Title

The Synthesis and Reactivity of 1-Nitro-1,3-dienes and the Synthesis of Cyclic β-Silylalkenyl Triflates Through Highly Reactive Vinyl Cation Intermediates

Author

Lee, Craig

Publication Date

2017

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

The Synthesis and Reactivity of 1-Nitro-1,3-dienes and the Synthesis of Cyclic β-Silylalkenyl Triflates Through Highly Reactive Vinyl Cation Intermediates

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Craig James Lee

2017

ABSTRACT OF THE DISSERTATION

The Synthesis and Reactivity of 1-Nitro-1,3-dienes and the Synthesis of Cyclic β-Silylalkenyl Triflates Through Highly Reactive Vinyl Cation Intermediates

by

Craig James Lee

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2017

Professor Ohyun Kwon, Chair

The synthesis and reactivity of substituted conjugated nitrodienes was investigated. We have prepared β-alkoxymethyl substituted nitrodienes via electrophilic nitration of 1,3-butadienes to employ in a tandem 6π-electrocyclization/[3 + 2] dipolar cycloaddition sequence with dipolarophiles to generate bicyclic nitroso acetals. Additionally, a series of β-alkenyl tethered nitrodienes was synthesized via a trimethylsilyl chloride (TMSCl) assisted organocuprate addition/elimination into 2-bis(methylthio)nitroethylene to give β-ethylthio nitroalkenes. A palladium catalyzed desulfitative cross-coupling of the β-ethylthio nitroalkenes with vinyl boronic acids gave a variety of acyclic β-substituted conjugated nitrodienes. This highly modular methodology allowed for access to a wide range of acyclic nitrodienes that could be exposed to 6π-electrocyclization/intramolecular [3 + 2] dipolar cycloaddition conditions to provide many

multicyclic nitroso acetals. Disappointingly, after screening a multitude of reaction conditions and substituient effects, the substituted nitrodienes failed to give nitroso acetal products.

Formation of highly reactive cyclic vinyl cations and the subsequent trapping by a triflate ion is described. Generation of 6-(trimethylsilyl)hex-5-yn-1-ols through organolithium addition to benzyl- or alkenyl- aldehydes gave a multitude of benzylic and allylic alcohols. Treatment of these alcohols with triflic acid induced stabilized benzylic or allylic cation formation which could be intercepted by a tethered alkyne to provide a vinyl cation intermediate. By taking advantage of the high reactivity of alkenyl cations, typically dissociative anions such as triflate ions can trap the cation, providing 1-(trimethylsilyl)-1-cyclohexenyl-2-triflates. This reactivity can also be extended to produce 3-(trimethylsilyl)-1,4-dihydronaphthalen-2-yl triflates. Using the methodology, the total synthesis of the aryl tetralin lactone *β*-Apopicropodophyllin was completed, hinging on a key Diels–Alder/retro-Diels–Alder reaction trapping of an intermediate cyclic alkyne.

The dissertation of Craig James Lee is approved.

Fuyuhiko Tamanoi

Michael E. Jung

Ohyun Kwon, Committee Chair

University of California, Los Angeles

2017

To my loving wife, Monica,

who has been at my side throughout this journey.

TABLE OF CONTENTS

CHAPTER 2

The Synthesis of Cyclic β-Silylalkenyl Triflates Through Highly Reactive Vinyl Cation Intermediates

LIST OF FIGURES

CHAPTER 1

CHAPTER 2

LIST OF SCHEMES

CHAPTER 1

CHAPTER 2

LIST OF TABLES

CHAPTER 1

CHAPTER 2

ACKNOWLEDGEMENTS

Chapter 1 contains unpublished results. Chapter 2 contains unpublished results that is under preparation for a manuscript to be published as: The Synthesis of Cyclic β-Silylalkenyl Triflates Through Highly Reactive Vinyl Cation Intermediates. Lee, C. J.; Kwon, O.

VITA

Craig James Lee

Undergraduate Education

University of California, San Diego

Major: Molecular Synthesis

Bachelors of Science, 2011

Publication

Nanoformulation of geranylgeranyltransferase-I inhibitors for cancer therapy: Liposomal encapsulation and pH-dependent delivery to cancer cells. Lu, J.; Yoshimura, K.; Goto, K.; Lee, C.; Hamura, K.; Kwon, O.; Tamanoi, F. *PLoS One* **2015**, *10*, 10e0137595.

Manuscript in Preparation

The Synthesis of Cyclic β-Silylalkenyl Triflates Through Highly Reactive Vinyl Cation Intermediates. Lee, C.J.; Kwon, O.

Chapter 1

The Synthesis and Reactivity of 1-Nitro-1,3-dienes

1.1 Introduction: Conjugated Nitrodienes

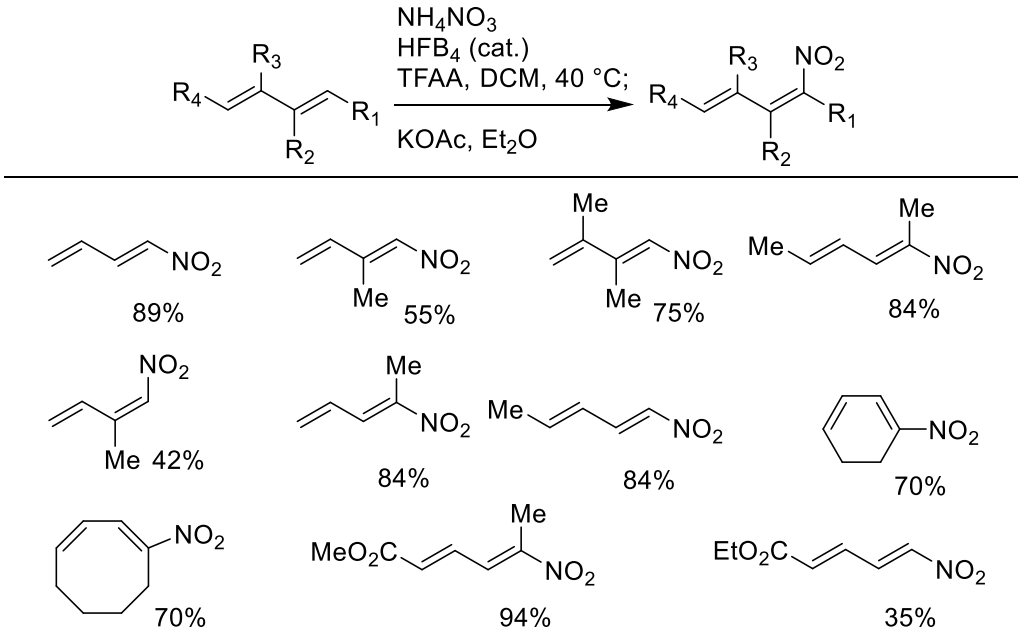
Conjugated electron-deficient dienes are powerful tools in organic synthesis, particularly for use in a variety of pericyclic reactions, with the Diels–Alder reaction garnering a majority of synthetic endeavors in this mode of reactivity. The ability of the conjugated diene system to rapidly undergo highly regio- and diastereoselective reactions exemplifies its synthetic utility in various pericyclic reactions. In contrast to the use of esters as an electron-withdrawing group, employment of conjugated nitrodienes remains limited.[1] Presumably, this limited exploration is due to the instability of many nitrodienes,[2] which can readily dimerize or oligomerize, oxidize, or decompose in the presence of acids or bases. In addition to the relative lack of investigation into the synthesis of nitrodienes, conjugated 1-nitro-1,3-dienes proves to be even more scarce. Compounding the problem of a lack of literature precedent for the synthesis of conjugated nitrodienes, the procedures for their synthesis was also found to be problematic.[3]

1.2 The Synthesis of 1-nitro-1,3-dienes

Electrophilic Nitration of 1,3-dienes

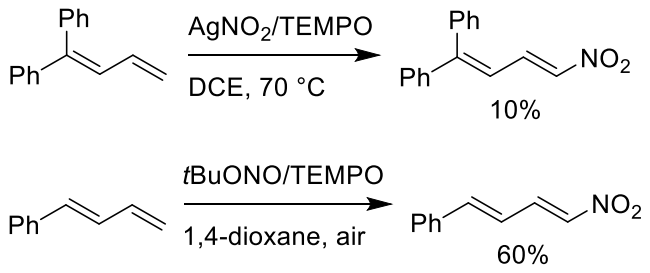
One of the pioneering methods for the synthesis of a variety conjugated nitrodienes was by Mellor,[3] utilizing a nitronium ion *in situ* generated from ammonium nitrate and trifluoroacetic anhydride (Scheme 1.2.1). Starting from substituted 1,3-dienes, several conjugated nitrodienes were synthesized in this manner, in moderate to excellent yields. Nitrotrifluoroacetoxylation and elimination of 1,3-butadiene cleanly gave the corresponding nitrodiene in 89% yield. In the case of isoprene, use of potassium acetate (KOAc) or trimethylamine (Et_3N) as the base yielded a 1:1 mixture of nitrodienes in low yield. However, when sodium hydride (NaH) was used as the base, the single *E*-nitrodiene was formed in 55% yield. More highly substituted dienes were well

tolerated, giving the *E*-nitrodienes in high yields. This reaction was extended to cyclic dienes, providing nitrocyclohexa-1,3-diene and nitrocycloocta-1,3-diene in good yields. *E*-Ethyl penta-2,4-dienoate was successfully converted to the nitrodiene, albeit in a low yield. However, high yield was seen in the synthesis of the hexa-2,4-dienoate analog. This methodology remains restricted, as the harshly acidic and oxidizing conditions limit the substrate scope to mainly aliphatic dienes, with only ester functionalities being tolerated.



Scheme 1.2.1 Mellor's synthesis of nitrodienes

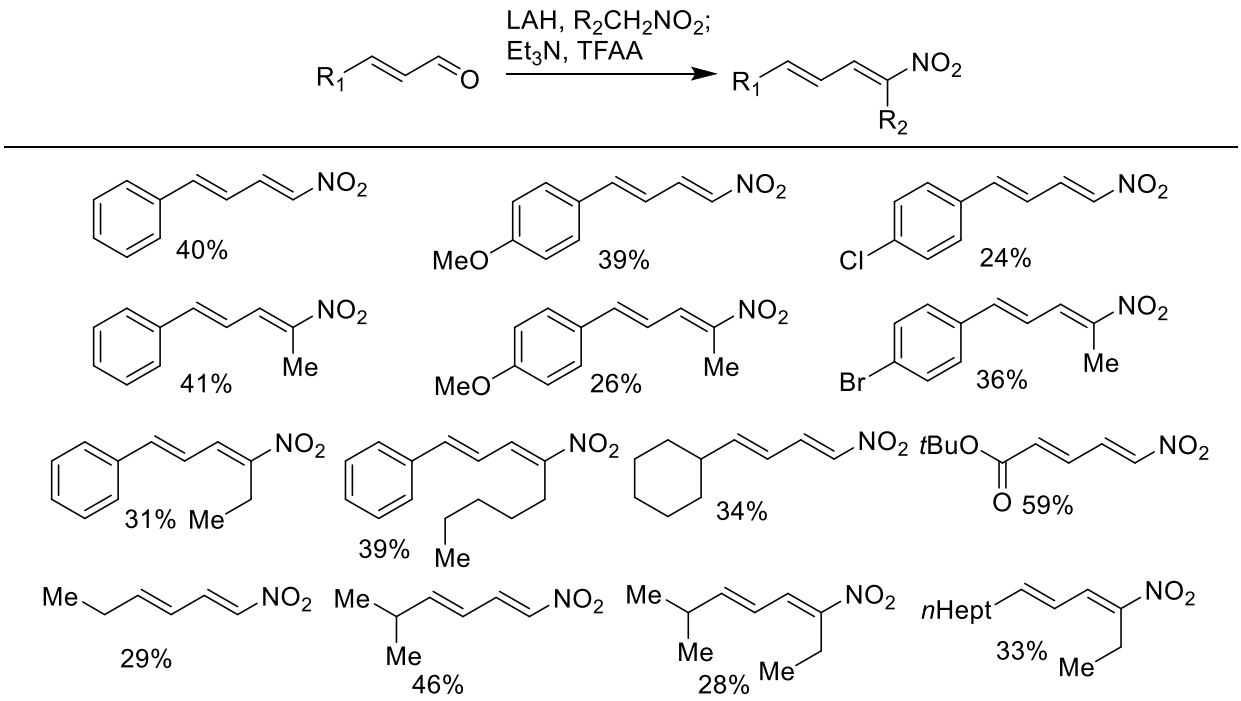
Recently, Maiti has developed an elegant method for the nitration of a wide variety of alkenes that is presumed to proceed through a radical intermediate.[4] Employing either silver(I) nitrite or *t*-butyl nitrite and TEMPO, this method avoids the necessity for harshly acidic conditions and strong oxidizing agents, allowing for a broad range of aryl and aliphatic nitroolefin products. However, when applied to the synthesis of nitrodienes, this methodology proves to be inefficient or restricted to only mono- or bis-phenyl substitution (Scheme 1.2.2).



Scheme 1.2.2 Radical nitration of conjugated dienes

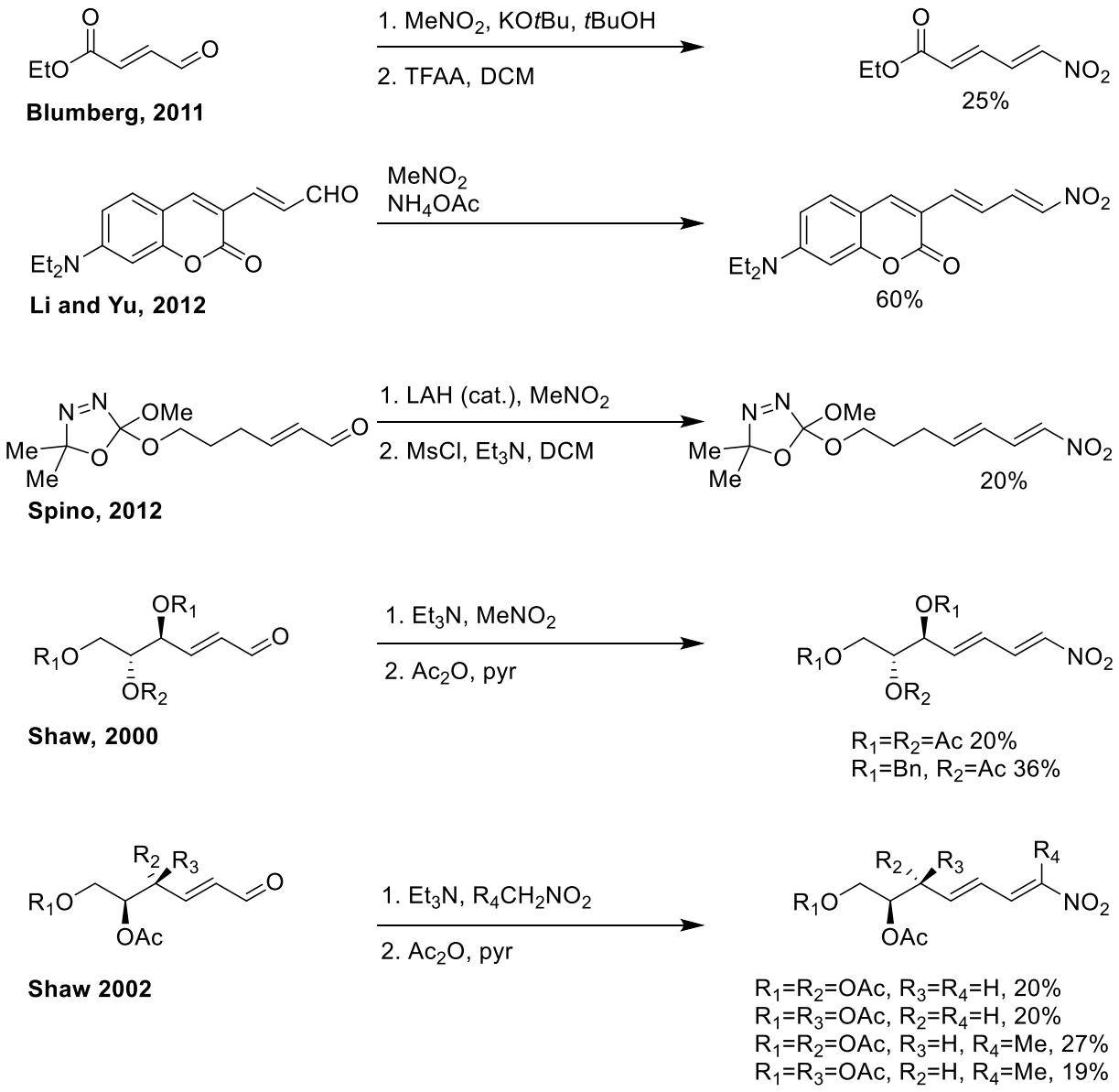
Henry Reaction/Dehydration to Generate Nitrodienes

A sequence of a Henry reaction followed by a dehydration has seen a rise for the synthesis of 1-nitro-1,3-dienes recently. Exemplified by Alexakis, this method reacts nitro alkanes with conjugated aldehydes forming the β-nitro alcohols in the presence of catalytic lithium aluminum hydride (LAH),[5] which in turn undergo an elimination after acetyl or trifluoroacetyl protection.[6] The Kim–Alexakis method was useful for the synthesis of cinnamaldehyde derived nitrodienes; however low yields are often seen in the synthesis of aliphatic nitrodienes (Scheme 1.2.3). Henry reaction of nitromethane and cinnamaldehyde and subsequent dehydration produced (1*E*, 3*E*)-1-nitro-4-phenylbuta-1,3-diene in 40% yield. The low yield was also observed for both methoxy and chloro substituted substrates. Homologating the pronucleophile to nitroethane proved to be amenable; however yields of the 1,3-nitropentadienes remained low. Reacting with nitropropane and nitrohexane also gave the desired nitrodienes, again in moderate yields. Moving on from conjugated aromatic aldehydes, this methodology was extended to alkyl substituted α,β-unsaturated aldehydes. Nitrodienes bearing cyclohexyl, ethyl, isopropyl, and *n*-heptyl substituents were all generated in low yield, but interestingly *t*-butyl (2*E*, 4*E*)-5-nitropenta-2,4-dienoate was isolated in good yield.



Scheme 1.2.3 Kim–Alexakis method to generate nitrodienes

In addition to the Kim–Alexakis methodology to create β-nitro alcohols, both organic and inorganic bases have been employed. Importantly, this general approach for the synthesis of nitrodienes has proven to tolerate a range of functionalities, including ester,[7] amine,[8] and 2,2-dialkoxy-Δ^3-1,3,4-oxadiazoline,[9] all in moderate yields (Scheme 1.2.4). While the moderate yields are acceptable for the synthesis of a single desired product, they fail to be synthetically useful in the development of a methodology built around the rapid elaboration of many different substrates.

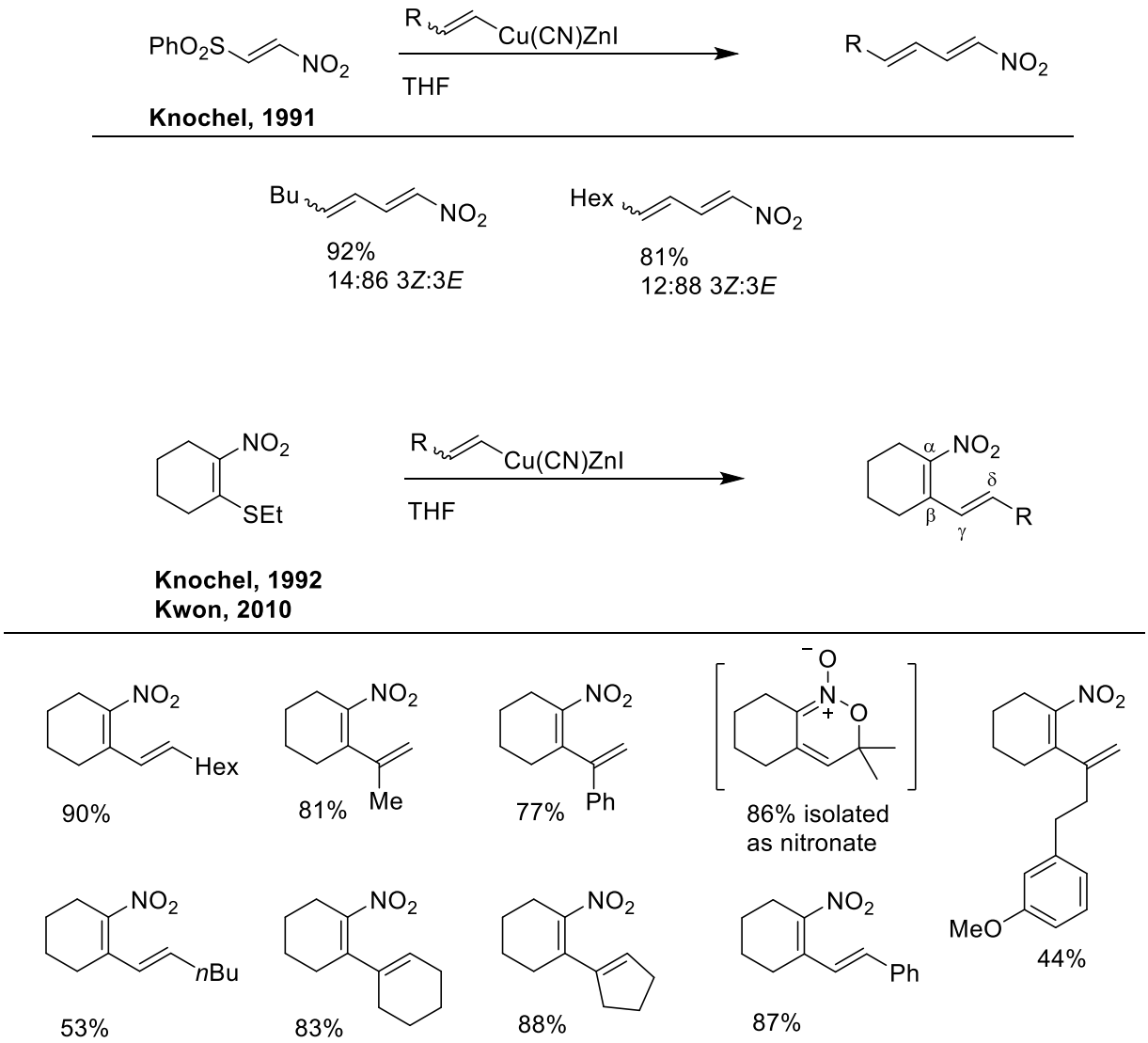


Scheme 1.2.4 Nitrodienes synthesized through Henry/dehydration under basic conditions

Addition/Elimination Pathway to Synthesize Nitrodienes

Although the Kim–Alexakis method for the synthesis of conjugated nitroolefins and nitrodienes has seen abundant use in organic synthesis, the requirement for an α,β-unsaturated aldehyde and a sterically undemanding nitro alkane limits the possible partners in the reaction sequence. In an alternative approach to the synthesis of nitrodienes, Knochel pioneered the

development of an efficient addition/elimination sequence. Addition of vinyl zinc cuprates into *β*-(phenylsulfonyl)-nitroethylene followed by elimination of the sulfenyl group gave the nitrodienes in good yields (Scheme 1.2.5).[10] Somewhat limited in substrate scope, this methodology was extended to generate nitrodienes with an internal *Z*-olefin geometry. First shown by Knochel, (*E*)-1-nitro-2-(oct-1-enyl)cyclohexene was synthesized in excellent yield after addition of the corresponding octenyl zinc cuprate to 2-thioethyl nitrocyclohexene.[11] From this protocol describing the synthesis of a single nitrodiene, Creech and Kwon successfully extended this methodology to the synthesis of a variety of substituted nitrodienes. Nitrodienes bearing both 2-propenyl and α-styrenyl substituents were readily synthesized in this manner. Surprisingly, δ,δ-dimethyl substituted nitrodiene was never isolated but was instead isolated as the nitronate after silica gel chromatography, presumably undergoing a spontaneous 6π-electrocyclization upon exposure to the slightly acidic SiO_2. Following the methodology, δ-*n*-butyl nitrodiene was generated in good yield, and δ-phenyl nitrodiene was provided in great yield. Extending the method to cyclic alkenes, both cyclohexenyl and cyclopentenyl nitrodienes were synthesized in great yields. γ-Alkyl substituted nitrodienes bearing an anisyl group was also generated in moderate yield. Similarly, alkenyl aluminum reagents are employed to undergo addition to (*E*)-1-ethoxy-2-nitroethylene followed by elimination after acidic workup, giving nitrodienes in good yields.[12] Despite this reaction pathway providing an efficient and high yielding method for synthesizing nitrodienes, it necessitates air-free techniques and the use of pyrophoric organolithium and organoaluminum reagents. Due to this requirement, the methodology is incompatible with many electrophiles and acidic substrates, limiting the scope to the production of mainly aliphatic nitrodienes.

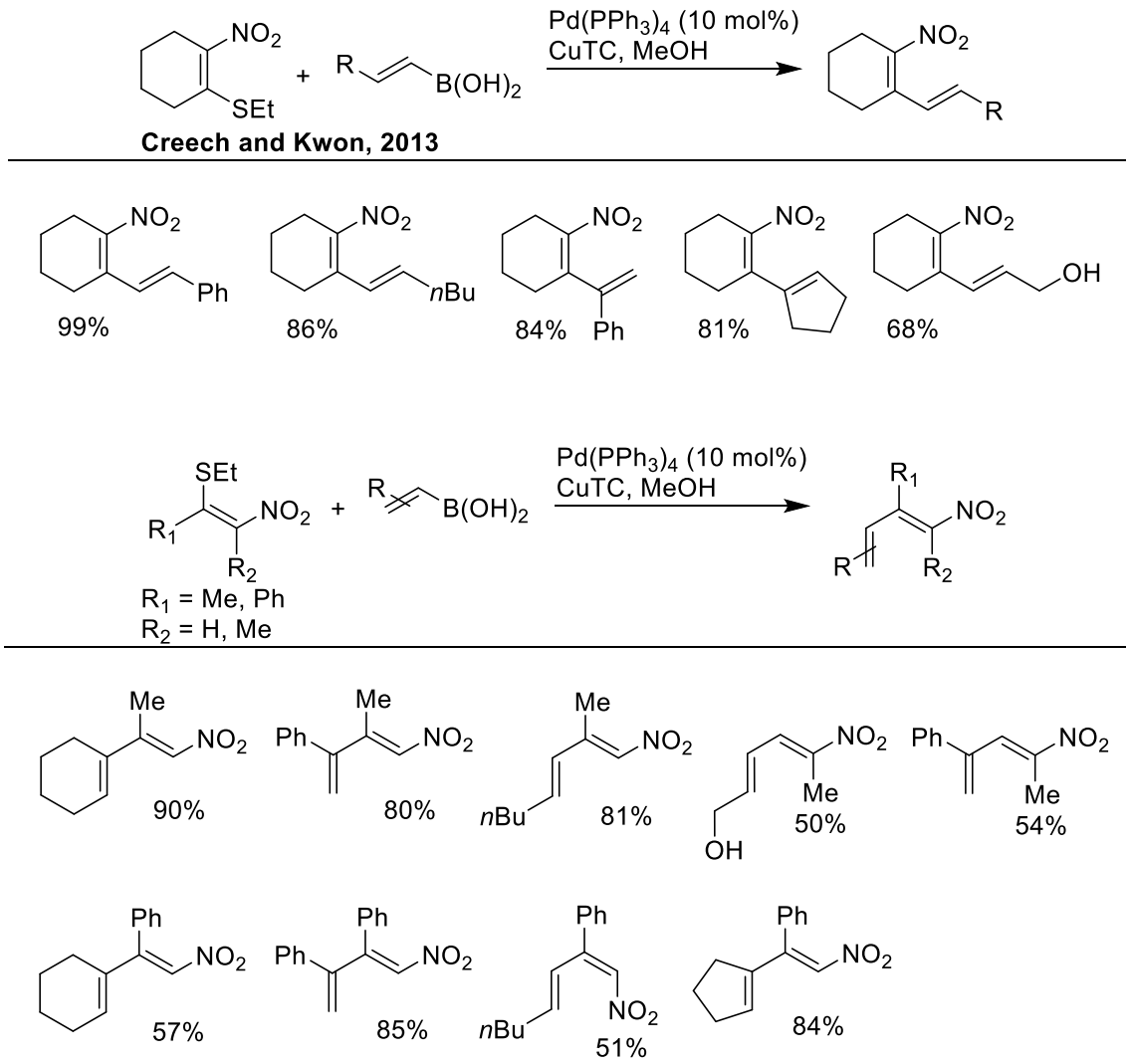


Scheme 1.2.5 Synthesis of conjugated nitrodienes by addition/elimination

Synthesis of Nitrodienes through Desulfitative Cross-Coupling

In order to overcome the limited substrate scope of the Knochel addition/elimination pathway, Creech and Kwon[13] devised an efficient, base-free, mild palladium-catalyzed desulfitative cross-coupling of vinyl thioethers and boronic acids (Scheme 1.2.6). In a similar fashion to Liebeskind–Srogl coupling of thioesters and boronic acids to form ketones, the C(sp^2)–S bond in a β-nitrothioether was believed to be sufficiently activated by the strongly electron

withdrawing nitro group for oxidative addition by palladium(0). Cross-couplings of the vinyl thioethers and vinyl boronic acids provided a variety of nitrodienes in good to excellent yields. δ-Phenyl and δ-*n*-butyl nitrodienes were synthesized in excellent yields with 2-thioethyl nitrocyclohexene as the coupling partner. Additionally, γ-phenyl substituted nitrodiene was generated in excellent yield, as was cyclopentenyl substituted nitro diene. Importantly, alcohol functionalities were now tolerated in synthetically useful yields, and in addition, previously inaccessible acyclic nitrodienes, were synthesized in good yields. Nitrothioethers bearing a β-methyl or a β-phenyl substituent were employed in the methodology to provide their corresponding nitrodienes. Cyclohexenyl nitrodienes were readily generated, as were γ-phenyl and δ-*n*-butyl nitrodienes. Capping off β-substituted nitrodienes is the cyclopentenyl nitrodiene in an 84% yield. As for α-methyl nitrodienes, both δ-hydroxymehtyl and γ-phenyl nitrodienes were synthesized in moderate yields. Most importantly, all nitrodienes utilized the *cis*-nitrothioether as the initial coupling partner. However, only for the synthesis of (1*E*,3*E*)-1-nitro-2-phenylocta-1,3-diene was this initial *cis* stereochemistry conserved. In all other cases, a complete loss of stereochemical information was observed.

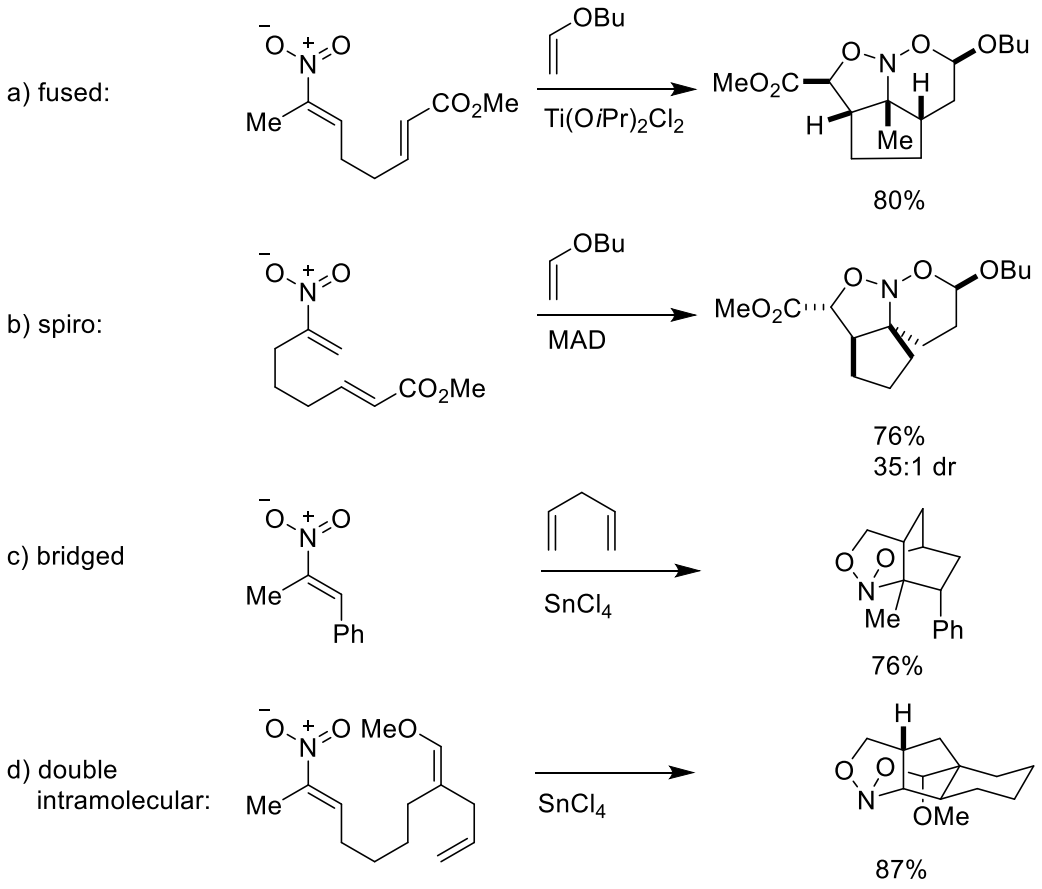


Scheme 1.2.6 Desulfitative cross-coupling of nitrothioethers and vinyl boronic acids

1.3 Pericyclic Reactivity of N=O π-bonds

Pericyclic reactions are among the most powerful of transformations in organic chemistry. Considerable molecular complexity can be generated in a single step, often from simple starting materials. In addition, pericyclic reactions quite often proceed through chemo-, regio-, and stereoselective pathways, giving only a sole product out of a multitude of possibilities.

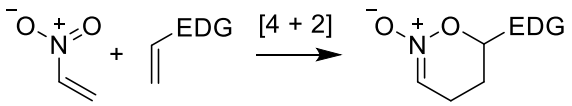
The literature is bountiful with examples of nitroolefins participating in pericyclic reactions, however, for the incorporation of the N=O π-bond the literature is considerably more scarce. Most notably, Denmark has developed a beautiful method for the synthesis of complex multicyclic nitroso acetals utilizing a hetero-Diels–Alder reaction of nitroalkenes to generate nitronate dipoles that are subsequently trapped through dipolar cycloadditions.[14] The tandem [4 + 2]/[3 + 2] sequence employed by Denmark encompasses four modes of reactivity: a) intermolecular [4 + 2] cycloaddition followed by β-tethered intramolecular [3 + 2] dipolar cycloaddition to give fused nitroso acetals; b) intermolecular [4 + 2] cycloaddition leading to α-tethered intramolecular [3 + 2] dipolar cycloaddition generating spirocyclic nitroso acetals; c) bridged nitroso acetal formation through intermolecular [4 + 2] with a dienophile tether; d) double intramolecular [4 + 2]/[3 + 2] providing a highly complex molecular skeleton (Scheme 1.3.1).



Scheme 1.3.1 Complex nitroso acetal products synthesized by [4 + 2]/[3 + 2] cycloadditions

Reactivity of Nitroalkenes in [4 + 2] Cycloaddition Reactions

Nitroalkenes have proven to be excellent compounds for use in a variety of cycloaddition reactions, mainly the Diels–Alder reaction.[15] Nitroalkenes typically react as a dienophile in a normal-electron-demand Diels–Alder reaction to yield nitrocyclohexenes. However, under inverse-electron-demand conditions, 6-membered cyclic nitronate products may be formed (Scheme 1.3.2).[14] Essential for the success of a nitroalkene [4 + 2] cycloaddition reaction is a low energy separation of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). In particular, for the inverse-electron-demand Diels–Alder of a nitroalkene and an electron-rich olefin, a Lewis acid is typically used to lower the energy of the $LUMO_{heterodiene}$ as well as increase the polarization of the FMO coefficients on the nitroalkene, leading to increased reaction efficiencies.

