Anion Relay Cyclopropanation and Aryl Vinyl Cyclopropane Cope Rearrangements

By

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Submitted to the graduate degree program in Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Abstract

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Department of Chemistry, July 2019

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Anion Relay Chemistry is a powerful tool for the rapid development of molecular complexity in an operationally simple manner. Much of the work in this field has been pioneered and developed by the Smith group, whose work has primarily focused on silicon and phosphorus Brook rearrangements to effect anion relay. Presented herein is the development of a retro-Claisen condensation protocol to effect anion relay in the synthesis of vinyl cyclopropanes, and subsequent aromatic Cope rearrangement of those vinyl cyclopropanes. This protocol provides a supplementary method of anion relay utilizing readily accessible nucleophiles, which obviates the need for synthesis of alkyl silanes or phosphines as starting materials.

Chapter 1 is a review of anion relay chemistry, which focuses on through-space anion relay over 3 or more bonds. It covers both new developments and applications to total synthesis of through-space anion relay more than three bonds since the field was last reviewed by Smith in 2008.

Chapter 2 begins with an overview of retro-Claisen activation of allylic alcohols and its application to decarboxylative and deacylative allylation reactions (DcA and DaA). This synopsis is followed by an overview of a novel anion relay cyclopropanation accomplished through a retro-Claisen activation of a nascent allylic alcohol following an initial Tsuji-Trost allylation between a carbon nucleophile and a vinyl epoxide. This reaction constitutes the latest example of retro-Claisen activation of allylic alcohols presented by our group, and a novel application of anion relay chemistry. Of note is that the anion relay is accomplished without a Brook rearrangement,

obviating the necessity to synthesize alkyl silanes or phosphonates. Furthermore, it is an example of [1,6]-anion relay, examples of which are much less common than [1,2]-and [1,4]-anion relay.

In chapter 3, aromatic vinyl cyclopropane Cope rearrangements are reviewed. This review is followed by a description of the aromatic Cope rearrangement of the vinyl cyclopropanes made using the methodologies outlined in Chapter 2. While divinyl cyclopropane Cope rearrangements are common and facile at room temperature, aryl vinyl cyclopropane Cope rearrangements are much less common, tend to require forcing conditions such as high temperatures and usually further require rigorously stereodefined starting materials to take advantage of the cyclopropane strain release to drive dearomatization. The reaction described in this document features a dynamic equilibrium of aryl vinyl cyclopropane diastereomers prior to Cope rearrangement, allowing the difficult Cope rearrangement to be accomplished even without stereodefined starting materials.

Acknowledgements

I would like to thank Dr. Jon Tunge for his profound influence on my life as a chemist and as a human. Without his fostering, I would not have been able accomplish the works described in this dissertation. He taught me to learn, how to think, and how to grow professionally. From Jon, I learned not to apologize, but to improve; refining oneself as one refines a chemical process.

I would like to thank my committee members; Dr. Helena Malinakova for the knowledge I gained in her organometallic chemistry class, Dr. Ryan Altman for his words of encouragement over the years. Dr. Michael Rubin has always given me excellent advice. I appreciate the lessons I learned in his class, as well as through his example and his advice over the years. Dr. Paul Hanson I admire for his curiosity and his passion. He has always fostered a sense of wonder and excitement in chemistry in myself and my fellow students.

I would like to thank my parents for moral and financial support. It's difficult to express my gratitude in text, as much of what I have gained from them is intangible and abstract, but they obviously have crafted me to a large extent into the person that I am today and are doing the same now for my own children. I wish to thank them for their constant faith in me and for believing in me even betting on my success has not always seemed logical.

Furthermore, I would like to thank my wife, Jamie Allegre, for her constant support and encouragement throughout my career. Without the support of her strength and character, the task of completing graduate school would have proved impossible. As a parent, my highest priority in life is supporting my children and fostering their happiness. While the endeavor of pursuing a PhD began with this goal in mind, my efforts would have been in vain without Jamie.

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Contents

Abbreviations

Ac – Acyl

Ar – Aryl

ARC – Anion Relay Chemistry

ASG – Anion Stabilizing Group

AVCPR – Aryl Vinyl Cyclopropane Cope Rearrangement

BINAP – (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)

BINOL – 1,1'-Bi-2-naphthol

Bn – Benzyl

Boc – *tert*-Butoxy Carbonyl

Bu – Butyl

cee – Conservation of Enantiomeric Excess [(ee of product)/(ee of reactant) * 100]

COD – Cyclooctadiene

DABCO – 1,4-Diazabicyclo[2.2.2]octane

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM – Dichloromethane or Methylene Chloride

DCE – 1,2-Dichloroethane

DKR – Dynamic Kinetic Resolution

DMAP – Dimethylamino Pyridine

DMPU – N,N′-Dimethylpropyleneurea

dppbz – 1,2-Bis(diphenylphosphanyl)benzene

dppe – 1,2-bis(diphenylphosphino)ethane

dppf – 1,1′-Ferrocenediyl-bis(diphenylphosphine)

dppm – bis(diphenylphosphino)methane

dppp – 1,3-bis(diphenylphosphino)propane

E^+ – Electrophile

ee – Enantiomeric Excess

Et – Ethyl

EtOAC – Ethyl Acetate

EWG – Electron Withdrawing Group

HMDS – Hexamethyl disilazane

HMPA – Hexamethyl Phosphoramide

LDA – Lithium Diisopropylamide

Me – Methyl

MIRC – Michael-Initiated Ring Closure

MOM – Methoxymethyl

Ms – Mesyl

NMR – Nuclear Magnetic Resonance Spectroscopy

Nu^- – Nucleophile

OTf – Triflate

Ph – Phenyl

PMB – Paramethoxybenzyl

PMP – Paramethoxy Phenyl

TBAF – Tetrabutyl Ammonium Fluoride

TBD – 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

TBS – *tert*Butyl Dimethyl Silyl

TBT – *tert*–Butyl Tetrazole

TEA – Triethylamine

TES – Triethylsilyl

THF – Tetrahydrofuran

TIPS – Triisopropylsilyl

TMS – Trimethylsilyl

Trt – Trityl

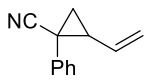
Ts – Tosyl

A note on compound numbering: Compounds are numbered in the order in which they are referred to *in the text* using an alpha-numeric code. The first character, a letter, indicates the major category of compound from the list below. The second character, a number, indicates the chapter in which the compound first appeared. The third character, a number, designates a specific class of compound based on important functional groups. Finally, the fourth character, a letter, designates a specific compound out of a class.

The meanings of the letters in the first digit are as follows; A designates a compound from a literature source, S designates a starting material, I indicates an intermediate, and P denotes a product.

An example compound number is shown below:

P2.1a – a product, first appearing in chapter 2, first class to appear, first listed within its class.



Note: even though vinyl cyclopropanes are starting materials in chapter 3, they will still be referred to by the number given to them in chapter 2. The initially observed benzocycloheptene will be named P3.1, even though it first appears in chapter 2.

Chapter 1: Review of Anion Relay Chemistry

§ 1.1 Introduction

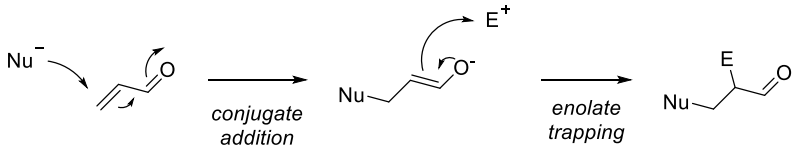
Anion relay is defined by Smith as a multicomponent coupling protocol wherein negative charge migrates from one part of a molecule to another through the transformation.[1] Smith categorizes anion relay into two major classes, through-bond and though-space, and reviewed the subject in 2008.[1] According to this definition, however, an extremely broad array of transformations can be considered "anion relay" including Michael/aldol chemistry, proton transfers, etc. Therefore, it is prudent to adjust this definition to cover a narrower field. As such, the working definition of through-space anion relay for the purposes of this review shall be the transfer of a group other than a proton involving the migration of negative charge through a molecule. While the validity of through-bond anion relay will not be entirely disregarded, it shall be considered a field much too broad for the scope of this review of anion relay. Therefore, we shall focus solely on what Smith calls through-space anion relay. The majority of through-space anion relay involves 1,2-Brook rearrangements, which are often not considered in the anion relay literature.[2] Herein, we present an updated review on through-space anion relay since 2008, which will focus on anionic migration over more than two bonds. First, an overview of different types of anion relay will be given, highlighting some examples. Then, recent developments in through-space anion relay over distances longer than two bonds will be presented. Finally, recent applications of anion relay chemistry to total synthesis will be reviewed.

1.1.1 – Types of Anion Relay

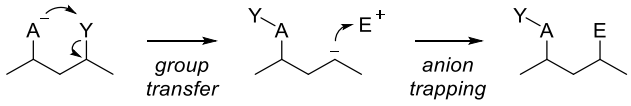
There are two major classes of anion relay reactions: through-bond and through-space transfers. The latter is further divided into two types:[1] type I and type II. Through-bond anion relay involves the migration of negative charge though the bonding network of a molecule, as in Michael

addition. This migration of negative charge is generally accomplished by formation of a sigma bond and movement of electrons through resonance in a π-system, resulting in anionic charge in a new locus on the molecule (Scheme 1.1). Through-space anion relay, on the other hand involves a migration of a group other than a proton, resulting in the breaking of a sigma bond and development of anionic charge at the atom where the sigma bond was broken, as in the Brook rearrangement (Scheme 1.2). Here, we present several examples typical of each type.

Scheme 1.1 – Through-Bond Anion Relay



Scheme 1.2 – Through-Space Anion Relay

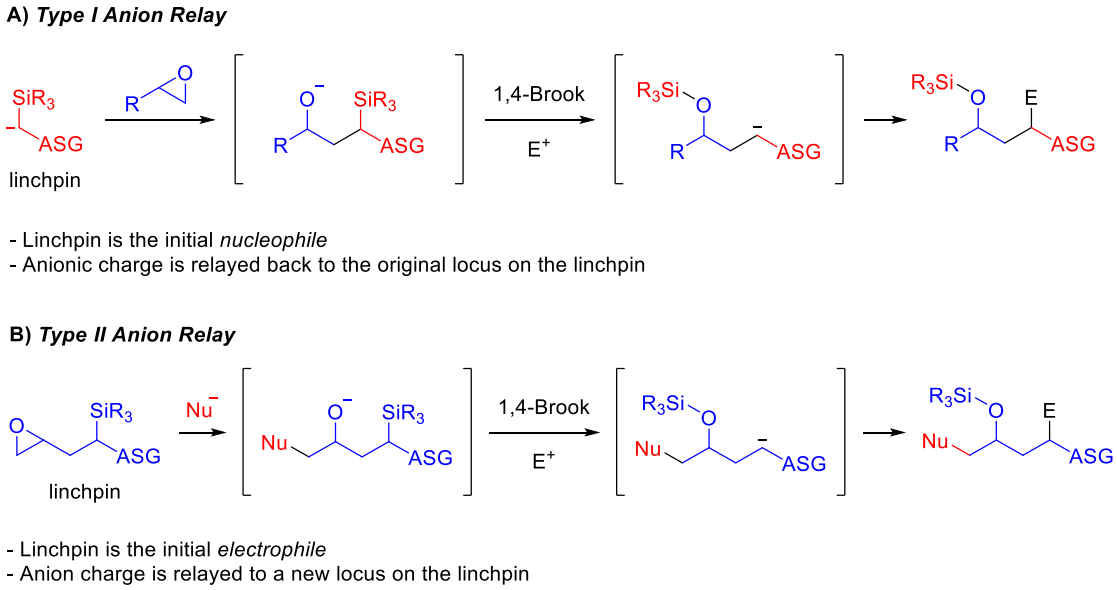


1.1.2 – Through-Space Anion Relay

Through-space anion relay comprises the relay of anionic charge within a molecule by the migration of some group through breaking of a sigma bond, which localizes anionic charge on the atom where the sigma bond was broken. Through-space anion relay can be roughly divided into two types (Scheme 1.3) distinguished by the nature and locus of anionic charge relative to the linchpin (the coupling partner containing the migrating group). In type I anion relay, the linchpin is the initial nucleophile. After coupling with an electrophile, anionic charge is relayed via a group migration back to the original locus on the linchpin (Scheme 1.3a).[1] Alternatively, type II anion

relay involves an electrophilic linchpin, which is activated by a nucleophile to undergo anion relay wherein anionic charge migrates to a new locus on the linchpin (Scheme 1.3b).[1]

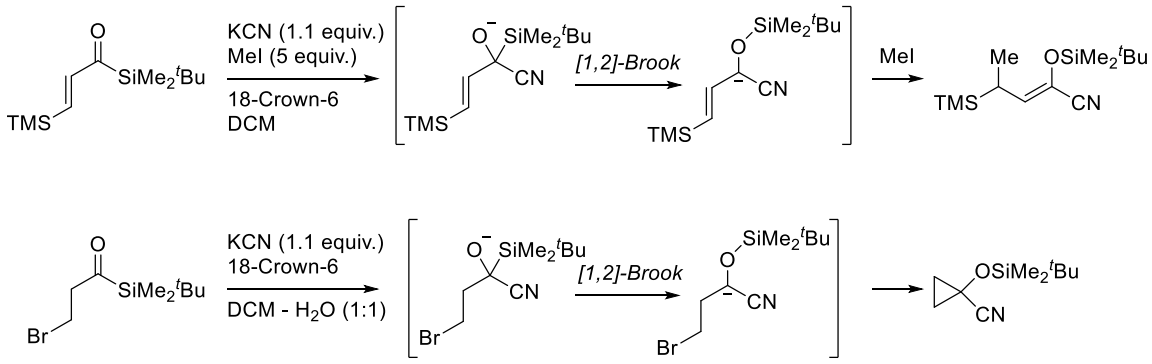
Scheme 1.3 – Types of Through-Space Anion Relay



By far, the most commonly employed reaction in through-space anion relay is the Brook rearrangement. Discovered by Brook in 1958, the initial examples were [1,2]-C to O silyl migrations.[3] Since then, [1,2]-Brook rearrangements continue to be the most commonly employed type of anion relay, especially [1,2]-Brook rearrangements induced by [1,2]-addition onto acyl silanes[4] and phosphonates.[5] For example, in 2000, the Ohnishi group demonstrated the ability of acylsilanes to undergo [1,2]-Brook rearrangements upon nucleophilic addition of cyanide (Scheme 1.4).[6] The nascent carbanion could then be utilized for nucleophilic addition reactions or intramolecular nucleophilic cyclizations to form cyclopropanes.

Scheme 1.4 – [1,2]-Brook Rearrangement Induced by [1,2]-Addition onto Acyl Silanes

Ohnishi, 2000



Since the pioneering work of Brook, the rearrangement has been expanded to include [1,n]-C to O silyl migrations,[1] most commonly [1,4]- and [1,5]-migrations, which have 5- and 6-membered transition states respectively. The subject of this review shall be primarily concerned with these longer range motifs (> 2 bonds) of through-space anion relay that have been developed in the last decade. The reactions used for anion relay, including Brook rearrangements as well as other reactions will be examined.

§ 1.2 Recent Developments in Through-Space [1, > 2]-Anion Relay

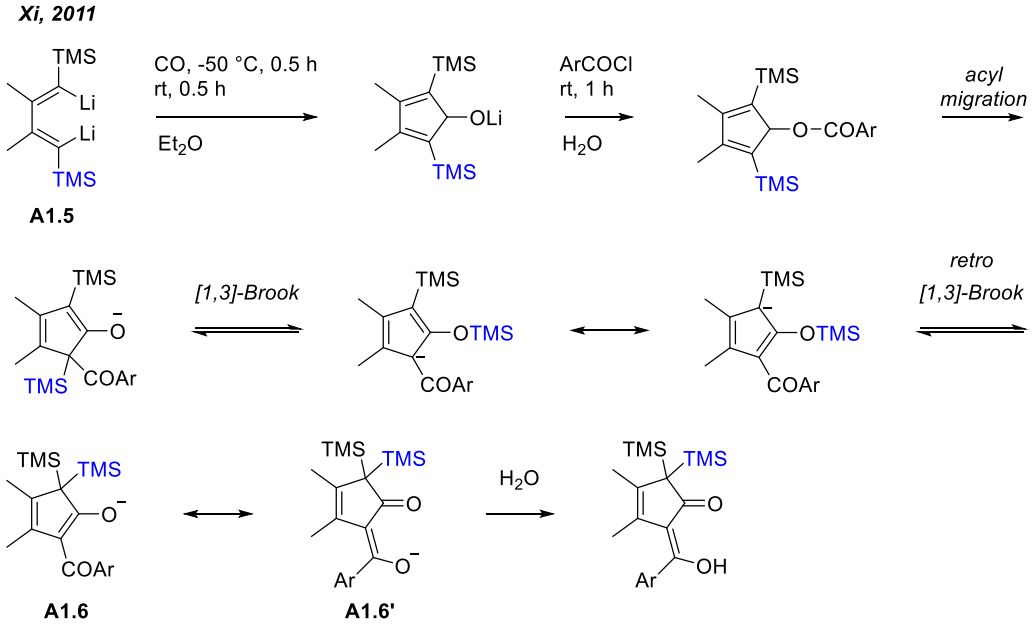
Herein shall be presented a review of through-space anion relay characterized by a charge migration of more than two bonds. These reactions will be primarily organized by the distance of anion relay and will be subdivided by class of migrating group.

1.2.1 – Through-Space [1,3]-Anion Relay

[1,3]-Brook rearrangements are much less common than [1,2]- or [1,4]-rearrangements, but they have seen some application in anion relay. In 2011, the Xi group reported an interesting example of the use of a [1,3]-Brook rearrangement in type I anion relay (Scheme 1.5).[7] A dianionic

bis(silyl)-butadiene, **A1.5** was carbonylated to form a type I anion relay linchpin. This bis-silylated alkoxycyclopentadiene was acetylated, and after an acyl migration, sequential 1,3-Brook rearrangement and retro-Brook rearrangements were initiated resulting in a *gem*-bis(trimethylsilyl)cyclopentadienone, **A1.6**. Of note is that the anion relay does not occur until after acylation of the initial anion and is initiated by an acyl transfer event rather than deprotonation or nucleophilic attack, as is common. The equilibrium of the Brook rearrangement depends on the stability of the carbanion and the relative strength of the silicon-oxygen bond.[1] The driving force of the retro-Brook rearrangement is likely thermodynamic as the extent of conjugation increases throughout the transformation.

Scheme 1.5 – Through-Space ARC via Sequential [1,3]-Brook and retro-Brook Rearrangement



1.2.2 – Through-Space [1,4]-Anion Relay

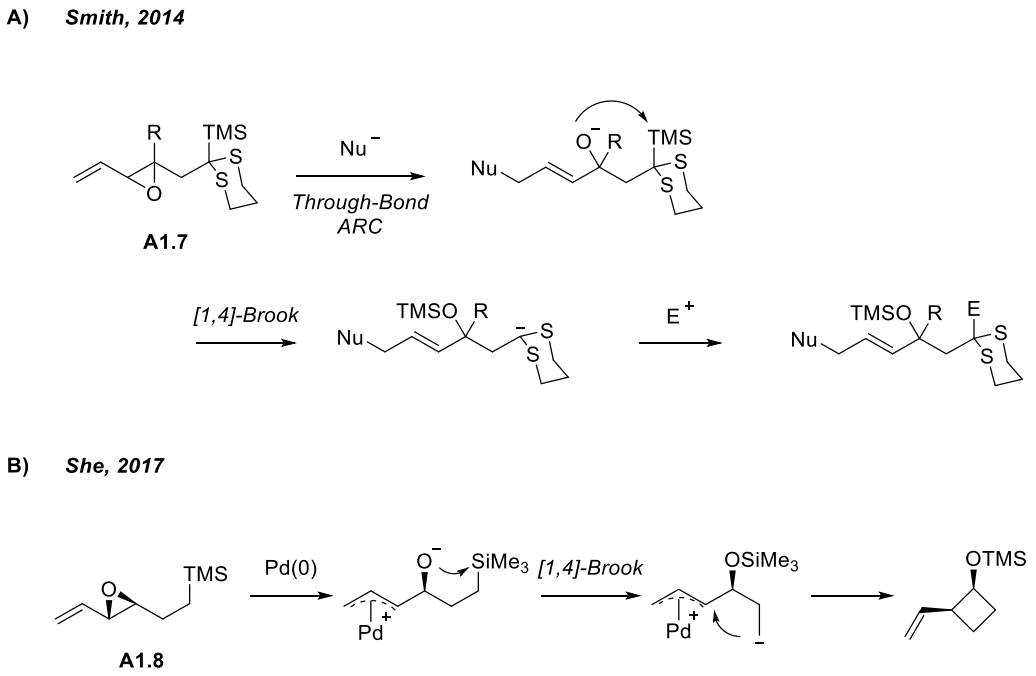
Perhaps not as common as through-space [1,2]-anion relay, but certainly more common than [1,3]-transfers, are through-space [1,4]-anion relays. As with [1,2]-rearrangements, the vast majority of applications in through-space [1,4]-ARC reactions has utilized Brook rearrangements.

1.2.2.1 – [1,4]-Brook Rearrangements

In Smith's type II anion relay chemistry, [1,4]-Brook rearrangements are ubiquitously employed. The first example of the combination of a [1,4]-Brook rearrangement with through-bond anion relay was reported by Smith and coworkers in 2014 (Scheme 1.6a).[8] Three vinyl epoxide linchpins (**A1.7)** were developed and were used to combine through-bond anion relay and through-space type II anion relay in 3-component coupling reactions. Through-bond anion relay was effected by the S_N2' opening of the vinyl epoxide, resulting in a vinyl alkoxide species, which is poised to undergo a [1,4]-Brook rearrangement. These linchpins complemented the existing epoxide linchpins developed in the Smith group, which were activated for anion relay by the direct opening of the epoxide via S_N2 reactions.

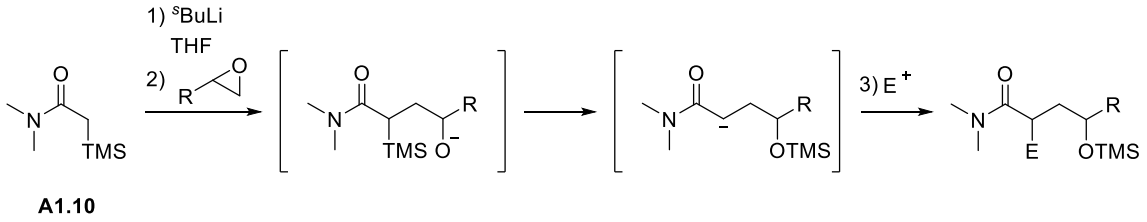
The She group was the first to use palladium-mediated opening of vinyl epoxides to effect anion relay (Scheme 1.6b).[9] Using a silane-containing vinyl epoxide linchpin (**A1.8)** similar to those developed by Smith, they utilized palladium to open the vinyl epoxide to form a Pd-π allyl alkoxide species that underwent anion relay via a [1,4]-Brook rearrangement. The resulting carbanion spontaneously cyclized, regenerating the palladium catalyst and forming a synthetically useful vinyl cyclobutane. Interestingly, the carbanion intermediates did not require stabilization by dithiane groups or other electron withdrawing groups.

Scheme 1.6 – [1,4]-Brook Rearrangement Combined with Through-Bond ARC



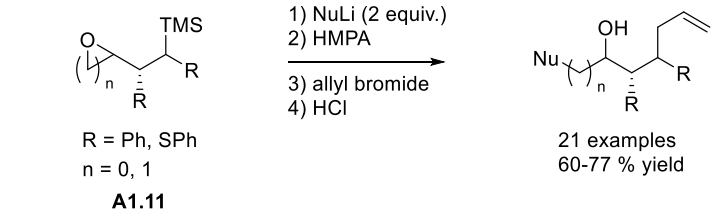
Compared with type II reactions, type I anion relay reactions have seen relatively less development over the last decade. Since 2008, only a few examples of new type I anion relay reactions have been developed. However, in 2017, Smith *et al*. described the use of α-silyl amides as linchpins (**A1.10**) for type I anion relay utilizing [1,4]-Brook rearrangements (Scheme 1.7).[10] These linchpins exhibited good reactivity with a variety of different epoxides and electrophiles in 3-component couplings (16 examples, 89-98 % yields). Furthermore, the amide was useful as a synthetic handle for subsequent functionalization. This amide linchpin demonstrated the utility of an alternative stabilizing group to the commonly utilized dithianes, thus expanding the scope of type I anion relay.

Scheme 1.7 – [1,4]-Brook Rearrangement with Type I Amide Linchpins



In 2010, Smith developed another new class of bifunctional type II linchpin that did not include dithianes (**A1.11**, Scheme 1.8).[11] In this publication, they introduced ten new linchpins, most of which were epoxides, but some examples of aldehyde linchpins were also provided. Phenyl and thiophenyl groups were used as anion stabilizers rather than dithianes, effectively expanding the scope of type II anion relay to a new class of compounds. The use of phenyl groups as anion stabilizing groups increased diastereoselectivities relative to use of the thiophenyl substrates, but the yields were acceptable in all cases.

Scheme 1.8 – Non-Dithiane Linchpins for Type II ARC

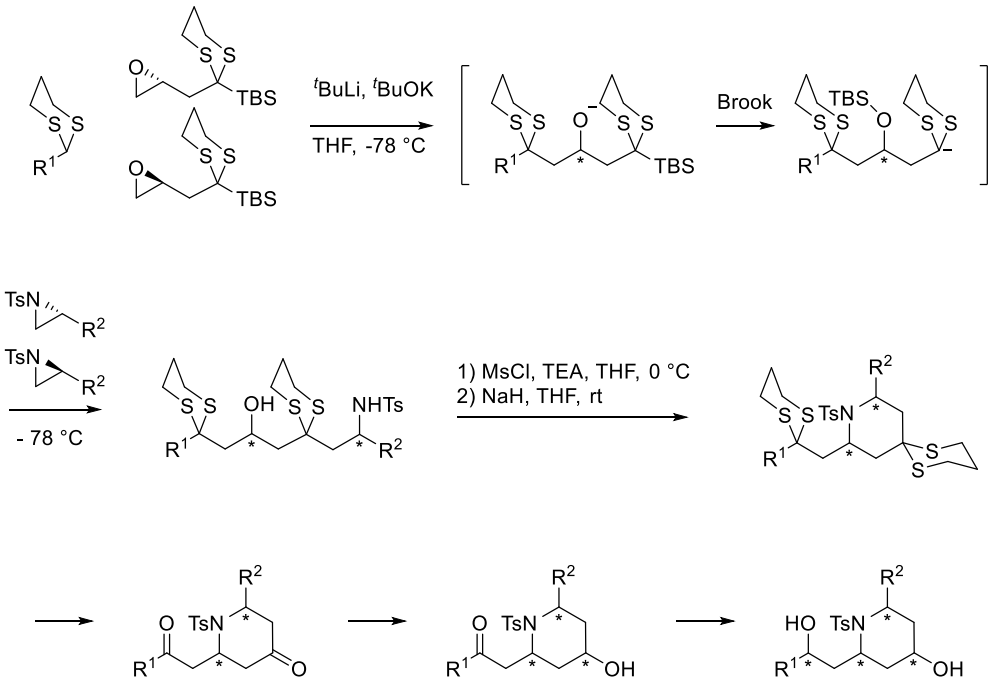


While a variety of electrophiles are useful in 3-component anion relay coupling reactions, Smith and coworkers demonstrated the first use of aziridines as the terminal electrophiles in type II ARC (Scheme 1.9) in 2011.[12] The 3-component amination reactions occurred in one pot, and

after mesylation of the alcohol and treatment with base, subsequently cyclized to form biologically relevant piperidines. As in other ARC protocols, these reactions were stereospecific, yielding chiral non-racemic material from enantiopure starting materials. The authors additionally showed conversion of the dithianes to ketones and subsequent reduction to provide alcohols.

Scheme 1.9 – [1,4]-Brook Rearrangement ARC Utilizing Aziridnes as the Terminal Electrophiles

Smith, 2011



The majority of these Brook rearrangement ARC reactions involve formation of C(sp^3) anions, but in 2008, Smith and Wuest developed a [1,4]-Brook rearrangement protocol to generate C(sp^2) anions from aryl silanes, **A1.12** for use in electrophilic aromatic substitution reactions (Scheme 1.10a).[13] This chemistry has enabled a new area of development for the Smith group, as many advancements in this motif have been made in the past decade (*vide infra*). A similar but complementary approach was developed by Smith and Maio in 2011 (Scheme 1.10b).[14] Rather

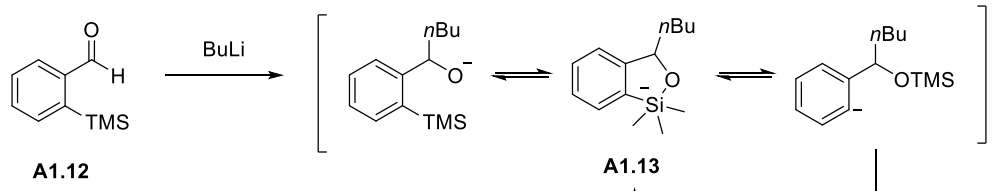
than generating an alkoxide via nucleophilic addition onto a carbonyl, the silicone "ate" intermediate of the Brook rearrangement, **A1.13** was generated via nucleophilic addition onto a 1-oxa-2-silacyclopentane, **A1.14**. The silicon "ate" complex was able to be trapped with electrophiles constituting a three-component coupling, and subsequently the trimethylsilyl group was easily removed to reveal functionalized benzyl alcohols.

Phenyl rings are not the only aromatic compounds that can be functionalized in this way. In 2009, Smith and Tong demonstrated that the same protocol could be used to functionalize furans and thiophenes (Scheme 1.10c).[15] These reactions again tolerated a variety of alkyl and aryl lithium nucleophiles. Furthermore, the authors demonstrated that when lithium ester enolates were utilized as the nucleophiles with thiophenes, the carbanion resulting from the Brook rearrangement could cyclize onto the ester to form bicyclic thiophenes **A1.15**.

In addition to electrophilic aromatic substitution, the aryl intermediates generated by O to C(sp^2) anion relay could also be utilized for palladium-catalyzed cross coupling reactions with a variety of allyl, aryl and benzyl halide electrophiles, as shown by Smith in 2010 (Scheme 1.10d).[16] In this work, six new linchpins were introduced and investigated, including both aldehyde and epoxide linchpins with β- or γ-electrophilic sites, which could be useful for downstream synthetic applications. This tactic of combining anion relay with palladium-catalyzed cross coupling greatly increases the scope of reactions for which type II ARC linchpins could potentially be used.

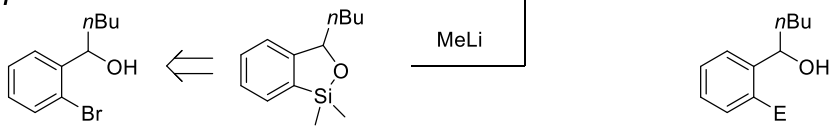
Scheme 1.10 – O-C(sp^2) Anion Relay

A) *Wuest, 2008*



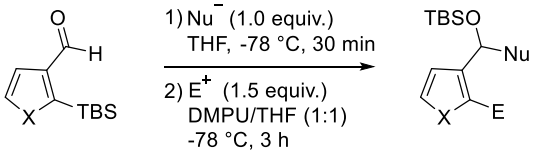
A1.12 **A1.13**

B) *Maio, 2011*

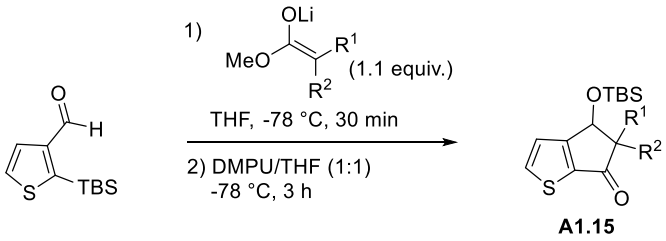


A1.14

C) *Smith, 2009*

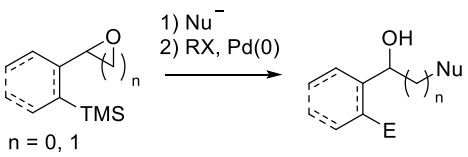


X = O, S



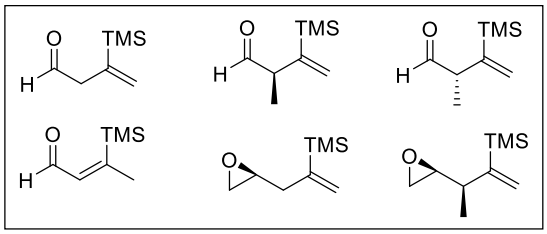
A1.15

D) *Smith, 2009*

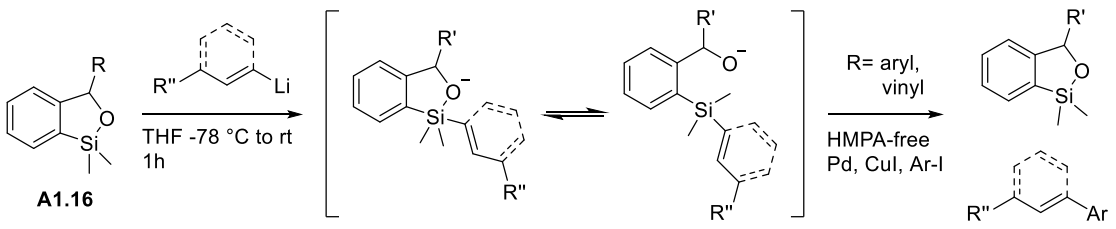


n = 0, 1

Linchpins



E) *Smith, 2012*



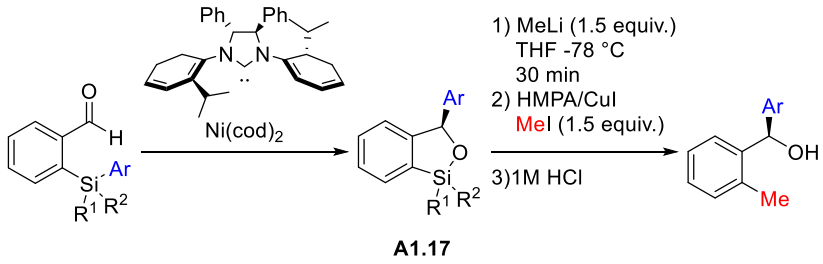
Beyond being used as reagents in coupling reactions, these aryl silane linchpins can be utilized as aryl transfer reagents. In 2012, Smith combined this same ARC tactic with Takeda and Hiyama cross coupling processes to lead to biaryl and allyl arene products, respectively (Scheme 1.10e).[17] In this case, the linchpin, **A1.16** was utilized as a stoichiometric aryl transfer reagent rather than a substrate. Continued efforts to develop a catalytic-in-silicon version are underway. If successful, these efforts could lead to a new form of transition metal-free catalytic cross-coupling reactions, greatly increasing the utility of anion relay linchpins.

Ogoshi *et al*. developed a related enantio- and diastereoselective synthesis of benzosiloles (**A1.17**) via a nickel/NHC-catalyzed intramolecular aryl transfer (Scheme 1.11).[18] They further showed enantiospecific functionalization of these benzosiloles via anion relay, constituting an asymmetric formal [1,4]-Brook rearrangement anion relay protocol.

While the above methods effectively demonstrate the migration of anionic charge by four bonds, even longer distances can be achieved by utilizing sequential Brook rearrangements. In 2012, Smith *et al*. developed a "long range" type II ARC tactic that involved two sequential [1,4]-Brook rearrangements prior to electrophile coupling, effectively migrating anionic charge five bonds away (Scheme 1.12).[19] The authors demonstrated the utility of this method for both nucleophilic alkylation and palladium-catalyzed cross coupling reactions.

Scheme 1.11 – Ni-Catalyzed Aryl Transfer/Anion Relay

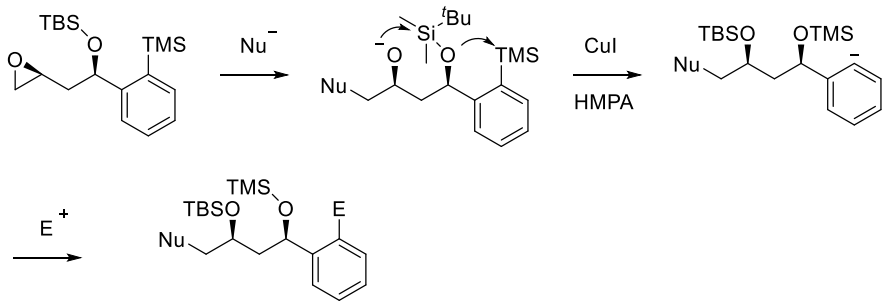
Ogoshi, 2015



A1.17

Scheme 1.12 – Long-Range O-C(sp^2) ARC

Smith, 2012



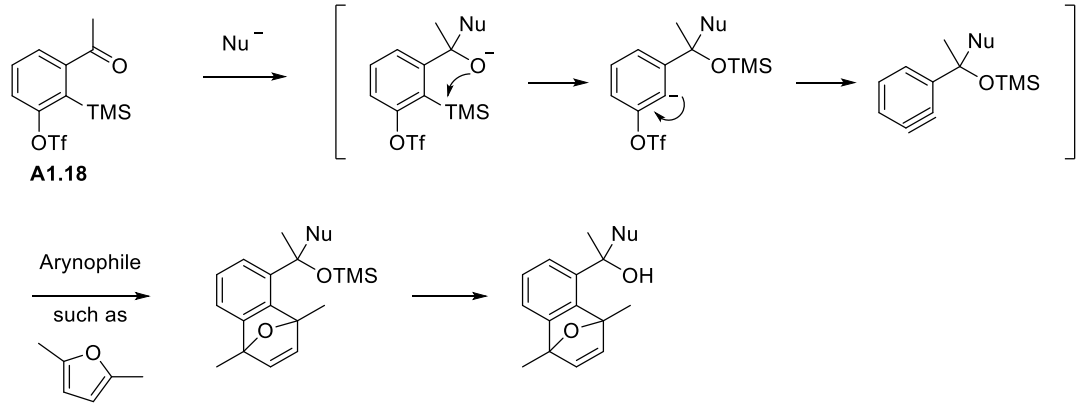
Additionally, this type of [1,4]-C(sp^2)-O Brook rearrangement ARC has been extended to reactions beyond electrophilic aromatic substitution. In 2011, Kim and Smith developed a linchpin (**A1.18**) that formed benzyne intermediates through anion relay. These linchpins were activated with Grignard or alkyllithium nucleophiles and were utilized in cyclization reactions with various arynophiles such as furans and azides (Scheme 1.13).[20]

In 2012, the Lin group developed a (bis)silyl enal as a useful linchpin (**A1.19**) for [1,2]-addition-initiated [1,4]-Brook rearrangement anion relay (Scheme 1.14a).[21] A variety of electrophiles were tolerated, such as alkyl aryl and benzyl halides, disulfides, aldehydes and

ketones. Alkyl, vinyl, aryl and propargyl lithium reagents were used as nucleophiles giving 14 examples with yields ranging between 62-81%. The reaction is γ-selective with respect to regioselectivity and was *E* selective with respect to the olefin geometry in all cases, often giving 100 % *E* selectivity.

Scheme 1.13 – O-C(sp^2) Anion Relay Linchpins with Benzyne Reactivity

Smith, 2011

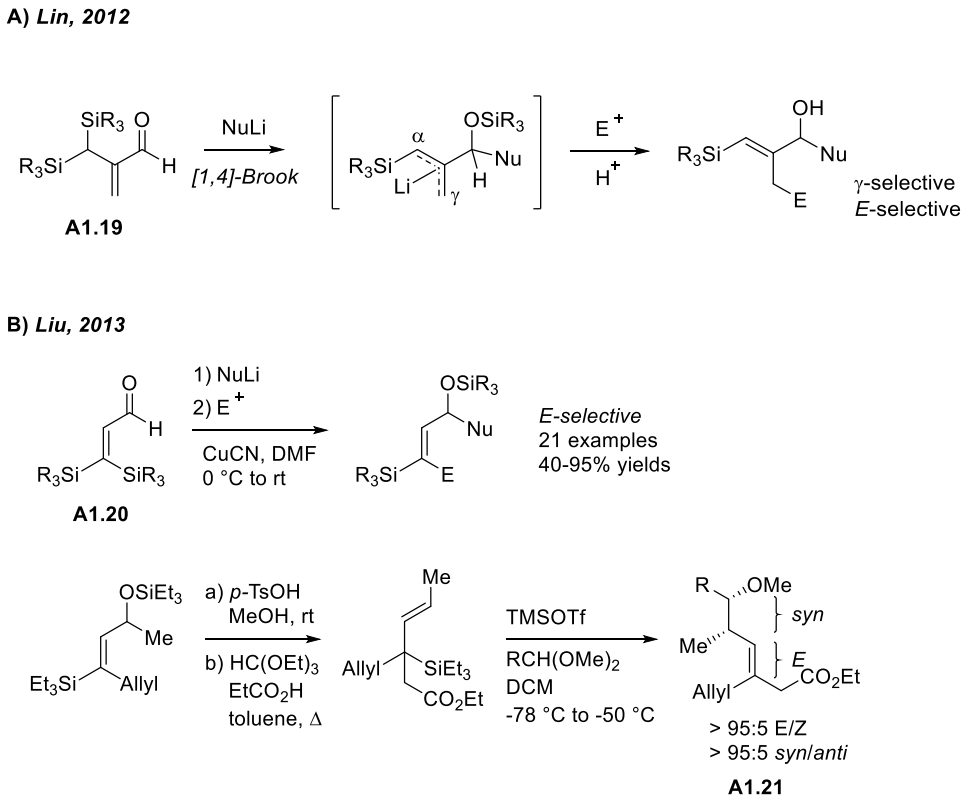


In 2015 Laali and co-workers performed DFT calculations on activation energies of the Brook rearrangement and subsequent nucleophilic addition reactions of these bissilylated enals (**A1.19**) (Scheme 1.14a).[22] They found the O-attack on silicon was essentially barrierless, and that the regio- and stereoselectivity was attributable to the steric environment about the bulky silyl group.

A similar reaction that utilized a complementary substrate class was developed by Liu *et al.* in 2013. Geminally γ-bissillyated enals (**A1.20**) were treated with a nucleophile followed by an electrophile in the presence of CuCN (Scheme 1.14b).[23] The authors demonstrated 21 examples with yields ranging from 40-95% and showed that the products could be further functionalized to

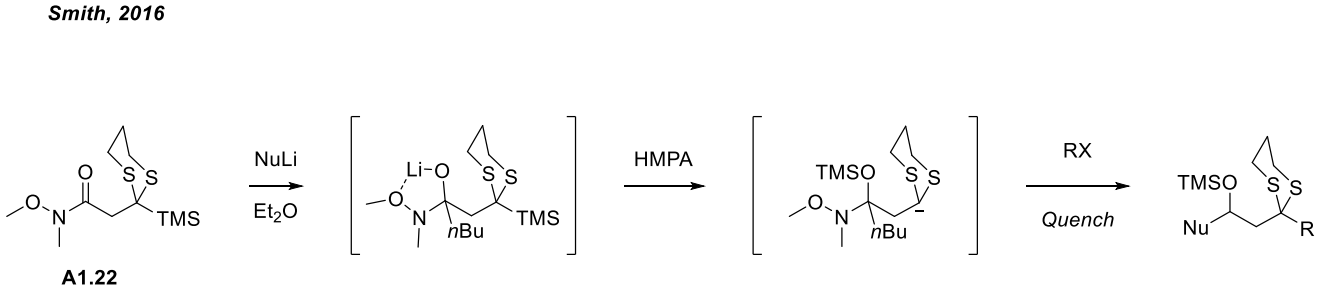
homoallylic methyl ethers (**A1.21**), which were *E*-selective with respect to the olefin geometry and *syn*-selective with respect to the nucleophilic addition.

Scheme 1.14 – Anion Relay with Bis(silyl)enals



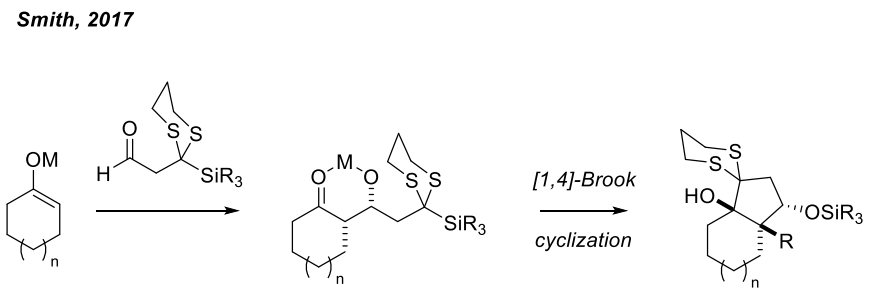
In 2016, the Smith group developed a class of synthetically useful Weinreb amide ARC linchpins (**A1.22**) that were utilized in three component coupling protocols (Scheme 1.15).[24] These linchpins were useful for the synthesis of [1,3]-diketones and decreased the need for protecting group and oxidation state manipulations, allowing for a more direct synthetic route than with previous linchpins. Furthermore, they developed a one-pot protocol for the synthesis of di- and tetrahydropyrans and spiroketals using the Weinreb amide linchpins.

Scheme 1.15 – Weinreb Amide Linchpins for Type II ARC



Finally, in 2017, the Smith group developed a formal [3+2]-cycloaddition tactic employing an anion relay aldol-Brook rearrangement-nucleophilic cyclization cascade (Scheme 1.16).[25] They provided 20 examples with yields ranging from 35-87% and excellent diastereoselectivities.

Scheme 1.16 – Aldol-Brook-Cyclization Cascade

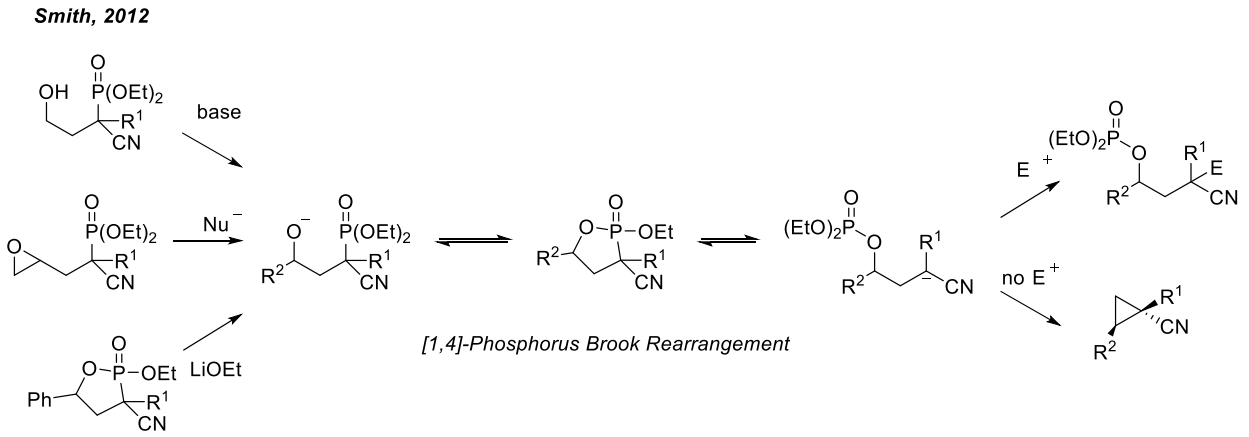


1.2.2.2 – [1,4]-Phosphorus Brook Rearrangement

While the majority of [1,4]-rearrangements in anion relay chemistry are Brook rearrangements involving silicon migration from carbon to oxygen, phosphorus Brook rearrangements are also known and have been applied to ARC in the same way. For example, in 2012, Smith and co-workers demonstrated the utility of phosphonate groups for anion relay via a [1,4]-phosphorus Brook rearrangement, thus expanding the scope of through-space anion relay beyond alkyl silanes (Scheme 1.17).[26] They demonstrated this [1,4]-phosphorus Brook

rearrangement anion relay with a variety of linchpins and utilized the intermediate nucleophile either for nucleophilic addition reactions or intramolecular nucleophilic cyclizations to form cyclopropanes.

Scheme 1.17 – Phosphorus Brook Rearrangement

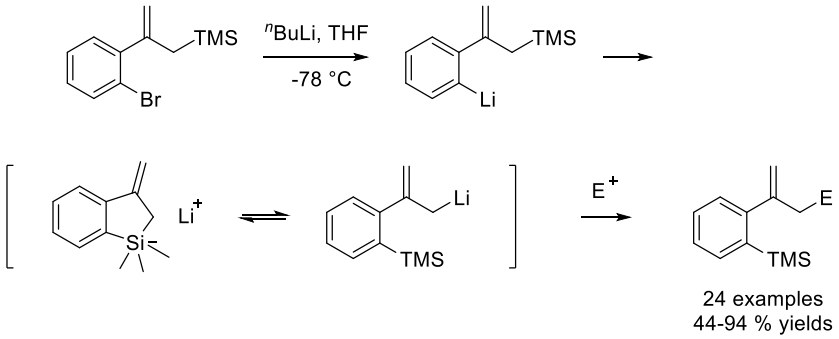


1.2.2.3 – [1,4]-C to C Anion Silyl Migration

While most examples of silyl migrations in anion relay occur between oxygen and carbon, in 2011, the Harmata group reported a two-component coupling involving a carbon-to-carbon [1,4]-silicon shift to generate a nucleophilic allyllithium species that were trapped with an electrophile (Scheme 1.18).[27] Their computational studies indicated that, although the pK_as of benzene and propene are similar, the reaction is exothermic.

Scheme 1.18 – [1,4]-C(sp^3) to C(sp^2) Anion Relay

Harmata, 2011



1.2.3 – Through-Space [1,5]-Anion Relay

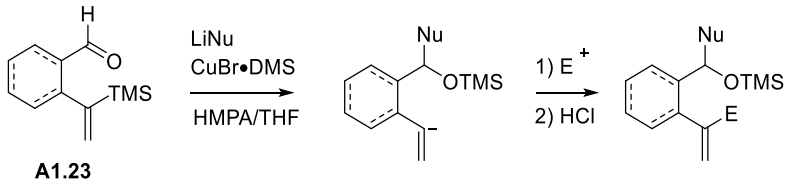
1.2.3.1 – [1,5]-Brook Rearrangements

In 2017, the Smith group demonstrated the first application of a [1,5]-Brook rearrangement in type II anion relay (Scheme 1.19).[28] These reactions utilized cyclic linchpins (**A1.23**) that forced the migrating silyl group within close proximity to the initially generated alkoxide anion. Both aryl and alkyl linchpins were competent for the reaction. DFT calculations were performed on the reaction with different substrates and reagents, compared with related [1,4]-Brook rearrangements. They found that, for [1,5]-Brook rearrangements vs. [1,4]-Brook rearrangements, the change in energy between the lithium alkoxide species and the copper coordinated intermediate (see ref. 28) is comparable, but the main difference is in a conformational change in the tether. There is a 15° conformational change in dihedral angle between the copper-coordinated intermediate and the transition state required for bond Cu-C bond formation in [1,5]-Brook rearrangements. This change in angle amounts to an energy difference of about 4 kcal/mol between the two transition states, which explains why [1,5]-Brook rearrangements are more challenging. However, through

the use of *cis*-cyclohexyl or phenyl linchpins, the activation energy of the [1,5]-Brook rearrangement is reduced by imposing conformational constraints on the tether.

