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The Studies of the Phosphine-Initiated General Base-Catalyzed Double-Michael Reaction and the Nitro-Nazarov Reaction

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Publication Date

2014

UNIVERSITY OF CALIFORNIA

Los Angeles

The Studies of the Phosphine-Initiated General Base-Catalyzed Double-Michael

Reaction and the Nitro-Nazarov Reaction

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Philosophy

in Chemistry

by

Judy Szeto

2014

ABSTRACT OF THE DISSERTATION

The Studies of the Phosphine-Initiated General

Base-Catalyzed Double-Michael Reaction and the Nitro-Nazarov Reaction

by

Judy Szeto

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2014

Professor Ohyun Kwon, Chair

General base-catalyzed double-Michael reactions of allenes with various dinucleophiles are described. The reactions are facilitated most efficiently by a catalytic amount of trimethylphosphine, affording six different types of benzannulated five-membered heterocycles: benzimidazolines, benzoxazolines, benzothiazolines, 1,3-benzodioxoles, 1,3-benzoxathioles, and 1,3-benzodithioles. This atom-economical reaction is operationally simple and provides the product heterocycles in good to excellent yields. Careful mechanistic studies unveiled the phosphine-triggered general base catalysis pathway. Furthermore, the double-Michael reaction can serve as an alternative method for the selective mono-ketalization of β-diketones.

We have employed a novel acid-mediated nitro-Nazarov reaction of conjugated nitrodienes to synthesize a variety of five-membered cyclic nitronates via a proposed nitro-allyl cation intermediate. An array of nitronates with varying alkyl and aryl substituents was isolated

in good to excellent yields. To verify the existence of the nitro-allyl cation intermediate, we synthesized nitrodienes tethered to an aromatic ring in hopes of trapping the cationic nitro-Nazarov reaction intermediate by electrophilic aromatic substitution. We were pleased that tetracyclic nitronates were constructed through an interrupted nitro-Nazarov cyclization reaction, which generated two new rings and an all carbon quaternary center. A five-membered cyclic nitronate was then subjected to a [3+2] dipolar cycloaddition with acrylates to obtain highly functionalized nitroso acetals. Reduction conditions were also performed on the cyclic nitronate to obtain a dihydroisoxazole and a four-membered cyclic nitrone.

Progress toward synthesizing α-aryl vinylboronic acids was fruitless. Transmetalation with trimethyl borate and aryl vinylaluminum intermediates did not transpire as hoped. The substrates that were successful based on thin layer chromatography (TLC) proved difficult to purify due to boronic acids being highly soluble in water. As of now, the condition in synthesizing and purifying α-aryl vinylboronic acids is still pending.

The dissertation of Judy Szeto is approved.

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2014

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ACKNOWLEDGMENTS

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Szeto, J.; Sriramurthy, V.; Kwon, O. *Org. Lett.* **2011**, *13*, 5420–5423

Manuscript in Preparation

Nitro-Nazarov Reaction
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Chapter 1

Phosphine-Initiated General Base-Catalyzed Double-Michael Reaction of Allenes

1.1 Introduction: Michael Addition

The Michael addition was first discovered by Arthur Michael in 1887 based on the work of Conrad and Kuthzeit in 1884. Conrad and Kuthzeit reacted ethyl 2,3-dibromopropionate with diethyl sodiomalonate forming a cyclopropane derivative (Scheme 1.1.1).[1] Michael replaced the propionate with ethyl 2-bromoacrylate and obtained the same cyclopropane product by malonate adding into the double bond of the acrylate (Scheme 1.1.1).
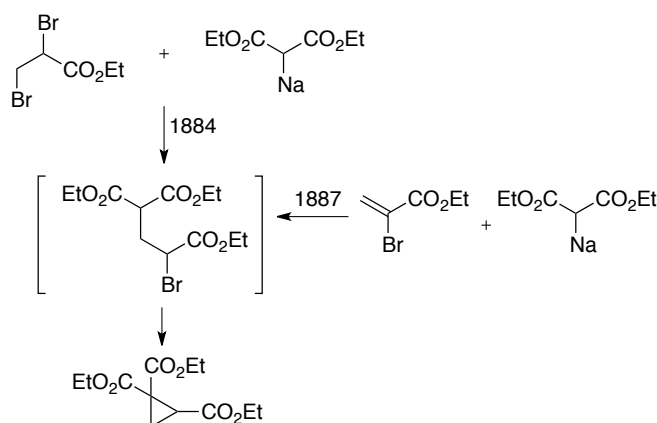
Scheme 1.1.1 The discovery of the Michael addition based on the work of Conrad and Kuthzeit

He then confirmed this observation by reacting diethyl malonate and ethyl cinnamate to obtain the first Michael adduct (Scheme 1.1.2).[2] Since the discovery, the Michael addition has become one of the most useful methods to form C–C bonds by the addition of an enolate of a ketone or aldehyde (Michael donor) to an α,β-unsaturated carbonyl compound (Michael acceptor). Currently, Michael donors are pronucleophiles that contain an electron-withdrawing group(s) to make the α-methylene protons more acidic for deprotonation by base. For example, malonates, β-cyanoesters, and β-ketoesters are some of the most commonly employed Michael donors used in organic synthesis.[3]
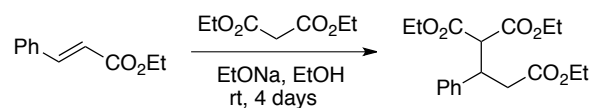
Scheme 1.1.2 The first Michael adduct

1.2 Phosphine-Initiated Michael Addition

One of the oldest tertiary phosphine-catalyzed reactions with pronucleophiles and activated olefins is the Michael addition. The first Michael addition with phosphine was demonstrated by White and Baizer in 1973.[4] 2-Nitropropane was added into ethyl acrylate, acrylonitrile, and methyl vinyl ketone in the presence of tertiary phosphine [e.g. tributylphosphine (PBu$_3$), triphenylphosphine (PPh$_3$), dimethylphenylphosphine (PPhMe$_2$), and methyldiphenylphosphine (PPh$_2$Me)] to obtain a Michael product. White and Baizer believed that the phosphine behaves as a nucleophile rather than as a base. In Scheme 1.2.1, tertiary phosphine was added into the activated alkene to provide a phosphonium enolate to serve as a base to deprotonate 2-nitropropane. The anion then attacked another activated alkene to form the Michael adduct.
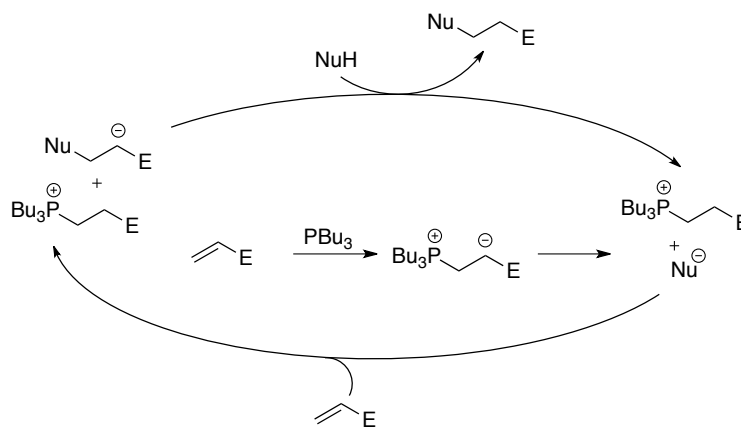
Scheme 1.2.1 The first Michael addition with phosphine

In 1993, Inanaga and co-workers were the first to report phosphine-catalyzed Michael addition between alcohols and methyl propiolate to form *E*-olefins (Scheme 1.2.2).[5] Alcohol

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substrates that were successful in the Michael addition in the presence of PBu_3 were primary, secondary allylic, benzylic, and homoallylic alcohols. Secondary and tertiary alcohols were not efficient nucleophiles. It seems that the acidity of the nucleophiles was important along with the steric hindrance of the alcohols for the efficiency of the Michael addition. Inanaga's Michael addition proceeded through a different mechanism than the one presented in Scheme 1.2.1. Similarly, the phosphine was added into the alkynoate and the intermediate zwitterion deprotonated the alcohol. However, instead of having the alkoxy anion add into another alkynoate, the anion added in a Michael fashion into the same phosphonium salt and the phosphine was eliminated to give the Michael adduct.

$$\text{CO}_2\text{Me} + \text{ROH} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{PBu}_3} \text{RO}\diagdown\text{CO}_2\text{Me}$$

R = primary, secondary allylic
benzylic, homoallylic
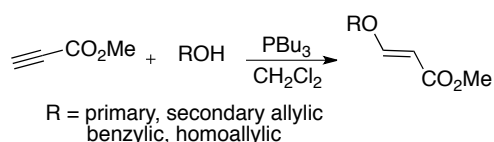
Scheme 1.2.2 Inanaga's phosphine-catalyzed Michael addition

Furthermore, Toste and Bergman demonstrated a conjugate addition of alcohols to α,β-unsaturated esters, enones, and acrylonitrile using 5 mol% trimethylphosphine (PMe_3) to provide the hydroalkoxylation product (Scheme 1.2.3).[6] The phosphonium enolate acted as a base to deprotonate the alcohol, and the alkoxide anion added into another α,β-unsaturated carbonyl. Interestingly, they were able to have water add into ethyl 2-methyl acrylate to give the hydration Michael adduct.

$$\underset{R^1}{\overset{\text{EWG}}{\diagup\!\!\!\diagdown}} \xrightarrow[R^2\text{OH}]{\text{PMe}_3 \ (5 \ \text{mol\%})} \underset{R^1}{\overset{\text{EWG}}{\diagdown\!\!\diagdown\text{OR}^2}}$$

EWG = COR, CO_2R, CN
R^1 = H, Me
R^2 = H, Me, Bn, *i*-Pr, Ph
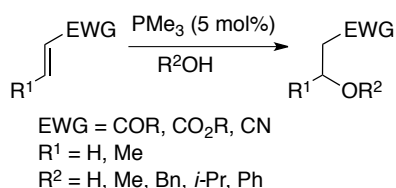
Scheme 1.2.3 Toste and Bergman's phosphine-catalyzed Michael addition

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Yavari and co-workers revealed that under phosphine-catalysis conditions the oxygen and the carbon of phenol derivatives can add into *tert*-butyl propiolate and provide a mixture of Michael adduct and the α-umpolung addition product (Scheme 1.2.4).[7] Phenol derivatives, such as 1-napthol, 2-napthol, or 3-hydroxybenzaldehyde provide an equal mixture of 2-arylacrylates and *tert*-butyl 3-aryloxypropenoates. After the phenol is deprotonated by the phosphonium enoate, the anion can resonate between the oxygen and the ortho carbon, thus causing an O- and C- addition to the propiolate and β-phosphonium enoate, respectively. However, when phenol, 3-hydroxy-4-methoxybenzaldehyde, 8-hydroxquinoline, and 7-hydroxycoumarin were employed to the same reaction condition only *tert*-butyl 3-aryloxypropenoates were observed, the O-addition to the propiolate.
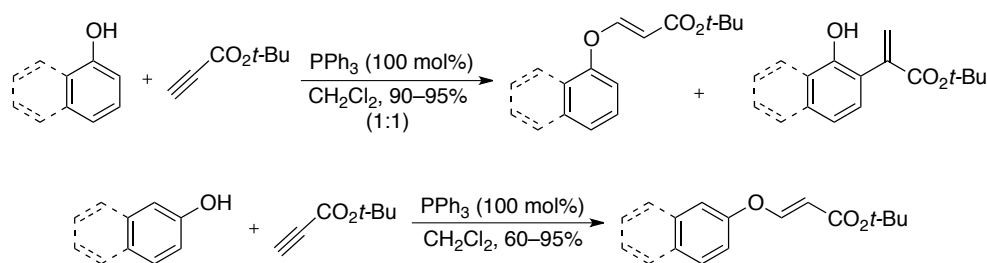
Scheme 1.2.4 Examples of Yavari's O- and C-addition to propiolate

Xia and co-workers reported a phosphine-catalyzed aza-Michael reaction. In the presence of 10 mol% of PPh$_3$ and trimethylsilyl chloride (TMSCl), the direct addition of carbamates to α,β-unsaturated ketones were observed in high yields (Scheme 1.2.5).[8] The role of the TMSCl is not completely understood, however it is believed that the silane is acting as a Lewis acid to activate the carbonyl group. Chalcones with electron-poor substituents were not efficient Michael acceptors for this reaction.

R¹, R² = alkyl, aryl   R³ = Et, Bn
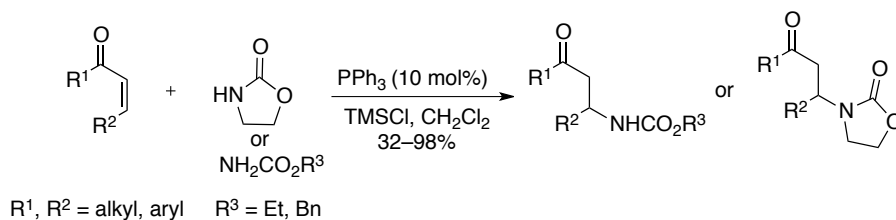
Scheme 1.2.5 Xia's phosphine-catalyzed aza-Michael reaction

Huang and co-workers demonstrated the first phosphine-catalyzed β-addition reaction of allenoates with hydrazones (Scheme 1.2.6).[9] Studies show that a less nucleophilic phosphine catalyst, tris(4-chlorophenyl)phosphine ((4-ClC₆H₄)₃P) caused the addition of the hydrazone to the β-carbon of the allenoate to provide the β,γ-unsaturated Michael adduct as the major product. When changing to a more nucleophilic phosphine, PBu₃, the α,β-unsaturated Michael adduct was the major product. The isomerization of the β,γ-double bond to the α,β-double bond is due to the basicity of the phosphonium dienolate (PBu₃ adding into allenoate), which can deprotonate the α-proton of the β,γ-unsaturated ester Michael adduct and then isomerize to the α,β-unsaturated ester Michael adduct.

R¹ = aryl   R² = Me, Et, Bn
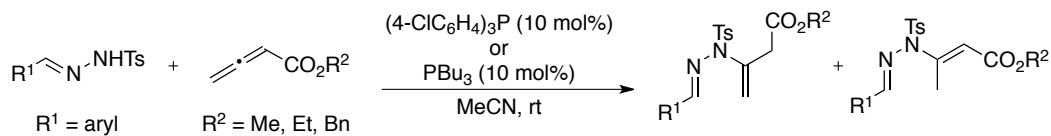
Scheme 1.2.6 Example of Huang's aza-Michael reaction

1.3 Double-Michael Addition into Acetylenes in the Presence of Phosphine

The double-Michael reaction is a powerful tool for synthesizing complex molecules from simple acyclic compounds. Electron-deficient acetylenes are used in double-Michel reactions in the presence of phosphine, however examples in the literature are limited. Grossman and co-workers have devoted their time to study the double-Michael addition of carbon pronucleophiles (Scheme 1.3.1).[10] Grossman synthesized tethered diesters with a variety of electron-withdrawing

groups (e.g. cyano, ester, nitro) to react in the double-Michael reaction. For example, in the presence of PPh$_3$, the double-Michael adduct was afforded in 46% yield with a 4:1 diastereomeric ratio. Due to Grossman's studies, he concluded that only one cyano group in the tethered diesters is necessary for the double-Michael reaction to proceed and the double-Michael adduct always has at least one axial cyano group.
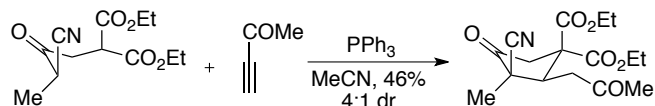
Scheme 1.3.1 An example of Grossman's double-Michael reaction

Endo and co-workers demonstrated a thia-double-Michael addition by reacting propane disulfide and methyl propiolate to obtain dithiane under PBu$_3$ (Scheme 1.3.2).[11] Endo performed kinetic studies and saw that the rate of the first attack of the thiol to propiolate is faster than that of the second attack. The second attack of thiol was found to be slower by 1.0×10^3 times in comparison with the first attack.
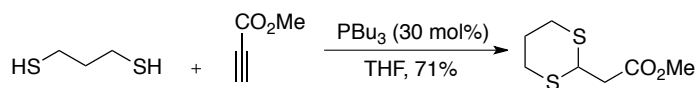
Scheme 1.3.2 An example of a thia-double-Michael

Yavari showed an example of a phosphine-mediated double-Michael reaction of catechol with methyl propiolate (Scheme 1.3.3).[12] This is the only example of an oxa-double-Michael reaction under phosphine with a low yield of the double-Michael product.
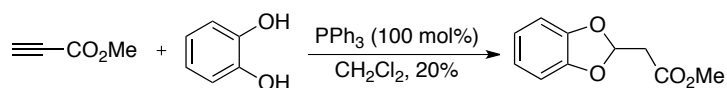
Scheme 1.3.3 Yavari's oxa-double-Michael reaction

Kwon and Sriramurthy were the first to demonstrate a phosphine-catalyzed mixed double-Michael reaction by reacting γ-amino malonates, β-amino alcohols, and β-amino thiols

with acetylenes and a bisphosphine (Scheme 1.3.4).[13] 1,3-Bis(diphenylphosphino)propane (DPPP) was important to facilitate the reaction by providing anchimeric assistance in stabilizing the reaction intermediate to provide highly functionalized pyrrolidines, oxazolidines, and thiazolidines in excellent yields and diastereoselectivities.

X = O, S, CH(CO$_2$Me)$_2$
E = COMe, CO$_2$Me, Ts
R = i-Pr, Bn, Ph
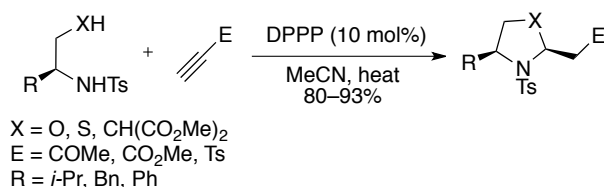
Scheme 1.3.4 Example of phosphine-catalyzed mixed double-Michael reaction

Furthermore, Kwon also reported that using the same phosphine, DPPP, aromatic dinucleophiles could be applied in the double-Michael reaction with acetylenes to provide bicyclic heterocycles, such as dihydropyrrolopyridine, indoline, benzimidazoline, dihydrobenzo-1,4-oxazine, dihydrobenzo-3,1-oxazine, tetrahydroquinoline, and tetrahydroisoquinoline (Scheme 1.3.5).[14] Some of the reactions required acetic acid (AcOH) and sodium acetate (NaOAc) as additives to facilitate the reactions.

n = 0, 1
X = C(O$_2$R)$_2$, NTs, CH$_2$O, CH$_2$(CO$_2$R)$_2$, OC(CO$_2$R)$_2$
E = COMe, COPh, CO$_2$Me
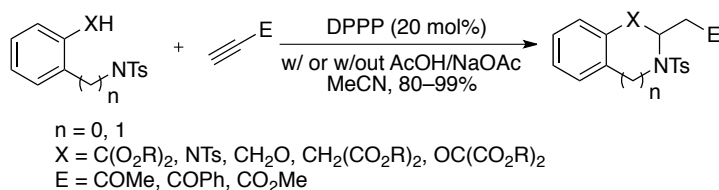
Scheme 1.3.5 Example of phosphine-catalyzed double-Michael using aromatic dinucleophiles

1.4 Double-Michael Addition into Allenes

Allenes have the same degree of unsaturation as acetylenes, however are more reactive Michael acceptors. Double-Michael reactions with allenes are scarce in the literature. To the best of our knowledge, there is no double-Michael onto allenes in the presence of phosphine reported in the literature. The first Michael reaction with allenes was described by Landor and

co-workers in 1979 (Scheme 1.4.1).[15] An addition of 1,2-diamine substrates to allenic nitriles gave imidazolines, benzimidazoles, or hexahydrobenzimidazoles. The isolable mono-Michael adducts, conjugated enaminic nitriles, were subjected to 300 °C for the cyclization and elimination of acetonitrile to obtain the imidazoline derivatives.
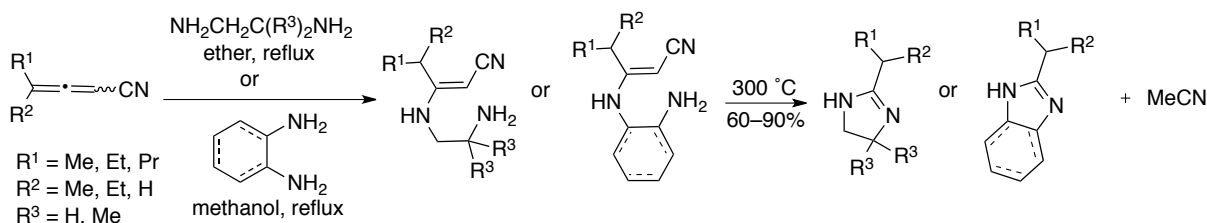
Scheme 1.4.1 The first Michael reaction with allenes

Years later, Landor reported using *ortho*-aminobenzyl alcohol as a dinucleophile for the Michael reaction to allenic nitriles. Again the cyclization and elimination of acetonitrile occurred at 300 °C to obtain benzoxazine derivatives (Scheme 1.4.2).[16] Excess amount of heating can lead to the formation of 3-cyanoquinoline by the dehydration of the enaminic nitrile to give the unstable triene. The triene undergoes electrocyclization follow by aromatization to give the quinoline species.
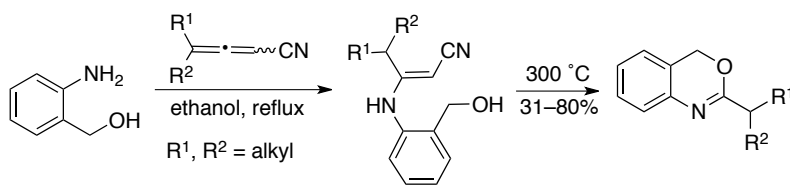
Scheme 1.4.2 Landor's double-Michael with allenic nitriles

Cabiddu and co-workers demonstrated that catechol, 2-mercaptophenol, and 1,2 benzenedithiol can react with α- or γ-substituted allenoates to afford 1,3-benzodioxoles, 1,3-benzoxathioles, and 1,3-benzodithioles, respectively, under potassium carbonate (Scheme 1.4.3).[17] However, the efficiency of the reaction was not excellent. Due to the isolation of mono-Michael adducts, only 4–68% yield of the double-Michael products were obtained.

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X = Y = O, S $R^1 = R^2 = R^3$ = alkyl
Z = H, Me
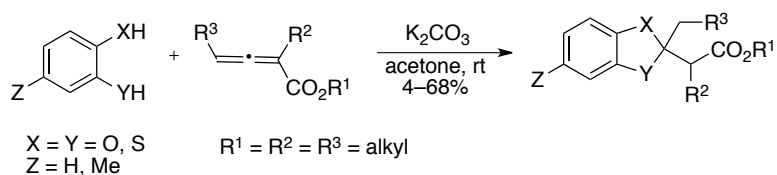
Scheme 1.4.3 Cabiddu's double-Michael reaction with 1,2-disubstituted benzenes

Since then, studies of double-Michael with allenes were not presented in literature until

2008. Ma presented a highly regio- and stereoselective double-Michael addition cyclization of

2,3-butadienoates (Scheme 1.4.4).[18] Michael addition of dialkyl zinc to enantiomerically pure

allenoate gave the optically active α-zincated 2-alkenoate, which undergoes another Michael

addition to another allenoate. The highly substituted cyclohexenone was formed by an

intramolecular 1,2-addition. Aryl groups with electron-donating and electron-withdrawing

groups both provided good yields of the cyclohexenone. The reaction proceeded at room

temperature when using diethylzinc or dibutylzinc. However, when dimethylzinc was employed

the product was obtained at 100 ˚C.

R = Me, Et, *n*-Bu
R^1, R^2 = Me, Et
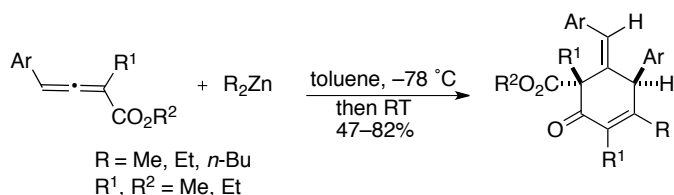
Scheme 1.4.4 Regio- and stereoselective double-Michael addition cyclization of 2,3-allenoates

Wang and co-workers described a highly enantioselective Michael-Michael sequence

when reacting aromatic alkynals with 2-(*E*)-(2-nitrovinyl) phenol in the presence of an amine

catalyst to obtain 4*H*-chromenes via a chiral iminium–allenamine intermediate (Scheme 1.4.5).[19]

The reaction created two C–C bonds, one new stereogenic center, and the incorporation of two

versatile functional groups, nitro and aldehyde, that can further be elaborated. Aromatic alkynals

that have electron-withdrawing or electron-donating substituents both proceeded with high

efficiency. This also holds true for having electron-donating or electron-withdrawing groups on the nitro phenol.
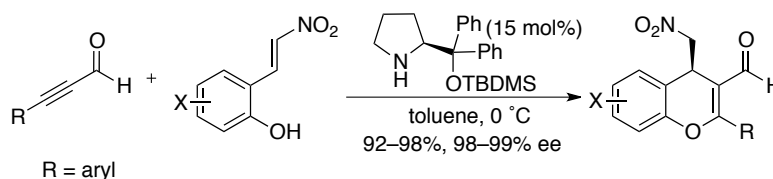
Scheme 1.4.5 Highly enantioselective Michael–Michael reaction

Lastly, Fan and co-workers demonstrated a one-pot double-Michael addition/intramolecular aldol reaction/decarboxylation of 1,2-allenenic ketones with cyanoacetates to synthesize highly functionalized benzenes (Scheme 1.4.6).[20] The deprotonated cyanoacetate adds to the β-carbon of allenone, and the resulting α-anion adds to another allenone. The cyano benzene was obtained after tautomerization, intramolecular aldol, and decarboxylation of an ethyl carbonate. γ-Substituted allenones were not as efficient as terminal allenones for the synthesis of cyano benzene. These substituted cyano benzenes can be transformed in one step to biphenyl tetrazoles, which are important pharmacophores.[21]
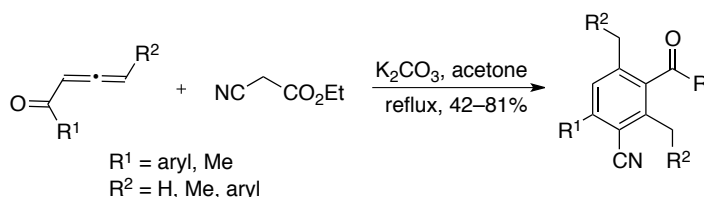
Scheme 1.4.6 Formation of highly substituted cyano benzenes

1.5 Phosphine-Catalyzed γ-Umpolung Addition

Activated allenes and 2-alkynoates are known to undergo γ-umpolung addition under phosphine-catalysis conditions (Scheme 1.5.1). For allenoates, the α,β-double bond is electron-deficient, while the β,γ-double bond is relatively electron-rich.[22] The reactivity of the β,γ-double

bond can be reversed in the presence of phosphine, making the γ-carbon behave as an electrophile.
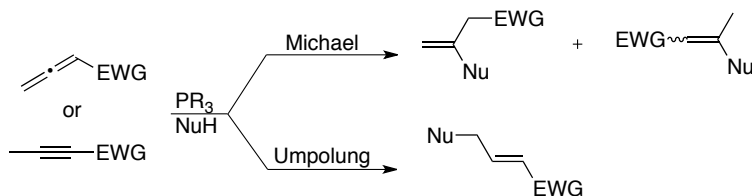
Scheme 1.5.1 Phosphine-catalyzed Michael addition and γ-umpolung addition

The phosphine-mediated γ-umpolung addition was first introduced by Cristau and co-workers through multi-step transformations.[23] First, the vinyl phosphonium ion is synthesized by stoichiometric amount of PPh$_3$ adding into 3,4-pentadien-2-one, followed by carbonyl protection and counter ion exchange (Scheme 1.5.2). Methanol was used as a nucleophile to verify the possibility of the γ-umpolung addition, providing the phosphonium ylide. The γ-umpolung product was obtained after a deprotection and elimination of phosphine.
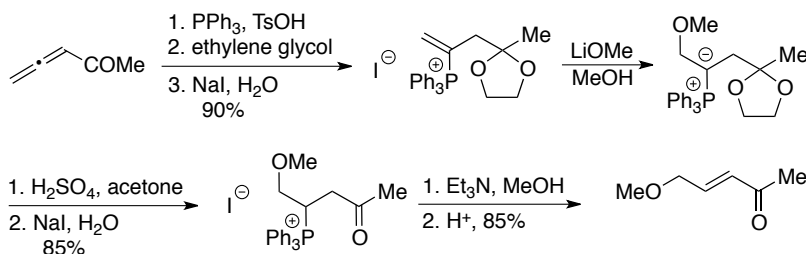
Scheme 1.5.2 Cristau's stepwise γ-umpolung addition

Twelve years later, Trost and co-workers demonstrated the first phosphine-catalyzed γ-umpolung addition of nucleophiles to 2-alkynoates. Trost investigated carbon, oxygen, and nitrogen pronucleophiles that could participate in the γ-umpolung reaction. Studies show that pronucleophiles with a pKa less than 16 were great nucleophiles for the reaction, such as malonate, benzyl alcohol, and amine (Scheme 1.5.3).[24] During his studies, Trost noticed that

alkyl phosphine appears to be too nucleophilic and led to oligomers. Lastly, a mixture of NaOAc/AcOH helped with the protonation-deprotonation at various stages of the reaction.
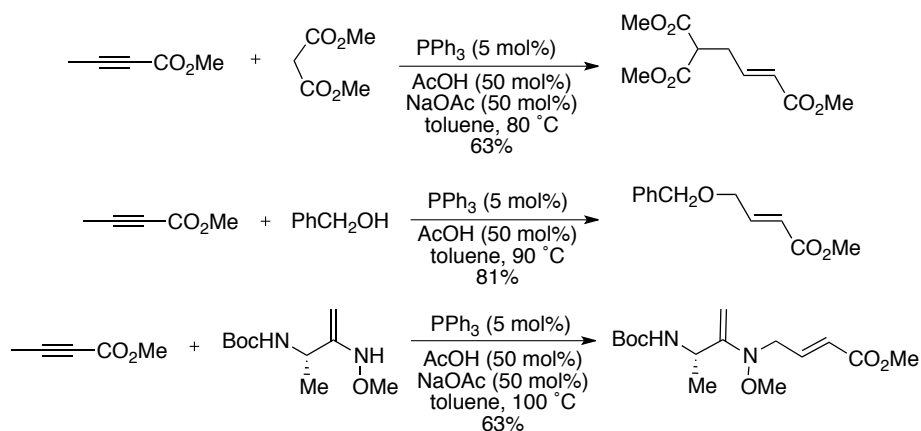
Scheme 1.5.3 Examples of Trost's γ-umpolung addition

The mechanism of the γ-umpolung reaction with acetylene begins with a β-addition of phosphine into propiolate to form a phosphonium enoate α-anion, which deprotonates the nucleophile (Scheme 1.5.4).[24a] The nucleophile adds into the vinylphosphonium to provide the phosphonium ylide. After proton transfer and elimination of phosphine the γ-umpolung product is obtained.
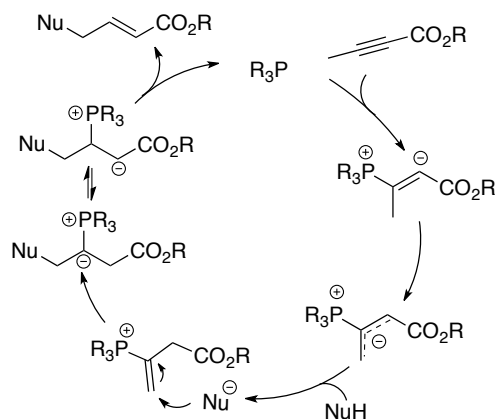
Scheme 1.5.4 Mechanism of γ-umpolung addition of acetylene

Similarly, Lu reported phosphine-catalyzed γ-umpolung addition on allenoates. Studies show that dimethyl malonate, 2,4-pentanedione, phenylsulfonyl acetonitrile, and methyl

acetoacetate were excellent pronucleophiles that gave the polarity-reversed addition products using methyl 2,3-butadienoate under 5 mol% PPh_3 (Scheme 1.5.5).[25] Allenoates with an α-substituent still gave the umpolung addition product, however under a more nucleophilic phosphine, PBu_3. Allenoates with γ-substituted alkyl groups failed to provide any product due to isomerization of the allene to diene.[26]
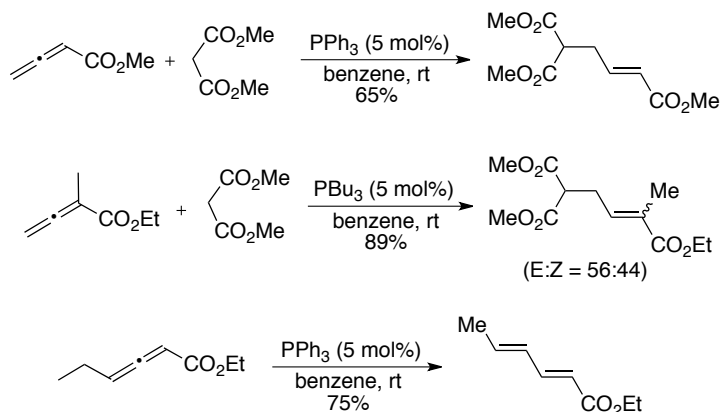
Scheme 1.5.5 Examples of Lu's γ-umpolung addition

The mechanism of the γ-umpolung reaction with allenoate begins similarly with β-addition of phosphine into allenoate to form phosphonium dienolate, which deprotonates the pronucleophile (Scheme 1.5.6).[25] The nucleophile anion adds into the vinylphosphonium to provide the phosphonium ylide. After the proton transfer and elimination of phosphine the γ-umpolung product is obtained.
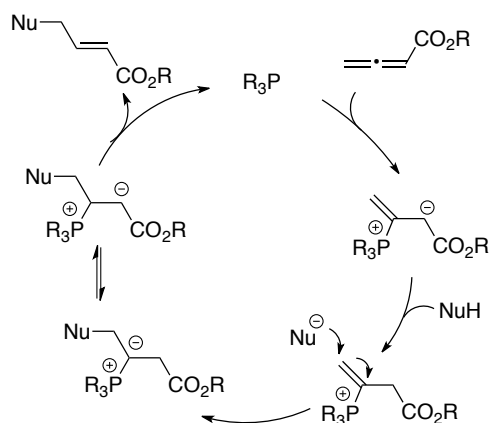
Scheme 1.5.6 Mechanism of γ-umpolung addition of allenoate

Alvarez-Ibarra and co-workers employed carboxylates as oxygen nucleophiles for the γ-umpolung addition into alkynoates and alkynones (Scheme 1.5.7).[27] The reaction was highly efficient when two-fold excess of the alkynoate or alkynone was utilized. Additionally, the presence of the conjugate acid was important for a buffer system.
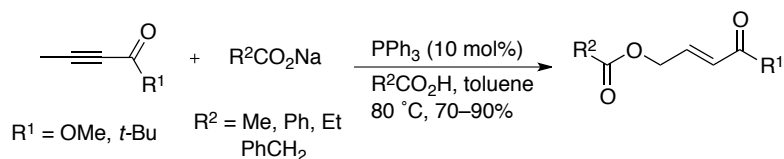
Scheme 1.5.7 Examples of Alvarez-Ibarra's γ-umpolung addition

Furthermore, Alvarez-Ibarra reported γ-umpolung addition of nitroacetates into ethyl 2-butynoates to provide only the *E*-isomer (Scheme 1.5.8).[28] The common NaOAc/AcOH buffer did not facilitate the γ-umpolung addition, a much more basic system was required, potassium *tert*-butoxide/*tert*-butanol (*t*-BuOK/*t*-BuOH).
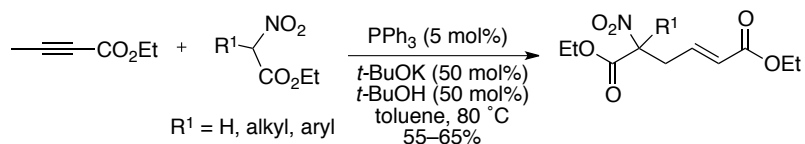
Scheme 1.5.8 Examples of Alvarez-Ibarra's γ-umpolung addition

1.6 Phosphine-Catalyzed Tandem Umpolung and Intramolecular Michael Additions

Heterocycles are important for both synthetic and pharmaceutical chemists.[29] An approach in forming heterocycles is by tandem nucleophilic additions, in which a bifunctional nucleophile adds into an electron-deficient alkyne or allene, followed by an intramolecular trapping of the intermediary monofunctional nucleophile to a newly formed electrophilic center. Cristau and co-workers reported the first γ-umpolung–Michael addition in a stepwise sequence (Scheme 1.6.1).[30] The vinyl phosphonium salt was reacted with *N,N*-dibenzyl-2-aminoethanol to give an O-addition umpolung product. The benzyl group on the amine was hydrogenolyzed, followed by an acidic removal of the acetal to provide the secondary amine phosphonium salt. Under triethylamine (Et$_3$N) the benzyl protected amine adds into the α,β-unsaturated ketone to provide a morpholine product. Reacting with *N*-benzyl-2-aminoethanol with the vinyl phosphonium salt, an *N*-addition umpolung product was obtained. Under acidic condition, the acetal was removed and the benzyl protected amine was protonated for the cyclization to the morpholine product.
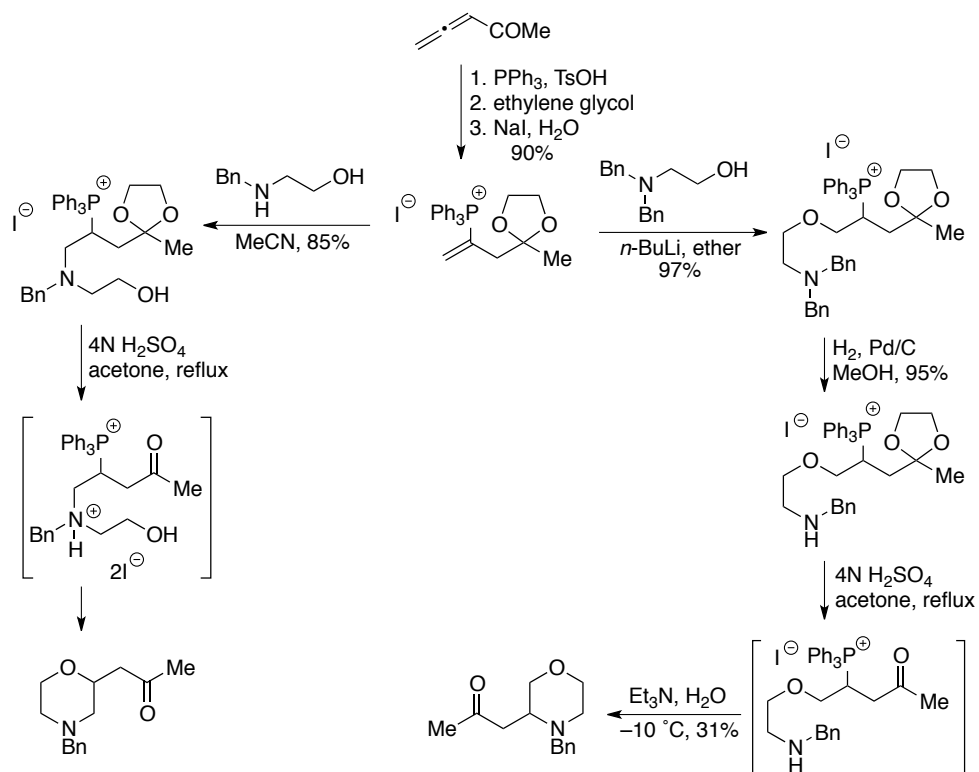
Scheme 1.6.1 Cristau's stepwise sequence of γ-umpolung–Michael addition

Lu and co-workers were the first to report phosphine-catalyzed tandem nucleophilic additions of bifunctional nucleophiles to electron-deficient alkynes or allenes. The tandem nucleophilic additions were successfully facilitated with 20 mol% of PPh$_3$. Carbon, oxygen, and nitrogen dinucleophiles reacted with propiolates and allenoates in good to excellent yields (Scheme 1.6.2).[31] The tandem nucleophilic additions favored a stronger electron-withdrawing group, from an ester to a ketone, which provided higher yields and a lower catalyst loading, 5 mol% of PPh$_3$.
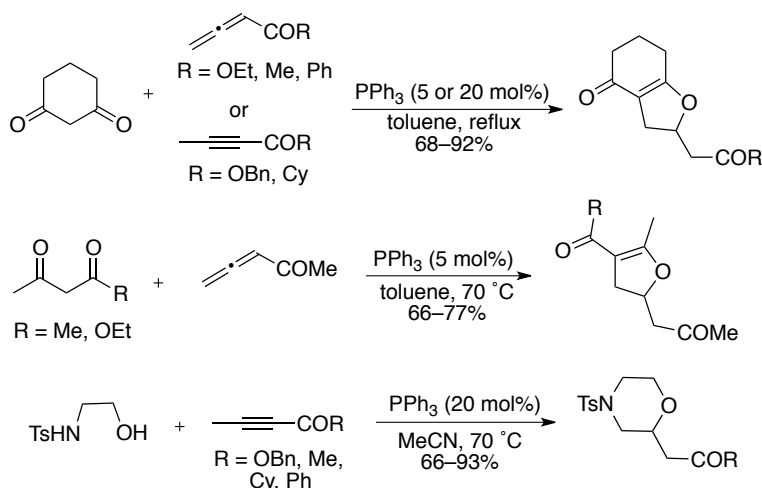
Scheme 1.6.2 Lu's tandem nucleophilic additions

Furthermore, Lu demonstrated the synthesis of highly substituted cyano cyclopentene scaffolds by tandem nucleophilic additions of ethyl 2,3-butadienoate and alkylidene malononitriles (Scheme 1.6.3).[32] The phosphonium dienolate deprotonates the methyl of the alkylidene malononitrile, which then adds into the phosphonium to give the γ-umpolung adduct after elimination of phosphine. The intermediate is deprotonated again at the most acidic carbon for a Michael addition to afford cyclopentene product.
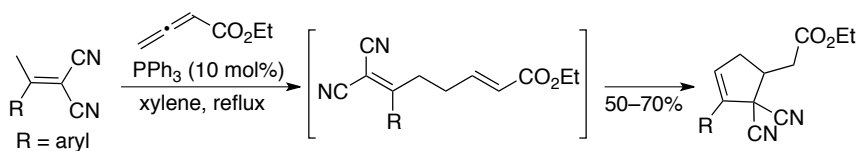
Scheme 1.6.3 Lu's tandem nucleophilic additions to synthesize cyclopentenes

Lastly, Liu and co-workers employed alkylthioamides, arylthioamides, and heteroaryl thioamides as dinucleophiles in the tandem nucleophilic additions with ethyl 2-butynoate to provide thiazoline derivatives (Scheme 1.6.4).[33] The nitrogen of the thioamide participates in the γ-umpolung addition follow by the sulfur adding in a Michael fashion to give thiazoline. The nitrogen added into the γ-carbon of the vinylphosphonium because the nitrogen is more

nucleophilic than sulfur. The electron-donating alkylthioamides (R = Me) were not great dinucleophiles due to decreased stabilization of the thioamide anion for the γ-umpolung addition.

R = aryl, Me, CF$_3$
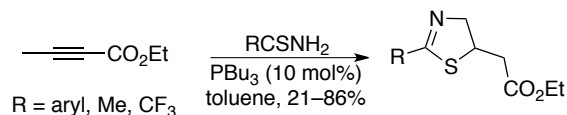
Scheme 1.6.4 Example of Liu's synthesis of thiazolines

1.7 Benzannulated 1,3-Diheteroatom Five-Membered Rings

Benzannulated 1,3-diheteroatom five-membered rings are valuable compounds for medicinal uses and in materials chemistry.[34] For example, 1,3-benzodioxoles exhibit endothelin antagonist, ant-inflammatory, antitumor, and antimicrobial activities.[35] Also, 1,3-benzothiazolines are used as antioxidants to advance the oxidative stability of polymers, rubbers, and plastics.[36] These motifs are generally synthesized through dehydrative condensation of 1,2-disubstituted benzenes with aldehydes or ketones in the presence of acid catalyst (Scheme 1.7.1).[37] However, the reaction conditions are often harsh, such as employing strong dehydrating agents or superstoichiometric amount of acid.[38]
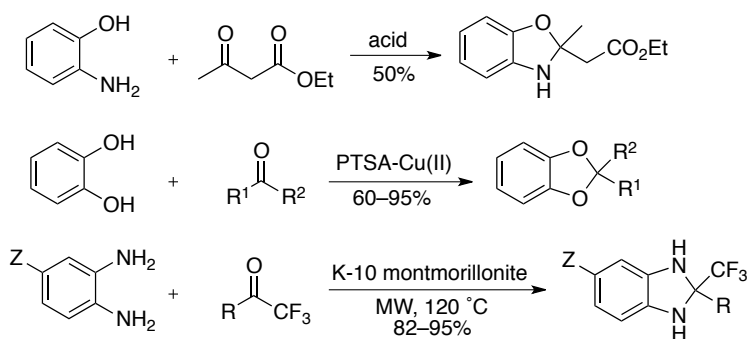
Scheme 1.7.1 Examples of acid catalyzed condensation of 1,2-disubstituted benzenes and carbonyls

Besides acid-catalyzed condensation reactions, the benzannulated 1,3-diheteroatom five-membered rings can be synthesized by a double-Michael reaction of allenes with potassium

carbonate (K$_2$CO$_3$), which was previously mentioned (Scheme 1.7.2).[17] Cabiddu and co-workers demonstrated that catechol, 2-mercaptophenol, and 1,2 benzenedithiol can react with α- or γ-substituted allenoates to afford 1,3-benzodioxoles, 1,3-benzoxathioles, and 1,3-benzodithioles, respectively.

X = Y = O, S   R^1 = R^2 = R^3 = alkyl
Z = H, Me
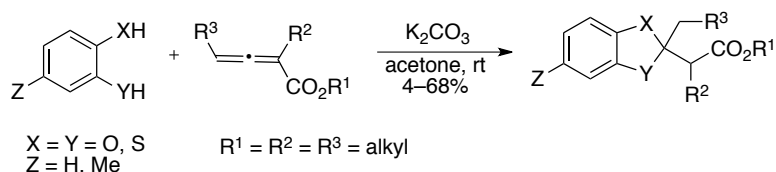
Scheme 1.7.2 Synthesis of benzannulated 1,3-diheteroatom by the double-Michael reaction

Furthermore, Olah and co-workers examined Lewis acids to facilitate the condensation reaction of 1,2-disubstituted benzenes and carbonyl compounds (Scheme 1.7.3).[39] Catalytic amount of gallium triflate [Ga(OTf)$_3$] afforded benzimidazolines and benzoxazolines in 75–98% yield. Lastly, there is no one condition reported in literature that can synthesize all six benzannulated 1,3-diheteroatom five-membered rings.

X = NH, O   R^1 = alkyl, aryl
Y = H, Me, Cl   R^2 = fluoroalkyl
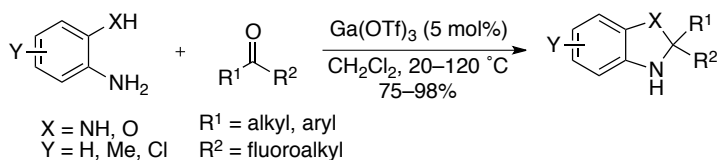
Scheme 1.7.3 Gallium triflate catalyzed condensation

1.8 Phosphine-Catalyzed Double-Michael Reaction of Allenes

As mentioned above, the tandem umpolung addition followed by intramolecular conjugate addition reaction is facilitated by PPh$_3$.[30–33] Reacting *N*-tosyl-2-aminophenol[40] (**1a**) and allenoate **2a** with PPh$_3$ (10 mol%) gave the benzomorpholine **3a**[41] in 88% yield (Scheme 1.8.1). However, studies of the tandem umpolung addition-Michael cyclization using γ-

substituted allenoates were not present in literature. Thus, investigation of the tandem umpolung-Michael reaction with γ-substituted allenoates was examined.
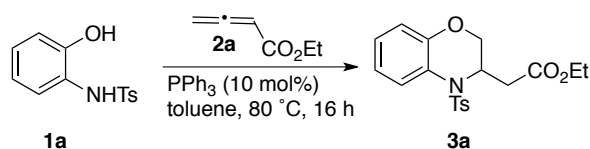
Scheme 1.8.1 Phosphine-catalyzed tandem umpolung-Michael reaction

N-Tosyl-2-aminophenol (**1a**) and allenoate **2b** were screened with different phosphines, solvents, temperatures, and additives to facilitate the tandem umpolung-Michael addition (Table 1.8.1). Reactions with PPh$_3$ in benzene at room temperature did not provide the desired product **3b** (entry 1). Switching the solvent to toluene and using NaOAc (50 mol%)/AcOH (50 mol%) as additives did not afford the desired benzomorpholine **3b** (entry 2). The reaction was then heated at 80 ˚C, however no product was obtained (entry 3). Surprisingly, switching to a more nucleophilic phosphine, PMe$_3$, and heating at 90 ˚C in a pressure tube gave a double-Michael product **4a** in 66% yield (entry 4). Changing the solvent to acetonitrile (MeCN) increased the yield of the double-Michael product to 78% (entry 5). At this point, the double-Michael reaction was investigated with substituted allenes instead of the unsuccessful tandem umpolung addition-Michael cyclization with substituted allenes.

Table 1.8.1 Screening conditions for the tandem umpolung–Michael reaction
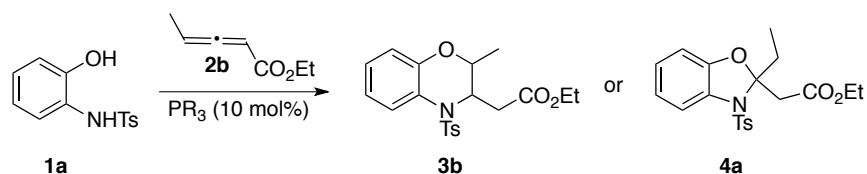
entry	catalyst	solvent	temp (˚C)	time (h)	additive	yield (%)[c]
1	PPh$_3$	benzene	22	48		0
2[a]	PPh$_3$	toluene	22	48	NaOAc/AcOH	0
3[a]	PPh$_3$	toluene	80	48	NaOAc/AcOH	0
4[b]	PMe$_3$	benzene	90	48		66 (**4a**)
5[b]	PMe$_3$	MeCN	90	30		78 (**4a**)

[a]Each additive was added in 50 mol% quantity. [b]Reaction was done in pressure tube. [c]Isolated yield.

Optimization of the double-Michael reaction

Optimization reactions were conducted with the model reaction of *N*-tosyl-2-aminophenol (**1a**) and 1.1 equivalents of allenoate **2b** in a pressure tube at 90 ˚C. The reaction in benzene with 10 mol% PMe$_3$ afforded benzoxazoline **4a** and a mixture of mono-Michael adduct **5a/b** in 66% and 4% yield, respectively (Table 1.8.2, entry 1). Changing to a more polar solvent, MeCN, increased the yield to 86%, with no mono-Michael adduct (entry 2). Additives were applied to the reaction [e.g. NaOAc, sodium trifluoroacetate (CF$_3$CO$_2$Na), and sodium benzoate (NaOBz)], which gave no improvement of the product yield (entries 3–5). Running the reaction at room temperature in MeCN did not provide any product (entry 6). Changing the phosphine, PBu$_3$ and PPh$_3$, provided a lower yield and no reaction, respectively (entries 7 and 8). Thus, PMe$_3$ is suggested to be the best phosphine for the double-Michael reaction. Lastly, adding more catalyst or allenoate provided diminished reaction efficiency (entries 9 and 10). The optimized condition was determined to be 1.1 equivalents of allenoate with 10 mol% PMe$_3$ at 90 ˚C in a pressure tube.