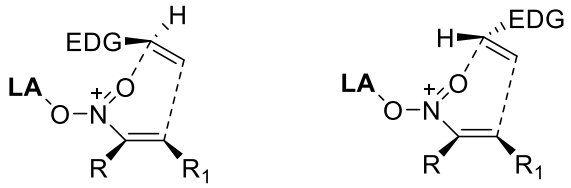


Scheme 1.3.2 [4 + 2] Cycloaddition of nitroalkene and olefin

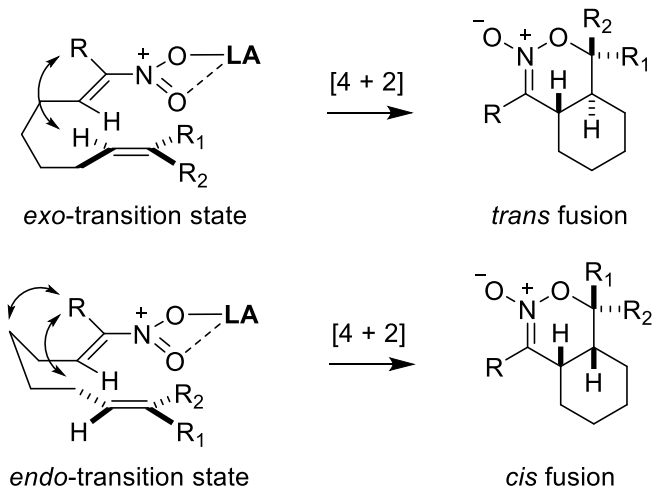
Importantly, due to the greater Lewis basicity of the product nitronate of the cycloaddition reaction, a stoichiometric amount of Lewis acid must be used, as the nitronate irreversibly binds to the Lewis acid. The products of the cycloaddition reaction typically display the characteristics of a pericyclic process. The *endo*-transition state is favored unless a large Lewis acid such as aluminum tris-(2,6-diphenylphenoxide) is employed (Figure 1.3.1). Additionally, in select cases where it is believed that the cycloaddition proceeds in a concerted, yet highly asynchronous process, minor products that do not preserve the starting olefin geometry can be observed. The

regioselectivity of the cycloaddition with dienophiles is easily predicted by analysis of the FMO coefficients. The β-carbon of the nitroalkene with the larger coefficient in the LUMO will align with the β-carbon of electron rich olefins with the larger coefficient in the HOMO.

Figure 1.3.1 *Endo* and *exo* transition state structures



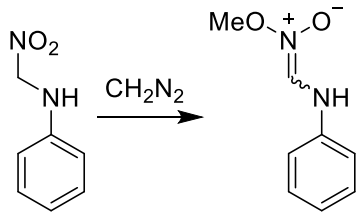
For nitroalkenes possessing a linked dienophile, the cycloaddition reaction can proceed in an intramolecular manner. Nitroalkenes bearing a β-tether can create a fused nitronate upon cycloaddition (Scheme 1.3.3). For compounds with a tethered dienophile, the diastereoselectivity is determined by the fold of the tether as the dienophile approaches the diene. Employing Lewis acids such as $SnCl_4$ favor an *exo* transition state, as this approach mediates steric congestion between the diene and substituents on the dienophile. Progression of the reaction through the *exo* transition state provides the corresponding *trans*-fused bicyclic nitronate, whereas reaction through the more hindered *endo* transition state give the *cis*-fused product.



Scheme 1.3.3 Tethered cycloadducts arising from steric interactions in the transition state

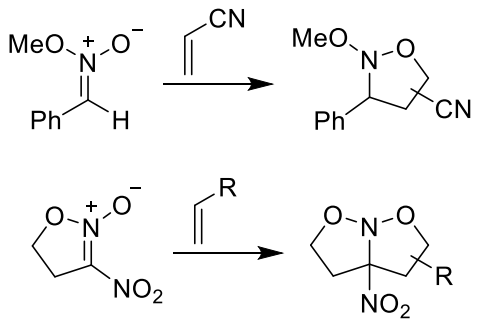
Nitronates and Their Use in Cycloadditions

Nef first described the synthesis of nitronates in 1894,[16] however, it was not until 1901 when Schmidt first reported on the isolation of a nitronate compound resulting from reacting diazomethane with phenylazonitromethane (Scheme 1.3.4).[17]



Scheme 1.3.4 First isolated nitronate

Despite disclosure of the nitronate structure in the early 1900's, the chemistry surrounding nitronates remained limited until the discovery of a nitronate dipolar cycloaddition reaction by Tartakovskii.[18] By reacting cyclic and acyclic nitronates with alkenes, a 1,3-dipolar cycloaddition reaction proceeded, providing products with a nitroso acetal functionality (Scheme 1.3.5).

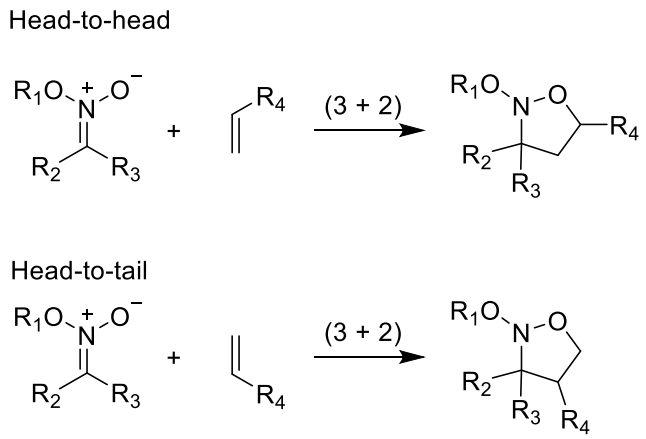


Scheme 1.3.5 First cycloaddition employing nitronates

Since the seminal report by Tartakovskii exemplifying dipolar cycloadditions with nitronates and alkenes, this mode of reactivity has seen a plethora of investigation due to the inherent ability of pericyclic reactions to form complex products in a predictable manner. The 1,3-dipolar cycloaddition reactions comprise a significant portion of cycloaddition reactions studied in organic chemistry. A 1,3 dipole, containing a formal positive charge at one terminus and a formal negative charge at the other will react with a corresponding dipolarophile, forming two new σ-bonds, producing a new five-membered ring. In line with other pericyclic reactions, the dipolar cycloaddition generally follows strict rules for cycloaddition.

Regioselectivity of the Nitronate Dipolar Cycloaddition

Two regioisomeric cycloaddition products are possible in the nitronate dipolar cycloaddition: head-to-head and head-to-tail, due to the inherent asymmetry of the dipole. However, in the case of nitronates reacting with dipolarophiles, the nitroso acetal product is formed almost exclusively in the head-to-head fashion (Scheme 1.3.6).[19]



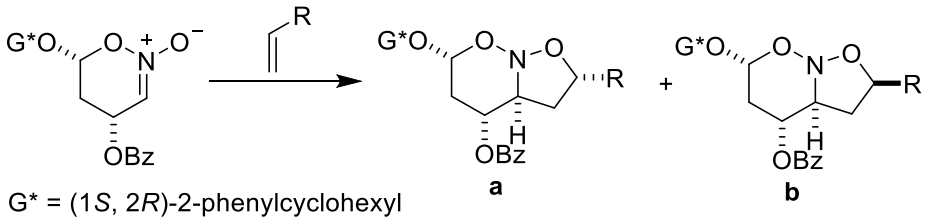
Scheme 1.3.6 Head-to-head and head-to-tail regioisomers

Thorough computational analysis has been employed to further explain the observed regioselectivity of the nitronate dipolar cycloaddition reaction. Intermediate Neglect of Differential Overlap (INDO) calculations of nitronates with electron-withdrawing groups were insufficient to definitively explain the orbital interactions.[20] When the electron-withdrawing group was removed, the higher coefficient for the nitronate lies on carbon in the HOMO and LUMO. As such, reacting a nitronate with a dipolarophile bearing an electron-withdrawing group results in head-to-head regioselectivity because the larger coefficient lies on the α-carbon of the dipolarophile.[21] As for electron-rich dipolarophiles, semiempirical calculations showed that the head-to-head approach of the dipolarophile is 5.91 kcal/mol more favorable than the head-to-tail approach, resulting in a cycloadduct that is 6.6 kcal/mol more stable.[22] Additionally, using density functional theory (DFT) calculations, electron-poor dipolarophiles showed a head-to-head favorability of 3.4 kcal/mol and electron-rich dipolarophiles showed a head-to-head favorability of 7.4 kcal/mol.[23]

Stereoselectivity of the Nitronate Dipolar Cycloaddition

In addition to following strict regioselectivity rules, the nitronate [3 + 2] dipolar cycloaddition reaction also benefits from predictable stereoselectivity. In addition to studying the head-to-head and head-to-tail approach of dipolarophiles, Denmark also studied the exo/endo selectivity of cyclic nitronates and monosubstituted dipolarophiles (Table 1.3.1).[21] Studies showed that the exo product is the major observed product, with a strong correlation between the steric size of the substituent on the dipolarophile and the preference for exo product. When reacting cyclic nitronates with sterically undemanding dipolarophiles like acrolein, the selectivity reverses, giving a majority of the endo product.

Table 1.3.1 Stereoselectivity of the cycloaddition of cyclic nitronate and dipolarophiles



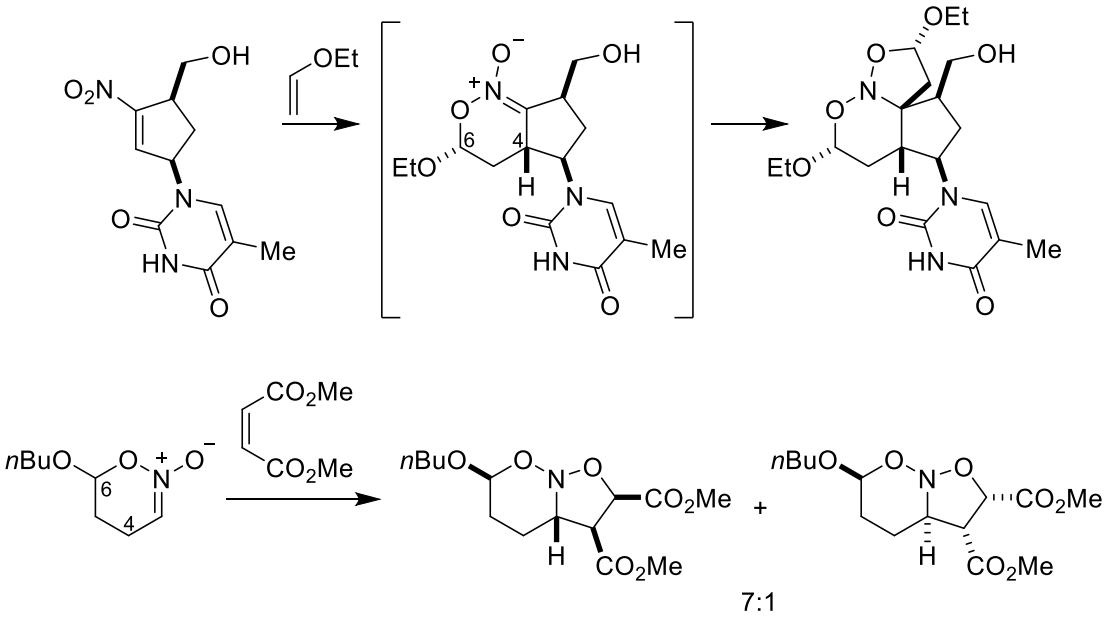
R	dr (a:b)
CO_2tBu	11.4:1
CO_2Me	6.5:1
COMe	6.2:1
$COCH_2OTDS^a$	5:1
$COCH_2OBn$	5.7:1
CH_2OH	1.3:1
CHO	1:2

[a]TDS = thexyldimethylsilyl

Facial Selectivity of the Nitronate Dipolar Cycloaddition

Along with regioselectivity and stereoselectivity, the nitronate dipolar cycloaddition also is generally governed by a facial selectivity preference. This occurs when the dipolarophile approaches from either the top or the bottom face of the nitronate, and is dictated by the steric

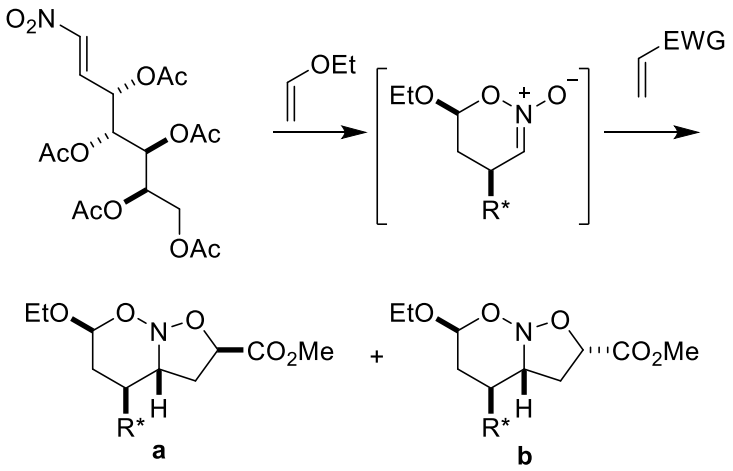
environment on that face. In particular, for cyclic nitronates, substituents at C4 and C6 exhibit steric and electronic effects that control the facial selectivity of the cycloaddition (Scheme 1.3.7).[24]



Scheme 1.3.7 C4 and C6 substituent effect on facial selectivity

Importantly, a lack of a substituent on the cyclic nitronate still provides for a high degree of facial selectivity.[25] As previously seen when increasing the steric environment around a dipolarophile increases the exo selectivity for the cycloaddition, so too does increasing the size of the dipolarophile raise the facial selectivity (Table 1.3.2).[26]

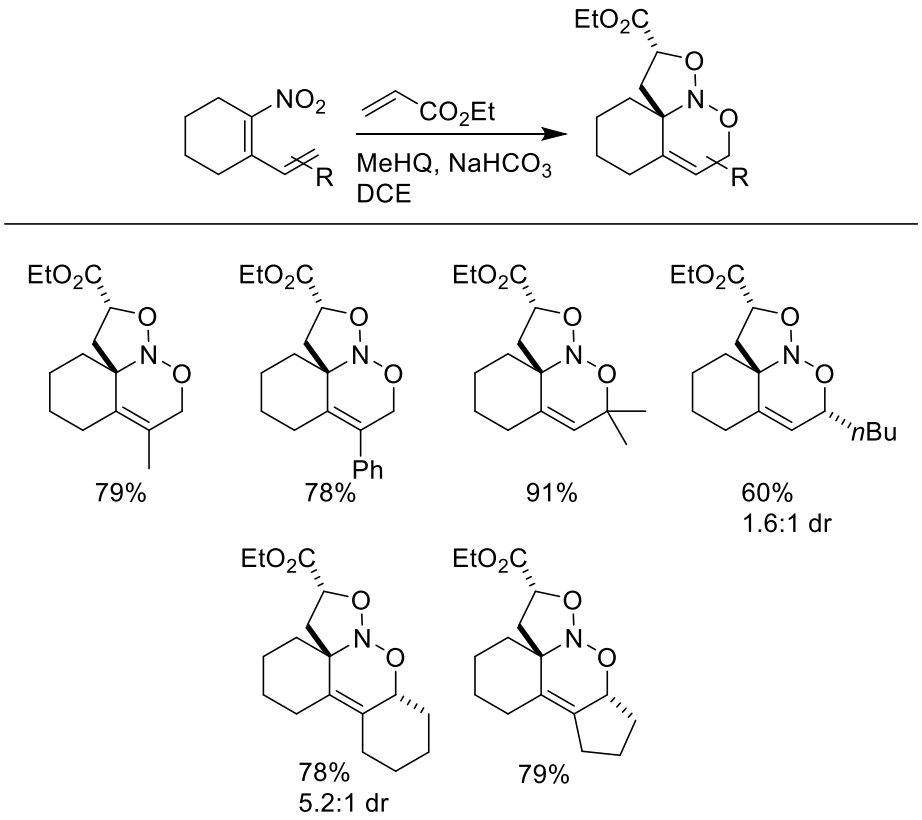
Table 1.3.2 Dipolarophile size and facial selectivity



EWG	yield (%)	dr (**a**:**b**)
COMe	79	1:0
CO_2Me	79	19:1
CN	70	6:1

Tandem 6π-Electrocyclization and Cycloaddition of Nitrodienes

Recently, Creech and Kwon reported on the synthesis of nitrodienes and their tandem 6π-electrocyclization/[3 + 2] dipolar cycloaddition to generate multicyclic nitroso acetals.[11b] By locking the internal olefin of the conjugated nitrodiene in the necessary *cis*-olefin geometry through using 2-thioethyl nitrocyclohexene, the desired nitrodienes were synthesized. Employment of the Knochel protocol for the synthesis of conjugated nitrodienes via conjugate addition/elimination of zinc cuprates readily gave access to a variety of nitrodienes (Scheme 1.3.8). γ-Substituted nitrodienes bearing methyl and phenyl substituents were efficiently synthesized. δ-Substituted nitrodienes were synthesized to give nitroso acetal products bearing an additional stereocenter. Additionally, δ-*n*-butyl, and δ-phenyl nitrodienes were generated, however in the case of *cis*-β-bromostyrene, only the *trans* product was observed. Cyclic alkenes were also tolerated, giving polycyclic nitrodienes in great yields. Most interestingly, δ,δ-dimethylnitrodiene was never isolated, but was found to spontaneously undergo 6π-electrocyclization over SiO_2.

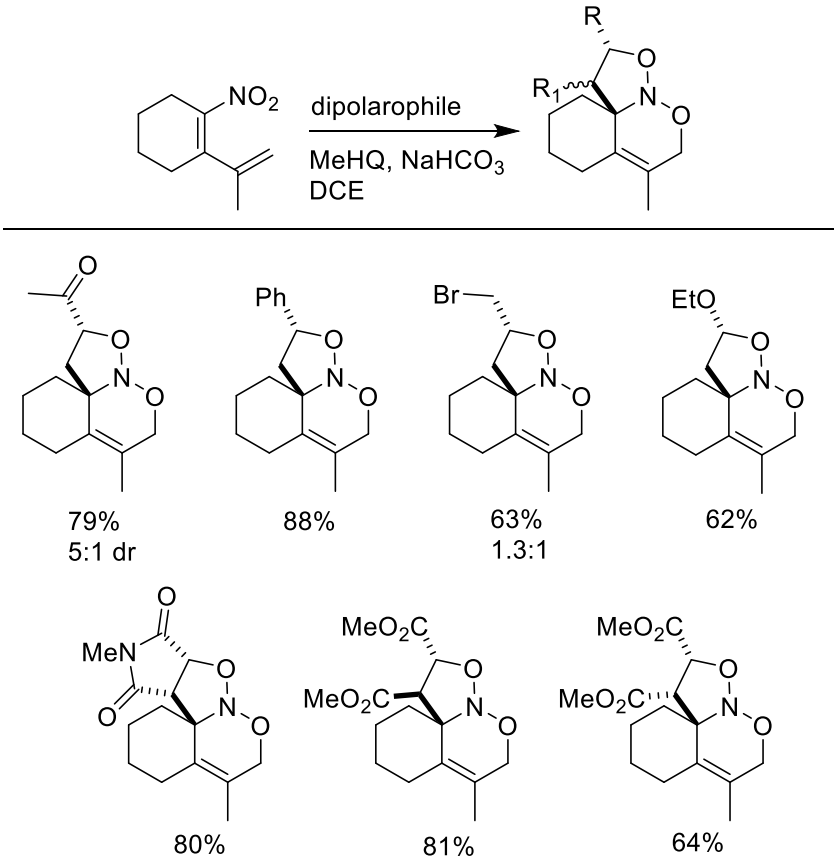


Scheme 1.3.8 Synthesis of nitroso acetals

Synthesis of various nitroso acetals by treatment of the nitrodienes with ethyl acrylate gave the tricyclic products in high yields with well-defined stereochemistry. For γ-substituted nitrodienes, tandem 6π-electrocyclization/[3 + 2] dipolar cycloaddition proceeded smoothly, giving the desired compounds. In the case of mono-δ-substituted nitrodienes, an additional stereogenic center is formed. For δ-*n*-butyl nitrodiene, the 6π-electrocyclization/[3 + 2] dipolar cycloaddition with ethyl acrylate resulted in a 1.6:1 mixture of diastereomers. With increased selectively, the 2-cyclohexenyl nitrocyclohexene can be transformed to the tetracyclic nitroso acetal in a 5.2:1 mixture of diastereomers. When applying the methodology to a cyclopentenyl nitrocyclohexane, only a single diastereomer is observed. Interestingly, the δ-phenyl nitrodiene did not undergo the rearrangement, which is postulated to be due to its increased stability via

extended conjugation. Based on the observed diastereoselectivities, the dipolarophile appears to approach from the face of the nitronate bearing the δ-hydrogen atom.

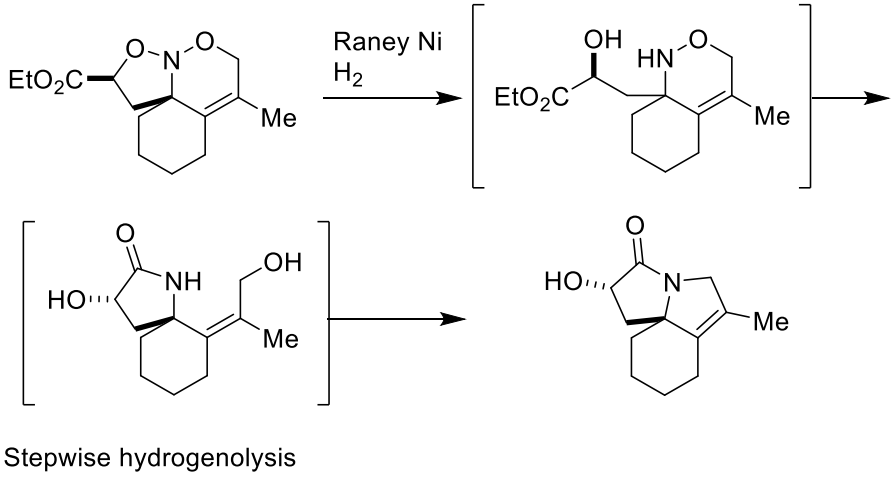
To further investigate the scope of the cycloaddition reaction, several dipolarophiles were screened under the reaction conditions (Scheme 1.3.9). Reaction with methyl vinyl ketone proceeded smoothly, however unlike ethyl acrylate, an erosion of the exo/endo selectivity was observed. More neutral dipolarophiles, styrene and allyl bromide, proved to be good dipolarophiles, giving nitroso acetals in good yields. Even electron-rich dipolarophile, ethyl vinyl ether, provides the nitroso acetal in good yield and excellent diasteroselectivity. Disubstituted olefins bearing electron-withdrawing groups reacted as expected, providing the multicyclic nitroso acetals in great yields and diastereoselectivities.

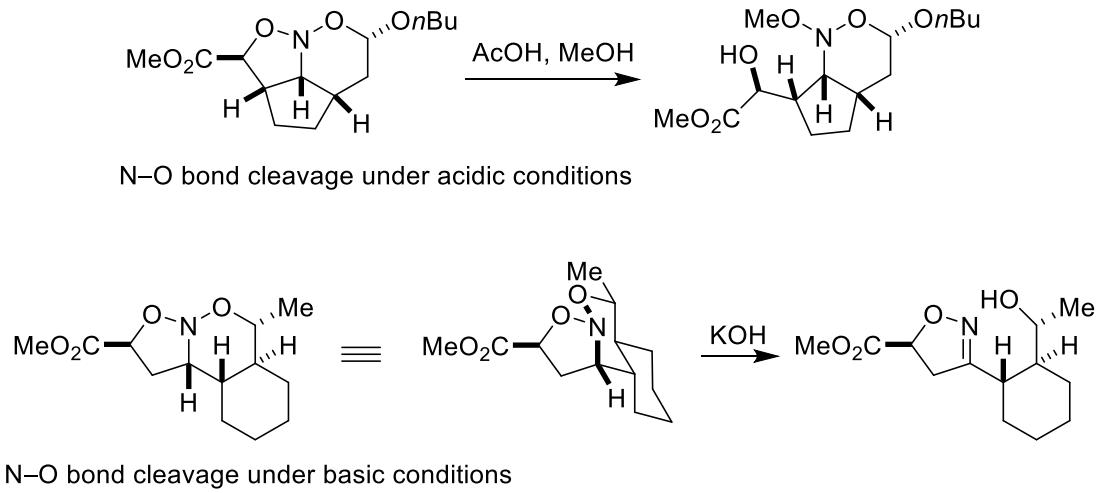


Scheme 1.3.9 Scope of dipolarophiles for the synthesis of nitroso acetals

Properties of Nitroso Acetals

The nitroso acetals produced by tandem pericyclic reactions are typically further processed into other functionalities via cleavage of the weak N–O bonds (Scheme 1.3.10). Stable at neutral conditions, the N–O bonds are weak (40–55 kcal mol^{-1}) and are typically cleaved to the amino diol by hydrogenolysis. The hydrogenolysis of the N–O bonds is accomplished in sequence, one N–O bond is cleaved followed by the second. In addition to being labile towards hydrogenolysis, nitroso acetals react in a similar manner to acetals/ketals. Under acidic conditions, one or both alkoxy groups may be exchanged. Under base catalyzed conditions, selective cleavage of a single N–O bond in bicyclic nitroso acetals is observed. This is explained by the requirement that the C–H bond must align in an antiperiplanar fashion with the fragmenting N–O bond. Aside reaction at the N–O bonds of nitroso acetals, other reactions at the periphery are also possible. The nitroso acetal is stable to both aluminum hydride and boron hydride reducing agents as well as mildly oxidizing conditions.





Scheme 1.3.10 Reactions of nitroso acetals

1.4 Pyrrolizidine Alkaloids

More than 660 pyrrolizidine alkaloids (PAs) are found widely throughout nature in over 6000 varieties of plants and possess a wide range of biological activities.[27] Mainly isolated from the extracts of plants, a unique feature of a majority of PAs is that they are synthesized, stored, and translocated as the corresponding *N*-oxides (Figure 1.4.1).[28] Although the isolation of alkaloids as their *N*-oxides is not an uncommon occurrence, isolation as *N*-oxides as the predominant form is unique to PAs. A majority of PAs (approximately 95%) are found in plants of the families

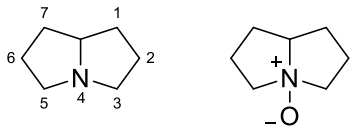


Figure 1.4.1 Pyrrolizidine and pyrrolizidine *N*-oxide

Asteraceae, Boraginaceae, Fabaceae, and Orchidaceae. Other families where PAs have been sparsely found include Apocynaceae, Celastraceae, Rhizophoraceae, Ranunculaceae, Santalaceae, Sapotaceae, and Convolvulaceae. In addition, PAs have been found in the family

Scrophulariaceae, however this root parasite does not synthesize PAs directly, but obtains them from its host. In general, PAs are found as ester alkaloids comprised of a necine base core and a necic acid (Figure 1.4.2).

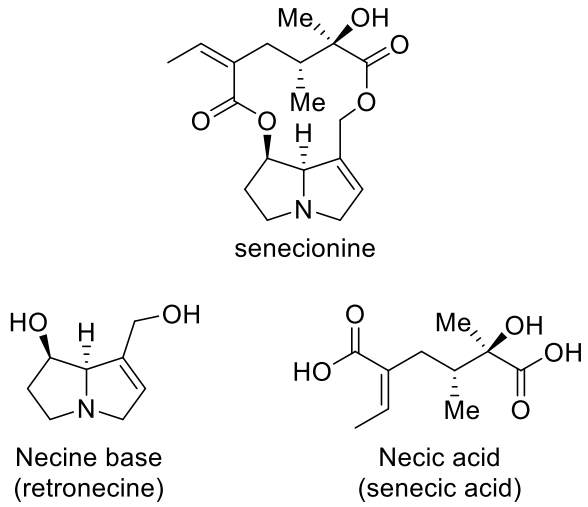


Figure 1.4.2 Necine base and necic acid

The two components can combine to form monoesters, open-chain diesters, and macrocyclic diesters. Because of this modularity, a great variety of compounds may be generated after various modifications of the necine base or necic acid structures. Drawing on the classifications pioneered by Culvenor[29] and Hartmann, PAs can be classified into seven types: senecionine, triangularine, lycopsamine, monocrotaline, phalaenopsine, loline, and miscellaneous (Figure 1.4.3).

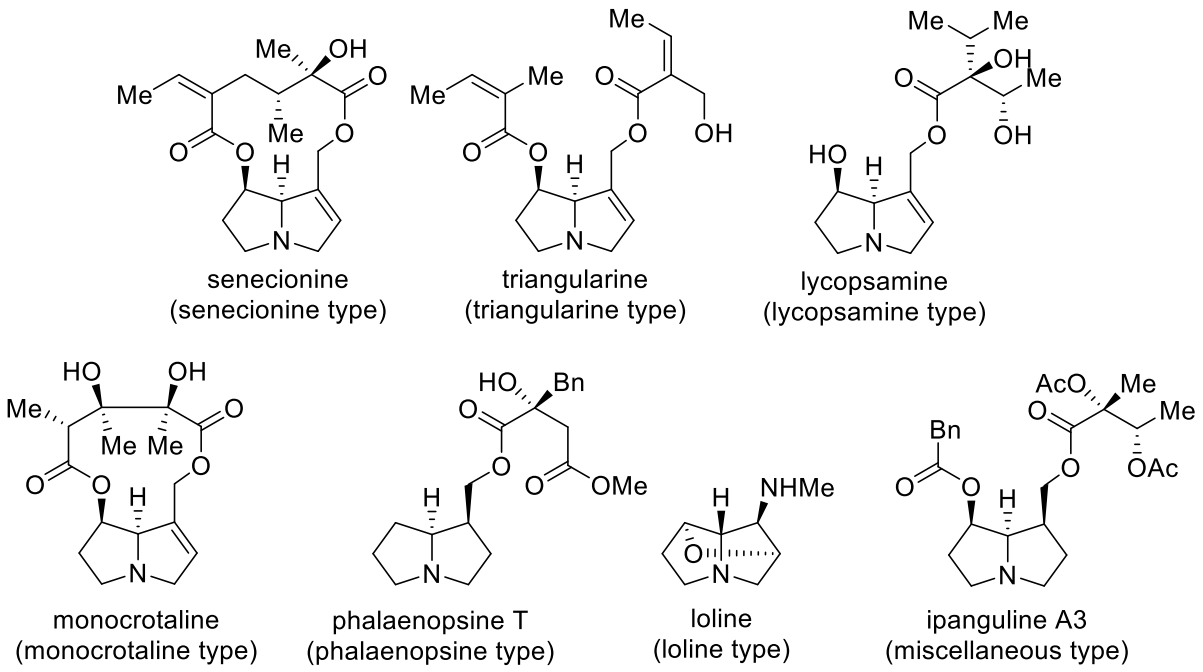


Figure 1.4.3 Classification of pyrrolizidine alkaloids

Senecionine Type

Structurally related to senecionine, this class is primarily composed of twelve-membered macrocyclic diesters, which can be further separated into four sub-classes: senecionine, senecivernine, nemorensine, and rosmarinine (Figure 1.4.4). The senecionine type of PAs is most characteristic of the tribe Senecioneae of the Asteraceae taxa as well as the Fabaceae taxa. The senecionine sub-group can be described as compounds that are derived from senecionine by manipulation of both the necine base and necic acid components, where the necic acid component is derived from isoleucine. Similar to the senecionine sub-group, the senecivernine sub-group is distinguished by a differing C–C linkage on the necic acid. PAs containing a thirteen-membered macrocycles with a necic acid derived from leucine and isoleucine are in the nemorensine sub-group. The final sub-group, rosmarinine, is comprised of C1- or C2-hydroxylated necine cores.

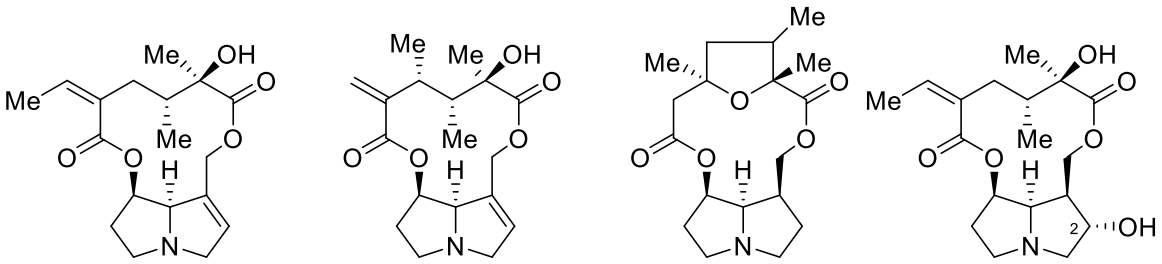


Figure 1.4.4 Senecionine type

Triangularine Type

The triangularine class of PAs contain either monoesters or diesters containing five-carbon acids and their hydroxylated derivatives (Figure 1.4.5). Alkaloids of this class are generally found in the family Senecioneae, and the monoesters are regularly found in the Eupatorieae and Boraginaaceae. The triangularine sub-group contains monoesters and diesters of either C7- and C9-hydroxylated alkaloids. The second sub-group, macrophylline, is composed of monoesters or diesters with C2- and C9-hydroxylated necines. senampeline sub-group is structurally similar to triangularine diesters, where the necine core is an acylpyrrole or a derivative with a C5 acetate.

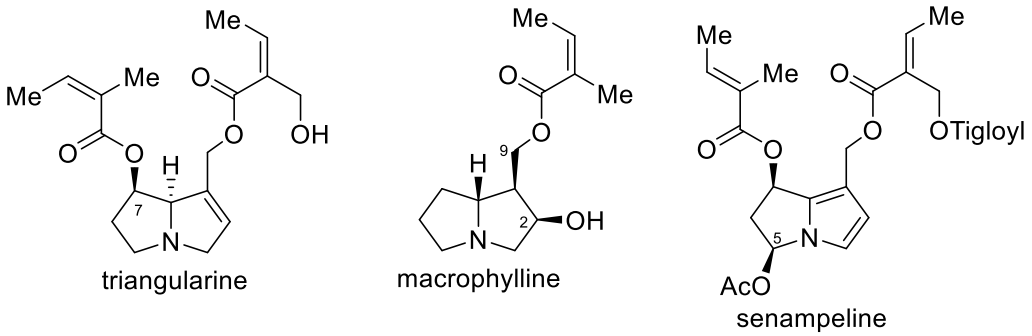


Figure 1.4.5 Triangularine type

Lycopsamine Type

Type three of PAs, the lycopsamine type, contain monoesters and diesters with a hydroxylated 2-isopropylbutyric acid as the necic acid, uniquely found in PAs. Overwhelmingly found in the Boraginaceae, PAs of this type are also found in the tribe Eupatorieae of Asteraceae. The lycopsamine types can be classified into four sub groups: lycopsamine, isolycopsamine, latifoline, and parsonsine (Figure 1.4.6). The first sub-class, lycopsamine, is exemplified by monoesters or diesters with a seven carbon acid esterified at the C9-OH. The diesters of this sub-class bear an acetate or five carbon acid attached to the C7-OH. Similar to the lycopsamine sub-class, the isolycopsamine sub-class contains alkaloids bearing monoesters or diesters with a seven carbon acid esterified exclusively at the C7-OH. Diesters in this sub-class have an acetate bound to the C9-OH. The latifoline sub-class is structurally analogous to the lycopsamine sub-class, but the seven carbon acid forms a five-membered lactone. The final sub-class, parsonsine, are macrocyclic PAs where the macrocyclic structure contains an ester linkage between two necic acids attached to the C7-OH and the C9-OH of retronecine. Additionally, at least one of the necic acids is a seven carbon acid.

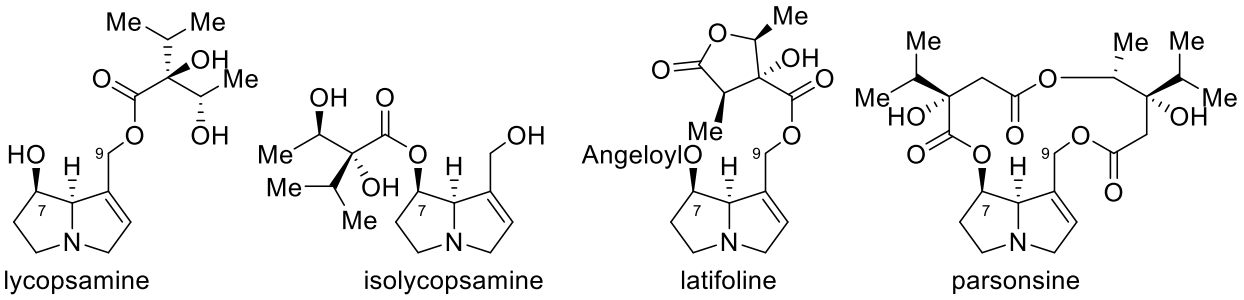
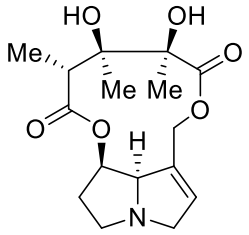


Figure 1.4.6 Lycopsamine type

Monocrotaline Type

Retronecine necine bases with eleven-membered macrocyclic diesters and a varied substitution of the necic acid make up the monocrotaline type of PAs (Figure 1.4.7). These PAs are characteristic of the genus *Crotalaria*, and are also found in select species of Boraginaceae.