Scheme 1.19 – [1,5]-Brook Rearrangement ARC

Smith, 2017

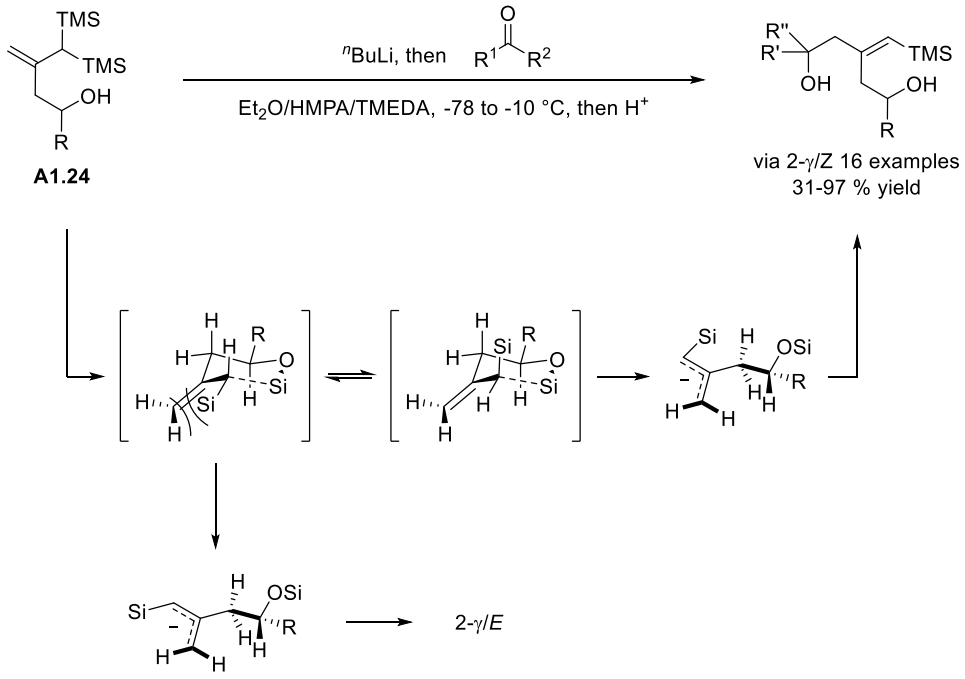


A1.23

In 2013, the Yin group reported a 2-component coupling featuring a [1,5]-Brook rearrangement following deprotonation of a bis(silyl)ene alcohol, **A1.24** (Scheme 1.20).[29] The reaction was compatible with a variety of aldehyde electrophiles, as well as ketones and aryl bromides. Yields were acceptable, the majority being above 50%, with bromobenzene giving a low yield of 31%. The reaction was generally regioselective, giving ≥ 95:5 selectivity in favor of γ-addition, except in the case of the aryl bromide, which gave 50:50 regioselectivity. Interestingly, the reaction was selective for *Z*-olefin geometry of the intermediate silyl ether giving a ratio of ≥ 95:5 in all cases. This stereoselectivity is based on steric influence of the bulky silyl group, as shown in Scheme 1.20.

Scheme 1.20 – [1,5]-Brook Rearrangement ARC with Bis(Silyl) Ene Alcohols

Yin, 2013

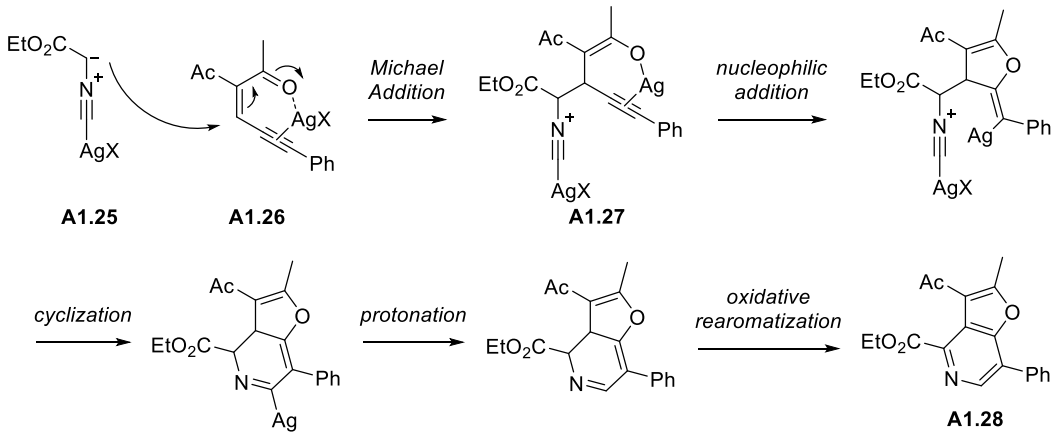


1.2.3.2 – Silver-Mediated [1,5]-Anion Relay

In 2018, Xu *et al.* utilized a combination of through-bond and type II through-space anion relay to effect a formal [3,3]-annulation between an active methylene isocyanide (**A1.25**) and ene-yne-ketone **A1.26** (Scheme 1.21).[30] The reaction was initiated by a silver-mediated Michael addition of the isocyanide onto the eneyne-containing ketone to generate a silver-alkoxide species, **A1.27**. The alkoxide then cyclized onto the propargyl moiety, constituting type II through-space ARC. The resulting vinyl silver species then underwent a second cyclization, followed by protonation and rearomatization to yield biologically relevant furo-[3,2-*c*]-pyridines, **A1.28**.

Scheme 1.21 – Silver-Mediated [1,5]-Anion Relay

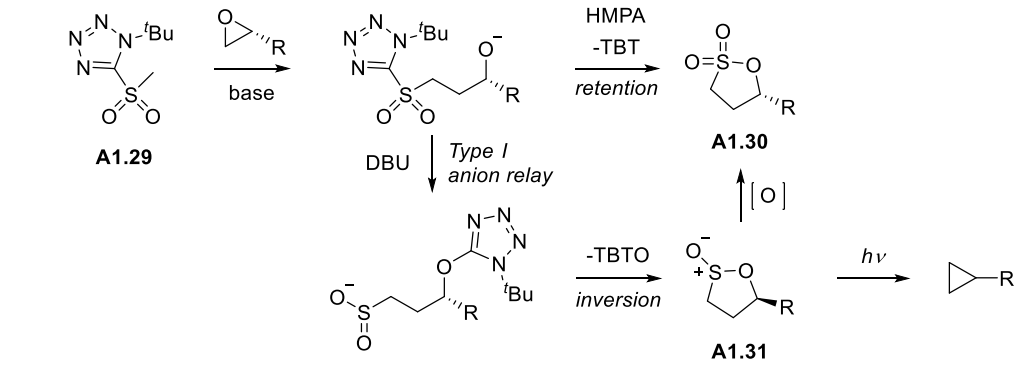
Xu, 2018



1.2.3.3 [1,5]-Anion Relay via Julia-Kociensky Reaction

Another anionic group transfer reaction that has been utilized in an anion-relay contest is the Julia-Kociensky reaction. In 2015, Bray *et al*. reported an interesting anion relay approach to sultines, using a homologous Julia-Kociensky reaction with epoxides (Scheme 1.22).[31] Under the normal course of the reaction, the Julia-Kociensky sulfone (**A1.29**) reacted with epoxides to form γ-alkoxy sulfones, which simply cyclized with loss of tert-butyl tetrazole (TBT) to form cyclic sulfones, **A1.30**. However, in the absence of HMDS and presence of DBU, the γ-alkoxy sulfones underwent anion relay to generate sulfinates, which underwent intramolecular cyclization to form sultines, **A1.31**. The sultines can subsequently be oxidized to sulfones or undergo photochemical ring contraction to form cyclopropanes.

Scheme 1.22 – [1,5]-Anion Relay via Julia-Kociensky Reaction



§ 1.3 Recent Applications of ARC to Total Synthesis

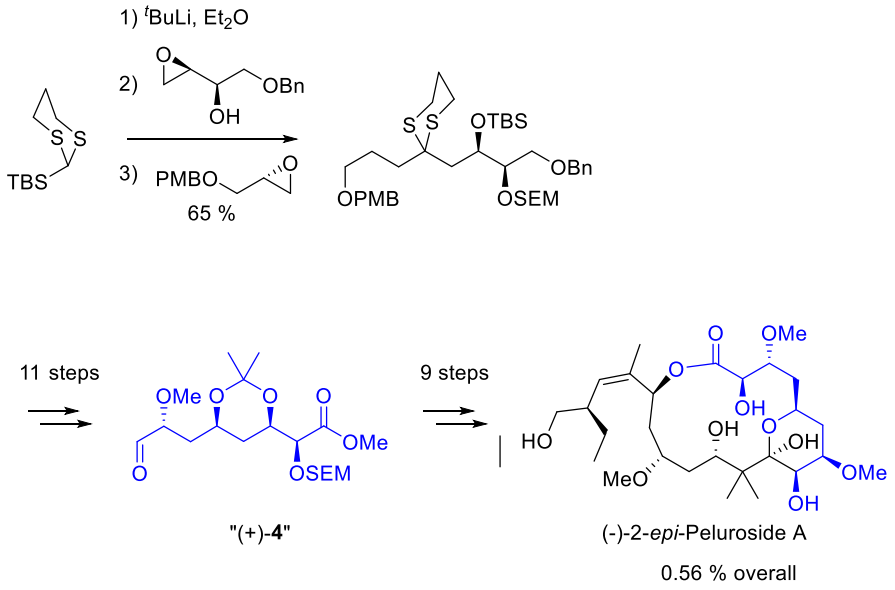
1.3.1 – Type I [1,4]-Brook Rearrangements

Type I anion relay has seen several applications to total synthesis in the last decade; not surprisingly most have been Brook rearrangements. Here, we will examine the applications of type I ARC [1,4]-Brook rearrangement protocols to total synthesis since 2008.

(-)-2-*epi*-Peluroside is a complex natural product isolated from the sea sponge *Mycale*. In 2008, the Smith group reported the total synthesis of (-)-2-*epi*-peluroside A in 25 steps (LLS) with an overall yield of 0.56% (Scheme 1.23).[32] The key step of this synthesis involved the type I anion relay three-component coupling of a dithiane linchpin and two enantiopure epoxide electrophiles in a stereospecific manner. The resulting intermediate was carried forward for the synthesis of the title compound in 20 additional steps.

Scheme 1.23 – Smith's Total Synthesis of (-)-2-*epi*-Peluroside A

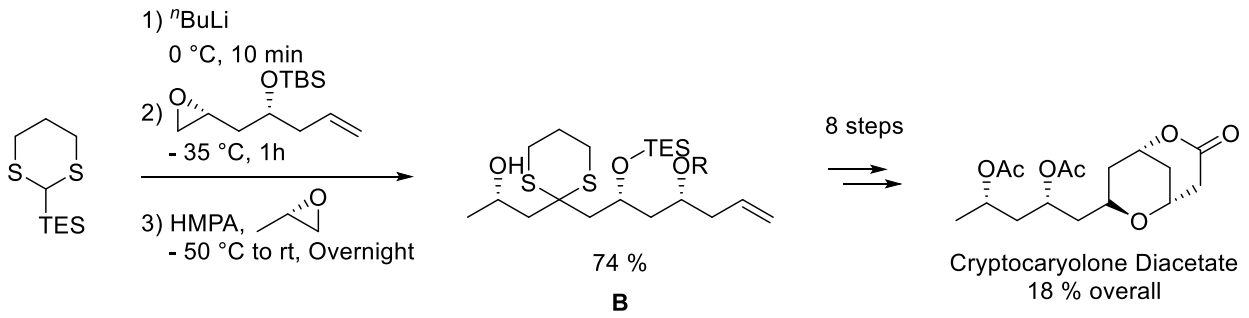
Smith, 2008



The *Cryptocarya* family of natural products come from the plant *Cryptocarya latifolia* and have biological activities and a variety of medicinal applications.[33] In 2009, the She group reported a unified path to the asymmetric total synthesis of three natural products of the *Cryptocarya* family including cryptocaryolone diacetate utilizing a three-component anion relay protocol in the first step (Scheme 1.24).[33] Starting from chiral starting materials, the Type I anion relay protocol allowed the stereospecific formation of material **B** in 74 % yield, which was carried forward to their target molecules in 6-8 additional steps.

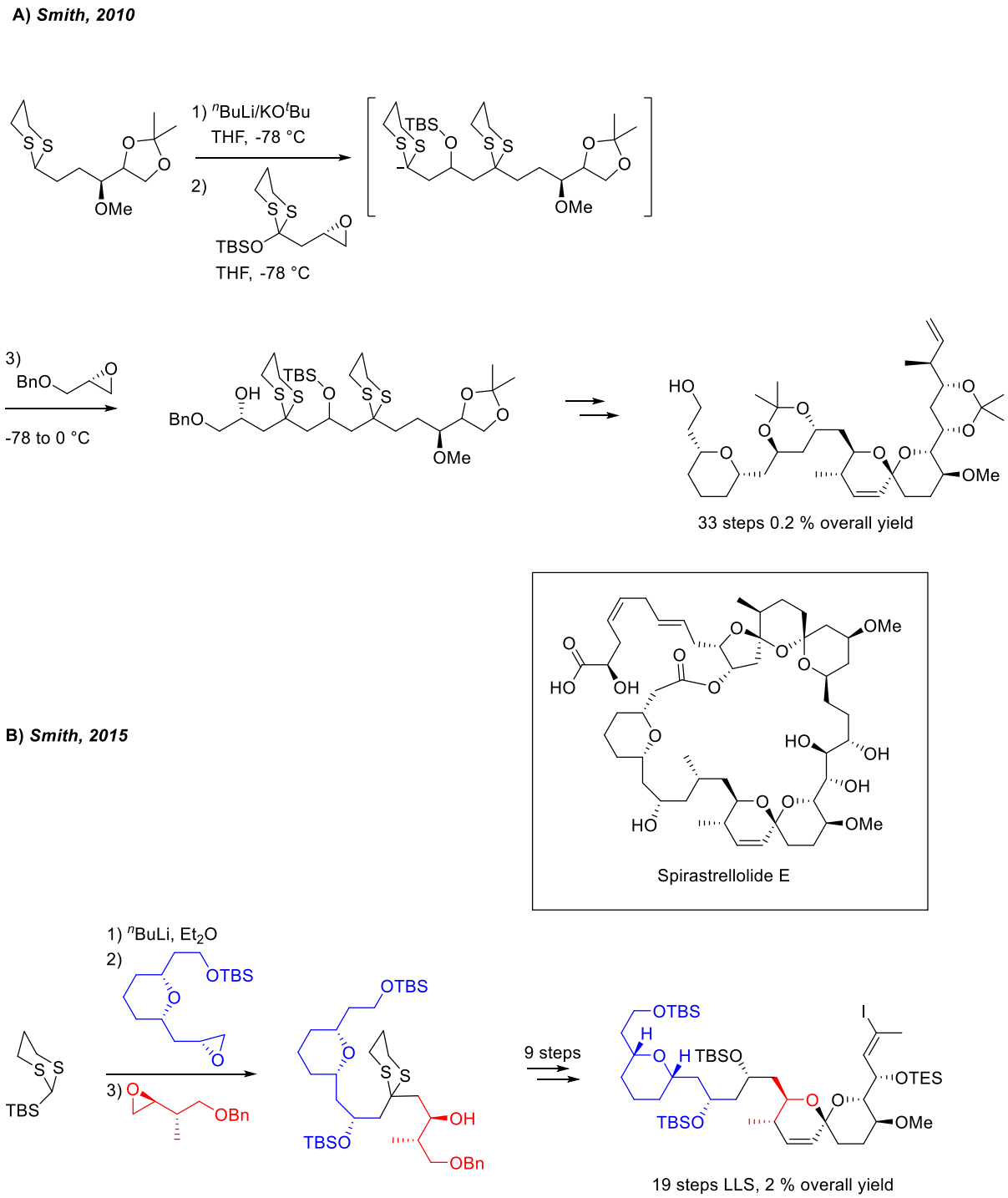
Scheme 1.24 – She's Total Synthesis of Cryptocaryolone Diacetate

She, 2009



Spirastrellolide is a complex natural product, which is a potent inhibitor of phosphatase 2A. In 2015, the Smith group published their work on synthesis of Spirastrellolide (Scheme 1.25).[34,35] After developing a lengthy synthesis of the southern hemisphere utilizing type II anion relay (33 steps LLS, Scheme 1.25a),[34] they used type I anion relay to improve their route by considerably reducing the step count and improving the yield (19 steps LLS, 2 % overall yield, Scheme 1.25b).[35]

Scheme 1.25 – Synthesis of Two Advanced Fragments of Spirastrellolide

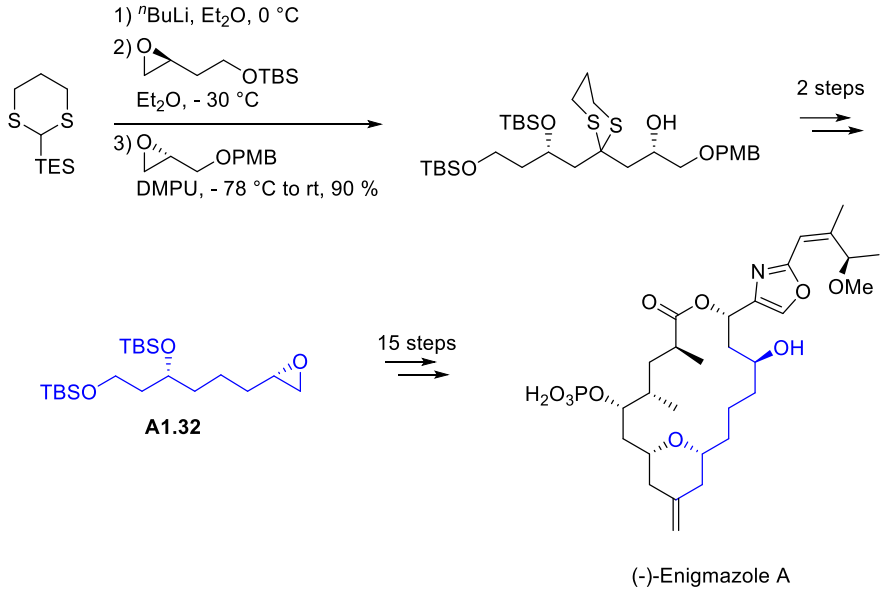


In 2015, the Smith group synthesized anti-tumor agent (-)-enigmazole A in 4.4 % overall yield with a longest linear sequence of 22 steps from commercially available chiral starting

materials (Scheme 1.26).[36] One of the key steps of this synthesis utilized a type I ARC tactic to stereospecifically synthesize chiral epoxide **A1.32**. This intermediate was successfully carried forward in the synthesis of the target in an additional 15 steps including a late-stage Petassis-Ferrier union/rearrangement protocol. They then published a more detailed account of this same synthesis three years later.[36b]

Scheme 1.26 – Smith's Total Syntheses of (-)-Enigmazole A

Smith, 2015



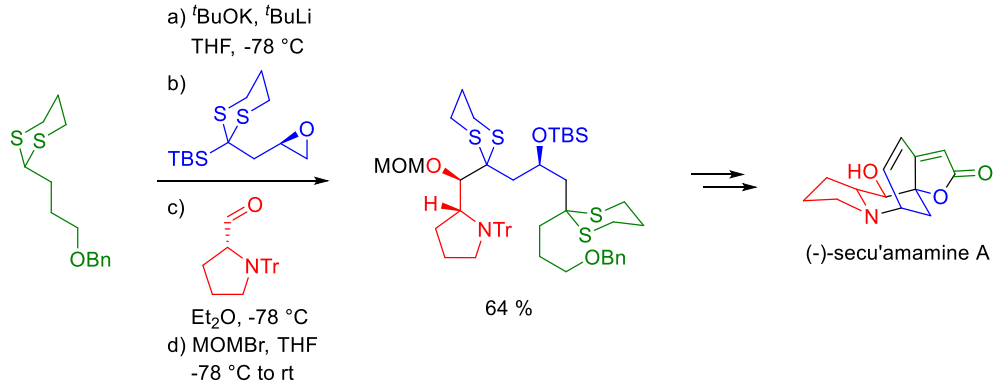
1.3.2 – Type II [1,4]-Brook Rearrangements

Type II anion relay has also been applied to a number of total syntheses in the last decade. Similar to type I anion relay, the application of type II anion relay in total synthesis has largely involved Brook rearrangements. Here, examples of type II [1,4]-Brook rearrangement ARC protocols applied to total synthesis in the last decade are presented.

Sec'uamamine A is a member of the *Securinega* alkaloids, a class of biologically active natural products isolated from the plants *Securinga* and *Phyllanthus*. In 2015, Smith *et al*. reported a formal synthesis of (-)-secu'amamine A, utilizing a type II anion relay protocol to couple four components in a single pot, generating the full linear carbon and nitrogen skeleton as the first and key step of the synthesis (Scheme1.27).[37] The reaction was stereospecific and led to the product in 64 % yield, which was then carried forward to complete the tetracyclic core of (-)-secu'amamine A in a further 5 steps.

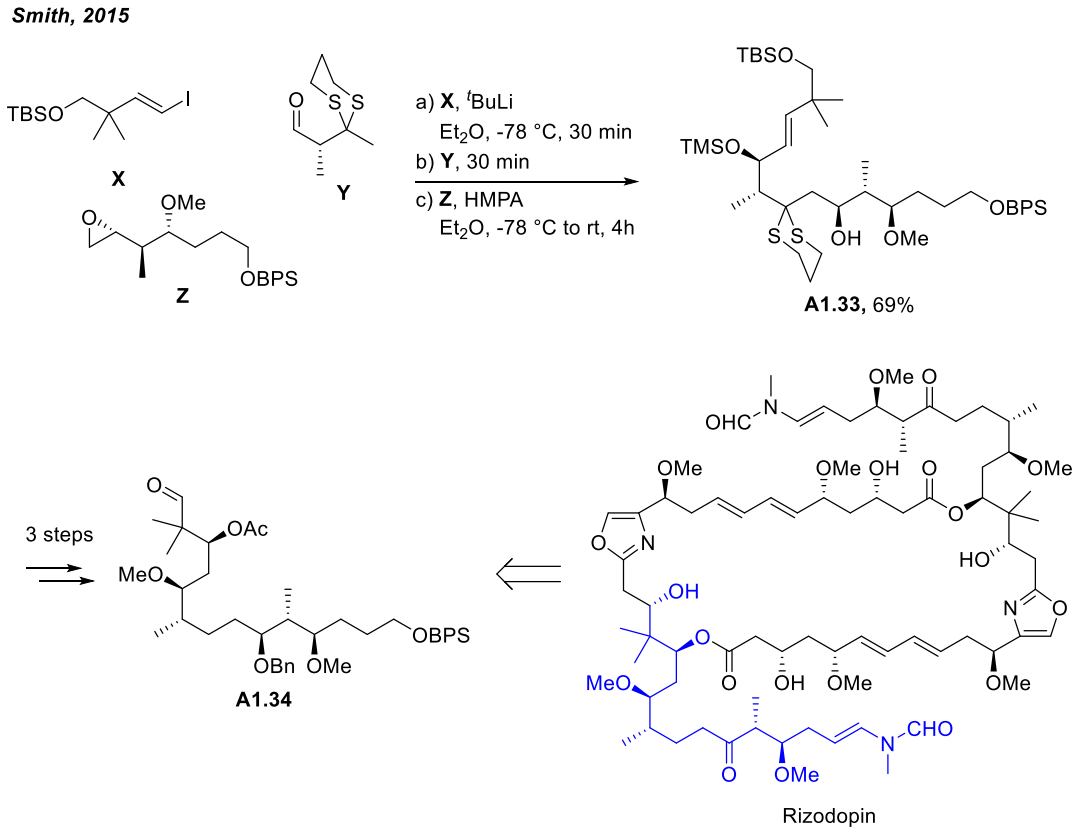
Scheme 1.27 – Total Synthesis of (-)-Secu'amamine A

Smith, 2015



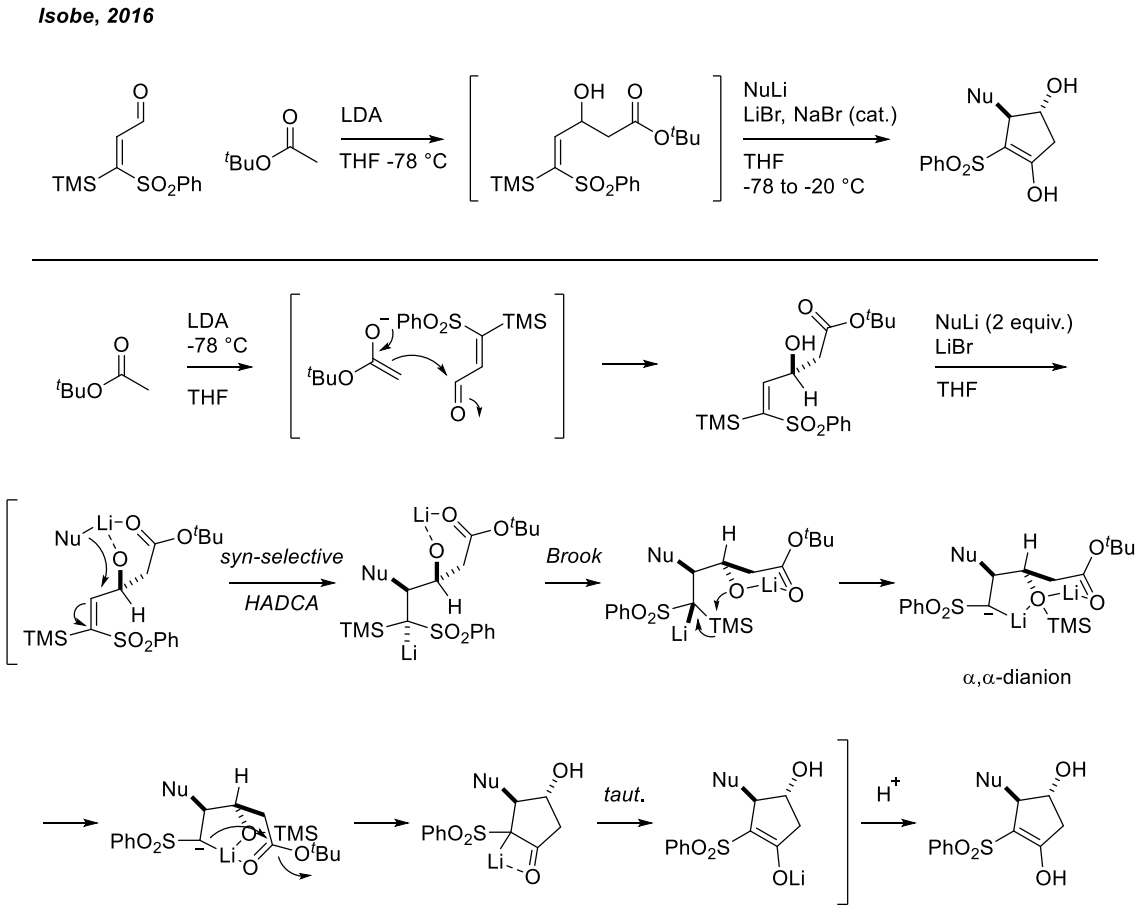
In 2015, Smith and co-workers constructed and advanced C16-C29 fragment of the actin-binding macrolide rizodopin (Scheme 1.28).[38] After somewhat arduous preparation of the starting materials for the ARC reaction, they elegantly coupled the fragments together in a single flask yielding the intermediate **A1.33** in 69 % yield. This intermediate was carried forward to their advanced fragment **A1.34** in a mere 3 additional steps.

Scheme 1.28 – Synthesis of C16-C29 Fragment of Rizodopin



In 2016 Isobe, *et al.* described a one-pot anion relay protocol to diastereoselectively generate substituted cyclopentanones (Scheme 1.29).[39] This protocol incorporated *syn*-selective heteroatom-directed conjugate addition (HADCA), and intramolecular anion relay cyclization via Brook rearrangement followed by intramolecular [1,2]-addition in a single pot. In the same paper, they utilized an asymmetric Reformatsky reaction to generate chiral vinyl sulfones, which stereoselectively underwent the anion relay cyclization and was carried forward for the asymmetric synthesis of prostaglandin E2 methyl ester.

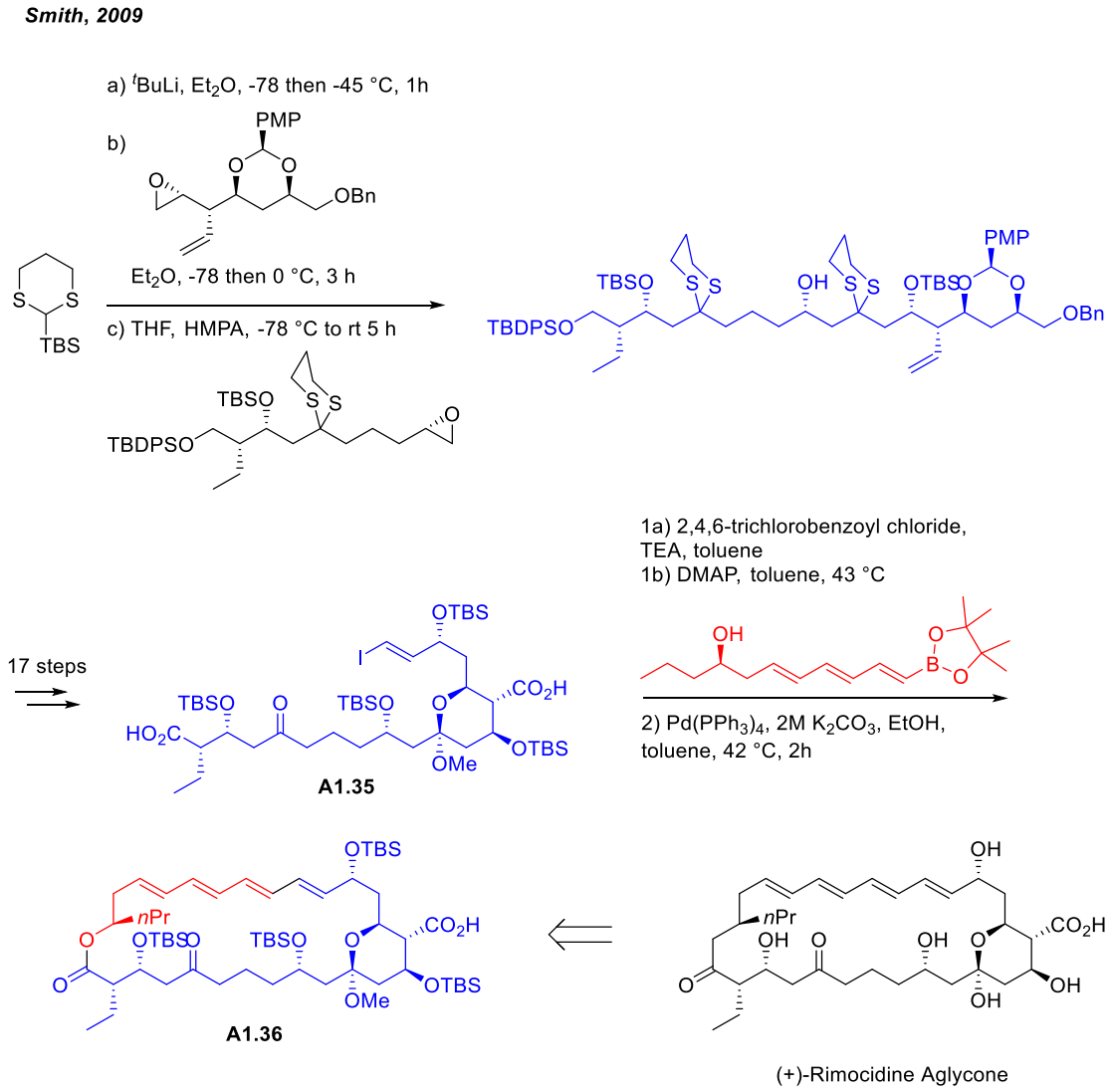
Scheme 1.29 – Synthesis of Prostaglandins Using Type II ARC



1.3.3 – Total Syntheses Employing both Type I and Type II [1,4]-Brook Rearrangements

(+)-Rimocidin aglycone is a member of a family of antifungals isolated from *Steptomyces rimosus* that are composed of polyene macrocycles. In 2009, Smith and Orbin undertook the synthesis of this complex molecule featuring an all-*trans* tetraene and 9 stereogenic centers (Scheme 1.30).[40] Although they did not complete the synthesis in this publication, they did complete the macrocyclic skeleton, including all 9 stereogenic centers with the correct configurations to form a molecule that is only a number of protecting group manipulations away from the target molecule. Their advanced intermediate **A1.35** was reached in 31 steps (LLS), and was carried forward to **A1.36** in 29% yield over two steps.

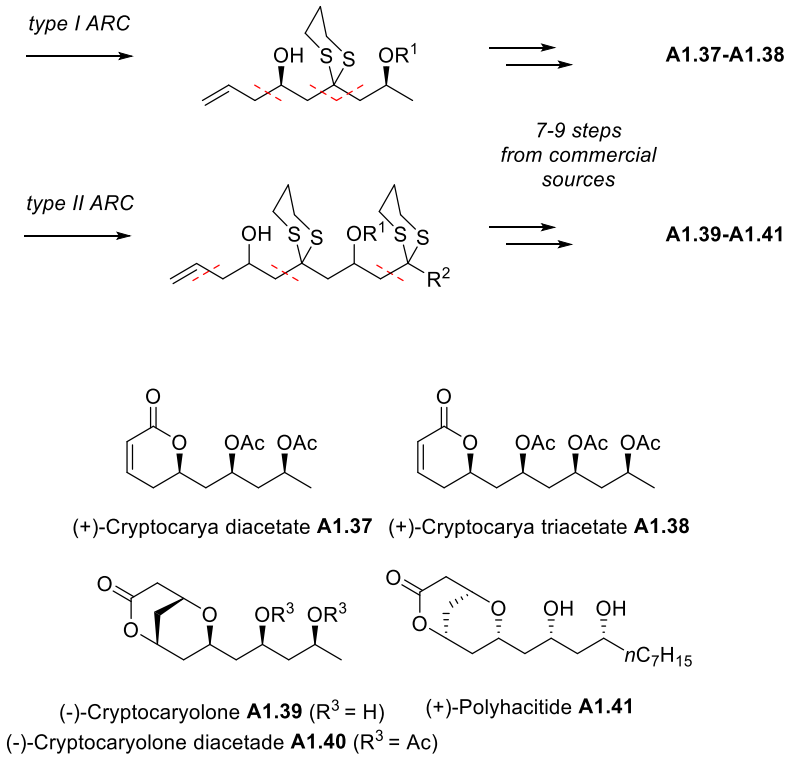
Scheme 1.30 – Synthesis of the Aglycone Skeleton



In 2013, Smith demonstrated the use of Type I and Type II ARC protocols for the synthesis of 5 members of the *Cryptocarya* class of natural products (**A1.37-A1.41**, Scheme 1.31).[41] The syntheses were relatively short, being only 5-7 steps from commercially available starting materials.

Scheme 1.31 – Type I and II Synthesis of Several Members of the Cryptocarya Family

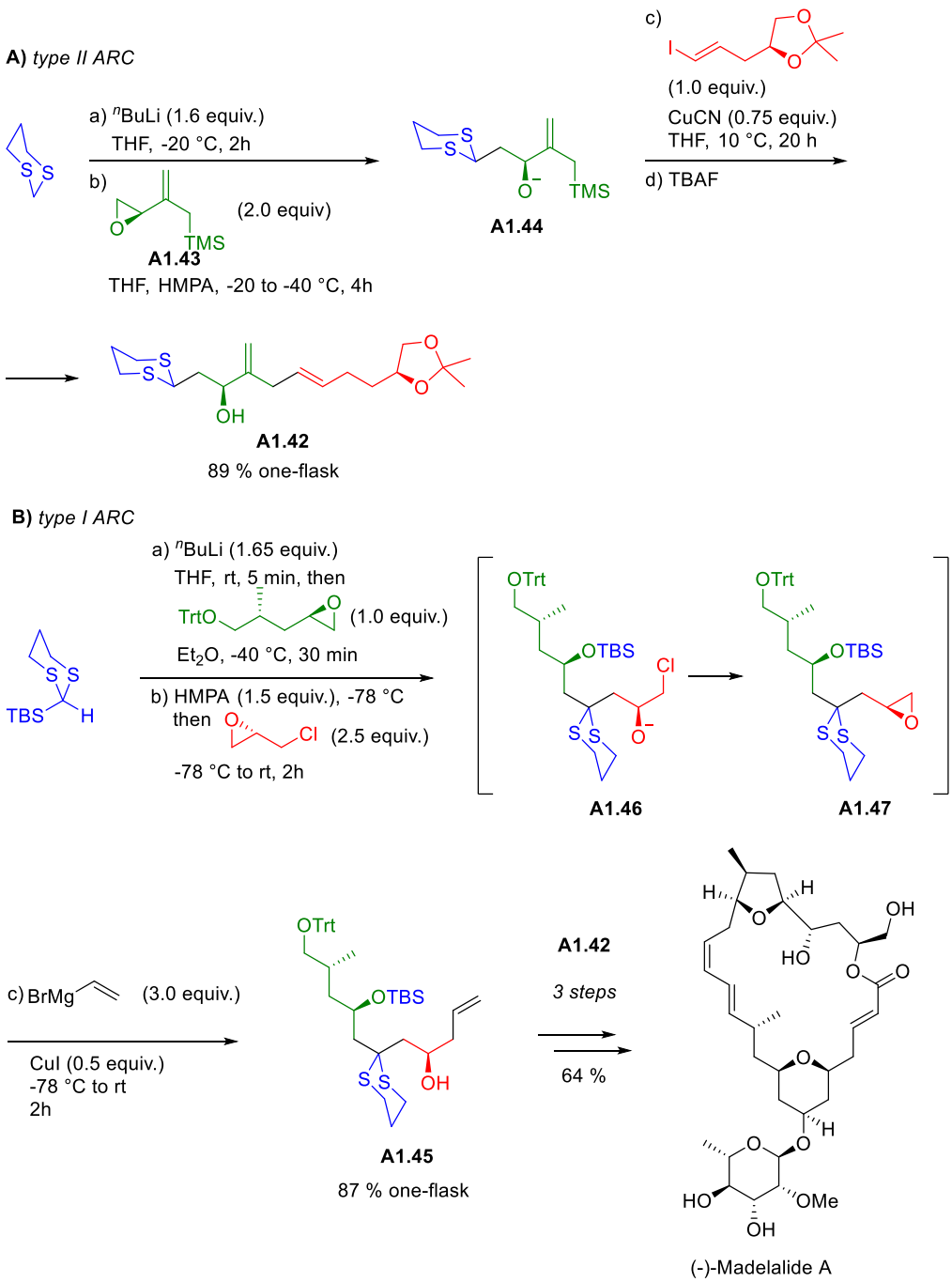
Smith, 2013



The combination of types I and II ARC also proved successful in the total synthesis of (-) madelalide, a cytotoxic marine macrolide (Scheme 1.32).[42] Type II ARC was utilized in the construction of fragment **A1.42** (Scheme 1.32a), wherein dithiane was deprotonated and nucleophilically added to the vinyl epoxide species **A1.43**, leading to alkoxide species **A1.44**. A vinyl iodide was added to this intermediate to complete the 3-component coupling protocol, giving intermediate **A1.42**. Intermediate **A1.45** was constructed utilizing a type I ARC 3-component coupling protocol to lead to deprotonated chlorohydrin species **A1.46** (Scheme 1.32b). Spontaneous ring closure followed to provide epoxide **A1.47**, to which vinyl Grignard was added to give intermediate **A1.45**. Finally, **A1.42** and **A1.45** were coupled and elaborated over to give the target molecule (-)-Madelalide A in 64% yield over three steps.

Scheme 1.32 – Total Synthesis of (-)-Madelalide A Using both Types of Through-Space ARC

Smith, 2016



§ 1.4 Conclusion

Anion Relay Chemistry is a powerful tool for the rapid development of molecular complexity in an operationally simple manner. The most common types of anion relay are through-bond anion relay via conjugate addition and [1,2]-Brook rearrangements. Here, through-space anion relay reactions exhibiting a negative charge migration over three or more bonds and their applications to total synthesis have been reviewed. By far, the most common motif for such reactions are [1,4]-Brook rearrangements, but there are some examples of silyl migration from atoms other than oxygen to carbon, and some examples of non-silyl migration being utilized for anion relay. Still, there seems to be a need for further development of the concept of anion relay beyond silyl migrations, which would allow chemists to capitalize on the rapid building of complexity possible with anion relay chemistry, without the need to synthesize alkylsilanes.

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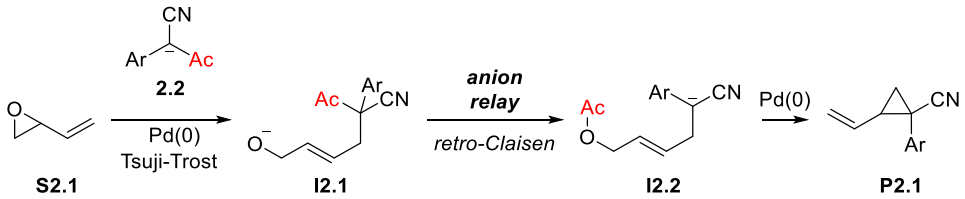
Chapter 2: Synthesis of Vinylcyclopropanes via Type I Anion Relay

§2.1 Introduction

As shown in Chapter 1, anion relay chemistry is an effective way to build molecular complexity in three-component coupling reactions. The majority of applications in anion relay involve Brook rearrangements, which necessitate the synthesis of alkyl silanes. Furthermore, examples of non-silyl migration anion relay are rare, so there is need for further development of anion relay beyond silyl migrations. Retro-Claisen condensation reactions provide an attractive potential alternative to Brook rearrangement chemistry, as they would involve acyl migration rather than silyl migration, obviating the need to synthesize alkyl silanes. Furthermore, since retro-Claisen reactions involve the nucleophilic substitution of a carbonyl with an alkoxide generating a carbanionic species, they can be utilized for further nucleophilic functionalization.

Described in this chapter is a type I anion relay protocol in which an allyl alcohol, formed from a Tsuji-Trost allylation between a vinyl epoxide and an acyl containing nucleophile, subsequently undergoes a TBD-mediated retro-Claisen condensation to generate a carbanion and an allyl acetate. This reaction is followed by intramolecular palladium-catalyzed allylation between the nascent carbanion and allyl acetate forming a vinyl cyclopropane. Hence, in one pot, Tsuji-Trost allylation, retro-Claisen activation and Tsuji-Trost cyclopropanation are combined to access synthetically useful vinyl cyclopropanes from vinyl epoxides using a mild and operationally simple procedure (Scheme 2.1). Where most examples of through-space anion relay chemistry involve [1,2]- or [1,4]-charge migration, this reaction utilizes TBD as an acyl transfer reagent to accomplish [1,6]-anion relay. Finally, this protocol provides an important novel complement to the ubiquitous Brook rearrangement anion relay tactics, in that it provides a way to achieve anion relay without the need to form alkyl silanes or phosphonates, but rather utilizes easily synthesized ketone linchpins.

Scheme 2.1 – Proposed Anion Relay Cyclopropanation

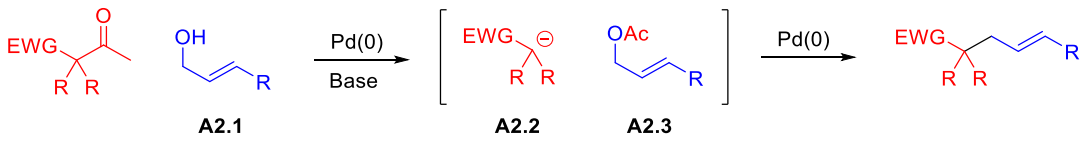


§2.2 Background

2.2.1 – Retro-Claisen Activation of Allyl Alcohols

The key enabling aspect of this chemistry is the retro-Claisen activation of the allylic alkoxide formed by the initial Tsuji-Trost reaction. Retro-Claisen activation of allyl alcohols (**A2.1**) allows the *in situ* generation of nucleophilic carbanions (**A2.2**) and simultaneous generation of an allyl acetate pro-electrophile (**A2.3**) for palladium-catalyzed cross-coupling reactions (Scheme 2.2).[43,44,45,46] The work described herein is the intramolecular version of chemistry that was coined as deacylative allylation (DaA), by Alex Grenning in 2011.[43a,b]

Scheme 2.2 – Retro-Claisen Activation Concept

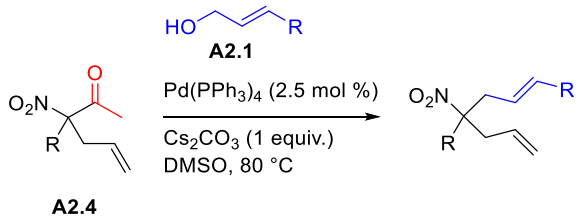


The publication by Grenning described the deacylative allylation of acyl-containing nitroalkanes (**A2.4**) with allyl alcohols (Scheme 2.3a).[43a] The retro-Claisen event was facilitated by the high pK_a of allylic alkoxides in DMSO (~30). In this way, nucleophiles having a pK_a lower than 25 in DMSO could be readily generated for use in DaA with the nascent allyl ester in the presence of palladium. Also in 2011, Grenning extended this concept to bisallylations using allyl esters (**A2.5**) and allyl alcohols with acyl nitroalkanes (**A2.6**) (Scheme 2.3b).[43b] The first

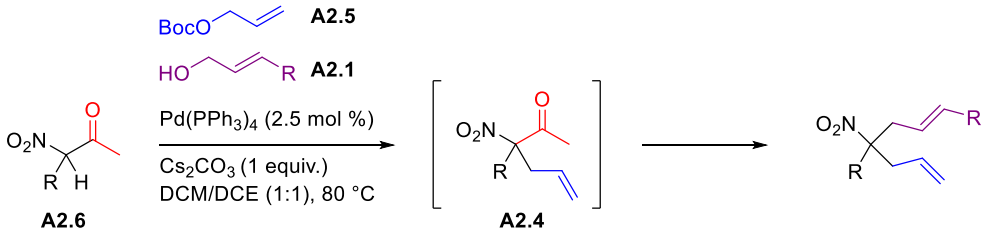
deacylative alkylation occurred with the boc allyl ester, being more facile and not requiring pre-activation to participate in coupling. Once the first allylation was complete, a retro-Claisen reaction transferred the acyl group from the nitroalkane to the allyl alcohol, simultaneously generating the nucleophile and pro-electrophile for a second deacylative alkylation. An asymmetric version of this chemistry was developed in 2013 (Scheme 2.3c).[43c] Using chiral PHOX ligands in the presence of a palladium(0) precatalyst, quaternary acyl bezocyclohexanones were asymmetrically allylated with allyl alcohols. To demonstrate the utility of this method, synthetically useful enantioenriched [1,6]-heptadienes were synthesized. Furthermore, the authors demonstrated the utility of asymmetric DaA to the synthesis of the Clive-Stoltz intermediate for the synthesis of (+)-hamigaren, synthesizing the intermediate in greater yield than Stoltz had using decarboxylative allylation.[47]

Scheme 2.3 – Retro-Claisen Chemistry in the Tunge Group

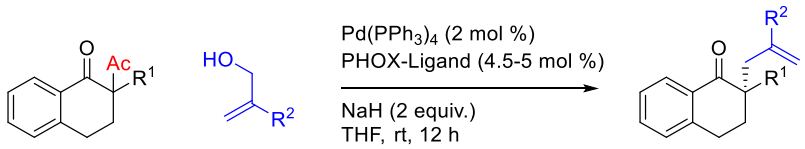
A) *Grenning, 2011*



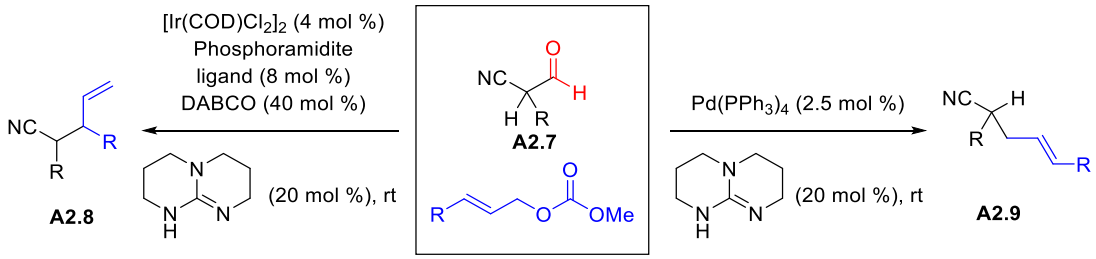
B) *Grenning, 2011*



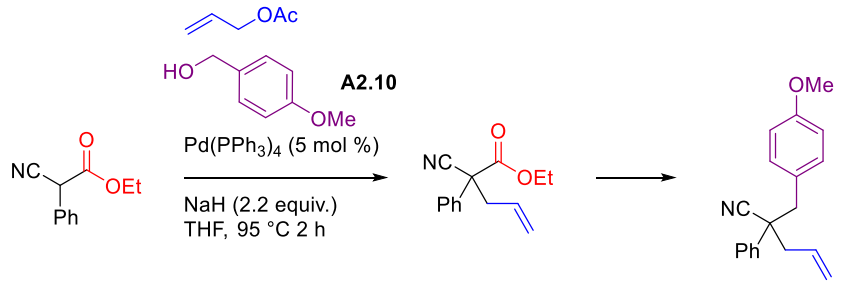
C) *Grenning, 2013*



D) *Maji, 2014*



E) *Maji, 2014*



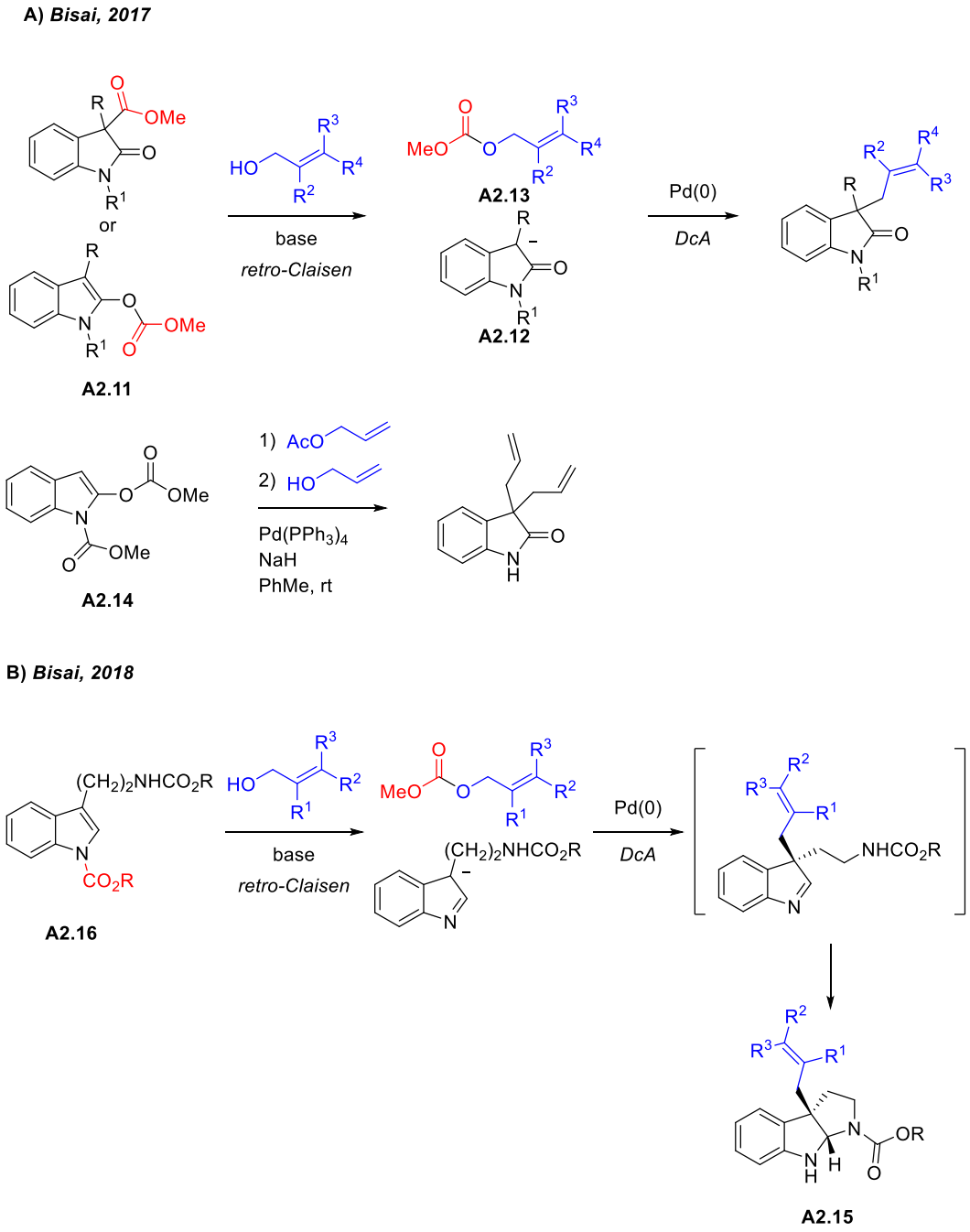
In 2014, Maji and Tunge developed a catalytic α-allylation of aryl acetonitriles, **A2.7** (Scheme 2.3d).[43d] In this reaction, an aldehyde group served to activate the aryl acetonitrile for α-allylation and prevented multiple allylations and was catalytically removed by 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD). The alcohol produced during decarboxylation subsequently removed the aldehyde, turning over TBD for additional formyl abstraction. The choice of metal catalyst controlled the regiochemistry, with iridium giving branched products (**A2.8**) and palladium giving linear products (**A2.9**).

