 (s, 1C), 134.26 (s, 1C), 134.23 (s, 1C), 134.12 (s, 1C), 132.02 (s, 1C), 129.78 (s, 1C), 129.41 (s, 1C), 128.21 (s, 1C), 122.63 (s, 1C), 55.07 (s, 1C), 41.47 (s, 1C), 29.45 (s, 1C). HRMS-ESI $^+$ calculated for $\text{C}_{19}\text{H}_{19}\text{NO}_2\text{Br}$ $[\text{M}+\text{H}]^+$: 372.0599, found 372.0595.

1-(2-Bromo-11-hydroxy-11-(1H-tetrazol-5-yl)-6,11-dihydro-5H-dibenzo[*b,e*]azepin-5-yl)-2,2-dimethylpropan-1-one (60)



To a flame dried flask under nitrogen, the pivalamide **59** (405 mg, 1.09 mmol, 1 equiv.) and morpholinotetrazole **56** (368 mg, 2.18 mmol, 2 equiv.) were added and dissolved in anhydrous THF (10 mL). The solution was cooled to -78°C (CO_2 :acetone). A freshly prepared solution of LiHMDS (473 mg, 2.83 mmol, 2.6 equiv.) in THF (3 mL) was added dropwise slowly with continuous stirring. The reaction was then kept at -78°C for 2 hours before being allowed to slowly reach room temperature overnight. Upon completion, the reaction was then concentrated, and the residue dissolved in 1 M HCl. The solution was then stirred for an hour before being transferred to a separatory funnel. The acidic layer was then extracted with ethyl acetate. The organics were then dried with sodium sulfate, decanted, and concentrated in vacuo. The product was purified by column chromatography on silica gel (1:1 acetone:hexanes) to provide **60** as a mixture of diastereomers (380 mg, 79%): white solid, FTIR_{max} 3232, 3172, 3132, 3062, 2968, 2930, 2870, 1735, 1718, 1655, 1619, 1597, 1508, 1480, 1450, 1398, 1375, 1280, 1267, 1228, 1216, 1198, 1116, 1097, 1026, 981, 929, 890, 868, 750, 734, 697, 662, 639, 612, 587, 572, 529, 514, 501, 486, 470, 454, 446, 440, 425, 413, 405 cm^{-1} ; $^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 8.30-8.23 (m, 3H), 8.12-8.09

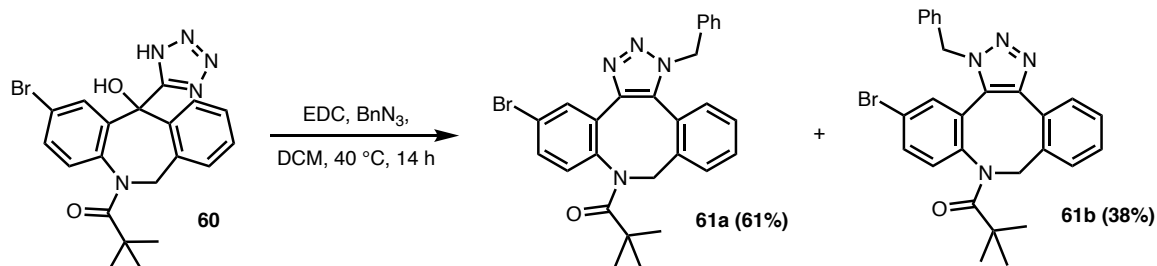
(m, 3H), 7.99-7.73 (m, 6H), 7.61-7.45 (m, 8H), 7.35-7.29 (m, 7H), 7.15 (d, $J = 7.8$ Hz, 1H), 5.59-5.56 (m, 1H), 4.54-4.50 (m, 1H), 4.09-4.05 (m, 4H), 2.02-1.94 (m, 9H), 1.01 (s, 9H). ^{13}C -NMR (126 MHz; CDCl_3): δ 177.39 (s, 1C), 170.48 (s, 1C), 143.33 (s, 1C), 143.26 (s, 1C), 136.55 (s, 1C), 135.30 (s, 1C), 135.02 (s, 1C), 134.26 (s, 1C), 132.52 (s, 1C), 131.52 (s, 1C), 130.92 (s, 1C), 130.36 (s, 1C), 130.23 (s, 1C), 129.49 (s, 1C), 129.36 (s, 1C), 129.00 (s, 1C), 128.89 (s, 1C), 128.50 (s, 1C), 128.36 (s, 1C), 127.96 (s, 1C), 127.27 (s, 1C), 127.05 (s, 1C), 126.93 (s, 1C), 126.36 (s, 1C), 126.11 (s, 1C), 125.87 (s, 1C), 125.53 (s, 1C), 125.08 (s, 1C), 124.41 (s, 1C), 123.53 (s, 1C), 122.96 (s, 1C), 121.49 (s, 1C), 120.99 (s, 1C), 112.70 (s, 1C), 67.60 (s, 1C), 60.09 (s, 1C), 53.24 (s, 1C), 28.62 (s, 1C), 27.79 (s, 1C), 27.31 (s, 1C), 20.39 (s, 1C). HRMS-ESI+ calculated for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_2\text{Br}$ $[\text{M}+\text{H}]^+$: 442.0879, found 442.0878.

4-Bromo-ADIBO (50)



4-Bromo-ADIBO (50, 99%)

To an oven-dried vial was added the hydroxytetrazole **60** (44.2 mg, 0.1 mmol, 1 equiv.) and EDC (23 mg, 0.12 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where it was transferred to a column for purification by column chromatography on silica gel (1:4 hexanes:EtOAc) to provide **50** (36.8 mg, 99%): oil, FTIR $_{\text{vmax}}$ 3292, 3063, 2971, 2929, 2867, 2803, 1733, 1671, 1643, 1601, 1584, 1565, 1541, 1505, 1477, 1455, 1430, 1396, 1365, 1344, 1288, 1261, 1190, 1181, 1157, 1117, 1095, 1073, 1036, 999, 986, 929, 886, 830, 806, 755, 736, 724, 699, 687, 650, 595, 580, 552, 524, 481, 463, 449, 442, 435, 429, 418, 411, 403 cm^{-1} ; ^1H -NMR (400 MHz; CDCl_3): δ 7.68 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 1.8$ Hz, 1H), 7.49-7.46 (m, 1H), 7.40-7.28 (m, 3H), 7.22 (d, $J = 8.3$ Hz, 1H), 5.28 (d, $J = 13.7$ Hz, 1H), 3.42 (d, $J = 13.6$ Hz, 1H), 0.89 (s, 9H). ^{13}C -NMR (101 MHz; CDCl_3): δ 152.14 (s, 1C), 149.20 (s, 1C), 132.74 (s, 1C), 131.18 (s, 1C), 131.05 (s, 1C), 130.87 (s, 1C), 130.21 (s, 1C), 128.93 (s, 1C), 128.21 (s, 1C), 128.05 (s, 1C), 126.05 (s, 1C), 125.87 (s, 1C), 123.09 (s, 1C), 118.44 (s, 1C), 107.19 (s, 1C), 57.52 (s, 1C), 41.81 (s, 1C), 29.66 (s, 1C). HRMS-ESI+ calculated for $\text{C}_{20}\text{H}_{19}\text{NOBr}$ $[\text{M}+\text{H}]^+$: 368.0650, found 368.0645.



To an oven-dried vial was added the hydroxytetrazole **60** (36.3 mg, 0.1 mmol, 1 equiv.), benzyl azide (0.06 mL, 0.5 mmol, 5 equiv.) and EDC (23 mg, 0.12 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where

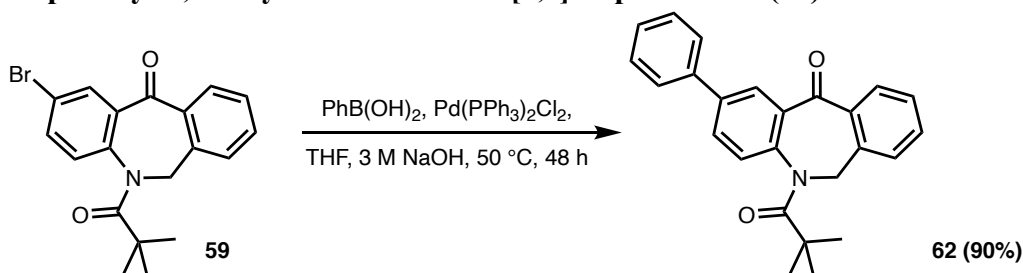
it was transferred to a column for purification by column chromatography on silica gel (1:2 hexanes:EtOAc) to provide a separable mixture of regioisomers:

61a (29.7 mg, 61%): oil, FTIR_{max} 3063, 3031, 2972, 2932, 2907, 2868, 1733, 1714, 1638, 1574, 1505, 1497, 1481, 1455, 1396, 1342, 1286, 1259, 1237, 1218, 1201, 1178, 1150, 1114, 1077, 1042, 1030, 1004, 990, 886, 822, 796, 774, 759, 730, 714, 693, 668, 586 cm⁻¹; ¹H-NMR (500 MHz; CDCl₃): δ 7.84 (dt, *J* = 8.5, 2.8 Hz, 1H), 7.58-7.54 (m, 1H), 7.39-7.15 (m, 9H), 7.02-6.99 (m, 1H), 5.72 (dd, *J* = 64.9, 15.4 Hz, 3H), 4.37-4.12 (m, 1H), 0.84 (s, 9H). ¹³C-NMR (126 MHz; CDCl₃): δ 178.39 (s, 1C), 142.76 (s, 1C), 141.21 (s, 1C), 136.20 (s, 1C), 135.87 (s, 1C), 135.52 (s, 1C), 135.09 (s, 1C), 133.21 (s, 1C), 133.17 (s, 1C), 131.54 (s, 1C), 130.83 (s, 1C), 130.46 (s, 1C), 129.93 (s, 1C), 129.33 (s, 1C), 128.69 (s, 1C), 127.71 (s, 1C), 127.54 (s, 1C), 124.74 (s, 1C), 123.02 (s, 1C), 56.11 (s, 1C), 53.19 (s, 1C), 41.94 (s, 1C), 29.63 (s, 1C). HRMS-ESI⁺ calculated for C₂₇H₂₆BrN₄O [M+H]⁺: 501.1290, found 501.1285.

61b (18.9 mg, 38%): oil, FTIR_{max} 3063, 3031, 2972, 2932, 2907, 2868, 1733, 1714, 1638, 1574, 1505, 1497, 1481, 1455, 1396, 1342, 1286, 1259, 1237, 1218, 1201, 1178, 1150, 1114, 1077, 1042, 1030, 1004, 990, 886, 822, 796, 774, 759, 730, 714, 693, 668, 586 cm⁻¹; ¹H-NMR (500 MHz; CDCl₃): δ 7.71-7.69 (m, 1H), 7.64-7.61 (m, 1H), 7.45-7.40 (m, 5H), 7.35-7.28 (m, 3H), 7.24-7.11 (m, 2H), 6.94-6.93 (m, 1H), 5.85 (dd, *J* = 33.9, 16.3 Hz, 2H), 5.00 (dd, *J* = 144.9, 16.0 Hz, 2H), 1.10 (s, 9H). ¹³C-NMR (126 MHz; CDCl₃): δ 177.61 (s, 1C), 145.06 (s, 1C), 143.23 (s, 1C), 136.27 (s, 1C), 134.84 (s, 1C), 134.80 (s, 1C), 133.85 (s, 1C), 133.64 (s, 1C), 133.58 (s, 1C), 132.86 (s, 1C), 130.11 (s, 1C), 129.46 (s, 1C), 129.34 (s, 1C), 128.98 (s, 1C), 128.87 (s, 1C), 128.21 (s, 1C), 127.93 (s, 1C), 127.85 (s, 1C), 121.49 (s, 1C), 56.46 (s, 1C), 52.73 (s, 1C), 39.79 (s, 1C), 28.54 (s, 1C). HRMS-ESI⁺ calculated for C₂₇H₂₆BrN₄O [M+H]⁺: 501.1290, found 501.1285.

2.4 4-Phenyl-ADIBO (51)

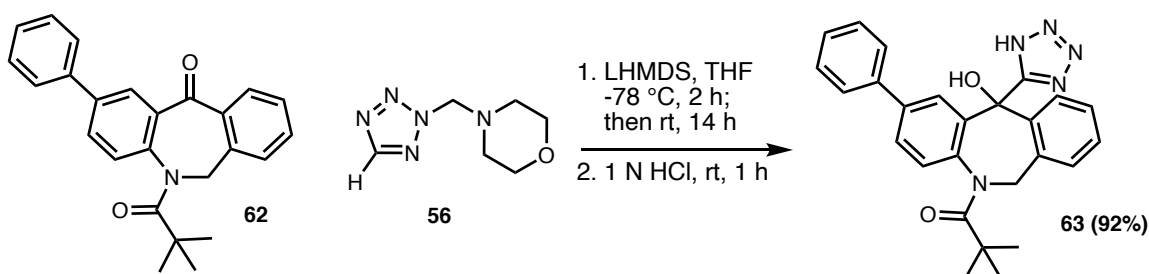
2-Phenyl-5-pivaloyl-5,6-dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (62)



To oven-dried vial equipped with a teflon cap was added pivalamide **59** (500 mg, 1.34 mmol, 1 equiv.), phenylboronic acid (246mg, 2.01 mmol, 1.5 equiv.), and bis(triphenylphosphine)palladium dichloride (178 mg, 0.269 mmol, 0.2 equiv.). The vial was evacuated and backfilled with nitrogen thrice. THF (17 mL) and 1 M NaOH (3 mL) was added by syringe and the reaction was heated to 50 °C with stirring for 2 days. Upon completion, the reaction was partitioned between water and ethyl acetate and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organics were then washed with brine, dried with sodium sulfate, decanted, and concentrated in vacuo. Purification of the product was achieved by column chromatography on silica gel (1:4 ethyl

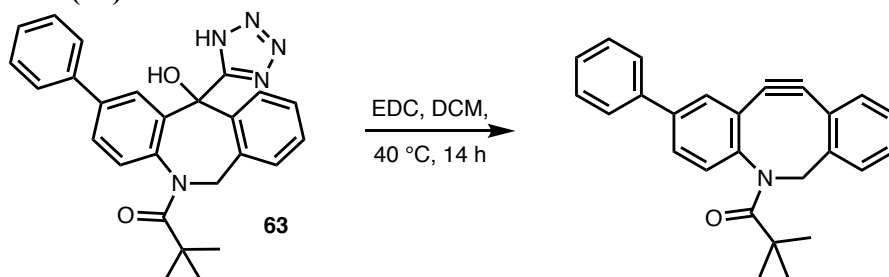
acetate:hexanes) to provide **62** (447 mg, 90%): $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.32 (dd, $J = 11.6$, 8.0 Hz, 1H), 8.17 (d, $J = 1.9$ Hz, 1H), 7.93-7.79 (m, 1H), 7.66 (d, $J = 7.2$ Hz, 2H), 7.58-7.37 (m, 9H), 7.29-7.28 (m, 1H), 5.07 (s, 1H), 1.03 (dd, $J = 19.8$, 0.5 Hz, 9H). $^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 192.38 (s, 1C), 177.34 (s, 1C), 142.45 (s, 1C), 142.43 (s, 1C), 141.85 (s, 1C), 141.78 (s, 1C), 139.62 (s, 1C), 139.42 (s, 1C), 134.62 (s, 1C), 133.98 (s, 1C), 133.93 (s, 1C), 132.98 (s, 1C), 132.59 (s, 1C), 131.93 (s, 1C), 131.87 (s, 1C), 131.31 (s, 1C), 130.11 (s, 1C), 130.04 (s, 1C), 129.73 (s, 1C), 129.41 (s, 1C), 129.35 (s, 1C), 129.15 (s, 1C), 128.92 (s, 1C), 128.58 (s, 1C), 128.54 (s, 1C), 128.46 (s, 1C), 128.07 (s, 1C), 128.02 (s, 1C), 127.45 (s, 1C), 127.11 (s, 1C), 126.78 (s, 1C), 126.44 (s, 1C), 55.16 (s, 1C), 55.10 (s, 1C), 49.83 (s, 1C), 41.49 (s, 1C), 41.44 (s, 1C), 29.59 (s, 1C), 29.55 (s, 1C), 29.49 (s, 1C).

1-(11-Hydroxy-2-phenyl-11-(1*H*-tetrazol-5-yl)-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl)-2,2-dimethylpropan-1-one (63**)**



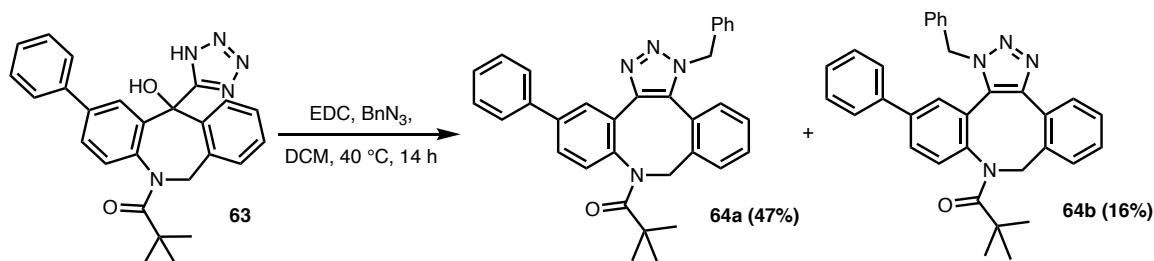
To a flame dried flask under nitrogen, the pivalamide **62** (185 mg, 0.501 mmol, 1 equiv.) and morpholinotetrazole **56** (176 mg, 1 mmol, 2 equiv.) were added and dissolved in anhydrous THF (5 mL). The solution was cooled to -78 °C (CO_2 :acetone). A freshly prepared solution of LiHMDS (176 mg, 1.05 mmol, 2.1 equiv.) in THF (1 mL) was added dropwise slowly with continuous stirring. The reaction was then kept at -78 °C for 2 hours before being allowed to slowly reach room temperature overnight. Upon completion, the reaction was then concentrated, and the residue dissolved in 1 M HCl. The solution was then stirred for an hour before being transferred to a separatory funnel. The acidic layer was then extracted with ethyl acetate. The organics were then dried with sodium sulfate, decanted, and concentrated in vacuo. The product was purified by column chromatography on silica gel (1:1 acetone:hexanes) to provide **63** as a mixture of diastereomers (202 mg, 92%): white solid, $\text{FTIR}_{\text{vmax}}$ 3275, 3198, 3133, 3062, 2969, 2929, 2868, 1739, 1718, 1655, 1643, 1619, 1602, 1597, 1509, 1479, 1449, 1397, 1375, 1292, 1267, 1228, 1218, 1197, 1116, 1097, 1073, 1028, 984, 929, 892, 879, 751, 732, 697, 662, 634, 612, 585, 572, 527, 514, 502, 486, 469, 454, 446, 440, 425, 413, 405 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.15 (s, 1H), 8.42 (s, 1H), 8.12 (dd, $J = 21.4$, 6.0 Hz, 2H), 7.71 (d, $J = 7.0$ Hz, 3H), 7.48 (t, $J = 7.4$ Hz, 2H), 7.40-7.19 (m, 6H), 5.66-5.48 (m, 2H), 4.58-4.41 (m, 1H), 1.01 (d, $J = 19.0$ Hz, 9H). $^{13}\text{C-NMR}$ (101 MHz; CDCl_3): δ 177.75 (s, 1C), 161.40 (s, 1C), 143.31 (s, 1C), 140.59 (s, 1C), 140.48 (s, 1C), 135.27 (s, 1C), 129.82 (s, 1C), 129.56 (s, 1C), 129.34 (s, 1C), 129.18 (s, 1C), 128.95 (s, 1C), 128.76 (s, 1C), 128.68 (s, 1C), 128.04 (s, 1C), 127.90 (s, 1C), 127.83 (s, 1C), 127.30 (s, 1C), 127.20 (s, 1C), 127.10 (s, 1C), 126.38 (s, 1C), 125.74 (s, 1C), 124.37 (s, 1C), 72.04 (s, 1C), 53.50 (s, 1C), 53.37 (s, 1C), 40.13 (s, 1C), 28.82 (s, 1C).

4-Phenyl-ADIBO (51)



4-Phenyl-ADIBO (51, 52%)

To an oven-dried vial was added the hydroxytetrazole **63** (44 mg, 0.1 mmol, 1 equiv.) and EDC (23 mg, 0.12 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where it was transferred to a column for purification by column chromatography on silica gel (1:4 hexanes:EtOAc) to provide **51** (18.9 mg, 52%): oil, ¹H-NMR (500 MHz; CDCl₃): δ 7.71-7.65 (m, 3H), 7.59-7.58 (m, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.44-7.28 (m, 6H), 5.35-5.29 (m, 1H), 3.54-3.46 (m, 1H), 0.92 (d, *J* = 23.8 Hz, 9H). ¹³C-NMR (126 MHz; CDCl₃): δ 179.37 (s, 1C), 179.33 (s, 1C), 153.30 (s, 1C), 152.33 (s, 1C), 149.20 (s, 1C), 141.48 (s, 1C), 139.74 (s, 1C), 132.73 (s, 1C), 132.69 (s, 1C), 130.02 (s, 1C), 129.82 (s, 1C), 129.39 (s, 1C), 128.62 (s, 1C), 128.54 (s, 1C), 128.42 (s, 1C), 128.17 (s, 1C), 127.95 (s, 1C), 127.92 (s, 1C), 127.46 (s, 1C), 127.26 (s, 1C), 126.58 (s, 1C), 125.95 (s, 1C), 125.91 (s, 1C), 125.74 (s, 1C), 124.26 (s, 1C), 123.90 (s, 1C), 123.61 (s, 1C), 123.57 (s, 1C), 116.98 (s, 1C), 116.70 (s, 1C), 109.98 (s, 1C), 108.79 (s, 1C), 108.71 (s, 1C), 57.74 (s, 1C), 57.64 (s, 1C), 41.80 (s, 1C), 41.74 (s, 1C), 29.69 (s, 1C), 29.63 (s, 1C).

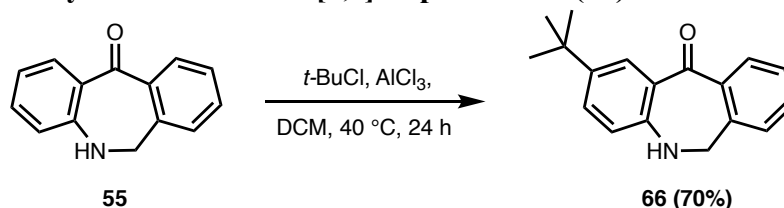


To an oven-dried vial was added the hydroxytetrazole **63** (36.3 mg, 0.1 mmol, 1 equiv.), benzyl azide (0.06 mL, 0.5 mmol, 5 equiv.) and EDC (23 mg, 0.12 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where it was transferred to a column for purification by column chromatography on silica gel (1:2 hexanes:EtOAc) to provide an inseparable mixture of regioisomers: **64a** and **64b** (30 mg, 63%): oil, FTIR_{νmax} 3061, 3023, 3013, 2975, 2931, 2889, 2875, 1645, 1508, 1497, 1488, 1457, 1455, 1433, 1398, 1380, 1369, 1282, 1250, 1188, 1133, 1079, 1049, 1045, 1021, 1018, 972, 909, 822, 775, 749, 734, 691, 642, 610, 573, 569, 545, 496, 449, 423, 419, 413, 410 cm⁻¹; ¹H-NMR (500 MHz; CDCl₃): δ 7.92 (d, *J* = 1.9 Hz,), 7.78-7.72 (m, 2H), 7.69-7.62 (m, 2H), 7.53-7.12 (m, 25H), 7.02-7.00 (m, 1H), 6.03-5.60 (m, 5H), 5.31-4.86 (m, 2H), 4.50-4.13 (m, 1H), 1.11 (d, *J* = 14.6 Hz, 8H), 0.86 (d, *J* = 24.1 Hz, 9H). ¹³C-NMR (126 MHz; CDCl₃): δ 178.58 (s, 1C), 177.65 (s, 1C), 144.31 (s, 1C), 143.92 (s, 1C), 143.89 (s, 1C), 143.23 (s, 1C), 142.17 (s, 1C), 142.14 (s, 1C), 141.14 (s, 1C), 140.88 (s, 1C), 139.71 (s, 1C), 139.22 (s, 1C), 136.96 (s, 1C), 136.57 (s, 1C), 135.76 (s, 1C), 135.71 (s, 1C), 134.26 (s, 1C), 134.23 (s, 1C), 133.57 (s, 1C), 133.53 (s, 1C), 133.23 (s, 1C), 132.63 (s, 1C), 131.85 (s, 1C), 131.68 (s, 1C), 131.55 (s, 1C), 131.51 (s, 1C),

130.47 (s, 1C), 130.39 (s, 1C), 130.35 (s, 1C), 130.28 (s, 1C), 130.18 (s, 1C), 130.08 (s, 1C), 130.04 (s, 1C), 129.76 (s, 1C), 129.70 (s, 1C), 129.60 (s, 1C), 129.42 (s, 1C), 129.32 (s, 1C), 129.26 (s, 1C), 129.14 (s, 1C), 129.00 (s, 1C), 128.80 (s, 1C), 128.74 (s, 1C), 128.61 (s, 1C), 128.55 (s, 1C), 128.50 (s, 1C), 128.33 (s, 1C), 128.26 (s, 1C), 128.14 (s, 1C), 128.02 (s, 1C), 127.95 (s, 1C), 127.85 (s, 1C), 127.68 (s, 1C), 127.63 (s, 1C), 127.48 (s, 1C), 127.37 (s, 1C), 127.30 (s, 1C), 127.16 (s, 1C), 126.86 (s, 1C), 125.02 (s, 1C), 125.00 (s, 1C), 56.77 (s, 1C), 56.75 (s, 1C), 56.23 (s, 1C), 53.13 (s, 1C), 53.10 (s, 1C), 52.48 (s, 1C), 52.25 (s, 1C), 41.93 (s, 1C), 39.92 (s, 1C), 29.67 (s, 1C), 29.58 (s, 1C), 29.51 (s, 1C), 28.68 (s, 1C), 28.54 (s, 1C), 28.47 (s, 1C).

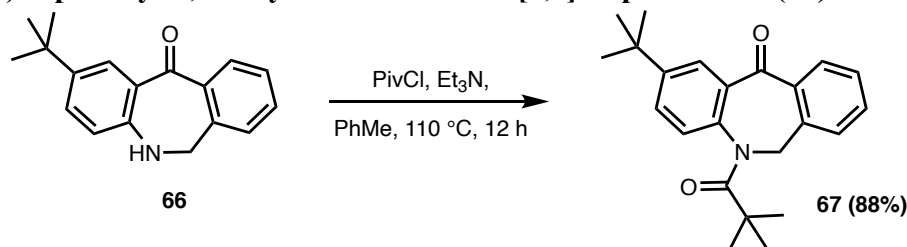
4.5 4-*tert*-Butyl-ADIBO (53)

2-(*Tert*-butyl)-5,6-dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (66)



To an oven-dried vial was added amine **55** (130 mg, 0.621 mmol, 1 equiv.). In a glovebox, aluminum trichloride (109 mg, 1.18 mmol, 1.5 equiv.) was added. To the vial, anhydrous DCM (5 mL) and *tert*-butyl chloride (109 mg, 1.18 mmol, 1.9 equiv.) was added and the reaction was stirred at room temperature for 24 hours. The vial was then diluted in water and the aqueous phase was extracted with DCM. The organics were then combined, washed with brine, dried with sodium sulfate, decanted, and concentrated in vacuo to provide, after purification by column chromatography on silica gel (1:4 ethyl acetate:hexanes) **66** (115 mg, 70%): oil, ¹H-NMR (400 MHz; CDCl₃): δ 8.19 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.50 (td, *J* = 7.4, 1.3 Hz, 1H), 7.42-7.37 (m, 2H), 7.22 (d, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 4.28 (s, 2H), 1.35 (s, 9H). ¹³C-NMR (101 MHz; CDCl₃): δ 194.61 (s, 1C), 148.72 (s, 1C), 141.70 (s, 1C), 141.44 (s, 1C), 137.88 (s, 1C), 132.62 (s, 1C), 132.48 (s, 1C), 129.48 (s, 1C), 128.32 (s, 1C), 127.84 (s, 1C), 126.56 (s, 1C), 121.79 (s, 1C), 118.67 (s, 1C), 50.20 (s, 1C), 34.52 (s, 1C), 31.69 (s, 1C).

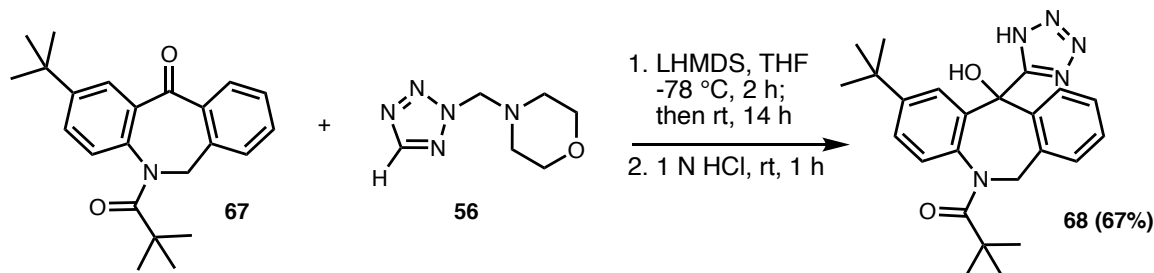
2-(*Tert*-butyl)-5-pivaloyl-5,6-dihydro-11*H*-dibenzo[*b,e*]azepin-11-one (67)



To a flame-dried flask equipped with a stir bar and condenser, amine **66** (450 mg, 1.7 mmol, 1 equiv.), triethylamine (0.284 mL, 2.03 mmol, 1.2 equiv.), and pivaloyl chloride (0.313 mL, 2.54 mmol, 1.5 equiv.) was added and dissolved in toluene (10 mL). The reaction was refluxed overnight nitrogen. The solution was cooled and quenched with water. The biphasic system was rapidly stirred for 20 minutes before being transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate. The organics were then combined, washed with brine, dried with sodium sulfate, decanted, and concentrated in vacuo. Purification by column chromatography on silica gel (1:4 ethyl acetate:hexanes) to provide **67** (520 mg, 88%): oil, ¹H-NMR (400 MHz;

CDCl₃): δ 8.27 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.58 (dd, J = 8.3, 2.3 Hz, 1H), 7.48 (td, J = 7.4, 1.0 Hz, 1H), 7.34 (dt, J = 18.7, 6.5 Hz, 3H), 5.05 (s, 1H), 1.36 (s, 9H), 0.98 (s, 9H). ¹³C-NMR (101 MHz; CDCl₃): δ 193.01 (s, 1C), 177.32 (s, 1C), 152.25 (s, 1C), 142.50 (s, 1C), 140.11 (s, 1C), 138.89 (s, 1C), 134.72 (s, 1C), 133.75 (s, 1C), 131.79 (s, 1C), 130.09 (s, 1C), 129.30 (s, 1C), 127.89 (s, 1C), 127.86 (s, 1C), 127.64 (s, 1C), 55.03 (s, 1C), 41.33 (s, 1C), 35.29 (s, 1C), 31.63 (s, 1C), 29.46 (s, 1C), 26.90 (s, 1C).

1-(2-(*tert*-butyl)-11-hydroxy-11-(1*H*-tetrazol-5-yl)-6,11-dihydro-5*H*-dibenzo[*b,e*]azepin-5-yl)-2,2-dimethylpropan-1-one (68)



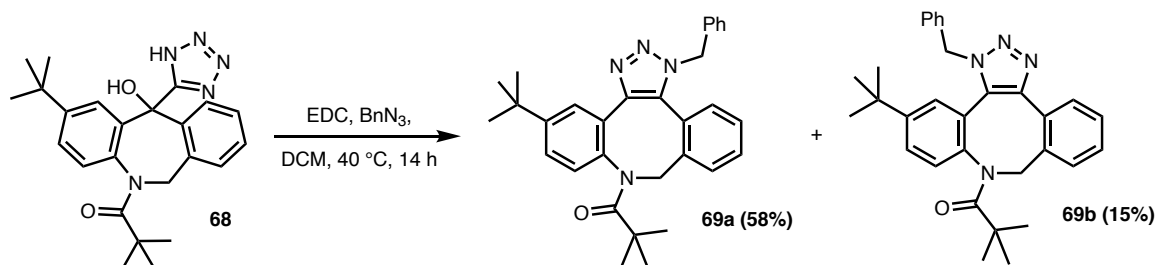
To a flame dried flask under nitrogen, the pivalamide **67** (520 mg, 1.49 mmol, 1 equiv.) and morpholinotetrazole **56** (755 mg, 4.46 mmol, 3 equiv.) were added and dissolved in anhydrous THF (20 mL). The solution was cooled to -78 °C (CO₂:acetone). A freshly prepared solution of LiHMDS (797 mg, 4.76 mmol, 3.2 equiv.) in THF (5 mL) was added dropwise slowly with continuous stirring. The reaction was then kept at -78 °C for 2 hours before being allowed to slowly reach room temperature overnight. Upon completion, the reaction was then concentrated, and the residue dissolved in 1 M HCl. The solution was then stirred for an hour before being transferred to a separatory funnel. The acidic layer was then extracted with ethyl acetate. The organics were then dried with sodium sulfate, decanted, and concentrated in vacuo. The product was purified by column chromatography on silica gel (1:1 acetone:hexanes) to provide **68** as a mixture of diastereomers (420 mg, 67%): white solid, FTIR_{max} 3338, 3201, 3133, 3067, 2976, 2951, 2942, 2868, 1735, 1729, 1657, 1619, 1692, 1508, 1479, 1448, 1398, 1364, 1295, 1274, 1230, 1216, 1198, 1114, 1097, 1021, 972, 929, 915, 891, 868, 749, 734, 697, 662, 634, 612, 585, 572, 527, 514, 502, 486, 469, 454, 446, 440, 425, 413, 405 cm⁻¹; ¹H-NMR (500 MHz; CDCl₃): δ 9.21 (s, 1H), 8.18-8.09 (m, 3H), 7.45 (dd, J = 8.2, 2.3 Hz, 1H), 7.32 (ddd, J = 8.6, 6.1, 2.2 Hz, 3H), 7.28-7.25 (m, 1H), 7.13 (d, J = 8.2 Hz, 1H), 5.62-5.59 (m, 1H), 4.49-4.46 (m, 1H), 1.33 (s, 9H), 0.97 (s, 9H). ¹³C-NMR (126 MHz; CDCl₃): δ 161.39 (s, 1C), 150.75 (s, 1C), 143.26 (s, 1C), 135.36 (s, 1C), 132.86 (s, 1C), 129.29 (s, 1C), 128.94 (s, 1C), 128.80 (s, 1C), 128.65 (s, 1C), 128.61 (s, 1C), 127.02 (s, 1C), 126.37 (s, 1C), 125.55 (s, 1C), 122.40 (s, 1C), 71.96 (s, 1C), 53.30 (s, 1C), 35.01 (s, 1C), 31.18 (s, 1C), 29.83 (s, 1C), 27.45 (s, 1C). HRMS-ESI⁺ calculated for C₂₄H₃₀N₅O₂ [M+H]⁺: 420.2400, found 420.2395.

4-*tert*-Butyl-ADIBO (52)



4-*tert*-Butyl-ADIBO (52, 70%)

To an oven-dried vial was added the hydroxytetrazole **68** (42 mg, 0.1 mmol, 1 equiv.) and EDC (23 mg, 0.12 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where it was transferred to a column for purification by column chromatography on silica gel (1:4 hexanes:EtOAc) to provide **52** (24.2 mg, 70%): oil, $^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 7.68-7.67 (m, 1H), 7.42-7.29 (m, 6H), 5.27 (d, J = 13.6 Hz, 1H), 3.47 (d, J = 13.4 Hz, 1H), 1.38 (s, 9H), 0.88 (s, 9H). $^{13}\text{C-NMR}$ (126 MHz; CDCl_3): δ 179.35 (s, 1C), 151.92 (s, 1C), 150.73 (s, 1C), 149.23 (s, 1C), 132.67 (s, 1C), 129.26 (s, 1C), 128.41 (s, 1C), 127.83 (s, 1C), 125.85 (s, 1C), 125.08 (s, 1C), 124.28 (s, 1C), 123.72 (s, 1C), 123.22 (s, 1C), 116.19 (s, 1C), 109.17 (s, 1C), 57.71 (s, 1C), 41.64 (s, 1C), 35.16 (s, 1C), 31.70 (s, 1C), 29.61 (s, 1C). HRMS-ESI⁺ calculated for $\text{C}_{24}\text{H}_{28}\text{NO}$ $[\text{M}+\text{H}]^+$: 346.2171, found 346.2168.



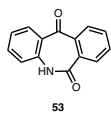
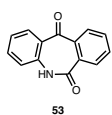
To an oven-dried vial was added the hydroxytetrazole **68** (42 mg, 0.1 mmol, 1 equiv.), benzyl azide (0.06 mL, 0.5 mmol, 5 equiv.) and EDC (23 mg, 0.12 mmol, 1.2 equiv.). The solids were dissolved in anhydrous DCM (1.5 mL). The reaction was then heated to 38 °C overnight to where it was transferred to a column for purification by column chromatography on silica gel (1:2 hexanes:EtOAc) to provide an inseparable mixture of regioisomers: **69a** and **69b** (35.1 mg, 73%): oil, FTIR_{max} 3058, 3017, 2985, 2973, 2943, 2871, 2845, 2833, 1649, 1517, 1496, 1484, 1459, 1341, 1383, 1369, 1286, 1253, 1188, 1139, 1079, 1039, 1032, 1012, 1009, 979, 906, 832, 777, 762, 732, 699, 641, 615, 584, 572, 543, 489, 479, 428, 420, 414, 408 cm^{-1} ; $^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 7.80 (d, J = 7.4 Hz,), 7.68 (d, J = 2.0 Hz, 1H), 7.54-7.49 (m, 1H), 7.45-7.41 (m, 1H), 7.40-7.27 (m, 5H), 7.25-7.14 (m, 2H), 7.00 (d, J = 7.7 Hz,), 6.94 (d, J = 1.6 Hz,), 5.93-5.81 (m, 1H), 5.72-5.59 (m, 1H), 5.22-5.19 (m,), 4.90-4.84 (m,), 4.41-4.36 (m,), 1.34 (s, 4H), 1.09 (d, J = 8.2 Hz, 9H), 0.83 (d, J = 0.3 Hz, 3H). $^{13}\text{C-NMR}$ (126 MHz; CDCl_3): δ 178.65 (s, 1C), 177.58 (s, 1C), 152.73 (s, 1C), 151.38 (s, 1C), 148.57 (s, 1C), 144.72 (s, 1C), 144.18 (s, 1C), 143.67 (s, 1C), 141.49 (s, 1C), 140.11 (s, 1C), 139.48 (s, 1C), 139.38 (s, 1C), 137.06 (s, 1C), 136.85 (s, 1C), 135.77 (s, 1C), 135.55 (s, 1C), 134.52 (s, 1C), 133.61 (s, 1C), 133.05 (s, 1C), 132.71 (s, 1C), 132.37 (s, 1C), 131.66 (s, 1C), 130.32 (s, 1C), 129.73 (s, 1C), 129.60 (s, 1C), 129.39 (s, 1C), 129.27 (s, 1C), 129.23 (s, 1C), 129.08 (s, 1C), 129.01 (s, 1C), 128.70 (s, 1C), 128.65 (s, 1C),

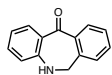
128.62 (s, 1C), 128.54 (s, 1C), 128.41 (s, 1C), 128.15 (s, 1C), 128.07 (s, 1C), 127.93 (s, 1C), 127.83 (s, 1C), 127.65 (s, 1C), 127.49 (s, 1C), 127.34 (s, 1C), 127.30 (s, 1C), 127.18 (s, 1C), 127.13 (s, 1C), 126.92 (s, 1C), 126.44 (s, 1C), 124.93 (s, 1C), 56.80 (s, 1C), 56.18 (s, 1C), 53.08 (s, 1C), 52.11 (s, 1C), 35.24 (s, 1C), 34.94 (s, 1C), 31.69 (s, 1C), 31.35 (s, 1C), 29.57 (s, 1C), 28.69 (s, 1C). HRMS-ESI⁺ calculated for C₃₁H₃₅N₄O [M+H]⁺: 479.2811, found 479.2810.

3. References

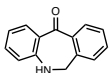
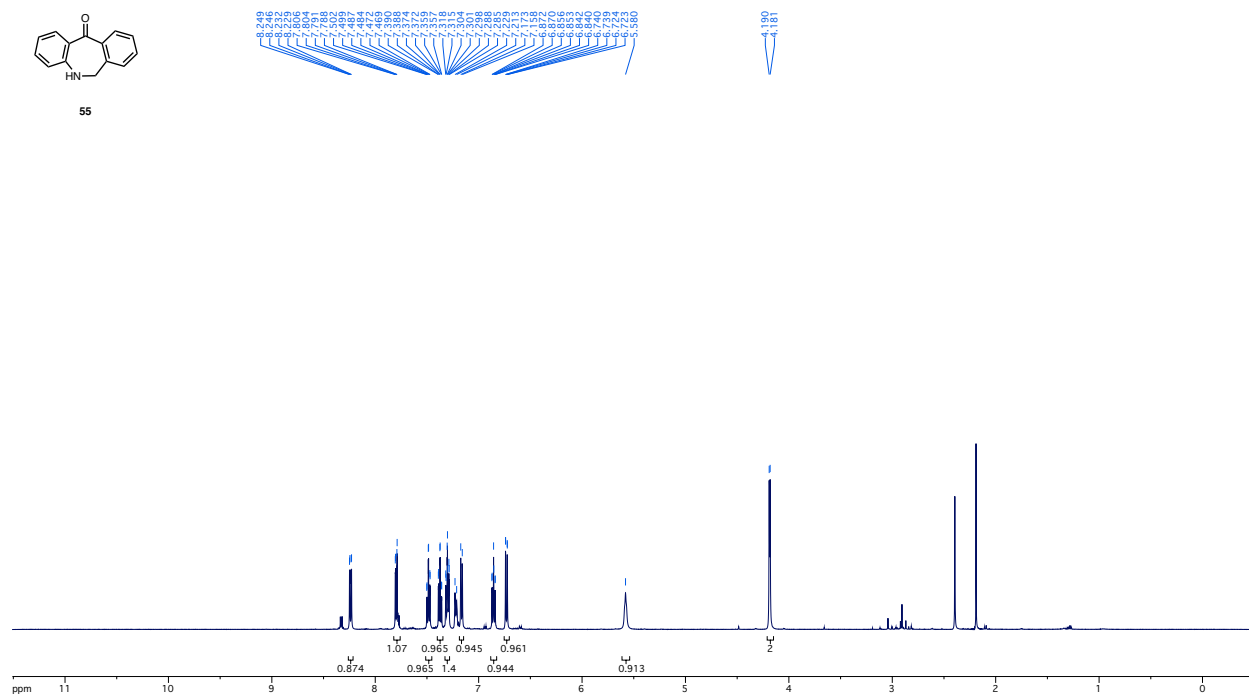
- (1) Rapid Chromatographic Technique for Preparative Separations With Moderate Resolution Still, W. C.; Kahn, M.; Mitra, A. *The Journal of Organic Chemistry* **1978**, *43*, 2923-2925.
- (2) Tetracyclic Derivatives of the 11-Oxodibenzo[b,e]azepnic Series Irurre, P. *Afinidad* **1988**, *45*, 443-446.