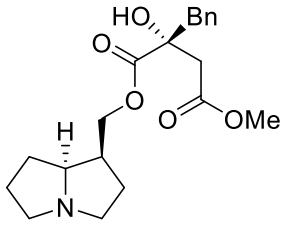


monocrotaline

Figure 1.4.7 Monocrotaline type

Phalaenopsine Type

The phalaenopsine type of PAs are monoesters of (–)-isoretronecanol, lindelfoline, laburnine or (–)-trachelanthamidine with an aryl or in scarce cases an alkyl necic acid (Figure 1.4.8). These alkaloids are typically found in Orchidaceae, which are solely produced as PAs with a 1,2-saturated necine core.

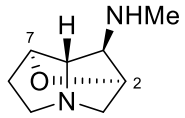


phalaenopsine T

Figure 1.4.8 Phalaenopsine type

Loline Type

The loline class is biogenetically unrelated to 1-hydroxymethylpyrrolizidines, however these pyrrolizidine derivatives bear an ether bridge between C2 and C7 (Figure 1.4.9). Loline type alkaloids can be found in tribe Genisteae of Fabaceae (genus *Adenocarpus*).

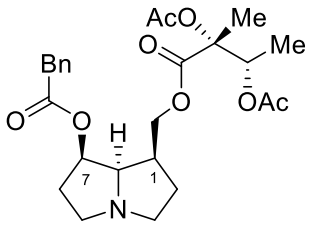


loline

Figure 1.4.9 Loline type

Miscellaneous Type

The final type consists of simple structures that do not fit into the above types (Figure 1.4.10). Some unusual compounds include the ipangulines, which are diesters of the necine base turneforcidine, where one necic acid is an alkyl acid, and the other necic acid is either benzoic or phenylacetic acid. Another sub-class includes the simple necine base derivatives which are not esterified. Some compounds belonging to this sub-class are thought to arise as postmortal degradation products.



ipanguline A3

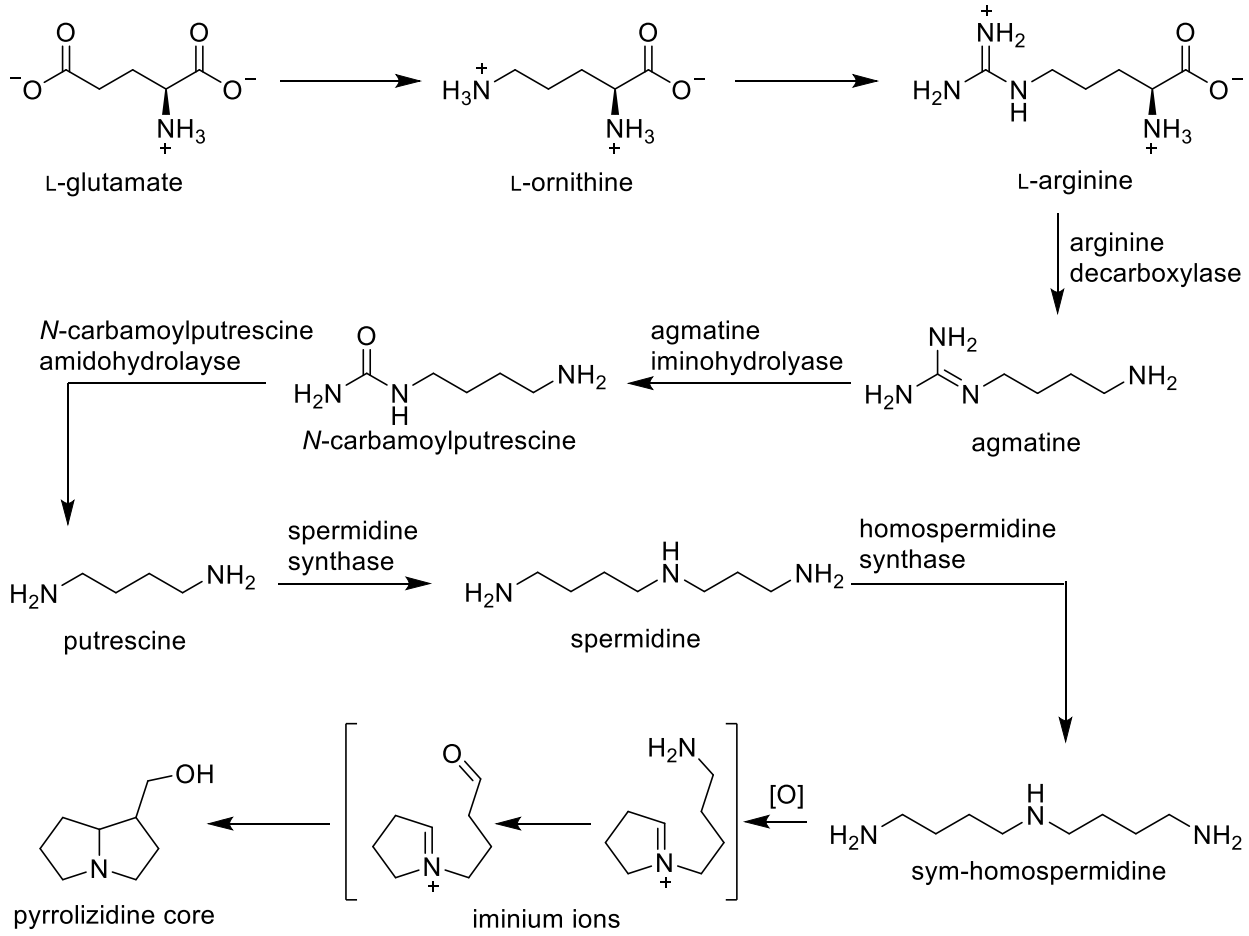
Figure 1.4.10 Miscellaneous type

1.5 Biology of Pyrrolizidine Alkaloids

The biosynthesis of PAs has been thoroughly investigated through a series of isotopic labeling studies.[30] Preliminary studies showed that L-ornithine is incorporated solely into the necine base and acetate or propionate are incorporated into the necic acid moiety. Further studies elucidated that either two molecules of L-ornithine or L-arginine combine to form the necine base via transformation to putrescine through the arginine-agmatine pathway.[31] Ornithine is converted to arginine which is then converted to agmatine with the aid of arginine decarboxylase. Agmatine iminohydrolayse then converts agmatine to *N*-carbamoylputrescine, which is subsequently transformed to putrescine with the aid of *N*-carbamoylputrescine amidohydrolyase. A series of experiments performed by Robbins and Spenser using isotopically labeled precursors elucidated the mechanism of biosynthesis (Scheme 1.5.1). ^{15}N- And ^{13}C-labeled putrescine was shown to form sym-homospermidine, a compound with C_{2v} symmetry. Based on experiments with the root cultures of *Senecio vulgaris*, it is likely that putrescine is converted to sym-homospermidine with the enzyme homospermidine synthase. In biomimetic studies, sym-homospermidine was oxidixed with diamino oxidase to the corresponding dialdehyde, however it is unlikely that diamino oxidase is responsible for the formation of sym-homospermidine *in vivo*, as sym-homospermidine is generated in the presence of β-hydroxyethylhydrazine, a known inhibitor of diamine and polyamine oxidases.[32] Consecutive oxidative deaminations then lead to a dialdehyde intermediate which is in equilibrium with an iminium ion that can be trapped under cyclization conditions to give 1-formylpyrrolizidine.[33] Reduction would then provide the necine base core structure.

Although less stable than the corresponding tertiary amines, PA *N*-oxides are the predominant form found in nature. Great care must be taken during the extraction procedure to avoid reduction of the *N*-oxides. For *Senecio* species, PAs are found exclusively in the *N*-oxide

form. It is believed that the polar *N*-oxides are more readily transported and stored in the cell vacuole than the tertiary amine form, which can pass through biomembranes more readily.



Scheme 1.5.1 Biosynthesis of 1-hydroxymethylpyrrolizidine

Although pyrrolizidine alkaloids themselves are generally nontoxic to mammals, a majority of PAs are known to cause diseases in both animals and humans. This is attributed to the toxicity of pyrrolic metabolites that are formed via oxidase enzymes found in liver microsomes, mainly cytochrome P-450 monooxygenases. PA pyrroles are highly unstable and are excellent alkylating agents, forming covalent bonds to essential biological nucleophiles such as proteins and nucleic acids. This leads to altered cell function, which, in turn, can bring about cell damage or

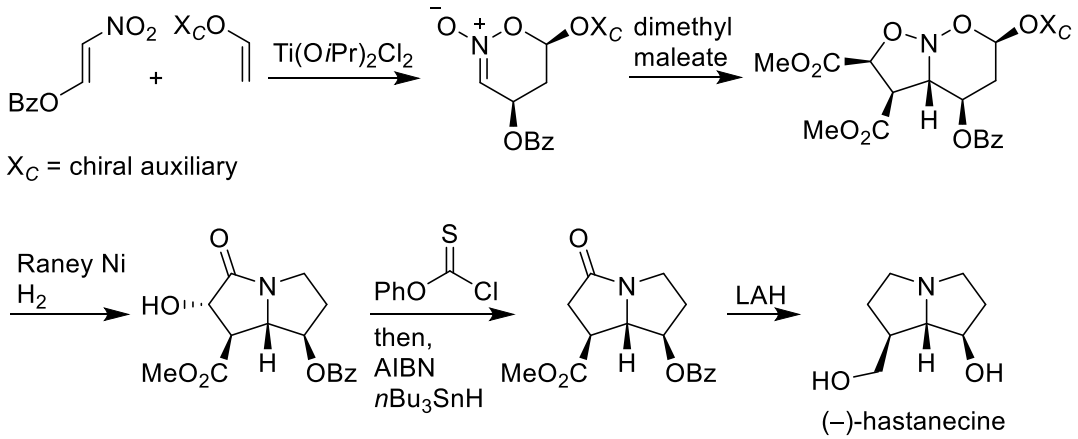
cell death, or even lead to cancer formation. In the liver, PAs can also be metabolized to their *N*-oxides, which are generally unreactive and can be safely excreted in urine due to their increased water solubility. However, PA *N*-oxides still present potential toxicity to animals due to the fact that they are easily reduced by intestinal flora of the ingesting animal and are then easily absorbed as the tertiary PA.

It is generally accepted that PAs are employed as protective chemicals for plants against mammalian herbivores and insects. In animals, the toxicity of the PAs only is apparent after an extended amount of time, which in some cases can be up to 18 months. This slow action is insufficient to explain the viability of PAs as defense compounds towards mammals. In fact, herbivores are observed to avoid ingesting PA producing plants unless there is a shortage of food, implicating a deterrent flavor as the primary defense mechanism. This same feeding aversion is observed in insects such as locusts, ants, and cockroaches. Although PAs can be used as deterrents, a large amount of insects in various orders are actually attracted to PA producing plants. These insects are known to sequester and store PAs from plants and subsequently use them as defense chemicals against predators.

1.6 Synthesis of Pyrrolizidine Alkaloids by Tandem Pericyclic Reactions

The utility of tandem pericyclic reactions towards the synthesis of a multitude of natural products is thoroughly explored in the synthesis of a number of pyrrolizidine alkaloids by Denmark and co-workers.[25, 34] By reacting various nitro alkenes with dienophiles, a cyclic nitronate is formed, which is then able to undergo a dipolar cycloaddition yielding a bicyclic nitroso acetal product. The pioneering synthesis for the application of tandem pericyclic reactions was accomplished by Denmark for the synthesis of (–)-hastanecine (Scheme 1.6.1). [4 + 2]

Cycloaddition between nitro alkene and chiral vinyl ether smoothly provided the desired nitronate product. The nitronate was then subjected to dipolar cycloaddition reaction conditions with



Scheme 1.6.1 Total synthesis of (–)-hastanecine

dimethyl maleate to give the desired nitroso acetal product as a single diastereomer. After N–O bond hydrogenolysis and cyclization with Raney Nickel the pyrrolizidine core was formed, and after deoxygenation of the C6 hydroxy group and global reduction, the natural product (–)-hastanecine was produced. This general reaction sequence was extended to the synthesis of a multitude of pyrrolizidine alkaloids and related natural products (Figure 1.6.1).

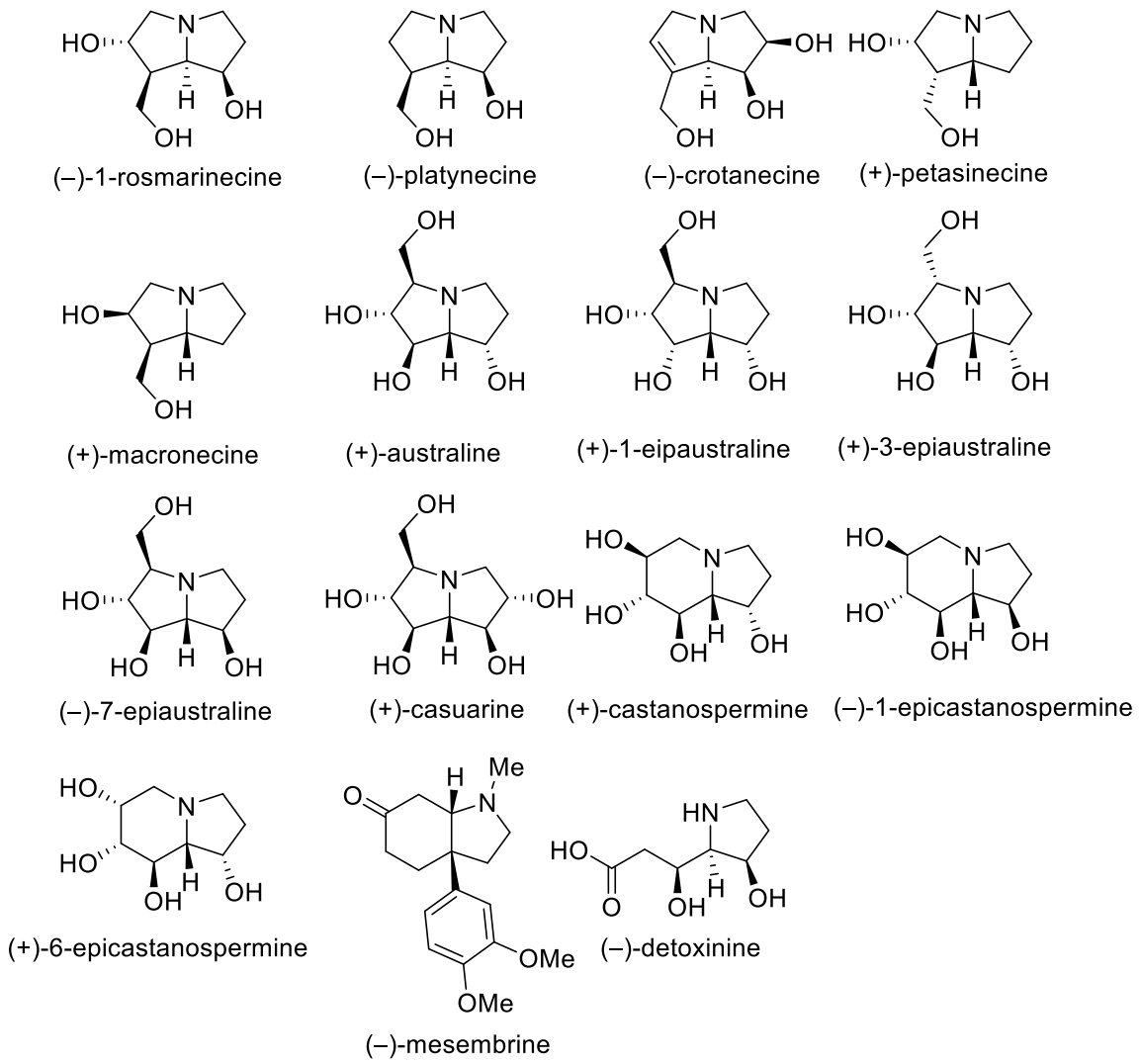
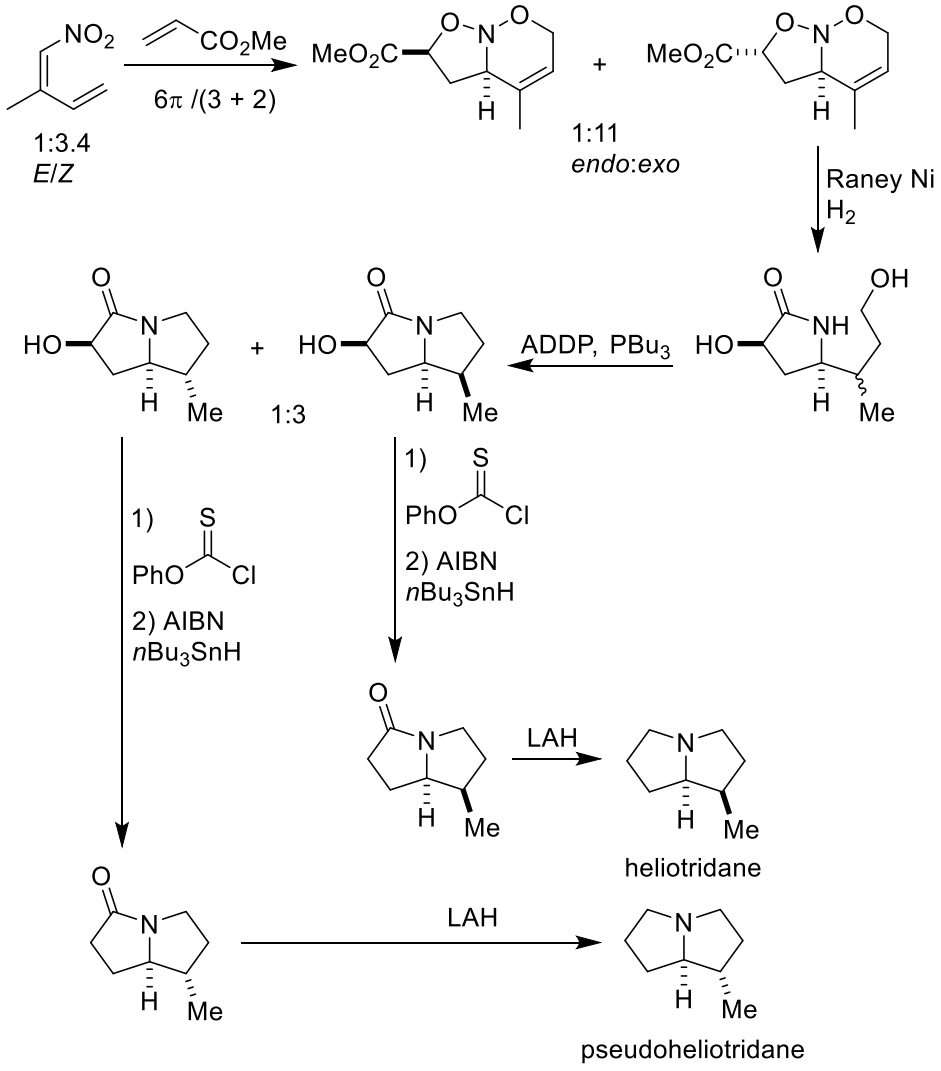


Figure 1.6.1 Natural products made by nitroalkene [4 + 2]/[3 + 2] cycloaddition

Drawing from the power of pericyclic reactions to rapidly install high molecular complexity from simple starting materials, Koc and Kwon devised a synthesis of heliotridane and pseudoheliotridane exploiting the versatility of a tandem 6π-electrocyclization/[3 + 2] dipolar cycloaddition of nitrodienes (Scheme 1.6.2).[35] Reaction of isoprene derived nitrodiene and methyl acrylate proceeded through the expected 6π-electrocyclization to provide the nitronate intermediate which was subsequently trapped to give the nitroso acetal product. Interestingly, the 1:3.4 mixture of *E* and *Z* isomers of the nitrodiene was able to undergo *in situ* isomerization during

the reaction to give the nitroso acetal product with a 1:11 ratio of *endo* to *exo*. Hydrogenolysis with Raney Ni, quickly followed by ring closure brought about the pyrrolizidine core structure, a 3:1 mixture of diastereomers. Individually taking the pyrrolizidinones forward through a sequence of deoxygenation and reduction, the natural products heliotridane and pseudoheliotridane were generated.

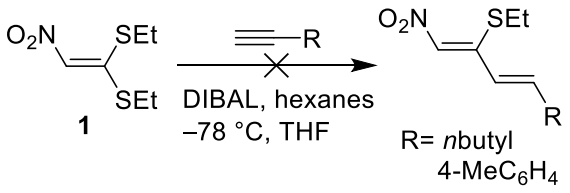


Scheme 1.6.2 Kwon's tandem 6π-electrocyclization/[3 + 2] dipolar cycloaddition for the synthesis of pyrrolizidine alkaloids

1.7 Results and Discussion

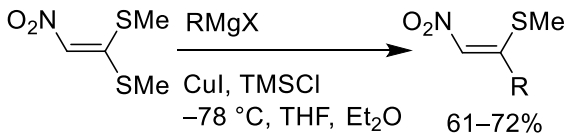
As part of our burgeoning program investigating the reactivity of conjugated nitrodienes, we wished to expand upon the scope of acyclic nitrodienes. We envisioned developing a highly modular reaction sequence that could rapidly provide access to a multitude of nitrodienes bearing a dipolarophile tether in order to generate a variety of medium ring compounds through this methodology. Four classes of intramolecular dipolar cycloaddition reactions can be performed based on the point (α, β, γ, δ) of attachment. We envisioned a modular approach to the various nitrodienes, beginning from known dithioketene acetal **1**,[36] which would provide access to β, γ, and δ substituted nitrodienes. Through a sequence of addition/elimination, Liebeskind–Srogl coupling, and cyclization, a variety of multicyclic nitroso acetals could be targeted.

Inspired by the addition/elimination methodology developed by Malanga,[12] we envisioned the simple preparation of conjugated nitrodienes via hydroalumination of various alkynes (Scheme 1.7.1). To probe the viability of this reaction we treated 1-hexyne and 4-ethynyltoluene with diisobutylaluminum hydride (DIBAL), generating the vinyl aluminum species, and subsequently reacting with **1**. Disappointingly, no desired product was formed under the reaction conditions, and extensive screening of varied reaction conditions and additives failed to give the desired nitrodiene products. Not to be discouraged, we sought alternative methods for the synthesis of nitrodienes.



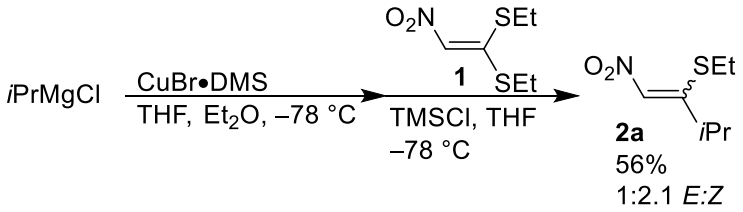
Scheme 1.7.1 Attempted conjugate addition/elimination

Ila and Junjappa[37] have reported on the trimethylsilyl chloride assisted conjugate addition/elimination of organocopper reagents to 2-bis(methylthio)nitroethylene (Scheme 1.7.2). Reacting Grignard reagents and copper(I) iodide in the presence of trimethylsilyl chloride (TMSCl) gave the corresponding β-alkyl-β-methylthionitroethylenes in good yields. Importantly, no bis-addition was observed and the nitro alkenes all formed the *Z* isomer as the sole product.



Scheme 1.7.2 TMSCl Assisted conjugate addition/elimination

Inspired by this report, we sought to investigate its application to our desired synthetic plan. Treatment of **1** under the reaction conditions proceeded smoothly, however both *Z* and *E* isomers (**2a**) were isolated (1:2.11 *E*:*Z*) in 56% yield (Scheme 1.7.3).

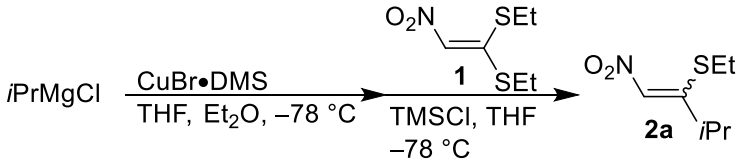


Scheme 1.7.3 Conjugate addition/elimination into 2-bis(ethylthio)nitroethylene

We noted that the reaction appeared to proceed a bit sluggishly and sought to improve upon this by screening the reactivity with the analogous organocuprate reagent (Table 1.7.1). By using copper(I) bromide dimethyl sulfide, the more soluble reagent was prepared and reacted with **1**. Surprisingly, we saw a marked improvement in yield when TMSCl was omitted in the reaction; however no *E:Z* selectivity was observed (Table 1.7.1, entry 1). Use of TMSCl in the reaction led

to a 1:1.7 *E:Z* selectivity and 96% yield (entry 2). Decreasing the reagent load of the reaction provided the desired product, albeit in lower yield and selectivity (entry 3).

Table 1.7.1 Optimization of the conjugate addition/elimination

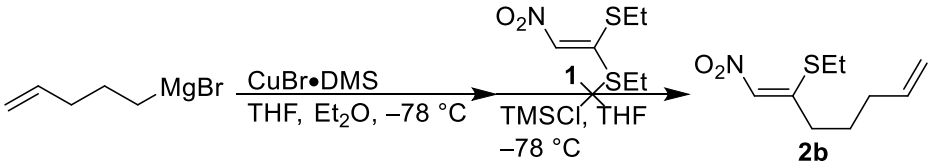


entry	CuBr·DMS (equiv.)	*i*PrMgCl (equiv.)	TMSCl (equiv.)	Yield **2a** (%) (*E:Z*)[a]
1	2	4	0	97 (1:1)
2	2	4	1	97 (1:1.7)
3	1	2	0	90 (1:1.25)

[a]Isolated yield.

Synthesis of β-Tethered Nitrothioethers

With an optimized reaction condition in hand for the conjugate addition/elimination reaction, we sought to synthesize β-tethered nitrothioethers that bore a pendant alkene for reaction in a dipolar cycloaddition reaction. Interestingly, reaction of the 4-pentenylmagnesium bromide failed to give any desired product (Scheme 1.7.4).

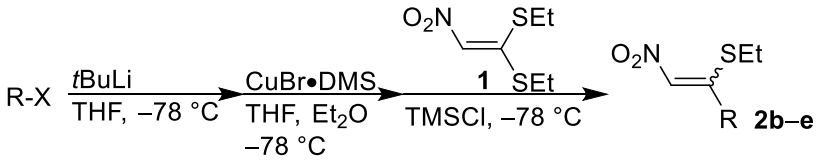


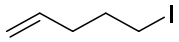
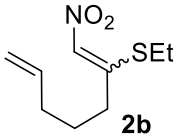
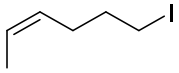
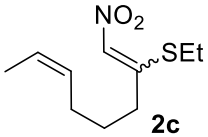
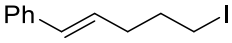
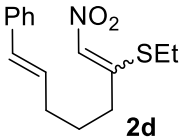
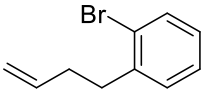
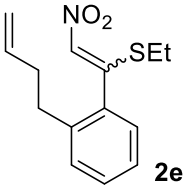
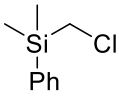
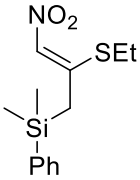
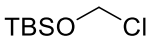
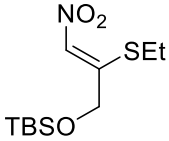
Scheme 1.7.4 Cuprate formation from Grignard reagent

However, when lithium-halogen exchange was performed on 4-pentenyl iodide, the cuprate addition gave the desired product **2b** in good yield. Unfortunately, this increased reactivity was also met with an erosion in the *E:Z* selectivity (Table 1.7.2, entry 1). The lack of selectivity was seen in all substrates (entries 1–4), with **2c** being slightly favored for the desired *Z* olefin (entry 2).

β-Tether containing a styrenyl motif produced compound **2d** in moderate yield, and phenyl linked tether **2e** was efficiently produced, albeit with a preference for the undesired isomer (entries 3–4). Interested in access to nitrodienes bearing a β-hydroxymethyl motif for the possible synthesis of various pyrrolizidine alkaloids, we attempted the synthesis of nitrothioethers bearing dimethyl phenyl methylene and TBS ether motifs.

Table 1.7.2 Synthesis of tethered nitrothioethers

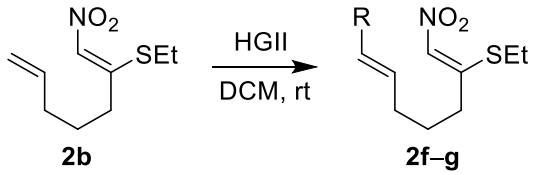


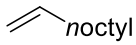
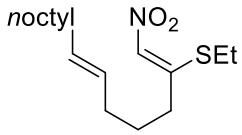
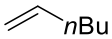
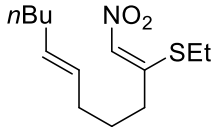
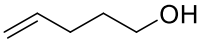
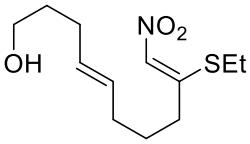
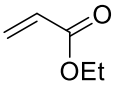
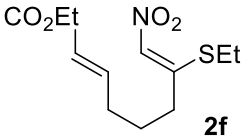
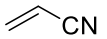
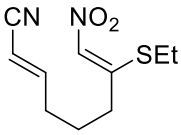
entry	halide	nitrothioether **2**	yield (%) (*E:Z*)[a]
1		 **2b**	70 (1:1)
2		 **2c**	76 (1:1.2)
3		 **2d**	50 (1:1)
4		 **2e**	84 (1.7:1)
5			0
6			0

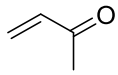
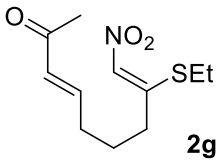
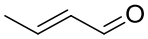
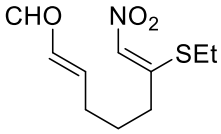
[a]Isolated yield. TBS=*tert*butyldimethyl silyl.

In order to incorporate functional groups that are incompatible with the basic organocuprate addition/elimination sequence, we planned on appending these electrophilic moieties via olefin metathesis. Exposing **2b** to Grubbs–Hoyveda 2nd generation olefin metathesis catalyst in the presence of various monosubstituted alkenes allowed for access to new nitrothioethers (Table 1.7.3).

Table 1.7.3 Appending tethers by olefin metathesis



entry	olefin	nitrothioether **2**	yield (%)[a]
1			0
2			0
3			0
4		 **2f**	85
5			0

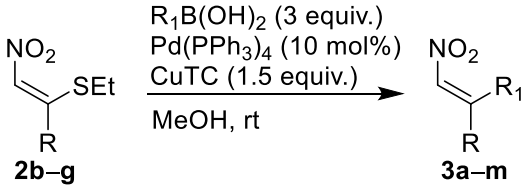
6		 **2g**	80
7			0

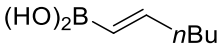
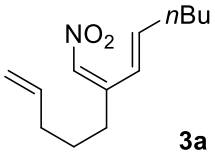
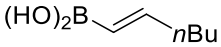
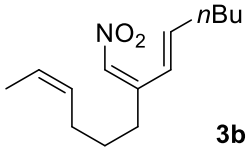
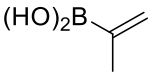
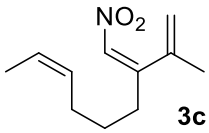
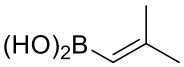
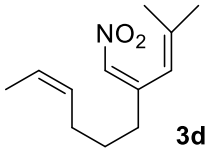
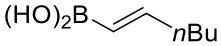
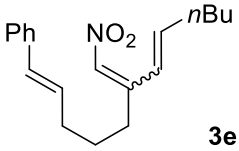
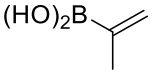
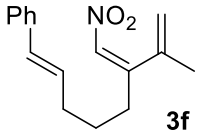
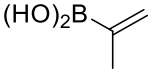
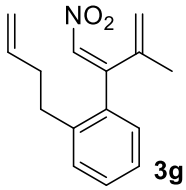
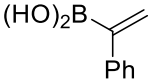
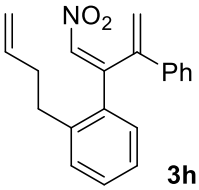
[a]Isolated yield.

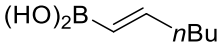
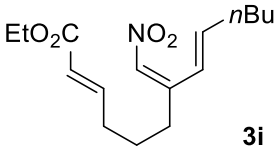
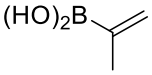
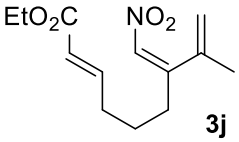
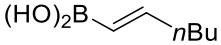
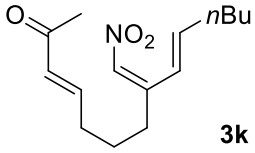
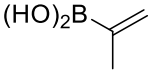
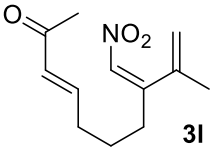
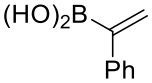
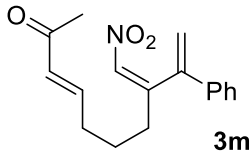
Preliminary reactions with terminal alkenes such as 1-decene and 1-hexene (Table 1.7.3, entries 1–2) failed to produce and desired product. Other alkenes, such as 4-pentenol also were resistant to the olefin metathesis reaction (entry 3). However, when employing an electron deficient alkene such as ethyl acrylate, the desired product **2f** was formed in 85% yield (entry 4). Screening other electron deficient alkenes (entries 5–7) only provided compound **2g**, the metathesis product of methyl vinyl ketone and **2b**, in 80% yield.

With nitrothioethers **2b–g** in hand, we were then able to focus on the formation of various nitrodienes through our established palladium-catalyzed desulfitative cross-coupling of boronic acids and vinyl thioethers (Table 1.7.4). Cross-coupling with hexenyl boronic acid under the standard reaction conditions with **2b** smoothly provided conjugated nitrodiene **3a** in excellent yield (Table 1.7.4, entry 1). Expanding the nitrothioether scope to contain the *Z*-substituted tether **2c**, the expected coupled products were observed in moderate yields (entries 2–4). Surprisingly, the cyclic nitronate product was not isolated in the case of **3d**, only the nitrodiene. Proceeding to nitrodienes derived from **2d** (entries 5–6), cross coupling proved to be a smooth transformation. Unexpectedly, a 1:2.3 mixture of *E*/*Z* isomers of nitrodiene **3e** was seen (entry 5), but no *cis*/*trans* mixture was observed for the other nitrodiene derived from **2d**. Nitrodiene **3f** was cleanly produced in an 85% yield (entry 6). When using the aryl-linked tether **2e** (entries 7–8), formation of γ-substituted nitrodienes **3g** and **3h** was accomplished with great efficiencies, 82% and 92% yield.

Table 1.7.4 Substrate scope for the cross-coupling reaction



entry	nitrothioether **2**	boronic acid	product **3**	yield (%)[a]
1	**2b**		 **3a**	94
2	**2c**		 **3b**	43
3	**2c**		 **3c**	63
4	**2c**		 **3d**	24
5	**2d**		 **3e**	98 1:2.3 *E*/*Z*
6	**2d**		 **3f**	85
7	**2e**		 **3g**	82
8	**2e**		 **3h**	98

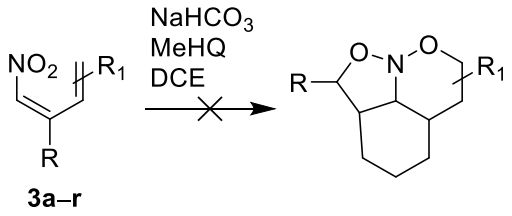
9	**2f**		 **3i**	99
10	**2f**		 **3j**	55
11	**2g**		 **3k**	70
12	**2g**		 **3l**	35
13	**2g**		 **3m**	75

[a]Isolated Yield.

We also sought to probe the reactivity of nitrodienes bearing an electron-withdrawing substituent on the alkene tether (entries 9–13). After cross metathesis with the corresponding alkene, the tethered α,β-unsaturated ester (**2f**) and α,β-unsaturated ketone (**2g**) were employed in the cross-coupling reaction. Formation of mono β,δ- and β,γ-substituted nitrodienes **3i** and **3j** was quickly accomplished. Moving to the nitrodiene bearing a tethered ketone (**2g**), we also probed the compatibility of the cross coupling reaction. γ-Methyl substituted nitrodiene **3l** was produced in moderate yield, and γ-phenyl nitrodiene **3m** was formed in good yield. With a plethora of nitrodienes and nitronates in hand, we sought to investigate the viability of the tandem 6π-electrocyclization/[3 + 2] dipolar cycloaddition reaction.

