

**New Methods for Allylic Functionalization:  
Selenium- and Palladium-Catalyzed Reactions**

By

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B.S. Chem. Creighton University, 2002

Submitted to the Department of Chemistry and the Faculty of the Graduate School of  
the University of Kansas in partial fulfillment of the requirements of the degree of  
Doctor of Philosophy

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## Abstract

Shelli R. Waetzig, Ph.D.

Department of Chemistry, April 2007

University of Kansas

The selenium- and palladium-catalyzed synthesis of new carbon—carbon and carbon—heteroatom bonds is the focus of the research described in this dissertation. Specifically, oxidative halogenation of olefins was catalyzed by PhSeCl in the presence of *N*-chlorosuccinimide. Using sterics and electronics to bias regioselectivity, the reaction afforded a variety of functionalized allyl chlorides in good yields. Furthermore, the selenium-catalyzed bromolactonization of unsaturated carboxylic acids was also achieved with increased regioselectivities as compared to the uncatalyzed reaction. Also reported are new methods for palladium-catalyzed allylic functionalization. First, the formation of new C—N bonds is detailed in the Pd-catalyzed decarboxylative coupling of carbamates producing allylated heteroaromatic amines. A new method for the construction of C—Se bonds is also reported through the palladium-catalyzed decarboxylation of selenoformates. Using chiral ligands, high enantioselectivities of the allyl selenide products could be obtained. The cross-coupling of allyl species is also detailed in this manuscript. To begin, allyl dicyanobutenoates underwent decarboxylative coupling to afford  $\alpha$ -allylated compounds as the kinetic hexadiene product upon treatment with palladium(0) catalysts. Isolation of the thermodynamic  $\gamma$ -allylation product was also possible through a Cope rearrangement or *via* a tandem decarboxylative

allylation/Cope rearrangement. High enantioselectivities and moderate diastereoselectivities were obtained using chiral ligands and microwave irradiation. Lastly, the palladium-catalyzed allylation of heteroaromatic alkanes is also described. Unusual regioselectivities and high diastereoselectivities were observed for this process and are explained *via* a mechanism involving a tandem decarboxylative dearomatization/aza-Cope rearrangement.

To my husband,

Josh

## Acknowledgements

At the culmination of a long journey it is often difficult to find the appropriate words to express the gratitude to all of those who have helped and supported your endeavors in numerous ways. My five years as a graduate student have been filled by interactions with many people who have contributed to my learning, development and success as a graduate student. They have helped make this possible and so I hope to give a small token back to those who have offered so much.

Josh, your support has made all of this possible. I have always considered myself lucky to be able to spend so much time with my best friend. It is not easy to find the words to tell you exactly how much you mean to me. But, I hope that you know just how much I appreciate your companionship. Having you in my life is truly a blessing. You are always willing to discuss anything, including work, and are always so rational and caring. Your hard work and dedication is something I have admired since we met, and you have made me a better graduate student because of that. Going through this process together has not always been easy when schedules are full, but we have always found a way to make time for us. To me, nothing is more perfect than spending the evening with you. You always know how to make me smile! Thank you for everything you have done. I hope you know that I am *your* biggest fan. As I write these acknowledgements, I also reflect fondly upon our past, cherish today, and look forward to our future, whatever that holds. I love you, Joshua.

Jon, I could not have asked for a better mentor. Working in your lab has been a terrific experience. Your passion for chemistry and desire to explore new avenues has been contagious. It has been fun to watch our group grow and I think that is a tribute to how friendly and personable you are, as well as a hard worker. Although it may not have always seemed like it, I have the utmost respect for you and am continually amazed at the vast amount of knowledge that you have. Thanks for teaching me all the little stuff, such as tricks for ChemDraw, as well as the “big” stuff, and for making fun of me when I least expected it. I know that you will do great

things in the future and I am excited to watch the new directions that the research will take. Best of luck and thanks again for everything.

I also wish to express my gratitude to the rest of my committee who have also contributed to my learning while here at KU. Dr. Givens, you were one of the first teachers that I had as a graduate student. I have always been impressed at your organization as a professor and how you made seemingly difficult concepts easy to understand. Dr. Carlson, I had the pleasure of teaching under you for multiple semesters. During this time, I was amazed at the respect the students gave you and it was a statement of how you were truly dedicated to the students. Along with chemistry discussions, I also enjoyed our conversations about Jayhawk basketball. Rock Chalk! Helena, thank you for the opportunity to work as a head TA for your lab classes. I think you have a great approach toward teaching basic concepts in a lab class, which can sometimes be difficult. I hope to do the same when I am teaching in the future. I also enjoyed your synthesis class as you presented creative new ways to look at old synthetic problems. Jeff, thanks for making problem set an open, learning environment. Your questions were always thought provoking, and made it a fun challenge to go up to the board. Again, thanks to all of my committee members for their time, effort and contribution.

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I have had the luxury of being in close proximity to my family over the past five years and I really treasure the time that I spend with them. First, to my sister, Jolene Dueringer, you are always so cheerful and giving. Thank you for being so supportive and for just being a fantastic older sister. Also, to my mother-in-law, Kathy Bowen, you have been a tremendous supporter of both Josh and I. Thanks for everything. It has been wonderful to spend more time with you since you moved to Lawrence.

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**New Methods for Allylic Functionalization:  
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## Abbreviations

Ac	acetyl
AIDS	Acquired Immune Deficiency Syndrome
Ar	aryl
Bn	benzyl
Bu	butyl
cat.	catalytic
COSY	correlation spectroscopy
Cp	cyclopentadienyl
dba	dibenzylidene acetone
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	<i>N, N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppb	diphenylphosphinobutane
dppe	diphenylphosphinoethane
dppp	diphenylphosphinopropane
dr	diastereomeric ratio
ee	enantiomeric excess
<i>ent</i>	enantiomer
Et	ethyl
EWG	electron-withdrawing group
GC	gas chromatography
Het	heteroaryl
HIV-1	Human Immunodeficiency Virus-1
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry

IR	infrared radiation
L <sub>L</sub>	large ligand
L <sub>n</sub>	ligand
L <sub>S</sub>	small ligand
Me	methyl
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -BuLi	<i>n</i> -butyl lithium
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
Np	naphthyl
NXS	<i>N</i> -halosuccinimide
Nuc	nucleophile
Pd	palladium
Ph	phenyl
ppm	part per million
SARS	Severe Acute Respiratory Syndrome
Se	selenium
<i>sec</i> -BuLi	<i>sec</i> -butyl lithium
Succ	succinimide
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
<sup>t</sup> Bu	<i>tert</i> -butyl
Tf	triflate
TMEDA	tetramethylethylene diamine
TMG	tetramethylguanidine
TMSCl	trimethylsilyl chloride
tol	toluene
Ts	tosyl
μW	microwave

## **Chapter 1**

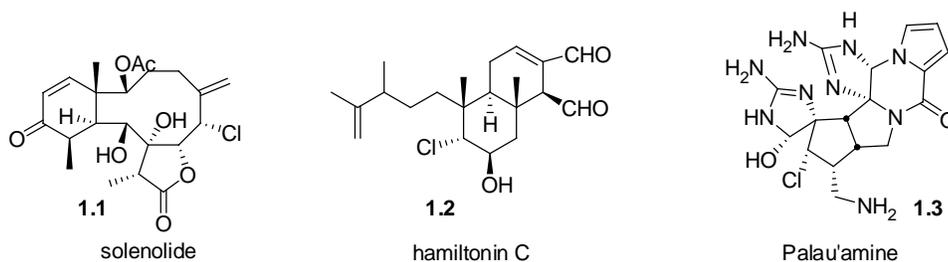
### *Selenium-Catalyzed Oxidative Halogenation*

## 1.1 Application and Significance of Halogenation

### *Halometabolites from Haloperoxidase Enzymes*

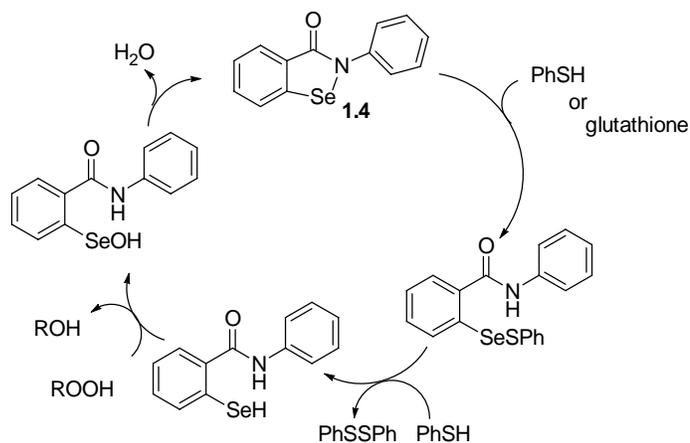
The isolation of halogen-containing natural products from marine organisms has illustrated that the simple oxidation of a C—H bond to a more functional C—X bond is a desirable transformation. These complex natural products incorporate one or several halogens in their structures (**1.1-1.3**).<sup>1,2</sup> Some have shown biological relevance, including protein phosphatase inhibition,<sup>3</sup> cytotoxicity,<sup>4</sup> anti-fouling properties,<sup>5</sup> and antimicrobial activities.<sup>6</sup> Given the biological potential for these compounds and their derivatives, it is plain to see why a simple, yet effective way to selectively incorporate halides into organic compounds is desirable.

Marine organisms possess a distinct way of catalyzing the oxidation NaX salts, present in high concentrations in the ocean, to electrophilic (“X<sup>+</sup>”) halogenating species, which can then be incorporated into organic substrates.<sup>7</sup> Enzymes, such as vanadium haloperoxidase and FeHeme haloperoxidase,<sup>8</sup> have set the standard oxidative halogenation of C—H bonds of organic substrates. The vanadium haloperoxidase enzymes have received more attention as they exhibit better thermal stability, thus making them easier to handle.<sup>8</sup> However, the low availability of these enzymes limits their synthetic utility.



**Scheme 1.1**

Some selenium-containing enzymes, such as glutathione peroxidase, are known for their antioxidant properties in biological systems and aid in protecting cells and lipid membranes from harmful H<sub>2</sub>O<sub>2</sub>.<sup>9</sup> Ebselen (**1.4**) is a selenium-containing compound which exhibits antioxidant activity<sup>10</sup> and can be used in place of glutathione peroxidase for reaction and mechanistic studies.<sup>11</sup> A proposed mechanism for ebselen-catalyzed oxidation of thiols is depicted in Scheme 1.2. Organoselenium compounds are also known to catalyze other types of oxidation. For example, a recent report utilized selenium reagents as catalysts for the oxidation of NaX salts to electrophilic “X<sup>+</sup>” reagents in the presence of H<sub>2</sub>O<sub>2</sub>.<sup>12</sup> These findings show that organoselenium compounds are not only antioxidants, but also mimics of the haloperoxidase enzymes found in marine organisms. Since the regioselectivity of halogen addition by the haloperoxidase enzymes can be unselective, organoselenium compounds could facilitate incorporation of halogens into complex molecules.

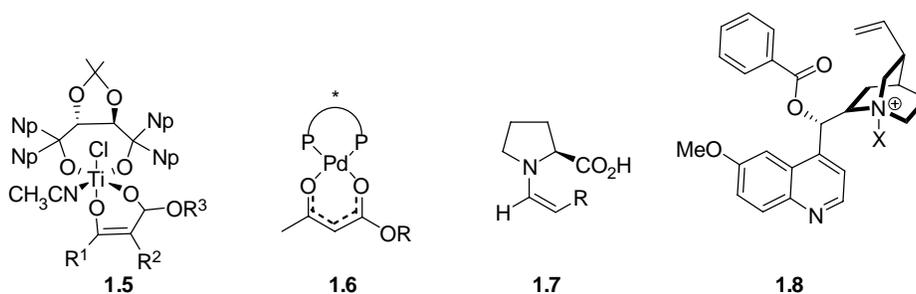


**Scheme 1.2**

### *Current Methods for Halogenation*

Not only do marine organisms use the haloperoxidase enzymes to synthesize halogenated compounds, but many of these are also produced in enantioenriched form. Since, further applications of these biologically active natural products could require multi-gram quantities of an enantiopure compound, the ability to mimic these stereoselective transformations using simpler methods is desirable. Traditional methods of halogenation rely on the use of reagents such as HOX or X<sub>2</sub>. However, controlling the regio- and stereoselective addition of halogens with HOX and X<sub>2</sub> has been difficult due to their propensity to undergo radical reactions.<sup>13</sup> Ideally, catalysis by a simple organic compound could be a way to direct the regio- and stereoselectivity by tempering the highly reactive nature of these reagents. Many of the current enantioselective halogenation reactions utilize ketones to introduce α-halogens through chiral enolates, their derivatives, or delivery from chiral

halogenating reagents (Scheme 1.3). Chiral ligands on metal centers allow for the generation of chiral, metal-bound enolates that undergo asymmetric C—Cl bond forming reactions with electrophilic halogen sources (1.5, 1.6).<sup>14</sup> Organocatalysis has been used in generating chiral enamine derivatives with amines, such as proline (1.7), that react similarly to chiral enolates.<sup>15</sup> Other groups have installed  $\alpha$ -halogens enantioselectively through halogen transfer from a chiral, halogen reagent (i.e. **1.8**), to achiral enolates.

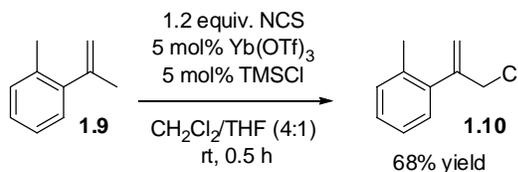


**Scheme 1.3**

While these techniques are useful for the halogenation of enolates, new routes are undoubtedly necessary to produce structures that mimic the diversity of halogenated natural products. Furthermore, the new methods which are developed should ideally be extended toward enantioselective variants.

Allylic halogenation is a useful tool that has potential application in synthesis. The *N*-halosuccinimide (NXS) reagents promote this type of transformation, but are better known for their radical-type reaction pathways, which can make enantioselectivity difficult to achieve. While there has been a surge to find new

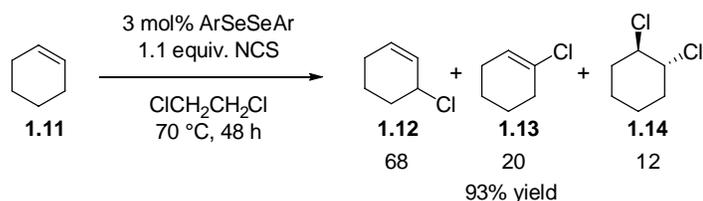
routes to  $\alpha$ -halogenated ketones, the field of catalytic allylic halogenation has been slower to develop.



#### Scheme 1.4

In 2002, Nakagawa and coworkers reported the Yb(OTf)<sub>3</sub>-TMSCl catalyzed allylic halogenation with NCS (Scheme 1.4).<sup>16</sup> The reaction was selective for the allylic over benzylic halogenation, as was shown by **1.9** selectively reacting to give the product of allylic halogenation (**1.10**). Although complete mechanistic details have not been reported, the lack of chlorination at the highly reactive benzylic position suggests that this reaction was a non-radical process. Substrates in this report were limited to those containing isopropenyl groups, as 1,2-disubstituted alkenes were unreactive.

Prior to this work, Sharpless disclosed the ability of aryl diselenides to catalyze the non-radical addition of *N*-chlorosuccinimide (NCS) to olefins such as **1.11**, ultimately yielding the product of allylic chlorination (**1.12**) as the major product.<sup>17</sup> Vinyl- (**1.13**) and dichlorination (**1.14**) products were also isolated, illustrating the common selectivity problem notorious with halogenation reactions (Scheme 1.5). While the reaction lacked selectivity for the allylic chlorinated products, it demonstrated selenium's capability of mimicking the two electron oxidation/reduction cycle notorious to transition metal chemistry.



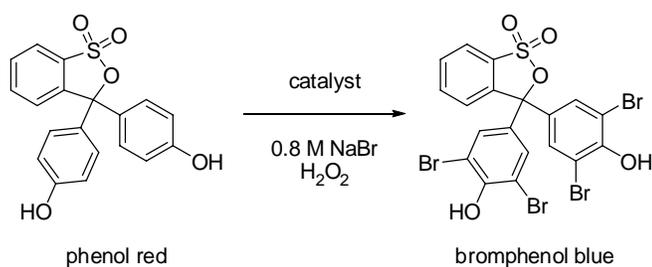
## Scheme 1.5

As mentioned, the progress of allylic halogenation has been slow and underrepresented in the literature. In fact, there are currently no reports on the subject of catalytic, enantioselective allylic halogenation. It is obvious that efforts should be directed toward filling this void and advancing this area of synthesis.

## 1.2 Selenium-Catalyzed Allylic Halogenation

### *Catalyst Screening*

To begin work on our initial goal of allylic halogenation, it was important to identify potential catalysts that can promote oxidative halogenation. To this end, various reagents were screened for their ability to catalyze oxidation of bromide by observing the reaction between an indicator (phenol red), NaBr and H<sub>2</sub>O<sub>2</sub> (Scheme 1.6). If bromination of phenol red occurred, another indicator, bromphenol blue was produced. As the names indicate, the reaction color proceeded from red to blue when the halogenation reaction occurred.



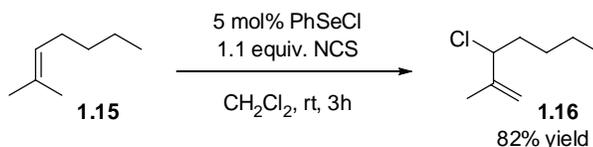
### Scheme 1.6

This electrophilic halogenation reaction requires that a source of “Br<sup>+</sup>” be produced in the reaction mixture. The control reaction with only hydrogen peroxide and sodium bromide showed no activity and the color remained unchanged. A number of potential catalysts for oxidative halogenation were identified, such as CuSO<sub>4</sub>, MnCl<sub>3</sub>, Pd(OAc)<sub>2</sub>, PhSeCl, and ebselen (Scheme 1.2, 1.4) as they promoted the color change over a period of 24 hours. The presence of bromphenol blue indicated that electrophilic “Br<sup>+</sup>” had been produced. Given the precedence of selenium compounds facilitating a two electron oxidation/reduction cycle, we chose to begin our study with selenium-based catalysts.<sup>18</sup> To simplify the reaction and better understand the reaction mechanism, we chose to use the preoxidized halogen source, *N*-halosuccinimide. This seemed advantageous as we could minimize the amount of freely diffusing halogen sources (HOX, X<sub>2</sub>) which make regio- and chemoselectivity difficult to control.

#### *Method Development with Prenyl Substituted Olefins*

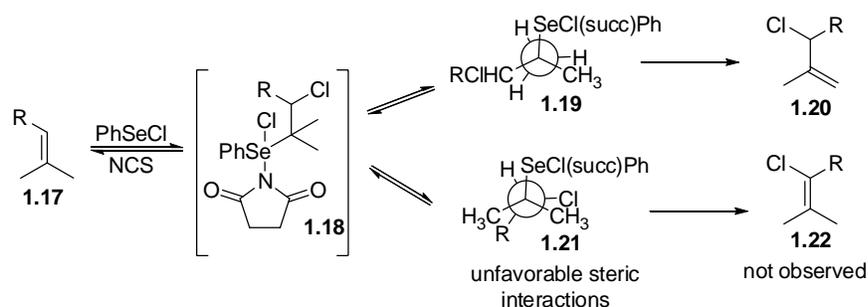
In previous work by Sharpless, it was noted that *N*-chlorosuccinimide oxidizes PhSeSePh to produce two separate species, PhSeCl and PhSe-succinimide. To

prevent multiple catalysts from being present in the reaction, we chose to start with PhSeCl, which was active in our initial screening and is commercially available. With the catalyst and halogen source chosen, we proceeded to test the reaction of 2-methyl-2-heptene (**1.15**) with 5 mol% PhSeCl and 1.1 equivalents NCS in CH<sub>2</sub>Cl<sub>2</sub> at room temperature (Scheme 1.7). After 3 hours, the product of allylic halogenation (**1.16**) was isolated. In contrast to the work done by Sharpless, allyl chloride **1.16** was the only product formed. Vinyl chlorides and dichlorides were not observed.



### Scheme 1.7

Intrigued by the isolation of a single isomer of the allyl chloride **1.16**, we aimed to provide rationale to account for the selectivity of this reaction. It seemed logical that regeneration of the double bond was caused by a *syn*-elimination of H and Se atoms, as is known for these types of conditions.<sup>19</sup> Therefore, upon further inspection of the conformational isomers (**1.19** vs. **1.21**) of selenium addition to the olefin, it seemed reasonable that allyl halide **1.20** was favored due to the minimal steric interactions present for *syn* elimination in the transition state. Conversely, intermediate **1.21** must overcome a high energy barrier caused by increased steric interactions, disfavoring the formation of **1.22** (Scheme 1.8).



### Scheme 1.8

Based on this model, we reasoned that other prenyl substituted olefins would react similarly, and subjected similar substrates to these conditions (Table 1.1). These substrates incorporated various functional groups, such as alcohols and ketones. While the functional groups were distal to the olefin, some had significant effects on the reaction times and yields. For example, prenyl (**1.23a**) reacted much more slowly and gave reduced yields, but heating the alcohol to 50 °C allowed for a more reasonable reaction time without compromising the yield. Protection of the free alcohol was advantageous showing decreased reaction times and increased yields. Ketone **1.23c** afforded a significantly lower yield, and the loss was attributed to the competing  $\alpha$ -halogenation reaction.<sup>20,18c</sup> Fortunately, protection of the ketone as an acetal (**1.23d**) allowed for swift reaction and **1.24d** was isolated in 85% yield. Subsequent deprotection to afford the ketone was achieved with 4N HCl in 88% yield. In the case of myrcene (**1.23e**), the unconjugated olefin reacts selectively to form allylic chloride **1.24e**.

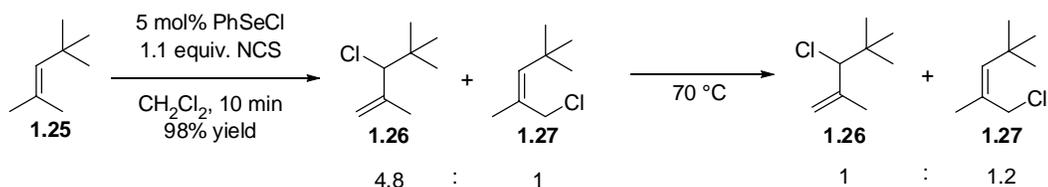
**Table 1.1** Allylic Chlorination of Prenyl Olefins

Reaction scheme:  $\text{1.23} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{5 mol\% PhSeCl, 1.1 equiv. NCS}} \text{1.24}$

Substrate	R	Time (h)	% yield
<b>1.23a</b>	CH <sub>2</sub> OH	48	72
<b>1.23a</b>	CH <sub>2</sub> OH	24	68 <sup>a</sup>
<b>1.23b</b>	CH <sub>2</sub> OBn	3	84
<b>1.23c</b>	CH <sub>2</sub> CH <sub>2</sub> COMe	4	50
<b>1.23d</b>		4	85
<b>1.23e</b>		24	69

<sup>a</sup> Reaction run at 35 °C.

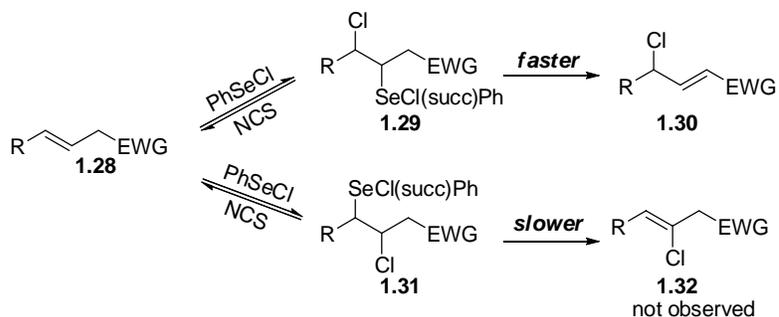
We were particularly interested by the reaction with *tert*-butyl substituted olefin **1.25** (Scheme 1.9). This reaction proceeded very quickly, affording a 98% yield and a 4.8:1 mixture of isomers (**1.26** and **1.27**, respectively) in just 10 minutes. Moreover, the minor isomer did not show transposition of the olefin that occurred for all other substrates. Sharpless also reported a similar reaction with  $\beta$ -pinene where the olefin was not transposed and concluded that another selenium species was active and PhSeCl was not the active catalyst.<sup>21</sup> However, in our case, only PhSeCl was added and catalyst speciation alone cannot explain the remarkably fast reaction times for **1.25**. The product mixture was heated to 70 °C to determine if equilibration of the two products was possible. The ratio did, in fact, change to a 1:1.2 ratio of the same products, demonstrating that **1.26** is the kinetic product of the reaction. Further studies would have to be done on this substrate to determine if another mechanism were operative.



**Scheme 1.9**

*Method Development with Electronically Biased Olefins*

Once we had established the ability to selectively form the allyl chloride products biased by sterics, it seemed logical to screen substrates which could facilitate elimination using an electronic bias by incorporating an electron withdrawing group (EWG) (Scheme 1.10). Since selenium reversibly adds across the olefin to form two regioisomers that can subsequently be oxidized by NCS (**1.29** and **1.31**), the one which can eliminate the more acidic  $\alpha$ -proton to the EWG should react faster to form the  $\alpha,\beta$ -unsaturated allyl chloride (**1.32**).<sup>22</sup>



**Scheme 1.10**

To begin, *trans*-3-hexenoic acid (**1.33a**) was used as a model substrate to test the validity of the aforementioned electronic argument. Unfortunately, the reaction

conditions used for the prenyl olefins were not compatible with this substrate. Reaction times were considerably longer (up to 3 days) and results were erratic and irreproducible. The addition of 4Å molecular sieves was helpful and the conversion of **1.33a** to allyl chloride **1.34a** was complete in 24 hrs. In the process of evaluating reaction conditions, it was seen that high concentrations of NCS inhibited the reaction. To keep the concentration of NCS in the reaction low, slow addition was attempted. Due to the low solubility of NCS in CH<sub>2</sub>Cl<sub>2</sub>, other solvents were tested for increased NCS solubility in an effort to keep the reaction concentration manageable for slow addition. A drastic difference in solubility of NCS was found among three solvents: CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, and MeOH. CH<sub>3</sub>CN possessed the highest NCS solubility (181 mg/mL), followed by CH<sub>2</sub>Cl<sub>2</sub> (70 mg/mL), while NCS was almost completely insoluble in MeOH, leaving CH<sub>3</sub>CN as the optimal solvent. To our delight, syringe pump addition of a solution of NCS in CH<sub>3</sub>CN over 16 hours provided reproducible results, decreased reaction times, and cleaner reaction mixtures. Once a set of reaction conditions had been established, several other unsaturated acids, esters, arenes, and nitriles were screened (Table 1.2). Despite the challenges presented by the unsaturated acids, switching to methyl ester derivatives (**1.33d-f**), significantly reduced reaction times (4 h) and boosted yields, although slow addition was still necessary. Other types of EWG's were introduced with substrates **1.33g** and **1.33h**, albeit higher catalyst loading (20 mol %) was necessary to reach complete conversion. 3-Pentenenitrile (**1.33h**) gave a crude 3:1 mixture of *E/Z* isomers, which was improved to 9:1 upon chromatography. This was the only substrate where *E/Z*

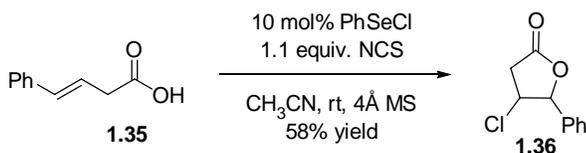
selectivity was an issue as all other substrates afforded solely the *E*-isomer, as determined by  $^1\text{H}$  NMR spectroscopy.

**Table 1.2** Allylic Chlorination of Allylic Acids, Esters, Arenes, and Nitriles

Substrate	R	EWG	Time (h)	% yield
<b>1.33a</b>	Et	CO <sub>2</sub> H	16	83
<b>1.33b</b>	Bu	CO <sub>2</sub> H	16	75
<b>1.33c</b>	H	CO <sub>2</sub> H	16	82
<b>1.33d</b>	Et	CO <sub>2</sub> Me	4	88
<b>1.33e</b>	Bu	CO <sub>2</sub> Me	4	89
<b>1.33f</b>	Ph	CO <sub>2</sub> Me	4	77
<b>1.33g</b>	H	Ph	48	66 <sup>a</sup>
<b>1.33h</b>	Me	CN	48	62 <sup>a,b</sup>

<sup>a</sup> 20 mol % PhSeCl <sup>b</sup> Isolated 9:1 *E/Z* mixture

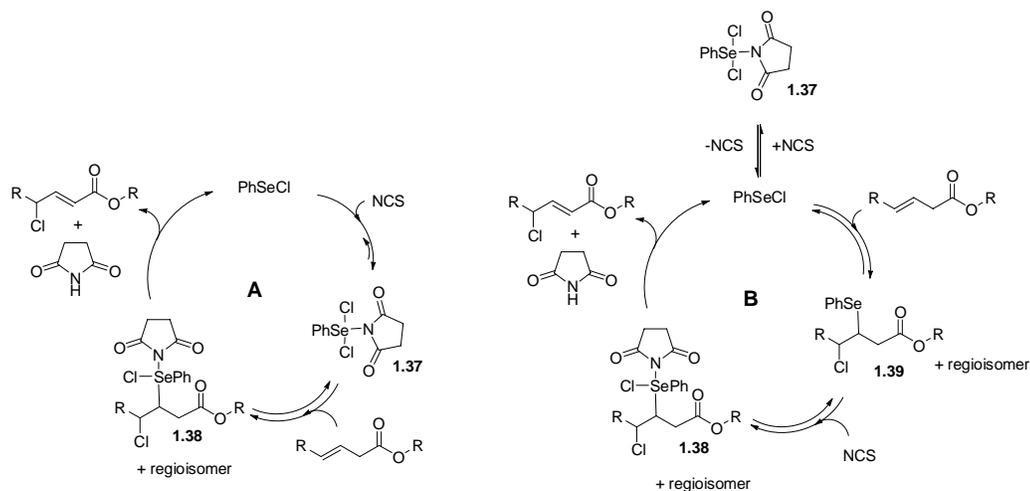
It is particularly noteworthy that when *trans*-styryl acetic acid (**1.35**) was treated under the standard reaction conditions, only chlorolactone **1.36** was isolated (Scheme 1.11). The formation of this product was interesting but not consistent with our goal for allylic halogenation and will be discussed later in more detail.



**Scheme 1.11**

### *Proposed Mechanisms*

Although we had a grasp on the role of sterics and electronics in the reaction, we lacked a complete mechanistic understanding. Based on the precedence of similar processes and our initial observations, it seemed that catalytic cycles **A** and **B** were viable mechanistic explanations (Scheme 1.12). Cycles **A** and **B** are distinguishable by the oxidation state of selenium when addition to the olefin occurs. The oxidation of PhSeCl with NCS is known to be a facile and rapid process,<sup>17</sup> so the selenium (IV) species (**1.37**) is considered to be the resting state of the catalyst in both cycles. In cycle **A**, addition of the selenium (IV) chloride (**1.37**) to the olefin produces alkyl selenide **1.38** (and its regioisomer),<sup>23</sup> which can undergo elimination of the  $\alpha$ -proton to liberate the allyl chloride, succinimide, and concomitantly regenerate PhSeCl. In Cycle **B**, the addition of selenium to the olefin occurs from the selenium (II) species, PhSeCl. At this point, alkyl selenide **1.39** is oxidized by NCS to form the same selenium (IV) complex, **1.38**, as in cycle **A**. Elimination can then ensue generating the expected allyl chloride, succinimide, and recycling the PhSeCl catalyst. Although these cycles are very similar, it seemed to us that appropriate mechanistic experiments might support or rule out one of these mechanisms.

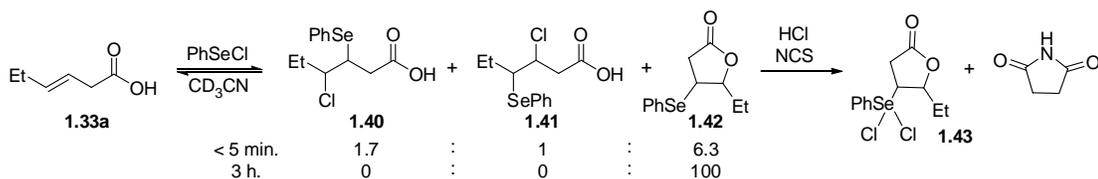


**Scheme 1.12**

### *Stoichiometric Studies of the Elementary Steps of Catalysis*

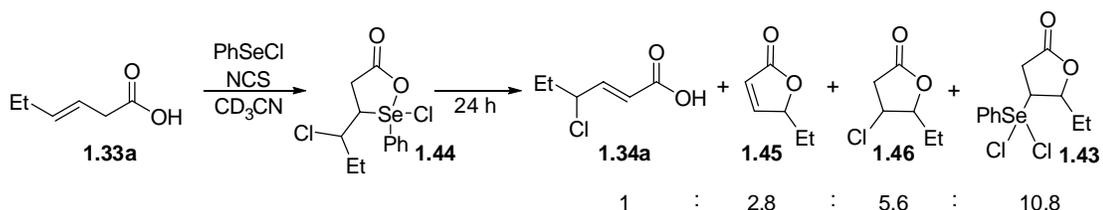
With this in mind, simple experiments were run with stoichiometric  $\text{PhSeCl}$  as a way of characterizing intermediates in the catalytic cycle. Reactions of this nature were run on small scale in deuterated solvents so as to be monitored by  $^1\text{H}$  NMR spectroscopy (Scheme 1.13). First, 3-hexenoic acid (**1.33a**) was treated with one equivalent  $\text{PhSeCl}$ , as a way to mimic the addition step of cycle B. The addition of  $\text{PhSeCl}$  to olefins is well preceded and is known to equilibrate between the two regioisomers of addition.<sup>17,24</sup> This is also evident with our model substrate, as **1.40** and **1.41** were formed in a 1.7:1 ratio, respectively. However, a third compound (**1.42**) was actually the major product of the initial reaction, as selenolactonization proved to be a relatively fast process in  $\text{CD}_3\text{CN}$ . After 3 hours, the reaction had completely equilibrated to selenolactone **1.42**. The cyclization step liberates a molecule of  $\text{HCl}$ , which upon the addition of an equivalent of  $\text{NCS}$ , immediately

reacts to form **1.43** and succinimide. The resulting inactivity of complex **1.43** after 16 hours hinted that this cyclization event might contribute to the loss of catalyst activity by producing HCl.



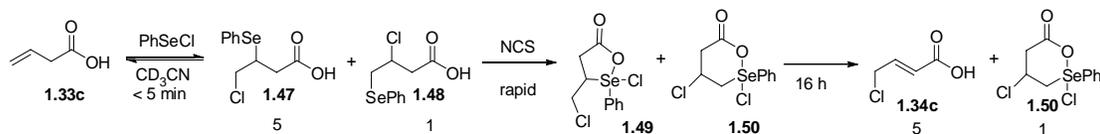
### Scheme 1.13

Next, **1.33a** was treated with 1.0 equivalent PhSeCl, and the addition of a stoichiometric amount of NCS immediately followed (Scheme 1.14). Based on the  $^1\text{H}$  NMR spectrum, it appeared that the kinetic addition product (**1.40**) was oxidized and the carboxylic acid cyclized onto the selenium atom forming selenurane **1.44**. After 24 hours, selenurane **1.44** had completely converted to a host of products which included allyl halide **1.34a**, butenolide **1.45**, chlorolactone **1.46**, and selenolactone **1.43**. The chlorolactone product can be explained by the 1,2-shift of chlorine from selenium to carbon, generating the chlorolactone and PhSeCl. Previous work has shown that the reduction of selenium (IV) to selenium (II) occurs by a similar process.<sup>23c,25</sup>



### Scheme 1.14

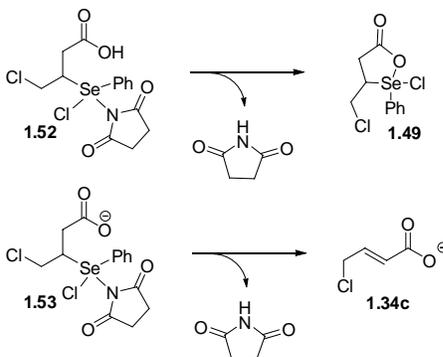
A similar reaction was performed on vinyl acetic acid (Scheme 1.15). Initial addition of PhSeCl afforded a 5:1 mixture of regioisomers, **1.47** and **1.48**, respectively. Within minutes, an equivalent of NCS was added and the reaction was further monitored by  $^1\text{H}$  NMR spectroscopy. Apparently, the addition of NCS oxidized both products to their respective selenuranes (**1.49**, **1.50**), but productive reaction occurred only with selenurane **1.49**. Consequently, after 16 hours, **1.49** had completely converted to allyl halide **1.34c**, but remained in a 5:1 ratio with unreacted selenurane **1.50**, suggesting that formation of the selenurane intermediates is essentially irreversible.



### Scheme 1.15

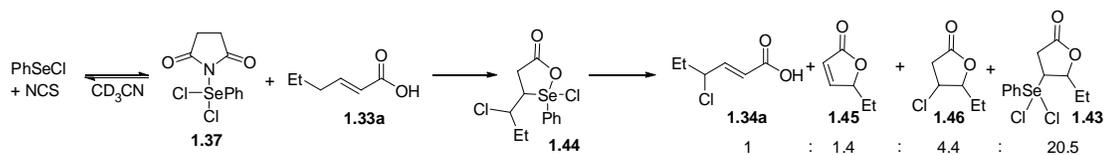
The selenurane (**1.49**) is a very long lived species and relative to the time scale of catalysis takes a significantly longer time to convert to product.<sup>26</sup> Given this, it is presumed that this is not a productive intermediate, but perhaps an inhibitor of the catalytic cycle. We speculate that the addition of molecular sieves might be a necessary additive to prevent the production of **1.49**. If the acid were deprotonated by a mild base (such as the molecular sieves),<sup>27</sup> the protonation of succinimide by the carboxylic acid would not occur, formation of the selenurane would not be facilitated and productive allylic chlorination would occur (Scheme 1.16). In all, the production of allyl chlorides by stoichiometric addition reactions of PhSeCl followed by NCS

oxidation case gives a complete picture of a productive catalytic pathway as well as plausible reaction intermediates.