Appendix B, ADIBO and its Analogs

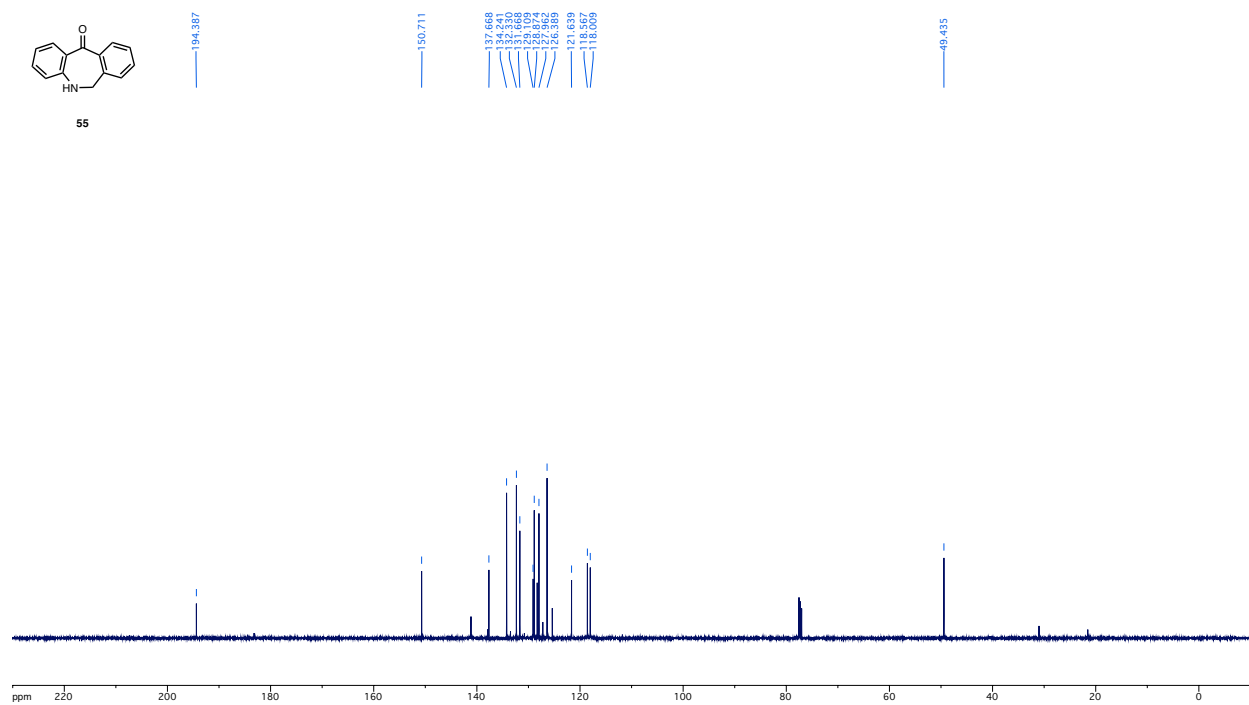


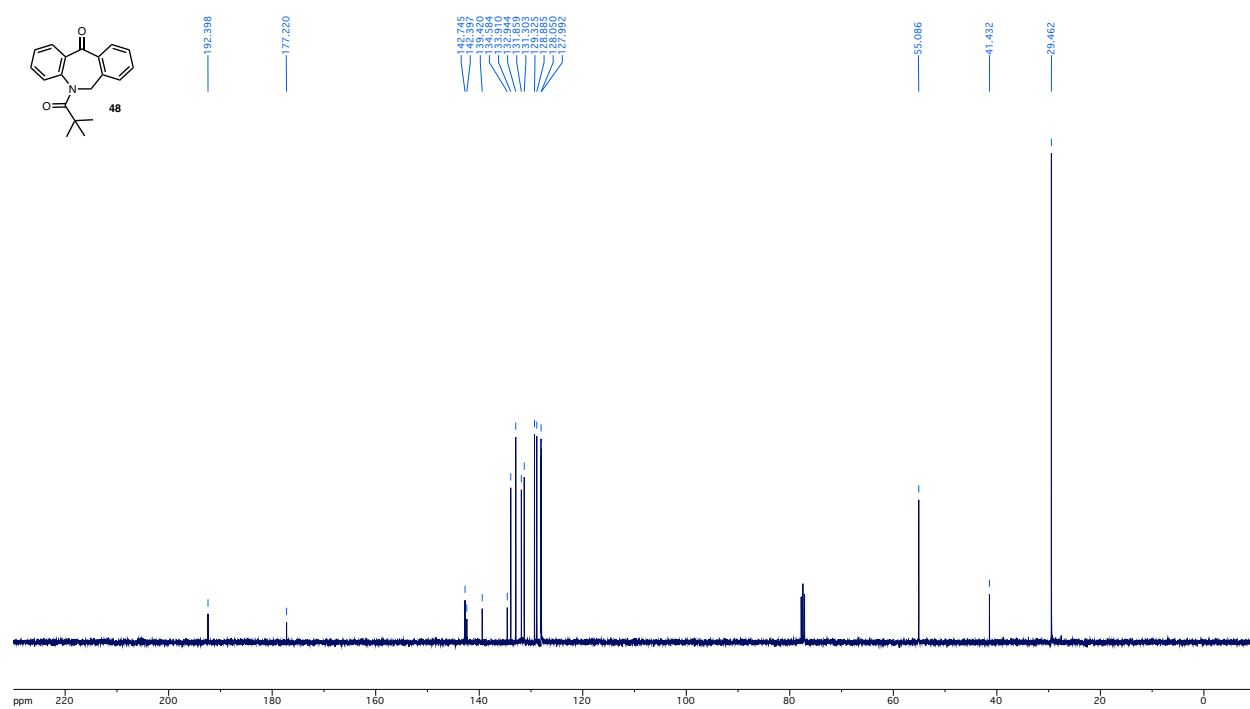
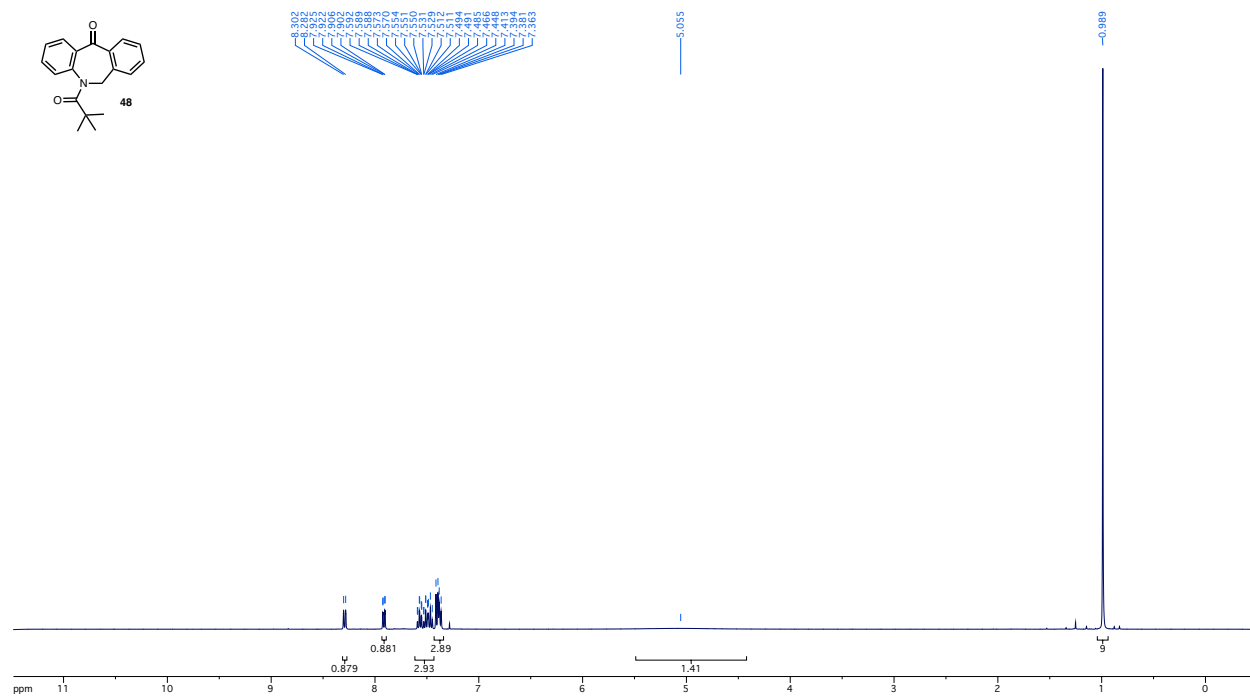


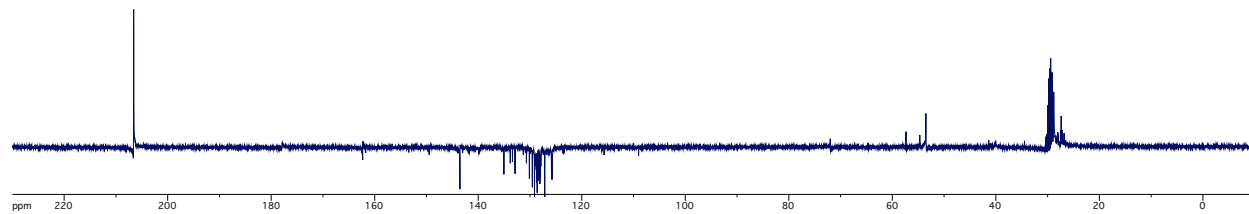
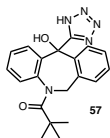
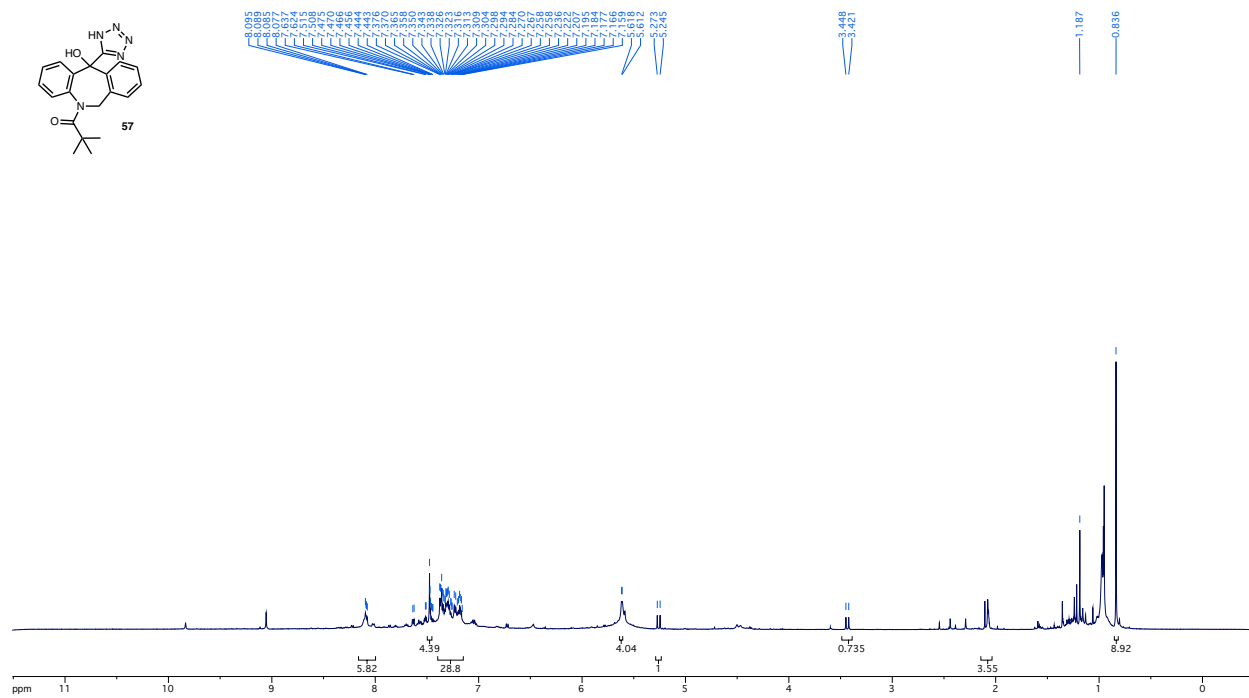
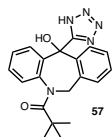
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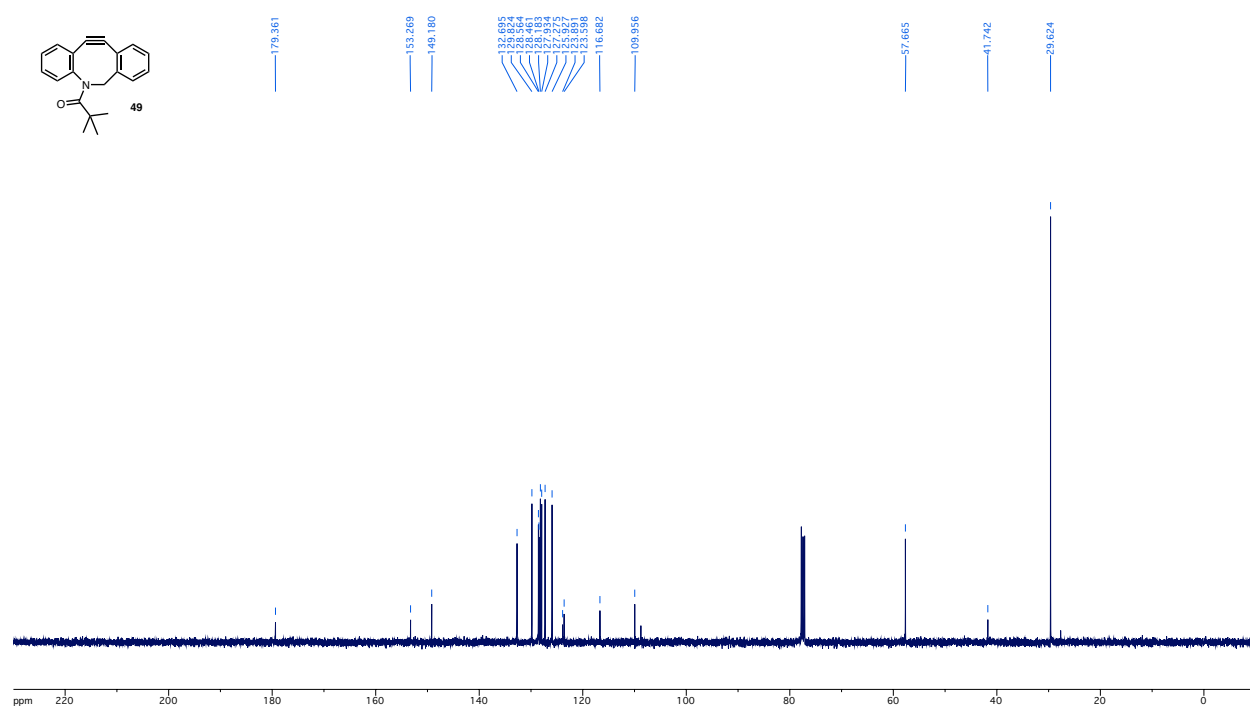
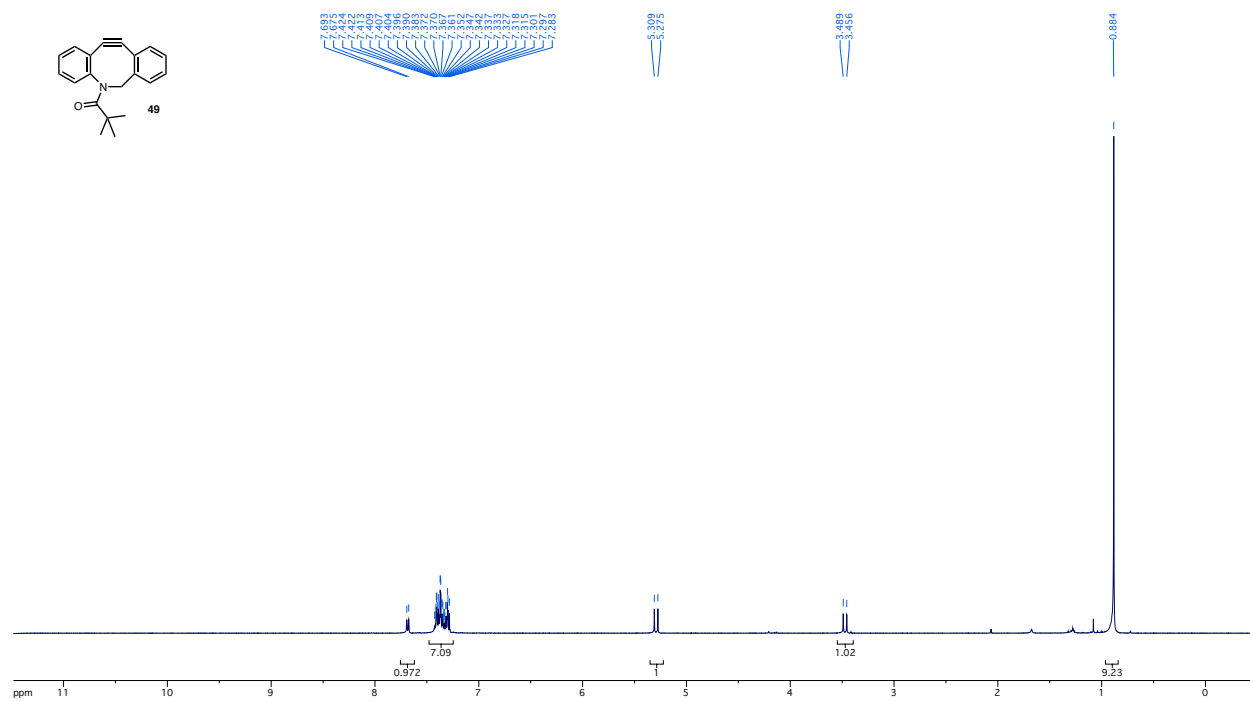


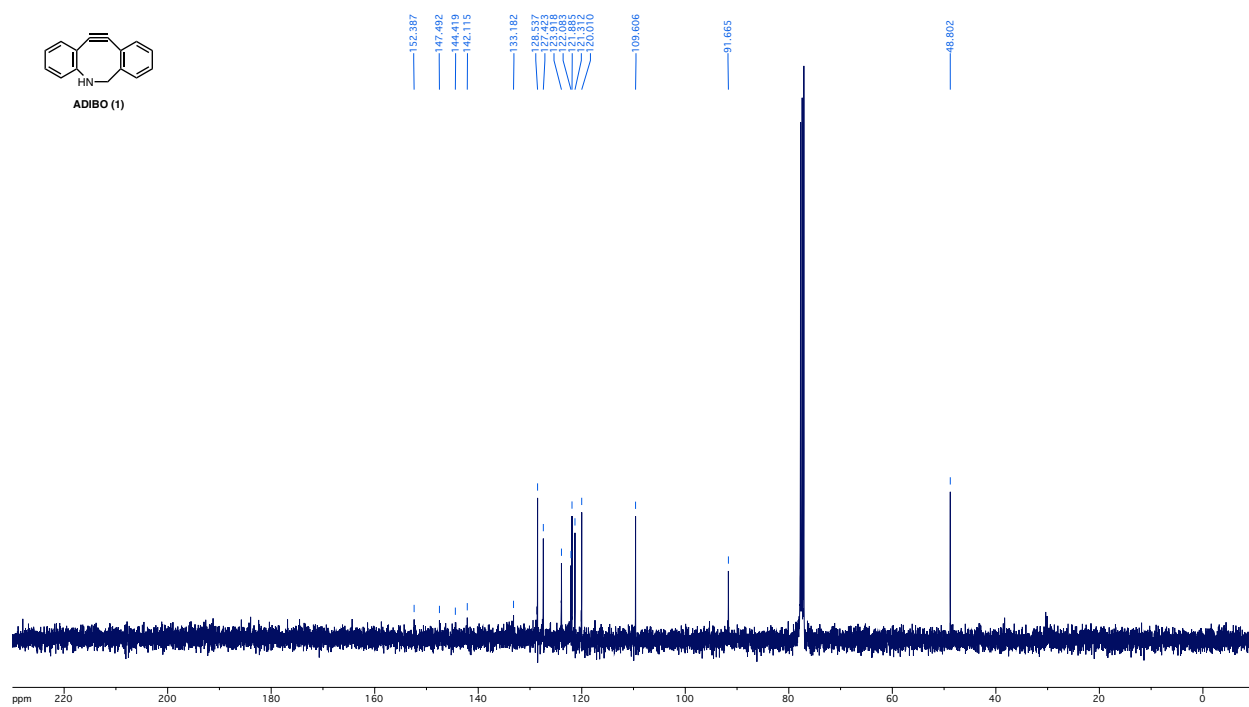
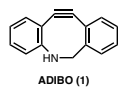
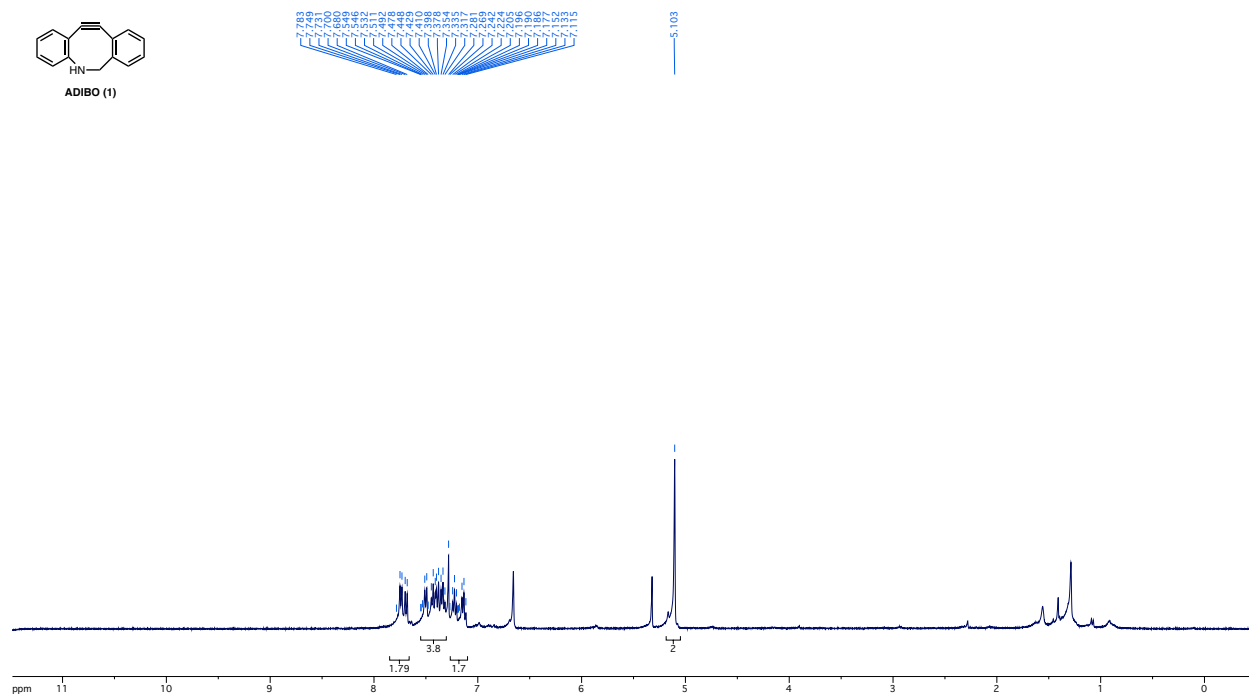
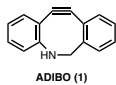
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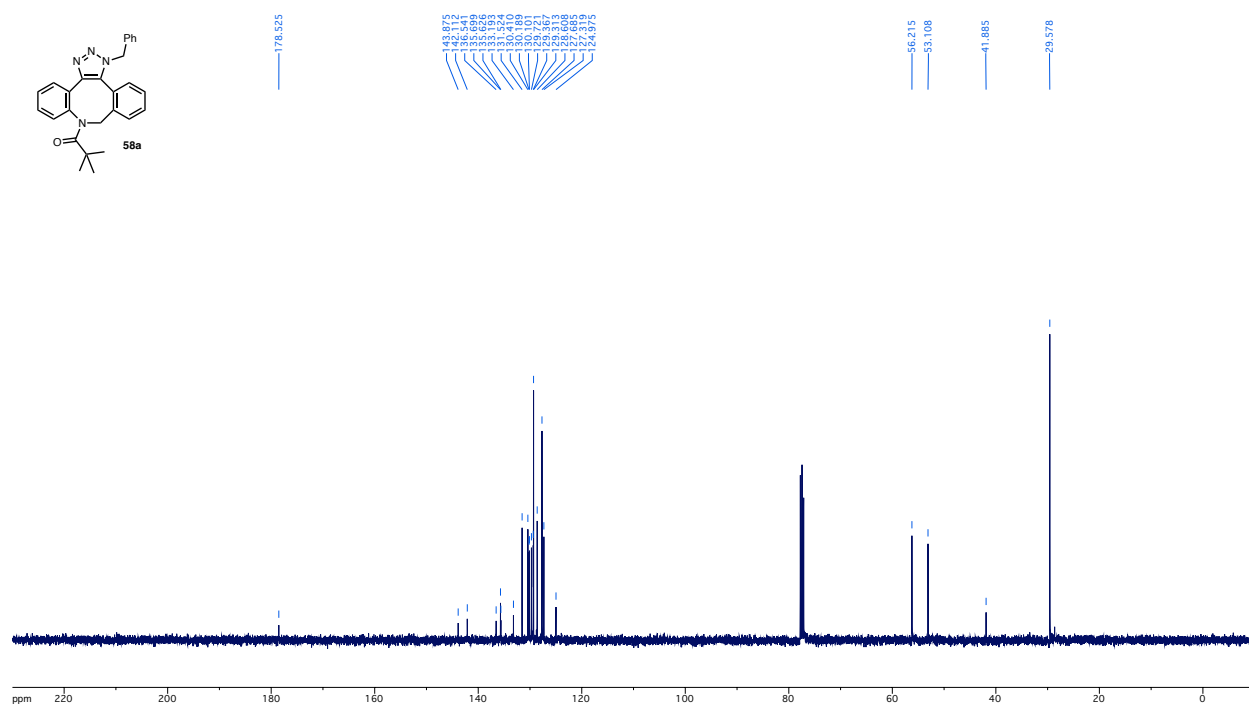
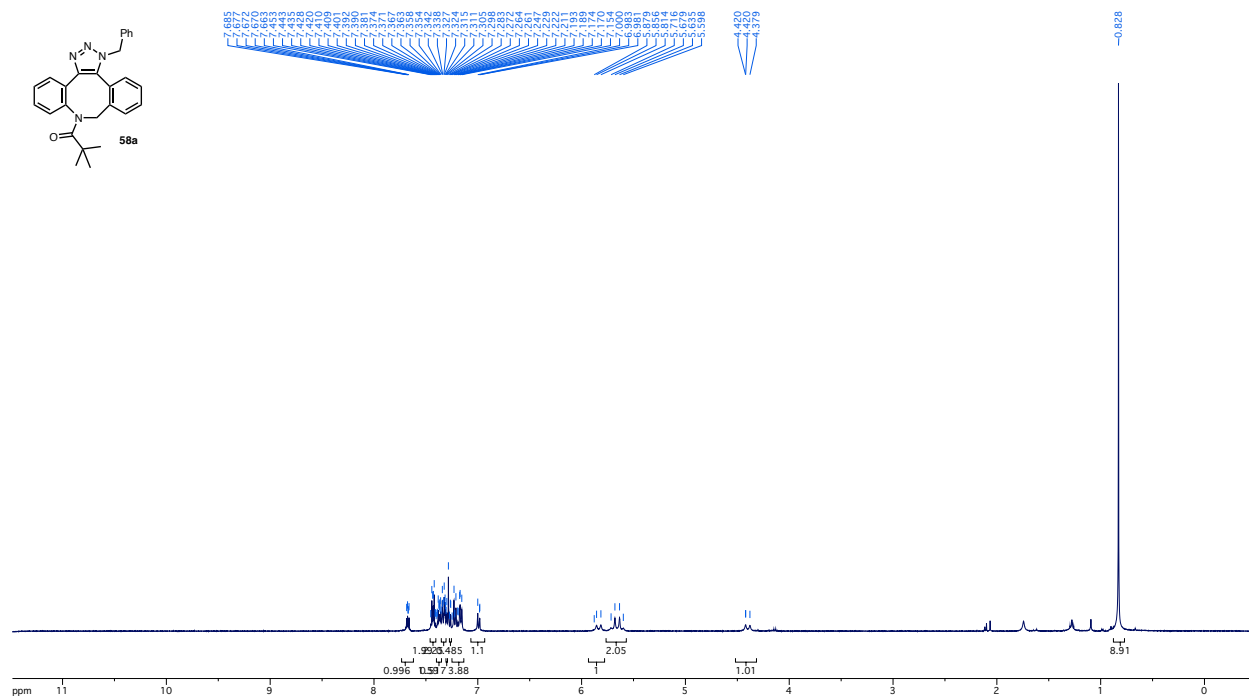


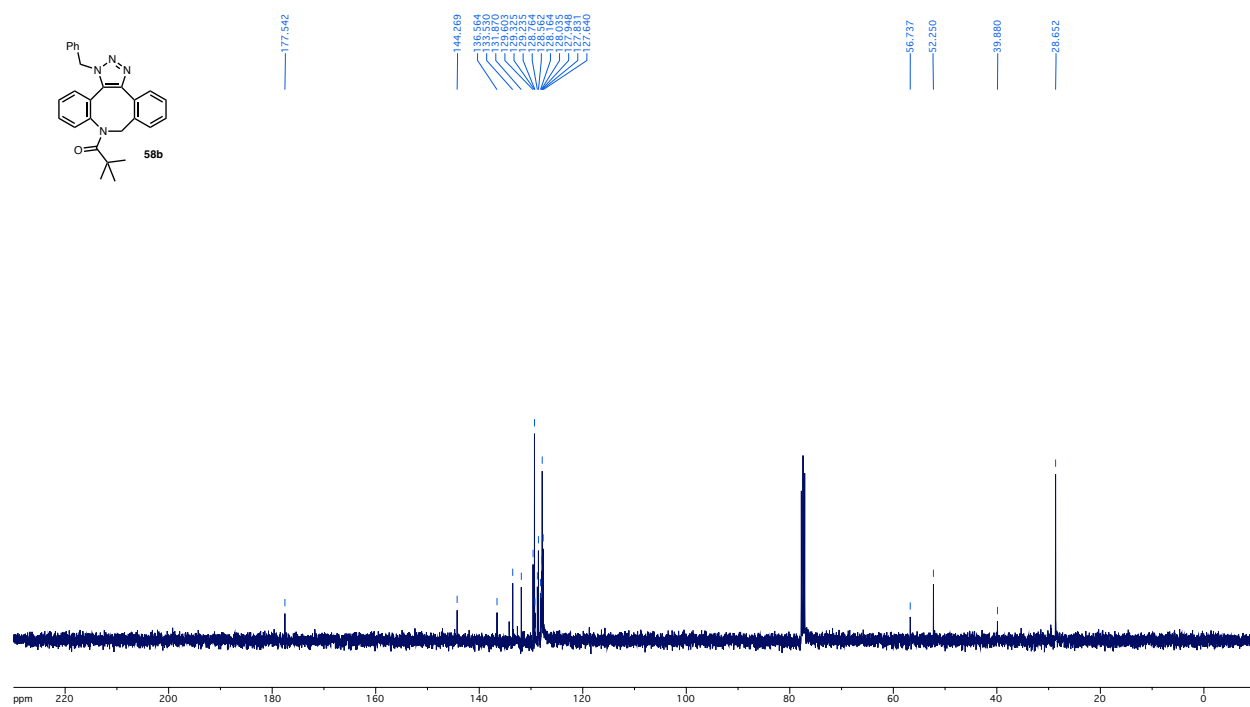
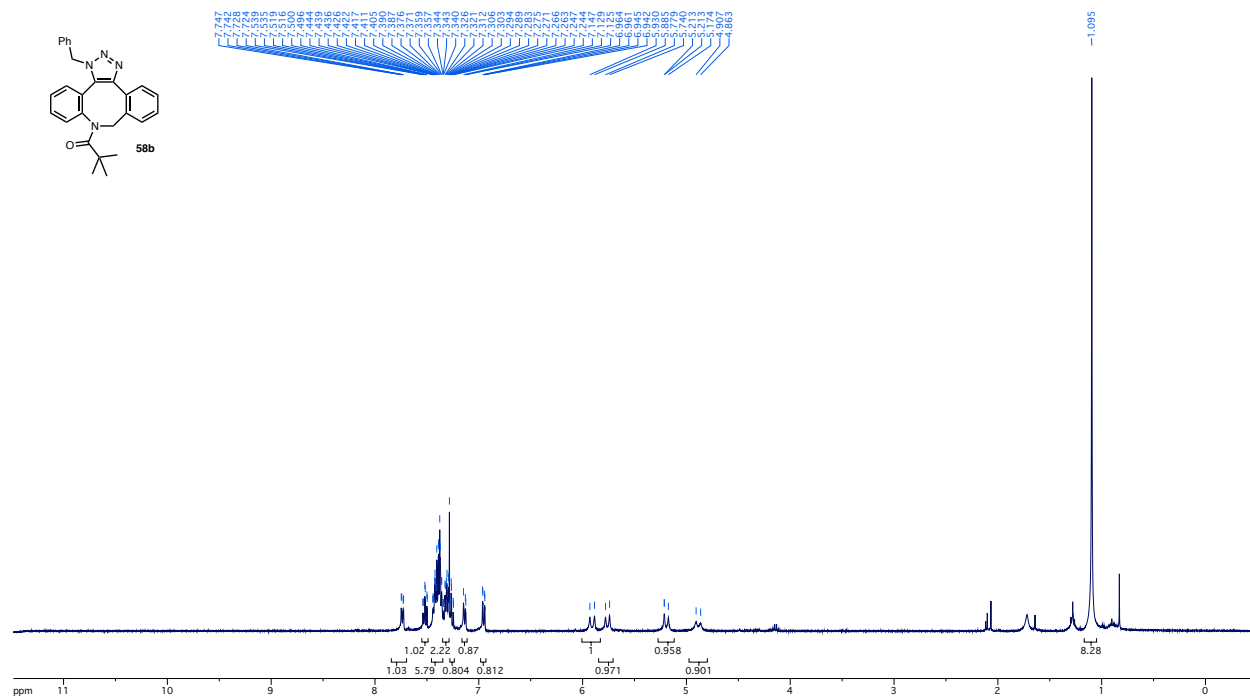


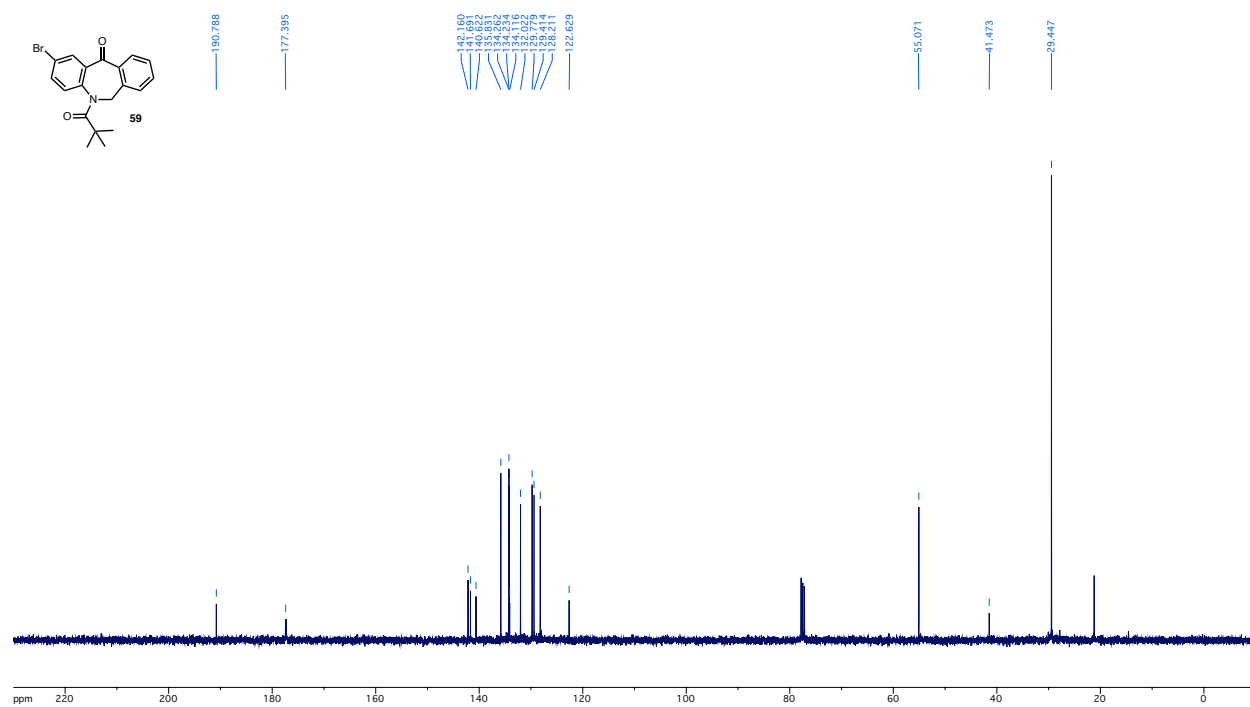
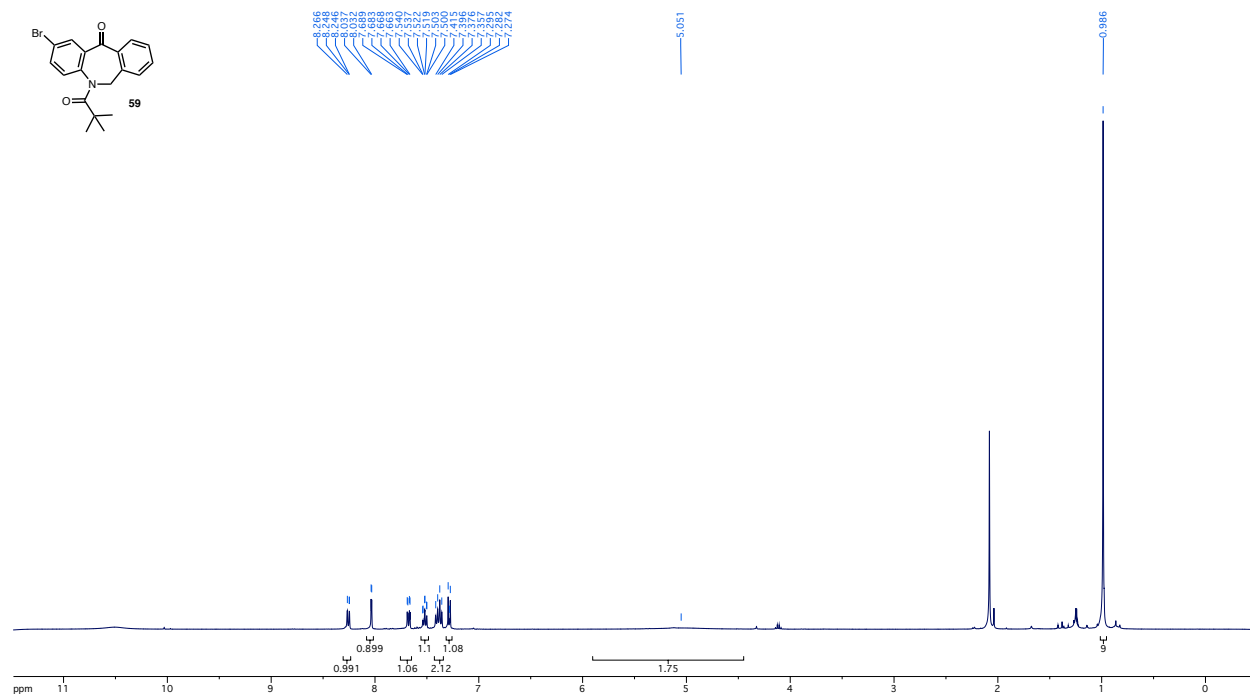


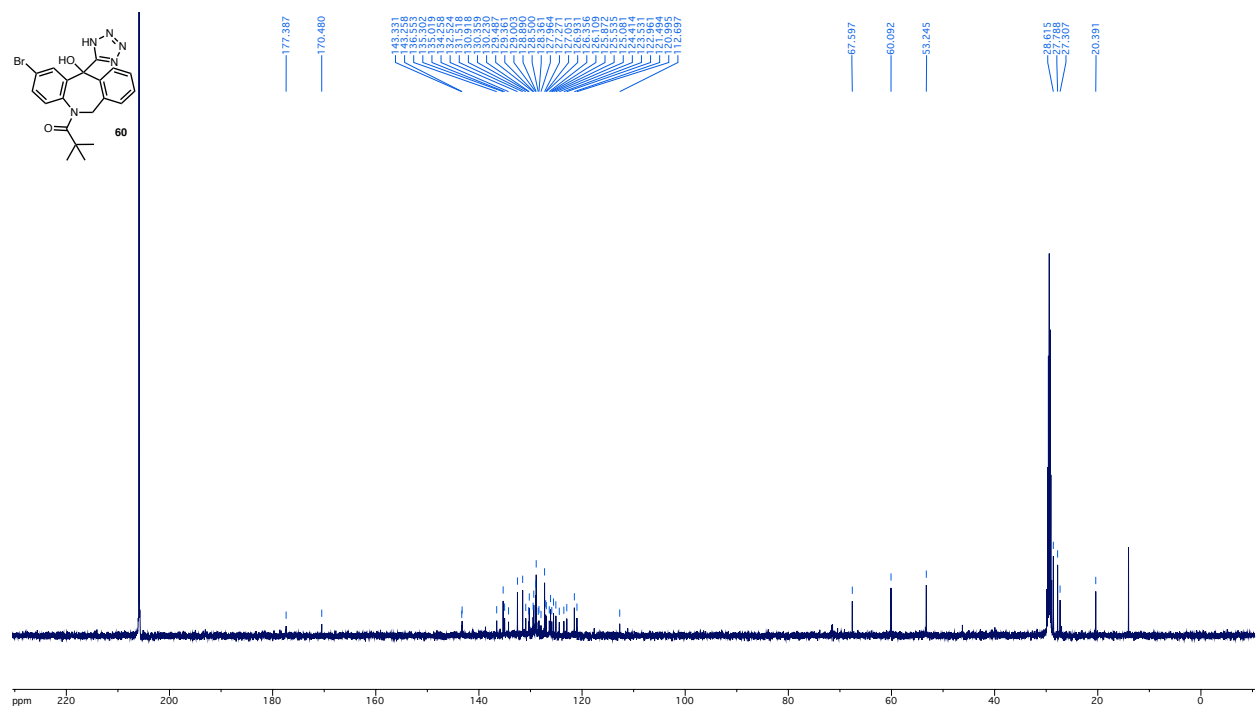
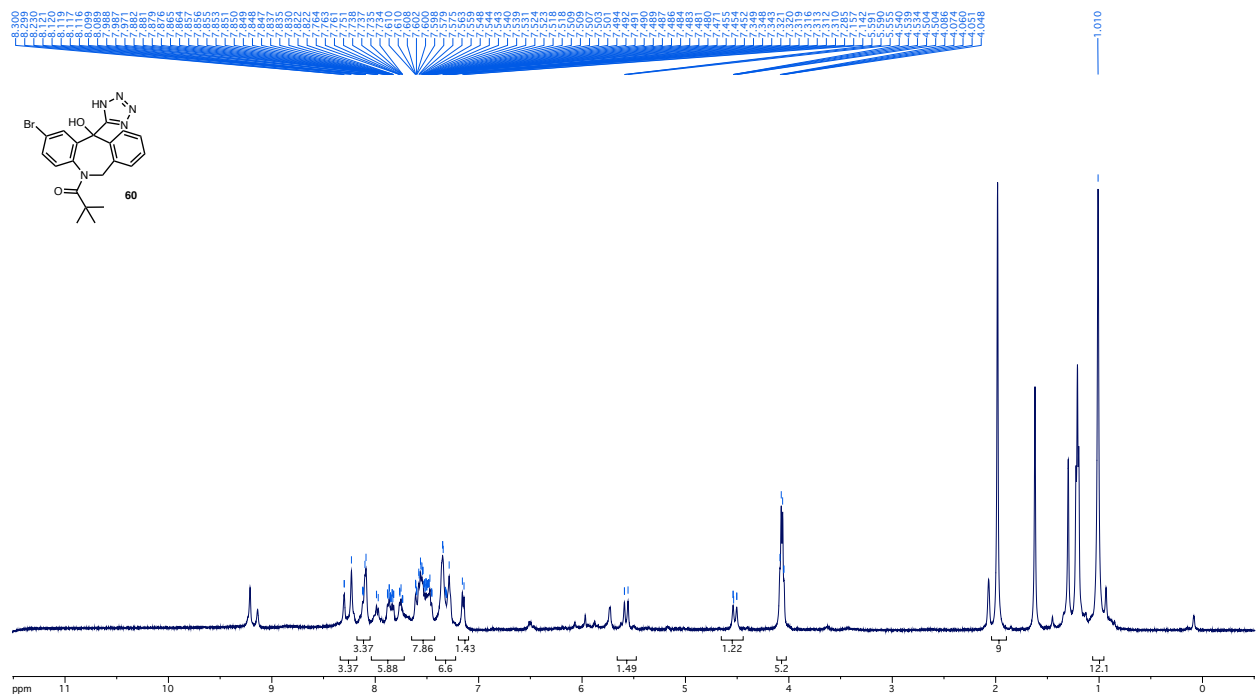