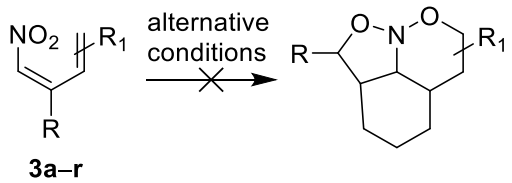
Upon exposure to the standard tandem 6π-electrocyclization/[3 + 2] dipolar cycloaddition reaction conditions, nitrodiene **3a** failed to give any desired product (Scheme 1.7.5). Further

screening of the remaining nitrodienes also showed a surprising lack of reactivity for the formation of nitroso acetals under the standard conditions. Additionally, heating the nitronate products in 1,2-dichloroethane (DCE) proved unsuccessful. Not to be discouraged by this unanticipated problem, we began screening alternative reaction conditions to aid in the dipolar cycloaddition.



Scheme 1.7.5 Tandem reaction under the standard conditions

We began to screen a multitude of varied reaction conditions to engender the nitroso acetal product (Scheme 1.7.6). First we began by altering the reaction temperatures, reaching temperatures as high as 250 °C, but disappointingly only starting material was recovered from the reaction. We then moved to screening a variety of Lewis and Brønsted acid additives in the tandem reaction. Unfortunately no desired product could be observed from these reactions either. Even reacting under photochemical conditions failed to yield any identifiable nitroso acetal product.



Scheme 1.7.6 Various conditions for the 6π-electrocyclization/[3 + 2] dipolar cycloaddition

In concert with providing a general scope for the synthesis of tethered nitrodienes, we also explored the viability of this reaction for the synthesis of pyrrolizidine alkaloids. Specifically, we targeted the pyrrolizidine alkaloids macronecine, isoretronecanol and trachlanthamidine, for their similarities to heliotridane and pseudoheliotridane (Figure 1.7.1).

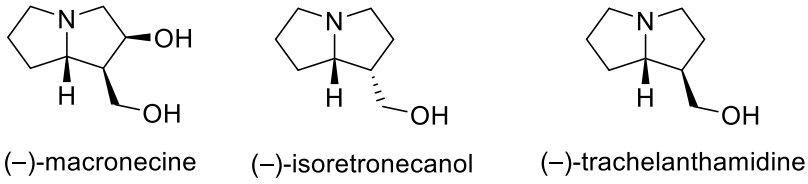
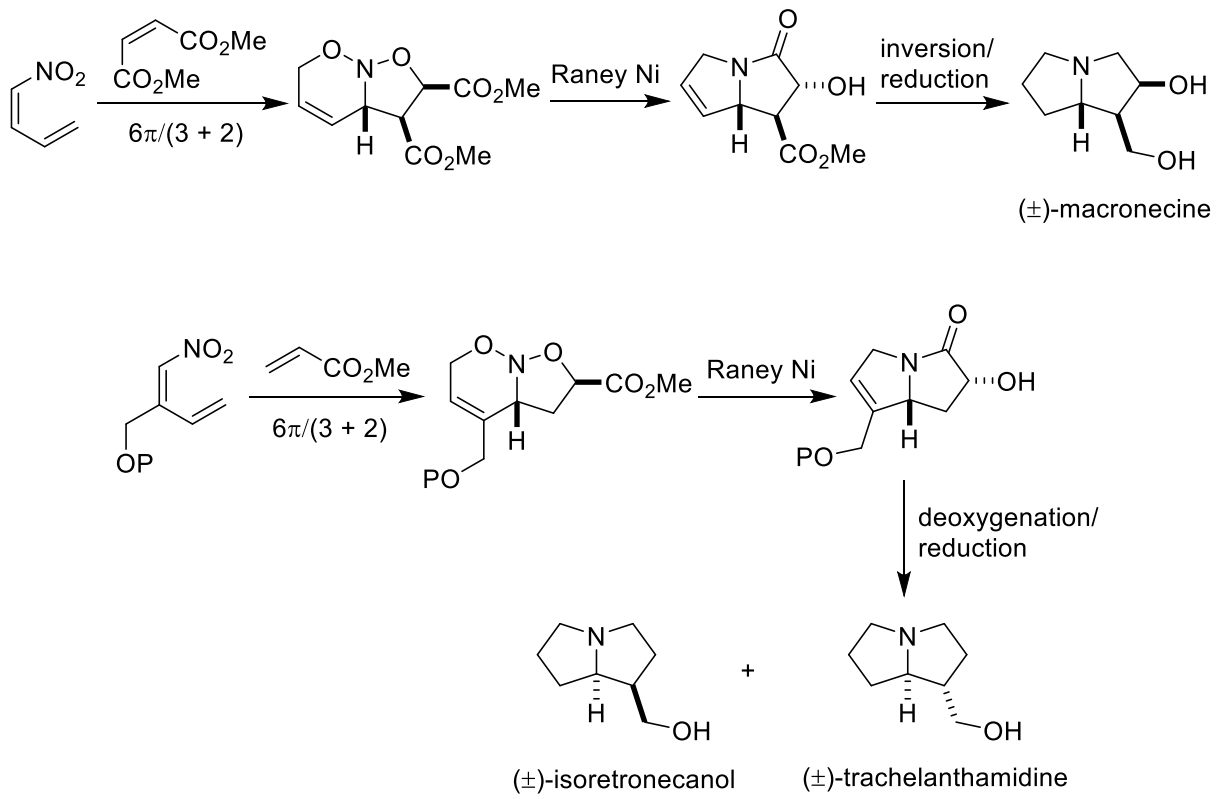


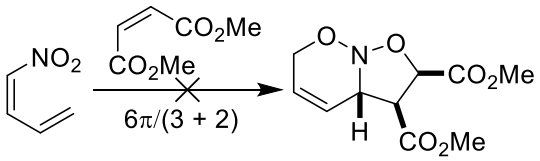
Figure 1.7.1 Macronecine, isoretronecanol and trachlanthamidine

Our proposed synthesis of macronecine was thought to proceed through tandem 6π-electrocycilzation/[3 + 2] dipolarcycloaddition of known 1-nitro-1,3-diene with dimethyl maleate (Scheme 1.7.7). After reduction of the resulting nitroso acetal, the bicyclic lactam should be formed, and finally after C6-stereoinversion and reduction, the desired natural product should be formed. As for isoretronecanol and trachlanthamidine, we envisioned these pyrrolizidine alkaloids to arise from the nitration of a protected 2-hydroxymethyl-1,3-butadiene. Formation of the nitroso acetal with ethyl (*E*)-2-benzyloxyacrylate followed by lactam formation under reducing conditions would likely give a mixture of C1-diastereomers, as in our synthesis of heliotridane and pseudoheliotridane. After ring closure and deprotection, the products isoretronecanol and trachlanthamidine should be formed.



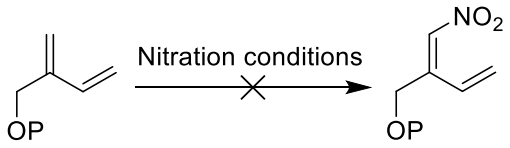
Scheme 1.7.7 Proposed synthesis of necine bases

Beginning from 1-nitro-1,3-butadiene,[3a] we tested the viability of the tandem 6π-electrocycilzation/[3 + 2] dipolarcycloaddition reaction (Scheme 1.7.8). Disappointingly, reaction with dimethyl maleate under the standard conditions did not yield any desired product. We then began an exhaustive investigation into the usage of a plethora of additives and reaction conditions. All manner of Lewis acid activators, isomerization facilitating nucleophiles, and alternate reaction temperatures failed to provide the desired product.



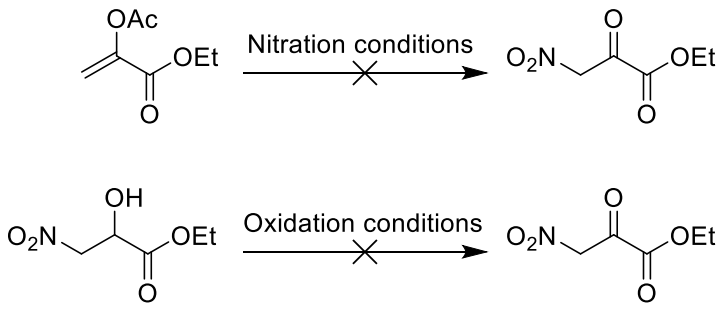
Scheme 1.7.8 6π-electrocycilzation/[3 + 2] dipolarcycloaddition reaction on 1-nitro-1,3-butadiene

Moving on to the synthesis of isoretronecanol and trachlanthamidine, we began by synthesizing known protected 2-hydroxymethyl-1,3-butadienes.[38] With dienes in hand, we screened a variety of nitration conditions for the synthesis of conjugated nitrodienes (Scheme 1.7.9). Interestingly, when the benzyl and benzoyl protected dienes were treated under Mellor's nitration conditions, no olefin nitration was seen, only nitration on the aromatic ring could be detected in small amounts. In general, the electrophilic nitration conditions proved to be too harsh for the starting material, oftentimes leading to extensive degradation of the starting material even at low temperatures.



Scheme 1.7.9 Failed nitration of 2-hydroxymethyl-1,3-butadienes

With the inability to install the nitro group after formation of the diene, we decided to attempt to access the desired nitrodiene through our palladium-catalyzed desulfitative cross-coupling of boronic acids and vinyl thioethers. We surmised that we could gain access to the necessary nitro thioether via nitration and subsequent dithioacetal formation of ethyl pyruvate (Scheme 1.7.10). Formation of the enol acetate from ethyl pyruvate yielded the necessary starting material for the nitration reaction.[39] Unfortunately, exposure to nitration conditions did not provide any desired product, only recovered ethyl pyruvate. We then focused on obtaining the necessary α-nitro ketone by oxidation of an analogous nitro alcohol.[40] None of the typical oxidizing conditions for alcohols gave the desired ketone product. We found that the alcohol was resistant to the oxidizing conditions, and even when employing harshly acidic transition-metal oxidants only the starting material could be recovered.



Scheme 1.7.10 Alternative routes to isoretronecanol and trachlanthamidine

Conclusion

We have successfully synthesized a variety of β-tethered conjugated nitrodienes via a cuprate addition/elimination reaction followed by a palladium-catalyzed cross-coupling reaction of vinyl boronic acids. Both alkyl and aryl tethers could be installed during the addition/elimination sequence, as well as both alkyl and aryl substituted vinyl boronic acids for the cross-coupling reaction. Electron deficient groups such as ketone and ester could be appended through olefin metathesis reaction. Although in some specific cases the necessary nitronate intermediate could be isolated, the ultimately desired nitroso acetal products could not be detected after exhaustive reaction screening. Additionally, when expanding the methodology towards the synthesis of pyrrolizidine natural products, we were unable to make sufficient progress towards their syntheses.

Experimental

General Information

All reactions were performed under Ar atmosphere with dry solvents in flame-dried round-bottom flasks containing stir bars. Toluene, methylene chloride, triethylamine, and 1,2-dichloroethane were distilled afresh from CaH_2 , methanol was distilled afresh from Mg(0); tetrahydrofuran, and diethyl ether were distilled from Na with benzophenone indicator. All reagents except for the alkyl halides and nitro dithioketeneacetals were purchased from commercial sources and used without further purification.

TLC: Thin layer chromatography (TLC) was performed on 0.25-mm Silicycle Glass-Backed Extra-Hard-Layer, 60-Å silica gel plates (TLG-R10011B-323) and visualized under UV light, permanganate staining, or anisaldehyde staining.

Chromatography: Flash column chromatography was performed using Silicycle SiliaFlash® P60 (230–400 mesh, R12030B) and compressed air.

M.P.: Melting points (m.p.) were recorded using an Electrothermal capillary melting point apparatus; they are uncorrected.

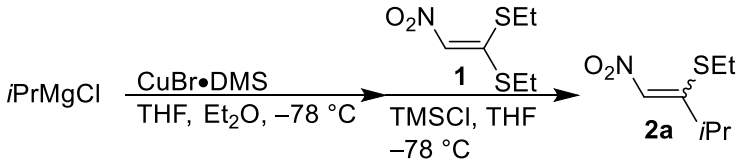
IR Spectroscopy: IR spectra were recorded using Thermo Nicolet Avatar 370 FT-IR spectrometer or a JASCO FT/IR-4100 spectrometer with an ATR-PRO 450-S accessory.

NMR Spectroscopy: NMR spectra were recorded using Bruker ARX-400, Avance-300, and Avance-500 instruments calibrated to $CH(D)Cl_3$ as an internal reference (7.26 and 77.0 ppm for ^1H and ^{13}C NMR spectra, respectively). Data for ^1H NMR spectra are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ, ppm). The following abbreviations are used to denote the multiplicities: s = singlet; d = doublet; dd = doublet of doublets; dt = doublet of triplets; ddd =

doublet of doublet of doublets; t = triplet; td = triplet of doublets; tt = triplet of triplets; q = quartet; qd = quartet of doublets; m = multiplet; p = pentet; sep = septet.

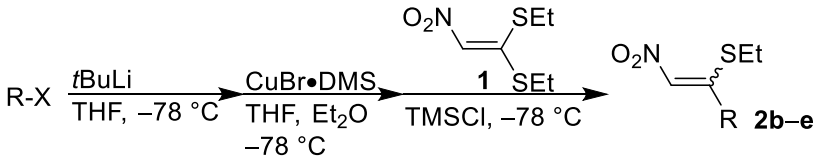
Mass Spectrometry: Mass spectra were recorded using a Waters LCT Premier XE Time-of-Flight Instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the Multi Mode Ionization source. The lock mass standard for accurate mass determination was Leucine Enkephalin (Sigma L9133).

Conjugate Addition/Elimination Into 2-Bis(ethylthio)nitroethylene



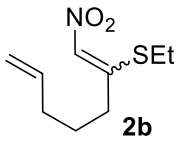
2-Ethylthio-3-methyl-1-nitrobutene 2a. Following the modified procedure developed by Ila,[37] *i*PrMgCl (20 mL, 2.0 M solution in THF, 40 mmol, 4 equiv.) was added dropwise to a solution of CuBr·DMS (4.112 g, 20 mmol, 2 equiv.) in THF (120 mL) and Et_2O (30 mL) at –78 °C and stirred 1 hr. A solution of nitro thioether **1** (1.93 g, 10 mmol, 1 equiv.) and TMSCl (1.27 mL, 10 mmol, 1 equiv.) in THF (30 mL) was added dropwise at –78 °C and stirred at the same temperature for 1 hr. The reaction was allowed to slowly warm to 0 °C and was quencehed with saturated aqueous NH_4Cl (100 mL) and allowed to stir vigorously for 1 hr. The aqueous layer was washed with Et_2O (3 x 75 mL) and the combined organic layers were washed with H_2O (150 mL) and brine (150 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (0–25% EtOAc/hexanes) to give **2a** as a pale yellow oil (1.695 g, 97% yield, 1:1.7 *E*/*Z*). **(*E*) 2a** IR (ν, cm^{-1}) 2975, 2873, 1568, 1497, 1463, 1334, 1314, 1000, 728; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.73 (s, 1H), 4.21 (sep, *J* = 6.8 Hz, 1H), 4.18 (q, *J* = 6.8 Hz, 2H), 1.37 (t, *J* = 7.4 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 169.1,

127.4, 30.8, 25.8, 21.5, 12.2; HRMS (ESI) HRMS (ESI) cacld for $C_7H_{13}NNaO_2S$ $[M + Na]^+$ *m/z* 198.0565, found 198.0024; **(*Z*) 2a** IR (ν, cm^{-1}) 2973, 2933, 1557, 1464, 1314, 1252, 795; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.21 (s, 1H), 2.98 (sept, *J* = 6.8 Hz, 1H), 2.91 (q, *J* = 7.5 Hz, 2H), 1.36, (t, *J* = 7.5 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 167.5, 130.2, 31.8, 24.8, 23.0, 13.5; HRMS (ESI) cacld for $C_7H_{13}NNaO_2S$ $[M + Na]^+$ *m/z* 198.0565, found 198.0073.

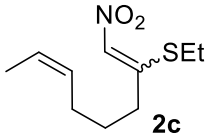


Synthesis of Tethered Nitro thioethers 2b–e

t-BuLi (14.1 mL, 24 mmol, 4.8 equiv) was added dropwise to a solution of tethered halide in THF (20 mL) at –78 °C and slowly warmed to 0 °C over 1 hr. The mixture was cannulated into a solution of CuBr·DMS (2.467 g, 12 mmol, 2.4 equiv.) in THF (20 mL) and Et_2O (20 mL) at –78 °C and stirred 1 hr. A solution of nitrothioether **1** (0.966 g, 5 mmol, 1 equiv.) and TMSCl (0.63 mL, 5 mmol, 1 equiv.) in THF (20 mL) was added dropwise at –78 °C and stirred at the same temperature for 1 hr. The reaction was allowed to slowly warm to 0 °C and was quencehed with saturated aqueous NH_4Cl (75 mL) and allowed to stir vigorously for 1 hr. The aqueous layer was washed with Et_2O (3 x 50 mL) and the combined organic layers were washed with H_2O (100 mL) and brine (100 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (0–25% EtOAc/hexanes) to give **2b–e**.



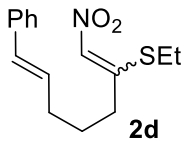
Ethyl(1-nitrohepta-1,6-dien-2-yl)sulfane 2b. Pale yellow oil (0.704 g, 70% yield, 1:1 *E*:*Z*). **(*E*) 2b** IR (ν, cm^{-1}) 2932, 1557, 1498, 1317, 1256, 914, 720; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.78 (s, 1H), 5.80 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, 1H), 5.07 (ddd, *J* = 17.1 Hz, *J* = 3.3 Hz, *J* = 1.6 Hz, 1H), 5.01–4.99 (m, 1H), 2.83–2.79 (m, 4H), 2.17 (q, *J* = 7.1 Hz, 2H), 1.76–1.71 (m, 2H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.3, 137.6, 128.0, 115.5, 33.7, 33.5, 28.5, 26.3, 12.3; HRMS (ESI) cacld for $C_9H_{15}NNaO_2S$ $[M + Na]^+$ *m/z* 224.0721, found 224.0128; **(*Z*) 2b** IR (ν, cm^{-1}) 2932, 1640, 1556, 1473, 1317, 1253, 992, 702; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.20 (s, 1H), 5.77 (ddt, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 6.8 Hz, 1H), 5.07 (ddd, *J* = 12.5 Hz, *J* = 3.3 Hz, *J* = 1.5 Hz, 1H), 5.05–5.04 (m, 1H), 2.90 (q, *J* = 7.5 Hz, 2H), 2.51–2.48 (m, 2H), 2.16 (q, *J* = 7.1 Hz, 2H), 1.70 (p, *J* = 7.5 Hz, 2H), 1.35 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.4, 136.8, 130.9, 116.3, 33.1, 32.8, 28.9, 24.8, 13.5; HRMS (ESI) cacld for $C_9H_{15}NNaO_2S$ $[M + Na]^+$ *m/z* 224.0721, found 224.0005.



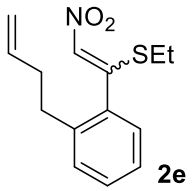
2c

Ethyl((6*Z*)-1-nitroocta-1,6-dien-2-yl)sulfane 2c. Pale yellow oil, (0.815 g, 76% yield 1:1.2 *E*:*Z*). **(*E*) 2c** IR (ν, cm^{-1}) 3013, 2935, 2862, 1632, 1517, 1456, 1338, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.78 (s, 1H) 5.53–5.47 (m, 1H), 5.42–5.36 (m, 1H), 2.83–2.79 (m, 4H), 2.15 (q, *J* = 7.3 Hz, 2H), 1.73–1.67 (m, 2H), 1.62–1.60 (m, 3H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.4, 129.2, 128.0, 125.1, 33.9, 29.2, 26.7, 26.2, 12.9, 12.3; HRMS (ESI) cacld for $C_{10}H_{17}NNaO_2S$ $[M + Na]^+$ *m/z* 238.0878, found 238.1636; **(*Z*) 2c** IR (ν, cm^{-1}) 3015, 2933, 1557, 1474, 1320, 1253, 750, 666; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.20 (s, 1H), 5.58–5.51 (m, 1H), 5.39–5.32 (m, 1H), 2.90 (q, *J* = 7.5 Hz, 2H), 2.50–2.48 (m, 2H), 2.15 (q, *J* = 7.0 Hz, 2H), 1.70–1.64 (m, 2H), 1.63–1.60 (m, 3H), 1.35 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

(ppm) 161.5, 130.9, 128.5, 125.9, 33.3, 29.6, 24.8, 13.5, 12.9; HRMS (ESI) cacld for $C_{10}H_{17}NNaO_2S$ $[M + Na]^+$ *m/z* 238.0878, found 238.1216

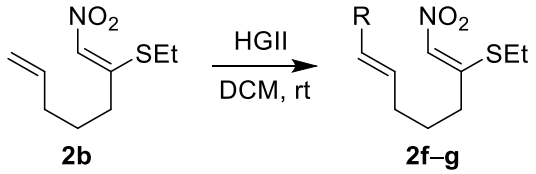


Ethyl((6*E*)-1-nitro-7-phenylhepta-1,6-dien-2-yl)sulfane 2d. Pale yellow oil, (0.698 g, 50% yield 1:1 *E*:*Z*). **(*E*) 2d** IR (ν, cm^{-1}) 2932, 1557, 1473, 1321, 1253, 693; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35–7.18 (m, 5H), 6.79 (s, 1H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8 Hz, *J* = 6.9 Hz, 1H), 2.88–2.84 (m, 2H), 2.82 (q, *J* = 7.4 Hz, 2H), 2.33 (q, *J* = 7.2 Hz, 2H), 1.86–1.80 (m, 2H), 1.36 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.3, 137.6, 130.9, 129.4, 128.5, 128.1, 127.0, 126.0, 33.8, 32.7, 29.0, 26.3, 12.3; HRMS (ESI) cacld for $C_{15}H_{19}NNaO_2S$ $[M + Na]^+$ *m/z* 300.1034, found 300.2577; **(*Z*) 2d** IR (ν, cm^{-1}) 2927, 1556, 1473, 1320, 966, 741; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35–7.30 (m, 4H), 7.24–7.21 (m, 1H), 7.23 (s, 1H), 6.44 (d, *J* = 15.8, 1H), 6.17 (dt, *J* = 15.8 Hz, *J* = 7.0 Hz, 1H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.57–2.53 (m, 2H), 2.33 (qd, *J* = 7.1 Hz, *J* = 1.3 Hz, 2H), 1.80 (p, *J* = 7.5 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 161.2, 137.1, 131.7, 131.0, 128.6, 128.4, 127.4, 126.0, 33.2, 32.1, 29.4, 24.9, 13.5; HRMS (ESI) cacld for $C_{15}H_{19}NNaO_2S$ $[M + Na]^+$ *m/z* 300.1034, found 300.2608.

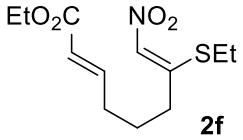


(1-(2-(But-3-en-1-yl)phenyl)-2-nitrovinyl)(ethyl)sulfane 2e. Pale yellow oil, (1.109 g, 84% yield 1.7:1 *E*:*Z*). **(*E*) 2e** IR (ν, cm^{-1}) 3073, 2930, 1556, 1489, 1474, 1319, 1255, 995, 912, 730; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.39–7.22 (m, 3H), 7.16 (s, 1H), 7.10–7.09 (m, 2H), 5.79 (ddt, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 6.7 Hz, 1H), 5.04–4.98 (m, 2H), 2.74–2.66 (m, 2H), 2.37–2.32 (m,

2H), 2.35 (q, J = 7.6 Hz, 2H), 1.11 (t, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.2, 138.8, 137.2, 132.9, 131.8, 129.8, 129.6, 128.3, 126.4, 115.8, 34.7, 32.0, 26.7, 13.2; HRMS (ESI) cacld for $C_{14}H_{17}NNaO_2S$ $[M + Na]^+$ *m/z* 286.0878, found 286.1960; **(*Z*) 2e** IR (ν, cm^{-1}) 2931, 1580, 1504, 1453, 1323, 993, 757; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.36–7.33 (m, 1H), 7.29–7.28 (m, 1H), 7.25–7.22 (m, 1H), 7.09–7.08 (m, 1H), 7.04 (s, 1H), 5.84 (ddt, J = 17.0 Hz, J = 10.4 Hz, J = 6.6 Hz, 1H), 5.03 (ddt, J = 17.1, J = 1.6 Hz, J = 1.6 Hz, 1H), 4.99–4.96 (m, 1H), 2.89–2.85 (m, 2H), 2.73–2.62 (m, 2H), 2.41–2.30 (m, 2H), 1.39 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 157.6, 138.7, 137.9, 133.4, 129.4, 129.1, 128.9, 127.5, 126.1, 115.1, 34.3, 32.0, 27.1, 12.5; HRMS (ESI) cacld for $C_{14}H_{17}NNaO_2S$ $[M + Na]^+$ *m/z* 286.0878, found 286.1931.

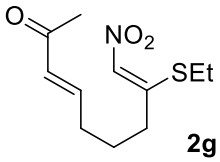


Olefin Metathesis of Nitro Thioethers. A mixture of **2b** (100 mg, 0.5 mmol, 1 equiv.), Hoveyda–Grubbs 2nd Generation Catalyst (6.2 mg, 0.01 mmol, 0.02 equiv.), and olefin (0.5 mL) in DCM (0.5 mL) was stirred at rt for 24 hr. The mixture was concentrated and purified by silica gel flash column chromatography (0–25% EtOAc/hexanes) to give **2f** and **2g**.

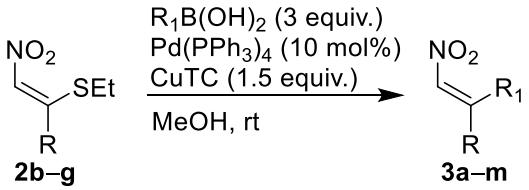


Ethyl (2*E*,7*Z*)-7-(ethylthio)-8-nitroocta-2,7-dienoate 2f. Pale yellow oil, (0.116 g 85% yield). IR (ν, cm^{-1}) 2933, 1721, 1552, 1451, 1368, 1322, 1186, 1044, 525; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.19 (s, 1H), 6.91 (dt, J = 15.6 Hz, J = 7.0 Hz, 1H), 5.87 (dt, J = 15.6 Hz, J = 1.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.89 (q, J = 7.5 Hz, 2H), 2.53–2.50 (m, 2H), 2.30 (qd, J = 7.2 Hz, J = 1.5 Hz, 2H), 1.81–1.75 (m, 2H), 1.35 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ (ppm) 166.2, 160.3, 146.5, 131.0, 122.9, 60.4, 33.1, 31.1, 28.0, 24.9, 14.3, 13.5; HRMS (ESI) cacld for $C_{12}H_{19}NNaO_4S$ $[M + Na]^+$ *m/z* 296.0932, found 296.1266.



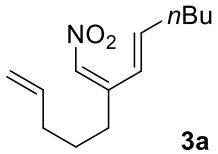
(3*E*,8*Z*)-8-(Ethylthio)-9-nitronona-3,8-dien-2-one 2g. Pale yellow oil, (0.097 g, 80% yield). IR (ν, cm^{-1}) 2932, 1672, 1626, 1557, 1473, 1361, 1321, 1255, 977, 795, 702; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.19 (s, 1H), 6.75 (dt, *J* = 15.9, *J* = 6.9 Hz, 1H), 6.13 (dt, *J* = 15.9 Hz, *J* = 1.5 Hz, 1H), 2.89 (q, *J* = 7.5 Hz, 2H), 2.54–2.51 (m, 2H), 2.31 (qd, *J* = 2.4 Hz, *J* = 1.2 Hz, 2H), 2.25 (s, 3H), 1.83–1.77 (m, 2H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 198.1, 160.1, 145.3, 132.2, 131.1, 33.2, 31.4, 28.0, 27.3, 24.9, 13.5; HRMS (ESI) cacld for $C_{11}H_{17}NNaO_3S$ $[M + Na]^+$ *m/z* 266.0827, found 266.0837.



Vinyl Nitro Thioether Cross-Coupling 3a–m

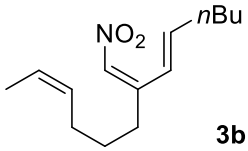
Following the procedure developed by Creech and Kwon,[13b] A dry, Ar-replenished reaction vessel was charged with copper(I) thiophene carboxylate (29 mg, 0.15 mmol, 1.5 equiv.), boronic acid (3 mmol, 3.0 equiv.), and palladiumtetrakis(triphenylphosphine) (12 mg, 0.01 mmol, 0.10 equiv.). The solid mixture was vacuum-replenished with argon prior to the addition of a solution of nitro thioether (0.01 mmol, 1.0 equiv) in distilled MeOH (3.75 mL). The solution was stirred under a positive pressure of argon at rt; it turned from red/yellow to dark brown within ca. 2 min. The reaction's progress was monitored by TLC (15% EtOAc/hexanes), with complete consumption of the starting thioether typically within 2 h. The reaction was quenched by the addition of EtOAc

(15 mL) and saturated ammonium chloride (10 mL). The layers were separated and the organic phase washed successively with water (10 mL) and brine (2 x 15 mL). The combined aqueous layers were then back-extracted with EtOAc (10 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (0–10% EtOAc/hexanes) to give **3a–m**.



3a

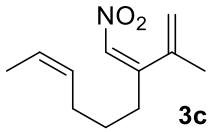
(6*Z*,7*E*)-6-(Nitromethylene)dodeca-1,7-diene 3a. Pale yellow oil, (21 mg, 94% yield). IR (ν, cm^{-1}) 2931, 1596, 1510, 1333, 972, 643; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.00 (s, 1H), 6.39 (dt, *J* = 14.8 Hz, *J* = 7.4 Hz, 1H), 5.95 (d, *J* = 15.6 Hz, 1H), 5.83 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* =6.7 Hz, 1H), 5.05 (ddt, *J* = 17.1 Hz, *J* = 1.6 Hz, *J* = 1.6 Hz, 1H), 5.02–5.00 (m, 1H), 2.80–2.77 (m, 2H), 2.23 (q, *J* = 6.8 Hz, 2H), 2.18 (q, *J* = 7.1 Hz, 2H), 1.62 (p, *J* = 7.7 Hz, 2H), 1.44 (p, *J* = 7.4 Hz, 2H), 1.38–1.30 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 151.5, 142.7, 137.9, 136.1, 127.8, 115.4, 33.9, 33.2, 30.8, 28.3, 26.8, 22.3, 13.9; HRMS (ESI) cacld for $C_{26}H_{42}N_2NaO_4$ $[2M + Na]^+$ *m/z* 469.3042, found 469.3070.



3b

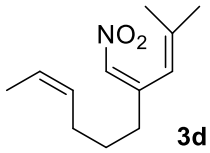
(2*Z*,7*Z*,8*E*)-7-(Nitromethylene)trideca-2,8-diene 3b. Pale yellow oil, (10 mg, 43%). IR (ν, cm^{-1}) 2931, 2856, 1593, 1510, 1461, 1334, 1032, 972, 637; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.00 (s, 1H), 6.40 (dt, *J* = 14.9 Hz, *J* = 7.4 Hz, 2H), 5.95 (d, *J* = 15.6 Hz, 1H), 5.55–5.48 (m, 1H), 5.44–5.38 (m, 1H), 2.80–2.77 (m, 2H), 2.23 (q, *J* = 6.9 Hz, 2H), 2.17 (q, *J* = 7.3 Hz, 2H), 1.63–1.57 (m, 5H), 1.45–1.41 (m, 2H), 1.37–1.30 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ (ppm) 151.6, 142.6, 136.1, 129.5, 127.8, 125.0, 33.2, 30.9, 29.0, 27.1, 27.0, 22.3, 13.9, 12.9; HRMS (ESI) cacld for $C_{13}H_{21}NNaO_2$ $[M + Na]^+$ *m/z* 246.1470, found 260.1656.



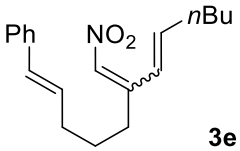
3c

(3*Z*,7*Z*)-2-Methyl-3-(nitromethylene)nona-1,7-diene 3c. Pale yellow oil, (12 mg, 63% yield). IR (ν, cm^{-1}) 3018, 2933, 1595, 1551, 1520, 1463, 1338, 915, 690; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.09 (s, 1H), 5.54–5.38 (m, 2H), 5.52 (s, 1H), 5.37 (s, 1H), 2.80–2.75 (m, 2H), 2.19–2.12 (m, 2H), 1.94 (s, 3H), 1.63–1.58 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 152.9, 140.1, 135.6, 129.4, 125.0, 121.1, 28.9, 27.7, 27.0,. 20.8, 12.8; HRMS (ESI) cacld for $C_{11}H_{18}NO_2$ $[M + H]^+$ *m/z* 196.1338, found 196.1312.



3d

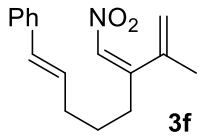
(4*Z*,8*Z*)-2-Methyl-4-(nitromethylene)deca-2,8-diene 3d. Pale yelow oil (5 mg, 24% yield). IR (ν, cm^{-1}) 2933, 1605, 1556, 1512, 1444, 1335, 857, 698; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.88 (s, 1H), 5.64 (d, *J* = 1.3 Hz, 1H), 5.52–5.45 (m, 1H), 5.41–5.35 (m, 1H), 2.67–2.64 (m, 2H), 2.11 (q, *J* = 7.4 Hz, 2H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.61–1.53 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 152.1, 142.4, 136.1, 129.6, 124.8, 123.2, 32.1, 27.7, 27.1, 26.9, 20.2, 12.8; HRMS (ESI) cacld for $C_{12}H_{20}NO_2$ $[M + H]^+$ *m/z* 210.1494, found 210.1481.



3e

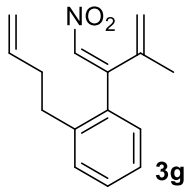
((1*E*)-6-(Nitromethylene)dodeca-1,7-dien-1-yl)benzene 3e. Yellow oil, (29 mg, 98% yield, 1:2.3 *E*/*Z*). **(*E*) 3e** IR (ν, cm^{-1}) 2952, 2868, 1553, 1334, 701; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm)

7.37–7.17 (m, 5H), 7.01 (s, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.41 (dt, *J* = 15.6 Hz, *J* = 7.1 Hz, 1H), 6.24 (dt, *J* = 15.8 Hz, *J* = 6.8 Hz, 1H), 5.97 (d, *J* = 15.6 Hz, 1H), 2.87–2.82 (m, 2H), 2.35 (q, *J* = 7.1 Hz, 2H), 2.23 (q, *J* = 6.8 Hz, 2H), 1.77–1.67 (m, 2H), 1.48–1.26 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 151.5, 142.7, 137.6, 136.1, 130.8, 129.7, 128.5, 127.7, 127.0, 126.0, 33.2, 33.2, 30.8, 28.8, 26.9, 22.3, 13.9; HRMS (ESI) cacld for $C_{19}H_{26}NO_2$ $[M + H]^+$ *m/z* 300.1964, found 300.1918; **(*Z*) 3e** IR (ν, cm^{-1}) 2958, 2930, 2860, 1554, 1333, 1047, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42–7.18 (m, 6H), 6.88 (s, 1H), 6.45–6.35 (m, 2H), 6.17 (dt, *J* = 15.7 Hz, *J* = 6.9 Hz, 1H), 2.43–2.38 (m, 2H), 2.31–2.24 (m, 2H), 1.78–1.66 (m, 2H), 1.48–1.31 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 148.3, 144.5, 137.4, 133.2, 131.2, 129.2, 128.6, 127.2, 126.0, 123.7, 33.4, 32.5, 31.4, 30.8, 29.0, 22.3, 13.9; HRMS (ESI) cacld for $C_{19}H_{26}NO_2$ $[M + H]^+$ *m/z* 300.1964, found 300.1938.



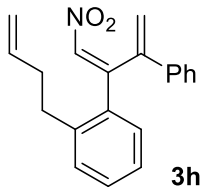
3f

((1*E*,6*Z*)-7-Methyl-6-(nitromethylene)octa-1,7-dien-1-yl)benzene 3f. Yellow oil, (22 mg, 85% yield). IR (ν, cm^{-1}) 2947, 2923, 1593, 1514, 1335, 968; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37–7.18 (m, 5H), 7.11 (s, 1H), 6.43 (d, *J* = 16.3 Hz, 1H), 6.22 (dt, *J* = 15.7, *J* = 6.8 Hz, 1H), 5.52 (s, 1H), 5.38 (s, 1H), 2.56–2.80 (m, 2H), 2.33 (q, *J* = 6.8 HZ, 2H), 1.95 (d, *J* = 0.6 HZ, 3H), 1.76–1.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 152.8, 140.1, 137.6, 135.7, 130.8, 129.6, 128.5, 127.0, 126.0, 121.2, 33.1, 28.7, 27.7, 20.8; HRMS (ESI) cacld for $C_{16}H_{20}NO_2$ $[M + H]^+$ *m/z* 258.1494, found 258.1357.