Table 1.8.2 Optimization for the double-Michael reaction
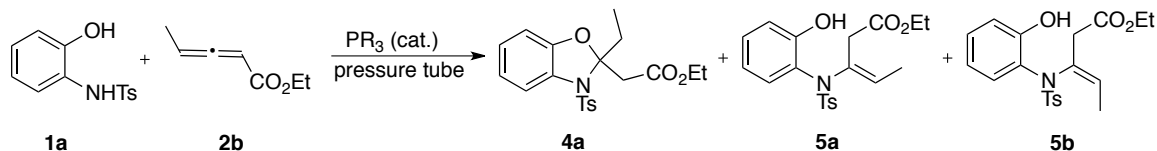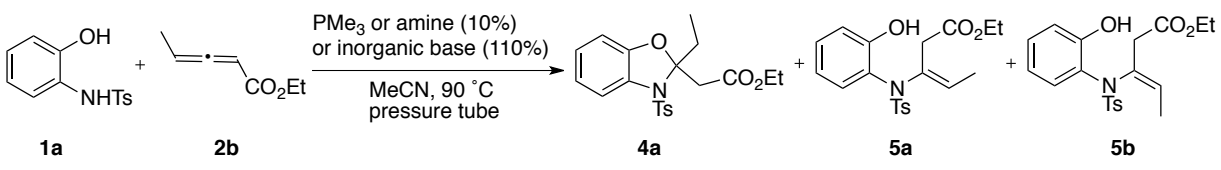
entry	catalyst[a]	solvent	additive[b]	temp (°C)	time (h)	yield (%)[c] 4a	5a/5b
1	PMe$_3$	benzene		90	45	66	4
2	PMe$_3$	MeCN		90	46	86	0
3	PMe$_3$	MeCN	NaOAc	90	24	86	trace
4	PMe$_3$	MeCN	CF$_3$O$_2$Na	90	40	73	trace
5	PMe$_3$	MeCN	NaOBz	90	15.5	73	trace
6	PMe$_3$	MeCN		rt	2 days	No reaction	
7	PBu$_3$	MeCN		90	42	51	4
8	PPh$_3$	MeCN		90	41	No reaction	
9	PMe$_3$[d]	MeCN		90	40	61	4
10[e]	PMe$_3$	MeCN		90	40	70	4

[a]10 mol% was added unless otherwise mentioned. [b]50 mol% was added. [c]Isolated yield. [d]5 mol% was used. [e]2.1 equiv of allenoate **2b** used.

The addition of PMe$_3$ to allenoate **2b** is speculated to form a phosphonium enolate that acts as a general base and promotes the formation of the double-Michael product **4a**. To test this hypothesis, the double-Michael reaction was examined using amines and inorganic bases. *N*-Tosyl-2-aminophenol (**1a**) and allenoate **2b** were reacted in the presence of an amine (0.1 equiv) or an inorganic base (1.1 equiv) in MeCN at 90 °C (Table 1.8.3). Among the common nucleophilic amine bases, quinuclidine provided the double-Michael adduct **4a** in only 26% yield (entry 2). Switching the base to 3-hydroxyquinuclidine (3-HQD) and 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded the product in a higher yield, 54% and 77%, respectively (entries 3 and 4). 4-Dimethylaminopyridine (DMAP) gave the best yield of the double-Michael product **4a** compared to the other amines and it is comparable with that of PMe$_3$ (entry 5). Neither the basicity[42] or the nucleophilicity[43] of the amine bases followed the same trend as the reaction efficiency, which means that the reaction follows a complex multistep

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mechanism. Also, the inorganic bases [e.g. sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), and NaOAc] facilitated the double-Michael reaction, however with diminished efficiency (entries 6–8). Lastly, CF_3CO_2Na did not provide the double-Michael product, only the mono-Michael (entry 9). Based on these results, phosphonium enolate is most likely acting as a general base in the formation of the double-Michael products. Focusing on the double-Michael reaction with PMe_3 and DMAP, we investigated a variety of nucleophiles and allenes for the construction of benzannulated 1,3-diheteroatom five-membered rings.

Table 1.8.3 Double-Michael reactions of the aminophenol **1a** and the allene **2b** mediated by different bases[a]

entry	base	time (h)	$pK_a(H_2O)$[b]	nucleophilicity[c]	yield (%)[d] 4a	yield (%)[d] 5a/5b
1	PMe_3	46	8.7	15.49[e]	86	
2	quinuclidine	24	11.3	20.54[f]	26	56
3	3-HQD	24	9.9		54	30
4	DABCO	24	8.7	18.80[f]	77	10
5	DMAP	24	9.2	15.80[g] (14.95)[f]	82	trace
6	Na_2CO_3	20	10.3		35	20
7	$NaHCO_3$	24	6.3		16	61
8	NaOAc	24	4.8		53	12
9	CF_3CO_2Na	24	−0.25		0	26

[a]Reactions were performed using 0.4 mmol of **1a** and 1.1 equiv of **2b**. [b]Reference 42. [c]Reference 43. [d]Isolated yield. [e]The value is the nucleophilicity of PBu_3 (in CH_2Cl_2). [f]Nucleophilicity in MeCN. [g]Nucleophilicity in CH_2Cl_2.

Double-Michael annulations of various dinucleophiles

The PMe_3-mediated double-Michael reaction was pertinent to a variety of ortho-substituted phenol, aniline, and thiophenol dinucleophiles (Table 1.8.4). The optimized condition of heating the dinucleophile at 90 °C in MeCN and in the presence of the allenoate **2a** and PMe_3

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(10 mol%) or DMAP (10 mol%) afforded benzannulated 1,3-diheteroatom five-membered rings. *N*-Tosyl-2-aminophenol (**1a**) provided the benzoxazoline **4b** in 92% yield (entry 1). The 1,3-benzoxathiol **4c**, the 1,3-benzodioxole **4d**, and the 1,3-benzodithiol **4e** were also formed readily in good yields (entries 2–4). In contrast, *N*-tosyl-2-aminothiophenol[44] and *N,N'*-ditosyl-1,2-diaminobenzene[45] produced only their mono-Michael adducts at 90 ˚C. To facilitate the second double-Michael addition, the reaction temperature was raised to 120 ˚C to obtain benzothiazoline **4f** and benzimidazoline **4g** in good yields (entries 5 and 6). Starting the reaction at 120 ˚C did not convert **1e** and **1f** to the double-Michael adduct. Thus, the reaction was run at 90 ˚C to facilitate the mono-Michael product, and then the temperature was raised to 120 ˚C to convert to the double-Michael product. DMAP was subjected to the reaction condition, in hopes of obtaining the full conversion of the double-Michael product **4f** and **4g** at 90 ˚C. Unfortunately, the mono-Michael product was again obtained and the temperature was raised to 120 ˚C for the second Michael addition to afford benzothiazoline **4f** and benzimidazoline **4g** at a much lower yield (entries 5 and 6). The presence of a chlorine substituent did not affect the double-Michael reaction of **1g**, giving the benzoxazoline **4h** in 84% yield (entry 7).

Table 1.8.4 Double-Michael annulations of various dinucleophiles[a]
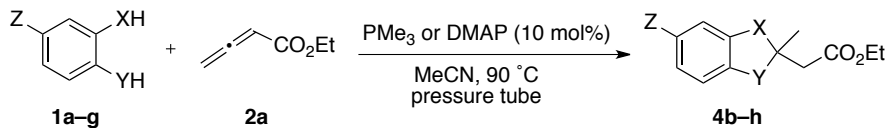
| entry | X, Y | Z | time (h) | product | yield (%)[b] | |
					PMe$_3$	DMAP
1	O, NTs (**1a**)	H	20	**4b**	92	
2	O, S (**1b**)	H	12	**4c**	93	
3	O, O (**1c**)	H	12	**4d**	80	
4	S, S (**1d**)	H	13	**4e**	74	
5[c]	S, NTs (**1e**)	H	60 (41)[d]	**4f**	68	53
6[c]	NTs, NTs (**1f**)	H	60 (41)[d]	**4g**	79	38
7	O, NTs (**1g**)	Cl	12	**4h**	84	

[a]Reactions were performed using 0.4 mmol of **1** and 1.1 equiv of **2a**. [b]Isolated yield. [c]Reaction performed initially at 90 °C to obtain the mono-Michael adduct; the temperature was then raised to 120 °C for full conversion to the double-Michael product. [d]Reaction times for the DMAP reaction.

Double-Michael annulations of substituted allenoates

α- and γ-Substituted allenoates[46,47] were subjected to the double-Michael reaction with *N*-tosyl-2-aminophenol (**1a**), 2-mercaptophenol (**1b**), and catechol (**1c**) to afford a variety of substituted benzoxazolines, 1,3-benzoxathioles, and 1,3-benzoxodioles, respectively (Table 1.8.5). Reacting *N*-tosyl-2-aminophenol (**1a**) with γ-phenyl, benzyl, and *tert*-butyl allenoates **2c–e** afforded benzoxazolines **4i–k** in good yields (entries 1–3). Similarly, reacting 2-mercaptophenol (**1b**) and catechol (**1c**) with γ-methyl, phenyl, benzyl, and *tert*-butyl allenoates **2b–e** provided 1,3-benzoxathioles **4l–o** and 1,3-benzoxodioles **4p–s**, respectively, in good yields (entries 4–11). Subjecting α-methyl, benzyl, and methylene ester allenoates **2f–h** with catechol (**1c**) produced 1,3-benzodioxoles **4t–v** in excellent yields (entries 12–14). With *N*-tosyl-2-aminophenol (**1a**) as the dinucleophile, α-substituted allenoates generated a mixture of diastereoisomers with poor selectivity, however in excellent yields (entries 15–17). Based on the yields of the double-Michael products in the presence of PMe$_3$, DMAP was added to the

reactions with γ-methyl, benzyl, and *tert*-butyl allenoates **2b**, **d**, and **e**. In general, DMAP was a less-efficient catalyst then PMe$_3$, with some exceptions (entries 2, 4, and 6). The noteworthy improvement in the product yield was when DMAP was used for the reaction of the γ-benzyl allenoate **2d** (entries 2 and 6). The lower yield with PMe$_3$ was likely due to isomerization of the γ-benzyl allenoate **2d** to the corresponding diene.[48] The superior performance of PMe$_3$ over DMAP might be due to the higher spectator coutercation property of phosphonium cation versus pyridinium cation in a general base catalysis.

Table 1.8.5 Double-Michael annulations of substituted allenoates[a]
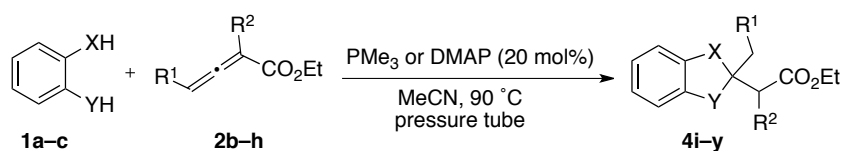
entry	X, Y	R^1, R^2	time (h)	product	yield (%)[b] PMe$_3$	DMAP
1	O, NTs	Ph, H (**2c**)	48	**4i**	83	
2	O, NTs	Bn, H (**2d**)	65 (33)[c]	**4j**	61	77
3	O, NTs	*t*-Bu, H (**2e**)	40 (48)[c]	**4k**	69	51
4	O, S	Me, H (**2b**)	46 (13)[c]	**4l**	74	76
5	O, S	Ph, H	48	**4m**	86	
6	O, S	Bn, H	65 (24)[c]	**4n**	65	89
7	O, S	*t*-Bu, H	40 (48)[c]	**4o**	58	48
8	O, O	Me, H	40 (13)[c]	**4p**	70	68
9	O, O	Ph, H	48	**4q**	77	
10	O, O	Bn, H	65 (33)[c]	**4r**	89	74
11	O, O	*t*-Bu, H	40 (48)[c]	**4s**	82	68
12	O, O	H, Me (**2f**)	35	**4t**	89	
13	O, O	H, Bn (**2g**)	40	**4u**	86	
14	O, O	H, CH$_2$CO$_2$Et (**2h**)	41	**4v**	80	
15[d]	O, NTs	H, Me	35	**4w**	81[e]	
16[d]	O, NTs	H, Bn	40	**4x**	73[e]	
17[d]	O, NTs	H, CH$_2$CO$_2$Et	41	**4y**	84[e]	

[a]Reactions were performed using 0.4 mmol of **1** and 1.35 equiv of **2**. [b]Isolated yield. [c]Reaction times for the DMAP reaction. [d]NaOAc (50 mol%) was added. [e]Diastereoisomeric ratio determined using ^{1}H NMR spectroscopy. Diastereoisomeric ratios 1:1, 2:1, and 1.2:1 for **4w**, **4x**, **4y**, respectively.

Mechanistic studies

In order to unequivocally prove the structure of the mono-Michael adducts, the reaction of *N*-tosyl-2-amino-5-chlorophenol (**1g**) with ethyl 2,3-pentadienoate (**2b**) was stopped prematurely to provide the mono-Michael adducts (Scheme 1.8.2). The mono-Michael adduct **5c** provided single crystals amenable to X-ray crystallographic analysis, which unequivocally proved its structure (Appendix). However, the minor mono-Michael adduct **5d** did not provide crystals. The mono-Michael adduct **5d** structure was assigned as shown based on its ^{1}H and ^{13}C NMR data and the fact that both **5c** and **5d** exhibit a sharp singlet as the signal for the phenolic OH unit in their ^{1}H NMR spectra; the signal for the aniline proton appears as a broad singlet. With the structure of the mono-Michael adduct in hand, it can be utilized in further mechanistic studies.
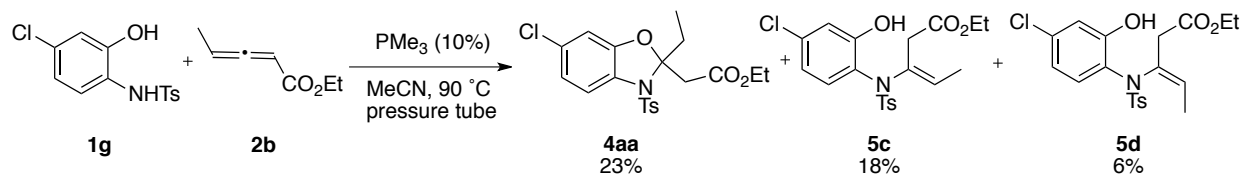
Scheme 1.8.2 Formation and isolation of mono-Michael adducts **5c/d**

To understand the mechanism of this new phosphine-mediated double-Michael reaction, the mono-Michael **5a**[41] was subjected to various reaction conditions (Table 1.8.6). There was almost no cyclized product **4a** when the mono-Michael **5a** was heated in MeCN in the presence of catalytic phosphine (entry 1). TLC analysis revealed a very faint spot corresponding to the cyclized product **4a**, with the majority of the compound **5a** remaining unreacted. Treatment of **5a** in MeCN with 1.1 equiv of the allenoate **2b** also did not lead to a facile conversion to **4a** (entry 2). However, exposure of **5a** to catalytic PMe$_3$ and 0.1 equivalents of allenoate **2b** in MeCN at 90 °C provided the double-Michael product **4a** in 80% yield (entry 3). Most interestingly, treatment of **5a** with catalytic PMe$_3$ and 1.1 equivalents of the allenoate **2a** also provided

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formation of the benzoxazoline **4a** (entry 4). Notably, the double-Michael product **4b** was not detected from the elimination of **1a** from **5a** and subsequent double-Michael reaction of the allenoate **2a**.

Table 1.8.6 Mechanistic studies with the mono-Michael adduct
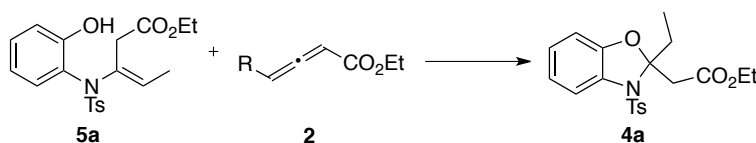
entry	PMe$_3$ (mol %)	R	yield (%)^a
1	10		0
2		Me	0
3	10	Me^b	80
4	10	H^c	82

^{a}Isolated yield. ^{b}0.1 equiv of allenoate **2b**. ^{c}1.1 equiv of allenoate **2a**.

Based on these results, the following mechanism for the double-Michael reaction is proposed (Scheme 1.8.3). Nucleophilic addition of the phosphine to the allenoate **2** provides the phosphonium dienolate **6**. Protonation of **6** by pronucleophile **1** leads to the formation of a nucleophile/phosphonium salt pair **7•8**, which undergoes γ-umpolung addition to yield the ylide **9** when PPh$_3$ is employed as the catalyst.[30–33] In contrast, the more-electron-rich phosphine PMe$_3$ does not facilitate umpolung addition.[49] Instead, the nucleophile **7** adds into the allenoate **2**. The resulting dienolate **11** undergoes γ-protonation to form the α,β-unsaturated enoate **13**, which is ready for a second Michael addition. The cyclic enolate **14** can further facilitate the double-Michael reaction cycle by deprotonating the pronucleophile **1** (or mono-Michael product **5a** in Table 1.8.6) to produce the product **4**, supporting the notion of a general base catalysis.[50] The observation of no cyclized product derived from the allenoate **2a** in Table 1.8.6 also suggests that the second Michael addition is facile and the intermediate **11** does not revert back to the allenoate **2** and the nucleophile **7**.

29
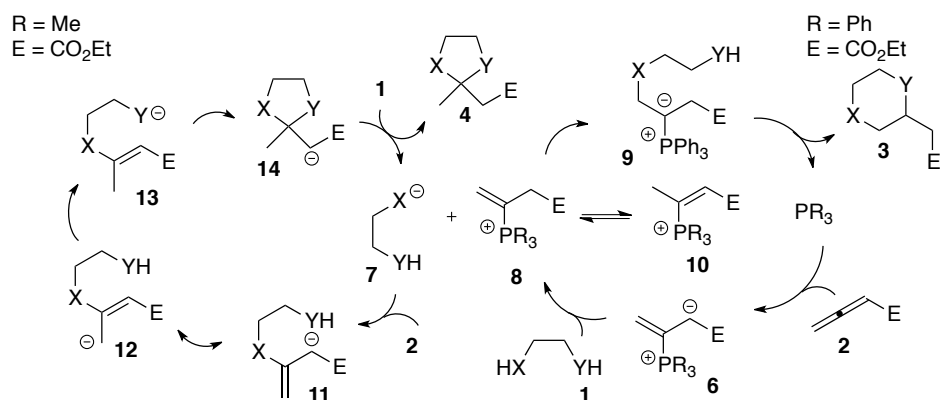
Scheme 1.8.3 Mechanism of the double-Michael reactions of allenes

Selective ketalization on allenones

Selective ketalization of dicarbonyls (e.g. diketones, dialdehydes, and ketoaldehydes) is difficult to accomplish. Mixture of ketalized products is obtained when asymmetric dicarbonyls are used. However, allenones can be surrogates to 1,3-dicarbonyls. To see if the double-Michael reaction is applicable to allenones, catechol (**1c**) was reacted with penta-3,4-dien-2-one (**15**) in MeCN in the presence of PMe$_3$ at 90 ˚C (Scheme 1.8.4). Pleasingly, the double-Michael product **16a** was obtained in 68% yield. The ketalization of the β-diketone **17** with catechol would produce a mixture of the acetals **16b** and **16c**. Conversely, the double-Michael reaction of catechol with the allenone **15b** produced only the acetal **16b** in 90% yield.[51] Thus, this method can be analogues for a selective ketalization of dicarbonyls by using allenones.
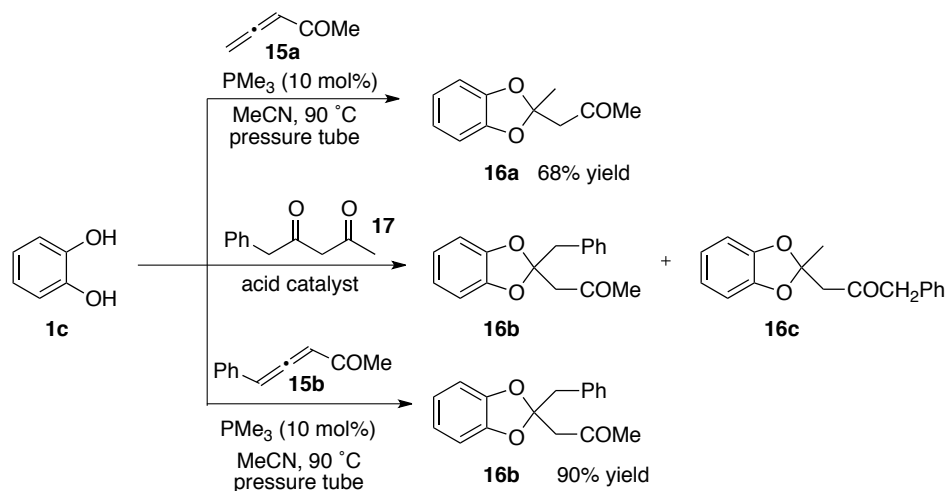
Scheme 1.8.4 Selective ketalization by the double-Michael reaction

Amino alcohols as alternative double-Michael pronucleophiles

As mentioned previously, β-amino alcohols were successfully used to demonstrate a phosphine-catalyzed mixed double-Michael reaction with acetylenes. We envisioned treating the amino alcohols with allenes in the presence of PMe₃ to obtain highly substituted oxazolidines. Subjecting isopropyl amino alcohol **18a** and γ-methyl allenoate **2b** in the presence of PMe₃ with NaOAc as an additive did not provide the desired double-Michael product (Table 1.8.7, entry 1). Switching the pronucleophile to methyl amino alcohol **18b** also did not obtain any product (entry 2). Examining benzyl amino alcohol **18c** with ethyl 2,3-butadienoate (**2a**) at 120 ˚C did not successful produce any oxazolidine product (entry 3). Thus, it was reasoned that amino alcohols are not good pronucleophiles for the double-Michael reaction with allenes because aliphatic amino alcohols are less acidic than anilines and phenols.

Table 1.8.7 Attempts of the double-Michael reaction with β-amino alcohols and allenoates[a]
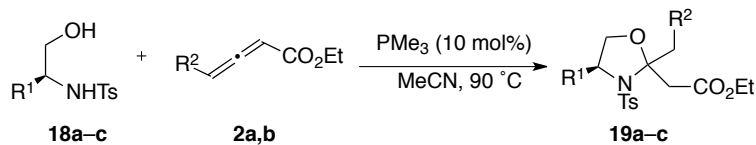
entry	R^1	R^2	additive	yield (%)
1	i-Pr	Me	NaOAc	0
2	Me	Me	NaOAc	0
3[b]	Bn	H		0

[a]Reactions were performed using 0.4 mmol of **18a–c** and 1.1 equiv of **2**. [b]Reaction ran at 120 ˚C.

Ortho-substituted benzyl alcohol or benzyl amine as alternative double-Michael pronucleophiles

Without any success with amino alcohols, we test the use of *ortho*-substituted benzyl alcohols and benzyl amines as the pronucleophiles. 2-Hydroxylbenzyl alcohol (**20a**) was reacted with ethyl 2,3-butadienoate (**2a**) in the presence of phosphine and NaOAc, which provided no double-Michael product (Table 1.8.8, entry 1). Under the same condition, *N*-tosyl-2-aminobenzyl alcohol (**20b**) and *N,N*-ditosyl-2-aminobenzyl amine (**20c**) produced the mono-Michael adducts in 43% and 30% yield, respectively (entries 2, 3). Replacing NaOAc with a much stronger base, potassium *tert*-butoxide (KO*t*-Bu), did not afford any product for benzyl alcohol **20a** (entry 4) and benzyl alcohol **20b** and benzyl amine **20c** produced the mono-Michael adducts, which were not isolated (entries 5, 6). Changing the base to sodium ethoxide (NaOEt), yet again the benzyl alcohol **20a** produced no product (entry 7), whereas the benzyl alcohol **20b** and benzyl amine **20c** consumed two allenoates (entries 8, 9). Using stronger bases did not facilitate the reaction, but caused decomposition of the benzyl alcohol **20a**. It seems that the *N*-tosylanilinamido proton is more acidic than the phenol proton, which is why we observe the mono-Michael product when using *N*-tosyl-2-aminobenzyl alcohol (**20b**) and *N,N*-ditosyl-2-aminobenzyl amine (**20c**) under NaOAc. However, the presence of stronger bases caused a consumption of two allenoate

molecules instead of forming the double-Michael products. To further examine the double-Michael reaction with 1,2-disubstituted benzyl alcohols, Lewis acids were subjected to the reaction. However, no fruitful double-Michael product was obtained (entries 10–12). Thus, along with amino alcohols, 1,2-disubstituted benzyl alcohol and benzyl amine are not suitable pronucleophiles for the double-Michael reaction.

Table 1.8.8 Attempts of the double-Michael reactions of disubstituted benzyl alcohol and benzyl amines with allenoate[a]
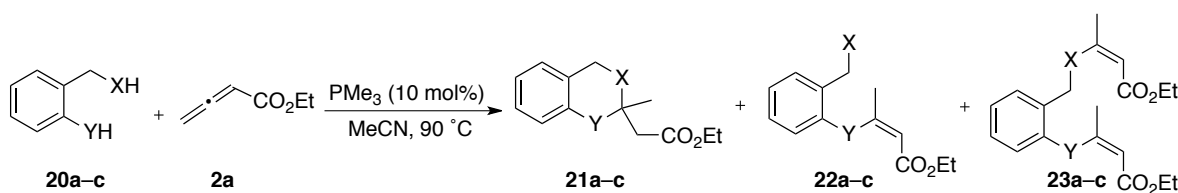
entry	X, Y	additive	Lewis acid	yield (%)[b]
1	O, O (**20a**)	NaOAc		0
2	O, NTs (**20b**)	NaOAc		43 (**22b**)
3	NTs, NTs (**20c**)	NaOAc		30 (**22c**)
4	O, O	KOt-Bu		0
5	O, NTs	KOt-Bu		No isolation
6	NTs, NTs	KOt-Bu		No isolation
7	O, O	NaOEt		0
8	O, NTs	NaOEt		15 (**23b**)
9	NTs, NTs	NaOEt		10 (**23c**)
10[c]	O, O		Yb(OTf)$_3$	0
11[c]	O, O		AlCl$_3$	0
12[c]	O, O		Y(OTF)$_3$	0

[a]Reactions were performed using 0.4 mmol of **20a–c** and 1.1 equiv of **2a**. [b]Isolated yield. [c]Reactions were performed in CH$_2$Cl$_2$ at room temperature.

Double-Michael reaction on α,γ-substituted allenoates and allenes

Aniline-, phenol-, and benzenethiol-derived dinucleophiles thus far are the only substrates that have been successful in the double-Michael reaction. In order to expand the substrate scope, a variety of elaborated allenes were examined with catechol and *ortho*-tosylamidophenol to produce more highly substituted heterocycles. First, α,γ-dimethyl allenoate

2i was reacted with catechol (**1c**) under the optimized double-Michael condition, which is in the presence of 10 mol% PMe$_3$ in MeCN at 90 ˚C and no product was obtained (Table 1.8.9, entry 1). Switching to α-methyl-γ-*tert*-butyl allenoate **2j** did not afford any desired product (entry 2). Also, α-methyl allenylphosphonate **2k** and α-methyl allenylsulfone **2l** did not generate any product (entries 3, 4). Switching to PBu$_3$ did not facilitate the reaction (entry 5). Lastly, examining *N*-tosyl-2-aminophenol (**1a**) with α,γ-dimethyl allenoate **2i** did not give any product (entry 6). Thus, even elaborated allenes could not facilitate the double-Michael reaction.

Table 1.8.9 Attempts of the double-Michael reaction with a variety of elaborated allenes[a]
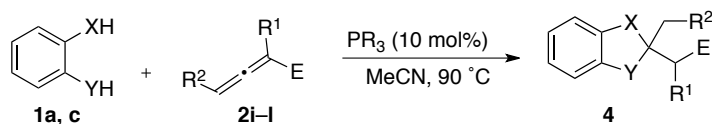
entry	X, Y	R^1, R^2	E	PR$_3$	yield (%)
1	O, O (**1c**)	Me, Me (**2i**)	CO$_2$Et	PMe$_3$	0
2	O, O	Me, *t*-Bu (**2j**)	CO$_2$Et	PMe$_3$	0
3	O, O	H, Me (**2k**)	PO(OEt)$_2$	PMe$_3$	0
4	O, O	H, Me (**2l**)	SO$_2$Ph	PMe$_3$	0
5	O, O	Me, Me	CO$_2$Et	PBu$_3$	0
6	O, NTs (**1a**)	Me, Me	CO$_2$Et	PMe$_3$	0

[a]Reactions were performed using 0.4 mmol of **1a**, **c** and 1.1 equiv of **2i–l**.

Double-Michael reaction with carbon pronucleophiles and allenoates

Besides heteroatom pronucleophiles, we examined carbon pronucleophiles to probe the scope of the double-Michael reaction. Subjecting pronucleophile **24a** to the reaction condition with ethyl 2,3-butadienoate (**2a**) in MeCN in the presence of PMe$_3$ at 90 ˚C did not give the desired indoline product. However, what was obtained was an oxindole compound **26a** in 19% yield (Table 1.8.10, entry 1). Switching to the γ-methyl allenoate **2b** did not prevent the oxindole from forming (entry 2). Trying bulkier pronucleophiles, the isopropyl and the *tert*-butyl esters did lead to the double-Michael product, however along with the mono-Michael product, which

were inseparable (entries 3, 4). Lastly, the mixture was resubjected to the same condition and was heated at 120 °C to facilitate the mono-Michael product to the double-Michael product. However, a second Michael addition did not occur (entry 5). Overall, the double-Michael reaction is more successful in subjecting aniline-, phenol-, and benzenethiol-derived dinucleophiles with γ- and α-substituted allenoates to produce benzannulated five-membered heterocycles.

Table 1.8.10 Attempts of the double-Michael with carbon pronucleophiles[a]
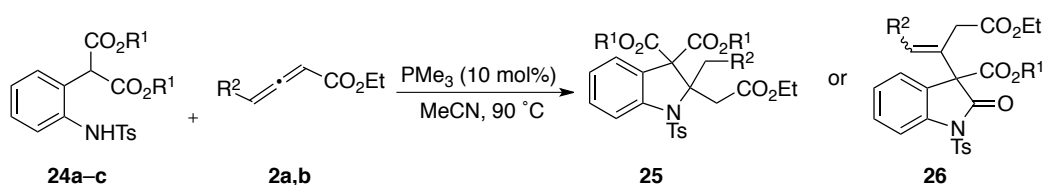
entry	R^1	R^2	yield (%)
1	Me (**24a**)	H (**2a**)	19 (**26a**)
2	Me	Me (**2b**)	36 (**26b**)
3	i-Pr (**24b**)	H	50 (**25b**/mono)
4	t-Bu (**24c**)	H	61 (**25c**/mono)
5[b]	i-Pr (**24b**)	H	0

[a]Reactions were performed using 0.4 mmol of **24a–c** and 1.1 equiv of **2a,b**. [b]Reaction ran at 120 °C.
[c]Isolated yield.

Tandem umpolung–Michael addition reaction of 1,2-disubstituted benzenes on allenoate

Experiencing little success in affording double-Michael products with β-amino alcohols or disubstituted benzyl alcohol and benzyl amine, we went back to examine the tandem umpolung-Michael reaction. *N*-Tosyl-2-aminophenol (**1a**) worked perfectly forming the benzomorpholine **3a** by the tandem umpolung-Michael reaction (Scheme 1.8.1). Now, 2-mercaptophenol (**1b**) and catechol (**1c**) were tested to see if the tandem umpolung-Michael reaction was successful with ethyl 2,3-butadienoate (**2a**). Subjecting 2-mercaptophenol (**1b**) to different amounts of PPh₃ in toluene at 80 °C or 110 °C did not facilitate the tandem umpolung-Michael addition (Table 1.8.11, entries 1–3). Using additives, AcOH/NaOAc, did not help the

reaction (entry 4). Subjecting catechol (**1c**) to the condition also was unable to facilitate the reaction (entries 5–7). Lastly, using one more pronucleophile, *N,N'*-ditosyl-1,2-diaminobenzene (**1f**), also did not produce the desired product (entry 8).

Table 1.8.11 Attempts of the tandem umpolung–Michael reaction with 1,2-disubstituted benzenes
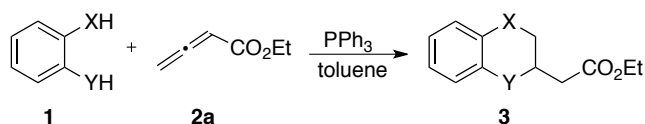
entry	X, Y	PPh$_3$ (mol%)	temp (˚C)	yield (%)
1	O, S (**1b**)	10	80	0
2	O, S	20	110	0
3	O, S	100	80	0
4[b]	O, S	10	80	0
5	O, O (**1c**)	20	110	0
6	O, O	100	80	0
7	O, O	20	110	0
8	NTs, NTs (**1f**)	10	80	0

*[a]*Reactions were performed using 0.4 mmol of **1** and 1.1 equiv of **2a**.

Conclusion

We have developed a phosphine-triggered general base-catalyzed double-Michael reaction that enables the syntheses of six different benzannulated 1,3-dihetereoatom five-membered rings from 1,2-disubstituted benzenes and allenes. The reported processes are operationally simple and atom-economical, minimize the generation of chemical waste, and employ mild reaction conditions. Based on the results of experiments performed using an isolated mono-Michael adduct, we have established a general-base catalysis mechanism for what appears to be a phosphine catalysis reaction. This highly efficient methodology also circumvents the synthetic problem of nonselective ketalization of β-diketones.

Experimental

General Information

All reactions were performed under Ar atmosphere with dry solvents in flame-dried round-bottom flasks containing stir bars. All reagents, except for the tosylated pronucleophiles and allenoates/allenones, were obtained commercially and used without further purification. Toluene and acetonitrile were distilled afresh from CaH_2; benzene was distilled from Na with benzophenone indicator.

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 a Thermo Nicolet Avatar 370 FT-IR spectrometer.

NMR Spectroscopy: NMR spectra were recorded using Bruker ARX-400 and AV-300 instruments calibrated to $CH(D)Cl_3$ as an internal reference (7.26 and 77.00 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; dq =

doublet of quartets; dq = doublet of pentets; t = triplet; td = triplet of doublets; q = quartet; m = multiplet.

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).

X-ray Crystallography: X-ray crystallographic data were collected using a Bruker SMART CCD-based diffractometer equipped with a low-temperature apparatus operated at 100 K.

Umpolung Addition/Michael Reaction
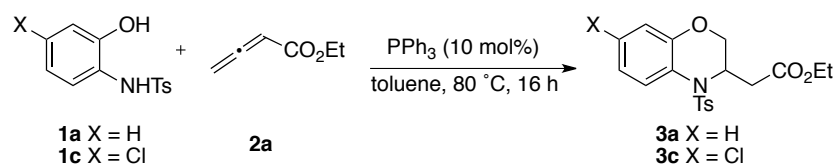
Ethyl 2,3-butadienoate (**2a**, 49.7 mg, 0.44 mmol, 1.1 equiv) and PPh$_3$ (10.6 mg, 0.04 mmol, 10 mol%) were added sequentially to a solution of the pronucleophile (**1a** or **1c**, 0.40 mmol, 1.0 equiv) in anhydrous toluene (2 mL) under an Ar atmosphere. The mixture was stirred at 80 °C for 12 h before an additional allenoate **2a** (11.2 mg, 0.10 mmol, 10 mol%) was added. Heating was continued for additional 4 h. After the noted disappearance (TLC) of the pronucleophile **1a** or **1c**, the solvent was evaporated under reduced pressure and the crude reaction product was purified through flash column chromatography (hexanes/EtOAc, 10:1) to afford **3a** or **3c**.

To unequivocally establish the connectivity of the umpolung addition/Michael product, single crystals suitable for X-ray crystallography were grown. Benzomorpholine **3c** (20 mg) was dissolved in MeOH (0.4 mL) in a 4 mL vial. EtOAc (3 mL) was added to this solution, followed

by hexanes (1 mL). The resulting solution was left to undergo slow evaporation for 1 day, which formed clear colorless needle-shaped free-floating crystals. The remaining mother liquor was decanted and the crystals were used for the X-ray crystallographic analysis without further washing. It was critical that MeOH was used because using EtOAc and hexanes mixture resulted only in the formation of powdery solids (Appendix).
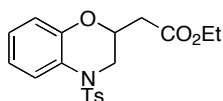
Ethyl 2-(4-Tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)acetate (3a). White solid (133.3 mg, 88% yield); m.p. 86–88 °C; IR (v, cm^{-1}): 3060, 2973, 2920, 2889, 1730, 1485, 1345, 1298, 1246, 1164; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.85 (dd, J = 8.2, 1.3 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.04 (dt, J = 8.1, 1.4 Hz, 1H), 6.92 (dt, J = 8.3, 1.4 Hz, 1H), 6.78 (dd, J = 8.1, 1.3 Hz, 1H), 4.44 (dd, J = 14.3, 2.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.85–3.77 (m, 1H), 3.17 (dd, J = 14.3, 9.9 Hz, 1H), 2.65 (dd, J = 16.2, 5.8 Hz, 1H), 2.46 (dd, J = 16.2, 7.4 Hz, 1H), 2.37 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 169.3, 146.6, 144.3, 135.5, 129.9, 127.4, 126.2, 124.3, 123.5, 121.1, 117.5, 68.2, 61.0, 48.0, 37.7, 21.6, 14.2; HRMS (ESI) calcd for C$_{19}$H$_{22}$NO$_5$S [M + H]$^+$ 376.1213, found 376.1202.
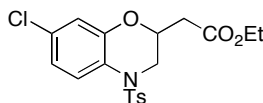
Ethyl 2-(7-Chloro-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)acetate (3c). White solid (135.3 mg, 82% yield); m.p. 93–95 °C; IR (v, cm^{-1}): 2979, 2932, 2868, 1736, 1596, 1572, 1485, 1193, 1088; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.80 (d, J = 8.9 Hz, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 6.90 (dd, J = 8.9, 2.4 Hz, 1H), 6.80 (d, J = 2.3 Hz, 1H), 4.44 (dd, J

= 14.5, 2.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 1H), 3.80–3.71 (m, 1H), 3.13 (dd, J = 14.5, 9.9 Hz, 1H),

2.63 (dd, J = 16.3, 5.8 Hz, 1H), 2.45 (dd, J = 16.3, 7.4 Hz, 1H), 2.39 (s, 3H), 1.28 (t, J = 7.1 Hz,

3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 169.1, 147.1, 144.6, 135.2, 131.2, 130.0, 127.4,

125.3, 122.3, 121.3, 117.6, 68.4, 61.1, 47.8, 37.5, 21.6, 14.2; HRMS (ESI) calcd for

C$_{19}$H$_{20}$ClNO$_5$SNa [M + Na]$^+$ 432.0643, found 432.0648.

General Procedure for the Double-Michael Reaction
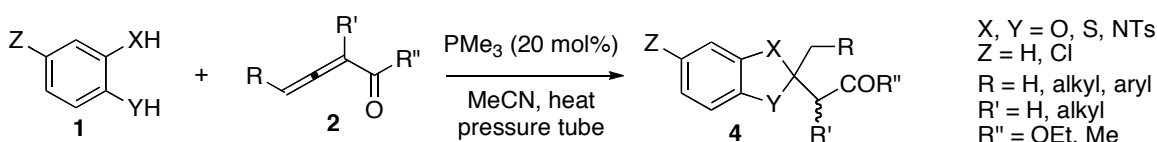
The allene (**2a–h**, **15a**, or **15b**, 0.44 mmol, 1.1 equiv) and PMe$_3$ (0.04 mmol, 10 mol%)—and

NaOAc (50 mol %) for **4w–y**—were added to a degassed solution of the pronucleophile (**1a–g**,

0.40 mmol, 1.0 equiv) in anhydrous MeCN (2 mL) in a sealed tube under an Ar atmosphere. The

reaction mixture was stirred at 90 °C [except for **4f** and **4g**, where heating at 120 °C was required

with additional allenoate (0.10 mmol) and PMe$_3$ (0.04 mmol) for 12 h] for the time indicated in

Table 1.8.4 and 1.8.5. Additional charges of the allenoate (0.10 mmol) and PMe$_3$ (0.04 mmol)

were added after 12 h for the complete consumption of the pronucleophile during the reactions

affording the double-Michael products **4i–4y**. Upon disappearance (TLC) of the nucleophiles

1a–g, the solvent was evaporated under reduced pressure and the residue purified through flash

column chromatography (5–10% EtOAc/hexanes) to produce the double-Michael products **4a–y**,

16a, and **16b** (except for **4g**, which was chromatographed using 10–33% EtOAc/hexanes).

General Procedure of the Double-Michael Reaction using DMAP

The allene (**2**, 0.44 mmol, 1.1 equiv) and DMAP (0.04 mmol, 0.1 equiv) were added to a solution of the pronucleophile (**1**, 0.40 mmol, 1.0 equiv) in anhydrous MeCN (2 mL) in a sealed tube under an Ar atmosphere. The reaction mixture was stirred at 90 °C [except for **4f** and **4g**, where heating at 120 °C was required with additional allenoate (0.10 mmol) and DMAP (0.04 mmol) for 12 h] for the time indicated in Table 1.8.4 and 1.8.5. Additional charges of the allenoate (0.10 mmol) and DMAP (0.04 mmol) were added after 12 h for the complete consumption of the pronucleophile during the reactions affording the double-Michael products **4j–l**, **4n–p**, **4r**, and **4s**. Upon disappearance (TLC) of the nucleophiles **1a–c**, **f**, **g**, the solvent was evaporated under reduced pressure and the residue purified through flash column chromatography (5–10% EtOAc/hexanes) to produce the double-Michael products **4f**, **4j–l**, **4n–p**, **4r**, and **4s**, (except for **4g**, which was chromatographed using 10–33% EtOAc/hexanes).

Physical and Spectroscopic Data for the Double-Michael Products

To assign the sets of peaks corresponding to each diastereoisomer for compounds **4w–y**, DEPT, HMQC, and HMBC NMR spectroscopy experiments were used.
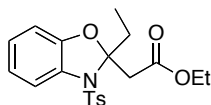
Ethyl 2-(2-Ethyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetate (4a). White solid (127.3 mg, 86% yield); m.p. 86–88 °C; IR (ν, cm⁻¹): 3060, 2979, 2932, 2880, 1736, 1596, 1474, 1363, 1164; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.86 (d, *J* = 8.4 Hz, 2H), 7.34–7.31 (m, 1H), 7. 28 (d, *J* = 8.4 Hz, 2H), 6.90–6.80 (m, 2H), 6.73–6.70 (m, 1H), 3.95–3.80 (m, 2H), 3.33 (d, *J* = 15.6 Hz, 1H), 3.10 (d, *J* = 15.6 Hz, 1H), 2.40 (s, 3H), 2.30 (dq, *J* = 15.0, 7.2 Hz, 1H), 2.25 (dq, *J* = 15.0,

7.2 Hz), 0.98 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 168.1, 149.4, 144.3, 137.6, 130.6, 129.8, 127.0, 123.4, 121.1, 111.9, 108.5, 105.1, 60.7, 43.5, 32.6, 29.7, 21.5, 13.7, 7.0; HRMS (ESI) calcd for C$_{20}$H$_{24}$NO$_5$S [M + H]$^+$ 390.1370, found 390.1369.
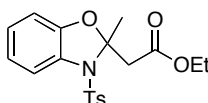
Ethyl 2-(2-Methyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetate (4b). White solid (130.9 mg, 92% yield); m.p. 76–78 °C; IR (ν, cm^{-1}): 3066, 2984, 2932, 2897, 1736, 1596, 1479, 1363, 1252, 1158; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.79 (d, J = 8.4 Hz, 2H), 7.39 (dd, J = 7.2, 1.2 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 6.95–6.84 (m, 2H), 6.74 (dd, J = 7.2, 1.5 Hz, 1H), 4.04 (q, J = 6.9 Hz, 2H), 3.23 (d, J = 15.0 Hz, 1H), 3.13 (d, J = 15.0 Hz, 1H), 2.39 (s, 3H), 1.92 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 168.1, 148.6, 144.4, 137.8, 129.9, 129.7, 126.9, 123.9, 121.5, 113.1, 109.4, 102.5, 60.8, 45.4, 24.9, 21.6, 13.9; HRMS (ESI) calcd for C$_{19}$H$_{22}$NO$_5$S [M + H]$^+$ 376.1213, found 376.1202.
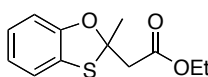
Ethyl 2-(2-Methylbenzo[*d*][1,3]oxathiol-2-yl)acetate (4c). Colorless oil (88.1 mg, 93% yield); IR (ν, cm^{-1}): 3056, 2979, 1736, 1461, 1374, 1339, 1234, 1176; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.10 (d, J = 7.5, 1.3 Hz, 1H), 6.99 (dt, J = 7.7, 1.4 Hz, 1H), 6.87 (dt, J = 7.5, 1.2 Hz, 1H), 6.79 (dd, J = 8.0, 1.0 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.16 (d, J = 15.7 Hz, 1H), 3.07 (d, J = 15.6 Hz, 1H), 1.97 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 169.1, 154.4, 126.2, 125.8, 122.3, 122.0, 110.7, 96.5, 60.9, 47.3, 28.5, 14.1; HRMS (ESI) calcd for C$_{12}$H$_{14}$O$_3$SNa [M + Na]$^+$ 261.0556, found 261.0549.
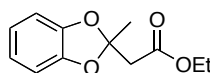
Ethyl 2-(2-Methylbenzo[*d*][1,3]dioxol-2-yl)acetate (4d). Colorless oil (72.8 mg, 80% yield); IR (ν, cm⁻¹): 3060, 2979, 2932, 2903, 1736, 1485, 1374, 1223; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 6.82–6.75 (m, 4H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.95 (s, 2H), 1.82 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 168.2, 146.9, 121.4, 115.6, 108.7, 60.9, 44.0, 24.6, 14.0; HRMS (ESI) calcd for C₁₂H₁₄O₄Na [M + Na]⁺ 245.0784, found 245.0783.
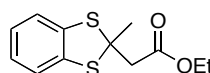
Ethyl 2-(2-Methylbenzo[*d*][1,3]dithiol-2-yl)acetate (4e). Colorless oil (73.2 mg, 74% yield); IR (ν, cm⁻¹): 3049, 2979, 2915, 2845, 1724, 1444, 1363, 1334, 1188; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.19–7.15 (m, 2H), 7.05–6.99 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.16 (s, 2H), 2.02 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 169.4, 137.7, 125.6, 122.6, 64.5, 60.9, 47.5, 28.6, 14.2; HRMS (ESI) calcd for C₁₂H₁₄O₂S₂Na [M + Na]⁺ 277.0327, found 277.0327.
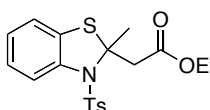
Ethyl 2-(2-Methyl-3-tosyl-2,3-dihydrobenzo[*d*]thiazol-2-yl)acetate (4f). Yellow oil (106.4 mg, 68% yield); IR (ν, cm⁻¹): 3060, 2979, 2926, 2862, 1730, 1596, 1672, 1461, 1362; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.66–7.63 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.10–7.00 (m, 3H), 4.20–4.09 (m, 2H), 3.35 (d, *J* = 15.3 Hz, 1H), 3.13 (d, *J* = 15.3 Hz, 1H), 2.38 (s, 3H), 2.18 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 169.1, 144.1, 138.8, 138.1, 129.8, 129.6, 126.8, 125.5, 125.4, 122.4, 119.1, 78.2, 60.9, 47.9, 26.0, 21.6, 14.1; HRMS (ESI) calcd for C₁₉H₂₁NO₄S₂Na [M + Na]⁺ 391.5043, found 391.5040.
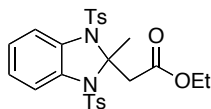
Ethyl 2-(2-Methyl-1,3-ditosyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)acetate (4g). White solid (169.1 mg, 79% yield); m.p. 194–196 °C; IR (v, cm^{-1}): 3060, 2973, 2921, 2891, 1730, 1590, 1479, 1369, 1257; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.67 (d, J = 8.3 Hz, 4H), 7.52–7.46 (m, 2H), 7.18 (d, J = 8.4 Hz, 4H), 6.98–6.92 (m, 2H), 3.80 (q, J = 7.1 Hz, 2H), 3.49 (s, 2H), 2.37 (s, 6H), 2.14 (s, 3H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 168.1, 144.2, 137.9, 131.9, 129.7, 126.9, 123.7, 113.6, 88.8, 60.7, 45.6, 25.4, 21.6, 13.6; HRMS (ESI) calcd for C$_{26}$H$_{29}$N$_2$O$_6$S$_2$ [M + H]$^+$ 529.1462, found 529.1442.
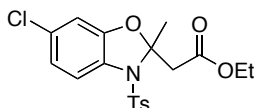
Ethyl 2-(6-Chloro-2-methyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetate (4h). White solid (139.5 mg, 84% yield); m.p. 70–72 °C; IR (v, cm^{-1}): 3054, 2985, 2926, 2856, 1736, 1590, 1474, 1363, 1246; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.76 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.5 Hz, 1H), 6.85 (dd, J = 8.4, 2.0 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 4.04 (q, J = 7.14 Hz, 2H), 3.23 (d, J = 15.3 Hz, 1H), 3.09 (d, J = 15.3 Hz, 1H), 2.40 (s, 3H), 1.89 (s, 3H), 1.14 (t, J = 7.14 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 167.9, 149.4, 144.7, 129.9, 128.9, 128.8, 126.9, 121.3, 113.4, 110.2, 103.5, 60.9, 45.2, 25.0, 21.6, 13.9; HRMS (ESI) calcd for C$_{19}$H$_{21}$ClNO$_5$S [M + H]$^+$ 410.0823, found 410.0824.
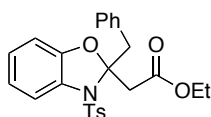
Ethyl 2-(2-Benzyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetate (4i). Colorless oil (141.9 mg, 83% yield); IR (ν, cm^{-1}): 3062, 3025, 2979, 2923, 2868, 1740, 1594, 1481, 1363; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.81 (d, J = 8.4 Hz, 2H), 7.42–7.17 (m, 8H), 6.86–6.68 (m, 3H), 3.88–3.71 (m, 2H), 3.60 (d, J = 14.0 Hz, 1H), 3.43 (d, J = 13.9 Hz, 1H), 3.40 (d, J = 16.2, 1H), 3.06 (d, J = 16.3 Hz, 1H), 2.38 (s, 3H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 167.8, 149.0, 144.4, 137.7, 133.9, 131.2, 130.3, 129.8, 128.1, 127.2, 127.0, 123.5, 121.2, 112.2, 108.8, 103.8, 60.6, 45.7, 41.6, 21.6, 13.7; HRMS (ESI) for C$_{25}$H$_{26}$NO$_5$S [M + H]$^+$ 452.1526, found 452.1513.
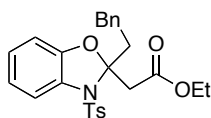
Ethyl 2-(2-Phenethyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetate (4j). White solid (114.2 mg, 61% yield); m.p. 79–81 °C; IR (ν, cm^{-1}): 3061, 3026, 2979, 2932, 2868, 1736, 1596, 1479, 1369, 1252, 1164, 1106; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.88 (d, J = 8.3 Hz, 2H), 7.39–7.14 (m, 6H), 7.07 (d, J = 8.0 Hz, 2H), 6.9 (dq, J = 7.7, 1.6 Hz, 2H), 6.76 (dd, J = 6.9, 1.9 Hz, 1H), 3.82–3.99 (m, 2H), 3.37 (d, J = 15.9 Hz, 1H), 3.14 (d, J = 15.6 Hz, 1H), 2.62 (m, 4H), 2.40 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 167.9, 149.2, 144.5, 140.6, 137.6, 130.5, 130.0, 128.4, 127.1, 126.0, 123.5, 121.3, 112.0, 108.7, 104.2, 60.7, 43.6, 41.3, 28.7, 21.6, 13.7; HRMS (ESI) calcd for C$_{26}$H$_{28}$NO$_5$S [M + H]$^+$ 466.1683, found 466.1672.
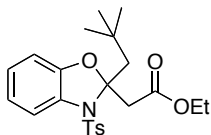
Ethyl 2-(2-Neopentyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetate (4k). White solid (120.1 mg, 69% yield); m.p. 82–84 °C; IR (ν, cm^{-1}): 2950, 2897, 2862, 1713, 1631, 1503, 1491, 1368,

1339; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm); 7.84 (d, J = 8.4 Hz, 2H), 7.41–7.38 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 6.92–6.84 (m, 2H), 6.71–6.68 (m, 1H), 3.87–3.68 (m, 2H), 3.29 (d, J = 16.0 Hz, 1H), 3.13 (d, J = 16.0 Hz, 1H), 2.39 (s, 3H), 2.36 (d, J = 15.2 Hz, 1H), 2.22 (d, J =15.2 Hz, 1H), 0.99 (s, 9H), 0.93 (t, J = 7.1 Hz, 1H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 167.9, 149.2, 144.3, 137.8, 130.0, 129.7, 127.2, 123.5, 121.1, 112.3, 108.8, 105.1, 60.5, 51.3, 44.4, 31.0, 21.5, 13.6; HRMS (ESI) calcd for C$_{23}$H$_{29}$NO$_5$SNa [M + Na]$^+$ 454.1659, found 454.1658.
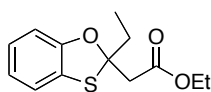