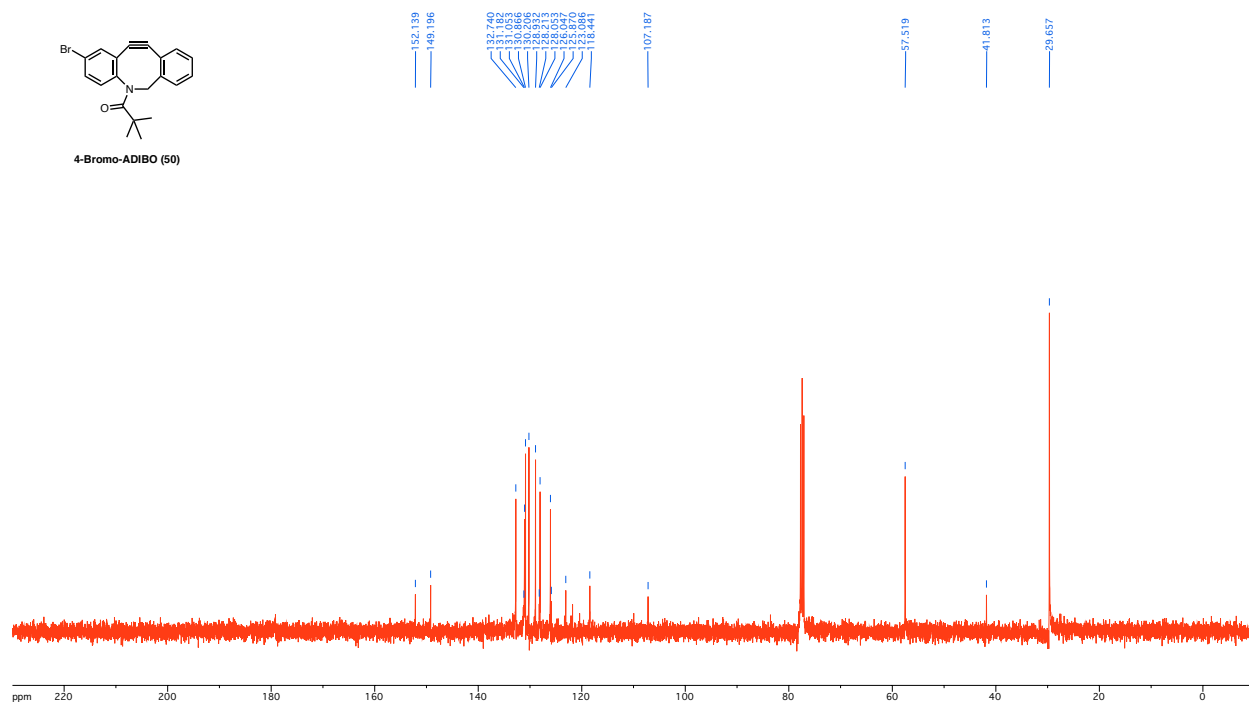


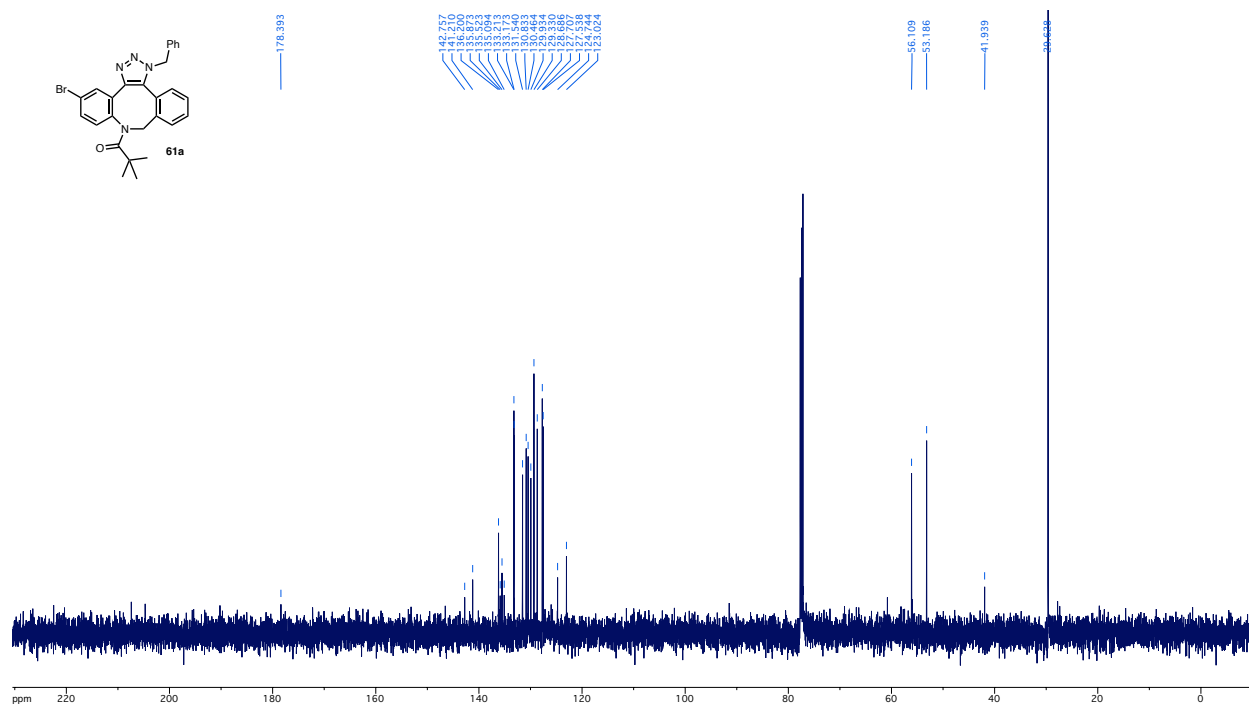
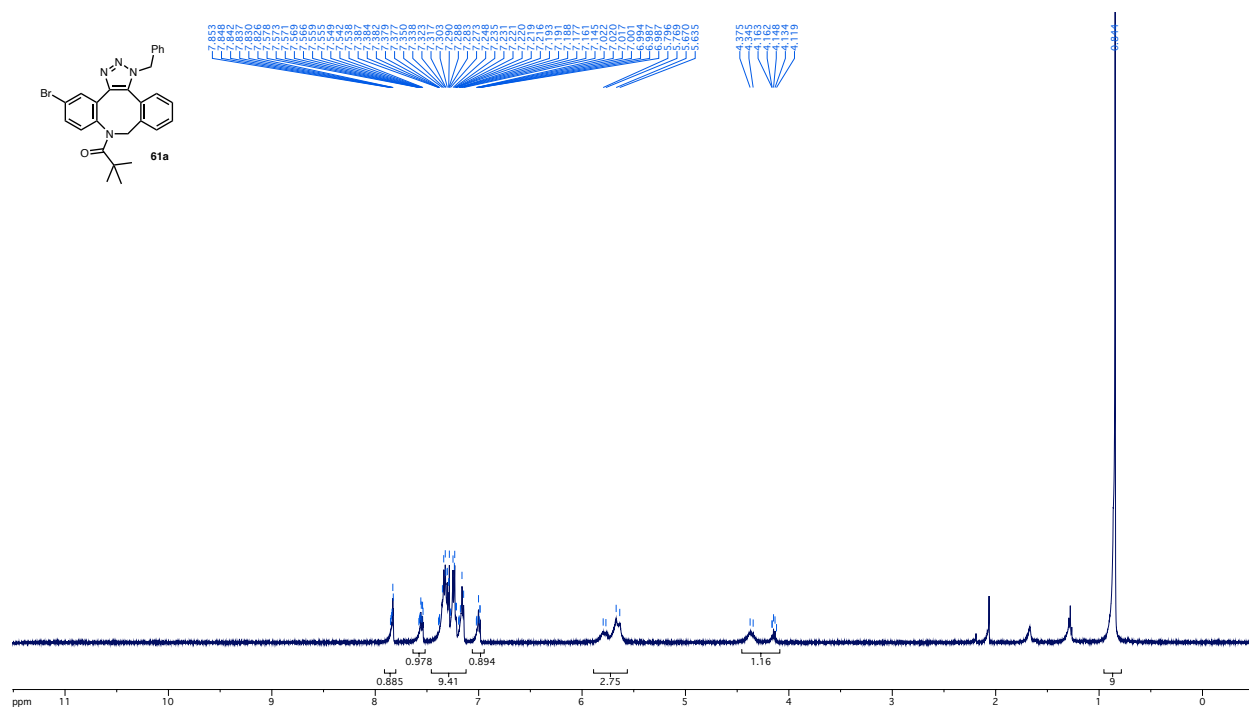


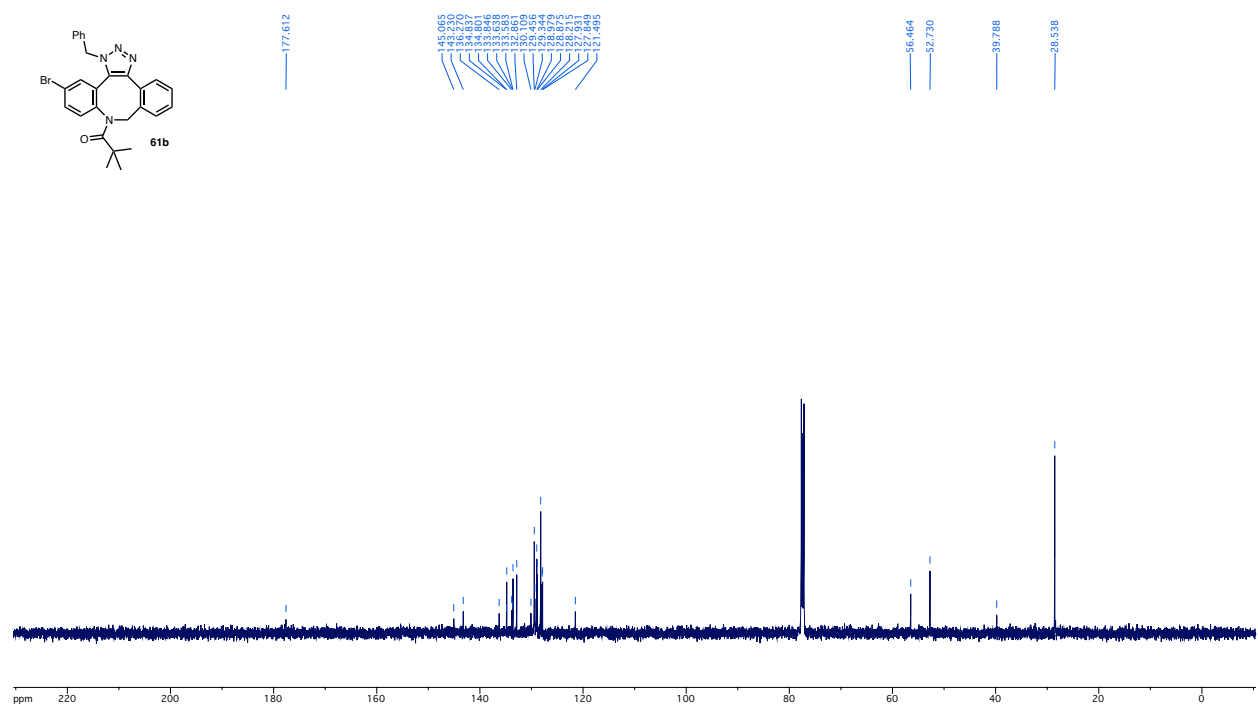
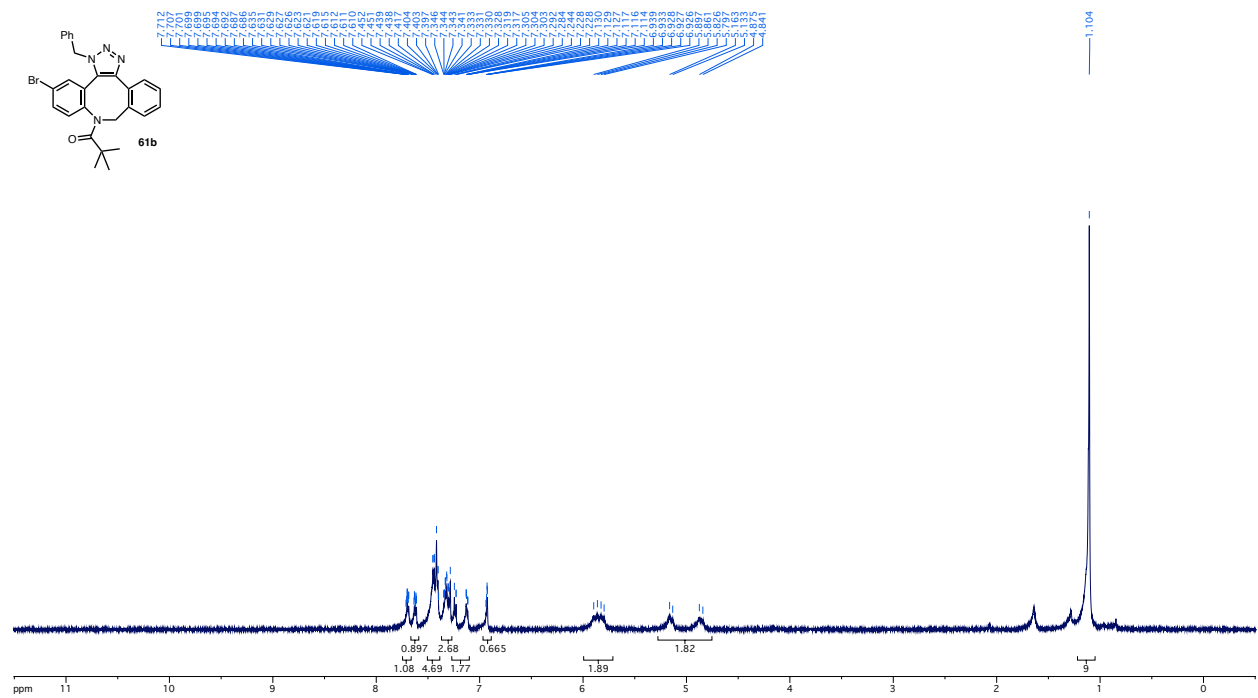


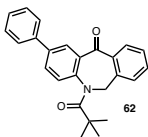
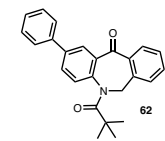


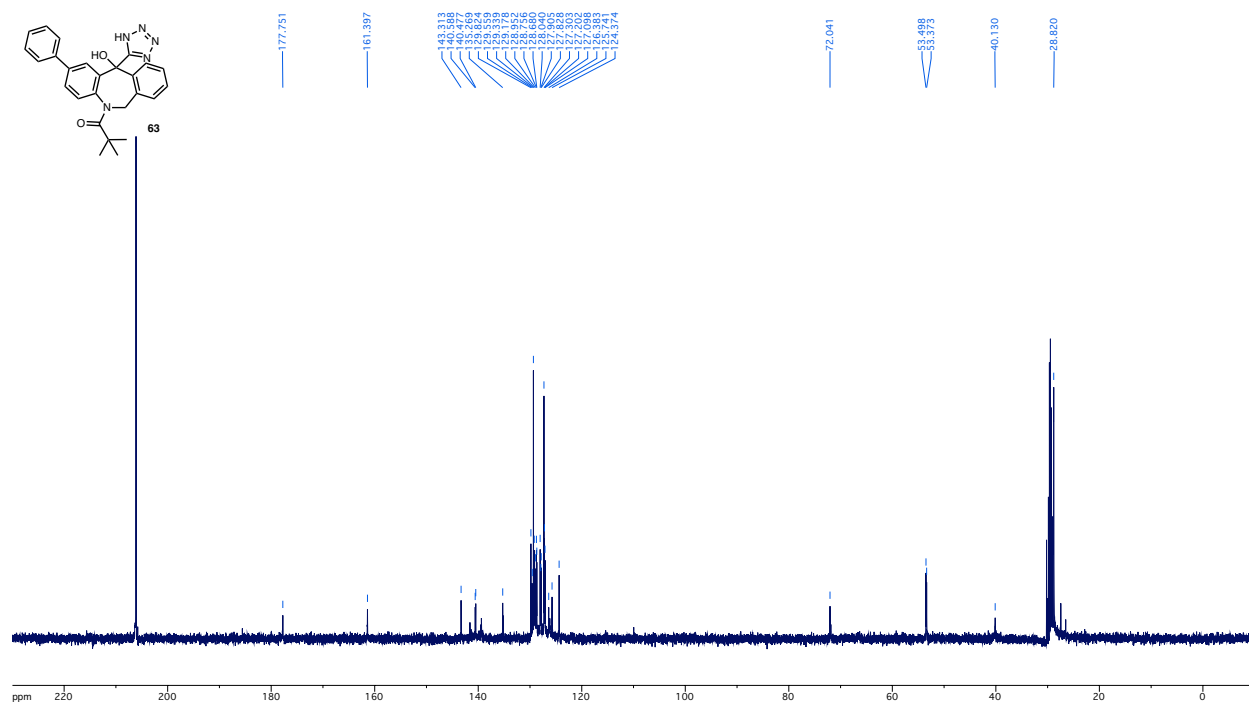


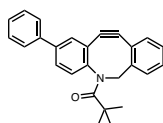




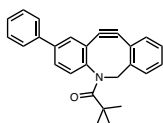
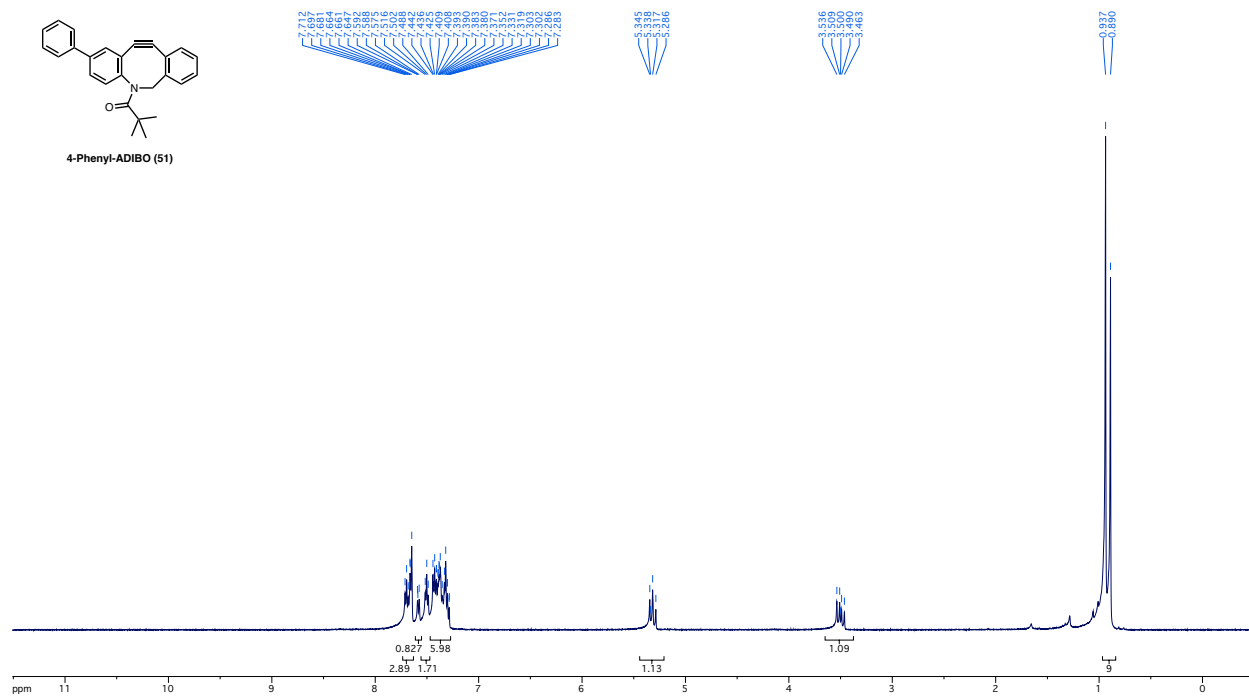




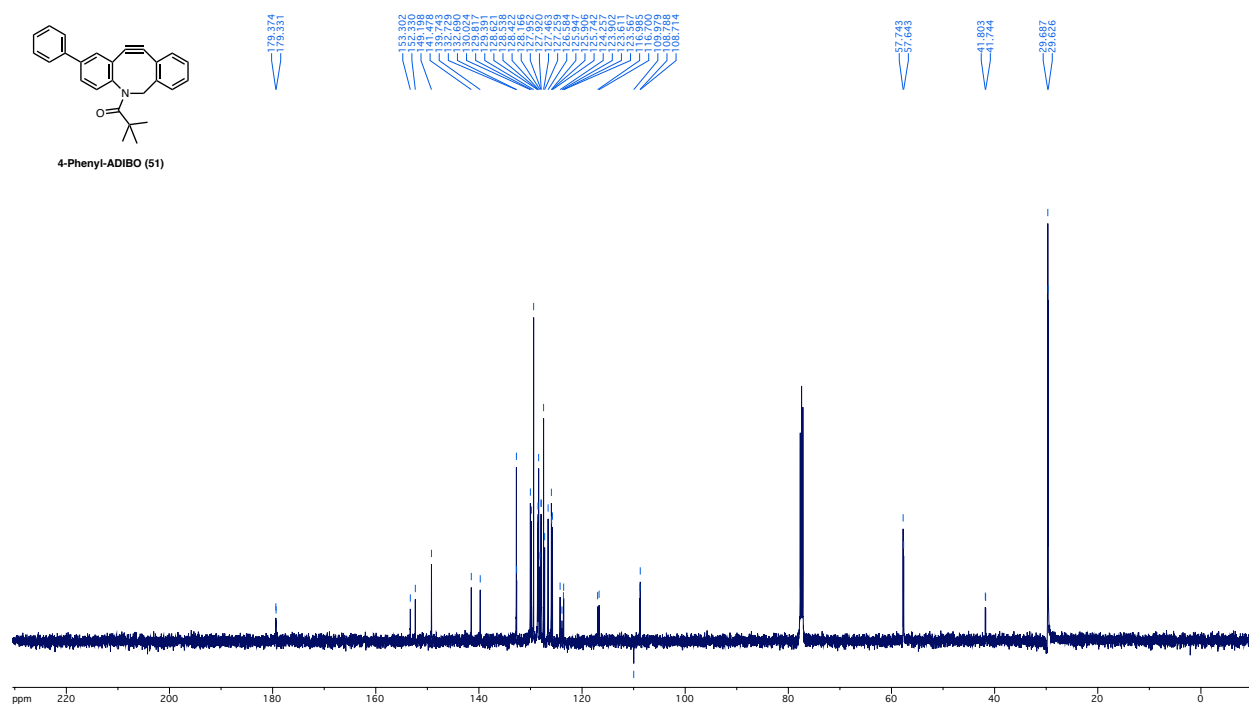


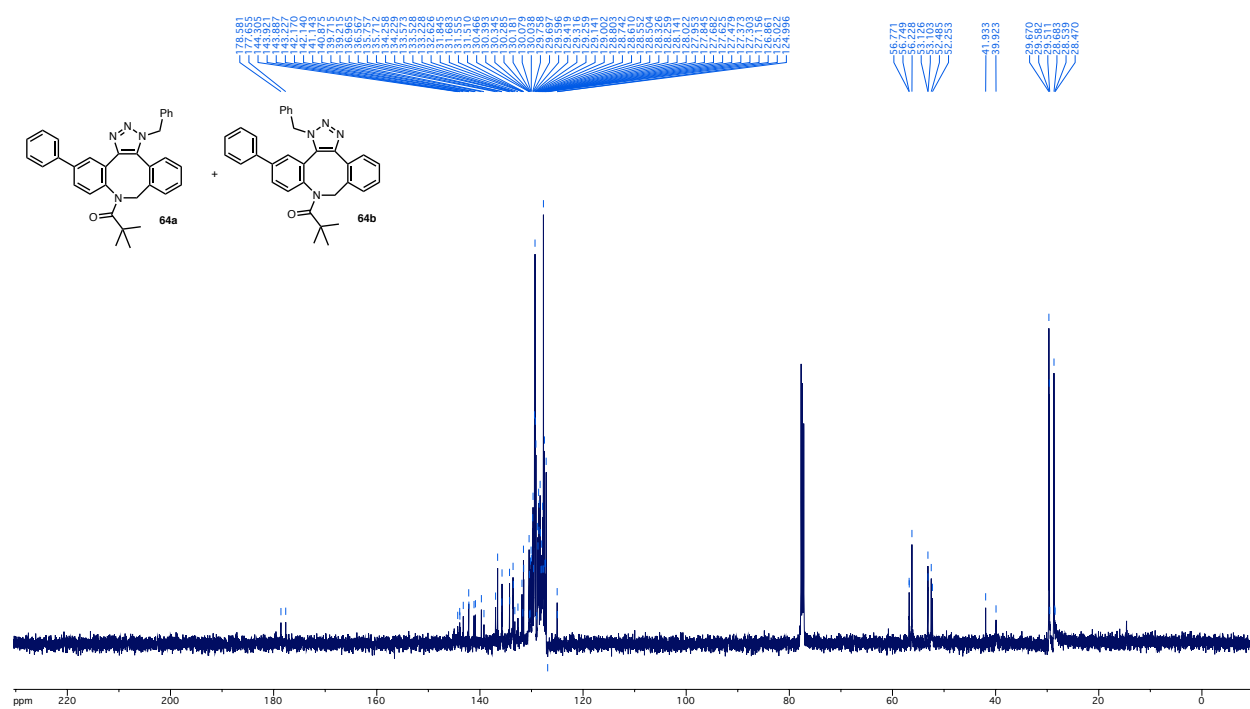
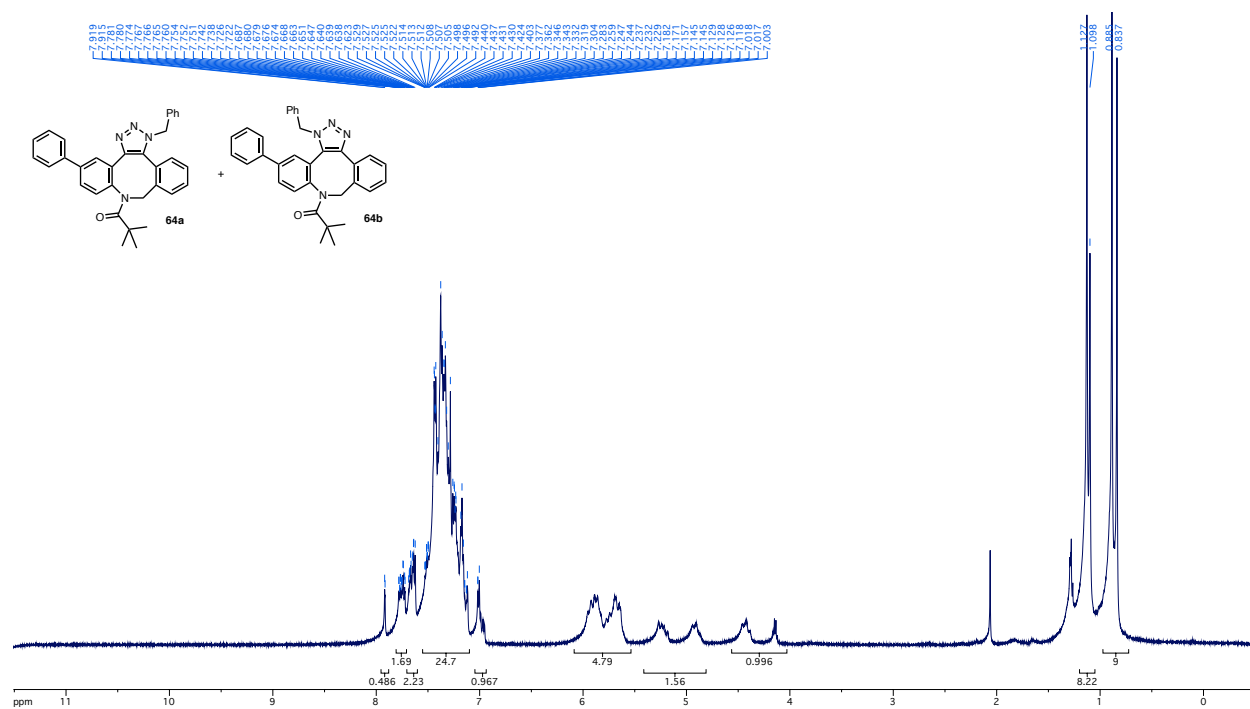


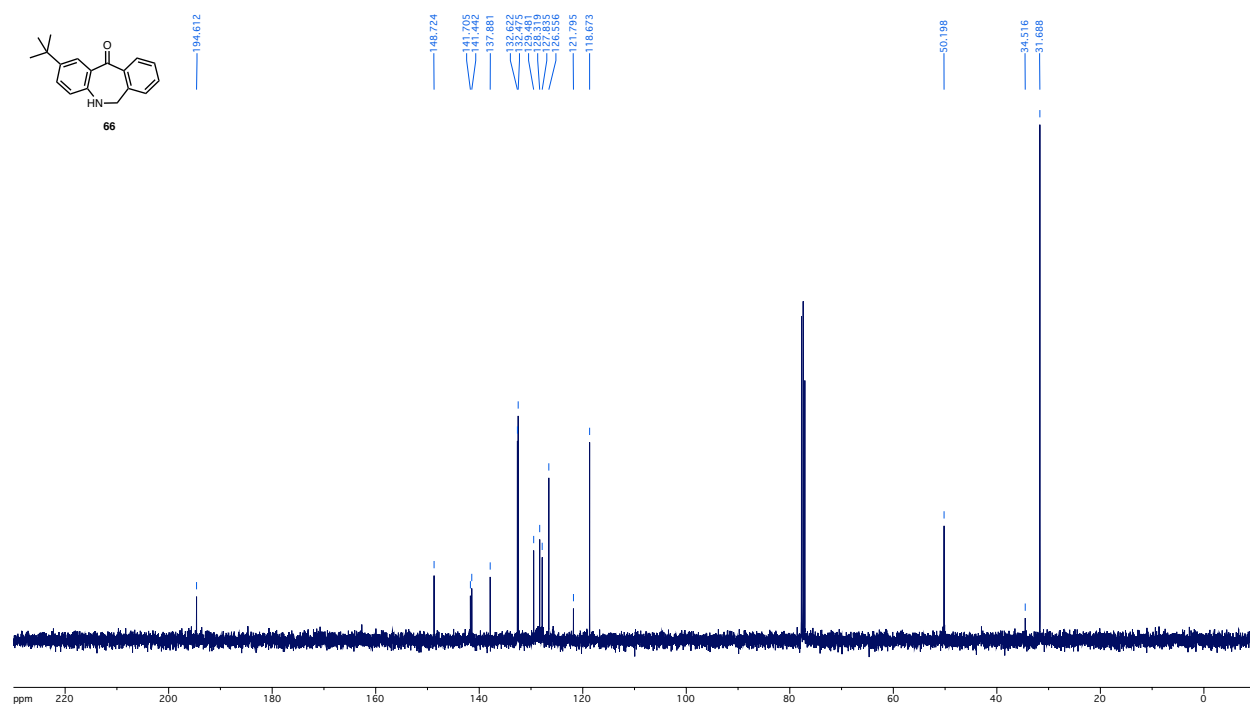
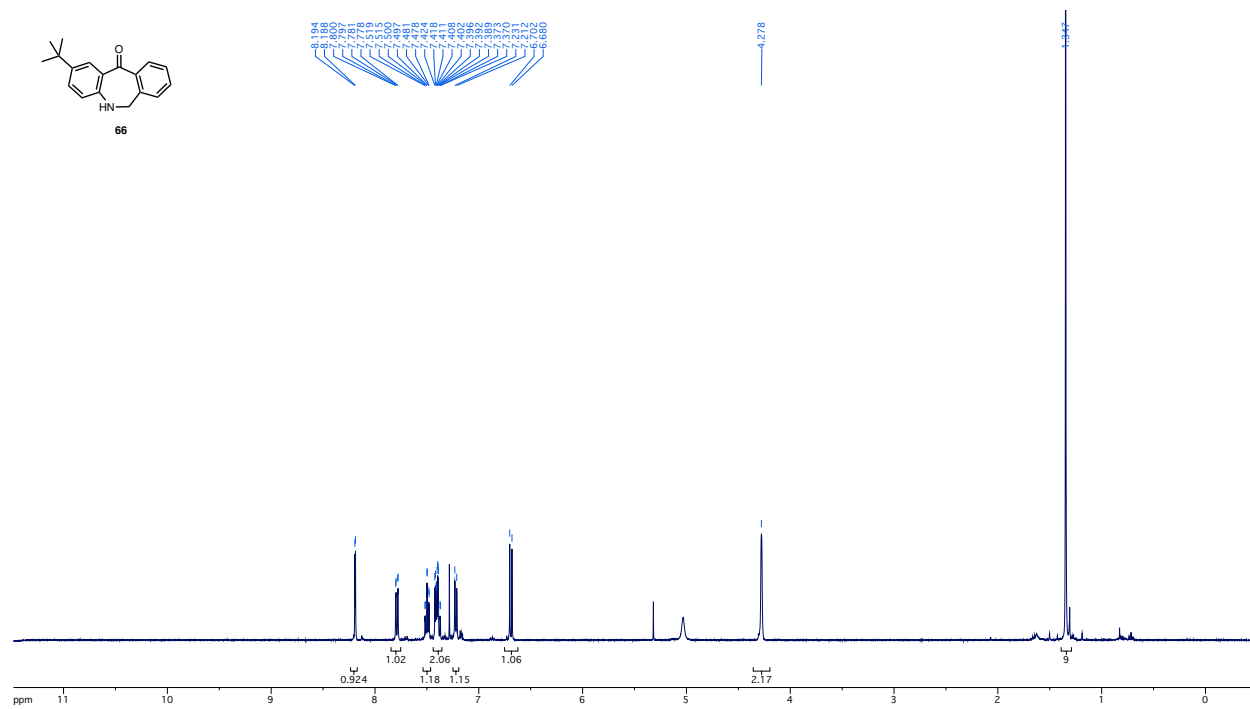
4-Phenyl-ADIBO (51)

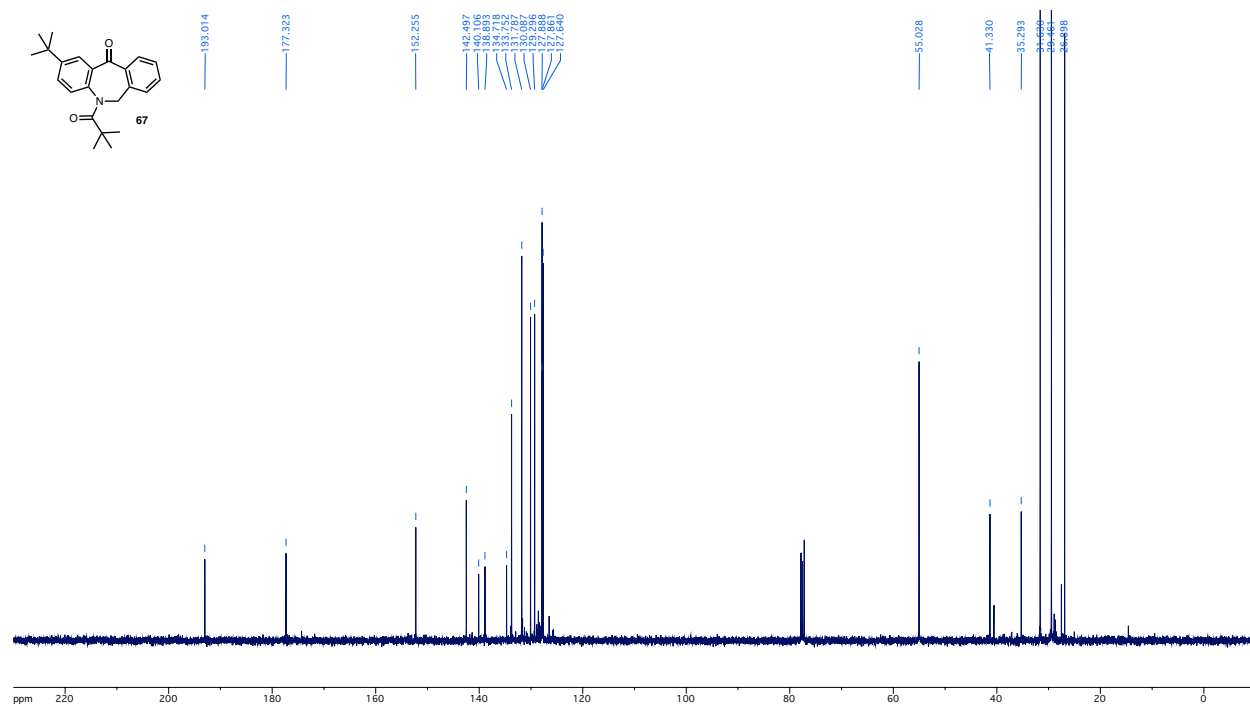
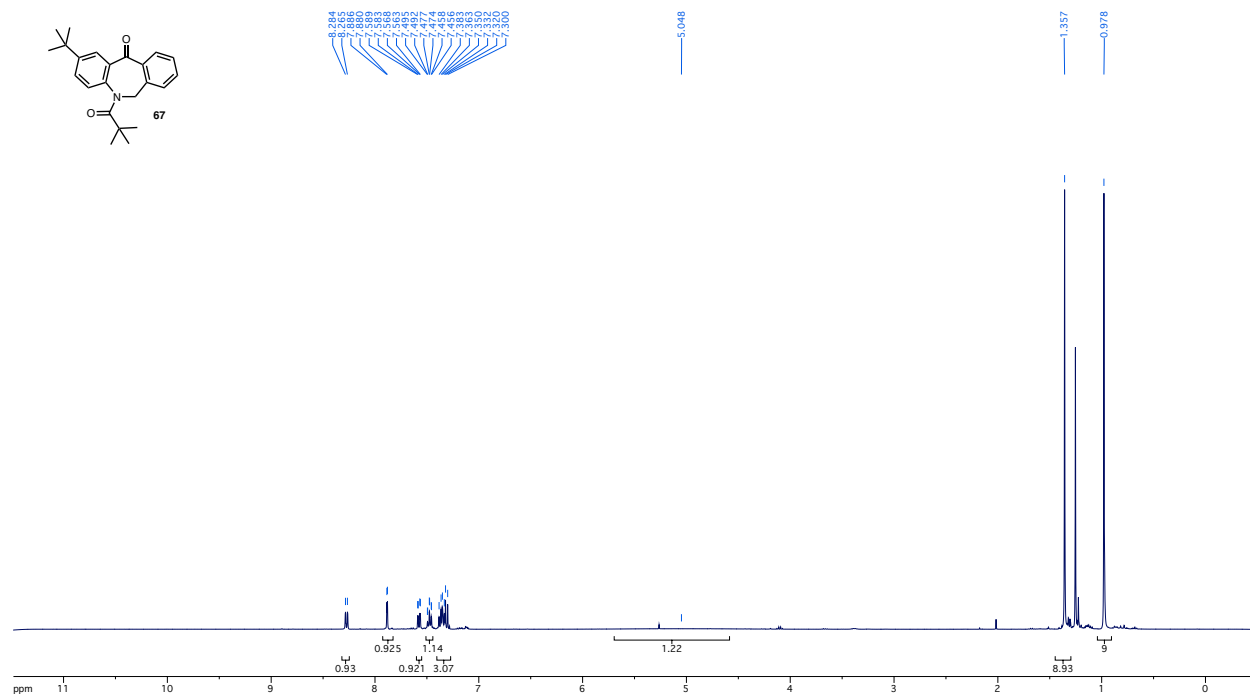