### Scheme 1.16

Since selenium(II) is easily oxidized to selenium(IV) in the presence of NCS, we thought it would be worthwhile to test the effects of this oxidation prior to olefin addition. Consequently, an experiment where stoichiometric amounts of PhSeCl and NCS were mixed for 30 minutes and then one equivalent 3-hexenoic acid was added to the reaction mixture (Scheme 1.17). Similar to the reaction where NCS addition was rapid, selenurane **1.44** was initially formed. After 18 hours, the reaction produced the same products in only modestly different ratios, albeit with only 37% conversion. Conversely, the reaction where PhSeCl and NCS were added sequentially was complete in 24 hours. Clearly, the order of addition is crucial for the rate of reaction, suggesting that initial formation of PhSeCl<sub>2</sub>(succinimide) complex, **1.37**, is not beneficial.



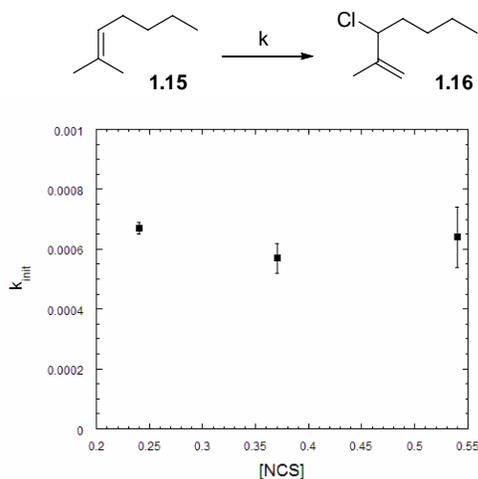
### Scheme 1.17

Collectively, the assortment of substrate-bound selenium intermediates observed demonstrated that making a selenium-carbon bond is necessary for allylic halogenation. These experiments have shed light on the fact that appropriate timing of NCS addition is vital to the reaction success. If added after too long a period, the reaction struggles to reach completion. Also, if the NCS is added all at once, producing a high concentration of NCS in solution, the reaction can also be inhibited by the formation of the selenium (IV) complex (**1.37**), which is likely an inactive form of the catalyst. Relatively inactive selenuranes may also inhibit the reaction and the faster reaction times of the esters also correspond with the inability to generate the cyclic selenurane species, allowing for quicker addition of the NCS.

#### *Reaction Kinetics*

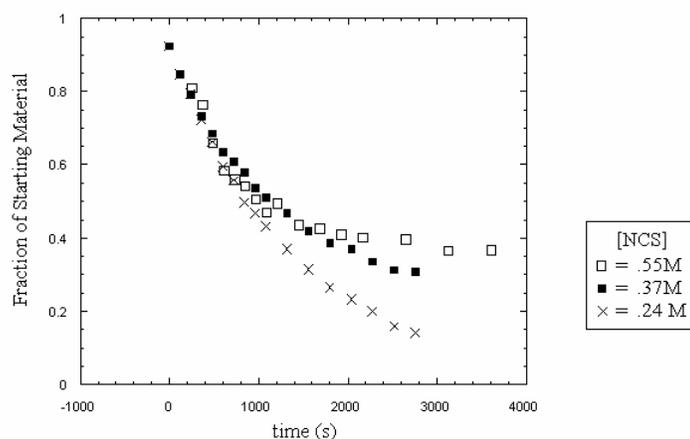
As an additional step toward determining a reasonable mechanism, reaction kinetics were performed to determine the reaction order of catalyst and NCS. Since the reaction kinetics with the unsaturated acid could be quite complex if slow addition was necessary, we chose a less complicated substrate, 2-methyl-2-heptene (**1.15**), on which to perform the kinetics experiments. Despite our choice of substrate, this process proved to be anything but simple. Many trials were run, but results were

inconsistent for various reasons, which included but were not limited to: order and timing of addition of PhSeCl, NCS, and the olefin, wet solvent due to the lack of molecular sieves in the NMR tubes, solvent effects, and variations in standard stock solutions used. After working through these problems, a trio of experiments was run where the olefin concentration was 0.016 M, with 5 mol% PhSeCl, while NCS was tested at three different concentrations, 0.24 M, 0.37 M, and 0.55 M. Note that all reactions were run with pseudo-first order concentrations of NCS, where the [NCS] is in large excess (constant) throughout the reaction. Initial rates of reaction were effectively the same (within error) indicating the reaction is zero order in NCS (Scheme 1.18). The observation of zero order kinetics in [NCS] is most consistent with catalytic cycle B since a molecule of NCS must be lost from PhSeCl<sub>2</sub>(succinimide) to form the active catalyst PhSeCl. Another molecule of NCS must be gained in the oxidation of the alkyl selenide before the rate determining elimination step is possible, thus accounting for the overall zero order.



**Scheme 1.18** Effect of [NCS] on the initial rate of reaction

Plots of the complete kinetic traces showed that as [NCS] increased, conversion and rate of the overall reaction decreased, promoting the idea that catalyst degradation is occurring after longer reaction times (Scheme 1.19). First order dependence on catalyst was also suggested by changing catalyst loading from 2.5 to 5 mol% PhSeCl, which essentially doubled the initial rate from  $3.6(5) \times 10^{-4} \text{ s}^{-1}$  to  $6.7(3) \times 10^{-4} \text{ s}^{-1}$ . The half-life of the reaction with 5 mol% PhSeCl was 17 minutes. It should also be noted that in the absence of catalyst, a single half-life of the reaction took 72 hours, showing that PhSeCl is indeed catalyzing the reaction. Exponential decay of the starting olefin was observed in cases where [NCS] was lower than 0.24 M, signifying first order kinetic dependence on the alkene as well. The rate law which can be extrapolated from this data is  $-d[2\text{-methyl-2-heptene}]/dt = k[\text{PhSeCl}][2\text{-methyl-2-heptene}]$ .



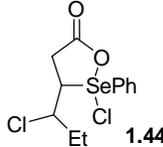
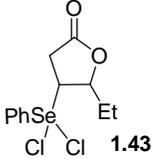
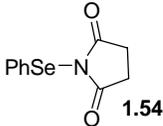
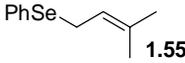
**Scheme 1.19** Effect of altering [NCS] on reaction conversion as a function of time

### *Selenium Catalyst Speciation*

Given the observation that the reaction was inhibited by high concentrations of NCS, we looked to  $^{77}\text{Se}$  NMR spectroscopy as an attempt to identify selenium species which might account for the inhibition of the reaction. Table 1.3 contains a list of reagents we initially characterized by  $^{77}\text{Se}$  NMR spectroscopy to aid in the identification of selenium species present in the reaction. This list also includes selenurane **1.44** and oxidized selenolactone **1.43**, which were characterized during the stoichiometric addition reactions.

Our first experiments were aimed at comparing chemical shifts of simple selenium compounds obtained with our methods, to the known values for these organoselenium compounds. Sharpless reported the reaction of PhSeSePh with NCS produces PhSeCl and PhSe(succinimide) (**1.54**).<sup>17</sup> Interestingly, when stoichiometric quantities of PhSeSePh and NCS were mixed and allowed to stand overnight, no new resonances were observed in the  $^{77}\text{Se}$  NMR spectrum. However, if pyridine was added, an immediate reaction occurred and new resonances were seen at  $\delta$  1022 ppm, and  $\delta$  698 ppm, indicating two new products had been formed. The  $\delta$  698 ppm resonance correlates with the expected PhSe(succinimide) complex. The  $\delta$  1022 ppm resonance is slightly farther upfield than expected for PhSeCl, but given the broadness of the  $^{77}\text{Se}$  NMR resonances and the fact that pyridine could complex this species in some way, it seemed reasonable to assume that PhSeCl had also been generated.

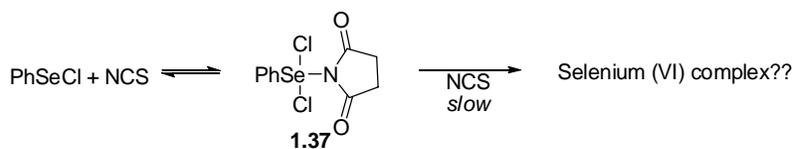
**Table 1.3**  $^{77}\text{Se}$  NMR Chemical Shifts of Selenium Containing Compounds

Compound	$\delta$ (ppm)	Compound	$\delta$ (ppm)
PhSeSePh	449		712
PhSeCl	1042		619
	698		
	316		

To characterize the oxidation of selenium (II) to selenium (IV) *via* NCS addition, two equivalents of PhSeCl were mixed with one equivalent of NCS. Upon initial addition, a resonance at  $\delta$  701 ppm was present, with a minimal resonance present at  $\delta$  1042 ppm. After one hour, the  $\delta$  701 ppm resonance had grown in intensity with no visible peak left at  $\delta$  1042 ppm. This experiment was rather confusing as it seemed that all of the PhSeCl has reacted to form a single species, despite the addition of only half an equivalent of NCS. Simultaneous observation of the reaction by  $^1\text{H}$  NMR showed at least two distinct aromatic species present, which does not correlate with a single resonance in the  $^{77}\text{Se}$  NMR spectrum. This led us to believe that perhaps not all species in solution were being observed by  $^{77}\text{Se}$  NMR. Another experiment was run with two equivalents of NCS relative to PhSeCl. Within 30 minutes, two new resonances had grown in and the PhSeCl resonance had almost completely disappeared. The major resonance was observed at  $\delta$  698 ppm, while a broader and less intense resonance was observed at  $\delta$  905 ppm. After an hour of reacting, the PhSeCl was completely gone, and both the observed resonances at  $\delta$  905

ppm and  $\delta$  698 ppm had grown more intense. A third, less intense resonance at  $\delta$  728 ppm had also emerged. It seemed to us that a likely explanation of this scenario was that oxidation of PhSeCl with NCS formed the PhSeCl<sub>2</sub>(succinimide) species whose resonance could correspond with the  $\delta$  701 ppm (and most likely the  $\delta$  698 ppm resonance which could be due to fluctuations of chemical shifts because of the lack of an internal standard). Although the correlation with the PhSe(succinimide) complex could be made, the formation of this type of species is not expected and is not a productive catalyst. The  $\delta$  905 ppm resonance could be explained by the formation of a selenium (VI) species, which over time, breaks down into a complex that has chemical shift of  $\delta$  728 ppm (Scheme 1.20).

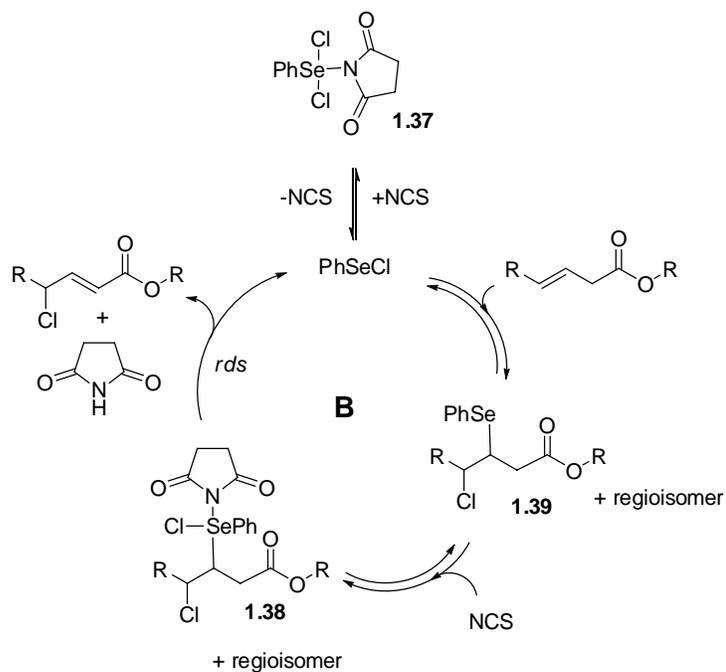
With limited resources available on this subject, we reasoned that initial inhibition of the catalyst was probably the formation of the PhSeCl<sub>2</sub>(succinimide) complex **1.37**, although the NCS dependent inhibition over longer times must be attributed to other selenium species as well. The inability to correlate chemical shift with the structure or oxidation state using <sup>77</sup>Se NMR spectroscopy made concrete identification of our complexes impossible, partly due to the complexity of the different selenium oxidation states and to the lack of differentiated chemical shifts in the <sup>1</sup>H NMR spectra.<sup>28</sup> Qualitatively, the NMR studies showed us that PhSeCl does in fact decay irreversibly to a species which is not an active catalyst.



### Scheme 1.20

#### *Mechanistic Conclusions*

In total, the stoichiometric reactions,  $^{77}\text{Se}$  NMR chemical shifts, and the reaction kinetics present a somewhat distorted set of data which does not combine to form a clear picture of a single operative mechanism. Perhaps this is due to the possibility that more than one mechanism is operative. However, in order to align some of the data into an interpretable catalytic cycle, it was necessary to focus less on the ambiguous  $^{77}\text{Se}$  NMR studies and place more attention on the stoichiometric addition reactions, where standard NMR techniques were used to positively identify structures of viable reaction intermediates. The kinetics were helpful in defining that the reaction was zero order in NCS, which ultimately discounts catalytic cycle **A**, as this reaction would have shown first order kinetics in NCS. Also, the dramatic decrease in reaction rate if PhSeCl and NCS were first mixed, suggests that the resulting Se(IV) species is not an operative catalyst, which also discredits cycle **A**. Overall, the data supports catalytic cycle **B** (Scheme 1.21) and this is our current working hypothesis.

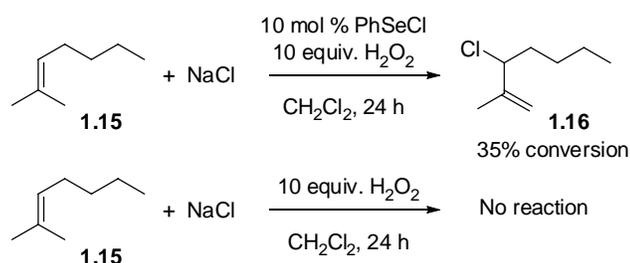


**Scheme 1.21**

### *Reagent Modifications*

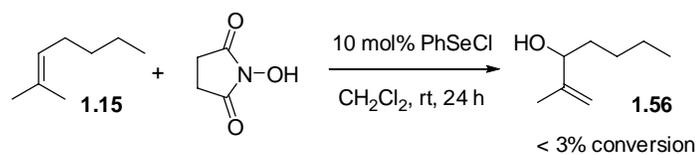
Once the allylic chlorination reaction was developed and better understood, the next step was to vary the reaction conditions to promote related halogenations. For example, we have shown that PhSeCl catalyzes the oxidation of Br<sup>-</sup> to this “Br<sup>+</sup>”, as well as the addition of the preoxidized halogen to olefins. These two processes mimic those known by haloperoxidase enzymes. Therefore, we altered the halogen source from the “preoxidized” NCS to the NaCl salt in the presence of H<sub>2</sub>O<sub>2</sub> to determine whether this oxidation would be possible. 2-Methyl-2-heptene was treated with 10 mol% PhSeCl, 10 equivalents H<sub>2</sub>O<sub>2</sub> as a 30% solution and saturated NaCl in CH<sub>2</sub>Cl<sub>2</sub>. The biphasic reaction was stirred overnight, after which it had proceeded to

35% conversion to the allylic chloride (Scheme 1.22). The formation of product in this reaction showed potential for this type of selenium-catalysis, as when run in the absence of catalyst, **1.15** did not react to form any product nor was degradation of the starting material observed. However, the biphasic nature of this reaction might have been somewhat limiting in terms of rate and conversion. Therefore, TBAF was substituted for NaCl, which is soluble in both organic and aqueous media, but this experiment proved to be unsuccessful as no products were observed.



### Scheme 1.22

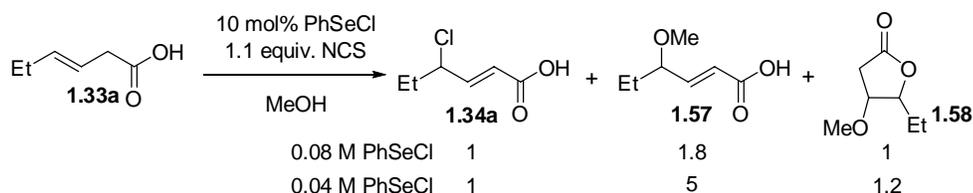
Then, we thought the ability to substitute chlorine for another halogen or nucleophile would also be particularly useful. To this end, 2-methyl-2-heptene (**1.15**) was treated with catalytic PhSeCl, 1.1 equivalents NCS and one equivalent of an external halide source [tetrabutylammonium fluoride (TBAF) or tetrabutylammonium bromide (TBAB)]. Neither halide source proved competent as a nucleophile, with the TBAF producing only the allyl chloride product, and the TBAB providing an intractable mixture as ascertained by <sup>1</sup>H NMR spectroscopy. Attempts to replace the *N*-halosuccinimides with a similar reagent, such as *N*-hydroxysuccinimide, were also unsuccessful (Scheme 1.23). The reaction went to less than 3% conversion to allylic alcohol **1.54**, showing this reagent was also not compatible with this process.



**Scheme 1.23**

### *Solvent Modification*

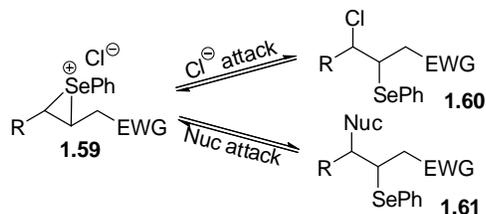
Despite the especially low solubility of NCS in MeOH, a few reactions were attempted in this solvent and it was found that the reactions occurred as fast as the rate of dissolution of NCS. Since MeOH is relatively nucleophilic, competition between the solvent and the Cl<sup>-</sup> was observed and a mixture of allyl chloride **1.34a**, allyl methoxide **1.57**, and methoxy lactone **1.58** products were obtained (Scheme 1.24). The observation of product **1.57** was not surprising as related methoxyselenations are known.<sup>29</sup>



**Scheme 1.24**

Since the addition of MeOH appeared much more facile than our attempts with the halide nucleophiles, it seemed likely that the concentration of MeOH relative to [Cl<sup>-</sup>] played an important role. Two-fold dilution of PhSeCl to 0.04 M favored the formation of **1.57**. This suggests that initial attack of MeOH on seleniranium **1.59** was competitive despite the rapid addition of PhSeCl to an olefin (Scheme 1.25). The

product of MeOH addition was interesting and could use further optimization, but was somewhat less pertinent than allylic halogenation at the time.

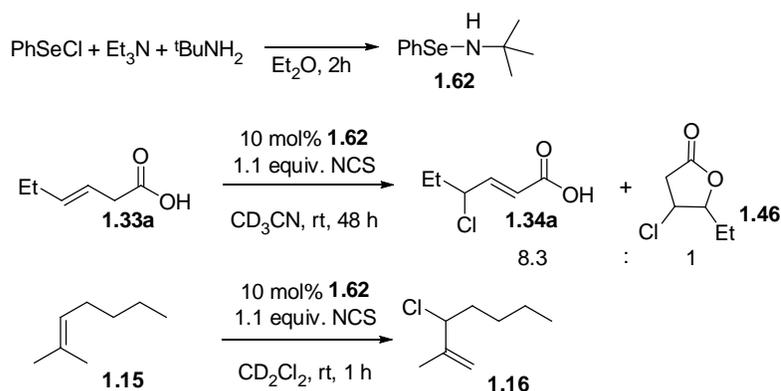


### Scheme 1.25

#### *Catalyst Modification*

After completing these reactions with other nucleophiles, we investigated the effect of catalyst modification. In 2002, Kitagawa and Mukaiyama reported the catalytic oxidation of alcohols using *N-tert*-butylbenzene sulfonamide in the presence of a terminal oxidant such as chloramine-T.<sup>30</sup> Given the similar reactivity patterns of sulfur and selenium, we became curious as to whether a selenium derivative of this catalyst would catalyze oxidative allylic halogenation of our substrates with NCS (Scheme 1.26). Therefore, **1.62** was synthesized from PhSeCl, Et<sub>3</sub>N and *tert*-butylamine. An initial NMR experiment was run with 3-hexenoic acid, 10 mol% PhSeNH<sup>t</sup>Bu, and 1.1 equivalents NCS in CD<sub>3</sub>CN. Surprisingly, the reaction had gone to 50% completion within 4 hours, where the major product was allyl halide **1.34a** and the minor product was chlorolactone **1.46**. Upon completion of this reaction these products had formed in an 8.3:1 ratio, respectively. The first half-life of the reaction with catalyst **1.62** was much faster than with PhSeCl, although the reaction

eventually took 48 hours to reach completion. A similar reaction was run with 2-methyl-2-heptene and this reaction was completed in one hour to give **1.16**. Since further studies with this catalyst after two weeks were considerably slower for both tested substrates, we were suspicious that catalyst degradation was occurring. Thus, other substrates have not been tested with this catalyst at this time.

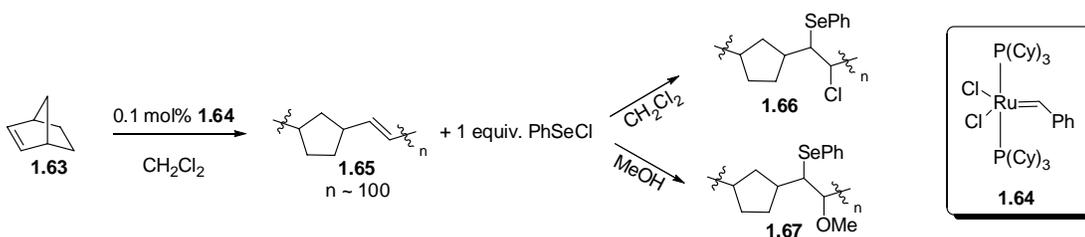


**Scheme 1.26**

### *Polymer-Supported Selenium Catalysts*

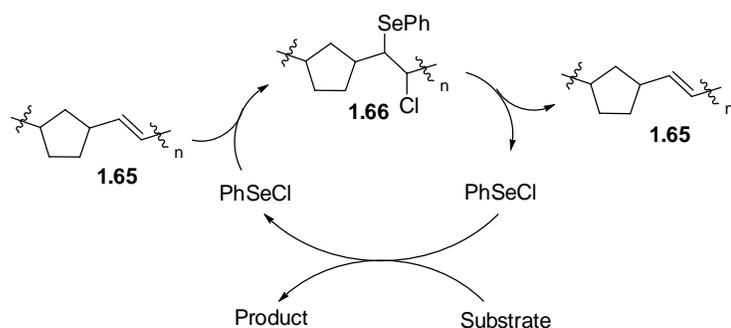
Lately, the use of polymer bound reagents has increased dramatically; particularly for those reagents which might cause adverse health effects if residual amounts remain in the isolated product.<sup>31</sup> Despite the presence of selenium in some enzymes, external sources of selenium have been reported to be carcinogenic.<sup>32</sup> The idea of trapping the selenium onto a polymer to prevent selenium leaching into the reaction mixture was one which merited further investigation. Although stoichiometric polymer-supported selenium reagents are becoming more prevalent in the literature,<sup>33</sup> there are currently no reports of polymer-supported selenium

catalysts. Initially, we thought that a norbornene-derived solid support would be an ideal support due to their solubility in  $\text{CH}_2\text{Cl}_2$ , allowing for homogeneity in the reaction (Scheme 1.27).<sup>34</sup> The polymer backbone (**1.65**) was synthesized via standard ring-opening metathesis polymerization of norbornene (**1.63**) with Grubbs I catalyst (**1.64**). PhSeCl was added to a solution of the polymer and it reacted with the olefin very quickly as the solution changed color from orange (PhSeCl) to colorless (RSePh) almost instantly.



**Scheme 1.27**

Since it is known that addition of PhSeCl to olefins is rapid and reversible, it was expected that the catalyst would be released from the polymer during the reaction. However, we reasoned that the once all of the substrate molecules had reacted, the catalyst would again add to the polymeric olefins, in a “boomerang” fashion (Scheme 1.28), allowing it to be retrieved from the reaction mixture.<sup>35</sup>

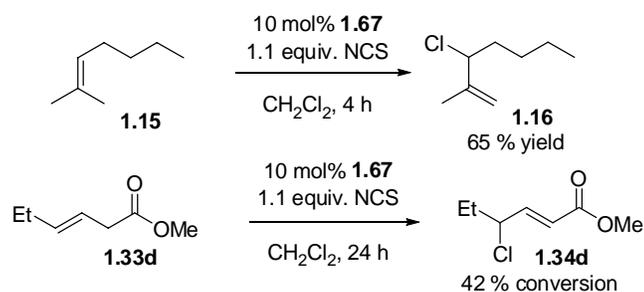


### Scheme 1.28

Preliminary reactions of 2-methyl-2-heptene, **1.15** with 10 mol% **1.66** and 1.1 equivalents NCS demonstrated that complete conversion occurred after two hours. The crude product was allyl halide **1.16**, but it was observed by  $^1\text{H}$  NMR that about 12% PhSeCl, relative to the crude product, was present in the unpurified mixture after precipitation of the polymer. Although this was somewhat disappointing, attempts were made to effect this reaction with other substrates. 3-hexenoic acid (**1.33a**) and methyl-4-phenylbutanoate (**1.33f**) were subjected to the comparable conditions except that slow addition of NCS was used and it was observed that both reactions struggled to achieve even 15% completion in 24 hours. The use of  $\text{CH}_2\text{Cl}_2$  as the reaction solvent could probably be attributed to the stunted reaction times, but was necessary as the polymer was insoluble in  $\text{CH}_3\text{CN}$ . As a last resort, the unselenated polymer (**1.65**) was added to crude reaction mixtures containing PhSeCl, as an attempt to scavenge the PhSeCl catalyst. This proved to be unsuccessful as the product mixture showed the presence of the selenium catalyst.

A new approach was needed to solve the problem of selenium not returning to the polymer upon reaction completion. Therefore, PhSeCl was added to the polymer

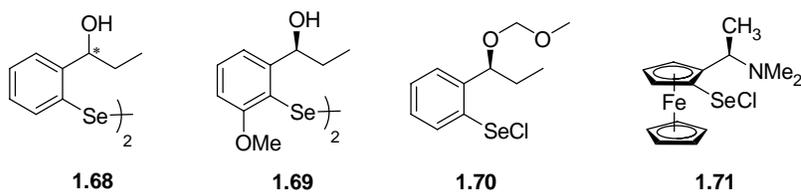
in methanolic solvent (Scheme 1.27). Since the methanol substitutes the intermediate seleniranium species faster than chloride, and this addition is irreversible, the end product will be polymer **1.67**. Polymer **1.67** was then used as the source of the catalytic selenium with 2-methyl-2-heptene in  $\text{CD}_2\text{Cl}_2$  (Scheme 1.29). The optimized reaction completed within 4 hours with a 65% yield relative to an internal standard. After crude workup, only 1.5% selenium was left in the reaction mixture, as determined by  $^1\text{H}$  NMR spectroscopy. In an attempt to recycle the catalyst, the polymer was isolated and used again. Just a single half-life with the recycled catalyst on the second cycle took much longer (20 hours). When ester substrate **1.33d** was treated with catalyst **1.67**, the reactions were very sluggish, even when slow addition of NCS was employed. The dramatic decrease in reaction times was not surprising given the additional steric hindrance caused by the polymer backbone encompassing the selenium atom.



**Scheme 1.29**

### Enantioselective Variants

Despite previous catalyst modifications, we had still not examined the effectiveness of chiral catalysts. To date, several asymmetric selenium catalysts had been used for stoichiometric additions to olefins, selenocyclizations and 2,3-rearrangements.<sup>36</sup> We chose chiral selenium compounds that somewhat resembled the ArSeCl framework, whereby appendages on the aryl ring could provide a source of chirality in the molecule. A few of these compounds, shown in Scheme 1.30, were chosen as their syntheses were fairly straightforward.

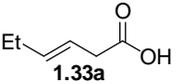
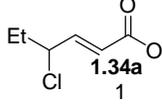
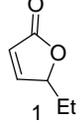
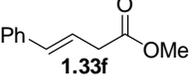
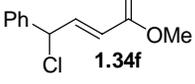
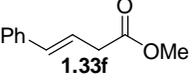
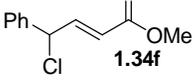


### Scheme 1.30

Catalyst **1.68** was first tried as a chiral, racemic catalyst to verify catalytic activity of the compound. 2-methyl-2-heptene (**1.15**) was treated with 10 mol% of diselenide **1.68** with 1.1 equivalents NCS (Table 1.4). The reaction was complete within 4 hours and allyl chloride **1.16** was isolated in 75% crude yield. Despite the slightly slower reaction compared to PhSeCl (4 h vs. 3 h), the new catalyst still afforded the product cleanly. It is necessary to point out that the precatalyst was the diselenide, which must undergo reaction with NCS to generate *in situ* the Ar<sup>\*</sup>SeCl catalyst. Despite the 10 mol% catalyst loading in this reaction, only 5 mol% of active catalyst was actually generated. Since many of these substrates have different

reactivities with the standard PhSeCl catalyst, it was necessary to explore the activity with other compounds as well.

**Table 1.4** Allylic Chlorination Utilizing a Chiral, Racemic Catalyst **1.68**

Entry	Substrate	Mol% Catalyst	Solvent	Time (h)	Product(s)
1		10	CH <sub>2</sub> Cl <sub>2</sub>	4	 78 % crude yield
2 <sup>b</sup>		10	CH <sub>2</sub> Cl <sub>2</sub>	4	
3		20	CH <sub>3</sub> CN	48	 + 
4		20	CH <sub>3</sub> CN	72	
5 <sup>c</sup>		20	CH <sub>3</sub> CN	72	

<sup>a</sup> Reactions were run using the specified amount of catalyst **1.68**, 1.1 equiv. NCS at room temperature in the specified solvent <sup>b</sup> After 4 h, reaction had reached 56 % conversion <sup>c</sup> syringe pump addition of NCS over 8 h.

Reactions with these substrates required longer reaction times as well as an excess of NCS. Intrigued by the rationale for needing extra equivalents of NCS, we thought it would be worthwhile to generate the selenyl chloride prior to addition to the reaction. Thus, catalyst **1.68** was then treated with SO<sub>2</sub>Cl<sub>2</sub>, which afforded two equivalents of Ar<sup>\*</sup>SeCl **1.72**. This compound was isolated and similar experiments were run with this catalyst on various substrates to determine its catalytic activity (Table 1.5).

Although the reactions were still slower, as compared to PhSeCl as the catalyst, the crude product mixtures were relatively clean, which was promising. The

reactions required much less NCS and usually completed with the standard 1.1 equivalents, giving credibility to the rationale for pregeneration of the Ar<sup>\*</sup>SeCl species. With these promising results, it looked as if chiral, nonracemic catalysts for this process should be pursued.

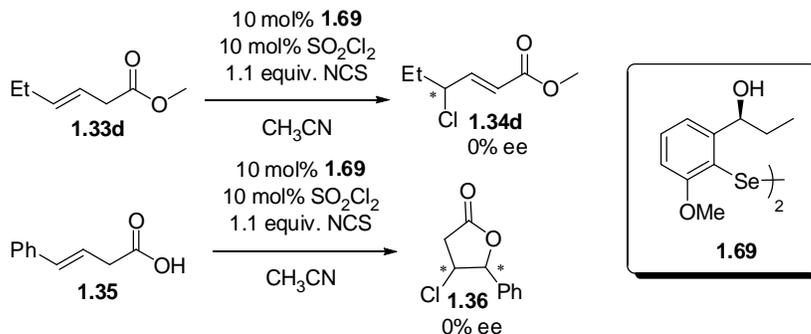
**Table 1.5** Reaction of Substrates with Chiral, Racemic Catalyst **1.72**

Entry	Substrate	Solvent	Time (h)	Product(s)
1 <sup>a</sup>		CH <sub>2</sub> Cl <sub>2</sub>	3.5	
2		CH <sub>2</sub> Cl <sub>2</sub>	1.5	 5 : 1
3		CH <sub>3</sub> CN	96	 2 : 1
4		CH <sub>3</sub> CN	60	 85 % crude yield

<sup>a</sup> After 3.5 h, reaction had reached 69 % conversion

Test reactions were run on alkenes **1.33d** and **1.35**, in the presence of 10 mol% catalyst **1.69**, 10 mol% SO<sub>2</sub>Cl<sub>2</sub>, and 1.1 equivalents NCS (Scheme 1.31). The diselenide was first treated with the sulfuryl chloride to generate the Ar<sup>\*</sup>SeCl species *in situ*. Then the olefin and NCS were added and the reactions were monitored by chiral gas chromatography (GC). The reactions formed the expected products,

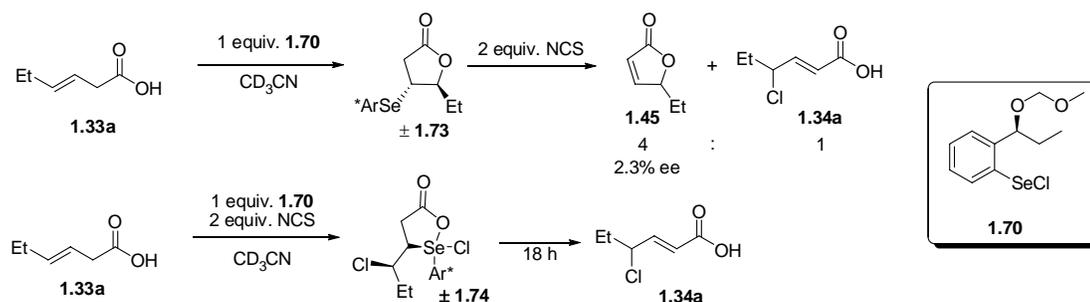
however the GC integrations showed that the products were racemic mixtures and no enantioselectivity had been achieved in either case.



**Scheme 1.31**

Chiral, non-racemic catalyst **1.70**, which differs from **1.68** only by MOM-protection, was synthesized and isolated. The protection of the alcohol would serve to increase sterics of the catalyst, as well as prevent oxygen coordination to the selenium atom center. A stoichiometric reaction was run with 3-hexenoic acid (**1.33a**) and catalyst **1.70** to determine the diastereoselectivity of addition to the olefin (Scheme 1.32). The  $^1\text{H}$  NMR spectrum showed no diastereoselectivity of the products formed upon addition of catalyst to the olefin. A stoichiometric amount of NCS was then added to the reaction mixture. After reacting overnight, butenolide was afforded the major product in approximately 4:1 ratio with allyl halide **1.34a**. To ensure that the enantioselectivity matched the poor diastereoselectivity of addition, the butenolide was isolated and subjected to chiral GC where 2.3% enantiomeric excess was observed. A similar reaction was run where olefin **1.33a** and catalyst **1.70** were mixed stoichiometrically, followed by rapid addition of excess NCS. Initial observation of the chiral reaction by  $^1\text{H}$  NMR again showed the formation of products

was not diastereoselective. After standing overnight, the reaction went cleanly to allyl halide **1.34a**. Since no diastereoselectivity was observed upon addition to the olefin, the enantiomeric excess of the product was not determined.



**Scheme 1.32**

A ferrocene-based catalyst (**1.71**) was reported by Uemura to have induced high enantioselectivities in the asymmetric 2,3-selenoxide rearrangement.<sup>37</sup> Since elimination of the selenium in our reaction could likely follow a similar mechanism, we thought it worthwhile to try this catalyst as well. Initial screenings of this catalyst with substrate 2-methyl-2-heptene demonstrated that slow reaction times would be a limiting factor. It was reasoned that the extra steric bulk of the ferrocene was hindering reaction completion, perhaps by slowing the process of selenium elimination. No further reactions were tried with this catalyst.

#### *Summary of Allylic Halogenation*

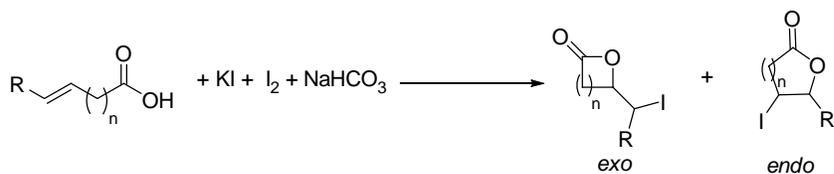
In the end, we were unable to establish an effective method for asymmetric allylic halogenation. However, a methodology for regioselective allylic halogenation *via* selenium catalysis was successfully developed. Selective allylic chlorination was

possible using both steric and electronic influences. Using PhSeCl as a catalyst allowed for the prevention of side reactions such as vinyl- and dichlorination, which have previously been reported with similar substrates. Mechanistic studies were performed and reaction intermediates were identified. Variations of the reaction components (halogen source, catalyst and solvent) were successful, yet could require further investigation. Overall, this reaction has been surveyed in depth to understand the limits and mechanism of this process. There is still much to be learned, but the establishment of selenium-catalyzed oxidative halogenation provides synthetic chemists with an alternative route for the conversion of C—H bonds to C—X bonds. Moreover, we have shown that selenium is capable of catalyzing 2-electron oxidations which are more characteristic of transition metals.