Ethyl 2-(2-Ethylbenzo[d][1,3]oxathiol-2-yl)acetate (4l). Colorless oil (80.7 mg, 74% yield); IR (ν, cm^{-1}): 3066, 2967, 2926, 2874, 1730, 1573, 1462, 1369, 1234, 1182; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.09 (dd, J = 7.5, 0.9 Hz, 1H), 6.98 (td, J = 7.8, 1.2 Hz, 1H), 6.85 (td, J = 7.5, 1.2 Hz, 1H), 6.78 (dd, J = 7.8, 0.9 Hz, 1H), 4.14 (q, J = 6.9 Hz, 2H), 3.14 (d, J = 15.6 Hz, 1H), 3.08 (d, J = 15.6 Hz, 1H), 2.27 (dq, J = 14.4, 7.2 Hz, 1H), 2.23 (dq, J = 14.4, 7.2 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 169.1, 155.1, 126.0, 125.6, 122.1, 121.8, 110.3, 100.3, 60.9, 45.6, 33.6, 14.1, 8.9; HRMS (ESI) calcd for C$_{13}$H$_{16}$O$_3$SNa [M + Na]$^+$ 275.0712, found 275.0709.
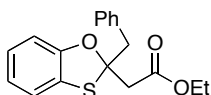
Ethyl 2-(2-Benzylbenzo[d][1,3]oxathiol-2-yl)acetate (4m). Yellow oil (106.9 mg, 86% yield); IR (ν, cm^{-1}): 3062, 3030, 2978, 2933, 1730, 1572, 1455, 1373, 1233; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.32–7.27 (m, 5H), 7.11 (dd, J = 7.5, 1.4 Hz, 1H), 7.00 (td, J = 7.7, 1.4 Hz, 1H), 6.88 (td, J = 7.5, 1.2 Hz, 1H), 6.84 (dd, J = 7.5, 1.1 Hz, 1H), 4.25–4.15 (m, 2H), 3.64 (d, J = 14.0

Hz, 1H), 3.46 (d, *J* = 14.0 Hz, 1H), 3.10 (d, *J* = 16.3 Hz, 1H), 2.98 (d, *J* = 16.3 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 169.4, 154.4, 135.5, 130.7, 128.3, 127.2, 126.2, 125.8, 122.3, 122.0, 110.7, 99.1, 61.0, 46.3, 43.8, 14.2; HRMS (ESI) calcd for C$_{18}$H$_{19}$O$_3$S [M + H]$^+$ 315.1049, found 315.1038.
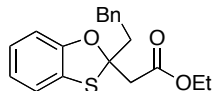
Ethyl 2-(2-Phenethylbenzo[*d*][1,3]oxathiol-2-yl)acetate (4n). Colorless oil (85.0 mg, 65% yield); IR (ν, cm^{-1}): 3072, 3026, 2973, 2926, 2851, 1730, 1602, 1573, 1462, 1369; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.31–7.27 (m, 2H), 7.22–7.17 (m, 3H), 7.13 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.01 (td, *J* = 7.6, 1.4 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.82 (dd, *J* = 7.9, 0.9 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.20 (d, *J* = 15.7 Hz, 1H), 3.14 (d, *J* = 15.7 Hz, 1H), 3.01–2.93 (m, 1H), 2.86–2.79 (m, 1H), 2.60–2.45 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 169.0, 154.9, 141.1, 128.5, 126.0, 125.9, 125.8, 125.8, 122.2, 121.9, 110.4, 99.2, 60.9, 46.1, 42.3, 30.9, 14.1; HRMS (ESI) calcd for C$_{19}$H$_{20}$O$_3$SNa [M + Na]$^+$ 351.1025, found 351.1020.
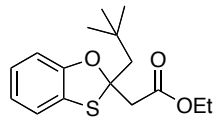
Ethyl 2-(2-Neopentylbenzo[*d*][1,3]oxathiol-2-yl)acetate (4o). Colorless oil (67.5 mg, 58% yield); IR (ν, cm^{-1}): 3067, 2951, 2904, 2865, 1733, 1574, 1465, 1368, 1236; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.10 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.98 (td, *J* = 7.7, 1.4 Hz, 1H), 6.86 (td, *J* = 7.5, 1.2 Hz, 1H), 6.78 (dd, *J* = 7.9, 0.9 Hz, 1H), 4.21–4.10 (m, 2H), 3.22 (s, 2H), 2.33 (d, *J* = 15.3 Hz, 1H), 2.22 (d, *J* = 15.3 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.1 (s, 9H); ^{13}C NMR (75.5 MHz,

CDCl$_3$) δ (ppm) 169.4, 154.3, 126.5, 125.6, 122.1, 121.7, 110.7, 99.7, 60.8, 51.4, 47.0, 31.8, 31.0, 14.1; HRMS (ESI) calcd for C$_{16}$H$_{23}$O$_3$S [M + H]$^+$ 295.1362, found 295.1354.
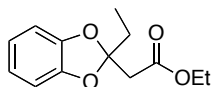
Ethyl 2-(2-Ethylbenzo[*d*][1,3]dioxol-2-yl)acetate (4p). Colorless oil (97.5 mg, 70% yield); IR (ν, cm^{-1}): 3066, 2979, 2932, 1742, 1596, 1479, 1369; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.78 (s, 4H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.93 (s, 2H), 2.13 (q, *J* = 7.4 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 168.2, 147.5, 121.3, 117.4, 108.4, 60.8, 42.5, 30.9, 13.9, 6.9; MS (EI) calcd for C$_{13}$H$_{16}$O$_4$Na [M + Na]$^+$ 259.0941, found 259.0937.
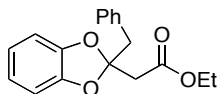
Ethyl 2-(2-Benzylbenzo[*d*][1,3]dioxol-2-yl)acetate (4q). Colorless oil (94.8 mg, 77% yield); IR (ν, cm^{-1}): 3062, 3030, 2981, 2925, 1736, 1485, 1333, 1234, 1088; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.36–7.23 (m, 5H), 6.77 (s, 4H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.41 (s, 2H), 2.88 (s, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 168.3, 147.1, 134.2, 130.7, 128.3, 127.2, 121.4, 116.5, 108.6, 60.9, 43.5, 41.6, 14.0; HRMS (ESI) calcd for C$_{18}$H$_{18}$O$_4$Na [M + Na]$^+$ 321.1097, found 321.1098.
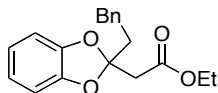
Ethyl 2-(2-Phenethylbenzo[*d*][1,3]dioxol-2-yl)acetate (4r). Colorless oil (111.9 mg, 89% yield); IR (ν, cm^{-1}): 3060, 3019, 2976, 2932, 2862, 1736, 1479, 1234, 1099; ^{1}H NMR (300 MHz,

CDCl$_3$) δ (ppm) 7.32–7.27 (m, 2H), 7.23–7.17 (m, 2H), 6.84 (s, 4H), 4.14 (q, J = 7.1 Hz, 2H),

2.99 (s, 2H), 2.87–2.82 (m, 2H), 2.50–2.44 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.5

MHz, CDCl$_3$) δ (ppm) 168.1, 147.4, 141.0, 128.5, 128.4, 126.1, 121.5, 116.6, 108.6, 61.0, 43.0,

39.6, 28.9, 14.0; HRMS (ESI) calcd for C$_{19}$H$_{20}$O$_4$ [M + Na]$^+$ 335.1254, found 335.1243.
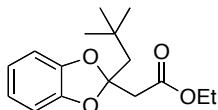
Ethyl 2-(2-Neopentylbenzo[*d*][1,3]dioxol-2-yl)acetate (4s). Colorless oil (92.6 mg, 82% yield);

IR (ν, cm^{-1}): 3066, 2953, 2906, 2867, 1735, 1495, 1365, 1234, 1087; ^{1}H NMR (300 MHz,

CDCl$_3$) δ (ppm) 6.82–6.75 (m, 4H), 4.09 (q, J = 7.1 Hz, 2H), 2.88 (s, 2H), 2.14 (s, 2H), 1.16 (t, J

= 7.1 Hz, 3H), 1.00 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 168.4, 147.0, 121.4, 117.7,

108.7, 60.8, 48.5, 45.0, 30.8, 30.7, 14.0; HRMS (ESI) calcd for C$_{16}$H$_{22}$O$_4$Na [M + Na]$^+$

301.1410, found 301.1404.
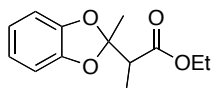
Ethyl 2-(2-Methylbenzo[*d*][1,3]dioxol-2-yl)propanoate (4t). Colorless oil (85.4 mg, 89%

yield); IR (ν, cm^{-1}): 3066, 2984, 2938, 2903, 1736, 1485, 1374, 1339, 1234, 1199; ^{1}H NMR (300

MHz, CDCl$_3$) δ (ppm) 6.81–6.74 (m, 4H), 4.20–4.10 (m, 2H), 3.06 (q, J = 7.2 Hz, 1H), 1.73 (s,

3H), 1.32 (d, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm)

172.0, 147.2, 121.3, 117.8, 108.5, 60.8, 48.1, 21.9, 14.1, 12.3; HRMS (ESI) calcd for

C$_{13}$H$_{16}$O$_4$Na [M + Na]$^+$ 259.0941, found 259.0937.
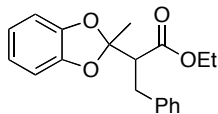
Ethyl 2-(2-Methylbenzo[*d*][1,3]dioxol-2-yl)-3-phenylpropanoate (4u). Colorless oil (108.2 mg, 86% yield); IR (ν, cm^{-1}): 3061, 3029, 2978, 2937, 1736, 1484, 1375, 1240; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.27–7.15 (m, 5H), 6.83–6.79 (m, 4H), 4.02 (q, J = 7.1 Hz, 2H), 3.28 (t, J = 6.9 Hz, 1H), 3.08 (d, J = 6.7 Hz, 2H), 1.80 (s, 3H), 1.04 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 170.8, 147.1, 147.0, 138.3, 128.8, 128.5, 126.5, 121.5, 121.4, 117.3, 108.8, 108.7, 60.8, 56.4, 33.4, 22.2, 14.0; HRMS (ESI) calcd for C$_{19}$H$_{20}$O$_4$Na [M + Na]$^+$ 335.1254, found 335.1241.
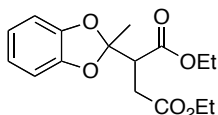
Diethyl 2-(2-Methylbenzo[*d*][1,3]dioxol-2-yl)succinate (4v). Colorless oil (99.1 mg, 80% yield); IR (ν, cm^{-1}): 3072, 2984, 2932, 2903, 1736, 1485, 1368, 1245, 1158, 1029; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.82–6.75 (m, 4H), 4.28–4.19 (m, 2H), 4.17–4.08 (m, 2H), 3.45 (dd, J = 10.9, 3.9 Hz, 1H), 2.93 (dd, J = 16.9, 10.9 Hz, 1H), 2.70 (dd, J = 16.9, 3.9 Hz, 1H), 1.71 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 171.5, 170.3, 146.9, 146.8, 121.6, 121.6, 116.6, 108.8, 108.7, 61.3, 60.9, 50.2, 31.7, 22.9, 14.1, 14.0; HRMS (ESI) calcd for C$_{16}$H$_{20}$O$_6$Na [M + Na]$^+$ 331.1152, found 331.1136.
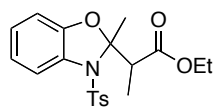
Ethyl 2-(2-Methyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)propanoate (4w). Yellow solid (126.9 mg; d.r. = 1:1; 81% yield); m.p. 72–74 °C; IR (ν, cm^{-1}): 3060, 2978, 2944, 2886, 1736,

1479, 1363, 1251, 1164. Diastereoisomer 1: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.75 (d, $J =$ 8.4 Hz, 2H), 7.48–7.47 (m, 1H), 7.26–7.20 (m, 2H), 6.99–6.89 (m, 2H), 6.76 (dd, $J =$ 7.7, 1.7 Hz, 1H), 4.11–3.90 (m, 2H), 3.26 (q, $J =$ 7.2 Hz, 1H), 2.37 (s, 3H), 1.83 (s, 3H), 1.37 (d, $J =$ 7.2 Hz, 3H), 1.10 (t, $J =$ 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 171.9, 149.4, 144.4, 137.7, 130.0, 129.7, 127.0, 124.3, 121.4, 113.6, 109.4, 104.9, 60.7, 48.8, 22.3, 21.5, 13.9, 12.3. Diastereoisomer 2: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.67 (d, $J =$ 8.4 Hz, 2H), 7.51–7.50 (m, 1H), 7.26–7.20 (m, 2H), 6.87–6.70 (m, 2H), 6.72 (dd, $J =$ 7.7, 1.3 Hz, 1H), 4.25–4.13 (m, 2H), 3.41 (q, $J =$ 6.9 Hz, 1H), 2.38 (s, 3H), 1.86 (s, 3H), 1.26 (t, $J =$ 7.2 Hz, 3H), 1.23 (d, $J =$ 7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 171.8, 149.5, 144.3, 137.7, 130.0, 129.7, 127.0, 124.9, 121.5, 114.8, 109.2, 104.7, 60.9, 49.9, 21.5, 20.4, 14.1, 11.6. HRMS (ESI) calcd for C$_{20}$H$_{24}$NO$_5$S [M + H]$^+$ 390.1370, found 390.1371.
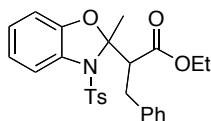
Ethyl 2-(2-Methyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)-3-phenylpropanoate (4x). Yellow solid (129.1 mg; d.r. = 2:1; 73% yield); m.p. 92–97 °C; IR (ν, cm^{-1}): 3066, 3026, 2973, 2926, 2856, 1736, 1596, 1479, 1363, 1252, 1164. Major diastereoisomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.79 (d, $J =$ 8.4 Hz, 2H), 7.64 (d, $J =$ 8.4 Hz, 2H), 7.60–7.53 (m, 2H), 7.39–7.15 (m, 5H), 7.05–6.92 (m, 2H), 3.98–3.79 (m, 2H), 3.37 (dd, $J =$ 12.0, 3.3 Hz, 1H), 3.29 (dd, $J =$ 13.5, 3.0 Hz, 1H), 3.13–3.01 (m, 1H), 2.37 (s, 3H), 1.99 (s, 3H), 0.99 (t, $J =$ 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 170.8, 149.8, 144.4, 138.5, 137.6, 130.0, 129.8, 128.9, 128.4, 127.1, 126.5, 125.6, 116.2, 109.7, 104.4, 60.7, 57.1, 33.2, 21.5, 19.6, 13.9. Minor diastereoisomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.79 (d, $J =$ 8.4 Hz, 2H), 7.64 (d, $J =$ 8.4

Hz, 2H), 7.39–7.15 (m, 5H), 7.05–6.92 (m, 2H), 6.91–6.74 (m, 2H), 4.12–4.00 (m, 2H), 3.64 (dd, J = 10.2, 4.8 Hz, 1H), 3.13–3.01 (m, 2H), 2.36 (s, 3H), 1.84 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm); 170.6, 149.2, 144.5, 138.5, 137.8, 130.0, 129.9, 129.0, 128.3, 127.0, 126.4, 124.5, 114.0, 109.5, 104.2, 60.9, 58.2, 32.5, 22.3, 19.6, 14.0. HRMS (ESI) calcd for C$_{26}$H$_{27}$NO$_5$SNa [M + Na]$^+$ 466.1683, found 466.1671.
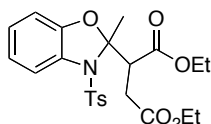
Diethyl 2-(2-Methyl-3-tosyl-2,3-dihydrobenzo[d]oxazol-2-yl)succinate (4y). Yellow solid (147.4 mg; d.r. = 1.2:1; 84% yield); m.p. 127–130 °C; IR (ν, cm^{-1}): 3066, 2979, 2903, 2868, 1742, 1590, 1468, 1363, 1246, 1164. Major diastereoisomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.75 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.56–7.51 (m, 1H), 7.27–7.12 (m, 2H), 6.76–6.74 (m, 1H), 4.28–4.20 (m, 2H), 3.50 (dd, J = 11.1, 3.9 Hz, 1H), 3.04–2.85 (m, 2H), 2.35 (s, 3H), 1.86 (s, 3H), 1.26–1.16 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 171.4, 170.5, 149.5, 144.4, 137.4, 129.9, 129.8, 127.0, 125.6, 121.9, 116.2, 109.8, 103.5, 61.2, 60.9, 50.7, 32.1, 21.5, 19.7, 14.1, 13.9. Minor diastereoisomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.75 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.25–7.04 (m, 2H), 7.04–6.88 (m, 2H), 4.16–4.01 (m, 2H), 3.75 (dd, J = 11.1, 3.9 Hz, 1H), 3.04–2.85 (m, 1H), 2.61 (dd, J = 17.1, 3.3 Hz, 1H), 2.37 (s, 3H), 1.83 (s, 3H), 1.32 (t, J = 8.1 Hz, 3H), 1.26–1.16 (m, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 171.4, 170.3, 148.7, 144.5, 137.5, 129.9, 129.6, 127.0, 124.5, 121.8, 113.9, 109.5, 103.7, 61.4, 60.8, 51.7, 31.6, 22.8, 19.7, 14.1, 14.0. HRMS (ESI) calcd for C$_{23}$H$_{28}$NO$_7$S [M + H]$^+$ 462.1581, found 462.1594.
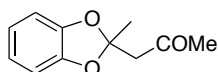
1-(2-Methylbenzo[*d*][1,3]dioxol-2-yl)propan-2-one (16a). Colorless oil (53.0 mg, 68% yield); IR (v, cm^{-1}): 3050, 2991, 2929, 1713, 1485, 1363, 1265, 1237, 730, 703; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 6.83–6.81 (m, 1H), 6.80–6.78 (m, 2H), 6.78–6.76 (m, 1H), 3.05 (s, 2H), 2.22 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 204.1, 146.8, 121.6, 115.8, 108.9, 51.8, 31.6, 24.3; MS (ESI) calcd for C$_{11}$H$_{12}$O$_3$Na [M + Na]$^+$ 215.0684, found 215.0677.
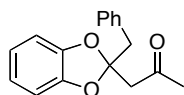
1-(2-Benzylbenzo[d][1,3]dioxol-2-yl)propan-2-one (16b). White solid (53.0 mg, 90% yield); m.p. = 76–78 °C; IR (v, cm^{-1}): 3061, 3019, 2909, 2844, 1718, 1479, 1357, 1229; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.34–7.24 (m, 5H), 6.80 (s, 4H), 3.37 (s, 2H), 2.98 (s, 2H), 2.17 (s, 2H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 204.1, 146.9, 134.3, 130.7, 128.3, 127.2, 121.6, 116.8, 108.8, 49.2, 43.3, 31.7; MS (ESI) calcd for C$_{17}$H$_{16}$O$_3$Na [M + Na]$^+$ 291.0092, found 291.1000.
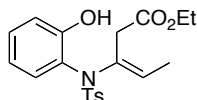
(*E*)-Ethyl 3-[*N*-(2-Hydroxyphenyl)-4-methylphenylsulfonamido]pent-3-enoate (5a). Colorless oil (4.4 mg, 3% yield); IR (v, cm^{-1}): 2979, 2921, 2862, 1730, 1684, 1602, 1497, 1170; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.30 (s, 1H), 7.75 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.68 (d, *J* = 8.3, 2H), 7.16 (d, *J* = 8.1, 2H), 7.10 (dt, *J* = 7.6, 1.5 Hz, 1H), 6.98 (dt, *J* = 8.0, 1.6 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.0 Hz, 1H), 3.30 (s, 2H), 2.34 (s, 3H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 171.1, 148.5, 143.4, 143.0, 136.8, 130.6, 129.3, 127.3, 125.6, 124.3, 122.3, 120.4, 100.9, 61.8, 34.8, 21.5, 14.3, 11.5; HRMS (ESI) calcd for C$_{20}$H$_{23}$NO$_5$SNa [M + Na]$^+$ 412.1189, found 412.1200.
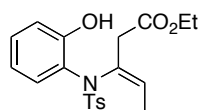
(*Z*)-Ethyl 3-[*N*-(2-Hydroxyphenyl)-4-methylphenylsulfonamido]pent-3-enoate (5b).
Colorless oil (1.5 mg, 1% yield); IR (ν, cm^{-1}): 3056, 2979, 2873, 1736, 1630, 1461, 1450, 1176;
^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.38 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.25–7.18 (m, 3H),
6.95 (d, *J* = 8.0, 1.1 Hz, 2H), 6.76 (dt, *J* = 7.4, 1.5 Hz, 1H), 5.69 (q, *J* = 7.0 Hz, 1H), 4.22 (q, *J* =
7.1 Hz, 2H), 3.34 (s, 2H), 2.41 (s, 3H), 1.69 (d, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C
NMR (75.5 MHz, CDCl$_3$) δ (ppm) 170.4, 147.6, 144.9, 143.5, 135.8, 129.5, 128.3, 127.9, 125.8,
123.7, 122.1, 116.9, 114.6, 62.8, 39.0, 20.5, 14.1, 10.6; HRMS (ESI) calcd for C$_{20}$H$_{23}$NO$_5$SNa
[M + Na]$^{+}$ 412.1189, found 412.1194.
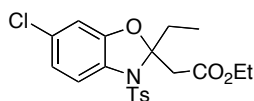
Ethyl 2-(6-Chloro-2-ethyl-3-tosyl-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetate (4aa). White solid
(39.9 mg, 23% yield); m.p. 106–108 °C; IR (ν, cm^{-1}): 3072, 2979, 2938, 2886, 1736, 1590,
1485, 1363, 1246, 1156; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.82 (d, *J* = 8.4 Hz, 2H), 7.29 (d,
J = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H),
3.94–3.83 (m, 2H), 3.32 (d, *J* = 16.0, 1H), 3.07 (d, *J* = 16.0, 1H), 2.40 (s, 3H), 2.35–2.14 (m,
2H), 1.01 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm)
167.8, 150.2, 144.6, 137.3, 129.9, 129.8, 128.2, 127.0, 120.8, 112.0, 109.3, 106.1, 60.8, 43.2,
32.8, 21.6, 13.7, 6.9; HRMS (ESI) calcd for C$_{20}$H$_{23}$ClNO$_5$S [M + H]$^{+}$ 424.0985, found 424.0979.
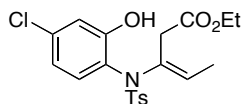
(**E**)-Ethyl 3-[**N**-(4-Chloro-2-hydroxyphenyl)-4-methylphenylsulfonamido]pent-3-enoate

(**5c**). White solid (30.1 mg, 18% yield); m.p. 118–121 °C; IR (ν, cm^{-1}): 2984, 2926, 2856, 1718, 1584, 1479, 1350, 1158; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.30 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.06 (dd, J = 8.8, 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 4.23 (q, J = 7.0 Hz, 1H), 3.28 (s, 2H), 2.35 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 171.0, 148.2, 143.7, 143.6, 136.5, 129.5, 129.3, 129.0, 127.3, 125.5, 122.4, 121.3, 102.1, 61.8, 34.6, 21.5, 14.2, 11.5; HRMS (ESI) calcd for C$_{20}$H$_{22}$ClNO$_5$SNa [M + Na]$^+$ 466.0799, found 446.0812.
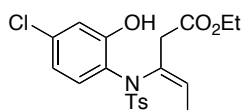
(**Z**)-Ethyl 3-[**N**-(4-Chloro-2-hydroxyphenyl)-4-methylphenylsulfonamido]pent-3-enoate

(**5d**). Colorless oil (10.4 mg, 6% yield); IR (ν, cm^{-1}): 2956, 2902, 2869, 1715, 1568, 1480, 1397, 1160; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.65 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 6.95 (dd, J = 8.6, 2.3 Hz, 1H), 6.70 (d, J = 2.3 Hz, 1H), 5.26 (q, J = 6.9 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.93 (s, 2H), 2.36 (s, 3H), 1.31 (dt, J = 6.9, 1.0 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 169.4, 146.6, 143.9, 143.5, 136.3, 130.5, 129.6, 127.3, 125.7, 123.3, 122.9, 116.0, 114.9, 61.4, 38.0, 21.5, 14.1, 10.6; HRMS (ESI) calcd for C$_{20}$H$_{22}$ClNO$_5$SNa [M + Na]$^+$ 466.0799, found 446.0806.
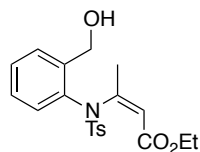
(Z)-Ethyl 3-{N-[2-(hydroxymethyl)phenyl]-4-methylphenylsulfonamido}but-2-enoate (22b).

Colorless oil (67.0 mg, 43% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.69 (t, J = 7.9 Hz, 3H), 7.46 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.2 Hz, 3H), 6.93 (d, J = 7.9 Hz, 1H), 5.66 (s, 1H), 4.84–4.81 (m, 1H), 4.67–4.59 (m, 1H), 4.08 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 2.25 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 166.7, 154.1, 144.9, 142.1, 136.3, 135.8, 130.7, 130.1, 130.0, 129.9, 128.7, 128.4, 108.6, 61.0, 60.0, 21.7, 17.7, 14.3.
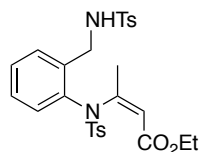
(Z)-ethyl 3-(4-methyl-N-{2-[(4-methylphenylsulfonamido)methyl]phenyl}phenylsulfon-amido)but-2-enoate (22c). Colorless oil (66.1 mg, 30% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.70–7.64 (m, 5H), 7.44 (t, J = 7.2 Hz, 1H), 7.30–7.22 (m, 5H), 6.80 (dd, J = 7.9, 1.0 Hz, 1H), 5.60 (s, 1H), 4.88–4.79 (m, 1H), 4.60–4.55 (m, 1H), 4.00 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 2.46 (s, 3H), 2.25 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H).
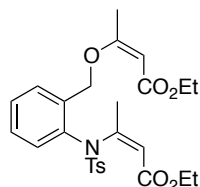
(Z)-ethyl 3-({2-[N-((Z)-4-ethoxy-4-oxobut-2-en-2-yl)-4-methylphenylsulfonamido]benzyl}-oxy)but-2-enoate (23b). Colorless oil (29.8 mg, 15% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ

(ppm) 7.69 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 7.7, 1.5 Hz, 1H), 7.47 (td, J = 7.6, 1.1 Hz, 1H), 7.39 (dd, J = 7.7, 1.7 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 7.8, 1.2 Hz, 1H), 5.73 (s, 1H), 5.09 (s, 1H), 4.87–4.85 (m, 1H), 4.76–4.72 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H).
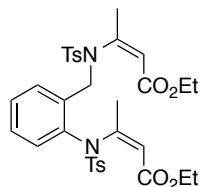
(Z)-ethyl 3-(N-{2-[N-((Z)-4-ethoxy-4-oxobut-2-en-2-yl)-4-methylphenylsulfonamido]benzyl}-4-methylphenyl-sulfonamido)but-2-enoate (23c). Colorless oil (26.6 mg, 10% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.71–7.63 (m, 5H), 7.46 (t, J = 7.2 Hz, 1H), 7.36–7.24 (m, 5H), 6.90 (dd, J = 7.9, 1.0 Hz, 1H), 5.81 (s, 1H), 5.68 (s, 1H), 4.95–4.89 (m, 1H), 4.77–4.71 (m, 1H), 4.09 (q, J = 6.9 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 2.46 (s, 3H), 2.45 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 166.6, 166.0, 153.4, 152.9, 144.9, 144.4, 138.3, 136.3, 135.8, 135.6, 130.3, 130.0, 129.9, 128.9, 128.3, 128.1, 127.5, 116.4, 108.5, 60.1, 60.0, 48.4, 21.7, 18.0, 17.7, 14.3, 14.2.
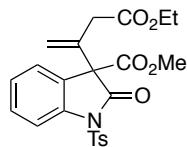
Methyl 3-(4-ethoxy-4-oxobut-1-en-2-yl)-2-oxo-1-tosylindoline-3-carboxylate (26a). Colorless oil (34.5 mg, 19% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.97–7.93 (m, 3H), 7.44–7.38 (m, 1H), 7.31 (d, J = 8.0 Hz, 3H), 7.20 (td, J = 7.6, 0.9 Hz, 1H), 5.36 (s, 1H), 5.08 (s, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.53 (s, 3H), 3.24 (d, J = 16.5 Hz, 1H), 3.16 (d, J = 16.5 Hz, 1H), 2.41 (s,

3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 170.3, 169.8, 167.6, 145.7, 139.6, 135.5, 134.8, 130.3, 129.7, 128.1, 126.1, 125.2, 125.0, 121.4, 114.2, 64.6, 60.8, 53.4, 38.4, 21.7, 14.1.
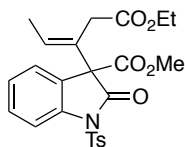
Methyl 3-(5-ethoxy-5-oxopent-2-en-3-yl)-2-oxo-1-tosylindoline-3-carboxylate (26b). Colorless oil (67.0 mg, 36% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.96–7.92 (m, 3H), 7.40 (ddd, J = 8.6, 7.1, 1.2 Hz, 1H), 7.32–7.28 (m, 3H), 7.19 (td, J = 7.6, 1.1 Hz, 1H), 5.48 (q, J = 6.9 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.51 (s, 3H), 3.34 (d, J = 17.1 Hz, 1H), 3.12 (d, J = 17.1 Hz, 1H), 2.41 (s, 3H), 1.61 (d, J = 6.9 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); 170.4, 170.0, 168.1, 145.6, 139.6, 134.6, 131.7, 130.1, 129.6, 129.1, 128.2, 128.0, 127.2, 126.3, 125.5, 125.3, 124.9, 114.2, 65.3, 60.7, 53.2, 34.2, 21.7, 14.5, 14.1.

Reference

(1)   Conrad, M.; Kuthzeit, M. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1185.

(2)   (a) Michael, A. *J. Prakt. Chem.* **1887**, *35*, 349–356. (b) Tokoyama, T. *Eur. J. Org. Chem.* **2010**, 2009.

(3)   (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, **1991**; Vol. 4, Chapter 1.1, pp 1–68. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Elsevier Science: New York, **1992**.

(4)   White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, *14*, 3597.

(5)   Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241.

(6)   Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

(7)   Yavari, I.; Souri, S.; Sirouspour, M.; Djahaniani, H.; Nasiri, F. *Synthesis*, **2005**, 1761.

(8)   Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2004**, *45*, 4507.

(9)   Li, E.; Xie, P.; Yans, L.; Liang, L.; Huang, Y. *Chem. Asian J.* **2013**, *8*, 603.

(10)   (a) Grossman, R. B. *Synlett* **2001**, 13–21. (b) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871.

(11)   Kuroda, H.; Tomita, I.; Endo, T. *Synth. Commun.* **1996**, *26*, 1539.

(12)   Yavari, I.; Souri, S.; Sirouspour, M.; Djahaniani, H. *Synthesis* **2006**, 3243.

(13)   Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928.

(14)   Sriramurthy, V.; Kwon, O. *Org. Lett.* **2010**, *12*, 1084.

(15)   Landor, S. R.; Landor, P. D.; Formum, Z. T.; Mpango, G. W. B. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2289.

(16)   Landor, S. R.; Johnson, A.; Formum, Z. T.; Nkengfack, A. E. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 609.

(17)   Cabiddu, S.; Cadoni, E.; Ciuffarin, E.; Fattuoni, C.; Floris, C. *J. Heterocycl. Chem.* **1991**, *28*, 1573.

(18)   Lu, Z.; Chai, G.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6054.

(19)   Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem, Int. Ed.* **2010**, *49*, 1481.

(20)   Zhang, X.; Jia, X.; Fang, L.; Liu, N.; Wang, J.; Fan, X. *Org. Lett.* **2011**, *13*, 5024.

(21)   (a) Kivrakidou, O.; Bräse, S.; Hulshorst, F.; Griebenow, N. *Org. Lett.* **2004**, *6*, 1143. (b) Toney, J. H.; Cleary, K. A.; Hammond, G. G.; Yuan, X. L.; May, W. J.; Hutchins, S. M.; Ashton, W. T.; Vanderwall, D. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2741.

(22)   (a) Pawa, A.; Yeske, P. E. *J. Org. Chem.* **1991**, *56*, 6386. (b) Landor, S. R.; In The Chemistry of Allene, Vol. 2; Landor, S. R., Ed.; Academic Press: New York 1982; p 361.

(23)   Cristau, H.-J.; Viala, J.; Christol, H. *Bull. Soc. Chem. Fr.* **1985**, 980.

(24)   (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819. (c) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670.

(25)   Zhang, C.; Lu, X. *Synlett* **1995**, 645.

(26)   Fourteen years later, Fu demonstrated asymmetric γ-umpolung addition to allenoates using catalytic phosphine, see: (a) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231. (b) Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225. (c) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568. (d) Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20652. (e) Fujiwara, Y.; Sun, J.; Fu, G. C. *Chem. Sci.* **2011**, *2*, 2196. (f) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 2525.

(27)   Alvarez-Ibarra, C.; Csáky, A. G.; de la Oliva, C. G. *Tetrahedron Lett.* **1999**, *40*, 8465.

(28)   Alvarez-Ibarra, C.; Csáky, A. G.; de la Oliva, C. G. *J. Org. Chem.* **2000**, *65*, 3544.

(29)   Newkome, G. R.; Paudler, W. W. Contemporary Heterocyclic Chemistry: Syntheses, Reactions and Application; Wiley: New York, **1982**.

(30)   Cristau, H.-J.; Fonte, M.; Torreilles, E. *Synthesis* **1989**, 301.

(31)   Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677.

(32)   Lu, Z.; Zheng, S.; Zhang, X., Lu, X. *Org. Lett.* **2008**, *10*, 3267.

(33)   Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595.

(34)   Boshta, N. M.; Bomkamp, M.; Waldvogel, S. R. *Tetrahedron* **2009**, *65*, 3773.

(35)   (a) Jae, H.-S.; Winn, M.; von Geldern, T. W.; Sorensen, B. K.; Chiou, W. J.; Nguyen, B.; Marsh, K. C.; Opgenorth, T. J. *J. Med. Chem.* **2001**, *44*, 3978. (b) Ullrich, T.; Baumann,

K.; Welzenbach, K.; Schmutz, S.; Camenisch, G.; Meingassner, J. G.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2483. (c) Leite, A. C. L.; da Silva, K. P.; de Souza, I. A.; de Araújo, J. M.; Brondani, D. J. *Eur. J. Med. Chem.* **2004**, *39*, 1059.

(36)   Robert, D. P.; Frank, A. H. U.S. Patent 4708810, **1987**.

(37)   (a) Biekert, E.; Hoffman, D.; Meyer, F. J. *Chem. Ber.* **1961**, *94*, 1664. (b) Xuezheng, L.; Shan, G.; Wenjuan, W.; Wenping, C; Jianguo, Y. *Chin. J. Chem. Eng.* **2008**, *16*, 124. (c) Toeroek, B. *J. Fluorine Chem.* **2007**, *128*, 587. (d) Hurtley, W. R. H.; Smiles, S. *J. Chem. Soc.* **1926**, 2263.

(38)   (a) Iwagami, H.; Yatagai, M.; Nakazawa, M.; Orita, H.; Honda, Y.; Ohnuki, T.; Yukawa, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 175. (b) Chan, T. H.; Brook, M. A.; Chaly, T. *Synthesis* **1983**, 203.

(39)   Prakash, G. K. S.; Mathew, T.; Panja, C.; Vaghoo, H.; Venkataraman, K.; Olah, G. A. *Org. Lett.* **2007**, *9*, 179.

(40)   Andersen, K. K.; Gowda, G.; Jewell, L.; McGraw, P.; Phillips, B. T. *J. Org. Chem.* **1982**, *47*, 1884.

(41)   The structures of **3c** (5-chlorobenzene variant of **3a**), **4a**, and **5c** (5-chlorobenzene variant of **5a**) were established unequivocally through X-ray crystallographic analyses. See the Experimental and Appendix for details.

(42)   (a) Streuli, C. A. *Anal. Chem.* **1960**, *32*, 985. (b) Ripin, D. H.; Evans, D. A. *Evans pK$_a$ Table.* http://www2.lsdiv.harvard.edu/labs/evans/index.html (accessed June 2011).

(43)   (a) Ofial, A.; Mayr. H. *Reactivity Scales.* http://www.cup.unimuenchen.de/oc/mayr/CDpublika.html (accessed June 2011). (b) Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr. H. *Chem.–Eur. J.* **2007**, *13*, 336.

(44)   Mizukami, S.; Kono, M. *Chem. Pharm. Bull.* **1965**, *13*, 33.

(45)   Kato, T.; Masu, H.; Takayangi, H.; Kaji, E.; Katagiri, K.; Tominaga, M.; Azumaya, I. *Tetrahedron* **2006**, *62*, 8458.

(46)   Lang, R. W.; Hansen, H.-J. *Org. Synth.* **1984**, *62*, 202.

(47)   Phosphine catalysis using α-substituted allenoates: (a) Kumar, K.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 787. (b) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (c) Tran, Y. S.; Kwon. O. *Org. Lett.* **2005**, *7*, 4289. (d) Zhao, G.-L.; Shi, M. *Org. Biomol. Chem.* **2005**, *3*, 3686. (e) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. (f) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (g) Lu, K.; Kwon, O. *Org. Synth.* **2009**, *86*, 212. (h) Guo, H.; Xu, Q.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318.

(i) Wang, T.; Ye, S. *Org. Lett.* **2010**, *12*, 4168. (j) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550. (k) Wang, Z.; Castellano, S.; Kinderman, S. S.; Argueta, C. E.; Beshir, A. B.; Fenteany, G.; Kwon, O. *Chem. Eur. J.* **2011**, *17*, 649. (l) Guan, X.-Y.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, 2673. (m) Cruz, D.; Wang, Z.; Kibbie, J.; Modlin, R.; Kwon, O. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6769. (n) Baskar, B.; Dakas, P.-Y.; Kumar, K. *Org. Lett.* **2011**, *13*, 1988. (o) Martin, T. J.; Vakhshori, V. G.; Tran, Y. S.; Kwon, O. *Org. Lett.* **2011**, *13*, 2586.

(48)   Xu, S.; Zhou, L.; Zeng, S.; Ma, R.; Wang, Z.; He, Z. *Org. Lett.* **2009**, *11*, 3498.

(49)   Tricyclohexylphosphine, which is comparable in size to triphenylphosphine, produced only the double-Michael product **4b** (in yields of 93%) when mixed with the allene **2a** and nucleophile **1a**.

(50)   (a) Reference 4. (b) Yoshida, T.; Saito, S. *Chem. Lett.* **1982**, 1587. (c) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553. (d) Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A.; Lago, E.; Molins, E. *Eur. J. Org. Chem.* **2001**, 2321. (e) Ref. 6.

(51)   Kumar, K.; Kaur, S.; Ishar, M. P. S. *Synlett* **1999**, 1237.

Chapter 2

Nitro-Nazarov Reaction with Nitrodienes

2.1 Introduction: Significance of Nitro Groups

In organic synthesis, the chemistry of nitro compounds has a long and copious history.[1] The high oxidation state of the nitro group provides many physical properties that have chemical importance. For example, the electron-withdrawing capability of the nitro group results from both dipolar and resonance effects. This allows for nucleophilic addition and reduction to proceed on aromatic and olefinic nitro compounds. Secondly, the α-protons of aliphatic nitro compounds are acidic, which gives rise to tautomers (Scheme 2.1.1).[2] The *aci*-nitro or isonitro tautomer is typically present in minor concentrations, with the equilibrium constant between 10^{-5} and 10^{-7}.[3] The alkylation of the tautomer provides both α-substituted nitro compounds and the regioisomeric nitronic esters (nitronates).
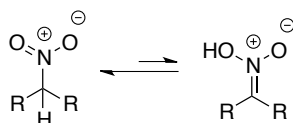
Scheme 2.1.1 Equilibrium of the nitro compound and its tautomer

2.2 The Discovery of Nitronates

Nitronates were described as early as 1894.[4] However, it was not until 1901 that the first isolation of a nitronate compound was disclosed, which resulted from the addition of diazomethane to phenylazonitromethane (Scheme 2.2.1).[5]
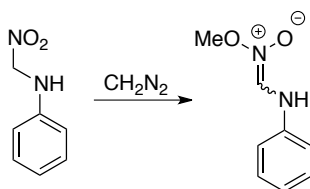
Scheme 2.2.1 The first isolation of a nitronate

The chemistry of nitronates remained unexplored during the early 1900's until Tartakovskii discovered that alkyl nitronates were excellent partners for dipolar cycloaddition with alkenes.[6]

Both acyclic and cyclic nitronates were reacted with olefins to obtain cycloadducts, which provided a new functional group where the nitrogen atom is at the center of an acetal[7], referred to as nitroso acetals[8] or nitrosals[9] (Scheme 2.2.2).
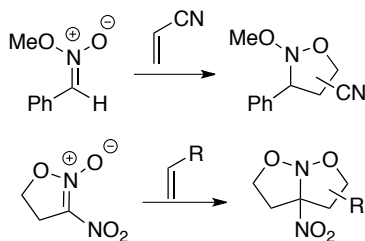
Scheme 2.2.2 Examples of cyclic and acyclic nitronates reacting with dipolarophiles

Eight years later, Loffe demonstrated that silyl nitronates could also react with alkenes in a dipolar cycloaddition reaction to provide silylated isoxazolidine cycloadducts (Scheme 2.2.3).[10] Tartakovskii's and Loffe's work was the foundation of developing new nitronate chemistry.
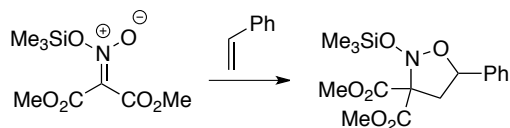
Scheme 2.2.3 Silyl nitronate reacting with styrene in a dipolar cycloaddition

2.3 Preparation of Cyclic Nitronates

Alkylation

The most common way of synthesizing cyclic nitronates was the intramolecular alkylation of a nitronate salt. Nitro compounds that contained γ- or δ-halides can cyclize under basic conditions to provide five- or six-membered cyclic nitronates, repectively.[11] The drawback to the alkylation reaction was that the nitro compounds without an electron-withdrawing group were found to be unstable.[12] Similarly, γ- or δ-hydroxy nitro compounds can cyclize under Mitsunobu conditions to produce cyclic nitronates (Scheme 2.3.1).[13]
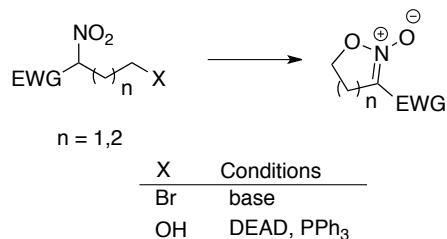
Scheme 2.3.1 γ- or δ-Hydroxy or halo nitro compounds were used to synthesize five- or six-membered nitronates

Another method for making cyclic nitronates is the addition of the potassium salt of dinitromethane to an α-malealdehyde to provide a nitro aldol intermediate that can undergo an intramolecular O-alkylation (Scheme 2.3.2).[14] The tandem reaction also applies to α-nitroacetals and unfunctionalized nitroalkenes reacting with other electrophiles, such as α-epoxyaldehyde[15], α-haloenones[16], and α-halosulfonium salts.[17]
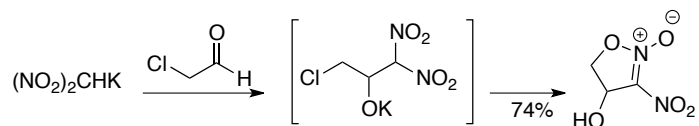
Scheme 2.3.2 Intramolecular O-alkylation via a nitro aldol intermediate

Lastly, addition of stabilized sulfonium ylide to a variety of nitroalkenes produced an intermediate nitronic acid, which upon displacement of dimethyl sulfide provides a mixture of nitrocyclopropane and cyclic nitronate (Scheme 2.3.3).[18] The ratio of products is highly dependent on the structure of alkene. For a nitroalkene without a substituent on the α-position, only the cyclopropane is observed. As of 1-nitrocylcopentene, only the nitronate product is observed.
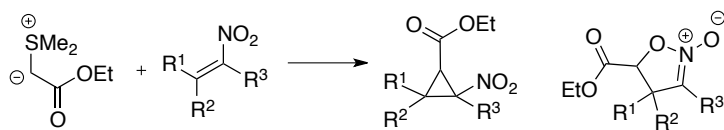
Scheme 2.3.3 Formation of nitronate by sulfonium ylide and nitroalkene

[4+2] Cycloaddition or 6π-electrocylcization

Nitroalkenes can react with dienophiles to afford cyclic nitronates by the [4+2] cycloaddition.[19] One of the N–O bonds of the nitro group participates as part of the 4π-fragment. Due to the electron-deficiency of the heterodiene, the electron-rich alkenes would react more efficiently than electron-poor alkenes. Enamines[20] and vinyl ethers[21] were the dienophiles that were studied the most (Scheme 2.3.4).
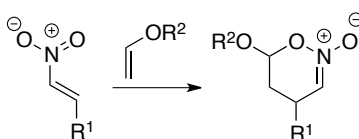
Scheme 2.3.4 [4+2] Cycloaddition between nitroalkenes and vinyl ethers

Lastly, our group demonstrated two methodologies to synthesize nitronates. First, a phosphine-catalyzed Michael addition of the nitrostyrenyl substrate followed by proton transfers to provide the nitrodiene moiety for a 6π-electrocyclization (Scheme 2.3.5).[22] Secondly, a tandem 6π-electrocyclization, [3+2] cycloaddition of nitrodienes was described. The nitrodiene performs a 6π-electrocyclization that provides the nitronate product, which then reacts with dipolarophiles to give nitroso acetals (Scheme 2.3.5).[23]
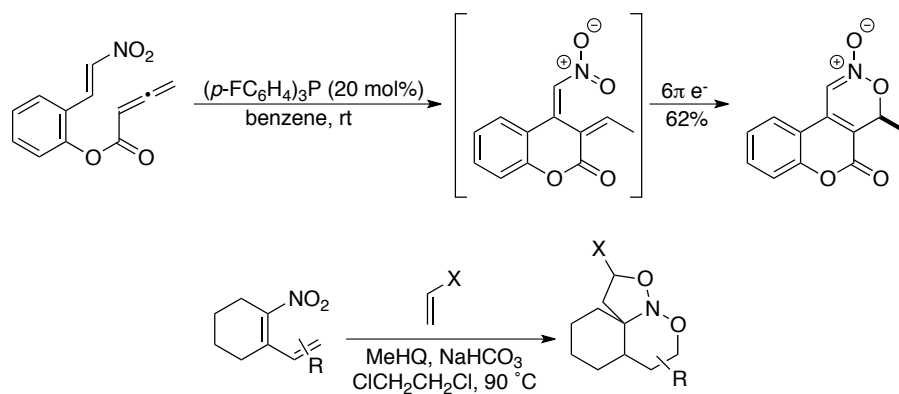
Scheme 2.3.5 Examples of Kwon's 6π-electrocyclization to form nitronates

Radical cyclization

Lastly, another method for synthesizing cyclic nitronates is the cyclization of nitro-stabilized radicals. Oxidation of the *aci*-form of the nitroalkene with ceric ammonium nitrate generates the α-carbon radical, which adds into the tethered olefin to provide the cyclic nitronate (Scheme 2.3.6).[24]
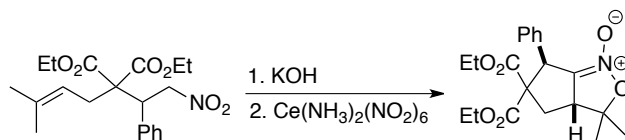
Scheme 2.3.6 Formation of a cyclic nitronate by radical cyclization

2.4 [3+2] Dipolar Cycloaddition of Nitronates

In a cycloaddition reaction, σ bonds are formed between the ends of two π systems to give a cyclic product. [3+2] Cycloaddition is one of the most common cycloaddition reactions in organic chemistry. 1,3-Dipoles react with alkenes or alkynes to produce five-membered heterocycles. All 1,3-dipoles have a formal positive charge at one terminus and a negative charge at the other terminus with a heteroatom (N or O) in the center in order to help stabilize the electron-deficient terminus. However, some 1,3-dipoles are not stable, and therefore need to be generated *in situ*.

Regioselectivity

Due to the asymmetry of some 1,3-dipoles there exists two possible regioisomeric cycloaddition products; head-to-head or head-to-tail. Nitronates reacting with dipolarophiles in a [3+2] cycloaddition fashion form exclusively head-to-head cycloadducts with only a few exceptions (Scheme 2.4.1).[25]

68

Head-to-head:

Head-to-tail:
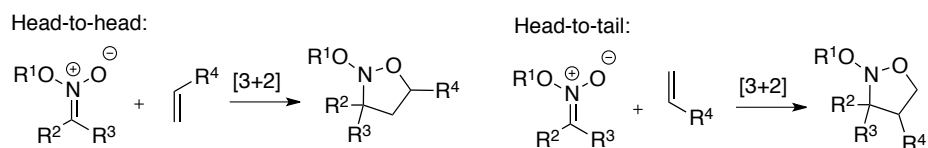
Scheme 2.4.1 Two possible regioisomers during the [3+2] dipolar cycloaddition

Computational analysis has been used to understand the observed regioselectivity. Intermediate neglect of differential overlap (INDO) calculations of nitronates with electron-withdrawing groups provided the energy difference between the two possible outcomes to be too small to determine definitively the orbital interaction.[26] Studies showed that without the electron-withdrawing groups attached to the nitronate the larger coefficient for the nitronate resides on the carbon atom in both the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). Thus, combining a nitronate with electron-deficient dipolarophiles where the larger coefficient resides on the α-carbon in both frontier orbitals resulted in a head-to-head orientation.[27] However, electron-rich dipolarophiles do not give the same results because the larger coefficient changes between the HOMO and the LUMO.[28] The head-to-head orientation was confirmed by two independent calculations. Semiempirical calculation showed that the approach of the electron-rich dipolarophile in a head-to-head fashion is 5.91 kcal/mol more favorable than the head-to-tail orientation. This difference resulted in the cycloadduct to be 6.6 kcal/mol more stable.[28] Also, using density functional theory the electron-poor dipolarophiles resulted in a head-to-head transition state more favorable by 3.4 kcal/mol and 7.4 kcal/mol for electron-rich dipolarophiles.[29]

Stereoselectivity

Beside regioselectivity of the cycloaddition, there is also stereoselectivity of the dipolarophile, exo or endo orientation. Studies have been done with cyclic nitronates and

monosubstituted dipolarophiles (Table 2.4.1).[27] The exo cycloadducts were the major product

observed due to the size of the substituents on the dipolarophile. The endo product was favored

when reacting with acrolein, which is believed to be due to the absence of steric hindrance.

Table 2.4.1 Stereoselectivity observed for the cycloaddition of the nitronate with various dipolarophiles
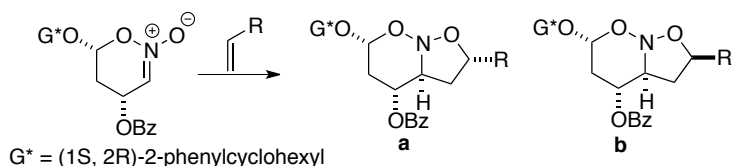
R	dr (a:b)
$CO_2 t Bu$	11.4:1
$CO_2 Me$	6.5:1
COMe	6.2:1
$COCH_2 OTDS^a$	5:1
$COCH_2 OBn$	5.7:1
$CH_2 OH$	1.3:1
CHO	1:2

^{a}TDS = thexyldimethylsilyl

INDO and HF/6-31G* calculations proposed that secondary orbital interaction of the

dipolarophile and the lone pair of electrons on the dipole nitrogen would favor the endo

isomer.[28,30] However, this is not shown experimentally, which suggests that stereoselectivity

must be based on sterics. B3LYP/6-31G* calculation show that the exo transition state is

preferred by 5.88 kcal/mol.[28]

Facial selectivity

Lastly, the facial selectivity of the [3+2] dipolar cycloaddition has two possibilities; the

dipolarophile reacts on top or bottom of the nitronate. The steric environment of the two faces

dictates the facial selectivity. For cyclic nitronates, the substituent on C4 and C6 of the nitronate

provides important steric and electronic effects that control the dipolar cycloaddition (Scheme

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2.4.2).[31] The absence of a substituent on C4 of the nitronate will still afford a high facial

selectivity upon addition of dipolarophile (Scheme 2.4.2).[32]
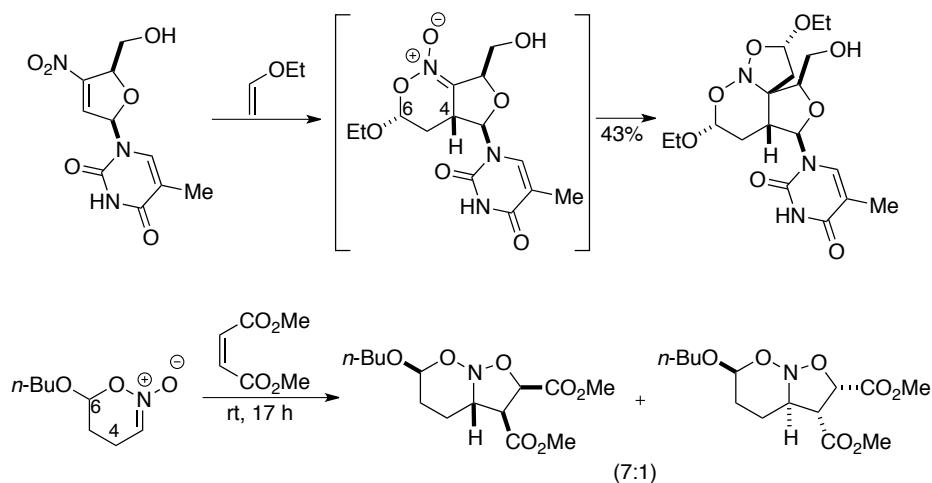
Scheme 2.4.2 Facial selectivity due to C4 and C6 of the cyclic nitronate

Furthermore, the size of the dipolarophile along with the substituent on C4 and C6 can enhance

the facial selectivity (Table 2.4.2).[33] Methyl acrylate provided a better diastereoselectivity of the

[3+2] cycloadduct than the methyl vinyl ketone and acrylonitrile.