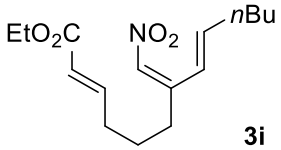
3g

(*E*)-1-(But-3-en-1-yl)-2-(3-methyl-1-nitrobuta-1,3-dien-2-yl)benzene 3g. Yellow oil, (20 mg, 82% yield). IR (ν, cm^{-1}) 2929, 1596, 1553, 1519, 1450, 1337, 915, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34–7.19 (m, 4H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.79 (ddt, *J* = 16.8 Hz, *J* = 10.1 Hz, *J* = 6.5 Hz, 1H), 5.49 (s, 1H), 5.01–4.93 (m, 3H), 2.52–2.45 (m, 2H), 2.29–2.25 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 149.6, 140.5, 138.9, 138.0, 135.8, 133.8, 128.8, 128.4, 127.9, 127.7, 125.8, 115.0, 34.1, 32.4, 20.1; HRMS (ESI) cacld for $C_{30}H_{35}N_2O_4$ $[2M + H]^+$ *m/z* 487.2597, found 487.2616.



3h

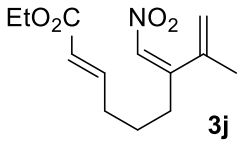
(*E*)-1-(But-3-en-1-yl)-2-(1-nitro-3-phenylbuta-1,3-dien-2-yl)benzene 3h. Yellow oil, (30 mg, 98% yield). IR (ν, cm^{-1}) 2931, 1596, 1520, 1337, 912, 757, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.45–7.33 (m, 7H), 7.27–7.26 (m, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 5.85 (ddt, *J* = 17.1 Hz, *J* = 10.1 Hz, *J* = 6.6 Hz, 1H), 5.59 (s, 1H), 5.21 (s, 1H), 5.04 (dd, *J* = 17.1 Hz, *J* = 1.6 Hz, 1H), 4.99 (dd, *J* = 10.3 Hz, *J* = 1.3 Hz, 1H), 2.74–2.61 (m, 2H), 2.39–2.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 154.7, 147.4, 139.2, 139.1, 138.8, 137.9, 133.6, 129.2, 128.8, 128.8, 128.7, 128.6, 128.2, 127.9, 126.1, 115.1, 34.3, 32.6; HRMS (ESI) cacld for $C_{20}H_{20}NO_2$ $[M + H]^+$ *m/z* 306.1494, found 306.1458.



3i

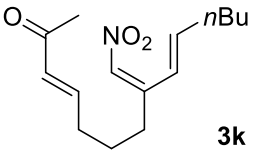
Ethyl (2*E*,7*Z*,8*E*)-7-(nitromethylene)trideca-2,8-dienoate 3i. Yellow oil, (16 mg, 55% yield). IR (ν, cm^{-1}) 2927, 1719, 1654, 1510, 1461, 1334, 1182, 973; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.01 (s, 1H), 6.96 (dt, *J* = 15.6 Hz, *J* = 6.9 Hz, 1H), 6.37 (dt, *J* = 15.5 Hz, *J* = 7.1 Hz, 1H), 5.96 (d,

J = 15.6 Hz, 1H), 5.86 (dt, *J* = 15.7 Hz, *J* = 1.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.82–2.79 (m, 2H), 2.32 (q, *J* = 6.8 Hz, 2H), 2.23 (q, *J* = 6.9 Hz, 2H), 1.73–1.67 (m, 2H), 1.47–1.41 (m, 2H), 1.37–1.30 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 166.5, 150.7, 147.8, 142.8, 136.3, 127.6, 122.2, 60.3, 33.2, 32.2, 30.1, 27.5, 26.9, 22.3, 14.3, 13.9; HRMS (ESI) cacld for $C_{16}H_{25}NNaO_4$ $[M + Na]^+$ *m/z* 318.1681, found 318.1623.



3j

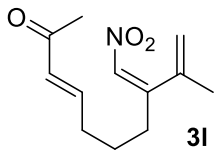
Ethyl (2*E*,7*Z*)-8-methyl-7-(nitromethylene)nona-2,8-dienoate 3j. Yellow oil, (14 mg, 55% yield). IR (ν, cm^{-1}) 2936, 1710, 1654, 1445, 1367, 1266, 1177, 1042, 891; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.10 (s, 1H), 6.95 (dt, *J* = 15.6 Hz, *J* = 6.9 Hz, 1H), 5.85 (dt, *J* = 15.6 Hz, *J* = 1.5 Hz, 1H), 5.49 (s, 1H), 5.38 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.81–2.77 (m, 2H), 2.31 (qd, *J* = 6.8 Hz, *J* = 1.5 Hz, 2H), 1.94 (d, *J* = 0.7 Hz, 3H), 1.72–1.66 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 166.7, 149.0, 147.2, 142.5, 121.5, 112.7, 112.5, 60.2, 33.1, 31.9, 27.0, 21.2, 14.3; HRMS (ESI) cacld for $C_{13}H_{19}NNaO_4$ $[M + Na]^+$ *m/z* 276.1212, found 276.1198.



3k

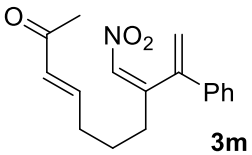
(3*E*,8*Z*,9*E*)-8-(Nitromethylene)tetradeca-3,9-dien-2-one 3k. Yellow oil, (18 mg, 70% yield). IR (ν, cm^{-1}) 2930, 2871, 1673, 1631, 1554, 1511, 1461, 1333, 1254, 976, 858; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.01 (s, 1H), 6.81 (dt, *J* = 15.9 Hz, *J* = 6.9 Hz, 1H), 6.38 (dt, *J* = 15.4 Hz, *J* = 7.1 Hz, 1H), 6.10 (dt, *J* = 16.0 Hz, *J* = 1.4 Hz, 1H), 5.97 (d, *J* = 15.6 Hz, 1H), 2.82–2.79 (m, 2H), 2.35 (qd, *J* = 7.2 Hz, *J* = 1.2 Hz, 2H), 2.26 (s, 3H), 2.23 (qd, *J* = 7.6 Hz, *J* = 1.0 Hz, 2H), 1.74–1.68 (m, 2H), 1.47–1.41 (m, 2H), 1.37–1.30 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ (ppm) 198.6, 150.7, 147.0, 142.8, 136.3, 132.0, 127.6, 33.2, 32.4, 30.8, 27.5, 26.9, 26.8, 22.3, 13.9; HRMS (ESI) cacld for $C_{15}H_{23}NNaO_3$ $[M + Na]^+$ *m/z* 288.1576, found 288.1589.



3l

(3*E*,8*Z*)-9-Methyl-8-(nitromethylene)deca-3,9-dien-2-one 3l. Yellow oil, (8 mg, 35% yield). IR (ν, cm^{-1}) 2930, 2856, 1674, 1518, 1335, 1254, 980, 543; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.10 (s, 1H), 6.80 (dt, *J* = 16.0 Hz, *J* = 6.9 Hz, 1H), 6.10 (dt, *J* = 16.0 Hz, *J* = 1.5 Hz, 1H), 5.50 (s, 1H), 5.39 (s, 1H), 2.81–2.78 (m, 2H), 2.33 (qd, *J* = 7.7 Hz, *J* = 1.5 Hz, 2H), 2.25 (s, 3H), 1.94 (d, *J* = 0.75 Hz, 3H), 1.74–1.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 198.7, 154.6, 146.9, 136.0, 134.5, 132.0, 121.3, 32.4, 27.5, 27.5, 26.9, 20.8; HRMS (ESI) cacld for $C_{12}H_{17}NNaO_3$ $[M + Na]^+$ *m/z* 246.1106, found 246.1102.



3m

(3*E*,8*Z*)-8-(Nitromethylene)-9-phenyldeca-3,9-dien-2-one 3m. Yellow oil, (21 mg, 75% yield). IR (ν, cm^{-1}) 2934, 1673, 1628, 1522, 1448, 1346, 1255, 978, 760, 701; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40–7.24 (m, 5H), 7.07 (s, 1H), 6.72 (dt, *J* = 16.0 Hz, *J* = 6.8 Hz, 1H), 6.03 (dt, *J* = 16.0 Hz, *J* = 1.5 Hz, 1H), 5.54 (d, *J* = 0.5 Hz, 1H), 5.50 (d, *J* = 0.5 Hz, 1H), 2.78–2.73 (m, 2H), 2.30–2.19 (m, 2H), 2.21 (s, 3H), 1.72–1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 199.0, 152.1, 146.5, 145.1, 137.4, 132.0, 129.5, 129.3, 129.0, 127.5, 113.1, 54.9, 32.3, 28.8, 26.9; HRMS (ESI) cacld for $C_{17}H_{17}NNaO_3$ $[M + Na]^+$ *m/z* 308.1263, found 308.1241.

References

1. Ballini, R.; Araújo, N.; Gil, M. V.; Román, E.; Serrano, J. A. *Chem. Rev.* **2013**, *113*, 3493.

2. (a) Bäckvall, J. E.; Karlsson, U.; Chinchilla, R. *Tetrahedron Lett.* **1991**, *32*, 5607. (b) Bäckvall, J. E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.

3. (a) Bloom, A. J.; Mellor, J. M. *Tetrahedron Lett.* **1986**, *27*, 873. (b) Bloom, A. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2737.

4. (a) Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. *J. Am. Chem. Soc.* **2013**, *135*, 3355. (b) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384.

5. Youn, S. W.; Kim, Y. H. *Synlett* **2000**, *2000*, 880.

6. (a) Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. *Org. Lett.* **2008**, *10*, 4557. (b) Tissot, M.; Müller, D.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 2770. (c) Tissot, M.; Alexakis, A. *Chem. Eur. J.* **2013**, *19*, 11352.

7. (a) Pathak, R.; Shaw, A. K.; Bhaduri, A. P. *Synth. Commun.* **2000**, *30*, 3595. (b) Pathak, R.; Shaw, A. K.; Bhaduri, A. P.; Chandrasekhar, K. V. G.; Srivastava, A.; Srivastava, K. K.; Chaturvedi, V.; Srivastava, R.; Srivastava, B. S.; Arora, S.; Sinha, S. *Bioorg. Med. Chem.* **2002**, *10*, 1695. (c) Blumberg, L. C.; Costa, B.; Goldstein, R. *Tetrahedron Lett.* **2011**, *52*, 872.

8. Wu, M.-Y.; Li, K.; Hou, J.-T.; Huang, Z.; Yu, X.-Q. *Org. Biomol. Chem.* **2012**, *10*, 8342.

9. Beaumier, F.; Dupuis, M.; Spino, C.; Legault, C. Y. *J. Am. Chem. Soc.* **2012**, *134*, 5938.

10. Retherford, C.; Knochel, P. *Tetrahedron Lett.* **1991**, *32*, 441.

11. (a) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5431. (b) Creech, G. S.; Kwon, O. *J. Am. Chem. Soc.* **2010**, *132*, 8876.

12. Menicagli, R.; Guagnano, V.; Malanga, C. *Gazz. Chim. Ital.* **1992**, *122*, 487.

13. (a) Creech, G. S. The Phosphine-catalyzed Synthesis of 2-Dihydropyrones, and the development of a Program Illuminating the Latent Pericyclic Propensity of 1-Nitro-1,3-dienes. Ph.D., University of California, Los Angeles, Ann Arbor, 2011. (b) Creech, G. S.; Kwon, O. *Chem. Sci.* **2013**, *4*, 2670.

14. Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

15. Baiazitov, R. Y.; Denmark, S. E., Tandem [4+2]/[3+2] Cycloadditions. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*, John Wiley & Sons, Inc.: 2014; p 471.

16. Nef, J. U. *Justus Liebigs Ann, Chem.* **1894**, *280*, 263.

17. Bamberger, E.; Schmidt, O. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 574.

18. Tartakovskii, V. A.; Chlenov, I. E.; Smagin, S. S.; Novikov, S. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, *13*, 549.

19. Kanemasa, S.; Kaga, S.; Wada, E. *Tetrahedron Lett.* **1998**, *39*, 8865.

20. Grée, R.; Tonnard, F.; Carrie, R. *Tetrahedron* **1976**, *32*, 675.

21. Denmark, S. E.; Seierstad, M.; Herbert, B. *J. Org. Chem.* **1999**, *64*, 884.

22. Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *Chem. Eur. J.* **2000**, *6*, 267.

23. Domingo, L. R. *Theor. Chem. Acc.* **2000**, *104*, 240.

24. Papchikhin, A.; Agback, P.; Plavec, J.; Chattopadhyaya, J. *J. Org. Chem.* **1993**, *58*, 2874.

25. Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045.

26. Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **1999**, *64*, 1494.

27. (a) Robins, D. J. *Nat. Prod. Rep.* **1984**, *1*, 235. (b) Robins, D. J. *Nat. Prod. Rep.* **1985**, *2*, 213. (c) Robins, D. J. *Nat. Prod. Rep.* **1986**, *3*, 297. (d) Robins, D. J. *Nat. Prod. Rep.* **1987**, *4*, 577. (e) Robins, D. J. *Nat. Prod. Rep.* **1989**, *6*, 577. (f) Robins, D. J. *Nat. Prod. Rep.* **1990**, *7*, 377. (g) Robins, D. J. *Nat. Prod. Rep.* **1991**, *8*, 213. (h) Robins, D. J. *Nat. Prod. Rep.* **1992**, *9*, 313. (i) Robins, D. J. *Nat. Prod. Rep.* **1993**, *10*, 487. (j) Robins, D. J. *Nat. Prod. Rep.* **1994**, *11*, 613. (k) Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413. (l) Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187. (m) Liddell, J. R. *Nat. Prod. Rep.* **1997**, *14*, 653. (n) Liddell, J. R. *Nat. Prod. Rep.* **1998**, *15*, 363. (o) Liddell, J. R.; Liddell, J. R.; Liddell, J. R. *Nat. Prod. Rep.* **1999**, *16*, 499. (p) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (q) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455. (r) Liddell, J. R. *Nat. Prod. Rep.* **2001**, *18*, 441. (s) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (t) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014**, *31*, 1721. (u) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2017**, *34*, 62.

28. Hartmann, T.; Witte, L., Chapter Four - Chemistry, Biology and Chemoecology of the Pyrrolizidine Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S. W., Ed. Pergamon: 1995; Vol. Volume 9, p 155.

29. Culvenor, C. C. J. *Bot. Notiser* **1978**, *131*, 473.

30. (a) Nowacki, E.; Byerrum, R. U. *Life Sci.* **1962**, *5*, 157. (b) Hughes, C. A.; Letcher, R.; Warren, F. L. *J. Chem. Soc.* **1964**, 4974. (c) Bottomley, W.; Geissman, T. A. *Phytochemistry* **1964**, *3*, 357. (d) Bale, N. M.; Crout, D. H. G. *Phytochemistry* **1975**, *14*, 2617. (e) Robins, D. J.; Sweeney, J. R. *J. Chem. Soc., Chem. Commun.* **1979**, 120. (f) Robins, D. J.; Sweeney, J. R. *J. Chem. Soc., Perkin Trans. I* **1981**, 3083. (g) Robins, D. J.; Sweeney, J. R. *Phytochemistry* **1983**, *22*, 457.

31. Hartmann, T.; Sander, H.; Adolph, R. D.; Toppel, G. *Planta* **1988**, *175*, 82.

32. Böttcher, F.; Adolph, R.; Hartmann, T. *Phytochemistry* **1993**, *32*, 679.

33. Facchini, P. J., Chapter 1 Regulation of Alkaloid Biosynthesis in Plants. In *The Alkaloids: Chemistry and Biology*, Geoffrey, A. C., Ed. Academic Press: 2006; Vol. Volume 63, p 1.

34. (a) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672. (b) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266. (c) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (d) Denmark, S. E.; Parker, D. L., Jr.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 435. (e) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (f) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125. (g) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357. (h) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046. (i) Denmark, S. E.; Hurd, A. R. *Org. Lett.* **1999**, *1*, 1311. (j) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875. (k) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887. (l) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276.

35. Koc, E.; Kwon, O. *Tetrahedron* **2017**, http://dx.doi.org/10.1016/j.tet.2016.12.056.

36. Rao, H. S. P.; Sakthikumar; Vanitha; Kumar, S. S. *Tetrahedron Lett.* **2003**, *44*, 4701

37. Terang, N.; Mehta, B. K.; Ila, H.; Junjappa, H. *Tetrahedron* **1998**, *54*, 12973.

38. (a) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91*, 3281 . (b) Najera, C.; Sansano, J. M. *Tetrahedron Lett.* **1993**, *34*, 3781. (c) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271

39. Bernier, D.; Brueckner, R. *Synthesis* **2007**, 2249

40. Addo, J. K.; Teesdale-Spittle, P.; Hoberg, J. O. *Synthesis* **2005**, 1923

Chapter 2

The Synthesis of Cyclic β-Silylalkenyl Triflates Through Highly Reactive Vinyl Cation Intermediates

2.1 Introduction: Vinyl Cations

The understanding of reactive intermediates is an essential aspect of the study of chemical reactions. Among the best studied reactive intermediates for organic chemists are intermediates derived from formerly tetracoordinated carbon: carbocations, carbanions, radicals, and carbenium ions (Table 2.1.1). In contrast, the study of the unsaturated variants of these species has garnered significantly less attention.[1] In particular, vinyl cations, the unsaturated variant of carbocations–perhaps the most thoroughly investigated carbon based reactive intermediate–have been studied the least. This extreme gap was forged by the thought that vinyl cations were of high energy and that simple hydrocarbon based vinyl cations could not be readily produced under solvolysis conditions. In fact, the related acylium cations were widely accepted as reactive intermediates well before vinyl cations became accepted. Despite the fact that hydration of propyne or allene in aqueous sulfuric acid has been known since the 1870's,[2] vinyl cations were not proposed as viable reaction intermediates until 1944 by Jacobs and Searles.[3] They postulated that the vinyl cation was a possible intermediate in the formation of alkyl acetate from the acid-catalyzed hydration of alkoxy acetylenes. In 1964 Grob and Cseh reported the first formation of vinyl cations through the solvolysis of arylvinyl halides.[4] Soon after, the use of superior leaving groups such as trifluoromethanesulfonate allowed for the direct solvolytic formation of simple vinyl cations. The ability to readily generate and investigate a multitude of unique vinyl cations led many to pursue this unique reactive intermediate. In the subsequent years, reactions of vinyl cations were investigated, exposing this intermediate as an excellent electrophilic reagent that can participate with both *n*- and π-donors with a higher reactivity than their saturated counterparts.

Table 2.1.1 Carbon based reactive intermediates

Intermediate	Structure	Intermediate	Structure
Carbocation		Vinyl cation	
Carbanion		Vinyl anion	
Radical		Vinyl radical	
Carbene		Alkylidene carbene	

2.2 Thermodynamics of Vinyl Cation

The properties of reaction intermediates can be more easily studied and understood if the intermediates exist for a long enough time that they could be examined for measurement.[5] Typically, reaction intermediates can be observed and measured through spectral methods. In the case of vinyl cations however, the lifetime is typically extremely short thus making direct observation quite difficult. Despite this difficulty, important thermodynamic data can be obtained from the gas phase mass spectrometry or ion cyclotron resonance experiments. By using the standard enthalpy of formation and the isodesmic hydride transfer of two hydrocarbon species, the relative stabilities between two cationic intermediates can be calculated.[6] In the gas phase, the ethenyl cation is actually calculated to be 25 kcal/mol more stable than methyl cation. However, this cation is 15 kcal/mol less stable than ethyl cation. When comparing the disubstituted propenyl cation to *n*-propyl cation, the relative stabilities are similar, but again it is 15 kcal/mol less stable than the isopropyl cation analogue.

Table 2.2.1 Heat of formation of simple hydrocarbons

$$R^+ + R_1H \longrightarrow RH + R_1^+$$

Isodesmic Hydride Transfer

Species	ΔH°_f (kcal/mol)	Species	ΔH°_f (kcal/mol)
$\overset{+}{C}H_3$	261	CH_4	–18
$\overset{+}{C}H_2$	219	$H_3C{-}CH_3$	–20
$\overset{+}{C}H_2$	208	$H_3C{-}CH_3$	–25
$\overset{+}{C}H$	192	$H_2C{=}CH_2$	12
$\overset{+}{C}H_2$	226	$H_3C{-}CH_2$	5
$\overset{+}{C}H$	266	$HC{\equiv}CH$	54
$\overset{+}{C}$	237	$H_3C{-}{\equiv}CH$	44

Theoretical Calculations

Preliminary calculations for ethenyl cation showed that both the linear and bridged structures of the vinyl cation have similar energies and that the barrier to interconversion is quite small, about 1 to 3 kcal/mol.[7] Weber and McLean performed bond length calculations for both the linear and bridged forms of ethenyl cation (Figure 2.2.1). For the open form, the C=C bond was calculated to be 1.263 Å, between the values of ethylene (1.330 Å) and acetylene (1.203 Å). The C_1–H_1 bond length of 1.075 Å is comparable to the analogous C–H bond in ethylene, whereas the C_2–H_2 bond is considerably longer at 1.086 Å. As for the bridged form, the calculated C=C bond length is 1.210 Å, similar to acetylene, but the C_1–H_1 bond length of 1.276 Å implies that the bridged form must be structurally related to a π-complexed protonated acetylene. The calculations predict a sp-hybridization for vinyl cations over sp^2-hybridization, showing that the linear cation is 50 kcal/mol lower in energy than the bent sp^2 structure.

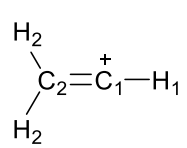
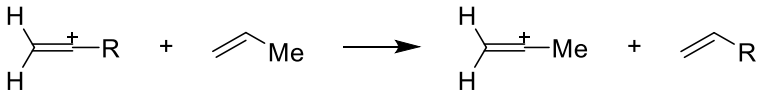


Figure 2.2.1 Properties of ethenyl cation

For substituted vinyl cations, calculations show that an α-substituent can impart great stabilization on the reactive intermediate (Table 2.2.2). Employment of STO-3G and 4-31G level calculations on α-substituted vinyl cations with methyl-, ethenyl-, ethynyl-, cyclopropyl-, and phenyl-substituted vinyl cations displayed a large increase in stability in comparison to the parent ethenyl cation.[8] A simple methyl substituent makes the resulting propenyl cation 26 kcal/mol more stable than ethenyl cation, and employment of an α-phenyl group lowers the energy by 60 kcal/mol.[9] A β-substitution, while providing some stability to the vinyl cation, give much less total stabilization energy than their α-substituted counterparts.[10]

Table 2.2.2 Energetic effects of substituents



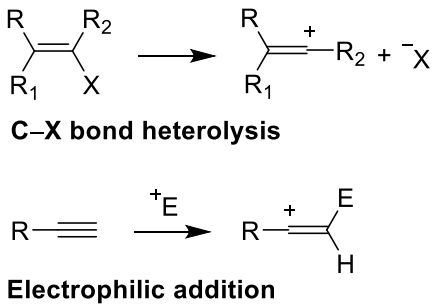
Isodesmic Hydride Transfer

R	STO-3G (kcal/mol)	4-31G (kcal/mol)
H	–25.9	–25.2
CH_3	0.0	0.0
$CH{=}CH_2$	15.1	14.3
C≡CH	2.0	–0.1
c-C_3H_5	15.8	17.3
C_6H_5	34.2	-

2.3 Formation of Vinyl Cations

Initially, vinyl cations were formed solely by the solvolysis of alkenes bearing good leaving groups, as shown by Grob. As work progressed in the field, new methods developed, which can broadly be categorized as heterolysis of the (C=)C–X bond and electrophilic addition (Scheme

2.3.1). Concerning bond heterolysis, methods of forming vinyl cations can be placed into the categories of solvolysis, photochemical, electron impact, and nuclear chemical. As for electrophilic addition methods, vinyl cations can be generated by electrophilic addition to allenes and alkynes.[11]

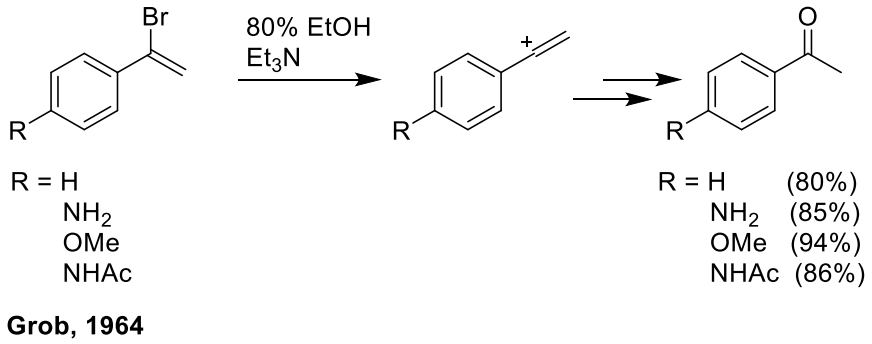


Scheme 2.3.1 Generalized techniques for vinyl cation formation

Bond Heterolysis Reactions to Form Vinyl Cations

The solvolysis of vinyl compounds proceeds through the same S_N1 type mechanism as their aliphatic counterparts, however the community was slow to accept this mechanism of formation.[12] This was due to the perceived instability of the vinyl cation intermediate in comparison to the trisubstituted carbocation analogue. However, calculations proved this to be untrue. Additionally, employment of silver salts in reactions with vinyl halides under solvolysis reaction conditions showed low reactivity, casting doubt on the formation of a vinyl cation intermediate. It was found that the increased C–X bond strength in vinyl halides was responsible for the lower reactivity towards silver salts. The increased σ character of the C–X bond as well as the partial double bond character leads to a much shorter C–X bond than in aliphatic halides. In fact, the C–Br bond in vinyl bromide is 1.86 Å, shortened from 1.91 Å in bromomethane and the C–Cl bond in vinyl chloride is 1.69 Å, compared to 1.76 Å in chloromethane.[13]

Generally accepted as the first example of a vinyl cation intermediate in a solvolysis reaction, Grob's solvolytic generation of α-arylvinyl cations from substituted α-bromostyrenes in ethanol led the way for studies of vinyl cations (Scheme 2.3.2).[4] Heating various para-substituted α-bromostyrenes in ethanol buffered with triethylamine yielded the acetophenone products in good yields. Notably, electron-donating substituents were well tolerated, providing the acetophenone products in an efficient manner. In contrast, the electron-withdrawing *p*-nitro group did not provide the acetophenone product, only the phenylacetylene product could be detected. It is apparent that for α-arylvinyl cations, increased stabilization due to electron donating groups greatly lead to increased stability of this reactive intermediate. In an α-arylvinyl system, the ground state is stabilized by the extended π(Ar)–π(C=C) conjugation, and the resulting cation is developed in a perpendicular p-orbital.[14] The vinyl cation in a vacant p-orbital can then be stabilized by overlap of the empty orbital and the aromatic π system. However, this necessitates a deconjugation of the π(Ar)–π(C=C) alignment.[15]



Scheme 2.3.2 First vinyl cation formation by Grob

After the initial report by Grob, a wide investigation into the generation of vinyl cations by solvolysis began. It became rapidly apparent that two criteria must be met if efficient vinyl cation formation was to be accomplished: employment of improved good leaving groups such as

trifluoromethanesulfonate or nonafluorobutanesulfonate and designing substrates so that the vinyl cation could be stabilized by electron-donating α-substituents or charge-dispersing β-substituents (Figure 2.3.1).[16] Substituents that can efficiently stabilize trigonal carbocations are also capable of stabilizing vinyl cations. Alkyl, aryl, alkenyl, alkynyl, and even cyclopropenyl substituents can help stabilize the vinyl cation.

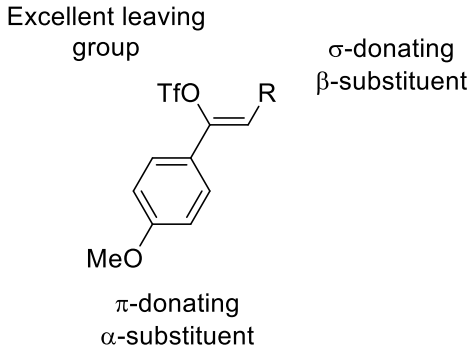
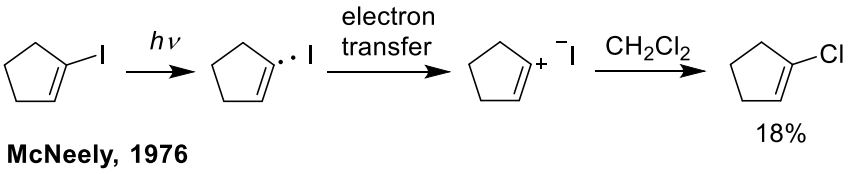


Figure 2.3.1 Criteria for efficient vinyl cation formation

Photochemical methods to generate vinyl cations generally involve C–X homolysis to form the radical pair followed by electron transfer to give the resulting vinyl cation (Scheme 2.3.3).[17] By utilizing bond homolysis instead of heterolysis, the energy required for the vinyl cation formation is less, oftentimes leading to reactions of higher efficiency. Another advantage to the use of photochemical methods for the formation of vinyl cations is the availability of a wider variety of intermediates, including primary cations. Generally the reaction conditions are mild, avoiding strong acids, non-nucleophilic solvents, and high temperatures.



Scheme 2.3.3 Photochemical methods for vinyl cation formation

Exposure of vinyl compounds to an electron beam and controlling the fragmentation has been employed as an important technique for the study of the thermodynamic properties of vinyl cations.[18] Likewise, the nuclear chemical method is used as a technique for studying the properties of vinyl cations.[19] β-Decay of tritium leads to the conversion of a positively charged RHe^+ ion where the positive charge resides on the helium atom. Electron transfer from carbon to helium then provides the vinyl cation.[20]

Electrophilic Addition Reactions to Form Vinyl Cations

Like the acid-catalyzed hydration of alkynes, the hydration of allene has been known since the late 1800's.[21] Despite this, there are considerably fewer investigations into reactions involving allenes than alkynes, due to difficulties in their preparation.[22] The structure of allene is symmetric with a sp hybridized central carbon and two terminal sp^2 carbon atoms (Figure 2.3.2). This places the two double bonds in perpendicular planes, allowing for hyperconjugation between the σ(C–H) bonds and the π(C=C) bonds. The effect of this hyperconjugation is a shorter C=C bond (1.34 Å).

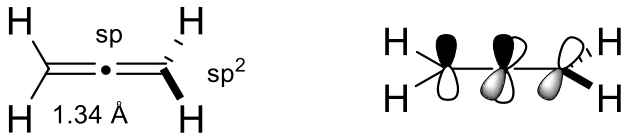
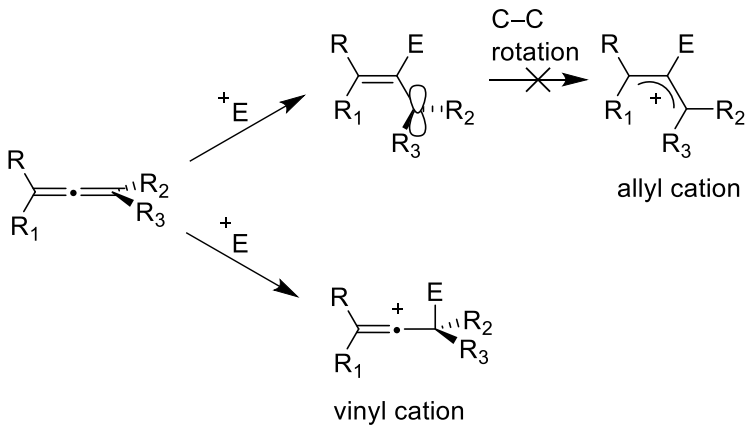


Figure 2.3.2 Properties of allene

The mechanism of addition to allenes follows the same pathway as addition to alkenes and alkynes with one main difference, the possibility for an electrophilic attack at either the terminal carbon, giving a vinyl cation, or the central carbon, giving the allyl cation (Scheme 2.3.4). Although the formation of the allyl cation via central carbon attack seems more likely than formation of the vinyl cation, the latter is the preferred reaction pathway. Due to the fact that the double bonds in allene are perpendicular to each other, C–C bond rotation is necessary to achieve

allylic stabilization, necessitating an energetic gain for the formation of the allyl cation from allene. As such, the general trend for the formation of intermediate ions is 3° allyl cation > vinyl cation ≈ 2° allyl cation > 1° allyl cation. Allene substituents, the nature of the electrophile, and the solvent all play important roles in differentiating between a vinyl cation and a 2° allyl cation. As with other reactions that proceed through a vinyl cation intermediate, the rate-determining step for electrophilic addition to allenes is the formation of the vinyl or allyl cation. Interestingly, addition of halo acids to allene gives the same products as reaction with propyne by way of the intermediate vinyl cation.[23]



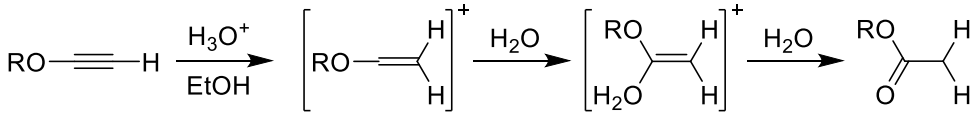
Scheme 2.3.4 Electrophilic attack of allene

In contrast to allenes, the study of alkynes and their reactivities has drawn considerably more attention from chemists.[24] The electrophilic addition to alkynes is a well-known process and the first electrophilic hydration of propyne was found in 1875 by Fittig and Schrohe and the first metal-catalyzed addition to alkynes was developed by Kucherov in 1881.[11] Despite the knowledge of this reaction for many years, the mechanism of the reaction remained elusive for quite some time. It was not until work by Grob concerning the solvolysis of vinyl halides that acceptance of

the vinyl cation intermediate began. In comparison to alkenes, alkynes typically undergo electrophilic additions at a greater rate due to their increased electron density.

The acid catalyzed addition of water to alkynes proceeds through a general acid-catalyzed mechanism with the protonation of the triple bond as the rate determining step. Jacobs and Searles first studied the acid-catalyzed hydration of ethynyl ethers to determine the mechanism of formation (Scheme 2.3.6).[3] It was discovered that both vinyl and phenyl substituted ethynyl ethers react 10^3 times slower than their alkyl counterparts. As a possible mechanism for the formation of the ester products, Jacobs and Searles proposed the intermediacy of a vinyl cation aided by resonance from the neighboring oxygen atom. The protonation of the triple bond was determined to be the rate determining step.

Jacobs and Searles proposed mechanism, 1944

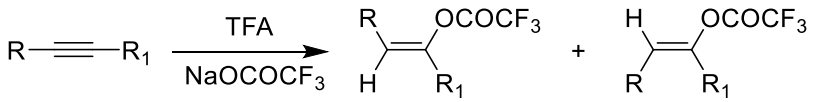


R = Et, *n*Bu, Ph, vinyl

Scheme 2.3.5 Mechanistic aspects of acid-catalysed hydration of alkynyl ethers

Like forming vinyl cations via solvolysis, the existence of stabilizing groups on the triple bond lead to increased stability of the vinyl cation. In addition, employment of trifluoroacetic acid (TFA) because of its high acidity and low nucleophilicity could lead to a mixture of vinyl trifluoroacetate isomers (Table 2.3.1).[16b] In general, the *Z* product is favored when reacting symmetrical alkynes with TFA. Although the *syn*-addition to give the *E* isomer is favored because of steric reasons when reacting with acids other than TFA, it was proposed that an hyperconjugation with the *β*-alkyl group and the incoming trifluoroacetate ion leads to the observed selectivity.