Finally, in 2014, Maji and Tunge showed that in addition to allyl alcohols, benzyl alcohols (**A2.10**) could be activated for palladium catalyzed DaA by a retro-Claisen reaction (Scheme 2.3e).[43e] The retro-Claisen reaction generated a benzylic ester that was activated to participate in

Tsuji-Trost allylation with the nascent α-nitrile nucleophile. Furthermore, the retro-Claisen benzylation could also be combined with DaA of phenyl acetonitriles to perform a three-component coupling reaction.

Other groups have applied the retro-Claisen activation of allylic alcohols to the functionalization of indole and oxindole derivatives.[44,45] Bisai, *et al.* have done so utilizing retro-Claisen activation in combination with DcA (Scheme 2.4).[44] In 2017, they demonstrated a retro-Claisen reaction between carboxylated oxindoles (**A2.11**) and allyl alcohols to generate nucleophilic enolates (**A2.12**) and allyl carbonates (**A2.13**), which then spontaneously underwent DcA in the presence of palladium (Scheme 2.4a).[44a] Furthermore, starting from oxindole derivatives, that were both *N*- and *O*-carboxylated (**A2.14**), they achieve a three-component coupling. Retro-Claisen benzylations were also demonstrated in the same publication. In 2018, the same group extended the concept to synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids (**A2.15**) from *N*-acyl indole derivatives (**A2.16**) utilizing a reactive carboxamide handle to effect cyclization after the initial DcA reaction (Scheme 2.4b).[44b] Also in 2018, they reported the application of their hexahydropyrrolo[2,3-*b*]-indole alkaloid synthesis protocol to the total synthesis of racemic (±)-deoxyeseroline, and (±)-esermethole.[44c]

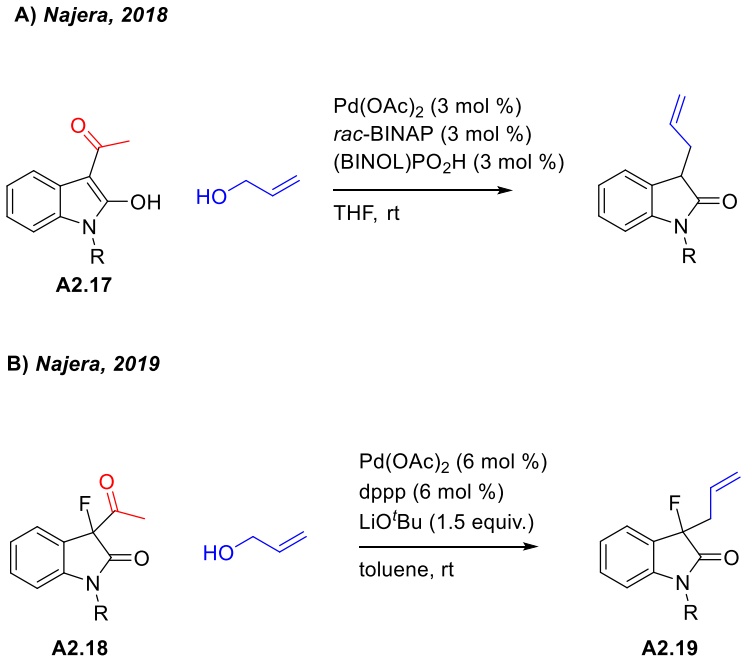
Scheme 2.4 – Bisai's Retro-Claisen DcA of Indoles and Oxindoles



The use of retro-Claisen initiated DaA for the functionalization of oxindoles was reported in 2018 by Najera (Scheme 2.5a).[45a] In this report, retro-Claisen reactions between acylated oxindoles (**A2.17**) and allyl alcohols to generated nucleophilic enolates and allyl acetates for DaA

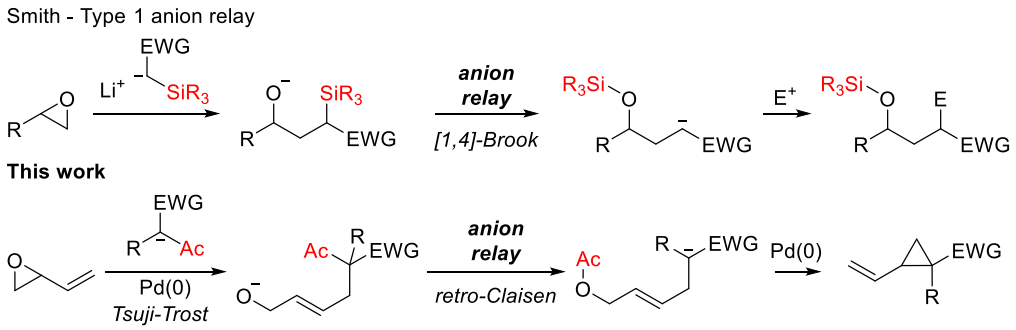
in the presence of palladium. In 2019, they demonstrated a similar protocol utilizing fluorinated oxindoles (**A2.28**), for the synthesis of 3-functionalized fluorinated oxindole species, **A2.19** (Scheme 2.5b).[45b]

Scheme 2.5 – Najera's Retro-Claisen DaA of oxindoles



Clearly, retro-Claisen activation of allylic alcohols has been shown to be effective in palladium-catalyzed allylic alkylations. To extend this concept to anion relay reactions, we envisioned that an acyl-stabilized nucleophile could couple with a vinyl epoxide to form an acyl-containing alkoxide.[48] If this alkoxide were to undergo a retro-Claisen reaction, migrating the negative charge from the oxygen to form a nucleophilic carbanion, it would constitute type I anion relay (Scheme 2.6). Moreover, the resulting allylic acetate would be activated for palladium-catalyzed intramolecular Tsuji-Trost-type cyclopropanation.[49] The resulting vinyl cyclopropanes would be synthetically useful molecules, giving us sufficient motivation to move forward. These types of Tsuji-Trost cyclopropanations are well known and have been accomplished in a variety of contexts, as shall be elucidated in the following section.

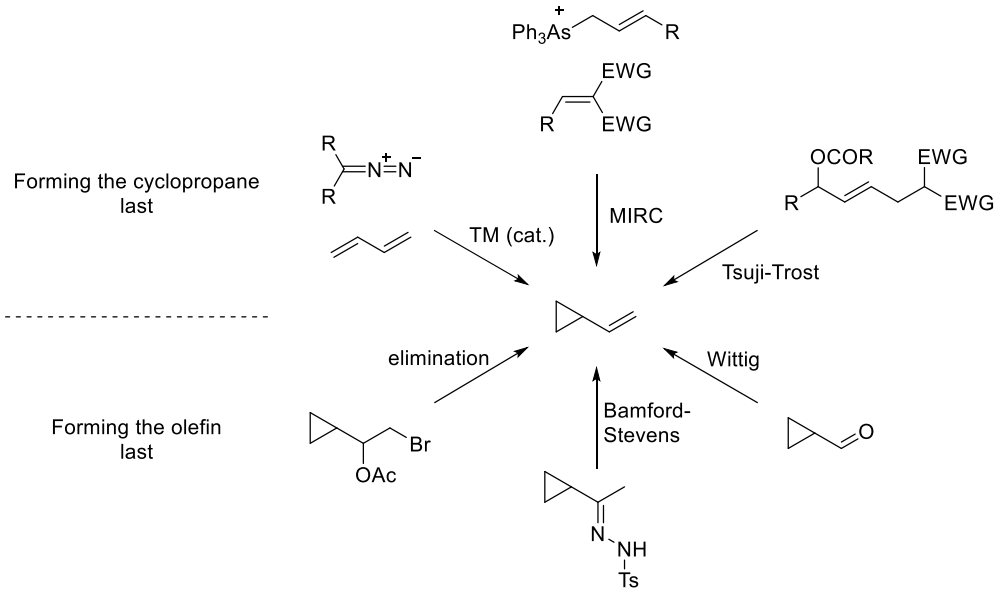
Scheme 2.6 – Envisioned Retro-Claisen Anion Relay Strategy



2.2.2 – Intramolecular Pd-catalyzed Cyclopropanation

Vinyl cyclopropanes are synthetically tractable molecules that can undergo a variety of useful transformations, including nucleophilic ring opening reactions,[50] cycloadditions,[49,51] and rearrangements.[50,52,53] Consequently, vinyl cyclopropanes are valuable intermediates in the synthesis of biologically active compounds.[51,54] Previous methods of making vinyl cyclopropanes involve metal carbenoids derived from diazo compounds[55] or Simmons-Smith-like reactions,[56] Michael-initiated ring closure (MIRC) reactions of ylides,[57] or functional group interconversion of appropriately functionalized cyclopropanes.[54,58,59] (Scheme 2.7) These methods can suffer from poor atom-economy,[57] poor step-economy,[52,58] or involve the use of dangerous/toxic reagents.[55,56] Thus, the direct conversion of readily-available vinyl epoxides to vinyl cyclopropanes could complement these existing methods.

Scheme 2.7 – Ways of making cyclopropanes



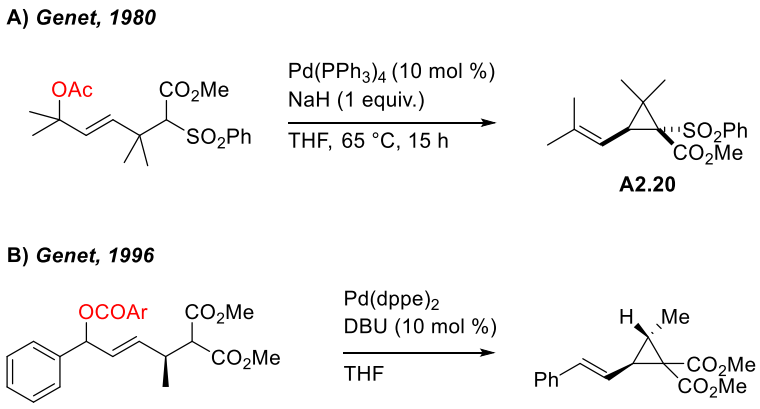
Tsuji-Trost cyclopropanation utilizing bis-electrophiles with stabilized carbon nucleophiles was originally demonstrated in a stepwise fashion by Genêt in 1980 (Scheme 2.8a).[60] In this initial application, a (±)-*trans*-crysanthemic acid derivative (**A2.20**) was synthesized utilizing an intramolecular deacylative allylation reaction to form the cyclopropane. Although palladium was not required for this reaction, it did increase the rate while not significantly affecting the stereochemical outcome of the reaction. Later, in 1996, the same group utilized a similar reaction to stereospecifically form vinyl cyclopropanes (Scheme 2.8b).[60e]

In 1987, Bäckvall and coworkers showed that the stereochemical outcome of the cyclopropanation was dependent on the geometry of the starting allyl acetate (Scheme 2.8c).[61] Allyl acetates with the pro-nucleophilic carbon and the acetate group *syn* to one another (**A2.21**) provided to the *trans* cyclopropanes in the presence of palladium, whereas, the epimeric acetates (**A2.22**) afforded the *cis* cyclopropanes. The reactions were *E*-selective in terms of olefin geometry, but in some cases *Z*-crotyl cyclopropanes were also observed.

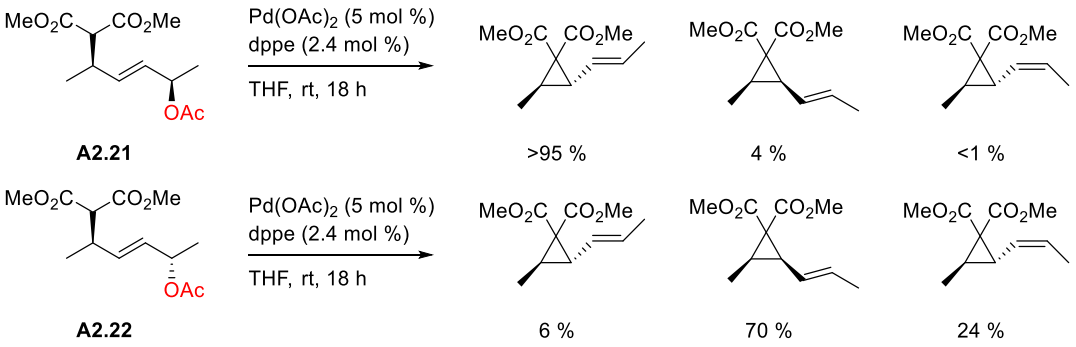
One-pot cyclopropanations incorporating sequential Tsuji-Trost reactions were later reported by Ito[62] in 1988 and Salaun[63] in 1999 (Scheme 2.8d, e). Ito performed the reaction asymmetrically using palladium in the presence of the chiral ferrocene ligand, (*R*),(*S*)-BPPFA, achieving modest to good enantioselectivities (up to 70 % ee Scheme 2.8d). Salaun also achieved asymmetric cyclopropanation using either a chiral catalyst or a chiral ketimine auxiliary as the electron withdrawing group, but only modest enantioselectivities were induced in this way (≤ 32% ee). However, the reactions were stereospecific, and enantioenriched cyclopropanes were obtained by using chiral starting materials (> 83% ee, > 88% cee, Scheme 2.8e).

In 2015, Nemoto demonstrated a similar decarboxylative allylic cyclopropanation reaction beginning from α-aryl lactones, **A2.23** (Scheme 2.8f).[64] They demonstrated a substrate scope of 12 examples with various substituents on the aryl ring with yields ranging from 81-94% and diastereomeric ratios as high as 15.1:1. However, α-alkyl lactones were incompetent for the reaction. In the same paper, the authors put forth an asymmetric version of the reaction utilizing chiral phosphoramidite ligands on palladium and achieved modest enantioselectivities (as high as 55 % ee), albeit with slightly lower diastereoselectivity (10:1).

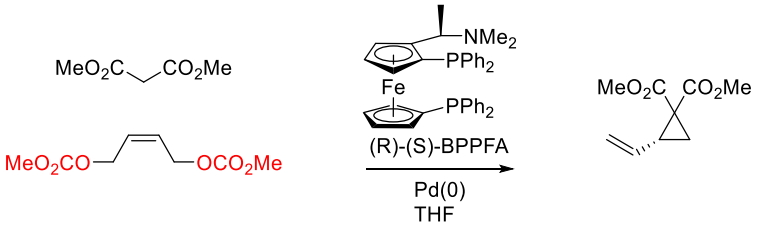
Scheme 2.8 – Intramolecular Tsuji-Trost Cyclopropanation



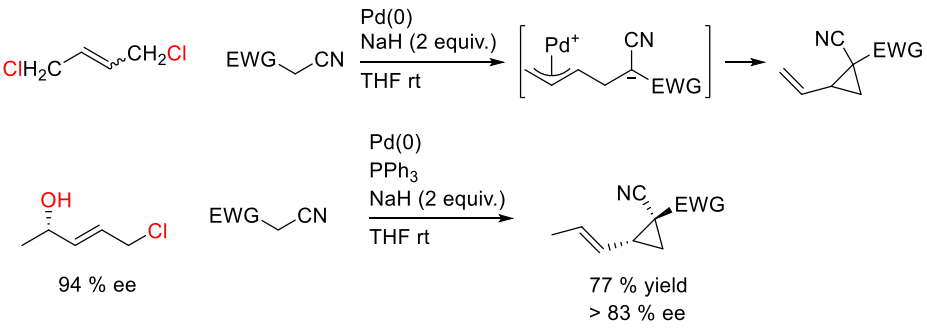
C) *Baekvall, 1987*



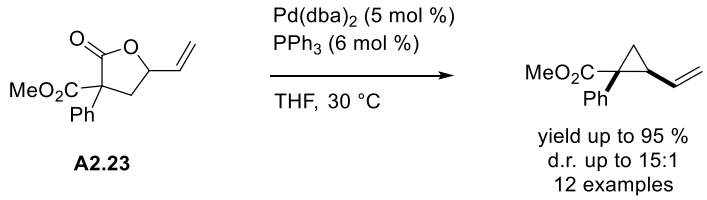
D) *Ito, 1988*



E) *Salaun*, *1999*



F) *Nemoto, 2015*



As can be seen, formation of vinyl cyclopropanes by intramolecular Tsuji-Trost reactions is well known. However, one common feature of most of the above reactions is that they utilize highly stabilized carbon nucleophiles, such as malonates and other active methylene compounds.

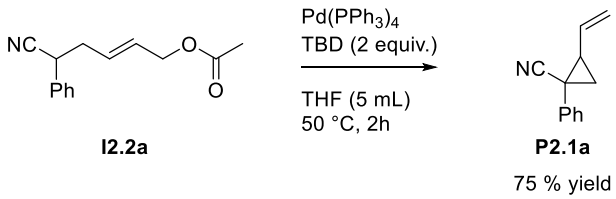
Herein, we report that less stabilized carbon nucleophiles can be used for the synthesis of vinyl cyclopropanes via a Tsuji-Trost/ARC/Tsuji-Trost sequence from readily available vinyl epoxides.[64] Furthermore, the cyclopropanation reaction presented below constitutes a new form of through-space anion relay that provides a new complement to the ubiquitous silyl migrations utilized in anion relay, and furthermore achieves a heretofore uncommon [1,6]-anion relay. As such, the methodology described herein constitutes a relatively mild and operationally simple procedure that constructs synthetically useful vinyl cyclopropanes from easily accessible starting materials, combining three reactions in a single pot.

§2.3 Synthesis of Vinylcyclopropanes via Anion Relay Chemistry

2.3.1 – Reaction Optimization

Initial experiments revealed that formation of the vinyl cyclopropane was feasible starting from the corresponding allyl ester in the presence of palladium(0) (Scheme 2.9). This experiment demonstrated that the desired Tsuji-Trost cyclopropanation reaction was possible starting from the phenyl acetonitrile containing allyl ester, **I2.2a**. In order to combine the cyclopropanation with retro-Claisen activation chemistry, we then sought to develop conditions for the acyl transfer.

Scheme 2.9 – Initial observation



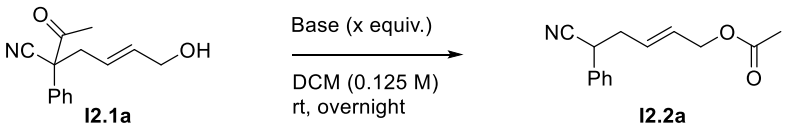
I2.2a **P2.1a**

75 % yield

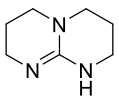
The base required for the retro Claisen reaction was then explored (Table 2.1). DABCO, imidazole, and benzimidazole were not competent for the retro-Claisen reaction (entries 1, 3, 4).

Sodium hydride only led to acyl transfer in 17% yield (entry 2). Interestingly, in the absence of any base, the acyl transfer occurred in 6 % yield (entry 5). TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) was the only base that was effective (entries 6, 7) at transacylation. Notably, it was equally effective when used stoichiometrically or in catalytic amounts.

Table 2.1 – Base Screening



Entry	Base (equiv)	yield (%)
1	DABCO (1.1)	no rxn
2	NaH (2)	17
3	Imidazole (1)	no rxn
4	Benzimidazole (1)	no rxn
5	n/a	6
6	TBD (1)	64
7	TBD (0.1)	67

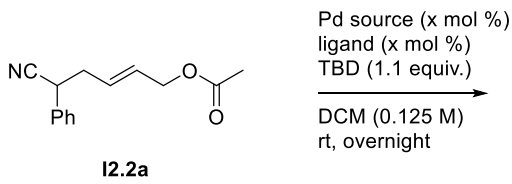


1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBD

Having found an optimal acyl transfer agent, the conditions for the terminal Tsuji-Trost cyclopropanation were further investigated (Table 2.2). Using $Pd(dba)_2$ as the palladium source, various ligands were screened for their ability to promote the reaction. Without any ligands, $Pd(dba)_2$ did not catalyze the reaction (entry 1). Monodentate phosphine ligands performed the best (entries 2-4). Bidentate phosphine ligands were capable of catalyzing the reaction, but the reactions were more sluggish (entries 6-10). The hemilabile ligand DavePhos performed quite well (entry 5). Pyridine based ligands were not competent at all for the reaction (entries 11-12).

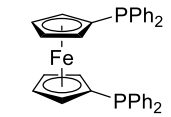
Ultimately, it was determined that the optimal conditions for the reaction were with 2.5 mol % $Pd(PPh_3)_4$ with no additional ligands (entry 13).

Table 2.2 – Ligand Screening

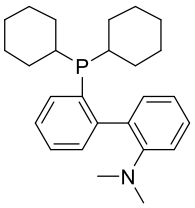


I2.2a **P2.1a**

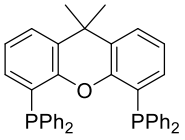
Entry	Pd Source (mol %)	Ligand (mol %)	Yield (%)	dr (cis:trans)
1	$Pd(dba)_2$ (2.5)	n/a	no rxn	n/a
2	$Pd(dba)_2$ (2.5)	PPh_3 (6)	38	76:24
3	$Pd(dba)_2$ (5)	PBu_3 (3.4)	69	80:20
4	$Pd(dba)_2$ (2.5)	PBu_3 (10)	37	81:19
5	$Pd(dba)_2$ (2.5)	DavePhos (10)	60	72:28
6	$Pd(dba)_2$ (5)	dppf (3.4)	8	63:38
7	$Pd(dba)_2$ (2.5)	dppe (10)	1	n/a
8	$Pd(dba)_2$ (2.5)	dppm (10)	23	74:26
9	$Pd(dba)_2$ (2.5)	dppbz (10)	no rxn	n/a
10	$Pd(dba)_2$ (2.5)	XantPhos (10)	11	64:36
11	$Pd(dba)_2$ (2.5)	2-picoline (10)	no rxn	n/a
12	$Pd(dba)_2$ (2.5)	2-methoxy pyridine (10)	no rxn	n/a



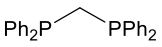
dppf



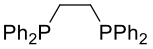
DavePhos



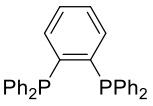
XantPhos



dppm



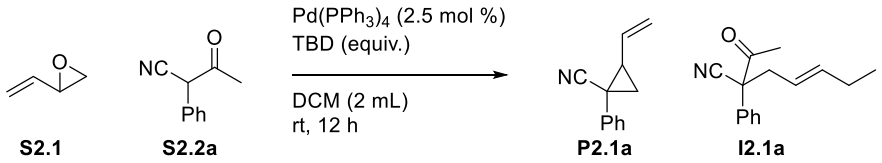
dppe



dppbz

Attention was then turned to optimization of the one-pot sequential allylation, retro-Claisen, cyclopropanation (Scheme 2.10). When TBD was omitted, the Tsuji-Trost allylation of **S2.2a** with **S2.1** proceeded readily in DCM in the presence of 2.5 mol % $Pd(PPh_3)_4$, however, the reaction stopped at the allyl alcohol intermediate. The addition of 1.1 equiv. of TBD to facilitate acyl migration led to the vinyl cyclopropane,[43d,65] albeit in only 14 % yield (entry 4).

Scheme 2.10 – Initial Attempts at One-Pot Reactions

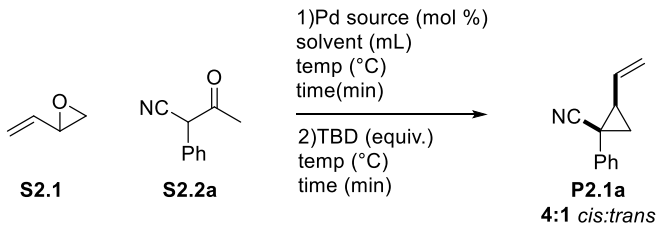


TBD (equiv.)	conversion to **P2.1a** (%)
0	0 %*
1.1	14 %

Nitrile (**S2.2a**, 0.25 mmol), Pd source, TBD, solvent and vinyl oxirane (**S2.1**, 1 equiv.) were mixed in that order and allowed to stir at the indicated temperature for the indicated amount of time. *89 % of the alcohol intermediate (**I2.1a**) was formed, but no vinyl cyclopropane was observed. rt = room temperature ~22 °C.

Gratifyingly, when addition of TBD was delayed until after the formation of the allyl alcohol intermediate, the product was formed in appreciable yield (75 %, table 2.3 entry 1). Further optimization was conducted, exploring different solvents, temperatures, catalyst loading and base loading, but ultimately the optimal conditions were determined to be those shown in entry 1 (Table 2.3).

Table 2.3 – Reaction Optimization



S2.1 **S2.2a** **P2.1a**
4:1 *cis:trans*

Entry	time step 1 (min) time step 2 (min)	Pd Source (mol %)	Ligand (mol %)	temp. step 1 (°C) temp. step 2 (°C)	solvent (mL)	TBD (equiv.)	conversion to **P2.1a** (%)
1	30 60	$Pd(PPh_3)_4$ (2.5)	n/a	RT RT	DCM (2)	1.1	75
2	5 30	$Pd(PPh_3)_4$ (10)	n/a	RT 80	Dioxane (2.5)	2	36
3	5 30	$Pd(PPh_3)_4$ (10)	n/a	RT 80	Dioxane (1.5)	2	0
4	10 30	$Pd(PPh_3)_4$ (10)	n/a	RT 80	Dioxane (2.5)	2	0
5	10 30	$Pd(PPh_3)_4$ (10)	n/a	RT 80	DMSO (2.5)	2	0
6	10 120	$Pd(PPh_3)_4$ (10)	n/a	RT 50	THF (1)	2	12
8	5 240	$Pd(PPh_3)_4$ (10)	n/a	RT RT	Dioxane (1)	1.1	42
9	5 120	$Pd(PPh_3)_4$ (10)	n/a	RT RT	DCM (1)	1.1	30
10	5 120	$Pd_2(dba)_3$ (5)	PPh_3 (30)	RT RT	THF (2.5)	1.1	24
11	30 120	$Pd(PPh_3)_4$ (1)	n/a	RT RT	DCM (2)	1.1	0
12	10 30	$Pd(PPh_3)_4$ (5)	n/a	RT RT	DCM (2)	1.1	75

Nitrile (**S2.2a**, 0.25 mmol), Pd source, solvent and vinyl oxirane (**S2.1a**, 1 equiv.) were mixed in that order and allowed to stir at the temperature indicated and for the amount of time indicated for the first step. Then TBD was added and the reaction was allowed to stir at the temperature indicated and for the amount of time indicated for the second step.

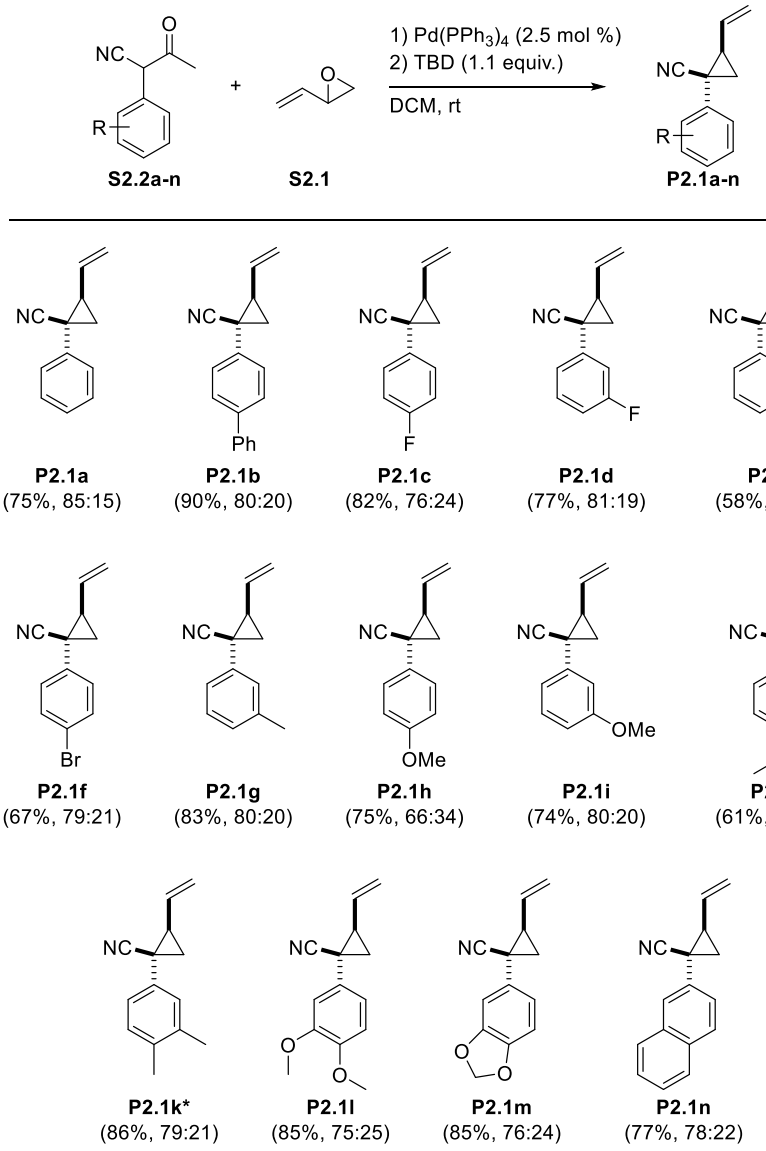
In order to demonstrate that the reaction could be performed on a preparative scale, it was performed on a 4.24 mmol scale using the prototypical substrates **S2.1** and **S2.2a**. For convenience,

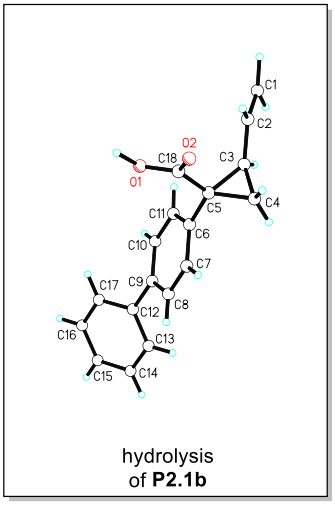
the reaction was carried out at a slightly higher concentration of 0.21 M. Under these conditions, the product **P2.1a** was obtained in 81 % yield with a dr of 81:19. Furthermore, the reaction was conducted under these same conditions with 2-(3,4-dimethylphenyl)-3-oxobutanenitrile (**S2.2k**) on gram scale, and the corresponding cyclopropane, **P2.1k** was obtained in 85 % yield (0.946 g, 79:21 d.r.).

2.3.2 – Reaction Scope

Next, the most successful conditions were used to explore the scope of the reaction. First, the scope of nitriles that undergo anion relay cyclopropanation with butadiene monoxide was explored (Scheme 2.11). Toward this end, the reactions of 2-phenyl-2-acetylacetonitriles that contained various substituents on the phenyl ring were examined. Compared with the unsubstituted substrate, which formed product **P2.1a** in 75 % yield, mono-substituted substrates bearing electron-withdrawing groups led to similar yields (**P2.1b-d**, 77-90 %), except in the case of the more strongly withdrawing *m*-CF_3 substituent (**P2.1e**, 58 %). Of note, a *p*-Br substrate that could suffer from competing C–Br oxidative addition provided the product in acceptable yield (**P2.1f**, 67 %). Electron-donating groups also provided similar yields of vinyl cyclopropanes **P2.1g-j**, indicating that the reaction efficiency is not strongly dependent on the electronic character of the nitrile. The diastereoselectivities of the substituted products also did not show a strong dependence on electronic character and were consistently in the range of 75:25–81:19. However, the most electron-rich substrate (*p*-OMe) did furnish the corresponding vinyl cyclopropane **P2.1h** with significantly lower diastereoselectivity (66:34). Disubstituted phenylacetonitriles were also briefly explored. Again, these substrates were all well-tolerated and provided the vinyl cyclopropanes **P2.1k-n** in good yield and moderate diastereoselectivity.

Scheme 2.11 - Scope of Nitriles



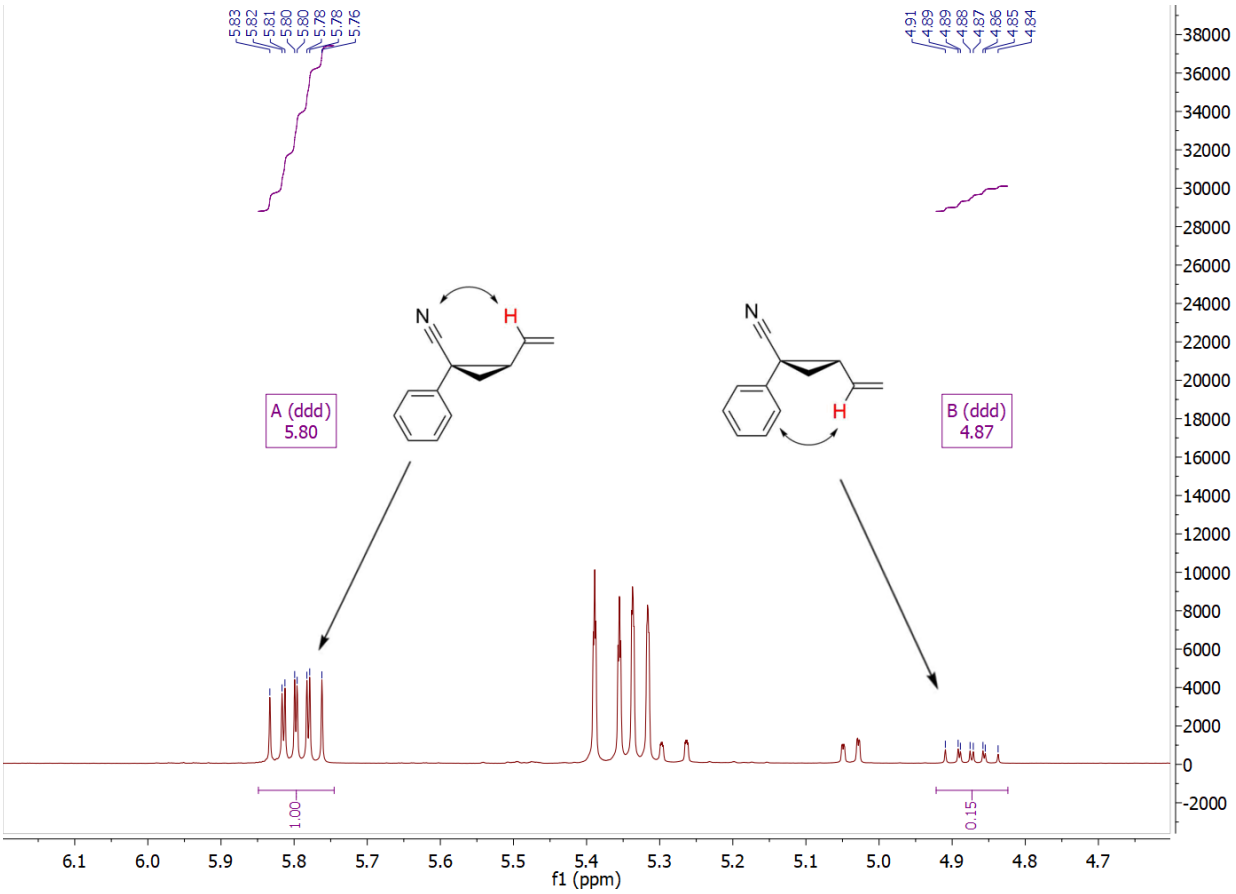


Reaction conditions: nitrile (**S2.2,** 0.25 mmol), $Pd(PPh_3)_4$ (2.5 mol %), DCM (1.9 mL), butadiene monoxide (**S2.1** 0.1 mL 2.5 M in DCM), rt, 30 min, then TBD (1.1 equiv.), rt, 1 h. Isolated yields. *gram scale

In order to determine the stereochemistry of the major diastereomer, compound **P2.1b** was hydrolyzed by treatment with NaOH/EtOH, at 105 °C overnight, followed aqueous workup and recrystallization from hot Et_2O. The resulting carboxylic acid formed X-ray quality crystals, which were analyzed to reveal the *cis* stereochemistry of the major product (Scheme 2.11 inset). The

relative stereochemistry can also be straightforwardly determined by analysis of the ^{1}H NMR spectroscopy; the internal alkene proton of the *trans* diastereomer is shifted significantly upfield (4.75-5.0 ppm) of its corresponding terminal protons, while the internal proton of the *cis* diastereomer has a normal shift of ca. 5.75 ppm and is downfield of its terminal protons (Figure 2.1).[66] Presumably, this is due to shielding of this proton by the electron cloud of the aromatic ring when the vinyl and phenyl groups are *cis* to one another. This observation was used diagnostically in the assessment of diastereoselectivity of the cyclopropanes. Ultimately, the stereochemistry is under thermodynamic control. Thus, treatment of either pure *cis* or pure *trans* vinyl cyclopropane with palladium leads to rapid equilibration to the thermodynamic ratio of diastereomers. [67]

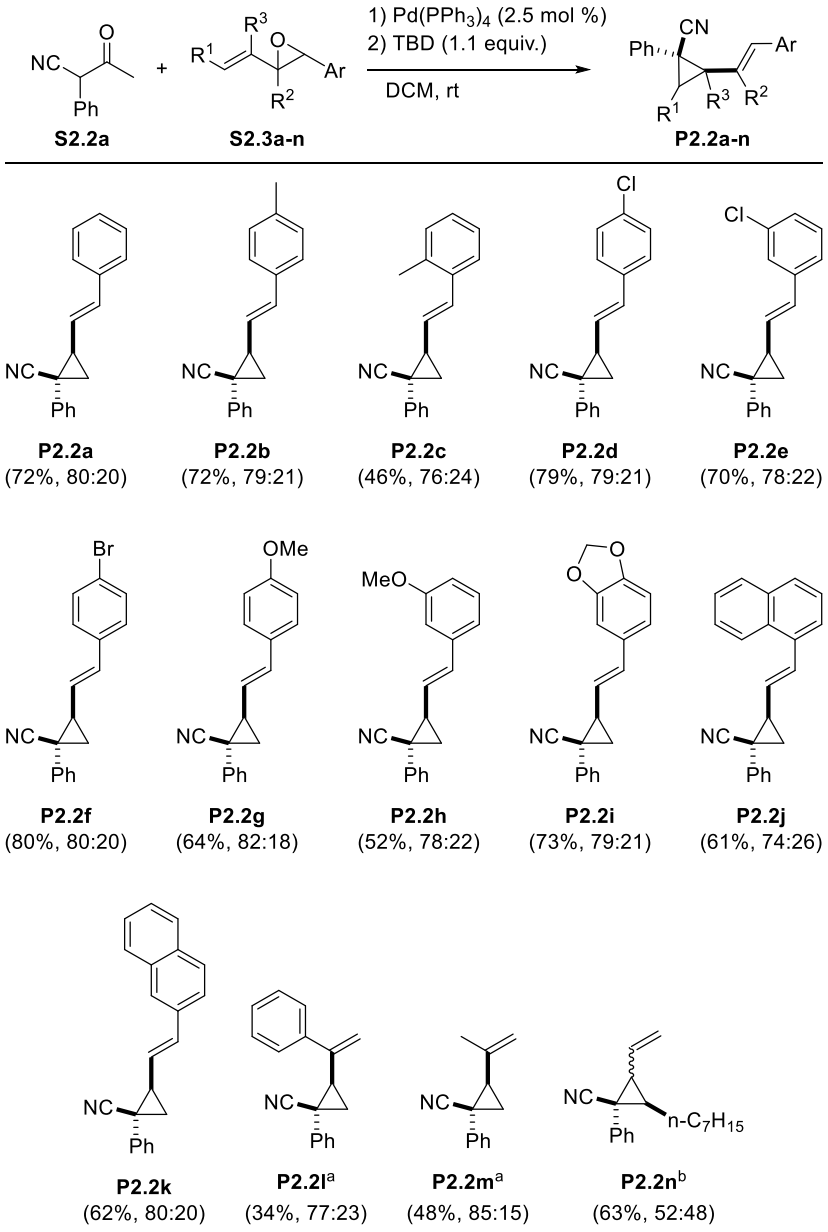
Figure 2.1 – Diagnostic ^{1}H NMR Resonances for Diastereoselectivity



Internal Olefin Proton Resonances in **3a**: Major (*cis*) isomer - ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.80 (ddd, *J* = 16.9, 10.3, 8.3 Hz, 1H). Minor (*trans*) isomer - 4.87 (ddd, *J* = 17.0, 10.3, 8.8 Hz, 1H).

Next, various 4-aryl-3,4-butadiene monoxides (**S2.3**) were evaluated in the reaction with 2-phenyl-2-acetylacetonitrile, **S2.2a** (Scheme 2.12). The prototypical example, with an unsubstituted phenyl substituent, resulted in a 72 % yield of the cyclopropane as an 80:20 mixture of diastereomers **P2.2a**. Again, substitution at the *para*-position of the arene (**P2.2b, d, f, g**) had little effect on the yield or diastereoselectivity of the transformation, while ortho substitution had a deleterious effect on the yield (**P2.2c**), and the diastereoselectivity was slightly decreased (76:24). Importantly, functionally useful aryl bromides and chlorides **P2.2d-f** were tolerated by the anion relay cyclization. In all cases where geometric isomers were possible with respect to the olefin, the *E* isomer was obtained exclusively as determined by ^{1}H NMR spectroscopy (**P2.2a-k**, >95:5).

Scheme 2.12 – Scope of Epoxides

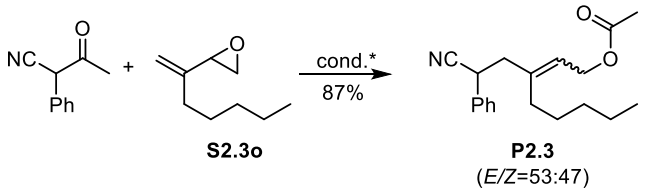


Reaction conditions: nitrile (0.25 mmol), $Pd(PPh_3)_4$ (2.5 mol %), DCM (1.9 mL), butadiene monoxide (0.1 mL 2.5 M in DCM), rt, 30 min, then TBD (1.1 equiv.), rt, 1 h. Isolated yields.a)1.5 h after addition of TBD b) 45 °C, 3.5 h after addition of TBD. Observed diastereomers of **P2.2n** are C_3-epimers, differing at the vinylic carbon.

Disubstitution of the arene was also tolerated (**P2.2i**), however, the naphthyl substituents led to lower yield of the cyclopropane **P2.2j** and **P2.2k**. Vinyl epoxides that bear a 3-substituent

reacted more sluggishly (**S2.2l, m**). Nonetheless, the R^2 phenyl-substituted reactant provided the cyclopropane **P2.2l** in 34 % yield, while the smaller R^2 methyl substituent furnished the cyclopropane **P2.2m** in 48 % yield. In this case, presumably, slow palladium-catalyzed cyclization is responsible for the lack of formation of the cyclopropane.[43a] Long-chain alkanes were tolerated at the R^1-position. As such, the reaction of (*E*)-2-(non-1-enyl)oxirane with 2-phenyl-2-acetylacetonitrile furnished the desired cyclopropane in acceptable yield, but the diastereoselectivity was low (**P2.2n**, 63 %, dr = 52:48). Unfortunately, a longer-chain alkyl substituent at the R^3-position failed to produce the desired product. Instead, the reaction stopped after acyl transfer, providing compound **P2.3**, as an *E/Z* mixture of olefins, in good yield (Scheme 2.13). Finally, the spirocyclic vinyl epoxide, 2-vinyl-1-oxaspiro[2.5]octane, did not lead to the desired product, but instead led to product **P2.4** (Scheme 2.13). Inspection of this product revealed that the reaction did not proceed due to a failed transacylation.[65] We hypothesize that the acyl group was effectively transferred to TBD, but the resulting intermediate was not capable of acylating the bulky tertiary alkoxide.[43e]

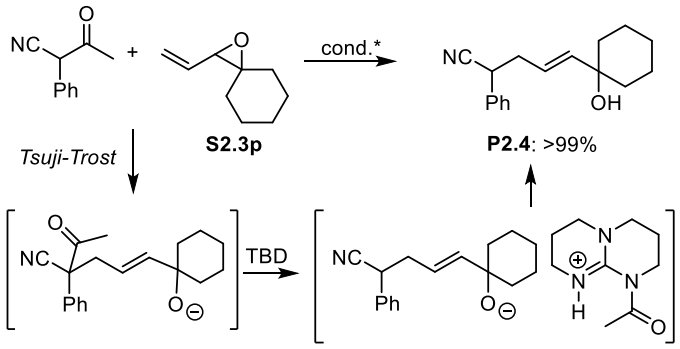
Scheme 2.12 – Failed cyclization



S2.3o **P2.3** (*E/Z*=53:47)

*Same conditions as those used in Scheme 2.11

Scheme 2.13 – Interrupted Transacylation

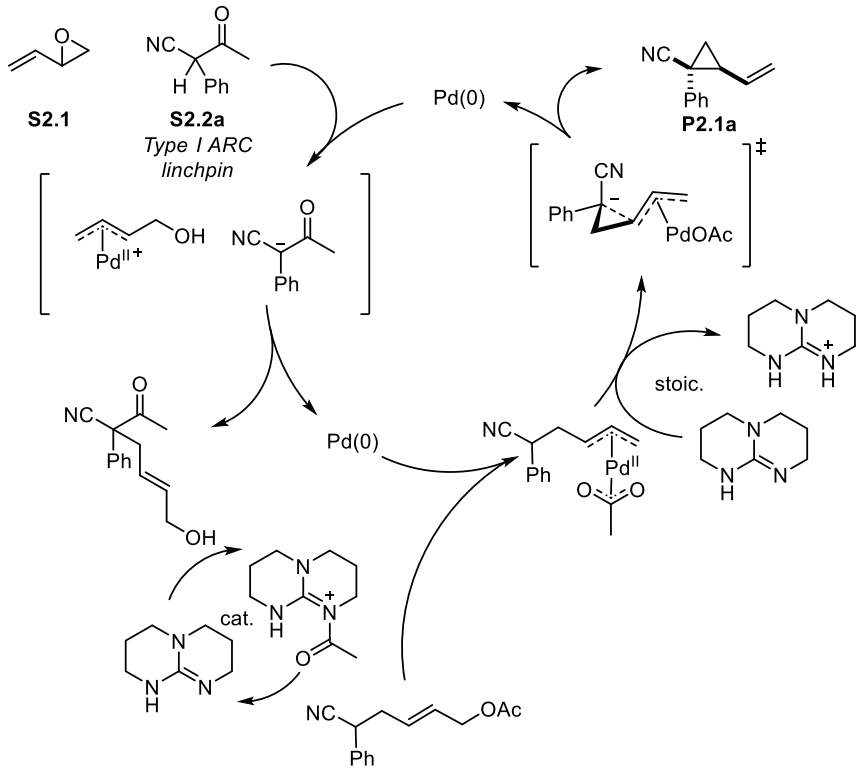


*Same conditions as those used in Scheme 2.11

2.3.3 – Mechanistic Considerations

Ultimately, these observations support a reaction sequence involving Tsuji-Trost allylation followed by deprotonation of the resultant alcohol in the presence of TBD to form an allyl alkoxide, **I2.1a** (Scheme 2.14). TBD catalyzes the anion relay via retro-Claisen reaction and transacylation, yielding an allyl ester, **I2.2a**.[65] The allyl ester is then activated to undergo oxidative addition and alkylation in the presence of palladium. Reversible ring-closure forms the thermodynamically favored cis arrangement of the vinyl group with the small nitrile substituent. Use of this strategy allows the direct conversion of readily-available vinyl epoxides and cyanoketones into versatile vinyl cyclopropanes.