Table 2.4.2 Facial selectivity of cyclic nitronate
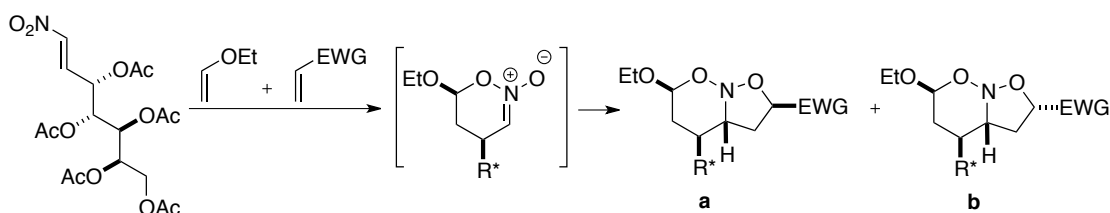
entry	EWG	time (day)	yield (%)	dr (**a**:**b**)
1	COMe	6	70	1:0
2	CO$_2$Me	4	79	19:1
3	CN	4	70	6:1

Forward to section 2.5

Six-membered nitronates are commonly studied and synthesized, but five-membered

nitronates are scarce in the literature. The Nazarov reaction affords five-membered cyclic

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compounds, which could be potentially used to synthesize five-membered nitronates. Thus, it would be appropriate to introduce the Nazarov cyclization reaction in the thesis.

2.5 Nazarov Cyclization

In an electrocyclic ring closing reaction, a σ bond forms between the termini of a conjugated π system. The reverse reaction is when a C–C σ bond breaks to give a conjugated π system. Electrocyclic reactions are subclassified as 2π-electrocyclic, 4π-electrocyclic, etc, which is determined by how many electrons are involved in the reaction. The stereochemical outcome of any electrocyclic ring opening or closing reaction can be predicted by the Woodward–Hoffmann rules. Electrocyclic reactions involving an odd number of electron pairs proceed though a disrotatory transition state under thermal conditions and conrotatory transition state under photochemical conditions. For an even number of electron pairs, it is the reverse, conrotatory transition state under thermal conditions and disrotatory transition state under photochemical conditions.

An example of a 4π electrocyclization is the Nazarov reaction, which was first discovered by the Russian chemist I. N. Nazarov in 1941.[34] The Nazarov cyclization undergoes electrocyclic ring closing with a divinyl ketone under a Lewis acid or Brønsted acid condition. The oxyallyl cation intermediate obtained upon 4π-electrocyclic ring closing can undergo an elimination of a proton to give a Lewis acid bound enolate, which gets protonated to provide the cyclopentenone (Scheme 2.5.1). The Nazarov reaction has been widely investigated due to its reactivity and selectivity patterns. For example, cyclization is often promoted in the presence of a strong Lewis acid in high quantity. The elimination of the proton is not regioselective and leads to a loss of stereochemistry. Lastly, the protonation of the enolate is not stereoselective. Some of these issues

were addressed by Denmark's silicon-directed Nazarov cyclization.[35] In addition, other groups also have contributed in solving these issues.[36]
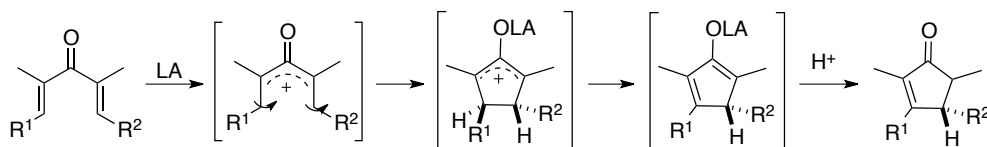
Scheme 2.5.1 Nazarov cyclization of divinyl ketone

Enhancement of the Nazarov cyclization by α-substituents

Denmark undertook an investigation into substituent effects on the divinyl ketone. He postulated that a cation-stabilizing substituent at the α-positions (R^1 and R^4) would stabilize the oxyallyl cation product, which lowers the activation barrier for the cyclization. However, substituents on the β-positions (R^2 and R^3) would stabilize the pentadienyl cation, thus raising the activation barrier for the cyclization (Figure 2.5.1).[35b] While, the presence of alkyl substitution on either β-position of the divinyl ketone slows down the reaction, a good percent yield of the Nazarov products is still obtained (Table 2.5.1, entries 1 and 2). However, the α-allyl or α-aryl group on the substrate enhanced the cyclization, which the reactions were able to cyclized at –25 ˚C for both substrates (entries 3 and 4). Thus, great insight was obtained from Denmark's remarkable findings, which allows the Nazarov reaction to be improved.
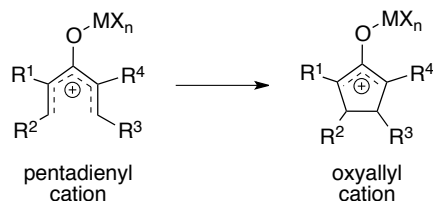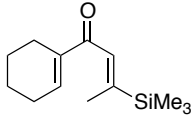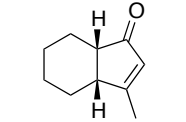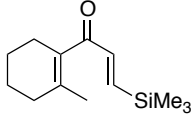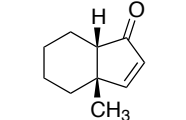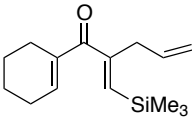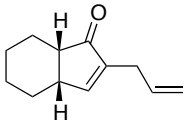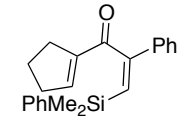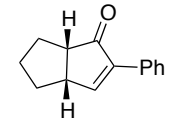
Figure 2.5.1 Denmark's substituent effects on cation stabilization

Table 2.5.1 Substituent effects on cation stabilization[a]

entry	substrate	time (h)	temp (°C)	product	yield (%)
1		13	20		70
2		12	20		70
3		1	−25		76
4		3	−25		86

[a]All reactions were ran at 0.08M CH_2Cl_2 with 1.05 equiv $FeCl_3$

In an effect to apply the insight gained from Denmark's studies, chemists investigated the effects of α-electron-donating substituents on the divinyl ketone. Tius and coworkers were one of the first to synthesize α-alkoxy substituted divinyl ketones for the Nazarov cyclization. The cyclization proceed efficiently due to the polarization of the intermediate ketone and the small steric hinderance during the approach of the allene carbon (Scheme 2.5.2).[37]
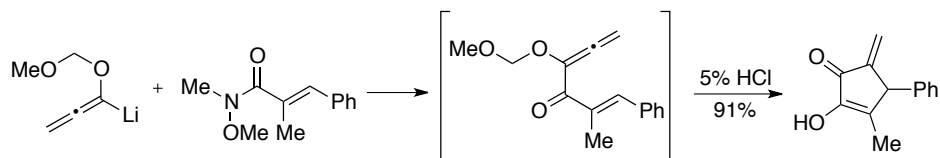
Scheme 2.5.2 Tius's α-alkoxy substituted divinyl ketones for the Nazarov cyclization

Cha and co-workers observed a successful cyclization of the α-ethoxy divinyl ketone substrate (Scheme 2.5.3).[38] They suggest that the Lewis acid, diethyl aluminium chloride (Et₂AlCl) chelates to the ethoxy and carbonyl groups for an efficient conrotatory ring closure. This synthetic strategy allows for a rapid construction of the cephalotaxine core.
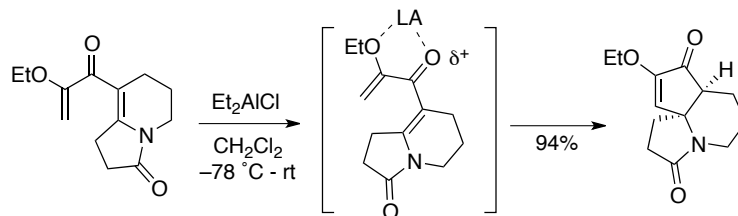
Scheme 2.5.3 Cha's α-alkoxy substituted divinyl ketones for the Nazarov cyclization

Occhiato and Prandi developed a new synthetic route of synthesizing cyclopenta-fused N- and O- containing heterocycles from tetrahydropyridine and dihydropyran derivatives, respectively (Scheme 2.5.4).[39] The presence of a heteroatom, such as oxygen or nitrogen, is important in stabilizing the oxyallyl cation in the transition state. To compare, under the same condition the analogue carbocycle divinyl ketone did not proceed to the Nazarov product.

X = O, NCbz, NTs
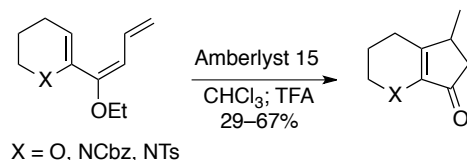
Scheme 2.5.4 Occhiato and Prandi's cyclopenta-fused N- and O- containing heterocycles

Frontier further advanced the α-electron-donating concept by synthesizing a push-pull system.[40] She designed polarized divinyl ketones that consist of a "vinyl nucleophile" and a "vinyl electrophile". Under Lewis acid the electron-donating and electron-withdrawing groups polarize the π system of the oxyallyl cation intermediate, which causes a rapid cyclization (Scheme 2.5.5). The regioselectivity of the elimination is controlled by having the positive charge adjacent to the oxygen atom for stabilization.
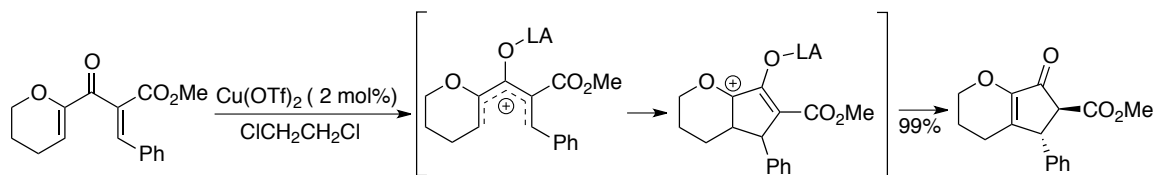
Scheme 2.5.5 Frontier's push-pull system

Lastly, Frontier expanded the scope of the polarized divinyl ketones to include heteroaromatic rings (Scheme 2.5.6).[41] Under scandium triflate a variety of cyclopentanone-fused heteroaromatic systems can be synthesized. Benzofuran divinyl ketone and 2-furan divinyl ketone were not feasible substrates for the cyclization.
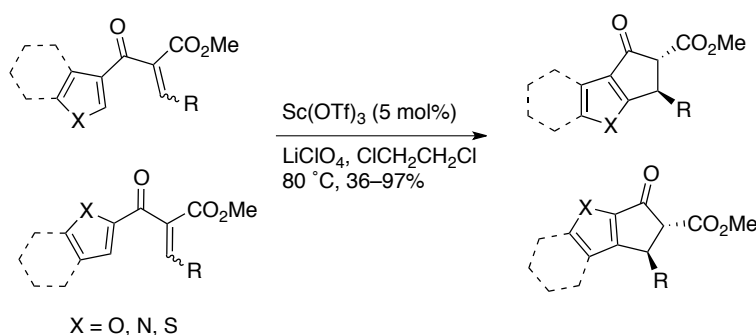
Scheme 2.5.6 Frontier's cyclopentanone-fused heteroaromatic compounds

Imino-and aza-Nazarov cyclization

Divinyl ketones are not the only substrates that can perform the Nazarov cyclization. There are few studies on subjecting imino and aza compounds to the Nazarov reaction. The first imino-Nazarov reaction was described by Tius and co-workers. The reaction with α,β-unsaturated nitriles and lithio(methoxy)methoxyallene reacted to give lithioimine, which cyclized to aminocyclopentenone by ammonium dihydrogen phosphate [(NH$_4$)H$_2$PO$_4$] (Scheme 2.5.7).[42]
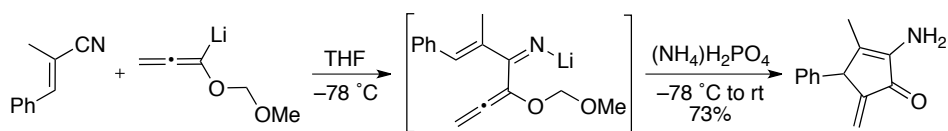
Scheme 2.5.7 An example of Tius's imino-Nazarov cyclization

Furthermore, Tius reported an asymmetric imino-Nazarov cyclization reaction of α-diketones. The diamine catalyst forms an enamine–iminium ion intermediate with the α-diketone

to undergo the Nazarov cyclization, which furnished α-hydroxycyclopentenones in high enantiomeric ratio (Scheme 2.5.8).[43]
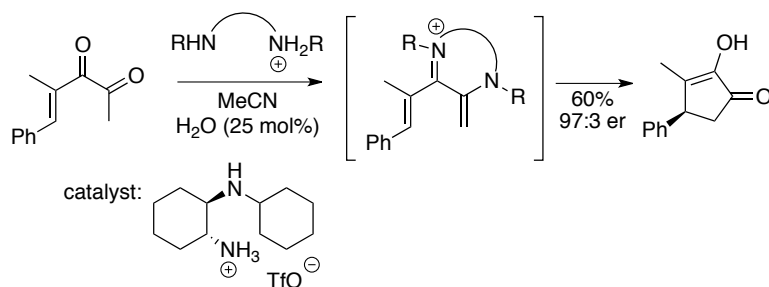
Scheme 2.5.8 Tius's asymmetric imino-Nazarov cyclization

Another example, Hsung and co-workers demonstrated a gold (I)-catalyzed imino-Nazarov cyclization using α-aryl-substituted allenamide to synthesize aromatic ring fused cyclopentenamide. They discovered that having an electron-withdrawing group on the nitrogen of the allenamide would destabilize the pentadienyl cation, such that the Nazarov cyclization can occur (Scheme 2.5.9).[44]
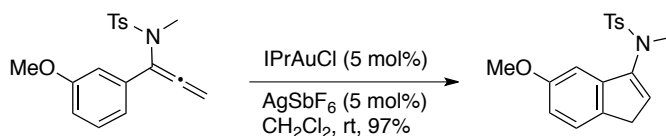
Scheme 2.5.9 An example of Hsung's imino-Nazarov cyclization

Aza-Nazarov is another type of heteroatom Nazarov that few groups have been studying. In one example, Tius and co-workers reacted an azirine dienone substrate with an amine catalyst to facilitate an asymmetric aza-Nazarov reaction. After trapping the intermediate with water, the substrate rearranged to cyclize to give nitrogen heterocycles (Scheme 2.5.10).[45]
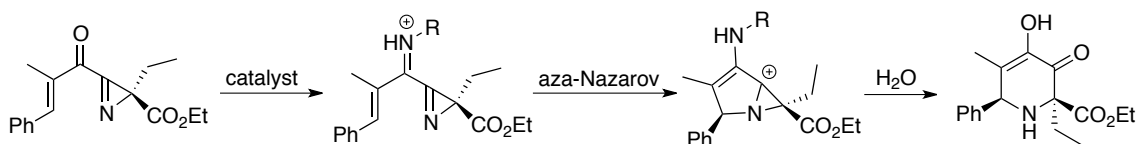
Scheme 2.5.10 An example of Tius's asymmetric aza-Nazarov cyclization

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Klumpp and co-workers reported that *N*-acyliminium ion salts could undergo the Nazarov cyclization in the presence of triflic acid (TfOH). The triflic acid forms a dicationic superelectrophilic intermediate that proceeds through a 4π-electrocyclization to form nitrogen heterocycles (Scheme 2.5.11).[46]
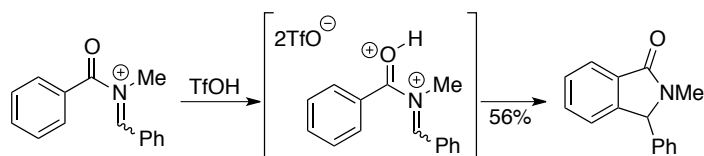
Scheme 2.5.11 Klumpp's dicationic superelectrophilic Nazarov cyclization

Furthermore, Klumpp demonstrated that benzamides with tethered acetal groups undergo an aza-Nazarov cyclization reaction in the presence of TfOH (Scheme 2.5.12).[47] The reaction proceeds through an *N*-acyliminium intermediate to obtain ring fused isoindolinone derivatives.
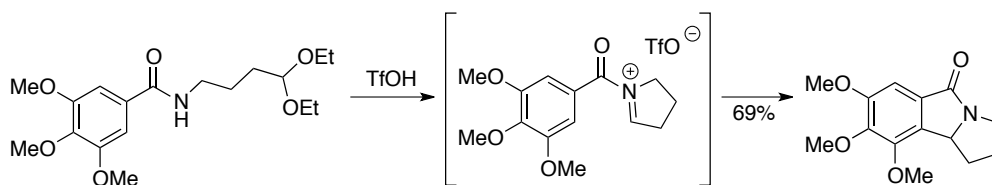
Scheme 2.5.12 Klumpp's synthesis of isoindolinone derivatives by aza-Nazarov cyclization

Lastly, Würthwein and co-workers convey a synthesis of highly substituted pyrrole derivatives through an aza-Nazarov cyclization reaction using indole as a neutral leaving group (Scheme 2.5.13).[48] The reaction must be under strongly acidic conditions (superelectrophilic solvation) for the N–N bond to cleave.
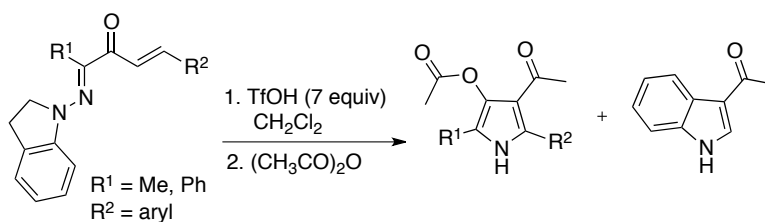
Scheme 2.5.13 Würthwein's synthesis of pyrrole by aza-Nazarov cyclization

Interrupted Nazarov cyclization

The stable oxyallyl cation intermediate is susceptible to nucleophilic trapping. The first interrupted Nazarov cyclization was discovered by West and co-workers. They synthesized divinyl ketone substrates tethered to an alkene, which the alkene trapped the oxyallyl cation after the 4π-electrocyclization (Scheme 2.5.14).[49] The secondary cation is then captured by the enolate oxygen followed by hydration. This interrupted Nazarov reaction works for substrates with a two-carbon tether between the alkene and dienone, and having electron-donating substituent on both α-positions of the dienone.
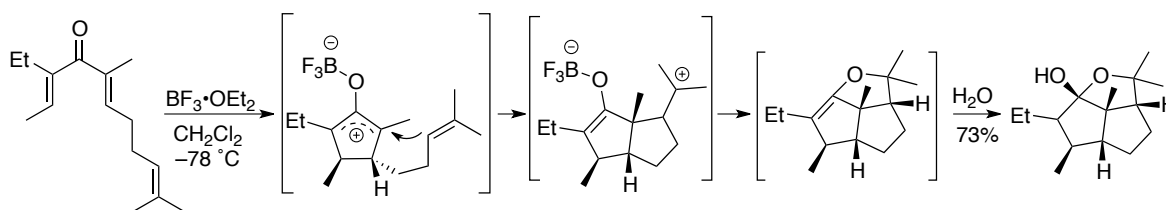
Scheme 2.5.14 An example of an interrupted Nazarov cyclization that is trapped by a tethered alkene

In addition, West demonstrated that electron-rich arenes can trap the oxyallyl cation to provide tri- and tetracyclic compounds with four new stereocenters at a low temperature (Scheme 2.5.15).[50] This reaction is highly stereoselective and chemoselective, and side-products were not observed.
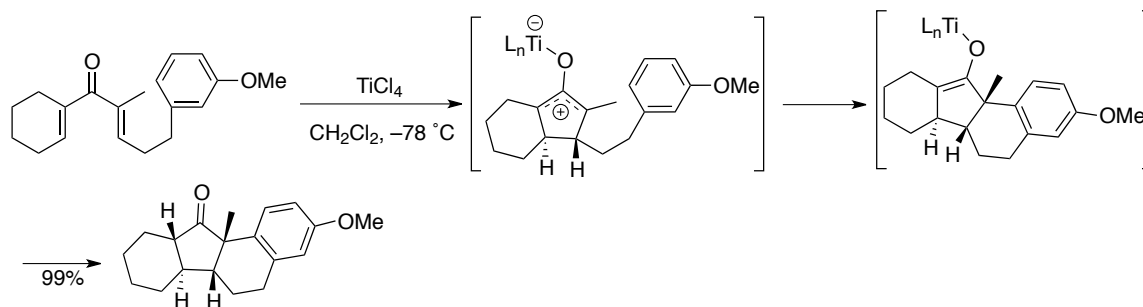
Scheme 2.5.15 Interrupted Nazarov trapping with tethered aryl

Furthermore, West demonstrated that the oxyallyl cation undergoes a [4+3] cycloaddition with a 1,3 diene tethered to the dienone. Studies show that a four-carbon tether gave exclusively exo product, while a three-carbon tether gave a mixture of exo and endo products (Scheme 2.5.16).[51]
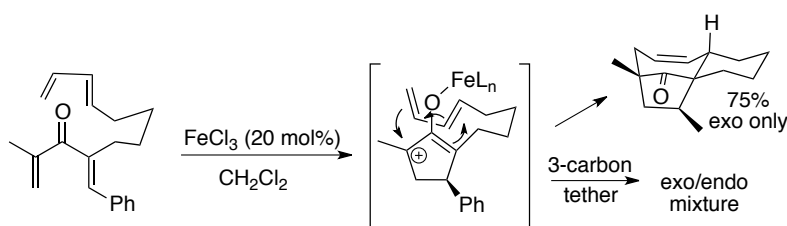
Scheme 2.5.16 Interrupted Nazarov trapping with tether 1,3-diene

Similarly, West showed that intermolecular alkene trapping of the oxyallyl cation using allylsilanes provided a [3+2] cycloadduct instead of undergoing desilylation (Scheme 2.5.17).[52] Using allyl trimethylsilane as the trapping agent, a mixture of two products was isolated as a 1:1 mixture. However, using a bulky allylsilane (triisopropylsilane) forms exclusively the [3+2] cycloadduct.
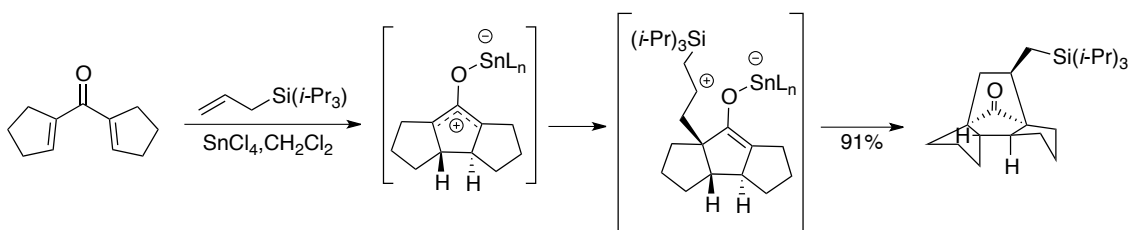
Scheme 2.5.17 West's intermolecular alkene trapping of the oxyallyl cation

Lastly, West did studies on using hydride to trap (reduce) the oxyallyl cation with trialkylsilane to give a saturated cyclopentane (Scheme 2.5.18).[53] Reduction is regioselective for unsymmetrical substituted dienone because the hydride attacked at the less-substituted position of the oxyallyl cation. The drawback is the isolation of a mixture of isomeric compounds at the α-position due to epimerization during acidic workup.
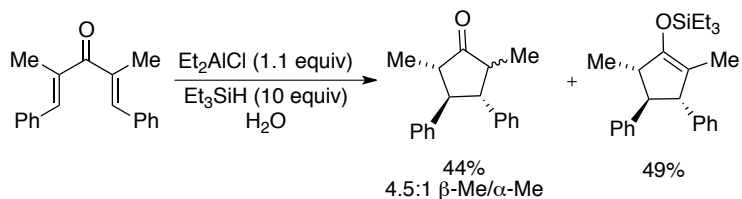
Scheme 2.5.18 Interrupted Nazarov trapping with hydride

Beside carbon nucleophiles, a pendant oxygen substituent could trap the oxyallyl cation. De Lera reported that under protic or Lewis acid, a pentadienyl cation intermediate is generated from a Z-vinyl acetal. The resultant cation after the cyclization is trapped by the pendant oxygen substituent to provide a dioxane product (Scheme 2.5.19).[54]
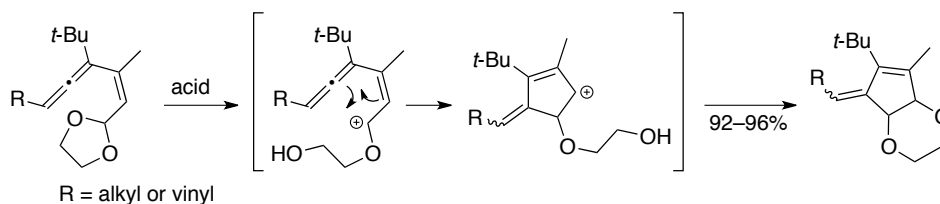
Scheme 2.5.19 An example of De Lera's interrupted Nazarov oxygen atom trapping

Similarly, Nair show that under Lewis acid, a pentadienyl cation intermediate is generated from a cyclic orthoester (Scheme 2.5.20).[55] Then, the cation is trapped by the oxygen to afford a lactone product after hydrolysis.
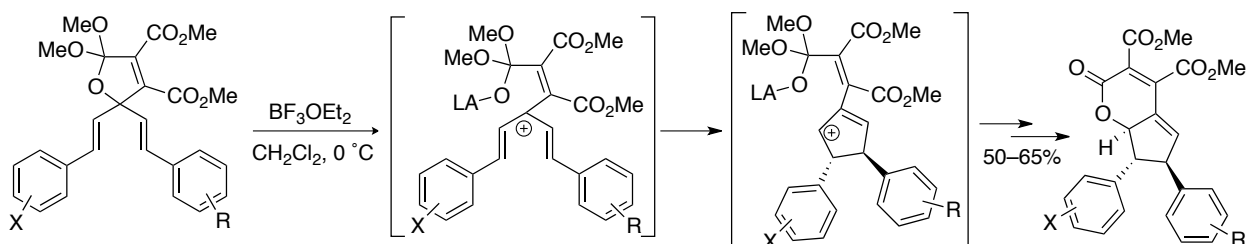
Scheme 2.5.20 An example of Nair's interrupted Nazarov oxygen atom trapping

West reported an interrupted Nazarov cyclization with azide. In the presence of TfOH, the tetrasubstituted 1,4-dien-3-ones underwent Nazarov cyclization follow by [3+3]

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cycloaddition between the resultant 2-hydroxycyclopentenyl cation and the azide (Scheme 2.5.21).[56] The bridged bicyclic triazenes were synthesized in high regioselectivity.

R[1] = aryl
R[2] = R[3] = Me
R[4] = aryl, t-Bu

R[5] = CH$_2$Ph
     CH$_2$CH$_2$Ph
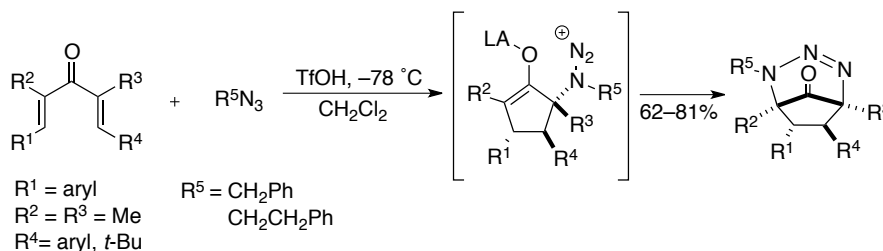
Scheme 2.5.21 West's interrupted Nazarov with azides

Furthermore, according to West's studies, the relative rates of competing Nazarov pathways are trapping by a π-system, reduction (trapping with a hydride), and then elimination (no trapping of the intermediate cation).[36g] This means that trapping the oxyallyl cation with a π-system substituent is faster than the elimination of the proton in the Nazarov reaction. Lastly, all interrupted Nazarov cyclizations preserved the relative stereochemistry created during the conrotatory cyclization.

2.6 Nitro-Nazarov Reaction

As mentioned before, five-membered nitronates are understudied due to the limited methods of synthesizing nitronates. The scope of nitronates is also limited due to the necessity of an electron-withdrawing group on the substrate for stabilization. Thus, it is still warranted to develop new methodologies to overcome these limitations. Our group reported a 6π-electrocyclization of nitrodienes to provide six-membered nitronates. Similarly, we would like to have nitrodienes also undergo a 4π-electrocyclization to provide five-membered nitronates.

The nitrodienes were synthesized by a conjugated addition/elimination of zinc cuprates,[57] which were derived from vinyl bromides **1a–i** (either commercially available or prepared through hydrobromination of the corresponding acetylene or by known methods)[58] into 2-

ethylthio nitrocyclohexene[59] (**2**). The conjugate addition/elimination reaction of α-alkyl and

phenyl vinyl bromides **1a–f** to 2-ethylthio nitrocyclohexene (**2**) provided good to excellent yields

of the nitrodienes **3a–f** within one hour (Table 2.6.1, entries 1–6). However, α-(*para*-

methoxy)phenyl, α-(*para*-methyl)phenyl, and α-(*ortho*-fluoro)phenyl vinylbromides resulted in

poor yields of the nitrodiene products **3g–i** with long reaction times (entries 7–9). The poor

yields can be contributed to the zinc cuprate reactions being very moisture sensitive. Purification

of these vinylbromides **1g–i** was not an easy task due to their low molecular weight and their

instability on silica gel during flash chromatography. Thus, the impurities and wetness of the

vinylbromides **1g–i** could have affected the yields of their corresponding nitrodiene substrates.

Changing the substrate to a substituted phenyl vinylboronic acid[60] **1j** provided the nitrodiene **3j**

in a good yield through the Liebeskind–Srogl[61] coupling reaction, a less sensitive reaction. The

synthesis of other substituted phenyl vinylboronic acids was not feasible (*vide infra*).

Table 2.6.1 Synthesis of various nitrodienes
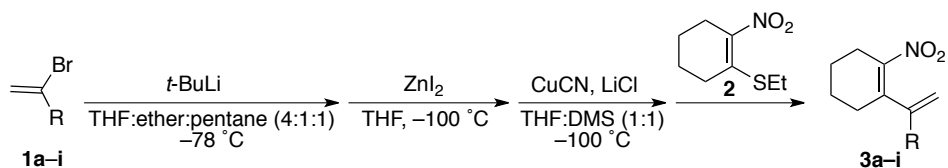
entry	R	time (h)	yield (%)[a]
1	Me (**1a**)	1	88 (**3a**)
2	Et (**1b**)	1	84 (**3b**)
3	*i*-Pr (**1c**)	1	87 (**3c**)
4	*n*-Bu (**1d**)	1	79 (**3d**)
5	*t*-Bu (**1e**)	1	60 (**3e**)
6	Ph (**1f**)	1	92 (**3f**)
7	p-MeOC$_6$H$_4$ (**1g**)	4.5	36 (**3g**)
8	p-MeC$_6$H$_4$ (**1h**)	2	10 (**3h**)
9	o-FC$_6$H$_4$ (**1i**)	1.5	14 (**3i**)
10[b]	p-CF$_3$C$_6$H$_4$ (**4**)	3	87 (**3j**)

[a]Isolated yield. [b]Nitrodiene synthesized by the Liebeskind–Srogl coupling reaction with vinylboronic acid **4**, 2-ethylthio nitrocyclohexene, 20% Pd(PPh$_3$)$_4$, copper thiophene carboxylate in methanol.

Optimization of nitro-Nazarov reaction

Optimization reactions were conducted for the model reaction of nitrodiene **3b** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and trifluoromethanesulfonic acid (TfOH). The substrate was dissolved in anhydrous methylene chloride (5 mL) and was cooled to the temperature indicated in Table 2.6.2. Different ratios and stoichiometries of TMSOTf and TfOH were added to the reaction, and it was stirred for the time indicated. Starting with 4 equivalents of TMSOTf and running the reaction at −78, −40, and 0 ˚C provided the nitronate product **5b** with good yields (entries 1–3). Using a mixture of TMSOTf and TfOH (10:1) provided similar production of the nitronate **5b**, but in a much shorter reaction time (entry 4). Increasing the TfOH up to 10 fold provided a slightly higher yield of the nitronate product **5b** (entries 5–6). Using a mixture of TMSOTf:TfOH (1:5) provided an excellent yield of 84% in 15 min (entry 7). Decreasing or increasing the equivalents of the acid mixture did not improve the product yield (entries 8–11). Also, doubling the TfOH in the mixture did not improve the reaction efficiency (entry 12). However, using only TfOH provided a good yield of the nitronate product **5b** (entry 13). Lastly, decreasing the equivalents of TfOH did not provide a better yield (entry 14). Therefore, the optimized condition involved the reaction of nitrodiene with 4 equivalents of TMSOTf:TfOH (1:5) mixture.

Table 2.6.2 Optimization of the nitro-Nazarov reaction
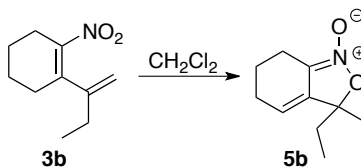
entry	total equiv	TMSOTf:TfOH	temp (˚C)	time (h)	yield (%)[a]
1	4	100:0	−78	5.3	72
2	4	100:0	−40	5.3	74
3	4	100:0	0	5.3	72
4	4	10:1	−78	1.5	72

5	4	5:1	−78	1.5	69
6	4	1:1	−78	1.5	76
7	4	1:5	−78	15 min	84
8	3	1:5	−78	1	76
9	2	1:5	−78	1.5	70
10	1.1	1:5	−78	1.5	72
11	6	1:5	−78	1	71
12	4	1:10	−78	50 min	69
13	4	0:100	−78	10 min	80
14	1.5	0:100	−78	1.25	69

[a]Isolated yield.

Subjecting alkyl nitrodienes **3a–e** to the optimized reaction condition, a mixture of TMSOTf:TfOH (1:5) produced alkyl nitronates **5a–e** in good yields within 20 minutes (Table 2.6.3, entries 1–5). Completion of phenyl nitronate **5f** took an hour with an 84% yield. The speed of this conversion cannot be made faster by warming the reaction because decomposition occurs if the reaction is removed from the dry ice bath. However, decomposition does not happen for the alkyl nitronates **5a–e** when the reactions were removed from the dry ice bath. The electron donating α-(*para*-methoxy)phenyl, α-(*para*-methyl)phenyl, and α-(*ortho*-fluoro)phenyl nitrodienes afforded good yields of the nitronates **5g–i** within 30 min of reaction time (entries 7–9). The electron-poor trifluoromethylphenyl nitrodiene **3j** also provided a good yield of nitronate **5j**, although a much longer reaction time compared to phenyl nitrodiene **3f** (entry 10) was required. After one hour the reaction could be removed from the dry ice bath to facilitate a faster reaction. Thus, various alkyl and substituted phenyl nitrodienes were applicable to the nitro-Nazarov reaction.

Table 2.6.3 Synthesis of various nitronates[a]
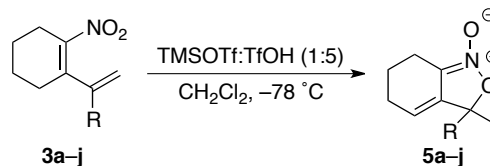
entry	R	time (min)	yield (%)[b]
1	Me	20	89 (**5a**)[c]
2	Et	15	83 (**5b**)
3	*i*-Pr	20	83 (**5c**)
4	*n*-Bu	15	77 (**5d**)
5	*t*-Bu	20	70 (**5e**)
6	Ph	60	84 (**5f**)
7	*p*-MeOC$_6$H$_4$	15	87 (**5g**)
8	*p*-MeC$_6$H$_4$	20	74 (**5h**)
9	*o*-FC$_6$H$_4$	30	72 (**5i**)
10[d]	*p*-CF$_3$C$_6$H$_4$	70	76 (**5j**)

[a]Reactions were preformed using 0.3 mmol of **3**. [b]Isolated yield. [c]Ref. 62. [d]Reaction removed from dry ice bath after 1 h and the reaction was completed after 10 min.

Mechanistic studies by interrupted nitro-Nazarov reaction

We believe that the nitro-Nazarov reaction proceeds through a nitro-allyl cation intermediate **A** from the protonation of the nitrodiene **3** (Scheme 2.6.1). Then intermediate **A** undergoes a 4π-electrocyclization to afford intermediate **B**, follow by a deprotonation to obtain the nitronate product **5**.
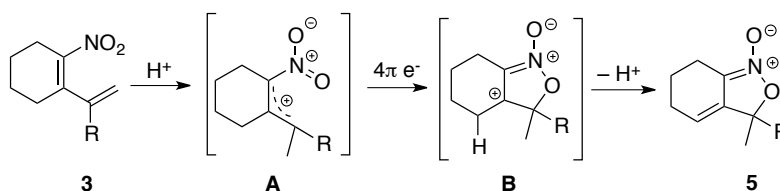
Scheme 2.6.1 Proposed mechanism via a nitro-allyl cation intermediate **A**
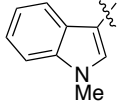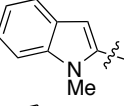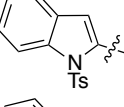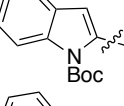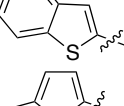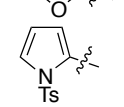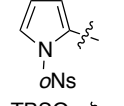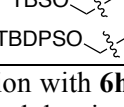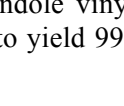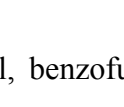
To test this hypothesis, we designed to interrupt the nitro-Nazarov reaction by quenching intermediate **B** with an electrophile. We synthesized various nitrodienes tethered to an aromatic ring by two carbons in hopes of trapping the cation intermediate **B** by electrophilic aromatic

substitution or by a heteroatom. Again, the nitrodienes were synthesized by a conjugated addition/elimination of zinc cuprates from vinylbromides **1k–y** into 2-ethanethio nitrocyclohexene (**2**). The vinylbromide **1k** was synthesized by forming *m*-methoxybenzyl magnesium bromide, which does an addition into 2,3-dibromopropene.[63] The vinylbromides **1l–y** were synthesized by hydrobromination[58] of the corresponding acetylene **6** in good to excellent yields (Table 2.6.4, entries 2–13). However, the hydrobromination with *N*-(*tert*-butoxycarbonyl) indole acetylene produced only 17% yield of the desired vinylbromide **1s** (entry 9). The side-product was the deprotected *N*-(*tert*-butoxycarbonyl) indole vinylbromide, which can be subjected to a di-*tert*-butyl dicarbonate and DMAP condition to get 99% yield of the desired vinylbromide **1s**. Lastly, the *tert*-butyldimethyl silyl (TBS) alcohol vinylbromide **1x** and *tert*-butyldiphenyl silyl (TBDPS) alcohol vinylbromide **1y** were obtained by reacting the corresponding silylchloride with 4-bromopent-4-en-1-ol in 76% yield and 94% yield, respectively (entries 14, 15).[64]

Table 2.6.4 Synthesis of vinylbromides **1k–y**

entry	R	yield (%)^a
1	MeO—C$_6$H$_4$— (**1k**)	60^b (**1k**)
2	methylenedioxyphenyl	96 (**1l**)
3	benzofuran	82 (**1m**)
4	thiophene	51 (**1n**)
5	dimethylphenyl	79 (**1o**)

6		97 (**1p**)
7		69 (**1q**)
8		80 (**1r**)
9		99^c (**1s**)
10		78 (**1t**)
11		73 (**1u**)
12		89 (**1v**)
13		93 (**1w**)
14	TBSO	76^d (**1x**)
15	TBDPSO	94^d (**1y**)

[a]Isolated yields. [b]Ref. 63. [c]Hydrobromination with **6h** produced on 17% yield of **1s**. The side-product was the deprotected *N*-(*tert*-butoxycarbonyl) indole vinyl bromide, which can be reprotected under di-*tert*-butyl dicarbonated and DMAP condition to yield 99% of **1s**. [d]Silyl protection of 4-bromopent-4-en-1-ol to obtain vinylbromide **1x** and **1y**.
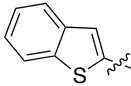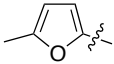
Then, the substituted phenyl, benzofuran, thiophene, *N*-methyl indole and *N*-(*para*-methyl)benzenesulfonyl (Ts) indole vinylbromides **1k–r** were subjected to the conjugate addition/elimination condition with 2-ethanethio nitrocyclohexene (**2**) and gave good to excellent yields of their corresponding nitrodienes (Table 2.6.5, entries 1–8). However, *N*-(*tert*-butoxycarbonyl) indole vinylbromide **1s** gave no nitrodiene product (entry 9). Many attempts have been sought to obtain the nitrodiene **3s**, but all were unsuccessful. Furthermore, benzothiophene and methyl furan vinylbromides provided excellent yields of their nitrodienes **3t** and **3u** in 74% yield and 86% yield, respectively (entries 10, 11). Unexpectedly, *N*-Ts pyrrole nitrodiene **3v** and *N*-(*ortho*-nitro)benzenesulfonyl (Ns) pyrrole nitrodiene **3w** were not obtained

(entries 12, 13). When the vinylbromide **1w** was subjected to the lithium-halogen exchange the reaction solution turned black, instead of the usual yellow solution. Unfortunately, the *tert*-butyllithium must have reacted with the nosyl group on the pyrrole. Lastly, besides trapping the cation by electrophilic aromatic substitution, we wanted to see if an alcohol or silylether could be employed as an internal nucleophile. The protected TBS alcohol vinylbromide **1x** and TBDPS alcohol vinylbromide **1y** provided nitrodienes **3x** and **3y** in 88% yield and 29% yield, respectively (entries 14, 15).

Table 2.6.5 Synthesis of various two carbon tethered nitrodienes

entry	R	yield (%)[a]
1	MeO-aryl	80 (**3k**)
2	methylenedioxyphenyl	70 (**3l**)
3	benzofuranyl	61 (**3m**)
4	thienyl	54 (**3n**)
5	methylphenyl	40 (**3o**)
6	N-Me indol-3-yl	81 (**3p**)
7	N-Me indol-2-yl	20 (**3q**)
8	N-Ts indol-2-yl	87 (**3r**)
9	N-Boc indol-2-yl	0

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10		74 (**3t**)
11		86 (**3u**)
12		0
13		0
14	TBSO	88 (**3x**)
15	TBDPSO	29 (**3y**)

[a]Isolated yield.

Our first attempt using nitrodiene **3k** and the optimal reaction condition, TMSOTf:TfOH (1:5), did not provide the interrupted nitro-Nazarov product as hoped, but gave an dihydroisoxazole product **8a** in 42% yield (Table 2.6.6, entry 1).[62] However, we believe the dihydroisoxazole product **8a** was obtained by first producing the desired interrupted nitro-Nazarov product. Then a ring opening occurred to form a nitrile oxide, which undergoes a [3+2] dipolar cycloaddition with the *para*-quinone methide (Scheme 2.6.2). Next, using TMSOTf showed no consumption of starting material at −78 ˚C after 4 h, which the reaction was then warmed up to room temperature for 2 h. Observation of the reaction showed that the starting material decomposed as shown by a baseline spot on the TLC (entry 2). Switching to *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and TfOH, the reaction did not provide any cyclized product, but the rearranged product **8a** (entries 4, 5). Finally, using 6 equivalents TfOH gave the cyclized product **7a** in 58% yield (entry 6).[62] Increasing the reaction time helped the efficiency of the reaction (entry 7). However, decreasing the equivalents did not provide any product (entry 8). Thus, the optimized condition involved the reaction of nitrodiene **3k** and 6 equivalents of TfOH.

Table 2.6.6 Optimization of the interrupted nitro-Nazarov reaction
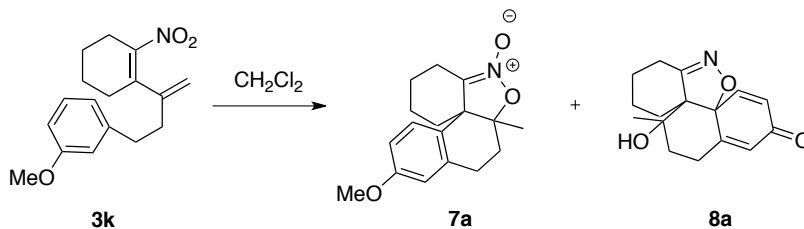
entry	equiv	acid	temp (°C)	time (h)	yield (%)[a]	
					7a	**8a**
1	4	TMSOTf:TfOH (1:5)	−78	3	0	42
2	4	TMSOTf	−78 to 22	6	0	0
4	4	TBSOTf	−78	6	0	13
5	4	TfOH	−78	3.5	0	32
6	6	TfOH	−78	1	58	0
7	6	TfOH	−78	2	66	0
8	1.2	TfOH	−78	5	0	0

[a]Isolated yield.
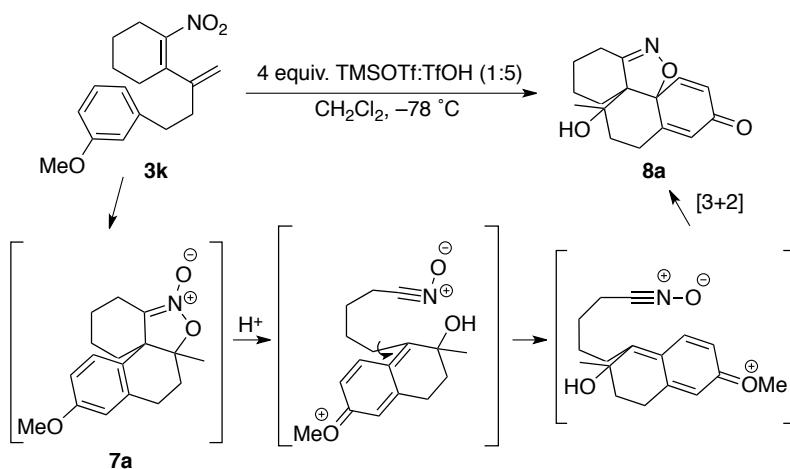
Scheme 2.6.2 Rearrangement of nitronate **7a** to dihydroisoxazole **8a**

Subjecting the optimized condition, 6 equivalents of TfOH, to benzo[d][1,3]dioxole, benzofuran, and thiophene nitrodienes **3l-n** provided the cyclized nitronates in good to excellent yields (Table 2.6.7, entries 1–3).

Table 2.6.7 Synthesis of various interrupted nitro-Nazarov nitronates[a]
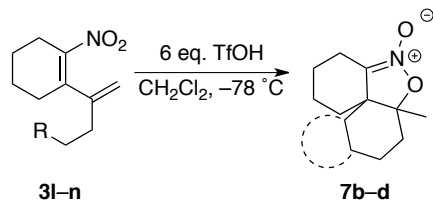
entry	R	yield (%)[b]
1	(1,3-benzodioxole)	66 (**7b**)
2	(benzofuran)	63 (**7c**)
3	(thiophene)	88 (**7d**)

[a]Reactions were preformed using 0.09 mmol of **3**. [b]Isolated yields.

However, employing *meta*-methylphenyl nitrodiene **3o** to the reaction condition did not afford the cyclized nitrodiene, instead only the nitro-Nazarov cyclization occurred **5k** (Table 2.6.8, entry 1). This can be due to the possibility that the methyl substituent on the phenyl is not electron-donating enough to cause the second cyclization to occur. Likewise, C3 *N*-methyl indole nitrodiene **3p** did not provide the trapping product, but the nitronate **5l** in 43% yield (entry 2). Other conditions were employed (e.g. various equivalents of TMSOTf:TfOH, TMSOTf, and TfOH, and temperature) to no avail. It was thought that the carbon tethered on C3 was not an ideal position, thus C2 *N*-methyl indole nitrodiene **3q** was employed. Again, no trapping product was obtained, only the Nazarov product **5m** in 40% yield (entry 3). Now, it was believed that the TfOH might be protonating the nitrogen of the indole because of the *N*-methyl protecting group, deactivating the iminium indole for the trapping of the cation after the nitro-Nazarov cyclization. Thus, electron-deficient *N*-Ts indole nitrodiene **3r** was synthesized in hopes of preventing the nitrogen of the indole from being protonated. Subjecting the *N*-Ts indole nitrodiene **3r** to 6 equivalents of TfOH gave a Michael-type product **9a** instead of the nitronate product (entry 4).

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Switching to an electron-withdrawing group, tosyl, did activate the indole for electrophilic aromatic substitution, however it was too active. The next step would be synthesizing *N*-Ns indole nitrodiene to see if the electron-withdrawing group on the benzenesulfonyl would cause the indole to be less active, but more active than the protonated *N*-methyl indole nitrodiene. However, with many attempts the *N-ortho*-Ns indole vinylbromide and the *N-para*-Ns indole vinylbromide were never obtained. Moving on to benzothiophene nitrodiene **3t**, surprisingly, a Michael-type product **9b** was also produced (entry 5). Many attempts were performed to get the cyclized nitronate of the methylfuran nitrodiene **3u**, however the nitrodiene was not reactive enough to obtain the desired product (entry 6). Lastly, the TBS protected alcohol nitrodiene **3x** also did not produce any desired product (entry 7). The major product was the desilylated nitrodiene alcohol and a rearranged product **8b** in 61% yield and 15% yield, respectively.[62] Another attempt was made utilizing a more bulky silyl protected alcohol nitrodiene, such as TBDPS protected alcohol nitrodiene **3y**, in hopes that it would prevent desilylation and obtain the trapping nitronate, however it did not produce the desired product (entry 8). **8b** was obtained similarly to **8a**, which entailed producing the desired interrupted nitro-Nazarov product. Then a ring opening occurred to form a nitrile oxide, which undergoes a [3+2] dipolar cycloaddition with the enol ether (Scheme 2.6.3). Therefore, the interrupted nitro-Nazarov reaction is very substrate specific for the reaction to occur successfully.

Table 2.6.8 Attempted nitrodienes to form interrupted nitro-Nazarov nitronates[a]
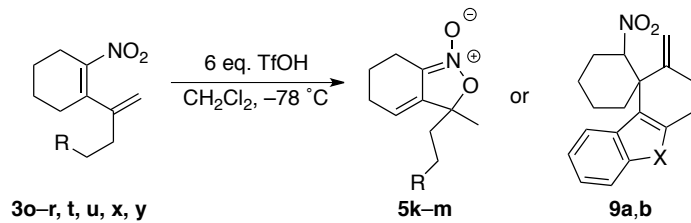
entry	R	isolated yield (%)[b]
1	(3o)	33% (5k)
2	(3p)	43% (5l)
3	(3q)	40% (5m)
4	(3r)	77% (9a)
5	(3t)	50% (9b)
6	(3u)	0
7	TBSO (3x)	15% (8b)
8	TBDPSO (3y)	0

[a]Reactions were preformed using 0.09 mmol of **3**. [b]Isolated yields.