Table 2.3.1 Stereochemical outcome of reacting alkynes with TFA



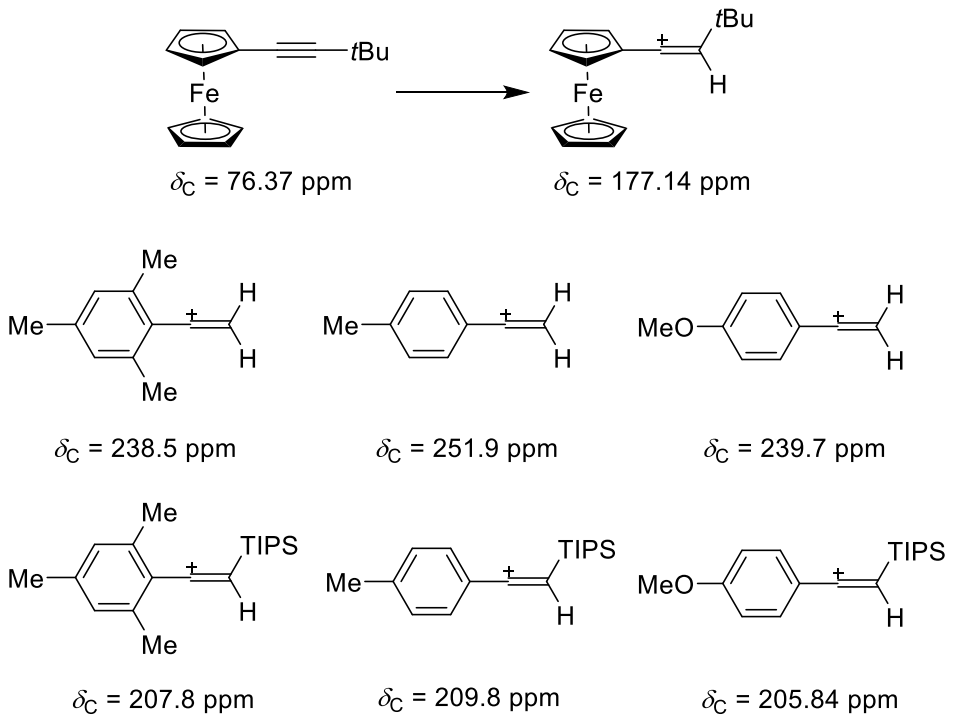
Schleyer, 1973

R	R_1	Ratio *Z*/*E*
Me	Me	3.33:1
Et	Et	0.91:1
*n*Pr	*n*Pr	0.77:1
*n*Pr	H	2:1
*n*Bu	H	2.06:1

Improving upon the higher reactivity of TFA towards vinyl cation formation, the use of superacid reagents greatly expanded the ability to generate vinyl cation intermediates. Brønsted superacids possess an extremely high acidity, oftentimes making it possible to generate organic species with a charge ≥ 2.[25] In addition, these superacids are extremely non-nucleophilic, allowing for even sluggish nucleophiles to be used in the reaction sequence. Usage of CF_3CO_2H–SO_2ClF system and a highly stabilized alkyne by Siehl and coworkers allowed for the detection of a vinyl cation by NMR spectroscopy.[26] Employment of α-ferrocenyl and β-*t*-butyl substituents allowed for the direct NMR observation of the intermediate vinyl cation.

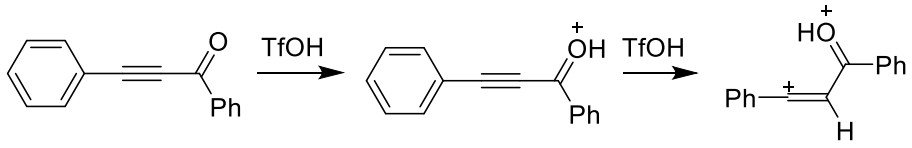
The ^{13}C NMR signal (δ_C) for the positively charged carbon atom occurs at 177.14 ppm, shifted downfield by more than 100 ppm from the parent neutral compound (Scheme 2.3.6). Progressing to substituted arylacetylenes, the stabilizing effect of various substituents can be seen.[27] A 2,4,6-trimethylphenyl group was found to give a vinyl cation with a chemical shift of 238.5 ppm, whereas a simple *p*-tolyl-substituted cation has a chemical shift of 251.9 ppm. Interestingly, a *p*-anisyl-substituted cation showed a chemical shift of 239.7 ppm. Variations of the aromatic moiety had much less effect on the vinyl cation chemical shift than adjustment of the

β-substituent. Inclusion of a trialkylsilyl group greatly alters the chemical shift, lowering the demand for charge delocalization into the aromatic ring by providing stabilization through hyperconjugation. In most cases, the presence of a β-silyl causes a great upfield shift, oftentimes 30–45 ppm changes.



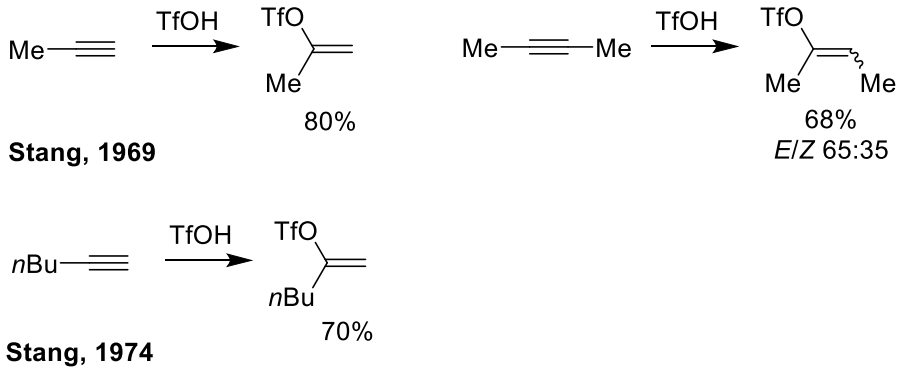
Scheme 2.3.6 Chemical shift (δ_C) for vinyl cations

For acetylene compounds bound to a heteroatom containing electron-withdrawing substituent, the protonation with superacids proceeds first at the heteroatom and then at the triple bond giving the dication (Scheme 2.3.7). The sequence of protonation of 1,3-diarylpropynones by HSO_3F was revealed by NMR studies and DFT calculations.[28] Protonation of the ketone oxygen proceeds first forming the oxocarbenium ion, where the charge can be delocalized into the aromatic substituents. A second protonation at the triple bond gives the superelectrophilic dication product. This pattern continues in arylpropynoic acids as well as arylbutynones.[29]



Scheme 2.3.7 Generalized protonation of electron poor acetylene compounds

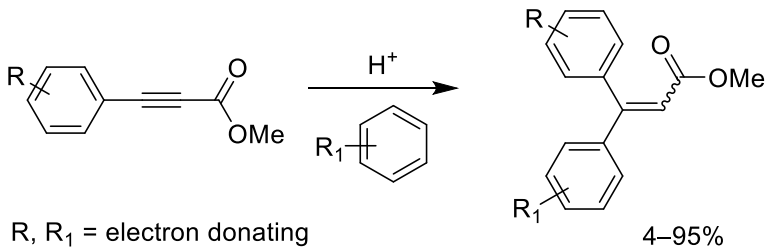
One of the more powerful transformations of vinyl cations with superacids is the generation and subsequent formation of vinyl fluorosulfonates and triflates.[16b, 30] Stang and Summerville showed the first addition of triflic acid to alkynes to generate vinyl triflate compounds via the vinyl cation intermediate. Reaction of simple alkyl substituted terminal alkynes produced the desired vinyl triflates in high yields (Scheme 2.3.8). It was seen that for the terminal alkynes, the addition of the proton and triflate occurs in a *syn* fashion. However when the alkyne scope was expanded to internal alkynes, a mixture of both *syn* and *anti* products was observed, with the *anti* product being favored.



Scheme 2.3.8 Synthesis of vinyl triflates by Stang and Summerville

α-Arylvinyl cations generated by superacids can be trapped by a number of aromatic molecules through electrophilic aromatic substitution. As noted by Vasilyev,[11] this reaction may be considered a hydroarylation reaction about the triple bond. Reaction of arylacetylene compounds with superacids at low temperatures to generate the vinyl cation followed by addition

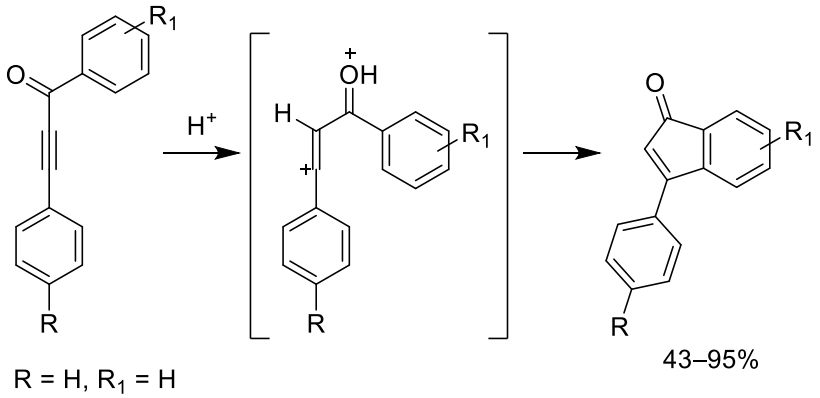
of various aromatic compounds cleanly provided a variety of 1,1-bisaryl substituted alkenes (Scheme 2.3.9).[29b, 31] A number of superacids may be employed, although fluorosulfonic acid and triflic acid dominate as the acids of choice. Numerous aromatic compounds are also tolerated, including benzene, alkylbenzenes, hydroxy, methoxy, and halogenated benzenes are all tolerated. Additionally, arylammonium ions, *N*-arylacetamides, and mildly electron poor aromatic groups can participate in the reaction. It is apparent that strongly electron-withdrawing substituents are not tolerated in the reaction.



Scheme 2.3.9 Trapping vinyl cation by S_EAr

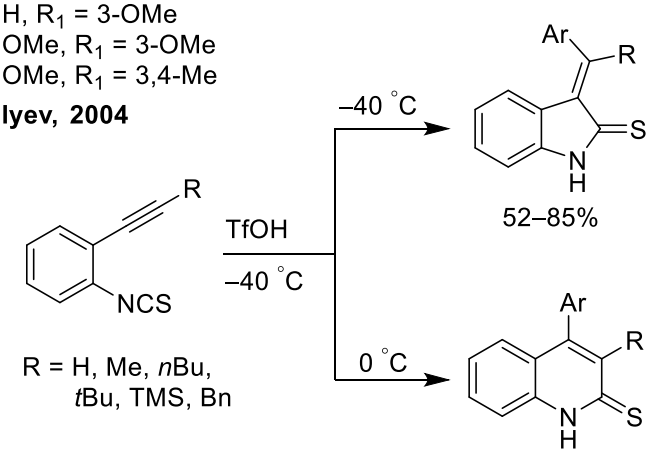
The intramolecular trapping of vinyl cations can be exploited to give a plethora of cyclic products (Scheme 2.3.10). 1,3-Diarylpropynones can be reacted with superacids to generate the dication intermediate which is intercepted by the pendant aryl group to give 3-arylindenone products in good yields.[32] Protonation of arylisothiocyanates bearing an *ortho* alkyne with triflic acid can efficiently give two cyclized products in good to great yields, depending on the temperature of the reaction.[33] Warmer temperatures favor the formation of the dication species which leads to the production of 4-arylquinone-2-thiones. Low reaction temperatures favor the generation of the corresponding indole-2-thione product. Reaction of benzylpropargylamines at room temperature in benzene with triflic acid can cleanly generate cyclic amine products in excellent yields.[34] Importantly, at room temperature the trimethylsilyl group could not be preserved in the product compound. Much like polyene cyclization reactions and radical cascade

reactions, vinyl cations also can participate in cascade cyclization reactions. 1,7-Enynes, when treated with triflic acid, provide polycyclic products in good to excellent yields.[35] Silylynol ethers bearing tethered alkenes and alkynes can be efficiently transformed to cyclic enone products.[36] After protonation of the silylynol ether and cyclization, the cyclic ketone is formed. In the case of siloxy alkynes bearing pendant alkynes, a second vinyl cation is formed, which is sufficiently reactive to incorporate a halogen atom from the solvent into the product.[37]



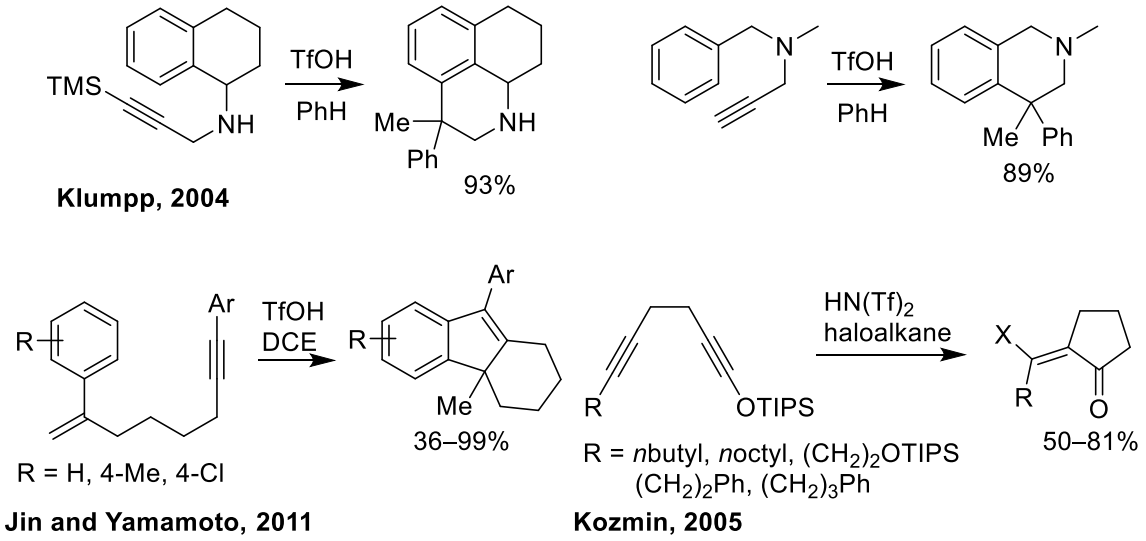
R = H, R_1 = H
R = Me, R_1 = H
R = OMe, R_1 = H
R = H, R_1 = 3-OMe
R = OMe, R_1 = 3-OMe
R = OMe, R_1 = 3,4-Me

Vasilyev, 2004



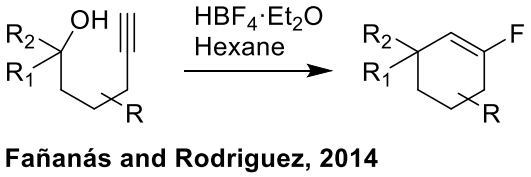
R = H, Me, *n*Bu, *t*Bu, TMS, Bn

Otani and Saito, 2009



Scheme 2.3.10 Various products made by intramolecular trapping of the vinyl cation

Recently, work by Fañanás and Rodriguez showed the simple generation of cyclic vinyl fluorides from enynes or alkynols by employment of tetrafluoroboric acid activation.[38] Formation of a stabilized cation from either the alcohol or olefin followed by intramolecular trapping by the terminal alkyne would quickly lead to the desired cyclohexenyl vinyl cation (Scheme 2.3.11). Trapping by fluoride would then lead to their desired vinyl fluoride products.



Scheme 2.3.11 Synthesis of cyclohexenyl fluorides

The methodology was shown to efficiently synthesize numerous 3-substituted cyclohexenyl fluorides in excellent yields (Figure 2.3.2). Essential to the reaction is the need for the initial carbocation to be stabilized as a 2° benzyl or 3° alkyl cation. With these constraints, 3-aryl cyclohexenyl fluorides could be synthesized. Importantly, the substitution on the aromatic

ring is restricted to electron-donating groups. As for 3,3-disubstituted products, both electron-donating aryl and alkyl groups efficiently give the desired products. Deviating from the standard cyclohexene core, this methodology can be extended to give dihydronaphthalene and tetrahydropyridine products as well. Finally, as in the case of many cation cyclization reactions, this method can be used in a cascade sequence, providing geraniol and nerol derived fluorinated bicyclic meroterpenes.

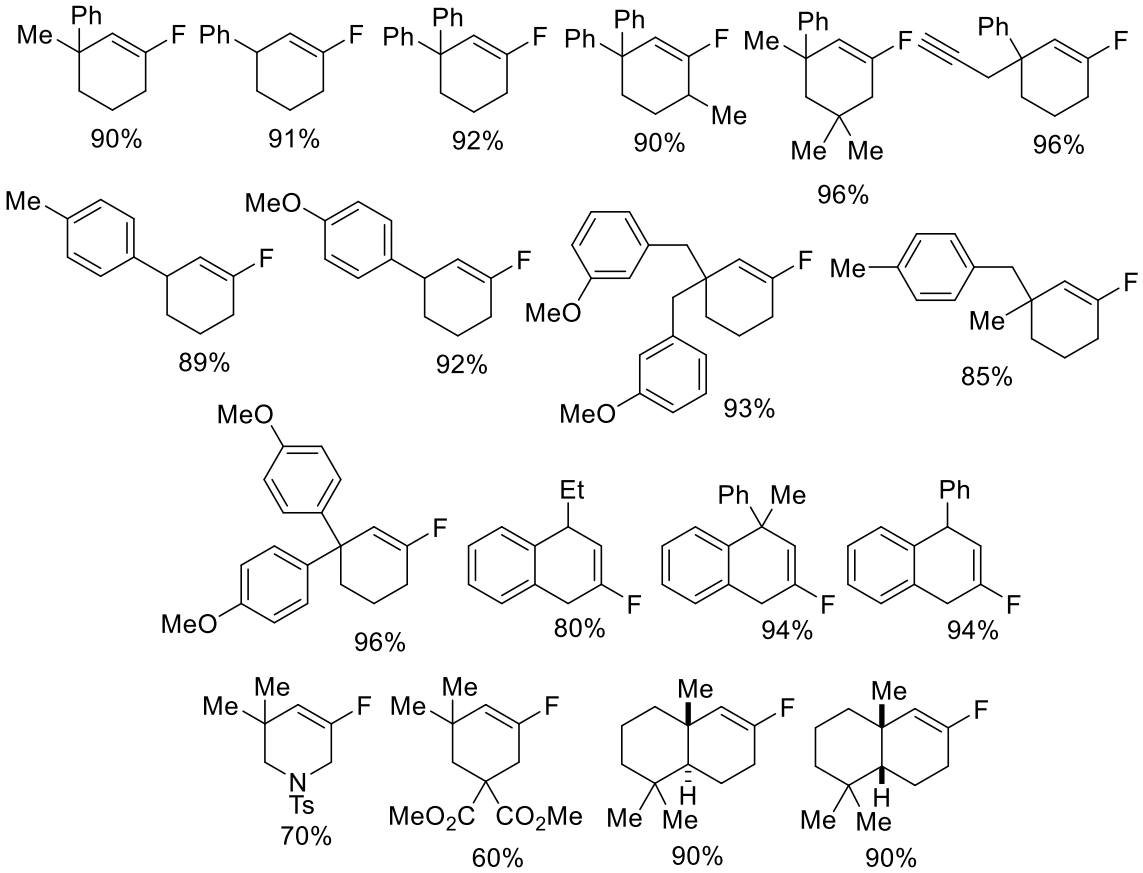
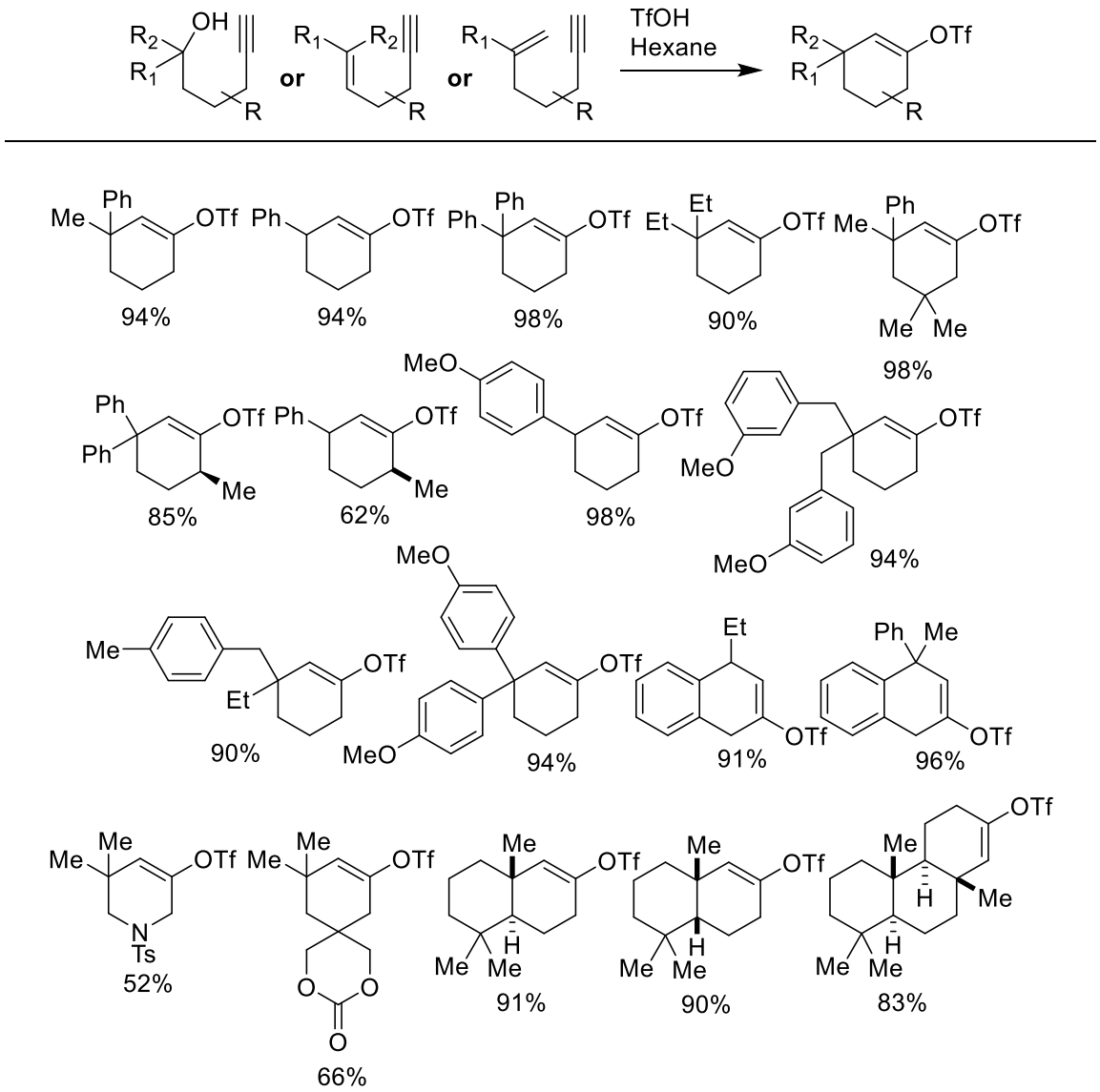


Figure 2.3.2 Cyclic alkenyl fluorides synthesized by Fañanás and Rodriguez

This efficient process was also expanded to generate vinyl triflates.[39] By replacing tetrafluoroboric acid with triflic acid, cyclic alkenyl triflates could be produced in the same highly efficient manner. Much like the substrate scope for the synthesis of cyclic alkenyl fluorides, this

method necessitates a stabilized carbocation intermediate to be intercepted by the pendant alkyne and subsequently trapped by triflate ion (Scheme 2.3.12). Electron-rich aryl groups are well tolerated, as well as inductively donating alkyl substituents. This method can also be used to give dihydronaphthalene derivatives as well as tetrahydropyridine compounds. Biomimetic cyclizations may also be performed, providing several terpenoids bearing vinyl triflate functional handles.

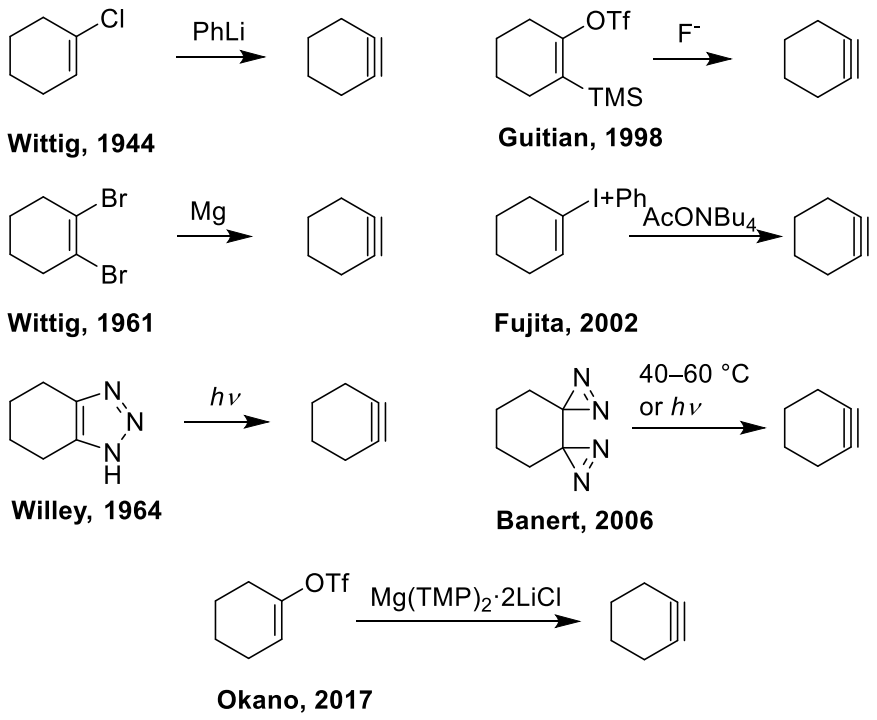
Fañanás and Rodriguez, 2015



Scheme 2.3.12 Synthesis of cyclic alkenyl triflates

2.4 Synthesis of Cyclohexyne

Due to their high reactivities, small strained organic molecules such as arynes[40] and cycloalkynes[41] have recently garnered much attention. Despite this attention, there are few reports on the synthesis and reactions of cyclohexyne and related strained cyclic alkynes. To compound this problem, a majority of the reported syntheses and reactions of cyclohexyne only involve the simple unsubstituted parent compound. The synthesis and trapping of cyclohexyne is well established, however the first methods generally involved the usage of harsh conditions. Work by Wittig and Roberts showed that cyclohexyne could be produced by dehydrohalogenation from the corresponding vinyl halide (Scheme 2.4.1).[42] The photochemical activation of aminotriazole to give cyclohexyne was developed by Willey and coworkers,[43] and the thermal or photochemical decomposition of bis(diazirine) to generate cyclohexyne was elucidated by Banert.[44] By far the most commonly accessed methodologies to obtain cyclohexyne are the desilylation/elimination of cyclohexenyl β-silyl triflate[45] and the decomposition of cyclohexenyl iodonium salts.[46] These methods have proven to be amenable to usage in complex molecule synthesis, however are generally limited to the generation of unsubstituted cyclohexyne.[41d, 41f, 41g, 47] Recently, Okano has disclosed a simple method for the generation of substituted cyclohexynes through the direct elimination of cyclic enol triflates using magnesium bisamides.[48] Although somewhat limited in substrate scope, several cyclohexynes could be generated and subsequently trapped in moderate to good yields.



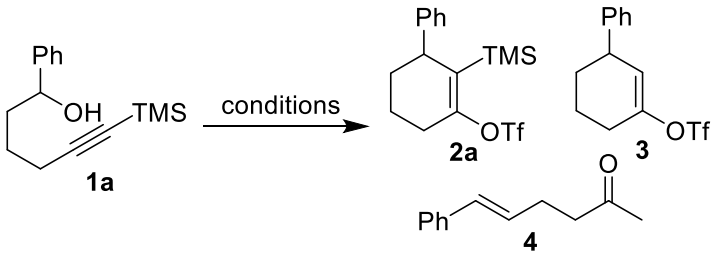
Scheme 2.4.1 Methods to synthesize cyclohexyne

2.5 Results and Discussion

Inspired by the work of Fañanás and Rodriguez, we sought to develop a method that could intercept the highly reactive vinyl cation intermediate to yield cyclic β-silylvinyl triflates. We began by synthesizing the silylated analogue (**1a**)[49] of the simple phenyl alkynol that was employed previously. Exposure of this compound to the conditions developed by Fañanás and Rodriguez failed to yield and desired product (Table 2.5.1, entry 1). Interestingly, this condition only led to complete decomposition of the starting material, with no identifiable products (entry 1). We believed that this increased reactivity might be due to the increased stability of the vinyl cation due to a β-silyl effect. Not to be discouraged, we then performed the transformation at lower temperatures (–78 °C) followed by slow warming to room temperature using dichloromethane (DCM) as a solvent (entry 2). Gratifyingly, we were able to obtain the desired cyclization product

2a, albeit in a 1:1 ratio with the desilylated product **3**. By adding the triflic acid as a solution in DCM to the alkynols, we reduced the amount of desilylated product formed; however, a rearranged ketone **4** was formed in its place (entry 3). Increasing the dilution of the reaction nearly eliminated the formation of **3**, but we noted a stark increase in the formation of **4** (entries 4–9). Believing this ketone to be the byproduct of hydration of the alkyne, we devised a strategy to eliminate adventitious water in the reaction. As noted by Fañanás and Rodríguez, hexane was used as the solvent in order to prevent side reactions with water. By adding trifluoromethylsulfonic anhydride (Tf_2O) to the reaction to react with any water formed during the dehydration sequence, we found that the amount of ketone byproduct was drastically reduced (entry 10). Super stoichiometric amounts of Tf_2O improved upon this, generating **2a** as the sole product (entries 12 and 13). Warming the reaction to –20 °C instead of to room temperature allowed for the use of a higher reaction concentration (entries 14–16).

Table 2.5.1 Optimization of the cationic cyclization

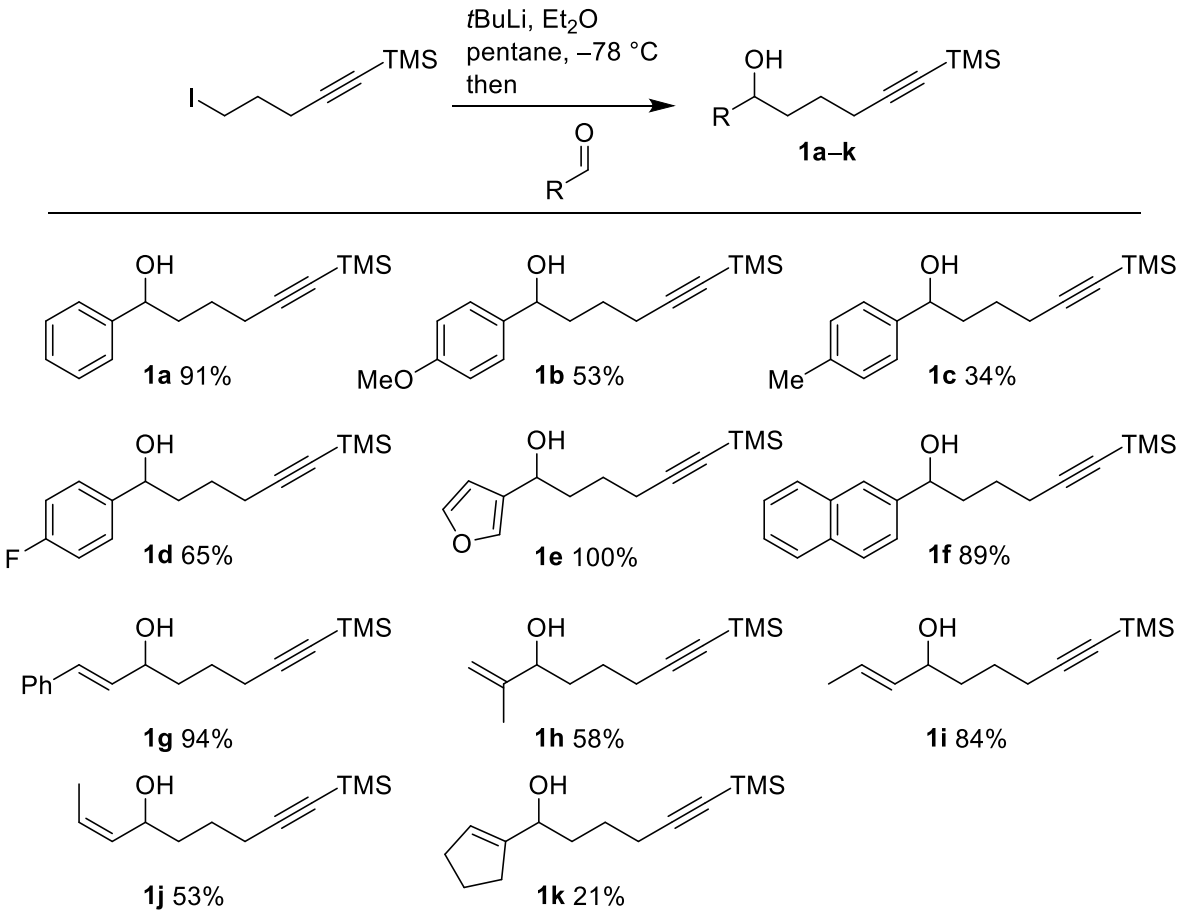


entry	concentration (M)	Tf_2O (equiv.)	ratio **2a**:**3**:**4**[b]	conversion (%)[c]
1[d, e, f]	0.1	-	-	0
2[f]	0.1	-	1:1:0	100
3	0.1	-	1:0.6:0.1	100
4	0.075	-	1:0.3:0.1	100
5	0.063	-	1:0.3:0.15	100
6	0.05	-	1:0.26:0.13	100
7	0.038	-	1:0.23:0.23	100
8	0.025	-	1:0.16:0.29	100
9	0.013	-	1:0.06:0.46	99

10	0.0063	0.5	1:0.04:0.28	99
11	0.01	2	1:0:0.18	100
12	0.01	5	1:0:0	100
13	0.01	10	1:0:0	100
14[g]	0.1	1	1:0:0	99
15[g]	0.1	5	1:0:0	100
16[g]	0.067	1.2	1:0:0	100

[a]A solution of TfOH and Tf_2O in DCM was added dropwise to a solution of **1a** in DCM at –78 °C and was warmed to room temperature over 2 hours. [b]Ratios determined through crude nmr analysis. [c]Conversion determined through crude nmr analysis. [d]Hexanes used as solvent. [e]Reaction run at rt. [f]Neat TfOH added directly to reaction mixture. [g]Reaction warmed to –20 °C.

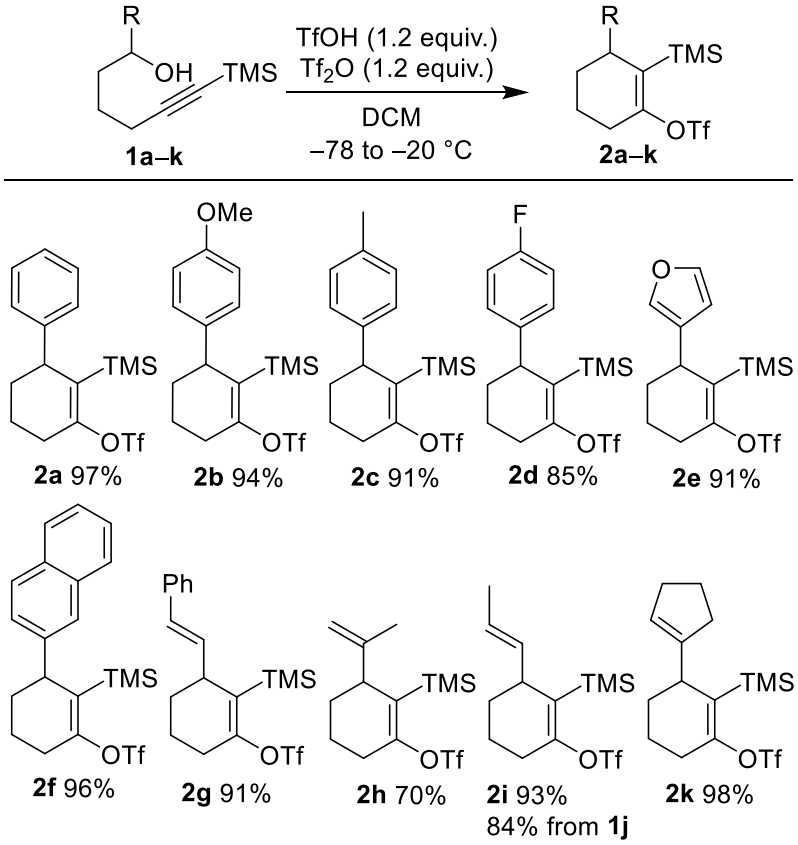
With optimized conditions in hand, we synthesized a variety of alkynols to employ in the cationic cyclization reaction (Scheme 2.5.1).[49] Simple lithium-halogen exchange and addition to an aldehyde was chosen for its synthetic ease for the synthesis of the necessary alkynols. By employing different 4-substituted benzaldehyde derivatives, we were able to access both electron-rich and electron-poor benzyl alcohols. In addition, we gained access to heterocyclic aryl alcohols in good yields using this methodology. Expanding this further, we desired to move past aromatic alcohols and pursue the synthesis of allylic alcohols. Again using the established methodology, we obtained several allylic alcohols in moderate to good yields.