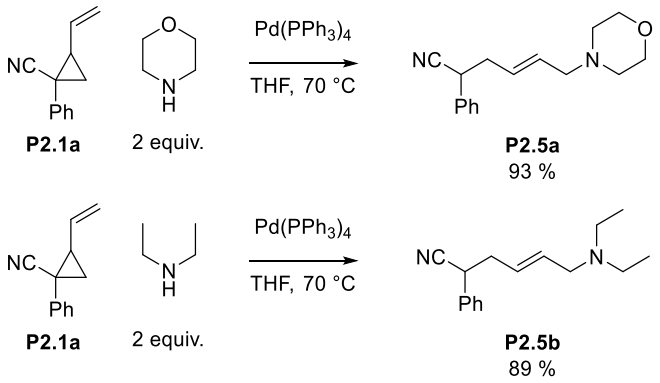
Scheme 2.14 – Proposed mechanism.



§2.4 Utilization of Cyclopropanes

Generally, cyclopropanes formed using intramolecular Tsuji-Trost reactions are produced from dicarboxylate pro-nucleophiles. Because these cyclopropanes are formed using significantly less activated pro-nucleophiles, it was of interest to demonstrate the ability of these cyclopropanes to participate in reactions typical of donor-acceptor cyclopropanes. In fact, they readily participated in ring-opening amination reactions.[68] Two examples are provided (Scheme 2.15).

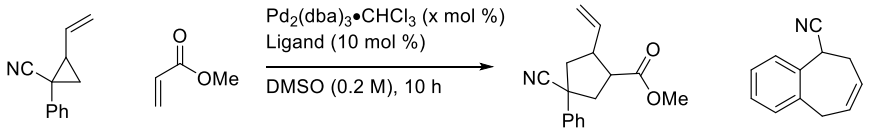
Scheme 2.15 – Utility of Vinyl Cyclopropanes in Ring Opening Amination



Reaction conditions: 2.5 mol % $Pd(PPh_3)_4$ was added to a flame dried vial under argon. 0.63 mL of 0.32 M vinyl cyclopropane solution in THF was added. Then 2 equiv. morpholine was added and the reaction was heated to 70 °C overnight. The reaction was quenched by running through a plug of silica in EtOAc. Yields reported are isolated yields after flash chromatography.

The ability of these vinyl cyclopropanes to participate in [3+2]-cycloadditions with methyl acrylate was explored. Initial attempts using conditions previously reported for a similar cycloaddition with 2,2-dicarboxylate-1-vinyl cyclopropanes were not successful.[69] Results of our optimization of this reaction are given in table 2.4.[70] When the cyclopropanes were combined with methyl acrylate in the presence of palladium with dppe at 150 °C, the [3+2]-cycloaddition only occurred to a small extent, and the majority of the product was ascribed to an interesting aryl vinyl cyclopropane Cope rearrangement product (**P3.1a**) (Table 2.4, entry 1). Interestingly, under the same conditions using PHOX ligands in place of dppe, the cycloaddition proceeded at room temperature (Table 2.4, entry 2). Increasing the temperature to 70 °C allowed the reaction to proceed to completion (Table 2.4, entry 3). Other PHOX ligands did not perform as well (Table 2.4, entries 4-5). Finally, it was found that heating to only 50 °C was sufficient for full conversion to the cycloaddition product **(P2.6**, Table 2.4, entry 6).

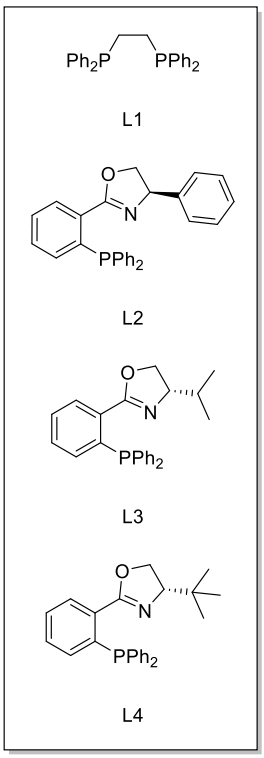
Table 2.4 – Optimization of Cycloaddition



P2.1a **P2.6** **P3.1a**

Entry	Pd (mol %)	Ligand (mol %)	temp. (°C)	**P2.6***	**P3.1a****
1	2.5	L1	150	8	79
2	2.5	L2	RT	89	0
3	2.5	L2	70	100	0
4	2.5	L3	70	18	2
5	2.5	L4	70	15	5
6	2.5	L2	50	100	0
7	2.5	none	150	3	97
8	0	none	150	3	96
9	0	none	150	0	100
10	2.5	L2	70	94***	0

Ligands



Conditions: $Pd_2(dba)_3$•$CHCl_3$ (x mol %), ligand (10 mol %) and DMSO were added to a flame dried flask under argon. Methyl acrylate and cyclopropane were added via syringe. The reaction was stirred at the given temperature for 10 h. * area % a on GC. ** area % b on GC. *** isolated yield, d.r. 57:29:14:0, determined by ^{1}H NMR.

Aryl vinyl cyclopropane Cope rearrangements are quite rare, so we optimized the transformation for formation of the benzocycloheptene side product (Table 2.4, entry 1). Interestingly, when the reaction was run in the absence of ligand, we saw nearly full conversion to the benzocycloheptene (Table 2.4, entry 7). Indeed, when the reaction was run in the absence of any catalyst, the reaction still proceeded almost completely to the benzocycloheptene, with small amounts of cycloaddition product (Table 2.4, entry 8). Under the same conditions, but in the absence of methyl acrylate the reaction proceeded fully to the benzocycloheptene and no other products were observed by GC (Table 2.4, entry 9). This rare aryl vinyl cyclopropane Cope

reaction was explored in greater depth and will be elaborated upon in Chapter 3. On the basis of these observations, the optimal conditions were used for the isolation of the cycloaddition product, which was thus obtained in 94% isolated yield (Table 2.4, entry 10).

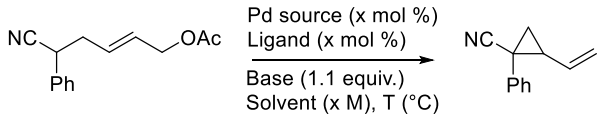
§2.5 Attempts at Asymmetric Cyclopropanation

Attempts were made to develop conditions for an asymmetric cyclopropanation. The cyclopropanation from the ester, being the potential enantio-determining step in the above one-pot protocol was isolated for optimization (Table 2.5). We began our investigation using a PHOX ligand, which was successful in the cyclopropanation developed by Nemoto *et al.*[64] Using a 4-^{t}butyl-substituted PHOX ligand with $Pd_2(dba)_3$ and otherwise standard conditions for the above developed cyclopropanation, we observed 24% yield of the cyclopropane **P2.1a** by NMR, with an approximately 4:1 dr in favor of the *cis* isomer. After a brief catalyst screen (Table 2.5, entries 2-4), the three dibenzylideneacetone palladium complexes were found to be acceptable, and a cost analysis revealed that $Pd(dba)_2$ was the optimal choice. A brief ligand screen (Table 2.5, entries 5-6) revealed that *bis*-phosphine ligand BINAP was not competent for the reaction, whereas the slightly less strongly coordinating (R)-MOP led to a greater yield (50 %, Table 2.5, entry 6). Using DBU as the base led to no conversion to the cyclopropane (Table 2.5, entry 7). Higher temperatures were not beneficial to the reaction (Table 2.5, entries 8-9). Increasing the amount of palladium from 2.5 mol % to 5 mol % increased the yield by 20 % with no significant effect on diastereoselectivity (Table 2.5, entry 10). A brief solvent screen revealed that DCM was an optimal solvent (Table 2.5, entries 10-13). Next, the loadings of the catalyst and ligands were explored in more detail (Table 2.5, entries 14-18). In order to see if increasing the amount of (*R*)-MOP had the same effect as increasing the amount of catalyst, the reaction was run with 20 mol % (*R*)-MOP and 2.5 mol % catalyst (see Table 2.5, entries 6, 10, 14). Indeed, increase in yield by doubling the

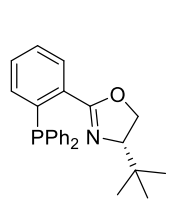
amount of ligand was comparable to that when the catalyst was increased two-fold. However, since (*R*)-MOP is more expensive than the palladium catalyst, increasing the catalyst two-fold was a more economical decision. Decreasing the amount of catalyst by half did not have the same effect as doubling the ligand (Table 2.5, entry 17). Lower loadings of ligand were explored, and 3.4 mol mol % ligand to mol 5 mol % catalyst was settled upon (Table 2.5, entries 15-16, 18). Higher loading of TBD was explored, to see if greater amounts of base could push the ester to higher conversion, however, adding additional base had detrimental effects to the yield (Table 2.5, entries 19-20). With these conditions in hand, the ligand screening was revisited in more detail (Table 2.5, entries 21-27), but it was determined that (*R*)-MOP was best, with RajPhos being a close second. It appears that bidentate ligands featuring a strongly coordinating phosphine in combination with a less strongly coordinating handle such as an ester are optimal for this transformation. Finally, slightly more dilute conditions were tried, and a very slight increase to the yield was observed (Table 2.5, entry 27). This optimization was done in the absence of an acceptable chiral HPLC separation method, so enantioselectivities were not routinely determined.

Subsequently, an HPLC method was developed and the enantioselectivity was determined for some of these conditions. First, the diastereomers of the cyclopropane had to be separated. This separation was accomplished on a flash column that was ½ in. wide and 10 in. tall. Initially packing the column with hexane and eluting the product with 0.5 % EtOAc in hexane, collecting fractions in 100x13 mm tubes, then flushing with EtOAc if recovery of the ester was desired. The isolated *cis* diastereomer of cyclopropane was injected on HPLC. The HPLC method used was isocratic, 2% isopropanol in hexane with a flow rate of 1 mL per minute through an IA column (Daicel Chiralpak IA, 4.6 X 250 mm, 5 mic) with 2 μL injections. One enantiomer eluted at about 6.5 minutes and the other eluted at 10 minutes using this method. The enantiomeric excess was

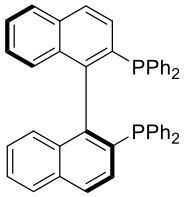
Table 2.5 – Attempted Asymmetric Cyclopropanation



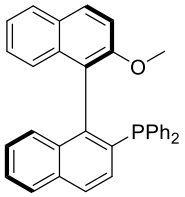
Entry	base (equiv.)	Catalyst (mol %)	Ligand (mol %)	Solvent (M)	Temp (°C)	Yield (%)	dr (*cis:trans*)	ee
1	TBD (1.1)	$Pd(dba)_2$ (2.5)	(S)-4-^{t}Bu-PHOX (10)	DCM (0.125)	rt	23	78:22	
2	TBD (1.1)	$Pd(dmba)_2$ (2.5)	(S)-4-^{t}Bu-PHOX (10)	DCM (0.125)	rt	8	75:25	
3	TBD (1.1)	$Pd_2(dba)_3$ (2.5)	(S)-4-^{t}Bu-PHOX (10)	DCM (0.125)	rt	20	75:25	
4	TBD (1.1)	$Pd_2(dba)_3$•$CHCl_3$ (2.5)	(S)-4-^{t}Bu-PHOX (10)	DCM (0.125)	rt	22	77:23	
5	TBD (1.1)	$Pd(dba)_2$ (2.5)	(S)-BINAP (10)	DCM (0.125)	rt	0		
6	TBD (1.1)	$Pd(dba)_2$ (2.5)	(R)-MOP (10)	DCM (0.125)	rt	50	78:22	
7	DBU (1.1)	$Pd(dba)_2$ (2.5)	(R)-MOP (10)	DCM (0.125)	rt	0		
8	TBD (1.1)	$Pd(dba)_2$ (2.5)	(R)-MOP (10)	DCM (0.125)	40	17	82:18	
9	TBD (1.1)	$Pd(dba)_2$ (2.5)	(R)-MOP (10)	DCM (0.125)	70	16	81:19	
10	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (10)	DCM (0.125)	rt	70	77:23	
11	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (10)	THF (0.125)	rt	6	83:17	
12	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (10)	CH_2Cl_2 (0.125)	rt	<1	100:0	
13	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (10)	DCE (0.125)	rt	14	79:21	
14	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (20)	DCM (0.125)	rt	71	79:21	
15	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (2.5)	DCM (0.125)	rt	47	77:23	4.2
16	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (5)	DCM (0.125)	rt	57	81:19	
17	TBD (1.1)	$Pd(dba)_2$ (1.25)	(R)-MOP (5)	DCM (0.125)	rt	8	88:13	
18	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (3.4)	DCM (0.125)	rt	75	79:21	
19	TBD (4)	$Pd(dba)_2$ (5)	(R)-MOP (3.4)	DCM (0.125)	rt	29	76:24	
20	TBD (2)	$Pd(dba)_2$ (5)	(R)-MOP (3.4)	DCM (0.125)	rt	54	76:24	
21	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-(R)-Me-RajPhos (3.4)	DCM (0.125)	rt	66	77:23	-1.5
22	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-(S)-BPPFA (3.4)	DCM (0.125)	rt	0		
23	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-4-Ph-PHOX (3.4)	DCM (0.125)	rt	16	75:25	
24	TBD (1.1)	$Pd(dba)_2$ (5)	(S)-4-^{t}Bu-PHOX (3.4)	DCM (0.125)	rt	19	74:26	
25	TBD (1.1)	$Pd(dba)_2$ (5)	(Ra,S)-Ph-Bn-SIPHOX (3.4)	DCM (0.125)	rt	20	75:25	
26	TBD (1.1)	$Pd(dba)_2$ (5)	(S)-(S)-DACH-Phenyl Trost (3.4)	DCM (0.125)	rt	17	59:41	
27	TBD (1.1)	$Pd(dba)_2$ (5)	(R)-MOP (3.4)	DCM (0.167)	rt	74	77:23	7.2



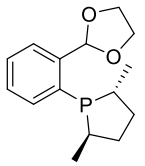
(S)-4-^{t}Bu-PHOX



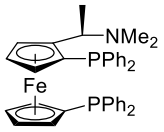
(S)-BINAP



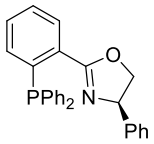
(R)-MOP



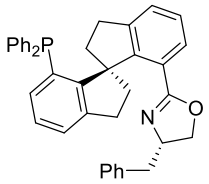
(R)-(R)-Me-RajPhos



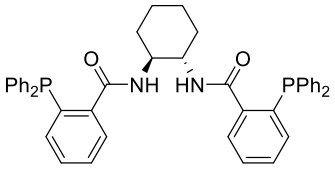
(R)-(S)-BPPFA



(*R*)-4-Ph-PHOX



(Ra,S)-Ph-Bn-SIPHOX



(S)-(S)-DACH-Phenyl Trost

determined for entries 15, 21 and 27 (Table 2.5,), and were 4.6, -1.5 and 7.2 % respectively. Therefore, while an enantioselective transformation is possible, acceptable enantioselectivities have not been achieved. Furthermore, bidentate phosphine ligands inhibit the reaction to some extent, whereas monodentate phosphine ligands containing another weakly coordinating heteroatom, such as oxygen, allow the reaction to proceed, but may not be optimal in terms of inducing enantioselectivity.

During the course of mechanistic studies on the aryl Cope rearrangement (see Chapter 3, Figure 3.17), it became apparent that palladium phosphine complexes catalyze the reversible ring opening of these vinyl cyclopropanes and under these conditions the reaction will inevitably progress toward the racemate over time. Therefore, at that time it was determined that our efforts were best focused elsewhere.

§2.6 Conclusion

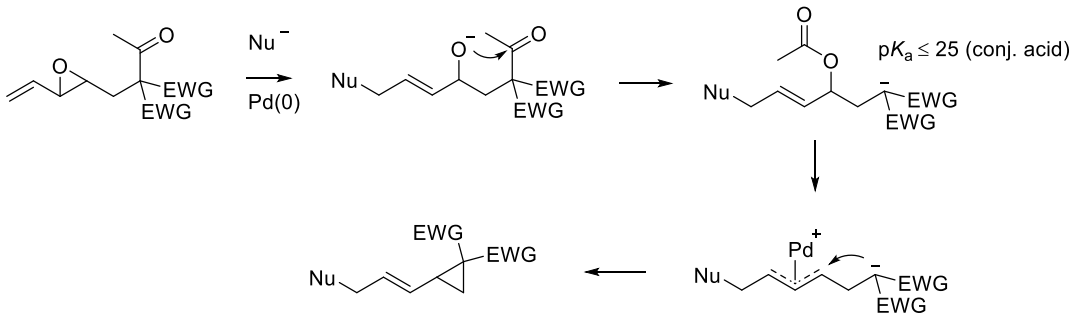
We have developed an effective type I anion relay protocol that utilizes retro-Claisen condensation reactions to relay anionic charge. Beginning from α-cyano acyl nucleophiles and vinyl epoxides, this protocol combines Tsuji-Trost allylation, retro-Claisen anion relay and

intramolecular Tsuji-Trost cyclopropanation in a single pot to afford synthetically useful vinylcyclopropanes. Furthermore, these vinylcyclopropanes were utilized in amination reactions and [3+2]-cycloadditions typical of donor-acceptor cyclopropanes. This new anion relay protocol obviates the need to synthesize alkyl silanes and complements existing non-silyl migration ARC tactics.

2.4.1 – Potential Future Directions

Further development of the retro-Claisen ARC concept is certainly possible and may prove fruitful for future research endeavors. One potential area of development could be the extension of the retro-Claisen anion relay concept to type-II anion relay. Such a project would necessitate the synthesis of a linchpin, such as the one shown in Scheme 2.16. As found previously, retro-Claisen reactions are not effective unless the pK_a of the conjugate acid of the resultant carbanion is less than about 25.[43a] Therefore, such a linchpin will have to be designed with electron-withdrawing groups that would impart an appropriately low pK_a.

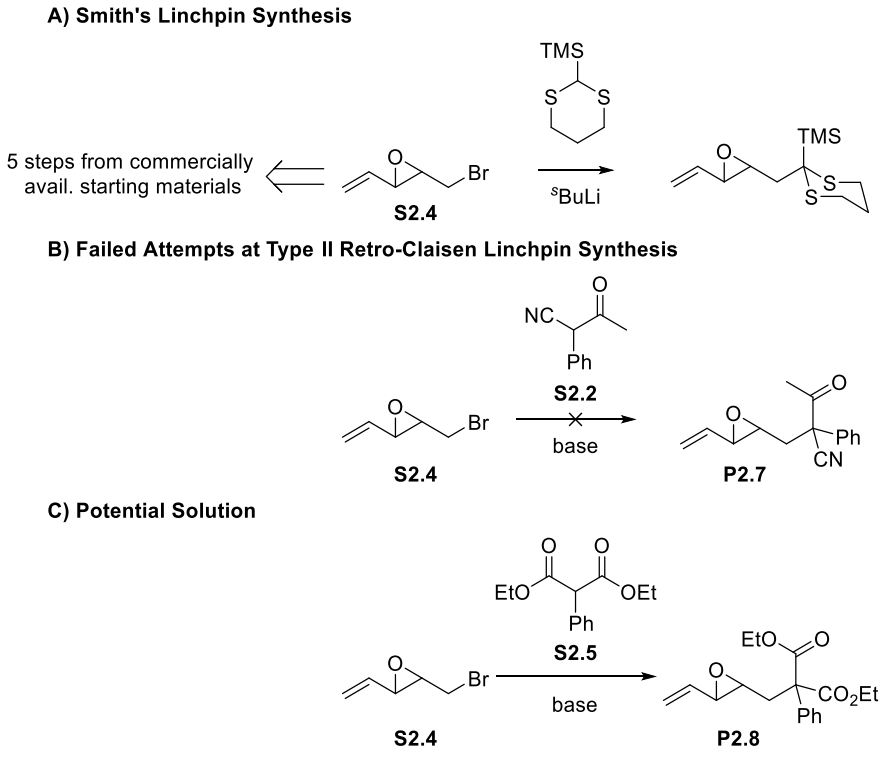
Scheme 2.16 – Type II Retro-Claisen ARC Concept



Smith has developed a similar type of linchpin for his [1,4]-Brook rearrangement chemistry using a dithiane group as an anion stabilizing moiety. In 5 steps, starting from commercially available starting materials, Smith *et al.* synthesized the brominated vinyl epoxide

shown in scheme 2.17a.[8] However, dithianes would not impart the anion stability required to drive a retro-Claisen reaction. Nonetheless, initial efforts in synthesizing a type II linchpin for retro-Claisen anion relay were done following a route similar to that used by Smith for the synthesis of his type II Brook rearrangement linchpins. Several attempts were made to synthesize an acceptable linchpin for retro-Claisen ARC using a similar strategy, but all attempts failed (*unpublished results*). In some cases, the epoxide was opened via the S_N2 or S_N2' pathways, and in other cases the kinetic enolate was formed preferentially and led to isomeric products. This problem of kinetic enolate formation could be prevented by using a diester, such as that shown in Scheme 2.17c.

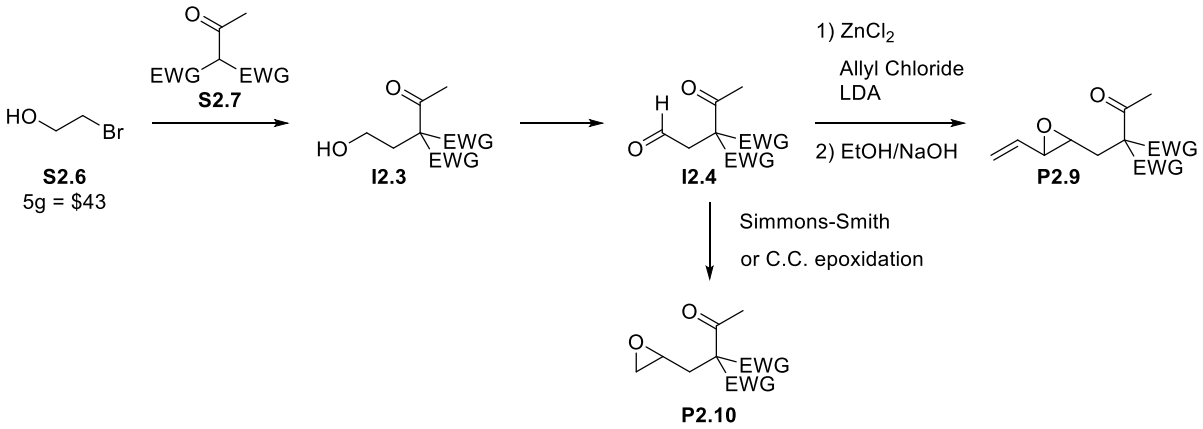
Scheme 2.17 – Attempts to Synthesize a Type II retro-Claisen ARC linchpin



Other types of linchpins could also be developed for use in retro-Claisen anion relay for use in both type I and type II protocols, such as aldehyde linchpins. Outlined in Scheme 2.18 is a

potential alternate route to type II linchpins that avoids both problems encountered above. Starting from commercially available brominated alcohol **S2.6**, the bromine could be displaced by an appropriately functionalized acyl containing nucleophile. The alcohol could then be oxidized to give an aldehyde **I2.4**, which itself could be a useful linchpin for retro-Claisen anion relay or could be epoxidized to make additional linchpins **P2.9** and **P2.10**.

Scheme 2.18 – Other Potential Routes to Type II retro-Claisen ARC Linchpins



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[70] Percentages reported in the table are percentages of the area of the corresponding peak in the GC trace, considering the total (100 %) to be the sum of the areas of the starting vinyl cyclopropane, all the isomers of the cycloaddition product and the benzocycloheptene. No other products or significant peaks were observed. Therefore, this data does not truly represent an accurate measurement of conversion or yield, but rather provides a qualitative assessment of the relative quality of the conditions.

Chapter 2 Appendix

Experimental methods and spectral analysis for chapter 2

§2.A.1 General Information

All reactions were performed in flame dried glassware under an argon atmosphere unless otherwise noted. THF was dried over sodium in the presence of benzophenone. Cyanoketones were prepared according to a literature procedure (*vide infra*). Preparation of 2-aryl-3-vinyl oxiranes was accomplished according to a literature procedure (*vide infra*).

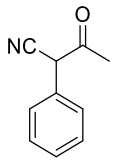
All other materials were obtained from Sigma-Aldrich, Acros Organics, Alfa Aesar or Fisher Scientific and were used without further purification. Reactions were monitored using either GC/MS on a Shimadzu GCMS-QP2010 SE or TLC on silica gel HL TLC plates w/UV254 from Sorbent Technologies. Compound purification was affected by flash chromatography using 230x400 mesh, 60 A porosity silica, using mixtures of hexane and EtOAc (EA) as eluent as noted. 1H NMR and 13C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer equipped with a QNP Cryoprobe and referenced to residual protio solvent signals. Structural assignments are based on ^{1}H, ^{13}C, DEPT135, COSY and NOESY techniques. J values are reported in Hz. High resolution mass spectral analysis was done on a Waters LCT Premeir mass spectrometer with a quadrupole and time of flight tandem mass analyzer and an electrospray ion source, or via LCMS using a Waters Q-Tof Premier in tandem with an Aquity UPLC using toluene assisted atmospheric pressure chemical ionization (TAPCI), as noted. Infrared analysis was performed on a Shimadzu FTIR-8400S infrared spectrometer. Melting points were obtained on a Digimelt MPA160 melting point apparatus.

§2.A.2 Synthesis and Characterization of Starting Materials

2.A.2.1 – Cyanoketone Preparation[43a]

General Procedure 2.B: Lithium hydride (96.5 mg, 12 mmol, 2 equiv.) was added to a flame dried flask in a glove box. DMSO (3 mL, 2.0 M) and a benzyl cyanide (0.705 g, 6 mmol, 1 equiv.) were added, and the flask was removed from the glove box and sealed. The suspension was cooled to 0 ℃ with stirring and N-acetyl imidazole (0.723 g, 6.6 mmol, 1.1 equiv.) was added. The solution was stirred for one hour, and then diluted with diethyl ether (~3X) and quenched with aqueous HCl (2 N). The aqueous layer was extracted with diethyl ether, then EtOAc. The combined organic layer was washed with hydrochloric acid, then brine and dried over magnesium sulfate. After filtration, the solvent was removed by rotary evaporation at 40 °C. The solid thus obtained was purified by recrystallization from Et_2O/hexane three times. A white solid was generally obtained (62% yield for **1a**).

S2.2a



2-phenyl-2-acetylacetonitrile

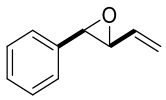
0.598 g, white solid, m.p.:84.4-86.5 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.29 (m, 5H), 4.68 (s, 1H), 2.27 (s, 3H).

2.A.2.2 – Preparation of 2-aryl-3-vinyl oxiranes[71a]

General Procedure 2.C: To a flame dried flask was added $ZnCl_2$ (2 equiv.) and diluted to 0.1 M with THF. This was followed by addition of 1.5 equiv. of allyl chloride. The flask was cooled to -78 °C in a dry ice/ acetone bath. With stirring, 2 equiv. LDA was added, and the reaction was allowed to stir for 30 minutes. At the same temperature 1 equiv. of aryl aldehyde was added and

the reaction was allowed to stir for 30 minutes. *Note*: removing the cold bath and quenching the reaction at 30 minutes, and not later, was crucial to the yield. The reaction was allowed to warm to room temperature followed by quenching with saturated aqueous sodium bicarbonate. The layers were separated, and the aqueous layer was extracted 3 times with ether. The combined organic layer was washed with brine. The solvent was removed from the organic layer *en vacuo*, and the residue was treated with saturated ethanolic KOH at room temperature in an open flask for 30 minutes. The mixture was placed on a rotary evaporator to remove the ethanol. Water and diethyl ether were added, the layers were separated and the aqueous layer was extracted with ether 3x. The combined organic layers were washed with brine and then dried over magnesium sulfate. The solvent was removed en vacuo and the product was purified by chromatography on silica gel using an EtOAc/hexane mixture as eluent (generally 1 % to 2 % EtOAc).

S2.3a

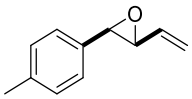


2-phenyl-3-vinyloxirane[71a,72]

Prepared from 0.51 mL benzaldehyde (5 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1 % triethylamine. Obtained 0.259 g colorless oil, yield: 35 % *cis*:*trans* ratio: 94:6. Spectral data was in agreement with published results. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.27 (m, 5H aromatic), 5.76 (ddd, *J* = 17.5, 10.4, 7.4 Hz, 1H minor alkene C*H*), 5.64 – 5.24 (m, 3H overlapping major and minor alkene C*H* and CH_2), 4.28 (d, *J* = 4.2 Hz, 1H major epoxide C*H*), 3.80 (d, *J* = 1.9 Hz, 1H

minor epoxide C*H*), 3.69 (dd, *J* = 8.1, 4.3 Hz, 1H major epoxide C*H*), 3.39 (dd, *J* = 7.5, 1.9 Hz, 1H minor epoxide C*H*).

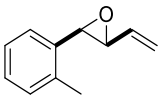
S2.3b



2-(p-tolyl)-3-vinyloxirane[71a]

Prepared from 1.77 mL *p*-tolualdehyde (15 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1 % triethylamine. Obtained 0.918 g colorless oil, yield: 38 % *cis*:*trans* ratio: 91:9. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (d, *J* = 7.9 Hz, 2H aromatic), 7.17 (d, *J* = 7.8 Hz, 2H aromatic), 5.74 (ddd, *J* = 17.6, 10.4, 7.4 Hz, 1H minor alkene C*H*), 5.61 – 5.23 (m, 3H overlapping major and minor alkene C*H* and CH_2), 4.23 (d, *J* = 4.2 Hz, 1H major epoxide C*H*), 3.75 (d, *J* = 2.0 Hz, 1H minor epoxide C*H*), 3.66 (dd, *J* = 8.1, 4.3 Hz, 1H major epoxide C*H*), 3.37 (dd, *J* = 7.4, 1.9 Hz, 1H minor epoxide C*H*), 2.36 (s, 3H CH_3).

S2.3c

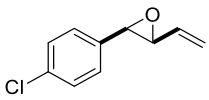


2-(*o*-tolyl)-3-vinyloxirane [71b]

Prepared from 1.2 mL *o*-tolualdehyde according to general procedure 2.C. Purified by flash chromatography on silica with EA:Hexane. Obtained 0.217 g yellow oil, yield: 13.4 % *cis*:*trans* ratio: 94:6. ^{1}H NMR ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.34 (m, 1H aromatic), 7.23 –

7.18 (m, 2H aromatic), 7.17 – 7.13 (m, 1H aromatic), 5.78 (ddd, *J* = 17.7, 10.4, 7.5 Hz, 1H alkene C*H*, minor), 5.57 – 5.47 (m, 1H alkene C*H*, major), 5.36 (d, *J* = 10.6 Hz, 2H alkene CH_2, minor), 5.28 – 5.17 (m, 2H alkene CH_2, major), 4.22 (d, *J* = 4.2 Hz, 1H epoxide C*H*, major), 3.91 (d, *J* = 2.1 Hz, 1H epoxide C*H*, minor), 3.74 (ddd, *J* = 6.0, 4.2, 1.2 Hz, 1H epoxide C*H*, major), 3.26 (dd, *J* = 7.6, 2.1 Hz, 1H epoxide C*H*, minor), 2.39 (s, 3H methyl CH_3, minor), 2.30 (s, 3H methyl CH_3, major). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 133.8, 132.7, 129.8, 127.8, 126.5, 125.8, 121.7, 59.3, 58.1, 18.9. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3084, 3069, 3028, 2994, 2972, 2926, 2861, 1491, 1460, 1441, 1381, 1044, 988, 945, 928, 882, 775, 741, 610. HRMS (ESI, m/z) calcd. for $C_{10}H_{10}O$, [M+] 146.0732; found 146.0732.

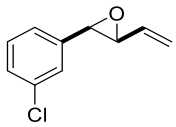
S2.3d



2-(4-chlorophenyl)-3-vinyloxirane [71a,72]

Prepared from 2.110 g *p*-chlorobenzaldehyde (15 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1% triethylamine. Obtained 1.848 g colorless oil, yield: 68 % *cis*:*trans* ratio: 92:8. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.19 (m, 4H aromatic), 5.73 (ddd, *J* = 17.5, 10.3, 7.3 Hz, 1H minor alkene C*H*), 5.62 – 5.49 (m, 1H overlapping 1H major and minor alkene CH_2), 5.43 – 5.26 (m, 2H overlapping 1H major alkene C*H* and 1H alkene CH_2), 4.22 (d, *J* = 4.2 Hz, 1H major epoxide C*H*), 3.76 (d, *J* = 2.0 Hz, 1H minor epoxide C*H*), 3.72 – 3.64 (m, 1H major epoxide C*H*), 3.33 (dd, *J* = 7.4, 1.9 Hz, 1H minor epoxide C*H*).

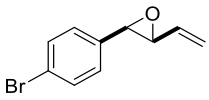
S2.3e



2-(3-chlorophenyl)-3-vinyloxirane

Prepared from 1.70 mL *m*-chlorobenzaldehyde (15 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1 % triethylamine. Obtained 1.565 g colorless oil, yield: 58 % *cis*:*trans* ratio: 92:8. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.16 (m, 4H aromatic), 5.71 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 0H minor alkene C*H*), 5.62 – 5.48 (m, 1H overlapping major and minor alkene CH_2), 5.43 – 5.26 (m, 2H overlapping 1H major alkene C*H* and 1H alkene CH_2), 4.21 (d, J = 4.2 Hz, 1H major epoxide C*H*), 3.74 (d, J = 1.9 Hz, 1H minor epoxide C*H*), 3.70 – 3.63 (m, 1H major epoxide C*H*), 3.33 (dd, J = 7.4, 1.9 Hz, 1H minor epoxide C*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 134.9, 134.5, 131.7, 130.0, 129.7, 128.6, 128.2, 126.8, 125.7, 124.9, 124.0, 122.67, 120.4, 63.3, 60.0, 59.7, 58.4. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 3069, 3030, 2994, 1946, 1867, 1640, 1600, 1574, 1481, 1429, 1385, 1337, 1180, 1094, 1076, 1042, 986, 931, 887, 779, 719, 683. HRMS (ESI, m/z) calcd. for $C_{10}H_9ClO$, [M+Na] 203.0240; found 203.0242

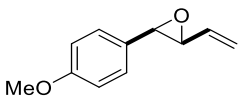
S2.3f



2-(4-bromophenyl)-3-vinyloxirane

Prepared from 0.463 g *p*-bromobenzaldehyde (2.5 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1% triethylamine. Obtained 0.191 g colorless oil, yield: 34 % *cis*:*trans* ratio: 93:7. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.47 (m, 2H aromatic), 7.27 – 7.16 (m, 2H aromatic), 5.74 (ddd, *J* = 17.2, 10.4, 7.4 Hz, 1H minor alkene C*H*), 5.62 – 5.50 (m, 1H overlapping major and minor alkene CH_2), 5.42 – 5.27 (m, 2H overlapping major and minor alkene CH_2 and major alkene C*H*), 4.22 (d, *J* = 4.2 Hz, 1H major epoxide C*H*), 3.76 (d, *J* = 1.9 Hz, 1H minor epoxide C*H*), 3.73 – 3.65 (m, 1H major epoxide C*H*), 3.34 (ddd, *J* = 7.4, 1.6, 0.7 Hz, 1H minor epoxide C*H*). ^{13}C NMR (126 MHz, CDCl3) δ 136.3, 134.9, 134.4, 131.9, 131.8, 131.5, 128.4, 127.4, 122.5, 122.3, 121.9, 120.2, 63.2, 60.0, 59.9, 58.6. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 3030, 2994, 1908, 1867, 1638, 1595, 1487, 1441, 1410, 1379, 1337, 1300, 1248, 1179, 1105, 1071, 1040, 1011, 986, 930, 872, 814, 762, 723, 689, 635. HRMS (TAPCI, m/z) calcd. for $C_{10}H_9BrO$ [M+H] 224.9915, found 224.9902

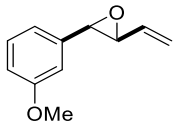
S2.3g



2-(4-methoxyphenyl)-3-vinyloxirane [71a,72]

Prepared from 1.83 mL *p*-anisaldehyde (15 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1 % triethylamine. Obtained 1.712 g colorless oil, yield: 65 % *cis*:*trans* ratio: 91:9. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.18 (m, 2H aromatic), 6.93 – 6.85 (m, 2H aromatic), 5.73 (ddd, *J* = 17.6, 10.3, 7.4 Hz, 1H minor alkene C*H*), 5.59 – 5.23 (m, 3H overlapping major alkene C*H* and CH_2), 4.20 (d, *J* = 4.2 Hz, 1H major epoxide C*H*), 3.81 (s, 3H OCH_3), 3.72 (d, *J* = 1.9 Hz, 1H minor epoxide C*H*), 3.63 (dd, *J* = 8.1, 4.2 Hz, 1H major epoxide C*H*), 3.36 (dd, *J* = 7.4, 2.0 Hz, 1H minor epoxide C*H*).

S2.3h

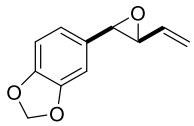


2-(3-methoxyphenyl)-3-vinyloxirane

Prepared from 1.83 mL m-anisaldehyde (15 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1 % triethylamine. Obtained 1.138 g colorless oil as an 85:15 mixture of diastereomers, yield: 43 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.23 (m, 1H aromatic), 6.95 – 6.80 (m, 3H aromatic), 5.72 (ddd, *J* = 17.3, 10.4, 7.5 Hz, 1H minor alkene C*H*), 5.60 – 5.49 (m, 1H overlapping major and minor alkene CH_2), 5.42 (ddd, *J* = 17.1, 10.4, 8.3 Hz, 1H major alkene C*H*), 5.35 (ddd, *J* = 10.4, 1.3, 0.6 Hz, 1H minor alkene CH_2), 5.29 (ddd, *J* = 10.4, 1.6, 0.6 Hz, 1H major alkene CH_2), 4.23 (d, *J* = 4.3 Hz, 1H major epoxide C*H*), 3.81 (d, *J* = 1.5 Hz, 3H OCH_2), 3.76 (d, *J* = 2.0 Hz, 1H minor epoxide C*H*), 3.66 (dd, *J* = 8.3, 4.3 Hz, 1H major epoxide C*H*), 3.37 – 3.32 (m, 1H minor epoxide C*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 159.7, 138.9, 137.0, 135.2, 132.3, 129.8, 129.5, 122.3, 120.0, 119.0, 118.2, 114.3, 113.7, 111.9, 110.6, 63.2, 60.4, 60.1, 59.0, 55.50, 55.48. IR ($\bar{\nu}$ –

$\bar{\nu}_{IR}$, neat) 3086, 2997, 2963, 2837, 1940, 1858, 1605, 1487, 1435, 1385, 1317, 1277, 1261, 1234, 1155, 988, 928, 787, 739, 698. HRMS (TAPCI, m/z) calcd. for $C_{11}H_{12}O_2$ [M-H] 175.0759, [M+H]M 177.0916, found 175.0752, 177.0906

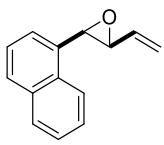
S2.3i



5-(3-vinyloxiran-2-yl)benzo[d][1,3]dioxole [71c]

Prepared from 2.25 g piperonal (15 mmol) according to general procedure 2.C, with the exception that the material was not treated with KOH/EtOH. Purified by flash chromatography on deactivated silica with 10 % EA:Hexane containing 1 % triethylamine. Obtained 1.92 g white solid, m.p.: 44.3-48.9 °C, yield: 67 % *cis*:*trans* ratio: 92:8. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.86 – 6.77 (m, 3H aromatic), 5.97 (s, 2H acetal CH_2), 5.72 (ddd, *J* = 17.5, 10.3, 7.4 Hz, 1H minor alkene C*H*), 5.62 – 5.24 (m, 3H overlapping alkene C*H* and CH_2), 4.17 (d, *J* = 4.1 Hz, 1H major epoxide C*H*), 3.70 (d, *J* = 2.0 Hz, 1H minor epoxide C*H*), 3.62 (dd, *J* = 8.0, 4.2 Hz, 1H major epoxide C*H*), 3.32 (dd, *J* = 7.3, 2.0 Hz, 1H minor epoxide C*H*).

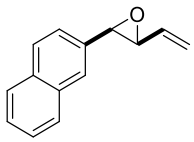
S2.3j



2-(naphthalen-1-yl)-3-vinyloxirane [71c]

Prepared from 0.784 g 1-napthaldehyde (5 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 1 % EA:Hexane. Obtained 0.832 g white solid, m.p.: 35.7-38.2 °C, yield: 84 % *cis*:*trans* ratio: 93:7. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 7.95 (m, 1H aromatic), 7.93 – 7.86 (m, 1H aromatic), 7.81 (d, *J* = 8.2 Hz, 1H aromatic), 7.60 – 7.44 (m, 4H aromatic), 5.90 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H minor alkene C*H*), 5.64 – 5.39 (m, 1H overlapping major and minor alkene CH_2), 5.35 – 5.07 (m, 2H overlapping alkene C*H* and CH_2), 4.71 (d, *J* = 4.2 Hz, 1H major epoxide C*H*), 4.40 (s, 1H minor epoxide C*H*), 3.92 (dd, *J* = 8.0, 4.2 Hz, 1H major epoxide C*H*), 3.37 (d, *J* = 6.2 Hz, 1H minor epoxide C*H*).

S2.3k

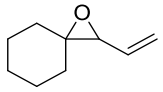


2-(naphthalen-2-yl)-3-vinyloxirane [71d]

Prepared from 0.788 g 2-napthaldehyde (5 mmol) according to general procedure 2.C. Purified by flash chromatography on deactivated silica with 1 % EA:Hexane. Obtained 0.769 g colorless oil, yield: 78 % *cis*:*trans* ratio: 89:11. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 – 7.77 (m, 4H aromatic), 7.61 – 7.34 (m, 3H aromatic), 5.81 (ddd, *J* = 17.2, 10.5, 7.5 Hz, 1H minor alkene C*H*), 5.67 – 5.56 (m, 1H overlapping major and minor alkene CH_2), 5.54 – 5.35 (m, 1H overlapping major alkene C*H* and minor alkene CH_2), 5.34 – 5.21 (m, 1H alkene CH_2), 4.44 (dd, *J* = 4.3, 0.8 Hz, 1H major epoxide C*H*), 3.97 (d, *J* = 1.9 Hz, 1H minor epoxide C*H*), 3.77 (dd, *J* = 8.4, 4.3 Hz, 1H major epoxide C*H*), 3.50 (dd, *J* = 7.5, 2.0 Hz, 1H minor epoxide C*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.3, 134.7, 133.5, 133.4, 133.2, 133.2, 132.9, 132.3, 128.6, 128.12, 128.11, 128.02, 128.00, 126.63, 126.56, 126.3, 126.2, 125.6, 125.3, 124.5, 123.0, 122.4, 120.0, 63.3, 60.7, 60.3,

59.3. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 3055, 3022, 2986, 1695, 1634, 1603, 1510, 1435, 1397, 1366, 1333, 1271, 1238, 1165, 1126, 140, 986, 943, 928, 862, 808, 752, 723, 897, 887. HRMS (ESI, m/z) calcd. for $C_{14}H_{12}O$ [M+H] 197.0966; found 197.0968

S2.3p



2-vinyl-1-oxaspiro[2.5]octane [71a]

Prepared from 1.97 g cyclohexanone according to general procedure 2.C. Purified by flash chromatography on silica with 5 % EA:Hexane. Obtained 0.876 g colorless oil, yield: 32 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.76 (ddd, *J* = 17.5, 10.5, 7.3 Hz, 1H alkene C*H*), 5.45 (dt, *J* = 17.2, 1.0 Hz, 1H alkene CH_2), 5.35 – 5.28 (m, 1H alkene CH_2), 3.19 (d, *J* = 7.3 Hz, 1H epoxide C*H*), 1.85 – 1.65 (m, 3H cyclohexane ring), 1.64 – 1.40 (m, 7H cyclohexane ring). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.4, 120.2, 65.0, 64.7, 35.7, 29.6, 25.8, 25.3, 25.0. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 2934, 2666, 1842, 1640, 1447, 1398, 1301, 1119, 986, 895, 821, 797, 727, 681. HRMS (TAPCI, m/z) calcd. for C9H14O [M+H] 139.1123; found 139.1122

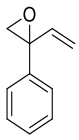
2.A.2.3 – Preparation of 2-aryl-2-vinyl oxiranes

General Procedure E: Acetophenone was added to acetonitrile (0.125 M) at room temperature and stirring was initiated. *N*-chlorosuccinimide (1 equiv.) and *p*-toluenesulfonic acid monohydrate (1 equiv.) were added. The reaction was allowed to stir for 1 hour at room temperature, followed by reflux (~77 °C) for 3 hours. The solvent was removed *en vacuo*, and water was added. The resulting mixture was extracted 3x with EtOAc, washed with brine and dried over magnesium

sulfate. The chloroacetophenone was purified by chromatography on silica gel using an EtOAc and hexane mixture as eluent. (2-5 %) often the starting material co-eluted with the mono-chlorinated product under these conditions. The chloroacetophenone/acetophenone mixture was used for the next step without further purification.[73]

Vinyl Grignard (1 equiv. as 1 M solution in THF) was diluted in THF to a concentration of 0.67 M and was cooled to ~ 0 °C in an ice/salt water bath. The product mixture from the previous step was added and allowed to stir in the bath for ½ hour. The reaction was allowed to warm to room temperature over ½ hour. It was then quenched with saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with ether three times. The combined organic fractions were treated with 1 N NaOH, and the mixture was allowed to stir for 3 hours. The layers were separated, and the aqueous layer extracted with ether. The combined organic layers were washed with brine, dried and concentrated by rotary evaporation. Some chlorohydrin remained and the residue was reconstituted in ether, and treated again with NaOH (1 N) for 3 hours at room temperature. Worked up as before and the product was purified by chromatography on silica gel using an EtOAc hexane mixture as eluent.[74]

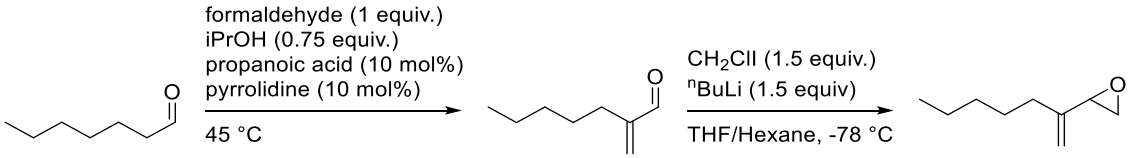
S2.3l



2-phenyl-2-vinyloxirane [74]

18 % over 2 steps. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 5H), 6.06 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.34 (dt, *J* = 10.7, 1.0 Hz, 1H), 5.26 (d, *J* = 17.1 Hz, 1H), 3.10 (dd, *J* = 5.7, 0.8 Hz, 1H), 3.03 (dd, *J* = 5.7, 0.8 Hz, 1H).

Synthesis of 2-(hept-1-en-2-yl)oxirane **S2.3o**



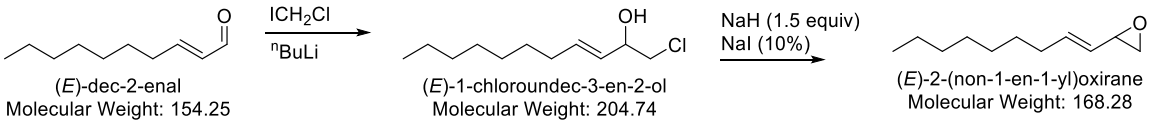
Heptanal was obtained from Alfa Aesar and was used without purification. To a flask was added formaldehyde (1.62 g, 37 wt % in water, 20 mmol, 1 equiv.), 20 mmol of heptanal (2.28 g, 20 mmol, 1 equiv.) and 1 mL iPrOH (13.1 mmol). Then 2 mmol of each of propanoic acid (0.148 g, 2 mmol, 10 mol %) and pyrrolidine (0.142 g, 2 mmol, 10 mol %) were added. The reaction was heated to 45 °C and left to stir and monitored for the disappearance of the starting material. The reaction was allowed to cool, and the reaction was quenched by addition of water. The aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated by rotary evaporation. 2-methyleneheptanal was obtained with a yield of 30% and was used without further purification.[75] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.55 (s, 1H) δ 6.25 (s, 1H), 5.99 (s, 1H), 2.24 (t, *J* = 7.7 Hz, 2H), 1.51 – 1.40 (m, 2H).

To a flask was added 50 mmol 2-methyleneheptanal (6.31 g) and 90 mL THF and cooled to -78 °C. Chloroiodomethane (12.8 g, 75 mmol, 1.5 equiv.) was added followed by the slow addition of 1.5 equiv. ^{n}BuLi over about 30 minutes (46.5 mL, 75 mmol, 1.6 M in hexanes). The reaction was held at the same temperature and monitored for disappearance of the starting material. After about

1 hour the starting material had been consumed. The reaction was removed from the bath and allowed to stir as it warmed to room temperature and overnight. The following day the reaction was quenched with saturated aqueous ammonium chloride. The reaction mixture was separated in a separatory funnel, rinsing in with additional ammonium chloride solution. The layers were separated and the aqueous layer extracted with ether. The combined organic layer was dried with magnesium sulfate, the mixture was filtered and concentrated by rotary evaporation. 2-(hept-1-en-2-yl)oxirane 27 % yield over 2 steps.[76,77] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.17 – 5.11 (m, 1H), 4.95 (q, *J* = 1.5 Hz, 1H), 3.38 – 3.30 (m, 1H), 2.88 (dd, *J* = 5.5, 4.2 Hz, 1H), 2.65 (dd, *J* = 5.5, 2.7 Hz, 1H), 2.04 – 1.89 (m, 2H), 1.54 – 1.20 (m, 6H), 0.98 – 0.81 (m, 3H).