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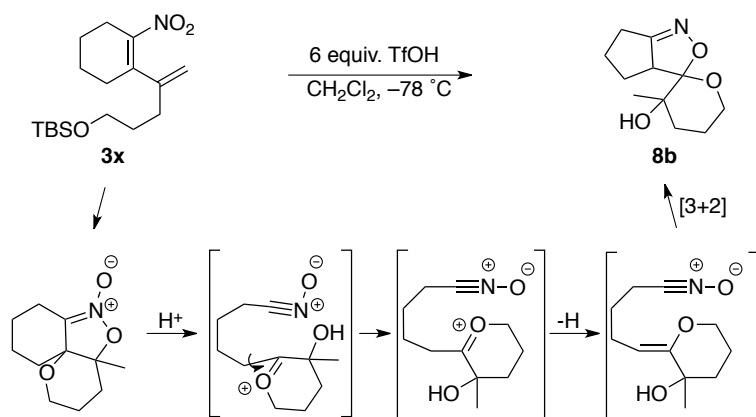
Scheme 2.6.3 Rearrangement of nitronate to dihydroisoxazole **8b**

[3+2] Dipolar cycloaddition with five-membered nitronates

Based on our success performing the [3+2] dipolar cycloaddition on the six-membered nitronates,[23] we found that the [3+2] dipolar cycloaddition also worked on the five-membered nitronates **5a** and **7a** (Table 2.6.9). Reacting nitronate **5a** and **7a** with ethyl acrylate as the dipolarophile produced cycloadduct **10a** and **11a** in 94% yield (dr 5:1) and 95% yield (dr 3:1), respectively (entry 1). Changing the ester to a bulkier *tert*-butyl group increased the diastereoselectivity, albeit with a slightly lower yield of the cycloadduct **10b** and **11b** (entry 2). Employing an electron neutral dipolarophile, styrene was not an efficient dipolarophile for the [3+2] dipolar cycloaddition with nitronate **5a** with only a 22% yield of the cycloadduct **10c** (entry 3). Also, reacting styrene with nitronate **7a** did not produce the desired product **11c** (entry 3). *N*-Ethyl maleimide was a successful dipolarophile, however only at a higher temperature (entry 4). It was hypothesized that more electron-deficient dipolarophiles would be excellent for the [3+2] dipolar cycloaddition, such as diethyl maleate and diethyl fumarate. Surprisingly, they were not effective dipolarophiles for the [3+2] dipolar cycloaddition with five-membered nitronates possibly due to sterics (entries 5 and 6). Lastly, we wanted to see if an electron-donating dipolarophile could be used in the [3+2] dipolar cycloaddition because it works well

with six-membered nitronates. Employing ethyl vinyl ether with nitronate **5a** and **7a** did not

provide any desired product (entry 7). Thus, five-membered cyclic nitronates are not as versatile

in the [3+2] dipolar cycloaddition when compared to the six-membered ring nitronates.

Table 2.6.9 [3+2] Dipolar cycloaddition with five-membered nitronate **5a** and **7a**[a]
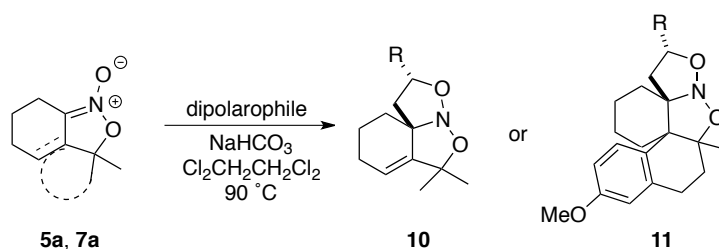
entry	dipolarophile	Nitroso acetal **10** isolated yield (%)[b]	Nitroso acetal **11** isolated yield (%)[b]
1	⌇CO₂Et	94% (dr 5:1)	95% (dr 3:1)
2	CO₂t-Bu	82% (dr 10:1)	80% (dr 4.5:1)
3	Ph	22%	0
4	(N-Ts maleimide)	64%[c]	58%[d]
5	CO₂Et / CO₂Et	0	

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| 6 | EtO$_2$C$\diagup$$\diagdown$CO$_2$Et | 0 |
| 7 | $\diagup$$\diagdown$OEt | 0 |

[a]Reactions were preformed using 0.08 mmol of **5a** or **7a**. [b]Isolated yield. [c]Reaction was preformed at 120 ˚C. [d]Reaction was preformed at 100 ˚C.

Reduction of nitronate 5a

We then explored the possibility of hydrogenolyzing nitronate **5a** to obtain cyclohexenone **12** or oxime compound **13** (Scheme 2.6.4).[65] However, reduction conditions unveiled unexpected reactivity. Reduction of nitronate **5a** with zinc/AcOH cleaved the exocyclic N–O bond, providing dihydroisoxazole **14** (Scheme 2.6.5).[65] Exposure to lithium aluminium hydride (LiAlH$_4$) produced a four-membered nitrone adduct **15** (Scheme 2.6.4). Both compounds **14** and **15** have the same molecular weight, 151.1 g/mol, by gas chromatography/mass spectrometer (GCMS). Thus, both molecules have lost only one oxygen atom during the hydrogenolysis reaction.
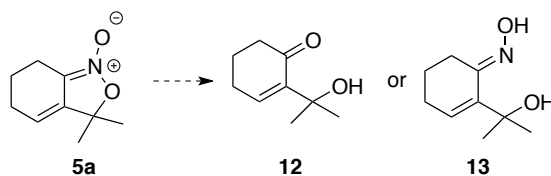
Scheme 2.6.4 Reduction of nitronate **5a** to form cyclohexenone **12** or oxime **13**
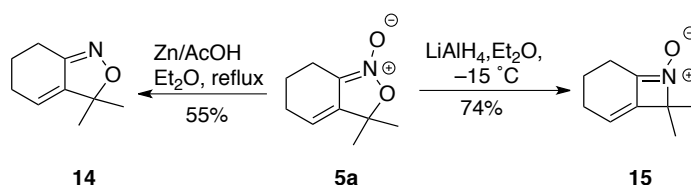
Scheme 2.6.5 Reduction of nitronate **5a** to form dihydroisoxazole **14** and nitrone **15**

The zinc/AcOH condition cleavage of the exocyclic N–O bond of nitronate **5a** instead of the endocyclic N–O bond is based on the proton and carbon chemical shifts in the ^{1}H and ^{13}C NMRs between nitronate **5a** and dihydroisoxazole **14**. The vinyl proton H$_a$ of dihydroisoxazole **14** did

not change dramatically when compared to the vinyl proton H_a of nitronate **5a** in the ^1H NMR (Figure 2.6.1). In the ^{13}C NMR, C1 of the dihydroisoxazole **14** also did not change chemical shift compared to C1 of nitronate **5a** (Figure 2.6.2). This suggests that C1 must be still bonded to the oxygen atom. Lastly, the C2 peak of dihydroisoxazole **14** shifted downfield compared to the C2 peak of nitronate **5a**, suggesting that the nitronate moiety has been removed because the chemical shift of C2 appears between 115.0–118.6 ppm for nitronate compounds.[65] Also, the removal of the negatively charged oxygen atom of the nitronate **5a** would cause C2 to be more deshielded and would move more downfield, such as the C2 of dihydroisoxazole **14**. Thus, based on the NMRs between nitronate **5a** and dihydroisoxazole **14**, it is strongly believed that zinc/AcOH condition cleaved the exocyclic N–O bond.
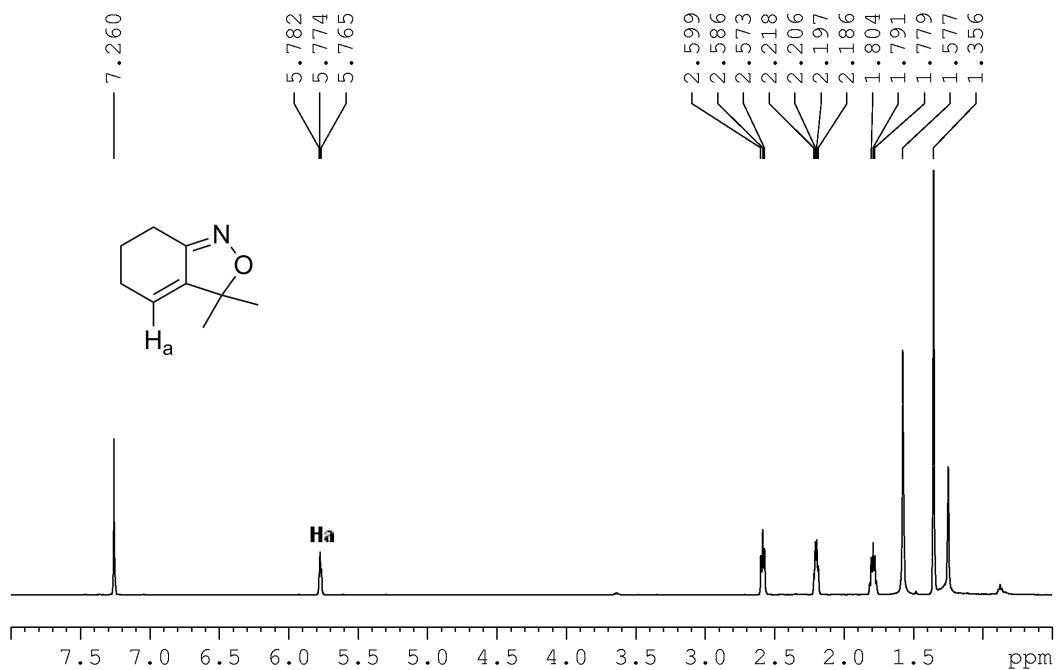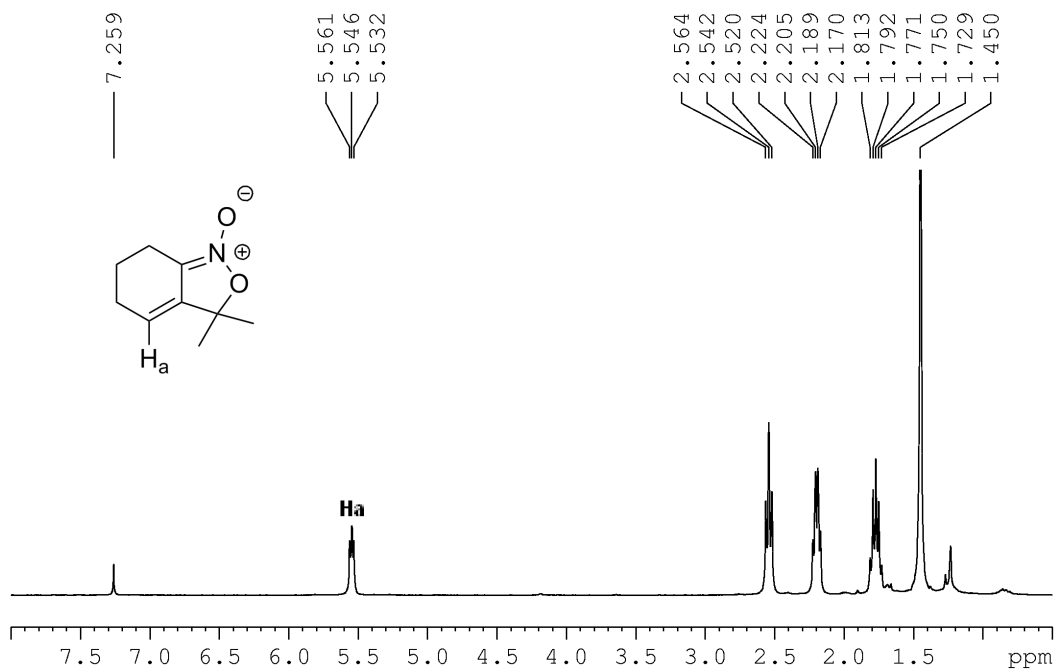
Figure 2.6.1 ^{1}H NMR of nitronate **5a** and dihydroisoxazole **14**
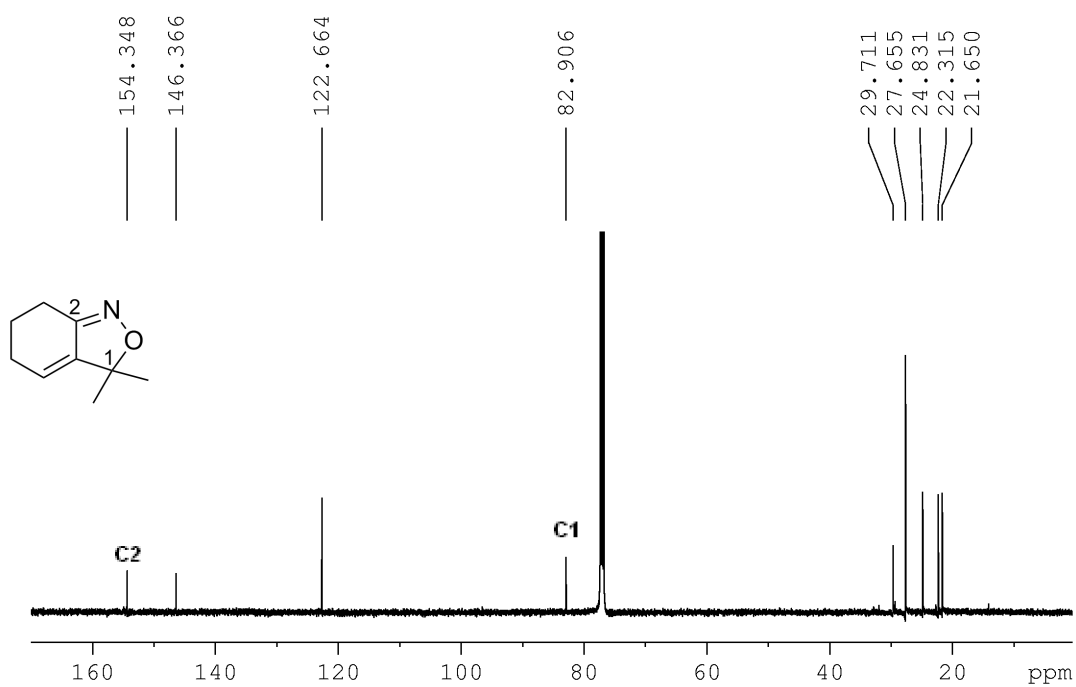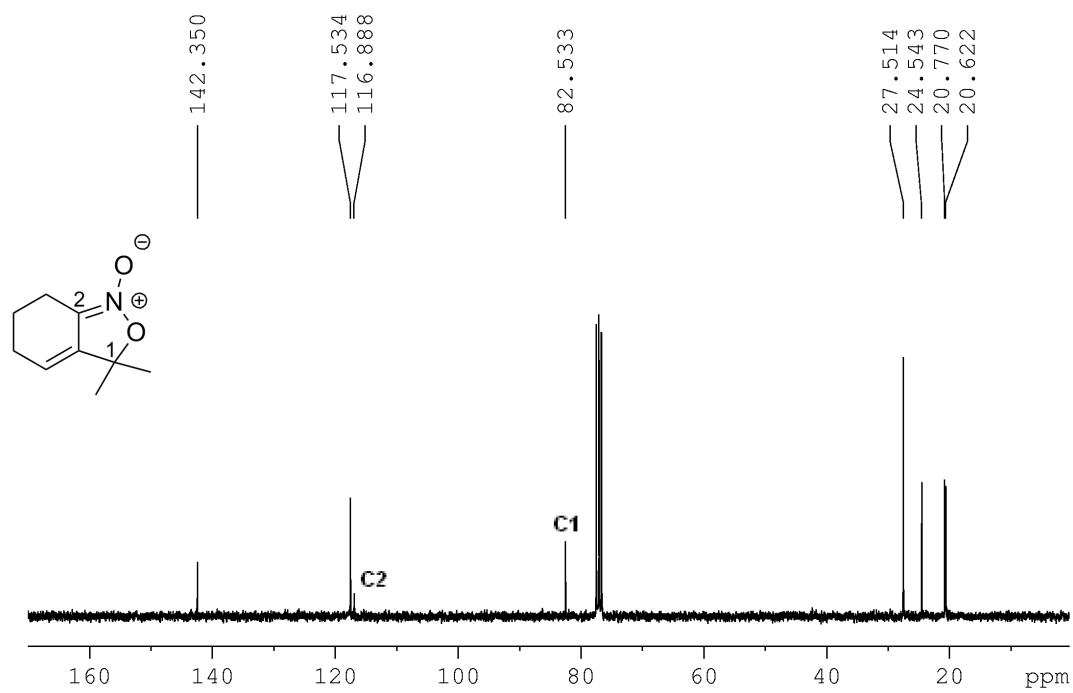
Figure 2.6.2 ^{13}C NMR of nitronate **5a** and dihydroisoxazole **14**

Exposure to LiAlH$_4$ produced a four-membered nitrone adduct **15** by cleavage of the endocyclic N–O bond. In the ^{1}H NMR, the vinyl proton H$_a$ of the nitrone **15** shifted downfield compared to the vinyl proton H$_a$ of the nitronate **5a** (Figure 2.6.3). The downfield shift can be due to the constraint of the four-membered ring. In the ^{13}C NMR, C1 of the nitrone **15** shifted upfield compared to C1 of the nitronate **5a** (Figure 2.6.4). This suggests that the oxygen atom is not bonded to C1, but C1 is bonded to a nitrogen atom that causes an upfield shift of the C1 peak. Lastly, the C2 peak has shifted downfield to 139.9 ppm in the nitrone **15**, which correlates to the chemical shifts of nitrone compounds.[66] Thus, based on the NMRs between nitronate **5a** and nitrone **14**, it is strongly believed that LiAlH$_4$ condition cleaved the endocyclic N–O bond, in which the tertiary alcohol could be leave to give a tertiary cation, such that the nitrogen atom added to the tertiary cation to give the four-membered nitrone **15**.
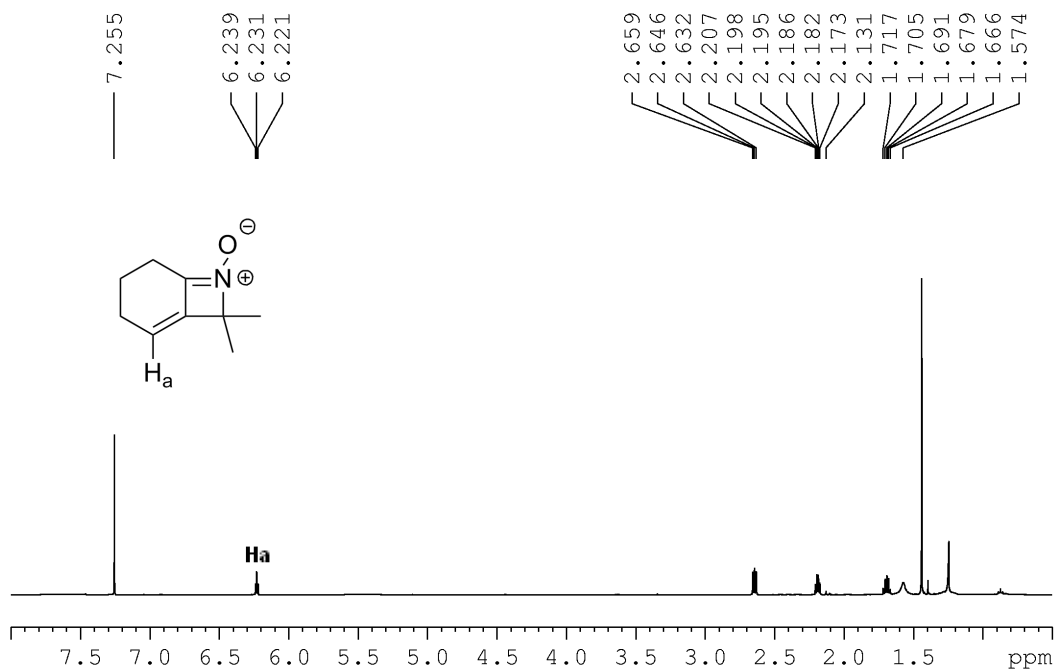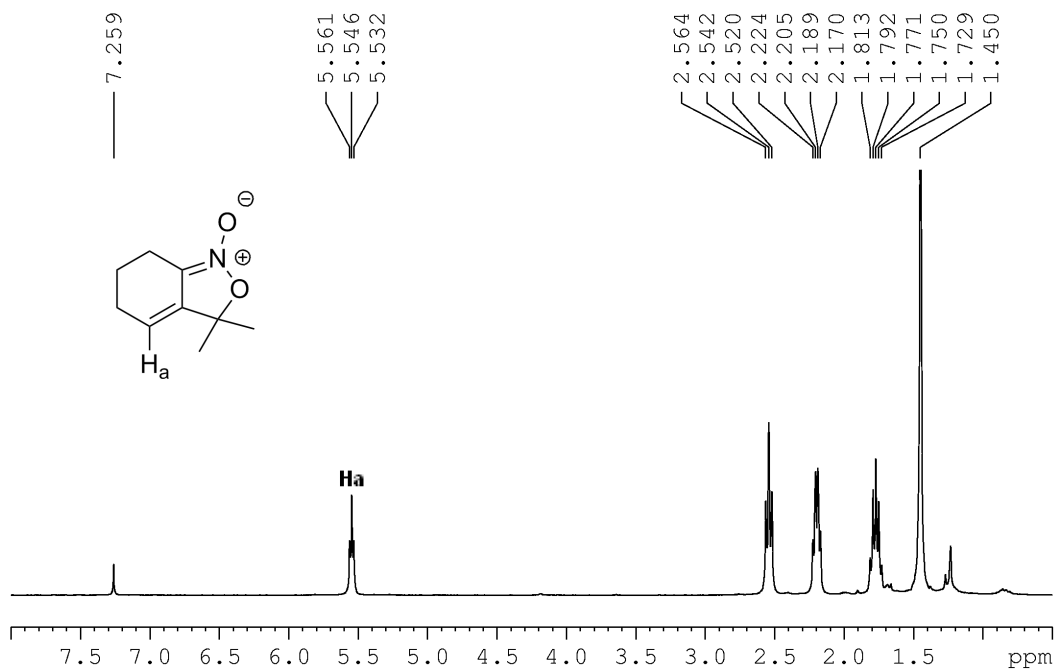
Figure 2.6.3 ^{1}H NMR of nitronate **5a** and nitrone **15**
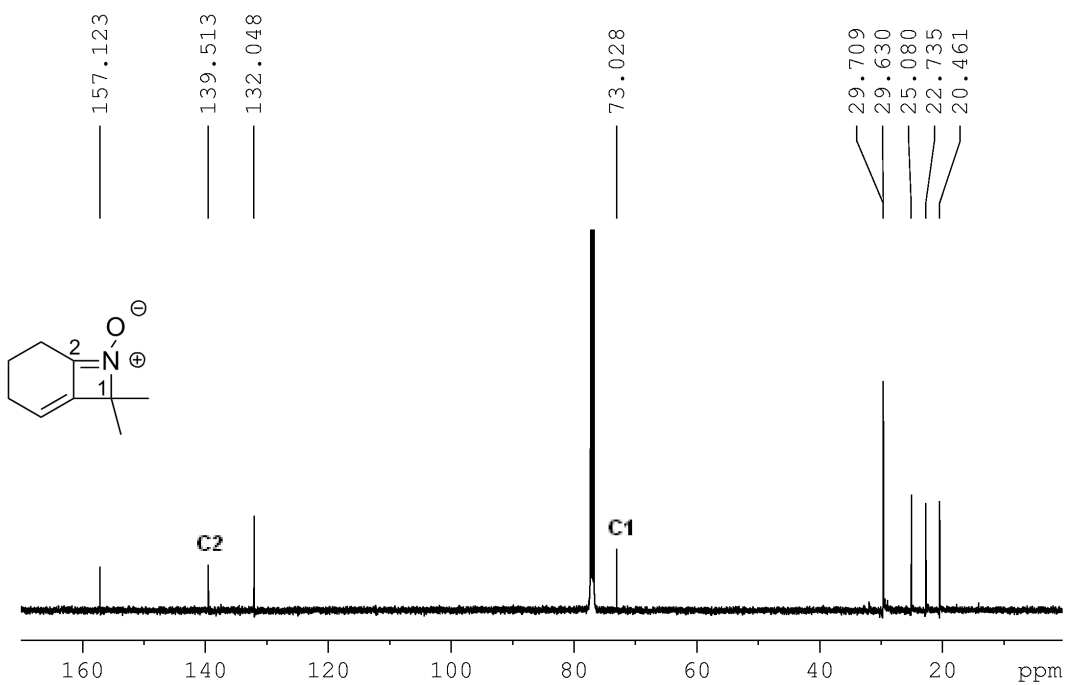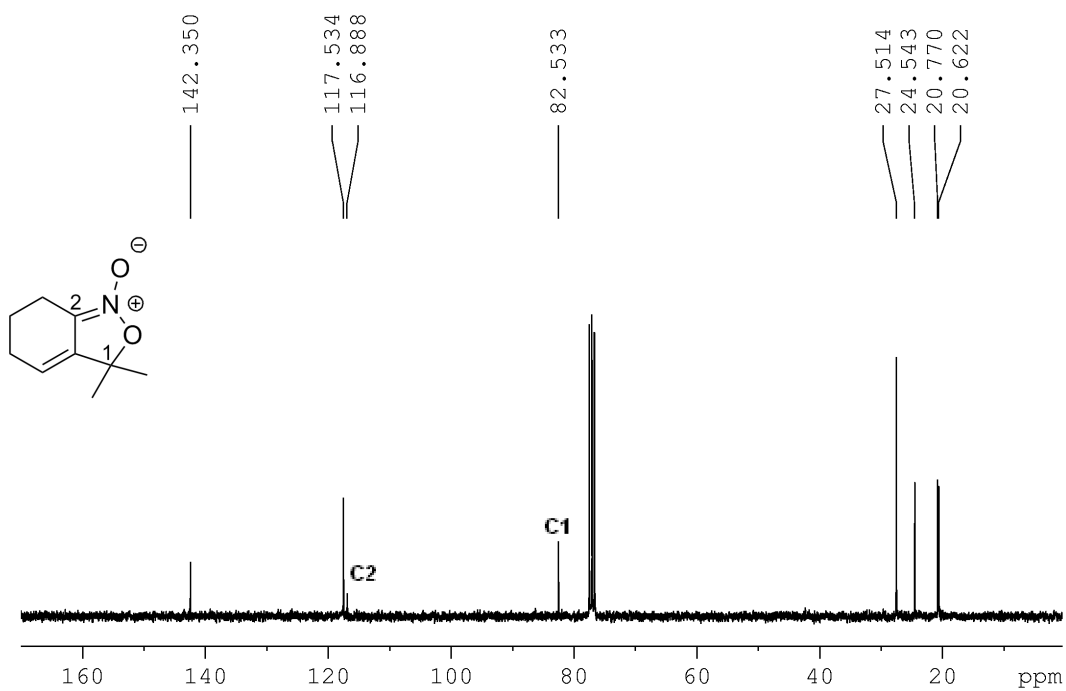
Figure 2.6.4 ^{13}C NMR of nitronate **5a** and nitrone **15**

Conclusion

We have developed an acid-mediated nitro-Nazarov reaction of conjugated nitrodienes to synthesize five-membered nitronates. Electron-withdrawing groups on these nitronates were not necessary for their stability. Thus, the nitro-Nazarov reaction is very useful in synthesizing alkyl and aryl substituted nitronates. Even though the interrupted nitro-Nazarov reaction was substrate specific, through the successful trapping experiments, we verified that the nitro-Nazarov reaction proceeds through a nitro-allyl cation intermediate. Synthesizing suitable nitrodiene substrates, the interrupted nitro-Nazarov reaction can be a powerful reaction to construct highly complex molecules, which can be further manipulated. Lastly, [3+2] dipolar cycloaddition was also successful for five-membered nitronates with only sterically accessible and electron-deficient dipolarophiles to obtain nitroso acetals. And the reduction of nitronate **5a** provided unexpected substrates, a dihydroisoxazole and a nitrone, whose structures were deduced by MS, and ^{1}H and ^{13}C NMR spectroscopic data.

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); dimethyl sulfide, tetrahydrofuran, and diethyl ether were distilled from Na with benzophenone indicator. Prior to use, the distilled dimethyl sulfide was stored in a Schlenk flask over 4Å molecular sieves. 2-Bromopropene and 2-bromo-1-butene were purchased from Alfa Aesar and α-bromostyrene was purchased from Acros Organics. The chemicals were stored over 4Å molecular sieves. Ethyl acrylate, *t*-butyl acrylate, and styrene were purchased from commercial sources and distilled prior to use; N-ethylmaleimide was recrystallized from diethyl ether.

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; 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). Mass-analyzed laser desorption/ionization (MALDI) mass spectra were recorded using an AB/PerSpective DE-STR TOF instrument with 2,5 dihydroxybenzoic acid as the matrix. An Agilent Technologies 5975 inert XL mass-selective detector GCMA was also used.

X-ray Crystallography: X-ray crystallographic data were collected using a Bruker SMART CCD-based diffractometer equipped with a low-temperature apparatus operated at 100 K.

Synthesis of Vinylbromides 1c and 1d

$$R\text{---}\!\equiv\quad \xrightarrow[\substack{CH_2Cl_2,\ 0\ ^\circ C;\\ AcOH;\ H_2O_2\\ 3\ M\ NaOH}]{B\text{-Br-9-BBN}}\quad R\diagdown\!\diagup Br$$

16 → 1c, 1d

R = *i*-Pr, *t*-Bu
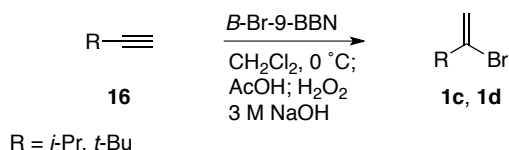
2-Bromo-3-methylbut-1-ene (**1c**). A round-bottom flask was charged with B-Br-9-BBN (1M in CH₂Cl₂, 8.8 mL, 8.8 mmol, 1.2 equiv) in CH₂Cl₂ (48 mL) and then cooled to 0 ˚C. A solution of commercially available 3-methylbut-1-yne (0.75 mL, 7.3 mmol, 1 equiv) in CH₂Cl₂ (33 mL) was added dropwise and was stirred for 3 h at 0 ˚C. Upon disappearance of the alkyne, (TLC; pentane:benzene (5:1), if the alkyne was not consumed additional 0.25 equiv of B-Br-9-BBN was added) acetic acid (4 mL) was added and stirred for 1 h at 0 ˚C. Then, 3M NaOH (49 mL)

and 30% hydrogen peroxide (8 mL) was added at 0 °C and stirred for 30 min at room temperature. The product was extracted with hexanes (3 x 30 mL), washed with water, NaHCO₃, and water again, and dried over Na₂SO₄. The solvent was distilled and the product was collected under reduced pressure to give the title compound as colorless oil (515 mg, 47% yield). Spectral data matches those reported in the literature.[68]

2-Bromo-3,3-dimethylbut-1-ene (**1d**). The procedure was followed as above using commercially available 3,3-dimethylbut-1-yne. The title compound was a colorless oil (700 mg, 66% yield). Spectral data matches those reported in the literature.[69]
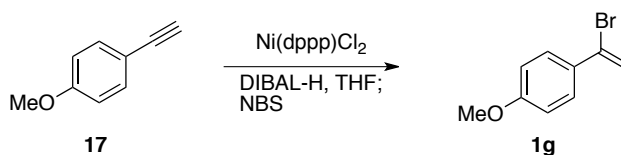
1-(1-Bromovinyl)-4-methoxybenzene (**1g**). To a suspension of 1,3-bis(diphenylphosphino)-propane nickel(II) chloride [Ni(dppp)Cl₂, 50.0 mg, 0.092 mmol, 0.03 equiv] in 10.2 mL THF was added DIBAL-H (4 mL, 4.0 mmol, 1.3 equiv) dropwise at room temperature. The resulting black solution was cooled to 0 °C before 1-ethynyl-4-methoxybenzene (0.4 g, 3.0 mmol, 1.0 equiv) was added slowly over five minutes and then was stirred for 2 h at room temperature. After the two hours, a solution of *N*-bromosuccinimide (NBS) (1.0 g, 6 mmol, 3.0 equiv) in THF (9 mL) was added dropwise into the reaction at 0 °C. The mixture is allowed to warm to room temperature and stir for 1 h before quenching the solution with a saturated solution of Rochelle's salt (15 mL) and is extracted with Et₂O (10 mL x 3), and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue purified through basified (with triethylamine) silica gel flash column chromatography (15% EtOAc/hexanes) to give the title compound as colorless oil (300 mg, 50% yield). Spectral data matches those reported in the literature.[70]

Synthesis of Vinylboronic Acid 4
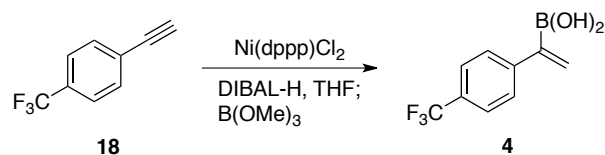
{1-[4-(Trifluoromethyl)phenyl]vinyl}boronic acid (4). To a suspension of 1,3-bis(diphenylphosphino)propane nickel(II) chloride [Ni(dppp)Cl$_2$, 50.0 mg, 0.092 mmol, 0.03 equiv] in 10.2 mL THF was added DIBAL-H (4 mL, 4.0 mmol, 1.3 equiv) dropwise at room temperature. The resulting black solution was cooled to 0 ˚C before 4-ethynyl trifluorotoluene (0.5 mL, 3.0 mmol, 1.0 equiv) was added slowly over five minutes and then was stirred for 2 h at room temperature. After the two hours, trimethylborate (1 mL, 9 mmol, 3.0 equiv) was added dropwise into the reaction at 0 ˚C. The resulting solution was allowed to be heated to 80 ˚C and stir for 24 h before the reaction is quenched by dropwise addition of water (9 mL) at 0 ˚C. The mixture is allowed to warm to room temperature and stir for 1 h before it is extracted with Et$_2$O (10 mL x 3), and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the residue purified through flash column chromatography (30% EtOAc/hexanes) to give the title compound as colorless oil (475 mg, 72% yield); IR (ν, cm^{-1}) 3098, 3052, 2931, 1617, 1322, 1164, 1115, 849; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.54 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 5.63 (d, J = 1.1 Hz, 1H), 5.42 (d, J = 1.1 Hz, 1H), ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 148.2, 143.2, 129.8 (q, J = 130.3 Hz), 127.8, 125.4 (q, J = 865.1 Hz), 118.7; ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) –62.7; HRMS (ESI) calcd for C$_9$H$_8$BF$_3$O$_2$ [M]$^+$ m/z 216.0569, found 216.0516.

Synthesis of vinylbromides 1l–w
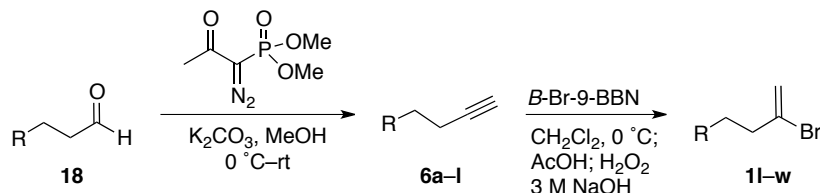
The synthesis of the two-carbon vinylbromides **1l–w** were produced by first synthesizing the corresponding acetylenes **6a–l** from known aldehyde compounds **18**.[71] Acetylenes **6b–l** were synthesized according to the procedure of **6a**. Also, vinylbromides **1m–w** were synthesized according to the procedure of **1l**.
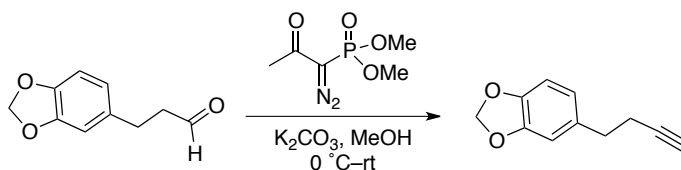
5-(But-3-yn-1-yl)benzo[d][1,3]dioxole (6a). To a suspension of K_2CO_3 (315 mg, 2.3 mmol, 2.1 equiv) in MeOH (17 mL) was added 3-(benzo[d][1,3]dioxol-5-yl)propanal[72] (193 mg, 1.1 mmol, 1 equiv). The mixture was cooled to 0 ˚C and then dimethyl 1-diazo-2-oxopropylphosphonate (250 mg, 1.3 mmol, 1.2 equiv) was added dropwise. The mixture was warm to room temperature. After 12 h, the reaction was quench with 5% $NaHCO_3$ (20 mL). The reaction was extracted with EtOAc (3 x 20 mL), and the organic layer was washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified through flash column chromatography (3% EtOAc/hexanes). Colorless oil (147 mg, 77% yield); IR (ν, cm^{-1}) 3292, 2928, 2901, 2144, 1503, 1487, 1442, 1242, 1037, 934, 808; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.74 (d, J = 8.0, 1.7 Hz, 1H), 6.73 (d, J = 7.8, 1.7 Hz, 1H), 5.93 (s, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.44 (td, J = 7.4, 2.6 Hz, 2H), 1.98 (t, J = 2.7 Hz, 1H); ^{13}C NMR (125 MHz,

CDCl$_3$) δ (ppm) 147.6, 146.0, 134.3, 121.3, 108.9, 108.2, 100.9, 83.7, 69.0, 34.6, 20.9; GCMS (EI+) calcd for C$_{11}$H$_{10}$O$_2$ [M]$^+$ *m/z* 174.1, found 174.1.
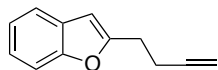
2-(But-3-yn-1-yl)benzofuran (6b). Colorless oil (260 mg, 91% yield); IR (ν, cm^{-1}) 3296, 2919, 2846, 2148, 1587, 1455, 1251, 1147, 943, 798, 741; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.52–7.49 (m, 1H), 7.43–7.37 (m, 1H), 7.25–7.15 (m, 2H), 6.49 (d, *J* = 0.9 Hz, 1H), 3.02 (t, *J* = 7.3 Hz, 2H), 2.65 (td, *J* = 7.4, 2.6 Hz, 2H), 2.00 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 157.0, 154.7, 128.7, 123.5, 122.6, 120.5, 110.8, 102.8, 82.9, 69.3, 27.9, 17.4; GCMS (EI+) calcd for C$_{12}$H$_{10}$O [M]$^+$ *m/z* 170.1, found 170.1.
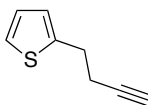
2-(But-3-yn-1-yl)thiophene (6c). Orange oil (100 mg, 92 % yield); IR (ν, cm^{-1}) 3295, 3072, 2118, 2914, 2852, 1438, 1259, 1130, 849; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.15 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.0, 3.4 Hz, 1H), 6.87 (dd, *J* = 3.4, 0.9 Hz, 1H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.54 (td, *J* = 7.4, 2.6 Hz, 2H), 2.01 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 142.9, 126.8, 124.8, 123.6, 83.2, 69.3, 29.2, 21.1; GCMS (EI+) calcd for C$_8$H$_8$S [M]$^+$ *m/z* 136.0, found 136.0.
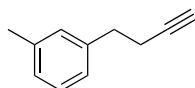
1-(But-3-yn-1-yl)-3-methylbenzene (6d). Colorless oil (210.3 mg, 76% yield); IR (ν, cm^{-1}) 3312, 2984, 2907, 2156, 1447, 1372, 1233, 1097, 1043, 937, 847; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.41–7.21 (m, 1H), 7.09–7.07 (m, 3H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.52 (td, *J* = 7.6, 2.6 Hz,

2H), 2.03 (t, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 140.4, 138.0, 129.3, 128.4, 127.2, 125.5, 83.9, 68.9, 34.9, 21.5, 20.6; GCMS (EI+) calcd for C$_{10}$H$_{12}$ [M]$^+$ m/z 144.1, found 144.0.
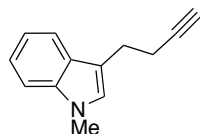
3-(But-3-yn-1-yl)-1-methyl-1H-indole (**6e**). Colorless oil (374.4 mg, 76% yield); IR (ν, cm^{-1}) 3289, 3052, 2914, 2115, 1615, 1555, 1472, 1322, 1247, 736; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.70 (d, J = 7.9 Hz, 1H), 7.40–7.37 (m, 1H), 7.33 (td, J = 7.5, 1.0 Hz, 1H), 7.21 (td, J = 7.3, 1.2 Hz, 1H), 7.00 (s, 1H), 3.82 (s, 3H), 3.11 (t, J = 7.5 Hz, 2H), 2.66 (td, J = 7.5, 2.6 Hz, 2H), 2.11 (t, J = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 137.1, 127.7, 126.5, 121.7, 118.9, 118.8, 113.5, 109.3, 84.7, 68.7, 32.7, 24.7, 20.0; GCMS (EI+) calcd for C$_{13}$H$_{12}$N [M]$^+$ m/z 183.1, found 183.1.
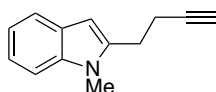
2-(But-3-yn-1-yl)-1-methyl-1H-indole (**6f**). White solid (240.2 mg, 79% yield); m.p. 66–68 ˚C; IR (ν, cm^{-1}) 3298, 2934, 2842, 2178, 1738, 1468, 1365, 1260, 1216, 1011, 845; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.59–7.57 (m, 1H), 7.30–7.28 (m, 1H), 7.22–7.18 (m, 1H), 7.12–7.08 (m, 1H), 6.35 (s, 3H), 3.69 (s, 3H), 3.03 (t, J = 7.6 Hz, 2H), 2.66–2.63 (m, 2H), 2.05 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 139.1, 137.4, 127.8, 120.1, 120.0, 119.4, 108.9, 99.1, 83.3, 69.3, 29.5, 26.2, 18.3; GCMS (EI+) calcd for C$_{13}$H$_{12}$N [M]$^+$ m/z 183.1, found 183.1.
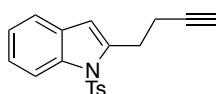
2-(But-3-yn-1-yl)-1-tosyl-1*H*-indole (6g). White solid (121.4 mg, 86% yield); m.p. 94–96 ˚C; IR (ν, cm^{-1}) 3294, 2967, 2864, 2155, 1596, 1453, 1370, 1264, 1175, 1091, 749; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 8.15 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, *J* = 6.7, 1.7 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.27 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.21 (td, *J* = 7.5, 1.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 0.8 Hz, 1H), 3.25 (t, *J* = 6.9 Hz, 2H), 2.68 (td, *J* = 7.2, 2.7 Hz, 2H), 2.32 (s, 3H), 2.00 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 144.8, 139.7, 137.2, 136.0, 129.9, 129.6, 126.3, 124.2, 123.6, 120.4 114.9, 109.9, 83.2, 69.4, 28.5, 21.6, 18.6; GCMS (EI+) calcd for C$_{19}$H$_{17}$NO$_2$S [M]$^+$ *m/z* 323.1, found 323.0.
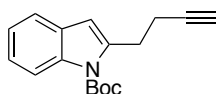
***tert*-Butyl 2-(but-3-yn-1-yl)-1*H*-indole-1-carboxylate (6h)**. Colorless oil (79.2 mg, 94% yield); IR (ν, cm^{-1}) 3300, 2981, 2931, 2120, 1730, 1455, 1371, 1334, 1157, 1089, 740; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 8.10 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.19 (td, *J* = 7.4, 0.8 Hz, 1H), 6.44 (s, 1H), 3.26 (t, *J* = 7.2 Hz, 2H), 2.61 (td, *J* = 7.4, 2.5 Hz, 2H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 150.4, 139.8, 136.6, 129.1, 123.6, 122.7, 120.0, 115.7, 108.1, 84.0, 83.5, 69.1, 29.5, 28.3, 18.6; GCMS (EI+) calcd for C$_{17}$H$_{19}$NO$_2$ [M]$^+$ *m/z* 269.1, found 269.1.
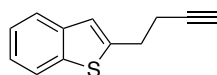
2-(but-3-yn-1-yl)benzo[*b*]thiophene (6i). Yellow oil (194.8 mg, 91% yield); IR (ν, cm^{-1}) 3297, 3057, 2916, 2849, 2119, 1457, 1435, 826, 746 ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.77 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.32–7.29 (m, 1H), 7.28–7.25 (m, 2H), 7.09 (s, 1H), 3.14

(t, J = 7.4 Hz, 2H), 2.64–2.61 (m, 2H), 2.03 (d, J = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ

(ppm) 143.8, 140.0, 139.4, 124.2, 123.7, 123.0, 122.2, 121.4, 83.0, 69.5, 30.0, 20.5; GCMS (EI+)

calcd for C$_{12}$H$_{10}$S [M]$^+$ m/z 186.3, found 186.2.
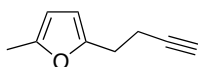
2-(But-3-yn-1-yl)-5-methylfuran (6j). Yellow oil (209.9 mg, 55% yield); IR (ν, cm^{-1}) 3300,

3107, 2920, 2850, 2120, 1570, 1445, 1219, 1024, 781, 630 ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm)

5.95 (d, J = 2.9 Hz, 1H), 5.85 (dd, J = 2.9, 1.0 Hz, 1H), 2.81 (t, J = 7.5 Hz, 2H), 2.50 (td, J = 7.5,

2.7 Hz, 2H), 2.25 (s, 3H), 1.97 (t, J = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 152.2,

150.7, 106.2, 106.0, 83.5, 68.8, 27.5, 17.8, 13.5; GCMS (EI+) calcd for C$_9$H$_{10}$O [M]$^+$ m/z 134.0,

found 134.1.
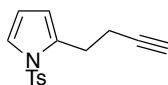
2-(But-3-yn-1-yl)-1-tosyl-1H-pyrrole (6k). Colorless oil (216.7 mg, 92% yield); IR (ν, cm^{-1})

3301, 2917, 2849, 2166, 1567, 1435, 1385, 1274, 1177, 751; ^{1}H NMR (500 MHz, CDCl$_3$) δ

(ppm) 7.64 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 3H), 6.21 (t, J = 3.3 Hz, 1H), 6.09 (d, J = 1.0

Hz, 1H), 2.92 (t, J = 7.4 Hz, 2H), 2.45 (td, J = 7.4, 2.4 Hz, 2H), 2.40 (s, 3H), 1.95 (t, J = 2.6 Hz,

1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 144.9, 136.3, 133.4, 130.1, 126.7, 122.7, 112.9,

111.4, 83.3, 69.0, 26.6, 21.6, 18.5; GCMS (EI+) calcd for C$_{15}$H$_{15}$NO$_2$S [M]$^+$ m/z 273.0, found

273.1.
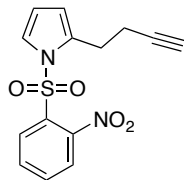
2-(But-3-yn-1-yl)-1-[(2-nitrophenyl)sulfonyl]-1*H*-pyrrole (**6l**). Yellow oil (248.0 mg, 91% yield); IR (ν, cm^{-1}) 3298, 3098, 2923, 2852, 2160, 1542, 1488, 1441, 1373, 1266, 1181, 1149, 1064, 851, 732; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.89 (dd, J = 8.0, 1.2 Hz, 1H), 7.75 (td, J = 7.8, 1.3 Hz, 1H), 7.63 (td, J = 7.8, 1.3 Hz, 1H), 7.28 (dd, J = 3.4, 1.7 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.32 (t, J = 3.4 Hz, 1H), 6.26–6.25 (m, 1H), 2.86 (t, J = 7.1 Hz, 2H), 2.46 (td, J = 7.2, 2.7 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 134.5, 134.4, 133.8, 133.1, 128.4, 125.4, 124.1, 113.7, 111.9, 82.9, 69.4, 26.6, 18.1; GCMS (EI+) calcd for C$_{13}$H$_{12}$N [M]$^+$ m/z 183.1, found 183.1; GCMS (EI+) calcd for C$_{14}$H$_{12}$N$_2$O$_4$S [M]$^+$ m/z 304.3, found 304.3.