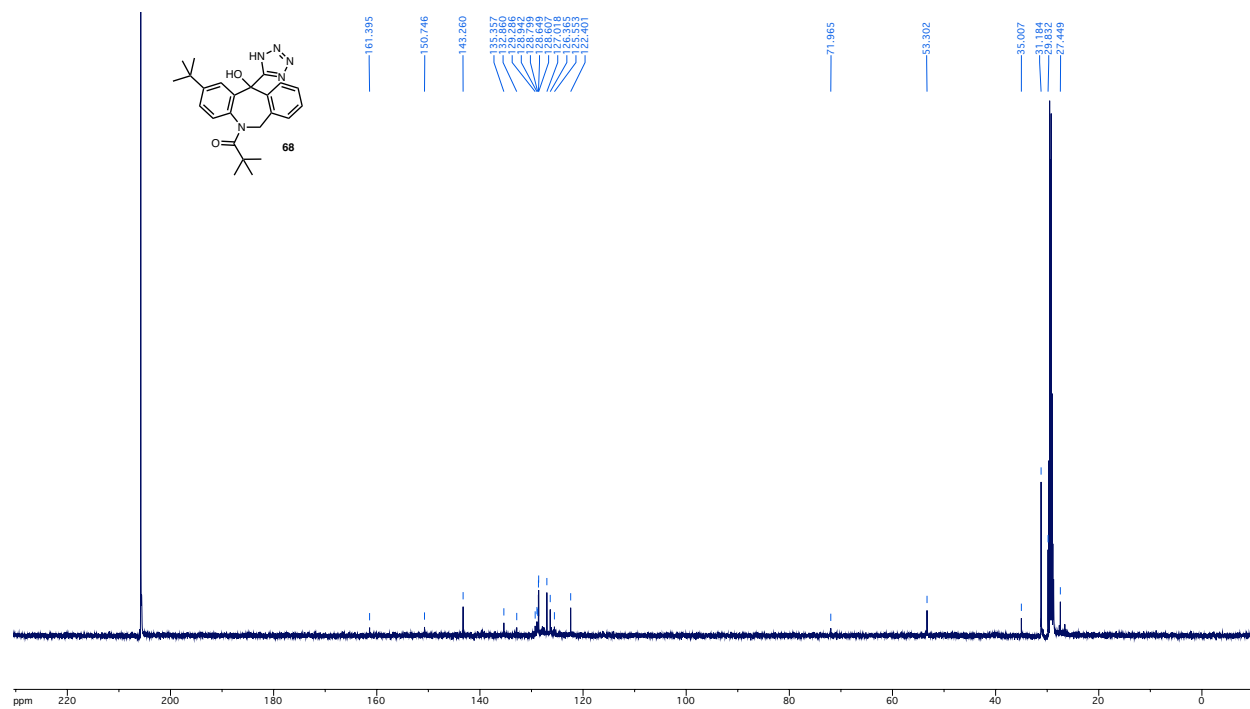
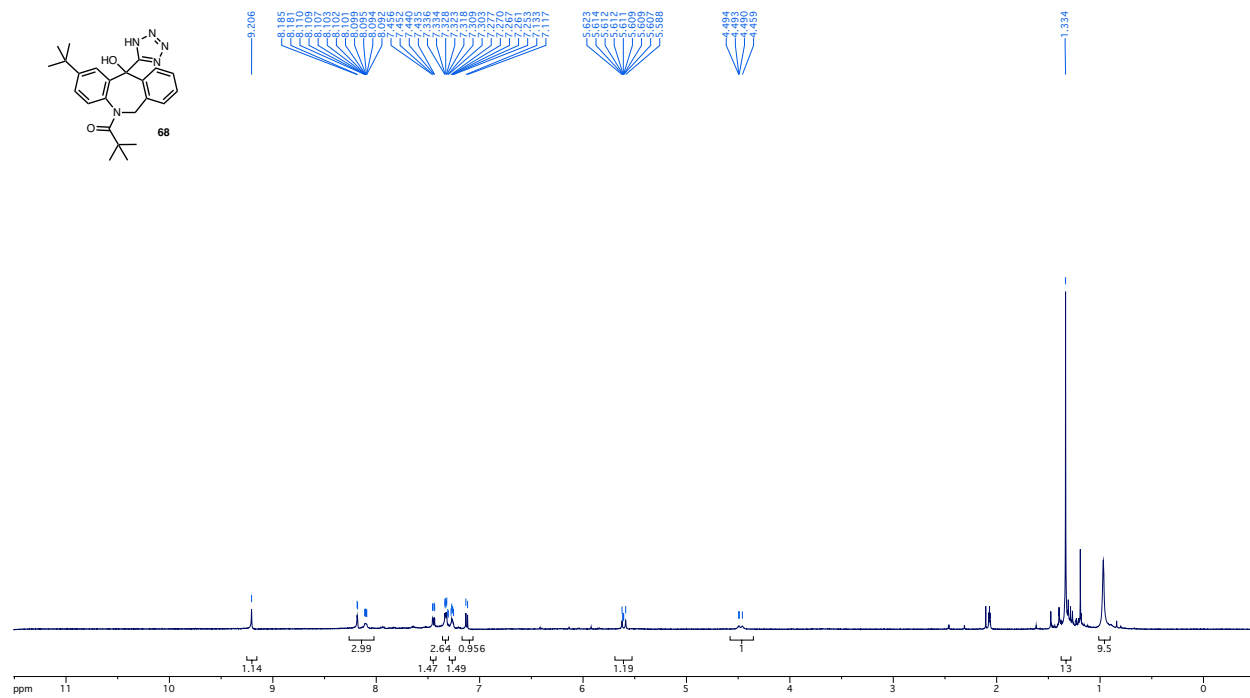
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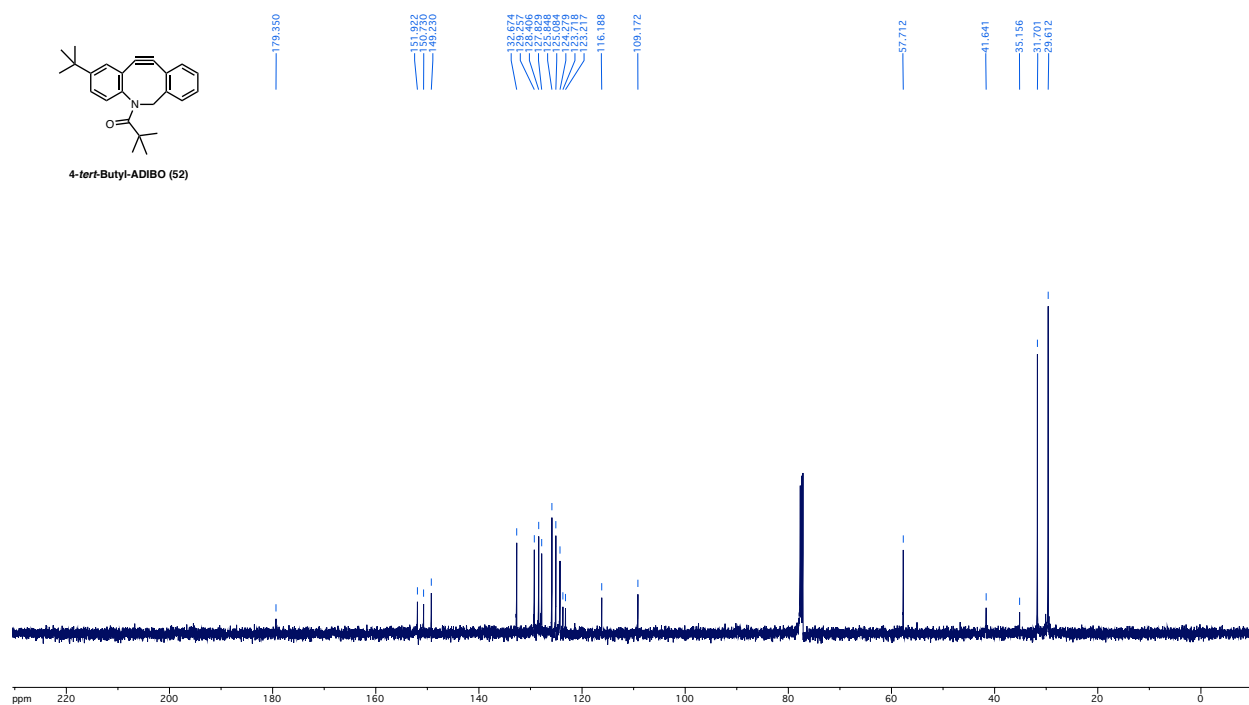


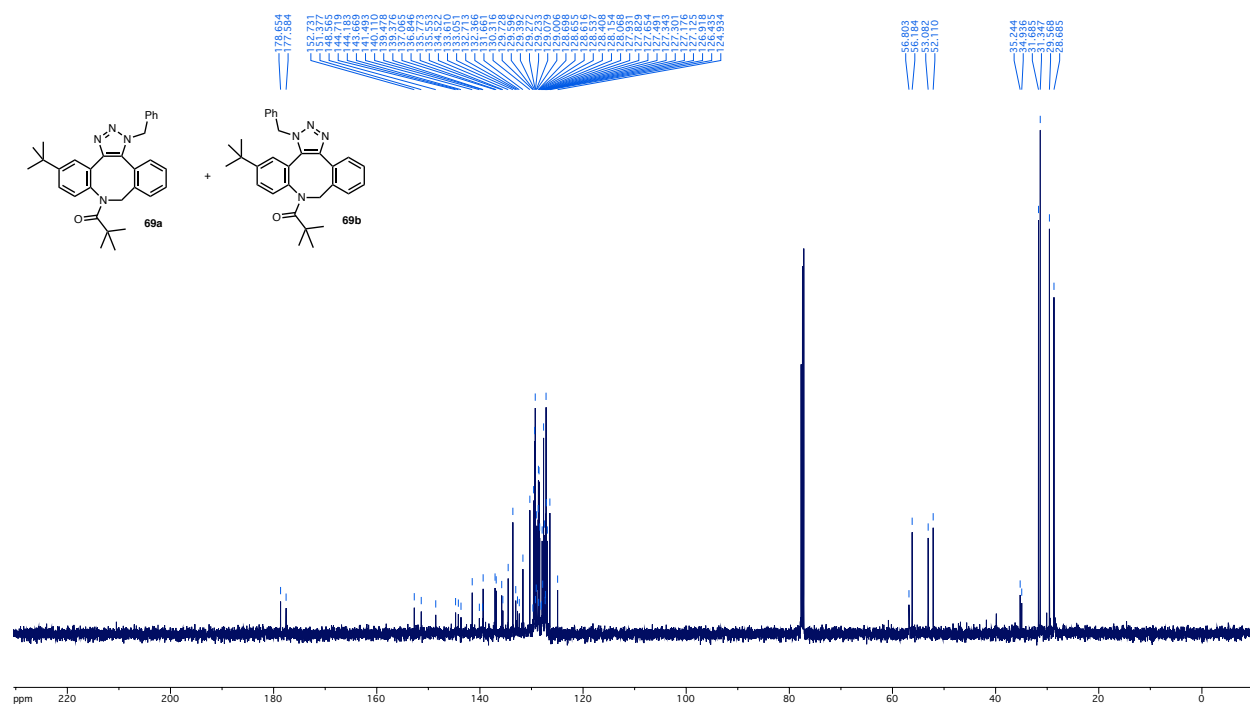












Chapter 5. Cyclopentynes

1. Structure of Cyclopentyne

When comparing the lifetime of cycloalkynes, there is an exponential trend in stability as the ring size is reduced.¹ Cyclooctynes (**4**) and larger alkynes are known to be the smallest cycloalkynes stable at ambient conditions, however there are numerous exceptions that are due to physical properties manipulation such as the addition of sp^2 centers. Cycloheptyne (**3**) has been found to have an appreciable lifetime of a few hours at $-75\text{ }^{\circ}\text{C}$ at dilute concentrations.² The same applies for cyclohexyne (**2**), but its lifetime is limited to a few minutes.² Cyclopentyne's lifespan has not been appreciably measured.³ As one of the most reactive compounds in organic chemistry, cyclopentynes (**1**) have largely eluded synthetic chemists. Despite this, the potential of cyclopentynes have been realized to some degree in materials science⁴ and synthetic inorganic chemistry.⁵

Due to the structural nature of the five-membered ring, the alkyne, cyclopentynes are transient alkynes and highly reactive, holding up to 74 kcal/mol in strain energy.⁶ Cyclooctyne (**4**) has been the smallest cycloalkyne that is stable (Figure 1). While cyclopentyne (**1**) is unstable under ambient conditions, a crystal structure of a zirconium complex of cyclopentyne has been reported.⁷ The alkyne bond is remarkably deformed to 116° , from the ideal bond angle of 180° . Due to the tight bond angle, cyclopentyne has been found to react as both a classical cycloalkyne and as a diradical.⁸

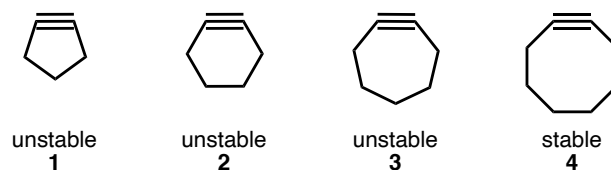


Figure 1. Geometry and resonance contributors of cyclopentyne.

2. General Reactivity of Cyclopentynes

Due to the high instability of cyclopentyne, these strained alkynes readily react with a wide range of partners (Figure 2). For example, **1** reacts with solvents that contain acidic protons such as alcohols to form enol ethers **5** (Figure 2).^{9 10} More significantly, cyclopentyne **1** has been found to frequently react with itself to dimerize **6**, trimerize **7**, and polymerize **8**.¹¹

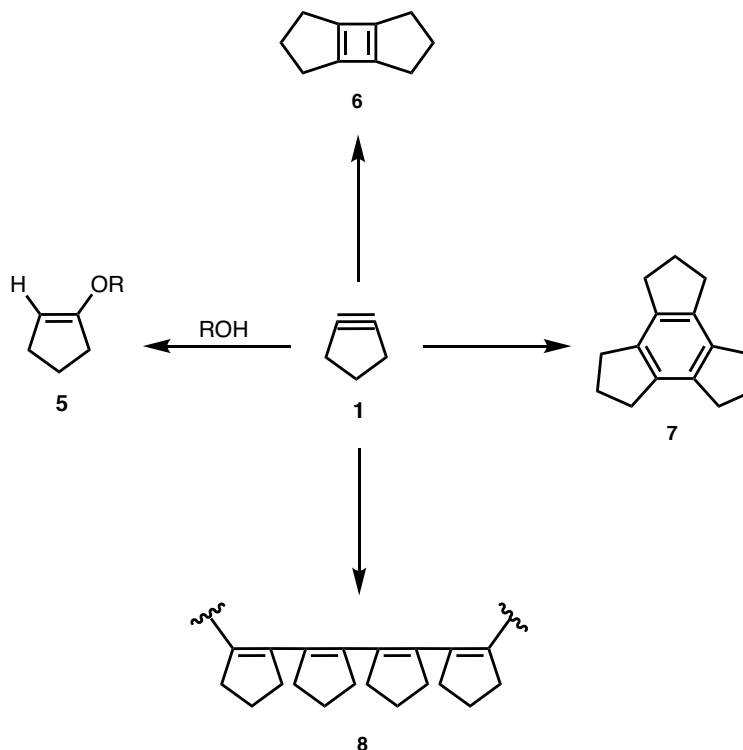


Figure 2. Reactivity of Cyclopentynes

3. Methods of Preparation

Due to the transient nature of strained, small-ring cycloalkynes, cyclopentynes must be intercepted *in situ* with an alkynophile. Unfortunately the trapping of cyclopentyne adducts has proven to be not very efficient. Synthetic methods for the preparation of cyclopentynes mirror

those employed for cyclooctynes. Below is a brief overview on existing methods of generation of cyclopentynes.

3.1 Photochemical Methods

The photolytic transformation α,α' -(bis)diazoketone **9** to form cyclopropenone **10**, followed by subsequent decarbonylation was used by Trost to prepare phenylacetylenes **11** in good yields (Figure 3).¹² This method was then later utilized by Popik towards his synthesis of cyclooctynes.¹³

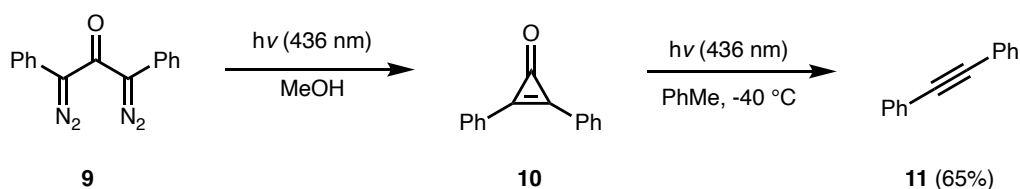


Figure 3. Preparation of phenylacetylenes via photolytic decarbonylation of cyclopropenones (Trost)

This method was subsequently utilized by Chapman for the preparation of strained alkynes from 2,6-diazocyclohexanone (**12**) and its derivatives (Figure 4).¹⁴ Irradiation of **12** at cryogenic temperatures ($< 10\text{ K}$) resulted in the sequential formation of diazoketene **13** and cyclopropenone **14**, which were characterized by IR spectroscopy. Continued irradiation of **14** promoted decarbonylation providing allene **15**, which was postulated to arise from cyclopentyne (**1**) via a [1,3]-sigmatropic shift. Chapman noted that the conversion of cyclopentyne (**1**) to allene **15** is faster than the fragmentation of cyclopropenone **14**, thus making characterization of cyclopentyne **1** difficult. To allow the characterization of cyclopentyne (**1**), Chapman immobilized this system by its fusion to a naphthalene ring.

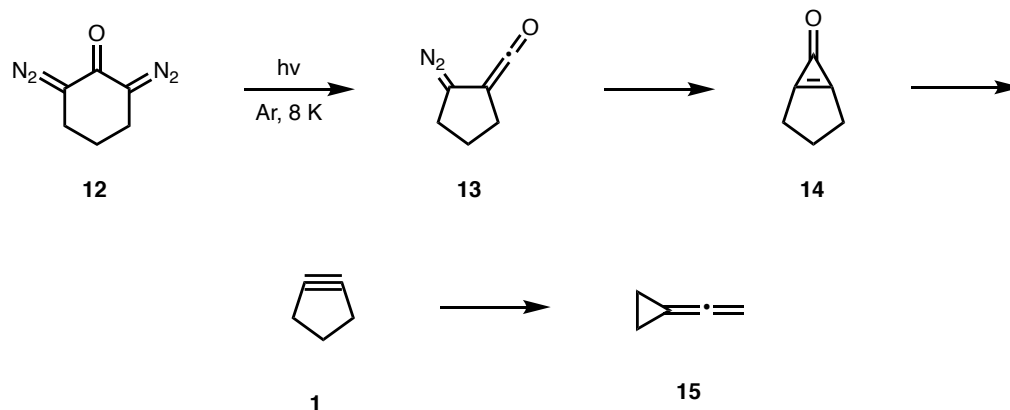


Figure 4. Preparation of cyclopentyne via photolytic decarbonylation of a cyclopropenone (Chapman)

To circumvent the sigmatropic rearrangement of cyclopentyne, Chapman utilized 1,3-bis(diazo)-1,2-dihydrophenalen-2-one (**16**) as it cannot undergo rearrangement. Irradiation of **16** formed cyclopropenone **18**, which underwent decarbonylation to form acenaphthyne (**19**) and allowing the first spectroscopic characterization (IR) of a cyclopentyne (Figure 5). Acenaphthyne (**19**) then was trapped with oxygen to form acenaphthoquinone **20**. Upon warming to room temperature, trimerization lead to formation of decacylene (**21**). The inclusion of trace amounts of water led to generation of acenaphthenone (**22**) and the acenaphthyne dimer-water complex **22**.

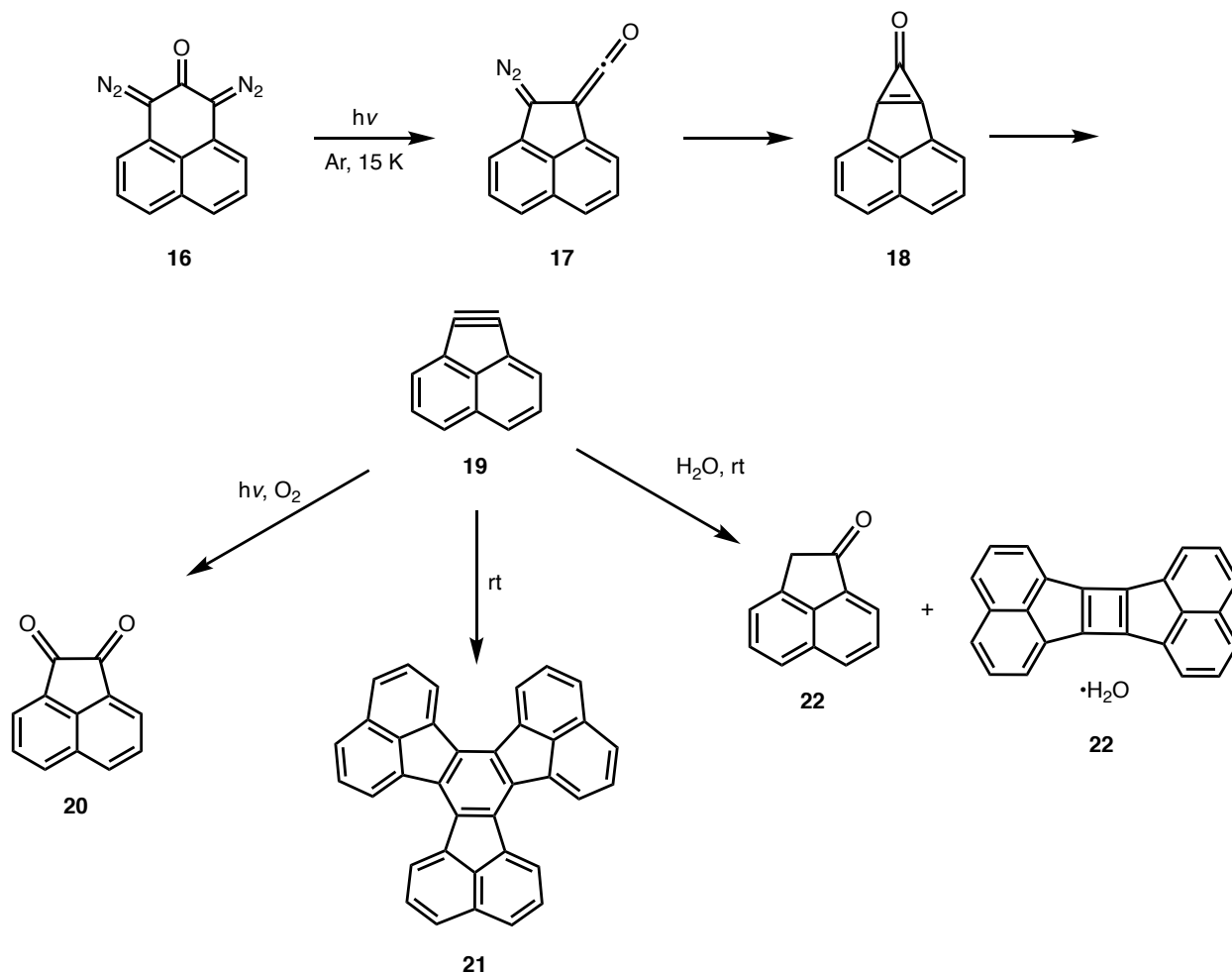


Figure 5. Preparation of acenaphthylene via photolytic decarbonylation of cyclopropanone (Chapman)

3.2 β -Elimination of Cyclopentene Derivatives

3.2.1 β -Elimination

One of the earliest methods of preparing cyclopentyne, reported by Wittig and co-workers in 1969, involves lithium-halogen exchange of dibromide **23** with *n*-butyllithium to form carbenoid **24**. Expulsion of lithium bromide then lead to the formation of cyclopentyne which through sequential [4+2] cycloaddition with isobenzofuran **25** to form benzopyran **26**. In this case, a small quantity of cyclopentyne trimer **27** was isolated (Figure 6). The employed isobenzofuran in this approach are limiting as cycloalkynes readily undergo reaction with strong nucleophiles.^{11, 15}

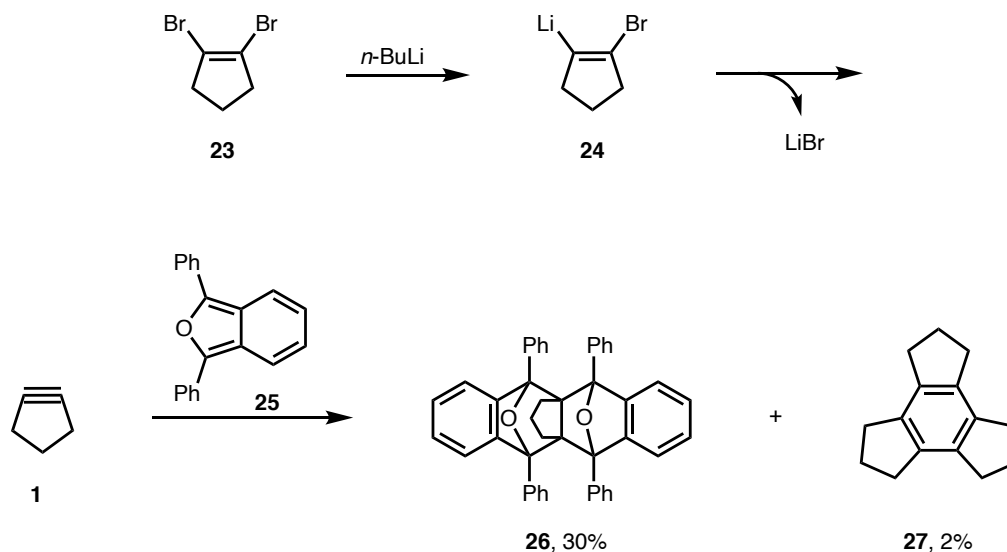


Figure 6. Wittig Approach

3.2.2 via Cyclobutylidenecarbene Expansion

The rearrangement of cyclobutylidenemethylene (**28**) to cyclopentyne (**1**) has been calculated by Daoust to be favorably exothermic by about 6.2 kcal/mol and have an activation barrier of about 1.5 kcal/mol (Figure 7).¹⁶

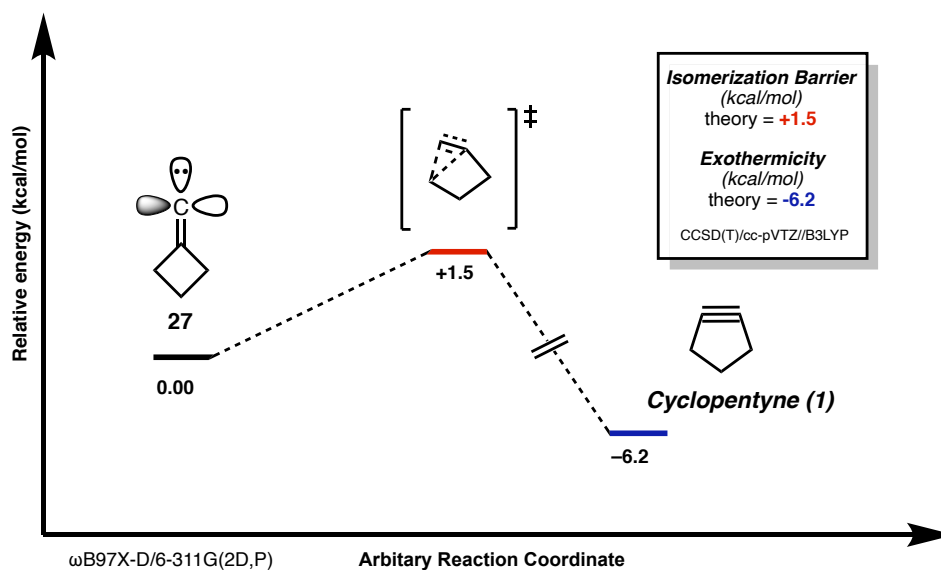
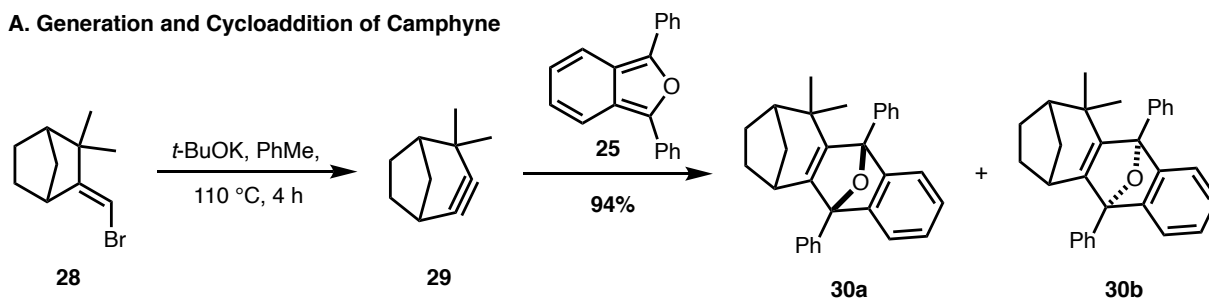


Figure 7. Energy profile of the rearrangement of cyclobutylidenemethylene (**27**) to cyclopentyne (**1**).

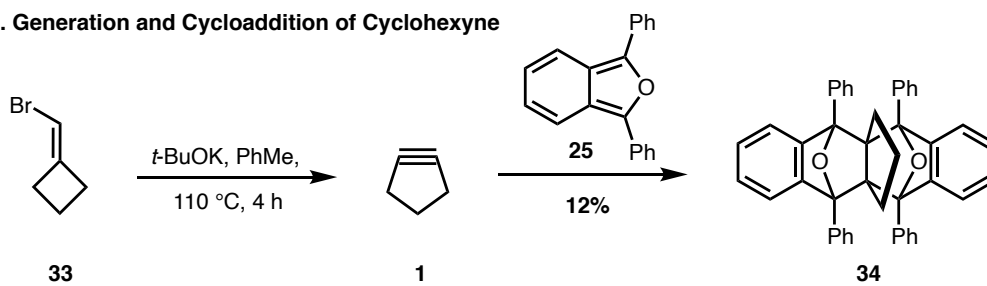
Studies by Tadros and Damico have shown that vinyl halides with both aromatic¹⁷ and aliphatic¹⁸ substituents can rearrange upon deprotonate. For example, Wolinsky treated ω -bromocamphene (**28**) to generate endocamphyne (**29**).¹⁹ Erickson has demonstrated that dehydrobromination of bromomethylenecycloalkanes with *tert*-butoxide generates smaller cycloalkynes. In this case, *in situ* trapping was accomplished with 1,3-diphenylisobenzofuran (**25**). A clear limitation of this method is the use of *t*-BuOK, a potential nucleophile. Other bases were evaluated, including organopotassium compounds that can allow for access towards milder conditions.²⁰

Wolinsky has reported similar reactivity with ω -bromocamphene (**28**) which upon treatment with *tert*-butoxide rearranged to form endocamphyne (**29**) and trapped with **25** to form cycloadduct **30a** and **30b** in high yield (Figure 8, A). Cyclopentyne (**1**) was produced from bromomethylenecyclobutane **31** and trapped with diminished efficiency to form **32** (Figure 8, B). Increasing ring size, bromomethylenecyclopentane **33** also rearranged into cyclohexyne (**2**) and isolated as a 1,3-diphenylisobenzofuran adduct **25** in low yield (Figure 8, C).

A. Generation and Cycloaddition of Camphyne



B. Generation and Cycloaddition of Cyclohexyne



C. Generation and Cycloaddition of Cyclopentyne

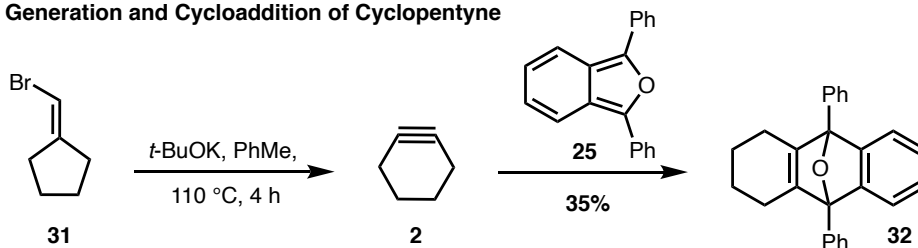
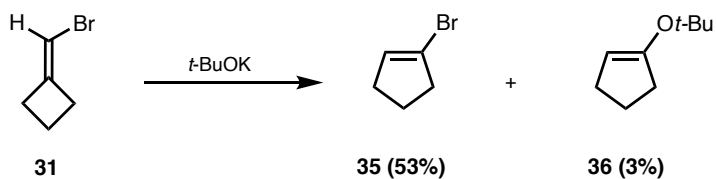


Figure 8. Preparation of cycloalkynes via dehydrobromination and ring expansion of bromomethylenecycloalkanes.

It is clear that as alkyne ring size decreases, the yield of cycloalkyne adduct decreases. While this may reflect increasing reactivity, Erickson has reported a different pathway that competes with alkyne formation. In the absence of an alkyne trapping reagent, treatment of **31** with *tert*-butoxide generated 1-bromocyclopentene (**35**) as the major product, together with a smaller amount of ether adduct **36** (Figure 9, A). Erickson posited that a bromide ion underwent nucleophilic addition to cyclopentyne to form the major product. Accordingly, an alkynophile **25** was employed to intercept the cycloalkyne. In this case, adduct **32** was formed in low yield, while vinyl bromide **35** was isolated as the major product. Interestingly, enol ether **36** was not formed under these

conditions (Figure 9, B), suggesting the rearrangement of 1-bromocyclopentene (**35**) is faster than formation of cyclopentyne (**1**).²¹

A. Generation and Trapping of Cyclopentyne (Erickson)



B. Generation and Trapping of Cyclopentyne (Erickson)

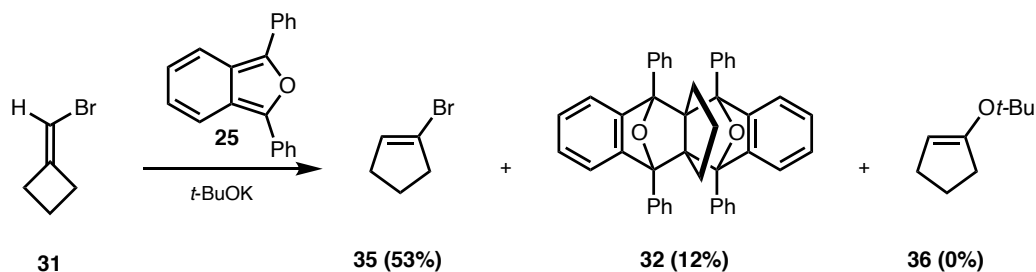


Figure 9. Generation and reactions of cyclopentyne.

Three mechanisms were proposed to account for the formation of vinyl bromide **35** and cyclopentyne (**1**) (Figure 10).²² Formally, the ring expansion of bromomethylenecyclobutane (**31**) to 1-bromocyclopentene (**35**) is analogous to the rearrangement of ethers and amines.²³

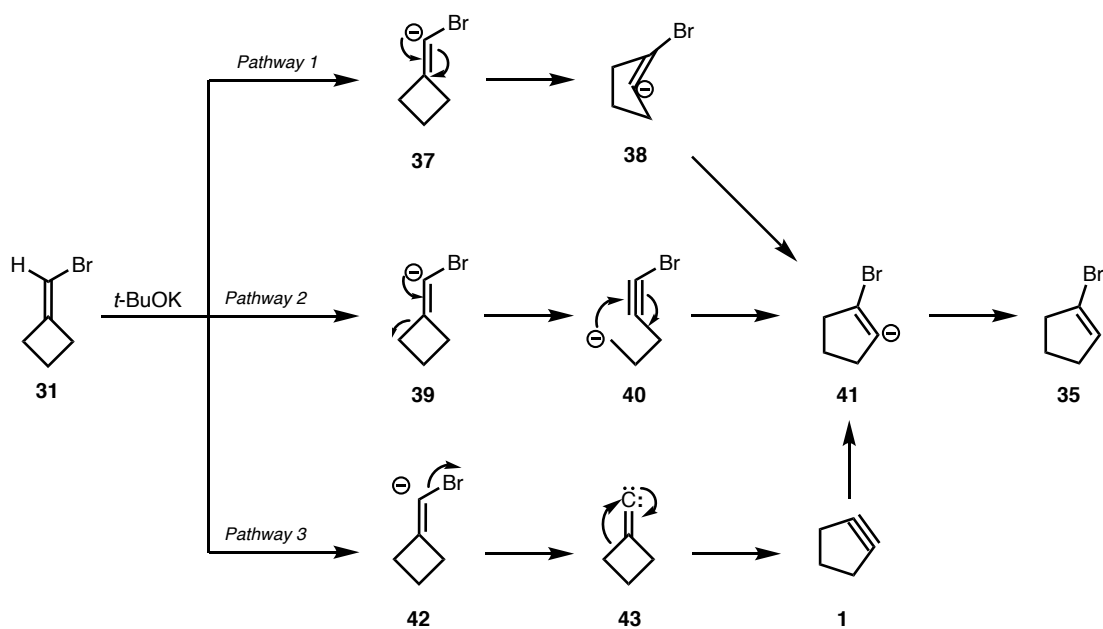


Figure 10. Proposed mechanistic pathways leading to the formation of vinyl bromide **35**.

Pathway 1 involves carbanion rearrangement involving a ring carbon migration to form **38**. While carbanion rearrangements are known in aromatic systems,²⁴ they are rare in aliphatic systems. Coupled with the fact that this pathway reasonably proceeds through a strained trans-cyclopentene intermediate, this mechanistic pathway seems implausible.

The second mechanistic rationale (Pathway 2) involves a cleavage-recombination strategy of the cyclobutyl ring to form unstable carbanion **40**, cyclizing to form vinyl anion **41**. This pathway also seems highly unlikely due to the high energy demand of the carbanion ring opening. That no non-cyclic products were isolated, suggests that this process is unlikely.

The final postulated pathway (Pathway 3) is arguably the most plausible, involving is the formation of alkylidenecarbene **43**, which undergoes 1,2-rearrangement to form cyclopentyne (**1**). While this mechanism is similar to that of larger cycloalkyne preparations, ring expanded vinyl halides are not the isolated products. Erickson later postulated that a combination of Pathways 1 & 3 are at play here.²⁵ Erickson suggests that since bromide **42** may not completely dissociate from carbenoid **42**, so carbenoid bromide complex **43** is a reaction intermediate that can take multiple resonance forms such as completely dissociated **44** and carbanion **45** (Figure 11).²²

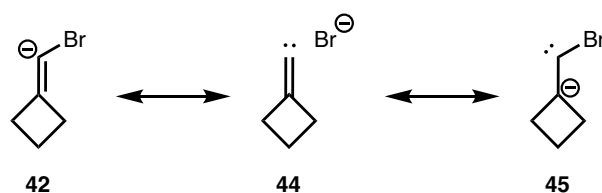


Figure 11. Proposed resonance structures of carbenoid bromide complex **42**

Erickson also examined the influence of leaving groups other than bromide on the rate of *ipso* elimination (Figure 12). Notably, vinyl chlorides (**31b**) provided similar yields to that of the bromide (**31a**); however, Erickson notes that the mass balance of remaining organic material was polymeric, which is in agreement to Wittig's observations of cyclopentyne polymerization.¹¹ The reaction of iodomethylenecyclobutane (**31c**) proceeded more cleanly, with higher efficiency. The

remaining substrates were found to be unreactive towards *tert*-butoxide, even at elevated temperatures.

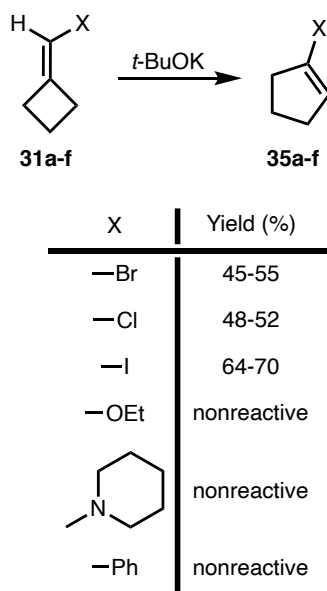


Figure 12. Influence of leaving group on the expansion of **31**

To confirm the presence of bromide-carbenoid complex **44**, Erickson determined the rates of bromide dissociation using deuterium-labeling studies.²¹ When bromomethylenecyclobutane (**31**) was heated at reflux in *tert*-butanol-OD for an hour, deuterium was incorporated at 45% (Figure 13). This suggests that loss of bromide is relatively slower in comparison to rearrangement of the alkylidenecarbene to cyclopentyne (**1**), thus promoting rearrangement towards 1-bromocyclopentene (**35**).

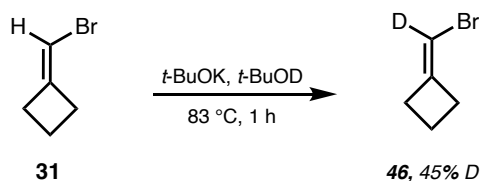


Figure 13. Deuterium incorporation of bromomethylenecyclobutane **31**

Lithium-halogen exchange has also been exploited for the synthesis of cyclopentyne, as in the case of both dibromomethylenecyclobutane (**50**),^{26, 27} and 1,2-dibromocyclopentene (**47**) (Figure

14).^{26, 28} 2-Bromocyclopentyllithium (**48**) was found to decay over time.²⁹ That this process was not accelerated when exposed to a trapping agent such as spirodiene **52**,^{11, 30} suggests that **51** must proceed through a separate reactive intermediate prior to trapping. Unencumbered cyclopentyne would be expected to undergo (1:1.5)²⁸ cycloaddition with no selectivity. However, the ratio of isolated cycloadducts **53a** and **53b** was found to be temperature dependent.²⁸ That the selectivity observed in this case implies that free cyclopentyne is not an intermediate, but rather, a LiBr complex of cyclopentyne **49** is.

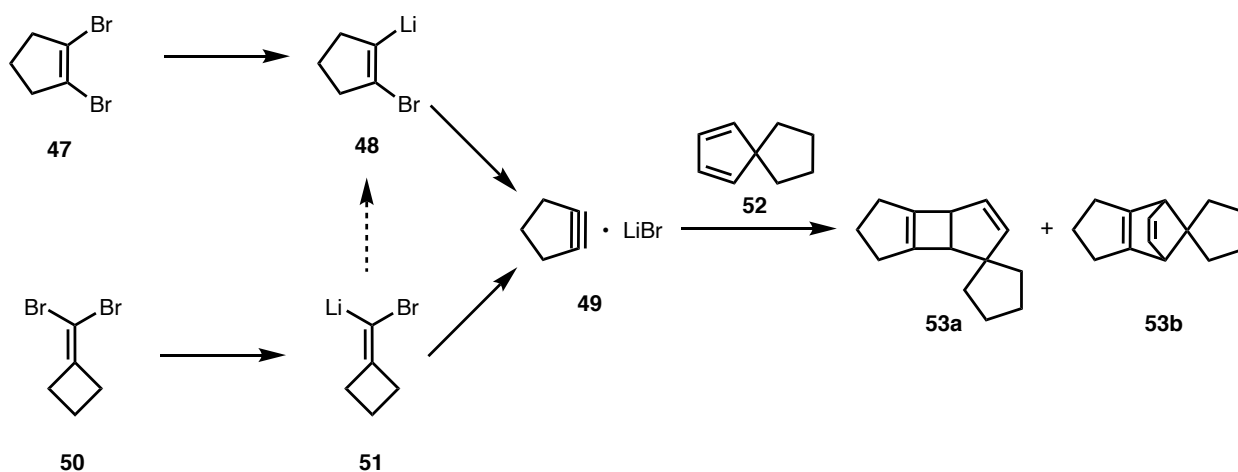


Figure 14. Cyclopentyne generation from dibromomethylenecyclobutane (**50**) and 1,2-dibromocyclopentene (**47**)

In the case of dibromomethylenecyclobutane (**50**), Br,Li-cyclobutylidenecarbenoid **51** was also found to be stable at -107 °C.²⁸ Erickson had previously demonstrated of the possible rearrangement towards 2-bromocyclopentyllithium **48** which can also be an intermediate in this pathway.²² The reaction was allowed to decay in the presence of spirodiene **52** to give products **53a** and **53b** in a stereoselective ratio of various degree depending on temperature. Despite the selectivity being similar to that observed in lithiocompounds **48** and **51**, further exploration may be required, but it was suspected that the lithium bromide cyclopentyne complex **44** is responsible for the observed selectivity.