2.A.2.4 – Other Vinyloxirane Syntheses

Synthesis of trans-2-(non-1-en-1-yl)oxirane **S2.3n**



Following a known procedure,[76] trans-2-decenal (3.08 g, 19.9 mmol) was added to 40 mL THF (distilled over Na/Benzophenone). The solution was cooled to -78 ° C in a dry ice/acetone bath. Chloroiodomethane (5.28 g) was added, followed by the slow addition of 12 mL of 2.5 M ^{n}BuLi solution in hexanes over 30 minutes. The reaction was quenched with 40 mL saturated aqueous ammonium chloride. The layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined and dried over magnesium sulfate, filtered and concentrated by rotary evaporation. The oil thus obtained was used without further purification. 1-chloroundec-3-en-2-ol ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 (dtd, *J* = 14.9, 6.7, 1.2 Hz, 1H), 5.46 (ddt, *J* = 15.4, 6.5, 1.5 Hz, 1H), 4.30 (dd, *J* = 7.5, 4.2 Hz, 1H), 3.61 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.49 (dd, *J*

= 11.0, 7.5 Hz, 1H), 2.17 (d, *J* = 4.1 Hz, 1H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.66 – 1.13 (m, 10H), 1.00 – 0.79 (m, 3H).[77]

To 25 mL THF was added 0.9 g NaH and 0.375 g NaI, and the suspension was cooled to 0 ° C and allowed to stir for 5 minutes. The oil obtained above was added slowly to avoid excessive bubbling and the reaction was allowed to warm to room temperature. The reaction was quenched with aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with Ether. The organic layers were combined and dried over magnesium sulfate, filtered and concentrated by rotary evaporation. Obtained 2-(non-1-en-1-yl)oxirane 2.80 g 16.6 mmol 83 % over 2 steps ^{1}H NMR (400 MHz, Benzene-d_6) δ 5.72 (dt, *J* = 15.5, 6.8 Hz, 1H), 5.08 (ddt, *J* = 15.4, 8.0, 1.5 Hz, 1H), 3.06 (ddd, *J* = 8.0, 4.0, 2.6 Hz, 1H), 2.52 (dd, *J* = 5.5, 4.0 Hz, 1H), 2.28 (dd, *J* = 5.4, 2.5 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.58 – 1.12 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H)[77]. (benzene referenced to 7.16)

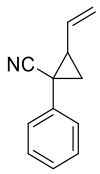
§2.A.3 General Procedure 2.A for Anion Relay Cyclopropanation

In a flame dried 20 mL sealable flask or vial $Pd(PPh_3)_4$ (7.2 mg, 2.5 mol%), nitrile, (0.25 mmol, 1 equiv.), and 1.9 mL of DCM were combined in the glove box. In a separate vial 38.2 mg (0.275 mmol, 1.1 equiv.) of TBD was added and sealed. A 2.5 M solution of vinyl epoxide in DCM was prepared in a resealable container under argon (*Note*: the exact concentration of the vinyl epoxide solution was unimportant as long as the molar quantity used in the next step was consistent). Under an argon atmosphere, 100 μL of the 2.5 M solution (0.25 mmol, 1 equiv.) was added and the reaction was allowed to stir for 30 to 60 min. or until all starting material was consumed (observed by GC/MS). TBD (1.1 equiv.) was then added to the reaction mixture and allowed to stir for 60 min. or until all of the intermediate was consumed. The reaction was quenched by filtering through

a 1" plug of silica in a pipette and washing the plug with EtOAc. The crude product was then purified by flash chromatography on silica using an eluent of 1-5 % EtOAc in hexanes.

§2.A.4 Characterization Data for Vinylcyclopropanes

P2.1a

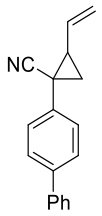


1-phenyl-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A.

32.7 mg, colorless oil, yield: 75 %, d.r.: 85:15. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.26 (m, 5H, overlapping major and minor, aromatic), 5.80 (ddd, *J* = 16.9, 10.3, 8.3 Hz, 1H major, alkene C*H*), 5.40 – 5.25 (m, overlapping 2H major alkene CH_2, 1H minor alkene CH_2), 5.04 (ddd, *J* = 10.3, 1.4, 0.6 Hz, 1H minor, alkene CH_2), 4.87 (ddd, *J* = 17.0, 10.3, 8.8 Hz, 1H minor alkene C*H*), 2.56 – 2.50 (m, 1H minor, cyclopropane C*H*), 2.24 – 2.16 (m, 1H major, cyclopropane C*H*), 1.92 (dd, *J* = 9.2, 5.9 Hz, 1H minor, cyclopropane CH_2), 1.83 (dd, *J* = 8.6, 5.9 Hz, 1H major, cyclopropane CH_2), 1.76 (dd, *J* = 7.3, 5.9 Hz, 1H major, cyclopropane CH_2), 1.65 (dd, *J* = 7.0, 5.9 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 134.5, 133.9, 133.5, 130.4, 129.7, 129.2, 129.1, 128.8, 128.6, 128.0, 125.8, 120.5, 119.0, 34.2, 31.9, 30.0, 23.5, 22.2, 19.4. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3063, 3030,

2236, 1723, 1694, 1640, 1601, 1493, 1451, 1111, 986, 953, 918, 754, 696. HRMS (TAPCI, m/z) calcd. for $C_{12}H_{11}N$ [M-H] 168.0813; found 168.0801.

P2.1b

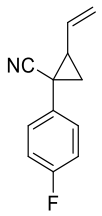


1-([1,1'-biphenyl]-4-yl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-([1,1'-biphenyl]-4-yl)-3-oxobutanenitrile.

55.1 mg, white solid, m.p.: 86.0-91.4 °C, yield: 90 %, d.r.: 80:20. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.54 (m, 4H overlapping major and minor aromatic), 7.48 – 7.34 (m, 5H overlapping major and minor aromatic), 5.82 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H major alkene C*H*), 5.39 (dt, *J* = 17.0, 0.9 Hz, 1H major alkene CH_2), 5.36 – 5.29 (m, 1H overlapping major and minor alkene CH_2), 5.08 (dd, *J* = 10.4, 1.4 Hz, 1H minor alkene CH_2), 4.94 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H minor alkene C*H*), 2.56 (td, *J* = 9.0, 7.0 Hz, 1H minor cyclopropane C*H*), 2.24 (td, *J* = 8.5, 7.5 Hz, 1H major cyclopropane C*H*), 1.96 (dd, *J* = 9.2, 5.9 Hz, 1H minor cyclopropane CH_2), 1.88 (dd, *J* = 8.6, 5.9 Hz, 1H major cyclopropane CH_2), 1.80 (dd, *J* = 7.4, 5.9 Hz, 1H major cyclopropane CH_2), 1.69 (dd, *J* = 7.0, 5.9 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 141.0, 140.4, 140.4,

134.9, 134.4, 133.5, 131.3, 130.1, 129.1, 129.1, 127.9, 127.9, 127.8, 127.3, 127.3, 126.2, 123.1, 120.5, 119.2, 119.1, 34.4, 32.1, 23.6, 22.0, 19.9, 19.5. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 3057, 3032, 2922, 2236, 1638, 1601, 1524, 1487, 1447, 1408, 1109, 986, 916, 847, 762, 729, 698. HRMS (ESI, m/z) calcd. for $C_{18}H_{15}N$ [M+Na] 268.1102, [M-CN] 219.1179; found 268.1112, 219.117.

P2.1c

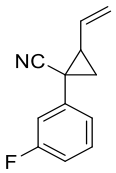


1-(4-fluorophenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(4-fluorophenyl)-3-oxobutanenitrile.

38.3 mg yellow oil, yield: 82 %, d.r.: 76:24. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.24 (m, 2H overlapping major and minor aromatic), 7.09 – 7.01 (m, 2H overlapping major and minor aromatic), 5.78 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H major alkene C*H*), 5.38 (dt, *J* = 17.0, 0.9 Hz, 1H major alkene CH_2), 5.33 (dt, *J* = 10.4, 0.8 Hz, 1H major alkene CH_2), 5.28 (ddd, *J* = 17.0, 1.4, 0.7 Hz, 1H minor alkene CH_2), 5.06 (ddd, *J* = 10.3, 1.4, 0.6 Hz, 1H minor alkene CH_2), 4.85 (ddd, *J* = 17.0, 10.3, 8.7 Hz, 1H minor alkene C*H*), 2.56 – 2.48 (m, 1H minor cyclopropane C*H*), 2.19 – 2.11 (m, 1H major cyclopropane C*H*), 1.93 (dd, *J* = 9.2, 5.9 Hz, 1H minor cyclopropane CH_2), 1.81 – 1.69 (m, 2H major cyclopropane CH_2), 1.63 – 1.57 (m, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 163.4, 161.8, 161.5, 134.3, 133.3, 131.8, 131.8, 131.7, 131.6, 128.27, 128.25, 128.0,

127.9, 122.9, 120.4, 119.3, 119.2, 116.3, 116.2, 116.10, 116.06, 33.8, 31.7, 30.0, 23.3, 21.5, 19.7, 19.4. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 3013, 2990, 928, 2857, 2236, 1640, 1605, 1514, 1449, 1412, 1236, 1165, 1109, 988, 921, 837, 808, 723, 700. HRMS (TAPCI, m/z) calcd. for $C_{12}H_{11}FN$ [M+H] 188.0876; found 188.0874.

P2.1d

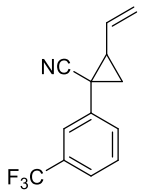


1-(3-fluorophenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(3-fluorophenyl)-3-oxobutanenitrile.

36.1 mg, yellow solid, m.p.: 38.0-43.2 °C, yield: 77 %, d.r.: 81:19. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.29 (m, 1H overlapping major and minor aromatic), 7.17 – 7.08 (m, 1H overlapping major and minor aromatic), 7.07 – 6.95 (m, 2H overlapping major and minor aromatic), 5.78 (ddd, *J* = 16.9, 10.3, 8.2 Hz, 1H major alkene C*H*), 5.39 (dt, *J* = 17.0, 0.9 Hz, 1H major alkene CH_2), 5.35 (dt, *J* = 10.4, 0.8 Hz, 1H major alkene CH_2), 5.30 (ddd, *J* = 16.9, 1.3, 0.8 Hz, 1H minor alkene CH_2), 5.08 (ddd, *J* = 10.4, 1.3, 0.6 Hz, 1H minor alkene CH_2), 4.90 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H minor alkene C*H*), 2.59 – 2.51 (m, 1H minor cyclopropane), 2.25 – 2.16 (m, 1H major cyclopropane), 1.94 (dd, *J* = 9.2, 6.0 Hz, 1H minor cyclopropane), 1.85 – 1.77 (m, 2H major cyclopropane), 1.65 (dd, *J* = 7.1, 6.0 Hz, 1H minor cyclopropane). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 164.0, 162.3, 162.0, 138.6, 138.5, 134.81, 134.75, 134.0, 132.9, 130.8, 130.8, 130.7, 130.6, 125.44, 125.41, 122.6,

121.44, 121.42, 120.0, 119.6, 119.5, 116.9, 116.7, 115.9, 115.7, 115.1, 114.9, 113.0, 112.8, 34.5, 32.2, 23.8, 21.97, 21.95, 19.90, 19.88, 19.5. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3090, 3015, 2990, 2926, 2846, 2238, 1640, 1616, 1589, 1495, 1451, 1275, 1244, 1190, 1167, 1109, 988, 924, 876, 858, 777, 708, 687. HRMS (TAPCI, m/z) calcd. for $C_{12}H_{11}FN$ [M+H] 188.0876; found 188.0876.

P2.1e

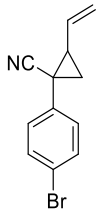


1-(3-(trifluoromethyl)phenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(3-(trifluoromethyl)phenyl)-3-oxobutanenitrile.

34.5 mg, yellow oil, yield: 58 % d.r.: 81:19. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 – 7.46 (m, 5H overlapping major and minor aromatic), 5.80 (ddd, *J* = 17.0, 10.3, 8.2 Hz, 1H major alkene C*H*), 5.41 (dt, *J* = 17.0, 1.0 Hz, 1H major alkene CH_2), 5.37 (dt, *J* = 10.3, 0.8 Hz, 1H major alkene CH_2), 5.31 (dt, *J* = 17.0, 1.0 Hz, 1H minor alkene CH_2), 5.09 (dt, *J* = 10.4, 0.9 Hz, 1H minor alkene CH_2), 4.86 (ddd, *J* = 17.0, 10.3, 8.6 Hz, 1H minor alkene C*H*), 2.60 (td, *J* = 9.0, 7.3 Hz, 1H minor cyclopropane), 2.24 (td, *J* = 8.4, 7.5 Hz, 1H major cyclopropane), 1.99 (dd, *J* = 9.2, 6.1 Hz, 1H minor cyclopropane), 1.91 – 1.81 (m, 2H major cyclopropane), 1.69 (dd, *J* = 7.1, 6.1 Hz, 1H minor cyclopropane) ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2, 133.8, 133.6, 133.31, 132.6, 131.9, 131.6, 129.8, 129.7, 129.4, 126.41, 126.38, 125.59, 125.56, 125.0, 124.91, 124.88, 124.85, 124.82, 122.9, 122.42, 122.39, 122.36, 122.33, 120.0, 119.8, 119.1, 34.5, 32.1, 23.7, 22.0, 19.9, 19.6. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3090,

3019, 2994, 2928, 2857, 2238, 1491, 1449, 1437, 1344, 1331, 1260, 1171, 1128, 1076, 988, 922, 808, 791, 700. HRMS (TAPCI, m/z) calcd. for $C_{13}H_{11}F_3N$ = [M+H] 238.0844; found 238.0849.

P2.1f

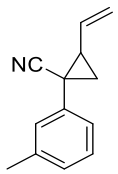


1-(4-bromophenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(4-bromophenyl)-3-oxobutanenitrile.

42.1 mg, yellow solid, m.p. 82.6-84.7 °C, yield: 67 %, d.r.: 79:21. Purified by flash chromatography on silica with 2 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.45 (m, 2H overlapping major and minor aromatic), 7.24 – 7.12 (m, 2H overlapping major and minor aromatic), 5.78 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H major alkene C*H*), 5.38 (dt, *J* = 17.0, 1.0 Hz, 1H major alkene CH_2), 5.34 (dt, *J* = 10.4, 0.9 Hz, 1H major alkene CH_2), 5.28 (ddd, *J* = 17.0, 1.3, 0.7 Hz, 1H minor alkene CH_2), 5.07 (ddd, *J* = 10.3, 1.4, 0.6 Hz, 1H minor alkene CH_2), 4.86 (ddd, *J* = 17.0, 10.4, 8.7 Hz, 1H minor alkene C*H*), 2.57 – 2.49 (m, 1H minor cyclopropane C*H*), 2.16 (tdd, *J* = 8.3, 7.6, 0.8 Hz, 1H major cyclopropane C*H*), 1.93 (dd, *J* = 9.2, 6.0 Hz, 1H minor cyclopropane CH_2), 1.84 – 1.74 (m, 2H major cyclopropane CH_2), 1.61 (dd, *J* = 7.1, 6.0 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 134.0, 133, 132.31, 132.29, 131.5, 131.4, 127.5, 122.8, 122.6, 121.9, 120.0, 119.6, 119.4, 34.3, 32.0, 30.0, 23.5, 21.8, 19.5. IR

($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 2963, 2926, 2853, 2236, 1640, 1491, 1447, 1400, 1261, 1109, 1076, 1011, 986, 920, 827, 789, 712 HRMS (TAPCI, m/z) calcd. for $C_{12}H_{10}BrN$ [M-H] 245.9918; found 245.9911.

P2.1g

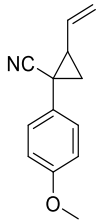


1-(*m*-tolyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(*m*-tolyl)-3-oxobutanenitrile.

38.1 mg, brown oil, yield: 83 %, d.r.: 80:20. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.25 – 7.22 (m, 1H overlapping major and minor aromatic), 7.17 – 7.04 (m, 3H overlapping major and minor aromatic), 5.79 (ddd, *J* = 17.0, 10.3, 8.4 Hz, 1H major alkene C*H*), 5.37 (dt, *J* = 17.0, 1.0 Hz, 1H major alkene CH_2), 5.32 (dt, *J* = 10.4, 0.8 Hz, 1H major alkene CH_2), 5.28 (ddd, *J* = 16.9, 1.5, 0.7 Hz, 1H minor alkene CH_2), 5.04 (dd, *J* = 10.3, 1.4 Hz, 1H minor alkene CH_2), 4.88 (ddd, *J* = 16.9, 10.3, 8.8 Hz, 1H minor alkene C*H*), 2.51 (td, *J* = 8.9, 6.9 Hz, 1H minor cyclopropane C*H*), 2.38 – 2.33 (m, 3H overlapping major and minor CH_3), 2.23 – 2.14 (m, 1H major cyclopropane C*H*), 1.90 (dd, *J* = 9.2, 5.9 Hz, 1H minor cyclopropane CH_2), 1.82 (dd, *J* = 8.6, 5.8 Hz, 1H major cyclopropane CH_2), 1.74 (dd, *J* = 7.3, 5.9 Hz, 1H major cyclopropane CH_2), 1.64 (dd, *J* = 7.0, 5.9 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.9, 135.8, 134.6, 133.6, 132.2, 130.5, 129.4, 129.1, 128.9, 128.7, 126.6, 123.3, 122.6, 120.7, 118.93, 118.86, 34.1, 31.9, 23.4, 22.1, 21.7, 21.6, 20.1,

19.3. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 2988, 2922, 2862, 2234, 1640, 1609, 1589, 1493, 1447, 986, 916, 795, 773, 708, 696 HRMS (ESI, m/z) calcd. for $C_{13}H_{13}N$, [M+] 183.1048, [M+H] 184.1126, [M+Na] 206.0946; found 183.1040, 184.1130, 206.0953.

P2.1h

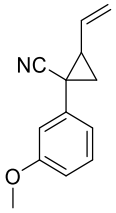


1-(4-methoxyphenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(4-methoxyphenyl)-3-oxobutanenitrile.

37.3 mg, yellow oil, yield: 75 %, d.r.: 66:34. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.20 (m, 2H overlapping major and minor aromatic), 6.90 – 6.86 (m, 2H overlapping major and minor aromatic), 5.78 (ddd, *J* = 17.0, 10.3, 8.4 Hz, 1H major alkene C*H*), 5.36 (dt, *J* = 17.0, 1.0 Hz, 1H major alkene CH_2), 5.31 (ddd, *J* = 10.3, 1.2, 0.6 Hz, 1H major alkene CH_2), 5.27 (ddd, *J* = 16.9, 1.5, 0.7 Hz, 1H minor alkene CH_2), 5.04 (ddd, *J* = 10.4, 1.5, 0.6 Hz, 1H minor alkene CH_2), 4.87 (ddd, *J* = 17.0, 10.3, 8.8 Hz, 1H minor alkene C*H*), 3.80 (s, 3H overlapping major and minor CH_3), 2.48 (td, *J* = 9.0, 6.9 Hz, 1H minor cyclopropane C*H*), 2.13 (tdt, *J* = 8.6, 7.3, 0.8 Hz, 1H major cyclopropane C*H*), 1.89 (dd, *J* = 9.2, 5.8 Hz, 1H minor cyclopropane CH_2), 1.75 (dd, *J* = 8.6, 5.8 Hz, 1H major alkene CH_2), 1.69 (dd, *J* = 7.3, 5.8 Hz, 1H major alkene CH_2), 1.57 (dd, *J* = 6.9, 5.8 Hz, 1H minor alkene CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 159.4, 134.7, 133.8, 131.1, 127.9, 127.6, 124.31, 123.3,

120.9, 118.7, 114.6, 114.5, 55.63, 55.55, 33.4, 31.7, 23.0, 21.5, 19.7, 19.4. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 3009, 2961, 2831, 2234, 2048, 1640, 1613, 1582, 1514, 1464, 1454, 1444, 1306, 1258, 1184, 1113, 1031, 988, 831, 786. HRMS (ESI, m/z) calcd. for $C_{13}H_{13}NO$ [M+H] 199.0997; found 199.0997.

P2.1i

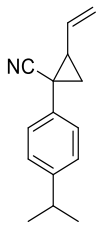


1-(3-methoxyphenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(3-methoxyphenyl)-3-oxobutanenitrile.

37.0 mg, brown oil, yield: 74 %, d.r.: 80:20. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.24 (m, 1H overlapping major and minor aromatic), 6.94 – 6.80 (m, 3H overlapping major and minor aromatic), 5.79 (ddd, *J* = 16.9, 10.3, 8.3 Hz, 1H major alkene C*H*), 5.37 (dt, *J* = 17.0, 1.0 Hz, 1H major alkene CH_2), 5.32 (dt, *J* = 10.3, 0.8 Hz, 1H major alkene CH_2), 5.28 (ddd, *J* = 16.9, 1.5, 0.7 Hz, 1H minor alkene CH_2), 5.05 (dd, *J* = 10.4, 1.4 Hz, 1H minor alkene CH_2), 4.90 (ddd, *J* = 17.0, 10.3, 8.8 Hz, 1H minor alkene C*H*), 3.82 (s, 3H major OCH_3), 3.81 (s, 3H minor OCH_3), 2.52 (td, *J* = 9.0, 7.0 Hz, 1H minor cyclopropane C*H*), 2.23 – 2.15 (m, 1H major cyclopropane C*H*), 1.90 (dd, *J* = 9.2, 5.9 Hz, 1H minor cyclopropane CH_2), 1.82 (dd, *J* = 8.6, 5.9 Hz, 1H major cyclopropane CH_2), 1.74 (dd, *J* = 7.4, 5.9 Hz, 1H major cyclopropane CH_2), 1.64 (dd, *J* = 7.1, 5.8 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 160.0, 137.5, 134.4, 133.8, 133.5, 130.3, 130.1, 123.1,

121.9, 120.5, 119.1, 119.0, 117.9, 115.5, 114.0, 113.2, 111.9, 55.59, 55.55, 34.2, 32.0, 29.9, 23.6, 22.2, 20.2, 19.5. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 3009, 2961, 2940, 2837, 2236, 1603, 1584, 1493, 1454, 1435, 1288, 1219, 1051, 988, 920, 790, 773, 708, 692. HRMS (TAPCI, m/z) calcd. for C13H14NO [M+H] 200.1075; found 200.1083.

P2.1j

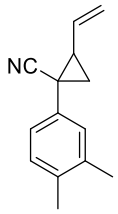


1-(4-isopropylphenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(4-isopropylphenyl)-3-oxobutanenitrile.

35.2 mg, yellow oil, yield: 61 %, d.r.: 80:20. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 18.6 Hz, 4H overlapping major and minor aromatic), 5.83 (ddd, *J* = 16.9, 10.3, 8.3 Hz, 1H major alkene C*H*), 5.39 (dt, *J* = 17.0, 0.9 Hz, 1H major alkene CH_2), 5.37 – 5.30 (m, 1H overlapping major and minor alkene CH_2), 5.08 (dd, *J* = 10.3, 1.4 Hz, 1H minor alkene CH_2), 4.93 (ddd, *J* = 17.0, 10.3, 8.9 Hz, 1H minor alkene C*H*), 2.94 (pd, *J* = 6.9, 1.8 Hz, 1H overlapping major and minor C*H*), 2.54 (td, *J* = 9.0, 6.9 Hz, 1H minor cyclopropane C*H*), 2.21 (q, *J* = 8.2 Hz, 1H major cyclopropane C*H*), 1.93 (dd, *J* = 9.2, 5.8 Hz, 1H minor cyclopropane CH_2), 1.84 (dd, *J* = 8.6, 5.8 Hz, 1H major cyclopropane CH_2), 1.76 (dd, *J* = 7.3, 5.8 Hz, 1H major cyclopropane CH_2), 1.65 (dd, *J* = 7.0, 5.8 Hz, 1H minor cyclopropane CH_2), 1.29 (s, 3H overlapping major and minor CH_3), 1.27 (s, 3H overlapping major

and minor C*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 148.8, 134.1, 133.8, 133.3, 129.7, 129.6, 127.3, 127.1, 125.8, 123.3, 120.7, 118.82, 118.75, 34.0, 34.0, 31.9, 30.0, 24.2, 24.11, 24.08, 23.4, 21.9, 19.8, 19.5. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 3051, 3028, 2963, 2930, 2872, 2236, 1629, 1516, 1458, 1438, 1420, 1120, 1057, 1018, 986, 918, 843. HRMS (ESI, m/z) calcd. for $C_{15}H_{17}N$ [M-CN] 185.1336; found 185.1343.

P2.1k

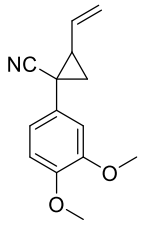


1-(3,4-dimethylphenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(3,4-dimethylphenyl)-3-oxobutanenitrile.

38.0 mg, yellow solid, m.p.: 43.0-49.0°C, yield: 77 %, d.r.: 79:21. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.14 – 7.07 (m, 2H overlapping major and minor aromatic), 7.02 (ddd, *J* = 17.1, 7.8, 2.2 Hz, 1H overlapping major and minor aromatic), 5.79 (ddd, *J* = 17.0, 10.3, 8.4 Hz, 1H major alkene C*H*), 5.36 (dt, *J* = 17.0, 1.0 Hz, 1H major alkene C*H*$_2$), 5.33 – 5.30 (m, 1H major alkene C*H*$_2$), 5.27 (dd, *J* = 16.6, 1.4 Hz, 1H minor alkene C*H*$_2$), 5.04 (dd, *J* = 10.4, 1.5 Hz, 1H minor alkene C*H*$_2$), 4.89 (ddd, *J* = 17.0, 10.4, 8.8 Hz, 1H minor alkene C*H*), 2.49 (td, *J* = 9.0, 6.9 Hz, 1H minor cyclopropane), 2.26 (d, *J* = 9.7 Hz, 6H), 2.15 (td, *J* = 8.4, 7.4 Hz, 1H major cyclopropane) 1.88 (dd, *J* = 9.2, 5.8 Hz, 1H minor cyclopropane), 1.79 (dd, *J* = 8.6, 5.8 Hz, 1H major cyclopropane), 1.71 (dd, *J* = 7.3, 5.8 Hz, 1H major cyclopropane), 1.62 (dd, *J* = 7.0, 5.8 Hz, 1H minor cyclopropane). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 137.4, 137.1, 136.5, 134.7, 133.8, 133.3, 130.9, 130.3, 130.2, 129.6, 127.3,

126.9, 123.4, 123.0, 120.8, 118.7, 118.7, 33.9, 31.8, 23.2, 21.8, 20.05, 20.02, 19.8, 19.7, 19.6, 19.3. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 3015, 2972, 2922, 2864, 2234, 1638, 1616, 1506, 1450, 1136, 986, 916, 824, 787, 718, 704. HRMS (ESI, m/z) calcd. for $C_{14}H_{15}N$ [M+Na] 220.1102, [M-CN] 171.1179; found 220.1109, 171.1174.

P2.1l

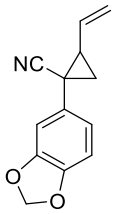


1-(3,4-dimethoxyphenyl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(3,4-dimethoxyphenyl)-3-oxobutanenitrile.

48.6 mg, brown oil, yield: 85 %, d.r.: 75:25. Purified by flash chromatography on silica with 10 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.89 – 6.76 (m, 3H overlapping major and minor aromatic), 5.79 (ddd, *J* = 17.2, 10.4, 8.5 Hz, 1H major alkene C*H*), 5.37 (dt, *J* = 17.0, 0.9 Hz, 1H major alkene CH_2), 5.32 (dd, *J* = 10.3, 1.0 Hz, 1H major alkene CH_2), 5.30 – 5.26 (m, 1H minor alkene CH_2), 5.04 (dd, *J* = 10.3, 1.3 Hz, 1H minor alkene CH_2), 4.88 (ddd, *J* = 17.0, 10.3, 8.9 Hz, 1H minor alkene C*H*), 3.93 – 3.85 (m, 6H overlapping major and minor OCH_3), 2.48 (td, *J* = 9.0, 6.9 Hz, 1H minor cyclopropane C*H*), 2.14 (q, *J* = 8.2 Hz, 1H major cyclopropane C*H*), 1.89 (ddd, *J* = 9.1, 5.8, 0.8 Hz, 1H minor cyclopropane CH_2), 1.77 (dd, *J* = 8.6, 5.8 Hz, 1H major cyclopropane CH_2), 1.69 (dd, *J* = 7.2, 5.8 Hz, 1H major cyclopropane CH_2), 1.57 (dd, *J* = 6.9, 5.8 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 149.3, 149.3, 149.0,

134.6, 133.8, 128.4, 124.7, 123.3, 122.1, 120.9, 118.8, 118.7, 118.3, 113.0, 111.5, 111.2, 110.0, 56.3, 56.23, 56.21, 56.1, 33.5, 31.7, 22.9, 21.8, 19.81, 19.76. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3007, 2961, 2938, 2839, 2234, 1605, 1591, 1520, 1464, 1454, 1416, 1250, 1223, 1177, 1150, 1026, 990, 920, 851, 810, 766, 708. HRMS (TAPCI, m/z) calcd. for $C_{14}H_{15}NO_2$ [M-H] 228.1025, [M+H] 230.1181; found 228.1029, 230.1175.

P2.1m

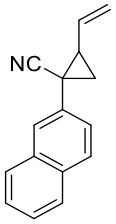


1-(benzo[*d*][1,3]dioxol-5-yl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(benzo[*d*][1,3]dioxol-5-yl)-3-oxobutanenitrile.

45.2 mg, brown solid, m.p.: 53.6-56.0 °C, yield: 85 %, d.r.: 76:24. Purified by flash chromatography on silica with 10 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.85 – 6.73 (m, 3H overlapping major and minor aromatic), 6.00 – 5.95 (m, 2H overlapping major and acetal CH_2), 5.77 (ddd, *J* = 16.9, 10.3, 8.4 Hz, 1H major alkene C*H*), 5.36 (dt, *J* = 17.0, 1.0 Hz, 1H major alkene CH_2), 5.33 – 5.25 (m, 1H overlapping major and minor alkene CH_2), 5.06 (ddd, *J* = 10.4, 1.4, 0.5 Hz, 1H minor alkene CH_2), 4.90 (ddd, *J* = 17.0, 10.3, 8.8 Hz, 1H minor alkene C*H*), 2.47 (td, *J* = 9.0, 7.0 Hz, 1H minor cyclopropane C*H*), 2.15 – 2.08 (m, 1H major cyclopropane C*H*), 1.88 (dd, *J* = 9.2, 5.8 Hz, 1H minor cyclopropane CH_2), 1.73 (dd, *J* = 8.6, 5.8 Hz, 1H major cyclopropane CH_2), 1.68 (dd, *J* = 7.3, 5.8 Hz, 1H major cyclopropane CH_2), 1.54 (dd, *J* = 7.0, 5.8 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 148.2, 148.0, 147.6, 134.5, 133.6, 129.7, 126.0, 123.6, 123.1, 120.7, 120.2, 118.9, 118.9, 110.3, 108.72, 108.68, 107.1,

101.7, 33.4, 31.1, 23.0, 21.9, 19.9, 19.8. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 3011, 2988, 2903, 2780, 2235, 1682, 1640, 1613, 1504, 1445, 1233, 1039, 932, 920, 815. HRMS (ESI, m/z) calcd. for $C_{13}H_{11}NO_2$ [M+Na] 236.0687; found 236.0696.

P2.1n

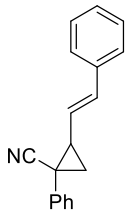


1-(naphthalen-2-yl)-2-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(napthalen-2-yl)-3-oxobutanenitrile.

42.0 mg, brown oil, yield: 77 %, d.r.: 78:22. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 – 7.79 (m, 3H aromatic), 7.56 – 7.45 (m, 2H aromatic), 7.33 (dd, *J* = 8.6, 2.0 Hz, 1H aromatic), 7.25 – 7.11 (m, 3H aromatic, minor), 6.75 – 6.64 (m, 2H aromatic, minor), 5.85 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H, alkene C*H*, major), 5.70 (ddtd, *J* = 13.5, 8.4, 2.6, 1.8 Hz, 1H alkene CH_2 minor), 5.56 (ddt, *J* = 11.4, 5.5, 2.7 Hz, 1H alkene CH_2, minor), 5.41 (dt, *J* = 17.0, 1.0 Hz, 1H, alkene CH_2, major), 5.36 (dt, *J* = 10.3, 0.8 Hz, 1H alkene CH_2, major), 4.66 (dd, *J* = 12.6, 3.5 Hz, 1H alkene C*H*, minor), 3.56 (dtt, *J* = 18.0, 5.1, 2.9 Hz, 1H cyclopropane CH_2, minor), 2.74 (ddd, *J* = 17.8, 8.5, 1.0 Hz, 1H cyclopropane CH_2, minor), 2.46 – 2.33 (m, 1H cyclopropane C*H*, minor), 2.36 – 2.24 (m, 1H cyclopropane C*H*, major), 1.96 (dd, *J* = 8.7, 5.9 Hz, 1H, cyclopropane CH_2, major), 1.84 (dd, *J* = 7.4, 6.0 Hz, 1H cyclopropane CH_2, major). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 138.4, 134.5, 133.4, 133.2, 132.8, 131.2, 129.9,

129.2, 129.1, 128.08, 128.05, 128.0, 127.9, 127.5, 127.1, 126.7, 125.2, 124.7, 123.4, 123.2, 120.6, 119.3, 119.1, 109.2, 40.4, 36.4, 34.1, 28.9, 23.4, 22.4. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3084, 3059, 3025, 2924, 2851, 2236, 1634, 1601, 1510, 1435, 1354, 1200, 988, 737, 704. HRMS (TAPCI, m/z) calcd. for $C_{16}H_{13}N$ [M+Na] 242.0946; found 242.0945.

P2.2a

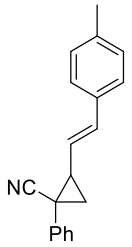


(E)-1-phenyl-2-styrylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-phenyl-3-vinyloxirane.

44 mg, colorless oil, yield: 72 %, d.r.: 80:20. Purified by flash chromatography on silica with 2 % EA:Hexane. Major diastereomer (syn) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 – 7.29 (m, 10H aromatic), 6.71 (d, *J* = 15.8 Hz, 1H alkene C*H*), 6.14 (dd, *J* = 15.7, 8.7 Hz, 1H alkene C*H*), 2.35 (ddd, *J* = 9.0, 8.1, 7.1 Hz, 1H cyclopropane C*H*), 1.95 (dd, *J* = 8.6, 6.0 Hz, 1H cyclopropane CH_2), 1.87 (dd, *J* = 7.3, 5.9 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 135.9, 134.2, 129.2, 128.9, 128.1, 128.0, 126.5, 126.1, 125.7, 120.6, 34.4, 24.1, 22.5. Minor diastereomer (anti) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.31 (m, 5H aromatic), 7.25 – 7.15 (m, 3H aromatic), 7.13 – 7.08 (m, 2H aromatic), 6.63 (d, *J* = 15.8 Hz, 1H alkene C*H*), 5.21 (dd, *J* = 15.8, 9.1 Hz, 1H alkene C*H*), 2.69 (tdd, *J* = 9.1, 7.0, 0.7 Hz, 1H cyclopropane C*H*), 2.02 (dd, *J* = 9.2, 5.9 Hz, 1H cyclopropane CH_2), 1.74 (dd, *J* = 7.0, 5.9 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7, 133.9, 132.4, 129.8, 129.2, 128.8, 128.7, 127.0, 126.3, 125.1, 123.1, 31.9, 20.5, 20.1. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3082, 3059, 3028, 2932, 2228, 1599, 1497, 1448, 959, 748, 696.

HRMS (ESI, m/z) calcd. for $C_{18}H_{15}N$ [M+H] 246.1283, [M-CN] 219.1179; found 246.1287, 219.1173.

P2.2b

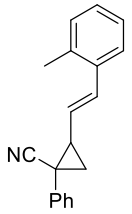


(E)-2-(4-methylstyryl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(*p*-tolyl)-3-vinyloxirane.

major (syn): white solid, m.p.: 91.0-95.2 °C, minor (anti): white solid, m.p.: 95.0-97.4 °C. 47 mg, yield: 72 %, d.r.: 79:21 Purified by flash chromatography on silica with 2 % EA:Hexane. Major (syn) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.36 (m, 2H), 7.35 – 7.29 (m, 5H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.67 (d, *J* = 15.7 Hz, 1H), 6.09 (dd, *J* = 15.7, 8.8 Hz, 1H), 2.35 (s, 3H), 2.33 (dd, *J* = 7.6, 0.9 Hz, 1H), 1.94 (dd, *J* = 8.6, 5.9 Hz, 1H), 1.85 (dd, *J* = 7.4, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 136.0, 134.0, 133.8, 129.6, 129.2, 127.9, 126.4, 125.7, 125.0, 120.7, 34.6, 24.1, 22.4, 21.5. Minor (trans) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 5H), 7.06 – 6.97 (m, 4H), 6.59 (d, *J* = 15.8 Hz, 1H), 5.16 (dd, *J* = 15.8, 9.1 Hz, 1H), 2.68 (tdd, *J* = 9.0, 7.0, 0.7 Hz, 1H), 2.28 (s, 3H), 2.01 (dd, *J* = 9.2, 5.9 Hz, 1H), 1.72 (dd, *J* = 7.0, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 133.9, 133.8, 132.5, 129.8, 129.5, 129.1, 128.7, 126.2, 124.0, 123.2, 32.0, 21.4, 20.4, 20.1. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 3026, 2920, 2860, 2228, 1601, 1514, 1448, 960, 800,

764, 698. HRMS (ESI, m/z) calcd. for $C_{19}H_{17}N$ 260.1441 [M+H], 2802.1266 [M+Na], 233.1336 [M-CN]; found 260.1441, 282.1266, 233.1336.

P2.2c

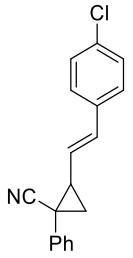


(E)-2-(2-methylstyryl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(*m*-tolyl)-3-vinyloxirane.

30 mg, white solid, m.p.: 78.2-84.3 °C, yield: 46 %, d.r.: 76:24. Purified by flash chromatography on silica with 2 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 – 6.96 (m, 9H overlapping major and minor aromatic), 6.94 (d, *J* = 15.6 Hz, 1H major alkene C*H*), 6.83 (d, *J* = 15.7 Hz, 1H minor alkene C*H*), 6.05 (dd, *J* = 15.6, 8.7 Hz, 1H major alkene C*H*), 5.13 (dd, *J* = 15.6, 8.9 Hz, 1H minor alkene C*H*), 2.75 (tdd, *J* = 9.1, 7.1, 0.8 Hz, 1H minor alkene C*H*), 2.44 – 2.36 (m, 4H overlapping major CH_3 and cyclopropane C*H*), 2.30 (s, 3H minor CH_3), 2.05 (dd, *J* = 9.1, 5.9 Hz, 1H minor cyclopropane CH_2), 1.98 (dd, *J* = 8.6, 6.0 Hz, 1H major cyclopropane CH_2), 1.90 (dd, *J* = 7.3, 5.9 Hz, 1H major cyclopropane CH_2), 1.78 (dd, *J* = 7.0, 5.9 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.94, 135.88, 135.7, 135.4, 135.4, 132.4, 132.1, 131.9, 130.52, 130.48, 129.8, 129.2, 129.2, 128.7, 128.0, 127.9, 127.8, 127.4, 126.5, 126.4, 126.2, 126.1, 125.72, 125.66, 123.2, 120.6, 34.7, 32.0, 24.2, 22.6, 20.6, 20.10, 20.05, 20.0. IR ($\bar{\nu}$ –

$\bar{\nu}_{IR}$, neat) 3011, 2928, 2868, 2234, 1946, 1915, 1800, 1601, 1381, 1265, 1192, 1159, 1113, 1080, 1055, 1038, 961, 909, 839. HRMS (TAPCI, m/z) calcd. for $C_{19}H_{17}N$ [M-H] 258.1283; found 258.1291.

P2.2d

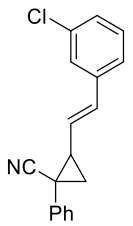


(E)-2-(4-chlorostyryl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(4-chlorophenyl)-3-vinyloxirane.

55mg, white solid, m.p.: 78.2-89.3 °C, yield: 79 %, d.r.: 79:21. Purified by flash chromatography on silica with 2-5 % EA:Hexane. Major (syn) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.34 (m, 2H aromatic), 7.38 – 7.25 (m, 7H aromatic), 6.65 (d, *J* = 15.7 Hz, 1H alkene C*H*), 6.11 (dd, *J* = 15.7, 8.7 Hz, 1H alkene C*H*), 2.33 (tdd, *J* = 8.6, 7.3, 0.7 Hz, 1H cyclopropane C*H*), 1.95 (dd, *J* = 8.6, 6.0 Hz, 1H cyclopropane CH_2), 1.86 (dd, *J* = 7.3, 6.0 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 135.1, 133.7, 132.9, 129.3, 129.0, 128.0, 127.7, 126.8, 125.8, 120.6, 34.2, 24.0, 22.6. Minor (anti) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.29 (m, 5H aromatic), 7.22 – 7.15 (m, 2H aromatic), 7.05 – 6.98 (m, 2H aromatic), 6.57 (d, *J* = 15.8 Hz, 1H alkene C*H*), 5.17 (dd, *J* = 15.8, 9.1 Hz, 1H alkene C*H*), 2.68 (tdd, *J* = 9.2, 7.0, 0.7 Hz, 1H cyclopropane C*H*), 2.07 – 1.96 (m, 1H cyclopropane CH_2), 1.74 (dd, *J* = 7.0, 5.9 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 133.5, 132.7, 132.3, 129.8, 129.2, 129.0, 128.8, 127.5, 125.9, 123.0,

31.7, 20.6, 20.1. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3090, 3063, 3030, 2930, 2233, 1601, 1492, 1450, 1089, 961, 812, 750, 696. HRMS (ESI, m/z) calcd. for $C_{18}H_{14}ClN$ 253.0787 [M-CN]; found 253.0787.

P2.2e

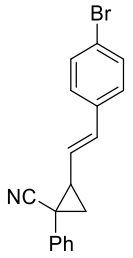


(E)-2-(3-chlorostyryl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(3-chlorophenyl)-3-vinyloxirane.

37 mg, yellow oil, yield: 70 %, d.r.: 78:22. Purified by flash chromatography on deactivated silica with 5 % EA:Hexane containing 1% triethylamine. Major (syn) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.18 (m, 9H aromatic), 6.64 (d, *J* = 15.7 Hz, 1H alkene C*H*), 6.14 (dd, *J* = 15.7, 8.7 Hz, 1H alkene C*H*), 2.33 (q, *J* = 8.3 Hz, 1H), 1.96 (dd, *J* = 8.6, 6.0 Hz, 1H), 1.87 (dd, *J* = 7.3, 6.0 Hz, 1H). Minor (anti) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.30 (m, 5H aromatic), 7.18 – 7.10 (m, 2H aromatic), 7.07 (d, *J* = 1.4 Hz, 1H aromatic), 6.97 (td, *J* = 4.6, 1.7 Hz, 1H), 6.56 (d, *J* = 15.7 Hz, 1H alkene C*H*), 5.22 (dd, *J* = 15.8, 9.1 Hz, 1H alkene C*H*), 2.74 – 2.60 (m, 1H cyclopropane C*H*), 2.03 (dd, *J* = 9.2, 5.9 Hz, 1H cyclopropane CH_2), 1.74 (dd, *J* = 7.0, 6.0 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.4, 135.6, 134.8, 134.7, 132.8, 132.6, 132.2, 130.1, 130.0, 129.8, 129.3, 129.2, 128.9, 128.1, 128.0, 127.8, 127.7, 126.8, 126.5, 126.2, 125.8, 124.7, 124.5, 122.9, 120.5, 34.2, 31.7, 24.0, 22.6, 20.7, 20.1. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088,

3061, 3030, 2937, 2233, 1682, 1593, 1566, 1497, 1450, another at about 1400, 1027, 1078, 959, 880, 779, 750, 696. HRMS (ESI, m/z) calcd. for $C_{18}H_{14}ClN$ [M-CN] 253.0790; found 253.0791.

P2.2f

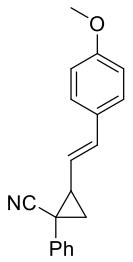


(E)-2-(4-bromostyryl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(4-bromophenyl)-3-vinyloxirane.

61 mg, white solid, m.p. 70.0-85.4 °C, yield: 80 %, d.r.: 80:20. Purified by flash chromatography on silica with 2 % EA:Hexane. Major (syn) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 – 7.24 (m, 9H aromatic), 6.63 (d, *J* = 15.7 Hz, 1H alkene C*H*), 6.12 (dd, *J* = 15.7, 8.7 Hz, 1H alkene C*H*), 2.36 – 2.28 (m, 1H cyclopropane C*H*), 1.96 (dd, *J* = 8.6, 6.0 Hz, 1H cyclopropane CH_2), 1.86 (dd, *J* = 7.3, 6.0 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 135.5, 133.0, 132.0, 129.3, 128.1, 127.0, 126.9, 125.8, 121.9, 120.6, 34.3, 24.0, 22.5. Minor (anti) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.30 (m, 7H aromatic), 6.99 – 6.94 (m, 2H aromatic), 6.56 (d, *J* = 15.8 Hz, 1H alkene C*H*), 5.19 (dd, *J* = 15.8, 9.1 Hz, 1H alkene C*H*), 2.67 (tdd, *J* = 9.1, 6.9, 0.7 Hz, 1H cyclopropane C*H*), 2.02 (dd, *J* = 9.2, 5.9 Hz, 1H cyclopropane CH_2), 1.74 (dd, *J* = 7.0, 5.9 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 132.7, 132.3, 131.9, 129.8, 129.2,

128.8, 127.8, 126.0, 122.9, 121.7, 31.7, 20.6, 20.1. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 3061, 3028, 2234, 1601, 1487, 1448, 1404, 1072, 1009, 959, 808, 747, 969. HRMS (ESI, m/z) calcd. for $C_{18}H_{14}BrN$ [M+] 323.310, [M+Na] 346.0207; found 323.0310, 346.0199.

P2.2g

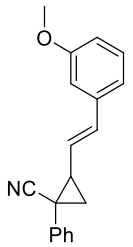


(E)-2-(4-methoxystyryl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(4-methoxyphenyl)-3-vinyloxirane.

44 mg, white solid, m.p: 68.1-75.6 °C, yield: 64 %, d.r.: 82:18. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.28 (m, overlapping 7H major, 5H minor, aromatic), 7.08 – 7.01 (m, 2H, aromatic, minor), 6.91 – 6.84 (m, 2H, aromatic, major), 6.76 (dd, *J* = 8.8, 2.0 Hz, 2H, aromatic, minor), 6.64 (d, *J* = 15.7 Hz, 1H, alkene C*H*, major), 6.57 (d, *J* = 15.7 Hz, 1H, alkene C*H*, minor), 6.00 (ddd, *J* = 15.8, 8.6, 1.8 Hz, 1H, alkene C*H*, major), 5.07 (ddd, *J* = 15.7, 9.0, 1.6 Hz, 1H, alkene C*H*, minor), 3.82 (s, 3H, CH_3, major), 3.76 (s, 3H, CH_3, minor), 2.67 (td, *J* = 9.0, 7.0 Hz, 1H, cyclopropane C*H*, minor), 2.32 (q, *J* = 8.2 Hz, 1H, cyclopropane C*H*, major), 2.00 (dd, *J* = 9.1, 5.9 Hz, 1H, cyclopropane CH_2, minor), 1.93 (dd, *J* = 8.6, 6.0 Hz, 1H, cyclopropane, CH_2 , major), 1.84 (dd, *J* = 7.3, 6.0 Hz, 1H,

cyclopropane, CH_2 , major), 1.71 (dd, *J* = 7.1, 5.9 Hz, 1H, cyclopropane, CH_2 , minor). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 159.5, 136.0, 133.6, 133.4, 132.5, 129.8, 129.5, 129.4, 129.2, 129.1, 128.6, 128.3, 127.87, 127.8, 127.5, 127.0, 125.7, 123.7, 123.2, 122.8, 120.7, 114.3, 114.2, 34.6, 32.0, 24.1, 22.4, 20.3, 20.1. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 3030, 3007, 2957, 2936, 2837, 2234, 1607, 1514, 1450, 1304, 1252, 1178, 1109, 1031, 959, 818, 762, 741, 696. HRMS (TAPCI, m/z) calcd. for $C_{19}H_{17}NO$ [M-H] 274.1232; found 274.1234.

P2.2h

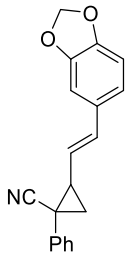


(E)-2-(3-methoxystyryl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(3-methoxyphenyl)-3-vinyloxirane.

36 mg colorless oil, yield: 52 %, d.r.: 78:22. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 6.56 (m, 10H overlapping major and minor 9H aromatic, 1H alkene C*H*), 6.19 – 6.07 (m, 1H major alkene C*H*), 5.25 – 5.16 (m, 1H minor alkene C*H*), 3.83 (d, *J* = 1.5 Hz, 3H major OCH_3), 3.74 (d, *J* = 1.5 Hz, 3H minor OCH_3), 2.68 (td, *J* = 9.1, 8.6, 6.8 Hz, 1H minor cyclopropane C*H*), 2.39 – 2.29 (m, 1H major cyclopropane C*H*), 2.02 (dd, *J* = 9.2, 6.0 Hz, 1H minor cyclopropane CH_2), 1.98 – 1.92 (m, 1H major cyclopropane CH_2), 1.86 (td, *J* = 6.7, 5.8, 1.4 Hz, 1H major cyclopropane CH_2), 1.77 – 1.71 (m, 1H minor cyclopropane CH_2) ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 159.9, 138.1, 138.0, 135.9, 134.1, 133.8, 132.4, 129.9, 129.8, 129.8, 129.3, 129.2, 128.8, 128.0, 126.4, 125.8, 125.6, 123.1,

120.6, 119.2, 118.9, 113.8, 113.2, 111.9, 111.8, 55.5, 55.4, 34.4, 31.8, 24.1, 22.5, 20.5, 20.2. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 3028, 2957, 2940, 2835, 2234, 1599, 1580, 1495, 1452, 1290, 1267, 1157, 1040, 961, 777, 760, 694. HRMS (ESI, m/z) calcd. for $C_{19}H_{17}NO$ [M+H] 276.1388, M-CN = 249.1285; found 276.1388, 249.1282.

P2.2i

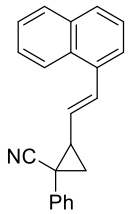


(E)-2-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 5-(3-vinyloxiran-2-yl)benzo[d][1,3]dioxole.

52 mg, white solid, m.p.: 111.4-114.3 °C, yield: 73 %, d.r.: 79:21. Purified by flash chromatography on silica with 5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.28 (m, 5H overlapping major and minor aromatic), 6.98 – 6.49 (m, 4H overlapping major and minor 3H aromatic 1H alkene C*H*), 6.01 – 5.86 (m, 3H overlapping major and minor 2H acetal CH_2 and 1H major alkene C*H*), 5.03 (dd, *J* = 15.7, 9.0 Hz, 1H minor alkene C*H*), 2.65 (tdd, *J* = 9.1, 7.0, 0.7 Hz, 1H minor cyclopropane C*H*), 2.30 (tdd, *J* = 8.5, 7.3, 0.7 Hz, 1H major cyclopropane C*H*), 2.00 (dd, *J* = 9.2, 5.9 Hz, 1H minor cyclopropane CH_2), 1.93 (dd, *J* = 8.6, 6.0 Hz, 1H major cyclopropane CH_2), 1.84 (dd, *J* = 7.4, 6.0 Hz, 1H major cyclopropane CH_2), 1.71 (dd, *J* = 7.0, 6.0

Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.7, 135.9, 133.7, 133.5, 132.4, 131.2, 131.1, 129.8, 129.2, 129.1, 128.7, 127.9, 126.9, 125.7, 124.2, 123.2, 121.2, 121.1, 120.6, 108.54, 108.52, 108.45, 105.9, 105.4, 101.5, 101.4, 101.3, 34.5, 31.8, 24.0, 22.4, 20.4, 20.1. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 3028, 3009, 2895, 2234, 1601, 1505, 1487, 1447, 1350, 1252, 1196, 1105, 1037, 959, 928, 802, 746, 696. HRMS (ESI, m/z) calcd. for $C_{19}H_{15}NO_2$ [M+Na] 312.1000; found 312.1002.