### **1.3 Overview of Halolactonization**

#### *Historical Timeline*

Halolactonization is a reaction that has been known since the early 1900's, and has proven to be a versatile reaction in organic synthesis.<sup>38</sup> The production of small or medium size lactones is particularly useful as these are often used as building blocks in the synthesis of natural products.<sup>39</sup> Initial work done in this area by Bougault utilized a weak base, KI, and I<sub>2</sub> to promote cyclization of carboxylic acids bearing  $\gamma,\delta$ -unsaturation (Scheme 1.33).<sup>38a</sup>

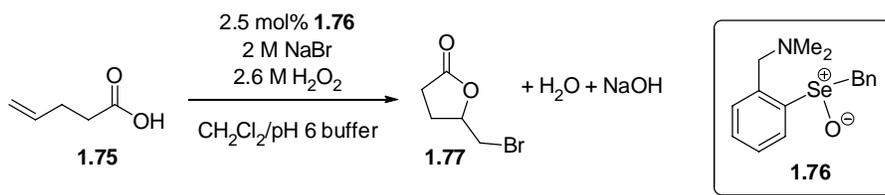


**Scheme 1.33**

Of the halogens, cyclizations with iodine are the most well known.<sup>40</sup> Despite the large body of work on iodolactonization, these reactions are most generally carried out with molecular iodine or *N*-iodosuccinimide as the source of the “I<sup>+</sup>”.<sup>35,41</sup> In contrast, very few examples of chlorolactonization have been reported due to the competing nature of dichlorination.<sup>42</sup> On the other hand, a number of different sources of electrophilic bromine have been identified as compatible reagents for bromolactonization. Reagents such as *N*-bromosuccinimide (NBS),<sup>43</sup> Br<sub>2</sub>,<sup>44</sup> H<sub>2</sub>O<sub>2</sub>/NaBr,<sup>45</sup> CuBr<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub>,<sup>46</sup> Ti<sub>2</sub>CO<sub>3</sub>/Br<sub>2</sub>,<sup>47</sup> and ZnBr<sub>2</sub>/Pb(OAc)<sub>4</sub><sup>48</sup> have all been reported to effect bromolactonization of unsaturated carboxylic acids. Although this does not represent a complete profile, it depicts the diversity of methods for the lactonization with bromine, particularly as compared to chlorine and perhaps iodine as well. While bromolactonization is well studied with different sources of electrophilic bromine, it suffers from a lack of regiocontrol in the formation of the halocyclized products (i.e. mixtures of *endo*- and *exo*-cyclization products). Iodocyclizations also have regiochemical issues which must be overcome, but they are much less pronounced than their bromine counterparts in most cases. Although an increased number of reports are appearing on the stereoselectivity of these reactions, asymmetric halolactonization is still a problem which has not yet been

solved. Furthermore, catalytic bromolactonization had not been reported at the time of our investigation.<sup>49</sup>

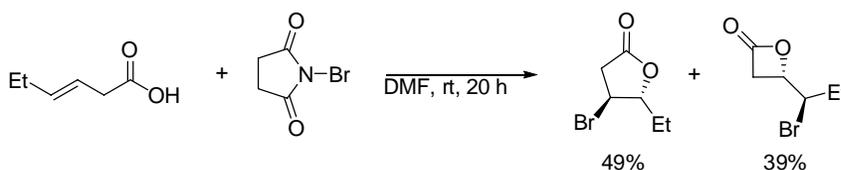
In regard to catalysis, Detty has developed a selenium-catalyzed system for the bromolactonization of unsaturated acids with NaBr/H<sub>2</sub>O<sub>2</sub> (Scheme 1.34). While it does show the oxidative capabilities of selenium in the presence of H<sub>2</sub>O<sub>2</sub>, this method is best characterized as the catalytic oxidation of Br<sup>-</sup> to “Br<sup>+</sup>”, producing freely diffusing electrophilic bromine species rather than catalytic halolactonization. Per the proposed mechanism, the selenium catalyst is not shown to be involved in the delivery of the bromine atom to the substrate. Therefore, attempting to control regio- and stereoselective processes via this catalyst would be futile.



**Scheme 1.34**

*N*-bromosuccinimide has garnered much attention in the area of bromocyclizations. NBS is particularly useful, as it provides not only a source of the electrophilic bromine atom, but also a base which can deprotonate the carboxylic acid to allow for cyclization. In 1979, a detailed report on the reaction of unsaturated acids with *N*-haloimides demonstrated that NBS was capable of effecting bromolactonization (Scheme 1.35).<sup>50</sup> The isolated yields with NBS were good, but the reaction times were generally long (20 h) and the regioselectivities were poor for

substrates that did not possess an electronic bias the formation of a single isomer. Subsequent reports broadened the scope of this reaction with a large variety of substrates as well as incorporating other NXS reagents, such as NCS and NIS; while NCS failed to yield the chlorolactone product, NIS did afford iodolactones albeit with more modest yields.



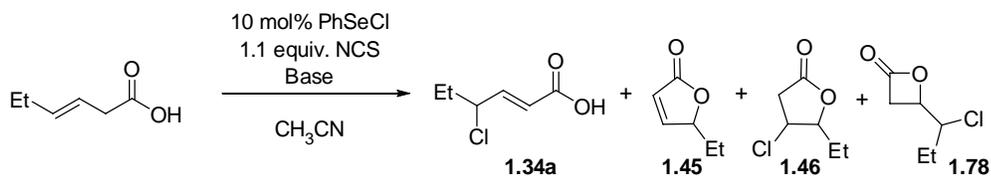
### Scheme 1.35

Mechanistically, it is generally accepted that these pathways proceed through a three-membered halonium intermediate, which is stereospecifically opened by the carboxylic acid in an *anti*-addition fashion. Therefore, in order to facilitate an enantioselective cyclization reaction, one of two scenarios is necessary. Either a chiral, nonracemic halonium intermediate must be generated via reagent control or the free acid must preferentially attack one face of the halonium ion through substrate control. Some groups have recognized this issue and have made progress toward chiral reagents which are capable of delivering the electrophilic halogen, but enantioselectivities of these processes remain moderate (< 65% ee).<sup>51</sup>

## 1.4 Selenium-Catalyzed Halolactonization

### *Selenium-Catalyzed Chlorolactonization*

The goal to develop a halolactonization procedure catalyzed by selenium originated from the observation that styryl acetic acid afforded only the  $\gamma$ -chlorolactone product when treated with PhSeCl and NCS, and the product of allylic halogenation was not observed (Scheme 1.11).<sup>52</sup> Given the lack of instances of chlorolactone formation in the literature, the ability to form these types of products was somewhat desirable. In an attempt to favor formation of the cyclic product with other unsaturated acids, a host of different bases were tested. As seen in Table 1.6, the product ratios varied extensively depending on the base used. Reactions with Et<sub>3</sub>N or DIEA in the presence of molecular sieves, but without slow addition of the NCS were the only reactions that formed the  $\gamma$ -chlorolactone product (**1.46**). When DMAP was used,  $\beta$ -chlorolactone **1.78** constituted 45% of the products isolated, although the reaction only went to 70% conversion. Some of the reactions were moderately successful, but at the time of the study, the formation of the  $\beta$ -lactone was not identified, so these reactions did not appear as productive. Even the best reactions still produced mixtures of products and so this method of halolactonization was not pursued further.

**Table 1.6** Effects of Base-Promoted Chlorolactonization

Base	1.34a	1.45	1.46	1.78
Pyridine, 4Å MS	1.6	1	0	0
4Å MS	5.9	1	0	0
Et <sub>3</sub> N, 4Å MS <sup>a</sup>	1	2	0	0
Et <sub>3</sub> N <sup>a</sup>	1	10	0	0
Et <sub>3</sub> N, 4Å MS	0	1	1.3	2.4
DIEA, 4Å MS	1	2.4	2.4	1.7
DMAP, 4Å MS <sup>b</sup>	0	1.25	0	1.0
Proton sponge, 4Å MS <sup>c</sup>	1	0	0	0
NaOAc, 4Å MS <sup>d</sup>	0	1	0	0
Cs <sub>2</sub> CO <sub>3</sub>	NR			

<sup>a</sup> Added NCS via syringe pump <sup>b</sup> Reaction only went to 70% completion after 24 h

<sup>c</sup> Reaction went to 66% completion after 48 h <sup>d</sup> Reaction went to 15% completion after 4 d

Interestingly, Massanet's group has since published a report on the synthesis of β- and γ-chlorolactones from unsaturated acids in the presence of NaOCl and a stoichiometric amount of Lewis acid. Although cyclization did not occur with ring sizes larger than 5, the yields were very high for most Lewis acids used (CeCl<sub>3</sub>·7H<sub>2</sub>O, FeCl<sub>3</sub>·6H<sub>2</sub>O, CuCl<sub>2</sub>·2H<sub>2</sub>O, ZnCl<sub>2</sub>, and Ce(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O). In this way, they have demonstrated a route to get to these chlorolactone structures which are still sparsely cited in the current literature.

#### *Development of Catalytic Bromolactonization*

Since NBS is an established reagent for bromolactonization, we were curious to see if selenium reagents had any catalytic effect on this reaction. Initially, a control experiment was run with 3-hexenoic acid and NBS in CD<sub>3</sub>CN at room

temperature to reproduce the results of the initial reports. The products obtained were the  $\gamma$ - and  $\beta$ -bromolactones in a 1.6:1 ratio, respectively; however we noticed a somewhat increased rate than was previously reported. Our choice of solvent might have impacted the reaction rate (DMF vs.  $\text{CH}_3\text{CN}$ ), but since  $\text{CH}_3\text{CN}$  is more volatile than DMF, handling the reactions was more facile with  $\text{CH}_3\text{CN}$ . The increased rates led us to decrease the reaction temperature to  $-30\text{ }^\circ\text{C}$  so that if catalysis were occurring, the impact on reaction rate should be observable. When run at this temperature, the control reaction with only NBS and 3-hexenoic acid still afforded the same ratio of products. Next,  $\text{PhSeSePh}$  was tested for catalytic activity by adding 5 mol% of  $\text{PhSeSePh}$  relative to 3-hexenoic acid and NBS at  $-30\text{ }^\circ\text{C}$  in  $\text{CD}_3\text{CN}$ . Interestingly, this reaction was not only faster, but also gave different product ratios. An 8.5:1 mixture of  $\gamma$ -bromolactone **1.79** and dibrominated product **1.81**, respectively, was obtained, while almost completely diminishing the formation of  $\beta$ -bromolactone **1.80** as compared to the uncatalyzed reaction (Table 1.7).

**Table 1.7** Catalyst Screening for Bromolactonization Reaction with NBS

	$\pm$ <b>1.79</b>	$\pm$ <b>1.80</b>	$\pm$ <b>1.81</b>
no catalyst	2	1	0
5 mol% $\text{PhSeSePh}$	17	1	2
5 mol% $\text{PhSeBr}$	4	0	1
5 mol% $\text{PhSe(phthalimide)}$	2	1	0

The observation of different product ratios and increased reaction rates were evidence the reaction was catalyzed by selenium. While it is known that  $\text{PhSeSePh}$

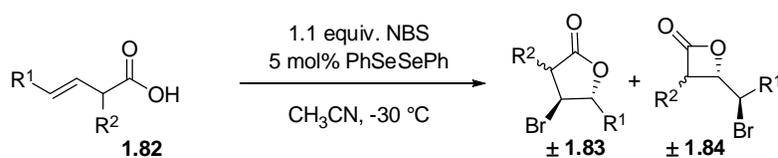
reacts with NCS to form two species, PhSeCl and PhSe(succinimide), it was unclear whether this same reaction occurs in the presence of NBS. If so, the active catalyst may not be PhSeSePh, but could have been one of the two species formed by oxidative cleavage of the diselenide bond, PhSeBr or PhSe(succinimide). Therefore, PhSeBr and PhSe(phthalimide) were tested for catalytic activity. It is worth noting that PhSe(phthalimide) is a derivative of PhSe(succinimide) which is thermally stable<sup>53</sup> and commercially available, and was therefore used in place of the PhSe(succinimide). Both reagents were used in catalytic amounts (5 mol%) for the same reaction as PhSeSePh. The PhSe(phthalimide) did not appear to increase the rate nor did it offer a different ratio of products as compared to the control reaction, providing only a 2:1 ratio of **1.79** and **1.80**, respectively. PhSeBr exhibited much better catalytic activity as the product ratios were altered to a 4:1 mixture of **1.79** and **1.81**. Still, the results did not reproduce the results of the PhSeSePh catalyst. This indicated that oxidative cleavage of the PhSeSePh was not occurring, and that PhSeSePh *was* the active catalyst.

#### *Bromolactonization of Various Substituted Olefins*

Once catalysis had been established and it was observed that the regioselectivity of the cyclization was greatly improved, we thought it would be worthwhile to examine the regioselectivity of other unsaturated acids. Control reactions were run in each case to determine the rates and regioselectivities of the reactions. In all cases when catalytic PhSeSePh was employed, the rates were

sufficiently enhanced. However, the regioselectivities were not necessarily affected, particularly in the cases where electronics biased the formation of one regioisomer in the absence of catalyst. A variety of  $\beta,\gamma$ -unsaturated acids were reacted with 5 mol% PhSeSePh and 1.1 equivalents NBS in CH<sub>3</sub>CN at -30 °C (Table 1.8). The regioselectivity for 3-octenoic acid (**1.82b**) was improved in the catalytic reaction from 2:1 to a 3:1 ratio of  $\gamma$ - and  $\beta$ -bromolactones, respectively. Interestingly, when a methyl substituent was placed at the  $\alpha$ -position to the carboxylic acid (**1.82e**), a 5:1 mixture of diastereomers was obtained.

**Table 1.8** Halolactonization of  $\beta,\gamma$ -Unsaturated Acids

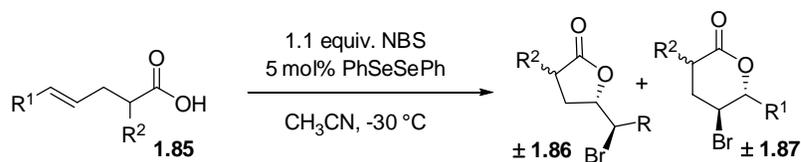


Substrate	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Selectivity ( $\gamma$ vs $\beta$ )	% Yield
<b>1.82a</b>	Et	H	2	94:6	52 <sup>a</sup>
<b>1.82b</b>	Bu	H	1	75:25	61 <sup>b</sup>
<b>1.82c</b>	Ph	H	4	100:0	90
<b>1.82d</b>	H	H	6	0:100	48
<b>1.82e</b>	H	CH <sub>3</sub>	5	0:100	34 <sup>c</sup>

<sup>a</sup> Isolated yield of major product only <sup>b</sup> Combined isolated yield of isomers

<sup>c</sup> 5:1 mixture of diastereomers

Next,  $\gamma,\delta$ -unsaturated acids were treated under the standard reaction conditions (Table 1.9). It was interesting to note that while reaction rates increased with these substrates, the regioselectivities for any of these substrates were not altered from the uncatalyzed reaction. Despite previous success with 1,1-disubstituted olefins, 4-hexenoic acid (**1.85a**), did not show any increase in regioselectivity. Again, an  $\alpha$ -substituent provided a 3:1 mixture of diastereomers of **1.86c**.

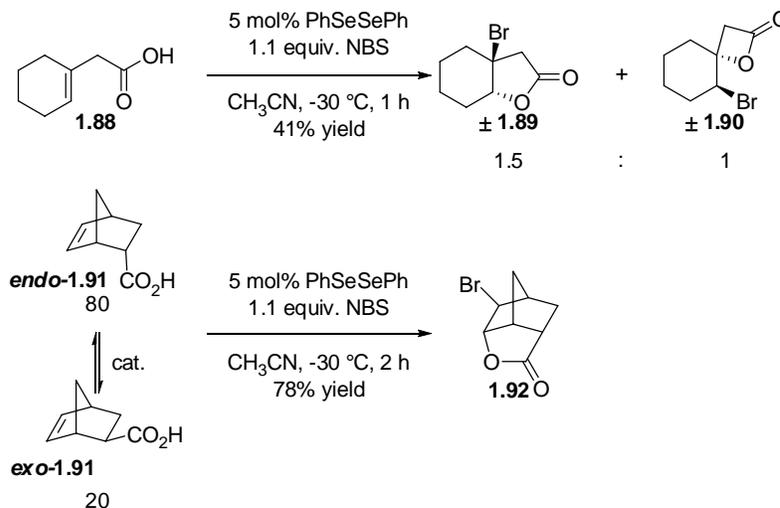
**Table 1.9** Halolactonization of  $\gamma,\delta$ -Unsaturated Acids

Substrate	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Selectivity ( $\gamma$ vs $\delta$ )	% Yield
<b>1.85a</b>	Me	H	2	66:34	33 <sup>a,b</sup>
<b>1.85b</b>	H	H	2	100:0	55
<b>1.85c</b>	H	CH <sub>3</sub>	3.5	100:0	90 <sup>c</sup>

<sup>a</sup> Combined isolated yield of isomers <sup>b</sup> Mixture of diastereomers reflecting the *E/Z* ratio of the starting material <sup>c</sup> 3:1 mixture of diastereomers

Two cyclic unsaturated acids were also tested for reactivity under the standard reaction conditions (Scheme 1.36). First, 2-cyclohexenyl acetic acid (**1.88**) was allowed to react with the catalyst and NBS and upon completion afforded a 1.5:1 mixture of **1.89** and **1.90** in a combined 41% yield. This substrate demonstrated the greatest change in regioselectivity as the uncatalyzed reaction afforded only **1.90**, suggesting that the catalytic reaction favors formation of the  $\gamma$ -bromolactones, which has been observed with other substrates as well (**1.82a**, **1.82b**). Next, a 1:4 mixture of *exo*- and *endo*-isomers, respectively, of 5-norbornene-2-carboxylic acid (**1.91**) was treated under the conditions of catalysis and only the  $\gamma$ -bromolactone **1.92** was formed. Interestingly, when the catalyzed and uncatalyzed reactions were followed by <sup>1</sup>H NMR spectroscopy, it was observed that the uncatalyzed reaction only formed product from the *endo*-carboxylic acid. However, when PhSeSePh was used as the catalyst, all of the starting material reacted to product, suggesting the conversion of *exo*- to *endo*- was possible with PhSeSePh present. This also explains the rather high yield as compared to the initial ratio of isomers of the starting material, which would

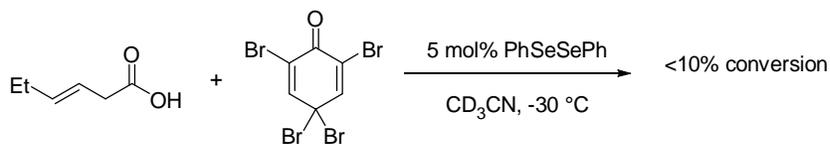
only have a theoretical yield of 80% if the *endo*-isomer was the only reactive substrate.



**Scheme 1.36**

### Reagent Modifications

In an effort to broaden the scope of this methodology, other halogenating reagents were investigated for their ability to produce halolactones. First, 2,4,4-tetrabromo-2,5-cyclohexadienone has been reported by Lectka as a source of “ $\text{Br}^+$ ” for  $\alpha$ -halogenation.<sup>14d</sup> We thought it would be worthwhile to test this reagent with our model substrate, 3-hexenoic acid, in the presence of 5 mol% PhSeSePh in  $\text{CD}_3\text{CN}$  at room temperature (Scheme 1.37). The reaction was followed by  $^1\text{H}$  NMR spectroscopy, where less than 10% conversion was observed after 5 hours. This showed that it was not as effective as NBS, so further tests with this reagent were not performed.

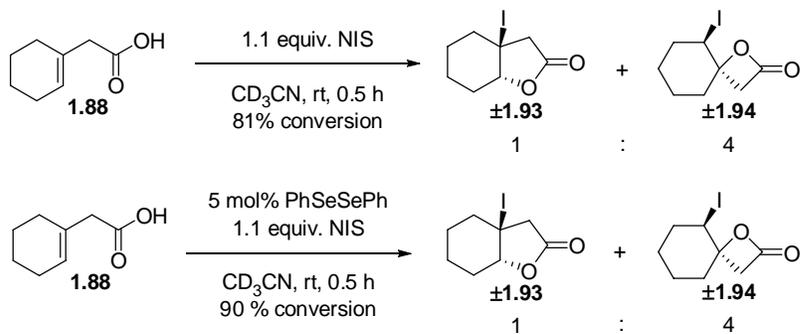


**Scheme 1.37**

### *Selenium-Catalyzed Iodolactonization Studies*

Iodolactonization is also an important reaction in organic synthesis. Since NIS has been widely used for this transformation, we thought selenocatalytic iodolactonization might be possible as well. These reactions proved to be much more difficult than their NBS counterparts. This could be attributed to the dramatic increase in reactivity of NIS vs. NBS. Despite running these reactions at very low temperatures (-78 °C, -30 °C) we could not ascertain that PhSeSePh was actually increasing the reaction rate due to the low solubility of NIS at such low temperatures. Therefore, the reactions had to be run at room temperature to ascertain catalysis. 2-cyclohexenyl acetic acid (**1.88**) was then treated with NIS in the absence and presence of PhSeSePh (Scheme 1.38). The uncatalyzed reaction had reached 81% conversion, while the catalyzed reaction had reached 90% conversion within 30 minutes. Although it appeared that the catalyzed reaction was slightly faster, completion of both reactions afforded identical regioselectivities. The selenium-catalyzed variant of this reaction with NBS gave  $\gamma$ -bromolactone **1.93** as the major product. Neither a significant rate enhancement nor change in regioselectivity were demonstrated in the

reaction with the selenium catalyst so further reactions with *N*-iodosuccinimide were not pursued.

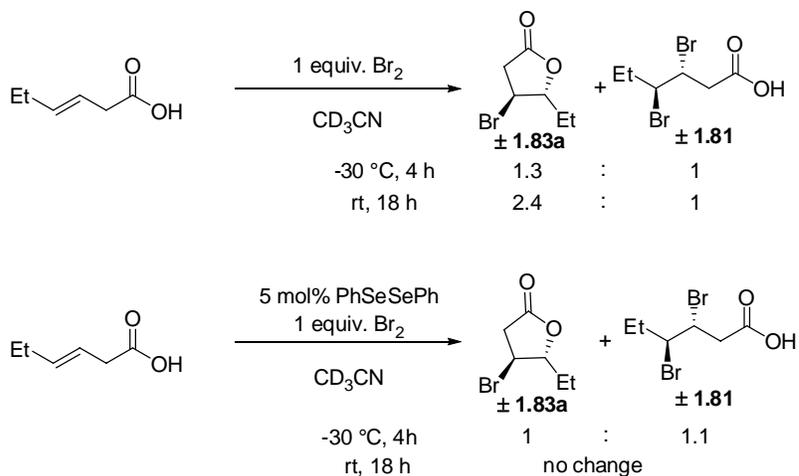


**Scheme 1.38**

### *Mechanistic Studies*

To begin our mechanistic studies, we felt that it was necessary to address the nature of the bromine electrophile that is added to the substrate. As previously mentioned, the selenium-catalyzed oxidation of NaBr to electrophilic “Br<sup>+</sup>” produces freely diffusing halogen species, which are not bound to selenium upon delivery to the substrate. The observation of dibrominated product **1.81** indicated the presence of a freely diffusing bromine source in our reaction as well. Therefore, the reaction of 3-hexenoic acid and molecular bromine was carried out at -30 °C in CD<sub>3</sub>CN (Scheme 1.39). Within four hours, the reaction had gone to completion and formed a 1.3:1 ratio of the  $\gamma$ -bromolactone (**1.83a**) and dibrominated acid (**1.81**), respectively. Interestingly, after allowing the reaction to warm to room temperature and stand overnight, the product ratios had equilibrated to a 2.4:1 mixture of the same products. A similar reaction with 5 mol% PhSeSePh also added was run simultaneously. This

reaction was also complete within four hours, although the product ratios differed slightly. Dibromination was slightly favored in this case with a 1:1.1 ratio of **1.83a** and **1.81**. However, after standing at room temperature overnight, this reaction did not equilibrate, but maintained the starting ratios of products.



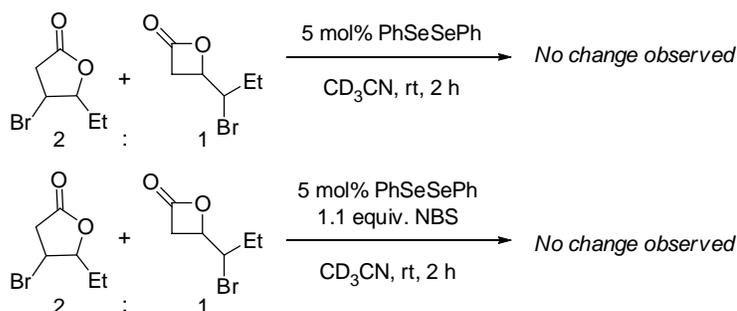
### Scheme 1.39

The results of these experiments do not discount the possibility of freely diffusing bromine being formed *in situ*, but it also does not reproduce the product ratio (17:1) of the catalytic reaction when NBS is used. Therefore, bromine is formed, it is not the main source of halogenation products.

#### Product Equilibration Studies

Since a variety of substrates had been tested and other halogen sources had been examined, we turned our focus back to the mechanistic details of the selenocatalytic bromolactonization reaction. In the bromolactonization reactions where the regiocontrol was altered, it seemed possible that the favored  $\gamma$ -lactone

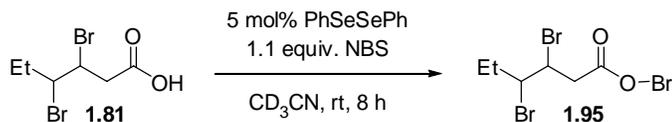
could be a result of equilibration of the  $\beta$ -lactone to the more thermodynamically stable  $\gamma$ -lactone, rather than a result of kinetic control. To test this hypothesis, a 2:1 mixture of the  $\gamma$ - and  $\beta$ -bromolactones, isolated from the uncatalyzed reaction of 3-hexenoic acid with NBS, was treated with 5 mol% PhSeSePh in CD<sub>3</sub>CN (Scheme 1.40). On the time scale of catalysis, no equilibration of the mixture was observed. 1.1 equivalents NBS were then added to reproduce the standard conditions of catalysis. Again, no equilibration of the starting materials occurred, suggesting that the change in regioselectivity between the catalyzed and uncatalyzed reactions was not caused by a thermodynamic equilibration of the products, but was rather a result of the kinetic product formation.



**Scheme 1.40**

These experiments did not take into account that the dibrominated product (**1.81**), could be cyclizing to form the  $\gamma$ -bromolactone. So, dibrominated product **1.81** was synthesized and resubmitted to the catalytic conditions (Scheme 1.41). Interestingly, it appeared that the NBS was reacting, but no obvious changes could be identified for the starting material by the <sup>1</sup>H NMR spectrum. We speculated that the reaction responsible for the liberation of succinimide was nucleophilic attack of the

carboxylic acid onto the electrophilic bromine, followed by deprotonation of oxonium by the succinimide anion, giving rise to **1.95**. It was concluded that cyclization of **1.81** to form halolactone **1.79a** was not occurring in the catalytic reaction.



### Scheme 1.41

#### *Catalyst Rate Enhancement Studies*

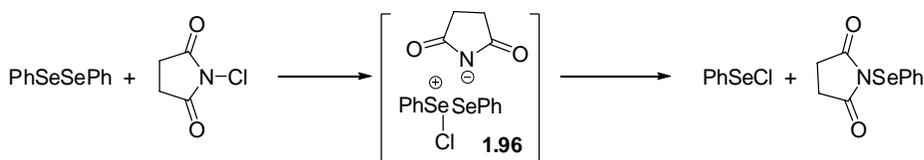
Although the change in product ratios between the catalyzed and uncatalyzed reactions in many cases was strong evidence that catalysis was occurring, we sought to obtain more data to test this claim. Therefore, variable-temperature NMR (vtNMR) was utilized as a way to observe reaction conversion at low temperatures. For the first experiment, a 0.32 M solution of 3-hexenoic acid and 5 mol% PhSeSePh in CD<sub>3</sub>CN was cooled to -30 °C. At this point, 1.1 equivalents NBS were added and the sample was inserted into the precooled NMR probe maintained at -30 °C. It is noteworthy that NBS is only sparingly soluble at such low temperatures, without the aid of stirring. At the time of the first spectrum, taken just after insertion into the instrument, all of the dissolved NBS been consumed and the bromolactonization had reached 32% conversion. The reaction was maintained at -30 °C, but further reaction occurred much slower suggesting that the rate was limited by dissolution of NBS. Over the course of 30 minutes the reaction was warmed to -20

°C and the reaction proceeded to 44% conversion. We were concerned that a lack of stirring was preventing reaction progression, so the sample was ejected and quickly shaken as an attempt to increase the solubility of the NBS. Once the reaction was reinserted into the NMR probe, a spectrum was immediately taken and the reaction had reached 90% completion, confirming that the rate of dissolution of NBS was limiting the rate of the catalyzed reaction.

Another reaction, identical to the first albeit without PhSeSePh, was then run. When the first spectrum was taken for this sample, only 5% of the NBS in solution had been consumed. After ten minutes of reacting, only 7% conversion had been achieved, although more than half of the NBS added was still present in solution. Ejecting the sample as an attempt to dissolve the NBS by shaking the sample tube, was ineffective as the reaction did not progress after doing so. At this point the NMR probe was warmed to 0 °C, because the reaction had still only proceeded to 10% conversion. This did not increase the reaction rate substantially. In fact, it was not until the probe was warmed to room temperature that a reasonable reaction rate was achieved. After reacting 10 minutes at room temperature, the reaction had progressed another 16%, but had still only reached 31% conversion. Clearly, the difference in rate between these two reactions was evidence that PhSeSePh was indeed catalyzing the reaction, and the rate of the reaction at -30 °C is dependent on the rate of dissolution of NBS. It is worth mentioning that when the reaction is stirred on larger scale, the rate of dissolution of NBS and thus the reaction is much faster.

### Selenium Catalyst Speciation

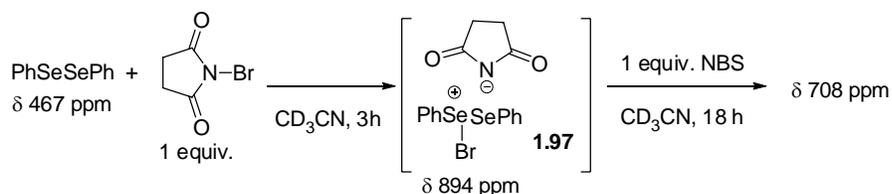
Altogether, selenium's role in the delivery of the halogen is not completely understood. Since the oxidative cleavage of PhSeSePh is known with NCS, we thought that some insight could be gained by considering the mechanism of the oxidative cleavage (Scheme 1.42). The first step in oxidative cleavage of the diselenide bond with NCS is likely nucleophilic attack on a chlorine atom by selenium. This is followed by nucleophilic displacement of the second selenium atom by the succinimide anion which breaks the diselenide bond, generating two distinct selenium species, PhSeCl and PhSe(succinimide). Since cleavage does not occur with NBS, we envisioned an ion pair similar to intermediate **1.96** could be an activated form of NBS with enhanced bromine electrophilicity.



### Scheme 1.42

Although  $^{77}\text{Se}$  NMR spectroscopy was inconclusive in the process of determining selenium speciation for allylic halogenation, we thought it would be worthwhile to run similar experiments for future use. First, PhSeSePh was allowed to react with one equivalent of NBS in  $\text{CD}_3\text{CN}$ . An initial spectrum was taken after 40 minutes of reaction. Two resonances were observed at  $\delta$  467 ppm, which can be attributed to PhSeSePh, and one which was less intense at  $\delta$  894 ppm (Scheme 1.43). After three hours, (the average timescale of catalysis) no new resonances were

observed. At this point another equivalent of NBS was added to the reaction and allowed to stand overnight. A new minor resonance was identified at  $\delta$  708 ppm, while the resonance for PhSeSePh at  $\delta$  467 ppm had almost completely disappeared. Since the halolactonizations were complete much before 24 hours, we were not concerned about the structure which correlated to the resonance at  $\delta$  708 ppm. Again, we did not have conclusive structural evidence of the selenium species that were generated, but it was interesting to know that in the presence of NBS, PhSeSePh does react to give a new selenium species which supports the idea that selenium can activate NBS to catalyze the reaction. The chemical shift of PhSeBr is  $\delta$  867 ppm,<sup>54</sup> which does not correlate with any of the species observed, again showing that this is probably not the active catalyst. The chemical shift changes observed support the hypothesis that the catalyst could be a species where selenium is bound to the bromine atom, rather than just a rapid transformation of NBS to freely diffusing bromine.

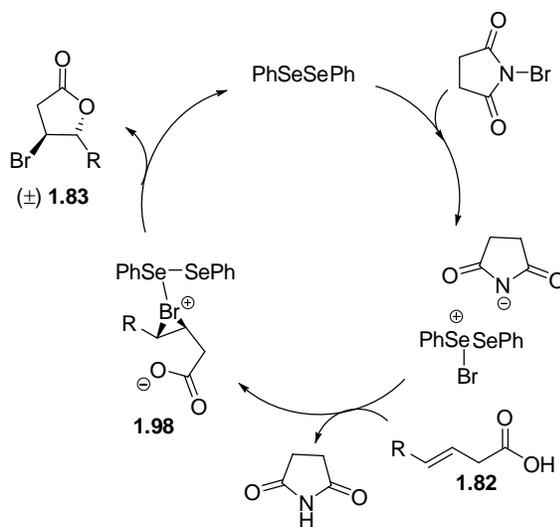


**Scheme 1.43**

### *Mechanistic Proposal*

We have proposed the mechanism in Scheme 1.44 for this transformation. If selenium was activating NBS, it seemed likely that nucleophilic attack on the

bromine atom of NBS was a plausible first step, generating the ion pair. At this point, proton transfer from the carboxylic acid to the succinimide anion should occur rapidly to produce the free carboxylate. The olefin can then attack the selenium bound bromine providing bromonium ion **1.98**. We suggest that the selenium catalyst remains coordinated to the bromonium species, since selenium affects the regioselectivity. Similarly, pyridine is also known to remain coordinated to the halogen during halolactone formation.<sup>55</sup> The carboxylate will then attack the bromonium cation in an *anti*-addition fashion, affording the *trans*-bromolactone products. In this step, the PhSeSePh is regenerated.

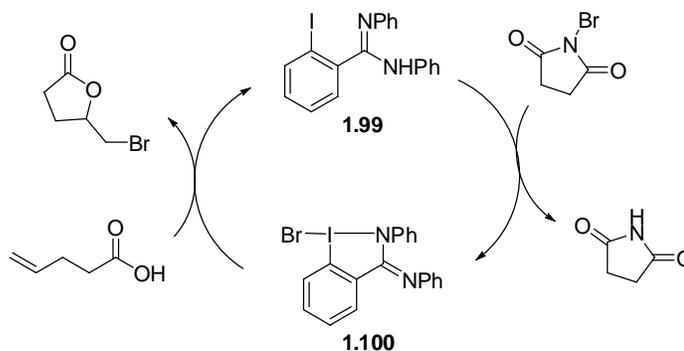


**Scheme 1.44**

### *Recent Developments in Catalytic Bromolactonization*

Recent work by Braddock and coworkers, published since our reports on this topic, also demonstrates the nucleophilic activation of NBS for the halolactonization

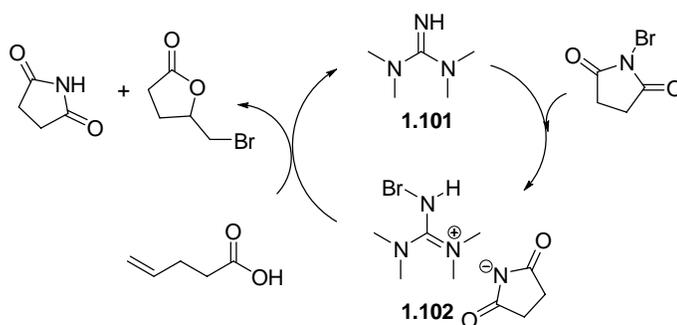
of unsaturated acids using *ortho*-substituted iodobenzenes as catalysts (Scheme 1.45).<sup>49a</sup> This report and the one following, both detail mechanisms whereby a nucleophilic atom activates NBS. In the first report, the most nucleophilic aryl substituents provided the most enhanced rates. They attribute this to the formation of bromoindinane complex **1.100** upon reaction with NBS. The reaction rates were most noticeably increased in the presence of the amidine substituted iodobenzene (**1.99**), though other functional groups with similar electron donors were also very effective. However, for substrates where regioselectivity has proven to be difficult they were also unable to control the regioselectivity of cyclization.



### Scheme 1.45

This group also published a report on the organocatalytic effects of dimethylformamide (DMF), dimethylacetamide (DMA), and tetramethylguanidine (TMG) on the halolactonization reaction (Scheme 1.46).<sup>49b</sup> The rate enhancements observed with these catalysts present were significant. Bromolactonization of 4-pentenoic acid in the absence of catalyst only reached 15% conversion in 15 hours when treated with one equivalent of NBS. Although all catalysts showed significant

increase in rate, TMG (**1.101**) proved to be most effective, reaching 100% conversion to the product in only 15 minutes. The isolated yields of most reactions were between 85-92%. Clearly, these recent advances in the field of bromolactonization are significant. However, they fail to address substrates which are notorious for yielding poor regioselectivities upon lactonization. Both reports detail the activation of the already electrophilic NBS reagent, which lends support to our proposed mechanism, where PhSeSePh is the activating nucleophile.