Scheme 2.5.1 Synthesis of alkynols

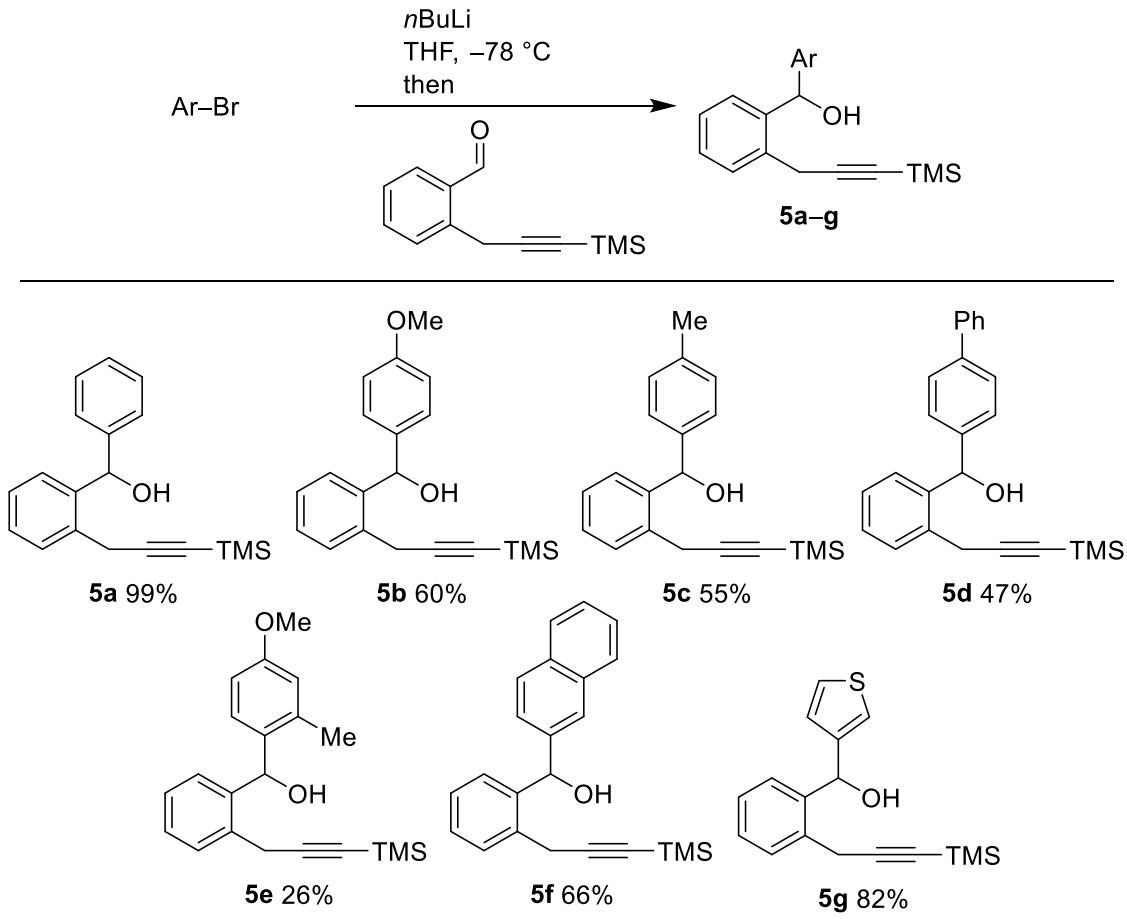
With numerous alkynols in hand, we then began to explore the scope of the cationic cyclization reaction (Scheme 2.5.2). Treatment of alcohol **1a** under the established conditions cleanly provided the desired β-silyl triflate product **2a** in 97% yield. Progressing to more electron-rich substrates bearing 4-methoxy (**1b**) and 4-methyl (**1c**) substituents, the desired products **2b** and **2c** were obtained in 94% and 91% yield, respectively. Even the electron-withdrawing fluoro group was well tolerated in the reaction, providing the product **2d** in 85% yield. Both 3-furyl (**2e**) and 2-naphthyl (**2f**) substitutions gave the cyclohexenyl products in excellent yields. Reacting numerous allylic alcohols also gave the β-silyl triflate products in good yields. Cinnamyl alcohol derivative **1g** cleanly provided the corresponding cyclohexene **2g** in 91% yield and allylic alcohol **1h** gave

cyclic alkenyl triflate **2h** in good yield. Interestingly, both *E* and *Z* isomers **1i** and **1j** converged on a single product, **2i**, when reacted under the standard conditions. Cyclic alkenes were also well tolerated, giving cyclopentenyl substituted product **2k** in excellent yield.



Scheme 2.5.2 Generation of cyclohexenyl silyl triflates

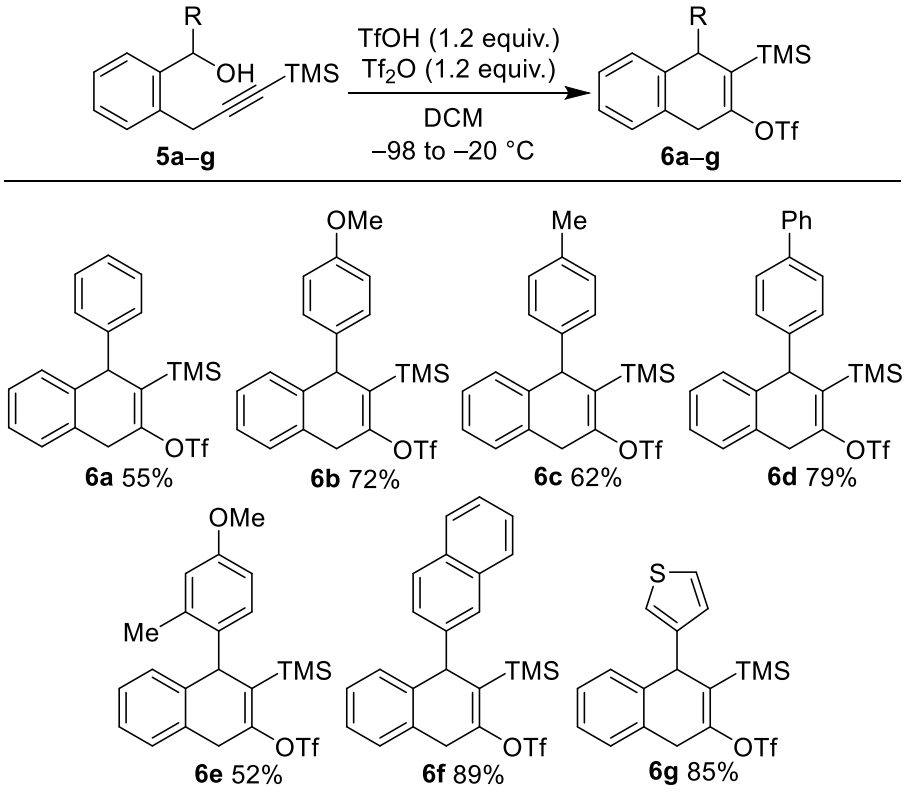
We then sought to explore another molecular scaffold through this methodology, the 1,4-dihydronaphthalene core. We began by synthesizing various benzhydrol derivatives via addition to the corresponding aryl aldehyde (Scheme 2.5.3). Addition to benzaldehyde cleanly gave the unsubstituted benzhydrol **5a**. Along the same lines, 4-methoxy (**5b**), 4-methyl (**5c**), 4-phenyl (**5d**), and 4-methoxy-2-methyl (**5e**) substituted benzhydrols were also synthesized. Access to 2-naphthyl (**5f**) and 3-thiophenyl (**5g**) substituted alcohols was also possible using this reaction sequence.



Scheme 2.5.3 Synthesis of alkynyl tethered benzhydrols

With a suitable amount of alkynyl benzhydrols in hand, we began the synthesis of 1,4-dihydronaphthalene derivatives using our established methodology (Scheme 2.5.4). We found improved efficiencies when performing the reaction at –98 °C, presumably due to the fact that the initially formed cation is readily formed because of the increased stability imparted by the bis-benzylic moieties. Alcohol **5a** cleanly underwent cationic cyclization/vinyl cation formation/triflate ion trapping, but **6a** was isolated in moderate yield. Progressing to substituted bis-benzylic alcohols, good yields could be obtained for electron-rich substrates, exemplified by 4-methoxy (**6b**), 4-methyl (**6c**), and 4-phenyl (**6d**) substituted derivatives. The presence of an *ortho* substituent was found to have a profound effect on the overall yield of the reaction, providing **6e**

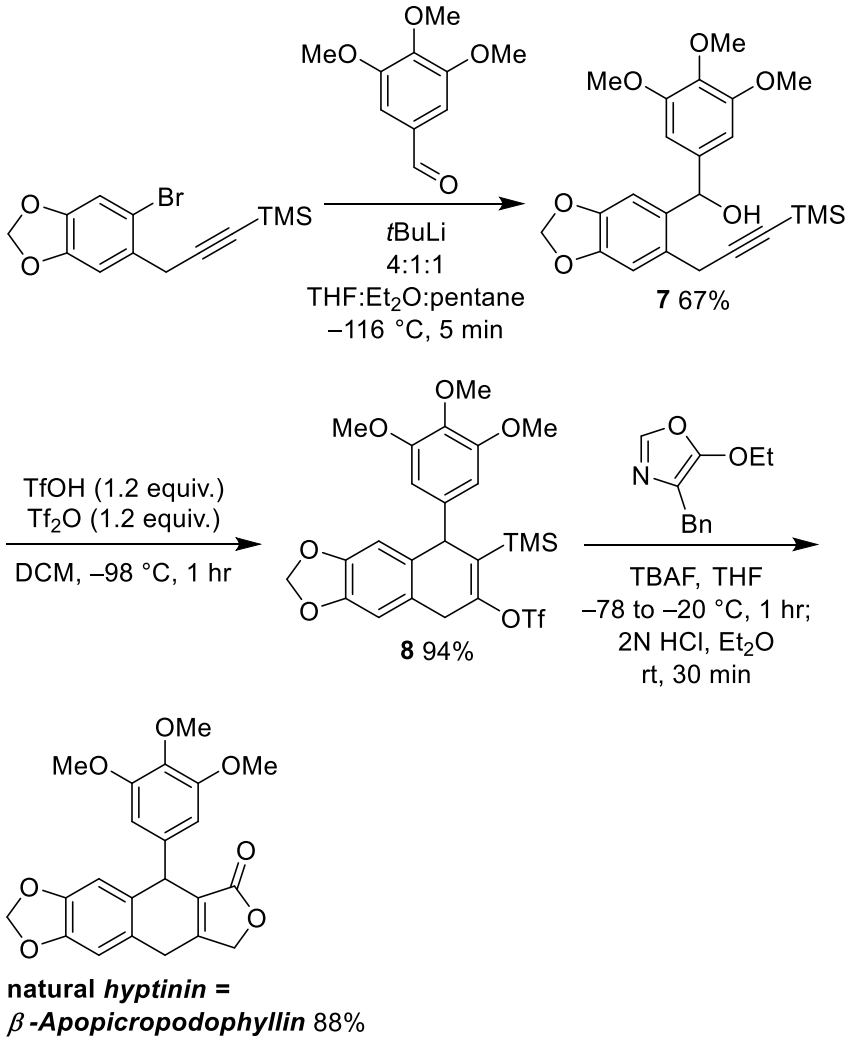
in moderate yield. Both 2-naphthyl (**6f**) and 3-thiophenyl (**6g**) substituted 1,4-dihydronaphthalene products were isolated in good yields.



Scheme 2.5.4 Synthesis of 1,4-dihydronaphthalene derivatives

Formation of the 1,4-dihydronaphthalene skeleton allows for access to a variety of aryltetralin lactones. To demonstrate the utility of this reaction, we report a concise synthesis of the cytotoxic lignin hyptinin, which has recently been structurally reassigned to match the compound *β*-Apopicropodophyllin (Scheme 2.5.5).[50] Isolated from the Jamaican plant *Hyptis verticillata*, natural hyptinin (*β*-Apopicropodophyllin) has shown inhibitory effects on S1T, an adult T-cell leukemia cell line.[51] Beginning from known aryl bromide,[52] addition to 3,4,5-trimethoxybenzaldehyde quickly produced alkynol **7** necessary for cyclization. Employment of the methodology efficiently provided β-silylvinyl triflate **8** in excellent yield. Cyclohexyne formation

induced by tetrabutylammonium fluoride and subsequent trapping by known oxazole in a Diels–Alder/retro Diels–Alder sequence and subsequent treatment with aqueous HCl provided the synthetic target β-Apopicropodophyllin in a rapid manner.[53]



Scheme 2.5.5 Total synthesis of β-Apopicropodophyllin

Conclusion

We have developed an efficient method for the synthesis of numerous cyclic β-silylvinyl triflates through triflate ion trapping of intermediate vinyl cations. The method is high yielding and can be used to access both cyclohexenyl and 1,4-dihydronaphthyl based substrates bearing

both aryl and vinyl substituents. In addition, this method can be employed in the rapid total synthesis of aryl tetralin lactones, exemplified by the natural product β-Apopicropodophyllin.

Experimental

General Information

All reactions were performed under Ar atmosphere with dry solvents in flame-dried round-bottom flasks containing stir bars. Toluene, methylene chloride, triethylamine, and 1,2-dichloroethane were distilled afresh from CaH_2 , methanol was distilled afresh from Mg(0); tetrahydrofuran, and diethyl ether were distilled from Na with benzophenone indicator. All reagents except for the alkyl halides were purchased from commercial sources and used without further purification.

TLC: Thin layer chromatography (TLC) was performed on 0.25-mm Silicycle Glass-Backed Extra-Hard-Layer, 60-Å silica gel plates (TLG-R10011B-323) and visualized under UV light, permanganate staining, or anisaldehyde staining.

Chromatography: Flash column chromatography was performed using Silicycle SiliaFlash® P60 (230–400 mesh, R12030B) and compressed air.

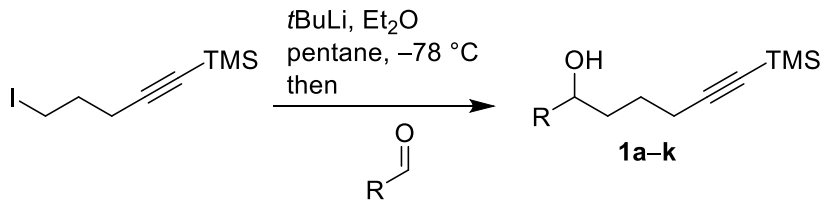
M.P.: Melting points (m.p.) were recorded using an Electrothermal capillary melting point apparatus; they are uncorrected.

IR Spectroscopy: IR spectra were recorded using Thermo Nicolet Avatar 370 FT-IR spectrometer or a JASCO FT/IR-4100 spectrometer with an ATR-PRO 450-S accessory.

NMR Spectroscopy: NMR spectra were recorded using Bruker ARX-400, Avance-300, and Avance-500 instruments calibrated to $CH(D)Cl_3$ as an internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C NMR spectra, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ, ppm). The following abbreviations are used to denote the multiplicities: s = singlet; d = doublet; dd = doublet of doublets; dt = doublet of triplets; ddd = doublet of doublet of doublets; ddq = doublet of doublet of quartets; dqd = doublet of quartet of

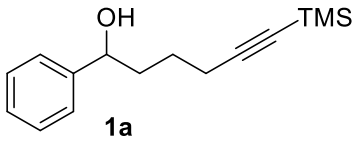
doublets; t = triplet; td = triplet of doublets; tt = triplet of triplets; q = quartet; qd = quartet of doublets; m = multiplet; p = pentet; pd = pentet of doublets.

Mass Spectrometry: Mass spectra were recorded using a Waters LCT Premier XE Time-of-Flight Instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the Multi Mode Ionization source. The lock mass standard for accurate mass determination was Leucine Enkephalin (Sigma L9133).

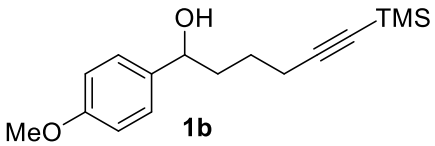


Synthesis of Alkynols 1a–k

Following the modified procedure developed by Inaba,[49] *t*BuLi (1.2 mL, 1.7 M solution in pentane, 2.05 mmol, 2.05 equiv.) was added dropwise to 5-iodo-1-(trimethylsilyl)pent-1-yne (0.266 g, 1 mmol, 1 equiv.) in a solution of pentane (6 mL) and ether (4 mL) at –78 °C. After 1 hr, an ether solution (2 ml) of aldehyde (1.25 equiv.) was added dropwise and the mixture was allowed to slowly warm to rt over 1 hr. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with H_2O (5 mL) and brine (5 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (0–10% EtOAc/hexanes) to give **1a**–**k**.

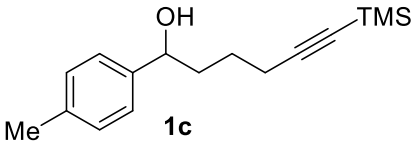


1-Phenyl-6-(trimethylsilyl)hex-5-yn-1-ol 1a. Colorless oil, (0.224 g, 94%); The spectral data matches those reported in the literature.[49]



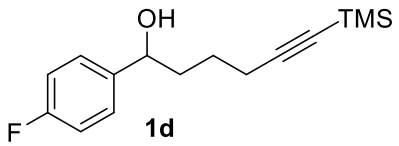
1b

1-(4-Methoxyphenyl)-6-(trimethylsilyl)hex-5-yn-1-ol 1b. Colorless oil, (0.146 g, 53%); IR (ν, cm^{-1}) 3363, 2953, 2172, 1611, 1511, 1245, 1174, 1035, 834, 758, 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.66 (td, *J* = 6.7 Hz, *J* = 3.1 Hz, 1H), 3.80 (s, 3H), 2.25 (td, *J* = 7.1 Hz, *J* = 2.0 Hz, 2H), 1.93–1.77 (m, 2H), 1.74 (s, 1H), 1.67–1.58 (m, 1H), 1.53–1.45 (m, 1H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 159.1, 136.7, 127.2, 113.9, 107.1, 84.8, 73.7, 55.3, 37.9, 24.9, 19.9, 0.2; HRMS (ESI) cacld for $C_{16}H_{23}OSi$ $[M – OH]^+$ *m/z* 259.1513, found 259.1533.



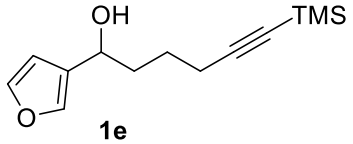
1c

1-(*p*-Tolyl)-6-(trimethylsilyl)hex-5-yn-1-ol 1c. Colorless oil, (0.089 g, 34% yield); IR (ν, cm^{-1}) 3355, 2953, 2173, 1437, 1248, 1028, 837, 758, 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 4.67 (td, *J* = 6.6 Hz, *J* = 3.3 Hz, 1H), 2.34 (s, 3H), 2.25 (td, *J* =7.1 Hz, *J* = 2.1 Hz, 2H), 1.92–1.78 (m, 2H), 1.77 (s, 1H), 1.68–1.59 (m, 1H), 1.53–1.46 (m, 1H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 141.6, 137.3, 129.2, 125.9, 107.1, 84.8, 73.9, 37.9, 24.8, 21.1, 19.7, 0.2; HRMS (ESI) cacld for $C_{16}H_{23}Si$ $[M – OH]^+$ *m/z* 243.1564, found 243.1515.



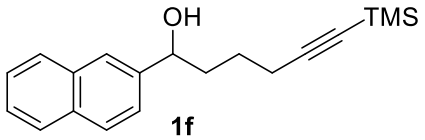
1d

1-(4-Fluorophenyl)-6-(trimethylsilyl)hex-5-yn-1-ol 1d. Colorless oil, (0.171 g, 65% yield); IR (ν, cm^{-1}) 3357, 2955, 2174, 1605, 1509, 1249, 1223, 1027, 834, 759. 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.33–7.30 (m, 2H), 7.05–7.01 (m, 2H), 4.72–4.69 (m, 1H), 2.25 (td, *J* = 7.0 Hz, *J* = 2.1 Hz, 2H), 1.91–1.77 (m, 3H), 1.67–1.57 (m, 1H), 1.54 (s, 1H), 1.52–1.46 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.2 (d, *J* = 243.7 Hz), 140.3, 127.5 (d, *J* = 8.0 Hz), 115.3 (d, *J* = 21.3 Hz), 106.9, 85.0, 73.4, 38.1, 24.7, 19.6, 0.1; HRMS (ESI) cacld for $C_{15}H_{21}FNaOSi$ $[M + Na]^+$ *m/z* 287.1243, found 287.1367.



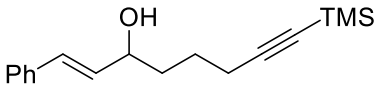
1e

1-(Furan-3-yl)-6-(trimethylsilyl)hex-5-yn-1-ol 1e. Colorless oil, (0.236 g, 100% yield); IR (ν, cm^{-1}) 3341, 2955, 2172, 1503, 1249, 1161, 1021, 837, 758, 600; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.39–7.38 (m, 2H), 6.41–6.40 (m, 1H), 4.71–4.68 (m, 1H), 2.27 (td, *J* = 7.0 Hz, *J* = 1.9 Hz, 2H), 1.91–1.80 (m, 2H), 1.69–1.61 (m, 1H), 1.68 (s, 1H), 1.58–1.52 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 143.4, 139.1, 129.0, 108.4, 107.0, 85.0, 66.5, 36.7, 24.6, 19.6, 0.1; HRMS (ESI) cacld for $C_{13}H_{19}OSi$ $[M – OH]^+$ *m/z* 219.1200, found 219.1137.



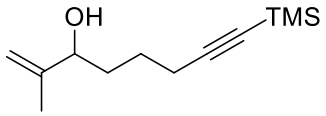
1f

1-(Naphthalen-2-yl)-6-(trimethylsilyl)hex-5-yn-1-ol 1f. Colorless solid, (0.264 g, 89% yield); m.p. 54 °C; IR (ν, cm^{-1}) 3342, 2951, 2830, 2172, 1409, 1249, 1024, 840, 757, 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.85–7.82 (m, 3H), 7.50–7.45 (m, 3H), 4.91–4.88 (m, 1H), 2.27 (td, *J* = 7.0 Hz, *J* = 1.8 Hz, 2H), 2.04–1.90 (m, 2H), 1.94 (s, 1H), 1.72–1.63 (m, 1H), 1.60–1.51 (m, 1H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 141.9, 133.3, 133.0, 128.4, 128.0, 127.8, 126.2, 125.9, 124.6, 124.0, 107.0, 85.0, 74.2, 37.9, 24.7, 19.7, 0.2; HRMS (ESI) cacld for $C_{19}H_{23}Si$ [M – OH]$^{+}$ *m/z* 279.1564, found 279.1538.



1g

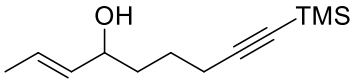
(*E*)-1-Phenyl-8-(trimethylsilyl)oct-1-en-7-yn-3-ol 1g. Colorless oil, (0.256 g, 94% yield); IR (ν, cm^{-1}) 3422, 2958, 2173, 1449, 1373, 1246, 1044, 839, 694; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38 (t, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.26–7.23 (m, 1H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* = 15.9 Hz, *J* = 6.8 Hz, 1H), 4.33–4.32 (m, 1H), 2.28 (t, *J* = 6.9 Hz, 2H), 1.77–1.58 (m, 4H), 1.56 (s, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 136.6, 134.0, 128.6, 127.7, 127.0, 126.5, 107.1, 84.9, 72.6, 36.3, 24.5, 19.8, 0.2; HRMS (ESI) cacld for $C_{17}H_{23}Si$ [M – OH]$^{+}$ *m/z* 255.1564, found 255.1552.



1h

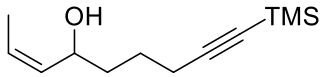
2-Methyl-8-(trimethylsilyl)oct-1-en-7-yn-3-ol 1h. Colorless oil, (0.122 g, 58% yield); IR (ν, cm^{-1}) 3362, 2954, 2174, 1450, 1249, 1043, 900, 837, 759, 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.95 (br s, 1H), 4.85 (br s, 1H), 4.09 (t, *J* = 6.0 Hz, 1H), 2.26 (td, *J* = 6.9 Hz, *J* = 2.4 Hz, 2H), 1.73

(s, 3H), 1.71–1.57 (m, 3H), 1.53–1.48 (m, 1H), 1.50 (s, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 147.4, 111.2, 107.2, 84.9, 75.4, 33.8, 24.5, 19.7, 17.5, 0.1; HRMS (ESI) cacld for $C_{12}H_{21}Si$ $[M – OH]^+$ *m/z* 193.1407, found 193.1375.



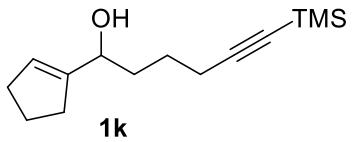
1i

(*E*)-9-(Trimethylsilyl)non-2-en-8-yn-4-ol 1i. Colorless oil, (0.177 g, 84% yield); IR (ν, cm^{-1}) 3342, 2957, 2173, 1450, 1249, 1054, 965, 837, 758, 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.68 (dqd, *J* = 15.3 Hz, *J* = 5.4 Hz, *J* = 0.8 Hz, 1H), 5.48 (ddq, *J* = 15.2 Hz, *J* = 7.1 Hz, *J* = 1.5 Hz, 1H), 4.06 (q, *J* = 5.3 Hz, 1H), 2.25 (t, *J* = 6.5 Hz, 2H), 1.70 (dd, *J* = 6.5 Hz, *J* = 1.1 Hz, 3H), 1.64–1.52 (m, 4H), 1.41 (br s, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 134.1, 127.1, 107.2, 84.7, 72.7, 36.3, 24.6, 19.8, 17.7, 0.2; HRMS (ESI) cacld for $C_{12}H_{21}Si$ $[M – OH]^+$ *m/z* 193.1407, found 193.1384.

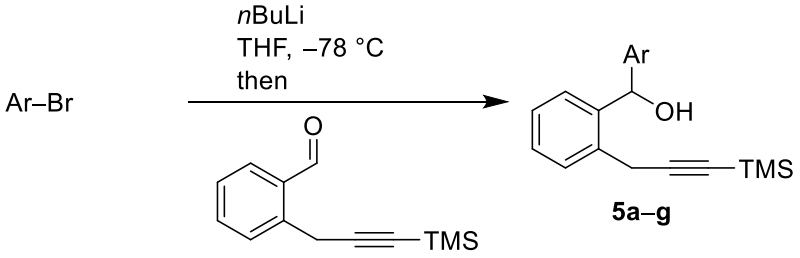


1j

(*Z*)-9-(Trimethylsilyl)non-2-en-8-yn-4-ol 1j. Colorless oil, (0.112 g, 53%);); IR (ν, cm^{-1}) 3355, 2956, 2173, 1430, 1249, 990, 837, 758, 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.56–5.55 (m, 1H), 5.42–5.38 (m, 1H), 4.52–4.48 (m, 1H), 2.29–2.25 (m, 2H), 1.73–1.65 (m, 1H), 1.68 (dd, *J* = 7.0 Hz, *J* = 1.6 Hz, 3H), 1.62–1.53 (m, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 133.3, 126.5, 107.2, 84.8, 66.9, 36.4, 24.4, 19.7, 13.3, 0.1; HRMS (ESI) cacld for $C_{12}H_{21}Si$ $[M – OH]^+$ *m/z* 193.1407, found 193.1443.

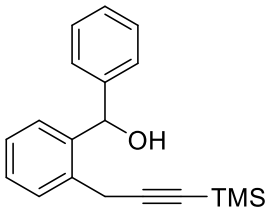


1-(Cyclopent-1-en-1-yl)-6-(trimethylsilyl)hex-5-yn-1-ol 1k. Colorless oil, (0.050 g, 21% yield); IR (ν, cm^{-1}) 3357, 2953, 2848, 2173, 1373, 1248, 1045, 838, 759, 638; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.60 (br s, 1H), 4.29 (t, *J* = 5.9 Hz, 1H), 2.35–2.30 (m, 2H), 2.26 (t, *J* = 6.7 Hz, 2H), 1.89 (m, 2H), 1.74–1.48 (m, 6H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 146.9, 125.7, 107.2, 84.8, 70.9, 34.4, 32.2, 31.0, 24.5, 23.3, 19.7, 0.2; HRMS (ESI) cacld for $C_{14}H_{23}Si$ $[M - OH]^+$ *m/z* 219.1564, found 219.1540.



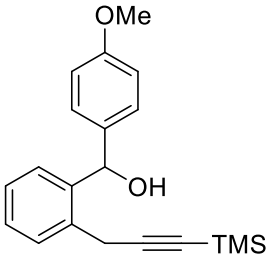
Synthesis of Alkynols 5a–g

To a solution of aryl halide (1.1 equiv.) in THF (5 mL) was added *n*-BuLi (0.67 mL, 1.6 M solution in hexane, 1.1 mmol, 1.1 equiv.) dropwise at –78 °C and stirred for 1 hr. A solution of 2-(3-(trimethylsilyl)prop-2-yn-1-yl)benzaldehyde (0.216 g, 1 mmol, 1 equiv.) in THF (10 mL) was added dropwise and the mixture was let slowly warm to rt. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with EtOAc (30 mL) and the organic layer was extracted with H_2O (5 mL) and brine (5 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (0–10% EtOAc/hexanes) to give **5a-g**.



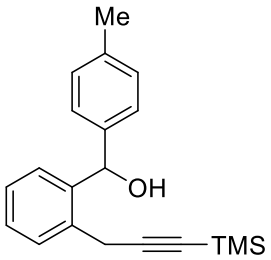
5a

Phenyl(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)methanol 5a. Colorless solid, (0.292 g, 99% yield); m.p. 48–50 °C; IR (ν, cm^{-1}) 3342, 2957, 2174, 1603, 1451, 1249, 1015, 838, 757, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.47–7.42 (m, 2H), 7.35–7.26 (m, 7H), 6.13 (d, *J* = 4.0 Hz, 1H), 3.62 (d, *J* = 18.9 Hz, 1H), 3.55 (d, *J* = 18.8 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.5, 141.1, 134.0, 129.2, 128.5, 128.1, 127.6, 127.4, 127.3, 126.9, 104.2, 87.7, 72.8, 24.0, 0.03; HRMS (ESI) cacld for $C_{19}H_{21}Si$ $[M – OH]^+$ *m/z* 277.1407, found 277.1349.



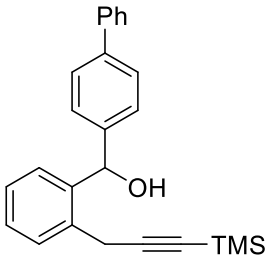
5b

(4-Methoxyphenyl)(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)methanol 5b. Colorless oil, (0.195 g, 60% yield); IR (ν, cm^{-1}) 3342, 2957, 2174, 1609, 1509, 1303, 1247, 1017, 837, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.52–7.45 (m, 2H), 7.31–7.27 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.06 (s, 1H), 3.79 (s, 3H), 3.60 (d, *J* = 18.9 Hz, 1H), 3.48 (d, *J* = 18.9 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 159.1, 141.2, 134.6, 133.7, 129.0, 128.3, 127.9, 127.1, 126.9, 113.9, 104.1, 87.7, 72.4, 55.2, 23.9, 0.06; HRMS (ESI) cacld for $C_{20}H_{23}OSi$ $[M – OH]^+$ *m/z* 307.1513, found 307.1550.



5c

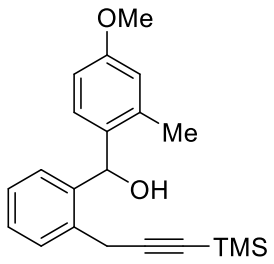
***p*-Tolyl(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)methanol 5c.** Colorless oil, (0.170 g, 55% yield); IR (ν, cm^{-1}) 3340, 2958, 2174, 1453, 1249, 1015, 838, 756, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.46–7.27 (m, 4H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.08 (d, *J* = 2.9 Hz, 1H), 3.62 (d, *J* = 18.8 Hz, 1H), 3.51 (d, *J* = 18.9 Hz, 1H), 2.33 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 141.2, 139.5, 137.3, 133.8, 129.2, 129.0, 127.9, 127.2, 127.1, 126.9, 104.2, 87.7, 72.7, 23.9, 21.2, 0.07; HRMS (ESI) cacld for $C_{20}H_{23}Si$ $[M – OH]^+$ *m/z* 291.1564, found 291.1588.



5d

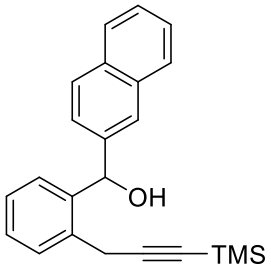
[1,1'-Biphenyl]-4-yl(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)methanol 5d. Colorless oil, (0.234 g, 55% yield); IR (ν, cm^{-1}) 3355, 3030, 2956, 2175, 1602, 1487, 1250, 1017, 840, 758, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.59–7.55 (m, 4H), 7.49–7.48 (m, 2H), 7.45–7.40 (m, 4H), 7.36–7.34 (m, 1H), 7.33–7.30 (m, 2H), 6.17 (br s, 1H), 3.66 (d, *J* = 18.9 Hz, 1H), 3.59 (d, *J* = 18.8 Hz, 1H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 141.5, 141.1, 140.8, 134.0, 129.2,

128.8, 128.1, 127.4 (2C), 127.3 (3C), 127.1 (2C), 104.2, 87.8, 72.6, 24.1, 0.05; HRMS (ESI) cacld for $C_{25}H_{25}Si$ $[M – OH]^+$ *m/z* 353.1720, found 353.1678.



5e

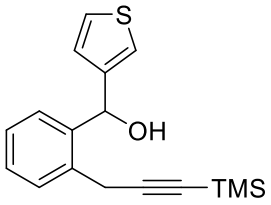
(4-Methoxy-2-methylphenyl)(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)methanol 5e. Pale yellow oil, (0.088 g, 26% yield); IR (ν, cm^{-1}) 3311, 2958, 2174, 1607, 1499, 1248, 1014, 838, 756, 640; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.44–7.42 (m, 1H), 7.35–7.31 (m, 2H), 7.30–7.23 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.22 (d, *J* = 3.6 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 18.6 Hz, 1H), 3.50 (d, *J* = 18.7 Hz, 1H), 2.26 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 159.0, 140.8, 137.5, 134.0, 132.7, 129.1, 127.9, 127.8, 127.2, 126.9, 116.3, 110.9, 104.2, 87.6, 69.3, 55.2, 23.9, 19.3, 0.02; HRMS (ESI) cacld for $C_{21}H_{25}OSi$ $[M – OH]^+$ *m/z* 321.1669, found 321.1661.



5f

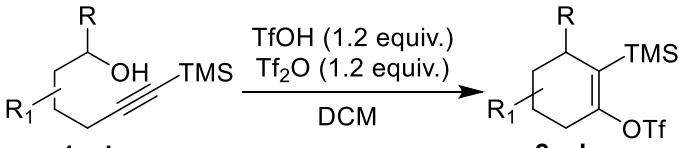
Naphthalen-2-yl(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)methanol 5f. Colorless oil, (0.227 g, 55% yield); IR (ν, cm^{-1}) 3312, 3059, 2957, 2175, 1603, 1453, 1249, 1018, 839, 754, 476; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.88 (br s, 1H), 7.84–7.81 (m, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.50–7.47 (m, 3H), 7.46–7.43 (m, 1H), 7.38–7.36 (m, 1H), 7.35–7.27 (m, 2H), 6.30 (d, *J* = 3.6 Hz,

1H), 3.68 (d, J = 18.8 Hz, 1H), 3.61 (d, J = 18.8 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 141.0, 140.0, 134.2, 133.2, 132.9, 129.3, 128.3, 128.2, 128.1, 127.8, 127.7, 127.4, 126.2, 126.0, 125.4, 125.1, 104.3, 87.8, 72.9, 24.1, 0.03; HRMS (ESI) cacld for $C_{23}H_{23}Si$ [M – OH]$^+$ *m/z* 327.1564, found 327.1544.



5g

Thiophen-3-yl(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)methanol 5g. Colorless oil, (0.246 g, 82% yield); IR (ν, cm^{-1}) 3342, 2957, 2174, 1604, 1439, 1249, 1015, 967, 839, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.55–7.53 (m, 1H), 7.47–7.45 (m, 1H), 7.34–7.31 (m 2H), 6.87 (d, J = 3.75 Hz, 1H), 6.56 (dd, J = 3.7 Hz, J = 0.6 Hz, 1H), 6.22 (d, J = 4.2 Hz, 1H), 3.63 (d, J = 18.8 Hz, 1H), 3.58 (d, J = 18.8 Hz, 1H), 2.52 (d, J = 4.2 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 148.4, 139.9, 133.8, 129.5, 129.4, 128.7, 127.5, 126.8, 125.5, 112.5, 103.7, 87.9, 69.2, 23.9, –0.05; HRMS (ESI) cacld for $C_{17}H_{19}SSi$ [M – OH]$^+$ *m/z* 283.0971, found 283.1006.

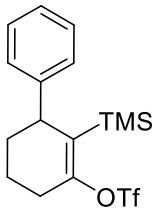


1a–k or 5a–g → **2a–k or 6a–g**

Synthesis of Cyclic Silyl Triflates 2a–k and 6a–g

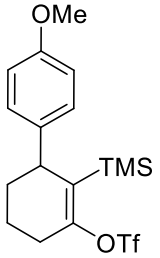
To a solution of alkynol (0.1 mmol, 1 equiv.) in DCM (1 mL) at –78 °C (–98 °C for benzhydrols) was added dropwise 0.5 mL of a 0.24 M solution of TfOH (11 μL, 0.12 mmol, 1.2 equiv.) and Tf_2O (20 μL, 0.12 mmol, 1.2 equiv.) and was slowly warmed to –20 °C over 3 hr. Saturated

aqueous $NaHCO_3$ (2 mL) was slowly added with vigorous stirring. The aqueous layer was extracted with DCM (3 x 2 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (0–10% EtOAc/hexanes) to give **2a–k** and **6a–g**.