3.3 Unencumbered Cyclopentynes

3.3.1 Cyclobutylidenecarbenes

Transition metal-alkyne complexes are well known. Recent studies of intramolecular π -interactions between lithium cations and acetylenes, from the X-ray crystal structure of the Li-OCMe₂CCH hexamer.³¹ Calculations have also been conducted that shows of lithium and acetylene the π -interaction stabilize the complex by about 20 kcal/mol.²⁸

Gilbert in his studies posited that the lithium cation must be directly involved in the cycloaddition of cyclopentyne (**1**) and adduct **58**. In this case, he proposed that the temperature product dependent ratios were related by differing aggregations of the lithium-cyclopentyne complex.³² As a control experiment, unencumbered cyclopentyne (**1**) was generated via Seyferth-Gilbert homologation of cyclobutanone (Figure 15).^{33, 34} Treatment of cyclobutanone (**54**) with diethyl-diazomethyl phosphonates (DAMP) and KH generated cyclopentyne (**1**) via deprotonation of diazonium ylide **56**. In situ trapping with dihydrofuran (**57**), via [2+2] cycloaddition, provided **58** in low yield.¹⁰ Subsequent NMR studies with ¹³C-enriched DAMP provided a nearly statistically equal distribution of label in the vinylic carbons of **58**; implicating cyclopentyne (**1**) is the symmetrical intermediate.

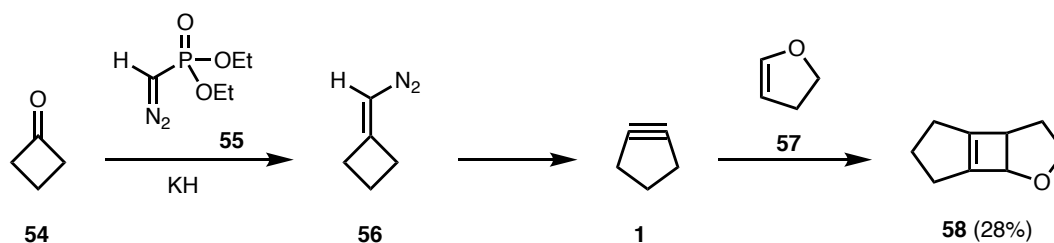


Figure 15. Generation and trapping of unencumbered cyclopentyne.

Gilbert also examined the stereochemistry of trapping with *cis*-1-methoxy-1-propene (**60**), which underwent cycloaddition with **1** to provide *cis*-cyclobutene **59** (Figure 16)³⁵. In contrast, trapping with *trans*-1-methoxy-1-propene (**61**), provided diene **62**, which was isolated after cycloaddition

with naphthazarin. Gilbert posited that the resulting stereochemistry of cycloaddition was a direct reflection of a concerted mechanism. The lack of selectivity, coupled with his ^{13}C -labeling studies, shows that free cyclopentyne could be generated.

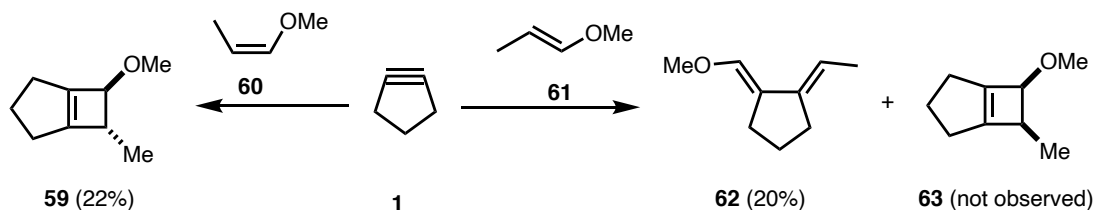


Figure 16. Trapping of unencumbered cyclopentyne with 1-methoxy-1-propene.

The use of diazomethylphosphonates to generate unencumbered cyclopentynes poses a disadvantage as the use of strong bases such as potassium hydride and more importantly, *tert*-butoxide, which can potentially intercept cyclopentynes. To circumvent these conditions, Gilbert proposed a developed an alternative synthetic route to cyclopentynes, relying on the fluoride-mediated α -desilylation of 1-(bromotrimethylsilylmethylene)cyclobutane (**64**) (Figure 17). This elimination had been previously reported to prepare their corresponding alkylidenecarbene intermediates, but they were not utilized to prepare a cycloalkyne.³⁶

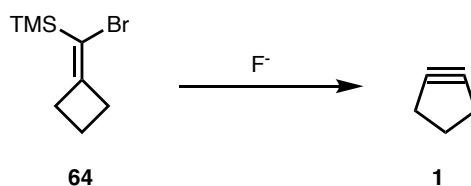


Figure 17. Generation of cyclopentyne from 1-(bromotrimethylsilylmethylene)cyclobutane (**64**)

1-(Bromotrimethylsilylmethylene)cyclobutane (**64**) was prepared by treatment of vinyl anion of bromoethylenecyclobutane (**31**) with trimethylsilyl chloride at low temperatures (Figure 18). The inefficient preparation of the cyclopentyne precursor is a major limitation to the synthetic route of cyclopentynes.

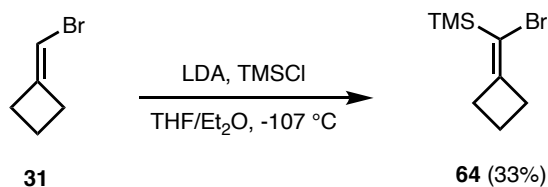


Figure 18. Preparation of 1-(bromotrimethylsilylmethylene)cyclobutane (**64**)

Addition of anhydrous benzyltrimethylammonium fluoride³⁷ to **64** resulted in the formation of a cyclopentyne intermediate which underwent cycloaddition with an alkynophile spiro[4.4]-nona-1,3-diene (**65**).^{38, 28} Isolation of products **66** and **67** also proved to be problematic as the cycloadducts are prone to thermal isomerization under GC conditions. The efficiency of this transformation was very low (4%) and displayed little selectivity (1:1.5) between the [2+2] and [2+4] cycloaddition products (Figure 19).

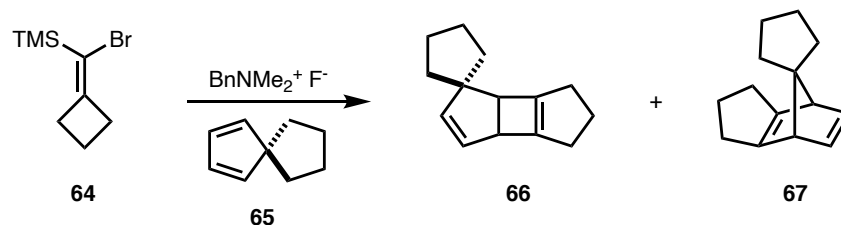
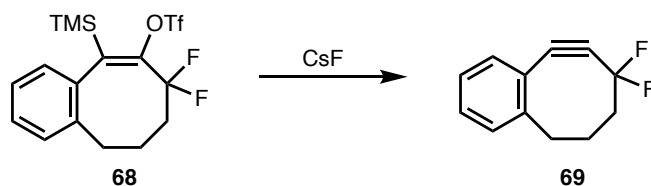


Figure 19. α -Elimination of 1-(bromotrimethylsilylmethylene)cyclobutane (**64**).

3.3.2 Classical β -Elimination Approach

Historically, most reported methods for the generation of cyclopentyne utilizes a β -elimination approach. Originally developed by Bertozzi for the preparation of cyclooctynes, fluoride-induced elimination of silyl enol triflates (Figure 20, A).³⁹ Garg has more recently adapted later adapted this methodology for the generation of cyclopentynes (Figure 20, B).⁴⁰

A. Fluoride-Induced Elimination of Silyl Enol Triflate (Bertozzi)



B. Adaptation towards Cyclopentyne Synthesis (Garg)

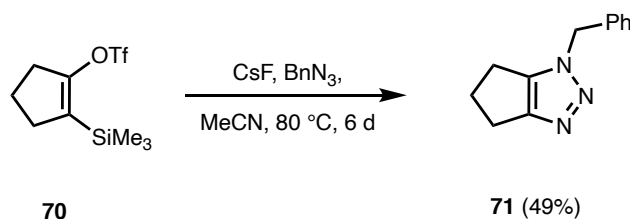


Figure 20. Preparation of cyclopentynes via fluoride induced elimination of vinyl enol triflates

Despite being the most recent and mildest synthesis for the generation of cyclopentynes, it is without limitation, mostly due to long reaction times. More importantly, preparation of the requisite precursor requires numerous steps with low overall yield. Silyl enol triflate **70** (Figure 21) is prepared by bromination of cyclopentenone (**72**) to form bromoketone **73**, then protection to form acetal **74**. The bromide group is then substituted via lithium-halogen exchange with *n*-BuLi and TMSCl. Subsequent deketalization and 1,4-migration to unsaturated cyclopentenone **75** followed by trapping with phenyl triflimide provided silyl enol triflate **70** in moderate yield.⁴¹

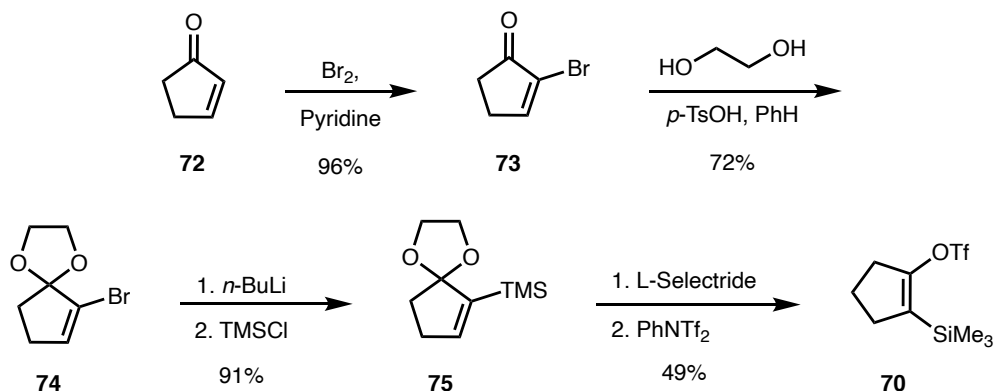


Figure 21. Preparation of vinyl enol triflate **70**.

4. Hypothesis

Numerous methods have been developed for the generation of cyclopentynes, yet limitations occur in each, including use of harsh reaction conditions such as organolithium reagents, inconvenient starting materials, and low yields. Fluoride induced elimination of silyl enol triflates is currently the method of choice for the generation of cycloalkynes, including cyclopentynes. However, this method involves extended reaction times (6 days) and necessitates a lengthy precursor synthesis, lowering overall efficiency. Having previously developed an efficient and practical ring-expansion methodology for the preparation of cyclooctynes, we wished to explore the extension of this method towards smaller cycloalkynes; specifically, cyclopentynes (Figure 22). Given Gilbert's observations,³⁴ we postulated that the putative diazoalkene intermediate **78** formed upon tetrazole fragmentation would undergo rearrangement. Calculation this process is energetically favorable by about 6 kcal/mol due to release of ring strain.⁶

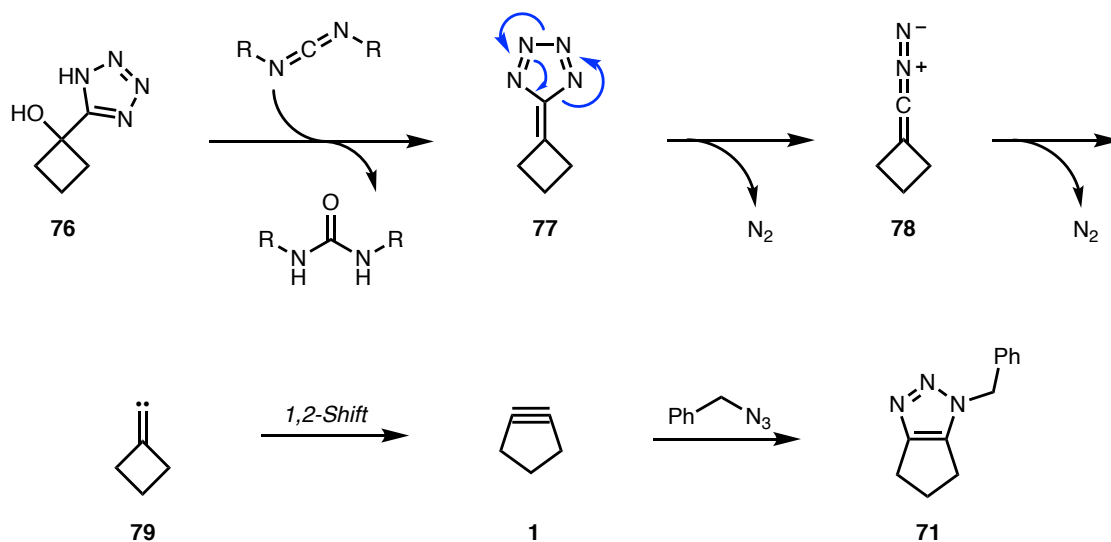


Figure 22. Proposed hypothesis for the generation of cyclopentynes via dehydrative fragmentation of 5-(1-hydroxycyclobutyl)tetrazole **76**.

5. Results and Discussion

5.1 Preliminary Results

For the preparation of requisite cyclobutyl tetrazole substrates, we opted to employ the 3,3'-diphenyl analog **82** for our exploratory studies (Figure 23). The higher molecular weight of **82** was chosen to avoid any issues pertaining to volatility. Compound **81** was prepared by the cycloaddition of 1,1-diphenylethylene (**80**) and dichloroketene, generated by trichloroacetyl chloride with zinc. The resulting dichloride was then treated with zinc to mediate dehalogenation and provide **81** in moderate yield.⁴² Tetrazole **82** was prepared using our standard conditions described⁴³ in moderate efficiency. The dehydrative fragmentation of **82** was conducted using the method standardized for cyclooctyne preparation in the presence of 5 equivalents of benzyl azide as an alkyne trap. Under these conditions, **83** was isolated in 22% yield. Despite the low yield, we were delighted that the extension of our methodology to the generation of cyclopentynes was viable and sought to optimize the efficiency of this methodology.

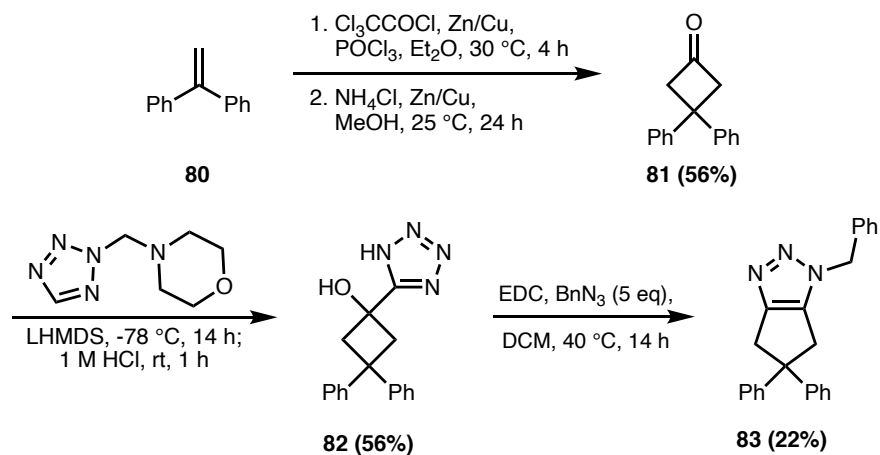


Figure 23. Preliminary studies

5.2 Optimization

Seeking to optimize our methodology, we evaluated a range of mild dehydrating agents, solvents, reaction temperatures, and effects of concentration. The results of this study are summarized in Figure 24.

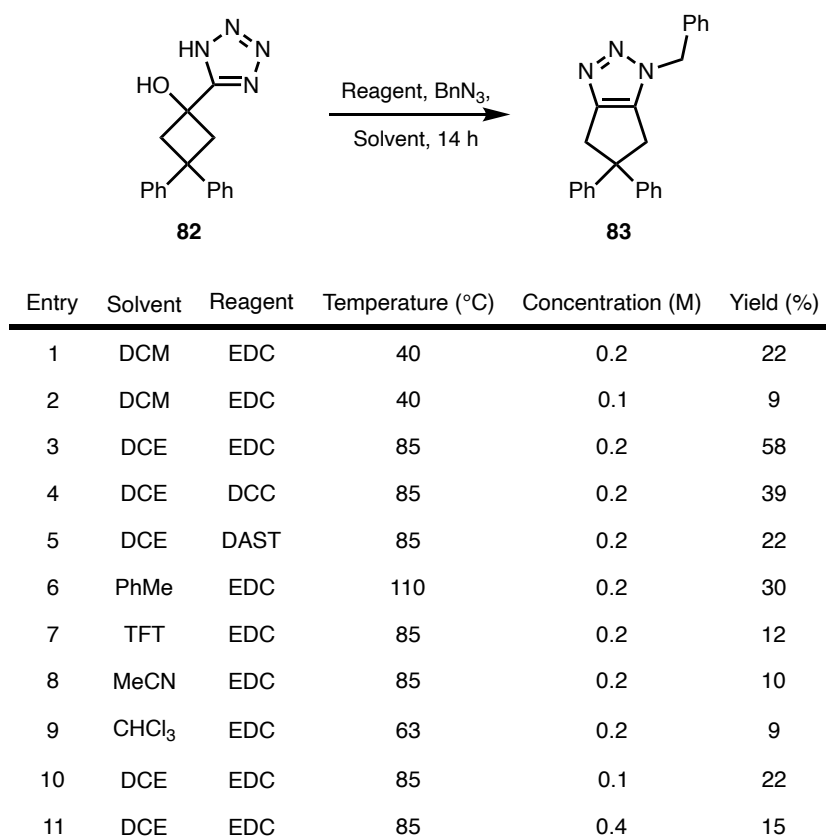


Figure 24. Optimization of 5-(1-hydroxycyclobutyl)tetrazole rearrangement and cyclopentyne trapping.

As with cyclooctynes, EDC was the favored to be the carbodiimide of choice despite screening other reagents such as DCC (Entry 4) and DAST (Entry 5) that were included in our screen of cyclooctyne preparation. An evaluation of solvents, including DCE (Entry 3), toluene (Entry 6), trifluorotoluene (Entry 7), acetonitrile (Entry 8), and chloroform (Entry 9) were also examined, with dichloroethane providing the highest yield, thus opting it as the solvent of choice. Reducing the concentration of the reaction (Entry 10) failed to increase efficiency. Dilution of the reaction could have possibly slowed the rate cycloaddition of cyclopentyne and benzyl azide. Furthermore,

increasing the reaction concentration (Entry 11) also did not prove to be fruitful; increased concentration may facilitate cyclopentyne polymerization or decomposition. With our optimization complete, we found EDC to be the preferred dehydrating reagent, DCE the solvent of choice and a reaction temperature of 85 °C (boiling point of DCE) to be optimal.

5.3 Preparation of Cyclobutanone Substrates

The 5-(1-hydroxycyclobutyl)tetrazoles for substrate scope study were prepared via zinc catalyzed [2+2] cycloaddition of dichloroketene and their corresponding alkenes, with subsequent zinc-facilitated dehalogenation reduction (Figure 25).⁴² This synthesis was overall moderately efficient, requiring slow addition and reaction temperature control.

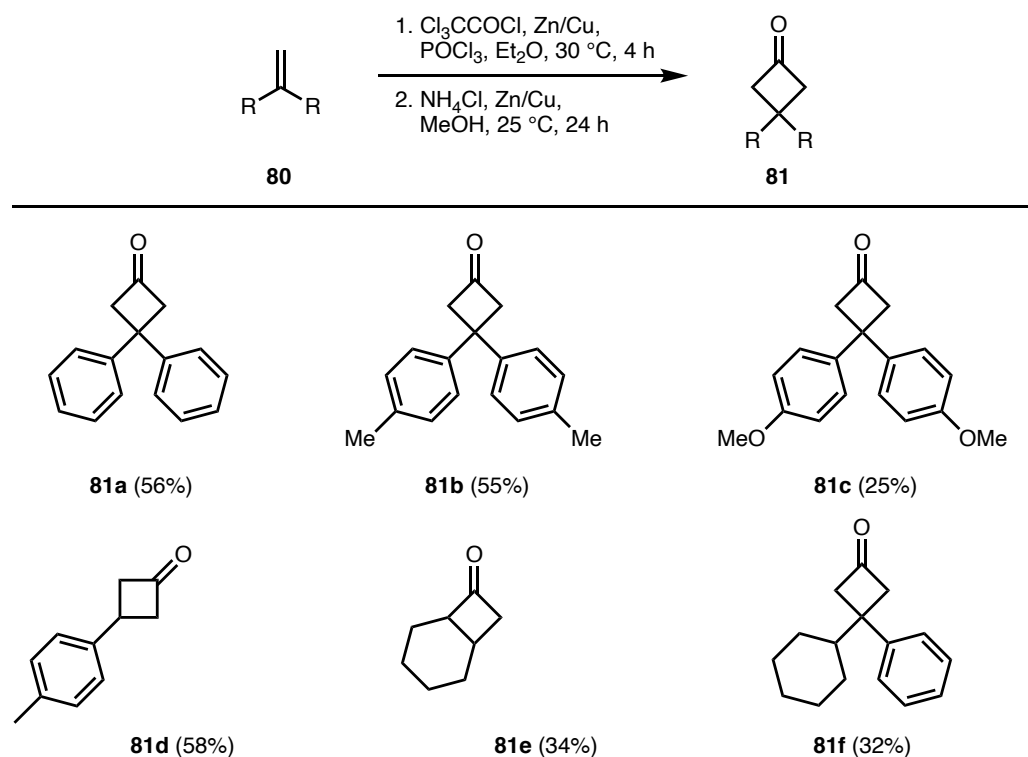


Figure 25. Preparation of 5-(1-hydroxycyclobutyl)tetrazole substrates

Addition onto the previously prepared cyclobutanones was performed using our previously reported protocol (Figure 26).⁴³ Yields varied from moderate to good with no change in procedure.

Substrates for the subsequent rearrangement were chosen to display the efficiency of the reaction as well as display functional group tolerance such as methoxy **82c**. Additionally, substrates with variable C–H substitution were also chosen such as **82e** and **82f** having tertiary C–H or **82b** and **82d** having benzylic hydrogens that could potentially be prone to insertion by an alkylidenecarbene.

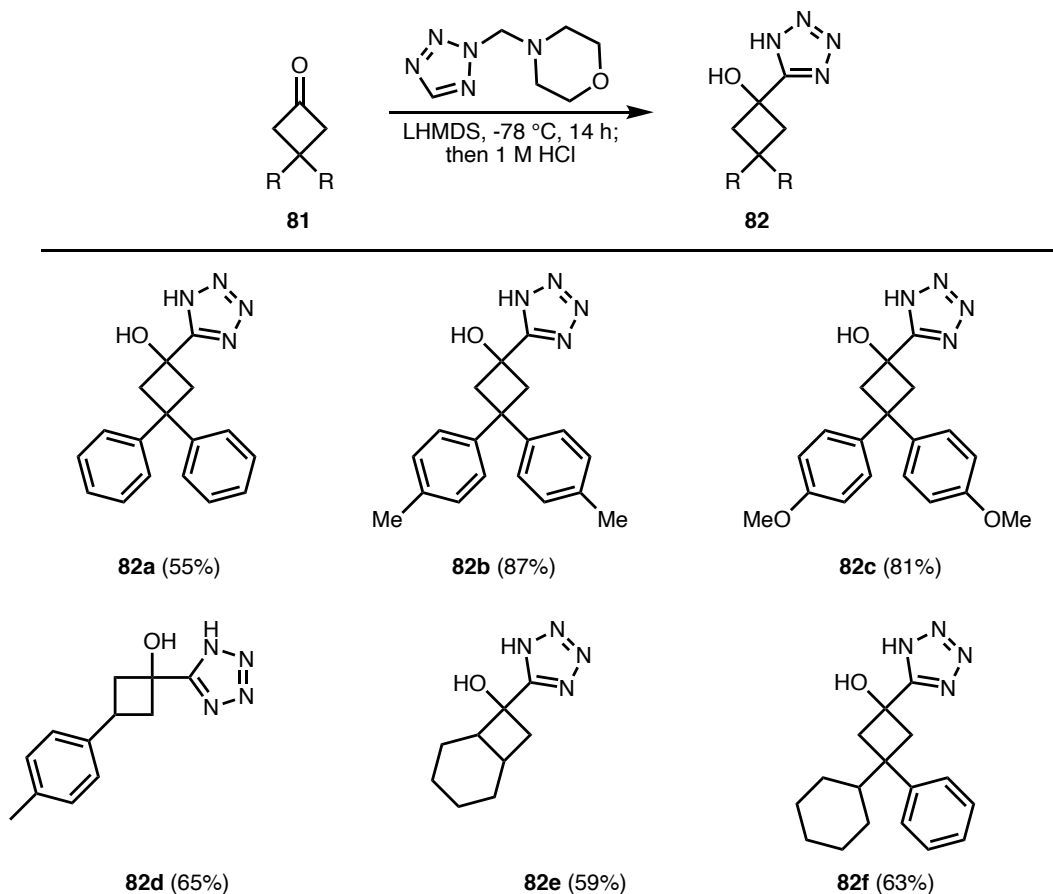


Figure 26. Substrate scope of cyclobutanone addition

5.4 Rearrangement of 5-(1-hydroxycyclobutyl)tetrazoles with in-situ trapping

Using the optimized rearrangement conditions previously mentioned in section 5.1, the 5-(1-hydroxycyclobutyl)tetrazoles were transformed into their corresponding cyclopentynes and trapped in situ with benzyl azide (Figure 27). Overall, the efficiency of this transformation was

low to moderate, but was at least comparable to previously reported methods including Garg.⁴⁰ Despite the limited scope, some inferences can be made. The addition of benzylic C–H may adversely effect the yield in the case of **83e**, due to the weakness of the benzylic bond, allowing the resulting alkylidenecarbene to abstract it, but this was not seen, as rearrangement and subsequent cycloaddition was far prevalent.

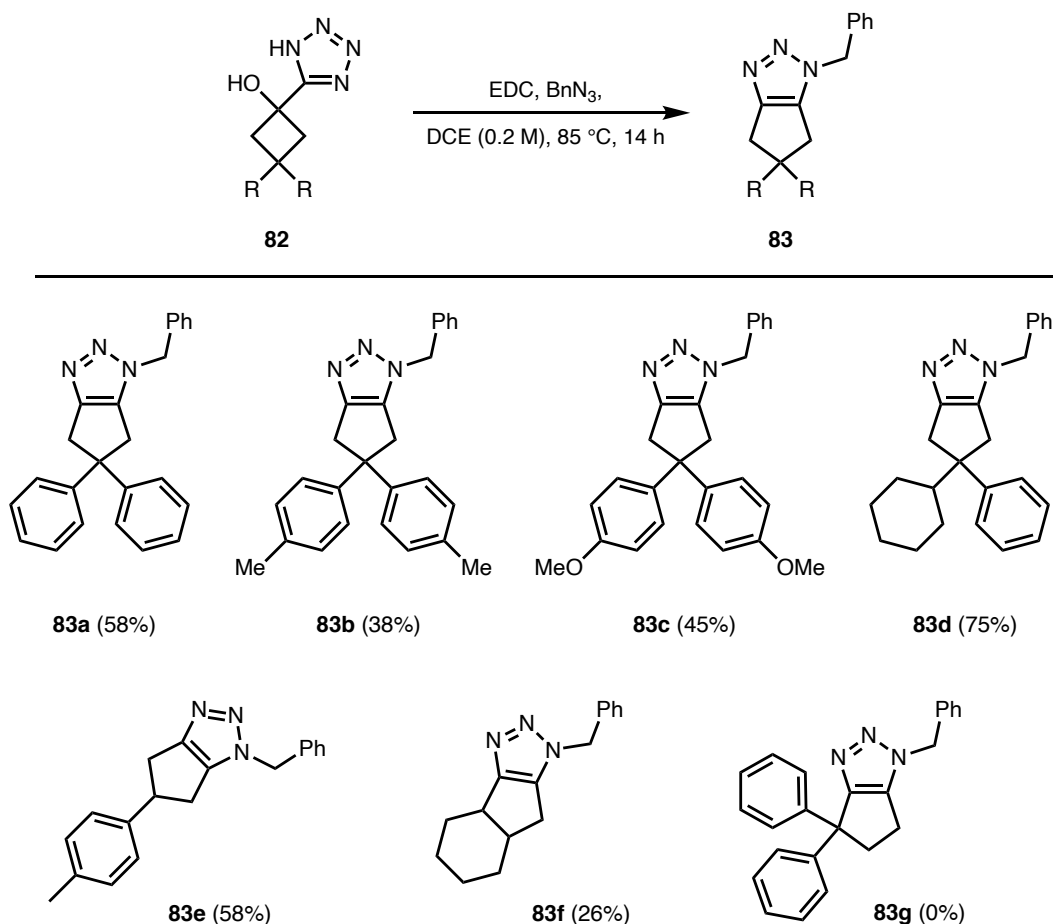


Figure 28. Substrate scope studies

6. Conclusion

Cyclopentynes have long eluded synthetic chemists due to their high reactivity and transient nature. Development of these transient species have been explored, yet their efficiency has not

been overall remarkable. Recent advancements are similar to the formation of cyclooctynes, where similar limitations take hold such as harsh reaction conditions or lengthy synthetic precursor routes, which hinders overall efficiency.

Using our previous methodology for the preparation of cyclooctynes, we were able to extend our protocol towards the synthesis of cyclopentynes under via the dehydrative fragmentation of 5-(1-hydroxycyclobutyl)tetrazoles as latent alkylidenecarbenes that will rearrange with ring expansion under mild reaction conditions. The synthesis of the precursors is easily accessible, stemming from easily prepared cyclobutanones in a much shorter route, providing an optimal route towards cyclopentynes.

7. References

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Appendix A, Cyclopentynes

1. General Comments

1.1 General Methods

All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F₂₅₄ indicator. Visualization was accomplished by UV light (254 nm), potassium permanganate solution, or phosphomolybdic acid solution. Flash column chromatography was performed according to the method of Still¹ using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

1.2 Materials

Anhydrous tetrahydrofuran (THF) was passed through a solvent dispensing system under a dry argon atmosphere. All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

1.3 Instrumentation

All melting points were determined in unsealed Pyrex capillaries with a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide disks, or thin films on sodium chloride or zinc selenide plates using an ATI Mattson Genesis series FTIR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 (400 MHz, ¹H, 100 MHz, ¹³C) or a Bruker Avance 500 (500 MHz, ¹H, 125 MHz, ¹³C) spectrometer. Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.26 ppm for ¹H; δ 78.0 ppm for ¹³C), methanol (δ 3.31 ppm for ¹H; δ 49.2 ppm for ¹³C), acetone (δ 2.05 ppm for ¹H; δ 29.9 ppm for ¹³C), and dimethyl sulfoxide (δ 2.50 ppm for ¹H; δ 39.5 ppm for ¹³C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), m (multiplet) and br (broad) app (apparent). The identification of ¹H and ¹³C signals was achieved using a combination of ¹H, ¹³C, DEPT, COSY, HMBC, HMQC and NOESY experiments. High-resolution electrospray ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass Q-ToF Ultima instrument at the University of Illinois Mass Spectrometry Laboratory. High-resolution electron ionization (HRMS-ESI) mass spectra were obtained on a Waters Micromass 70-VSE instrument at the University of Illinois Mass Spectrometry Laboratory.

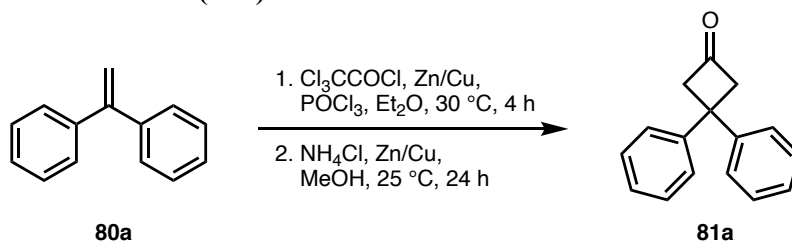
1.4 Safety Precautions!

While all procedures involving tetrazoles were conducted without incident, it is advisable to take appropriate safety precautions, such as the use of shields in a fume hood and personal protection equipment, when undertaking work with these potentially energetic heterocycles.

2. Experimental Details

2.1 Cyclobutanone Preparations

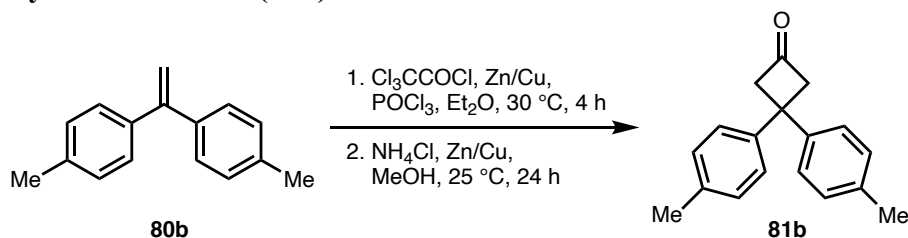
3,3-Diphenylcyclobutan-1-one (**81a**)



To a flame-dried flask equipped with a stir bar was added 1,1-diphenylethylene (**80a**) (3.39 mL, 19.2 mmol, 1 equiv.), Zn/Cu-couple (2.5 g, 38.4 mmol, 2 equiv.), and anhydrous diethyl ether (30 mL). A solution of trichloroacetyl chloride (2.8 mL, 25 mmol, 1.3 equiv.) and phosphorus oxychloride (3.59 mL, 38.4 mmol, 2 equiv.) in anhydrous ether (10 mL) was added dropwise. When addition was complete, the reaction was refluxed for 4 hours and filtered through celite. The filter cake was washed with ether and the filtrate was sequentially washed with water, saturated sodium bicarbonate, and brine. The organic layer was then dried with sodium sulfate, decanted and concentrated in vacuo.

The crude residue was then dissolved in methanol (55 mL) followed by addition of Zn/Cu-couple (2.5 g, 38.4 mmol, 2 equiv.) and ammonium chloride. The suspension was stirred overnight, and the reaction mixture was filtered through celite. The filter cake was washed with ether. The filtrate was then concentrated to remove most of the solvent and then diluted in ether. It was then transferred to a separatory funnel and sequentially washed with water, saturated sodium bicarbonate, and brine. The organics were then dried with sodium sulfate, decanted and concentrated in vacuo. Additional purification was achieved via column chromatography on silica gel (1:9 ethyl acetate/hexanes) to provide **81a** (2.40 g, 56%): clear liquid, ^1H -NMR (400 MHz; CDCl_3): δ 7.41-7.36 (m, 8H), 7.30-7.26 (m, 2H), 3.86 (s, 4H); ^{13}C -NMR (101 MHz; CDCl_3): δ 205.82 (s, 1C), 147.65 (s, 1C), 129.11 (s, 1C), 127.13 (s, 1C), 126.90 (s, 1C), 60.95 (s, 1C), 42.43 (s, 1C).

3,3-Di-*p*-tolylcyclobutan-1-one (**81b**)

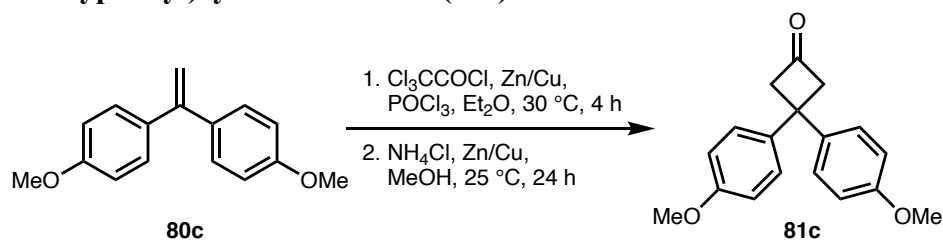


To a flame-dried flask equipped with a stir bar was added **80b** (3 g, 14.4 mmol, 1 equiv.), Zn/Cu-couple (2.07 g, 31.7 mmol, 2.2 equiv.), and anhydrous diethyl ether (14 mL). A solution of trichloroacetyl chloride (2.42 mL, 21.6 mmol, 1.5 equiv.) and phosphorus oxychloride (2.02 mL, 21.6 mmol, 1.5 equiv.) in anhydrous ether (7 mL) was added dropwise. When addition was complete, the reaction was refluxed for 4 hours and filtered through celite. The filter cake was

washed with ether and the filtrate was sequentially washed with water, saturated sodium bicarbonate, and brine. The organic layer was then dried with sodium sulfate, decanted and concentrated in vacuo.

The crude residue was then dissolved in methanol (41 mL) followed by addition of Zn/Cu-couple (2.07 g, 31.7 mmol, 2.2 equiv.) and ammonium chloride. The suspension was stirred overnight, and the reaction mixture was filtered through celite. The filter cake was washed with ether. The filtrate was then concentrated to remove most of the solvent and then dilute in ether. It was then transferred to a separatory funnel and sequentially washed with water, saturated sodium bicarbonate, and brine. The organics were then dried with sodium sulfate, decanted and concentrated in vacuo. Additional purification was achieved via column chromatography on silica gel (1:9 ethyl acetate/hexanes) to provide **81b** (1.98 g, 55%): clear liquid, $^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 7.30 (d, J = 8.1 Hz, 4H), 7.23 (d, J = 7.9 Hz, 4H), 3.86 (s, 4H), 2.41 (s, 6H). $^{13}\text{C-NMR}$ (126 MHz; CDCl_3): δ 206.26 (s, 1C), 145.01 (s, 1C), 136.42 (s, 1C), 129.79 (s, 1C), 127.02 (s, 1C), 60.95 (s, 1C), 41.82 (s, 1C), 21.41 (s, 1C).

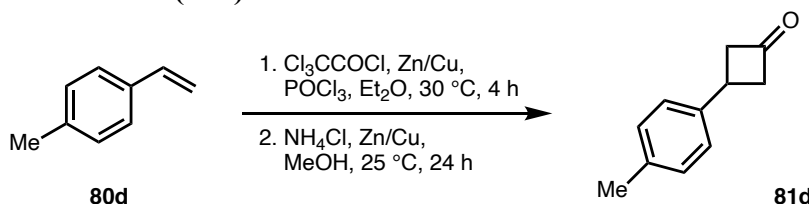
3,3-bis(4-methoxyphenyl)cyclobutan-1-one (**81c**)



To a flame-dried flask equipped with a stir bar was added **80c** (3.36 g, 14 mmol, 1 equiv.), Zn/Cu-couple (2.01 g, 30.8 mmol, 2.2 equiv.), and anhydrous diethyl ether (14 mL). A solution of trichloroacetyl chloride (2.35 mL, 21 mmol, 1.5 equiv.) and phosphorus oxychloride (1.96 mL, 21 mmol, 1.5 equiv.) in anhydrous ether (7 mL) was added dropwise. When addition was complete, the reaction was refluxed for 4 hours and filtered through celite. The filter cake was washed with ether and the filtrate was sequentially washed with water, saturated sodium bicarbonate, and brine. The organic layer was then dried with sodium sulfate, decanted and concentrated in vacuo.

The crude residue was then dissolved in methanol (40 mL) followed by addition of Zn/Cu-couple (2.01 g, 30.8 mmol, 2.2 equiv.) and ammonium chloride. The suspension was stirred overnight, and the reaction mixture was filtered through celite. The filter cake was washed with ether. The filtrate was then concentrated to remove most of the solvent and then dilute in ether. It was then transferred to a separatory funnel and sequentially washed with water, saturated sodium bicarbonate, and brine. The organics were then dried with sodium sulfate, decanted and concentrated in vacuo. Additional purification was achieved via column chromatography on silica gel (1:9 ethyl acetate/hexanes) to provide **81c** (0.99 g, 25%): clear liquid, $^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 7.70 (dd, J = 12.0, 7.4 Hz, 1H), 7.56 (t, J = 7.1 Hz, 1H), 7.47 (dd, J = 7.2, 5.3 Hz, 1H), 7.24-7.21 (m, 2H), 6.90-6.87 (m, 3H), 3.80 (s, 3H), 3.76 (s, 3H). $^{13}\text{C-NMR}$ (126 MHz; CDCl_3): δ 206.36 (s, 1C), 158.41 (s, 1C), 140.08 (s, 1C), 132.60 (s, 1C), 132.52 (s, 1C), 129.02 (s, 1C), 128.93 (s, 1C), 128.14 (s, 1C), 114.35 (s, 1C), 61.08 (s, 1C), 55.68 (s, 1C), 41.12 (s, 1C).

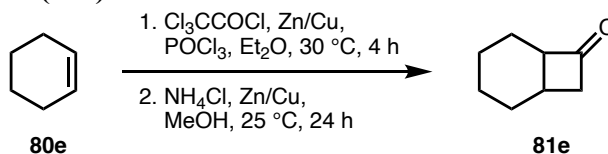
3-(*p*-Tolyl)cyclobutan-1-one (**81d**)



To a flame-dried flask equipped with a stir bar was added **80d** (2.5 mL, 19 mmol, 1 equiv.), Zn/Cu-couple (2.73 g, 41.8 mmol, 2.2 equiv.), and anhydrous diethyl ether (19 mL). A solution of trichloroacetyl chloride (3.2 mL, 28.5 mmol, 1.5 equiv.) and phosphorus oxychloride (2.66 mL, 28.5 mmol, 1.5 equiv.) in anhydrous ether (8 mL) was added dropwise. When addition was complete, the reaction as refluxed for 4 hours and filtered through celite. The filter cake was washed with ether and the filtrate was sequentially washed with water, saturated sodium bicarbonate, and brine. The organic layer was then dried with sodium sulfate, decanted and concentrated in vacuo.

The crude residue was then dissolved in methanol (54 mL) followed by addition of Zn/Cu-couple (2.73 g, 41.8 mmol, 2.2 equiv.) and ammonium chloride. The suspension was stirred overnight, and the reaction mixture was filtered through celite. The filter cake was washed with ether. The filtrate was then concentrated to remove most of the solvent and then dilute in ether. It was then transferred to a separatory funnel and sequentially washed with water, saturated sodium bicarbonate, and brine. The organics were then dried with sodium sulfate, decanted and concentrated in vacuo. Additional purification was achieved via column chromatography on silica gel (1:9 ethyl acetate/hexanes) to provide **81d** (1.76 g, 58%): clear liquid, FTIR ν_{max} 3083, 3056, 3025, 2956, 2921, 2865, 2828, 1950, 1875, 1780, 1601, 1582, 1540, 1496, 1444, 1379, 1331, 1301, 1274, 1225, 1217, 1185, 1156, 1141, 1130, 1099, 1079, 1041, 1028, 1000, 947, 911, 883, 871, 811, 762, 698, 651, 619, 587, 541, 524, 475, 448, 426, 404 cm^{-1} ; ^1H -NMR (400 MHz; CDCl_3): δ 7.23 (q, $J = 6.5$ Hz, 4H), 3.70-3.64 (m, 1H), 3.54-3.47 (m, 2H), 3.30-3.22 (m, 2H), 2.41-2.37 (m, 3H). ^{13}C -NMR (101 MHz; CDCl_3): δ 207.36 (s, 1C), 141.03 (s, 1C), 136.64 (s, 1C), 129.78 (s, 1C), 126.82 (s, 1C), 55.16 (s, 1C), 28.52 (s, 1C), 21.42 (s, 1C).