5-(3-Bromobut-3-en-1-yl)benzo[*d*][1,3]dioxole (**1l**). A round-bottom flask was charged with B-Br-9-BBN (1M in CH$_2$Cl$_2$, 0.7 mL, 0.7 mmol, 1.2 equiv) in CH$_2$Cl$_2$ (4 mL) and then cooled to 0 ˚C. A solution of 5-(but-3-yn-1-yl)benzo[*d*][1,3]dioxole (107 mg, 0.6 mmol, 1 equiv) in CH$_2$Cl$_2$ (2.8 mL) was added dropwise and was stirred for 4 h at 0 ˚C. Upon disappearance of the alkyne, (TLC; pentane:benzene (5:1), if the alkyne was not consumed additional 0.25 equiv of B-Br-9-BBN was added) acetic acid (0.3 mL) was added and stirred for 1 h at 0 ˚C. Then, 3M NaOH (4 mL) and 30% hydrogen peroxide (0.7 mL) was added at 0 ˚C and stirred for 30 min at room temperature. The reaction was extracted with hexanes (3 x 10 mL), and the organic layer was washed with water, NaHCO$_3$, and water again, and dried over Na$_2$SO$_4$. The solvent was

evaporated under reduced pressure and the residue purified through flash column chromatography (3% EtOAc/hexanes). Colorless oil (132.7 mg, 96% yield); IR (ν, cm^{-1}) 3296, 2915, 1627, 1503, 1487, 1441, 1242, 1097, 1038, 889; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.50–7.47 (m, 1H), 7.42–7.39 (m, 1H), 7.25–7.15 (m, 2H), 6.44 (d, J = 0.8 Hz, 1H), 5.61 (d, J = 1.6 Hz, 1H), 5.43 (d, J = 1.7 Hz, 1H), 3.06 (t, J = 7.4 Hz, 1H), 2.87 (t, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.6, 145.9, 134.2, 133.4, 121.3, 117.3, 108.9, 108.2, 100.8, 43.6, 34.1; GCMS (EI+) calcd for C$_{11}$H$_{11}$BrO$_2$ [M]$^+$ m/z 254.0, found 254.0
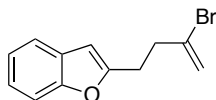
2-(3-Bromobut-3-en-1-yl)benzofuran (**1m**). Colorless oil (260 mg, 82% yield); IR (ν, cm^{-1}) 3111, 2958, 2917, 2847, 1587, 1455, 1251, 1104, 888, 797, 748; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.49 (dd, J = 7.3, 1.7 Hz, 1H), 7.42 (dd, J = 7.2, 1.0 Hz, 1H), 7.22 (td, J = 7.6, 1.5 Hz, 1H), 7.19 (td, J = 7.3, 1.2 Hz, 1H), 6.45 (d, J = 0.9 Hz, 1H), 5.62–5.61 (m, 1H), 5.44 (d, J = 1.8 Hz, 1H), 3.06 (t, J = 7.5 Hz, 2H), 2.87 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 156.9, 154.7, 132.5, 128.7, 123.4, 122.5, 120.4, 117.7, 110.8, 102.9, 39.6, 27.4; GCMS (EI+) calcd for C$_{12}$H$_{11}$BrO [M]$^+$ m/z 250.0, found 250.0.
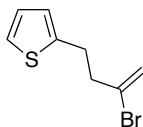
2-(3-Bromobut-3-en-1-yl)thiophene (**1n**). Colorless oil (121 mg, 51% yield); IR (ν, cm^{-1}) 3106, 3070, 2921, 2851, 1629, 1441, 1264, 1194, 1109, 1038, 889, 820, 696; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.13 (dd, J = 5.1, 1.2 Hz, 1H), 6.92 (dd, J = 5.1, 3.5 Hz, 1H), 6.84–6.82 (m, 1H), 5.57–5.56 (m, 1H), 5.42 (d, J = 1.8 Hz, 1H), 3.11 (t, J = 7.5 Hz, 2H), 2.77 (tt, J = 7.5, 0.8 Hz,

2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 142.8, 132.8, 126.8, 124.8, 123.4, 117.7, 43.4, 28.6; GCMS (EI+) calcd for C$_8$H$_9$BrS [M]$^+$ *m/z* 218.0, found 218.0.
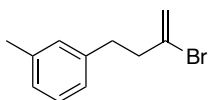
1-(3-Bromobut-3-en-1-yl)-3-methylbenzene (**1o**). Colorless oil (262.6 mg, 79% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.30–7.22 (m, 1H), 7.09–7.05 (m, 3H), 5.59 (d, *J* = 1.5 Hz, 1H), 5.46 (d, *J* = 1.6 Hz, 1H), 2.93–2.88 (m, 2H), 2.79–2.75 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 140.4, 138.0, 133.7, 129.3, 128.3, 126.9, 125.5, 117.0, 43.4, 34.4, 21.4.
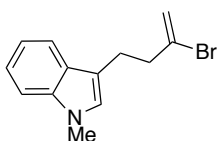
3-(3-Bromobut-3-en-1-yl)-1-methyl-1*H*-indole (**1p**). Colorless oil (295.1 mg, 97% yield); IR (ν, cm^{-1}) 3052, 2926, 2905, 2851, 1627, 1554, 1472, 1375, 1322, 1106, 1012, 885; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.74 (d, *J* = 7.9 Hz, 2H), 7.42–7.39 (m, 1H), 7.36 (td, *J* = 7.4, 1.1 Hz, 1H), 7.25 (ddd, *J* = 7.9, 6.6, 1.4 Hz, 1H), 5.67 (d, *J* = 1.5 Hz, 1H), 5.54 (d, *J* = 1.6 Hz, 1H), 3.82 (s, 3H), 3.16 (t, *J* = 7.5 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75.0 MHz, CDCl$_3$) δ (ppm) 137.1, 134.4, 127.8, 126.5, 121.7, 118.9, 118.8, 116.9, 113.2, 109.3, 42.5, 32.6, 24.1; GCMS (EI+) calcd for C$_{13}$H$_{14}$NBr [M]$^+$ *m/z* 263.0, found 263.0.
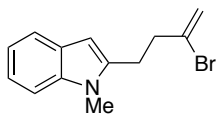
2-(3-Bromobut-3-en-1-yl)-1-methyl-1*H*-indole (**1q**). Colorless oil (240.2 mg, 69% yield); IR (ν, cm^{-1}) 3042, 2916, 2839, 2811, 1617, 1544, 1432, 1371, 1352, 1116, 1002, 880; ^{1}H NMR

(500 MHz, CDCl$_3$) δ (ppm) 7.54 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.17 (td, J = 7.6, 1.0 Hz, 1H), 7.07 (td, J = 7.4, 0.8 Hz, 1H), 5.64 (s, 1H), 5.46 (d, J = 1.8 Hz, 1H), 3.70 (s, 3H), 3.03 (t, J = 7.8 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 139.0, 137.4, 132.9, 127.8, 120.9, 119.9, 119.4, 117.6, 108.8, 99.2, 40.7, 29.5, 25.8; GCMS (EI+) calcd for C$_{13}$H$_{14}$NBr [M]$^+$ m/z 263.0, found 263.0.
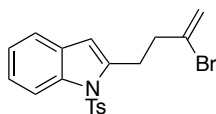
2-(3-Bromobut-3-en-1-yl)-1-tosyl-1H-indole (1r). White solid (525.5 mg, 80% yield); m.p. 93–95 ˚C; IR (ν, cm^{-1}) 2919, 2809, 1628, 1596, 1452, 1370, 1174, 1091, 812, 749; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 8.16 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 6.43 (s, 1H), 5.59 (s, 1H), 5.42 (d, J = 1.5 Hz, 1H), 3.27 (t, J = 7.4 Hz, 2H), 2.88 (d, J = 7.4 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 144.8, 139.7, 137.3, 135.9, 132.8, 129.9, 129.6, 126.3, 124.2, 123.6, 120.3, 117.9, 114.9, 110.0, 41.0, 28.0, 21.6; GCMS (EI+) calcd for C$_{19}$H$_{18}$NO$_2$SBr [M]$^+$ m/z 403.0, found 403.0.
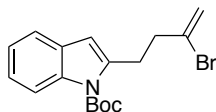
tert-Butyl 2-(3-bromobut-3-en-1-yl)-1H-indole-1-carboxylate (1s). Colorless oil (31.9 mg, 99% yield); IR (ν, cm^{-1}) 2981, 1732, 1455, 1370, 1333, 1259, 1159, 1116, 1086, 746; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 8.10 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.24–7.18 (m, 2H), 6.40 (s, 1H), 5.60 (s, 1H), 5.45 (d, J = 1.3 Hz, 1H), 3.30 (t, J = 7.5 Hz, 2H), 2.85 (t, J = 7.4 Hz, 2H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 150.5, 139.8, 136.6, 133.2, 129.2,

123.5, 122.7, 119.9, 117.3, 115.6, 107.9, 84.0, 40.8, 28.9, 28.3; GCMS (EI+) calcd for $C_{17}H_{20}NO_2Br$ [M]$^+$ m/z 350.3, found 350.2.
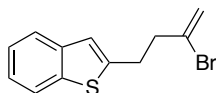
2-(3-Bromobut-3-en-1-yl)benzo[*b*]thiophene (1t). Colorless oil (200.0 mg, 78% yield); IR (ν, cm^{-1}) 3058, 2922, 2853, 1629, 1436, 1066, 1213, 889, 822; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.76 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.05 (s, 1H), 5.49 (d, J = 1.4 Hz, 1H), 5.43 (d, J = 1.4 Hz, 1H), 3.18 (t, J = 7.4 Hz, 2H), 2.8 (d, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 143.7, 140.0, 139.4, 132.5, 124.2, 123.7, 122.9, 122.1, 121.4, 118.0, 42.7, 29.4; GCMS (EI+) calcd for $C_{12}H_{11}SBr$ [M]$^+$ m/z 266.0, found 266.0.
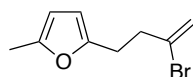
2-(3-Bromobut-3-en-1-yl)-5-methylfuran (1u). Colorless oil (234.4 mg, 73% yield); IR (ν, cm^{-1}) 3104, 2948, 2920, 1629, 1569, 1443, 1218, 1130, 1023, 888; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 5.90 (d, J = 2.9 Hz, 1H), 5.84 (dd, J = 2.9, 1.0 Hz, 1H), 5.58 (dd, J = 2.9, 1.2 Hz, 1H), 5.41 (d, J = 1.7 Hz, 1H), 2.84 (t, J = 7.5 Hz, 1H), 2.73 (t, J = 7.6 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 152.1, 150.6, 133.1, 117.2, 106.2, 105.9, 40.1, 27.0, 13.5; GCMS (EI+) calcd for $C_9H_{11}OBr$ [M]$^+$ m/z 214.0, found 213.9.
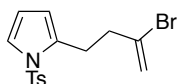
2-(3-Bromobut-3-en-1-yl)-1-tosyl-1*H*-pyrrole (**1v**). Colorless oil (248.3 mg, 89% yield); IR (ν, cm^{-1}) 2924, 2850, 1632, 1596, 1368, 1189, 1176, 1091, 814; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.65 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 3H), 6.19 (t, *J* = 3.3 Hz, 1H), 6.02 (s, 1H), 5.50 (d, *J* = 1.1 Hz, 1H), 5.39 (d, *J* = 1.6 Hz, 1H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 144.9, 136.3, 133.2, 133.0, 130.0, 126.8, 122.7, 117.5, 112.9, 111.4, 40.9, 26.2, 21.6.
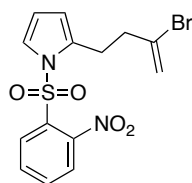
2-(3-Bromobut-3-en-1-yl)-1-[(2-nitrophenyl)sulfonyl]-1*H*-pyrrole (**1w**). Colorless oil (266.4 mg, 93% yield); ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.88 (d, *J* = 8.0 Hz, 1H), 7.75 (td, *J* = 7.8, 1.1 Hz, 1H), 7.65 (td, *J* = 7.8, 1.2 Hz, 1H), 7.29–7.28 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 5.53 (s, 1H), 5.39 (s, 1H), 2.88 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 134.6, 134.2, 133.6, 133.0, 132.6, 128.7, 125.4, 124.0, 117.9, 113.6, 111.7, 40.5, 26.2.

General Procedure for the Formation of Nitrodiene substrates
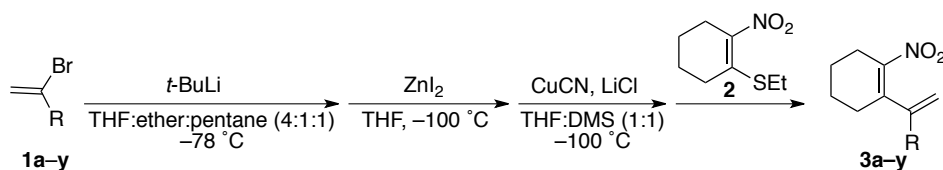
To a dry, Ar-replenished round-bottom flask equipped with a stir bar was added Trapp mixture (dry THF/diethyl ether/pentane, 4:1:1; 6.3 mL) and vinylbromides **1a–y** (2.7 mmol, 2 equiv). After cooling to −78 ˚C, *tert*-butyllithium (1.6 M in pentanes, 3.3 mL, 5.3 mmol, 4.0 equiv) was

added dropwise and the mixture was stirred at −78 ˚C for 30 min. The resulting solution was cannulated into a second round-bottom flask that was cooled to −100 ˚C, containing zinc (II) iodide (852.3 mg, 2.7 mmol, 2 equiv) in THF (8.3 mL). This vinyl zinc solution was then stirred at −100 ˚C for 10 min, which resulted in a milky white appearance. A third dry round-bottom flask charged sequentially with copper (I) cyanide (239.1 mg, 6.4 mmol, 2 equiv), LiCl (226.4 mg, 5.3 mmol, 4.0 equiv), THF (3.3 mL), and DMS (3.3 mL). This solution was light green and homogenous initially, and then a white precipitate formed upon addition of DMS, which was then cooled to −100 ˚C. The vinyl zinc solution was then cannulated into the copper solution at −100 ˚C, forming a brightly orange solution. The zinc cuprate solution was stirred for a few minutes before a THF solution of 1-ethylthio-2-nitrocyclohexene (250.0 mg, 1.3 mmol, 1 equiv) was added. The cooling bath was removed and the solution was gradually warmed to room temperature. Upon the disappearance of 1-thioethyl-2-nitrocyclohexene by TLC (2–4 h), saturated ammonium chloride solution (5 mL) was added to quench the remaining cuprate. The reaction mixture was filtered through a Celite pad and rinsed with EtOAc (50 mL). The biphasic solution was separated and then the organic phase was washed with water (20 mL) and brine (2 x 20 mL), and dried with Na_2SO_4. The solvents were removed in vacuo and the crude oil was purified by through flash column chromatography (0–5% EtOAc in hexanes).
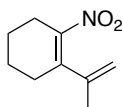
1-Nitro-2-(prop-1-en-2-yl)cyclohex-1-ene (3a). Yellow oil (196 mg, 88% yield); IR (v, cm^{-1}) 2945, 2864, 1519, 1439, 1346, 1329, 900, 773; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 4.88 (t, $J =$ 1.5 Hz, 1H), 4.73 (s, 1H), 2.63–2.57 (m, 2H), 2.34–2.28 (m, 2H), 1.93 (s, 3H), 1.83–1.75 (m,

2H), 1.73–1.65 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 144.6, 144.2, 143.3, 112.1, 30.3, 26.0, 22.0, 21.0; MS (MALDI) calcd for C$_9$H$_{13}$NO$_2$Na [M + Na]$^+$ m/z 190.08, found 190.08.
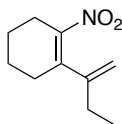
1-(But-1-en-2-yl)-2-nitrocyclohex-1-ene (3b). Yellow oil (203 mg, 84% yield); IR (ν, cm^{-1}) 2938, 2864, 1626, 1516, 1436, 1326, 901, 768; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 4.84 (s, 1H), 4.74 (s, 1H), 2.59–2.54 (m, 2H), 2.29–2.23 (m, 2H), 2.18 (q, J = 7.4 Hz, 2H), 1.79–1.71 (m, 2H), 1.69–1.61 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 149.7, 144.9, 142.8, 109.7, 30.8, 27.0, 26.1, 21.9, 21.4, 11.8; MS (MALDI) calcd for C$_{10}$H$_{15}$NO$_2$Na [M + Na]$^+$ m/z 204.10, found 204.08.
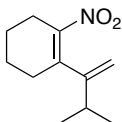
1-(3-Methylbut-1-en-2-yl)-2-nitrocyclohex-1-ene (3c). Colorless oil (78.7 mg, 87% yield); IR (ν, cm^{-1}) 2962, 2869, 1518, 1460, 1361, 1344, 1327, 903, 758; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 4.91 (s, 1H), 4.81 (s, 1H), 2.63–2.57 (m, 2H), 2.39 (sep, J = 6.8 Hz, 1H), 1.78 (tt, J = 8.9, 3.0 Hz, 2H), 1.67 (tt, J = 8.6, 2.9 Hz, 2H), 1.09 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 154.2, 145.1, 142.7, 109.5, 31.9, 31.6, 26.4, 22.1, 21.7, 21.7; MS (MALDI) calcd for C$_{11}$H$_{17}$NO$_2$Na [M + Na]$^+$ m/z 218.12, found 218.11.
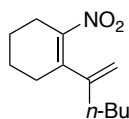
1-(Hex-1-en-2-yl)-2-nitrocyclohex-1-ene (3d). Yellow oil (38.7 mg, 79% yield); IR (ν, cm^{-1}) 2942, 2850, 1639, 1515, 1420, 1340, 899, 776; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 4.88 (d, J = 1.4 Hz, 1H), 4.78 (d, J = 1.0 Hz, 1H), 2.62–2.56 (m, 2H), 2.31–2.25 (m, 2H), 2.17 (t, J = 7.7 Hz, 2H), 1.81–1.73 (m, 2H), 1.70–1.63 (m, 2H), 1.50–1.27 (m, 6H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 148.5, 145.0, 142.7, 110.9, 34.2, 30.9, 29.8, 26.3, 22.5, 22.1, 21.6, 14.0; MS (MALDI) calcd for C$_{12}$H$_{19}$NO$_2$Na [M + Na]$^+$ m/z 232.13, found 232.10.
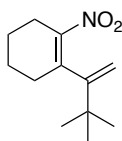
1-(3,3-Dimethylbut-1-en-2-yl)-2-nitrocyclohex-1-ene (3e). Colorless oil (40 mg, 60% yield); IR (ν, cm^{-1}) 2942, 2867, 1519, 1364, 1197, 965, 876, 731; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 4.97 (s, 1H), 4.74 (s, 1H), 2.76–2.70 (m, 1H), 2.47–2.46 (m, 2H), 2.15–2.11 (m, 1H), 1.79–1.75 (m, 2H), 1.68–1.64 (m, 2H), 1.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 157.6, 145.1, 143.7, 110.3, 35.5, 33.0, 30.8, 26.1, 22.0, 21.6; MS (MALDI) calcd for C$_{12}$H$_{20}$NO$_2$ [M + H]$^+$ m/z 210.15, found 210.14.
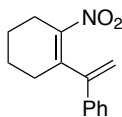
[1-(2-Nitrocyclohex-1-en-1-yl)vinyl]benzene (3f). Orange oil (237 mg, 92% yield); IR (ν, cm^{-1}) 2942, 2863, 1519, 1494, 1446, 1345, 1329, 779, 760, 708; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.39–7.29 (m, 5H), 5.47 (s, 1H), 5.08 (s, 1H), 2.71 (tt, J = 7.7, 2.7 Hz, 2H), 2.29 (tt, J = 7.6, 2.6 Hz, 2H), 1.89–1.82 (m, 2H), 1.73 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.2, 140.6,

137.4, 128.6, 128.4, 128.2, 126.5, 112.5, 30.8, 26.3, 22.1, 21.6; MS (MALDI) calcd for

$C_{14}H_{16}NO_2$ [M + H]$^+$ *m/z* 230.12, found 230.09.
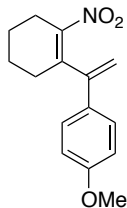
1-Methoxy-4-[1-(2-nitrocyclohex-1-en-1-yl)vinyl]benzene (**3g**). Colorless oil (20 mg, 36%

yield); IR (v, cm^{-1}) 2935, 2854, 1610, 1501, 1367, 1145, 1188, 997, 827, 678; ^{1}H NMR (400

MHz, CDCl$_3$) δ (ppm) 7.31 (dd, *J* = 6.7, 2.2 Hz, 2H), 6.87 (dd, *J* = 6.7, 2.1 Hz, 2H), 5.37 (s, 1H),

4.98 (s, 1H), 3.81 (s, 3H), 2.73–2.68 (m, 2H), 2.31–2.27 (m, 2H), 1.85 (tt, *J* = 9.1, 3.1 Hz, 2H),

1.69 (tt, *J* = 8.9, 3.0 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 159.7, 147.0, 146.6, 140.8,

130.0, 127.7, 113.9, 110.7, 55.3, 30.8, 26.2, 22.1, 21.6. MS (MALDI) calcd for $C_{15}H_{17}NO_3Na$

[M + Na]$^+$ *m/z* 282.11, found 282.10.
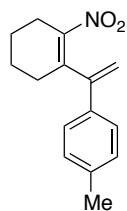
1-Methyl-4-[1-(2-nitrocyclohex-1-en-1-yl)vinyl]benzene (**3h**). Colorless oil (8.8 mg, 10%

yield); ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.27 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H),

5.43 (s, 1H), 5.02 (s, 1H), 2.72–2.67 (m, 2H), 2.35 (s, 3H), 2.31–2.27 (m, 2H), 1.87–1.82 (m,

2H), 1.85 (tt, *J* = 9.1, 3.1 Hz, 2H), 1.69 (tt, *J* = 8.9, 3.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ

(ppm) 147.0, 146.9, 140.8, 138.1, 134.5, 129.3, 126.3, 111.6, 30.9, 26.3, 22.1, 21.6, 21.2.
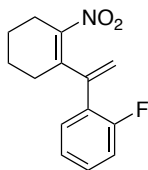
1-Fluoro-2-[1-(2-nitrocyclohex-1-en-1-yl)vinyl]benzene (3i). Colorless oil (15 mg, 14% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.34 (td, J = 7.8, 1.9 Hz, 1H), 7.30–7.22 (m, 1H), 7.11 (td, J = 7.6, 1.2 Hz, 1H), 7.03 (ddd, J = 8.2, 11.2, 1.2 Hz, 1H), 5.53 (s, 1H), 5.33 (s, 1H), 2.69–2.63 (m, 2H), 2.39–2.35 (m, 2H), 1.84–1.78 (m, 2H), 1.74–1.68 (m, 2H).
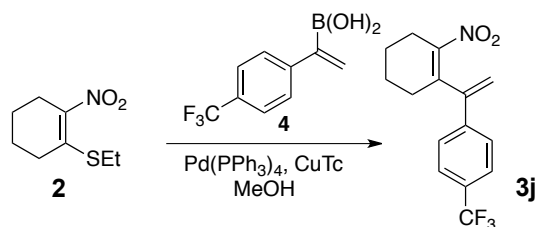
[1-(2-Nitrocyclohex-1-en-1-yl)vinyl]-4-(trifluoromethyl)benzene (3j). To a dry round-bottom flask equipped with a stir bar was added 1-ethylthio-2-nitrocyclohexene (100 mg, 0.53 mmol, 1 equiv), Pd(PPh$_3$)$_4$ (123.4 mg, 0.1 mmol, 0.2 equiv), copper(I) thiophene carboxylate (152.7 mg, 0.8 mmol, 1.5 equiv), and boronic acid **4** (346 mg, 1.6 mmol, 3.0 equiv) and was then Ar-replenished three times. Methanol (18 mL) was added to the reaction and was stirred until disappearance of 1-thioethyl-2-nitrocyclohexene by TLC (3 h). The reaction was quenched by saturated ammonium chloride solution (10 mL) and was filtered through a Celite pad that was rinsed with EtOAc (20 mL). The biphasic solution was separated and then the organic phase was washed with water (20 mL) and brine (2 x 20 mL), and dried with Na$_2$SO$_4$. The solvents were removed in vacuo and the crude oil was purified by through flash column chromatography (0–5% EtOAc in hexanes) to give the title compound as orange oil (138.8 mg, 87% yield); IR (ν, cm^{-1}) 2945, 2866, 1617, 1518, 1321, 1113, 1163, 1065, 847, 698; ^{1}H NMR (300 MHz, CDCl$_3$) δ

(ppm) 7.60 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 5.55 (s, 1H), 5.19 (s, 1H), 2.75–2.69 (m, 2H), 2.31–2.25 (m, 2H), 1.86 (tt, J = 9.0, 3.0 Hz, 2H), 1.71 (tt, J = 8.8, 2.9 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 147.7, 146.1, 140.9, 139.9, 130.1 (q, J = 129.2 Hz), 128.4 (t, J = 86.8 Hz), 126.8, 125.6 (q, J = 15.0 Hz), 114.5, 30.8, 26.2, 22.0, 21.5; ^{19}F NMR (376 MHz, CDCl$_3$) δ (ppm) −63.2; HRMS (ESI) calcd for C$_{15}$H$_{15}$F$_3$NO$_2$ [M + H]$^+$ m/z 298.1055, found 298.1057.
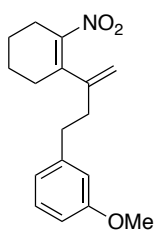
1-Methoxy-3-[3-(2-nitrocyclohex-1-en-1-yl)but-3-en-1-yl]benzene (**3k**). Colorless oil (73.6 mg, 80% yield); IR (ν, cm^{-1}) 2932, 2851, 1600, 1584, 1517, 1343, 1259, 1151, 903, 744, 775, 694; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.21 (t, J = 7.8 Hz, 2H), 6.83–6.73 (m, 3H), 4.98 (d, J = 1.0 Hz, 1H), 4.82 (d, J = 0.7 Hz, 1H), 3.80 (s, 3H), 2.80 (t, J = 8.2 Hz, 2H), 2.62–2.53 (m, 2H), 2.51 (t, J = 8.2 Hz, 2H), 2.29–2.23 (m, 2H), 1.75 (tt, J = 8.8, 3.0 Hz, 2H), 1.64 (tt, J = 8.7, 2.8 Hz, 2H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 159.6, 147.7, 145.2, 143.2, 142.3, 129.3, 120.6, 114.0, 111.4, 111.3, 55.1, 35.8, 34.0, 30.7, 26.1, 21.9, 21.4; HRMS (ESI) calcd for C$_{17}$H$_{22}$NO$_3$ [M + H]$^+$ m/z 288.1600, found 288.1600.
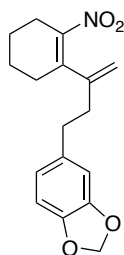
5-[3-(2-Nitrocyclohex-1-en-1-yl)but-3-en-1-yl]benzo[*d*][1,3]dioxole (3l). Colorless oil (68 mg, 70% yield); IR (ν, cm^{-1}) 2940, 2820, 1610, 1522, 1509, 1359, 1258, 900, 739, 780, 679; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.72 (d, *J* = 9.9 Hz, 1H), 6.71 (s, 1H), 6.65 (d, *J* = 9.4 Hz, 1H), 5.91 (s, 2H), 4.95 (s, 1H), 4.83 (s, 1H), 2.75–2.70 (m, 2H), 2.61–2.56 (m, 2H), 2.47–2.42 (m, 2H), 2.28–2.23 (m, 2H), 1.79–1.71 (m, 2H), 1.68–1.60 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 147.7, 147.6, 145.7, 145.3, 142.4, 135.5, 121.1 111.5, 108.8, 108.2, 100.8, 36.3, 33.8, 30.8, 26.2, 22.0, 21.6; HRMS (ESI) calcd for C$_{17}$H$_{20}$NO$_4$ [M + H]$^+$ *m/z* 302.1392, found 302.1354.
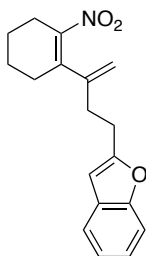
2-[3-(2-Nitrocyclohex-1-en-1-yl)but-3-en-1-yl]benzofuran (3m). Colorless oil (91 mg, 61% yield); IR (ν, cm^{-1}) 2939, 1516, 1454, 1325, 1251, 1164, 904, 826, 718, 740; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.50–7.47 (m, 1H), 7.43–7.40 (m, 1H), 7.25–7.16 (m, 2H), 6.44 (s, 1H), 4.99 (d, *J* = 0.8 Hz, 1H), 4.88 (d, *J* = 0.7 Hz, 1H), 3.02–2.97 (m, 2H), 2.70–2.64 (m, 2H), 2.60–2.55 (m, 2H), 2.31–2.26 (m, 2H), 1.77–1.66 (m, 2H), 1.64–1.58 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 158.3, 154.6, 146.9, 145.6, 141.9, 128.9, 123.3, 122.5, 120.3, 112.1, 110.7, 102.4, 32.2, 30.7, 26.9, 26.2, 21.9, 21.5; HRMS (ESI) calcd for C$_{18}$H$_{20}$NO$_3$ [M + H]$^+$ *m/z* 298.1442, found 298.1429.
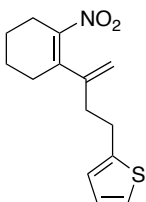
2-[3-(2-Nitrocyclohex-1-en-1-yl)but-3-en-1-yl]thiophene (3n). Red oil (39.6 mg, 54% yield); IR (ν, cm^{-1}) 2924, 2850, 1518, 1437, 1327, 849, 904, 695; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.12 (dd, J = 5.1, 1.2 Hz, 1H), 6.93–6.90 (m, 1H), 6.83–6.82 (m, 1H), 4.97 (d, J = 0.9 Hz, 1H), 4.86 (d, J = 0.9 Hz, 1H), 3.06–3.00 (m, 2H), 2.63–2.56 (m, 4H), 2.29–2.23 (m, 2H), 1.80–1.72 (m, 2H), 1.69–1.61 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.2, 145.4, 144.4, 142.2, 126.7, 124.3, 123.1, 111.9, 36.2, 30.8, 28.2, 26.2, 21.9, 21.5; MS (MALDI) calcd for C$_{14}$H$_{17}$NO$_2$SNa [M + Na]$^+$ m/z 286.09, found 286.08.
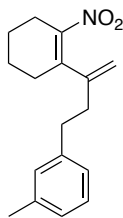
1-Methyl-3-[3-(2-nitrocyclohex-1-en-1-yl)but-3-en-1-yl]benzene (3o). Colorless oil (44.4 mg, 40% yield); IR (ν, cm^{-1}) 3018, 2929, 2861, 1517, 1449, 1343, 1091, 898, 775; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.17 (t, J = 7.5 Hz, 1H), 7.02–6.99 (m, 3H), 4.96 (s, 1H), 4.84 (s, 1H), 2.78–2.75 (m, 2H), 2.60–2.57 (m, 2H), 2.50–2.57 (m, 2H), 2.32 (s, 3H), 2.26–2.24 (m, 2H), 1.76–1.72 (m, 2H), 1.66–1.62 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 148.0, 145.2, 142.5, 141.6, 138.0, 129.1, 128.3, 126.7, 125.3, 111.3, 36.1, 34.0, 30.8, 26.2, 22.0, 21.5, 21.4; GCMS (EI+) calcd for C$_{17}$H$_{21}$NO$_2$ [M]$^+$ m/z 271.4, found 271.5.
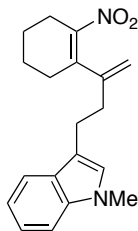
1-Methyl-3-[3-(2-nitrocyclohex-1-en-1-yl)but-3-en-1-yl]-1*H*-indole (**3p**). Colorless oil (79.5 mg, 81% yield); IR (ν, cm^{-1}) 3052, 2934, 2860, 1626, 1513, 1473, 1323, 1245, 900, 745; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.64 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.31 (ddd, *J* = 8.3, 7.3, 1.0 Hz, 1H), 7.26 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.15 (ddd, *J* = 7.9, 6.7, 1.2 Hz, 1H), 6.9 (s, 1H), 5.06 (dd, *J* = 2.6, 1.4 Hz, 1H), 4.91 (d, *J* = 1.0 Hz, 1H), 3.76 (s, 3H), 3.02–2.96 (m, 2H), 2.67–2.59 (m, 4H), 2.33–2.28 (m, 2H), 1.80–1.66 (m, 2H), 1.64–1.61 (m, 2H); ^{13}C NMR (75.0 MHz, CDCl$_3$) δ (ppm) 148.4, 145.2, 142.9, 137.1, 127.8, 126.2, 121.6, 119.0, 118.7, 114.5, 111.3, 109.2, 35.1, 32.6, 31.0, 26.3, 23.5, 22.1, 21.6; GCMS (EI+) calcd for C$_{19}$H$_{12}$N$_2$O$_2$ [M]$^+$ *m/z* 310.4, found 310.3.
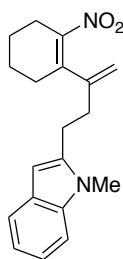
1-Methyl-2-[3-(2-nitrocyclohex-1-en-1-yl)but-3-en-1-yl]-1*H*-indole (**3q**). Colorless oil (20.0 mg, 20% yield); IR (ν, cm^{-1}) 2946, 1738, 1518, 1365, 1275, 1261, 763; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.55 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.29 (s, 1H), 5.03 (s, 1H), 4.91 (s, 1H), 3.70 (s, 3H), 2.97–2.94 (m, 2H), 2.65–2.61 (m, 4H), 2.32–2.30 (m, 2H), 1.79–1.77 (m, 2H), 1.69–1.66 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.4, 145.6, 142.3, 140.3, 137.4, 127.8, 120.7, 119.9, 119.3, 111.7, 108.8, 98.7, 33.1, 30.8, 29.5, 26.2, 25.1, 22.0, 21.5; GCMS (EI+) calcd for C$_{19}$H$_{12}$N$_2$O$_2$ [M]$^+$ *m/z* 310.4, found 310.4.
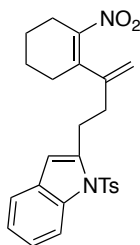
2-[3-(2-Nitrocyclohex-1-en-1-yl)but-3-en-1-yl]-1-tosyl-1*H*-indole (3r). Colorless oil (84.1 mg, 87% yield); IR (ν, cm^{-1}) 2917, 2949, 1541, 1453, 1368, 1173, 1090, 914; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 8.17 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.61 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.40 (dd, *J* = 7.0, 0.7 Hz, 1H), 7.26 (dd, *J* = 7.8, 0.4 Hz, 2H), 7.21 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 0.6 Hz, 2H), 6.44 (d, *J* = 0.8 Hz, 1H), 4.97 (d, *J* = 0.9 Hz, 1H), 4.87 (d, *J* = 0.8 Hz, 1H), 3.19–3.15 (m, 2H), 2.66–2.59 (m, 4H), 2.33–2.30 (m, 2H), 2.33 (s, 3H), 1.78–1.74 (m, 2H), 1.69–1.66 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.0, 145.6, 144.7, 141.9, 141.2, 137.3, 136.0, 129.9, 129.8, 126.3, 124.0, 123.5, 120.2, 114.9, 112.1, 109.3, 34.0, 30.5, 27.6, 26.3, 22.0, 21.6, 21.5; GCMS (EI+) calcd for C$_{25}$H$_{26}$N$_2$O$_4$S [M]$^+$ *m/z* 403.0, found 403.0.
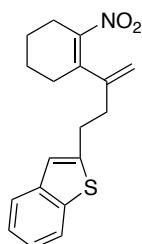
2-[3-(2-Nitrocyclohex-1-en-1-yl)but-3-en-1-yl]benzo[*b*]thiophene (3t). Colorless oil (87.0 mg, 74% yield); IR (ν, cm^{-1}) 2918, 2849, 1519, 1435, 1328, 1262, 839, 795, 748; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.76 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.31 (td, *J* = 7.8, 0.7 Hz, 1H), 7.26 (td, *J* = 7.5, 1.2 Hz, 1H), 7.05 (d, *J* = 0.7 Hz, 1H), 3.11 (td, *J* = 8.0, 0.9 Hz, 2H), 2.66 (d, *J* = 8.0 Hz, 2H), 2.60 (tt, *J* = 5.8, 2.1 Hz, 2H), 2.28 (tt, *J* = 5.7, 2.0 Hz, 2H), 1.77–1.73 (m, 2H), 1.67–1.62 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.0, 145.6, 145.4,

142.1, 140.1, 139.2, 124.2, 123.6, 122.8, 122.1, 120.9, 112.0, 35.5, 30.8, 29.1, 26.2, 22.0, 21.5; GCMS (EI+) calcd for $C_{18}H_{19}NO_2S$ [M]$^+$ m/z 313.1, found 313.0.
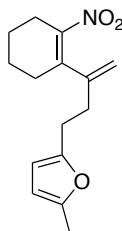
2-Methyl-5-[3-(2-nitrocyclohex-1-en-1-yl)but-3-en-1-yl]furan (**3u**). Colorless oil (96.2 mg, 86% yield); IR (ν, cm^{-1}) 2940, 2849, 1619, 1517, 1449, 1344, 1218, 1022, 910, 781; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 5.87 (d, J = 1.8 Hz, 1H), 5.83 (d, J = 1.8 Hz, 1H), 4.93 (dd, J = 1.5, 0.8 Hz, 1H), 4.83 (d, J = 0.5 Hz, 1H), 2.77–2.75 (m, 2H), 2.59–2.56 (m, 2H), 2.54–2.50 (m, 2H), 2.27–2.24 (m, 2H), 2.23 (s, 3H), 1.77–1.73 (m, 2H), 1.66–1.62 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 153.3, 150.3, 147.3, 145.3, 142.3, 111.7, 105.9, 105.7, 32.7, 30.8, 26.5, 26.2, 22.0, 21.5, 13.5; GCMS (EI+) calcd for $C_{15}H_{19}NO_3$ [M]$^+$ m/z 261.3, found 261.2.
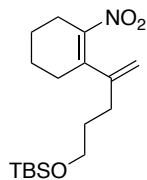
***tert*-Butyldimethyl{[4-(2-nitrocyclohex-1-en-1-yl)pent-4-en-1-yl]oxy}silane** (**3x**). Colorless oil (76.1 mg, 88% yield); IR (ν, cm^{-1}) 2930, 2857, 1520, 1253, 1100, 834, 774; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 4.88 (s, 1H), 4.79 (s, 1H), 3.63 (t, J = 6.3 Hz, 2H), 2.60–2.57 (m, 2H), 2.29–2.21 (m, 4H), 1.77–1.74 (m, 2H), 1.71–1.65 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.9, 145.2, 142.2, 111.3, 62.6, 30.9, 30.7, 30.6, 26.3, 26.0, 22.0, 21.6, 18.3, – 5.27; GCMS (EI+) calcd for $C_{17}H_{31}NO_3Si$ [M]$^+$ m/z 325.5, found 325.4.
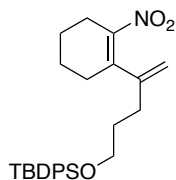
tert-Butyl{[4-(2-nitrocyclohex-1-en-1-yl)pent-4-en-1-yl]oxy}diphenylsilane (3y). Colorless oil (54.7 mg, 29% yield); IR (v, cm^{-1}) 2931, 2857, 1519, 1428, 1360, 1106, 823, 739, 700; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.66 (dd, J = 7.9, 1.4 Hz, 4H), 7.43–7.56 (m, 8H), 4.85 (s, 1H), 4.77 (s, 1H), 3.69 (t, J = 6.0 Hz, 2H), 2.59–2.56 (m, 2H), 2.29–2.22 (m, 4H), 1.79–1.71 (m, 2H), 1.66–1.62 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 147.9, 145.2, 142.3, 135.6, 135.5, 134.0, 129.6, 129.5, 127.7, 127.6, 111.3, 63.4, 30.7, 30.6, 26.9, 26.3, 22.0, 21.6, 19.2; GCMS (EI+) calcd for C$_{27}$H$_{35}$NO$_3$Si [M]$^+$ m/z 449.7, found 449.7.

General Procedure for the Syntheses of Nitronate Products 5a–5j
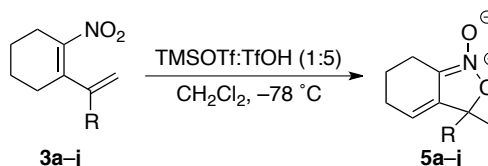
In a dry round-bottom flask with a magnetic stir bar under Ar atmosphere, a solution of nitrodiene **3a–j** (0.31 mmol, 1 equiv) in methylene chloride (16 mL) was cooled to −78 ˚C. TMSOTf and TfOH (38 μL:92 μL, 1:5, 4 equiv) was added sequentially to the cooled solution and then stirred at −78 ˚C. Upon disappearance of nitrodiene (10 min–1 h) by TLC, it was quenched using triethylamine (0.22 mL, 1.6 mmol, 5 equiv). The cooling bath was removed and the solution was gradually warmed to room temperature. The organic solution was washed with water (20 mL) and brine (2 x 20 mL), and dried with Na$_2$SO$_4$. The solvents were removed in vacuo and the crude oil was purified by through flash column chromatography (0–15% EtOAc in hexanes).
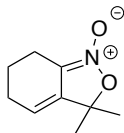
3,3-Dimethyl-3,5,6,7-tetrahydrobenzo[c]isoxazole 1-oxide (**5a**). White solid (46.6 mg, 89% yield); m.p. 56–58 ˚C; IR (ν, cm^{-1}) 2973, 2920, 2827, 1648, 1625, 1426, 1351, 1263, 1141, 854; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 5.55 (t, J = 4.4 Hz, 1H), 2.54 (t, J = 6.6 Hz, 2H), 2.20 (q, J = 5.4 Hz, 2H), 1.77 (pen, J = 6.3 Hz, 2H), 1.45 (s, 6H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 142.4, 117.5, 116.9, 82.5, 27.5 (2C), 24.5, 20.8, 20.6; HRMS (ESI) calcd for C$_9$H$_{14}$NO$_2$ [M + H]$^+$ m/z 168.1029, found 168.1024.
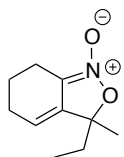
3-Ethyl-3-methyl-3,5,6,7-tetrahydrobenzo[c]isoxazole 1-oxide (**5b**). White solid (120 mg, 83% yield); m.p. 44–46 ˚C; IR (ν, cm^{-1}) 2967, 2926, 2879, 2838, 1648, 1619, 1460, 1353, 1263, 838; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 5.52 (t, J = 4.5 Hz, 1H), 2.56 (t, J = 6.3 Hz, 2H), 2.23 (q, J = 5.0 Hz, 2H), 1.84–1.72 (m, 2H), 1.66 (q, J = 7.2 Hz, 2H), 1.44 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 140.9, 117.9, 117.4, 85.3, 33.4, 25.8, 24.6, 20.7 (2C), 7.6; HRMS (ESI) calcd for C$_{10}$H$_{16}$NO$_2$ [M + H]$^+$ m/z 182.1181, found 182.1189.
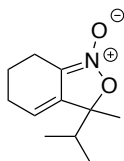
3-Isopropyl-3-methyl-3,5,6,7-tetrahydrobenzo[c]isoxazole 1-oxide (**5c**). White solid (26.6 mg, 83% yield); m.p. 32–34 ˚C; IR (ν, cm^{-1}) 2974, 2877, 2836, 1649, 1624, 1454, 1354, 1257, 833;

^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 5.52 (t, J = 4.5 Hz, 1H), 2.51 (t, J = 6.5 Hz, 2H), 2.23–2.17 (m, 2H), 1.86–1.70 (m, 3H), 1.40 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 140.4, 118.4, 117.5, 87.4, 37.1, 24.7, 24.0, 20.7, 20.6, 16.5, 16.4; HRMS (ESI) calcd for C$_{11}$H$_{18}$NO$_2$ [M + H]$^+$ m/z 196.1338, found 196.1343.
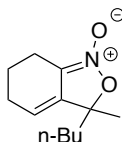
3-Butyl-3-methyl-3,5,6,7-tetrahydrobenzo[c]isoxazole 1-oxide (**5d**). Yellow oil (16.4 mg, 77% yield); IR (ν, cm^{-1}) 2926, 2856, 1647, 1622, 1451, 1350, 1286, 842, 779; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 5.51 (t, J = 4.5 Hz, 1H), 2.53 (t, J = 6.3 Hz, 2H), 2.21 (dd, J = 11.2, 5.2 Hz, 2H), 1.78 (q, J = 6.3 Hz, 2H), 1.73–1.55 (m, 2H), 1.41 (s, 3H), 1.31–1.23 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 141.2, 117.8, 117.4, 85.0, 40.4, 26.2, 25.3, 24.6, 22.7, 20.7, 20.6, 14.0; HRMS (ESI) calcd for C$_{12}$H$_{20}$NO$_2$ [M + H]$^+$ m/z 210.1494, found 210.1505.
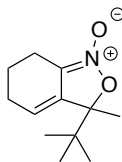
3-(*tert*-Butyl)-3-methyl-3,5,6,7-tetrahydrobenzo[c]isoxazole 1-oxide (**5e**). White solid (12.5 mg, 70% yield); m.p. 44–46 ˚C; IR (ν, cm^{-1}) 2955, 2908, 2873, 1648, 1619, 1426, 1356, 1257, 843; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 5.62 (t, J = 4.4 Hz, 1H), 2.61–2.51 (m, 2H), 2.32–2.15 (m, 2H), 1.83–1.72 (m, 2H), 1.43 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 140.0, 119.6, 117.8, 89.7, 38.2, 24.9, 24.4, 21.7, 20.8, 20.5; HRMS (ESI) calcd for C$_{12}$H$_{20}$NO$_2$ [M + H]$^+$ m/z 210.1494, found 210.1496.
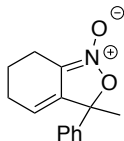
3-Methyl-3-phenyl-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-oxide (5f). Brown oil (150 mg, 84%

yield); IR (ν, cm^{-1}) 3061, 2924, 2853, 1650, 1624, 1557, 1446, 1267, 838, 765, 699; ^{1}H NMR

(400 MHz, CDCl$_3$) δ (ppm) 7.48–7.47 (m, 2H), 7.38–7.26 (m, 2H), 5.70 (t, *J* = 4.5 Hz, 1H),

2.65–2.51 (m, 2H), 2.24–2.22 (m, 2H), 1.83 (s, 3H), 1.81–1.71 (m, 2H); ^{13}C NMR (100.6 MHz,

CDCl$_3$) δ (ppm) 142.2, 141.6, 128.6, 128.1, 124.8, 120.1, 116.3, 84.7, 27.3, 24.8, 20.9, 20.5;

HRMS (ESI) calcd for C$_{14}$H$_{16}$NO$_2$ [M + H]$^+$ *m/z* 230.1181, found 230.1179.
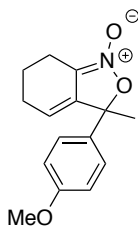
3-(4-Methoxyphenyl)-3-methyl-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-oxide (5g). Colorless

oil (17.2 mg, 87% yield); IR (ν, cm^{-1}) 3054, 2933, 2837, 1651, 1624, 1511, 1249, 1180, 1031,

837, 730; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.38 (dd, *J* = 6.9, 1.9 Hz, 2H), 6.88 (dd, *J* = 6.9,

1.9 Hz, 2H), 5.65 (dt *J* = 4.5 Hz, 1H), 3.80 (s, 3H), 2.65–2.54 (m, 2H), 2.25–2.22 (m, 2H), 1.83

(s, 3H), 1.81–1.76 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 159.4, 141.8, 134.1, 126.4,

120.0, 116.5, 113.9, 84.7, 55.3, 27.3, 24.8, 20.9, 20.6; HRMS (ESI) calcd for C$_{15}$H$_{18}$NO$_3$ [M +

H]$^+$ *m/z* 260.1287, found 260.1301.
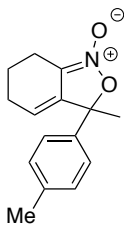
3-Methyl-3-(*p*-tolyl)-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-oxide (**5h**). Colorless oil (5.5 mg, 74% yield); IR (ν, cm^{-1}) 3030, 2923, 2866, 1650, 1623, 1512, 1354, 1451, 1267, 839, 817; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.35 (dd, *J* = 7.5, 2.7 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.67 (t, *J* = 4.5 Hz, 1H), 2.65–2.54 (m, 2H), 2.34 (s, 3H), 2.25–2.21 (m, 2H), 1.82 (s, 3H), 1.81–1.76 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 141.8, 139.3, 138.0, 129.3, 124.8, 119.8, 116.4, 84.7, 27.3, 24.8, 21.1, 20.9, 20.5; HRMS (ESI) calcd for C$_{15}$H$_{18}$NO$_2$ [M + H]$^{+}$ *m/z* 244.1338, found 244.1329.
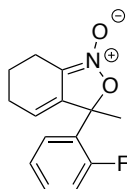
3-(2-Fluorophenyl)-3-methyl-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-oxide (**5i**). Colorless oil (5.9 mg, 72% yield); IR (ν, cm^{-1}) 3079, 2932, 1651, 1626, 1487, 1452, 1267, 837, 759; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.59 (td, *J* = 7.9, 1.7 Hz, 1H), 7.33–7.27 (m, 1H), 7.14 (td, *J* = 7.7, 1.2 Hz, 1H), 7.07 (ddd, *J* = 11.9, 8.2, 1.2 Hz, 1H), 5.87 (td, *J* = 4.5, 1.6 Hz, 1H), 2.66–2.52 (m, 2H), 2.25–2.20 (m, 2H), 1.92 (d, *J* = 1.5 Hz, 3H), 1.79 (p, *J* = 6.2 Hz, 2H); HRMS (ESI) calcd for C$_{14}$H$_{15}$FNO$_3$ [M + H]$^{+}$ *m/z* 248.1087, found 248.1089.
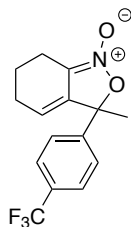
3-Methyl-3-[4-(trifluoromethyl)phenyl]-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-oxide (**5j**). Yellow oil (138.8 mg, 76% yield); IR (ν, cm^{-1}) 3057, 2982, 2935, 2873, 1651, 1625, 1409, 1325, 1118, 840; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.63 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 8.8 Hz,

2H), 5.74 (t, $J = 4.5$ Hz, 1H), 2.66–2.52 (m, 2H), 2.32–2.17 (m, 2H), 1.85 (s, 3H), 1.82–1.71 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 146.3, 141.1, 130.3 (q, $J = 129.3$ Hz), 125.7 (q, $J = 14.7$ Hz), 125.1, 122.6, 120.6, 115.9, 83.9, 27.2, 24.8, 20.9, 20.4; HRMS (ESI) calcd for C$_{15}$H$_{15}$F$_3$NO$_2$ [M + H]$^+$ m/z 298.1055, found 298.1040.

General Procedure for the Formation of 7a–d, 5k–m, 9a,b
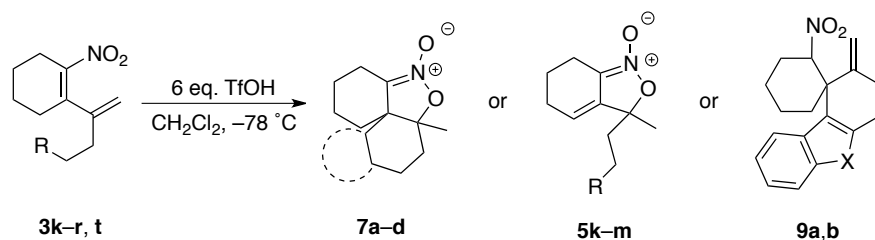
In a dry round-bottom flask with a magnetic stir bar under Ar atmosphere, a solution of nitrodiene **3k–r**, **t** (0.09 mmol, 1 equiv) in methylene chloride (5 mL) was cooled to −78 ˚C. TfOH (47 μL, 0.5 mmol, 6 equiv) was added to the cooled solution and then stirred at −78 ˚C. Upon disappearance of nitrodiene (2–4 h) by TLC, it was quenched using triethylamine (0.22 mL, 1.6 mmol, 7 equiv). The cooling bath was removed and the solution was gradually warmed to room temperature. The organic solution was washed with water (20 mL) and brine (2 x 20 mL), and dried with Na$_2$SO$_4$. The solvents were removed in vacuo and the crude oil was purified by through flash column chromatography (0–33% EtOAc in Hexanes).
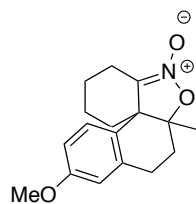
10-Methoxy-6a-methyl-2,3,4,6a,7,8-hexahydro-1H-benzo[c]naphtho[1,2-d]isoxazole 5-oxide (7a). White solid (16.8 mg, 66% yield); m.p. 178–180˚C; IR (ν, cm^{-1}) 2933, 2899, 1640, 1608,

1504, 1241, 825, 773; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.17 (d, J = 8.6 Hz, 1H), 6.74 (dd, J = 8.6, 2.7 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 3.77 (s, 3H), 2.95–2.82 (m, 2H), 2.65–2.45 (m, 2H), 2.10–1.90 (m, 4H), 1.76–1.55 (m, 4H), 1.52 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 158.1, 138.5, 130.8, 128.5, 120.1, 113.5, 111.9, 86.6, 55.1, 53.1, 32.7, 32.6, 26.4, 23.4, 23.0, 22.9, 21.4; HRMS (ESI) calcd for C$_{17}$H$_{22}$NO$_3$ [M + H]$^+$ m/z 288.1600, found 288.1596.
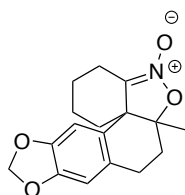
6a-Methyl-2,3,4,6a,7,8-hexahydro-1H-[1,3]dioxolo[4',5':6,7]naphtho[1,2d]benzo[c]isoxazole 5-oxide (7b). White solid (27.8 mg, 66% yield); m.p. 184–186°C; IR (ν, cm^{-1}) 2924, 2854, 1637, 1483, 1227, 1034, 829; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.72 (s, 1H), 6.61 (s, 1H), 5.91 (dd, J = 4.4, 1.4 Hz, 2H), 2.95–2.76 (m, 2H), 2.58–2.47 (m, 2H), 2.08–1.88 (m, 4H), 1.72–1.62 (m, 4H), 1.51 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 146.3, 146.1, 131.7, 130.6, 128.3, 119.9, 108.6, 107.9, 101.1, 86.7, 53.7, 32.7, 26.2, 23.4, 23.1, 22.9, 21.6; HRMS (ESI) calcd for C$_{17}$H$_{20}$NO$_4$ [M + H]$^+$ m/z 302.1392, found 302.1382.
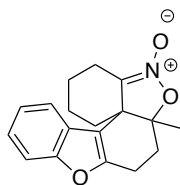
6a-Methyl-2,3,4,6a,7,8-hexahydro-1H-[1,3]dioxolo[4',5':6,7]naphtho[1,2d]benzo[c]isoxazole 5-oxide (7c). White solid (10 mg, 63% yield); m.p. 183–185°C; IR (ν, cm^{-1}) 2942, 2931, 1645, 1455, 1269, 1016, 854; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.61 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 6.3 Hz, 1H), 7.25–7.19 (m, 2H), 3.11–3.03 (m, 1H), 2.94–2.88 (m, 1H), 2.77 (dd, J = 17.0, 5.7

Hz, 1H), 2.73–2.66 (m, 1H), 2.34 (dd, J = 14.7, 5.3 Hz, 1H), 2.24–2.19 (m, 1H), 2.14–2.05 (m, 2H), 2.04–1.97 (m, 2H), 1.91–1.87 (m, 1H), 1.78–1.72 (m, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 154.9, 153.1, 126.4, 123.7, 122.5, 119.7, 119.4, 113.4, 111.6, 86.4, 49.9, 30.1, 28.2, 22.8, 22.3, 22.1, 21.6, 19.5; HRMS (ESI) calcd for C$_{18}$H$_{20}$NO$_3$ [M + H]$^+$ m/z 298.1443, found 298.1451.
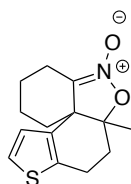
6a-Methyl-2,3,4,6a,7,8-hexahydro-1H-benzo[c]thieno[2',3':5,6]benzo[1,2-d]isoxazole 5-oxide (7d). White solid (15.9 mg, 88% yield); m.p. 151–153 ˚C; IR (ν, cm^{-1}) 2939, 2920, 1646, 1436, 1375, 1262, 1232, 830, 735; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.12 (d, J = 5.4 Hz, 1H), 7.05 (d, J = 5.3 Hz, 1H), 3.12–3.00 (m, 1H), 2.87–2.75 (m, 2H), 2.42–2.34 (m, 1H), 2.30 (ddd, J = 14.4, 5.4, 1.8 Hz, 1H), 2.13–2.04 (m, 1H), 2.02–1.97 (m, 1H), 1.96–1.84 (m, 2H), 1.83–1.76 (m, 2H), 1.62–1.53 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 135.8, 134.7, 125.9, 123.3, 119.5, 85.0, 50.9, 30.6, 29.6, 23.3, 23.01, 22.1, 21.9, 20.8; HRMS (ESI) calcd for C$_{14}$H$_{18}$NO$_2$S [M + H]$^+$ m/z 264.1058, found 264.1066.
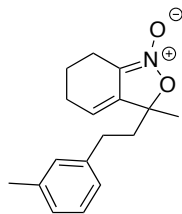
3-Methyl-3-(3-methylphenethyl)-3,5,6,7-tetrahydrobenzo[c]isoxazole 1-oxide (5k). Colorless oil (3.0 mg, 33% yield); IR (ν, cm^{-1}) 2924, 2860, 1650, 1623, 1454, 1354, 1267, 963, 841; ^{1}H

NMR (500 MHz, CDCl$_3$) δ (ppm) 7.15 (t, J = 7.5 Hz, 1H), 6.99–6.96 (m, 3H), 5.57 (t, J = 4.4 Hz, 1H), 2.72 (td, J = 12.8, 4.7 Hz, 1H), 2.58–2.55 (m, 3H), 2.31 (s, 3H), 3.23–3.20 (m, 2H), 2.07–2.00 (m, 1H), 1.96–1.90 (m, 1H), 1.82–1.75 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 141.2, 140.9, 138.0, 129.2, 128.4, 126.7, 125.3, 118.2, 117.3, 84.5, 42.5, 29.6, 26.4, 24.6, 21.4, 20.8, 20.6; GCMS (EI+) calcd for C$_{17}$H$_{21}$NO$_2$ [M]$^+$ m/z 271.4, found 271.4.
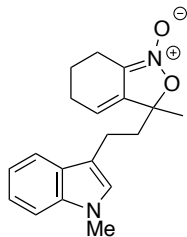
3-Methyl-3-[2-(1-methyl-1H-indol-3-yl)ethyl]-3,5,6,7-tetrahydrobenzo[c]isoxazole   1-oxide (5l). Colorless oil (3.0 mg, 43% yield); ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.53 (d, J = 7.8 Hz, 1H), 7.28–7.26 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.82 (s, 1H), 5.58 (t, J = 4.4 Hz, 1H), 3.73 (s, 3H), 2.93–2.86 (m, 1H), 2.77–2.71 (m, 1H), 2.58–2.54 (m, 2H), 2.22–2.02 (m, 4H), 1.81–1.74 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 141.0, 137.1, 127.6, 126.0, 121.6, 118.8, 118.7, 118.0, 117.4, 114.0, 109.2, 84.7, 41.4, 32.6, 26.5, 24.6, 20.8, 20.6 19.1.
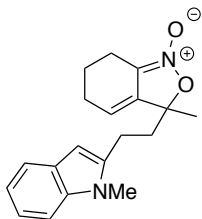
3-methyl-3-[2-(1-methyl-1H-indol-2-yl)ethyl]-3,5,6,7-tetrahydrobenzo[c]isoxazole   1-oxide (5m). Colorless oil (4.0 mg, 40% yield); IR (ν, cm^{-1}) 2920, 2849, 1650, 1624, 1542, 1468, 1353, 1267, 840; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.51 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.16 (td, J = 7.6, 1.1 Hz, 1H), 7.06 (td, J = 7.4, 0.9 Hz, 1H), 6.23 (s, 1H), 5.62 (t, J = 4.5

Hz, 1H), 3.66 (s, 3H), 2.90 (ddd, J = 15.4, 11.7, 4.1 Hz, 1H), 2.75 (ddd, J = 15.3, 11.6, 4.3 Hz, 1H), 2.59 (t, J = 6.6 Hz, 2H), 2.25–2.20 (m, 2H), 2.19–2.15 (m, 1H), 2.10–2.03 (m, 1H), 1.84–1.74 (m, 2H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ (ppm) 140.7, 139.7, 137.4, 127.7, 120.8, 119.8, 119.3, 118.4, 117.2, 108.8, 98.7, 84.1, 39.4, 29.5, 26.6, 24.6, 20.9, 20.8, 20.6; GCMS (EI+) calcd for $C_{19}H_{22}N_2O_2$ [M]$^+$ m/z 310.2, found 310.2.
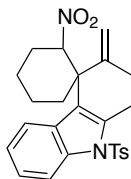
3-Methylene-2'-nitro-9-tosyl-1,2,3,9-tetrahydrospiro[carbazole-4,1'-cyclohexane] **(9a)**. Colorless oil (7.0 mg, 77% yield); ^{1}H NMR (500 MHz, CDCl₃) δ (ppm) 7.83 (dd, J = 7.6, 1.7 Hz, 2H), 7.66 (d, J = 8.3 Hz, 1H), 7.30 (ddd, J = 8.3 7.4, 1.2 Hz, 1H,); 7.25 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 6.99 (td, J = 6.99, 7.5, 0.9 Hz, 1H), 5.18 (d, J = 1.4 Hz, 1H), 4.75 (s, 1H), 3.85 (s, 1H), 2.93–2.86 (m, 2H), 2.55–2.52 (m, 2H), 2.40–2.34 (m, 1H), 2.35 (s, 3H), 2.23–2.17 (m, 1H), 2.08–2.04 (m, 1H), 1.93 (td, J = 13.3, 3.6 Hz, 1H), 1.75–1.66 (m, 2H), 1.50–1.47 (m, 2H); ^{13}C NMR (125 MHz, CDCl₃) δ (ppm) 164.3, 143.7, 141.2, 141.0, 138.1, 131.0, 129.5, 128.3, 127.2, 126.1, 125.5, 122.9, 114.7, 114.1, 94.8, 58.9, 31.0, 30.0, 25.7, 25.6, 25.4, 21.5, 21.0.
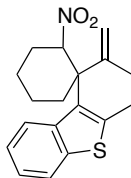
2'-methylene-2-nitro-3',4'-dihydro-2'H-spiro[cyclohexane-1,1'-dibenzo[b,d]-thiophene] **(9b)**. Colorless oil (5.5 mg, 50% yield); ^{1}H NMR (500 MHz, CDCl₃) δ (ppm) 7.29 (d, J = 6.1 Hz, 1H), 7.26 (d, J = 6.4 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.11 (td, J = 7.6, 0.7 Hz, 1H), 5.13 (s, 1H), 4.81 (s, 1H), 3.41 (s, 1H), 2.86 (dd, J = 15.3, 4.7 Hz, 1H), 2.63 (td, J = 13.5, 4.9 Hz, 1H),

2.43–2.37 (m, 2H), 2.36–2.35 (m, 1H), 2.19–2.14 (m, 1H), 1.91–1.87 (m, 1H), 1.79 (dd, J = 13.8, 1.5 Hz, 1H), 1.48–1.43 (m, 1H), 1.39 (tt, J = 13.5, 3.1 Hz, 1H), 1.06 (qt, J = 13.2, 4.2 Hz, 1H), 0.91 (td, J = 13.3, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 145.6, 137.1, 136.6, 130.0, 126.4, 125.2, 124.2, 113.6, 100.6, 96.1, 61.3, 34.8, 31.1, 28.9, 26.6, 24.6, 20.6.