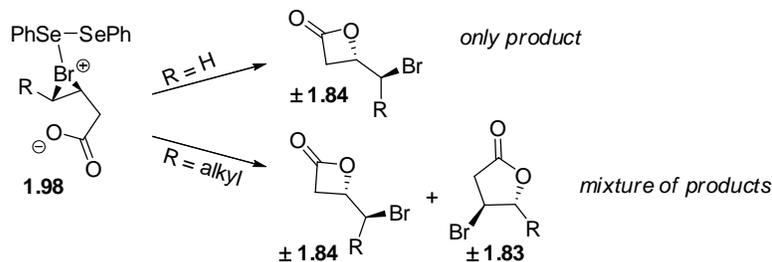


**Scheme 1.46**

### *Regioselectivity of Cyclization*

Our proposed catalytic cycle can help to explain the regioselectivity of bromination of certain unsaturated acids. In the cases where R = H, it will be electronically more favorable to attack the bromonium ion **1.98** at the carbon which bears the most positive charge, favoring  $\beta$ -lactone formation with the substrate shown in Scheme 1.47. Even for the catalyzed reaction, the effects of selenium are not large enough to affect the preference for the formation of the  $\beta$ -lactone. However, if R = alkyl, then both olefinic carbons are equally substituted, decreasing the influence of

electronics on regioselectivity. This is not unique to this methodology as this type of selectivity for cyclization has been reported much earlier.<sup>56</sup>

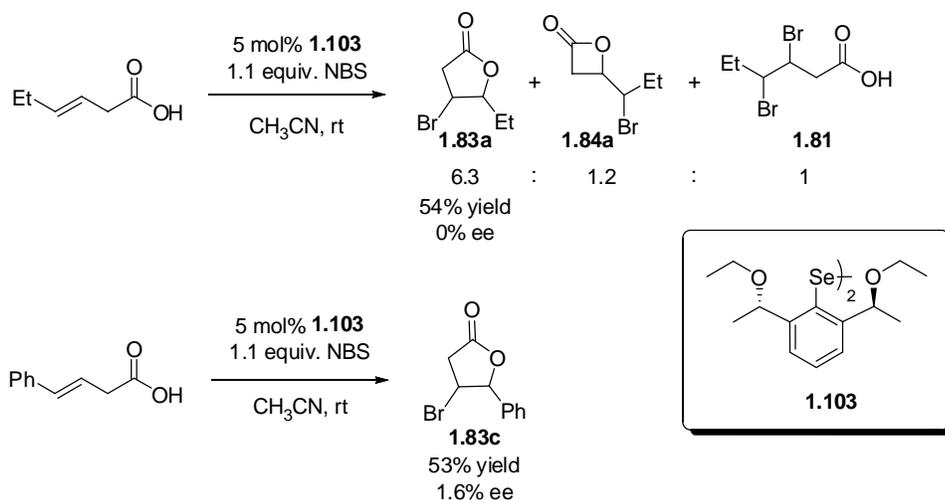


**Scheme 1.47**

### *Enantioselective, Catalytic Bromolactonization*

In the case of halocyclizations with halopyridinium reagents, it is proposed that the donor and the acceptor of the halogen are both in close enough proximity that stereochemical information could be transferred from the donor to the acceptor in the process.<sup>55a</sup> It seemed rational that selenium reagents might also be able to induce asymmetry in a similar fashion. Chiral selenium reagents are well known in the literature for their role in asymmetric addition reactions, such as selenolactonization and methoxyselenation, as well as other important transformations.<sup>40,57</sup> While these reactions lend promise by yielding products in high enantiomeric excess, they have not yet been extended to processes where the selenium reagents are catalytic. We attempted to use some of these chiral selenium reagents for the allylic halogenation reaction with little success. For bromolactonization and the intermediate from which chirality should be transferred, a chiral,  $C_2$ -symmetric diselenide seemed like a viable option. To this end, diselenide **1.103** was synthesized and used in the

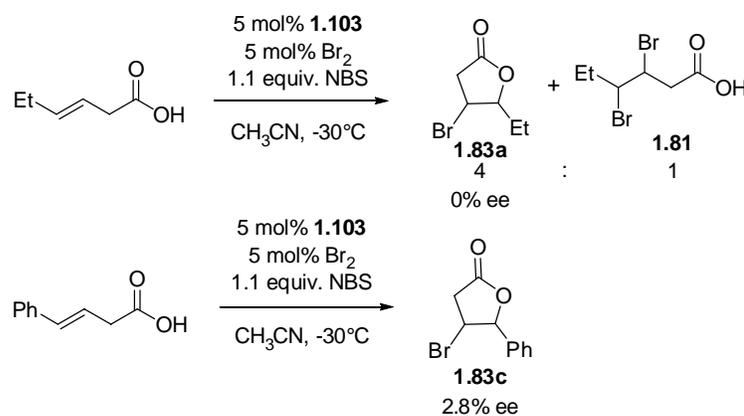
halolactonization reaction. The first reaction was run with 3-hexenoic acid, 5 mol% **1.103**, and 1.1 equivalents NBS in CH<sub>3</sub>CN at -30 °C (Scheme 1.48). Neither the catalyst nor the NBS were very soluble at this temperature so the reaction was allowed to warm to room temperature. After 1.5 hours the reaction was complete and afforded a mixture of products **1.83a**, **1.84a**, and **1.81**. Purification of the mixture revealed a 54% yield of  $\gamma$ -bromolactone **1.83a**. This was followed by chiral stationary phase GC analysis which, to our dismay, showed that no asymmetric induction had been achieved. We then thought a larger olefin substituent might be helpful, so a similar reaction was run with styryl acetic acid. After 5 hours, the reaction was complete and **1.83c** was isolated in 53% yield. Unfortunately, chiral GC analysis also showed that **1.83c** was present in only 1.6% enantiomeric excess.



**Scheme 1.48**

Although we were confident that the catalyst in the reaction was Ar<sup>\*</sup>SeSeAr<sup>\*</sup>, one last effort to induce asymmetry was made. Similar to the allylic halogenation

reactions, the catalyst was pretreated with Br<sub>2</sub> to liberate two molecules of the Ar<sup>\*</sup>SeBr complex from **1.103**. This was done prior to addition of the same two substrates as the previous examples, with 1.1 equivalents NBS in CD<sub>3</sub>CN. These reactions could be run at -30 °C due to the increased solubility of the Ar<sup>\*</sup>SeBr complex (Scheme 1.49). The reaction with 3-hexenoic acid produced only a 4:1 mixture of the **1.83a** and **1.81**, respectively. Again, **1.83a** was isolated and subjected to chiral stationary phase GC analysis; however the product was found to be racemic. Product **1.83c** was also isolated and was determined to have only 2.8% ee. Although these results were somewhat discouraging, it was not surprising that these types of enantioselective halogenations were difficult given the number of reports where only modest enantioselectivities have been obtained.<sup>51</sup>



**Scheme 1.49**

#### *Summary of Selenium-Catalyzed Bromolactonization*

The halolactonization reaction has truly advanced from the beginning stages of its development. Many different reagents and methods have been utilized to effect

the halocyclization event. Our selenocatalytic halolactonization was the first catalytic bromolactonization of its kind to be reported.<sup>39,43,51</sup> Few catalytic methods are reported which actually activate the halogen and serve as the halogen donor, although this seems to be a promising way to introduce halogens enantioselectively. Since the idea of catalytic halolactonization is relatively new and just beginning to gain more attention, only a few reports of catalytic, asymmetric halolactonization have been reported. Tempering the reactivity of the halogens in order to achieve selective addition to the substrate is not a trivial goal. Our attempts at inducing enantioselectivity were unfruitful, but we have still developed a methodology which is capable of altering the regioselectivity as well as the reaction rates of standard bromolactonization with NBS. The ability to induce high enantioselectivities in chloro-, bromo- and even iodolactonizations would be a powerful tool in organic synthesis and is still a field which requires further attention.

## **1.6 General Methods and Compound Characterization**

### *Materials*

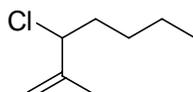
All air and moisture sensitive reactions were carried out in flame-dried glassware under argon using standard Schlenk techniques. Methylene chloride, toluene, and THF were dried over activated alumina columns on an Innovative Technology Solvent System.<sup>58</sup> Benzene was distilled over sodium prior to use. Acetonitrile was stored over activated 4Å molecular sieves. Commercially available reagents were used without additional purification unless otherwise stated. Flash column chromatography was performed with 230x400 mesh, 60 Å porosity, silica

obtained from Sorbent Technologies. Thin layer chromatography was performed on silica gel 60F<sub>254</sub> plates (EM-5715-7, EMD chemicals). Visualization of the plates was accomplished with a UV lamp (254 nm) or KMnO<sub>4</sub> stain. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer using the designated frequencies and referenced to residual protio solvent signals (some spectra were taken using a QNP Cryoprobe). <sup>77</sup>Se NMR spectra were obtained on a Bruker Avance 500 DRX spectrometer at 95.4 MHz and were externally referenced to PhSeSePh at 449 ppm. Variable temperature NMR (vtNMR) spectra were acquired on a Bruker Avance 400 DRX spectrometer. Structural assignments are based on <sup>1</sup>H, <sup>13</sup>C, DEPT-135, COSY, sEl-nOe and HMQC spectroscopies. FTIR spectra were recorded using either a ATI Mattson Genesis Series FTIR or Shimadzu 8400-S FTIR spectrometers. High Resolution Mass Spectrometry (HRMS) were performed using EI, ESI, and FAB techniques. EI MS spectra were obtained on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). ESI MS spectra were acquired either on a LCT Premier (Waters Corp., Milford, MA) or Q-ToF-2 (Microsmass Ltd, Manchester UK) spectrometers. FAB MS spectra were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd, Manchester UK). Elemental Analyses were performed by Desert Analytics Laboratory (Tucson, AZ). Chiral gas phase chromatography was performed on a Shimadzu GC-17A instrument with an AOC-20i autoinjector using TA Chiraldex or B-DM columns (Astec, Whippany, NJ). Chiral high pressure liquid

chromatography was performed on a Shimadzu SCL-10AVP instrument using Daicel Chiralpak AD and OD-H columns.

*General Procedures and Spectral Characterization*

**General procedure for allylic halogenation of prenyl olefins:** Phenyl selenium chloride (5 mol%, 0.026 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL), producing an orange solution. The prenyl substrate was added to the solution (0.52 mmol). The addition of the olefin resulted in an immediate color change from orange to pale yellow. *N*-chlorosuccinimide (0.57 mmol) was then added to the resulting solution. The reaction was allowed to stir at room temperature until completion of the reaction was confirmed by <sup>1</sup>H NMR. The reaction was then concentrated to < 1 mL, and diethyl ether (10 mL) was added. The ether was decanted from the solid and washed with H<sub>2</sub>O (2 × 3 mL). The resulting ether layer was dried over MgSO<sub>4</sub> and concentrated. Unless otherwise noted, the products obtained in this manner were > 95% pure and no purification was necessary. **1.16** was isolated in 82% yield. Isolated yields for all other compounds can be found in Table 1.1.

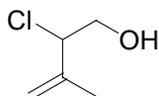


3-chloro-2-methylhept-1-ene

**1.16** (srm1012)

Yield: 82%

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 0.91 (t, 3H: *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.34 (m, 4H: CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>R), 1.75 (m, 5H: CH<sub>2</sub>CHCl and CH<sub>3</sub>C=CH<sub>2</sub>), 4.42 (t, 1H: *J* = 7.3 Hz, CHCl), 4.89 (p, 1H: *J* = 1.5 Hz, R<sub>2</sub>C=CHH), 5.02 (s, 1H: R<sub>2</sub>C=CHH).



2-chloro-3-methylbut-3-en-1-ol

**1.24a** (srm1193)

pale yellow oil

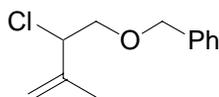
Yield: 72%

**Purification:** flash chromatography: (90:10 hexane:ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.28 (s, 1H: OH), 1.86 (s, 3H: CH<sub>3</sub>), 3.83 (d, 3H: *J* = 6.5 Hz, CH<sub>2</sub>O), 4.51 (t, 1H: *J* = 6.5 Hz, CHCl), 5.07 (s, 1H: CH<sub>2</sub>=C), 5.16 (s, 1H: CH<sub>2</sub>=C).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 18.5 (CH<sub>3</sub>), 65.7 (CH<sub>2</sub>OH), 67.5 (ClCH), 116.6 (CH<sub>2</sub>=C), 141.7 (CH<sub>2</sub>=C);

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>): ν = 3585, 3088, 2945, 1644, 1444, 1383.



((2-chloro-3-methylbut-3-enyloxy)methyl)benzene

**1.24b**<sup>59</sup> (srm1168)

pale yellow oil

Yield: 84%

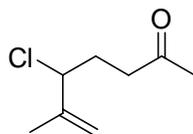
**Purification:** flash chromatography (97:3 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.83 (s, 3H: CH<sub>3</sub>), 3.71 (m, 2H: ClCHCH<sub>2</sub>O), 4.59 (m, 3H: CHCl and CH<sub>2</sub>Ph), 5.03 (q, 1H: *J* = 1Hz, CHH=CR<sub>2</sub>), 5.14 (s, 1H: CHH=C), 7.34 (m, 5H: Ar CH's).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 17.9 (CH<sub>3</sub>), 63.7 (CHCl), 72.4 (ClCHCH<sub>2</sub>O), 73.7 (OCH<sub>2</sub>Ph), 116.4 (CH<sub>2</sub>=C), 128.2 (Ar CH), 128.3 (Ar CH), 128.9 (Ar CH), 138.1 (CH<sub>2</sub>=C), 142.4 (quat. Ph C);

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>): ν<sub>max</sub> 3083, 3031, 2980, 2954, 1643, 1495, 1450, 1208, 1080.

**HRMS** calcd for C<sub>12</sub>H<sub>15</sub>ClO [M+Li] 217.0971, found 217.0980.

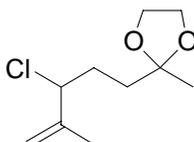


5-chloro-6-methylhept-6-en-2-one

**1.24c**<sup>60</sup> (srm1069)

Yield: 50%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.83 (s, 3H: CH<sub>3</sub>C=CH<sub>2</sub>), 2.11 (dq, 2H: *J* = 0.6, 7.3 Hz, RCH<sub>2</sub>CHCl), 2.18 (s, 3H: CH<sub>3</sub>COR), 2.60 (m, 2H: RCH<sub>2</sub>COCH<sub>3</sub>), 4.42 (t, 1H: *J* = 7.3 Hz, RCHCl), 4.93 (d, 1H: *J* = 1.2 Hz, R<sub>2</sub>C=CHH), 5.04 (s, 1H: R<sub>2</sub>C=CHH).



2-(3-chloro-4-methylpent-4-enyl)-2-methyl-1,3-dioxolane

**1.24d**<sup>61</sup> (srm1236)

colorless oil

Yield: 85%

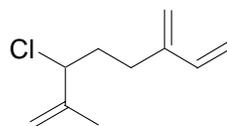
**Purification:** flash chromatography (97:3 hexane: ethyl acetate).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.30 (s, 3H: RC(OR)<sub>2</sub>CH<sub>3</sub>), 1.66 (m, 1H: ClCCH<sub>2</sub>), 1.78 (s, 3H: C=CCH<sub>3</sub>), 1.88 (m, 1H: ClCCH<sub>2</sub>), 2.06 (m, 2H: C(OR)<sub>2</sub>CH<sub>2</sub>), 3.58 (m, 4H: CO<sub>2</sub>C<sub>2</sub>H<sub>4</sub>), 4.37 (t, 1H: *J* = 7 Hz, ClCH), 4.78 (s, 1H: C=CH<sub>2</sub>), 4.92 (s, 1H: C=CH<sub>2</sub>).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 17.1 (C=CCH<sub>3</sub>), 24.3 (CO<sub>2</sub>CH<sub>3</sub>), 31.7 (CH<sub>2</sub>CO<sub>2</sub>), 36.8 (ClCHCH<sub>2</sub>), 64.9 (CO<sub>2</sub>C<sub>2</sub>H<sub>4</sub>), 64.8 (CO<sub>2</sub>C<sub>2</sub>H<sub>4</sub>), 67.1 (CHCl), 109.7 (CO<sub>2</sub>), 114.4 (C=CH<sub>2</sub>), 144.9 (C=CH<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>): ν<sub>max</sub> 3083, 2991, 2955, 1644, 1378, 1147, 1065.

**HRMS** calcd for C<sub>10</sub>H<sub>18</sub>ClO<sub>2</sub> [M+H] 205.0995, found 205.0999.



3-chloro-2-methyl-6-methyleneocta-1,7-diene

**1.24e**<sup>62</sup> (jat1231)

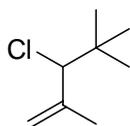
colorless oil

Yield: 69%

**Purification:** flash chromatography (99:1 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 1.86 (s, 3H: CH<sub>3</sub>), 2.08 (m, 2H: CClCH<sub>2</sub>), 2.24 (m, 1H: ClCCH<sub>2</sub>CHH), 2.47(m, 1H: ClCCH<sub>2</sub>CHH), 4.47 (dd, 1H: *J* = 6.4, 8.0 Hz, CHCl), 4.96 (s, 1H), 5.07 (s, 1H), 5.08 (s, 1H), 5.09 (d, 1H; *J* = 10.7 Hz, *cis*-CH=CHH), 5.29 (d, 1H: *J* = 17.5 Hz, *trans*-CH=CHH), 6.40 (dd, 1H: *J* = 10.8 Hz, 17.6 Hz, CH=CH<sub>2</sub>).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 17.4 (CH<sub>3</sub>), 29.0 (CH<sub>2</sub>C); 35.6 (ClCCH<sub>2</sub>); 67.1 (CHCl); 113.9 (HC=CH<sub>2</sub>), 114.6 (=CH<sub>2</sub>), 116.8 (=CH<sub>2</sub>), 138.9 (CH=CH<sub>2</sub>), 145.0 (C=CH<sub>2</sub>), 145.6 (C=CH<sub>2</sub>).



3-chloro-2,4,4-trimethylpent-1-ene (major isomer)

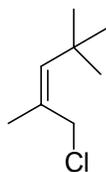
**1.26**<sup>63</sup> (srm1026)

Major and minor isomers were assigned based on reported spectra of all isomers.

Yield: 98% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.15 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>), 1.87 (s, 3H: C=CCH<sub>3</sub>), 3.99 (s, CH<sub>2</sub>Cl), 5.58 (s, 1H, C=CH).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 15.30(C=CCH<sub>3</sub>), 30.76 (C(CH<sub>3</sub>)<sub>3</sub>), 32.64 (C(CH<sub>3</sub>)<sub>3</sub>), 55.21 (CHCl), 130.61 (C=CH), 141.24 (C=CH)



(Z)-1-chloro-2,4,4-trimethylpent-2-ene (minor isomer)

**1.27** (srm1026)

colorless oil

Yield: 98% (combined isomers)

**Purification:** Vacuum Distillation

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.07 (s, 9H: C(CH<sub>3</sub>)<sub>3</sub>), 1.89 (s, 3H: C=CCH<sub>3</sub>), 4.28 (s, 1H: ClCH), 4.97 (t, *J* = 2 Hz, 1H: C=CH<sub>2</sub>), 4.98 (s, 1H: C=CH<sub>2</sub>).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ = 19.8 (C=CCH<sub>3</sub>), 27.8 (C(CH<sub>3</sub>)<sub>3</sub>), 36.5 (C(CH<sub>3</sub>)<sub>3</sub>), 77.8 (ClCH), 116.6 (ClCHCH<sub>2</sub>), 143.9 (H<sub>2</sub>C=C).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>): ν<sub>max</sub> 3073, 2929, 1654, 1367, 1024.

### **Kinetics experiments on the synthesis of 1.16**

*N*-chlorosuccinimide (19-43 mg) was dissolved in dry CD<sub>2</sub>Cl<sub>2</sub> (580 μL). Upon complete dissolution of the NCS, 2-methyl-2-heptene (10 μL of a 0.97M standard solution in CD<sub>2</sub>Cl<sub>2</sub>) was added. The NMR tube was sealed with a septum and immediately taken to the NMR spectrometer. Next, PhSeCl (10 μL of a 0.05M standard solution in CD<sub>2</sub>Cl<sub>2</sub>) was injected and the sample was mixed by shaking. The resulting solutions were quickly inserted into the spectrometer for analysis. Plots of this data were generated to determine the initial rate as well as overall conversion of the reaction. This procedure was twice repeated with [NCS] of 0.37 M and 0.55 M.

**Allylic chlorination of 2-methyl-2-heptene with H<sub>2</sub>O<sub>2</sub>, NaCl, and PhSeCl.**

To a solution of 2-methyl-2-heptene (0.783 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added PhSeCl (10 mol%, 0.783 mmol), and H<sub>2</sub>O<sub>2</sub> (783 mmol of a 30% aqueous solution). Enough NaCl was added to the reaction to make the solution saturated in the salt. The reaction was allowed to stand overnight, without stirring. The reaction proceeded to 41% conversion of **1.16**.

**Allylic chlorination of 2-methyl-2-heptene using selenamide catalyst 1.62.**

Selenamide Catalyst **1.62** was prepared using a modified procedure, where PhSeCl was used in place of PhSCl.<sup>64</sup> A dried NMR tube was charged with 2-methyl-2-heptene (0.655 mmol) and CD<sub>3</sub>CN (750 μL). Catalyst **1.62** (10 mol%, 0.065 mmol) was added to the solution, followed by the addition of NCS (0.721 mmol). The reaction was allowed to stir for 2 hours at room temperature, after which time reaction completion to **1.16** was confirmed by <sup>1</sup>H NMR spectroscopy.

**Allylic chlorination of 2-methyl-2-heptene using polymer bound PhSeCl.**

Polymer catalyst **1.66** was synthesized using a procedure for ruthenium-catalyzed ROMP of norbornene,<sup>65</sup> followed by the addition of PhSeCl (0.5 equivalents relative to the polymer) to the solution of polymer in CH<sub>2</sub>Cl<sub>2</sub>. Concentration of the solvent afforded polymer **1.66**. 2-methyl-2-heptene (0.32 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL). Polymer **1.66** (5 mol% Se) was added to the reaction, followed by the addition of NCS (0.35 mmol). The reaction was stirred for 2 hours at room temperature, and

then the solution was concentrated to < 1 mL and extracted with Et<sub>2</sub>O (15 mL) and washed with H<sub>2</sub>O (2 × 5 mL). The organic phase was then dried over MgSO<sub>4</sub> and concentrated. The crude reaction mixture had the desired product **1.16**, succinimide and polymer.

**Procedure for the hydrolysis of 1.24d to 1.24c.**

To a solution of **1.24d** (493 mg, 2.41 mmol) in THF (36 mL) was added 4M HCl (8.80 mL, 36 mmol). The solution was allowed to stir at room temperature for 6 hours, and was then diluted with Et<sub>2</sub>O (35 mL). The organic phase was extracted with H<sub>2</sub>O (2 × 10 mL) and NaHCO<sub>3</sub> (2 × 5 mL) and then dried over MgSO<sub>4</sub>. The solution was concentrated *in vacuo*, and the product was isolated in 88% yield.

**Allylic chlorination of 2-methyl-2-heptene using polymer 1.67.**

Polymer catalyst **1.67** was synthesized using a procedure for ruthenium-catalyzed ROMP of norbornene, followed by the addition of PhSeCl (0.5 equivalents relative to the polymer) to the solution of polymer in MeOH. Concentration of the solvent afforded polymer **1.67**. 2-methyl-2-heptene (0.32 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL). Polymer **1.67** (10 mol% Se) was added to the reaction, followed by the addition of NCS (0.35 mmol). The reaction was stirred for 4 hours at room temperature, and then the solution was concentrated to < 1 mL and extracted with Et<sub>2</sub>O (15 mL) and washed with H<sub>2</sub>O (2 × 5 mL). The organic phase was then dried over MgSO<sub>4</sub> and concentrated. The reaction afforded **1.16** in 65% yield.

#### **Allylic chlorination using chiral, racemic catalyst 1.68.**

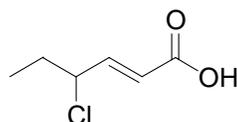
Racemic catalyst **1.68** was synthesized *via* known methods.<sup>66</sup> The catalyst (10 mol%, 0.070 mmol) was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Then, 2-methyl-2-heptene (0.703 mmol) and NCS (0.77 mmol) were added to the reaction which was allowed to stir at room temperature for 2.5 hours. The reaction was concentrated to < 1 mL and diluted with Et<sub>2</sub>O (15 mL). The organic phase was extracted with H<sub>2</sub>O (2 × 5 mL) and dried over MgSO<sub>4</sub>. **1.16** was isolated in 78% crude yield after concentration of the organic phase. **1.24b**, **1.34a**, and **1.34f** were also synthesized using a similar procedure (Table 1.4).

#### **Allylic chlorination using chiral, racemic catalyst 1.72.**

Racemic catalyst **1.68** (0.35 mmol) was initially treated with SO<sub>2</sub>Cl<sub>2</sub> (0.35 mmol) to generate catalyst **1.72**.<sup>67</sup> **1.72** (10 mol%, 0.064 mmol) was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Then, 2-methyl-2-heptene (0.64 mmol) and NCS (0.71 mmol) were added to the reaction which was allowed to stir for 2.5 hours at room temperature. The reaction was concentrated to < 1 mL and diluted with Et<sub>2</sub>O (15 mL). The organic phase was extracted with H<sub>2</sub>O (2 × 5 mL) and dried over MgSO<sub>4</sub>. **1.16** was isolated after concentration of the organic phase. **1.26**, **1.27**, and **1.34a** were also synthesized using a similar procedure (Table 1.5). **1.34e** was isolated in 85% crude yield.

### General procedure for allylic halogenation of $\beta,\gamma$ -unsaturated acids.

Phenyl selenium chloride (10 mol %, 0.052 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (3 mL that was stored over 4Å mol sieves), producing an orange solution. To this solution, 4Å mol sieves (4 beads, ~ 0.15 g) were added followed by addition of the  $\beta,\gamma$ -unsaturated acid (0.52 mmol). The addition of the olefin resulted in an immediate color change from orange to pale yellow. A solution of *N*-chlorosuccinimide (0.57 mmol, in 3 mL  $\text{CH}_3\text{CN}$ ) was prepared then drawn into a 5 mL GASTIGHT syringe equipped with a teflon needle. The solution of NCS was added via syringe pump at the rate of 0.191 mL/h. After 16 h, completion of the reaction was confirmed by  $^1\text{H}$  NMR. This solution was concentrated to < 1 mL, and diethyl ether (10 mL) was added. The ether was decanted from the solid and washed with  $\text{H}_2\text{O}$  ( $2 \times 3$  mL). The resulting ether layer was dried over  $\text{MgSO}_4$ , concentrated, and the residue was purified by flash chromatography (95:5 hexane:ethyl acetate). Isolated yields are reported in Table 1.2.



(*E*)-4-chlorohex-2-enoic acid

**1.34a** (srm1238)

pale yellow oil

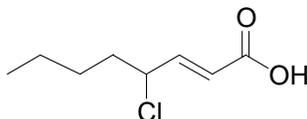
Yield: 83%

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.06 (t, 3H:  $J = 7$  Hz,  $\text{CH}_3$ ), 1.92 (m, 2H:  $\text{CH}_2$ ), 4.45 (app t, 1H:  $J =$  Hz,  $\text{CHCl}$ ), 5.95 (dd, 1H:  $J = 1.0, 15.0$  Hz,  $\text{CHCO}_2\text{H}$ ), 7.04 (dd, 1H:  $J = 7.5, 15.0$  Hz,  $\text{ClCHCH}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  11.1 ( $\text{CH}_3$ ), 31.2 ( $\text{CH}_2$ ), 61.4 ( $\text{ClCH}$ ), 122.2 ( $\text{CHCO}_2\text{H}$ ), 149.2 ( $\text{ClCHCH}=\text{CH}$ ), 171.8 ( $\text{CO}_2\text{H}$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ ):  $\nu_{\text{max}}$  2970(broad), 1700, 1654.

HRMS calcd for  $\text{C}_6\text{H}_{10}\text{ClO}_2$  [ $\text{M}+\text{H}$ ] 149.0369, found 149.0381.



(*E*)-4-chlorooct-2-enoic acid

**1.34b** (srm1227)

yellow oil

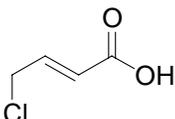
Yield: 75%

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94 (t, 3H:  $J = 6.5$  Hz,  $\text{CH}_3$ ), 1.38 (m, 4H:  $\text{CH}_3\text{CH}_2\text{CH}_2$ ), 1.88 (q, 2H:  $J = 7.5$  Hz,  $\text{ClCHCH}_2$ ), 4.48 (app q, 1H:  $J = 7$  Hz,  $\text{CHCl}$ ), 6.05 (dd, 1H:  $J = 1.0, 15.0$  Hz,  $\text{CHCO}_2\text{H}$ ) 7.03 (dd, 1H:  $J = 7.5, 15$  Hz,  $\text{ClCHCH}=\text{CH}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  14.3 ( $\text{CH}_3$ ), 22.5 ( $\text{CH}_3\text{CH}_2$ ), 28.7 ( $\text{CH}_3\text{CH}_2\text{CH}_2$ ), 37.7 ( $\text{ClCHCH}_2$ ), 60.0 ( $\text{CHCl}$ ), 122.0 ( $\text{CH}=\text{CHCO}_2\text{H}$ ), 149.4 ( $\text{CHClCH}=\text{CH}$ ), 171.8 ( $\text{CO}_2\text{H}$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ ):  $\nu_{\text{max}}$  3052 (broad), 2986, 1705, 1659.

HRMS calcd for  $\text{C}_8\text{H}_{14}\text{ClO}_2$  [ $\text{M}+\text{H}$ ] 177.0682, found 177.0681.



(*E*)-4-chlorobut-2-enoic acid

**1.34c**<sup>68</sup> (srm1187)

white crystalline solid

Yield: 82%

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.22 (dd, 2H:  $J = 1.5, 6.0$  Hz,  $\text{ClCH}_2$ ), 6.16 (dt, 1H:  $J = 1.5, 15$  Hz,  $\text{CHCO}_2\text{H}$ ), 7.12 (dt, 1H:  $J = 6, 15$  Hz,  $\text{CH}_2\text{CH}=\text{CH}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  42.7 ( $\text{CHCl}$ ), 123.6 ( $\text{C}=\text{CHCO}_2\text{H}$ ), 144.9 ( $\text{ClCH}_2\text{CH}=\text{CH}$ ) 171.3 ( $\text{CO}_2\text{H}$ ).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>):  $\nu_{\max}$  3006, 1700, 1654.

**Mp** = 75-79°C

**HRMS** calcd for C<sub>4</sub>H<sub>5</sub>ClO<sub>2</sub> [M+H] 121.0046, found 121.0056

**Allylic chlorination of 3-hexenoic acid using selenamide catalyst 1.62.**

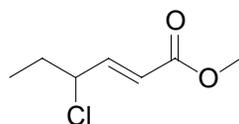
Selenamide Catalyst **1.62** was prepared using a modified procedure, where PhSeCl was used in place of PhSCl.<sup>64</sup> A dried NMR tube was charged with 3-hexenoic acid **1.33a** (0.437 mmol) in CD<sub>3</sub>CN (750  $\mu$ L), as well <sup>t</sup>BuOMe (0.218 mmol) which was used as an internal standard. Catalyst **1.62** (10 mol%, 0.044 mmol) was added to the solution, followed by the addition of NCS (0.721 mmol). The reaction was allowed to stir at room temperature for 48 hours, after which time reaction completion to **1.34a** was confirmed by <sup>1</sup>H NMR spectroscopy.

**Allylic chlorination of 3-hexenoic acid using chiral catalyst 1.70.**

Chiral catalyst **1.70** was synthesized *via* the reported method<sup>69</sup> followed by treatment with MOM-Cl and SO<sub>2</sub>Cl<sub>2</sub> to afford catalyst **1.70**. Catalyst **1.70** (0.034 mmol) was dissolved into CD<sub>3</sub>CN (600  $\mu$ L). 3-hexenoic acid (0.034 mmol) was then added to the solution. NCS (0.034 mmol) was added quickly to the solution. The reaction was observed by <sup>1</sup>H NMR spectroscopy and it was observed that **1.34a** was formed after 18 hours at room temperature. The enantiomeric excess was determined by chiral GC separation of the butenolide side product **1.45**.

### General procedure for allylic halogenation of $\beta,\gamma$ -unsaturated esters.

Phenyl selenium chloride (10 mol%, 0.052 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (3 mL, stored over 4Å mol sieves), producing an orange solution. To this solution, 4Å mol sieves (4 beads, ~ 0.15 g) were added followed by addition of the  $\beta,\gamma$ -unsaturated ester (0.52 mmol). The addition of the olefin resulted in an immediate color change from orange to pale yellow. A solution of *N*-chlorosuccinimide (0.57 mmol, in 6 mL  $\text{CH}_3\text{CN}$ ) was prepared then slowly added via addition funnel. After 4 h, completion of the reaction was confirmed by  $^1\text{H}$  NMR. This solution was concentrated to < 1 mL, and diethyl ether (10 mL) was added. The ether was decanted from the solid and washed with  $\text{H}_2\text{O}$  ( $2 \times 3$  mL). The resulting ether layer was dried over  $\text{MgSO}_4$ , and concentrated. Products obtained in this manner were ~ 95 % pure; the small amount of residual  $\text{PhSeCl}$  was removed by flash chromatography (95:5 hexane: ethyl acetate). Isolated yields are reported in Table 1.2.



(*E*)-methyl 4-chlorohex-2-enoate

**1.34d** (srml 147)

pale yellow oil

Yield: 88%

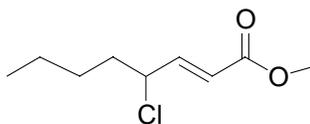
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.04 (t, 3H:  $J = 7$  Hz,  $\text{CH}_3$ ), 1.98 (m, 2H:  $\text{CH}_2$ ), 3.78 (s, 3H:  $\text{OCH}_3$ ), 4.41 (app q, 1H:  $J = 6$  Hz,  $\text{CHCl}$ ), 6.04 (dd, 1H:  $J = 1.0, 15.0$  Hz,  $\text{CHCO}_2$ ) 6.92 (dd, 1H:  $J = 7.7, 15.0$  Hz,  $\text{ClCHCH}=\text{CH}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  11.1 ( $\text{CH}_3$ ), 31.3 ( $\text{CH}_2$ ), 52.2 ( $\text{OCH}_3$ ), 61.8 ( $\text{ClCH}$ ), 122.6 ( $\text{CHCO}_2\text{H}$ ), 146.7 ( $\text{ClCHCH}=\text{CH}$ ), 166.7 ( $\text{CO}_2$ ).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>):  $\nu_{\max}$  3062, 2970, 2950, 1721, 1659, 1460, 1444.

**HRMS** calcd for C<sub>7</sub>H<sub>15</sub>NO<sub>2</sub>Cl [M+NH<sub>4</sub><sup>+</sup>] 180.0791, found 180.0764

**Chiral GC Column:** Chiraldex TA **Program:** Initial Hold at 50 °C for 5 min, ramp of 1 °C/minute until 120 °C, final hold for 50 minutes. **Retention Times:** 99.0 and 100.1 minutes.



(*E*)-methyl 4-chlorooct-2-enoate

**1.34e** (srm1212)

yellow oil

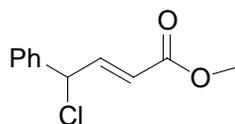
Yield: 89%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.92 (t, 3H:  $J$  = 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.36 (m, 4H: CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.86 (m, 2H: ClCHCH<sub>2</sub>), 3.78 (s, 3H: OCH<sub>3</sub>), 4.45 (app q, 1H:  $J$  = 7.5 Hz, CHCl), 6.03 (dd, 1H:  $J$  = 1.0, 15.0 Hz, CHCO<sub>2</sub>), 6.92 (dd, 1H:  $J$  = 8.1, 15.0 Hz, ClCHCH=CH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>)  $\delta$  14.3 (CH<sub>2</sub>CH<sub>3</sub>), 22.5 (CH<sub>3</sub>CH<sub>2</sub>), 28.7 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>), 37.8 (ClCHCH<sub>2</sub>), 52.2 (OCH<sub>3</sub>), 60.3 (CHCl), 122.4 (CH=CHCO<sub>2</sub>H), 147.0 (CHClCH=CH), 166.7 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>):  $\nu_{\max}$  3062, 2955, 2863, 1726, 1659, 1434, 1173.

**HRMS** calcd for C<sub>9</sub>H<sub>16</sub>ClO<sub>2</sub> [M+H] 191.0839, found 191.0840.



(*E*)-methyl 4-chloro-4-phenylbut-2-enoate

**1.34f** (srm1251)

orange oil

Yield: 77%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.78 (s, 3H: OCH<sub>3</sub>), 5.56 (d, 1H: *J* = 7.3 Hz, CHCl), 6.10 (d, 1H: *J* = 16 Hz, CHCO<sub>2</sub>), 7.18 (dd, 1H: *J* = 6.5, 15.0 Hz, ClCHCH), 7.38 (m, 5H: Ar CH's).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 52.3 (OCH<sub>3</sub>), 61.2 (CHCl), 122.8 (CHCO<sub>2</sub>), 128.0 (Ar CH), 129.4 (overlapping Ar CH's), 138.8 (quat. Ar C), 145.9 (ClCHCH), 166.6 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>): ν<sub>max</sub> 3062, 3032, 2955, 1721, 1660, 1490, 1280, 1168.

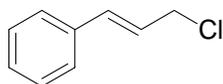
**HRMS** calcd for C<sub>11</sub>H<sub>12</sub>ClO<sub>2</sub> [M+H] 211.0526, found 211.0500.

#### **Allylic chlorination of 1.33d using chiral catalyst 1.69.**

Chiral catalyst **1.69** was synthesized *via* the reported method.<sup>69</sup> Catalyst **1.69** (0.021 mmol) was dissolved into CH<sub>3</sub>CN (3 mL) and SO<sub>2</sub>Cl<sub>2</sub> (0.021 mmol) was added to generate the Ar\*SeCl chloride *in situ*. Ester **1.33d** (0.41 mmol) was then added to the solution. NCS (0.906 mmol in 2 mL CH<sub>3</sub>CN) was added *via* syringe pump over 16 hours. The reaction was complete after two days. The solution was concentrated to < 1 mL, and diethyl ether (10 mL) was added. The organic phase was washed with H<sub>2</sub>O (2 × 5 mL). The resulting ether layer was dried over MgSO<sub>4</sub>, and concentrated. Compound **1.36** was formed using a similar procedure.