Bicyclo[4.2.0]octan-7-one (**81e**)

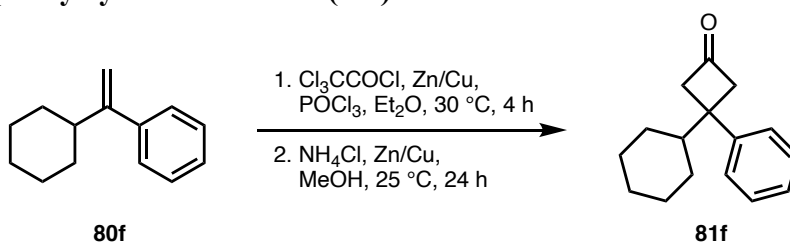


To a flame-dried flask equipped with a stir bar was added cyclohexene (**80e**) (1.92 mL, 19 mmol, 1 equiv.), Zn/Cu-couple (2.73 g, 41.8 mmol, 2.2 equiv.), and anhydrous diethyl ether (19 mL). A solution of trichloroacetyl chloride (3.2 mL, 28.5 mmol, 1.5 equiv.) and phosphorus oxychloride (2.66 mL, 28.5 mmol, 1.5 equiv.) in anhydrous ether (8 mL) was added dropwise. When addition was complete, the reaction as refluxed for 4 hours and filtered through celite. The filter cake was washed with ether and the filtrate was sequentially washed with water, saturated sodium bicarbonate, and brine. The organic layer was then dried with sodium sulfate, decanted and concentrated in vacuo.

The crude residue was then dissolved in methanol (54 mL) followed by addition of Zn/Cu-couple (2.73 g, 41.8 mmol, 2.2 equiv.) and ammonium chloride. The suspension was stirred overnight,

and the reaction mixture was filtered through celite. The filter cake was washed with ether. The filtrate was then concentrated to remove most of the solvent and then dilute in ether. It was then transferred to a separatory funnel and sequentially washed with water, saturated sodium bicarbonate, and brine. The organics were then dried with sodium sulfate, decanted and concentrated in vacuo. Additional purification was achieved via column chromatography on silica gel (1:9 ethyl acetate/hexanes) to provide **81e** (0.812 g, 34%): clear liquid; FTIR_{max} 2972, 2941, 2866, 1719, 1451, 1423, 1345, 1333, 1308, 1270, 1255, 1217, 1176, 1130, 1113, 1057, 990, 965, 838, 662, 551 cm⁻¹; ¹H-NMR (400 MHz; CDCl₃): δ 3.22-3.17 (m, 1H), 3.06 (ddd, *J* = 16.3, 9.1, 2.4 Hz, 1H), 2.41-2.36 (m, 2H), 2.11-2.06 (m, 1H), 1.87 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.53-1.44 (m, 2H), 1.41-1.31 (m, 1H), 1.16-0.99 (m, 3H). ¹³C-NMR (101 MHz; CDCl₃): δ 210.07 (s, 1C), 56.95 (s, 1C), 52.44 (s, 1C), 29.83 (s, 1C), 22.91 (s, 1C), 22.82 (s, 1C), 22.71 (s, 1C), 21.54 (s, 1C).

3-Cyclohexyl-3-phenylcyclobutan-1-one (**81f**)

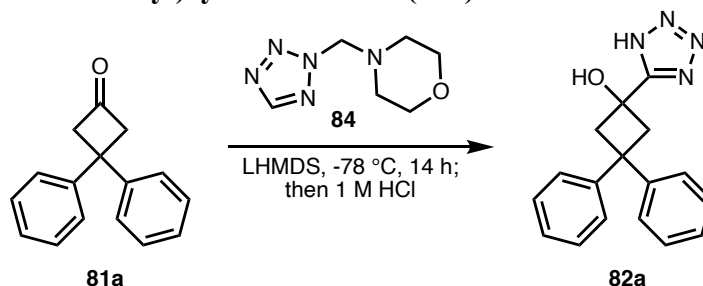


To a flame-dried flask equipped with a stir bar was added (1-cyclohexylvinyl)benzene (**80f**) (900 mg, 4.83 mmol, 1 equiv.), Zn/Cu-couple (695 mg, 10.6 mmol, 2.2 equiv.), and anhydrous diethyl ether (5 mL). A solution of trichloroacetyl chloride (0.813 mL, 7.25 mmol, 1.5 equiv.) and phosphorus oxychloride (0.675 mL, 7.25 mmol, 1.5 equiv.) in anhydrous ether (2 mL) was added dropwise. When addition was complete, the reaction was refluxed for 4 hours and filtered through celite. The filter cake was washed with ether and the filtrate was sequentially washed with water, saturated sodium bicarbonate, and brine. The organic layer was then dried with sodium sulfate, decanted and concentrated in vacuo.

The crude residue was then dissolved in methanol (14 mL) followed by addition of Zn/Cu-couple (695 mg, 10.6 mmol, 2.2 equiv.) and ammonium chloride. The suspension was stirred overnight, and the reaction mixture was filtered through celite. The filter cake was washed with ether. The filtrate was then concentrated to remove most of the solvent and then dilute in ether. It was then transferred to a separatory funnel and sequentially washed with water, saturated sodium bicarbonate, and brine. The organics were then dried with sodium sulfate, decanted and concentrated in vacuo. Additional purification was achieved via column chromatography on silica gel (1:9 ethyl acetate/hexanes) to provide **81f** (350 mg, 32%): clear liquid, ¹H-NMR (400 MHz; CDCl₃): δ 7.37-7.17 (m, 5H), 3.40-3.28 (m, 2H), 1.88-1.75 (m, 4H), 1.63-1.51 (m, 2H), 1.40-1.18 (m, 4H), 1.00-0.91 (m, 1H), 0.83-0.74 (m, 1H). ¹³C-NMR (101 MHz; CDCl₃): δ 208.07 (s, 1C), 144.56 (s, 1C), 128.59 (s, 1C), 128.01 (s, 1C), 127.37 (s, 1C), 127.02 (s, 1C), 126.56 (s, 1C), 57.26 (s, 1C), 48.01 (s, 1C), 42.18 (s, 1C), 33.13 (s, 1C), 28.48 (s, 1C), 27.23 (s, 1C), 26.93 (s, 1C), 26.84 (s, 1C), 26.33 (s, 1C).

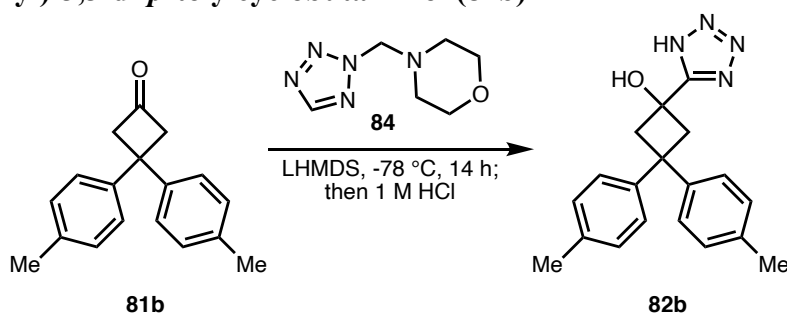
2.2 Tetrazole Additions

3,3-Diphenyl-1-(1*H*-tetrazol-5-yl)cyclobutan-1-ol (**82a**)



To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**84**) (338 mg, 2 mmol, 2 equiv) and cyclobutanone **81a** (222 mg, 1 mmol, 1 equiv) in THF (5.0 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (368 mg, 2.2 mmol, 2.2 equiv) in THF (2.0 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 25 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 50 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:4 acetone/hexanes) to provide **82a** (160 mg, 55%): white solid; FTIR ν_{max} 3419, 3022, 2995, 2948, 2848, 2776, 2627, 1598, 1580, 1537, 1496, 1444, 1430, 1410, 1386, 1318, 1249, 1223, 1206, 1181, 1128, 1095, 1063, 1032, 1016, 1000, 980, 908, 889, 852, 841, 806, 756, 706, 594, 623, 585, 574, 568, 504, 483, 444, 437, 425, 416, 405 cm⁻¹; ¹H-NMR (400 MHz; (CD₃)₂CO): δ 7.49 (dt, *J* = 8.3, 1.5 Hz, 2H), 7.38 (dt, *J* = 8.3, 1.5 Hz, 2H), 7.33-7.29 (m, 2H), 7.24-7.21 (m, 2H), 7.17-7.13 (m, 1H), 7.10-7.06 (m, 1H), 3.76 (d, *J* = 13.5 Hz, 2H), 3.42 (d, *J* = 13.5 Hz, 2H); ¹³C-NMR (101 MHz; (CD₃)₂CO): δ 150.45 (s, 1C), 128.63 (s, 1C), 128.50 (s, 1C), 126.58 (s, 1C), 126.53 (s, 1C), 125.87 (s, 1C), 125.83 (s, 1C), 66.56 (s, 1C), 49.40 (s, 1C), 44.10 (s, 1C). HRMS-ESI calculated for C₁₇H₁₇N₄O [M+H]⁺: 293.1402, found 293.1402.

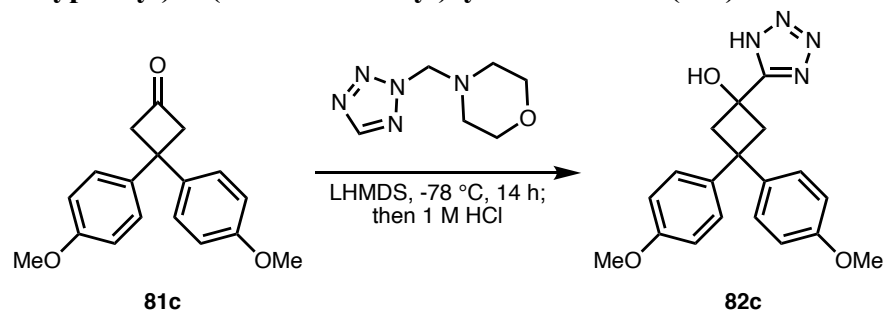
1-(1*H*-Tetrazol-5-yl)-3,3-di-*p*-tolylcyclobutan-1-ol (**82b**)



To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**84**) (2.678 g, 15.8 mmol, 2 equiv) and cyclobutanone **81a** (1.981 g, 7.91 mmol, 1 equiv) in THF (40 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (2.913 g, 17.4 mmol, 2.2 equiv) in THF (17 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 100 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 100 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was

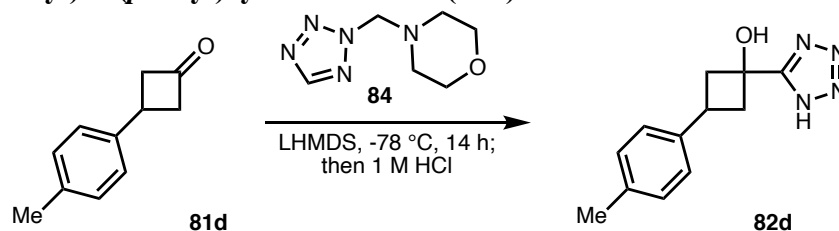
purified by flash column chromatography on silica gel (1:4 acetone/hexanes) to provide **82b** (2.20 g, 87%): white solid; FTIR ν_{max} 3343, 3201, 3031, 2973, 2934, 2906, 2834, 1711, 1654, 1608, 1580, 1507, 1462, 1453, 1441, 1417, 1381, 1299, 1290, 1242, 1176, 1115, 1095, 1027, 929, 932, 895, 825, 808, 759, 739, 702, 661, 636, 619, 566, 552, 485, 475, 460, 451, 442, 432, 416, 410 cm^{-1} ; ^1H -NMR (500 MHz; $(\text{CD}_3)_2\text{CO}$): δ 7.40-6.96 (m, 8H), 3.91 (d, J = 12.4 Hz, 1H), 3.59 (d, J = 0.2 Hz, 2H), 3.26-3.18 (m, 1H), 2.26 (d, J = 5.6 Hz, 3H), 2.21-2.18 (m, 3H). ^{13}C -NMR (126 MHz; $(\text{CD}_3)_2\text{CO}$): δ 170.55 (s, 1C), 134.92 (s, 1C), 129.29 (s, 1C), 129.21 (s, 1C), 129.11 (s, 1C), 126.75 (s, 1C), 126.66 (s, 1C), 126.06 (s, 1C), 126.01 (s, 1C), 80.52 (s, 1C), 66.70 (s, 1C), 49.75 (s, 1C), 48.86 (s, 1C).

3,3-Bis(4-methoxyphenyl)-1-(1*H*-tetrazol-5-yl)cyclobutan-1-ol (**82c**)



To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**84**) (1190 mg, 7.03 mmol, 2 equiv) and cyclobutanone **81c** (993 mg, 1 mmol, 1 equiv) in THF (17 mL), under nitrogen at $-78\text{ }^{\circ}\text{C}$ (acetone/ CO_2), was added a freshly prepared solution of LHMDS (1295 mg, 7.74 mmol, 2.2 equiv) in THF (17 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at $-78\text{ }^{\circ}\text{C}$, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 100 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 100 mL). The combined extracts were dried over Na_2SO_4 , filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:4 acetone/hexanes) to provide **82c** (1008 mg, 81%): white solid; FTIR ν_{max} 3232, 3090, 3046, 3018, 2990, 2943, 2919, 2859, 2211, 1710, 1654, 1574, 1509, 1445, 1417, 1375, 1359, 1314, 1255, 1206, 1188, 1172, 1114, 1090, 1068, 1047, 1017, 981, 941, 898, 865, 841, 808, 793, 763, 731, 667, 620, 561, 537, 522, 500, 476, 459, 451, 444, 435, 424, 417, 407 cm^{-1} ; ^1H -NMR (500 MHz; $(\text{CD}_3)_2\text{CO}$): δ 7.30 (dd, J = 51.3, 8.7 Hz, 8H), 6.88-6.77 (m, 8H), 3.76 (s, 3H), 3.72 (d, J = 6.0 Hz, 3H), 3.69-3.68 (m, 2H), 3.34 (d, J = 13.2 Hz, 2H). ^{13}C -NMR (126 MHz; $(\text{CD}_3)_2\text{CO}$): δ 161.93 (s, 1C), 157.92 (s, 1C), 142.82 (s, 1C), 141.78 (s, 1C), 127.67 (s, 1C), 127.64 (s, 1C), 113.92 (s, 1C), 113.80 (s, 1C), 66.43 (s, 1C), 55.01 (s, 1C), 54.92 (s, 1C), 49.66 (s, 1C), 42.73 (s, 1C).

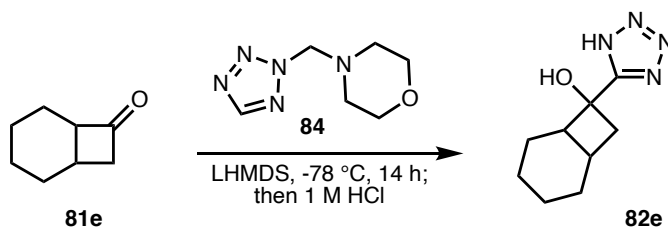
1-(1*H*-Tetrazol-5-yl)-3-(*p*-tolyl)cyclobutan-1-ol (**82d**)



To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**84**) (1732 mg, 10.2 mmol, 2 equiv) and cyclobutanone **81d** (820 mg, 5.12 mmol, 1 equiv) in THF (25 mL), under nitrogen at $-78\text{ }^{\circ}\text{C}$

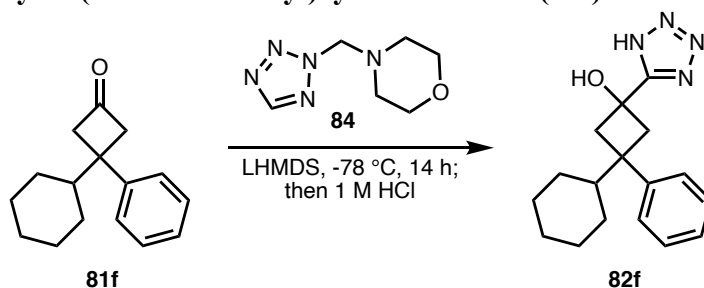
(acetone/CO₂), was added a freshly prepared solution of LHMDS (1884 mg, 11.3 mmol, 2.2 equiv) in THF (17 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 100 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 100 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:4 acetone/hexanes) to provide **82d** (767 mg, 65%): white solid; FTIR ν_{max} 3133, 2982, 2936, 2859, 2732, 1664, 1609, 1548, 1514, 1447, 1421, 1377, 1309, 1284, 1244, 1209, 1191, 1182, 1093, 1034, 1020, 954, 897, 808, 780, 757, 714, 698, 650, 624, 563, 540, 504, 485, 477, 454, 445, 439, 431, 423, 406 cm⁻¹; ¹H-NMR (400 MHz; (CD₃)₂CO): δ 7.23-7.14 (m, 5H), 3.59-3.58 (m, 1H), 3.09-3.04 (m, 2H), 2.68-2.63 (m, 2H), 2.29 (d, J = 4.9 Hz, 3H). ¹³C-NMR (101 MHz; (CD₃)₂CO): δ 161.93 (s, 1C), 141.82 (s, 1C), 135.85 (s, 1C), 129.37 (s, 1C), 126.93 (s, 1C), 67.13 (s, 1C), 45.53 (s, 1C), 29.82 (s, 1C), 20.57 (s, 1C). HRMS-ESI calculated for C₁₂H₁₅N₄O [M+H]⁺: 231.1246, found 231.1242.

7-(1*H*-Tetrazol-5-yl)bicyclo[4.2.0]octan-7-ol (**82e**)



To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**84**) (2213 mg, 13.1 mmol, 2 equiv) and cyclobutanone **81e** (812 mg, 6.54 mmol, 1 equiv) in THF (31 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (2407 mg, 14.4 mmol, 2.2 equiv) in THF (17 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 100 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 100 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:4 acetone/hexanes) to provide **82e** (748 mg, 59%): white solid; FTIR- ν_{max} 3311, 3139, 3082, 3055, 3023, 2997, 2946, 1731, 1659, 1651, 1633, 1621, 1614, 1596, 1557, 1538, 1491, 1445, 1417, 1372, 1318, 1252, 1186, 1155, 1092, 1043, 1027, 1001, 979, 909, 826, 773, 746, 695, 668, 638, 618, 584, 555, 523, 493, 487, 477, 457, 448, 440, 425, 417, 401 cm⁻¹; ¹H-NMR (500 MHz; (CD₃)₂CO): δ 9.23 (s, 1H), 2.77-2.72 (m, 1H), 2.60-2.56 (m, 1H), 2.46 (dd, J = 8.5, 1.7 Hz, 2H), 1.97-1.89 (m, 1H), 1.74-1.68 (m, 2H), 1.58-1.52 (m, 3H), 1.52-1.42 (m, 2H). ¹³C-NMR (126 MHz; (CD₃)₂CO): δ 162.67 (s, 1C), 69.58 (s, 1C), 43.93 (s, 1C), 38.24 (s, 1C), 25.96 (s, 1C), 23.99 (s, 1C), 22.67 (s, 1C), 21.83 (s, 1C), 21.53 (s, 1C). HRMS-ESI calculated for C₉H₁₅N₄O [M+H]⁺: 195.1246, found 195.1245.

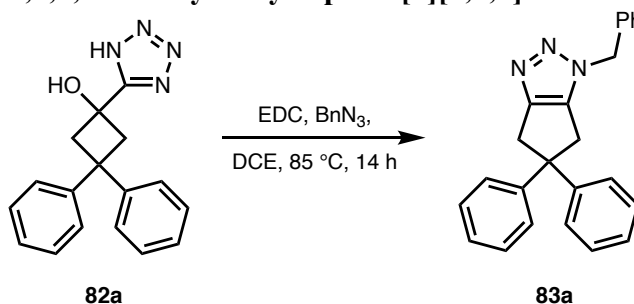
3-Cyclohexyl-3-phenyl-1-(1*H*-tetrazol-5-yl)cyclobutan-1-ol (**82f**)



To a stirred solution of 4-((*N*-tetrazolyl)methyl)morpholine (**84**) (519 mg, 3.07 mmol, 2 equiv) and cyclobutanone **81f** (350 mg, 1.53 mmol, 1 equiv) in THF (15 mL), under nitrogen at -78 °C (acetone/CO₂), was added a freshly prepared solution of LHMDS (564 mg, 3.37 mmol, 2.2 equiv) in THF (3 mL) dropwise via syringe over 5 min. The reaction was stirred for 2 h at -78 °C, allowed to warm to room temperature over 14 h, and then concentrated under reduced pressure. The remaining residue was treated with aqueous HCl (1 N, 25 mL), stirred at room temperature for 1 h, and the solution extracted with EtOAc (3 x 50 mL). The combined extracts were dried over Na₂SO₄, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:4 acetone/hexanes) to provide **82f** (288 mg, 63%): white solid; FTIR ν_{max} 3140, 3054, 3024, 2983, 2923, 2850, 1671, 1601, 1545, 1493, 1443, 1413, 1367, 1349, 1331, 1253, 1235, 1209, 1170, 1137, 1092, 1072, 1038, 1001, 980, 915, 891, 866, 838, 765, 702, 587, 541, 519, 465, 454, 436, 424, 418 cm⁻¹; ¹H-NMR (400 MHz; (CD₃)₂CO): δ 7.25 (m, 2H), 7.16-7.09 (m, 3H), 3.21 (d, *J* = 13.4 Hz, 2H), 2.90 (d, *J* = 13.4 Hz, 2H), 1.88 (s, 2H), 1.72 (d, *J* = 13.0 Hz, 3H), 1.59-1.56 (m, 1H), 1.30-1.21 (m, 3H), 0.87 (dddd, *J* = 17.1, 13.0, 8.9, 4.1 Hz, 1H), 0.58 (qd, *J* = 12.4, 2.7 Hz, 2H). ¹³C-NMR (101 MHz; (CD₃)₂CO): δ 162.53 (s, 1C), 145.53 (s, 1C), 128.14 (s, 1C), 127.42 (s, 1C), 125.78 (s, 1C), 66.54 (s, 1C), 48.85 (s, 1C), 47.19 (s, 1C), 43.22 (s, 1C), 30.27 (s, 1C), 27.46 (s, 1C), 26.96 (s, 1C), 26.68 (s, 1C).

2.3 In-Situ Trapping of Cyclopentynes with Benzyl Azide

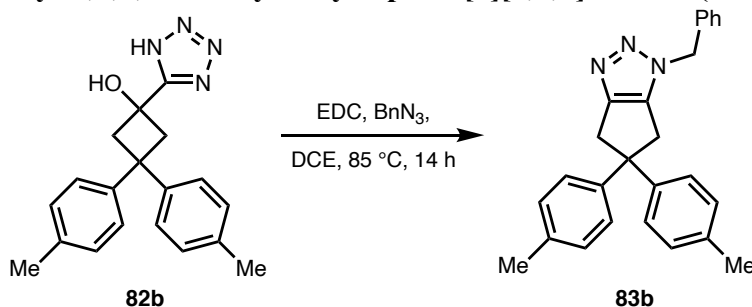
1-Benzyl-5,5-diphenyl-1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazole (**83a**)



To an oven-dried vial equipped with a teflon cap was added **82a** (146 mg, 0.5 mmol, 1 equiv), benzyl azide (0.309 mL, 2.5 mmol, 5 equiv), and EDC (115 mg, 0.6 mmol, 1.2 equiv) in anhydrous EDC (2.5 mL). The vial was flushed with nitrogen and capped. It was then refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **83a** (102 mg, 58 %): oil; FTIR ν_{max} 3290, 3056, 3023, 2926, 2854, 1708, 1650, 1596, 1528, 1492, 1445, 1358, 1312, 1254, 1219, 1204, 1157, 1090, 1045, 1026, 1001, 980, 909, 828, 747, 694, 632, 617, 584, 561, 528, 456, 433, 404 cm⁻¹; ¹H-NMR (400 MHz; CDCl₃): δ

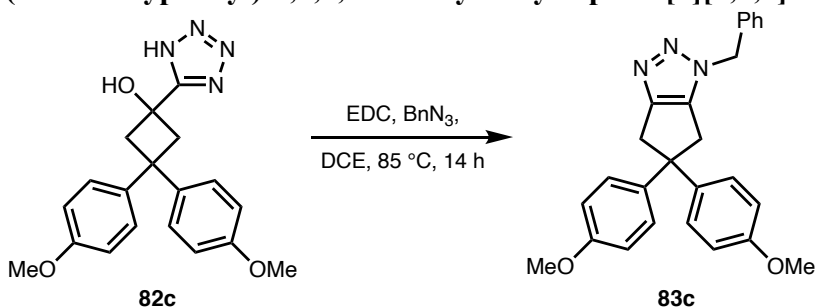
7.47-7.44 (m, 3H), 7.42-7.40 (m, 1H), 7.38-7.32 (m, 9H), 7.47-7.18 (m, 17H), 7.22-7.18 (m, 3H), 4.38 (s, 1H), 4.38 (s, 1H), 3.62 (d, $J = 14.4$ Hz, 2H), 3.62 (d, $J = 14.4$ Hz, 2H), 3.12 (d, $J = 14.4$ Hz, 2H), 3.12 (d, $J = 14.4$ Hz, 2H), 2.84 (s, 1H), 2.84 (s, 1H); ^{13}C -NMR (101 MHz; CDCl_3): δ 148.90 (s, 1C), 148.81 (s, 1C), 129.49 (s, 1C), 129.27 (s, 1C), 129.09 (s, 1C), 129.00 (s, 1C), 128.87 (s, 1C), 128.74 (s, 1C), 128.65 (s, 1C), 128.58 (s, 1C), 127.14 (s, 1C), 127.10 (s, 1C), 126.83 (s, 1C), 126.70 (s, 1C), 126.64 (s, 1C), 126.54 (s, 1C), 126.41 (s, 1C), 126.35 (s, 1C), 126.32 (s, 1C), 125.94 (s, 1C), 125.82 (s, 1C), 106.25 (s, 1C), 81.12 (s, 1C), 55.23 (s, 1C), 44.79 (s, 1C), 41.62 (s, 1C). HRMS-ESI calculated for $\text{C}_{24}\text{H}_{22}\text{N}_3$ $[\text{M}+\text{H}]^+$: 352.1814, found 352.1807.

1-Benzyl-5,5-di-*p*-tolyl-1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazole (**83b**)



To an oven-dried vial equipped with a teflon cap was added **82b** (160 mg, 0.5 mmol, 1 equiv), benzyl azide (0.309 mL, 2.5 mmol, 5 equiv), and EDC (115 mg, 0.6 mmol, 1.2 equiv) in anhydrous EDC (2.5 mL). The vial was flushed with nitrogen and capped. It was then refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **83b** (72.3 mg, 38 %): oil; FTIR ν_{max} 3296, 3087, 3019, 2990, 2920, 2855, 2732, 1716, 1654, 1607, 1572, 1509, 1452, 1376, 1356, 1314, 1293, 1231, 1205, 1189, 1175, 1115, 1089, 1043, 1017, 982, 941, 908, 808, 728, 702, 663, 645, 619, 559, 538, 524, 503, 478, 457, 423, 409, 403 cm^{-1} ; ^1H -NMR (500 MHz; CDCl_3): δ 7.38-6.93 (m, 15H), 5.48 (s, 2H), 3.51 (s, 2H), 3.14 (s, 2H), 2.31 (s, 6H). ^{13}C -NMR (126 MHz; CDCl_3): δ 154.57 (s, 1C), 145.67 (s, 1C), 136.27 (s, 1C), 129.67 (s, 1C), 129.59 (s, 1C), 129.54 (s, 1C), 129.44 (s, 1C), 129.36 (s, 1C), 129.24 (s, 1C), 129.10 (s, 1C), 129.04 (s, 1C), 128.42 (s, 1C), 126.98 (s, 1C), 126.87 (s, 1C), 126.70 (s, 1C), 126.61 (s, 1C), 126.48 (s, 1C), 126.35 (s, 1C), 125.98 (s, 1C), 53.68 (s, 1C), 49.14 (s, 1C), 38.57 (s, 1C), 38.41 (s, 1C), 37.38 (s, 1C), 21.33 (s, 1C), 21.26 (s, 1C). HRMS-ESI calculated for $\text{C}_{26}\text{H}_{26}\text{N}_3$ $[\text{M}+\text{H}]^+$: 380.2127, found 380.2121.

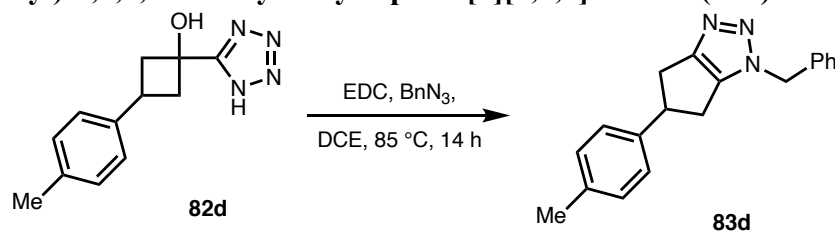
1-Benzyl-5,5-bis(4-methoxyphenyl)-1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazole (**83c**)



To an oven-dried vial equipped with a teflon cap was added **82c** (176 mg, 0.5 mmol, 1 equiv), benzyl azide (0.309 mL, 2.5 mmol, 5 equiv), and EDC (115 mg, 0.6 mmol, 1.2 equiv) in anhydrous EDC (2.5 mL). The vial was flushed with nitrogen and capped. It was then refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel

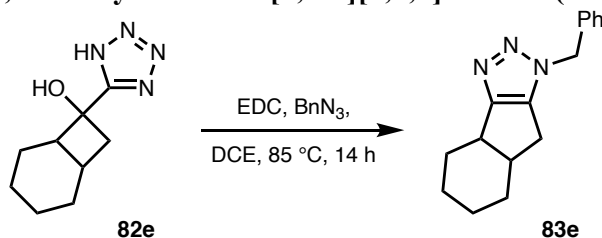
(EtOAc:Hex 1:3) **83c** (92.1 mg, 45 %): oil; FTIR ν_{max} 3327, 3058, 3030, 2996, 2930, 2852, 2834, 1712, 1647, 1605, 1579, 1507, 1454, 1440, 1360, 1291, 1242, 1176, 1120, 1098, 1028, 981, 908, 824, 756, 727, 704, 667, 645, 636, 617, 587, 563, 458, 437, 423 cm^{-1} ; ^1H -NMR (400 MHz; CDCl_3): δ 7.36 (t, J = 3.0 Hz, 4H), 7.23-7.21 (m, 4H), 6.94 (d, J = 8.7 Hz, 4H), 6.75 (d, J = 8.7 Hz, 5H), 5.48 (s, 2H), 3.77 (s, 7H), 3.48 (s, 2H), 3.10 (s, 2H). ^{13}C -NMR (101 MHz; CDCl_3): δ 158.29 (s, 1C), 154.63 (s, 1C), 140.90 (s, 1C), 129.43 (s, 1C), 129.03 (s, 1C), 128.40 (s, 1C), 128.13 (s, 1C), 114.20 (s, 1C), 113.97 (s, 1C), 62.93 (s, 1C), 60.78 (s, 1C), 55.62 (s, 1C), 53.67 (s, 1C), 38.84 (s, 1C), 37.65 (s, 1C). HRMS-ESI calculated for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 412.2025, found 412.2014.

1-Benzyl-5-(*p*-tolyl)-1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazole (**83d**)



To an oven-dried vial equipped with a teflon cap was added **82d** (115 mg, 0.5 mmol, 1 equiv), benzyl azide (0.309 mL, 2.5 mmol, 5 equiv), and EDC (115 mg, 0.6 mmol, 1.2 equiv) in anhydrous EDC (2.5 mL). The vial was flushed with nitrogen and capped. It was then refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **83d** (83.5 mg, 58%): oil; FTIR ν_{max} 3291, 3132, 3093, 3004, 2921, 2854, 1735, 1723, 1663, 1606, 1573, 1540, 1514, 1496, 1454, 1426, 1378, 1352, 1308, 1283, 1245, 1229, 1208, 1178, 1110, 1101, 1039, 1019, 958, 904, 809, 752, 735, 702, 673, 644, 575, 541, 513, 483, 473, 464, 456, 425, 412, 406, 400 cm^{-1} ; ^1H -NMR (400 MHz; CDCl_3): δ 7.40-7.07 (m, 10H), 5.47 (s, 1H), 4.15-3.99 (m, 1H), 3.51-3.39 (m, 1H), 3.25-3.19 (m, 1H), 2.90-2.80 (m, 1H), 2.69-2.48 (m, 1H), 2.36-2.34 (m, 3H). ^{13}C -NMR (101 MHz; CDCl_3): δ 155.18 (s, 1C), 136.81 (s, 1C), 129.75 (s, 1C), 129.44 (s, 1C), 129.07 (s, 1C), 128.66 (s, 1C), 127.05 (s, 1C), 127.01 (s, 1C), 126.95 (s, 1C), 126.85 (s, 1C), 53.75 (s, 1C), 51.01 (s, 1C), 32.22 (s, 1C), 31.31 (s, 1C), 21.38 (s, 1C). HRMS-ESI calculated for $\text{C}_{19}\text{H}_{20}\text{N}_3$ $[\text{M}+\text{H}]^+$: 290.1657, found 290.1648.

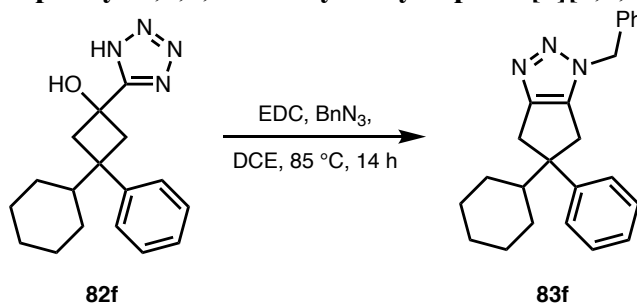
1-Benzyl-1,3b,4,5,6,7,7a,8-octahydroindeno[1,2-*d*][1,2,3]triazole (**83e**)



To an oven-dried vial equipped with a teflon cap was added **82e** (100 mg, 0.5 mmol, 1 equiv), benzyl azide (0.309 mL, 2.5 mmol, 5 equiv), and EDC (115 mg, 0.6 mmol, 1.2 equiv) in anhydrous EDC (2.5 mL). The vial was flushed with nitrogen and capped. It was then refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **83e** (33.4 mg, 26 %): oil; FTIR ν_{max} 3290, 3131, 2921, 2854, 1718, 1662, 1605, 1572, 1514, 1496, 1453, 1426, 1377, 1352, 1308, 1282, 1246, 1209, 1178, 1098, 1039, 1019, 960, 906, 809, 752, 703, 668, 643, 575, 541, 505, 483, 455, 422, 416, 403 cm^{-1} ; ^1H -NMR (500 MHz; CDCl_3): δ 7.41-7.24 (m, 5H), 5.50-5.43 (m, 2H), 3.05-3.01 (m, 1H), 2.92-2.87 (m,

2H), 2.79-2.70 (m, 2H), 2.62-2.53 (m, 2H), 2.42-2.36 (m, 2H), 2.18-2.14 (m, 1H). ^{13}C -NMR (126 MHz; CDCl_3): δ 164.82 (s, 1C), 163.71 (s, 1C), 145.86 (s, 1C), 145.58 (s, 1C), 129.35 (s, 1C), 129.29 (s, 1C), 128.88 (s, 1C), 128.48 (s, 1C), 128.11 (s, 1C), 53.54 (s, 1C), 53.35 (s, 1C), 45.73 (s, 1C), 45.58 (s, 1C), 36.33 (s, 1C), 36.16 (s, 1C), 28.89 (s, 1C), 28.17 (s, 1C), 27.89 (s, 1C), 27.66 (s, 1C), 23.23 (s, 1C), 23.07 (s, 1C), 22.95 (s, 1C), 22.39 (s, 1C).

1-Benzyl-5-cyclohexyl-5-phenyl-1,4,5,6-tetrahydrocyclopenta[*d*][1,2,3]triazole (**83f**)



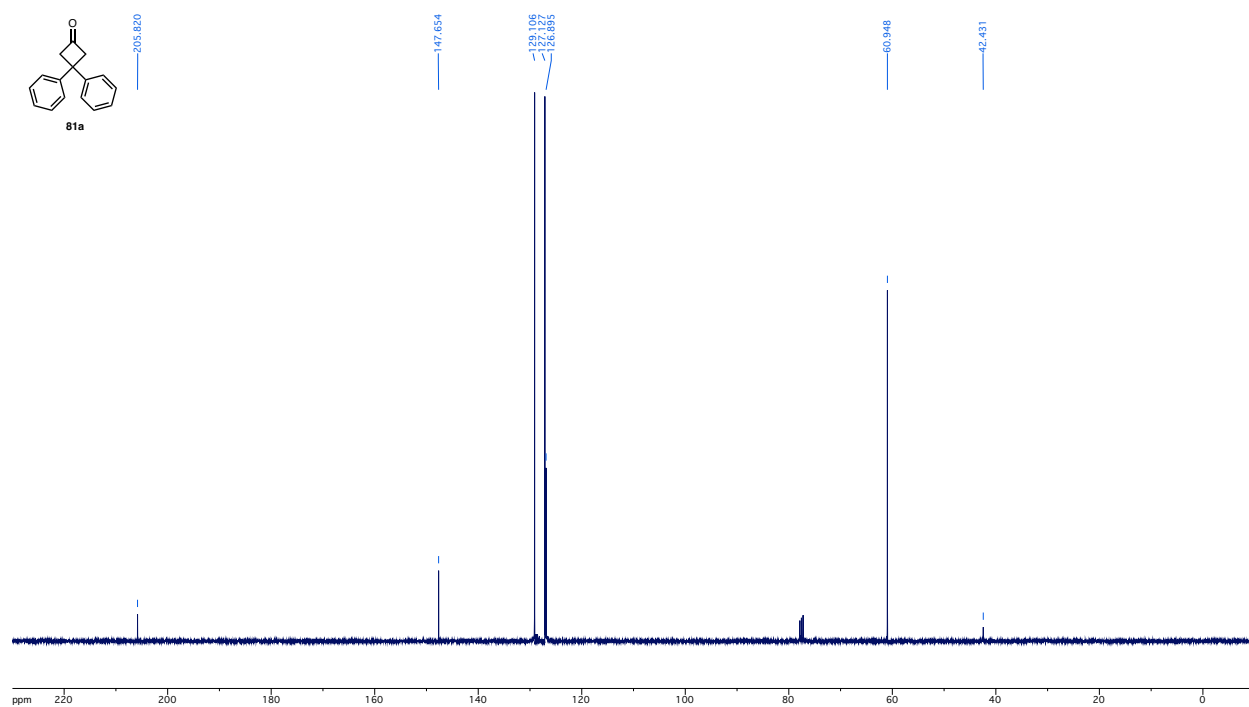
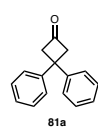
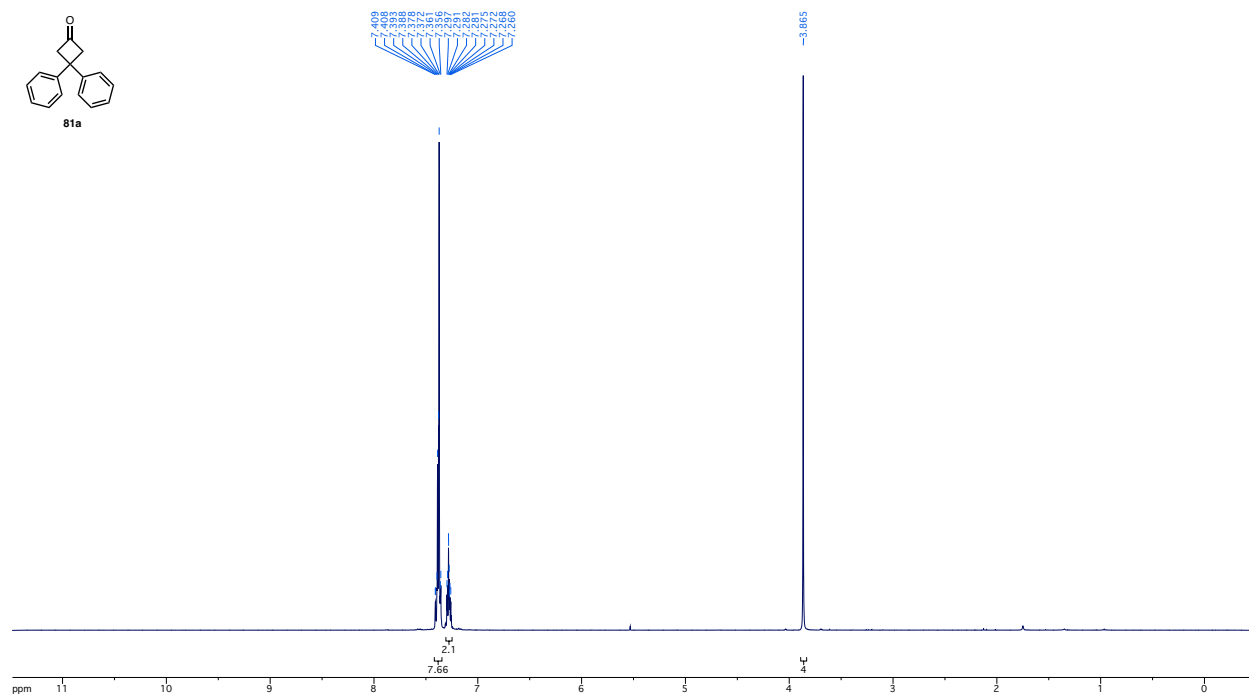
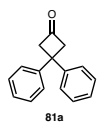
To an oven-dried vial equipped with a teflon cap was added **82f** (149 mg, 0.5 mmol, 1 equiv), benzyl azide (0.309 mL, 2.5 mmol, 5 equiv), and EDC (115 mg, 0.6 mmol, 1.2 equiv) in anhydrous DCE (2.5 mL). The vial was flushed with nitrogen and capped. It was then refluxed at 38 °C for 14 hours, to provide, after purification by column chromatography on silica gel (EtOAc:Hex 1:3) **83f** (134 mg, 75%) as an inseparable mixture of regioisomers: oil; FTIR ν_{max} 3299, 3082, 3058, 3028, 2973, 2924, 2851, 1740, 1713, 1645, 1601, 1537, 1493, 1450, 1444, 1380, 1364, 1349, 1300, 1255, 1219, 1182, 1151, 1116, 1076, 1027, 933, 912, 890, 841, 791, 766, 759, 725, 699, 603, 589, 561, 529, 511, 493, 471, 462, 453, 438, 425, 417, 411 cm^{-1} ; ^1H -NMR (500 MHz; CDCl_3): δ 7.36-7.18 (m, 16H), 5.73 (d, J = 0.5 Hz, 1H), 4.42 (dd, J = 32.6, 5.7 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 2.75-2.51 (m, 5H), 1.82-1.55 (m, 10H), 1.33-1.18 (m, 12H), 0.89 (dt, J = 17.1, 5.3 Hz, 6H). ^{13}C -NMR (126 MHz; CDCl_3): δ 175.23 (s, 1C), 171.54 (s, 1C), 148.04 (s, 1C), 144.82 (s, 1C), 138.86 (s, 1C), 138.76 (s, 1C), 129.06 (s, 1C), 128.59 (s, 1C), 128.16 (s, 1C), 127.83 (s, 1C), 127.64 (s, 1C), 127.60 (s, 1C), 127.29 (s, 1C), 126.05 (s, 1C), 125.68 (s, 1C), 60.79 (s, 1C), 50.10 (s, 1C), 46.54 (s, 1C), 43.97 (s, 1C), 36.82 (s, 1C), 35.32 (s, 1C), 35.10 (s, 1C), 35.07 (s, 1C), 34.44 (s, 1C), 32.00 (s, 1C), 27.95 (s, 1C), 27.45 (s, 1C), 27.22 (s, 1C), 26.89 (s, 1C), 26.66 (s, 1C), 23.05 (s, 1C), 21.44 (s, 1C), 21.10 (s, 1C), 14.60 (s, 1C), 14.52 (s, 1C), 11.83 (s, 1C).