P2.2j

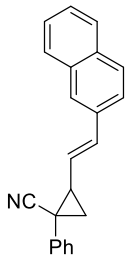


(E)-2-(2-(naphthalen-1-yl)vinyl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(naphthalen-1-yl)-3-vinyloxirane.

38mg, white solid, m.p.: 99.3-101.4 °C, yield: 61 %, d.r.: 74:26. Purified by flash chromatography on silica with 2 % EA:Hexane. Major (syn) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 – 7.29 (m, 13H overlapping 12H aromatic and 1H alkene C*H*), 6.21 (ddd, *J* = 15.5, 8.7, 2.7 Hz, 1H alkene C*H*), 2.49 (q, *J* = 8.3 Hz, 1H cyclopropane C*H*), 2.00 (ddd, *J* = 8.4, 6.0, 1.5 Hz, 1H cyclopropane CH_2), 1.94 (t, *J* = 6.7 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 134.3, 133.8, 131.4, 131.1, 129.24, 129.18, 128.79, 128.47, 127.96, 126.36, 126.03, 125.91, 125.68, 124.43, 123.86, 120.6, 34.6, 24.2, 22.6. Minor (anti) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 – 7.26 (m, 12H aromatic), 7.11 (dt, *J* = 7.2, 1.0 Hz, 1H alkene C*H*), 5.27 (dd, *J* = 15.6, 8.8 Hz, 1H

alkene C*H*), 2.84 (tdd, *J* = 9.1, 7.0, 0.8 Hz, 1H cyclopropane C*H*), 2.08 (dd, *J* = 9.1, 6.0 Hz, 1H cyclopropane CH_2), 1.83 (dd, *J* = 7.0, 6.0 Hz, 1H cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 133.7, 132.5, 131.4, 131.0, 129.9, 129.2, 128.8, 128.7, 128.4, 128.3, 126.3, 126.1, 125.7, 124.1, 123.9, 123.1, 32.0, 20.7, 20.0. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 3046, 2955, 2236, 1601, 1503, 1451, 1398, 1265, 1173, 1111, 957, 797, 775, 756, 733, 696. HRMS (ESI, m/z) calcd. for $C_{22}H_{17}N$ [M+Na] 318.1259; found 318.1265.

P2.2k

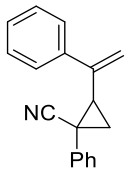


(E)-2-(2-(naphthalen-2-yl)vinyl)-1-phenylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-(naphthalen-2-yl)-3-vinyloxirane.

39 mg, white solid, m.p.: 131.0-140.1 °C, yield: 62 %, d.r.: 80:20. Purified by flash chromatography on silica with 2 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.87 – 7.19 (m, 12H overlapping major and minor aromatic), 6.86 (d, *J* = 15.7 Hz, 1H major alkene C*H*), 6.79 (d, *J* = 15.7 Hz, 1H minor alkene C*H*), 6.26 (dd, *J* = 15.7, 8.8 Hz, 1H major alkene C*H*), 5.37 – 5.29 (m, 1H minor alkene C*H*), 2.75 (tdd, *J* = 9.1, 7.0, 0.7 Hz, 1H minor cyclopropane C*H*), 2.40 (tdd, *J* = 8.6, 7.3, 0.7 Hz, 1H major cyclopropane C*H*), 2.06 (dd, *J* = 9.1, 6.0 Hz, 1H minor cyclopropane CH_2), 1.99 (dd, *J* = 8.6, 6.0 Hz, 1H major cyclopropane CH_2), 1.91 (dd, *J* = 7.3, 6.0

Hz, 1H major cyclopropane CH_2), 1.78 (dd, J = 6.9, 6.1 Hz, 1H minor cyclopropane CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 134.3, 134.0, 133.8, 133.3, 129.9, 129.3, 129.2, 128.8, 128.56 128.4, 128.3, 128.2, 128.0, 127.94, 127.85, 126.60, 126.58, 126.45, 126.3, 126.24, 126.22, 125.8, 125.5, 123.7, 123.3, 123.1, 120.7, 100.2, 34.6, 32.0, 24.2, 22.6, 20.6, 20.3. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3088, 3053, 3028, 3003, 2236, 1599, 1505, 1452, 1265, 1109, 959, 812, 746, 735, 696. HRMS (ESI, m/z) calcd. for $C_{22}H_{17}N$ [M+] 295.1361, [M+H] 296.1439, [M+Na] 318.1259; found 295.1357, 296.1435, 318.1263.

P2.2l

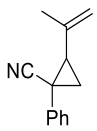


1-phenyl-2-(1-phenylvinyl)cyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-phenyl-2-vinyloxirane.

15 mg, slightly yellow needles, m.p.: 118.4-122.6 °C, yield: 34 %, d.r.: 77:23. Purified by flash chromatography on silica with 1 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.27 (m, 8H overlapping major and minor aromatic), 7.20 – 7.13 (m, 1H overlapping major and minor aromatic), 5.76 (s, 1H major methylene CH_2), 5.39 (s, 1H minor methylene CH_2), 5.28 (d, J = 1.4 Hz, 1H major methylene CH_2), 4.90 (d, J = 1.4 Hz, 1H minor methylene CH_2), 2.98 (ddd, J = 9.0, 7.6, 1.4 Hz, 1H minor cyclopropane CH), 2.55 (td, J = 8.2, 1.3 Hz, 1H major cyclopropane CH), 2.13 (dd, J = 7.8, 6.0 Hz, 1H major cyclopropane CH_2), 2.04 (dq, J = 9.1, 6.3 Hz, 2H minor cyclopropane CH_2), 1.91 (dd, J = 8.5, 6.1 Hz, 1H major cyclopropane CH_2). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 142.7, 140.4, 139.7, 139.6, 136.0, 131.2, 129.3, 128.80, 128.77, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 126.1, 126.0, 125.5, 123.4, 120.0, 115.4, 114.7, 35.7, 34.3, 23.9, 21.7, 21.1, 17.4. IR ($\bar{v} - \bar{v}_{IR}$, neat) 3061, 2926, 2236, 1726, 1694, 1601, 1495, 1449, 1317, 1279, 1111, 1071, 1026, 910, 758, 698. HRMS (ESI, m/z) calcd. for $C_{18}H_{15}N$ [M+H] 246.1283; found 246.1281.

P2.2m

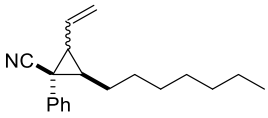


1-phenyl-2-(prop-1-en-2-yl)cyclopropane-1-carbonitrile was prepared following General Procedure 2.A with 2-methyl-2-vinyloxirane.

22 mg, yellow oil, yield: 48 %, d.r.: 85:15. Purified by flash chromatography on silica with 1 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H aromatic), 5.12 (h, *J* = 1.4 Hz, 1H major alkene C*H*$_2$), 4.95 (q, *J* = 1.1 Hz, 1H major alkene C*H*$_2$), 4.83 – 4.78 (m, 1H minor alkene C*H*$_2$), 4.71 (q, *J* = 1.3 Hz, 1H minor alkene C*H*$_2$), 2.54 – 2.47 (m, 1H minor cyclopropane C*H*), 2.17 – 2.06 (m, 1H major cyclopropane C*H*), 2.04 – 1.92 (m, 1H), 1.89 (dd, *J* = 7.7, 6.2 Hz, overlapping 1H major cyclopropane C*H*$_2$, 3H major C*H*$_3$), 1.83 (dd, *J* = 9.2, 6.2 Hz, 1H minor cyclopropane C*H*$_2$), 1.72 (dd, *J* = 8.5, 5.9 Hz, 1H minor cyclopropane C*H*$_2$). 1.43 (t, *J* = 0.9 Hz, 3H minor C*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9, 138.2, 136.5, 131.7, 129.3, 129.2, 128.63, 128.59, 128.2, 127.9, 126.0, 123.7, 120.4, 115.4, 114.2, 37.2, 36.1, 22.9, 22.5, 22.3, 21.6, 21.5,

19.9, 17.3. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 2974, 2939, 22341651, 1601, 1497, 1451, 1385, 1234, 1196, 1119, 902, 760, 721, 696. HRMS (ESI, m/z) calcd. for $C_{13}H_{13}N$ [M+H] 184.1126; found 184.1123.

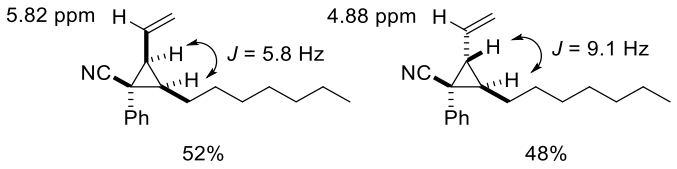
P2.2n



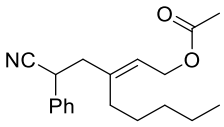
2-heptyl-1-phenyl-3-vinylcyclopropane-1-carbonitrile was prepared following General Procedure 2.A with (E)-2-(non-1-en-1-yl)oxirane.

42 mg, yellow oil, yield: 62 %, d.r.: 52:48. Purified by flash chromatography on silica with 0.5 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.26 (m, 5H aromatic), 5.82 (ddd, *J* = 17.0, 10.4, 9.4 Hz, 1H alkene C*H*), 5.41 (ddd, *J* = 16.9, 1.5, 0.7 Hz, 1H alkene CH_2), 5.35 (ddd, *J* = 10.4, 1.5, 0.6 Hz, 1H alkene CH_2), 5.24 (ddd, *J* = 16.9, 1.5, 0.6 Hz, 1H alkene CH_2), 5.05 – 4.98 (m, 1H alkene CH_2), 4.88 (ddd, *J* = 16.9, 10.3, 8.9 Hz, 1H alkene C*H*), 2.31 (t, *J* = 9.1 Hz, 1H cyclopropane C*H*), 2.19 (dd, *J* = 8.9, 5.8 Hz, 1H cyclopropane C*H*), 1.88 – 1.12 (m, 13H overlapping aliphatic CH_2 and cyclopropane C*H*), 0.89 (q, *J* = 7.1 Hz, 3H CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 133.9, 133.3, 132.4, 132.3, 132.20, 132.18, 131.4, 129.9, 129.2, 129.1, 129.0, 128.8, 128.7, 128.5, 127.8, 125.9, 121.6, 120.2, 119.2, 118.3, 38.9, 37.8, 34.7, 32.0, 32.0,

31.4, 30.8, 29.6, 29.5, 29.5, 29.4, 29.0, 28.9, 27.2, 26.5, 26.3, 22.90, 22.89, 14.4, 14.3. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3086, 3061, 3030, 2928, 2857, 2230, 1715, 1634, 1601, 1495, 1449, 1377, 1298, 1175, 1120, 1030, 986, 912, 696. HRMS (TAPCI, m/z) calcd. for $C_{19}H_{25}N$ [M-H] 266.1909, [M+H] 268.2065; found 266.1907, 268.2062



P2.3

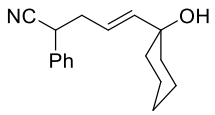


3-(2-cyano-2-phenylethyl)oct-2-en-1-yl acetate was prepared following General Procedure 2.A with 2-(hept-1-en-2-yl)oxirane at 0.75 mmol scale.

61mg, yellow oil, yield: 87 %, E:Z: 53:47. Purified by flash chromatography on silica with 2-10 % EA:Hexane. 1H NMR (500 MHz, Chloroform-d) δ 7.43 – 7.29 (m, 5H aromatic), 5.51 (tt, J = 7.1, 1.3 Hz, 1H alkene C*H*, major), 5.46 (tt, J = 6.9, 1.0 Hz, 1H), 4.59 (d, J = 6.9 Hz, 1H), 4.47 – 4.32 (m, 2H, CH_2, major), 3.89 (ddd, J = 8.7, 6.5, 5.0 Hz, 1H, C*H*, major), 2.80 (dd, J = 13.7, 8.7 Hz, 1H CH_2, major), 2.68 – 2.49 (m, 3H overlapping 1H CH_2, major and 2H CH_2, minor), 2.15 (dt, J = 13.7, 7.7 Hz, 1H CH_2, minor), 1.49 – 1.19 (m, 9H, overlapping 2H CH_2, 3H CH_3, major and 1H CH_2 minor 3H CH_3, minor), 0.89 (td, J = 7.1, 2.5 Hz, 6H overlapping CH_3 major and minor). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 171.0, 140.9, 140.5, 135.8, 135.6, 129.39, 129.35,

128.54, 128.45, 127.6, 127.5, 123.6, 123.3, 120.7, 120.6, 77.3, 60.9, 60.7, 43.1, 37.2, 36.9, 36.7, 36.7, 31.9, 31.7, 30.6, 28.4, 27.7, 22.7, 21.3, 21.2, 14.28, 14.25. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3065, 3032, 2957, 2932, 2861, 2241, 1732, 1667, 1601, 1497, 1454, 1374, 1233, 1078, 1024, 961, 754, 700, 608. LRMS (EI, m/z) parent mass 299.19 found 299.15 rel. intensity 0.06 HRMS via LCT ESI TOF MS and LC TAPCI QTOF MS was attempted.

P2.4



(E)-5-(1-hydroxycyclohexyl)-2-phenylpent-4-enenitrile was prepared following General Procedure 2.A with 2-vinyl-1-oxaspiro[2.5]octane.

68 mg, yellow oil, yield >99 %. Purified by flash chromatography on silica with 0-30 % EA:Hexane. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.35 (m, 2H), 7.35 – 7.29 (m, 3H), 5.75 – 5.60 (m, 2H), 3.84 (dd, *J* = 7.7, 6.6 Hz, 1H), 2.68 – 2.56 (m, 2H), 1.70 – 1.40 (m, 9H), 1.34 – 1.19 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 135.4, 132.4, 132.3, 129.3, 128.8, 128.7, 128.4, 127.6, 121.9, 120.6, 71.6, 38.8, 38.1, 38.1, 25.7, 22.3. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3452 (broad), 3063, 2932, 2857, 2241, 1601, 1497, 14541346, 1261, 1173, 1055, 1034, 972, 754, 698. HRMS (TAPCI, m/z) calcd. for $C_{17}H_{21}NO$ [M-H] 238.1596; found 238.1595.

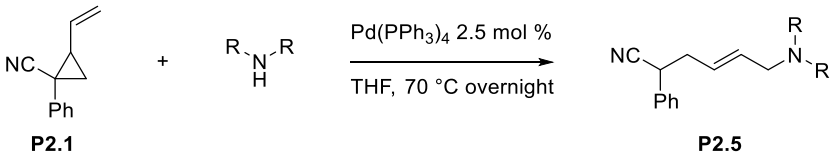
Large scale synthesis of **P2.1a**

3a was prepared on large scale by combining 0.675 g (4.24 mmol) of **1a**, 0.12 g $Pd(PPh_3)_4$ (0.107 mmol, 2.5 mol %) in 20 mL DCM (0.212 M) in a flame dried schlenk flask under argon. **2a** was added directly by syringe (0.308 g, 4.38 mmol, 1.03 equiv.) and the solution was allowed to stir at room temperature for 30 minutes. 0.682 g of TBD (4.91 mmol 1.16 equiv.) was added and the resulting solution was allowed to stir for 1 hour at room temperature. The solvent was evaporated at reduced pressure until it was mostly gone, and the mixture was quenched on the column.

0.717 g, colorless oil, yield: 81 %, d.r.: 81:19. Purified by flash chromatography on silica with 2 % EA:Hexane. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H, overlapping major and minor, aromatic), 5.80 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H major, alkene C*H*), 5.43 – 5.23 (m, overlapping 2H major alkene CH_2, 1H minor alkene CH_2), 5.04 (ddd, *J* = 10.3, 1.4, 0.5 Hz, 1H minor, alkene CH_2), 4.88 (ddd, *J* = 16.9, 10.3, 8.7 Hz, 1H minor alkene C*H*), 2.53 (td, *J* = 9.0, 7.0 Hz, 1H minor, cyclopropane C*H*), 2.20 (tdt, *J* = 8.2, 7.4, 0.7 Hz, 1H major, cyclopropane C*H*), 1.92 (dd, *J* = 9.2, 5.9 Hz, 1H minor, cyclopropane CH_2), 1.83 (dd, *J* = 8.6, 5.9 Hz, 1H major, cyclopropane CH_2), 1.76 (dd, *J* = 7.4, 5.9 Hz, 1H major, cyclopropane CH_2), 1.65 (dd, *J* = 7.0, 5.9 Hz, 1H minor cyclopropane CH_2).

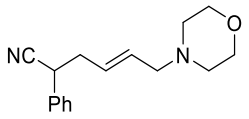
§2.A.5 Amination

General Method



Based on a previously developed method,[68] 5.8 mg of $Pd(PPh_3)_4$ (2.5 mol %) and 0.63 mL of a 0.32 M solution of 1-phenyl-2-vinylcyclopropane-1-carbonitrile in THF were added to a flame dried flask in a glove box. An excess (> 2 equiv.) of amine was added and the flask was sealed. The reaction was allowed to stir at room temperature for 48 hours, and was quenched on a silica plug in EtOAc. The eluate was evaporated, and diluted with EtOAc. The solution was acidified by adding 5 mL of 1M HCl, the layers were separated and the aqueous layer was extracted 4X with EtOAc. Solid NaOH was added until the aqueous layer was markedly basic and it was extracted again with EtOAc. The second extract was dried over $MgSO_4$, filtered and evaporated to yield the pure amination product.

P2.5a

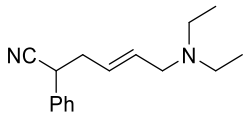


(E)-6-morpholino-2-phenylhex-4-enenitrile

Isolated yield, 93 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.28 (m, 5H), 5.69 – 5.53 (m, 2H), 3.86 (t, *J* = 7.2 Hz, 1H), 3.67 (t, *J* = 4.7 Hz, 4H), 2.99 – 2.91 (m, 2H), 2.70 – 2.61 (m, 2H), 2.44 – 2.29 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.29, 131.70, 129.31, 128.38, 128.34, 127.56, 120.53, 77.26, 67.15, 61.02, 53.69, 38.83, 37.83. HRMS (ESI, m/z) calcd for $C_{16}H_{20}N_2O$ [M+H] 257.1654, [M+Na] 279.1473; found 257.1655, 279.1484. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3032, 2957, 2855, 2808, 2241, 1601, 1495, 1454, 1354, 1285, 1117, 1071, 1005, 980, 866, 758, 700.

P2.5b



(E)-6-(diethylamino)-2-phenylhex-4-enenitrile

Isolated yield, 89 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.29 (m, 5H), 5.67 – 5.53 (m, 2H), 3.85 (t, *J* = 7.1 Hz, 1H), 3.06 (dd, *J* = 6.2, 1.0 Hz, 2H), 2.64 (ddt, *J* = 9.0, 6.7, 1.2 Hz, 2H), 2.47 (q, *J* = 7.2 Hz, 4H), 1.00 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.39, 132.66, 129.28, 128.35, 127.56, 127.27, 120.61, 54.91, 46.66, 38.92, 37.97, 11.77. HRMS (ESI, m/z) calcd. for $C_{16}H_{22}N_2$ [M+H] 243.1861, [M+Na] 256.1681; found 243.1864, 256.1686. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 2969, 2934, 2807, 2241, 1497, 1454, 1371, 1200, 1165, 1082, 974, 756, 698.

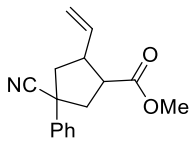
§2.A.6 Cycloaddition

General Procedure

To a flame dried flask in a glove box were added 2.7 mg of $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %), 4.4 mg (R)-Phenyl PHOX ligand (L2, 10 mol %) and 0.25 mL of DMSO. The solution was allowed to stir at room temperature for ½ hour. Then 0.1 mL of 1 M 1-phenyl-2-vinylcyclopropane-1-carbonitrile solution in DMSO was added, followed by 0.15 mL of 1M methyl acrylate solution in DMSO (1.5 equiv.). The resulting solution was heated to 70 ° C overnight (previous monitoring had shown 10 hours to be sufficient for disappearance of 1-phenyl-2-vinylcyclopropane-1-carbonitrile). The sample was quenched on a silica plug in EtOAc. The eluate was evaporated until only DMSO remained and it was loaded directly onto a silica gel

column (5 % EtOAc/Hexane). Evaporation of column fractions responsive to $KMnO_4$ yielded a mixture of diastereomers of methyl 4-cyano-4-phenyl-2-vinylcyclopentane-1-carboxylate.

P2.6



methyl 4-cyano-4-phenyl-2-vinylcyclopentane-1-carboxylate

Major Diastereomer

1H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.55 (m, 2H), 7.45 – 7.37 (m, 2H), 7.37 – 7.30 (m, 1H), 5.73 (ddd, *J* = 17.0, 10.2, 7.7 Hz, 1H), 5.17 (ddd, *J* = 17.1, 1.4, 0.8 Hz, 1H), 5.11 (ddd, *J* = 10.2, 1.4, 0.6 Hz, 1H), 3.69 (s, 3H), 3.49 – 3.36 (m, 2H), 2.77 – 2.69 (m, 1H), 2.64 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.54 (ddt, *J* = 12.8, 5.5, 1.5 Hz, 1H), 2.31 – 2.21 (m, 1H). 13C NMR (126 MHz, $CDCl_3$) δ 174.36, 138.41, 135.97, 129.55, 129.26, 128.44, 126.28, 126.07, 123.95, 117.66, 52.03, 47.99, 46.87, 45.94, 45.33, 42.87.

1st minor diastereomer

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.47 (m, 2H), 7.43 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 5.93 (ddd, *J* = 16.9, 10.2, 7.5 Hz, 1H), 5.14 (dt, *J* = 17.0, 1.1 Hz, 1H), 5.11 – 5.07 (m, 1H), 3.73 (s, 3H), 3.18 – 3.05 (m, 2H), 2.81 – 2.74 (m, 1H), 2.57 – 2.43 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.00, 139.42, 139.02, 129.34, 128.40, 126.29, 126.06, 124.29, 116.52, 52.38, 50.22, 47.18, 46.53, 46.39, 44.19.

2nd minor diastereomer

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.44 (m, 1H), 7.43 – 7.37 (m, 2H), 7.36 – 7.28 (m, 2H), 5.85 (ddd, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.20 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.12 (dt, *J* = 10.4, 1.1 Hz, 1H), 3.76 (s, 3H), 3.40 – 3.31 (m, 1H), 3.00 – 2.92 (m, 1H), 2.89 (td, *J* = 9.8, 7.1 Hz, 1H), 2.75 – 2.46 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.84, 137.87, 129.35, 128.78, 128.67, 128.40, 126.91, 126.02, 116.75, 52.50, 49.16, 47.65, 46.86, 43.13.

IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3065, 3030, 2953, 2234, 1732, 1643, 1601, 1495, 1449, 1435, 1371, 1206, 1173, 993, 922, 760, 698. LRMS (EI, m/z) parent mass 255.13; found 255.10 rel. int. 0.71. HRMS via LCT ESI TOF MS and LC TAPCI QTOF MS was attempted

§2.A.7 References

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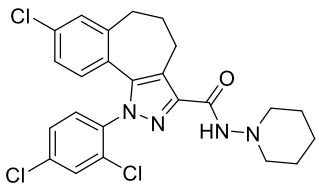
Chapter 3: Synthesis of Benzocycloheptenes via Aromatic Vinylcyclopropane Cope Rearrangements

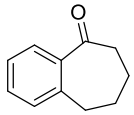
§3.1 Introduction

Vinyl cyclopropanes are synthetically useful molecules that undergo a variety of rearrangements. For example, vicinal *cis*-divinyl cyclopropanes undergo facile Cope rearrangements at room temperature. While the divinyl cyclopropane Cope rearrangement is well-known and has been broadly applied in synthesis,[78] examples of the aryl vinyl cyclopropane Cope rearrangement (AVCPR) are less common and generally limited in scope or reaction yield. Furthermore, these aryl vinyl cyclopropane Cope rearrangements generally require sterically predefined starting materials that place the vinyl and aryl groups *cis* to one another. This relatively rare rearrangement gives access to the benzocycloheptene scaffold. Benzocycloheptene derivatives and other benzo-fused 7-membered rings are found in a variety of medicinally relevant natural compounds (Figure 3.1). For example, NESS 0327 is a potent cannabinoid receptor agonist.[79a] Benzosuberone is an important chemical building block for the synthesis of various medicinally relevant compounds, such as colchicines. Colchicine itself and its derivatives are potent anticancer agents. For instance theaflavin, a compound isolated from black tea regulates the growth and survival of cancer cells and can also regulate metathesis. Brussonol is a compound isolated from salivabroussonetii that exhibits anticancer activity against murine cancer cells.[79b] Gamma-Lumicolchicine is a photodegradation product of colchicine, which does not exhibit the same biological effects, but has found use as a standard in colchicine activity studies.[79c] (Figure 3.1) . Herein, we report a method to obtain either of two regioisomeric benzocycloheptene products via an aryl vinyl cyclopropane Cope rearrangement, featuring additive-controlled regioselectivity. Mechanistic studies indicate a dynamic equilibration of cyclopropane stereoisomers, followed by rearrangement of the *cis* diastereomer.

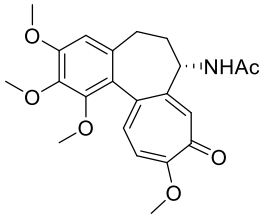
Figure 3.1 – Natural and Biologically Active Benzo-fused 7-membered Rings



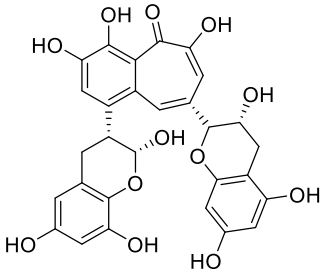
NESS 0327



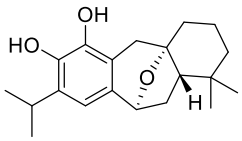
Benzosuberone



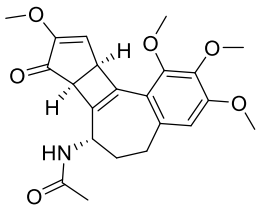
Colchicine



Theaflavin



Brussonol



gamma-Lumicolchicine

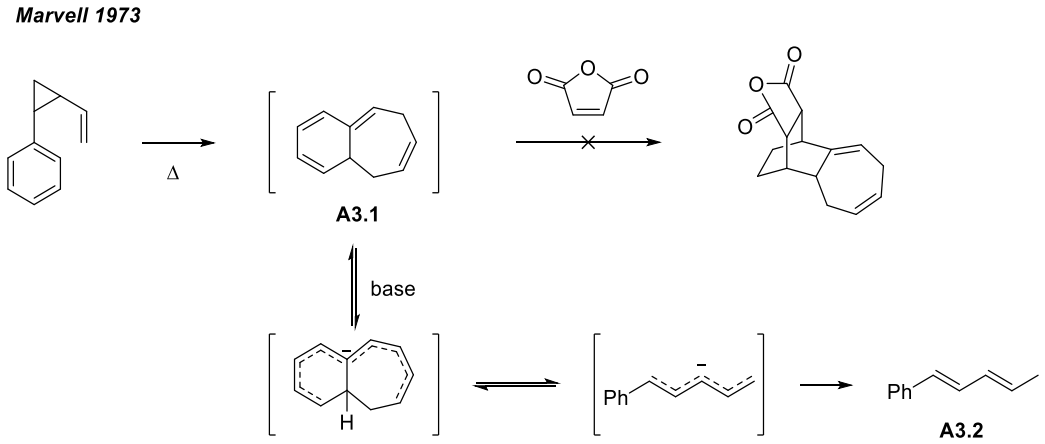
§3.2 Overview of Aromatic Vinylcyclopropane Cope Rearrangements

Cope rearrangements are well-known and powerfully useful reactions in organic synthesis.[80] The Cope rearrangements of *cis* divinyl cyclopropanes are particularly interesting because they are facile at relatively low temperatures due to the rigidity of the system and the strain release that provides a thermodynamic driving force.[78] The related *aromatic* Cope rearrangements, however, are less common due to the low reactivity of the aryl ring and the need to transiently destroy aromaticity.[81] Thus, aromatic Cope reactions tend to require forcing conditions and/or stereodefined starting materials, and suffer from low yield or limited scope.[81]

The first evidence for the possibility of aryl vinyl cyclopropane Cope rearrangements was presented by Marvell and Lin in 1973.[81a] The authors attempted to form and trap dearomatized intermediate **A3.1** via a Diels-Alder reaction with various dienophiles with no success. However,

treatment of the cyclopropane with *tert*-butoxide/*tert*-butyl alcohol, at 150 °C, mainly generated the conjugated diene product **A3.2**. Based on deuterium incorporation studies, they proposed the mechanism shown in Scheme 3.1 for the formation of the diene product. This experiment provided evidence in support of an aryl vinyl cyclopropane Cope rearrangement mechanism, although the rearomatized benzocycloheptene was not observed at that time.

Scheme 3.1 – Initial Evidence for Aryl Vinyl Cyclopropane Cope Rearrangement

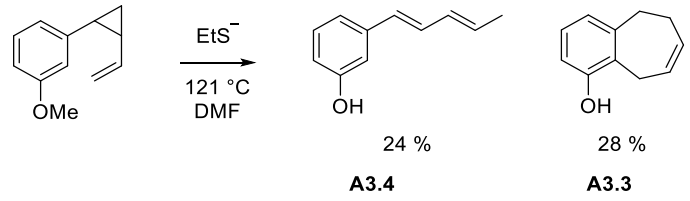


Continuing their studies in 1977, Marvell and Lin reported the first definitive example of the aryl vinyl cyclopropane Cope rearrangement (Scheme 3.2).[81b] Treatment of *m*-methoxy 2-phenyl-1-vinylcyclopropane with ethanethiolate at 121 °C in DMF led to the desired aryl vinyl cyclopropane Cope product **A3.3** in 28 % yield along with the diene (**A3.4**, 24 %), which form via the same intermediate, as well as the *cis*- and *trans*-isomers of the starting material (Scheme 3.2a). Interestingly, although there is a possibility for two different regioisomers to form in the aryl vinyl cyclopropane Cope rearrangement with these *m*-substituted aryl vinyl cyclopropanes, the authors only observed one of the two possibilities (Scheme 3.2b). They hypothesized that the retro-Cope rearrangement was more facile than prototropic conversion of intermediate **A3.5** to the rearomatized product **A3.4**.

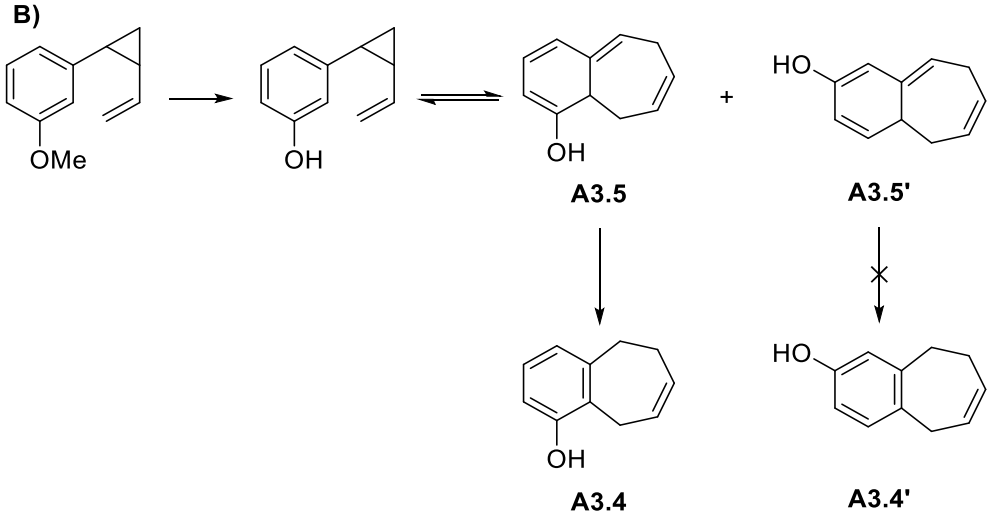
Scheme 3.2 – First Example of Aromatic Double Bond Participating in Cope Rearrangment

Marvell, 1977

A)



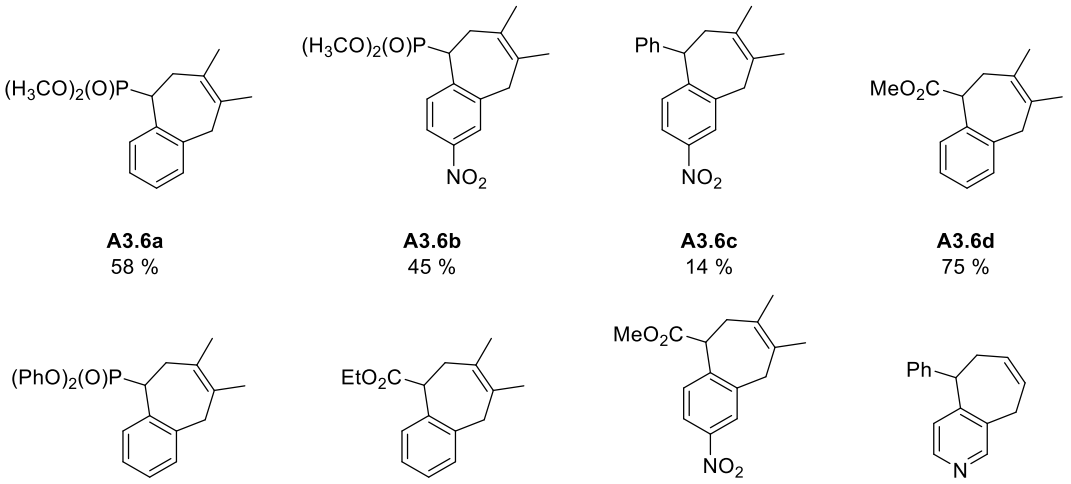
B)



In 1979, Maas *et al.* reported several examples of aryl vinyl cyclopropane Cope rearrangements in 1979 (Scheme 3.3).[82] This report included 8 examples (**A3.6a-h**) with yields ranging from trace amounts to 75 % and included some containing phosphonate and carbonate esters. Of note, a pyridinyl cyclopropane underwent the aryl Cope rearrangement (**A3.6h**), constituting the first example of a heteroaromatic ring participating in an aryl Cope rearrangement, further highlighting the synthetic utility of cyclopropane strain release as a driving force for dearomatization.

Scheme 3.3 – More Early Examples of AVCPR Including Heterocyclic ARVCP

Maas, 1979



A3.6a
58 %

A3.6b
45 %

A3.6c
14 %

A3.6d
75 %

A3.6e
74 %

A3.6f
trace

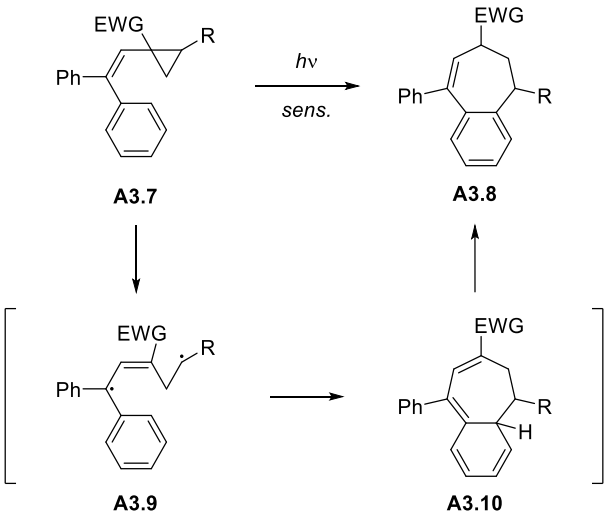
A3.6g
49 %

A3.6h
55 %

In 2000, Aggarabeitia reported the first photochemical aryl vinyl cyclopropane Cope rearrangement. They photochemically rearranged 1-(2,2-diphenylvinyl)cyclopropanes (**A3.7**) to benzocycloheptenes (**A3.8**), but only reported 4 examples with yields all below 20 % (Scheme 3.4).[83] The authors postulated that the reaction proceeded via a diradical intermediate (**A3.9**), which generated a dearomatized intermediate (**A3.10**) upon recombination of the radicals. Rearomatization by a proton transfer then led to the conjugated benzocycloheptene product. Without the electron withdrawing group in the C1 position as shown in Scheme 3.4, the benzocycloheptene products would not be observed, but rather only cyclopentenes would be formed.

Scheme 3.4 – Photochemical Aryl Vinyl Cyclopropane Cope Rearrangement

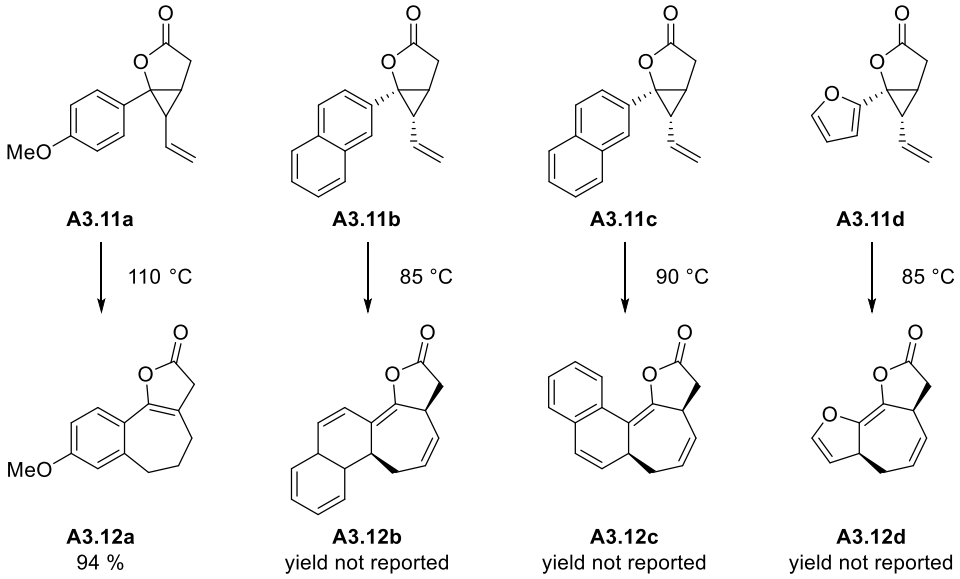
Aggarabeitia, 2000



Martin *et al*. reported the thermal rearrangement of several aryl vinyl cyclopropane fused lactones (**A3.11a-d**) to seven membered rings (Scheme 3.5).[84] Although spectroscopic data was given for four of the rearrangement products, the yield was only reported for one (**A3.12a**). Interestingly, in the case of those reported without yields, non-rearomatized structures were reported (**A3.12b-d**), possibly due to a slow [1,3]-proton transfer preventing rearomatization. Furthermore, the reactions did require stereodefined starting materials and were apparently stereospecific.

Scheme 3.5 – Isolation of Dearomatized Products from AVCPR

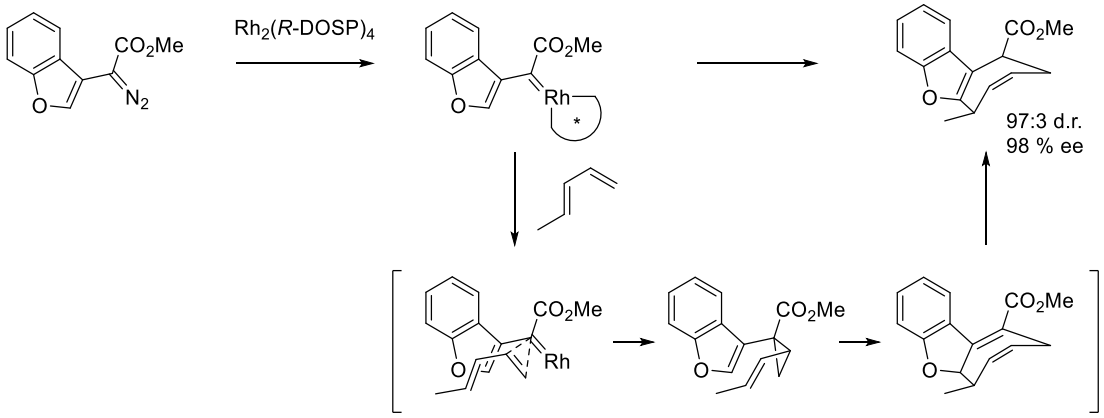
Martin, 2002



In 2008, Davies *et al*. reported the tandem Rh-catalyzed carbene cyclopropanation/aryl vinyl cyclopropane Cope rearrangement of diazo compounds with dienes (Scheme 3.6).[85] The diastereo and enantioselective synthesis of *cis* cyclopropanes was followed by the rearrangement to benzocycloheptenes at high temperatures in a single pot. The authors reported seven examples of the formal [4+3]-cycloadditions with yields ranging from 66 to 92 % with diastereoselectivities all above 97:3 d.r. and enantioselectivities all above 90 % ee. Furthermore, they applied this method to the formal synthesis of (+)-frondosin B.

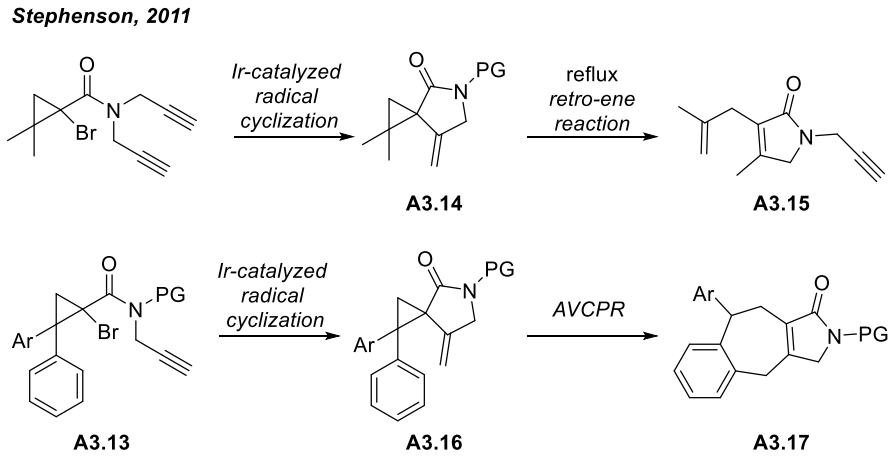
Scheme 3.6 – One-Pot Cyclopropanation/AVCPR protocol

Davies, 2010



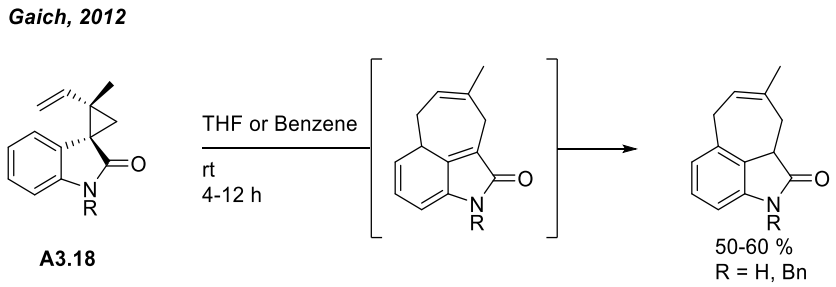
Aryl vinyl cyclopropane Cope rearrangements sometimes occur unexpectedly in the course of other pursuits. In 2011, the Stephenson group reported a tandem photochemical cyclization and aryl vinyl cyclopropane Cope rearrangement (Scheme 3.7).[86] Geminally substituted bromo cyclopropanes bearing propargyl amide substituents (**A3.13**) underwent an iridium-catalyzed photochemical cyclization leading to necessarily *cis* aryl vinylcyclopropanes. Initially, upon heating, the spirocyclic cyclopropanes (**A3.14**) would undergo a retro-ene reaction to form cyclopentenes, **A3.15**. In order to suppress this pathway, they synthesized geminally substituted diaryl cyclopropanes (**A3.16**) and subjected them to the reaction conditions. Rather than undergoing retro-ene reactions, these substrates readily rearranged to form benzocycloheptenes, **A3.17** via AVCPR reactions. The authors reported ten examples of the one-pot protocol, with yields ranging from 32 % to 91 %.

Scheme 3.7 – Stephenson's Tandem Radical Cyclization/Cope Rearrangment



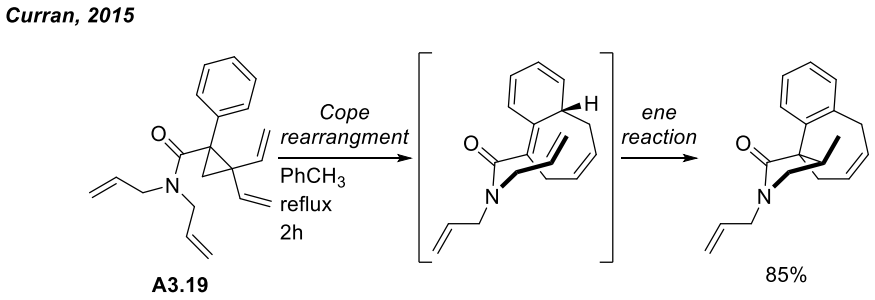
The biosynthesis of ergot alkaloids is initiated by prenylation of indole by DMAT synthase. An aryl Cope rearrangement mechanism has been proposed as a potential biosynthetic mechanism for this transformation.[87] Inspired by this hypothesis, Gaich and coworkers developed a prenylation of indole at the C4 position via an aryl vinyl cyclopropane Cope rearrangement (Scheme 3.8).[88] Utilizing stereochemically predefined spiro-fused vinylcyclopropane indoles (**A3.18**) to mimic the conformational restrictions likely imposed by the enzyme in the biosynthetic pathway, they accomplished the rearrangement at room temperature.

Scheme 3.8 – Gaich's Bioinspired C4 Prenylation of Indole



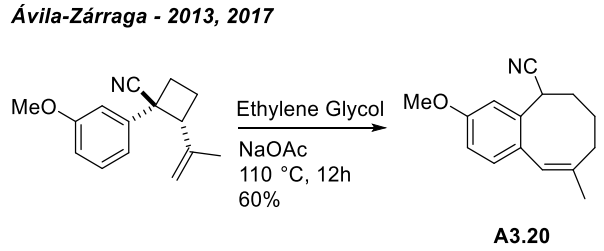
More recently, the Curran group disclosed a variety of rearrangements of 1,1-divinylcyclopropanes (**A3.19**), including five examples that underwent aromatic Cope rearrangements with yields ranging from 44 % to 73 % (Scheme 3.9).[89] Those reactions cleverly utilized an ene reaction to drive rearomatization after the initial Cope rearrangement. Typically in AVCPR, a [1,3]-proton transfer is exploited for the rearomatization;[86] however, with substrates that required [1,3]-proton transfer for rearomatization, rearrangement to form cyclopentenes was favored over AVCPR. Aryl vinyl cyclopropane Cope rearrangements were only observed in allyl and propargyl amide substrates where rearomatization by ene reaction was possible.

Scheme 3.9 – Curran's ene-driven Aryl Vinyl Cyclopropane Cope Rearrangement



Finally, Ávilla-Zárraga and coworkers reported an aryl vinyl cyclobutane rearrangement to form a benzocyclooctene (**A3.20**, Scheme 3.10).[90] In the initial report, a single product was obtained in an optimized yield of just 45 %. However, a subsequent publication in 2017 demonstrated an improved yield of 60 % *en route* to the synthesis of (+/-)-parvifoline.[91] Given the target-oriented nature of the synthesis, only a single example was demonstrated. To accomplish the reaction, control of the stereochemistry of the cyclobutanes was required to ensure that the aromatic ring and vinyl group were *cis* to one another.

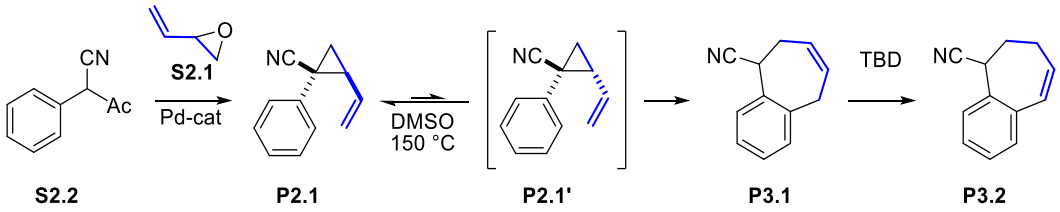
Scheme 3.10 – Ávilla-Zárraga's Cope Rearrangement of Aryl Vinylcyclobutanes



This chapter describes a method for the synthesis of benzocycloheptenes from aryl vinylcyclopropanes wherein dynamic equilibration of the diastereomers of the cyclopropane precedes the rearrangement, obviating the need to laboriously prepare cyclopropanes as a single diastereomer (Scheme 3.11).[92] Furthermore, a conjugation-driven isomerization of the initially formed benzocycloheptenes occurs in the presence of the base TBD. This protocol allows the

highly selective synthesis of either of two isomers of the benzocycloheptene products. Styrenyl vinylcyclopropanes underwent the more common vinylcyclopropane rearrangement to cyclopentenes, likely due to increased steric hindrance in the AVCPR transition state. This reaction constitutes an operationally simple and high-yielding complement to existing AVCPR protocols.

Scheme 3.11 – Dynamic Aryl Vinyl Cyclopropane Cope Rearrangements



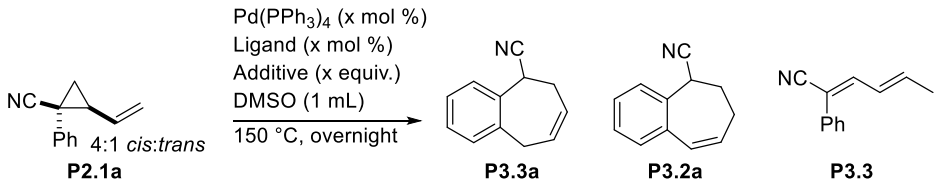
§3.3 Synthesis of Benzocycloheptenes via Dynamic Vinyl Cyclopropane Cope Rearrangements

3.3.1 – Optimization

During our optimization of the cycloaddition with vinylcyclopropanes (*vide supra*), it was noted that at elevated temperatures, the reaction formed an isomeric byproduct that was tentatively assigned as a benzocycloheptene. To further investigate benzocycloheptene formation, the vinylcyclopropane product was isolated and subjected to palladium catalysis at 150 °C. Indeed, the benzocycloheptene product (**P3.1a)** was formed in 73 % isolated yield (Table 3.1, entry 1).[93] This rearrangement warranted further investigation, since reports of such aromatic Cope rearrangements are generally limited in scope and produce products in low yield. Next, the same rearrangement was performed in the presence of TBD, which is also present during cyclopropane formation. Under these conditions, the desired benzocycloheptene was not observed, but rather the regioisomeric benzocycloheptene **P3.2a** was obtained in low yield (entry 2). The addition of dppe as a ligand increased the yield of **P3.2a** significantly (entry 3). This result could be interpreted to

mean that deactivation of Pd through chelation was beneficial to the reaction. Indeed, control reactions showed that palladium is not required for the isomerization (entries 4–5). In fact, conducting the reaction at 150 °C in the absence of palladium provided benzocycloheptenes in better yield than when palladium was present.