2a

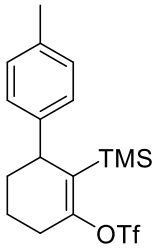
3-Phenyl-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2a. Colorless oil, (37 mg, 97% yield); IR (ν, cm^{-1}) 2958, 1410, 1210, 1143, 897, 839, 701; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.29 (m, 2H), 7.24–7.20 (m, 1H), 7.16–7.14 (m, 2H), 3.76–3.75 (m, 1H), 2.56–2.43 (m, 2H), 1.91–1.84 (m, 1H), 1.71–1.60 (m, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 157.2, 143.8, 129.6, 128.7, 128.3, 126.5, 118.4 (q, J = 319.8 Hz), 44.3, 31.1, 28.4, 18.3, –0.7; HRMS (ESI) cacld for $C_{16}H_{22}F_3O_3SSi$ $[M + H]^+$ *m/z* 379.1011, found 379.0923.



2b

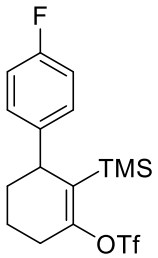
3-(4-Methoxyphenyl)-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2b. Colorless oil, (38 mg, 94% yield); IR (ν, cm^{-1}) 2952, 1686, 1611, 1512, 1246, 1035, 839, 640; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.06 (dd, J = 8.5 Hz, J = 1.6 Hz, 2H), 6.85 (dd, J = 8.6 Hz, J = 1.8 Hz, 2H), 3.79 (s, 3H), 3.71 (br s, 1H), 2.54–2.41 (m, 2H), 1.85–1.80 (m, 1H), 1.69–1.57 (m, 3H), 0.02 (s,

9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 158.3, 157.0, 135.7, 129.9, 129.7, 118.4 (q, *J* = 319.7 Hz), 113.6, 55.2, 43.4, 31.1, 18.2, –0.7; HRMS (ESI) cacld for $C_{17}H_{24}F_3O_4SSi$ $[M + H]^+$ *m/z* 409.1117, found 409.1254.



2c

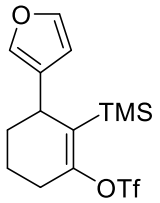
3-(4-Methylphenyl)-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2c. Colorless oil, (36 mg, 91% yield); IR (ν, cm^{-1}) 2943, 1646, 1512, 1411, 1245, 1208, 1144, 994, 898, 840, 630; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.12 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 3.72 (br s, 1H), 2.55–2.39 (m, 2H), 2.33 (s, 3H), 1.87–1.81 (m, 1H), 1.73–1.57 (m, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 157.1, 140.7, 136.1, 129.7, 129.0, 128.6, 118.4 (q, *J* = 319.8 Hz), 43.9, 31.1, 28.4, 21.0, 18.3, –0.7; HRMS (ESI) cacld for $C_{17}H_{24}F_3O_3SSi$ $[M + H]^+$ *m/z* 393.1168, found 393.1272.



2d

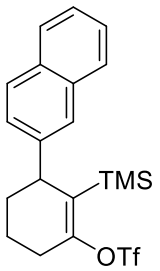
3-(4-Fluorophenyl)-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2d. Colorless oil, (34 mg, 85% yield); IR (ν, cm^{-1}) 2951, 1687, 1510, 1411, 1252, 1221, 898, 831, 653; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.12–7.09 (m, 2H), 7.03–6.98 (m, 2H), 3.75 (br s, 1H), 2.54–2.42 (m,

2H), 1.89–1.82 (m, 1H), 1.67–1.56 (m, 3H), 0.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.6 (d, *J* = 245.0 Hz), 157.2, 139.4, (d, *J* = 3.2 Hz), 130.1, (d, *J* = 9.8 Hz), 128.8, (d, *J* = 7.8 Hz), 118.4 (q, *J* = 319.8 Hz), 115.2 (d, *J* = 21.2 Hz), 43.5, 31.1, 28.3, 18.2, –0.7; HRMS (ESI) cacld for $C_{16}H_{21}F_4O_3SSi$ $[M + H]^+$ *m/z* 397.0917, found 397.2080.



2e

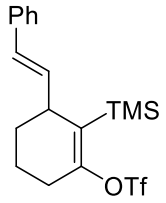
3-(3-Furanyl)-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2e. Colorless oil, (33 mg, 91% yield); IR (ν, cm^{-1}) 2951, 1649, 1410, 1243, 1207, 1144, 993, 897, 839, 624; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.37–7.36 (m, 1H), 7.09 (br s, 1H), 6.22 (br s, 1H), 3.60 (br s, 1H), 2.45–2.43 (m, 2H), 1.72–1.66 (m, 4H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 156.7, 143.8, 140.9, 129.5, 127.8, 118.3 (q, *J* = 319.9 Hz), 110.5, 34.9, 28.9, 28.0, 18.1, –0.8; HRMS (ESI) cacld for $C_{14}H_{19}F_3NaO_4SSi$ $[M + Na]^+$ *m/z* 391.0623, found 391.1747.



2f

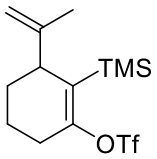
3-(2-Naphthyl)-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2f. Colorless oil, (41 mg, 96% yield); IR (ν, cm^{-1}) 2944, 1646, 1409, 1244, 1208, 1143, 993, 894, 839, 594; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.83–7.80 (m, 3H), 7.55 (s, 1H), 7.45 (pd, *J* = 1.7 Hz, *J* = 1.2 Hz, 2H), 7.32 (dd, *J* = 8.5 Hz, *J* = 1.5 Hz, 1H), 3.92 (s, 1H), 2.61–2.47 (m, 2H), 1.97–1.90 (m, 1H), 1.75–

1.63 (m, 3H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 157.4, 141.2, 133.2, 132.3, 129.6, 128.2, 127.8, 127.6, 127.5, 127.1, 126.2, 125.7, 118.4 (q, *J* = 319.8 Hz), 44.3, 30.7, 28.4, 18.2, –0.7; HRMS (ESI) cacld for $C_{20}H_{24}F_3O_3SSi$ $[M + H]^+$ *m/z* 429.1168, found 429.1820.



2g

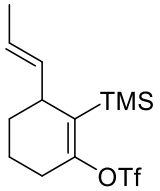
(*E*)-3-Styryl-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2g. Colorless oil, (37 mg, 91% yield); IR (ν, cm^{-1}) 2950, 1643, 1407, 1244, 1203, 1142, 1026, 893, 838, 748, 612; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.36–7.29 (m, 4H), 7.24–7.21 (m, 1H), 6.28 (d, *J* = 16.1 Hz, 1H), 6.20 (dd, *J* = 16.0 Hz, *J* = 6.6 Hz, 1H), 3.31 (br s, 1H), 2.45–2.42 (m, 2H), 1.83–1.61 (m, 4H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 156.6, 137.1, 132.7, 132.0, 129.3, 128.6, 127.4, 126.2, 118.3 (q, *J* = 319.8 Hz), 40.5, 28.3, 27.6, 18.3, –0.6; HRMS (ESI) cacld for $C_{18}H_{24}F_3O_3SSi$ $[M + H]^+$ *m/z* 405.1168, found 405.1302.



2h

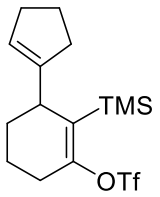
3-(2-Propenyl)-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2h. Colorless oil, (24 mg, 70% yield); IR (ν, cm^{-1}) 2933, 1412, 1246, 1209, 1145, 898, 838, 626; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.99 (s, 1H), 4.60 (s, 1H), 2.94 (d, *J* = 5.4 Hz, 1H), 2.38 (dd, *J* = 7.8 Hz, *J* = 4.7 Hz, 2H), 1.78 (s, 3H), 1.75–1.59 (m, 4H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)

156.6, 146.0, 129.5, 118.2 (q, J = 320.4 Hz), 114.9, 44.6, 31.6, 28.2, 22.7, 14.1, –0.9; HRMS (ESI) cacld for $C_{13}H_{22}F_3O_3SSi$ $[M + H]^+$ *m/z* 343.1011, found 343.1053.



2i

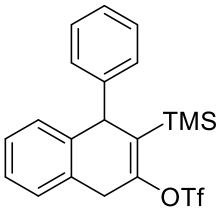
(*E*)-3-(1-Propenyl)-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2i. Colorless oil, (32 mg, 93% yield from **1i**, 29 mg, 84% field from **1j**); IR (ν, cm^{-1}) 2942, 1645, 1409, 1244, 1202, 1143, 987, 898, 838, 606; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.41 (ddq, J = 15.4 Hz, J = 6.5 Hz, J = 1.3 Hz, 1H), 5.34 (dqd, J = 15.4 Hz, J = 6.2 Hz, J = 0.8 Hz, 1H), 3.06 (br s, 1H), 2.39–2.36 (m, 2H), 1.80–1.71 (m, 1H), 1.71–1.63 (m, 1H), 1.68 (dt, J = 6.2 Hz, J = 1.1 Hz, 3H), 1.58–1.47 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 156.2, 133.0, 129.6, 128.0, 118.3, (q, J = 319.8 Hz), 40.1, 28.2, 27.6, 18.2, 17.9, –0.7; HRMS (ESI) cacld for $C_{13}H_{22}F_3O_3SSi$ $[M + H]^+$ *m/z* 343.1011, found 343.1306.



2k

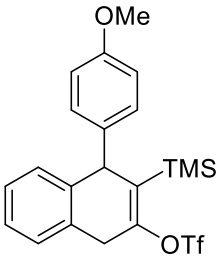
3-Cyclopentenyl-2-(trimethylsilyl)cyclohexenyl trifluoromethylsulfonate 2f. Colorless oil, (36 mg, 98% yield); IR (ν, cm^{-1}) 2944, 2847, 1651, 1409, 1245, 1202, 1143, 991, 890, 828, 763, 618; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.28 (br s, 1H), 3.06–3.05 (d, J = 3.7 Hz, 1H), 2.39–2.29 (m, 5H), 2.18–2.12 (m, 1H), 1.93–1.82 (m, 2H), 1.71–1.65 (m, 2H), 1.63–1.58 (m, 1H), 1.50–1.43 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 156.1, 145.5, 129.7,

129.0, 118.3 (q, J = 319.8), 39.6, 34.6, 32.6, 28.1, 25.0, 23.8, 18.4, –0.9; HRMS (ESI) cacld for $C_{30}H_{48}F_6O_6S_2Si_2$ $[2M + 2H]^+$ *m/z* 738.2335, found 733.3793.



6a

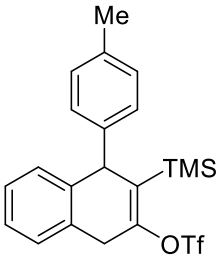
4-Phenyl-3-(trimethylsilyl)-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate 6a. Colorless oil, (24 mg, 55% yield); IR (ν, cm^{-1}) 2960, 1493, 1450, 1250, 841, 759, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.31–7.24 (m, 6H), 7.19–7.13 (m, 3H), 4.91 (dd, J = 3.1 Hz, J = 3.1 Hz, 1H), 4.12 (dd, J = 20.9 Hz, J = 3.7 Hz, 1H), 3.70 (dd, J = 20.9 Hz, J = 2.2 Hz, 1H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 153.2, 143.5, 136.9, 130.3, 129.9, 128.9, 128.1, 128.1, 128.0, 127.3, 127.1, 126.5, 118.4 (q, J = 319.8), 50.9, 32.8, –0.7; HRMS (ESI) cacld for $C_{20}H_{22}F_3O_3SSi$ $[M + H]^+$ *m/z* 427.1011, found 427.1259.



6b

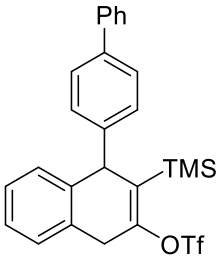
4-(4-Methoxyphenyl)-3-(trimethylsilyl)-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate 6b. Colorless oil, (33 mg, 72% yield); IR (ν, cm^{-1}) 2954, 1609, 1509, 1413, 1251, 1211, 1034, 888, 843, 619; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.29 (m, 1H), 7.22–7.18 (m, 1H), 7.19 (d, J = 8.7 Hz, 2H), 7.15–7.11 (m, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.84 (br s, 1H), 4.01 (dd, J = 20.9 Hz, J = 3.6 Hz, 1H), 3.75 (s, 3H), 3.66 (dd, J = 20.9 Hz, J = 1.9 Hz, 1H),

0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 158.6, 152.9, 137.2, 135.6, 130.2, 130.1, 129.0, 128.1, 128.0, 127.2, 126.3, 118.4 (q, *J* = 319.5 Hz), 114.2, 55.2, 50.4, 32.7, –0.7; HRMS (ESI) cacld for $C_{21}H_{24}F_3O_4SSi$ $[M + H]^+$ *m/z* 457.1117, found 457.0984.



6c

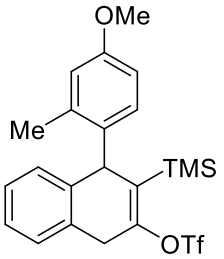
4-(*p*-Tolyl)-3-(trimethylsilyl)-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate 6c. Colorless oil, (27 mg, 62% yield); IR (ν, cm^{-1}) 2957, 1657, 1412, 1207, 1142, 1020, 887, 841, 619; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.24–7.22 (m, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.15–7.11 (m, 3H), 7.08 (d, *J* = 7.9 Hz, 2H), 4.87–4.86 (m, 1H), 4.10 (dd, *J* = 20.8 Hz, *J* = 3.7 Hz, 1H), 3.68 (dd, *J* = 20.8 Hz, *J* = 2.3 Hz, 1H), 2.27 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 153.0, 140.4, 137.2, 136.7, 130.3, 130.0, 129.5, 128.1, 128.0, 127.8, 127.3, 126.4, 118.4 (q, *J* = 319.8 Hz), 50.5, 32.8, 21.0, –0.7; HRMS (ESI) cacld for $C_{21}H_{24}F_3O_3SSi$ $[M – H]^-$ *m/z* 439.1016, found 439.1080.



6d

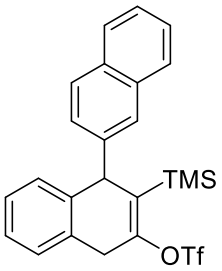
4-([1,1'-Biphenyl]-4-yl)-3-(trimethylsilyl)-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate 6d. Colorless oil, (40 mg, 79% yield); IR (ν, cm^{-1}) 2951, 1659,

1411, 1211, 1142, 1018, 839, 758, 620; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.56–7.52 (m, 4H), 7.43–7.36 (m, 4H), 7.33–7.29 (m, 3H), 7.18–7.15 (m, 2H), 4.96–4.95 (m, 1H), 4.15 (dd, *J* = 20.9 Hz, *J* = 3.7 Hz, 1H), 3.72 (dd, *J* = 20.9 Hz, *J* = 2.2 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 153.2, 142.4, 140.5, 140.0, 136.8, 130.4, 129.9, 128.7, 128.4, 128.2, 128.0, 127.8, 127.5, 127.3, 127.3, 126.9, 126.5, 118.4 (q, *J* = 319.8 Hz), 50.5, 32.8, –0.7; HRMS (ESI) cacld for $C_{26}H_{25}F_3O_3SSi$ $[M]^+$ *m/z* 502.1246, found 502.2708.



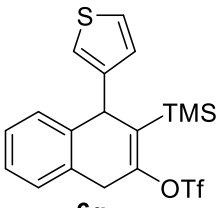
6e

4-(4-Methoxy-2-methylphenyl)-3-(trimethylsilyl)-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate 6e. Colorless oil, (24 mg, 52% yield); IR (ν, cm^{-1}) 2954, 1655, 1498, 1411, 1207, 1142, 1017, 885, 841, 621; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.25–7.09 (m, 5H), 6.68–6.65 (m, 2H), 5.16–5.15 (m, 1H), 4.09 (dd, *J* = 21.1 Hz, *J* = 4.4 Hz, 1H), 3.74 (s, 3H), 3.72 (dd, *J* = 21.1 Hz, *J* = 3.2 Hz, 1H), 2.51 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 158.2, 153.0, 137.2, 136.2, 133.9, 131.0, 130.2, 128.1 (2C), 127.6, 127.2, 126.4, 118.4 (q, *J* = 319.9 Hz), 116.6, 111.6, 55.1, 46.1, 32.6, 20.3, –0.5; HRMS (ESI) cacld for $C_{21}H_{25}OSi$ $[M – OTf]^+$ *m/z* 321.1669, found 321.1705.



6f

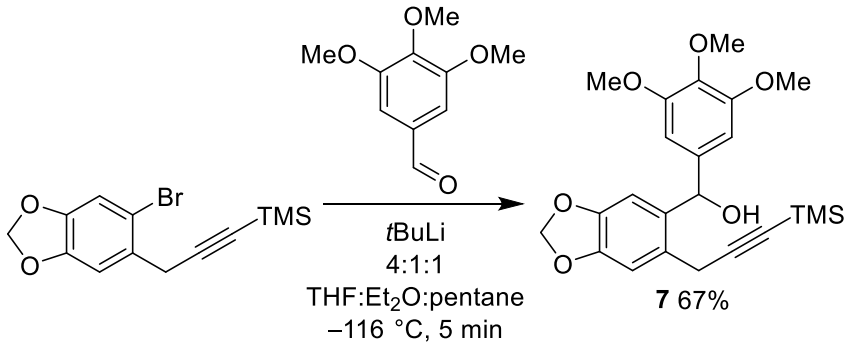
2-(Trimethylsilyl)-1,4-dihydro-[1,2'-binaphthalen]-3-yl trifluoromethanesulfonate 6f. Colorless oil, (42 mg, 89% yield); IR (ν, cm^{-1}) 3030, 2953, 1413, 1211, 1020, 842, 759; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.81–7.75 (m, 4H), 7.47–7.30 (m, 5H), 7.14–7.12 (m, 2H), 5.07 (dd, *J* = 3.0 Hz, *J* = 3.0 Hz, 1H), 4.17 (dd, *J* = 21.0 Hz, *J* = 3.7 Hz, 1H), 3.72 (dd, *J* = 21.0 Hz, *J* = 2.3 Hz, 1H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 153.3, 140.7, 136.7, 133.5, 132.5, 130.4, 129.9, 128.9, 128.2 (2C), 127.9, 127.6, 127.3, 126.5, 126.4, 126.2 (2C), 125.9, 118.5 (q, *J* = 319.7 Hz), 51.0, 32.9, –0.7; HRMS (ESI) cacld for $C_{24}H_{23}F_3NaO_3SSi$ $[M + Na]^+$ *m/z* 499.0987, found 499.2171.



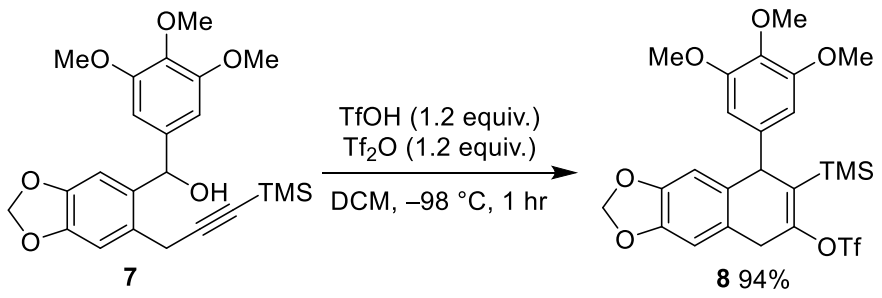
6g

4-(Thiophen-3-yl)-3-(trimethylsilyl)-1,4-dihydronaphthalen-2-yl trifluoromethanesulfonate 6g. Colorless oil, (37 mg, 85% yield); IR (ν, cm^{-1}) 2953, 1630, 1249, 965, 843, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.28–7.26 (m, 2H), 7.22–7.16 (m, 2H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 3.7 Hz, 1H), 6.57 (d, *J* = 3.7 Hz, 1H), 5.00 (s, 1H), 3.91 (d, *J* = 20.8 Hz, 1H), 3.61 (d, *J* = 20.8 Hz, 1H), 0.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 150.1, 141.8, 137.2, 134.0,

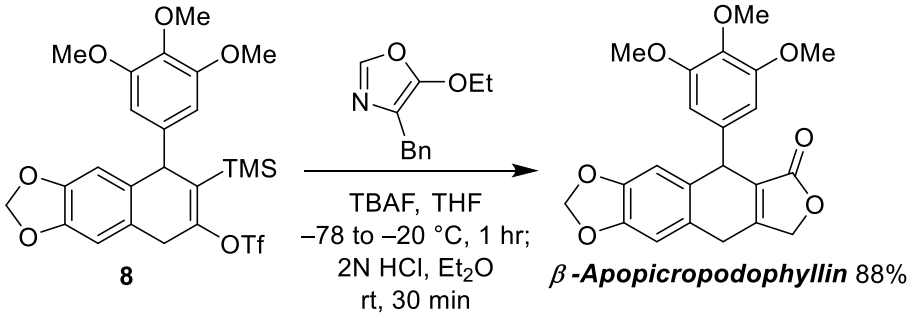
133.0, 129.6, 127.6 ,127.5, 127.0, 126.7, 123.9, 118.0 (q, J = 319.3 Hz), 110.6, 47.2, 39.8, –0.6; HRMS (ESI) cacld for $C_{18}H_{20}F_3O_3S_2Si$ $[M + H]^+$ *m/z* 433.0575, found 433.1433.



Synthesis of Alcohol 7. To a solution of (3-(6-bromobenzo[*d*][1,3]dioxol-5-yl)prop-1-yn-1-yl)trimethylsilane (1.79 g, 5.75 mmol, 1.15 equiv.) and 3,4,5-trimethoxybenzaldehyde (0.98 g, 5 mmol, 1 equiv.) in a 4:1:1 mixture of THF (33 mL), Et_2O (8 mL), and pentane (8 mL) at –116 °C was added *t*BuLi (4.1 mL, 1.7 M in pentane, 7 mmol, 1.4 equiv.) dropwise and stirred 5 min. The mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 x 50 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (25% EtOAc/hexanes) to give **7** (1.433 g, 3.3 mmol, 67% yield) as a colorless solid. IR (ν, cm^{-1}) 3357, 2942, 2834, 2174, 1592, 1483, 1417, 1231, 1124, 1033, 840, 730, 645; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.96 (s, 1H), 6.84 (s, 1H), 6.52 (s, 2H), 5.97–5.94 (m, 3H), 3.81 (s, 3H), 3.79 (s, 6H), 3.60 (d, J = 18.9 Hz, 1H), 3.49 (d, J = 18.9 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 153.2, 147.0, 146.6, 138.3, 137.2, 134.6, 127.7, 109.4, 107.9, 104.4, 103.7, 101.2, 87.6, 72.3, 60.8, 56.1, 23.7, 0.02; HRMS (ESI) cacld for $C_{23}H_{28}NaO_6Si$ $[M + Na]^+$ *m/z* 451.1553, found 451.1533.



Synthesis of Silyl Triflate 8. Following general procedure for the cyclization, the product was isolated as a colorless solid (1.055 g, 1.9 mmol, 94% yield); m.p. 55 °C, IR (ν, cm^{-1}) 2952, 1590, 1504, 1486, 1414, 1212, 1127, 1039, 937, 847, 635; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.69 (s, 1H), 6.55 (s, 1H), 6.49 (s, 2H), 5.93–5.89 (m, 1H), 5.87–5.84 (m, 1H), 4.67–4.66 (m, 1H), 3.97 (dd, *J* = 20.9 Hz, *J* = 3.8 Hz, 1H), 3.83 (s, 6H), 3.78 (s, 3H), 3.53 (dd, *J* = 20.9 Hz, *J* = 2.2 Hz, 1H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 153.4, 152.7, 147.0, 146.6, 138.9, 137.0, 130.2, 129.8, 123.0, 122.2, 118.4 (q, *J* = 319.7 Hz), 107.4, 107.3, 104.9, 101.1, 60.9, 56.2, 51.0, 46.2, –0.7; HRMS (ESI) cacld for $C_{24}H_{28}F_3O_8SSi$ $[M + Na]^+$ *m/z* 561.1226, found 561.1212.



Synthesis of *β*-Apopicropodophyllin. TBAF (12 μL, 1 M solution in THF, 0.012 mmol, 1.2 equiv.) was added to a mixture of silyl triflate **8** (5.6 mg, 0.01 mmol, 1 equiv.) and oxazole (20 mg, 0.1 mmol, 10 equiv.) in THF (0.5 mL) at –78 °C and let warm to –20 °C over 30 min. The mixture was diluted with Et_2O (1.5 mL) and 2N HCl (1.5 mL) was slowly added. Vigorous stirring

was continued for 1 hr at rt. The mixture was extracted with EtOAc (3 x 2 mL) and dried with Na_2SO_4. The solvent was evaporated and the residue purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give hyptinin (3.5 mg, 0.0088 mmol, 88% yield) as a colorless solid. The spectral data match those reported in the literature.[50b]

References

1. (a) Stang, P. J.; Rappoport, Z. V. I.; Hanack, M.; Subramanian, L. R., Introduction and Historical Background. In *Vinyl Cations*, Academic Press: 1979; p 1. (b) Nefedov, V. D.; Sinotova, E. N.; Lebedev, V. P. *Russ. Chem. Rev.* **1992**, *61*, 523.

2. Fittig, R.; Schrohe, A. *Chem. Ber.* **1875**, *8*, 367.

3. Jacobs, T. L.; Searles, S. *J. Am. Chem. Soc.* **1944**, *66*, 686.

4. Grob, C. A.; Cseh, G. *Helv. Chim. Acta* **1964**, *47*, 194.

5. Stang, P. J.; Rappoport, Z. V. I.; Hanack, M.; Subramanian, L. R., Thermodynamics and Theoretical Calculations. In *Vinyl Cations*, Academic Press: 1979; p 6.

6. (a) Lossing, F. P. *Can. J. Chem.* **1972**, *50*, 3973. (b) Lossing, F. P. *Can. J. Chem.* **1971**, *49*, 357. (c) Lossing, F. P.; Semeluk, G. P. *Can. J. Chem.* **1970**, *48*, 955. (d) Aue, D. H.; Davidson, W. R.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 6700. (e) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 289. (f) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 269.

7. (a) Hoffmann, R. *J. Chem. Phys.* **1964**, *40*, 2480. (b) Sustmann, R.; Williams, J. E.; Dewar, M. J. S.; Allen, L. C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1969**, *91*, 5350. (c) Hopkins, A. C.; Yates, K.; Csizmadia, I. G. *J. Chem. Phys.* **1971**, *55*, 3835. (d) Kollmar, H.; Smith, H. O. *Theor. Chim. Acta.* **1971**, *20*, 65. (e) Hariharan, P. C.; Lathan, W. A.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *14*, 385. (f) Lathan, W. A.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 808. (g) Zurawski, B.; Ahlirchs, R.; Kutzelnigg, W. *Chem. Phys. Lett.* **1973**, *21*, 309. (h) Weber, J.; Yoshimine, M.; McLean, A. D. *J. Chem. Phys.* **1976**, *64*, 4159. (i) Weber, J.; McLean, A. D. *J. Am. Chem. Soc.* **1976**, *98*, 875.

8. Apeloig, Y.; Schleyer, P. v. R.; Pople, J. A. *J. Org. Chem.* **1977**, *42*, 3004.

9. (a) Hehre, W. J.; Ditchfield, R.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4796. (b) Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1975.

10. Radom, L.; Hariharan, P. C.; Pople, J. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 6531.

11. Vasilyev, A. V. *Russ. Chem. Rev.* **2013**, *82*, 187.

12. Stang, P. J.; Rappoport, Z. V. I.; Hanack, M.; Subramanian, L. R., Bond Heterolysis. In *Vinyl Cations*, Academic Press: 1979; p 206.

13. (a) Brockway, L. O.; Beach, J. Y.; Pauling, L. *J. Am. Chem. Soc.* **1935**, *57*, 2693. (b) Hugill, J. A. C.; Coop, I. E.; Sutton, L. E. *Trans. Faraday Soc.* **1938**, *34*, 1518.

14. Stang, P. J.; Rappoport, Z. V. I.; Hanack, M.; Subramanian, L. R., Arylvinyl Cations Via Solvolysis. In *Vinyl Cations*, Academic Press: 1979; p 290.

15. Rappoport, Z. *Acc. Chem. Res.* **1976**, *9*, 265.

16. (a) Subramanian, L. R.; Hanack, M. *Chem. Ber.* **1972**, *105*, 1465. (b) Summerville, R. H.; Schleyer, P. V. R. *J. Am. Chem. Soc.* **1974**, *96*, 1110. (c) Hanack, M. *Acc. Chem. Res.* **1976**, *9*, 364. (d) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107.

17. (a) McNeely, S. A.; Kropp, P. J. *J. Am. Chem. Soc.* **1976**, *98*, 4319. (b) Kropp, P. J.; McNeely, S. A.; Davis, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 6907.

18. Lossing, F. P.; Holmes, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 6917.

19. (a) Cacace, F. *Adv. Chem. Sci.* **1981**, *97*, 33. (b) Speranza, M. *Gazz. Chim. Ital.* **1983**, *113*, 37.

20. Fornarini, S.; Speranza, M. *Tetrahedron Lett.* **1984**, *25*, 869.

21. Gustavson, G.; Demjanoff, N. *J. Prakt. Chem.* **1888**, *38*, 201.

22. Stang, P. J.; Rappoport, Z. V. I.; Hanack, M.; Subramanian, L. R., Electrophilic Additions to Allenes and Participation of the Allenyl Bond in Solvolysis. In *Vinyl Cations*, Academic Press: 1979; p 152.

23. (a) Griesbaum, K. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 697. (b) Griesbaum, K. *J. Am. Chem. Soc.* **1964**, *86*, 2301. (c) Griesbaum, K.; Naegele, W.; Wanless, G. G. *J. Am. Chem. Soc.* **1965**, *87*, 3151. (d) Griesbaum, K. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 933.

24. Stang, P. J.; Rappoport, Z. V. I.; Hanack, M.; Subramanian, L. R., Electrophilic Additions to Alkynes and Participation of the Triple Bond in Solvolysis. In *Vinyl Cations*, Academic Press: 1979; p 24.

25. Olah, G. A.; Klumpp, D. A., *Superelectrophiles and Their Chemistry*. Wiley: New York, 2008.

26. Koch, E. W.; Siehl, H. U.; Hanack, M. *Tetrahedron Lett.* **1985**, *26*, 1493.

27. (a) Siehl, H. U.; Kaufmann, F. P. *J. Am. Chem. Soc.* **1992**, *114*, 4937. (b) Siehl, H. U.; Kaufmann, F. P.; Hori, K. *J. Am. Chem. Soc.* **1992**, *114*, 9343. (c) Siehl, H. U.; Müller, T.; Gauss, J.; Buzek, P.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1994**, *116*, 6384.

28. (a) Vasilyev, A. V.; Walspurger, S.; Pale, P.; Sommer, J.; Haouas, M.; Rudenko, A. P. *Zh. Org. Khim.* **2004**, *40*, 1819. (b) Vasilyev, A. V.; Walspurger, S.; Haouas, M.; Sommer, J.; Pale, P.; Rudenko, A. P. *Org. Biomol. Chem.* **2004**, *2*, 3483.

29. (a) Walspurger, S.; Vasilyev, A. V.; Sommer, J.; Pale, P.; Savechenkov, P. Y.; Rudenko, A. P. *Zh. Org. Khim.* **2005**, *41*, 1516. (b) Aristov, S. A.; Vasilyev, A. V.; Fukin, G. K.; Rudenko, A. P. *Zh. Org. Khim.* **2007**, *43*, 696. (c) Vasilyev, A. V.; Aristov, S. A.; Fukin, G. K.; Kozhanov, K. A.; Bubnov, M. P.; Cherksasov, V. K. *Zh. Org. Khim.* **2008**, *44*, 802.

30. Stang, P. J.; Summerville, R. *J. Am. Chem. Soc.* **1969**, *91*, 4600.

31. (a) Savechenkov, P. Y.; Rudneko, A. P.; Vasilyev, A. V. *Zh. Org. Khim.* **2004**, *40*, 1106. (b) Rudenko, A. P.; Savechenkov, P. Y.; Vasilyev, A. V. *Zh. Org. Khim.* **2004**, *40*, 1424. (c) Savechenkov, P. Y.; Rudenko, A. P.; Vasilyev, A. V.; Fukin, G. K. *Zh. Org. Khim.* **2005**, *41*, 1341. (d) Shchukin, A. O.; Vasilyev, A. V.; Aristov, S. A.; Fukin, G. K.; Rudenko, A. P. *Zh. Org. Khim.* **2008**, *44*, 977. (e) Shchukin, A. O.; Vasilyev, A. V.; Rudenko, A. P. *Tetrahedron Lett.* **2008**, *64*, 6334. (f) Shchukin, A. O.; Vasilyev, A. V. *Appl. Catal. A* **2008**, *336*, 140.

32. Vasilyev, A. V.; Walspurger, S.; Pale, P.; Sommer, J. *Tetrahedron Lett.* **2004**, *45*, 3379.

33. Otani, T.; Kunimatsu, S.; Takahashi, T.; Nihei, H.; Saito, T. *Tetrahedron Lett.* **2009**, *50*, 3853.

34. Klumpp, D. A.; Rendy; Zhang, Y.; McElrea, A.; Gomez, A.; Dang, H. *J. Org. Chem.* **2004**, *69*, 8108.

35. Jin, T.; Uchiyama, J.; Himuro, M.; Yamamoto, Y. *Tetrahedron Lett.* **2011**, *52*, 2069.

36. Zhang, L.; Sun, J.; Kozmin, S. A. *Tetrahedron* **2006**, *62*, 11371.

37. Sun, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13512.

38. Alonso, P.; Pardo, P.; Fananas, F. J.; Rodriguez, F. *Chem. Commun.* **2014**, *50*, 14364.

39. Alonso, P.; Pardo, P.; Galván, A.; Fañanás, F. J.; Rodríguez, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 15506.

40. (a) Heaney, H. *Chem. Rev.* **1962**, *62*, 81. (b) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427. (c) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (d) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 502. (e) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550.

41. (a) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (b) Suzuki, N. *J. Synth. Org. Chem Jpn.* **2007**, *65*, 347. (c) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**,

48, 6974. (d) Gampe, C. M.; Carreira, E. M. *Chem. - Eur. J.* **2012**, *18*, 15761. (e) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766. (f) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2962. (g) Gampe, C. M.; Boulos, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4092. (h) Yoshida, S.; Karaki, F.; Uchida, K.; Hosoya, T. *Chem. Commun.* **2015**, *51*, 8745.

42. (a) Scardiglia, F.; Roberts, J. D. *Tetrahedron* **1957**, *1*, 343. (b) Wittig, G.; Pohlke, R. *Chem. Ber.* **1961**, *94*, 3276. (c) Montgomery, L. K.; Scardiglia, F.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 1917.

43. Willey, F. G. *Angew. Chem. Int. Ed.* **1964**, *94*, 3276.

44. Al-Omari, M.; Banert, K.; Hagedorn, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 309.

45. Atanes, N.; Escudero, S.; Perez, D.; Guitian, E.; Castedo, L. *Tetrahedron Lett.* **1998**, *39*, 3039.

46. Fujita, M.; Sakanishi, Y.; Kim, W. H.; Okuyama, T. *Chem. Lett.* **2002**, 908.

47. (a) Devlin, A. S.; Bois, J. D. *Chem. Sci.* **2013**, *4*, 1059. (b) Barber, J. S.; Styduhar, E. D.; Pham, H. V.; McMahon, T. C.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 2512.

48. Hioki, Y.; Okano, K.; Mori, A. *Chem. Commun.* **2017**, *53*, 2614.

49. Inaba, K.; Takaya, J.; Iwasawa, N. *Chem. Lett.* **2007**, *36*, 474

50. (a) Kuhnt, M.; Rimpler, H.; Heinrich, M. *Phytochemistry* **1994**, *36*, 485. (b) Maeda, K.; Hamada, T.; Onitsuka, S.; Okamura, H. *J. Nat. Prod.* **2017**, *80*, 1446.

51. Hamada, T.; White, Y.; Nakashima, M.; Oiso, Y.; Fujita, M. J.; Okamura, H.; Iwagawa, T.; Arima, N. *Molecules* **2012**, *17*, 9931.

52. Masters, K.-S.; Wallesch, M.; Bräse, S. *J. Org. Chem.* **2011**, *76*, 9060.

53. Boukouvalas, J.; Thibault, C. *J. Org. Chem.* **2015**, *80*, 681.