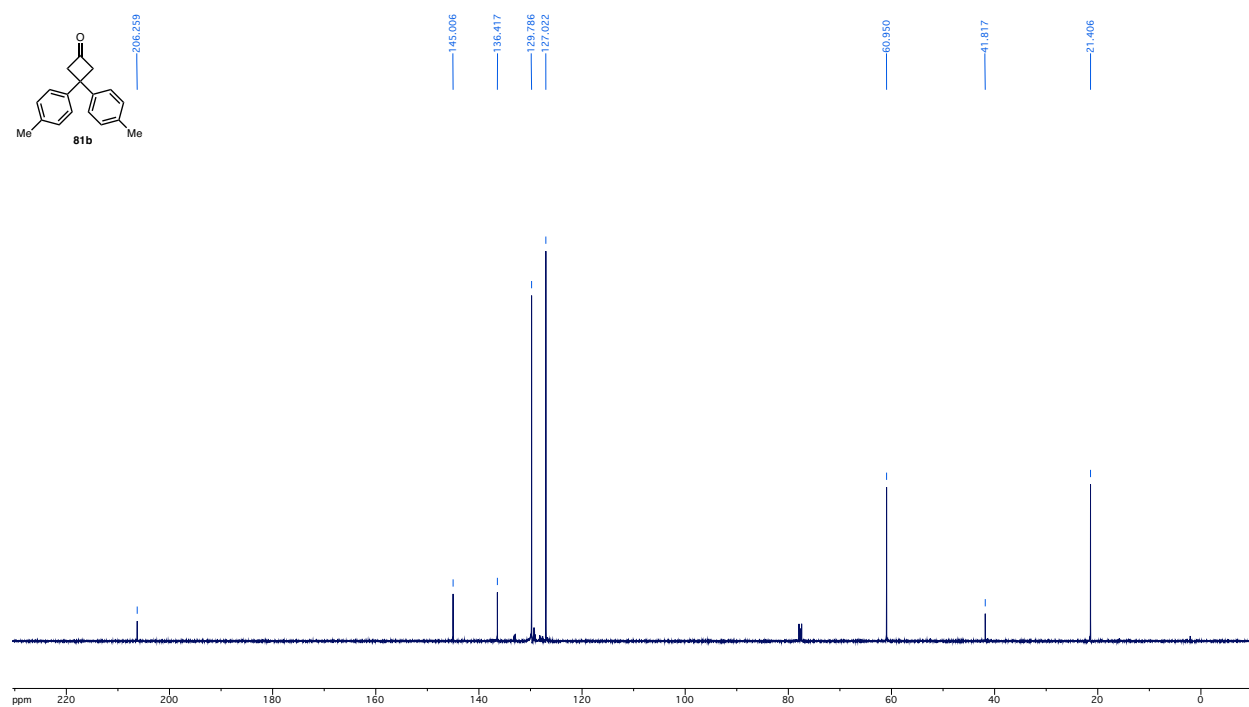
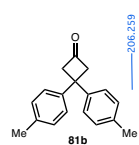
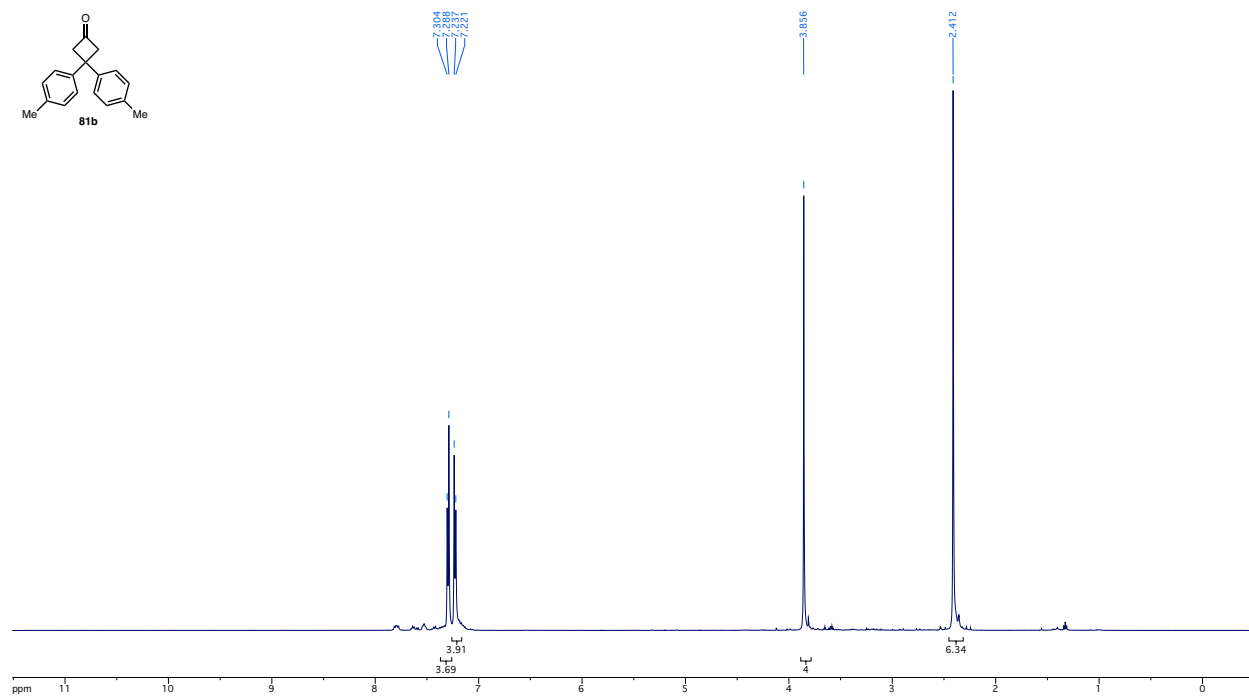
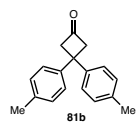
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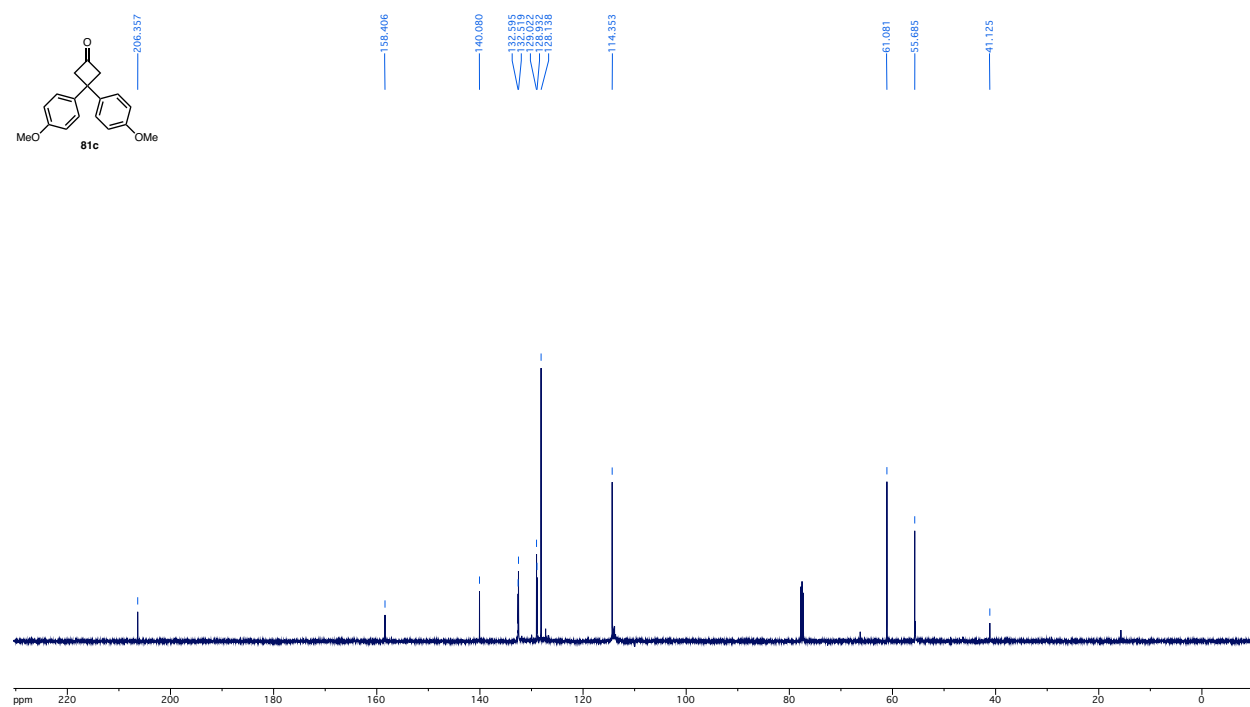
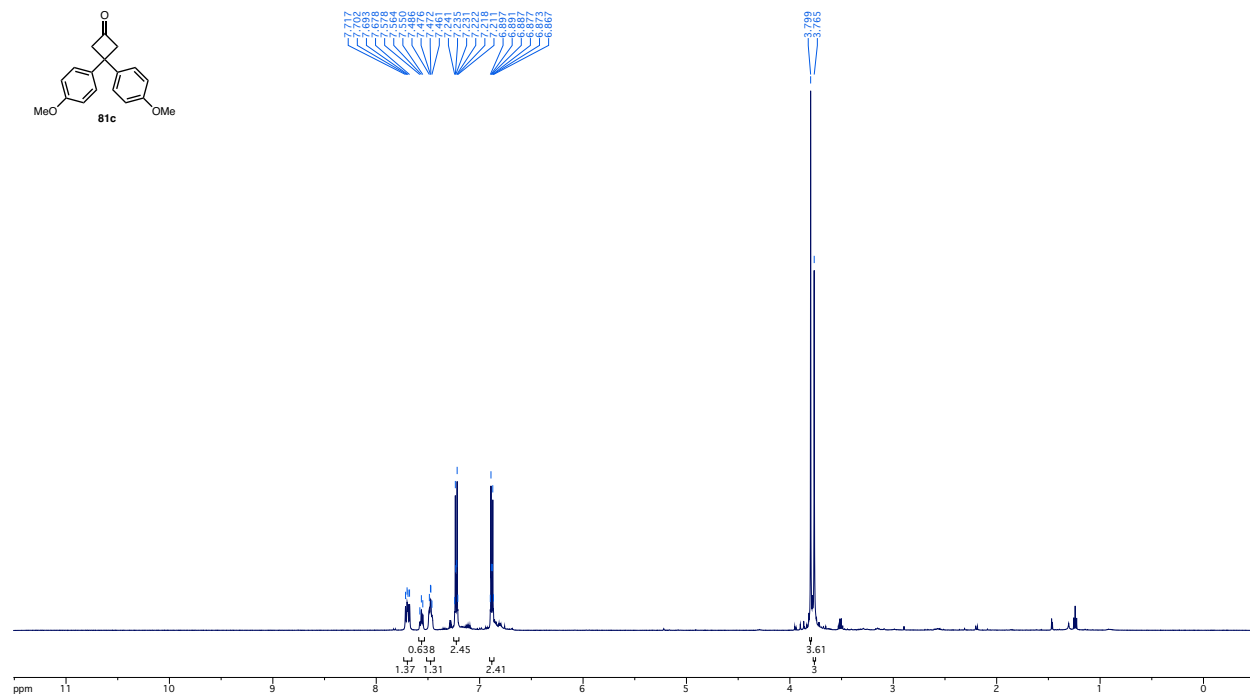
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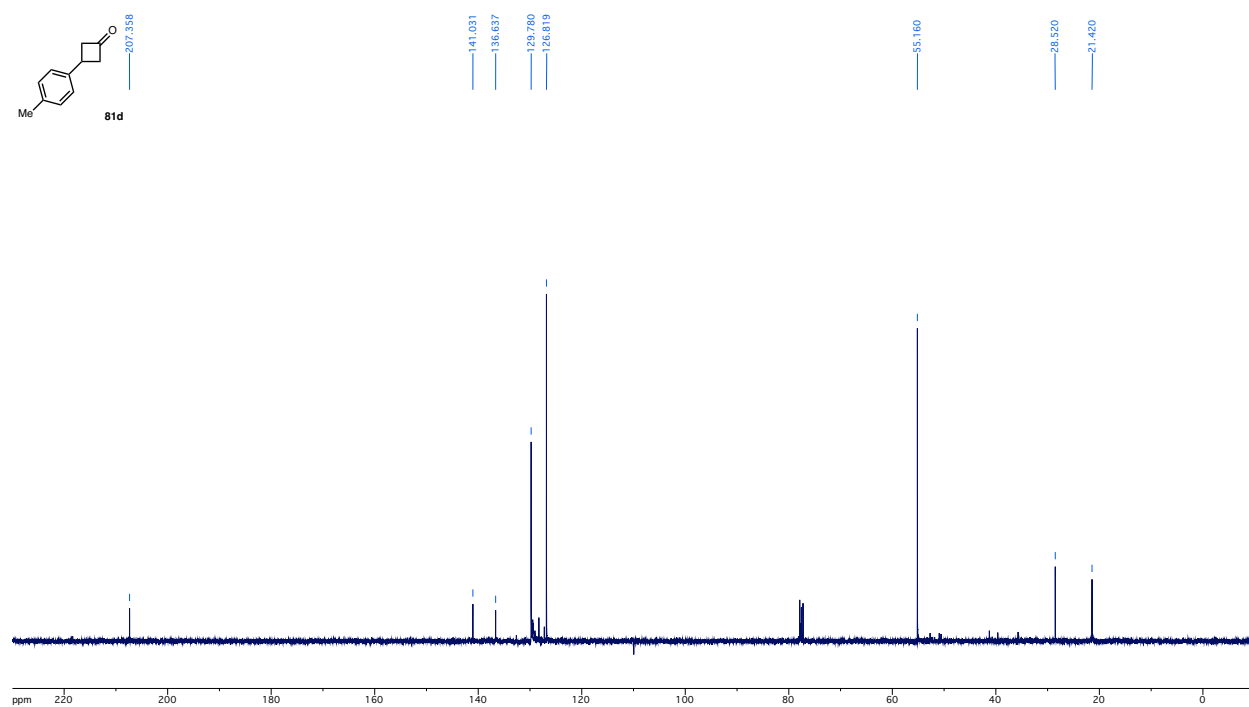
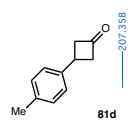
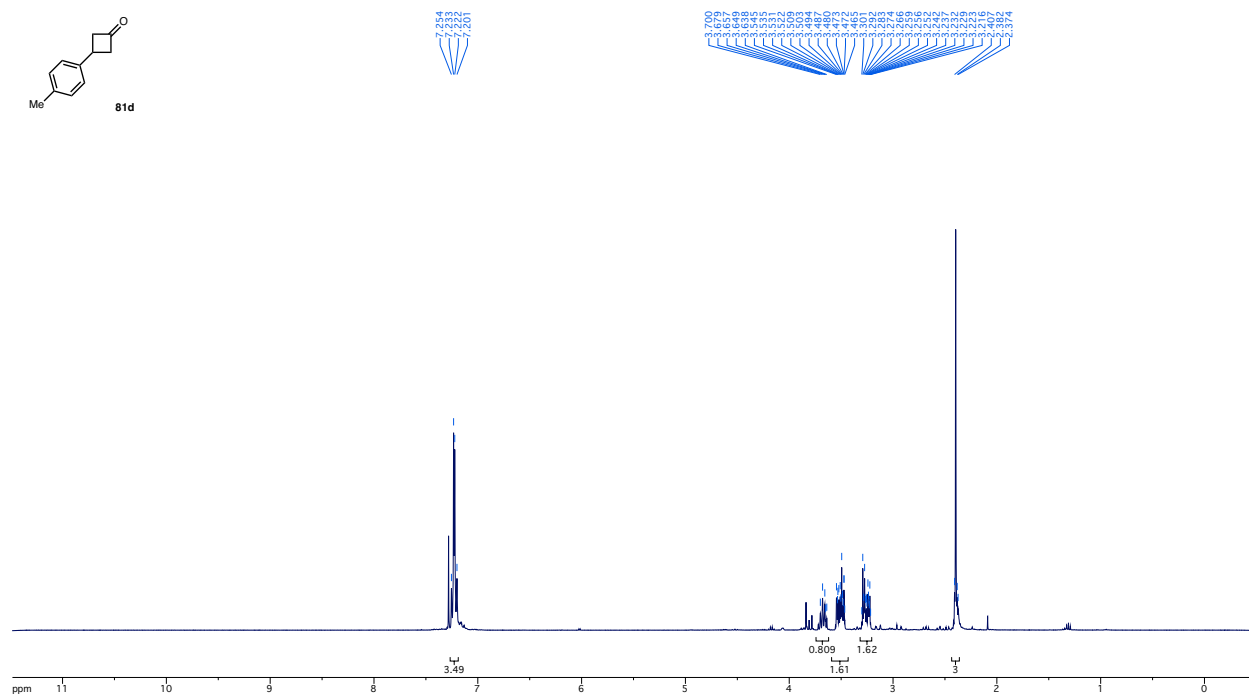
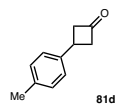
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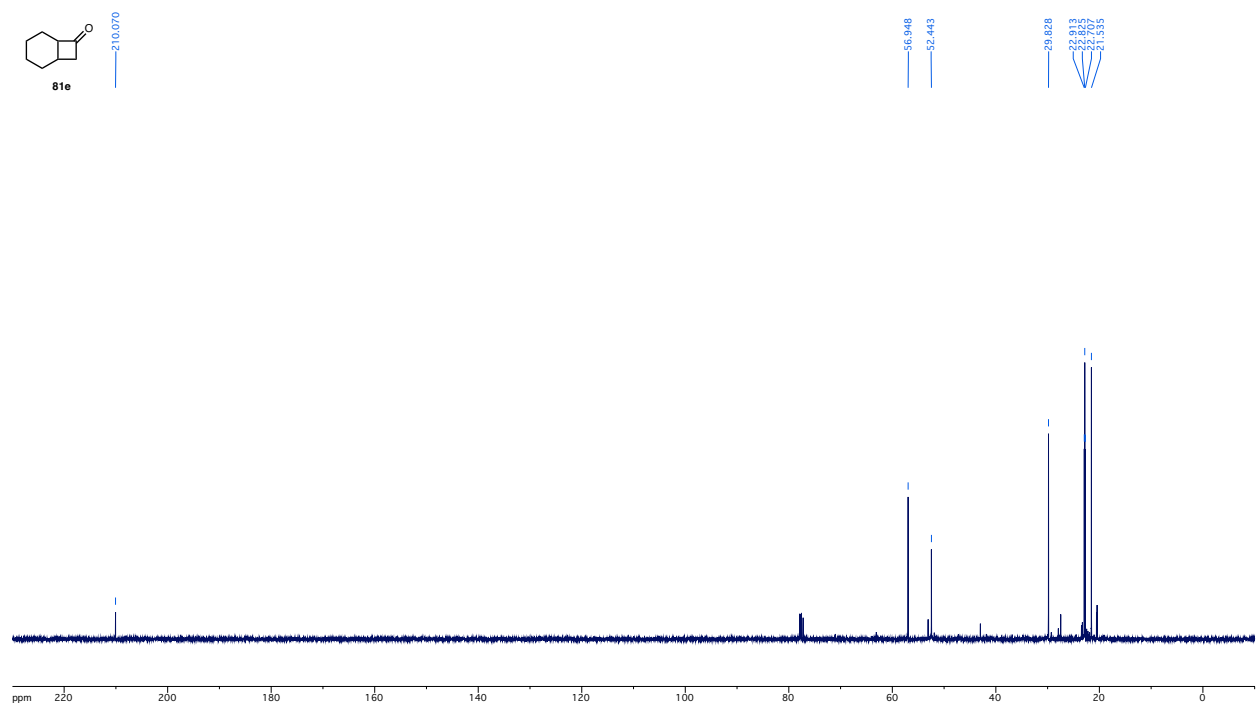
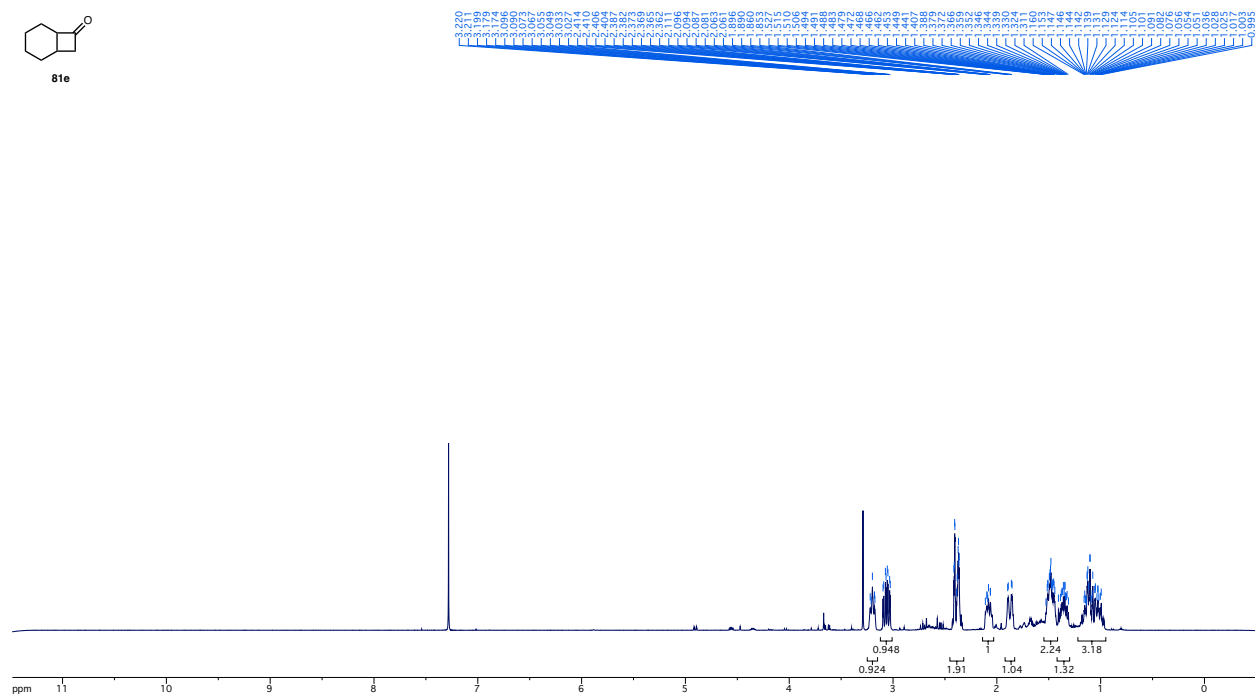
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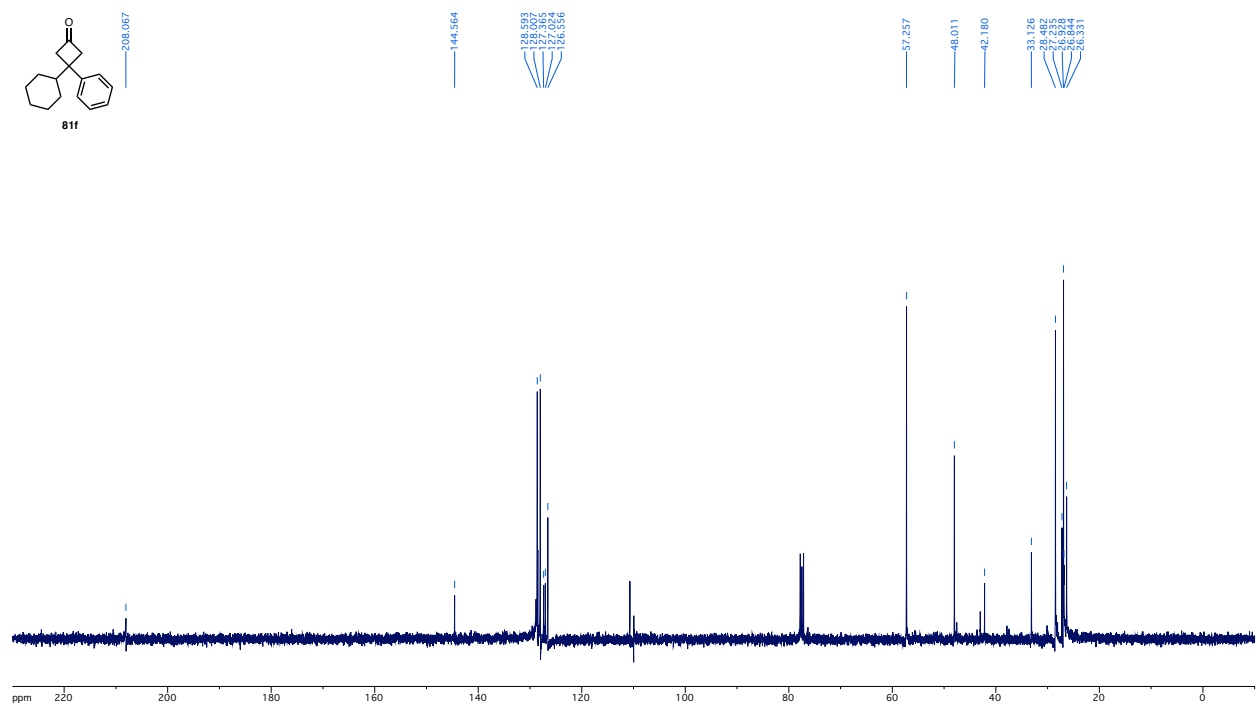
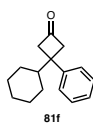
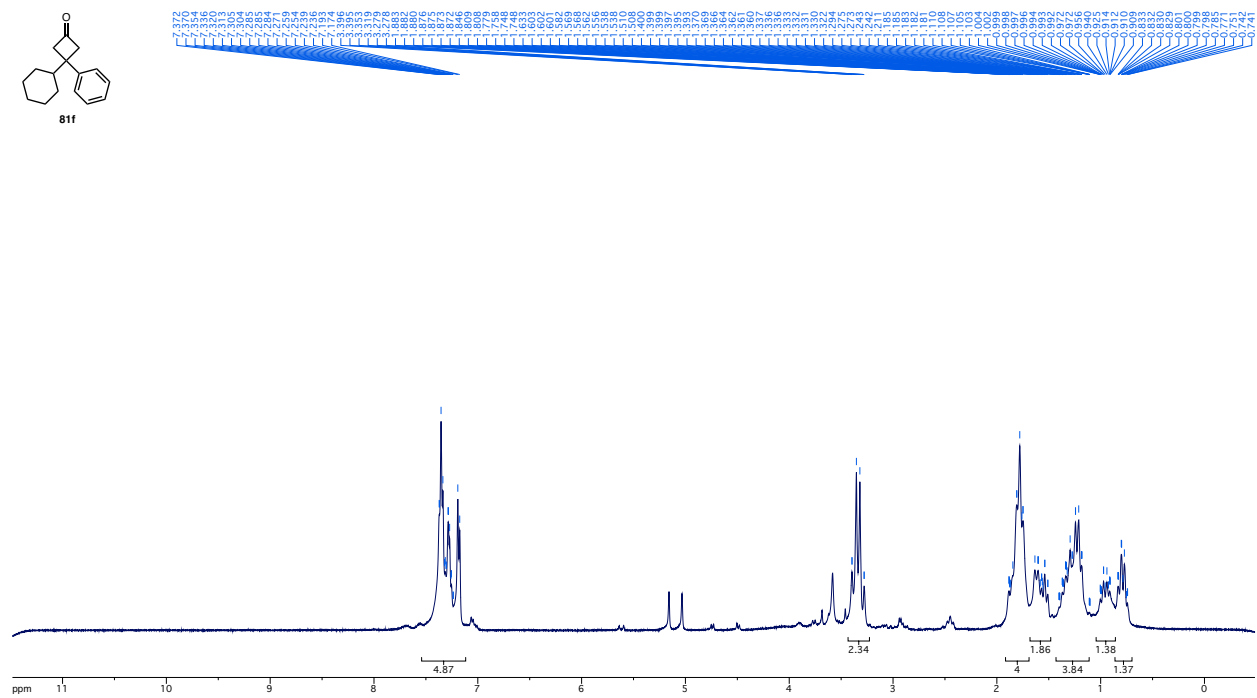
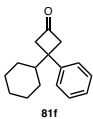


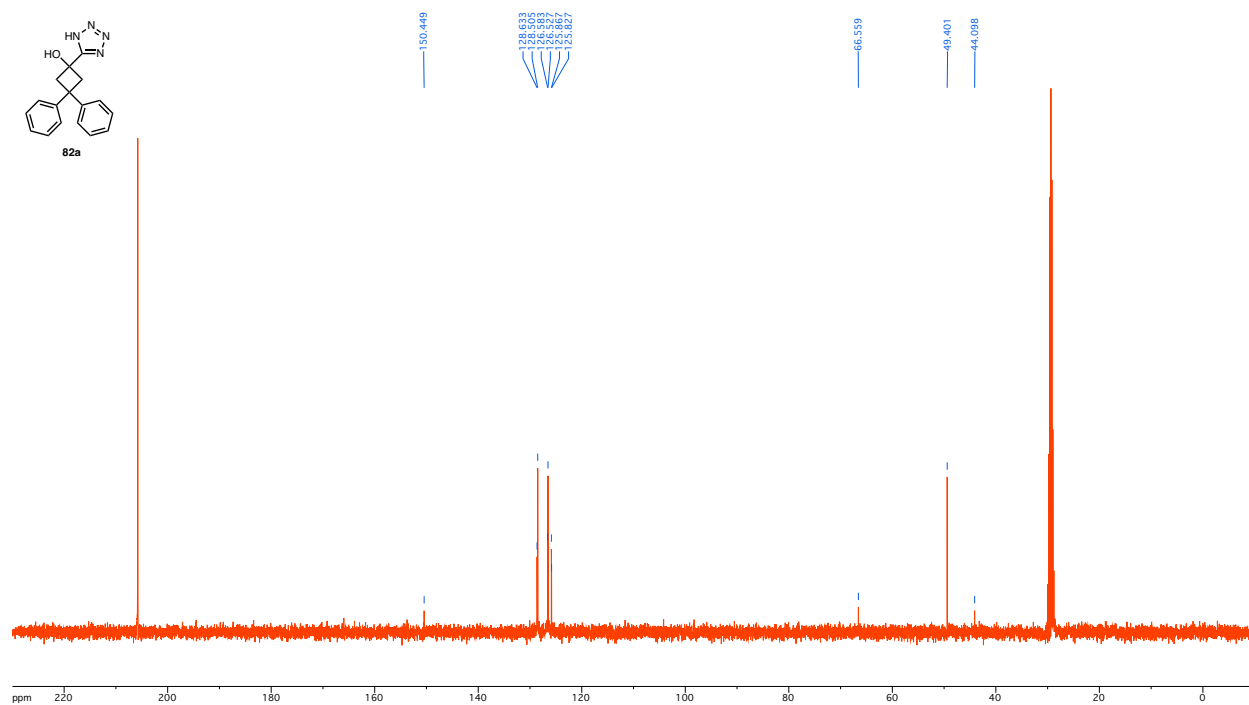
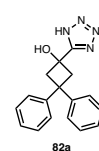
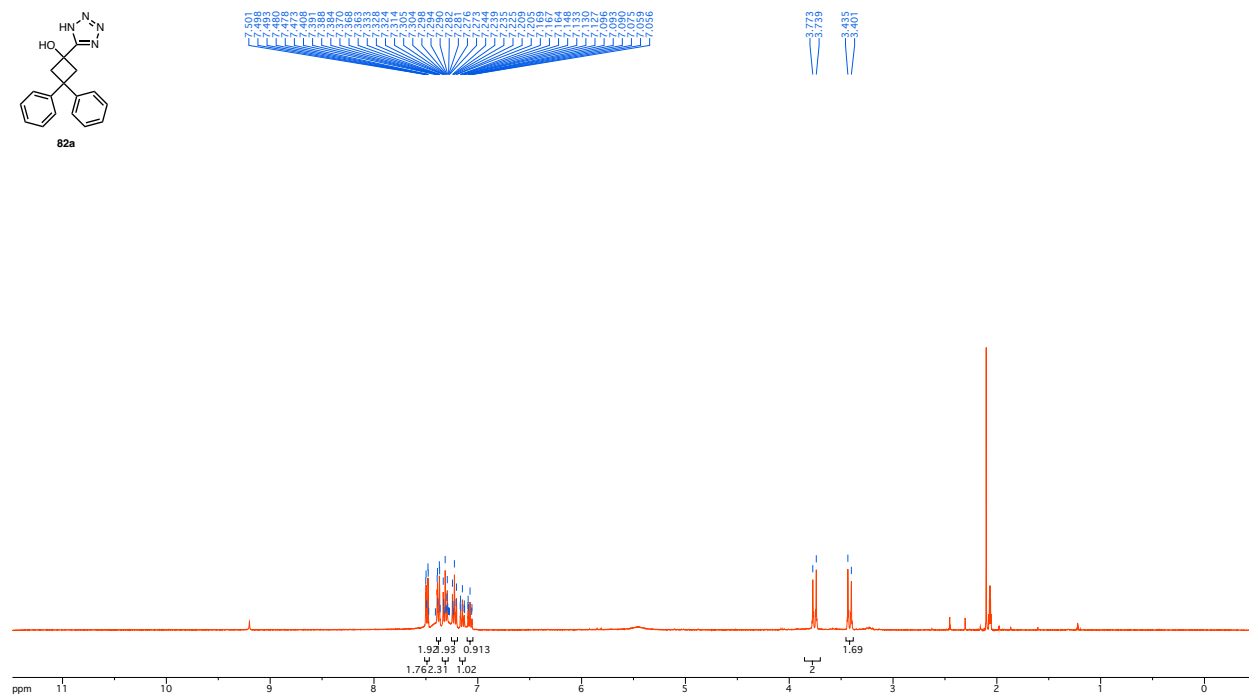
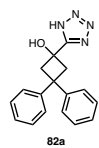


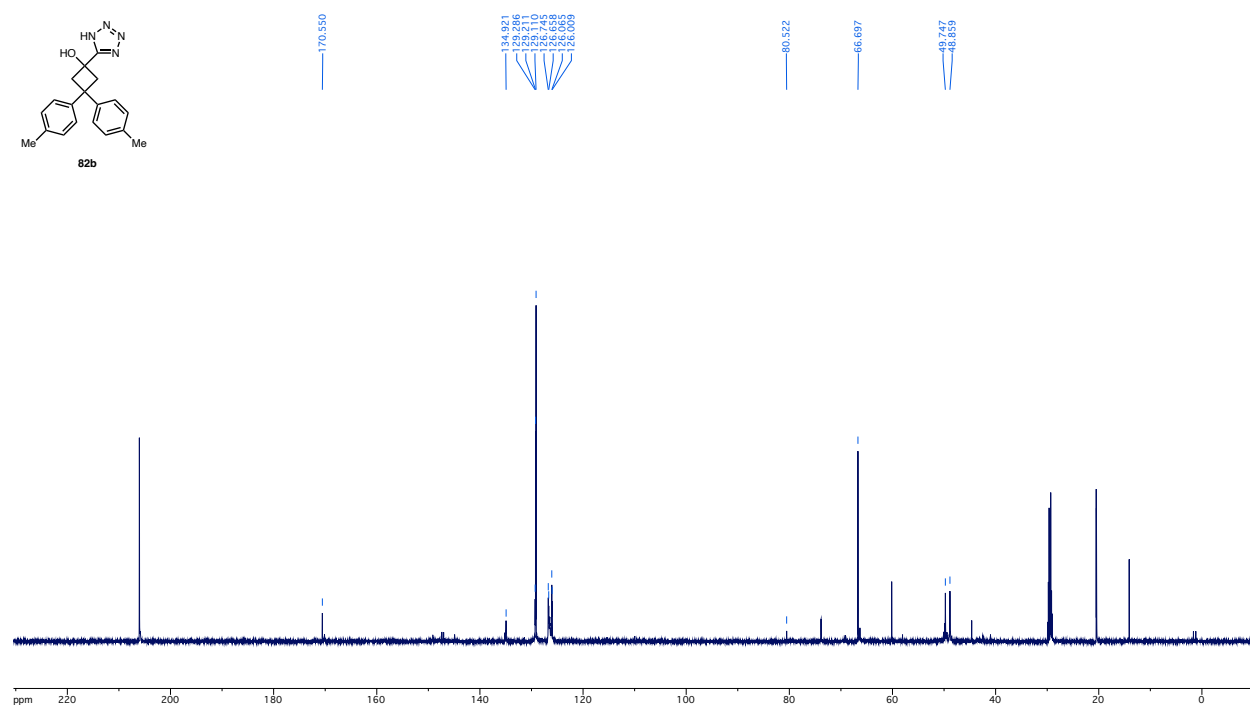
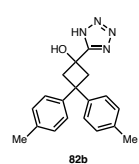
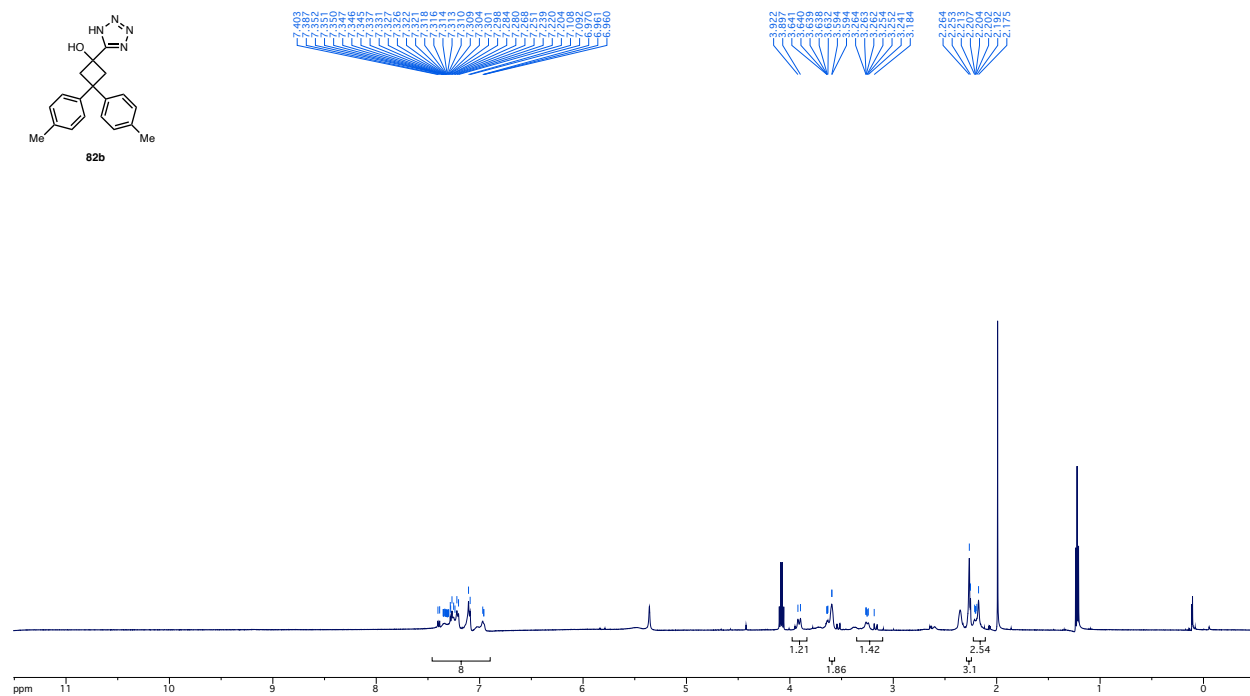
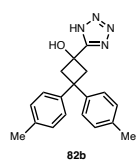


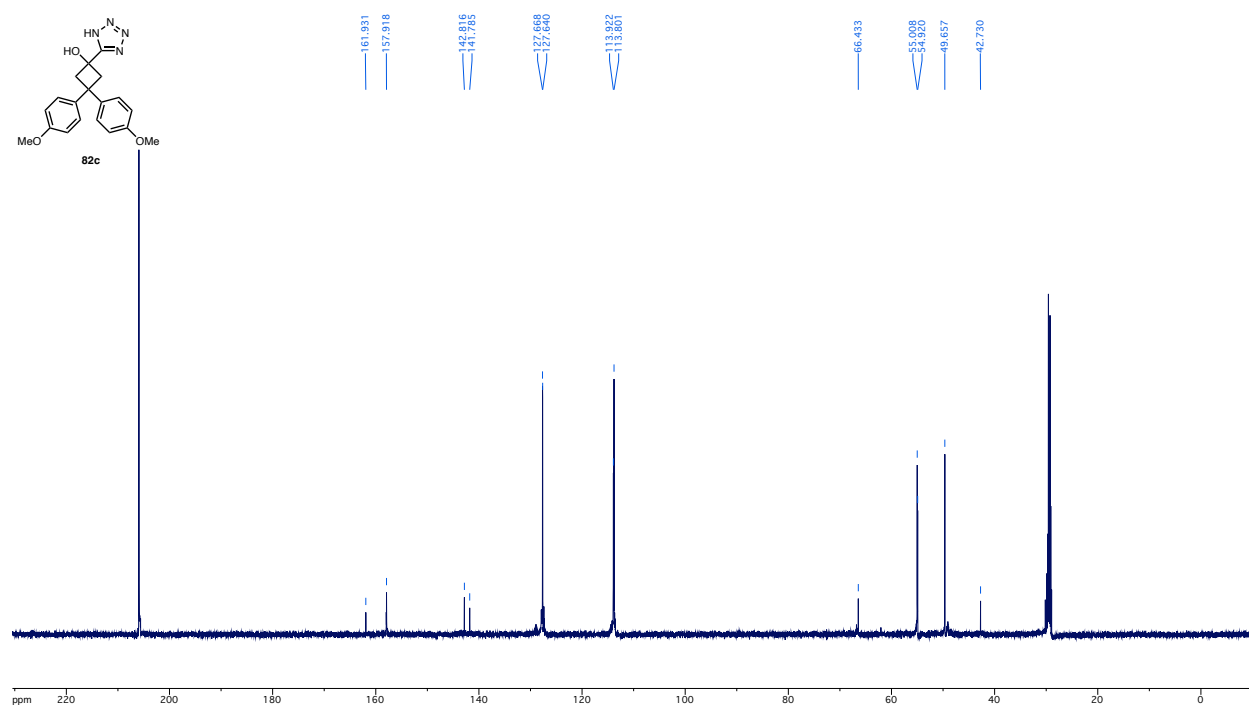
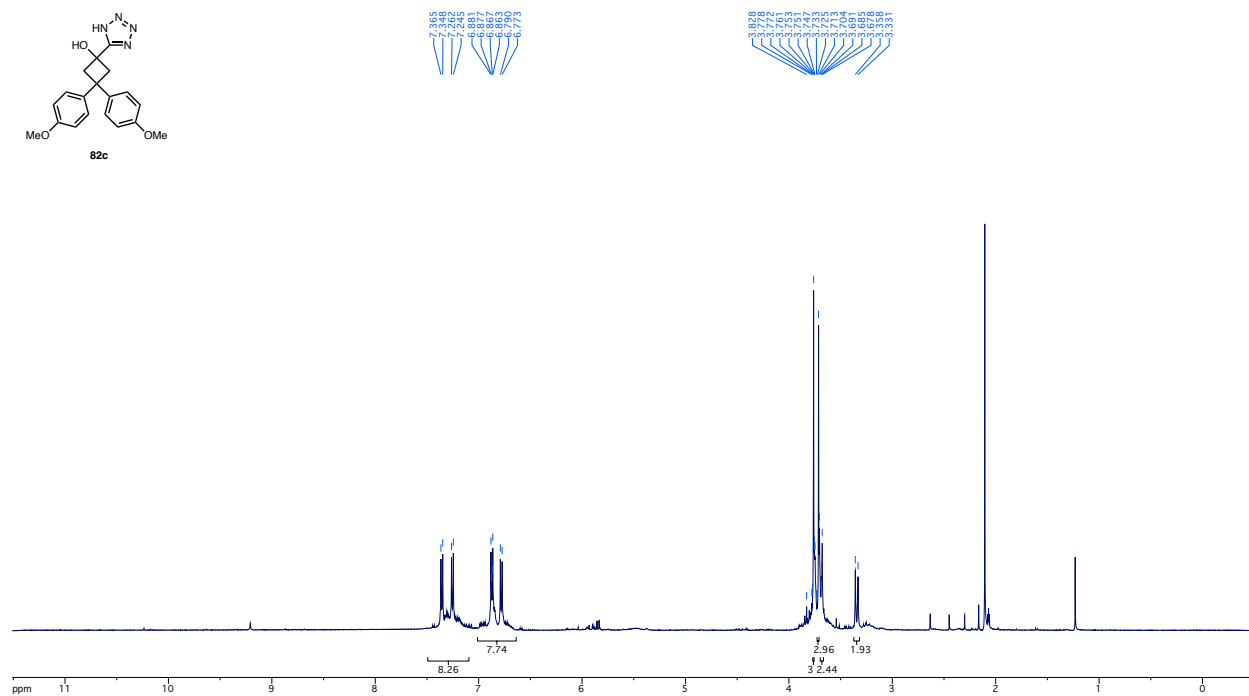
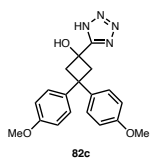