Procedure for the Formation of Hydroisoxazole 8a,b

Hydroisoxazole **8a** was obtained by following the procedure of the formation of nitronates **5a–j**.

Hydroisoxazole **8b** was obtained by following the procedure of the formation of nitronates **7a–d**.
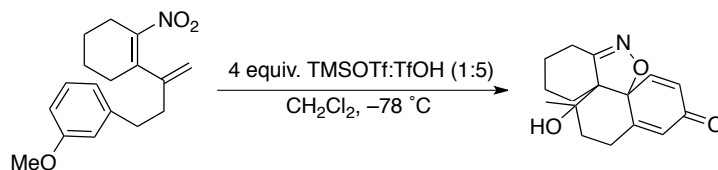
11-Hydroxy-11-methyl-7,8,9,10,12,13-hexahydrobenzo[c]naphtho[1,8a-d]isoxazol-2(11H)-one (8a) White solid (14.3 mg, 42% yield); m.p. 178–180˚C; IR (ν, cm^{-1}) 3441, 2934, 2863, 1667, 1629, 1293, 1132, 911, 732; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.77 (d, J = 10.2 Hz, 1H), 6.19 (s, 1H), 6.12 (d, J = 10.2 Hz, 1H), 2.96–2.88 (m, 1H), 2.80–2.64 (m, 2H), 2.54–2.42 (m, 1H), 2.34–2.24 (m, 1H), 2.00–1.81 (m, 3H), 1.67–1.31 (m, 4H), 1.26 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ (ppm) 184.9, 163.8, 156.4, 145.3, 128.6, 126.9, 85.8, 74.5, 66.8, 35.6, 29.2, 27.3, 26.3, 25.5, 25.0, 21.7; HRMS (ESI) calcd for C$_{16}$H$_{20}$NO$_3$ [M + H]$^+$ m/z 273.1365, found 273.1363.
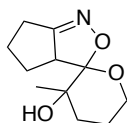
3'-Methyl-3a,3',4,4',5,5',6,6'-octahydrospiro[cyclopenta[c]isoxazole-3,2'-pyran]-3'-ol   (8b). Colorless oil (6.8 mg, 15% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 4.09–4.00 (m, 1H),

3.95–3.88 (m, 1H), 3.67–3.63 (m, 1H), 2.46–2.39 (m, 2H), 2.30–2.14 (m, 2H), 2.09 (d, J = 1.2 Hz, 1H), 1.95–1.78 (m, 4H), 1.72–1.61 (m, 2H), 1.53 (s, 3H).

General Procedure for [3+2] Cycloaddition
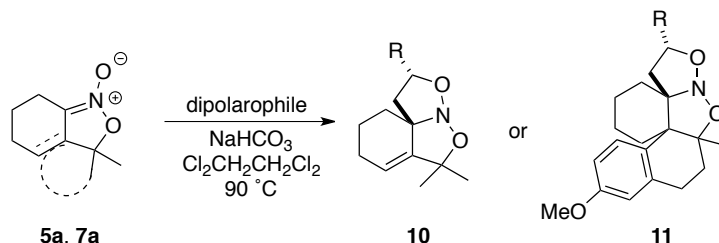
Nitronate **5a** or **7a** (0.08 mmol, 1 equiv), NaHCO$_3$ (0.1 mmol, 1.2 equiv), distilled dichloroethane (stored over 4-Å molecular sieves; 1 mL), and acrylate (distilled and stored over 4-Å molecular sieves and with 0.05% MeHQ as stabilizer, 1 mL) were added to a dry pressure tube with a magnetic stirrer under Ar atmosphere. The reaction vessel was closed and stirred at 90 ˚C. Upon disappearance of nitronate **5a** or **7a** (24–48 h) by TLC, the solvent was removed in vacuo and the crude oil was purified by flash column chromatography (0–10% EtOAc in Hexanes).
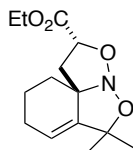
Ethyl 6,6-dimethyl-1,2,6,8,9,10-hexahydrobenzo[c]isoxazolo[2,3-b]isoxazole-2-carboxylate (10aa). Tan solid (17.5 mg, 79% yield); m.p. 38–40 ˚C; IR (ν, cm⁻¹) 2977, 2869, 1744, 1448, 1378, 1271, 1198, 1080, 1048, 942, 800; ¹H NMR (400 MHz, CDCl$_3$) δ (ppm) 5.55 (t, J = 3.5 Hz, 1H), 5.16 (dd, J = 10.1, 6.3 Hz, 1H), 4.23 (dq, J = 14.3, 0.9 Hz, 2H), 2.52 (dd, J = 12.5, 10.2 Hz, 1H), 2.20 (dd, J = 12.5, 6.3 Hz, 1H), 2.11–2.02 (m, 2H), 1.94–1.89 (m, 1H), 1.83 (dt, J = 11.8, 3.1 Hz, 1H), 1.61–1.52 (m, 1H), 1.50–1.45 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.29 (t, J =

7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 170.3, 146.9, 119.6, 80.8, 79.5, 78.2, 61.6, 41.7, 31.3, 29.5, 27.8, 23.7, 18.2, 14.1; GCMS (EI+) calcd for C$_{14}$H$_{21}$NO$_4$ [M]$^+$ m/z 267.1, found 267.1.
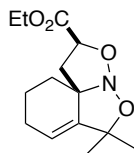
Ethyl 6,6-dimethyl-1,2,6,8,9,10-hexahydrobenzo[*c*]isoxazolo[2,3-*b*]isoxazole-2-carboxylate (10ab). Colorless oil (3.3 mg, 15% yield); IR (ν, cm^{-1}) 2933, 2809, 1733, 1460, 1370, 1267, 1223, 1053, 799, 735; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 5.54 (t, J = 3.4 Hz, 1H), 4.91 (dd, J = 9.8, 5.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.78 (dd, J = 12.9, 4.9 Hz, 1H), 2.24–2.19 (m, 1H), 2.18–2.10 (m, 1H), 2.09–2.03 (m, 1H), 1.95–1.91 (m, 1H), 1.71–1.69 (m, 1H), 1.57–1.56 (m, 2H), 1.55 (s, 3H), 1.34 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 171.6, 146.8, 119.3, 81.4, 79.7, 78.7, 61.6, 39.6, 31.3, 29.6, 27.2, 23.8, 18.2, 14.2; GCMS (EI+) calcd for C$_{14}$H$_{21}$NO$_4$ [M]$^+$ m/z 267.1, found 267.1.

major   minor
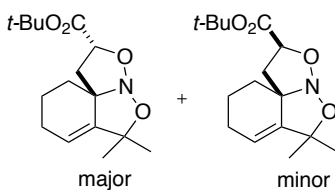
tert-**Butyl 6,6-dimethyl-1,2,6,8,9,10-hexahydrobenzo[*c*]isoxazolo[2,3-*b*]isoxazole-2-carboxylate (10b)**. Inseparable 10:1 mixture of diastereoisomers, white solid (14.6 mg, 82% yield); m.p. 54–60 ˚C; IR (ν, cm^{-1}) 2980, 2877, 1741, 1458, 1369, 1267, 1156, 948, 806; Major diastereoisomer: ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 5.53 (t, J = 3.5 Hz, 1H), 5.05 (dd, J = 10.0, 6.2 Hz, 1H), 2.47 (dd, J = 12.2, 10.3 Hz, 1H), 2.20–2.12 (m, 1H), 2.14–2.04 (m, 2H), 1.95–1.83 (m, 2H), 1.68–1.53 (m, 1H), 1.47 (s, 9H), 1.41 (s, 3H), 1.3 (s, 3H); ^{13}C NMR (125 MHz,

CDCl$_3$) δ (ppm) 169.4, 147.1, 119.4, 82.2, 81.6, 79.4, 78.2, 41.6, 31.3, 29.4, 27.9, 27.8, 23.7, 18.2; Minor diastereoisomer: ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 5.51 (t, J = 3.8 Hz, 1H), 4.81 (dd, J = 5.9, 3.1 Hz, 1H), 2.71(dd, J = 12.8, 5.1 Hz, 1H), 2.14–2.05 (m, 2H), 2.04–1.99 (m, 3H), 1.95–1.83 (m, 1H), 1.47 (s, 9H), 1.35 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 170.4, 147.0, 119.1, 81.9, 81.6, 79.6, 78.6, 39.4, 31.2, 29.6, 27.9, 27.4, 23.8, 18.27; GCMS (EI+) calcd for C$_{16}$H$_{25}$NO$_4$ [M]$^+$ m/z 295.2, found 295.1.
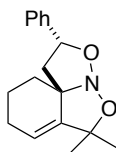
6,6-Dimethyl-2-phenyl-1,2,6,8,9,10-hexahydrobenzo[c]isoxazolo[2,3-b]isoxazole (**10c**). Colorless oil (5.3 mg, 22% yield); IR (ν, cm^{-1}) 3031, 2974, 2942, 2864, 1448, 1377, 1360, 1267, 1023, 941, 759; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.41–7.28 (m, 5H), 5.80 (dd, J = 9.0, 7.8 Hz, 1H), 5.55 (t, J = 3.5 Hz, 1H), 2.66 (dd, J = 12.5, 9.2 Hz, 1H), 2.20–2.09 (m, 2H), 2.02 (dd, J = 12.6, 7.7 Hz, 1H), 1.96–1.85 (m, 2H), 1.74 (td, J = 13.3, 3.4 Hz, 1H), 1.55–1.44 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 148.2, 139.4, 128.6, 128.0, 126.8, 118.9, 84.3, 79.4, 78.5, 47.2, 33.1, 29.6, 27.8, 23.7, 18.2; GCMS (EI+) calcd for C$_{17}$H$_{21}$NO$_2$ [M]$^+$ m/z 271.4, found 271.4.
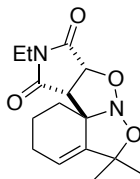
10-Ethyl-5,5-dimethyl-2,3,10,11a-tetrahydro-1H-benzo[3,4]isoxazolo[2,3-b]pyrrolo[3,4-d]isoxazole-9,11(5H,8aH)-dione (**10d**). White solid (13.0 mg, 64% yield); m.p 187–189 ˚C; IR (ν, cm^{-1}) 2985, 2938, 2871, 1709, 1450, 1402, 1356, 1330, 1225, 1147, 1016, 899, 797; ^{1}H NMR

(500 MHz, CDCl₃) δ (ppm) 5.71 (t, *J* = 3.5 Hz, 1H), 5.25 (d, *J* = 8.3 Hz, 1H), 3.53–3.44 (m, 2H), 3.17 (d, *J* = 8.3 Hz, 1H), 2.36 (ddd, *J* = 18.7, 6.9, 3.2 Hz, 1H), 2.17–2.09 (m, 1H), 2.03–1.99 (m, 1H), 1.77 (dt, *J* = 11.5, 3.0 Hz, 1H), 1.74–1.67 (m, 1H), 1.60 (td, *J* = 12.7, 2.8 Hz, 1H), 1.28 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 1.11 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 174.3, 173.8, 142.7, 123.1, 83.1, 82.9, 80.1, 53.9, 33.9, 32.0, 30.2, 24.0, 23.6, 17.5, 12.6; GCMS (EI+) calcd for C₁₅H₂₀N₂O₄ [M]⁺ *m/z* 292.3, found 292.2.

major + minor
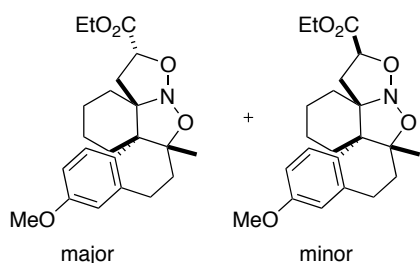
Ethyl 9-methoxy-5a-methyl-2,5a,6,7,12,13,14,15-octahydro-1*H*-benzo[*c*]isoxazolo[2,3-*b*]naphtho[1,2-*d*]isoxazole-2-carboxylate (11a). Inseparable 3:1 mixture of diastereoisomers, colorless oil (17.0 mg, 95% yield); IR (ν, cm⁻¹) 2938, 2869, 1750, 1609, 1500, 1466, 1375, 1266, 1197, 1042, 850, 737; Major diastereoisomer: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.46 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.66–6.65 (m, 1H), 4.87 (dd, *J* = 10.2, 6.0 Hz, 1H), 4.22–4.09 (m, 2H), 3.78 (s, 3H), 2.74–2.70 (m, 2H), 2.40 (dd, *J* = 10.3, 13.1 Hz, 1H), 2.19–2.11 (m, 2H), 2.05–1.99 (m, 2H), 1.97–1.91 (m, 1H), 1.90–1.82 (m, 2H), 1.79–1.72 (m, 2H), 1.70–1.64 (m, 1H), 1.51 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), ¹³C NMR (125 MHz, CDCl₃) δ (ppm) 170.6, 157.5, 138.6, 134.4, 128.7, 113.5, 112.2, 84.9, 82.6, 78.6, 61.4, 55.2, 51.6, 44.4, 37.1, 35.0, 34.2, 28.6, 25.2, 21.3, 20.6, 14.1; Minor diastereoisomer: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.38 (d, *J* = 8.7 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.66–6.65 (m, 1H), 4.68 (dd, *J* = 7.1, 8.9 Hz, 1H), 2.19–2.11 (m, 2H), 3.79 (s, 3H), 2.68–2.62 (m, 2H), 2.46 (dd, *J* = 11.7, 8.3 Hz, 1H), 2.19–

2.11 (m, 2H), 2.05–1.99 (m, 2H), 1.97–1.91 (m, 1H), 1.90–1.82 (m, 2H), 1.79–1.72 (m, 2H), 1.70–1.64 (m, 1H), 1.53 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 171.2, 157.4, 139.3, 134.7, 128.6, 113.4, 112.0, 84.9, 83.1, 79.1, 61.4, 55.2, 51.4, 42.9, 37.7, 35.4, 33.6, 28.3, 25.6, 20.9, 20.1, 14.1; GCMS (EI+) calcd for C$_{22}$H$_{29}$NO$_5$ [M]$^+$ m/z 387.5, found 387.5.

major   +   minor
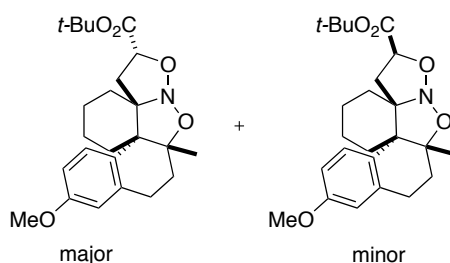
tert-Butyl   9-methoxy-5a-methyl-2,5a,6,7,12,13,14,15-octahydro-1*H*-benzo[*c*]isoxazolo[2,3-b]naphtho[1,2-*d*]isoxazole-2-carboxylate (11b). Inseparable 4.5:1 mixture of diastereoisomers, colorless oil (10.4 mg, 80% yield); IR (ν, cm^{-1}) 2935, 2871, 1742, 1609, 1500, 1465, 1365, 1241, 1157, 1042, 844, 735; Major diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.48 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 8.7, 2.8 Hz, 1H), 6.67–6.65 (m, 1H), 4.76 (dd, J = 10.2, 6.1 Hz, 1H), 3.79 (s, 3H), 2.74–2.69 (m, 2H), 2.35 (dd, J = 10.2, 13.0 Hz, 1H), 2.18–2.12 (m, 2H), 2.03–1.95 (m, 2H), 1.94–1.87 (m, 1H), 1.78–1.73 (m, 2H), 1.72–1.67 (m, 2H), 1.61–1.60 (m, 1H), 1.51 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 169.7, 157.5, 138.6, 134.5, 128.7, 113.4, 112.2, 84.7, 82.5, 82.0, 79.4, 55.2, 51.6, 44.4, 37.1, 35.1, 34.3, 28.6, 27.9, 25.3, 21.4, 20.7; Minor diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.38 (d, J = 8.7 Hz, 1H), 6.74 (dd, J = 8.7, 2.9 Hz, 1H), 6.67–6.65 (m, 1H), 4.57 (dd, J = 7.0, 8.9 Hz, 1H), 3.79 (s, 3H), 2.66–2.63 (m, 2H), 2.42 (dd, J = 12.9, 7.0 Hz, 1H), 2.18–2.12 (m, 2H), 2.03–1.95 (m, 2H), 1.94–1.87 (m, 1H), 1.78–1.73 (m, 2H), 1.72–1.67 (m, 2H), 1.61–1.60 (m, 1H), 1.52 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 170.4, 157.3, 139.3, 134.7, 128.6, 113.3, 112.0, 84.9, 83.1,

81.7, 79.6, 55.2, 51.4, 42.7, 37.7, 35.4, 33.7, 28.3, 27.9, 25.6, 20.9, 20.2; GCMS (EI+) calcd for C$_{24}$H$_{33}$NO$_5$ [M]$^+$ m/z 415.5, found 415.4.
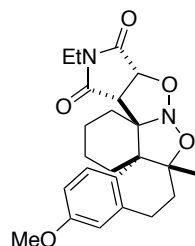
11-Ethyl-3-methoxy-6a-methyl-6,6a,11,12a,13,14,15,16-octahydrobenzo[*c*]naphtho[1,2-*d*]pyrrolo[3',4':4,5]isoxazolo[2,3-*b*]isoxazole-10,12(5*H*,9a*H*)-dione (10c). Colorless oil (10.0 mg, 58% yield); IR (ν, cm^{-1}) 2929, 2843, 1710, 1610, 1502, 1453, 1401, 1348, 1227, 1141, 1042, 734; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.68 (d, J = 8.8 Hz, 1H), 6.87 (dd, J = 8.8, 2.9 Hz, 1H), 6.65 (d, J = 2.8 Hz, 1H), 5.10 (d, J = 8.1 Hz, 1H), 3.80 (s, 3H), 3.54 (d, J = 8.0 Hz, 1H), 3.48 (q, J = 7.2 Hz, 2H), 2.76–2.72 (m, 2H), 2.34–2.27 (m, 1H), 2.15–2.21 (m, 1H), 2.06–2.02 (m, 1H), 1.93–1.86 (m, 1H), 1.82–1.78 (2H), 1.75–1.69 (m, 2H), 1.66–1.60 (m, 2H), 1.55 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 173.1, 171.5, 157.9, 138.4, 132.9, 130.5, 128.3, 113.5, 112.3, 86.2, 85.9, 81.1, 56.2, 55.2, 52.5, 36.9, 35.3, 33.9, 28.2, 28.1, 25.7, 20.6, 20.4, 12.9; GCMS (EI+) calcd for C$_{23}$H$_{28}$N$_2$O$_5$ [M]$^+$ m/z 412.2, found 412.2.

General Procedure for the Reduction of Nitronate 5a
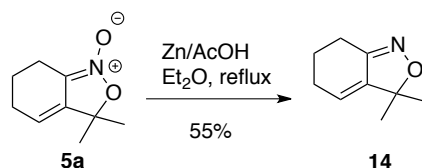
3,3-Dimethyl-3,5,6,7-tetrahydrobenzo[*c*]isoxazole (14). In a dry round-bottom flask with a magnetic stir bar under Ar atmosphere, Zn dust (39 mg, 0.6 mmol, 10 equiv) and 25% aq AcOH (92 μL) were added to the nitronate **5a** (10 mg, 0.06 mmol, 1 equiv) diethyl ether solution (2

mL). The reaction was heated to 50 ˚C for 24 h and during that time Zn dust and 25% aq AcOH was added twice to the reaction to be complete. The reaction was filtered and washed with NaHCO$_3$. The organic layer was removed in vacuo and the crude oil was purified by flash column chromatography (0–10% EtOAc in Hexanes) to provide hydroisoxazole **14** as a colorless oil (9 mg, 68% yield); IR (ν, cm^{-1}) 2953, 2924, 2849, 1730, 1267, 1460, 1267, 867; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 5.77 (t, J = 4.3 Hz, 1H), 2.58 (t, J = 6.6 Hz, 2H), 2.21–2.18 (m, 2H), 1.81–1.76 (m, 2H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 154.3, 146.4, 122.7, 82.9, 29.7, 27.7, 24.8, 22.3, 21.6; GCMS (EI+) calcd for C$_9$H$_{13}$NO [M]$^+$ m/z 151.1, found 151.1.
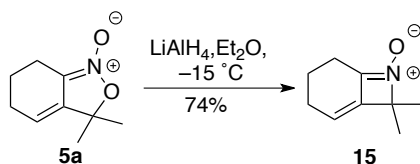
8,8-Dimethyl-7-azabicyclo[4.2.0]octa-1,6-diene 7-oxide (**15**). In a dry round-bottom flask with a magnetic stir bar under Ar atmosphere, a solution of LiAlH$_4$ (2.0 mg, 0.05 mmol, 1.5 equiv) in diethyl ether (0.5 mL) was cooled to –15 ˚C (ice/salt bath). A solution of nitrodiene **5a** (6 mg, 0.04 mmol, 1.0 equiv) in diethyl ether (0.5 mL) was added to the cooled solution. The reaction was quenched with 0.5 mL water and 0.5 mL 1M NaOH after the disappearance of starting material (1 h) by TLC. The reaction was then extracted with diethyl ether (2 x 5 mL) and washed with water follow by brine. The solvent was removed in vacuo and the crude oil was purified by flash column chromatography (0–15% EtOAc in Hexanes) to furnish nitrone **15** as colorless oil (4 mg, 74% yield); IR (ν, cm^{-1}) 2918, 2849, 1712, 1627, 1401, 1265, 1166, 967; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.27 (t, J = 4.5 Hz, 1H), 2.69 (t, J = 6.7 Hz, 2H), 2.23 (dt, J = 4.6, 6.1 Hz, 2H), 1.78–1.69 (m, 2H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm) 157.2, 139.5, 132.1, 73.0, 29.7, 29.6, 25.1, 22.7, 20.5; GCMS (EI+) calcd for C$_9$H$_{13}$NO [M]$^+$ m/z 151.1, found 151.1.

Reference

(1)   (a) Feuer, H. ed., "The Chemistry of the Nitro and Nitroso Groups", in *The Chemistry of Functional Groups*, Patai, S. ed., Wiley, New York, **1969**. (b) Coombes, R. G. "Nitro and Nitroso Compounds" in Comprehensive Organic Chemistry, Vol. 2, Sutherland, I. O. ed., Pergamon Press, New York, **1979**, pp. 303–382. (c) Patai, S. ed., "The Chemistry of Amino, Nitroso, and Nitro Compound and their derivatives," in *The Chemistry of Functional Groups*, Wiley, New York, **1982**. (d) Ono, N. *The Nitro Group in Organic Synthesis*, Wiley, New York, **2001**.

(2)   (a) Nielsen, A. T. "Nitronic Acids and Esters" in *The Chemistry of the Nitro and Nitroso Groups*, Feuer, H. ed., Wiley, New York, **1969**, pp. 349–486. (b) Breuer, E. "Nitrones and Nitronic Acid Derivatives: Their Structure and Their Role in Synthesis" in *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*, Patai, S. ed., Wiley, New York, **1982**, pp. 460–564.

(3)   Stewart, R. "The Proton: Applications to Organic Chemistry", in *Organic Chemistry*, Wasserman, H. H. ed., Vol. 46. Academic Press, New York, **1985**.

(4)   Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280*, 263.

(5)   Bamberger, E.; Schmidt, O. *Chem. Ber.* **1901**, *34*, 574.

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

(7)   Knunyants, I. L.; Bykhovskaya, E. G.; Frosin, V. N.; Kisel, Y. M. *Dokl. Chem.* **1960**, *132*, 455.

(8)   Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, *65*, 836.

(9)   Rudchenko, V. F.; Chervin, I. I.; Kostyanovsky, R. G. *Mendeleev Commun.* **1991**, 9.

(10)   Ioffe, S. L.; Kashutina, M. V.; Shitkin, V. M.; Levin, A. A.; Tartakovskii, V. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1972**, 1292.

(11)   (a) Kohler, E. P.; Barrett, G. R. *J. Am. Chem. Soc.* **1926**, *48*, 1770. (b) Gibson, M. S. *Tetrahedron*, **1962**, *18*, 1377. (c) Tartakovskii, V. A.; Gribov, B. G.; Novikov, S. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965**, 1034. (d) Chlenov, I. E.; Khudak, V. I.; Tartakovskii, V. A.; Novikov, S. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1969**, 2113. (e) Chlenov, I. E.; Khudak, V. I.; Kolymagina, L. N.; Morozova, N. S.; Tartakovskii, V. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1970**, 1757.

(12)   Chlenov, I. E.; Morozova, N. S.; Khudak, V. I.; Tartakovskii, V. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1970**, 2492.

(13) Falck, J. R.; Yu, J. *Tetrahedron Lett.* **1992**, *45*, 6723.

(14) Tartakovskii, V. A.; Onishchenko, A. A.; Chlenov, I. E.; Novikov, S. S. *Dokl. Chem.* **1966**, *167*, 406.

(15) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781.

(16) Calli, C.; Marotta, E.; Righi, P.; Rosini, G. *J. Org. Chem.* **1995**, *60*, 624.

(17) Chow, Y. L.; Shu, Y. Y.; Bakker, B. H.; Pillay, K. S. *Heterocycles* **1989**, *29*, 2245.

(18) Kumaran, G.; Kulkarni, G. H. *Synthesis* **1995**, 1545.

(19) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(20) (a) Risaliti, A.; Forchiassin, M.; Valentin, E. *Tetrahedron* **1968**, *24*, 1889. (b) Nielson, A. T.; Archibald, T. G. *Tetrahedron* **1970**, *26*, 3475. (c) Colonna, F. P.; Valentin, E.; Pitacco, G.; Risaliti, A. *Tetrahedron* **1973**, *29*, 3011. (d) Ferri, R. A.; Pitacco, G.; Valentin, E. *Tetrahedron* **1978**, *34*, 2537. (e) Benedetti, F.; Pitacco, G.; Valentin, E. *Tetrahedron* **1979**, *35*, 2293. (f) Barbarella, G.; Pitacco, G.; Russo, C.; Valentin, E. *Tetrahedron Lett.* **1983**, *24*, 1621. (g) Barbarella, G.; Brückner, S.; Pitacco, G.; Valentin, E. *Tetrahedron* **1984**, *40*, 2441. (h) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron* **1989**, *45*, 2099. (i) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron* **1989**, *45*, 5667. (j) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1645. (k) Huffman, J. W.; Cooper, M. M.; Miburo, B. B.; Pennington, W. T. *Tetrahedron* **1992**, *48*, 8213.

(21) (a) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4679. (b) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *98*, 4679. (c) Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284. (d) Seebach, D.; Brook, M. A. *Helv. Chem. Acta.* **1985**, *68*, 319. (e) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311. (f) Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *Tetrahedron Lett.* **1991**, *32*, 2517. (g) Bäckvall, J.-E.; Karlsson, U.; Chinchilla, R. *Tetrahedron Lett.* **1991**, *32*, 5607.

(22) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069.

(23) Creech, G. S.; Kwon, O. *J. Am. Chem. Soc.* **2010**, *132*, 8876.

(24) Arai, N.; Narasaka, K. *Chem. Lett.* **1995**, 987.

(25) Kanemasa, S.; Kaga, S.; Wada, E. *Tetrahedron Lett.* **1998**, *39*, 8865.

(26) Grée, R.; Tonnard, F.; Carrié, R. *Tetrahedron*, **1976**, *32*, 675.

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

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

(29) Domingo, L. R. *Theor. Chem. Acc.* **2000**, *104*, 240.

(30) Grée, R.; Tonnard, F.; Carrié, R. *Bull. Soc. Chim. Fr.* **1975**, 1325.

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

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

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

(34) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSS, Ser. Khim. 1941,* 211.

(35) (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta.* **1988**, *71*, 168.

(36) Reviews on Nazarov: (a) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. (b) Denmark, S. E.; In Paquette, L. A., Ed.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991, vol 5, pp 751. (c) Habermas, K. L.; Denmark, S. E. *Org. React.* **1994**, *45*, 1. (d) Harmata, M. *Chemtracts* **2004**, *17*, 416. (e) Tius, M. A. *Eur. J. Chem.* **2005**, 2193. (f) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (g) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.

(37) Tius, M. A.; Kwok, C.-K.; Gu, X.-Q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871.

(38) Kim, S. H.; Cha, J. K. *Synthesis* **2000**, 2113.

(39) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728.

(40) (a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278. (b) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003.

(41) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661.

(42) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419.

(43) Bow, W. F.; Basak, A. K.; Jolit, A.; Vicic, D. A. *Org. Lett.* **2010**, *12*, 440.

(44) Ma, Z.-X.; He, S.; Wangze, S.; Hsung, R. *Org. Lett.* **2012**, *14*, 5736.

(45) Shimada, N; Ashbum, B. O.; Basak, A. K.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *Chem. Commun.* **2010**, *46*, 3774.

(46) Klumpp, D. A.; Zhang, Y.; O'Connor, M. J.; Esteves, P. M.; de Almeida, L. S. *Org. Lett.* **2007**, *9*, 3085.

(47) Sai, K. K. S.; O'Connor, M. J.; Klumpp, D. A. *Tetrahedron Lett.* **2011**, *52*, 2195.

(48) Narayan, R.; Daniliuc, C.-G.; Würthwein, E.-U. *Eur. J. Org. Chem.* **2012**, 602.

(49) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430.

(50) (a) Browder, C. C.; Marmsater, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033. (b) Browder, C. C.; Marmsater, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375.

(51) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876.

(52) Giese, S.; Kastrup, L.; Steins, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970.

(53) (a) Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 8393. (b) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221.

(54) de Lera, A. R.; Rey, J. G.; Hrovat, D.; Iglesias, B.; Lopez, S. *Tetrahedron Lett.* **1997**, *38*, 7425.

(55) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821.

(56) Scadeng, O.; Ferguson, M. J.; West F. G. *Org. Lett.* **2011**, *13*, 114.

(57) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5431.

(58) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(59) (a) Özbal, H.; Zajac, W. W. Jr. *J. Org. Chem.* **1981**, *46*, 3082. (b) Node, M.; Kawabata, T.; Fujimoto, M.; Fuji, K. *Synthesis*, **1984**, 234.

(60) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961.

(61) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

(62) The structures of **4a**, **6a**, **7a**, and **7b** were established unequivocally through X-ray crystallographic analyses. See the Experimental and Appendix for details.

(63) Nelson, N. A.; Wollensak, J. C. *J. Am. Chem. Soc.* **1958**, *80*, 6626.

(64)   (a) Pihko, A. J.; Lundell, K.; Kanerva, L.; Koshinen, A. M. P. *Tetrahedron: Asymmetry* **2004**, *15*, 1637. (b) Gu, P.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y.; Zhang, F. *Org. Lett.* **2006**, *8*, 5271.

(65)   Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chem. Acta.* **1986**, *69*, 1971.

(66)   (a) Reference 65. (b) Liu, J.-T.; Lin, W.-W.; Jang, J.-J.; Liu, J.-Y.; Yan, M.-C.; Hung, C.; Kao, K.-H.; Wang, Y.; Yao, C.-F. *Tetrahedron*, **1999**, *55*, 7115.

(67)   (a) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816. (b) Verboom, W.; Van Eijk, P. J. S. S.; Conti, P. G. M.; Reinhoudt, D. N. *Tetrahedron* **1989**, *45*, 3131.

(68)   Goldschmidt, Z.; Finkel, D. *J. Chem. Soc. Perkin Trans. I* **1983**, 45.

(69)   Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem.* **2007**, *72*, 2216.

(70)   Rosia, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, 4044.

(71)   Synthesis of known aldehydes **18**, see: (a) Ferriera, E. M.; Stolz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (b) Masutani, K.; Minowa, T.; Hagiwara, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106. (c) van de Sande, M.; Gais, H.-J. *Chem. Eur. J.* **2007**, *13*, 1784. (d) Namba, K.; Yamamoto, H.; Sasaki, I, Mori, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2008**, *10*, 1767. (e) Jui, N. T.; Lee, E. C. Y.; MacMillian, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015.

(72)   Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 11606.

Chapter 3

Progress Towards the Synthesis of α-Aryl Vinylboronic Acids

3.1 Introduction to Boronic Acid

The structure of a boronic acid is a trivalent boron-containing organic compound that comprises a carbon substituent (alkyl or aryl) and two hydroxyl groups. The sp^2-hybridized boron atom has a vacant p-orbital that is orthogonal to the three substituents, which gives boronic acid compounds a trigonal planar geometry. The first isolation of a boronic acid was demonstrated by Frankland in 1860 by reacting diethylzinc with triethylborate to provide a highly air sensitive triethylborane.[1] Ethylboronic acid was then obtained by a two-fold oxidation of triethylborane in ambient air (Scheme 3.1.1).

$$Et_2Zn \ + \ (EtO)_3B \ \longrightarrow \ Et_3B \ \xrightarrow{air} \ EtB(OH)_2$$
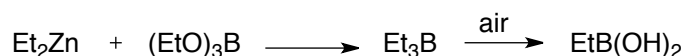
Scheme 3.1.1 The first preparation and isolation of a boronic acid

Boronic acid stability to atmospheric oxidation is superior to that of borinic acid (first oxidation of borane) (Figure 3.1.1). However, boronic acid can further oxidize to boric acid. For example, commercially available boronic acids may contain various amounts of boric acid residues. Recrystallization in water can purify the boronic acid from boric acid or the compounds can be separated through a partition between water and chilled diethyl ether. Lastly, boronic acids tend to exist as mixture of oligomeric anhydrides, in particular the cyclic six-membered boroxine.
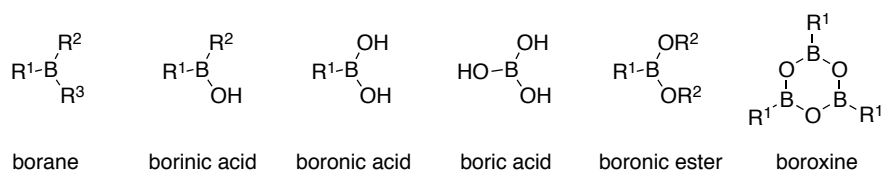
Figure 3.1.1 Various oxidation states of boron

There are four types of boronic acids; alkyl-, alkenyl-, alkynyl-, and arylboronic acids. Each has their own reactivity and properties, however our main focus is on alkenylboronic acids.

Alkenylboronic acids are more stable in water due to the coordination of water to boron, acting as a protection from oxidation.[2] However, alkenylboronic acids having a high water solubility can cause a purification problem during aqueous workup. A solution to this problem is to form the boronic anhydride to extract with organic solvent. The crude product is then diluted with water to precipitate the boronic acid for filtering. Another technique is adjusting the water phase to neutral or slightly acidic and then use a polar organic solvent for efficient partition. Luckily, some small boronic acid compounds that are dissolved in polar organic solvents can be precipitated by nonpolar organic solvents. Thus, it is common to purify the boronic ester instead of the boronic acid due to the high water solubility and potential oxidation of boronic acids. Lastly, alkenylboronic acids are highly resistant to protolysis of the C–B bond in neutral aqueous solutions and at high temperatures. However, protonolysis of alkenylboronic acids do occur in refluxing acetic acid.[3]

Alkenylboronic acids are useful synthetic intermediates in organic chemistry due to their low toxicity, such as cross-coupling reactions,[4] conjugate addition,[5] oxidation,[6] and homologation.[7] Thus, several methods are available for the preparation of a wide range of boronic acids. However, as mentioned before boronic acids are difficult to purify. There are methods of preparing boronic esters for isolation, which then can be hydrolyzed to obtain the boronic acid.[8] For example, catecholborane is commonly used in synthesizing boronic acids. Catecholborane is very Lewis acidic due to the opposing conjugation between the phenolic oxygens and the benzene ring, which cause it to be highly sensitive to hydrolysis.[9]

3.2 Preparation of β-Alkenylboronic Acids

One method is subjecting alkenyl bromides or iodides to *n*-butyllithium to form the alkenyllithium species followed by a metal-exchange with borate to provide alkenylboronic esters.[10] The esters are then hydrolyzed by acid to obtain alkenylboronic acids (Scheme 3.2.1). The limitation of this method is the synthesis of vinylhalides.

R = alkyl, aryl
X= Br, I
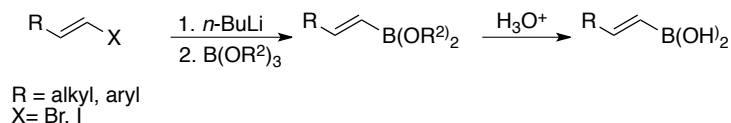
Scheme 3.2.1 Lithium halogen-exchange with borate

Internal or terminal alkynes can be subjected to hydroboration with catecholborane or borane reagents. For terminal alkynes, the reaction proceeds in a stereospecific cis-addition where the boron attacks the less hindered carbon of the triple bond. The cis-addition was determined by deuterium studies.[11] Similarly, to obtain the boronic acids the boronic esters are hydrolyzed (Scheme 3.2.2). Unfortunately, unsymmetrical internal alkynes usually give mixtures of regioisomeric alkenylborane compounds. Furthermore, it is important to use hindered boranes for hydroboration because small borane reagents tend to undergo dihydroboration with alkynes.[12] For alkenylborane compounds to provide alkenylboronic acids, the two C–B bonds are oxidized by trimethylamine oxide (Me₃NO) to provide the alkenylboronates (Scheme 3.2.2).[13]

R^1 = alkyl, aryl, H
R^2 = alkyl, aryl
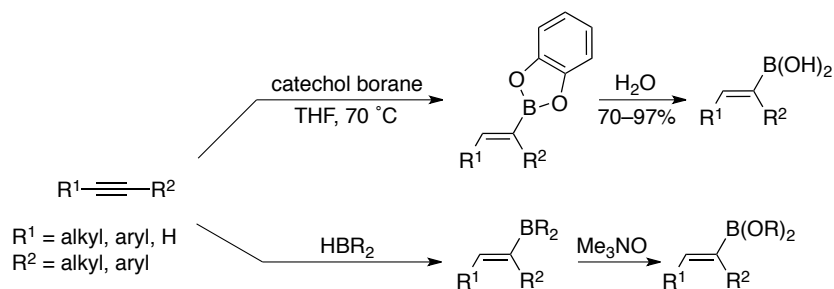
Scheme 3.2.2 Hydroboration of internal and terminal alkynes

Alkynes can also be subjected to dibromoborane dimethyl sulfide complex (HBBr$_2$•SMe$_2$) to obtain boronic acid compounds. For example, reacting 1-hexyne with HBBr$_2$•SMe$_2$ provided a mono-hydroboration of alkenyldibromoborane (Scheme 3.2.3).[14] The mono-hydroboration was achieved because the methyl sulfide binds tightly to the alkenyldibromoborane to provide steric hinderance. The alkenyldibromoborane was then hydrolyzed by two equivalents of sodium hydroxide to obtain 1-hexenylboronic acid. However, the borane reagent does not tolerate sensitive functional groups. A more suitable borane reagent to use instead is dichloroborane dioxane complex.[15]
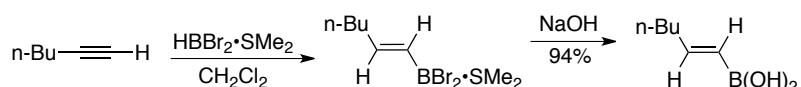
Scheme 3.2.3 Hydroboration using dibromoborane dimethyl sulfide complex

Transmetalation can also provide the same boronic ester compounds as hydroboration of alkynes with catecholborane. Transmetalation offers a more synthetically efficient route in synthesizing alkenylboronic compounds than hydroboration. For example, hydrozirconation is more functional group tolerant than the corresponding hydroboration of alkynes. Also, the regioselectivity of hydrozirconation process is better than that observed for hydroboration with hindered boranes. The alkenylzirconium compounds prepared through hydrozirconation of alkynes transmetalate with *B*-chlorocatechol borane to provide boronic esters (Scheme 3.2.4).[16]
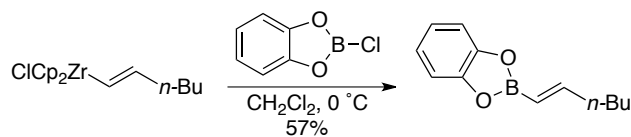
Scheme 3.2.4 Transmetalation of alkenylzirconium with *B*-chlorocatecholborane

Alkenyltrimethylsilanes can also be used to synthesize alkenylboronic acids by reacting alkenyltrimethylsilanes with boron halides (e.g. boron trichloride, BCl$_3$) through *ipso-*

borodesilylation. Addition of catecholborane to the alkenyldichloroborane forms the boronic ester, which can be easily isolated and then hydrolyzed to the boronic acid (Scheme 3.2.5).[17] Also, bis-silylated dienes and trienes can be converted to alkenylboronic ester silanes by a mono-*ipso*-borodesilylation with BCl_3. Sodium carbonate was used as an additive because it prevented the competing protodesilylation (Scheme 3.2.5).[18]
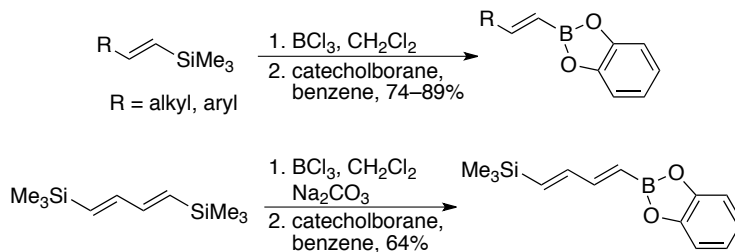
Scheme 3.2.5 *ipso*-Borodesilylation of alkenyltrimethylsilanes

Using a catalyst for hydroboration is beneficial because it allows for a very fast reaction under mild conditions for catecholborane and pinacolborane. Reactions without catalyst need elevated temperatures to facilitate the reaction, while reactions with catalyst can be run at ambient temperature. Many different types of catalysts have been shown to be efficient for hydroboration.

For example, cyclic or acyclic alkenyl halides or triflates are suitable substrates in the palladium-catalyzed borylation reaction with bis(pinacolato)diborane $[B_2(pin)_2]$ (Scheme 3.2.6).[19] Potassium phenoxide was found to be the most effective base and triphenylphosphine as the ligand in a less polar solvent, toluene. The starting alkenyl halide or triflate geometry is preserved in the product. The low yield of products is due to the formation of a mixture of several products (homocoupling or Heck coupling).
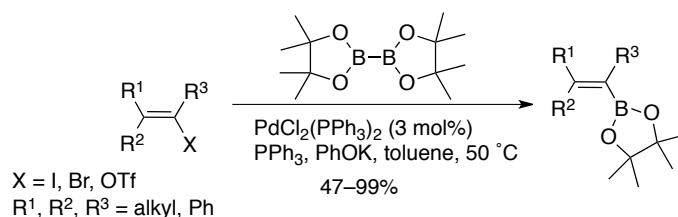
Scheme 3.2.6 Palladium-catalyzed borylation reaction with $B_2(pin)_2$

To prevent unwanted coupling products, Masuda reported an improved palladium-catalyzed borylation reaction (Scheme 3.2.7).[20] Cyclic alkenyl halides or triflates in the presence of 3 mol% [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) [$PdCl_2(dppf)$] reacted with pinacolborane to provide cycloalkenylboronates. Triphenylarsine ($AsPh_3$) was used as an additive to help weakly coordinate with palladium complex to stabilize the catalyst. Triethylamine was the most effective base to obtain the product.
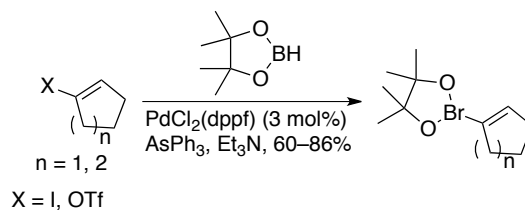
Scheme 3.2.7 Palladium-catalyzed borylation of cyclic coupling partners

Another method is hydroboration of alkyne with pinacolborane catalyzed by Schwartz's reagent (Cp_2ZrHCl) (Scheme 3.2.8).[21] The reaction is syn-selective and highly regioselective for terminal and internal alkynes. The condition is compatible with acid-sensitive functional groups. Only a slight excess of pinacolborane is needed to facilitate the hydroboration. And under the same condition without the catalyst hydroboration proceeded only 2–20%.
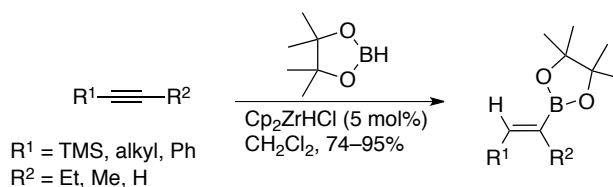
Scheme 3.2.8 Zirconium-catalyzed hydroboration of alkynes

Thioacetylenes can be used for hydroboration with catecholborane in the presence of 1,2-bis(diphenylphosphino)ethane nickel(II) chloride [NiCl$_2$(dppe)]. The reaction proceeds regio- and stereospecific with excellent yields of (β-thioalkyl)vinylboronates (Scheme 3.2.9).[22] Typically, the addition of boron is preferred on the carbon alpha to the sulfur for uncatalyzed-hydroboration of thioacetylenes. The nickel catalyst altered the regiochemical preference of the addition of boron.

R^{1}S———R^2

$\xrightarrow[\text{catecholborane, benzene}]{\text{NiCl}_2\text{(dppe) (3 mol\%)}}$ 63–99%

R^1 = Me, Ph, Et
R^2 = alkyl, Ph, H
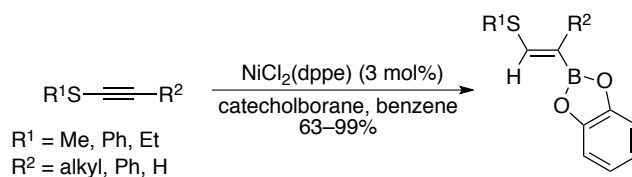
Scheme 3.2.9 Nickel-catalyzed hydroboration of alkynes

Allene substrates can be subjected to hydroboration conditions. Under platinum-catalyzed hydroboration, alkyl and aryl phosphines were effective for hydroboration of the internal double bond of allene (Scheme 3.2.10).[23] High yields were achieved by using bulky phosphine, such as tricyclohexylphosphine (Cy$_3$P) and tri(*tert*-butyl)phosphine (*t*-Bu$_3$P). However, *t*-Bu$_3$P demonstrated a higher regioselectivity than Cy$_3$P. Hydroboration of the terminal double bond of allene can be achieved by using a very bulky and basic phosphine, tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP). However, selectivity does depend on various allenes. TTMPP exhibit different stereochemical outcome because it is postulated that TTMPP ligand induces the insertion of the allene into the Pt-BX$_2$ bond rather than the H-Pt bond.