### General Procedure for allylic halogenation of 1.34g and 1.34h.

Phenyl selenium chloride (20 mol%, 0.104 mmol) was dissolved in CH<sub>3</sub>CN (3 mL, stored over 4Å mol sieves), producing an orange solution. To this solution, 4Å mol sieves (4 beads, ~ 0.15g) were added followed by addition of the substrate (0.52 mmol). The addition of the olefin resulted in an immediate color change from orange to pale yellow. A solution of *N*-chlorosuccinimide (0.57 mmol, in 3 mL CH<sub>3</sub>CN) was prepared then drawn into a 5 mL GASTIGHT syringe equipped with a teflon needle. The solution of NCS was added via syringe pump at the rate of 0.125 mL/h. After 48 h, completion of the reaction was confirmed by <sup>1</sup>H NMR. This solution was concentrated to < 1 mL, and Et<sub>2</sub>O (10 mL) was added. The ether was decanted from the solid and washed with H<sub>2</sub>O (2 × 3 mL). The resulting ether layer was dried over MgSO<sub>4</sub>, concentrated and the residue was purified *via* flash chromatography with the specified elution system. Isolated yields are reported in Table 1.2.



(*E*)-(3-chloroprop-1-enyl)benzene  
**1.34g**<sup>70</sup> (srml198)  
pale pink oil  
Yield: 66%

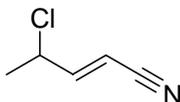
**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.28 (dd, 2H; *J* = 1, 7 Hz, CH<sub>2</sub>Cl), 6.36 (m, 1H: PhCH=CH), 6.69 (d, 1H: *J* = 15 Hz, ClCH<sub>2</sub>CH), 7.36 (m, 5H: Ar CH's).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 45.9 (CH<sub>2</sub>Cl), 125.3 (ClCH<sub>2</sub>CH), 127.2 (Ar CH), 128.7 (Ar CH), 129.1 (Ar CH), 134.6 (PhCH=CH), 136.3 (quat. Ar C).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>): ν<sub>max</sub> 3083, 3027, 2945, 1644, 1572.

**HRMS** calcd for C<sub>19</sub>H<sub>9</sub>Cl [M<sup>+</sup>] 152.0393, found 152.0382.



(*E*)-4-chloropent-2-enenitrile (major isomer)

***E*-1.34h**<sup>71</sup> (srm1264)

yellow oil

Yield: 62% (combined isomers)

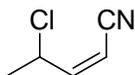
**Purification:** flash chromatography (95:5 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 1.67 (d, 3H: *J* = 7 Hz, CH<sub>3</sub>), 4.60 (m, 1H: CHCl), 5.66 (dd, 1H: *J* = 1.5, 16 Hz, CNCH), 6.75 (dd, 1H: *J* = 6, 16 Hz, CNCH=CH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 24.9 (CH<sub>3</sub>), 54.8 (ClCH), 101.4 (NCCH), 116.7 (CN), 153.8 (NCCH=CH);

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>): ν<sub>max</sub> 3053, 2986, 2685, 2304, 1421, 896.

**LRMS:** [M] = 115



(*Z*)-4-chloropent-2-enenitrile (minor isomer)

***Z*-1.34h** (srm1264)

yellow oil

Yield: 62% (combined isomers)

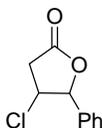
**Purification:** flash chromatography (95:5 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 1.67 (d, 3H: *J* = 7 Hz, CH<sub>3</sub>), 4.94 (m, 1H: CHCl), 5.38 (d, 1H: *J* = 10.9 Hz, CNCH), 6.50 (t, 1H: *J* = 10.6 Hz, CNCH=CH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 24.4 (CH<sub>3</sub>), 53.6 (ClCH), 99.7 (NCCH), 115.2 (CN), 153.4 (NCCH=CH).

**Procedure for chlorolactonization of *trans*-styrylacetic acid.**

Phenyl selenium chloride (10 mol %, 0.01 mmol) was dissolved in CH<sub>3</sub>CN (5 mL, stored over 4Å mol sieves), producing an orange solution. To this solution, the unsaturated acid (1.0 mmol) was added. The addition of the acid resulted in an immediate color change from orange to pale yellow. *N*-chlorosuccinimide (1.1 mmol) was then added to reaction. After 6 h, completion of the reaction was confirmed by <sup>1</sup>H NMR. This solution was concentrated to < 1 mL, and diethyl ether (10 mL) was added. The ether was decanted from the solid and washed with H<sub>2</sub>O (2 × 3 mL). The resulting ether layer was dried over MgSO<sub>4</sub>, concentrated and the residue was purified by flash chromatography (90:10 hexane:ethyl acetate). Chlorolactone **1.36** was isolated in 58% yield.



4-chloro-5-phenyldihydrofuran-2(3*H*)-one

**1.36**<sup>72</sup> (srm1053)

pale orange solid

Yield: 58%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.89 (dd, 1H: *J* = 5.5, 18.1 Hz, CHHCO<sub>2</sub>), 3.17 (dd, 1H: *J* = 7.2, 18.1 Hz, CHHCO<sub>2</sub>), 4.45 (ddd, 1H: *J* = 5.3, 7.2, 4.9 Hz, CHCl), 5.59 (d, 1H: *J* = 4.4 Hz, CHO) 7.43 (m, 5H: Ar CH's)

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 38.0 (CH<sub>2</sub>), 57.7 (CHCl), 87.4 (CHO), 125.1 (Ar CH), 129.0 (Ar CH) 129.2 (Ar CH), 135.7 (quat. Ar C) 172.7 (CO<sub>2</sub>).

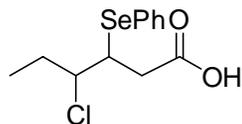
FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub> 2924, 1792, 1495, 1449, 1403, 1142.

HRMS calcd for C<sub>10</sub>H<sub>10</sub>ClO<sub>2</sub> [M+H] 197.0368, found 197.0362.

**Chiral GC Column:** Chiraldex TA **Program:** Initial Hold at 50 °C for 5 min, ramp of 1 °C/minute until 150 °C, final hold for 50 minutes. **Retention Times:** 53.0 and 53.3 minutes.

**General procedure for the formation of 1.40-1.43.**

To a dried NMR tube was added a solution of 3-hexenoic acid (0.104 mmol) in 600  $\mu\text{L}$   $\text{CD}_3\text{CN}$ . A stoichiometric amount of  $\text{PhSeCl}$  (0.104 mmol) was then added to the solution. The formation of **1.40-1.42** was observed immediately by  $^1\text{H}$  NMR spectroscopy. The reaction was allowed to stand for 3.5 hours, after which the reaction had converted completely to **1.42**. Then,  $\text{NCS}$  (0.104 mmol) was added to the reaction and the formation of **1.43** was observed by  $^1\text{H}$  NMR spectroscopy.

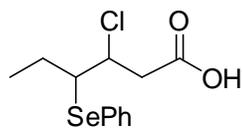


4-chloro-3-(phenylselanyl)hexanoic acid

**1.40** (srm2063)

yield: 52% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.04 (t, 1H:  $J = 7.5$  Hz,  $\text{CH}_3$ ), 1.86 (ddd, 1H:  $J = 7.3$ , 8.8, 14.6 Hz,  $\text{CHHCH}_3$ ), 2.25 (ddq, 1H:  $J = 3.2$ , 7.3, 10.5 Hz,  $\text{CHHCH}_3$ ), 2.88 (dd, 1H:  $J = 9.1$ , 17.0 Hz,  $\text{CHHCO}_2\text{H}$ ), 3.29 (dd, 1H:  $J = 4.1$ , 17.0 Hz,  $\text{CHHCO}_2\text{H}$ ), 3.66 (td, 1H:  $J = 4.2$ , 8.6 Hz,  $\text{R}_2\text{CHSePh}$ ), 4.13 (td, 1H:  $J = 3.2$ , 8.3 Hz,  $\text{R}_2\text{CHCl}$ ), 7.35 (m, 3H: Ar CH's), 7.67 (m, 2H: Ar CH's), 10.87 (br. s, 1H:  $\text{CO}_2\text{H}$ ).

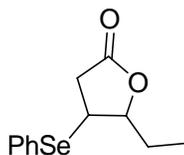


3-chloro-4-(phenylselanyl)hexanoic acid

**1.41** (srm2063)

yield: 10% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.18 (t, 3H:  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.74 (ddd, 1H:  $J = 7.3, 9.1, 14.6$  Hz,  $\text{CHHCH}_3$ ), 2.12 (ddd, 1H:  $J = 3.8, 7.3, 11.1$  Hz,  $\text{CHHCH}_3$ ), 2.88 (m, 1H:  $\text{CHHCO}_2\text{H}$ ), 3.27 (dd, 1H:  $J = 13.8, 17.5$  Hz,  $\text{CHHCO}_2\text{H}$ ), 3.46 (dd, 1H:  $J = 3.4, 16.5$  Hz,  $\text{R}_2\text{CHSePh}$ ), 4.50 (ddd, 1H:  $J = 3.2, 8.3, 9.8$  Hz,  $\text{R}_2\text{CHCl}$ ), 7.30 (m, 3H: Ar CH's), 7.63 (m, 2H: Ar CH's), 10.87 (br. s, 1H:  $\text{CO}_2\text{H}$ ).

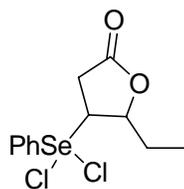


5-ethyl-4-(phenylselanyl)dihydrofuran-2(3H)-one

**1.42** (srm2121)

yield: 38% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.95 (t, 3H:  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.64 (sext, 1H:  $J = 7.3$  Hz,  $\text{CHHCH}_3$ ), 1.76 (m, 1H:  $\text{CHHCH}_3$ ), 2.58 (dd, 1H:  $J = 7.5, 18.2$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.03 (dd, 1H:  $J = 8.4, 18.3$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.74 (ddd, 1H:  $J = 6.6, 7.7, 8.1$  Hz,  $\text{R}_2\text{CHSePh}$ ), 4.38 (m, 1H:  $\text{R}_2\text{CHO}$ ), 7.39 (m, 3H: Ar CH's), 7.64 (m, 2H: Ar CH's).



**1.43** (srm2121)

yield: >95% by  $^1\text{H}$  NMR

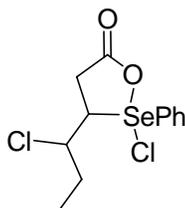
$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  1.11 (t, 3H:  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.95 (m, 2H:  $\text{RCH}_2\text{CH}_3$ ), 3.24 (dd, 1H:  $J = 2.9, 19.8$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.54 (dd, 1H:  $J = 9.2, 19.8$  Hz,  $\text{CHHCO}_2\text{R}$ ), 5.19 (ddd, 1H:  $J = 2.6, 5.4, 7.8$  Hz,  $\text{CHOR}_2$ ), 5.26 (dt, 1H:  $J = 2.8, 9.2$  Hz,  $\text{R}_2\text{CHSeCl}_2\text{Ph}$ ), 7.63 (m, 3H: Ar CH's), 8.01 (m, 2H: Ar CH's).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  9.1 ( $\text{CH}_3$ ), 29.6 ( $\text{CH}_2\text{CH}_3$ ), 33.4 ( $\text{CH}_2\text{CO}_2\text{R}$ ), 71.0 ( $\text{CHO}$ ), 83.1 ( $\text{R}_2\text{CHSe}$ ), 130.7 (Ar CH), 131.1 (Ar CH's), 132.8 (Ar CH), 139.80 (quat. Ar C), 173.5 ( $\text{C}=\text{O}$ ).

$^{77}\text{Se}$  NMR (95.4 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  618.8.

### General procedure for the formation of 1.44-1.46.

To a dried NMR tube was added a solution of 3-hexenoic acid (0.104 mmol) in 600  $\mu\text{L}$   $\text{CD}_3\text{CN}$ . A stoichiometric amount of  $\text{PhSeCl}$  (0.104) was then added to the solution and the reaction was shaken. Immediately, NCS (0.104 mmol) was added to the solution and the reaction was quickly observed by  $^1\text{H}$  NMR spectroscopy, and it was demonstrated **1.44** had been produced. After allowing the reaction to stand for 16 hours, **1.45** and **1.46** were also observed in the reaction solution.

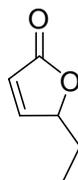


**1.44** (srm2122)  
yield: 90% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  1.16 (t, 3H:  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.98 (m, 2H:  $\text{CH}_2\text{CH}_3$ ), 2.97 (dd, 1H:  $J = 9.5, 17.6$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.16 (dd, 1H:  $J = 2.2, 17.6$  Hz,  $\text{CHHCO}_2\text{R}$ ), 4.96 (dt, 1H:  $J = 2.2, 9.5$  Hz,  $\text{R}_2\text{CHSe}$ ), 5.24 (ddd, 1H:  $J = 2.2, 6.1, 8.2$  Hz,  $\text{R}_2\text{CHCl}$ ), 7.65 (m, 3H: Ar CH's), 8.02 (m, 2H: Ar CH's).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  11.2 ( $\text{CH}_3$ ), 30.1 ( $\text{CH}_2\text{CH}_3$ ), 31.5 ( $\text{CH}_2\text{CO}_2\text{R}$ ), 63.1 ( $\text{CHCl}$ ), 71.7 ( $\text{R}_2\text{CHSe}$ ), 129.2 (Ar CH), 130.7 (Ar CH), 131.1 (quat. Ar C), 132.7 (Ar CH), 175.7 ( $\text{C}=\text{O}$ ).

$^{77}\text{Se}$  NMR (95.4 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  711.6.



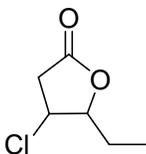
5-ethylfuran-2(5H)-one

**1.45** (srm1115)

Yield: 14%

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.01 (t, 3H: *J* = 7.7 Hz, CH<sub>3</sub>), 1.75 (m, H: CHHCH<sub>3</sub>), 1.83 (m, 1H: CHHCH<sub>3</sub>), 5.01 (ddt, 1H: 1.7, 5.6, 7.8 Hz, CHO), 6.12 (dd, 1H: *J* = 1.9, 5.8 Hz, CH=CHCO<sub>2</sub>R), 7.44 (dd, 1H: *J* = 1.3, 5.6 Hz, CH=CHCO<sub>2</sub>R).

**Chiral GC Column:** Chiraldex TA **Program:** Initial Hold at 50 °C for 5 min, ramp of 1 °C/minute until 120 °C, final hold for 50 minutes. **Retention Times:** 94.3 and 114.8 minutes.



4-chloro-5-ethyl-2(3H)-one

**1.46** (srm1238)

yield: 13%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.07 (t, 3H: *J* = 7.6 Hz, CH<sub>3</sub>), 1.86 (m, 1H: *J* = 6.9, 7.1, 14.4 Hz, CHHCH<sub>3</sub>), 2.04 (dt, 1H: *J* = 7.3, 14.4 Hz, CHHCH<sub>3</sub>), 2.88 (d, 1H: *J* = 17.8 Hz, CHHCO<sub>2</sub>R), 3.13 (dd, 1H: *J* = 6.1, 18.1 Hz, CHHCO<sub>2</sub>R), 4.45 (td, 1H: *J* = 3.7, 6.9 Hz, R<sub>2</sub>CHCl), 4.66 (dd, 1H: *J* = 3.5, 6.1 Hz, R<sub>2</sub>CHO).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 9.9 (CH<sub>3</sub>), 24.3 (CH<sub>2</sub>CH<sub>3</sub>), 41.54 (CH<sub>2</sub>CO<sub>2</sub>R), 58.0 (CHCl), 84.5 (CHO), 173.9 (C=O).

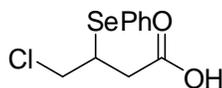
**Alternate procedure for the synthesis of 1.43-1.46 by premixing PhSeCl and NCS.**

To a solution of PhSeCl (0.109 mmol) in 600 μL CD<sub>3</sub>CN was added NCS (0.218 mmol) and an orange/yellow solution was produced. The reaction was allowed to

stand for 30 minutes, after which time the reaction had lightened to a more yellow solution. 3-hexenoic acid (0.109 mmol) was then added to the reaction and the formation of **1.44** was initially observed. After standing overnight **1.43**, **1.45**, and **1.46** formed along with allyl chloride **1.34a**.

#### General procedure for the synthesis of **1.47-1.50**.

To a dried NMR tube was added a solution of 3-butenic acid (0.104 mmol) in 600  $\mu\text{L}$   $\text{CD}_2\text{Cl}_2$ . A stoichiometric amount of  $\text{PhSeCl}$  (0.104 mmol) was then added to the solution. A 5:1 mixture of **1.47** and **1.48** was observed immediately by  $^1\text{H}$  NMR spectroscopy. To this solution  $\text{NCS}$  (0.104 mmol) was quickly added and the formation of selenuranes **1.49** and **1.50** were observed by  $^1\text{H}$  NMR spectroscopy.

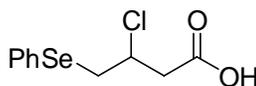


4-chloro-3-(phenylselanyl)butanoic acid

**1.47** (jat1011)

yield: 92% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  2.70 (dd, 1H:  $J = 8.6, 16.7$  Hz,  $\text{CHHCHSePh}$ ), 3.19 (dd, 1H:  $J = 4.3, 16.9$  Hz,  $\text{CHHCHSePh}$ ), 3.61 (m, 1H:  $\text{CHSePh}$ ), 3.67 (app. t, 1H:  $J = 10.4$  Hz,  $\text{CHHCl}$ ), 3.96 (dd, 1H:  $J = 3.8, 10.6$  Hz,  $\text{CHHCl}$ ), 7.34 (m, 3H: Ar CH's), 7.62 (d, 2H:  $J = 6.8$  Hz, Ar CH's), 10.70 (br. s, 1H:  $\text{CO}_2\text{H}$ )



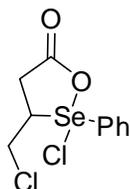
3-chloro-4-(phenylselanyl)butanoic acid

**1.48** (jat1011)

yield: 77% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  2.79 (dd, 1H:  $J = 9.1, 16.4$  Hz,  $\text{CHHCHCl}$ ), 3.22 (m, 1H:  $\text{CHHCHCl}$ ), 3.30 (dd, 1H:  $J = 3.5, 16.3$  Hz,  $\text{CHHSePh}$ ), 3.45 (dd, 1H:  $J =$

4.8, 13.1 Hz,  $\text{CHHSePh}$ ), 4.38 (dt, 1H:  $J = 4.4, 4.4, 9.1, 9.1$  Hz,  $\text{CHCl}$ ), 7.33 (d, 3H:  $J = 2.5$ , Ar CH's), 7.57 (dd, 2H:  $J = 2.3, 5.8$  Hz, Ar CH's), 11.00 (br. s, 1H:  $\text{CO}_2\text{H}$ ).

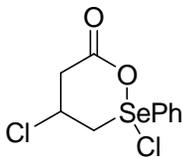


**1.49** (jat1018)

yield: ~90% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  2.87 (dd, 1H:  $J = 9.1, 17.4$  Hz,  $\text{CHHCHSePh}$ ), 3.17 (d, 1H:  $J = 17.4$  Hz,  $\text{CHHCHSePh}$ ), 4.22 (dd, 1H:  $J = 12.4$  Hz,  $\text{CHHCl}$ ), 4.62 (dd, 1H:  $J = 4.5, 12.4$  Hz,  $\text{CHHCl}$ ), 4.72 (br. s, 1H:  $\text{CHSePhClO}$ ), 7.58 (m, 3H: Ar CH's), 7.83 (d, 2H:  $J = 8.0$  Hz, Ar CH's).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  34.8 ( $\text{CH}_2\text{CO}_2$ ), 43.8 ( $\text{CH}_2\text{Cl}$ ), 69.6 ( $\text{CHSe}$ ), 129.3 (Ar CH), 130.5 (Ar CH), 132.6 (Ar CH), 134.5 (quat Ar C).



**1.50** (jat2066)

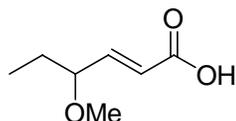
yield: 43% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  3.63 (m, 1H:  $\text{R}_2\text{CHCl}$ ), 3.81 (dd, 1H:  $J = 9.7, 11.0$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.98 (dd, 1H:  $J = 4.8, 11.0$  Hz,  $\text{CHH}_2\text{CO}_2\text{R}$ ), 5.33 (m, 2H:  $\text{CH}_2\text{Se}$ ), 7.65 (m, 3H: Ar CH's), 8.02 (m, 2H: Ar CH's)

### Procedure for allylic etherification (1.57) and methoxylactonization (1.58).

3-hexenoic acid (0.438 mmol) was dissolved in MeOH (1 mL). To this solution was added PhSeCl (10 mol%, 0.438 mmol) and NCS (0.531 mmol). The orange solution went colorless upon stirring and the mixture was allowed to react for 3.5 hours. The

reaction was diluted with  $\text{CH}_2\text{Cl}_2$  (4 mL) and extracted with  $\text{H}_2\text{O}$  ( $2 \times 2$  mL). The organic phase was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification of the crude mixture of allyl chloride **1.34a**, **1.57**, and **1.58** *via* flash chromatography (95:5 hexane:ethyl acetate) afforded an inseparable mixture of **1.57** and **1.58**. A similar reaction was also run in MeOH (2 mL) and the procedure was followed as above. This decreased the amount of allyl chloride product, **1.34a**, and increased the production of **1.57**.

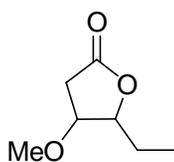


(*E*)-4-methoxyhex-2-enoic acid

**1.57** (srm2041)

Yield: 18% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.05 (t, 3H:  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.91 (m, 2H:  $\text{CH}_2\text{CH}_3$ ), 3.78 (s, 3H:  $\text{OCH}_3$ ), 4.40 (m, 1H:  $\text{OCHR}_2$ ), 6.05 (dd, 1H:  $J = 1.2, 15.5$  Hz,  $\text{CH}=\text{CHCO}_2\text{H}$ ), 6.92 (dd, 1H:  $J = 7.6, 15.5$  Hz,  $\text{CH}=\text{CHCO}_2\text{H}$ ).



5-ethyl-4-methoxydihydrofuran-2(3H)-one

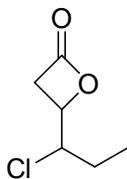
**1.58** (srm2041)

Yield: 18% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.11 (t, 3H:  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.85 (m, 1H:  $\text{CHHCH}_3$ ), 2.11 (dq, 1H:  $J = 7.3, 10.4$  Hz,  $\text{CHHCH}_3$ ), 2.84 (dd, 1H:  $J = 9.5, 16.5$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.18 (dd, 1H:  $J = 3.4, 16.2$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.77 (s, 3H:  $\text{OCH}_3$ ), 4.03 (td, 1H:  $J = 3.2, 8.2$  Hz,  $\text{R}_2\text{CHOCH}_3$ ), 4.40 (m, 1H:  $\text{R}_2\text{CHO}_2\text{CR}$ ).

### General procedure for the base-promoted chlorolactonization.

To a solution of 3-hexenoic acid (0.78 mmol) in CH<sub>3</sub>CN (3 mL) was added PhSeCl (10 mol%, 0.078 mmol) and the DIEA (0.78 mmol). Following this, NCS (0.86 mmol) was added to the reaction and it was allowed to stir for 2 days at room temperature. The reaction completion was verified by <sup>1</sup>H NMR spectroscopy and the solution was concentrated to < 1 mL, and diluted with Et<sub>2</sub>O (20 mL). The organic phase was extracted with 10% HCl (2 × 7 mL) and dried over MgSO<sub>4</sub>. Concentration of the reaction mixture afforded a mixture of **1.34a**, **1.45**, **1.46**, and **1.78** (1:2.4:2.4:1.7), respectively. A similar procedure was used for other bases as well the results are reported in Table 1.6.



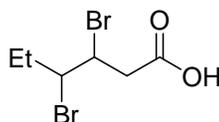
4-(1-chloropropyl)oxetan-2-one  
**1.78** (srm1214)  
yield: 23% by <sup>1</sup>H NMR

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.13 (t, 3H: *J* = 7.3 Hz, CH<sub>3</sub>), 1.90 (m, 1H: CHHCH<sub>3</sub>), 2.04 (m, 1H: CHHCH<sub>3</sub>), 3.40 (dd, 1H: *J* = 4.1, 16.7 Hz, CHHCO<sub>2</sub>R), 3.61 (dd, 1H: *J* = 5.8, 16.7 Hz, CHHCO<sub>2</sub>R), 4.00 (ddd, 1H: *J* = 3.5, 7.7, 9.0 Hz, R<sub>2</sub>CHCl), 4.52 (m, 1H: R<sub>2</sub>CHO<sub>2</sub>CR).

### Procedure for the formation of **1.81**.

To a solution of 3-hexenoic acid (200 mg, 1.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -78 °C was added Br<sub>2</sub> (1.8 mL of 0.97 M soln in CH<sub>2</sub>Cl<sub>2</sub>, 1.75 mmol) *via* syringe pump over 1 hour. The solution was allowed to warm to room temperature and stirred for 16

hours. The reaction was quenched with saturated NaHSO<sub>3</sub> solution (5 mL) and then diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The organic layer was extracted with H<sub>2</sub>O (2 × 3 mL) and dried over MgSO<sub>4</sub>. The solution was concentrated *in vacuo* and the crude acid **1.81** was isolated in 76% yield.



2,3-dibromohexanoic acid

**1.81** (srm2184)

colorless oil

yield: 76%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.12 (t, 3H: *J* = 7.3 Hz, CH<sub>3</sub>), 2.00 (sept, 1H: *J* = 7.4 Hz, CHHCH<sub>3</sub>), 2.25 (qd, 1H: *J* = 2.9, 7.3 Hz, CHHCH<sub>3</sub>), 3.05 (dd, 1H: *J* = 9.5, 17.0 Hz, CHHCO<sub>2</sub>) 3.55 (dd, 1H: *J* = 3.0, 17.1 Hz, CHHCO<sub>2</sub>), 4.25 (td, 1H: *J* = 3.0, 8.5 Hz, CHBr), 4.47 (td, 1H: *J* = 3.0, 9.2 Hz, CHBr) 10.6 (br. s, 1H: CO<sub>2</sub>H).

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 11.5 (CH<sub>3</sub>), 30.6 (CH<sub>2</sub>CH<sub>3</sub>), 43.4 (CH<sub>2</sub>CO<sub>2</sub>), 50.4 (BrCHCH<sub>2</sub>CO<sub>2</sub>H) 60.3 (CH<sub>3</sub>CH<sub>2</sub>CHBr), 176.6 (CO<sub>2</sub>).

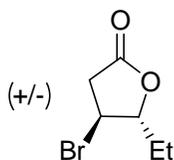
FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub> 3053 (broad), 2983, 1716, 1259, 1153.

HRMS calcd for C<sub>6</sub>H<sub>11</sub>Br<sub>2</sub>O<sub>2</sub> [M+H] 272.9126, found 272.9114

### General procedure for bromolactonization of β,γ- or γ,δ-unsaturated acids

Diphenyl diselenide (5 mol%, 0.05 mmol) was dissolved in CH<sub>3</sub>CN (5 mL, stored over 4Å mol sieves), producing a yellow solution. The unsaturated acid (1.00 mmol) was added, and the resulting mixture was cooled to -30 °C. Next, *N*-bromosuccinimide (1.1 mmol) was added and the resulting reaction mixture was stirred for the reported time. Completion of the reaction was confirmed by <sup>1</sup>H NMR spectroscopy. This solution was concentrated to < 1 mL, and Et<sub>2</sub>O (10 mL) was

added. The ether was decanted from the solid and washed H<sub>2</sub>O (2 × 3 mL). The resulting ether layer was dried over MgSO<sub>4</sub>, concentrated, and the residue was purified by flash chromatography (100% methylene chloride). Isolated yields are reported in Table 1.8.



4-bromo-5-ethyldihydrofuran-2(3*H*)-one  
**1.83a**<sup>73</sup> (<sup>1</sup>H: srm2227, <sup>13</sup>C: srm2114)  
colorless oil  
Yield: 52%

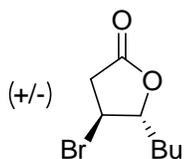
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.10 (t, 3H: *J* = 7.5 Hz, CH<sub>3</sub>), 1.71 (m, 1H: CHHCH<sub>3</sub>), 1.86 (m, 1H, CHHCH<sub>3</sub>), 2.92 (dd, 1H: *J* = 6.9, 18.3 Hz, CHHCO<sub>2</sub>) 3.20 (dd, 1H: *J* = 7.7, 18.2 Hz, CHHCO<sub>2</sub>), 4.19 (ddd, 1H: *J* = 5.6, 7.0, 7.9 Hz, CHBr), 4.60 (dt, 1H: *J* = 5.1, 8.0 Hz, CHO).

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 10.0 (CH<sub>3</sub>), 26.6 (CH<sub>2</sub>CH<sub>3</sub>), 39.7 (CH<sub>2</sub>CO<sub>2</sub>), 42.7 (CHBr) 89.4 (CHO), 173.5 (CO<sub>2</sub>);

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub> 2974, 1785, 1461, 1407, 1352, 1168, 1097.

HRMS calcd for C<sub>6</sub>H<sub>13</sub>NO<sub>2</sub>Br [M+NH<sub>4</sub>] 210.0130, found 210.0134.

**Chiral GC Column:** Chiraldex TA **Program:** Initial Hold at 50 °C for 5 min, ramp of 1 °C/minute until 120 °C, final hold for 50 minutes. **Retention Times:** 83.4 and 92.0 minutes.



4-bromo-5-butylidihydrofuran-2(3*H*)-one

**1.83b** (srm2241\_5)

colorless oil

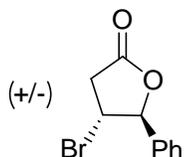
Yield: 61% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 0.95 (t, 3H: *J* = 7.1 Hz, CH<sub>3</sub>), 1.36-1.56 (m, 4H: CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.66 (m, 1H: CHHCHO), 1.81 (m, 1H: CHHCHO) 2.92 (dd, 1H: *J* = 7.9, 18.3 Hz, CHHCO<sub>2</sub>) 3.19 (dd, 1H: *J* = 7.7, 18.3 Hz, CHHCO<sub>2</sub>), 4.18 (m, 1H: CHBr), 4.64 (dt, 1H: *J* = 5.3, 7.9 Hz, CHO).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 14.2 (CH<sub>3</sub>), 22.7 (CH<sub>2</sub>CH<sub>3</sub>), 27.8 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 33.3 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 39.7 (CH<sub>2</sub>CO<sub>2</sub>), 43.3 (CHBr), 88.3 (CHO), 173.5 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub> 2960, 2935, 1787, 1259, 1207, 1168.

**HRMS** calcd for C<sub>8</sub>H<sub>14</sub>BrO<sub>2</sub> [M+H] 221.0177, found 221.0184.



4-bromo-5-phenyldihydrofuran-2(3*H*)-one

**1.83c**<sup>73,74</sup> (srm2131)

pale orange solid

Yield: 90%

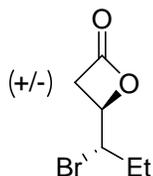
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.00 (dd, 1H: *J* = 6.4, 18.1 Hz, CHHCO<sub>2</sub>) 3.26 (dd, 1H: *J* = 7.3, 18.1 Hz, CHHCO<sub>2</sub>), 4.39 (ddd, 1H: *J* = 5.3, 6.4, 7.6 Hz, CHBr), 5.69 (d, 1H: *J* = 5.3 Hz, CHO) 7.42 (m, 5H: Ar CH's).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 39.2 (CHBr), 46.0 (CH<sub>2</sub>), 88.3 (CHO), 125.8 (Ar CH) 129.5 (Ar CH), 129.8 (Ar CH), 136.3 (quat. Ar C) 173.4 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub> 3064, 3067, 2927, 1789, 1496, 1406, 1261, 1159, 1047.

**HRMS** calcd for C<sub>10</sub>H<sub>10</sub>BrO<sub>2</sub> [M+H] 240.9864, found 240.9863.

**Chiral GC Column:** Chiraldex TA **Program:** Initial Hold at 50 °C for 5 min, ramp of 1 °C/minute until 120 °C, final hold for 200 minutes. **Retention Times:** 222.3 and 225.4 minutes.



4-(1-bromopropyl)oxetan-2-one

**1.84a**<sup>73,75</sup> (srm2223)

colorless oil

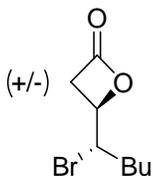
yield: 15% by <sup>1</sup>H NMR

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.14 (t, 3H: *J* = 7.4 Hz, CH<sub>3</sub>), 1.83 (m, 1H: CHHCH<sub>3</sub>), 2.13 (m, 1H: CHHCH<sub>3</sub>), 3.35 (dd, 1H: *J* = 4.2, 16.7 Hz, CHHCO<sub>2</sub>) 3.65 (dd, 1H: *J* = 5.7, 16.7 Hz, CHHCO<sub>2</sub>), 3.99 (td, 1H: *J* = 3.4, 8.9 Hz, CHBr), 4.54 (ddd, 1H: *J* = 4.1, 5.6, 8.8 Hz, CHO).

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 11.9 (CH<sub>3</sub>), 28.3 (CH<sub>2</sub>CH<sub>3</sub>), 44.2 (CH<sub>2</sub>CO<sub>2</sub>), 57.2 (CHBr), 71.7 (CHO), 167.2 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub> 2985, 1836, 1411, 1271, 1114.

**HRMS** calcd for C<sub>6</sub>H<sub>13</sub>NO<sub>2</sub>Br [M+NH<sub>4</sub>] calcd 210.0130, found 210.0132.



4-(1-bromopentyl)oxetan-2-one

**1.84b** (srm224\_4)

colorless oil

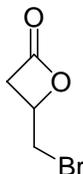
Yield: 61% (combined isomers)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.95 (t, 3H: *J* = 7.1 Hz, CH<sub>3</sub>), 1.42 (m, 2H: CH<sub>2</sub>CH<sub>3</sub>), 1.61 (m, 2H: CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.79 (m, 1H: CHHCHO), 2.06 (m, 1H: CHHCHO) 3.35 (dd, 1H: *J* = 4.2, 16.8 Hz, CHHCO<sub>2</sub>) 3.64 (dd, 1H: *J* = 5.7, 16.6 Hz, CHHCO<sub>2</sub>), 4.03 (td, 1H: *J* = 3.4, 9.1 Hz, CHBr), 4.53 (app. p, 1H: *J* = 4.7 Hz, CHO).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  14.3 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_2\text{CH}_3$ ), 29.4 ( $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 34.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 44.1 ( $\text{CH}_2\text{CO}_2$ ), 55.5 ( $\text{CHBr}$ ), 72.0 ( $\text{CHO}$ ), 167.3 ( $\text{CO}_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$  2960, 2933, 1834, 1265, 1114.

HRMS calcd for  $\text{C}_8\text{H}_{14}\text{BrO}_2$  [ $\text{M}+\text{H}$ ] 221.0177, found 221.0189.



4-(bromomethyl)oxetan-2-one

**1.84d**<sup>76,77</sup> (srm2144)

colorless oil

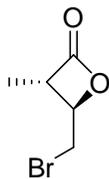
Yield: 48%

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.36 (dd, 1H:  $J = 4.1, 16.6$ ,  $\text{CHH}$ ), 3.62 (m, 2H: one of  $\text{CH}_2\text{Br}$ , one of  $\text{CH}_2\text{CO}_2$ ), 3.73 (dd, 1H:  $J = 4.8, 11.6$  Hz,  $\text{CHH}$ ), 4.73 (p, 1H:  $J = 4.6$  Hz,  $\text{CHO}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  31.7 ( $\text{CH}_2\text{CO}_2\text{R}$ ), 43.1 ( $\text{CH}_2\text{Br}$ ), 68.0 ( $\text{CHO}$ ), 166.1 ( $\text{CO}_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$  1838, 1403, 1111.

HRMS calcd for  $\text{C}_4\text{H}_6\text{BrO}_2$  [ $\text{M}+\text{H}$ ] 164.9551, found 164.9569.



4-(bromomethyl)-3-methyloxetan-2-one (major diastereomer)

*anti*-**1.84e**<sup>75</sup> (srm2292)

isolated as a 4.4:1 mixture of diastereomers

colorless oil

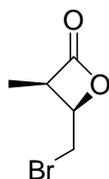
Yield: 34% (combined diastereomers)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.49 (d, 3H:  $J = 7.6$  Hz,  $\text{CH}_3$ ), 3.52 (dd, 1H:  $J = 4.1, 7.6$  Hz,  $\text{CHCH}_3$ ), 3.54 (dd, 1H:  $J = 7.9, 10.8$  Hz,  $\text{CHHBr}$ ), 3.73 (dd, 1H:  $J = 4.8, 10.7$  Hz,  $\text{CHHBr}$ ), 4.41 (m, 1H:  $\text{CHO}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  12.9 ( $\text{CH}_3$ ), 31.6 ( $\text{CH}_2\text{Br}$ ), 52.0 ( $\text{CHCH}_3$ ), 76.2 ( $\text{CHO}$ ), 170.5 ( $\text{CO}_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$  1832, 1458, 1384, 1209, 1110, 1051.

HRMS calcd for  $\text{C}_5\text{H}_8\text{BrO}_2$   $[\text{M}+\text{H}]$  178.9708, found 178.9716.