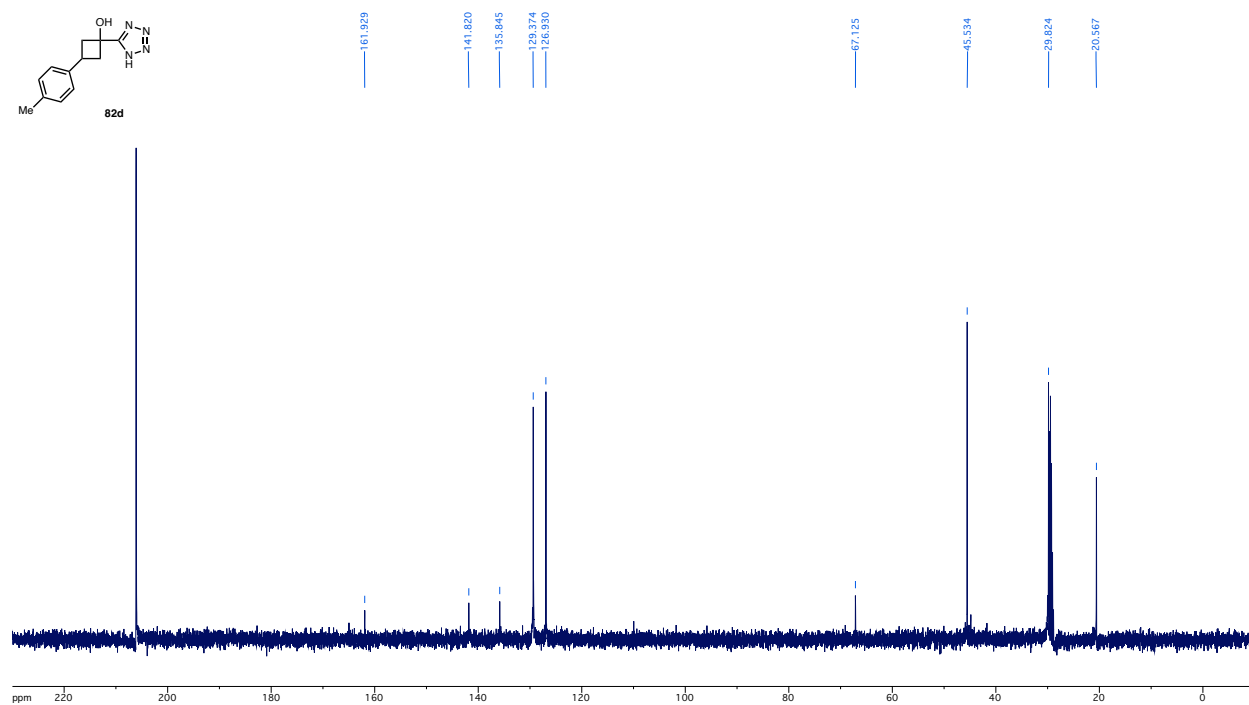
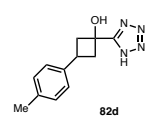
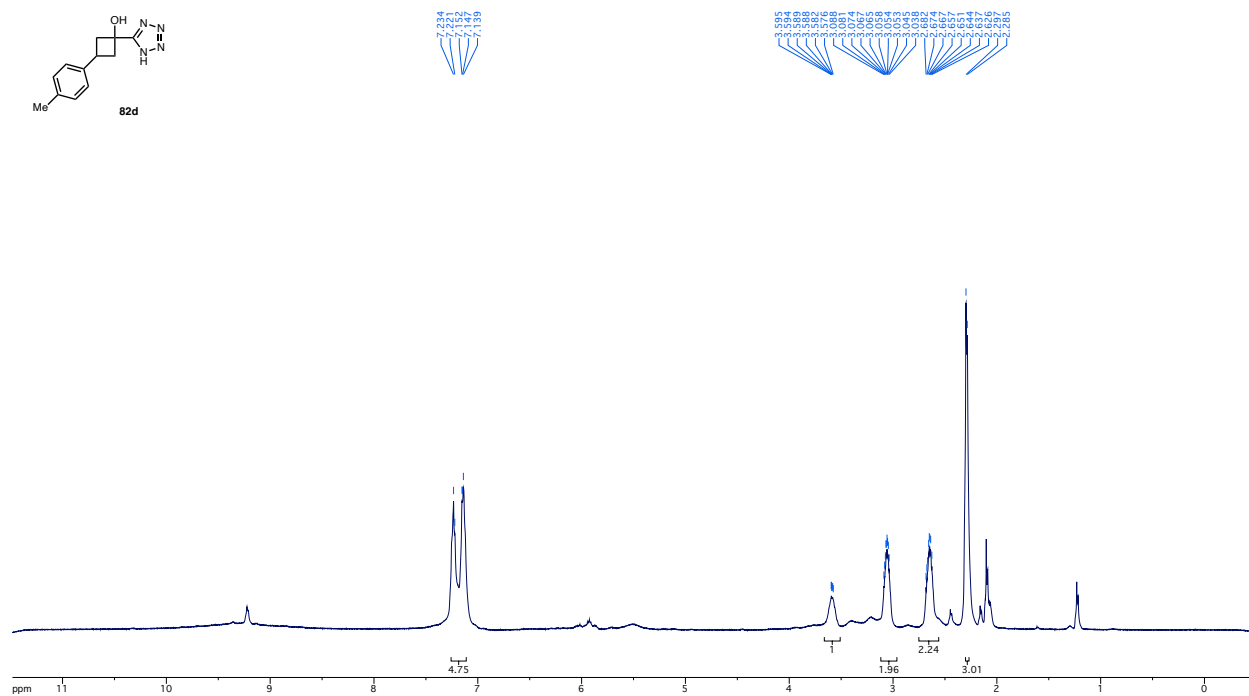
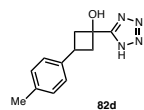


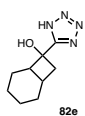




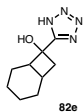
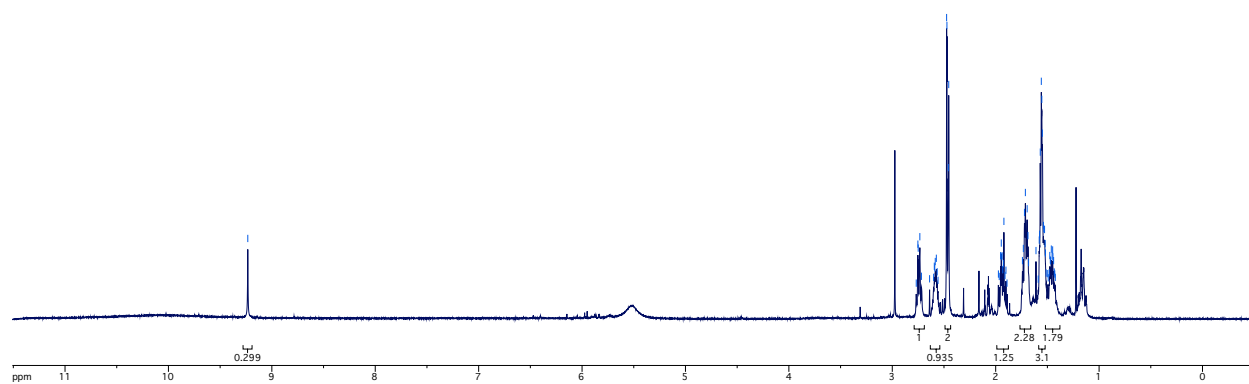








9.233



162.669

69.581

43.934

38.243

29.984

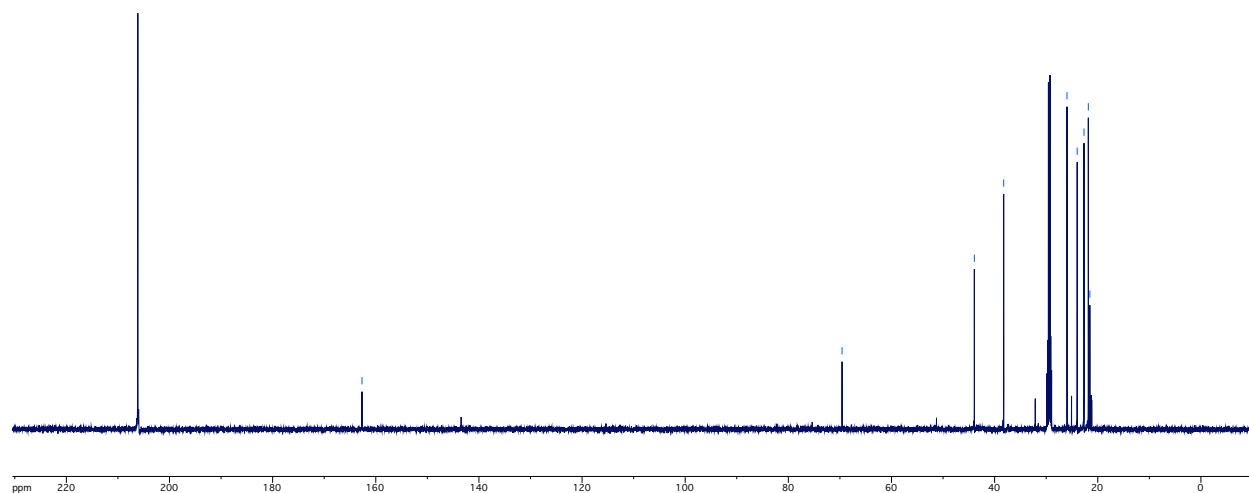
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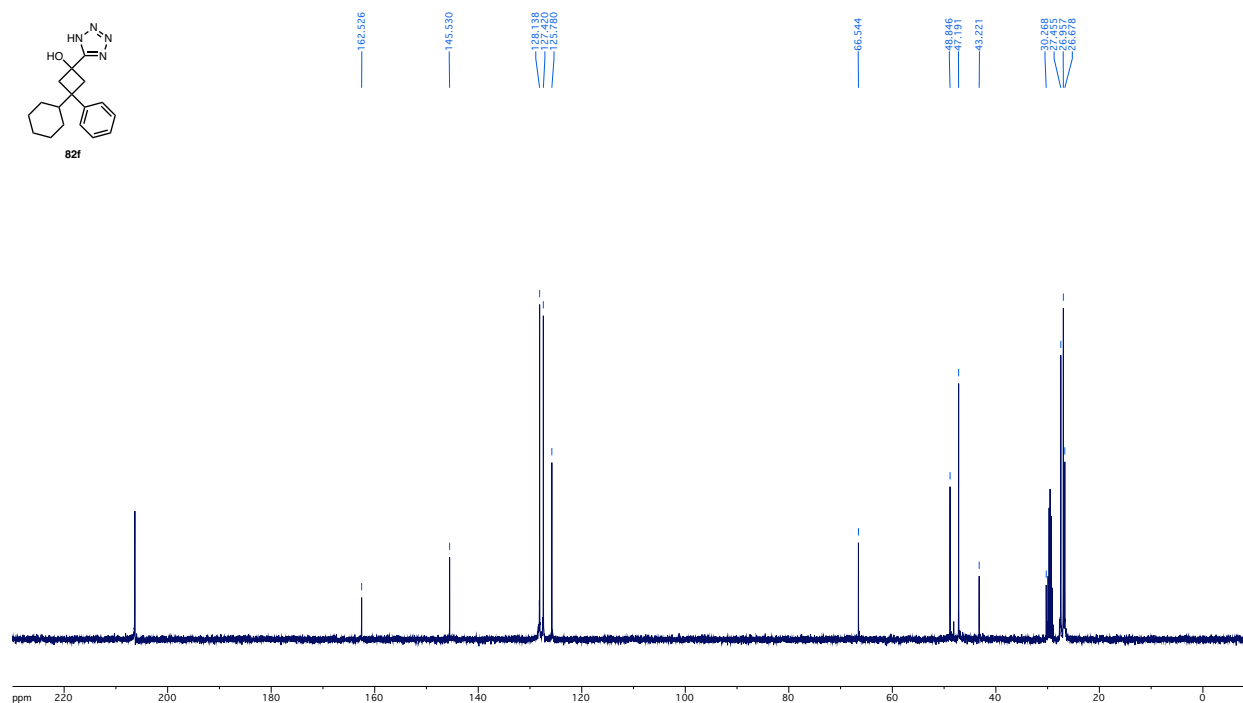
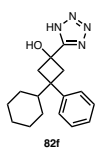
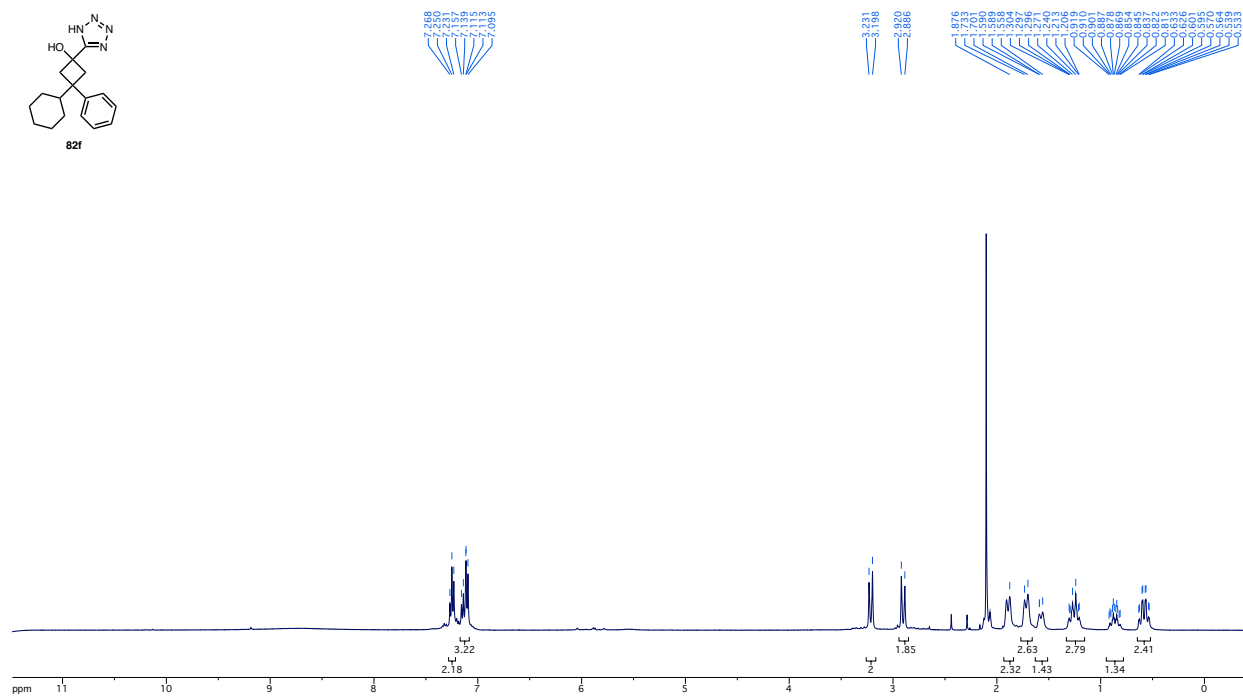
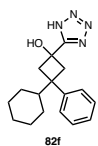
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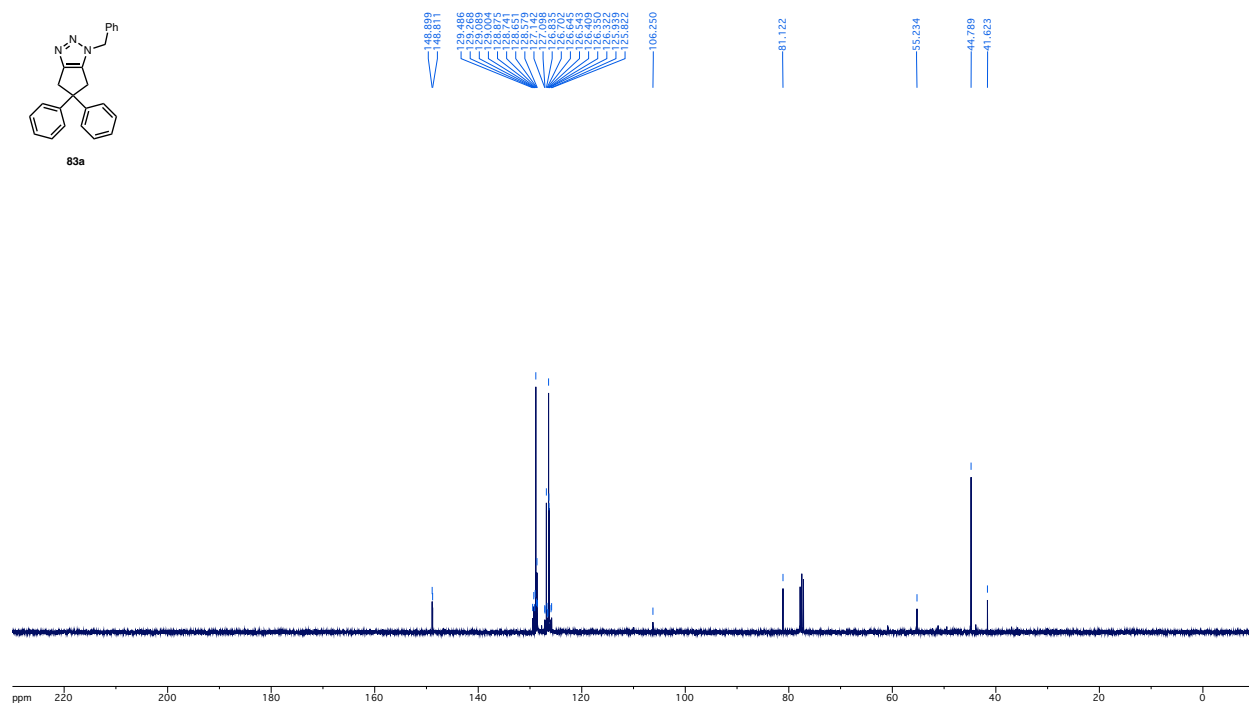
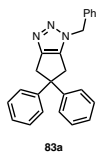
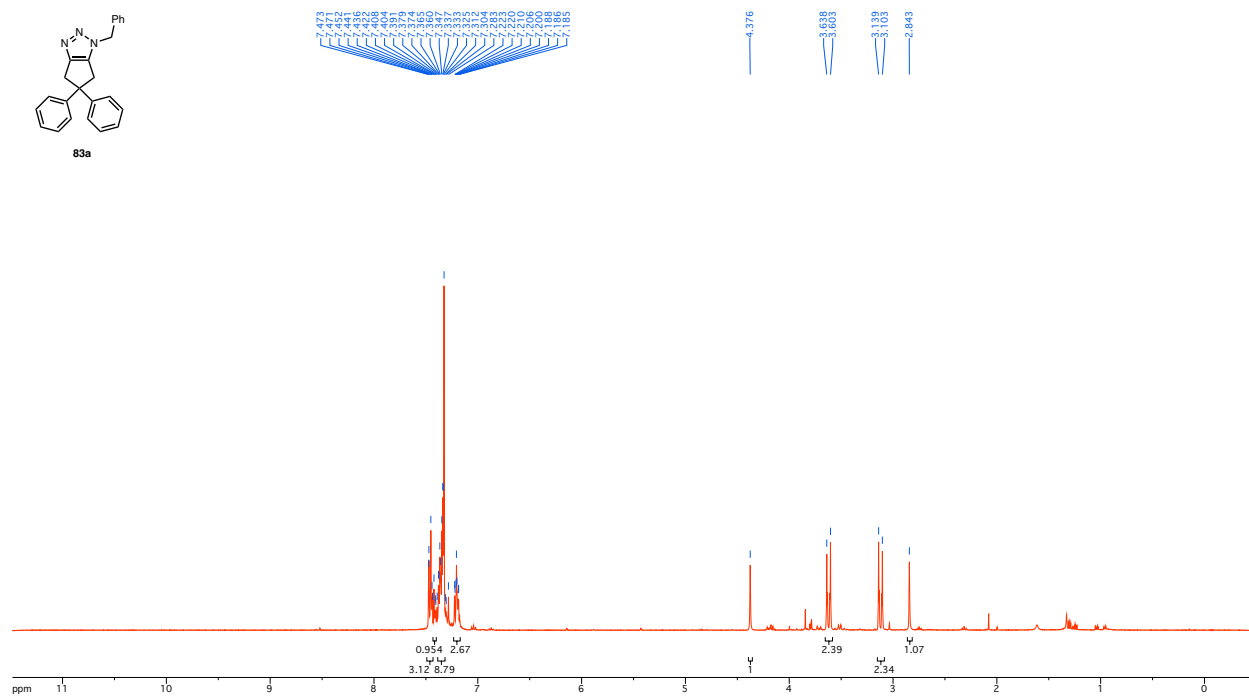
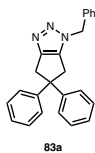
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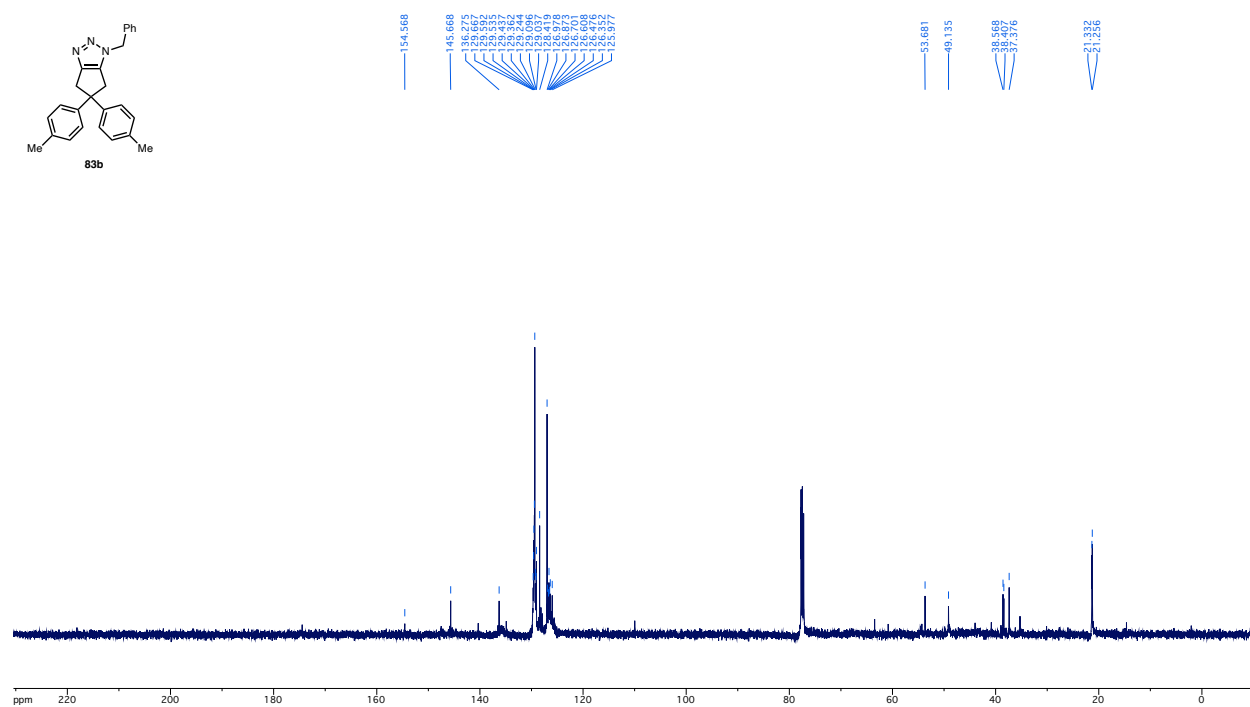
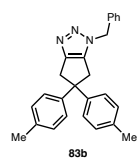
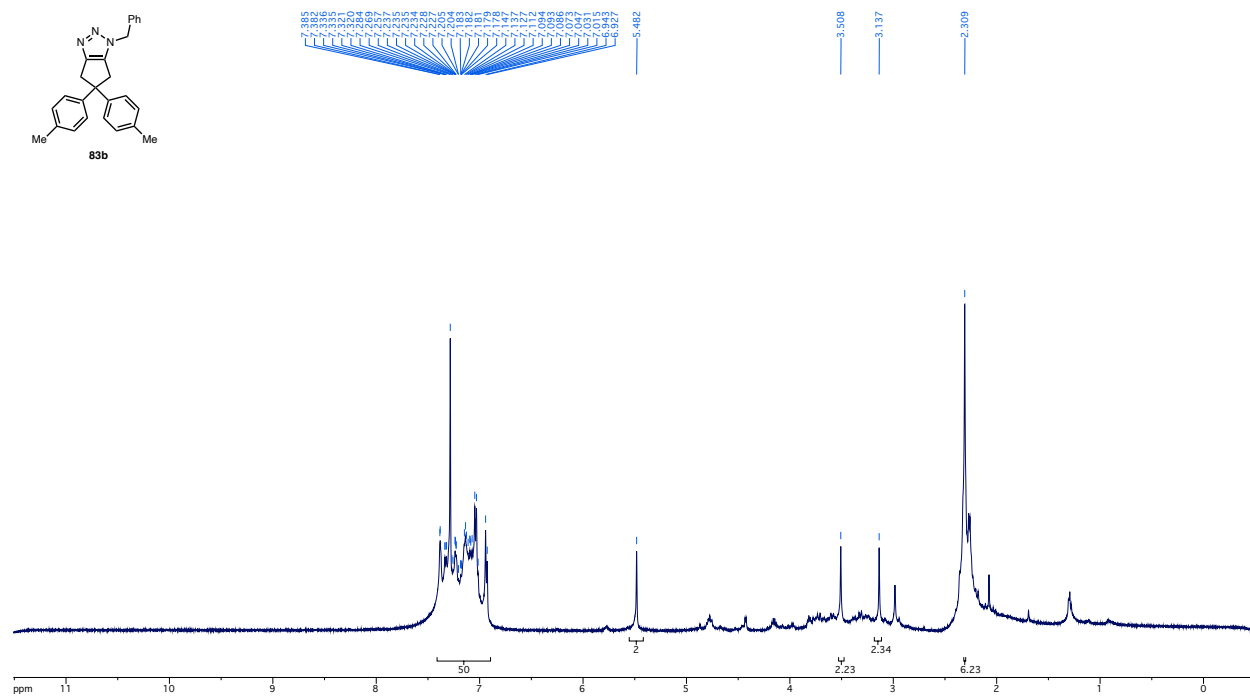
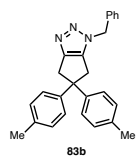
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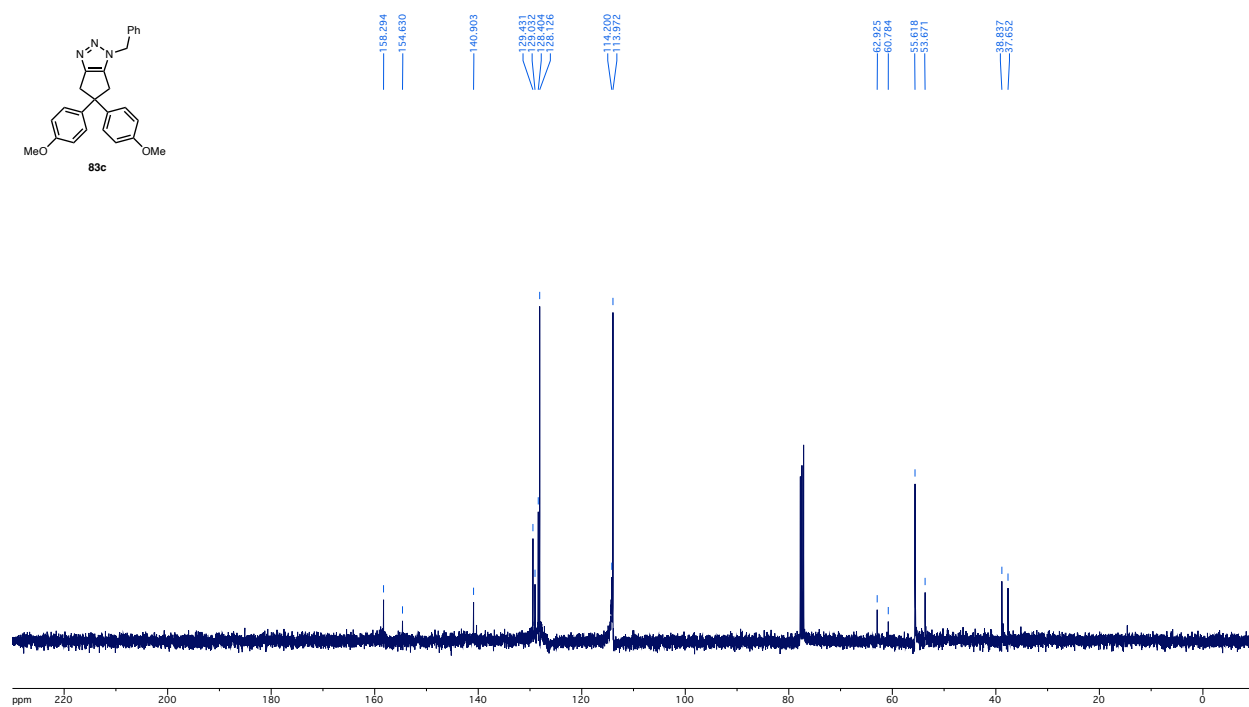
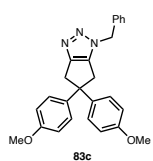
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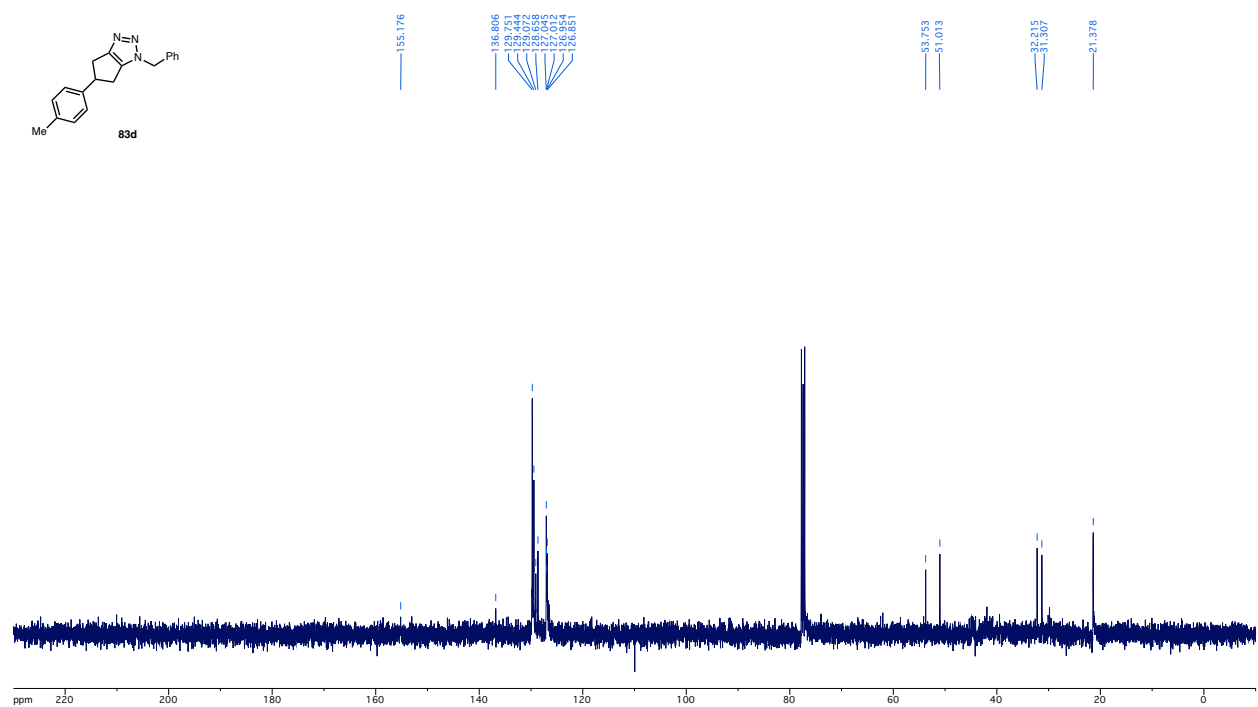
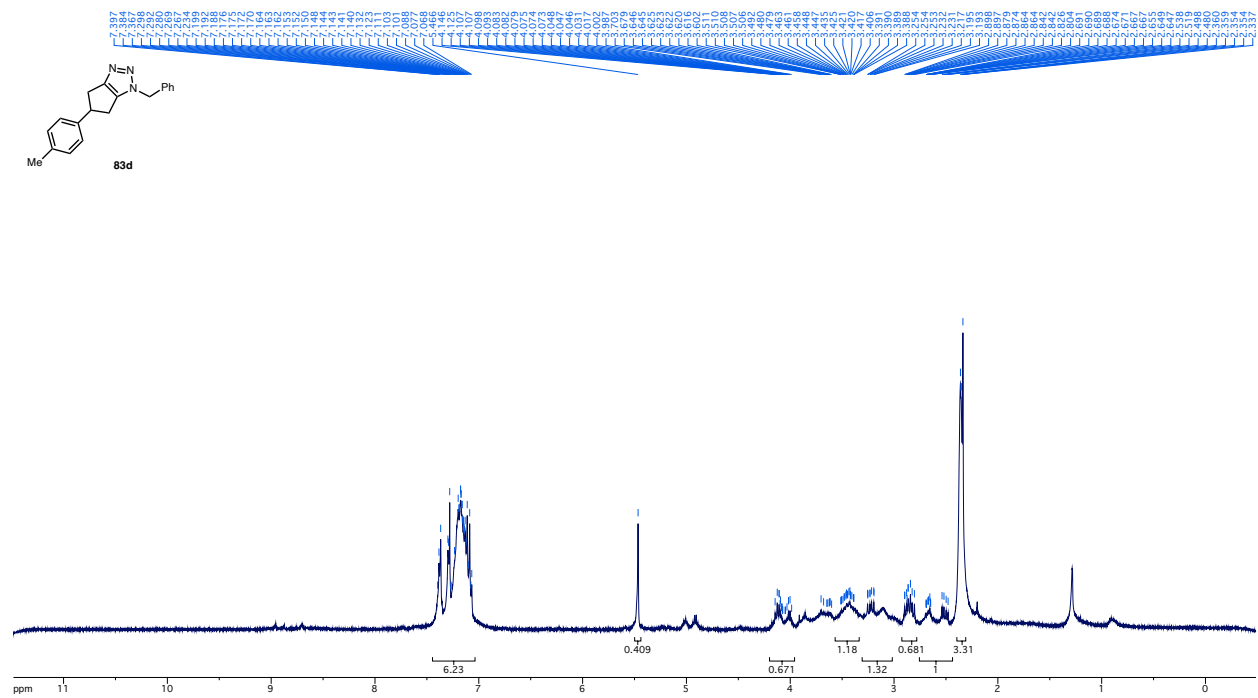














Panagiotis D. Alexakos, Ph.D.

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EDUCATION

8/2014-06/2021 Ph.D. (Organic Chemistry), University of Illinois at Chicago, Chicago, IL.

8/2009-5/2013 B.S. (Chemistry), University of Illinois at Chicago, Chicago, IL.

PROFESSIONAL EXPERIENCE

5/2021-present **Senior Chemist I (Adesis Inc)**

- Plans and executes various chemical reactions
- Develops synthetic routes towards large scale commercial use
- Devises alternative synthetic routes

8/2014-06/2021 **Research Assistant (University of Illinois at Chicago)**

w. Prof. Duncan J. Wardrop, Associate Professor

- Explored the reactivity of 1-(5-hydroxyalkyl)tetrazoles as latent alkylidenecarbenes towards the synthesis of cycloalkynes
- Established an efficient, one-pot synthesis to the direct access of 1-(5-hydroxyalkyl)tetrazoles
- Employed this methodology to explore the dehydrative fragmentation of 1-(5-hydroxyalkyl)tetrazoles to establish an efficient synthesis of cyclooctynes
- Synthesized a library of cyclooctynes including existing alkynes such as BARAC and DIBAC, including analogs of the latter
- Developed an *in-situ* trapping methodology with various alkynophiles
- Established an efficient route towards the synthesis of cyclopentynes

8/2014-05/2021 **Graduate Student Teaching Assistant (University of Illinois at Chicago)**

w. Prof. Lindsey McQuade, Clinical Professor

- Instructed and motivated a diverse undergraduate student body in organic chemistry, including lecture and lab
- Guided discussion amongst students in and beyond the classroom
- Administered, and returned completed assignments in a timely fashion
- Recognized by UIC in the form of 3 Teaching Awards

5/2013-5/2014 **Ophthalmic Technician (Midwest Glaucoma Center)**

w. Mildred Olivier, MD FACS, Department of Ophthalmology

- Performed initial patient screenings, ophthalmic testing procedures, and assisted physicians with related examinations as directed

- Ophthalmological testing and procedures including visual acuity, pupil assessment, Humphrey visual fields, Goldmann applanation, refractions, motility measurements were performed to provide optimal patient care
- Communicated with patients of proper care, notification of upcoming operations and appointments, answered any patient questions

1/2010-5/2013 **Research Assistant (Northwestern University)**
w. Debra A. Goldstein, MD, Department of Ophthalmology

- Collected and analyzed patient data diagnosed with acute retinal necrosis

PATENTS

1. Wardrop, D.; Alexakos, P.; *N*-Morpholinomethyl-5-lithiotetrazole and Use for the One-Pot Synthesis of 5-(1-Hydroxyalkyl)tetrazoles. U.S. Patent 62/745,572, October 15, 2018.

PUBLICATIONS

1. Alexakos, P.; Wardrop, D. *N*-Morpholinomethyl-5-lithiotetrazole: A Reagent for the One-Pot Synthesis of 5-(1-Hydroxyalkyl)tetrazoles. *J. Org. Chem.* **2019**, *84*, 12430-12436.
2. Alexakos, P.; Saraiya, N.; Goldstein, D; Drug-Induced Uveitis. *EyeWiki*. **2013**.

ORAL PRESENTATIONS

- 6/2021 Alexakos, P.; Wardrop, D. “A Mild, 2-Step Approach to Strained Cycloalkynes.” Presented at the 2021 ACS Great Lakes Regional Meeting, Virtual. Award Winner.
- 11/2020 Alexakos, P.; Wardrop, D. “7+1=8: A Ring Expansion Approach towards Cyclooctynes.” Presented at the UIC Chemistry Colloquium, Virtual.
- 10/2020 Alexakos, P.; Wardrop, D. “Tetrazole-Mediated Ring Expansion: A Mild Approach to Cyclooctynes.” Presented at the 2020 Midwest Chemistry Symposium, Virtual.
- 8/2020 Alexakos, P.; Wardrop, D. “New Methods in Alkylidenecarbene Chemistry: A Mild Route Towards Cycloalkynes.” Presented at the 2020 Discovery Abbvie Scholars Symposium, Virtual.
- 4/2019 Alexakos, P.; Wardrop, D. “*N*-Morpholinomethyl-5-lithiotetrazole: A Reagent for the One-Pot Synthesis of 5-(1-Hydroxyalkyl)tetrazoles.” Presented at the 2019 ACS Great Lakes Regional Meeting, Lisle, IL.

POSTER PRESENTATIONS

- 4/2020 Omega, M.; Alexakos, P.; Wardrop, D. “4 + 1 = 5: A New Approach to the Synthesis & Trapping of Cyclopentyne” Presented at UIC Impact and Research Day, Chicago, IL.
- 7/2019 LaFon, W.; Alexakos, P.; Cologna, S.; Wardrop, D. “Decomposition of 5-(1-Hydroxyalkyl)tetrazoles within Microdroplets via ESI-MS” Presented at Chicago Mass Spec Day, Chicago, IL.
- 6/2019 Alexakos, P.; Wardrop, D. “*N*-Morpholinomethyl-5-lithiotetrazole: A Reagent for the One-Pot Synthesis of 5-(1-Hydroxyalkyl)tetrazoles” Presented at the 46th Annual National Organic Symposium, Bloomington, IN.
- 6/2019 Alexakos, P.; Damiao, M.; Wardrop, D. “Tetrazole-Mediated Ring Expansion: A Mild Approach to Strained Cyclooctynes” Presented at the 46th National Organic Symposium, Bloomington, IN.
- 5/2013 Alexakos, P.; Goldstein, D.; Birnbaum, A.; “Delay of Diagnosis of ARN: Effect on Outcome” Presented at UIC Honors College Convocation, Chicago, IL

AWARDS

- | | |
|------|--------------|
| 2018 | UIC TA Award |
| 2016 | UIC TA Award |
| 2015 | UIC TA Award |

REFERENCES

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