Table 3.1 – Optimization of Cope Rearrangement



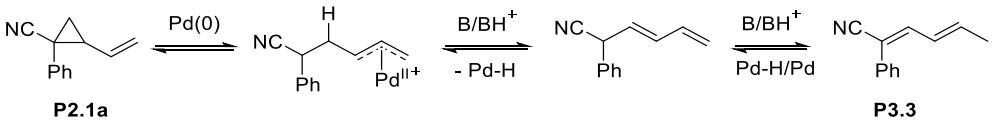
Entry	$Pd(PPh_3)_4$ (mol %)	Ligand (mol %)	Additive (equiv.)	yield **P3.1a** (%)	yield **P3.2a** (%)	yield **P3.3** (%)
1	2.5	n/a	n/a	73	0	0
2	2.5	n/a	TBD (1.1)	0	4	0
3	2.5	dppe (20)	TBD (1.1)	0	70	0
4	**0**	**n/a**	**n/a**	**98***	**0**	**0**
5	**0**	**n/a**	**TBD (1)**	**0**	**83**	**0**
6	2.5	n/a	AcOH (1)	0	7	36
7	0	n/a	AcOH (1)	71	0	0

* 2mL DMSO used

Interestingly, when acetic acid was used in place of TBD, the majority of the product obtained was a diene resulting from ring-opening of the vinylcyclopropane followed by β-hydride elimination and alkene isomerization (**P3.3**, entry 6). A control experiment in the absence of palladium showed that palladium was required for the formation of this diene (entry 7). The proposed mechanism for the formation of this diene is shown in Scheme 3.12.[94] The vinyl cyclopropane can undergo reversible ring opening in the presence of palladium. Subsequent β-hydride elimination from the resulting π-allyl species occurs via a base-mediated anti-elimination, resulting in a palladium hydride species. Then either the palladium

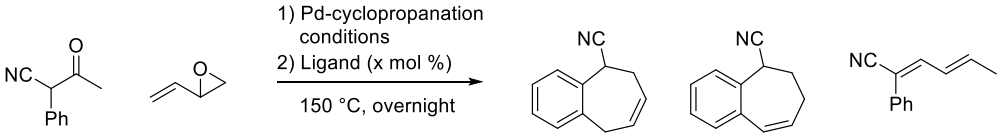
hydride or the base can isomerize the resulting diene to the lower energy conjugated isomer, **P3.3.**

Scheme 3.12 – Catalytic Formation of Diene



While the optimal conditions for the rearrangement are metal-free, the above studies show that the rearrangement is compatible with palladium. This observation led us to explore a protocol that would incorporate the anion relay cyclopropanation and aryl vinyl cyclopropane Cope rearrangements in a single pot (Table 3.2). In DCM containing $Pd(PPh_3)_4$, the benzocycloheptene **P3.1a** was formed in 20 % yield (entry 1). When the amount of palladium was increased, a mixture of the conjugated benzocycloheptene, **P3.2a** and the diene **P3.3** was obtained, but the yield of each was low (entry 2). Addition of dppe favored the non-conjugated isomer **P3.1a** and the yield was slightly improved (entry 3). Interestingly, by simply allowing less time for the cyclopropane formation, the yield of **P3.1a** was improved to 40 % (entry 4).

Table 3.2 – Sequential ARC/AVCPR



Entry	solvent (mL)	Pd source (mol %)	time	TBD (equiv.)	Ligand (mol %)	yield **P3.1a** (%)	yield **P3.2a** (%)	yield **P3.3** (%)
1	DCM (0.8)	$Pd(PPh_3)_4$ (2.5)	3 h	1.1	---	20	0	4
2	DCM (0.8)	$Pd(PPh_3)_4$ (10)	3 h	1.1	---	0	4	7
3	DCM (0.8)	$Pd(PPh_3)_4$ (10)	3 h	1.1	dppe (20)	24	0	4
4	DCM (0.8)	$Pd(PPh_3)_4$ (2.5)	5 min	1.1	---	40	0	4
5	DMSO (1)	$Pd(PPh_3)_4$ (2.5)	3 h	1.1	---	0	20	0
6	DMSO (1)	$Pd(PPh_3)_4$ (5)	3 h	1.1	---	0	25	0
7	DMSO (1)	$Pd(dba)_2$ (2.5)	---[a]	1.1	---	0	33	0
8	DMSO (1)	$Pd(dba)_2$ (2.5)	---[a]	1.1	dppe (10)	0	28	0
9	DMSO (1)	$Pd(dba)_2$ (2.5)	2 h	1.1	dppe (20)	0	30	0
10	DMSO (1)	$Pd(dba)_2$ (2.5)	3 h	1.1	dppe (20)	0	36	0
11	DCM (0.8)	$Pd(PPh_3)_4$ (10)	5 min	0.5	$P(OPh)_3$ (40)	0	0	30
12	DCM (0.8)	$Pd(PPh_3)_4$ (10)	5 min	0.5	P(o-tolyl)$_3$ (40)	0	0	32
13	DCM (0.8)	$Pd(PPh_3)_4$ (2.5) (7.5)[b]	30 min	0.5	---	0	0	35
14	DCM (0.8)	$Pd(PPh_3)_4$ (10)	5 min	0.5	P(1-naphthyl)$_3$ (40)	0	0	47

[a] Conditions: 1) **S2.2a** and the Pd source were dissolved in the solvent and allowed to stir under Argon. **S2.1** was then added, and the reaction was stirred at room temperature for the given time. TBD was added, and the reaction was stirred at room temperature overnight. 2) The ligand was added, and the reaction was stirred at 150 °C overnight. a) Monitored for completion of the Tsuji-Trost allylation before adding TBD. b) Additional palladium was added along with TBD in the second step.

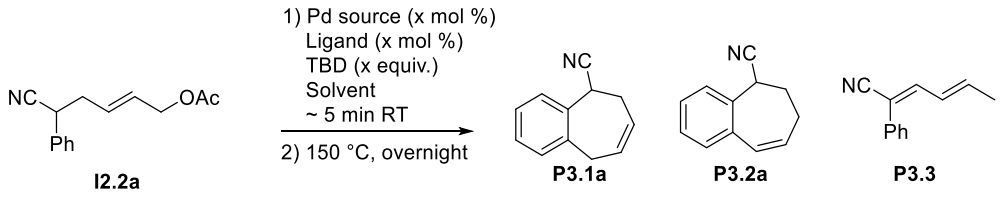
An improved yield of the conjugated isomer **P3.2a** was obtained when the reaction was carried out in DMSO (entry 5). Doubling the palladium concentration increased the yield slightly (entry 6). The yield of **P3.2a** was further improved by using $Pd(dba)_2$ instead of $Pd(PPh_3)_4$ to effect the cyclopropanation (entry 7). Addition of 10 mol % of dppe decreased the yield, but 20 mol %

of dppe increased the yield (entries 8-10). Unfortunately, while the one-pot ARC cyclopropanation–aromatic Cope rearrangement sequence was viable, the product yields were lower than desired.

Since the cyclopropane is an intermediate in formation of the benzocycloheptene, but the diene can be formed directly from the π-allyl complex formed from the ester and does not require the intermediacy of the cyclopropane, we hypothesized that avoiding formation of the cyclopropane while simultaneously increasing catalyst loading would favor β-hydride elimination and formation of the diene, **P3.3**. Operating under this hypothesis, the reaction was run in DCM with 10 mol % $Pd(PPh_3)_4$ and a catalytic amount of TBD in the presence of a bulky phosphine ligand. These conditions did indeed favor the formation of **P3.3** (entries 11-12). The reaction was run with 2.5 mol % catalyst for the formation of the ester, and then additional catalyst was added along with TBD prior to heating. This protocol slightly increased the yield (entry 13). Ultimately, the bulky 1-naphthyl phosphine formed **P3.3** in one pot with an appreciable yield of 47% (entry 14).

Next, in order to determine whether the initial Tsuji-Trost reaction contributed to the low yield of benzocycloheptenes, that process was circumvented by isolating and purifying the allylic acetate intermediate necessary for cyclopropane formation. From this intermediate (**I2.2a**), attempts were made to optimize a one-pot Tsuji-Trost cyclopropanation–aromatic Cope rearrangement protocol (Table 3.3).

Table 3.3 – Optimization of the Tsuji-Trost/Cope Rearrangement Sequence



Entry	Pd source (mol %)	Ligand (mol %)	TBD (equiv.)	solvent	yield **P3.1a** (%)	yield **P3.2a** (%)	yield **P3.3** (%)
1	$Pd(PPh_3)_4$ (1)	n/a	1.1	DCM	7	0	1
2	$Pd(PPh_3)_4$ (1)	n/a	0.5	DCM	24	0	1
3	$Pd(PPh_3)_4$ (2.5)	dppe (20)[a]	1.1	DCM/DMSO	38	6	10
4	$Pd(dba)_2$ (2.5)	n/a	1.1	DMSO	0	53	2
5	$Pd(dba)_2$ (2.5)	dppm (10)	1.1	DMSO	0	42	0
6	$Pd(dba)_2$ (2.5)	dppe (10)	1.1	DMSO	0	52	0
7	$Pd(PPh_3)_4$ (1)	n/a	1.1	DMSO	0	0	20
8	$Pd(PPh_3)_4$ (10)	n/a	0.6	DCM	0	0	51
9	$Pd(PPh_3)_4$ (10)	n/a	0.1	DCM	0	0	55
10	$Pd(PPh_3)_4$ (10)	n/a	0.1	DCM	0	0	62

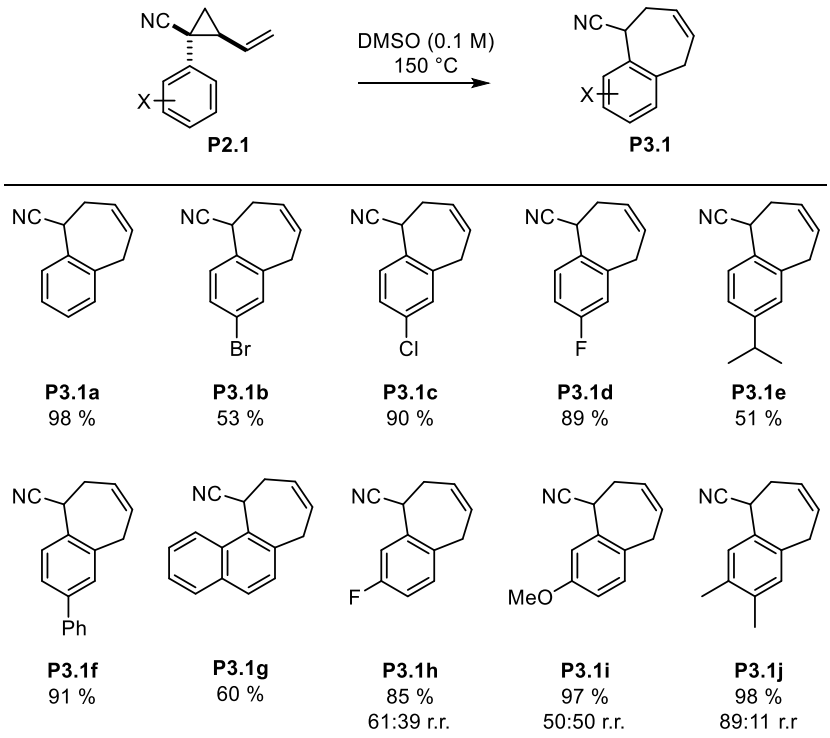
Conditions: 1) The Pd source, the ligand and TBD were dissolved in the solvent in a dry flask under Argon. **I2.2a** was added, and the reaction was stirred at room temperature for 5 minutes. 2) The reaction was stirred at 150 °C overnight. a) The first step was allowed to continue overnight, the ligand was added in a second step, and the solvent was changed from DCM to DMSO between first and second steps.

Initial attempts with conditions known to affect cyclopropanation generated the benzocycloheptene **P3.1a**, but the yield was low (entry 1). To investigate whether dppe could be used to inhibit palladium's interference with the aromatic Cope rearrangement, the cyclopropanation was performed first, followed by addition of dppe. Under these conditions, **P3.1a** was formed in 38 % yield, but that procedure also required a solvent swap prior to heating overnight (entry 3). However, when the catalyst was changed to $Pd(dba)_2$, formation of the conjugated benzocycloheptene was favored, resulting in 53 % of **P3.2a** (entry 4). A brief ligand

screen did not result in improved yields (entries 5-6). When the reaction was performed solely in DMSO with $Pd(PPh_3)_4$, benzocycloheptene did not form; instead, elimination to form the diene **P3.3** was favored (entry 7). When the reaction was performed in DCM with a higher loading of $Pd(PPh_3)_4$, the diene was always preferentially formed (compare entries 2,8), and catalytic loadings of TBD also seemed to contribute to the formation of the diene (entries 9-10). Under these conditions, **P3.3** could be formed selectively in appreciable amounts; however, it was not considered of interest to pursue the diene further, as β-hydride elimination from π-allyl complexes to form dienes is quite well known[94]. Ultimately, while a moderate yield of the benzocycloheptene could be obtained in a one-pot transformation, the focus was shifted to maximizing the yield of benzocycloheptene synthesis through a one-step procedure.

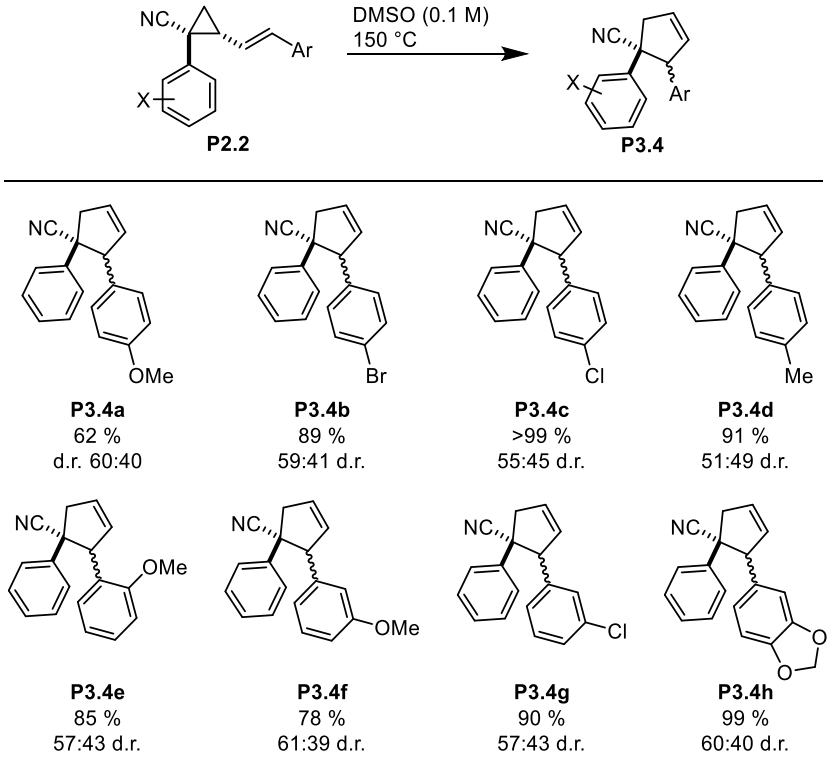
3.3.2 – Scope

Scheme 3.13 – Scope of Benzocycloheptene Formation



The scope of the aromatic Cope rearrangement was then investigated using various substituted vinylcyclopropanes, **P2.1** (Scheme 3.13). These studies showed that *para*-substituted aryl vinylcyclopropanes generally produced benzocycloheptenes in excellent yields (**P3.1b**–**e**). Substrates with extended aromatic systems performed equally well (**P3.1f, g**). *Meta*-substituted aryl rings were also well-tolerated but led to regioisomeric products resulting from aromatic Cope rearrangement at both the proximal and distal positions to the substituent. While relatively small substituents (F and OMe, **P3.1h, i**) imparted little regioselectivity, the larger methyl substituent more effectively forced reaction at the distal position (**P3.1j**, 89:11 regioselectivity).

Scheme 3.14 - Scope of Cyclopentene Formation

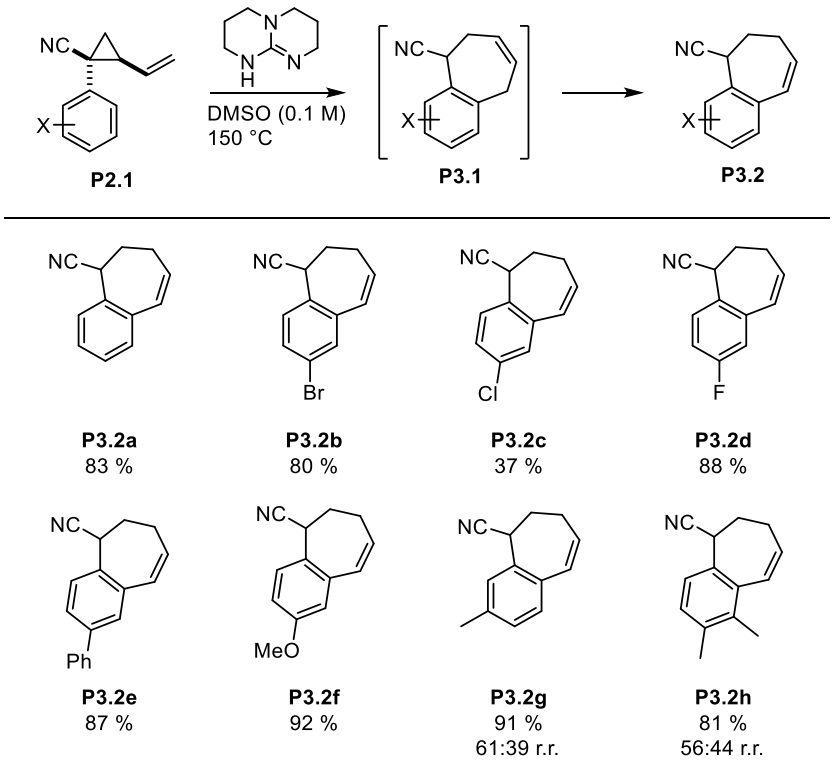


Interestingly, when styrenyl cyclopropanes were subjected to the conditions for aromatic Cope rearrangement, isomerization to cyclopentenes was observed instead (**P3.4a-h,** Scheme

3.14). [81b-d,91,52] Unfortunately, the products formed with low diastereoselectivity, indicating that this rearrangement occurs via an indiscriminate cyclization

Next, on the basis of our optimizations (*vide supra*), the use of triazabicyclodecene (TBD) base was expected to equilibrate the benzocycloheptene isomers to form the conjugated isomer. Indeed, applying these basic reaction conditions to aromatic Cope rearrangements of terminal vinylcyclopropanes had the same effect, leading to good yields of conjugated benzocycloheptenes **P3.2** (Scheme 3.15).

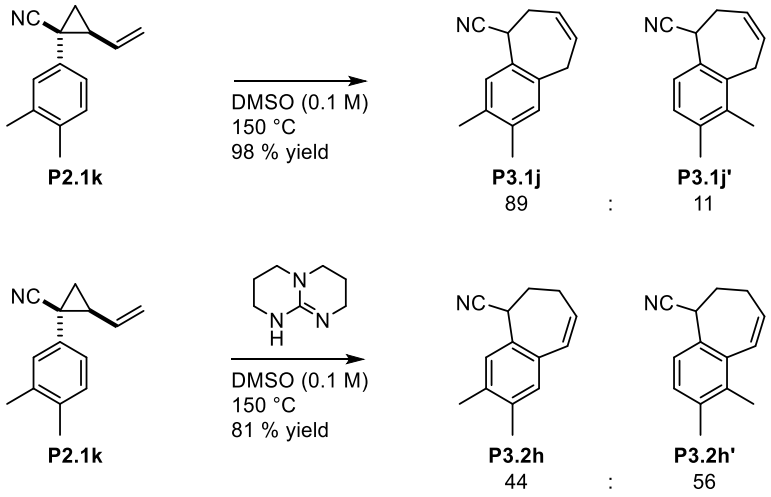
Scheme 3.15 - Scope of Conjugated Benzocycloheptenes



Interestingly, the presence of TBD affected the regiochemistry of the aromatic Cope rearrangement (Scheme 3.16). For example, **P3.1j** was obtained as an 89:11 mixture of regioisomers, but the conjugated analog **P3.2h** was formed with only 56:44 regioselectivity.

Furthermore, in the case of **P3.2h** the regioselectivity favored cyclization at the more sterically hindered carbon, indicating the presence of an electronic influence on regioselectivity.

Scheme 3.16 – Effect of TBD on Regioselectivity of AVCPR

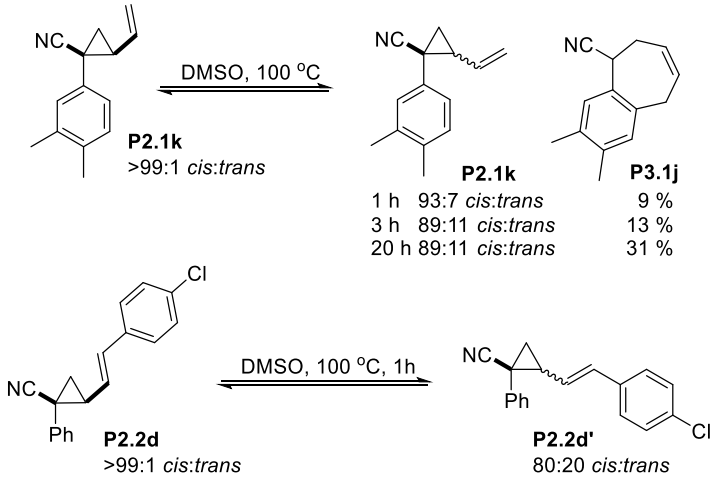


3.3.3 – Mechanistic Considerations

It is interesting that high yields of benzocycloheptenes are observed starting from reactants on which the vinyl and aryl groups primarily have a *trans* disposition; aromatic Cope rearrangements are known to require the *cis*-orientation of the aryl and vinyl groups.[81b] Thus, we hypothesized that the cyclopropane reactants were undergoing stereochemical equilibration on the timescale of the rearrangement.[81b] To investigate this potential isomerization, the stereochemical fidelity of a diastereomerically pure *cis* cyclopropane was investigated at various temperatures in DMSO (Scheme 3.17). While no isomerization occurred at room temperature, the cyclopropane epimerized at 100 °C, reaching the expected diastereomeric equilibrium within 3 hours. The aromatic Cope rearrangement was only slightly slower, having reached 13 % conversion at 3 hours and 31 % conversion after 20 hours. As expected,

a styrenyl cyclopropane underwent more rapid epimerization, reaching equilibrium after 1 hour at 100 °C. The fact that no cyclopentene was formed under these conditions indicates that cyclization to form the cyclopentene is the rate-limiting step in forming **P3.4c**. The thermal epimerization of cyclopropanes could occur through diradical[81b-d,52c] or zwitterionic intermediates.[82,50] We favor the latter pathway since cyclopropanes **P2.2d** are typical donor-acceptor cyclopropanes, which would be expected to form zwitterionic intermediates in DMSO at elevated temperature. Indeed, addition of 2.5 mol % $Pd(PPh_3)_4$, which can stabilize zwitterionic intermediates of ring opening,[48a,b,49,64,68,69,95] catalyzed the *cis*/*trans* equilibration of cyclopropane **P2.2d** in just 1 hour at room temperature.

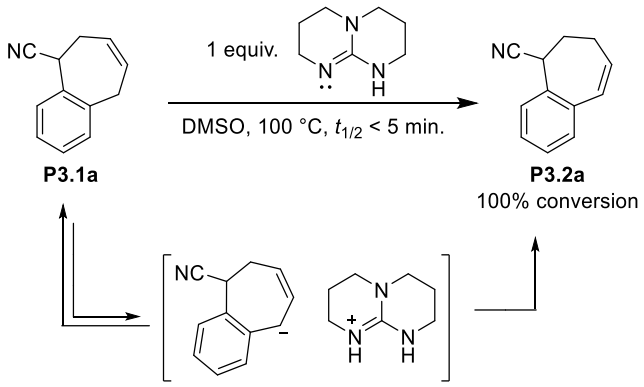
Scheme 3.17 – Stereochemical Fidelity of Cyclopropanes



It was hypothesized that TBD (pK_a ~ 26)[96] plays a role in the isomerization of the benzocycloheptene **P3.1a** (pK_a ~ 33)[97] to its conjugated form **P3.2a** by acting as a proton shuttle. This isomerization would clearly require the reversible deprotonation of the far more acidic proton alpha to the nitrile (pK_a ~ 22).[96] In order to investigate this hypothesis, the non-conjugated benzocycloheptene **P3.1a** was isolated and exposed to TBD in DMSO at different temperatures. The isomerization was slow at room temperature ($t_{1/2}$ ~ 12 h) but occurred rapidly at 60 °C ($t_{1/2}$ <

1 h) and 100 °C ($t_{1/2}$ < 5 min) (Scheme 3.18). This result indicates that, under the Cope rearrangement conditions, the non-conjugated benzocycloheptene is rapidly isomerized to the conjugated isomer in the presence of TBD.

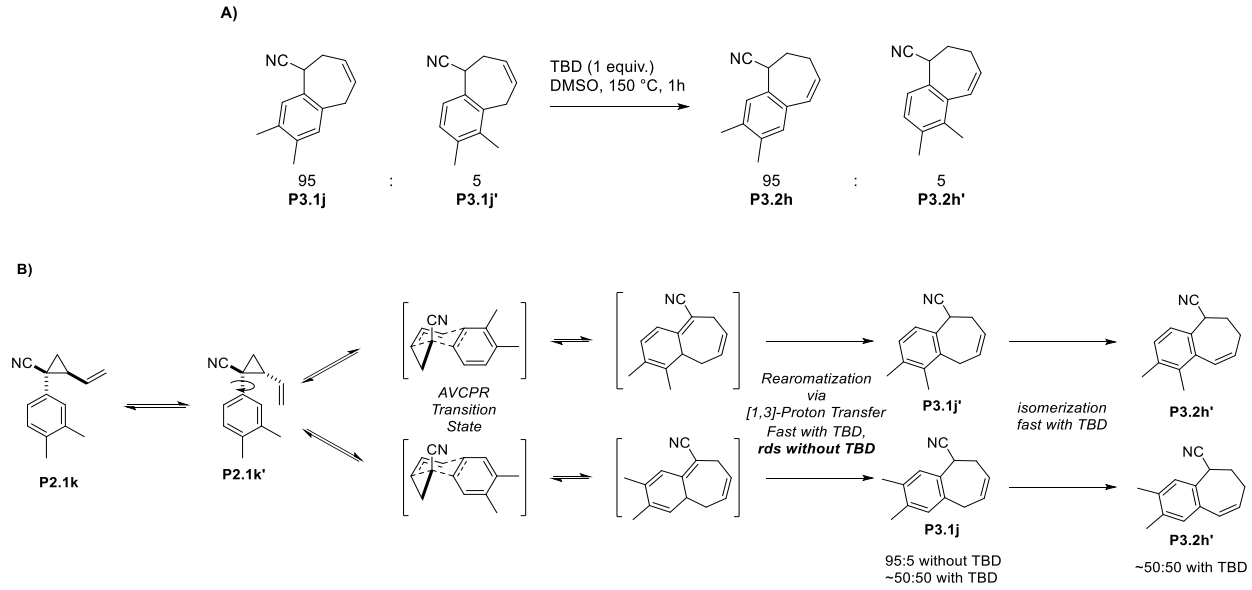
Scheme 3.18 – Role of TBD in the Observed Isomerization



As noted above, when TBD was used to effect the isomerization of the non-conjugated benzocycloheptenes to their conjugated isomers, the regioselectivity was markedly less (Scheme 3.16). In order to investigate the role of TBD in the regiochemical outcome of the AVCPR reaction, a control experiment was run wherein the isolated non-conjugated benzocycloheptene **P3.1a** was exposed to TBD in DMSO at 150 °C. Under these conditions, the regiochemistry of the Cope rearrangement was conserved (Scheme 3.19a). This observation suggested that the influence of TBD on the regiochemistry of the AVCPR reaction occurs through trapping of a non-equilibrium mixture of regioisomeric intermediates by catalyzing rearomatization, thus preventing the retro-Cope rearrangement (Scheme 3.19b). Initially, due to bond rotation about the C(sp^3)-C(sp^2) bond the aryl vinyl Cope rearrangement leads to a 50:50 mixture of regioisomeric intermediates. Under normal conditions, the slow [1,3]-proton transfer allows the retro-Cope rearrangement to occur, allowing the regioisomers to equilibrate and reach their thermodynamic ratio before

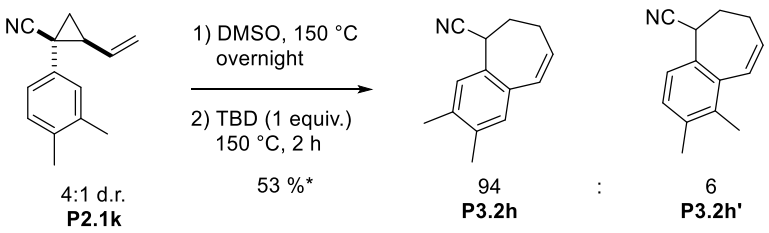
rearomatization occurs. On the other hand, in the absence of TBD, the [1,3]-proton transfer required for rearomatization is thought to be the rate limiting step, allowing the regioisomers of the Cope rearrangement to reach thermodynamic equilibrium prior to rearomatization.

Scheme 3.19 – Effect of TBD on Regiochemistry of AVCPR



In light of this new mechanistic insight into the origin of the regioselectivity of **P3.2h**, an attempt was made to improve the regioselectivity of the conjugated benzocycloheptene **P3.2h** by first forming the Cope product **P3.1j** prior to initiating the alkene isomerization by adding TBD. Indeed, when vinylcyclopropane **P2.1k** was heated to 150 °C overnight, then TBD was added in a second step, **P3.2h** formed in 53 % yield with 94:6 regioselectivity in favor of the distal regioisomer within two hours after TBD addition (Scheme 3.20).

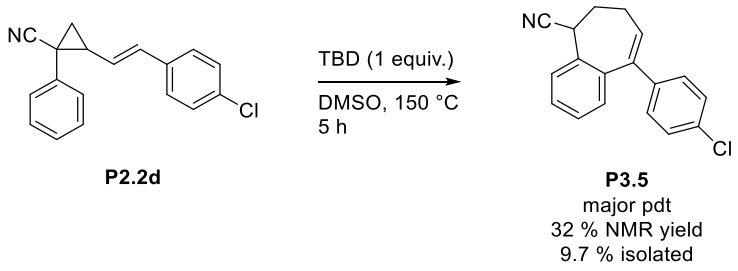
Scheme 3.20 – Improved Regioselectivity of 5h by Sequential AVCPR/Alkene Isomerization



*Yield was obtained by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Given these observations, we hypothesized that by utilizing TBD's ability to catalyze the rearomatizing [1,3]-proton transfer, and further isomerize the resulting benzocycloheptene to the lower energy conjugated isomer, it may be possible to trap the aryl vinyl cyclopropane Cope intermediate, even in the case of the styrenyl substrates. Indeed, when **P2.2d** was exposed to elevated temperatures in the presence of TBD, the conjugated benzocycloheptene **P3.5** was observed as the major product (Scheme 3.21). However, **P3.5** was only isolated in ~10 % yield, due in part to the difficulty of completely separating it from the isomeric by-products, and the yield could likely be improved with an optimized separation technique.

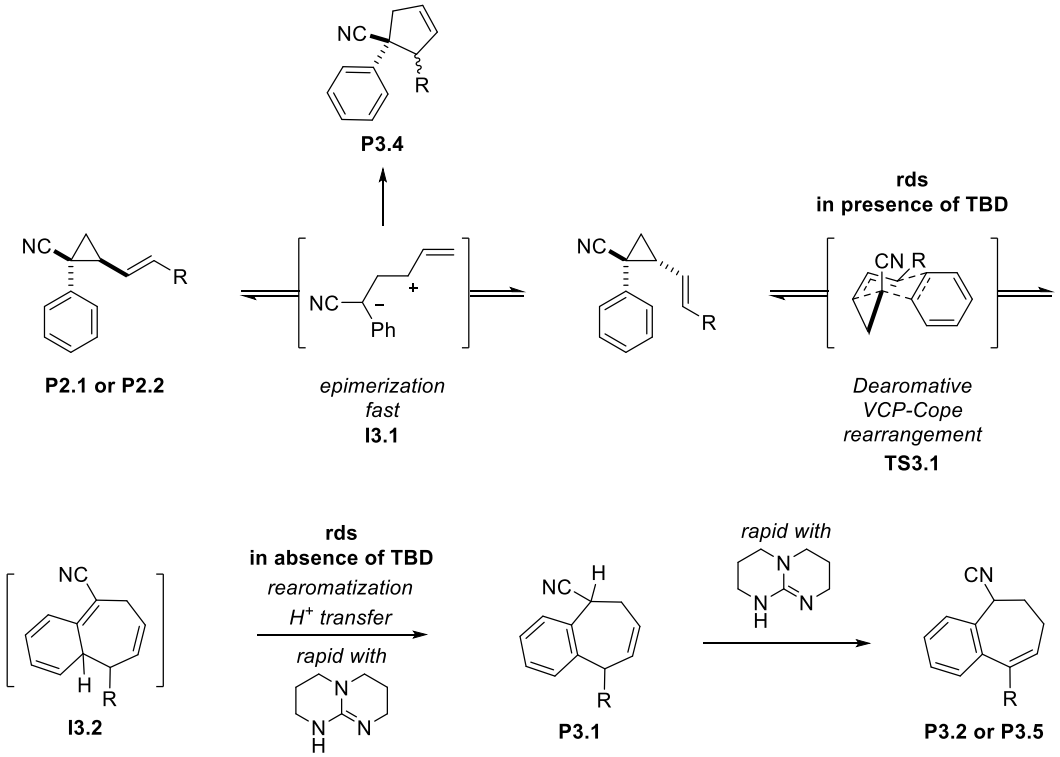
Scheme 3.21 – Synthesis of a Styrenyl Benzocycloheptene



Our observations led us to propose the following mechanism (Scheme 3.22). At high temperatures, the epimerization of the vinylcyclopropane via **I3.1** becomes facile. The *trans* isomer has the vinyl and aryl groups *cis* to one another, and at 150 °C, the Cope rearrangement via **TS3.1** leading to **I3.2** is facile. In the absence of TBD, the [1,3]-proton transfer required for rearomatization is slow. This situation allows the reverse Cope rearrangement to occur. In the case

of styrenyl substrates, the reverse Cope rearrangement and subsequent rearrangement to form cyclopentenes (**P3.4**) in low diastereoselectivity dominates. In the case of simple vinylcyclopropanes, however, the [1,3]-proton transfer dominates over cyclopentene rearrangement, and benzocycloheptenes **P3.1** are formed. Under these conditions the reverse Cope rearrangement is still more facile than proton transfer. However, in the presence of TBD, the rearomatizing [1,3]-proton transfer and subsequent isomerization to the more stable conjugated benzocycloheptene **P3.2** or **P3.5** is facile. This fast rearomatization makes the reverse Cope rearrangement less competitive, so conjugated benzocycloheptenes are selectively formed, even from styrenyl cyclopropanes.

Scheme 3.22 – Proposed Mechanism



§3.4 Conclusion

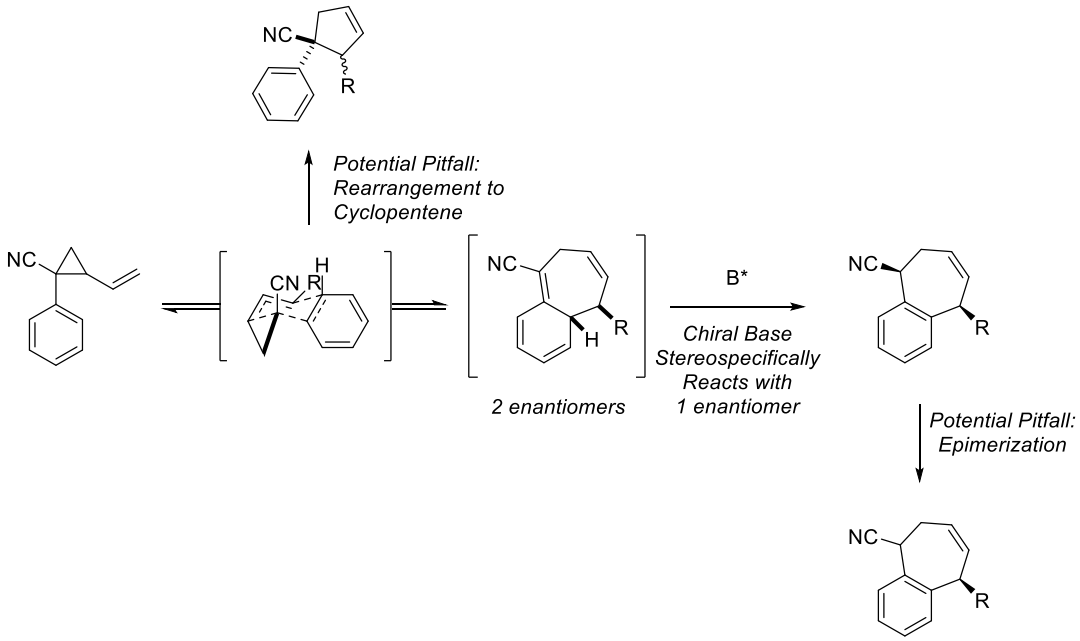
In conclusion, we have described an aryl vinyl cyclopropane Cope rearrangement protocol for the conversion of vinylcyclopropanes to benzocycloheptenes. A key feature of this reaction is the dynamic equilibration of the diastereomers of the starting vinylcyclopropane that obviates the need to laboriously synthesize vinylcyclopropanes of a particular diastereomer, yet still allows capitalization upon the thermodynamic driving force of the cyclopropane strain release to accomplish the difficult rearrangement. Furthermore, the base-mediated isomerization of the initially formed benzocycloheptenes is driven by conjugation. This isomerization provides a means of selectively forming either of two isomers of benzocycloheptene products depending solely on the presence or absence of base. As such, this transformation provides an important complement to currently known aryl vinyl cyclopropane Cope rearrangements.

3.4.1 – Potential Future Directions

The potential to control the stereochemistry of the product by controlling the rate of the retro-Cope rearrangement vs. the rearomatizing [1,3]-proton transfer could potentially provide a means of inducing asymmetry in the reaction. One could envision a chiral dynamic kinetic resolution situation in which the Cope rearrangement would give rise to a pair of enantiomeric intermediates. If an appropriate chiral base were used, it could catalyze an enantiospecific [1,3]-proton transfer, selectively reacting with only one of the two enantiomeric Cope intermediates. The other enantiomer would be able to undergo the retro-Cope rearrangement and racemize. Eventually, all the material could be asymmetrically rearomatized giving rise to chiral benzocycloheptenes. The challenge in executing such a strategy would lie in the careful control of the sterics of the base, to prevent epimerization of the α-nitrile stereocenter. Furthermore, careful control over the relative rates of the reverse Cope rearrangement and the [1,3]-proton transfer

would be required so that the proton transfer was slow enough to allow the reverse Cope reaction to occur, but fast enough to prevent rearrangement to the cyclopentene.

Scheme 3.23 – Enantioselective Aryl Cope via Asymmetric [1,3]-Proton Transfer DKR



§3.5 References

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Chapter 3 Appendix

Experimental methods and spectral analysis for chapter 3

§3.A.1 General Experimental Procedures

All reactions were performed in flame dried glassware under an argon atmosphere unless otherwise noted. THF was dried over sodium in the presence of benzophenone. All other materials were obtained from Sigma-Aldrich, Acros Organics, Alfa Aesar or Fisher Scientific and were used without further purification unless otherwise noted. Reactions were monitored in 50 μL aliquots, performing a simple aqueous workup, and observing the proton NMR spectrum in $CDCl_3$. Flash chromatography was performed using 230x400 mesh, 60 Å porosity silica, using mixtures of hexane (Hex) and ethyl acetate (EA) as eluent as noted. 1H NMR and 13C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer equipped with a QNP Cryoprobe and referenced to residual protio solvent signals.

Structural assignments are based on ^{1}H, ^{13}C, DEPT135, COSY and NOESY techniques. J values are reported in Hz. High resolution mass spectral analysis was done on a Waters LCT Premier mass spectrometer with a quadrupole and time of flight tandem mass analyzer and an electrospray ion source, or via LCMS using a Waters Q-Tof Premier in tandem with an Aquity UPLC using toluene assisted atmospheric pressure chemical ionization (TAPCI), as noted. Infrared analysis was performed on a Shimadzu FTIR-8400S infrared spectrometer. Melting points were obtained on a Digimelt MPA160 melting point apparatus.

3.A.1.1 General Experimental Procedures for Synthesis of Benzocycloheptenes

General Procedure 3.A for Synthesis of Benzocycloheptenes P3.1: A 100 mg/mL solution of vinylcyclopropane in DMSO was prepared, and 0.5 to 1 mL of this solution was added to a flame dried vial equipped with a stir bar and diluted to 0.2 M with DMSO. The vial was sealed and the atmosphere was replaced with argon by purging and refilling with argon 3×. The mixture was

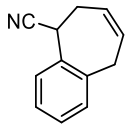
heated to 150 °C and monitored via NMR. Once the reaction was complete (generally 1–6 hours), the mixture was diluted with EtOAc (2 mL) and washed with water (5 mL). The first wash was back extracted with EtOAc (1mL), and the combined organic extracts were washed again with water (5 mL) and brine (1 mL). The organic layer was then dried with $MgSO_4$, filtered, and the solvents were evaporated to afford the non-conjugated benzocycloheptene. For most products, no further purification was needed. In some cases, additional purification via flash chromatography was required.

General Procedure 3.B for Synthesis of Conjugated Benzocycloheptenes P3.2: A 100 mg/mL solution of vinylcyclopropane in DMSO was prepared, and 0.5 to 1 mL of this solution was added to a flame dried vial equipped with a stir bar and diluted to 0.2 M with DMSO. TBD (1,5,7-Triazabicyclo[4.4.0]dec-5-ene) was added (0.5 mmol, 1 equiv.), the vial was sealed and the atmosphere was replaced with argon by purging and refilling with argon 3×. The mixture was heated to 150 °C and monitored via NMR. Once the reaction was complete (generally 1–6 hours), the mixture was diluted with EtOAc (2 mL) and washed with water (5 mL). The first wash was back extracted with EtOAc (1 mL), and the combined organic extracts were washed again with water (5 mL) and brine (1 mL). The organic layer was then dried with $MgSO_4$, filtered, and the solvents were evaporated to afford the non-conjugated benzocycloheptene. For most products, no further purification was needed. In some cases, additional purification via flash chromatography was required.

§3.A.2 Compound Characterization

*3.A.2.1 – Non-Conjugated Benzocycloheptenes **P3.1** Generated Using General Procedure 3.A:*

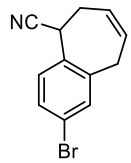
P3.1a



6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.057 g (0.34 mmol) 1-phenyl-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 0.056 g yellow of oil **P3.1a** (0.0.33 mmol, 98 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3029, 2903, 2903, 2839, 2241, 2225, 1660., 1602, 1492, 1456. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 (dd, *J* = 7.5, 1.5 Hz, 1H Aromatic C<u>H</u>), 7.31 – 7.21 (m, 2H Aromatic C<u>H</u>, solvent overlap), 7.15 – 7.11 (m, 1H, Aromatic C<u>H</u>), 5.82 (dddt, *J* = 11.5, 7.1, 4.3, 2.2 Hz, 1H, Alkene C<u>H</u>), 5.49 (ddddd, *J* = 11.6, 4.6, 3.5, 2.4, 1.0 Hz, 1H Alkene C<u>H</u>), 4.47 (dd, *J* = 10.4, 3.2 Hz, 1H α-CN C<u>H</u>), 3.67 (dp, *J* = 17.5, 3.4 Hz, 1H, Alkane C<u>H$_a$</u>H$_b$), 3.47 – 3.36 (m, 1H Alkane CH$_a$<u>H$_b$</u>), 2.83 – 2.74 (m, 1H Alkane C<u>H$_a$</u>H$_b$), 2.66 – 2.54 (m, 1H Alkane CH$_a$<u>H$_b$</u>).^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 134.5, 129.1, 128.3, 127.5, 126.9, 126.5, 126.0, 120.4, 34.1, 33.6, 33.1. HRMS (ESI, m/z) calcd. for $C_{12}H_{11}N$ [M+Na] 192.0784; found 192.0782.

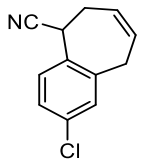
P3.1b



2-bromo-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.0747 g (0.301 mmol) 1-(4-bromophenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A. The crude product was purified by flash chromatography (silica gel, 2.5 % EtOAc in Hexanes) to yield 0.0393 g of white solid **P3.1b** (0.158 mmol, 53 %). Melting point 85.1-89.2 °C. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3026, 2921, 2850, 2238, 1695, 1584, 1484, 1397. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.23 (m, 3H Aromatic C<u>H</u>), 5.78 (dddt, *J* = 11.5, 6.6, 4.3, 2.2 Hz, 1H Alkene C<u>H</u>), 5.48 (ddddd, *J* = 11.6, 4.6, 3.5, 2.4, 0.9 Hz, 1H Alkene C<u>H</u>), 4.42 (dd, *J* = 10.4, 3.3 Hz, 1H α-CN C<u>H</u>), 3.63 (dp, *J* = 17.5, 3.4 Hz, 1H Alkane C<u>H$_a$</u>H$_b$), 3.40 – 3.28 (m, 1H Alkane CH$_a$<u>H$_b$</u>), 2.77 (dtdd, *J* = 18.0, 5.1, 3.5, 1.8 Hz, 1H Alkane C<u>H$_a$</u>H$_b$), 2.56 (ddtt, *J* = 17.9, 10.8, 3.7, 1.9 Hz, 1H Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 133.5, 132.0, 130.3, 128.5, 126.1, 125.7, 122.0, 119.8, 33.7, 33.3, 32.7. HRMS (ESI, m/z) calcd. for $C_{12}H_{10}BrN$ [M+Na] 269.9889; found 269.9898.

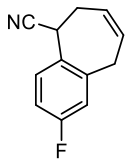
P3.1c



2-chloro-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.0833 g (0.409 mmol) 1-(4-chlorophenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 0.0747 g of yellow oil **P3.1c** (0.367 mmol, 90 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3025, 2917, 2846, 2243, 1661, 1597, 1574, 1487, 1407. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.2 Hz, 1H, Aromatic C<u>H</u>), 7.27 – 7.24 (m, 1H, Aromatic C<u>H</u>, solvent overlap), 7.14 (d, *J* = 2.2 Hz, 1H, Ar<u>H</u>), 5.79 (dddt, *J* = 11.4, 6.7, 4.2, 2.2 Hz, 1H, Alkene C<u>H</u>), 5.49 (dddd, *J* = 11.6, 4.7, 3.5, 2.4 Hz, 1H, Alkene C<u>H</u>), 4.43 (dd, *J* = 10.4, 3.3 Hz, 1H, α-CN C<u>H</u>), 3.67 – 3.59 (m, 1H, Alkane C<u>H$_a$</u>H$_b$), 3.36 (dd, *J* = 17.5, 7.2 Hz, 1H CH$_a$<u>H$_b$</u>), 2.77 (ddtd, *J* = 18.0, 6.8, 3.4, 1.7 Hz, 1H Alkane C<u>H$_a$</u>H$_b$), 2.57 (ddtd, *J* = 17.9, 10.7, 3.6, 1.9 Hz, 1H CH$_a$<u>H$_b$</u>). 13C NMR (126 MHz, CDCl3) δ 142.3, 133.9, 133.0, 129.2, 128.2, 127.3, 126.2, 125.8, 119.9, 33.7, 33.4, 32.8. HRMS (ESI, m/z) calcd. for $C_{12}H_{10}ClN$ [M+H] 204.0575; found 204.0569.

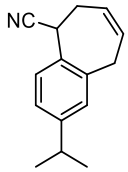
P3.1d



2-fluoro-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 64.6 mg (0.355 mmol) 1-(4-fluorophenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 57.7 mg of yellow oil **P3.1d** (0.317 mmol, 89 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3027, 2922, 2848, 2244, 1667, 1614, 1594, 1501. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (dd, *J* = 8.5, 5.5 Hz, 1H Aromatic C<u>H</u>), 6.95 (td, *J* = 8.4, 2.7 Hz, 1H Aromatic C<u>H</u>), 6.85 (dd, *J* = 9.1, 2.7 Hz, 1H Aromatic C<u>H</u>), 5.79 (dddt, *J* = 11.5, 6.7, 4.4, 2.2 Hz, 1H Alkene C<u>H</u>), 5.49 (dq, *J* = 11.2, 3.6 Hz, 1H Alkene C<u>H</u>), 4.42 (dd, *J* = 10.3, 3.3 Hz, 1H α-CN C<u>H</u>), 3.62 (dp, *J* = 17.6, 3.4 Hz, 1H Alkane C<u>H$_a$</u>H$_b$), 3.38 (dd, *J* = 17.5, 7.1 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.82 – 2.71 (m, 1H Alkane C<u>H$_a$</u>H$_b$), 2.57 (dddt, *J* = 19.5, 11.9, 3.5, 1.6 Hz, 1H Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.2 (d, *J* = 247.8 Hz), 142.9 (d, *J* = 7.9 Hz), 130.3 (d, *J* = 3.0 Hz), 128.6 (d, *J* = 8.9 Hz), 126.0 (d, *J* = 54.4 Hz), 125.8, 116.3 (d, *J* = 22.3 Hz), 113.9, 113.7, 33.6, 33.5, 33.0. HRMS (ESI, m/z) calcd. for $C_{12}H_{10}NF$ [M+Na] 210.0689; 210.0697.