4-(bromomethyl)-3-methyloxetan-2-one (minor diastereomer)

*syn*-**1.84e**<sup>75</sup> (srm2292)

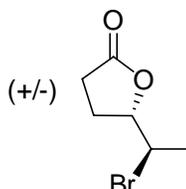
isolated as a 4.4:1 mixture of diastereomers

colorless oil

Yield: 34% (combined diastereomers)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.41 (d, 3H:  $J = 7.7$  Hz,  $\text{CH}_3$ ), 3.50 (m, 1H:  $\text{CHHBr}$ ), 3.67 (dd, 1H:  $J = 5.8, 10.5$  Hz,  $\text{CHHBr}$ ), 3.91 (dq, 1H:  $J = 6.4, 7.9$  Hz,  $\text{CHCH}_3$ ), 4.82 (dt, 1H:  $J = 5.8, 8.2$  Hz,  $\text{CHO}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  8.3 ( $\text{CH}_3$ ), 27.9 ( $\text{CH}_2\text{Br}$ ), 48.5 ( $\text{CHCH}_3$ ), 73.1 ( $\text{CHO}$ ), 171.2 ( $\text{CO}_2$ ).



5-(1-bromoethyl)dihydrofuran-2(3H)-one (major isomer)

*syn*-**1.86a** (srm2288)

isolated as a 5:1 *syn:anti* mixture resulting from a *cis:trans* mixture of starting olefin

colorless oil

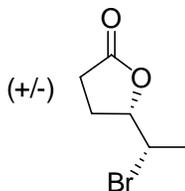
Yield: 33% (combined isomers)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.78 (d, 3H:  $J = 6.6$  Hz,  $\text{CH}_3$ ), 2.17 (m, 1H:  $\text{CHHCHO}$ ), 2.40-2.50 (m, 1H:  $\text{CHHCHO}$ ), 2.57 (dd, 1H:  $J = 8.7, 18.0$  Hz,  $\text{CHHCO}_2$ ), 2.63 (m, 1H:  $\text{CHHCO}_2$ ), 4.16 (p, 1H:  $J = 6.8$  Hz,  $\text{CHBr}$ ), 4.48 (q, 1H:  $J = 6.97$  Hz,  $\text{CHO}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  22.1 ( $\text{CH}_3$ ), 25.6 ( $\text{CH}_2\text{CHO}$ ), 28.5 ( $\text{CH}_2\text{CO}_2$ ), 50.4 ( $\text{CH}_2\text{Br}$ ), 82.5 (CHO), 176.3 ( $\text{CO}_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$  2993, 2977, 1780, 1176.

HRMS calcd for  $\text{C}_6\text{H}_{10}\text{BrO}_2$  [ $\text{M}+\text{H}$ ] 192.9864, found 192.9859.



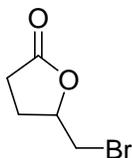
5-(1-bromoethyl)dihydrofuran-2(3H)-one (minor isomer)  
*anti*-**1.86a** (srm2288)

isolated as a 5:1 *syn:anti* mixture resulting from a *cis:trans* mixture of starting olefin  
colorless oil

Yield: 33% (combined isomers)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.78 (d, 3H:  $J = 6.6$  Hz,  $\text{CH}_3$ ), 2.17 (m, 1H:  $\text{CHHCHO}$ ), 2.39 (m, 1H:  $\text{CHHCHO}$ ), 2.50-2.54 (m, 2H:  $\text{CH}_2\text{CO}_2$ ), 4.22 (dd, 1H:  $J = 3.9, 7.2$  Hz,  $\text{CHBr}$ ), 4.61 (ddd, 1H:  $J = 3.7, 6.8, 7.9$  Hz, CHO).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  21.1 ( $\text{CH}_3$ ), 24.9 ( $\text{CH}_2\text{CHO}$ ), 28.3 ( $\text{CH}_2\text{CO}_2$ ), 50.1 ( $\text{CH}_2\text{Br}$ ), 81.7 (CHO), 176.1 ( $\text{CO}_2$ ).



5-(bromomethyl)dihydrofuran-2(3H)-one

**1.86b**<sup>76,78</sup> (srm2143)

colorless oil

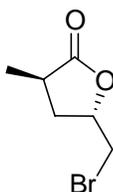
Yield: 55%

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.14 (m, 1H:  $\text{CHHCHO}$ ), 2.46 (m, 1H:  $\text{CHHCHO}$ ), 2.53-2.73 (m, 2H:  $\text{CH}_2\text{CO}_2$ ), 3.55 (dd, 1H:  $J = 5.9, 10.8$  Hz,  $\text{CHHBr}$ ), 3.59 (dd, 1H:  $J = 4.4, 10.8$  Hz,  $\text{CHHBr}$ ), 4.76 (p, 1H:  $J = 6.7$  Hz, CHO).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  26.6 ( $\text{CH}_2\text{CHO}$ ), 28.8 ( $\text{CH}_2\text{Br}$ ), 34.5 ( $\text{CH}_2\text{CO}_2$ ), 78.2 (CHO), 176.6 ( $\text{CO}_2$ ).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$  2965, 1781, 1421, 1167, 1023.

**HRMS** calcd for C<sub>5</sub>H<sub>8</sub>BrO<sub>2</sub> [M+H] 178.9708, found 178.9713.



5-(bromomethyl)-3-methyldihydrofuran-2(3*H*)-one (major diastereomer)

**1.86c**<sup>79</sup> (srm2287)

isolated as a 3:1 mixture of diastereomers

colorless oil

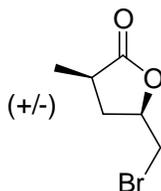
Yield: 90% (combined diastereomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.33 (d, 3H:  $J$  = 6.9 Hz, CH<sub>3</sub>), 1.73 (m, 1H: CHHCHO), 2.66 (m, 1H: CHHCHO), 2.75 (m, 1H: CHCH<sub>3</sub>), 3.51 (ddd, 1H:  $J$  = 1.0, 6.4, 10.7 Hz, CHHBr), 3.61 (ddd, 1H:  $J$  = 1.2, 4.7, 10.8 Hz, CHHBr), 4.59 (sext, 1H:  $J$  = 6.28 Hz, CHO).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>)  $\delta$  15.0 (CH<sub>3</sub>), 33.3 (CH<sub>2</sub>Br), 35.5 (CH<sub>2</sub>CHO), 35.6 (CHCH<sub>3</sub>), 75.8 (CHO), 178.3 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$  2977, 1778, 1423, 1178, 1157, 1018.

**HRMS** calcd for C<sub>6</sub>H<sub>10</sub>BrO<sub>2</sub> [M+H] 192.9864, found 192.9868.



5-(bromomethyl)-3-methyldihydrofuran-2(3*H*)-one (minor diastereomer)

**1.86c** (srm2287)

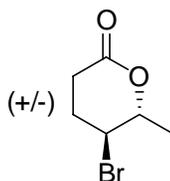
isolated as a 3:1 mixture of diastereomers

colorless oil

Yield: 90% (combined diastereomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.33 (d, 3H:  $J$  = 6.9 Hz, CH<sub>3</sub>), 2.11 (dt, 1H:  $J$  = 8.5, 13.5 Hz, CHHCHO), 2.43 (ddd, 1H:  $J$  = 4.1, 9.4, 13.0 Hz, CHHCHO), 2.85 (m, 1H: CHCH<sub>3</sub>), 3.53 (m, 2H: CH<sub>2</sub>Br), 4.77 (m, 1H: CHO).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  16.1 ( $\text{CH}_3$ ), 33.7 ( $\text{CH}_2\text{Br}$ ), 33.7 ( $\text{CHCH}_3$ ), 33.7 ( $\text{CH}_2\text{CHO}$ ), 75.7 ( $\text{CHO}$ ), 179.1 ( $\text{CO}_2$ ).



5-bromo-6-methyltetrahydro-2*H*-pyrano-2-one (major isomer)  
**1.87a** (srm2295)

isolated as a 10:1 *syn:anti* mixture resulting from a *cis:trans* mixture of starting olefin  
colorless oil

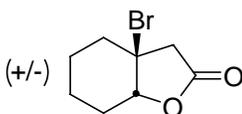
Yield: 33% (combined isomers)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.56 (d, 3H:  $J = 6.1$  Hz,  $\text{CH}_3$ ), 2.33 (m, 1H:  $\text{CHHCHBr}$ ), 2.51 (m, 1H:  $\text{CHHCHBr}$ ), 2.61 (m, 1H:  $\text{CHHCO}_2$ ), 2.81 (dt, 1H:  $J = 6.7, 17.8$  Hz,  $\text{CHHCO}_2$ ), 3.98 (td, 1H:  $J = 5.3, 8.5$  Hz,  $\text{CHBr}$ ), 4.59 (dq, 1H:  $J = 6.4, 8.5$  Hz,  $\text{CHO}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  20.8 ( $\text{CH}_3$ ), 29.5 ( $\text{CH}_2\text{Br}$ ), 29.9 ( $\text{CH}_2\text{CO}_2$ ), 47.4 ( $\text{CHBr}$ ), 80.8 ( $\text{CHO}$ ), 170.2 ( $\text{CO}_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$  1735, 1382, 1252, 1135.

HRMS calcd for  $\text{C}_6\text{H}_{10}\text{BrO}_2$  [ $\text{M}+\text{H}$ ] 192.9864, found 192.9868.



3a-bromohexahydrobenzofuran-2(3*H*)-one  
**1.89**<sup>76,78b</sup> (srm2216)

colorless oil

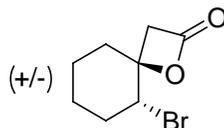
Yield: 41% (combined isomers)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.59 (m, 4H:  $\text{BrCCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO}$ ), 1.88-2.11 (m, 3H:  $\text{CH}_2\text{CHO}$  and one of  $\text{CH}_2\text{CBr}$ ), 2.22 (dt,  $J = 5.4, 14.8$  Hz, 1H:  $\text{CHHCHBr}$ ), 2.96 (d,  $J = 17.0$  Hz, 1H:  $\text{CHHCO}_2$ ), 3.08 (d,  $J = 17.1$  Hz, 1H:  $\text{CHHCO}_2$ ), 4.70 (t,  $J = 4.4$  Hz, 1H:  $\text{CHO}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  20.01 ( $\text{CH}_2$ ), 22.83 ( $\text{CH}_2$ ), 25.94 ( $\text{CH}_2$ ), 37.61 ( $\text{CH}_2$ ), 47.33 ( $\text{CH}_2\text{CO}_2$ ), 59.12 ( $\text{CBr}$ ), 84.82 ( $\text{CHO}$ ), 173.85 ( $\text{CO}_2$ ).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$  2948, 2867, 1789, 1450, 1260, 1161, 1105.

**HRMS** calcd for C<sub>8</sub>H<sub>12</sub>BrO<sub>2</sub> [M+H] 219.0021, found 221.0016.



5-bromo-1-oxaspiro[3,5]nonan-2-one  
**1.90**<sup>73,76,78b</sup> (srm2257)

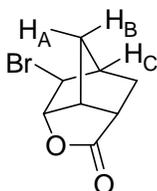
colorless oil

Yield: 41% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.50-1.70 (m, 4H: cyclohexyl CH's), 1.75 (m, 3H: cyclohexyl CH's), 2.33 (m, 1H: cyclohexyl CH's), 3.12 (d, 1H:  $J = 17.6$  Hz, CHHCO<sub>2</sub>), 3.47 (d, 1H:  $J = 17.6$  Hz, CHHCO<sub>2</sub>), 4.37 (dd, 1H:  $J = 3.8, 6.7$  Hz, CHBr).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>)  $\delta$  18.8 (cyclohexyl CH<sub>2</sub>), 22.0 (cyclohexyl CH<sub>2</sub>), 22.3 (cyclohexyl CH<sub>2</sub>), 32.5 (cyclohexyl CH<sub>2</sub>), 32.8 (CH<sub>2</sub>CO<sub>2</sub>), 47.0 (CHBr), 54.6 (R<sub>3</sub>CO), 166.9 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$  1828.



**1.92**<sup>80</sup> (srm2274)

colorless oil

Yield: 78%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.77 (dq, 1H:  $J = 1.73, 11.5$  Hz, CH<sub>B</sub>), 1.83 (dt, 1H:  $J = 2.0, 13.7$  Hz, *endo* CHHCHCO<sub>2</sub>), 2.17 (ddd, 1H:  $J = 4.2, 11.3, 13.7$  Hz, *exo* CHHCHCO<sub>2</sub>), 2.37 (dd, 1H:  $J = 1.9, 11.7$  Hz, CH<sub>A</sub>), 2.60 (dd, 1H:  $J = 4.7, 11.3$  Hz, CHCO<sub>2</sub>), 2.71 (d, 1H:  $J = 2.7$  Hz, CH<sub>C</sub>), 3.27 (tq, 1H:  $J = 1.5, 4.8$  Hz, CHCHO), 3.9 (d, 1H:  $J = 2.3$  Hz, CHBr), 4.96 (d, 1H:  $J = 5.0$  Hz, CHO).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>)  $\delta$  33.9 (CH<sub>2</sub>CO<sub>2</sub>), 35.7 (CH<sub>A</sub>H<sub>B</sub>), 37.5 (CHCO<sub>2</sub>), 45.4 (CHCHBr), 45.8 (CHCHO), 53.4 (CHBr), 87.6 (CHO), 179.1 (CO<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\text{max}}$  2981, 1785, 1184, 1170, 1014.

**HRMS** calcd for C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub> [M+NH<sub>4</sub>] 234.0130, found 234.0134

**Procedure for bromolactonization of 3-hexenoic acid using PhSeBr.**

PhSeBr (5 mol%, 0.02 mmol) was dissolved in CD<sub>3</sub>CN (600  $\mu$ L). The 3-hexenoic acid (0.17 mmol) was then added and the resulting mixture was cooled to -30 °C. Next, *N*-bromosuccinimide (0.18 mmol) was added and the resulting reaction mixture was stirred for 6 hours at -30 °C. Completion and the formation of **1.79** and **1.81** (4:1), respectively, was confirmed by <sup>1</sup>H NMR spectroscopy. A similar procedure was employed when using PhSe-phthalimide as the catalyst, where a mixture of **1.79** and **1.80** (2:1) was observed

**Procedure for the bromolactonization of 3-hexenoic acid using PhSeSePh and Br<sub>2</sub>.**

To a dried NMR tube was added 3-hexenoic acid (0.17 mmol) and PhSeSePh (5 mol%, 0.008 mmol) in CD<sub>3</sub>CN (600  $\mu$ L) and the resulting solution was cooled to -30 °C. Then bromine (0.18 mmol) was added to the solution which was allowed to react for 4 hours, after which time the products **1.83a** and **1.81** were observed by <sup>1</sup>H NMR spectroscopy. Then, the reaction was warmed to room temperature and allowed to react another 18 hours. The product ratio of **1.83a** and **1.81** were again determined by <sup>1</sup>H NMR spectroscopy. A similar procedure was run in the absence of

PhSeSePh and both products were obtained, albeit in different ratios. The ratios of the products are reported in Scheme 1.39.

**Procedure for bromolactonization of 3-hexenoic acid using chiral catalyst 1.103.**

To a solution of 3-hexenoic acid (1.0 mmol) in CH<sub>3</sub>CN (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added catalyst **1.103** (0.05 mmol) at room temperature. Then, NBS (1.1 mmol) was added to the reaction and it was stirred for 1.5 hours. After completion of the reaction was confirmed by <sup>1</sup>H NMR spectroscopy, the reaction was concentrated to <1 mL and diluted with Et<sub>2</sub>O (10 mL). The organic phase was extracted with H<sub>2</sub>O (2 × 5 mL), dried over MgSO<sub>4</sub> and concentrated. Bromolactones **1.83a**, **1.84a**, and **1.81** were isolated in the crude product mixture. Purification *via* flash chromatography afforded **1.83a** in 54% yield, and the enantiomeric excess was determined using chiral phase GC, where a 0% ee was observed. Bromolactone **1.83c** was also isolated in 53% yield and 1.6% ee using the same procedure.

**Procedure for bromolactonization of 3-hexenoic acid using chiral catalyst 1.103 and Br<sub>2</sub>.**

A solution of bromine (0.97 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.05 mmol) was added to catalyst **1.103** (0.05 mmol) dissolved in CH<sub>3</sub>CN (5 mL). The mixture was stirred for 5 minutes, and then 3-hexenoic acid (1.00 mmol) and NBS (1.10 mmol) were added to the solution. After stirring for 18 hours, the reaction was concentrated and the residue was diluted with Et<sub>2</sub>O (10 mL). The organic phase was extracted with H<sub>2</sub>O (2 × 5 mL) and dried

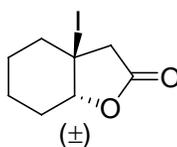
with MgSO<sub>4</sub>. The organic solution was concentrated and the products **1.831** and **1.81** were obtained. **1.83a** was subjected to chiral phase gas chromatography where a 0% ee was obtained. Product **1.83c** was also obtained using this procedure. Analysis of this compound *via* chiral stationary phase gas chromatography revealed a 2.8% ee.

**Procedure for variable temperature NMR studies.**

3-hexenoic acid (0.32 mmol) was added to a solution of PhSeSePh (0.016 mmol) in CD<sub>3</sub>CN (600 μL) and cooled to -30 °C. NBS (0.35 mmol) was then added and the mixture was immediately cooled to -78 °C to freeze the reaction and prevent reaction prior observation by the <sup>1</sup>H NMR spectrometer. The NMR probe was precooled to -30 °C, and the NMR tube was inserted into the probe. The reaction was periodically monitored and the probe was slowly warmed to room temperature by increasing the temperature in 10 °C intervals. A replica of this reaction was also run in the absence of PhSeSePh following the same protocol.

**Procedure for iodolactonization of 1.88.**

Diphenyl diselenide (5 mol%, 0.02 mmol) was dissolved in CD<sub>3</sub>CN (600 μL), producing a yellow solution. Acid **1.88** (0.32 mmol) was added at room temperature. Next, *N*-iodosuccinimide (0.35 mmol) was added and the resulting reaction mixture was allowed to react for 1.5 hours. At this point, products **1.93** and **1.94** were observed by <sup>1</sup>H NMR spectroscopy. A similar procedure was used without diphenyl diselenide where both products were also observed.

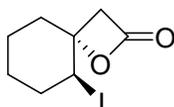


3a-iodohexahydrobenzofuran-2(3H)-one

**1.93** (srm2200)

yield: 63% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.56 -1.80 (m, 4H: cyclohexyl CH's), 1.89 - 2.00 (m, 2H: cyclohexyl CH's), 2.15 (m, 1H:  $\text{CHHCICH}_2\text{CO}_2\text{R}$ ), 2.48 (td, 1H:  $J = 4.2, 9.3$  Hz,  $\text{CHHCICH}_2\text{CO}_2\text{R}$ ), 3.19 (d, 1H:  $J = 16.4$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.41 (c, 1H:  $J = 16.4$  Hz,  $\text{CHHCO}_2\text{R}$ ), 4.59 (dd, 1H:  $J = 2.9, 3.5$  Hz,  $\text{CHO}$ ).



5-iodo-1-oxaspiro[3.5]nonan-2-one

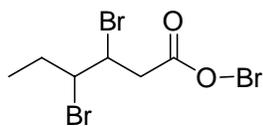
**1.94** (srm2200)

yield: 37% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.56 -1.80 (m, 4H: cyclohexyl CH's), 1.89 - 2.00 (m, 2H: cyclohexyl CH's), 2.25 (m, 1H:  $\text{CHHCHI}$ ), 3.00 (d, 1H:  $J = 17.0$  Hz,  $\text{CHHCO}_2\text{R}$ ), 3.19 (d, 1H:  $J = 17.0$  Hz,  $\text{CHHCO}_2\text{R}$ ), 4.83 (t, 1H:  $J = 3.9$  Hz,  $\text{R}_2\text{CHI}$ ).

#### Procedure for the synthesis of 1.95.

Dibrominated acid **1.81** (0.064) was isolated and dissolved in  $\text{CD}_3\text{CN}$  (600  $\mu\text{L}$ ). Then  $\text{PhSeSePh}$  (5 mol%, 0.03 mmol) and NBS (0.07 mmol) were added to the reaction and it was monitored by  $^1\text{H}$  NMR spectroscopy. Within 8 hours, the NBS was completely consumed and **1.95** was product identified.



3,4-dibromohexanoic hypobromous anhydride

**1.95** (srm2235)

yield: >95% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  1.09 (t, 3H:  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.95 (m, 1H:  $\text{CHHCH}_3$ ), 2.13 (m, 1H:  $\text{CHHCH}_3$ ), 2.94 (dd, 1H:  $J = 9.8, 17.1$  Hz,  $\text{CHHCO}_2\text{Br}$ ), 3.33 (dd, 1H:  $J = 3.2, 17.0$  Hz,  $\text{CHHCO}_2\text{Br}$ ), 4.36 (ddd, 1H:  $J = 3.2, 6.6, 9.2$  Hz,  $\text{BrCHCH}_2\text{CH}_3$ ), 4.56 (ddd, 1H:  $J = 2.9, 6.8, 9.9$  Hz,  $\text{BrCHCH}_2\text{CO}_2\text{Br}$ )

## 1.6 References

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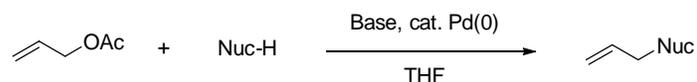
## **Chapter 2**

### *Palladium-Catalyzed Decarboxylative Allylic Functionalization*

## 2.1 Introduction to Tsuji-Trost Allylation

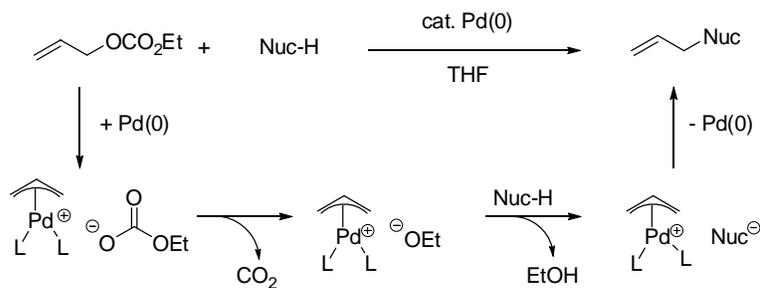
### *Historical Background of Pd-Catalyzed C-C Bond Forming Reactions*

Carbon—carbon bond formation plays a vital role in organic synthesis. To achieve the syntheses of more complex molecules, new methodologies are being developed which allow for the construction of new carbon—carbon bonds. Particular emphasis has been placed on those methods which utilize mild reaction conditions. In this way, transition metal-catalyzed processes have revolutionized organic synthesis. Palladium has received a great deal of attention due to its ability to effect a number of cross-coupling reactions, including the Stille,<sup>1</sup> Suzuki,<sup>2</sup> and Sonogashira<sup>3</sup> reactions.<sup>4</sup> These processes were first reported between 1975 and 1979, and have expanded the repertoire of carbon—carbon bond construction. Another important reaction of this type is the palladium-mediated allylic substitution reaction, otherwise known as the Tsuji-Trost reaction. Seminal work by Tsuji in 1965 disclosed the nucleophilic substitution of palladium- $\pi$ -allyl complexes with stabilized carbon nucleophiles, such as sodiomalonates.<sup>5</sup> However, it was not until 1970 that the reaction was rendered catalytic in Pd(0).<sup>6</sup> Initial research in this area used allylic acetates as the precursors to Pd- $\pi$ -allyl electrophiles, but this method required the addition of a stoichiometric amount of base to generate the necessary carbanion for nucleophilic attack (Scheme 2.1).<sup>7</sup>



### Scheme 2.1

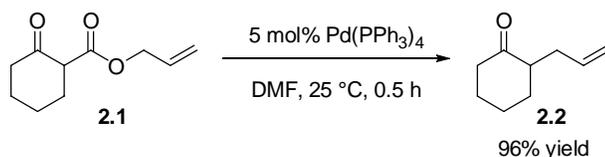
The use of allylic carbonates has improved this process by eliminating the addition of a base. Instead, the base is generated *in situ* upon decarboxylation of the carbonate anion, leaving behind the corresponding alkoxide (Scheme 2.2).<sup>8</sup> The alkoxide base can then deprotonate the nucleophile, which must be sufficiently acidic so that proton transfer can occur. The allylic carbonates provide the same product as allylic acetates upon nucleophilic attack. The use of carbonates is also advantageous as they are more reactive than the allylic acetates.



### Scheme 2.2

Further progress in this area led to the incorporation of allyl  $\beta$ -ketoesters as substrates for Pd(0)-catalyzed allylic substitution.<sup>9</sup> Here, decarboxylation reveals an enolate nucleophile *in situ*, which can then attack the electrophilic allyl moiety (Scheme 2.3). The ability to regioselectively allylate ketone enolates upon decarboxylation was particularly advantageous. The overall transformation of this process was similar to the original Carroll rearrangement, reported in 1940.<sup>10</sup> The

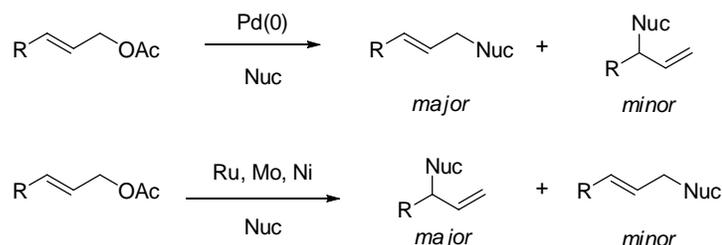
initial report of the Carroll rearrangement describe the thermal transformation which required extremely high temperatures (~240 °C), which the palladium-catalyzed variant could avoid as ambient temperature was sufficient for most substrates. Though these two reactions are mechanistically distinct, the two reactions afford the same products.



**Scheme 2.3**

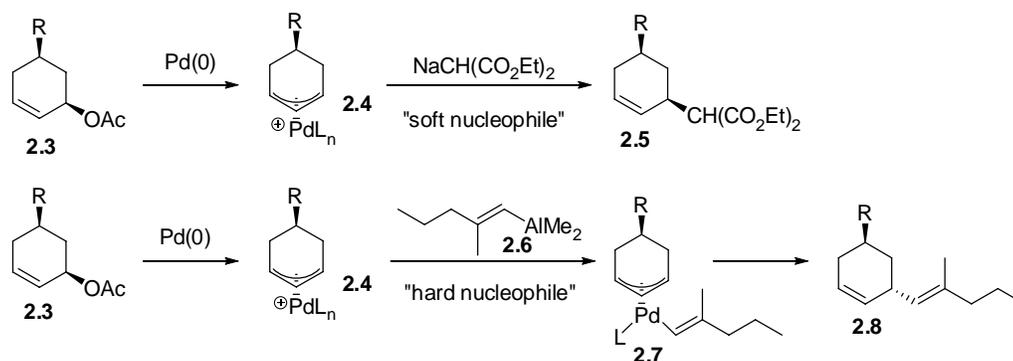
#### *Regio- and Stereoselectivity of Transition Metal-Catalyzed Allylic Alkylation*

Other transition metals have also been used to catalyze these allylic alkylations, including Ni,<sup>11</sup> Mo,<sup>12</sup> Rh,<sup>13</sup> and Ru.<sup>14</sup> These metals are distinguished from palladium in their regioselectivity of allylation. While palladium preferentially forms the linear product of allylation,<sup>15</sup> these other transition metals are more selective for the branched allylation product (Scheme 2.4). Palladium has, by far, received the most attention in this area and is the most well understood mechanistically.



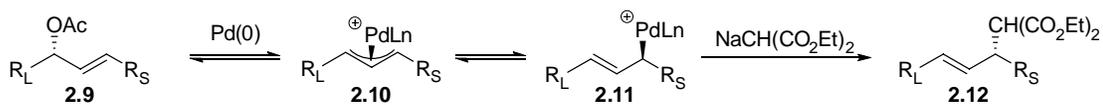
**Scheme 2.4**

A great deal of this mechanistic work on these systems has been completed by Trost and coworkers.<sup>16</sup> Importantly, they revealed the stereochemical outcome of allylic substitution on stereochemically “labeled” allylic acetates. First, upon treatment of a *cis*-allylic acetate with a palladium(0) catalyst, coordination of the olefin to palladium facilitates the displacement of the acetate through an S<sub>N</sub>2 process (Scheme 2.5). This affords the (η<sup>3</sup>-allyl)Pd(II) complex with stereochemical inversion (**2.4**). The mechanistic pathway then diverges depending on the type of nucleophile used. Soft nucleophiles (p*K*<sub>a</sub> < 25) directly attack the allylic carbon from the opposite face of the Pd-π-allyl complex (**2.4**), displacing the palladium atom through another inversion event, providing net retention of configuration in the product (**2.5**).<sup>16c,17</sup> On the contrary, hard nucleophiles (p*K*<sub>a</sub> > 25) prefer to attack the palladium, rather than the allylic carbon.<sup>18</sup> Then, reductive elimination of **2.7** couples the two fragments from the same face of the allyl on which palladium resides, and therefore gives **2.8** with a net inversion of stereochemistry.



**Scheme 2.5**

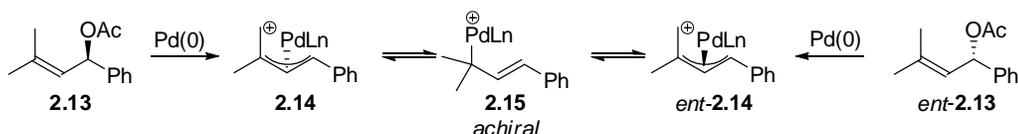
There are some exceptions to these stereochemical mnemonics, but overall, they provide insight for the stereochemical requirements of palladium-catalyzed allylic substitution. They are also important in terms of the enantioselective reaction. The stereospecific nature of this process allows for initial chirality of the molecule to be preserved to the product (Scheme 2.6). The addition of chiral ligands can not determine the stereochemical outcome of the product, but rather it is determined from the chirality of original substrate. Thus, a racemic mixture of an achiral allylic acetate will afford a racemic product mixture even if chiral ligands are employed.



**Scheme 2.6**

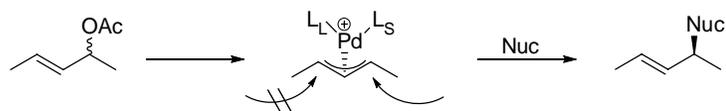
Therefore, the enantioselective allylic substitution of racemic acetates is a desirable transformation, as racemic mixtures are generally cheaper and easier to synthesize. This can be achieved if a substrate is employed that can slip from a chiral (η<sup>3</sup>-allyl)Pd(II) intermediate (2.14) to an (η<sup>1</sup>-allyl)Pd(II) species at a

nonstereogenic center, giving an achiral intermediate (**2.15**) (Scheme 2.7). Then, the original chiral information is lost and the stereochemistry of the product can be determined by the chiral ligand bound to palladium.<sup>19</sup> In this scenario, a racemic mixture can still give enantioenriched products in the presence of an effective chiral ligand.



### Scheme 2.7

Another option for asymmetric induction is the use of symmetrically substituted allyl groups.<sup>20</sup> Then, racemization occurs upon formation of the meso- ( $\eta^3$ -allyl)Pd(II) species (Scheme 2.8). Then, the chiral ligand can direct the position at which the allyl group is attacked by the nucleophile. One of the two enantiotopic positions of the allyl moiety must be selectively attacked for successful asymmetric induction. Common chiral ligands block the approach of the nucleophile from one angle while allowing attack from the opposite angle (Scheme 2.8). The nucleophile attacks from the angle where the ligand is sufficiently small. This reaction is still stereospecific, and the nature of hard and soft nucleophiles determines the face to which nucleophile is delivered. Many of the chiral ligands used are of the  $C_2$ -symmetric class, although  $C_1$  ligands have given some of the best results.<sup>16e,21</sup>



**Scheme 2.8**

These topics represent an overview of the general characteristics of palladium-catalyzed allylic alkylation. A tremendous effort has been expended to broaden the scope of this powerful reaction to include countless asymmetric variants, a variety of heteroatom and carbon nucleophiles, and ligand modifications as a means to improve the reactivity profiles. Prior to the discovery of the palladium-catalyzed allylic substitution, functionalization of the allylic position with carbon nucleophiles was very limited, but has since become a hallmark in organic synthesis. The rapidly increasing number of citations on the subject of palladium-catalyzed asymmetric allylic alkylation is a testament to the contribution that it has made to organic synthesis.<sup>22</sup>

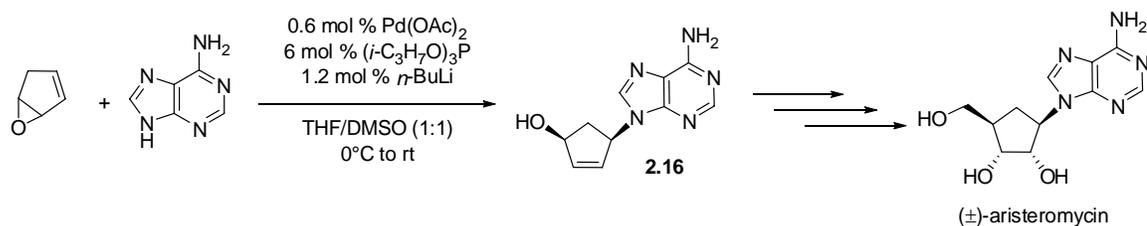
## 2.2 Synthetic Methods of Allylic Amination

### *Biological and Synthetic Applications of Allylic Amines*

Allylic amination is one of the fundamental methods for the construction of new carbon—nitrogen bonds. This “simple” transformation provides essential building blocks capable of a variety of synthetic manipulations. Over the years, the development of new routes to access allylic amines has been an important focal point in synthetic methodology. As a result, many different types of aminations, such as the Overman rearrangement,<sup>23</sup> Mitsunobu amination,<sup>24</sup> and transition metal-catalyzed

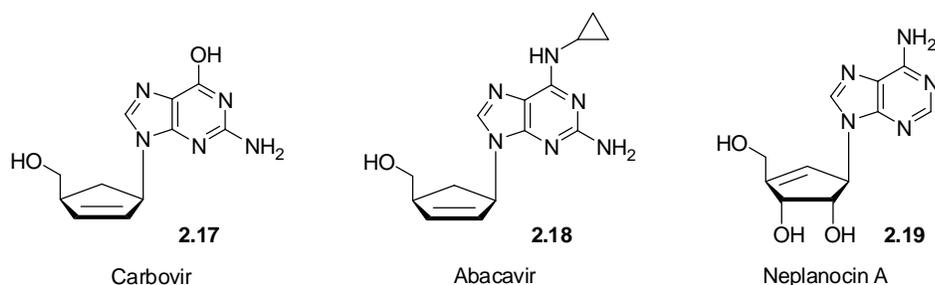
allylic amination have emerged.<sup>16b,25</sup> A particular advantage of the latter reaction is the mild reaction conditions, allowing for the selective transformation in the presence of a variety of other functional groups. While palladium-catalyzed allylic couplings have been widely explored since the discovery of the Tsuji-Trost reaction, the allylic amination reaction has benefited from the incorporation of a variety of other metals, such as Ir,<sup>26</sup> Ru,<sup>27</sup> and Ni<sup>28</sup>. The regiochemical preference of these metals is for branched allylic amines, rather than linearly substituted amines, which palladium is known to provide. One key advantage of this methodology, independent of the metal, is the ability to afford enantioenriched products by using chiral ligands.

The first example of palladium-catalyzed allylic amination of saturated amines was reported in 1970 by Manyik and coworkers.<sup>29</sup> Since this publication, numerous reports have appeared in the literature that expand the applications of this transformation. However, there have been only a limited number of examples which utilize heteroaromatic amines as the nucleophilic component. This is rather surprising considering the increasing number of pharmaceutical compounds which contain these units in their core structure.<sup>30</sup> The first report on the allylation of heteroaromatic amines did not appear until 1988 and was authored by Trost and coworkers (Scheme 2.9).<sup>31</sup> In this publication, they demonstrated the nucleophilic opening of vinyl epoxides with catalytic Pd(OAc)<sub>2</sub> to form the palladium- $\pi$ -allyl complex followed by nucleophilic attack by the nucleotide adenine, which afforded the desired precursor (**2.16**) in the synthesis toward the natural product, aristeromycin.



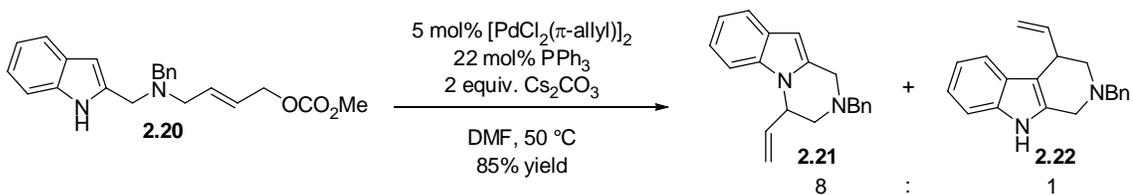
## Scheme 2.9

This catalytic allylation of heteroaromatic nucleotides became a facile way to install the important C—N bond in carbocyclic nucleosides,<sup>32</sup> some of which exhibit significant antiviral activity (Scheme 2.10).<sup>33</sup> Despite its rather simple structure, carbovir (**2.17**) is a potent inhibitor of HIV-1 (Human Immunodeficiency Virus-1) replication in human T-cells.<sup>34</sup> Initial synthetic efforts required several steps to synthesize the nucleotide following standard amination protocols,<sup>35</sup> although a shorter synthesis utilizing the palladium-catalyzed allylic amination allowed for the introduction of the whole nucleotide in a single step.<sup>36</sup> Carbovir is only one of many other nucleosides which are potent antiviral agents. Currently there are eight nucleoside analogs which are licensed for the treatment of AIDS (Acquired Immune Deficiency Syndrome) in the United States.<sup>37</sup> Abacavir (**2.18**), the prodrug for carbovir, is also used to treat AIDS and can also be synthesized using the palladium-catalyzed allylic amination procedure. Another antiviral agent, Neplanocin A (**2.19**), has been used to treat orthopoxviruses, as well as SARS (Severe Acute Respiratory Syndrome).<sup>38</sup> Thus, the addition of heteroaromatic amines is an important area of research not only for the synthesis of these natural products, but their derivatives as well.