R^1 = Ph, Me, CH$_2$CO$_2$Et
R^2 = H, Me

ligand = PCy$_3$ or *t*-Bu$_3$P or TTMPP

$\xrightarrow[\text{toluene, 50 °C}]{\substack{\text{Pt(dba)}_2 \text{ (30 mol\%)} \\ \text{pinacolborane, ligand}}}$

39–100%   43–100%
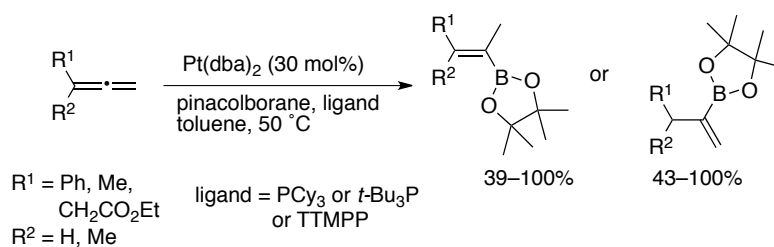
Scheme 3.2.10 Platinum-catalyzed hydroboration of allenes

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(*E*)-1-Alkenylboronic acids are readily obtained by methods already mentioned. However, (*Z*)-1-alkenylboronic acids are not trivial to synthesize. One method, a two-step process, is a hydroboration of 1-halo-1-alkynes with dialkylborane followed by addition of a hydride [e.g. lithium triethylborohyride (LiEt$_3$BH)] to boron, which then transfers with inversion of configuration at the vinyl carbon (Scheme 3.2.11).[24] An efficient synthesis of (*Z*)-1-alkenylboronic acids was demonstrated by Brown. Subjecting (*Z*)-1-bromo-1-alkenylboronic esters with potassium triisopropoxyborohydride (KIPBH) to provide (*Z*)-1-alkenylboronic esters (Scheme 3.2.11).[25] The reaction involved a hydride transfer from KIPBH to the boronate ester followed by hydride migration from boron to the vinylic carbon.

R^1 = alkyl
R^2 = Me, *i*-Pr, -(CH$_2$)$_2$-,
        -(CH$_2$)$_3$-
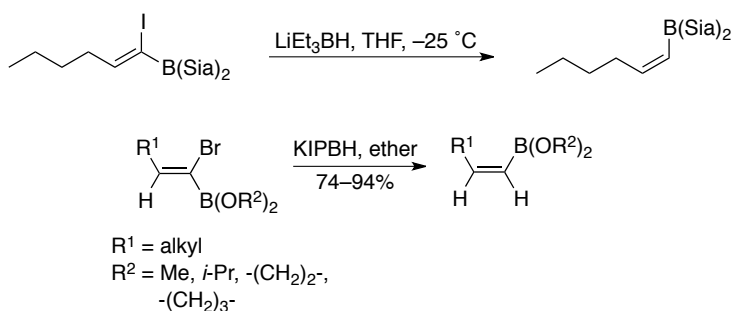
Scheme 3.2.11 Inversion of conformation by hydride

Beside hydroboration, hydrogenation of alkynylboronic esters can provide (*Z*)-alkenylboronic esters. Hydrogenation can be accomplished by using Lindlar's catalyst (5 mol% Pd/CaCO$_3$, poisoned by lead) under hydrogen atmosphere for a cis-addition onto alkynyldiisopropoxyboranes to give (*Z*)-1-alkenylboronates (Scheme 3.2.12).[26] The *Z:E* ratio can be further enhanced by hydrolyzing to the boronic acid followed by recrystallization from water.
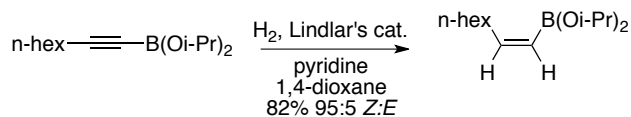
Scheme 3.2.12 Hydrogenation of alkynylboronic esters

Another method is hydrozirconation of alkynylboronic esters via syn-addition (Scheme 3.2.13).[27] The carbon-zirconium bond is more reactive than the carbon-boron bond toward various electrophiles. Thus, hydrolysis would prefer to break the carbon-zirconium bond and the geometry is retained.
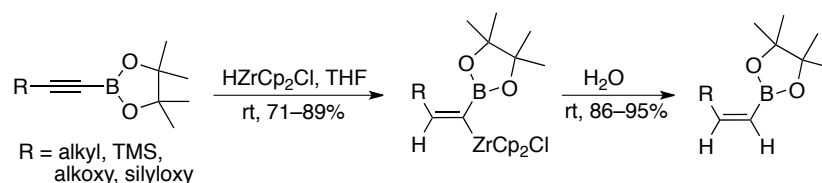
Scheme 3.2.13 Hydrolysis of carbon-zirconium bond

Rhodium can also be used to catalyze hydroboration of alkynes with pinacolborane to synthesize (*Z*)-alkenylboronic esters. Terminal alkynes were reacted with chloro(1,5-cyclooctadiene)rhodium(I) dimer [Rh(cod)Cl]$_2$ with greater then one equivalent of triethylamine and triisopropylphosphine [P(*i*-Pr)$_3$] to obtain high yields and high cis-selectivity of the alkenylboronic esters (Scheme 3.2.14).[28] Not having triethylamine in the reaction produced isomeric products. The trans-hydroboration product is dominant when excess alkyne is used relative to the borane reagent. It is believed that the cis product is formed initially, but an addition/elimination sequence of Rh–H species isomerizes the cis product to the trans product.
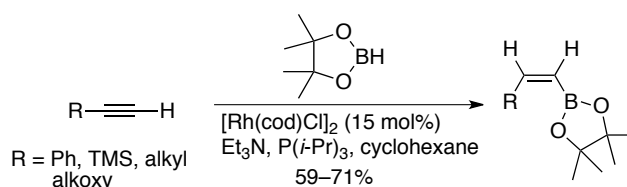
Scheme 3.2.14 Rhodium-catalyzed hydroboration of alkyne

Lastly, hydroboration with dialkylboranes followed by a selective protodeboronation of dialkylboranes resulted in (*Z*)-alkenyl pinacolboronates (Scheme 3.2.15).[29] Dialkylboranes and

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pinacolboronates have a large reactivity difference, which allows a selective protodeboronation on the dialkylborane with acetic acid.
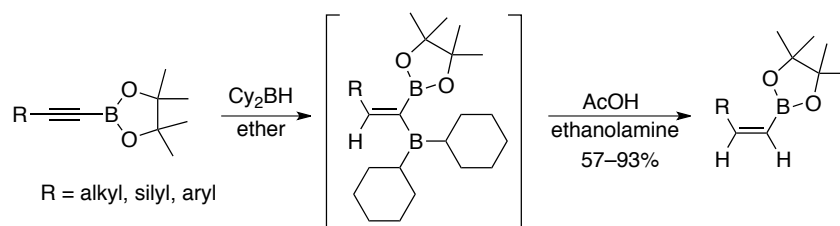
Scheme 3.2.15 Hydrolysis of alkynylborane

3.3 Preparation of α-Alkenylboronic Acids

The methods mentioned above apply only to the synthesis of β-substituted alkenylboronic acids. There are very few methods in synthesizing α-substituted alkenylboronic acids. The most common method is lithiation of α-substituted vinylhalide substrates followed by a transmetalation with catecholborane or pinacolborane to get the desired α-substituted vinylboronic esters. For example, the acetylene was converted to 2-iodoalkene with sodium iodide and trimethylsilyl chloride (Scheme 3.3.1).[30] The vinyliodide was then subjected to lithium halogen-exchange followed by transmetalation with pinacolborane derivative to afford the α-substituted alkenylboronic ester.[31] The disadvantage of this method is synthesizing the vinylhalides, which can be difficult for elaborate substrates. Thus, new methods in constructing α-substituted alkenylboronic acid are essential.
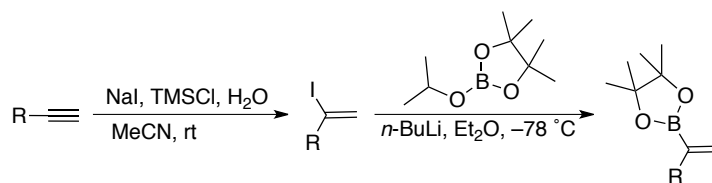
Scheme 3.3.1 Lithium halogen-exchange with pinacolborane derivative

It was not until 2011 that the development of new syntheses of α-substituted alkenylboronic esters was seen. The new methodologies consist of different types of copper mediated hydroboration. The first example was subjecting propargyl amines or propargyl alcohols with *N*-heterocyclic carbene-copper (NHC-Cu) complex and B$_2$(pin)$_2$, which afforded a regioselective addition of the copper to the less hindered carbon of the triple bond and the boron on the more hindered carbon of the triple bond (Scheme 3.3.2).[32] The copper–carbon bond was hydrolyzed by the addition of methanol to obtain α-substituted vinylboronates with good yields. Interestedly, the propargyl amines provided a higher α-selectivity than the propargyl alcohols.
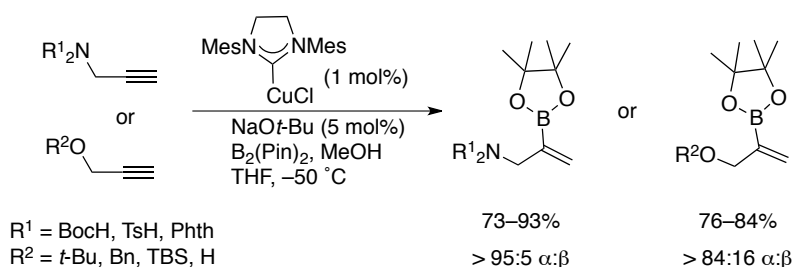
Scheme 3.3.2 NHC-Cu complex-catalyzed hydroboration of propargyl amines and alcohols

Aryl and alkyl allenes were also subjected to NHC-Cu complex and B$_2$(pin)$_2$, in which the addition was regioselective for the terminal double bond of the allene to provide α-substituted alkenylboronic esters (Scheme 3.3.3).[33] Bulky aryl groups on the NHC gave a higher selectivity of the α-substituted vinylboronates, while smaller functional groups on the NHC, such as alkyl substituents, favor the formation of the β-substituted vinylboronates with (*Z*)-selectivity. Interestingly, allene substrates with quaternary center were more α-selective than those containing a less hindered linear branch.
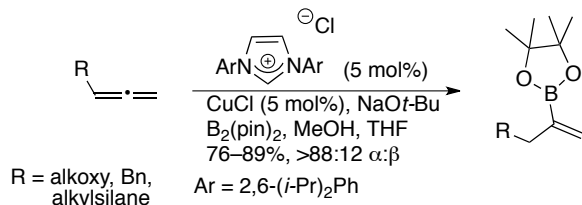
Scheme 3.3.3 NHC-Cu complex catalyzed hydroboration of allenes

A much bulkier NHC-Cu complex was demonstrated on allenes that contained primary, secondary, and tertiary alkyl groups and aryl groups to provide the α-substituted alkenylboronic esters in good to high yields and with higher selectivity than the NHC-Cu complex presented above (Scheme 3.3.4).[34] Electron-donating groups and electron-withdrawing groups on the aryl ring did not affect the yields or selectivities. The selectivity of the reaction is due to the bulky substituent on the NHC. The (Z)-σ-allyl copper species (formed by the boryl copper species inserting at the terminal double bond of allene) is protonated with methanol in a S_E2' fashion to afford α-substituted alkenylboronic esters from a bulky NHC. A less bulky NHC, the (Z)-σ-allyl copper species is protonated in a S_E2 fashion to afford 1,2-disubstituted vinylboronates.
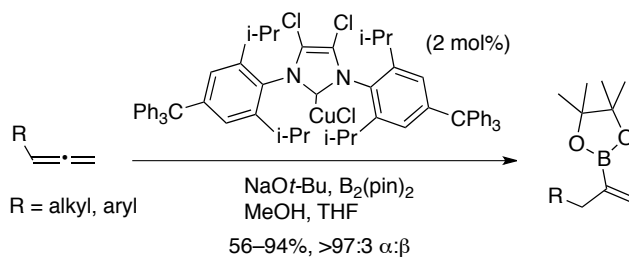
Scheme 3.3.4 Bulkier NHC-Cu complex-catalyzed hydroboration

Lastly, allenylic ethers were also subjected to NHC-Cu complex with $B_2(pin)_2$ to afford 1,3-butadiene boronate substrates (Scheme 3.3.5).[35] For this reaction the boryl copper species inserted into the internal double bond of the allene to provide the σ-allyl copper intermediate. 1,3-Butadiene boronates were obtained by a β-elimination of the benzyloxy moiety. Interestingly, borylation of unsymmetrical α,α-disubstituted allenes were highly stereoselective

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and afforded >90:10 E:Z of the (*E*)-1,3-butadiene boronates. Boc-protected piperidine and ketal moieties on allenes were tolerated under the condition.
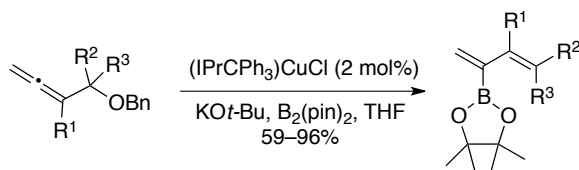
Scheme 3.3.5 NHC-Cu complex-catalyzed hydroboration of allenylic ethers

3.4 Applications Employing Boronic Acid (Carbon–Carbon Bond Formation)

In the past 10 years, boronic acids have grown to be valuable compounds in molecular recognition,[36] materials science,[37] and catalysis.[38] Furthermore, a drug containing a boronic acid moiety has been commercialized as an anticancer agent, Velcade.[39] Organoboranes are also important synthetic intermediates in forming carbon–carbon bonds through cross-coupling reactions. For example, Suzuki–Miyaura cross-coupling reaction involves aryl halides or vinyl halides coupling with boronic acid compounds in the presence of catalytic palladium complex (Scheme 3.4.1).[4a]

$$R^1\text{-}BY_2 \quad + \quad R^2\text{-}X \quad \xrightarrow[\text{base}]{\text{Pd catalyst}} \quad R^1\text{-}R^2$$

R^1, R^2 = aryl, alkenyl
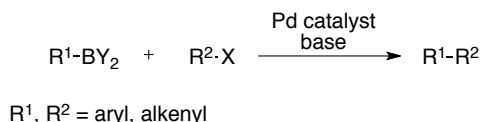
Scheme 3.4.1 Suzuki–Miyaura cross-coupling reaction

The mechanism of the Suzuki reaction begins with the oxidative addition of palladium to the halide to obtain the organopalladium intermediate with retention of stereochemistry (Scheme 3.4.2). Next, the base exchanges with the halide to provide a more active organopalladium species. The Pd–O bond is more reactive than a Pd–X bond (X = Br, I) during the transmetalation step due to the higher oxophilicity of boron.[40] Then, the boronate complex undergoes transmetalation with the organopalladium species follow by reductive elimination to

give the product. Studies have shown that the base has three important roles, which are the formation of the palladium complex [ArPd(OR)L$_2$], formation of the trialkyl borate, and facilitating the acceleration of the reductive elimination step.[41] Overall, the Suzuki cross-coupling reaction has been extremely useful in organic synthesis.
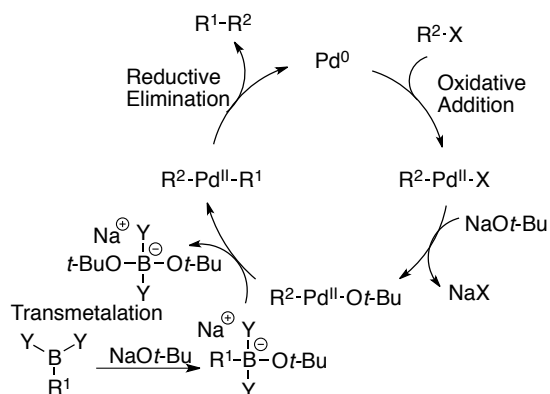
Scheme 3.4.2 Suzuki–Miyaura cross-coupling mechanism

Another carbon–carbon bond formation method that employs boronic acid is the Liebeskind–Srogl coupling reaction. This reaction involves thioesters coupling with boronic acid in the presence of palladium complex (Scheme 3.4.3).[4d] Also, tris(2-furyl)phosphine (TFP) is used as an additional ligand and copper(I) thiophene-2-carboxylate (CuTc) is used as a co-metal catalyst.
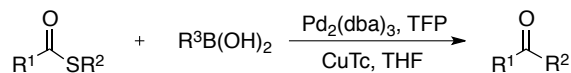
Scheme 3.4.3 Liebeskind–Srogl coupling reaction

The mechanism of the Liebeskind–Srogl coupling reaction begins with the thioester forming a complex with CuTc (Scheme 3.4.4).[42] Next, an oxidative insertion of palladium into the carbon sulfur bond followed by transmetalation with boronic acid, in which R^2 is transferred to the palladium metal center, while at the same time the sulfur atom is transferred to the copper

complex. Lastly, the ketone product was obtained by reductive elimination of the organopalladium species.
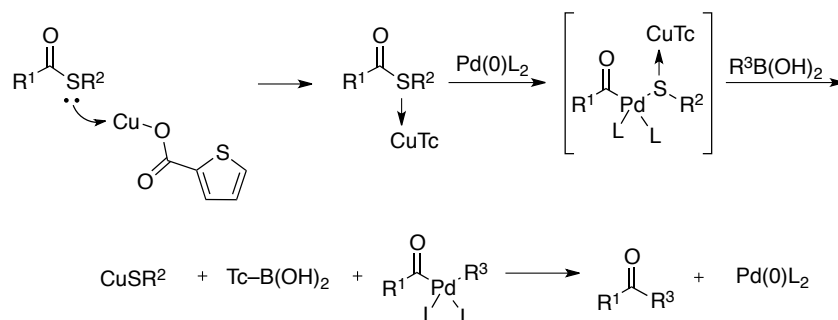
Scheme 3.4.4 Liebeskind–Srogl coupling mechanism

The CuTc serves the dual role of polarizing the Pd–S bond through the Cu(I) coordination to sulfur center and activating the trivalent boron compound simultaneously through coordination of the carboxylate to boron center (Figure 3.4.1).[42] Also, boronic acid is important because of the hydrogen bonding with CuTc strengthens the ternary complex. So, a bulky boronic acid will not be effective for the reaction because it prevents the dual activation of the copper(I) reagent to form the ternary complex. Lastly, the Liebeskind–Srogl coupling reaction not only synthesizes ketones, but has been expanded to synthesizing internal alkynes, nitriles, heteroaromatic compounds, and imines.
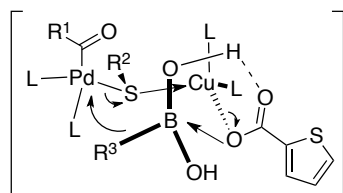
Figure 3.4.1 Ternary complex as the reactive intermediate

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3.5 Progress to the Synthesis of α-Aryl Vinylboronic Acid

As mentioned in Chapter 2, the Liebeskind–Srogl coupling reaction was one of the methods employed to synthesize nitrodienes. For the Liebeskind–Srogl coupling reaction to be a successful, boronic acid is required for its hydrogen-bonding capability to stabilize the ternary complex intermediate. α-Aryl vinylboronic acids were substrates needed for the reaction to provide nitrodiene scaffolds. However, 1-phenylvinylboronic acid is the only α-aryl vinylboronic acid commercially available and there is only one method in synthesizing this compound.[43] Thus, it is essential to develop a method to prepare α-aryl vinylboronic acids to be used in the Liebeskind–Srogl coupling reaction and also other cross-coupling reactions. There are two known methods in synthesizing α-aryl vinylboronic esters demonstrated by Hoveyda and co-workers.

In 2010, Hoveyda reported a nickel-catalyzed hydroalumination of arylacetylenes with dichloro[1,3-bis(diphenylphosphino)propane] nickel [Ni(dppp)Cl$_2$] and diisobutylaluminium hydride (DIBAL-H) as the aluminium source.[44] Arylacetylenes containing electron-donating or electron-withdrawing groups proceeded in high yields and high α-selectivity of the α-aryl vinylaluminium. Two examples of α-aryl vinylboronates were synthesized through a one-pot Ni-catalyzed hydroalumination on arylacetylenes with methoxy(pinacolato)borane [MeOB(pin)] (Scheme 3.5.1). The reaction provided excellent yield of the *meta*-fluorophenylvinylboronic ester, while a lower yield of the *ortho*-chlorophenylvinylboronic ester due to sterics. Most importantly, both products demonstrated excellent α-selectivity.
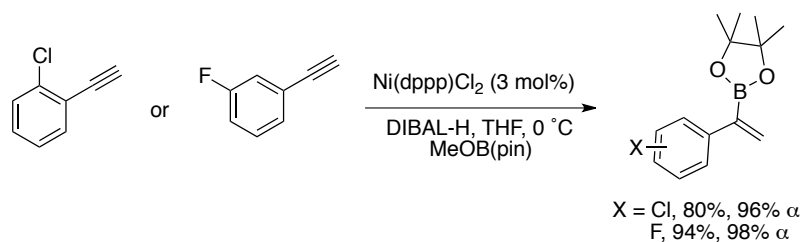
Scheme 3.5.1 Nickel-catalyzed hydroboration of arylacetylenes

A year later, Hoveyda described that a NHC-Cu complex could facilitate the formation of α-aryl vinylboronates with $B_2(pin)_2$ (Scheme 3.5.2).[32] Using the same substrates as mentioned previously, halogens and electron-withdrawing groups on the arylacetylenes provided a high α-selectivity of the desired boronates, >83:17 α:β. However, electron-donating groups, such as methoxy and methyl, on the arylacetylenes demonstrated poor α-selectivity (41:59 α:β, 70:30 α:β, respectively). Interesting, sterics can affect the selectivity for the (trifluoromethyl)phenyl acetylene. When the CF_3 group is ortho to the acetylene on the phenyl the α-selectivity is low, 83:17 α:β. As the sterics decrease (the CF_3 group on the meta or para to the acetylene) the α-selectivity increases (meta 89:11 α:β, ortho 96:4 α:β). This selectivity can be easily explained by the sterics between the *ortho*-CF_3 and the large (pinacolato)boron substituent at the benzylic carbon. As the CF_3 group moves farther away from the (pinacolato)boron substituent the better α-selectivity for the reaction.
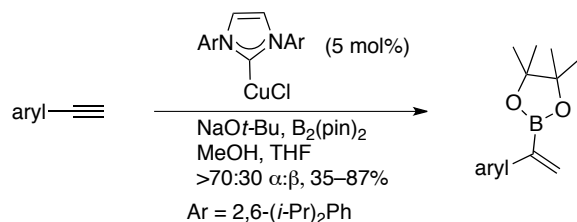
Scheme 3.5.2 NHC-Cu complex-catalyzed hydroboration of arylacetylenes

Results/Discussion

Based on the two methods presented, the Ni-catalyzed hydroalumination appeared to be the most promising method to improve upon to synthesize α-aryl vinylboronic acids. The Ni-catalyzed hydroalumination has a higher α-selectivity than the NHC-Cu complex hydroboration. A modification to the Ni-catalyzed hydroalumination would be changing the boron substituent. Pinacolborane is a stable ester and, therefore, is not easily hydrolyzed to provide the acid. Thus, to obtain the acid we needed to employ a boronic ester that is labile to hydrolysis, such as trimethyl borate. As mentioned previously, *para*-(trifluoromethyl)phenylvinylboronic acid **2a** was successfully incorporated into the Liebeskind–Srogl coupling reaction to construct the corresponding nitrodiene **3a** (Scheme 3.5.3). To expand the substrate scope, we wanted to examine various aryl-substituted acetylenes. Commercially available *para*-tolylacetylene (**1b**) was subjected to the modified Ni-catalyzed hydroalumination as the model system.
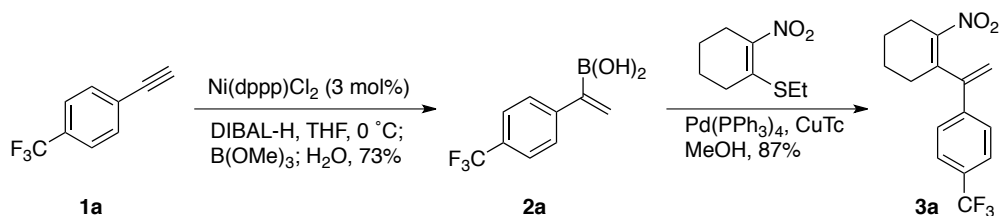
Scheme 3.5.3 Example of Liebeskind–Srogl coupling reaction with electron-withdrawing aryl vinylboronic acid

para-Tolylacetylene (**1b**) was subjected to the same condition as the *para*-(trifluoromethyl)phenyl acetylene (**1a**). The solution turned black when DIBAL-H in hexane (1.0 M, 1.3 equiv) was added to the nickel catalyst solution. The solution was cooled in an ice-water bath before *para*-tolylacetylene (**1b**) was added. After stirring the reaction for 12 hours at 0 °C, trimethyl borate was added followed by refluxing the reaction for 12 hours. After hydrolysis and purification the desired product was not obtained (Table 3.5.1, entry 1). Next, the acetylene **1b** was added at a slightly higher temperature and stirred at 4 °C for 12 hours to produce the

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hydroalumination product. After purification, no vinylboronic acid **2b** was isolated (entry 2). Furthermore, to increase the efficiency of the hydroalumination of the acetylene, the equivalence of DIBAL-H was increased (2 equiv). However, no product was obtained (entry 3). The transmetalation step of the reaction could be the issue in synthesizing the vinylboronic acid that trimethyl borate might not be a good electrophile. The amount of trimethyl borate was increase and the temperature of the oil bath was elevated to induce the formation of the vinylboronic ester. The desired product was unsuccessfully produced (entries 4 and 5).

Table 3.5.1 Attempts in synthesizing *para*-methylphenylvinylboronic acid
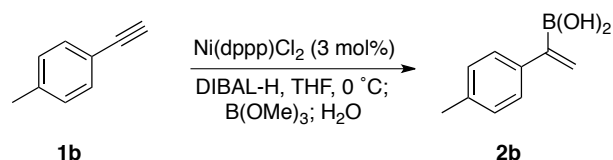
entry	DIBAL-H (eq)	temp (˚C)	B(OMe)$_3$	temp (˚C)	yield (%)
1	1.3	0	3.0	85	0
2	1.3	4	3.0	85	0
3	2.0	0	3.0	85	0
4	1.3	0	4.0	85	0
5	1.3	0	3.0	100	0

Switching to a more electron-donating arylacetylene, *para*-methoxyphenyl acetylene (**1c**), which can be synthesized by a homologation reaction of the corresponding aryl aldehyde,[45] was subjected to the same reaction conditions as *para*-(trifluoromethyl)phenyl acetylene (**1a**) (Scheme 3.5.4). After flash column chromatography (FCC), no desired product was obtained. Based on TLC, the desired boronic ester products for both *para*-tolylacetylene (**1b**) and *para*-methoxyphenyl acetylene (**1c**) were being produced during the reaction. However, after hydrolysis and purification by FCC no vinylboronic acid is isolated. Thus, the vinylboronic acid could have decomposed during the column purification. To avoid purification by FCC, hexane was added to the crude product mixture after the work-up and crystals appeared in the solution.

Without further purification of the crystals, **2c** was immediately subjected to the Liebeskind–Srogl coupling reaction in case the vinylboronic acid is not stable. The Liebeskind–Srogl coupling reaction produced the nitrodiene **3c** in 10% yield. Further optimization and purification of the formation of the aryl vinylboronic acid **2c** was unsuccessful. It seems that α-aryl vinylboronic acids are not stable and/or there is an issue with the hydrolysis step.
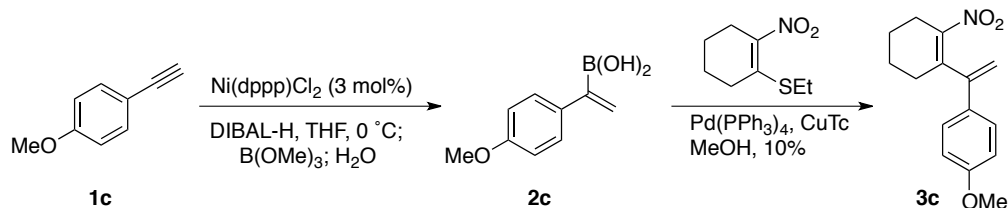
Scheme 3.5.4 Example of Liebeskind–Srogl coupling reaction with electron-donating aryl vinylboronic acid

Without any success of electron-donating arylacetylenes, electron-withdrawing 4-fluorophenyl acetylene (**1d**) was subjected to the reaction.[45] After the addition of trimethyl borate, the reaction was monitored by TLC and no boronic ester was produced during the reaction (Table 3.5.2, entry 1). An increased amount of trimethyl borate and elevated oil bath temperature did not induce transmetalation (entries 2 and 3). Thus, 4-fluorophenyl vinylaluminium species is not a good substrate for transmetalation with trimethyl borate.
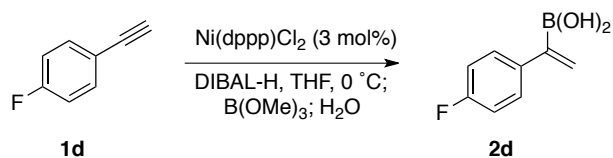
Table 3.5.2 Attempts in synthesizing 4-fluorophenylvinylboronic acid

entry	DIBAL-H (eq)	temp (˚C)	B(OMe)₃	temp (˚C)	yield (%)
1	1.3	0	3.0	85	0
2	1.3	0	4.0	85	0
3	1.3	0	3.0	100	0

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The last attempt of synthesizing boronic acid is using catecholborane instead of trimethyl borate because catecholborane might be a better boron source and it is more labile to hydrolysis than pinacolborane. Employing *para*-tolylacetylene (**1b**) to the reaction condition followed by catecholborane, no desired product was obtained (Scheme 3.5.5).
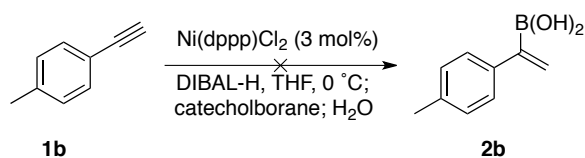
Scheme 3.5.5 Attempts of synthesizing *para*-methylphenylvinylboronic acid with catecholborane

Conclusion

Transmetalation of α-aryl vinylaluminium species with trimethyl borate or catecholborane was not successful with the exception of α-[*p*-(trifluoromethyl)phenyl] vinylaluminium and α-(*p*-methoxyphenyl) vinylaluminium species. With limited variety of borate esters available, finding a boric acid ester that is compatible with the vinylaluminium species for transmetalation and then hydrolysis of the vinylboronic ester seems unpromising. As such, attempts of alternating the amount of reagents and increasing temperature were fruitless in synthesizing α-aryl vinylboronic acids. However, it is still important to develop a methodology to synthesize α-aryl vinylboronic acids for cross-coupling reactions, especially Liebeskind– Srogl. As mentioned previously, boronic acids are difficult to purify due to their solubility in water and limited stability. Also, it could be a reason why substituted α-aryl vinylboronic acids are not commercially available and no available methods in synthesizing them.

Experimental

General Information

All reactions were performed under Ar atmosphere with dry solvents in flame-dried round-bottom flasks containing stir bars. All reagents, except for trimethylborate, were obtained commercially and used without further purification. Tetrahydrofuran was distilled from Na with benzophenone indicator, methanol was distilled afresh from Mg(0), and trimethylborate was purified by distillation prior to use.
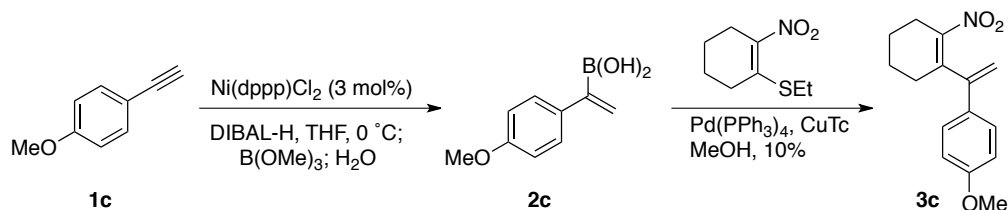
TLC: Thin layer chromatography (TLC) was performed on 0.25-mm Silicycle Glass-Backed Extra-Hard-Layer, 60-Å silica gel plates (TLG-R10011B-323) and visualized under UV light, permanganate staining, or anisaldehyde staining.

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

IR Spectroscopy: IR spectra were recorded using a Thermo Nicolet Avatar 370 FT-IR spectrometer.

NMR Spectroscopy: NMR spectra were recorded using Bruker ARX-400 and AV-300 instruments calibrated to $CH(D)Cl_3$ as an internal reference (7.26 and 77.00 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; dq = doublet of quartets; dq = doublet of pentets; t = triplet; td = triplet of doublets; q = quartet; m = multiplet.

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).

1-Methoxy-4-[1-(2-nitrocyclohex-1-en-1-yl)vinyl]benzene (**3c**) To a suspension of 1,3-bis(diphenylphosphino)propane nickel(II) chloride [Ni(dppp)Cl$_2$, 61.5 mg, 0.11 mmol, 0.03 equiv] in 13 mL THF was added DIBAL-H (5 mL, 5.0 mmol, 1.3 equiv) dropwise at room temperature. The resulting black solution was cooled to 0 ˚C before *p*-methoxyphenyl acetylene (0.5 g, 3.8 mmol, 1.0 equiv) was added slowly over five minutes and then was stirred for 2 h at room temperature. After the 2 hours, trimethylborate (1.3 mL, 11.3 mmol, 3.0 equiv) was added dropwise into the reaction at 0 ˚C. The resulting solution was allowed to be heated to 80 ˚C and stir for 12 h before the reaction was quenched by dropwise addition of water (9 mL) at 0 ˚C. The mixture is allowed to warm to room temperature and stir for 1 h before it is extracted with Et$_2$O (10 mL x 3), and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the residue was purified by adding hexanes to precipitate the aryl vinylboronic acid, which was immediately subjected to the Liebeskind–Srogl coupling reaction. To a dry round-bottom flask equipped with a stir bar was added 1-thioethyl-2-nitrocyclohexene (60 mg, 0.32 mmol, 1 equiv), Pd(PPh$_3$)$_4$ (74.1 mg, 0.064 mmol, 0.2 equiv), copper(I) thiophene carboxylate (91.6 mg, 0.48 mmol, 1.5 equiv), and boronic acid (185.0 mg, 0.96 mmol, 3.0 equiv) and was then Ar-

replenished three times. Methanol (11 mL) was added to the reaction and was stirred until disappearance of 1-thioethyl-2-nitrocyclohexene by TLC (3 h). The reaction was quenched by saturated ammonium chloride solution (10 mL) and was filtered through a Celite pad that was rinsed with EtOAc (20 mL). The biphasic solution was separated and then the organic phase was washed with water (20 mL) and brine (2 x 20 mL), and dried with Na_2SO_4. The solvents were removed in vacuo and the crude oil was purified by through flash column chromatography (0–5% EtOAc in hexanes) to give nitrodiene **3c** as colorless oil (8.3 mg, 10% yield); IR (v, cm^{-1}) 2935, 2854, 1610, 1501, 1367, 1145, 1188, 997, 827, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (dd, J = 6.7, 2.2 Hz, 2H), 6.87 (dd, J = 6.7, 2.1 Hz, 2H), 5.37 (s, 1H), 4.98 (s, 1H), 3.81 (s, 3H), 2.73–2.68 (m, 2H), 2.31–2.27 (m, 2H), 1.85 (tt, J = 9.1, 3.1 Hz, 2H), 1.69 (tt, J = 8.9, 3.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 159.7, 147.0, 146.6, 140.8, 130.0, 127.7, 113.9, 110.7, 55.3, 30.8, 26.2, 22.1, 21.6; MS (MALDI) calcd for $C_{15}H_{17}NO_3Na$ [M + Na]$^+$ m/z 282.11, found 282.10.

Reference

(1)   (a) Frankland, E.; Duppa, B. F. *Justus Liebigs Ann. Chem.* **1860**, *115*, 319. (b) Frankland, E.; Duppa, B. F. *Proc. R. Soc. Lond.* **1860**, *10*, 568. (c) Frankland, E. *J. Chem. Soc.* **1862**, *15*, 363.

(2)   (a) Synder, H. R.; Kuck, J. A.; Johnson, J. R. *J. Am. Chem. Soc.* **1938**, *60*, 105. (b) Johnson, J. R.; Van Campen, M. G. Jr. *J. Am. Chem. Soc.* **1938**, *60*, 121.

(3)   (a) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. *J. Org. Chem.* **1982**, *47*, 3808. (b) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Lee, H. D.; Negishi, E.–I.; Katz, J. J. *J. Org. Chem.* **1986**, *51*, 5270.

(4)   (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (c) Chan, D. M. T.; Manaco, K. L.; Wang, R.–P.; Winters, M. P.; Prokopcová, H.; Kappe, C. O. *Tetrahedron Lett.* **1998**, *39*, 2933. (d) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

(5)   (a) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214. (b) de la Herrán, G.; Segura, A.; Csák, A. G. *Org. Lett.* **2007**, *9*, 961.

(6)   Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068.

(7)   Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810.

(8)   (a) Matteson, D. S.; Michnick, T. J.; Willet, R. D.; Patterson, C. D. *Organometallics* **1989**, *8*, 726. (b) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590. (b) Matteson, D. S.; Sadhu, K. M.; Lienhard, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 5241. (c) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. S. *Organometallics* **1983**, *2*, 1536. (d) Matteson D. S.; Sadhu, K. M. *Organometallic* **1984**, *3*, 614. (e) Yuen, A. K. L.; Hutton, C. A. *Tetrahedron Lett.* **2005**, *46*, 7899. (f) Inglis, S. R.; Woon, E. C. Y.; Thompson, A. L.; Schofield, C. J. *J. Org. Chem.* **2010**, *75*, 468.

(9)   Ketuly, K. A.; Hadi, A. H. A. *Molecules* **2010**, *15*, 2347.

(10)   (a) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (b) Brown, H. C.; Bhat, N. G. *Tetrahedron Lett.* **1988**, *29*, 21. (c) Uenishi, J.; Matsui, K.; Wada, A. *Tetrahedron Lett.* **2003**, *44*, 3093.

(11)   Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370.

(12)   Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 3834.

(13)   Miyaura, N.; Suzuki, A. *Chem. Lett.* **1981**, 879.

(14)   Brown, H. C.; Campell, J. B. *J. Org. Chem.* **1980**, *45*, 389.

(15)   Josyula, K. V. B.; Gao, P.; Hewitt, C. *Tetrahedron Lett.* **2003**, *44*, 7789.

(16)   Cole, T. E.; Quintanilla, R.; Rodewald, S. *Organometallics* **1991**, *10*, 3777.

(17)   Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *J. Chem. Soc., Chem. Commun.* **1995**, 2523.

(18)   Badudri, F.; Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron* **1998**, *54*, 1085.

(19)   (a) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 126. (b) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.

(20)   Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *Synthesis* **2000**, 778.

(21)   Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.

(22)   Gridnev, I. D.; Miyaura, N.; Suzuki, A. *Organometallics* **1993**, *12*, 589.

(23)   Yamamoto, Y.; Fujikawa, R.; Yamada, A.; Miyaura, N. *Chem. Lett.* **1999**, 1069.

(24)   (a) Negishi, E.; Williams, R. M.; Lew, G.; Yoshida, T. *J. Organomet. Chem.* **1975**, *92*, C4. (b) Campell, J. B. Jr.; Molander, G. A. *J. Organomet. Chem.* **1978**, *156*, 71.

(25)   Brown, H. C.; Imai, T. *Organometallics* **1984**, *3*, 1392.

(26)   Srebnik, M.; Bhat, N. G.; Brown, H. C. *Tetrahedron Lett.* **1988**, *29*, 2635.

(27)   Deloux, L.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 6871.

(28)   Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990.

(29)   Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2008**, *73*, 6841.

(30)   (a) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett*, **1990**, *11*, 675. (b) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733.

(31)   Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995.

(32)   Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859.

(33)   Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414.

(34)   Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2013**, *19*, 7125.

(35)   Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 12400.

(36)   Whyte, G. F.; Vilar, R.; Woscholski, R. *J. Chem. Biol.* **2013**, *6*, 161.

(37)   Chorkendorff, I.; Niemantsverdriet, J. W. in *Concepts of Modern Catalysis and Kinetics: 2nd and completely revised and enlarged edition*, Wiley, Weinheim, **2007**.

(38)   (a) Rao, G.; Phillip, M. *J. Org. Chem.* **1991**, *56*, 1505. (b) Georgiou, I.; Ilyashenko, G.; Whiting, A. *Acc. Chem. Res.* **2009**, *42*, 756. (c) McCubbin, J. A.; Hosseini, H.; Krokhin, O. V. *J. Org. Chem.* **2010**, *75*, 959. (d) Li, M.; Yang, T.; Dixon, D. J. *Chem. Commun.* **2010**, *46*, 2191. (e) Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011**, *2*, 1305.

(39)   (a) Adams, J.; Kauffman, M. *Cancer Invest.* **2004**, *22*, 304. (b) Bonvivi, P.; Zorzi, E.; Basso, G.; Rosolen, A. *Leukemia* **2007**, *21*, 838. (c) Gelman, J. S.; Sironi, J.; Berezniuk, I.; Dasgupta, S.; Castro, L. M.; Gozzo, F. C.; Ferro, E. S.; Fricker, L.D. *PLoS One* **2013**, *8*, e53263.

(40)   Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

(41)   Amatore, C.; Jutand, A.; Lu Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492.

(41)   (a) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554. (b) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734.

(42)   Prokopcová, H.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2009**, *48*, 2276.

(43)   Arendsen, D. L.; Bhatia, P. US Patent 2000075145, 2000.

(44)   Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961.

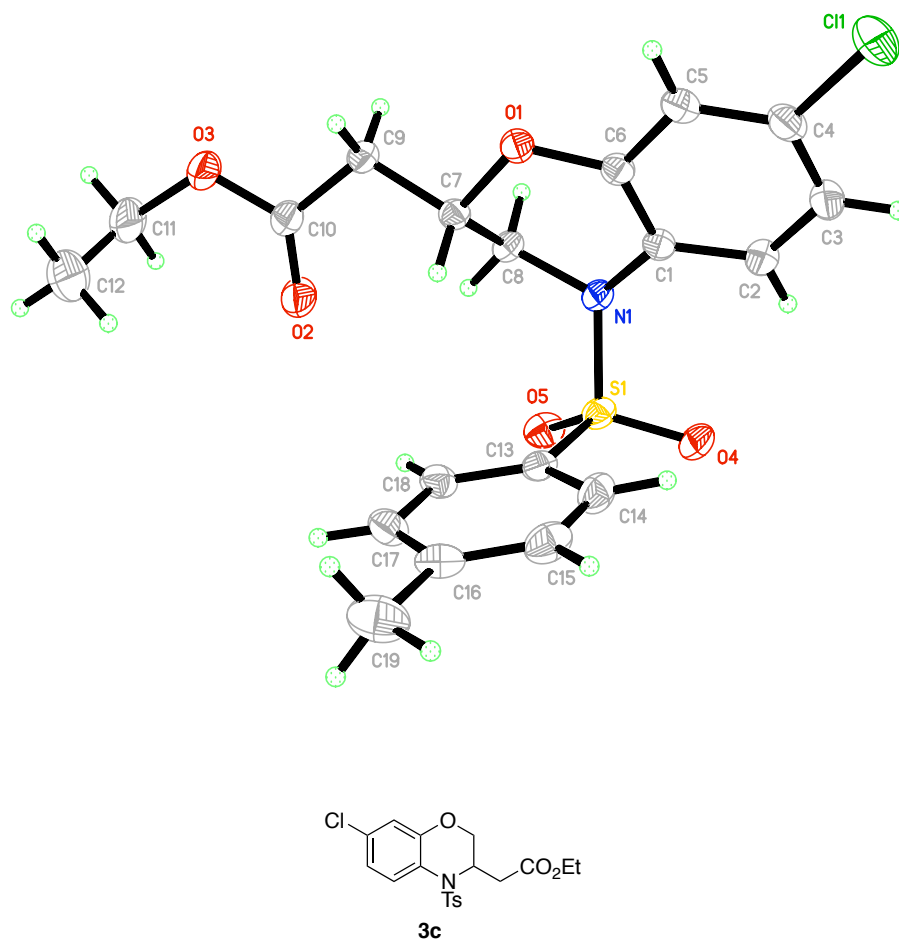(45)   Ganesh, M.; Namboothiri, I. N. N. *Tetrahedron* **2007**, *63*, 11973.

Appendix

Figure A.1.1 X-ray crystal structure of **3c** provided unambiguous assignment of the location of the oxygen and nitrogen atoms. This has been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC- 779839.
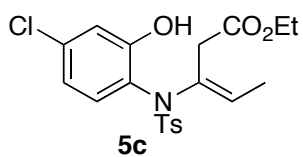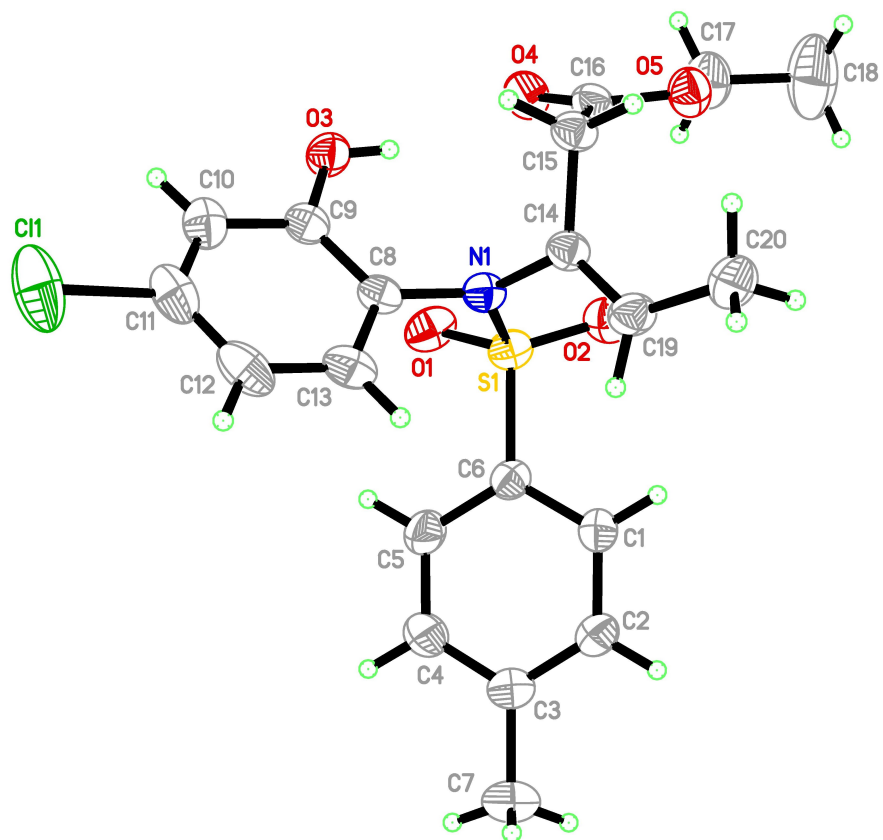
Figure A.1.2 X-ray crystal structure of **4a** provided unambiguous assignment of the double-Michael product. This has been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC- 779840.

Figure A.1.3 X-ray crystal structure of **5c** provided unambiguous assignment of the mono-Michael adduct. This has been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC- 779841.
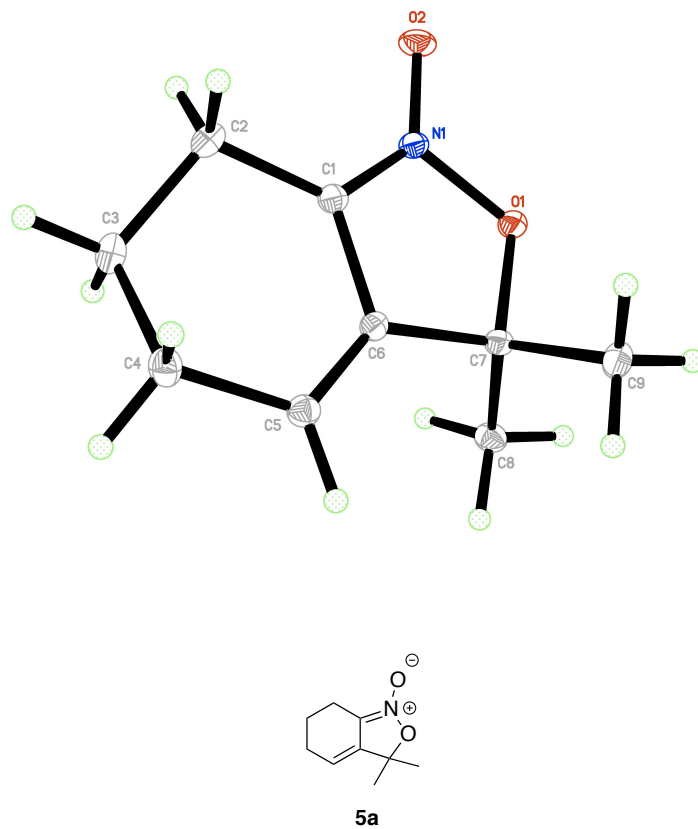
Figure A.2.1 X-ray crystal structure of **5a** provided unambiguous assignment of the nitronate product through the nitro-Nazarov reaction.
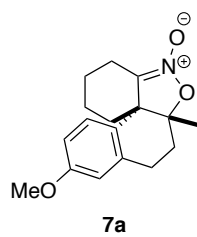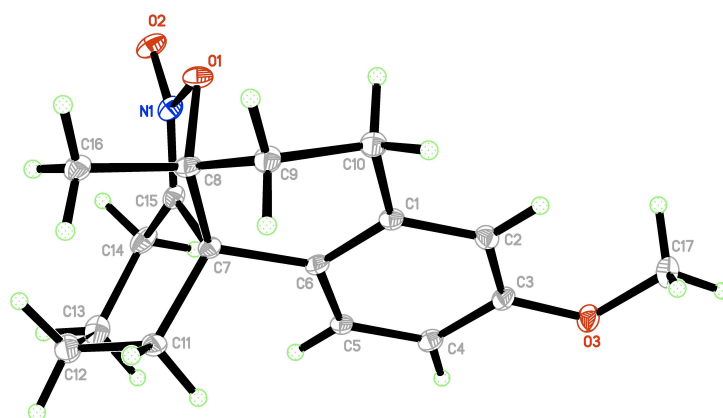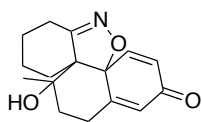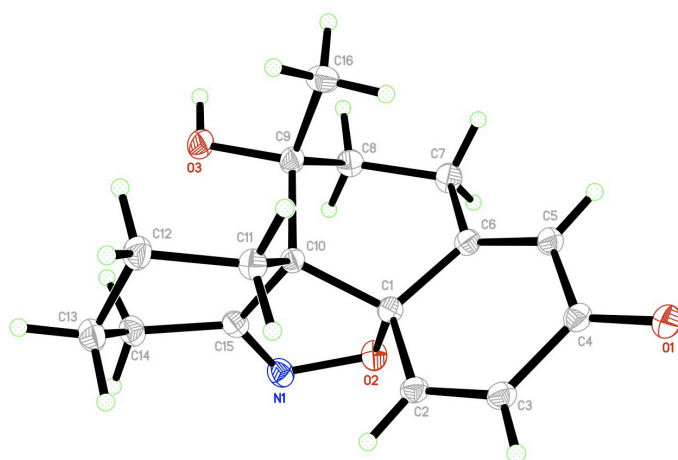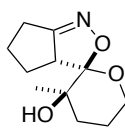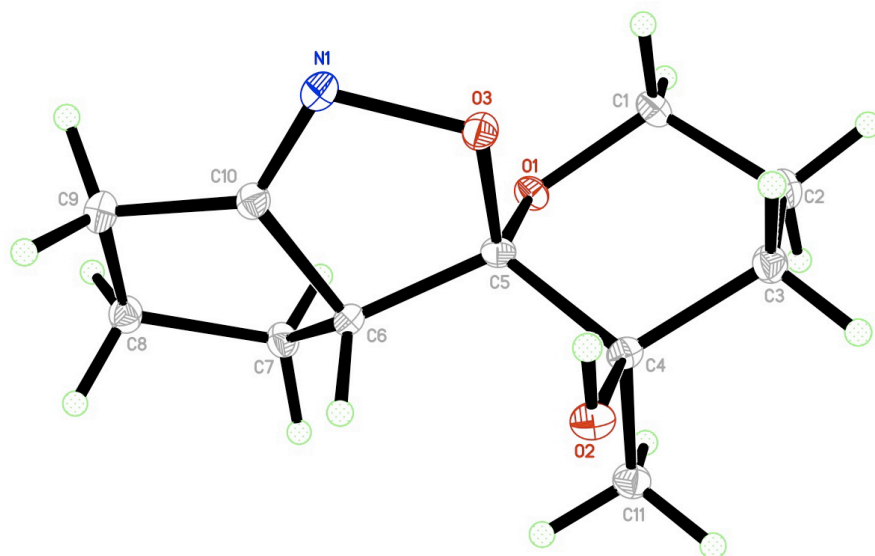
Figure A.2.2 X-ray crystal structure of **7a** provided unequivocal assignment of the interrupted nitro-Nazarov product.

8a

Figure A.2.3 X-ray crystal structure of **8a** provided unambiguous assignment of the rearranged product through the interrupted nitro-Nazarov reaction.

8b

Figure A.2.4 X-ray crystal structure of **8b** provided unambiguous assignment of the rearranged product through the interrupted nitro-Nazarov reaction.