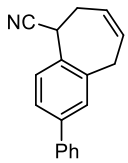
P3.1e



2-isopropyl-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.086 g (0.41 mmol) 1-(4-isopropylphenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A. The crude product was purified by flash chromatography (silica gel, 5 % EtOAc in Hexanes) to yield 0.044 g of brown oil **P3.1e** (0.21 mmol, 51 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3023, 2962, 2241, 1603, 1503, 2921, 2241, 1597, 1505. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (d, *J* = 7.8 Hz, 1H Aromatic C<u>H</u>), 7.13 (dd, *J* = 7.9, 1.9 Hz, 1H Aromatic C<u>H</u>), 6.98 (d, *J* = 1.8 Hz, 1H Aromatic C<u>H</u>), 5.83 (dddt, *J* = 11.5, 6.8, 4.4, 2.2 Hz, 1H Alkene C<u>H</u>), 5.54 – 5.40 (m, 1H Alkene C<u>H</u>), 4.42 (dd, *J* = 10.2, 3.3 Hz, 1H α-CN C<u>H</u>), 3.64 (dt, *J* = 17.5, 3.5 Hz, 1H, Alkane C<u>H$_a$</u>H$_b$), 3.40 (dd, *J* = 17.5, 7.0 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.88 (p, *J* = 6.9 Hz, 1H, Alkane C<u>H</u>), 2.76 (dtdd, *J* = 17.9, 5.1, 3.4, 1.8 Hz, 1H, Alkane C<u>H$_a$</u>H$_b$), 2.59 (ddtd, *J* = 19.6, 12.2, 3.6, 2.0 Hz, 1H, Alkane CH$_a$<u>H$_b$</u>), 1.24 (d, *J* = 6.9 Hz, 6H methyl C<u>H$_3$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 140.4, 131.9, 127.5, 126.9, 126.6, 126.0, 125.2, 120.5, 33.9, 33.9, 33.7, 33.4, 24.1, 24.0. HRMS (ESI, m/z) calcd. for $C_{15}H_{17}N$ [M+H] 212.1439; found 212.1436.

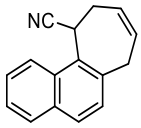
P3.1f



2-phenyl-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 68.4 mg (0.279 mmol) 1-([1,1'-biphenyl]-4-yl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 62.3 mg of yellow solid **P3.1f** (0.254 mmol, 91 %). Melting point 78.0-83.3 °C. IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3028, 2904, 2839, 2242, 1662, 1600, 1568, 1486. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.31 (m, 8H Aromatic C<u>H</u>), 5.86 (dddt, *J* = 11.5, 6.7, 4.3, 2.2 Hz, 1H Alkene C<u>H</u>), 5.60 – 5.45 (m, 1H Alkene C<u>H</u>), 4.51 (dd, *J* = 10.4, 3.3 Hz, 1H α-CN C<u>H</u>), 3.73 (dp, *J* = 17.6, 3.5 Hz, 1H, Alkane C<u>H$_a$</u>H$_b$), 3.48 (dd, *J* = 17.5, 7.1 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.82 (dddt, *J* = 17.9, 5.0, 3.4, 1.7 Hz, 1H, Alkane C<u>H$_a$</u>H$_b$), 2.70 – 2.58 (m, 1H Alkane CH$_a$<u>H$_b$</u>).^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 141.0, 140.5, 133.5, 129.0, 128.0, 127.7, 127.4, 127.3, 126.4, 126.1, 126.0, 120.3, 33.9, 33.6, 33.4. HRMS (ESI, m/z) calcd. for $C_{18}H_{15}N$ [M-CN] 219.1168; found 219.1163.

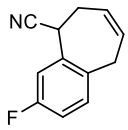
P3.1g



10,11-dihydro-7H-cyclohepta[a]naphthalene-11-carbonitrile.

Prepared from 0.0978 g (0.446 mmol) 1-(naphthalen-1-yl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A. The crude product was purified by flash chromatography (silica gel, 2.5 % EtOAc in Hexanes)to yield 0.0582 mg yellow oil **P3.1g** (0.266 mmol, 60 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3054, 3022, 2925, 2851, 2238, 1667, 1624, 1599, 1512, 1430. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.7 Hz, 1H Aromatic C<u>H</u>), 7.88 (d, *J* = 8.2 Hz, 1H Aromatic C<u>H</u>), 7.76 (d, *J* = 8.4 Hz, 1H Aromatic C<u>H</u>), 7.58 (t, *J* = 7.8 Hz, 1H Aromatic C<u>H</u>), 7.49 (t, *J* = 7.6 Hz, 1H Aromatic C<u>H</u>), 7.29 (d, *J* = 8.4 Hz, 1H Aromatic C<u>H</u>), 5.96 (t, *J* = 10.0 Hz, 1H Alkene C<u>H</u>), 5.63 (ddd, *J* = 11.7, 5.8, 2.8 Hz, 1H Alkene C<u>H</u>), 5.08 (d, *J* = 4.3 Hz, 1H α-CN C<u>H</u>), 4.58 (dt, *J* = 18.9, 3.7 Hz, 1H Alkane Alkane C<u>H$_a$</u>H$_b$), 3.42 (dd, *J* = 18.7, 8.0 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.87 (dd, *J* = 18.1, 5.0 Hz, 1H Alkane C<u>H$_a$</u>H$_b$), 2.63 (d, *J* = 17.6 Hz, 1H Alkane Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 133.0, 130.5, 129.3, 129.0, 128.9, 128.8, 127.2, 126.8, 125.5, 125.2, 121.7, 120.2, 34.7, 30.9, 28.3. HRMS (ESI, m/z) calcd. for $C_{16}H_{13}N$ [M+H] 220.1121; found 220.1127.

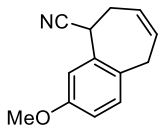
P3.1h



3-fluoro-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.0641 g (0.342 mmol) 1-(3-fluorophenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 0.0546 g of yellow oil **P3.1h** as a mixture of regioisomers (0.292 mmol, 85 %, r.r. 61:39). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3027, 2917, 2846, 2244, 1669, 1616, 1501, 1466. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 7.7 Hz, 1H major Aromatic C<u>H</u>), 7.25 – 7.18 (m, overlapping 1H major 1H minor Aromatic C<u>H</u>), 7.09 (dd, *J* = 8.4, 5.6 Hz, 1H minor Aromatic C<u>H</u>), 7.02 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H major Aromatic C<u>H</u>), 6.92 (td, *J* = 8.4, 2.7 Hz, 1H minor Aromatic C<u>H</u>), 5.80 (dddq, *J* = 11.5, 6.6, 4.3, 2.1 Hz, overlapping 1H major 1H minor Alkene C<u>H</u>), 5.56 – 5.41 (m, overlapping 1H major 1H minor Alkene C<u>H</u>). 4.48 (dd, *J* = 10.4, 3.3 Hz, 1H major α-CN C<u>H</u>), 4.44 (dd, *J* = 10.6, 3.3 Hz, 1H minor α-CN C<u>H</u>), 3.71 – 3.58 (m, 1H overlapping major and minor Alkane C<u>H$_a$</u>H$_b$), 3.48 (dp, *J* = 17.9, 3.5 Hz, 1H major Alkane CH$_a$<u>H$_b$</u>), 3.35 (dd, *J* = 17.7, 7.3 Hz, 1H minor Alkane CH$_a$<u>H$_b$</u>), 2.78 (ddtd, *J* = 16.4, 6.5, 3.3, 1.6 Hz, overlapping 1H major 1H minor Alkane C<u>H$_a$</u>H$_b$), 2.59 (ddtt, *J* = 18.0, 10.4, 3.8, 2.0 Hz, overlapping 1H major 1H minor Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8 (d, *J* = 246.0 Hz), 159.3 (d, *J* = 245.2 Hz), 137.0(d, *J* = 3.4 Hz),, 136.3 (d, *J* = 7.4 Hz), 136.2 (d, *J* = 2.9 Hz), 130.5 (d, *J* = 8.1 Hz), 128.1, 128.07, 127.5 (d, *J* = 16.1 Hz), 126.4, 126.4, 125.8, 125.6, 122.3, 122.3, 119.9, 119.8, 115.3 (d, *J* = 23.7 Hz), 114.6 (d, *J* = 20.8 Hz), 114.1 (d, *J* = 23.6 Hz), 34.0 (d, *J* = 2.8 Hz), 33.9 (d, *J* = 1.2 Hz), 33.3, 33.3, 32.2, 22.4 (d, *J* = 6.2 Hz). HRMS (ESI, m/z) calcd. for $C_{12}H_{10}NF$ [M-CN] 161.0761; found 161.0773.

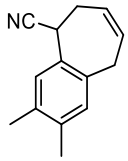
P3.1i



3-methoxy-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 49.2 mg (0.247 mmol) 1-(3-methoxyphenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 48.6 mg of brown oil **P3.1i** as a mixture of regioisomers (0.244 mmol, 97 % r.r. 50:50). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3007, 2939, 2839, 2244, 1661, 1608, 1503, 1265, 1039. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.23 (t, *J* = 8.0 Hz, 1H Aromatic C<u>H</u>), 7.13 (d, *J* = 7.7 Hz, 1H Aromatic C<u>H</u>), 7.06 (d, *J* = 2.6 Hz, 1H Aromatic C<u>H</u>), 7.04 (d, *J* = 8.3 Hz, 1H Aromatic C<u>H</u>), 6.86 (d, *J* = 8.4 Hz, 1H Aromatic C<u>H</u>), 6.76 (dd, *J* = 8.3, 2.7 Hz, 1H Aromatic C<u>H</u>), 5.82 (ddtt, *J* = 9.5, 5.7, 4.1, 2.1 Hz, overlapping 1H 1H Alkene C<u>H</u>), 5.47 (dp, *J* = 11.2, 3.7 Hz, overlapping 1H 1H Alkene C<u>H</u>), 4.50 (dd, *J* = 10.7, 3.2 Hz, 1H α-CN C<u>H</u>), 4.42 (dd, *J* = 10.4, 3.2 Hz, 1H α-CN C<u>H</u>), 3.82 (d, *J* = 1.4 Hz, overlapping 3H 3H OC<u>H</u>$_3$), 3.81 – 3.74 (m, 1H Alkane C<u>H$_a$</u>H$_b$), 3.59 (dp, *J* = 17.8, 3.5 Hz, 1H Alkane C<u>H$_a$</u>H$_b$), 3.43 (dq, *J* = 17.7, 3.5 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 3.33 (dd, *J* = 17.7, 7.1 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.77 (ddtd, *J* = 16.3, 4.9, 3.2, 1.6 Hz, overlapping 1H 1H Alkane C<u>H$_a$</u>H$_b$), 2.65 – 2.52 (m, overlapping 1H 1H Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 156.0, 136.2, 135.6, 132.6, 130.2, 129.1, 127.7, 127.0, 126.8, 126.3, 125.7, 120.5, 120.3, 119.0, 112.9, 110.7, 56.0, 55.6, 34.3, 34.1, 33.6, 32.3, 22.4. HRMS (ESI, m/z) calcd. for $C_{13}H_{13}NO$ [M+H] 200.1070; found 200.1080.

P3.1j

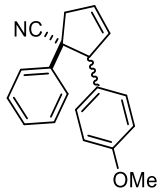


2,3-dimethyl-6,9-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.0738 g (0.374 mmol) 1-(3,4-dimethylphenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 0.0729 g of yellow oil **P3.1j** as a mixture of regioisomers (0.369 mmol, 98 %, r.r. 89:11). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3019, 2922, 2734, 2243, 1661, 1614, 1561, 1505.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.24 (s, 1H Aromatic C<u>H</u>), 6.90 (s, 1H Aromatic C<u>H</u>), 5.81 (dddd, *J* = 11.7, 6.9, 4.4, 2.1 Hz, 1H Alkene C<u>H</u>), 5.46 (dq, *J* = 11.4, 3.6 Hz, 1H Alkene C<u>H</u>), 4.39 (dd, *J* = 10.3, 3.2 Hz, 1H α-CN C<u>H</u>), 3.65 – 3.49 (m, 1H Alkane C<u>H$_a$</u>H$_b$), 3.34 (dd, *J* = 17.6, 7.0 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.75 (dddd, *J* = 19.5, 6.1, 3.6, 1.8 Hz, Alkane C<u>H$_a$</u>H$_b$), 2.64 – 2.48 (m, 1H Alkane CH$_a$<u>H$_b$</u>), 2.26 (s, 3H Methyl C<u>H$_3$</u>), 2.23 (s, 3H Methyl C<u>H$_3$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 136.4, 135.6, 132.3, 132.2, 131.7, 130.6, 128.7, 128.6, 128.2, 126.9, 126.7, 125.9, 120.6, 33.8, 33.7, 32.7, 19.4, 19.4. HRMS (ESI, m/z) calcd. for $C_{14}H_{15}N$ [M+Na] 220.1102; found 220.1102.

*3.A.2.2 – Cyclopentenes **P3.4** Generated Using General Procedure 3.A.*

P3.4a

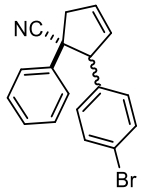


2-(4-methoxyphenyl)-1-phenylcyclopent-3-ene-1-carbonitrile.

Prepared from 0.116 g (0.421 mmol) (E)-2-(4-methoxystyryl)-1-phenylcyclopropane-1-carbonitrile (1b) according to General Procedure 3.A. The Product was purified by flash chromatography (silica gel, 5 % EtOAc in Hexanes) to yield 0.0716 g of yellow oil **P3.4a** as separable diastereomers (0.260 mmol, 62 %, 60:40 d.r.). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 3033, 3003, 2935, 2838, 2237, 1610, 1449, 1033. ^{1}H NMR (500 MHz, Chloroform-*d*) (major diastereomer) δ 7.52 – 7.48 (m, 2H Aromatic C<u>H</u>), 7.42 – 7.37 (m, 2H Aromatic C<u>H</u>), 7.37 – 7.31 (m, 1H Aromatic C<u>H</u>), 7.04 – 6.99 (m, 2H Aromatic C<u>H</u>), 6.88 – 6.82 (m, 2H Aromatic C<u>H</u>), 6.07 (dt, *J* = 6.6, 2.3 Hz, 1H Alkene C<u>H</u>), 5.89 (dq, *J* = 6.1, 2.1 Hz, 1H Alkene C<u>H</u>), 4.27 (p, *J* = 2.3 Hz, 1H Alkane C<u>H</u>, benzylic), 3.79 (s, 3H Methoxy C<u>H</u>$_3$), 3.37 (dq, *J* = 17.1, 2.3 Hz, 1H Alkane C<u>H</u>$_a$H$_b$), 3.16 (dq, *J* = 17.1, 2.2 Hz, 1H Alkane CH$_a$<u>H</u>$_b$).^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 159.4, 140.6, 132.6, 130.5, 129.6, 129.5, 129.1, 128.0, 125.9, 122.3, 114.0, 64.2, 55.3, 48.0, 29.9.^{1}H NMR (500 MHz, Chloroform-*d*) (minor diastereomer) δ 7.12 – 6.99 (m, 5H Aromatic C<u>H</u>), 6.75 – 6.65 (m, 2H Aromatic C<u>H</u>), 6.60 – 6.50 (m, 2H Aromatic C<u>H</u>), 6.19 (dq, *J* = 5.7, 2.4 Hz, 1H Alkene C<u>H</u>), 5.88 (dq, *J* = 6.1, 2.1 Hz, 1H Alkene C<u>H</u>), 4.65 (p, *J* = 2.3 Hz, 1H Alkane C<u>H</u>, benzylic), 3.69 (s, 2H Methoxy C<u>H</u>$_3$), 3.29 (q, *J* = 2.2 Hz, 2H Alkane C<u>H</u>$_2$).^{13}C NMR (126 MHz, $CDCl_3$) (minor diastereomer) δ 158.9, 136.2, 132.8, 130.4, 129.7, 129.0, 128.1,

127.6, 127.4, 125.5, 113.5, 62.7, 55.3, 51.4, 44.4. HRMS (ESI, m/z) calcd. for $C_{19}H_{17}NO$ [M+H] 276.1383; found 276.1374.

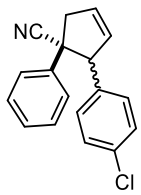
P3.4b



2-(4-bromophenyl)-1-phenylcyclopent-3-ene-1-carbonitrile.

Prepared from 100 mg (0.308 mmol) 2-(4-bromostyryl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 88.8 mg of yellow oil **P3.4b** as a mixture of diastereomers (0.274 mmol, 89 %, d.r. 59:41). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3063, 2924, 2854, 2240, 1698, 1595, 1489, 1449. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 (dt, *J* = 8.1, 1.0 Hz, 2H, major Aromatic C<u>H</u>), 7.46 – 7.38 (m, overlapping 2H major 3H minor Aromatic C<u>H</u>), 7.38 – 7.33 (m, 1H, major Aromatic C<u>H</u>), 7.15 (d, *J* = 8.1 Hz, 2H, minor Aromatic C<u>H</u>), 7.10 (d, J = 7.3 Hz, 2H minor Aromatic C<u>H</u>), 7.06 – 7.01 (m, 2H, minor Aromatic C<u>H</u>), 6.95 (d, *J* = 8.2 Hz, 2H, major Aromatic C<u>H</u>), 6.67 (d, *J* = 8.2 Hz, 2H minor Aromatic C<u>H</u>), 6.28 – 6.20 (m, 1H minor Alkene C<u>H</u>), 6.16 – 6.08 (m, 1H major Alkene C<u>H</u>), 5.92 – 5.81 (m, overlapping 1H major 1H minor Alkene C<u>H</u>), 4.66 (q, *J* = 2.3 Hz, 1H minor Alkane C<u>H</u>, benzylic), 4.27 (q, *J* = 2.4 Hz, 1H major Alkane C<u>H</u>, benzylic), 3.37 (dq, *J* = 17.2, 2.2 Hz, 1H major Alkane C<u>H$_a$</u>H$_b$), 3.32 (p, *J* = 2.6 Hz, 2H minor Alkane C<u>H$_2$</u>), 3.19 (dq, *J* = 17.2, 2.3 Hz, 1H major Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 137.3, 135.9, 135.7, 131.8, 131.7, 131.6, 131.2, 131.0, 130.3, 130.2, 130.0, 129.0, 128.1, 128.1, 127.8, 127.1, 125.8, 124.9, 122.1, 121.8, 121.3, 64.1, 62.7, 55.0, 48.0, 44.6. HRMS (ESI, m/z) calcd. for $C_{18}H_{14}BrN$ [M+H] 324.0382; found 324.0386.

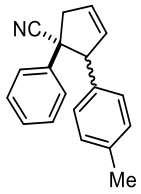
P3.4c



2-(4-chlorophenyl)-1-phenylcyclopent-3-ene-1-carbonitrile.

Prepared from 100 mg (0.357 mmol) (E)-2-(4-chlorostyryl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 100 mg of brown oil **P3.4c** as a mixture of diastereomers (0.357 mmol, 100 % d.r. 55:45). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3062, 2924, 2861, 2239, 1597, 1490, 1449. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.44 (m, 2H major Aromatic C<u>H</u>), 7.44 – 7.37 (m, 2H major Aromatic C<u>H</u>), 7.39 – 7.31 (m, 1H major Aromatic C<u>H</u>), 7.32 – 7.26 (m, 2H major Aromatic C<u>H</u>), 7.13 – 7.05 (m, 2H major Aromatic C<u>H</u>), 7.02 (ddd, *J* = 15.2, 7.9, 4.2 Hz, 7H minor Aromatic C<u>H</u>), 6.77 – 6.70 (m, 2H minor Aromatic C<u>H</u>), 6.24 (dq, *J* = 5.0, 2.3 Hz, 1H minor Alkene C<u>H</u>), 6.12 (dq, *J* = 4.9, 2.3 Hz, 1H major Alkene C<u>H</u>), 5.88 (tq, *J* = 6.3, 2.1 Hz, overlapping 1H major 1H minor Alkene C<u>H</u>), 4.68 (p, *J* = 2.3 Hz, 1H minor Alkane C<u>H</u>, benzylic), 4.29 (p, *J* = 2.3 Hz, 1H major Alkane C<u>H</u>, benzylic), 3.37 (dq, *J* = 17.2, 2.2 Hz, 1H major Alkane C<u>H$_a$</u>H$_b$), 3.32 (p, *J* = 2.5 Hz, 2H minor Alkane C<u>H$_2$</u>), 3.19 (dq, *J* = 17.1, 2.3 Hz, 1H major Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 136.9, 135.8, 135.5, 134.0, 133.3, 132.0, 131.8, 131.3, 130.4, 129.9, 129.8, 129.2, 128.9, 128.2, 128.2, 127.9, 127.3, 125.9, 125.0, 121.9, 64.1, 62.7, 55.2, 51.3, 48.1, 44.7. HRMS (ESI, m/z) calcd. for $C_{18}H_{14}ClN$ [M+H] 280.0888; found 280. 0902.

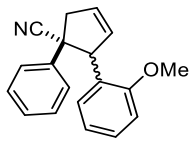
P3.4d



1-phenyl-2-(p-tolyl)cyclopent-3-ene-1-carbonitrile.

Prepared from 100 mg (0.386 mmol) (E)-2-(4-methylstyryl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 91.1 mg of yellow oil **P3.4d** as a mixture of diastereomers (0.351 mmol, 91.1 % d.r. 51:39). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3059, 3027, 2921, 2861, 2238, 1600, 1494, 1449. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.45 (m, 2H major Aromatic C<u>H</u>), 7.44 – 7.36 (m, 2H major Aromatic C<u>H</u>), 7.36 – 7.28 (m, 2H minor Aromatic C<u>H</u>), 7.25 (d, *J* = 5.5 Hz, 1H minor Aromatic C<u>H</u>), 7.12 (p, *J* = 6.8, 6.0 Hz, 2H major Aromatic C<u>H</u>), 7.04 (t, *J* = 5.5 Hz, overlapping 1H major 2H minor Aromatic C<u>H</u>), 7.02 – 6.92 (m, 2H major Aromatic C<u>H</u>), 6.83 (dd, *J* = 7.7, 4.8 Hz, 2H minor Aromatic C<u>H</u>), 6.67 (dt, *J* = 8.3, 5.3 Hz, 2H minor Aromatic C<u>H</u>), 6.18 (ddp, *J* = 7.1, 4.9, 2.4 Hz, 1H minor Alkene C<u>H</u>), 6.07 (tq, *J* = 8.4, 4.8, 3.5 Hz, 1H major Alkene C<u>H</u>), 5.89 (td, *J* = 5.6, 2.8 Hz, overlapping 1H major 1H minor Alkene C<u>H</u>), 4.66 (p, *J* = 4.0, 3.1 Hz, 1H minor Alkane C<u>H</u>, benzylic), 4.27 (h, *J* = 3.7, 3.0 Hz, 1H major Alkane C<u>H</u>, benzylic), 3.36 (ddt, *J* = 16.9, 5.0, 2.4 Hz, 1H major Alkane C<u>H$_a$</u>H$_b$), 3.29 (dp, *J* = 4.9, 2.4 Hz, 2H minor Alkane C<u>H$_2$</u>), 3.16 (ddq, *J* = 17.5, 5.5, 2.5 Hz, 1H major Alkane CH$_a$<u>H$_b$</u>), 2.32 (t, *J* = 5.3 Hz, 3H major C<u>H$_3$</u>), 2.22 – 2.11 (m, 3H minor C<u>H$_3$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 137.8, 137.0, 136.2, 135.4, 133.8, 132.8, 132.5, 132.3, 132.2, 132.1, 130.5, 129.6, 129.4, 129.1, 128.7, 128.6, 128.3, 128.0, 127.6, 127.4, 125.9, 125.5, 122.2, 64.5, 63.0, 55.0, 51.4, 48.1, 44.6, 21.3, 21.1. HRMS (ESI, m/z) calcd. for $C_{19}H_{17}N$ [M+Na] 282.1253; found 282.1265.

P3.4e

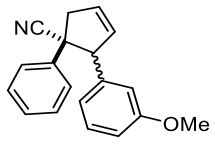


2-(2-methoxyphenyl)-1-phenylcyclopent-3-ene-1-carbonitrile.

Prepared from 0.0739 g (0.268 mmol) E)-2-(2-methoxystyryl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 0.0625 g of yellow oil **P3.4e** as a mixture of diastereomers (0.275 mmol, 85 %, d.r. 68:32). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 2940, 2836, 2237, 1601, 1491, 1451, 1270, 1158, 1049. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 – 7.48 (m, 2H major Aromatic C<u>H</u>), 7.44 – 7.36 (m, 2H major Aromatic C<u>H</u>), 7.39 – 7.31 (m, 2H minor Aromatic C<u>H</u>), 7.24 (d, *J* = 7.9 Hz, 1H minor Aromatic C<u>H</u>), 7.12 – 7.04 (m, overlapping 2H major 2H minor Aromatic C<u>H</u>), 6.97 (t, *J* = 7.9 Hz, 1H minor Aromatic C<u>H</u>), 6.85 (dd, *J* = 8.3, 2.6 Hz, 1H major Aromatic C<u>H</u>), 6.70 (dt, *J* = 7.6, 1.2 Hz, 1H major Aromatic C<u>H</u>), 6.63 (t, *J* = 2.1 Hz, 1H major Aromatic C<u>H</u>), 6.60 (dd, *J* = 8.3, 2.6 Hz, 1H minor Aromatic C<u>H</u>), 6.47 (dd, *J* = 7.6, 1.4 Hz, 1H minor Aromatic C<u>H</u>), 6.26 (t, *J* = 2.0 Hz, 1H minor Aromatic C<u>H</u>), 6.22 (dq, *J* = 4.9, 2.3 Hz, 1H minor Alkene C<u>H</u>), 6.10 (dt, *J* = 6.5, 2.3 Hz, 1H major Alkene C<u>H</u>), 5.91 (tq, *J* = 5.8, 2.1 Hz, overlapping 1H major 1H minor Alkene C<u>H</u>), 4.67 (p, *J* = 2.2 Hz, 1H Alkane C<u>H</u>, benzylic), 4.28 (p, *J* = 2.3 Hz, 1H Alkane C<u>H</u>, benzylic), 3.75 (s, 3H major OC<u>H</u>$_3$), 3.58 (s, 3H major OC<u>H</u>$_3$), 3.38 (dq, *J* = 17.1, 2.3 Hz, 1H major Alkane C<u>H</u>$_a$H$_b$), 3.31 (q, *J* = 2.2 Hz, 2H minor Alkane C<u>H</u>$_2$), 3.17 (dq, *J* = 17.1, 2.2 Hz, 1H major Alkane CH$_a$<u>H</u>$_b$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 159.4, 140.7, 140.0, 138.5, 136.1, 132.3, 132.2, 130.9, 130.0, 129.7, 129.1, 129.0, 128.1, 128.0, 127.7, 127.4, 125.9, 125.3, 122.1, 121.3, 120.9, 114.2, 114.0, 113.4, 113.3,

64.8, 63.3, 55.3, 55.2, 54.9, 51.4, 48.2, 44.6. HRMS (ESI, m/z) calcd. for $C_{19}H_{17}NO$ [M+] 275.1305; found 275.1314.

P3.4f

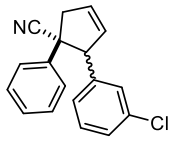


2-(3-methoxyphenyl)-1-phenylcyclopent-3-ene-1-carbonitrile.

Prepared from 50 mg (0.182 mmol) (E)-2-(3-methoxystyryl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 38.9 mg of pale yellow oil **P3.4f** as a mixture of diastereomers (0.141 mmol, 77.6 % d.r. 61:39). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 2939, 2836, 2238, 1600, 1584, 1491, 1450, 1269, 1157, 1036. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.49 (m, 2H major Aromatic C<u>H</u>), 7.40 (t, *J* = 7.7 Hz, 2H major Aromatic C<u>H</u>), 7.37 – 7.31 (m, 2H minor Aromatic C<u>H</u>), 7.24 (d, *J* = 7.9 Hz, 1H minor Aromatic C<u>H</u>), 7.12 – 7.03 (m, overlapping 2H major 2H minor Aromatic C<u>H</u>), 6.96 (t, *J* = 7.9 Hz, 1H minor Aromatic C<u>H</u>), 6.84 (dd, *J* = 8.3, 2.5 Hz, 1H major Aromatic C<u>H</u>), 6.70 (d, *J* = 7.6 Hz, 1H major Aromatic C<u>H</u>), 6.63 (d, *J* = 2.1 Hz, 1H major Aromatic C<u>H</u>), 6.60 (dd, *J* = 8.2, 2.6 Hz, 1H minor Aromatic C<u>H</u>), 6.47 (d, *J* = 7.5 Hz, 1H minor Aromatic C<u>H</u>), 6.26 (t, *J* = 2.0 Hz, 1H minor Aromatic C<u>H</u>), 6.22 (dq, *J* = 5.0, 2.4 Hz, 1H minor Alkene C<u>H</u>), 6.10 (dq, *J* = 6.2, 2.3 Hz, 1H major Alkene C<u>H</u>), 5.91 (tq, *J* = 5.6, 2.1 Hz, 1H overlapping 1H major 1H minor Alkene C<u>H</u>), 4.71 – 4.62 (m, 1H minor Alkane C<u>H</u>, benzylic), 4.28 (q, *J* = 2.3 Hz, 1H minor Alkane C<u>H</u>, benzylic), 3.75 (s, 3H major OC<u>H</u>$_3$), 3.58 (s, 3H minor OC<u>H</u>$_3$), 3.38 (dq, *J* = 17.1, 2.3 Hz, 1H major Alkane Alkane C<u>H</u>$_a$H$_b$), 3.31 (q, *J* = 2.2 Hz, 2H minor Alkane C<u>H</u>$_2$), 3.17 (dq, *J* = 17.1, 2.2 Hz, 1H major

Alkane $CH_a\underline{H}_b$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 159.4, 140.7, 140.0, 138.5, 136.1, 132.4, 132.2, 130.9, 130.0, 129.7, 129.1, 129.0, 128.1, 128.0, 127.7, 127.4, 125.9, 125.3, 122.1, 121.3, 120.9, 114.2, 114.0, 113.4, 113.3, 64.8, 63.3, 55.30, 55.25, 54.9, 51.4, 48.2, 44.6. HRMS (ESI, m/z) calcd. for $C_{19}H_{17}NO$ [M+Na] 298.1202; found 298.1204.

P3.4g

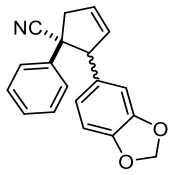


2-(3-chlorophenyl)-1-phenylcyclopent-3-ene-1-carbonitrile.

Prepared from 50 mg (0.179 mmol) (E)-2-(3-chlorostyryl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.A to yield 45 mg of yellow oil **P3.4g** as a mixture of diastereomers (0.161 mmol, 90 % d.r. 59:41). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3063, 2926, 2860, 2239, 1597, 1572, 1494, 1449. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 7.6 Hz, 2H major Aromatic C$\underline{H}$), 7.41 (t, *J* = 7.5 Hz, 2H major Aromatic C$\underline{H}$), 7.38 – 7.27 (m, overlapping 1H major 5H minor Aromatic C$\underline{H}$), 7.13 – 6.94 (m, overlapping 4H major 2H minor Aromatic C$\underline{H}$), 6.74 (s, 1H minor Aromatic C$\underline{H}$), 6.72 (d, *J* = 7.7 Hz, 1H minor Aromatic C$\underline{H}$), 6.25 (dt, *J* = 5.8, 2.4 Hz, 1H minor Alkene C$\underline{H}$), 6.13 (dd, *J* = 5.8, 2.7 Hz, 1H minor Alkene C$\underline{H}$), 5.88 (td, *J* = 5.8, 2.6 Hz, overlapping 1H major 1H minor Alkene C$\underline{H}$), 4.67 (t, *J* = 2.3 Hz, 1H minor Alkane C$\underline{H}$, benzylic), 4.27 (t, *J* = 2.3 Hz, 1H major Alkane C$\underline{H}$, benzylic), 3.39 (dd, *J* = 17.2, 2.5 Hz, 1H major Alkane $C\underline{H}_aH_b$), 3.33 (d, *J* = 2.4 Hz, 2H minor Alkane $C\underline{H}_2$), 3.18 (dd, *J* = 17.2, 2.4 Hz, 1H major Alkane $CH_a\underline{H}_b$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 140.3, 139.1, 135.7, 134.6, 134.0, 131.7, 131.6, 131.5, 130.6, 129.9, 129.3, 129.2, 129.0, 128.7, 128.5, 128.4, 128.24,

128.20, 128.0, 127.52, 127.48, 127.2, 127.0, 126.8, 125.8, 125.0, 121.8, 64.4, 63.0, 54.7, 51.3, 48.2, 44.7. HRMS (ESI, m/z) calcd. for $C_{18}H_{14}ClN$ [M+H] 280.0888; found 280. 0902

P3.4h



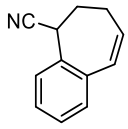
2-(benzo[d][1,3]dioxol-5-yl)-1-phenylcyclopent-3-ene-1-carbonitrile.

Prepared from 0.0699 g (0.242 mmol) (E)-2-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.A. Filtered through a silica gel plug in EtOAc. Yield 0.695 g brown oil **P3.4h** (0.240 mmol, 99 % d.r. 58:42). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3061, 3029, 2897, 2779, 2237, 1601, 1503, 1444, 1251, 1099, 1039.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.47 (m, 2H major Aromatic C<u>H</u>), 7.40 (t, *J* = 7.5 Hz, 2H major Aromatic C<u>H</u>), 7.34 (t, *J* = 7.3 Hz, 1H major Aromatic C<u>H</u>), 7.15 – 7.04 (m, overlapping 2H major 2H minor Aromatic C<u>H</u>), 6.76 (d, *J* = 7.8 Hz, 1H major Aromatic C<u>H</u>), 6.58 (s, 1H minor O-C<u>H</u>$_2$-O), 6.56 (d, *J* = 1.9 Hz, 1H minor Aromatic C<u>H</u>), 6.49 (d, *J* = 8.0 Hz, 1H minor Aromatic C<u>H</u>), 6.33 (dd, *J* = 8.0, 1.6 Hz, 1H minor Aromatic C<u>H</u>), 6.24 (d, *J* = 1.7 Hz, 1H minor Aromatic C<u>H</u>), 6.19 (dq, *J* = 5.0, 2.2 Hz, 1H minor Alkene C<u>H</u>), 6.08 (dq, *J* = 4.8, 2.2 Hz, 1H major Alkene C<u>H</u>), 5.95 (s, 2H major O-C<u>H</u>$_2$-O), 5.86 (dt, *J* = 6.1, 2.1 Hz, overlapping 1H major 1H minor Alkene C<u>H</u>), 5.83 – 5.79 (m, 1H minor Aromatic C<u>H</u>), 4.62 (t, *J* = 2.3 Hz, 1H minor Alkane C<u>H</u>, benzylic), 4.29 – 4.19 (m, 1H major Alkane C<u>H</u>, benzylic), 3.37 (dq, *J* = 17.1, 2.2 Hz, 1H major Alkane C<u>H$_a$</u>H$_b$), 3.29 (q, *J* = 2.2 Hz, 2H minor Alkane C<u>H</u>$_2$), 3.14 (dq, *J* = 17.1, 2.2 Hz, 1H major Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 147.5, 146.8, 140.7,

136.1, 132.6, 132.3, 130.74, 130.71, 129.8, 129.1, 128.7, 128.1, 128.0, 127.7, 127.4, 125.8, 125.4, 122.2, 122.1, 121.8, 108.9, 108.7, 108.4, 107.9, 101.2, 101.0, 64.7, 63.1, 54.8, 51.4, 48.1, 44.4. HRMS (ESI, m/z) calcd. for $C_{19}H_{15}NO_2$ [M+H] 290.1176; found 290.1192.

*3.A.2.3 – Conjugated Benzocycloheptenes **P3.2** Generated Using General Procedure 3.B:*

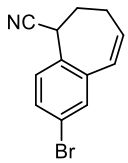
P3.2a



6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.0718 g (0.424 mmol) 1-phenyl-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B. The crude product was filtered through a silica gel plug in EtOAc to yield 0.0594 g of brown oil **P3.2a** (0.351 mmol, 83 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3060, 3022, 2934, 2895, 2830, 2239, 1644, 1599, 1495, 1450, 1425. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.38 (m, 1H Aromatic C<u>H</u>), 7.30 (td, *J* = 7.5, 1.4 Hz, 1H Aromatic C<u>H</u>), 7.23 (ddd, *J* = 9.7, 7.8, 1.7 Hz, 2H Aromatic C<u>H</u>), 6.48 (dt, *J* = 12.1, 2.0 Hz, 1H Alkene C<u>H</u>), 6.00 (dt, *J* = 12.1, 4.8 Hz, 1H Alkene C<u>H</u>), 4.05 (dd, *J* = 6.4, 4.3 Hz, 1H α-CN C<u>H</u>), 2.55 (ddddd, *J* = 24.2, 18.7, 13.0, 5.0, 2.1 Hz, 2H Alkane C<u>H</u>$_2$), 2.36 – 2.29 (m, 2H Alkane C<u>H</u>$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 134.2, 131.7, 131.6, 129.6, 128.3, 127.9, 127.5, 119.9, 36.1, 31.9, 29.1. LRMS (EI, m/z) parent mass 169.2 found 169.0 %TIC 5.80. HRMS (ESI, m/z) calcd. for $C_{12}H_{11}N$ [M+Na] 192.0784; found 192.0786.

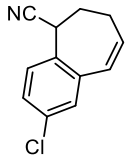
P3.2b



2-bromo-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 77.8 mg mg (0.313 mmol) 1-(4-bromophenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B to yield 62.4 mg of brown oil **P3.2b** (0.251 mmol, 80 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3024, 2934, 2828, 2239, 1645, 1562, 1486, 1448.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 9.2 Hz, 2H Aromatic C<u>H</u>), 7.27 (d, *J* = 8.0 Hz, 1H Aromatic C<u>H</u>), 6.39 (dt, *J* = 12.1, 1.8 Hz, 1H Alkene C<u>H</u>), 6.05 (dt, *J* = 11.9, 4.8 Hz, 1H Alkene C<u>H</u>), 3.99 (dd, *J* = 6.4, 4.5 Hz, 1H α-CN C<u>H</u>), 2.61 – 2.47 (m, 2H Alkane C<u>H</u>$_2$), 2.35 – 2.24 (m, 2H Alkane C<u>H</u>$_2$).^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 134.1, 133.4, 133.1, 130.2, 129.4, 128.3, 122.1, 119.4, 35.5, 31.7, 29.0. HRMS (ESI, m/z) calcd. for $C_{12}H_{10}NBr$ [M+H] 248.0069; found 248.0077.

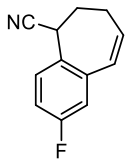
P3.2c



2-chloro-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.0482 g (0.237 mmol) 1-(4-chlorophenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B. The crude product was purified by flash chromatography (silica gel, 2.5% EtOAc in Hexanes) to yield 0.0179 g of pale yellow oil **P3.2c** (0.088 mmol, 37 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 2924, 2850, 2241, 1592, 1564, 1489, 1448. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.30 (m, 1H Aromatic C<u>H</u>), 7.20 (d, *J* = 7.6 Hz, 2H Aromatic C<u>H</u>), 6.40 (dd, *J* = 12.2, 2.0 Hz, 1H Alkene C<u>H</u>), 6.06 (ddd, *J* = 12.8, 7.3, 3.1 Hz, 1H Alkene C<u>H</u>), 4.01 (dd, *J* = 6.7, 4.3 Hz, 1H α-CN C<u>H</u>), 2.63 – 2.46 (m, 2H Alkane C<u>H</u>$_2$), 2.30 (qd, *J* = 7.0, 1.8 Hz, 2H Alkane C<u>H</u>$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 134.1, 133.4, 132.6, 131.2, 129.2, 128.5, 127.3, 119.5, 35.5, 31.8, 29.0. HRMS (ESI, m/z) calcd. for $C_{12}H_{10}NCl$ [M+H] 204.0575; found 204.0583.

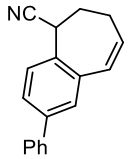
P3.2d



2-fluoro-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 54.9 mg (0.293 mmol) 1-(4-fluorophenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B to yield 48.3 mg of yellow oil **P3.2d** (0.258 mmol, 88 %). (KA7_115). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3025, 2935, 2898, 2240, 1675, 1610, 1584, 1425, 1394. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 (dd, *J* = 9.4, 5.4 Hz, 1H Aromatic C<u>H</u>), 6.84 (ddt, *J* = 8.0, 3.8, 2.0 Hz, 2H Aromatic C<u>H</u>), 6.33 (dt, *J* = 12.1, 1.9 Hz, 1H Alkene C<u>H</u>), 5.97 (dt, *J* = 12.0, 4.8 Hz, 1H Alkene C<u>H</u>), 3.94 (dd, *J* = 6.3, 4.5 Hz, 1H α-CN C<u>H</u>), 2.55 – 2.38 (m, 2H Alkane C<u>H</u>$_2$), 2.26 – 2.18 (m, 2H Alkane C<u>H</u>$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4 (d, *J* = 246.3 Hz), 137.8 (d, *J* = 8.1 Hz), 133.2, 130.1 (d, *J* = 3.5 Hz), 129.6 (d, *J* = 8.2 Hz), 128.6 (d, *J* = 1.8 Hz), 125.9 (d, *J* = 52.7 Hz), 119.7, 117.9 (d, *J* = 21.8 Hz), 114.0 (d, *J* = 21.7 Hz), 35.4, 31.8, 28.9. HRMS (ESI, m/z) calcd. for $C_{12}H_{10}NF$ [M-CN] 161.0761; found 161.0795.

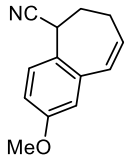
P3.2e



2-phenyl-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 28.8 mg (0.117 mmol) 1-([1,1'-biphenyl]-4-yl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B to yield 25.0 mg of yellow oil **P3.2e** (0.102 mmol, 87 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3029, 2932, 2240, 1667, 1600, 1485, 1449. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.56 (m, 2H Aromatic C<u>H</u>), 7.51 – 7.42 (m, 5H Aromatic C<u>H</u>), 7.42 – 7.33 (m, 1H Aromatic C<u>H</u>), 6.56 (dt, *J* = 12.2, 1.9 Hz, 1H Alkene C<u>H</u>), 6.05 (dt, *J* = 11.9, 4.8 Hz, 1H Alkene C<u>H</u>), 4.14 – 4.05 (m, 1H α-CN C<u>H</u>), 2.69 – 2.47 (m, 2H Alkane C<u>H</u>$_2$), 2.40 – 2.29 (m, 2H Alkane C<u>H</u>$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 140.3, 135.9, 133.1, 132.1, 130.4, 129.6, 129.0, 128.5, 127.8, 127.2, 126.0, 119.9, 35.8, 31.8, 29.1. HRMS (ESI, m/z) calcd. for $C_{18}H_{15}N$ [M-CN] 219.1168; found 219.1134.

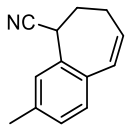
P3.2f



2-methoxy-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 96.8 mg (0.486 mmol) 1-(4-methoxyphenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B to yield 88.6 mg of brown oil **P3.2f** (0.445 mmol, 92 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3009, 2935, 2837, 2237, 1604, 1574, 1505, 1464, 1248, 1037. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.22 (m, 1H Aromatic C<u>H</u>), 6.74 (dd, *J* = 6.0, 2.8 Hz, 2H Aromatic C<u>H</u>), 6.41 (dt, *J* = 12.1, 1.9 Hz, 1H Alkene C<u>H</u>), 5.98 (dt, *J* = 12.0, 4.8 Hz, 1H Alkene C<u>H</u>), 4.00 (dd, *J* = 7.7, 3.0 Hz, 1H α-CN C<u>H</u>), 3.79 (d, *J* = 1.3 Hz, 3H OC<u>H</u>$_3$), 2.62 – 2.40 (m, 2H Alkane C<u>H</u>$_2$), 2.36 – 2.17 (m, 2H Alkane C<u>H</u>$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 136.8, 132.0, 129.4, 129.1, 126.5, 120.0, 116.9, 112.3, 55.3, 35.2, 31.6, 28.8. HRMS (ESI, m/z) calcd. for $C_{13}H_{13}NO$ [M+H] 200.1070; found 200.1077.

P3.2g

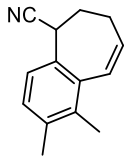


3-methyl-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

Prepared from 0.1047 g (0.572 mmol) 1-(3-methoxyphenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B to yield 0.0951 g of yellow oil **P3.2g** as a mixture of regioisomers (0.519 mmol, 91 %, r.r. 61:39). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3026, 2945, 2864, 2240, 1672,

1610, 1501, 1461. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 (dd, *J* = 6.9, 2.1 Hz, 1H major Aromatic C<u>H</u>), 7.20 (d, *J* = 18.4 Hz, overlapping 2H major 1H minor Aromatic C<u>H</u>), 7.10 (d, *J* = 1.7 Hz, 2H minor aromatic C<u>H</u>), 6.64 (dd, *J* = 11.1, 1.9 Hz, 1H major Alkene C<u>H</u>), 6.45 (dd, *J* = 12.1, 2.0 Hz, 1H minor Alkene C<u>H</u>), 6.22 (dt, *J* = 11.0, 6.2 Hz, 1H major Alkene C<u>H</u>), 5.93 (dt, *J* = 12.1, 4.7 Hz, 1H minor Alkene C<u>H</u>), 4.01 (dd, *J* = 6.5, 4.2 Hz, 1H minor α-CN C<u>H</u>), 3.93 (dd, *J* = 10.3, 5.1 Hz, 1H major α-CN C<u>H</u>), 2.62 – 2.44 (m, 1H Alkane C<u>H$_a$</u>H$_b$), 2.44 – 2.33 (m, overlapping 3H methyl C<u>H$_3$</u>, 1H Alkane C<u>H$_a$</u>H$_b$), 2.33 – 2.18 (m, overlapping 3H methyl C<u>H$_3$</u>, 1H Alkane CH$_a$<u>H$_b$</u>), 2.17 – 2.06 (m, 1H Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 136.9, 135.0, 134.0, 133.9, 132.6, 132.1, 132.1, 131.6, 131.2, 130.5, 129.8, 129.3, 128.8, 128.5, 127.3, 124.7, 120.8, 119.9, 38.0, 36.0, 34.2, 31.6, 29.0, 25.5, 21.1, 20.0. HRMS (ESI, m/z) calcd. for $C_{13}H_{13}N$ [M+H] 184.1121; found 184.1124.

P3.2h



2,3-dimethyl-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile.

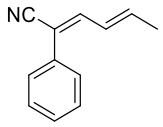
Prepared from 37.4 mg (0.190 mmol) 1-(3,4-dimethylphenyl)-2-vinylcyclopropane-1-carbonitrile according to General Procedure 3.B. Yield 30.2 mg yellow oil **P3.2 h** (0.153 mmol, 87 % r.r. 56:44). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3021, 2941, 2240, 1612, 1508, 1453. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 7.8 Hz, 1H major Aromatic C<u>H</u>), 7.15 (s, 1H minor Aromatic C<u>H</u>), 7.11 (d, *J* = 7.8 Hz, 1H major Aromatic C<u>H</u>), 6.99 (s, 1H minor Aromatic C<u>H</u>), 6.69 (dd, *J* = 10.7, 1.8 Hz, 1H major Alkene C<u>H</u>), 6.41 (dt, *J* = 12.1, 1.9 Hz, 1H minor Alkene C<u>Hz</u>), 6.24

(ddd, *J* = 10.8, 7.2, 6.3 Hz, 1H major Alkene C<u>H</u>), 5.91 (dt, *J* = 12.1, 4.7 Hz, 1H minor Alkene C<u>H</u>), 4.00 (t, *J* = 5.3 Hz, 1H minor α-CN C<u>H</u>), 3.88 (dd, *J* = 10.7, 5.8 Hz, 1H major α-CN C<u>H</u>), 2.64 – 2.44 (m, 1H Alkane C<u>H$_a$</u>H$_b$), 2.37 (dddd, *J* = 13.1, 11.0, 7.7, 3.5 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.31 (s, 3H methyl C<u>H$_3$</u>), 2.27 (s, 3H methyl C<u>H$_3$</u>), 2.24 (s, 3H methyl C<u>H$_3$</u>), 2.20 (s, 3H methyl C<u>H$_3$</u>), 2.14 (ddt, *J* = 14.2, 7.0, 3.5 Hz, 1H Alkane CH$_a$<u>H$_b$</u>), 2.04 – 1.95 (m, 1H Alkane CH$_a$<u>H$_b$</u>). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 136.4, 135.9, 135.3, 135.2, 133.0, 132.9, 131.5, 131.4, 130.8, 130.5, 129.9, 129.33, 129.30, 128.9, 124.1, 121.2, 120.2, 38.9, 35.7, 33.8, 31.6, 29.1, 24.6, 20.5, 19.4, 19.3, 15.8. HRMS (ESI, m/z) calcd. for $C_{14}H_{15}N$ [M+H] 198.1277; found 198.1282.

3.A.2.4 – Other Products

3.A.2.4.1 – Diene (P3.3)

P3.3



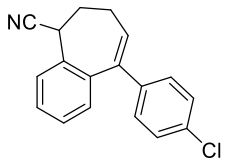
(2E,4E/Z)-2-phenylhexa-2,4-dienenitrile 96:5 mixture of E/Z isomers

IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3062, 3030, 2963, 2932, 2851, 2213, 1634, 1597, 1496, 1450, 1261. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.64 – 7.59 (m, 1H, minor Ar), 7.60 – 7.52 (m, 2H), 7.39 (tt, *J* = 8.8, 2.1 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.21 (d, *J* = 11.1 Hz, 1H), 6.96 (d, *J* = 11.3 Hz, 1H minor alkene), 6.73 (tdd, *J* = 15.1, 4.4, 2.8 Hz, 1H), 6.46 (ddt, *J* = 14.7, 11.4, 1.6 Hz, 1H minor alkene), 6.29 (dq, *J* = 14.1, 6.9 Hz, 1H), 6.11 (dd, *J* = 10.8, 7.3 Hz, 1H minor alkene), 1.97 (dt, *J* = 7.0, 1.4 Hz, 3H), 1.86 (dd, *J* = 6.9, 1.4 Hz, 3H minor C*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3,

140.8, 133.4, 129.3, 129.1, 129.0, 125.7, 117.1, 111.4, 19.1. HRMS (ESI, m/z) calcd. for $C_{14}H_{11}N$ [M+Na] 192.0789; found 198.0796.

3.A.2.4.2 – Styrenyl Benzocycloheptene P3.5 generated using General Procedure 3.B

P3.5



9-(4-chlorophenyl)-6,7-dihydro-5H-benzo[7]annulene-5-carbonitrile

Prepared from 0.0663 g (0.237 mmol) (E)-2-(4-chlorostyryl)-1-phenylcyclopropane-1-carbonitrile according to General Procedure 3.B. The Product was purified by flash chromatography (silica gel, 5 % EtOAc in Hexanes) to yield 0.0064 g of yellow oil **P3.5** (9.7 %). IR ($\bar{\nu} - \bar{\nu}_{IR}$, neat) 3060, 3027, 2946, 2862, 2240, 2592, 1489, 1444, 1401, 1265, 1901. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.22 – 7.15 (m, 2H), 7.03 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.47 (t, *J* = 7.4 Hz, 1H), 3.97 (dd, *J* = 10.8, 6.9 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.51 – 2.40 (m, 1H), 2.17 (dtd, *J* = 14.1, 7.3, 3.1 Hz, 1H), 1.89 (ddt, *J* = 14.0, 12.2, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 139.5, 138.7, 134.5, 133.8, 129.8, 129.3, 128.7, 128.4, 128.3, 127.7, 126.8, 120.9, 40.2, 33.4, 24.4. HRMS (ESI, m/z) calcd. for $C_{18}H_{14}NCl$ [M+H] 280.893; found 280.894.