### Scheme 2.10

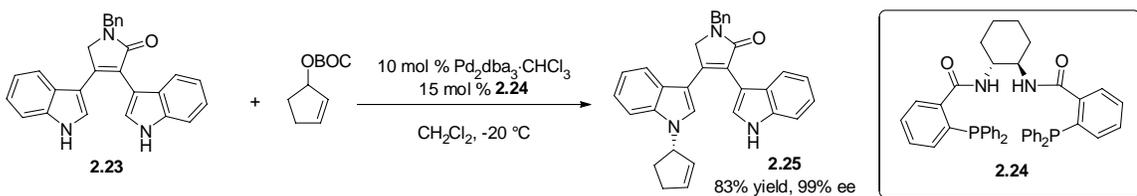
While the incorporation of the nucleotides is important, they are not the only heteroaromatic amines that can be found in pharmaceutical drugs. Thus, it has also been shown that other unsaturated amines, such as imidazole, have been utilized with this strategy.<sup>39</sup> Extensions of this chemistry beyond the sugar-derived allyl cores have received far less attention.<sup>40</sup> One example is the intramolecular allylation of indole which has recently been described, where acyclic allylic carbonates are used to form the Pd- $\pi$ -allyl intermediate.<sup>40b</sup> Since the indole possesses two nucleophilic sites, the nitrogen and the C-3 position, it is possible that either position could attack the Pd- $\pi$ -allyl intermediate. While the C-3 position is generally most nucleophilic in CH<sub>2</sub>Cl<sub>2</sub>, the reactivity could be altered to make the nitrogen the nucleophilic site by switching to a more polar solvent (Scheme 2.11). This exemplifies the ability of Pd-catalyzed allylic amination to synthesize molecular skeletons with the heteroaromatic functional groups. Further exploration of this type of chemistry would augment the already vast synthetic utility of the palladium-mediated allylic amination reaction.



**Scheme 2.11**

*Current Methods in Asymmetric Allylic Amination with Heteroaromatic Amines*

The asymmetric allylic amination reaction is a necessary tool for the synthesis of chiral, non-racemic nitrogen containing molecules. In terms of enantioselective processes, the transition metal-catalyzed allylic amination has had an enormous impact.<sup>26b,27c,28a</sup> While most of these examples have been restricted to saturated amines, the application of enantioselective heteroaromatic allylation has been demonstrated. Trost and coworkers showcased this in their enantioselective indole allylation (Scheme 2.12).<sup>17a</sup> The chemoselective allylation at the more acidic indole of **2.23**, which is linearly conjugated with the  $\alpha,\beta$ -unsaturated system, is a distinctive feature of this transformation. By employing the chiral Trost ligand (**2.24**), the product could be obtained in good yields with excellent enantioselectivity.

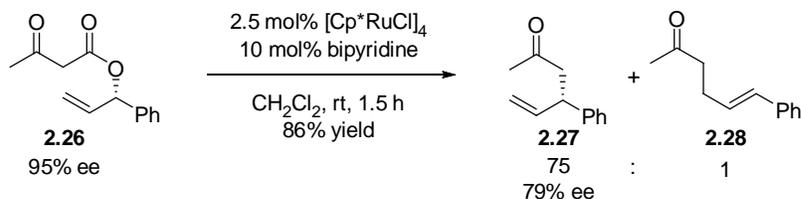


**Scheme 2.12**

The high enantioselectivity observed in this reaction lends promise toward being able to provide similar results with other types of systems. To date, there have been no reports on asymmetric allylations of other types of heteroaromatics, such as imidazole or pyrazole. The broader scope of the Pd-catalyzed allylic amination with nucleophilic heteroaromatic amines and their asymmetric variant has yet to be fully explored.

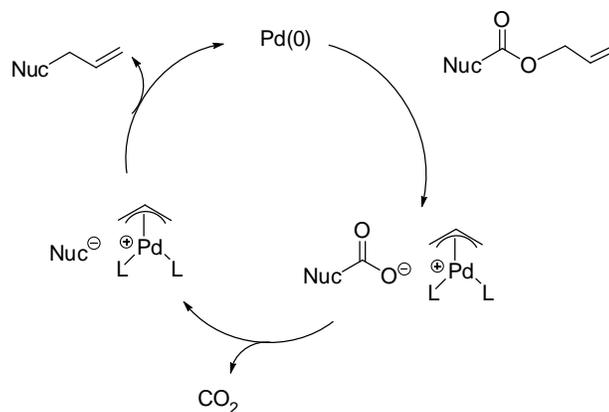
### *Decarboxylative Coupling Methods*

A focus in our group has been on carbon—carbon bond formation *via* transition metal-catalyzed decarboxylative coupling. Erin Burger, a member of our group, began this research by studying the Carroll-type rearrangement of allyl  $\beta$ -ketoesters with ruthenium and palladium catalysts.<sup>41</sup> Since Ru is known for the selective formation of the branched regioisomer, studies with chiral, non-racemic allyl  $\beta$ -ketoesters were completed (Scheme 2.13). These reactions showed that this reaction is also stereospecific, as high levels of enantiomeric excess were conserved from the starting allyl  $\beta$ -ketoester (**2.26**) to the product ketone (**2.27**).



**Scheme 2.13**

Although the palladium-catalyzed Carroll-type rearrangement had previously been reported,<sup>42</sup> it was also demonstrated by Erin Burger that high levels of enantioselectivity could be realized in the reaction with chiral ligand/palladium combinations.<sup>41b</sup> While the decarboxylation of the allyl  $\beta$ -ketoesters specifically forms ketone products, we began to wonder what other types of functionality would be compatible with the decarboxylative coupling strategy. Therefore, we took a more general approach to the decarboxylation of allyl  $\beta$ -ketoesters by simply viewing them as an electrophile appended to a nucleophile by a linker ( $\text{CO}_2$ ) (Scheme 2.14). When conditions are favorable, palladium is capable of facilitating the loss of  $\text{CO}_2$ , which is ideally followed by recombination of the nucleophile (i.e. enolates) and the electrophile ( $\text{Pd}$ - $\pi$ -allyl complex).

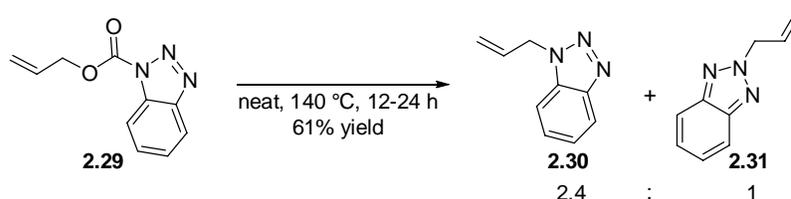


**Scheme 2.14**

It seemed to us that other types of stabilized nucleophiles should be compatible in this type of reaction as well, particularly saturated and heteroaromatic amines. However, the general approach used for most transition metal-catalyzed allylic aminations has been nucleophilic attack on the metal-allyl species with a

stoichiometric amount of an external nucleophile. In light of our previous observations, we were interested as to whether allylic carbamates would react similarly to the allyl  $\beta$ -ketoesters. If this were possible, it would eliminate the need for additional reagents in the reaction mixture, as the electrophile and the nucleophile would already be present in the starting carbamate.

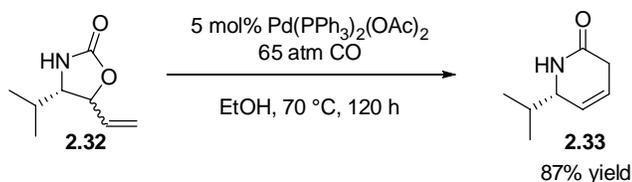
The thermal decarboxylation of allylic carbamates has been reported with some saturated and heteroaromatic amines to afford the allylic amination products stereo- and regiospecifically.<sup>43</sup> In this way, Katrizky and coworkers have demonstrated the thermal decarboxylation of carbamates which incorporate benzotriazole (Scheme 2.15).<sup>44</sup> After heating a neat solution of **2.29** at 140 °C, a mixture regioisomers (**2.30**, **2.31**) was obtained in 61% yield. Thermal decarboxylation methods are not synthetically useful because of the extremely high temperatures, or strong bases which are necessary in the cases of saturated amines.



### Scheme 2.15

The palladium-catalyzed decarboxylation of carbamates has also been reported. For example, Tsuji disclosed the use of molybdenum and nickel as catalysts for decarboxylative amination of a single substrate.<sup>45</sup> Generally though, the resulting amide generated is not used as a nucleophile, but rather as a base<sup>46</sup> where the allyl group is attacked by an external nucleophile. Others have facilitated carbonylation of

the amide, followed by cyclization onto the allyl moiety to synthesize vinyloxazolidinones, such as **2.33** (Scheme 2.16).<sup>47</sup> The insertion of carbon monoxide prior to protonation exhibits promise that allylation of the amide nucleophile generated might also be possible.



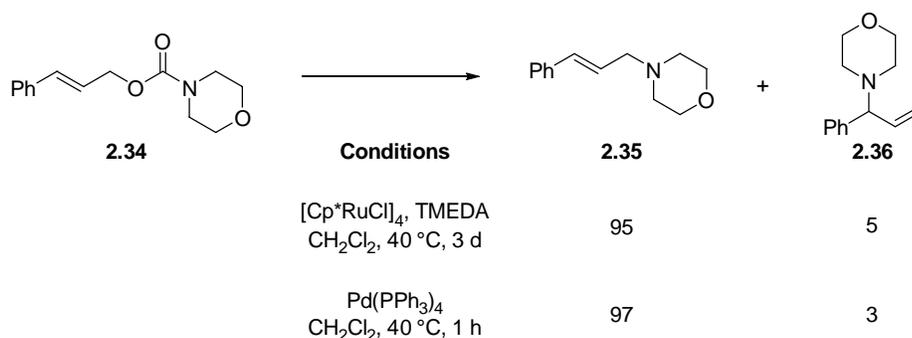
**Scheme 2.16**

These examples demonstrate palladium's ability to facilitate decarboxylation of carbamates at much lower temperatures as compared to the thermal conditions. If the transition metal-catalyzed decarboxylation of the carbamates was realized, the use of an external nucleophile would no longer be necessary, although regio- and stereochemical issues would also have to be investigated. The allylation of heteroaromatic amines is particularly underdeveloped and the establishment of this type of chemistry would aid in the synthesis of larger molecules containing these structures.

### 2.3 Palladium-Catalyzed C—N Bond Formation *via* Decarboxylative Coupling

### *Pd-Catalyzed Decarboxylative Amination with Saturated Amines*

In pursuit of a transition metal-catalyzed decarboxylative allylic amination, a coworker in our group, Dinesh Rayabarapu, began by synthesizing various allylic carbamates which incorporated saturated amines.<sup>48</sup> Ruthenium and palladium complexes were combined with various ligands and screened for catalytic activity with the allylic carbamates. Multiple catalysts provided the allylic amination products, most of the ruthenium complexes favored branched product (**2.36**) formation, although product ratios did not exceed 3:1 (**2.36**:**2.35**) (Scheme 2.8). The substituted allyl products are synthetically useful, but much higher regioselectivities were achieved with catalysts which favored linear product formation. Pd(PPh<sub>3</sub>)<sub>4</sub> and [Cp\*RuCl]<sub>4</sub>/TMEDA were two catalyst systems which gave particularly high regioselectivities of the linear product of allylation (**2.35**).

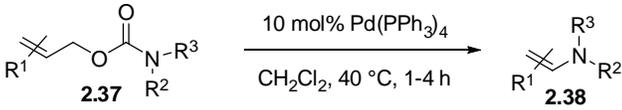
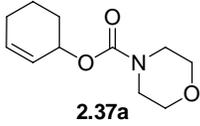
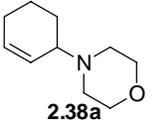
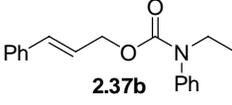
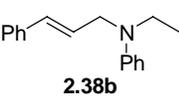
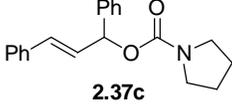
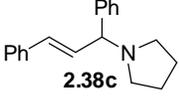
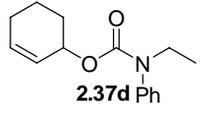


### **Scheme 2.17**

The Pd(PPh<sub>3</sub>)<sub>4</sub> catalyst was ultimately chosen for its short reaction times. An extensive survey of the allyl proelectrophiles was performed, including cyclic, branched and unsubstituted allyl carbamates. Likewise, the amines were varied to include morpholine, pyrrolidine, and secondary anilines. Most combinations of these

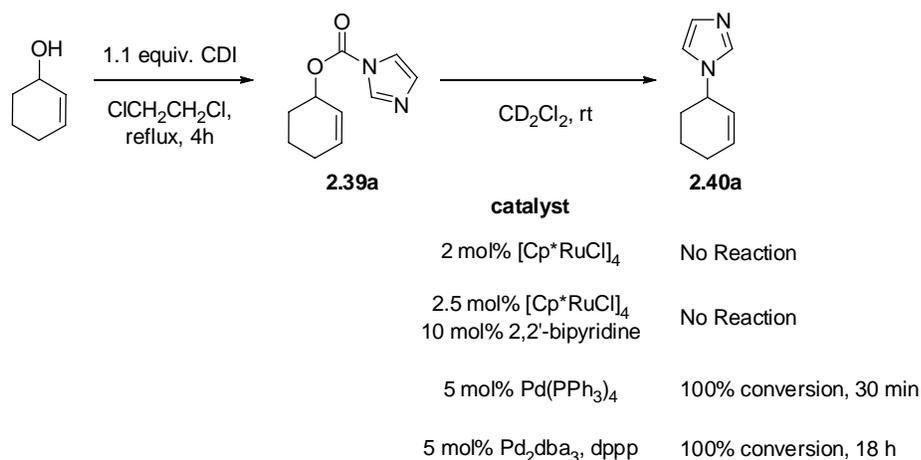
two subunits were compatible and proceeded in high yields (~70-90%). One exception was the **2.37d**, where only elimination products were observed. Table 2.1 provides a brief summary of the reaction scope. Altogether, the palladium-catalyzed decarboxylative method provided an easy route to allylic amines with high yields and regioselectivities.

**Table 2.1** Pd-Catalyzed Decarboxylative Allylation of Saturated Amines

		
Reactant	Product	Yield (%)
 <b>2.37a</b>	 <b>2.38a</b>	83
 <b>2.37b</b>	 <b>2.38b</b>	68
 <b>2.37c</b>	 <b>2.38c</b>	95
 <b>2.37d</b>		—

Our interest in the allylation of heteroaromatic amines led us to pursue these types of carbamates as substrates for decarboxylative coupling. To this end, **2.39a** was synthesized and reacted in the presence of ruthenium and palladium catalysts (Scheme 2.18). With the ruthenium catalyst, the reaction failed to proceed to product,

even in the presence of an additional ligand, such as 2,2'-bipyridine. Degradation of the starting materials was not observed in these reactions. To our delight, when palladium catalysts were employed, the reaction proceeded to the desired allylated imidazole product. Pd(PPh<sub>3</sub>)<sub>4</sub> was the optimal catalyst as the reaction was complete in only 30 minutes.



### Scheme 2.18

#### *Pd-Catalyzed Decarboxylative Amination with Heteroaromatic Amines*

Since multiple heteroaromatic amines are prevalent in pharmaceutically important compounds, we surveyed different heterocycles such as pyrazole, triazole and benzotriazole (Table 2.2). These carbamates were successfully allylated in the presence of 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>. The reactions with benzotriazole carbamates (**2.39d** and **2.39g**) afforded a mixture of regioisomers with allylations occurring at both the *N*-1 and *N*-2 positions. Previous reports of benzotriazole alkylations have also demonstrated a similar lack of selectivity.<sup>44,49</sup> Interestingly, the triazole carbamate

(**2.39c**) afforded only a single regioisomer with allylation only occurring at the *N*-1 position. Cycloheptenyl variants of these carbamates also afforded the allylic amines in good yields. Almost all substrates proceeded to completion within 1-4 hours (substrate **2.39f** required 8h), which corresponded with a color change in the reaction. Upon reaction completion, the colorless solution would turn bright yellow, suggesting the regeneration of the Pd(PPh<sub>3</sub>)<sub>4</sub> catalyst. Attempts to synthesize 2-cyclopentenyl derived carbamates were unsuccessful as silica gel appeared to promote decarboxylation or hydrolysis and the starting carbamates could not be easily obtained.

**Table 2.2** Pd-Catalyzed Decarboxylative Allylation of Heteroaromatic Amines

Substrate	Product(s)	Isolated Yield	Substrate	Product(s)	Isolated Yield
		90%			71%
		77%			65%
		88%			79% <sup>a</sup> 1:1.1
	 	81% <sup>a</sup> 1.6:1			

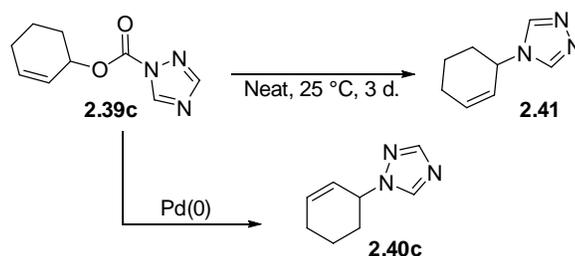
<sup>a</sup> Combined yield of regioisomers

The impressive biological activity of carbonucleosides<sup>32-36</sup> made the incorporation of nucleotides *via* the decarboxylative coupling methodology desirable. In light of this, attempts were made to synthesize carbamates from guanine and

purine. Unfortunately, the increased polarity of these bases due to the number of heteroatoms present decreased their solubility in many organic solvents. Neither base was soluble in the solvents that were used (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, Acetone), and we were unable to couple the amines with the allylic alcohols in the presence of triphosgene. Looking back on these reactions and related work, the synthesis of these carbamates might have been more successful if solvents such as DMSO were used.

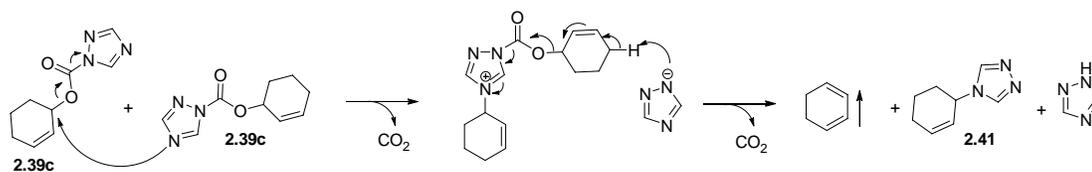
#### *Substrate Decomposition Studies*

In general, most of the starting carbamates were stable, particularly the imidazole and pyrazole compounds. However, the triazole and benzotriazole carbamates were more prone to decomposition after prolonged storage at room temperature. This process usually occurred after storing one to two weeks on the benchtop. The decomposition of benzotriazole substrates was obvious as white solids changed to yellowish liquids. We speculated that the degradation product was a result of hydrolysis of the carbamate by moisture in the air, affording the benzotriazole and cyclohexenol subunits. Observation of the degradation product of triazole carbamate **2.39c**, proved more interesting, as a crystalline solid slowly emerged from a colorless liquid upon standing (3-6 days) (Scheme 2.19). Using <sup>1</sup>H NMR spectroscopy, we were able to identify that the *N*-3 position had been allylated to provide the symmetrically substituted triazole product (**2.41**). This product was not observed in the palladium-catalyzed reaction.



**Scheme 2.19**

A large amount of triazole was also observed by  $^1\text{H}$  NMR spectroscopy in the degradation mixture. No cyclohexenol was present indicating hydrolysis was not the main source of decomposition. In contrast, when **2.39c** was stored as a solution in  $\text{CD}_2\text{Cl}_2$ , no degradation was observed. It seems that either the dilution of the substrate or storage in a dry solvent, prevented degradation. Close proximity of molecules due to the high local concentration during storage could facilitate nucleophilic attack of one substrate molecule onto another by the accessible *N*-3 nitrogen, beginning a cascade reaction. The release of free triazole can promote either nucleophilic displacement at the allylic carbamate or elimination of the carbamate to form cyclohexadiene. The presence of triazole in the  $^1\text{H}$  NMR spectrum leads us to believe that the elimination route is symbiotic with allylation (as shown in Scheme 2.20). Cyclohexadiene was not observed, but it is relatively volatile (bp = 80 °C) and could evaporate upon prolonged standing, and thus it was not observed by  $^1\text{H}$  NMR spectroscopy.



### Scheme 2.20

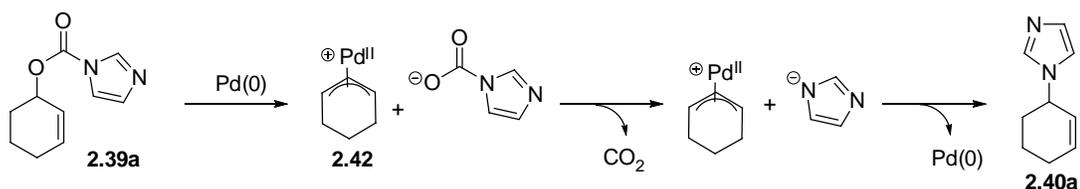
Although the *N*-3 allylated product was not observed in the palladium-catalyzed reaction, we wanted to ensure that the *N*-1 allylated product was not a result of equilibration between regioisomers facilitated by the palladium. So, a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to the crystalline material formed from substrate degradation and the mixture was allowed to react. Substrate **2.41** was left unchanged showing that the palladium catalyst was not equilibrating regioisomer **2.41** to **2.40c**. This confirms that the presence of palladium alters the regioselectivity of nucleophilic addition upon decarboxylation as compared to the uncatalyzed process.

### *Proposed Mechanisms*

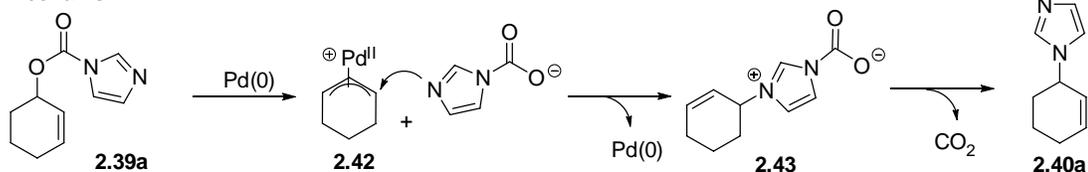
The formation of two regioisomers, particularly with the benzotriazole examples, led to further mechanistic investigations. All of the azole carbamates that had been tested contained at least two nucleophilic nitrogens. It was only possible to observe allylation of multiple nitrogens in the cases where they were chemically different (benzotriazole). We became curious whether the additional nitrogen(s) facilitated product formation. We chose to address this by studying the relative timing of decarboxylation. Scheme 2.21 shows two likely mechanisms which could be operating. Mechanism A represents a pathway where decarboxylation occurs

directly after formation of the palladium  $\pi$ -allyl complex (**2.42**). The negative charge can then be delocalized over both nitrogens, and then attack the metal-allyl complex to regenerate the Pd(0) catalyst. In contrast, mechanism B is distinguished by attack of the additional azole nitrogen atom onto the palladium- $\pi$ -allyl complex prior to decarboxylation to give intermediate **2.43**. This activation of the heteroaromatic amine would be expected to promote decarboxylation as a means of quenching the incipient charge of the imidazolium species.

**Mechanism A:**



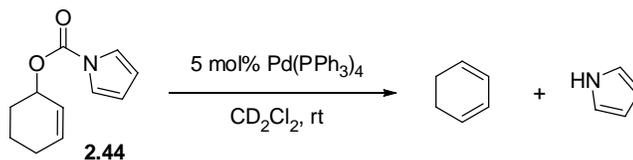
**Mechanism B:**



**Scheme 2.21**

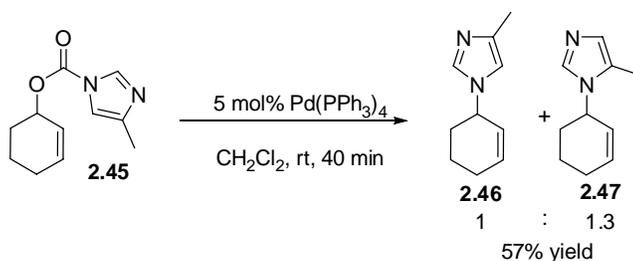
We first thought a reaction including a heteroaromatic amine with only a single nitrogen should aid in the mechanistic determination. Therefore, pyrrole carbamate **2.44** was synthesized and treated under the conditions of catalysis. The reaction did not afford the decarboxylatively coupled product, but rather produced only cyclohexadiene and pyrrole (Scheme 2.22). Although this was significant, we were hesitant to speculate on the operative mechanistic pathway, due to the high relative basicity of the pyrrolide ( $pK_a = 23$ ),<sup>50</sup> in contrast to the other azoles which

have lower  $pK_a$  values [imidazole (18.6), pyrazole (19.8), triazole (14.8) and benzotriazole (~12)].<sup>51</sup> Thus, elimination to form cyclohexadiene could have been an artifact of the difference in basicities.



### Scheme 2.22

Since the pyrrole example was mechanistically inconclusive, we relied on 4-methyl substituted imidazole for clarification. The methyl substituent provided an unsymmetrical imidazole, allowing us to determine which nitrogen was being allylated. Therefore, carbamate **2.45** was treated under standard conditions and a 1:1.3 mixture of products **2.46** and **2.47**, respectively, was obtained in a 57% isolated yield (Scheme 2.23).



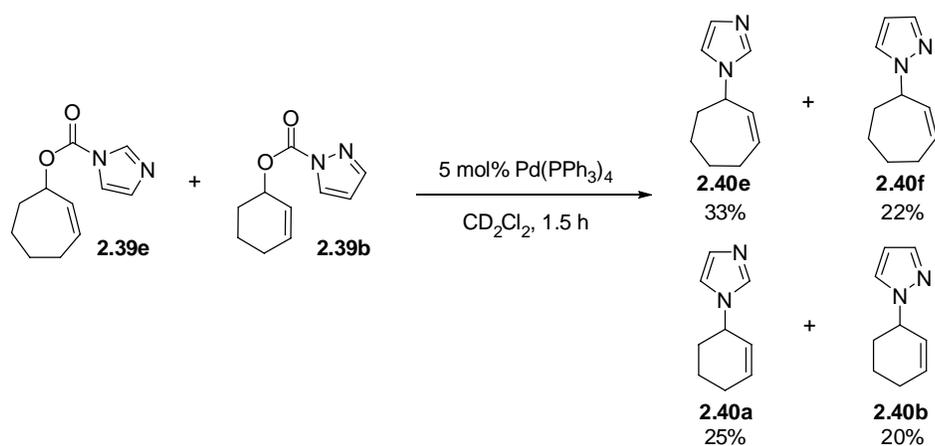
### Scheme 2.23

In a previous example on the palladium-catalyzed allylation of 4-substituted imidazoles, a mixture of regioisomers was also obtained.<sup>39d</sup> Perhaps the most notable observation was that the major product isolated was the product of allylation at the more sterically encumbered nitrogen. In terms of mechanistic rationale, the

observation of a mixture of products did not rule out either mechanism. Mechanism A could account for the formation of both products, although this does not discount that both pathways could be operative. If pathway A is the only active mechanism, then the ratio of products may simply reflect the charge distribution of the anionic imidazolyl species after decarboxylation. Mechanism B cannot explain the formation of **2.46**, and therefore mechanism A must be a contributing pathway to product formation.

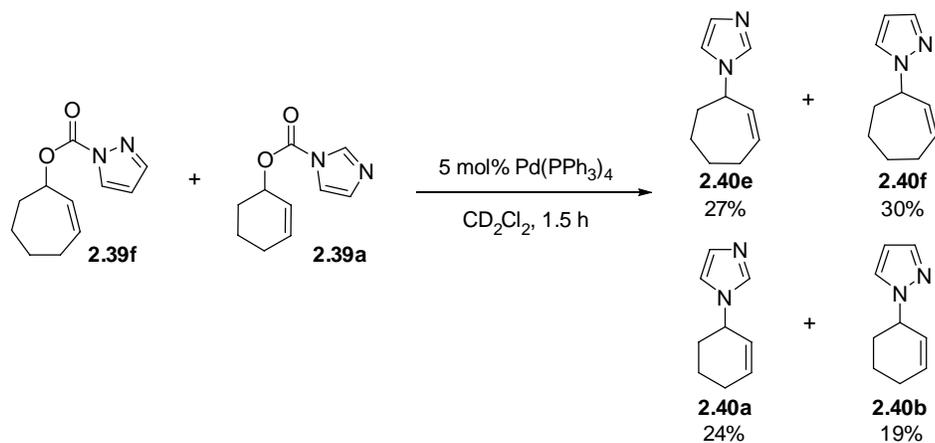
#### *Crossover Experiments*

Based on previous related investigations, we believed that the nucleophilic attack (prior to or after decarboxylation) on the Pd- $\pi$ -allyl species occurred in an intermolecular fashion, rather than through reductive elimination. To support this hypothesis, a crossover experiment was employed. Equimolar amounts of two different carbamates, **2.39e** and **2.39b**, were combined and allowed to react in the presence of the palladium catalyst (Scheme 2.24). After the reaction was complete, the product mixture was subjected to GC analysis and a statistical mixture of four products was obtained, indicating complete crossover had occurred. This confirmed our belief that the formed carboxylate was freely diffusing in solution rather than tightly coordinated to the palladium center.



**Scheme 2.24**

Since we only started with two carbamates and had observed all four possible products, it seemed like an interesting exercise to also run the crossover between carbamates **2.39f** and **2.39a** (Scheme 2.25). The reaction was run under identical conditions and completed in 1.5 hours. Again, a statistical mixture of products was obtained.

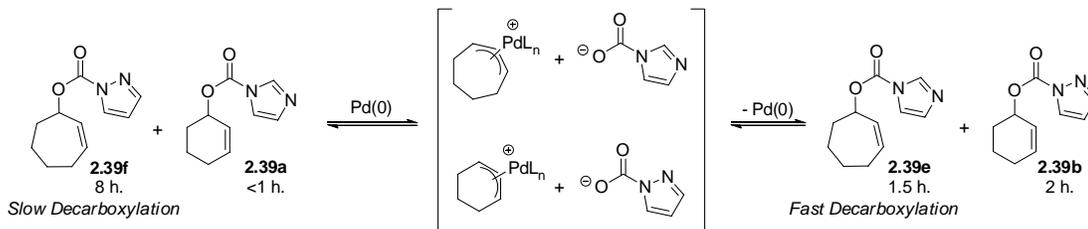


**Scheme 2.25**

### *Studies on Substrate Rate Enhancement*

Interestingly, the catalyzed reaction of **2.39f** alone took almost 8 hours. However, the crossover experiment using this substrate was complete in only 1.5 hours. Clearly, the reaction rate of this substrate was increased by the addition of a substrate with a faster reaction rate. Intrigued by the rate acceleration, two experiments were run simultaneously to qualitatively determine the effect of a faster reacting substrate on the rate of reaction of **2.39f**. Two experiments with **2.39f** were run under standard conditions of catalysis. Both were monitored after 1.5 hours by  $^1\text{H}$  NMR spectroscopy, and both reactions had independently reached 23% conversion to product **2.40f**. Then, one of the two experiments was spiked with 0.15 equivalents of **2.39a**. After reacting 45 minutes, the reactions were again monitored. The unspiked reaction had proceeded to 35% conversion, while the spiked reaction had reached 40% conversion based on the original starting material, **2.39f**. The increase in rate was not overwhelmingly high, so another 0.25 equivalents of **2.39a** was added to the spiked reaction. After one hour, the spiked reaction had progressed to 80% conversion (based on substrate **2.39f**), while the unspiked reaction had only proceeded to 56% conversion. When comparing the two conversions, it was obvious the addition of a substrate with a faster rate is also capable of increasing the rate of the slower substrate. Since crossover experiments showed that freely diffusing ions must have been present in the solution, one possible explanation of the rate amplification of **2.39f** is that the freely diffusing carboxylate species recombine with

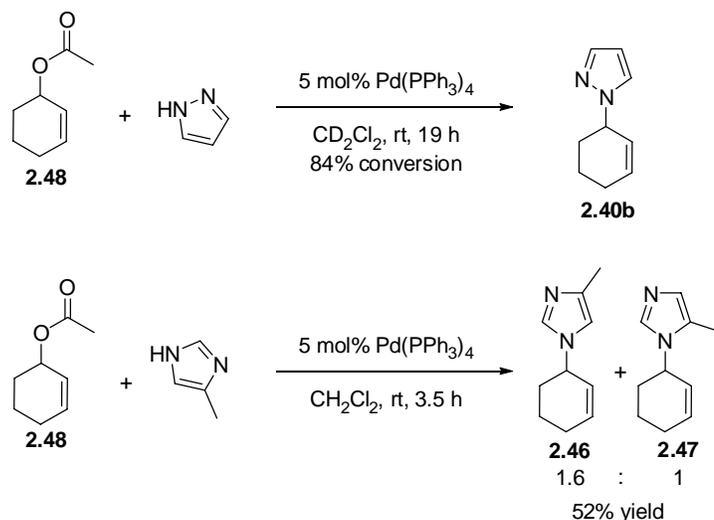
a different Pd-allyl species much faster than decarboxylation (Scheme 2.26). Then **2.39e** is formed and the rate of reaction for this carbamate is faster than **2.39f**.



**Scheme 2.26**

#### *Allylic Amination Utilizing Allylic Acetates and Heteroaromatic Amines*

Although the carbamates could be easily synthesized, we wondered if the reaction of an allylic acetate and a stoichiometric amount of the azoles would be feasible. To verify this concept, pyrazole and 4-methylimidazole were treated separately with one equivalent of 2-cyclohexenyl acetate (**2.48**) and 5 mol % of Pd(PPh<sub>3</sub>)<sub>4</sub>. The first half life of the pyrazole reaction was accomplished in 5 hours, however further observation showed that the reaction only proceeded to 84% conversion after 18 hours, after which time the reaction had shut down completely (Scheme 2.27). In contrast, the reaction with 4-methylimidazole attained 100% conversion after 3.5 hours, but gave only a slight difference in regioselectivity and yield as compared to the decarboxylative coupling.



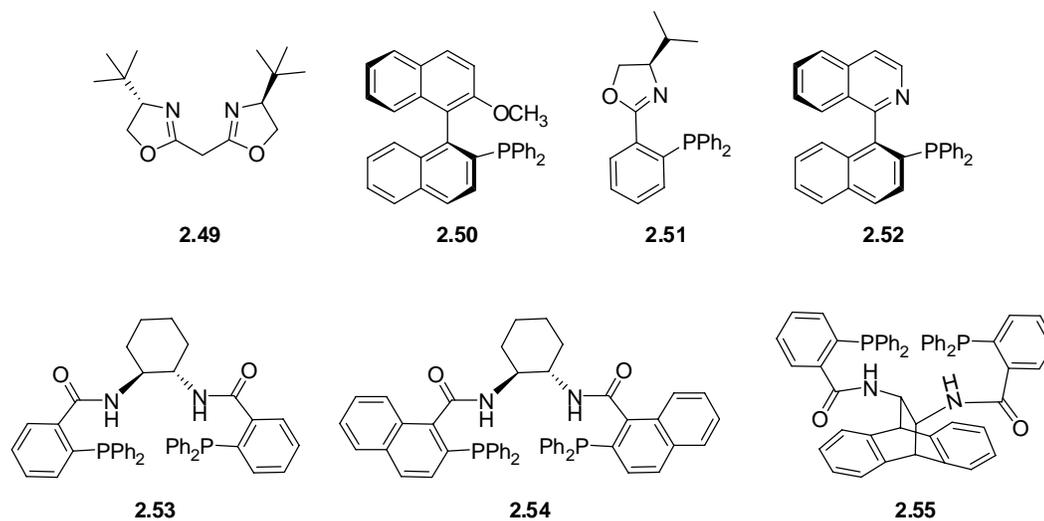
**Scheme 2.27**

While the “intermolecular” variant of this reaction could be a useful route to allylated azoles, it did not prove to be as successful as the decarboxylative allylic amination, particularly in terms of reaction rates. Without the advantage of increased yields or rates, it was not beneficial to continue the research in this direction.

#### *Enantioselective Decarboxylative Allylic Amination*

In terms of reaction scope, the lack of diversity of the allyl electrophiles investigated was unfortunate as elimination products were not observed with the cyclic allyl group and other alkyl-substituted allyls could have been examined. In retrospect, extensions of this chemistry to other substituted allyls could have easily been made. However, the initial reason for the use cyclohexenyl proelectrophile was early planning for the exploration of the asymmetric variant of this reaction. Since this is a metal mediated process, the use of chiral ligands could induce

enantioselectivity through a chiral palladium  $\pi$ -allyl complex, which directs the attack of the nucleophile. To begin the asymmetric endeavor, various chiral ligands were selected for screening (Scheme 2.28).

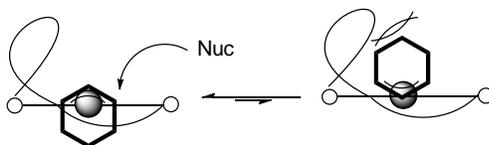


**Scheme 2.28**

The choice of ligands was based on their differential binding modes to palladium (Scheme 2.28). Ligand **2.49** is void of a phosphine donor, while **2.50-2.52** all have a single phosphine which can coordinate the metal center. The Trost ligand (**2.53**) and its derivatives (**2.54**, **2.55**) all possess a chelating diphosphine moiety. These ligands are known for their ability to induce enantioselectivity in cyclic allyl systems,<sup>16b</sup> which is the reason they were included in the screening.

The method by which the Trost ligand is capable of inducing enantioselectivity with cyclic allyl systems has been discussed in a report by Lloyd-Jones and coworkers.<sup>52</sup> The characteristic of the Trost ligand which is unique from other ligands is the formation of a 13-membered ring upon chelation of a palladium

atom by the phosphines. Although the unbound ligand is  $C_2$ -symmetric, Lloyd-Jones and coworkers explain that when the ligand chelates the palladium, the ring adopts a non- $C_2$ -symmetric conformation to alleviate ring strain, as represented in Scheme 2.29. When the cyclic allyl complex binds to palladium, equilibration to the rotamer where the ring is placed away from the ligand is preferred to avoid unfavorable steric interactions. The nucleophilic attack occurs from the least sterically hindered face to afford the allylated product. This representation of the Trost ligand chelation to palladium prompted us to begin our studies with cyclic allyl systems, rather than linear systems where these ligand types are known to be less effective.

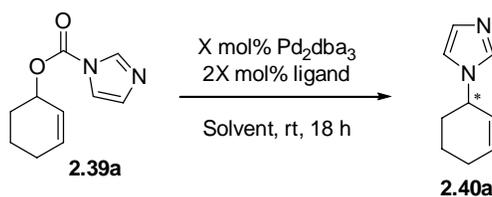


**Scheme 2.29**

The ligand screening was initiated with **2.39a** in the presence a catalytic  $Pd_2dba_3$  and the corresponding ligands (Table 2.3). Some of the ligand/catalyst combinations did not provide any reaction (entries 1-4), but we were encouraged to see that the Trost ligand (**2.53**) was suitable as the reaction reached completion in 18 hours (entry 5). Although this is long when compared with the  $Pd(PPh_3)_4$  system, the reaction still provided a clean product mixture. Once the reaction was complete, as observed by  $^1H$  NMR spectroscopy, the enantiomers were separated by chiral High Pressure Liquid Chromatography (HPLC) and compared with a racemic sample of product **2.40a**. The enantiomeric excess obtained was rather low (5.5%), but it did

provide a beginning framework. The naphthyl-Trost ligand (**2.54**) is a larger ligand and it afforded a significant increase in the enantioselectivity, up to 31% ee (entry 6). An even bulkier derivative of the Trost ligand, **2.55**, was also tested (entry 7-9). This ligand slightly improved the enantioselectivity, giving the highest ee observed in this screening. In comparing solvents, CD<sub>2</sub>Cl<sub>2</sub> was as efficient as C<sub>6</sub>D<sub>6</sub>, but the reaction in THF was completely shut down. In the future, it is important to note that all of these reactions were run at room temperature. Altering the reaction temperature could have an effect on the enantioselectivity as well. Also, different ligand/catalyst ratios could have been tested as a means of increasing the enantiomeric excess of the product. In this regard, this system was not optimized, but the initial survey of ligands did not project that a high level (>90% ee) of enantiopurity would eventually be obtained.

**Table 2.3** Palladium-Catalyzed Enantioselective Allylic Amination

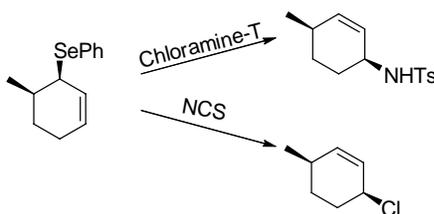


Entry	Catalyst Loading(mol %)	Ligand	Solvent	%ee
1	5	<b>2.49</b>	C <sub>6</sub> D <sub>6</sub>	NR
2	5	<b>2.50</b>	C <sub>6</sub> D <sub>6</sub>	NR
3	5	<b>2.51</b>	C <sub>6</sub> D <sub>6</sub>	NR
4	2.5	<b>2.52</b>	C <sub>6</sub> D <sub>6</sub>	NR
5	5	<b>2.53</b>	CD <sub>2</sub> Cl <sub>2</sub>	5.5
6	5	<b>2.54</b>	C <sub>6</sub> D <sub>6</sub>	31
7	2.5	<b>2.55</b>	C <sub>6</sub> D <sub>6</sub>	38
8	2.5	<b>2.55</b>	CD <sub>2</sub> Cl <sub>2</sub>	39
9	2.5	<b>2.55</b>	THF	NR

## 2.4 Palladium-Catalyzed Decarboxylative Selenation

### *Allyl Selenides as Precursor to Allylic Amines*

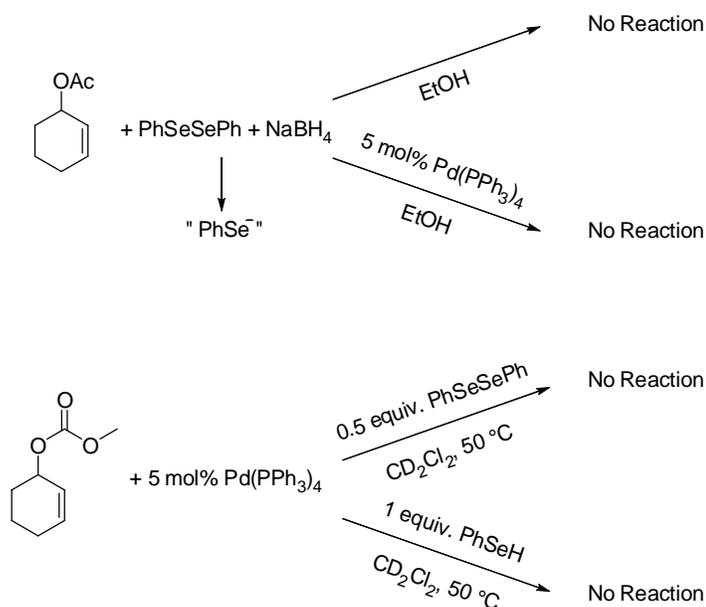
While the decarboxylative coupling proved to be a valid method for C—N bond formation, we had not yet reached our goal of effecting highly enantioselective allylic amination. The low enantioselectivities obtained from the decarboxylative amination procedure left us to approach this objective from a new angle. Our research in the area of selenium chemistry provided knowledge of the numerous transformations accessible with organoselenium compounds. For instance, allyl selenides are known for their ability to undergo the [2,3]-sigmatropic rearrangement under the appropriate conditions.<sup>53</sup> Treating the allyl selenides with Chloramine-T or NCS facilitates this rearrangement to afford allylic amines or chlorides, respectively (Scheme 2.30).<sup>54</sup> This [2,3]-rearrangement is a concerted process which proceeds through a cyclic transition state. Therefore, if we could synthesize enantioenriched allyl selenides, we could take advantage of this method en route to chiral, nonracemic allylic amine or allyl chloride products.



**Scheme 2.30**

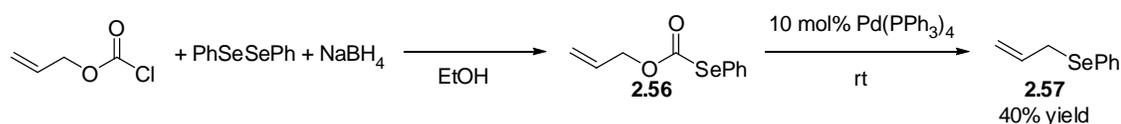
### Synthesis of Allyl Selenides

Multiple syntheses of allyl phenyl selenides have been reported, but many include stoichiometric quantities of transition metals, toxic reagents (Sn, Sm), or require basic or acidic conditions.<sup>55</sup> Our first attempt to synthesize the allyl selenide involved a nucleophilic displacement on 2-cyclohexenyl acetate with PhSeSePh in the presence of NaBH<sub>4</sub> in EtOH (Scheme 2.31). Although this procedure is applicable to the opening of epoxides, it was not capable of displacing the acetate group, as starting materials were recovered. Our attempts to reproduce a literature procedure for palladium-catalyzed allyl selenide formation were also unsuccessful.<sup>56</sup> Other attempts with allylic carbonates did not improve the reactivity, even in the presence of an aprotic solvent.



**Scheme 2.31**

Since attempts to synthesize allyl selenides were unsuccessful, we began to wonder if decarboxylative selenation would provide access to the desired allyl selenides, as it also had provided the allylic amines. For this reaction to be possible, the synthesis of selenoformates would be necessary. Interestingly, the reaction of allyl chloroformate and benzeneselenol has been reported to provide our desired selenoformate.<sup>57</sup> The procedure was fairly simple as the selenide anion was generated *in situ* by reacting PhSeSePh with NaBH<sub>4</sub> in EtOH, followed by the addition of allyl chloroformate (Scheme 2.32). After 4 hours, the product selenoformate was isolated. The purified allyl selenoformate (**2.56**) was subjected to 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in a variety of solvents (C<sub>6</sub>D<sub>6</sub>, CD<sub>3</sub>CN, Tol-*d*<sub>8</sub>). Although the reaction in benzene-*d*<sub>6</sub> was sluggish (<40% conversion after 18 hours), the reactions in acetonitrile-*d*<sub>3</sub> and toluene-*d*<sub>8</sub> both proceeded much faster. After only 15 minutes the reaction in CD<sub>3</sub>CN had reached 86% conversion to allyl selenide **2.57** while the reaction in Tol-*d*<sub>8</sub> had reached 20% conversion in the same time period. Both solvents showed complete conversion to the allyl selenide product in less than 5 hours. The reaction was scaled up in CH<sub>2</sub>Cl<sub>2</sub> and purified to obtain **2.57** in 40% yield, although the yield was unrepresentative of the clean conversion to product by observation of the <sup>1</sup>H NMR spectrum.

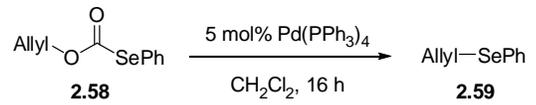


**Scheme 2.32**

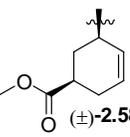
### Extension of the Pd-Catalyzed Decarboxylative Selenation

Since it seemed that we had developed a new extension of the decarboxylative coupling methodology, we were curious how applicable this type of process would be for other aryl- and alkyl-substituted, as well as cyclic allyl groups. Therefore several allyl selenoformates were synthesized<sup>58</sup> and reacted under the conditions of catalysis. We were pleased to note that much higher yields were obtained than for the simple allyl selenide **2.57** (Table 2.4). After 16 hours, the reactions proceeded cleanly to one product (or *E/Z* isomers of one product in the case of **2.58c** and **2.58f**). The *cis*-substituted cyclohexyl allyl substrate (**2.58g**) afforded only the *cis*-substituted product, as determined by <sup>1</sup>H NMR spectroscopic coupling constants, to give a net retention of stereochemistry. This type of stereospecificity has been previously demonstrated with other soft nucleophiles.<sup>59</sup>

**Table 2.4** Pd-Catalyzed Decarboxylative Selenation

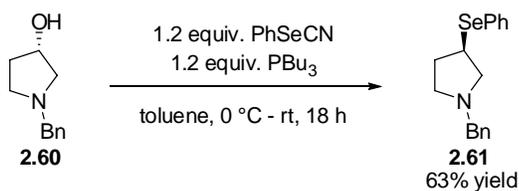


Reaction scheme showing the Pd-catalyzed decarboxylative selenation of allyl selenoformates (**2.58**) to allyl selenides (**2.59**). Conditions: 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 16 h.

Allyl	% Yield	Allyl	% Yield
 <b>2.58a</b>	82	 <b>2.58e</b>	83
 <b>2.58b</b>	66	 <b>2.58f</b>	72 <sup>b</sup>
 <b>2.58c</b>	95 <sup>a</sup>	 <b>(±)-2.58g</b>	99
 <b>2.58d</b>	90		

<sup>a</sup> Isolated as 3.9:1 mixture of *E/Z* isomers <sup>b</sup> Isolated as 10:1 mixture of *E/Z* isomers

We were a little surprised by the feasibility of this reaction. Sulfur and selenium containing compounds are known to “poison” palladium catalysts and we were concerned that this might be a problem for the decarboxylative coupling. The high conversions and good yields indicated that this did not hinder the reaction. We attributed this to the deactivation of the selenium lone pairs by the adjacent carbonyl which provides an electron deficient environment. While standard methods for the synthesis of allyl selenides have been modest at best in our hands, we were pleased to find a convenient route to these synthons by employing our simple decarboxylative coupling strategy. We were hopeful that the asymmetric synthesis of allyl selenides would be viable with the transition metal-catalyzed pathway. The asymmetric construction of carbon—selenium bonds utilizing electrophilic organoselenium reagents is widely known although the enantioselectivities of these reactions leave something to be desired.<sup>60</sup> However, there is much less precedence for asymmetric C—Se bond formation by means of a nucleophilic selenium reagent. One common strategy takes advantage of enantiospecific substitution reactions on chiral materials to interconvert functional groups (Scheme 2.33).<sup>60a</sup> This does not address the problem of generating new stereocenters at carbons which are bound to selenium.

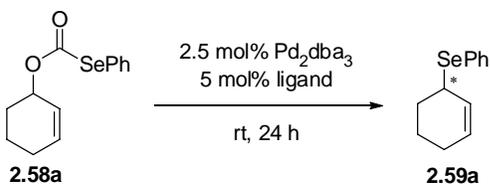
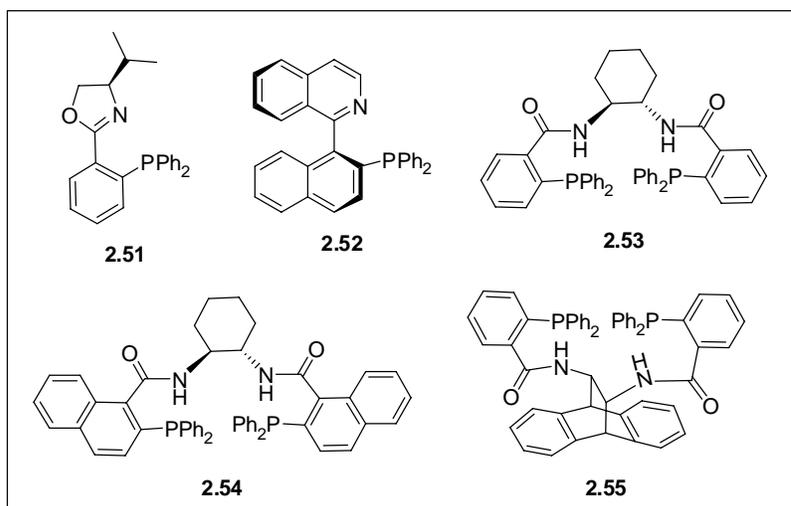


**Scheme 2.33**

### *Enantioselective Pd-Catalyzed Decarboxylative Selenation*

Therefore, we thought it a worthwhile attempt to extend the decarboxylative selenation toward asymmetric variants. To begin, **2.58a** was used as a model substrate to screen chiral ligands for their ability to induce enantioselectivity in the reaction (Table 2.5). While chiral ligands **2.51** and **2.52** did not react (entries 1-2), the Trost ligand (**2.53**) and its derivatives (**2.54**, **2.55**) proceeded to give products with moderately high enantioselectivities (entries 3-5). These reactions had problems with incomplete conversion and would slow down drastically after the first two to four hours of the reaction. In many cases, it was observed that the reaction had reached 50% conversion within the first two hours and then slow down severely, so as to only have reached 60-80% conversion after 24 hours. The naphthyl-Trost ligand (**2.54**) gave the highest enantiomeric ratios while still affording reasonable conversion.

**Table 2.5** Chiral Ligand Screening for Pd-Catalyzed Decarboxylative Selenation



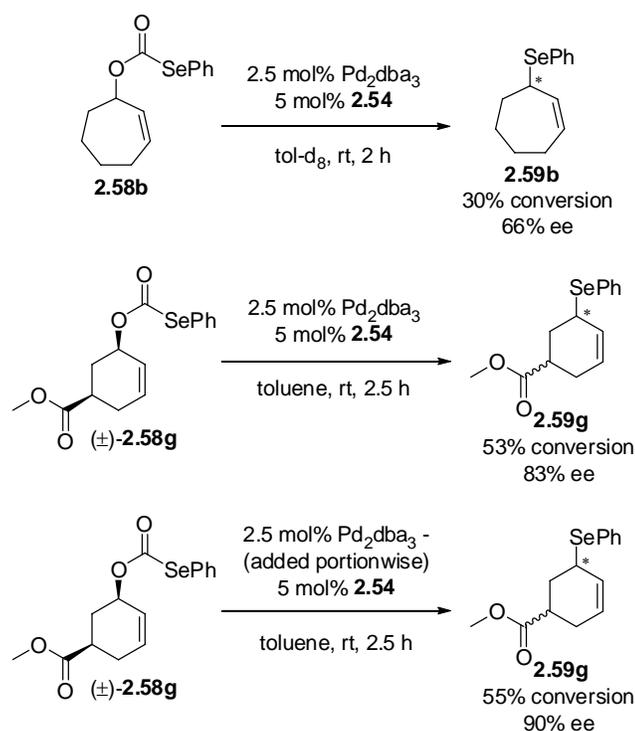
Entry	Ligand	Solvent	% Conversion	% ee
1	<b>2.51</b>	C <sub>6</sub> D <sub>6</sub>	12	ND
2	<b>2.52</b>	C <sub>6</sub> D <sub>6</sub>	NR	N/A
3	<b>2.53</b>	C <sub>6</sub> D <sub>6</sub>	78	28
4	<b>2.54</b>	C <sub>6</sub> D <sub>6</sub>	60	73
5	<b>2.55</b>	C <sub>6</sub> D <sub>6</sub>	88	14
6	<b>2.54</b>	Tol-d <sub>8</sub>	57	80
7	<b>2.54</b>	THF	50	69
8	<b>2.54</b>	CD <sub>2</sub> Cl <sub>2</sub>	92 <sup>a</sup>	60
9	<b>2.54</b>	C <sub>6</sub> D <sub>6</sub>	100 <sup>b</sup>	34
10	<b>2.54</b>	Tol-d <sub>8</sub>	60 <sup>c</sup>	80
11	<b>2.54</b>	Tol-d <sub>8</sub>	63 <sup>d</sup>	69
12	<b>2.54</b>	Tol-d <sub>8</sub>	59 <sup>e</sup>	87

<sup>a</sup> Reaction Run at 50 °C <sup>b</sup> Reaction run for 48 h <sup>c</sup> Premix catalyst and ligand prior to adding substrate <sup>d</sup> Reaction run at 0 °C <sup>e</sup> Ligand:Catalyst ratio = 2:1

As a means of trying to increase the conversion of the reaction, the reaction was heated to 50 °C in C<sub>6</sub>D<sub>6</sub> (entry 8). Indeed, this was enough to drive the reaction to completion, although a significant drop in enantioselectivity was observed. Longer

reaction times also allowed for complete conversion, but at the expense of the enantioselectivity (entry 9). Premixing the catalyst with the ligand prior to adding **2.58a** was unsuccessful in improving the conversion (entry 10). The reaction run at 0 °C in *tol-d*<sub>8</sub> surprisingly did not affect the conversion, but the enantiomeric excess of the product dropped to 69% (entry 11). Increasing the ligand to catalyst ratio did little to increase the conversion, but provided a slight boost in enantioselectivity (entry 12).

Two other compounds, **2.58b** and **2.58g**, were also tested for enantioselectivity. **2.58b** reacted to 30% conversion overnight with only a modest level of enantioinduction achieved (Scheme 2.34). Selenoformate **2.58g** was more successful with similar conversion and enantioselectivity as compared to the selenoformate **2.58a**. As a last attempt at effecting higher conversion, the palladium catalyst was added portionwise to the reaction mixture. This did not change the overall conversion, but did increase the enantiomeric excess to 90%, supporting the idea that increasing the ligand to palladium ratio is beneficial for asymmetric induction.



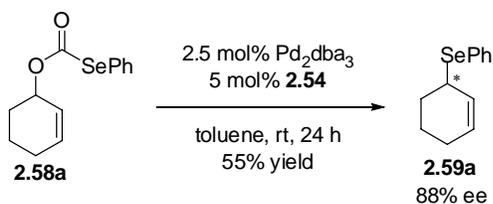
**Scheme 2.34**

### *Reaction Rate Suppression*

Although we have been unable to determine with confidence the reason for reaction rate suppression, we suspect it might be correlated with the formation of allyl selenide product. Recently, selenium containing ligands have been shown to coordinate transition metals and have emerging in the literature.<sup>61</sup> As sulfur and selenium possess similar properties, selenium can also serve as a soft donor to transition metals, such as palladium. However, this coordination may be detrimental to our reaction, as the allyl selenide can coordinate palladium through the  $\pi$ -bond and the selenium atom. Therefore, the product could potentially inhibit the reaction if it

binds to palladium more tightly than the substrate allyl, which would explain the severe decrease in reaction efficiency as the conversion passes 50%. The strong donating nature of  $\text{PPh}_3$  may have enough of an effect to prevent this phenomenon from occurring in the case of the achiral reactions.

Despite the inability to effect full conversion without drastically lowering the enantioselectivity, the allyl selenides could be easily isolated from the selenoformates. With a convenient method for asymmetric allylic selenation, we focused on obtaining enantioenriched allylic amines via the [2,3]-sigmatropic rearrangement. The reaction with selenoformate **2.58a** was scaled up (0.27 mmol) so that a modest amount of product could be isolated and used further. Allyl selenide **2.59a** was isolated in 55% yield and 88% ee (Scheme 2.35). The yield is rather high considering that the reaction conversions generally only proceed to <60% with these conditions. This procedure provided enough allyl selenide to perform test reactions for the [2,3]-sigmatropic rearrangements.



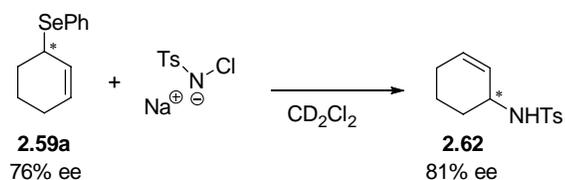
**Scheme 2.35**

### *Allylic Amination via [2,3]-Sigmatropic Rearrangement*

In 1972, Sharpless and Lauer first proposed the [2,3]-sigmatropic rearrangement with allyl selenides as a mechanism of the allylic oxidation of olefins with SeO<sub>2</sub>. Until this time, only sulfur derivatives had been reported to mediate this type of process.<sup>62</sup> Then, in 1979, Sharpless published a report which briefly included the oxidation of allyl selenides with reagents such as Chloramine-T and NCS to the allylic amines and chlorides, respectively.<sup>54</sup> The rearrangement of allyl phenyl sulfides with NCS was previously known,<sup>63</sup> but had not been applied to allyl phenyl selenides. Both the allylic amination and allylic chlorination were hypothesized to utilize the [2,3]-rearrangement to afford their respective products. Although reports on the chirality transfer from an enantioenriched allyl selenide to the respective allylic amine have not been disclosed, a previous example has been shown where a chiral ferrocenyl auxiliary on selenium afforded allylic amines with enantioselectivities as high as 87% upon treatment with [*N*-toluene-*p*-sulfonyl]imino]phenyliodinane.<sup>64</sup> We were hopeful that simple transfer of chirality would be possible in our system.

To begin, the racemic allyl selenide **2.59a** was treated with 2.5 equivalents of Chloramine-T in CD<sub>2</sub>Cl<sub>2</sub> and monitored by <sup>1</sup>H NMR spectroscopy. After only one hour the starting material had completely been consumed, but multiple products were present in the reaction mixture. Allowing the reaction to stand overnight did not provide any change. Since the reaction only proceeded to approximately 40% conversion, the crude product was partially purified on silica gel, although the product was contaminated with 28% *p*-tosyl amine. Next, we subjected our

enantioenriched allyl selenide (76% ee) to the same conditions. The reaction proceeded similarly to the achiral variant, but we were pleased to find that upon isolation of allyl amine **2.62** and separation via chiral HPLC, an enantiomeric excess of 81% was obtained (Scheme 2.36). The increase in enantiopurity could probably be attributed to the margin of error in the HPLC chromatogram integrations and was not a concern. This example demonstrates the ability to retain stereochemistry in the rearrangement from the allyl selenide, which is a potentially powerful synthetic tool. Further studies with Chloramine-T were discontinued as the reaction mixtures were not especially clean.

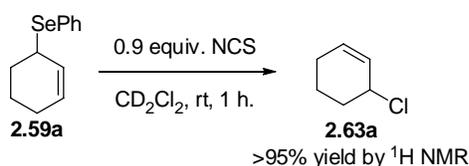


**Scheme 2.36**

#### *Allylic Chlorination via [2,3]-Sigmatropic Rearrangement*

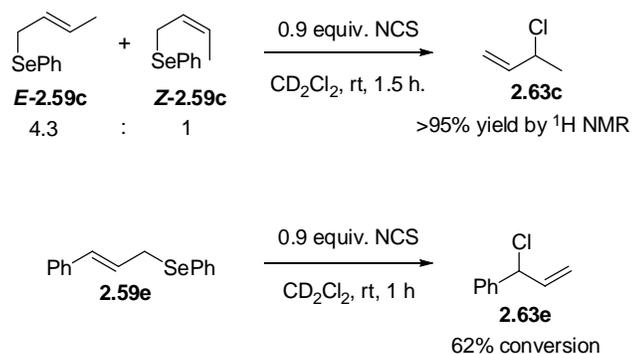
Previously, we attempted asymmetric allylic chlorination using selenium catalysts (Chapter 1, Section 1.2). Although this was unsuccessful, we were still interested in ways to obtain highly enantiopure allylic chlorides. As Sharpless previously reported, allyl selenides could easily be transposed to the allylic chlorides *via* [2,3]-sigmatropic rearrangement in the presence of NCS. Since we were able to transfer chirality from the allyl selenide to the allylic amine, we were hopeful that this reaction was possible for the allylic chlorination. First, NCS was added to **2.59a** in

$\text{CD}_2\text{Cl}_2$  as an attempt to reproduce the results of prior work (Scheme 2.37). We were pleased to find that allyl selenide **2.59a** had cleanly converted to allyl chloride **2.63a** in one hour at room temperature. Longer reaction times were detrimental to the formation of product, so close observation was necessary to determine completion. To prevent over-oxidation or over-chlorination of the resulting product, only 0.9 equivalents of NCS were used.



**Scheme 2.37**

The success of the achiral allylic chlorination prompted us to subject other substrates to the same conditions to determine if the transformation was general for other allyl selenides (Scheme 2.38). As expected, other substrates displayed similar behavior as **2.59a**. Allyl selenide **2.59c**, isolated as a mixture of *E/Z* isomers, afforded a single regioisomer of the terminal olefin (**2.63c**). Cinnamyl phenyl selenide (**2.59e**) was slower to react, reaching only 62% conversion in 1 hour, however it provided a very clean reaction mixture.



### Scheme 2.38

#### *Transfer of Chirality*

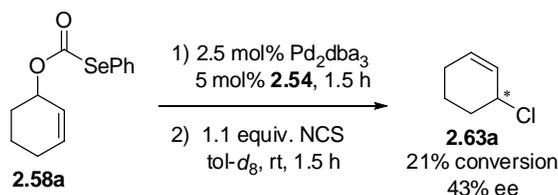
Enantioenriched allyl selenide **2.59a** (88% ee) was subjected to a limited screening of reaction conditions to determine if the chirality in the molecule would be maintained. The overall conservation of asymmetry was good in toluene, but significant racemization was observed in  $\text{CH}_2\text{Cl}_2$  (Table 2.6). Lowering the reaction temperature did not decrease racemization. With a higher conservation of asymmetry in toluene, it was demonstrated that a less polar solvent is beneficial for this reaction.

**Table 2.6** Chiral Allylic Chlorination from an Allyl Selenide

Solvent	Temperature (°C)	% ee
$\text{CH}_2\text{Cl}_2$	25	65
$\text{CH}_2\text{Cl}_2$	0	63
Toluene	25	82

The excellent retention of stereochemistry in toluene made us curious if both the decarboxylative selenation and [2,3]-sigmatropic rearrangement could be

performed in “one-pot”. These two reactions are compatible due to the oxidation of Pd(0) to Pd(II) by NCS. This is necessary to prevent reaction of Pd(0) species with the product allyl chloride. Therefore, selenoformate **2.58a** was treated with 2.5 mol% Pd<sub>2</sub>dba<sub>3</sub> and 5 mol% Np-Trost ligand (**2.54**) in tol-*d*<sub>8</sub> at room temperature (Scheme 2.39). After 1.5 hours, the reaction had reached 55% conversion to the allyl selenide. This reaction generally only proceeds to <60% conversion under these conditions, so at this point, 1.1 equivalents of NCS was added to the reaction mixture. Ideally, the excess NCS would oxidize the Pd(0) species to a Pd(II) species which would only be a spectator to the [2,3]-rearrangement. The reaction did afford allyl chloride, although in only 57% conversion from the allyl selenide (21% overall conversion from the starting selenoformate). It is plausible that the selenoformate was also reacting with the NCS, so additional equivalents of NCS might be necessary to effect complete conversion of allyl selenide **2.59a** to allyl chloride **2.63a**. The allyl chloride was determined to have a 43% ee. The enantioselectivity of the intermediate allyl selenide was not determined for this reaction, but if this step achieved a level of enantioselectivity similar to previous results (ca. 85%), then only ca. 50% of the chirality was conserved. This result did not reproduce previous “two-pot” results where the decarboxylative selenation and 2,3-sigmatropic rearrangement were run separately, but the results of the “one-pot” reaction provided a promising start as the conditions employed were completely unoptimized.



### Scheme 2.39

#### Summary

Our initial goal was to develop a methodology involving Pd-catalyzed decarboxylative allylation of heterocyclic amines. This reaction was a success as heterocyclic amines were readily allylated in the presence of catalytic Pd(PPh<sub>3</sub>)<sub>4</sub> and the products were obtained in high yields. The operative mechanism has yet to be completely understood, although initial support has been presented for a mechanism that incorporates decarboxylation prior to allylation. The asymmetric variant was somewhat limited in terms of enantioselectivity, as only modest enantiomeric excess was achieved. The ability to facilitate this allylic amination led us to other types of heteroatom allylation through decarboxylative coupling. Selenoformates proved to be exceptional substrates for the Pd-catalyzed decarboxylation strategy as high yields were obtained in most cases. The utility of this reaction was further increased by the good enantioselectivities that were achieved in the presence of chiral ligands, particularly the Np-Trost ligand (**2.54**). The stunted conversions of these reactants is an area which requires more attention as this would greatly increase the impact of the reaction. The allyl selenides are also useful intermediates for the synthesis of allylic amines and chlorides. While the allylic amination with Chloramine-T left something

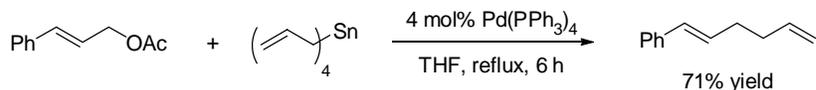
to be desired, the [2,3]-sigmatropic rearrangement facilitated by NCS was a fruitful endeavor. The formation of highly enantiopure allylic chlorides has not been previously reported and is worthy of further exploration. Altogether, we have developed a new decarboxylative allylic heteroatom coupling which could provide synthetic chemists with new possibilities in the area of allylic functionalization.

## **2.5 Background and Significance of Allyl-Allyl Coupling**

### *Hexadiene Synthesis via Allyl-Allyl Coupling*

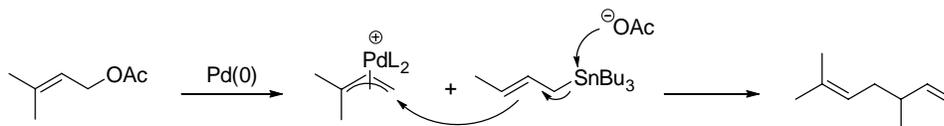
1,5-dienes are important class of molecules which have been identified as intermediates in a number of biosynthetic pathways.<sup>65</sup> This diene moiety can also be found in a variety of biologically active natural products.<sup>66</sup> Their biological significance makes their synthesis desirable. The synthesis of these hydrocarbon chains has been accomplished in a number of ways,<sup>67</sup> and palladium mediated allyl-allyl coupling has received much of the attention in this field.<sup>68</sup> The first catalytic allyl-allyl coupling was reported in 1968 by Corey and coworkers.<sup>69</sup> This reaction was catalytic in nickel, but this method was not synthetically useful as homocoupling was observed when different allyl groups were employed. Since the initial Tsuji report on electrophilic palladium- $\pi$ -allyl substitution the scope of carbon—carbon bond formation has expanded to include a variety of carbon nucleophiles. However, the coupling of two allyl groups is particularly challenging due to loss of geometrical integrity during the reaction as well as problems with homocoupling. In 1980, Trost reported the palladium-catalyzed coupling of an allylic acetate and an allylstannane

(Scheme 2.40).<sup>70</sup> The reaction proceeded in moderate yields, but was one of the first examples of allyl-allyl cross-coupling.



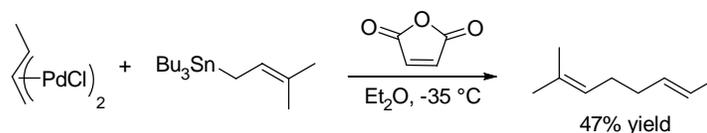
### Scheme 2.40

Separately, and almost simultaneously, Stille also published the palladium-catalyzed allyl-allyl coupling of allylstannanes with allylic acetates.<sup>71</sup> However, rather than using Pd(PPh<sub>3</sub>)<sub>4</sub>, allyl bromides were reacted in the presence of a palladium(II) precatalyst with a catalytic amount of ZnCl<sub>2</sub> to afford similar 1,5-hexadiene products. Interestingly, both methods exhibited decreased yields with increased substitution on the olefin of the allylstannane. In many cases where organostannanes are used in cross-coupling reactions, a generally accepted mechanism involves delivery of the alkyl group *via* transmetalation from tin to palladium, followed by reductive elimination to afford the coupled product. However, this mechanism did not explain branched product formation as the carbon distal from the tin was found to be the nucleophilic center that attacked the electrophilic  $\pi$ -allyl species (Scheme 2.41). It could also be possible that a similar attack onto palladium followed by reductive elimination could afford the same regioisomer.



### Scheme 2.41

While these contributions were a significant improvement in the area of allylic cross-coupling, the limits of the reaction were still not well defined. Following this, Schwartz communicated the synthesis of unsymmetrical bis(allyl)Pd complexes, which was made possible *via* the addition of an allyl Grignard reagent to a preformed Pd- $\pi$ -allyl species. Although this reaction was not catalytic, it showed that the bis(allyl)Pd complex was stable to reductive elimination. The addition of a  $\pi$ -acidic ligand, such as maleic anhydride, initiated reductive coupling of the two allyl species, forming the hexadiene product, where the new bond was formed between the two least hindered carbons. Schwartz also studied the addition of organostannanes to the preformed allyl-Pd(II) species and observed similar results as the allylic Grignard reagents in terms of yields and the need for maleic anhydride. Lastly, the reaction was rendered catalytic by employing only 1 mol%  $[(\eta^3\text{-allyl})\text{PdCl}]_2$  with an allyl halide, allylstannane, and maleic anhydride, and observed the formation of the respective 1,5-dienes (Scheme 2.42). Since Schwartz again observed substitution at the least hindered allyl termini, he reasoned that a  $(\eta^3\text{-allyl})(\eta^1\text{-allyl})\text{Pd}$  species is formed and then reductive elimination can occur in the presence of maleic anhydride.



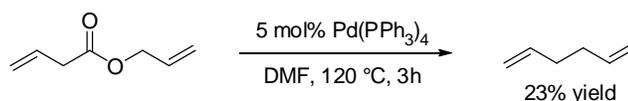
**Scheme 2.42**

The aforementioned methods are important advancements in the field of allyl-allyl coupling, but the reactions are still less than ideal since they require the use of

stoichiometric, toxic tin reagents and suffer from low yields. The use of Grignard reagents eliminates toxicity issues but these reagents are very basic, highly reactive and not compatible with catalytic coupling procedures. Allyl boronates<sup>72</sup> and allyl silanes<sup>73</sup> have also been used in Pd-catalyzed allylic cross-coupling resulting in hexadiene formation with reasonable regioselectivities and good yields. There are limited examples of these types of couplings, but they still fail to demonstrate coupling between highly substituted allyls.

#### *Decarboxylative Methods for Hexadiene Synthesis*

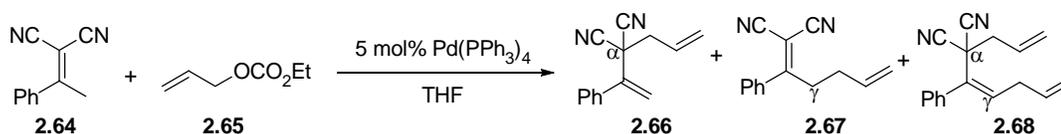
A different approach was taken by Saegusa in 1980.<sup>74</sup> The focus of the paper was on the generation of enolates via the Pd(0)-catalyzed decarboxylation of allyl  $\beta$ -ketoesters. However, a single example is included where a bisallylic ester was treated with 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in DMF and heated to 120 °C (Scheme 2.43). After three hours, 1,5-hexadiene was formed in a 23% yield as monitored by gas chromatography. Although the yield was low, the result was noteworthy as the nucleophilic allyl group was generated *via* decarboxylation rather than through transmetalation from tin and afforded CO<sub>2</sub> as the only byproduct.



#### **Scheme 2.43**

In 1999, Yamamoto and coworkers disclosed the Pd-catalyzed coupling of allyl ethyl carbonate (**2.65**) and the allylic position of activated olefins (**2.64**).<sup>75</sup>

Reaction of these two allyl moieties in the presence of catalytic Pd(0) afforded mixtures of  $\alpha$ -allylated (**2.66**) and  $\gamma$ -allylated (**2.67**) products, as well as the diallylated product (**2.68**). The ratio of these products was seemingly dependent on the amount of allyl ethyl carbonate in the reaction mixture relative to the olefin. Use of only one equivalent of allyl ethyl carbonate slightly decreased the yield, but gave a large increase of the  $\gamma$ -allylated product with a minimal amount of diallylation product. Increasing the temperature to just 50 °C completely reversed the selectivity, such that the  $\alpha$ -adduct was no longer observed. This phenomena was rationalized by a Pd(0)-catalyzed Cope rearrangement of the hexadiene products. Thermal<sup>76</sup> and Pd(II)-catalyzed<sup>77</sup> Cope rearrangements have been well documented in the literature, but this was the first example of a Pd(0)-catalyzed Cope rearrangement.



Equiv. 2.65	Temp (°C)	Yield (%)	2.66:2.67:2.68
1	25	82	68:24:8
2.5	25	100	78:0:22
2.5	50	76	0:11:89

#### Scheme 2.44

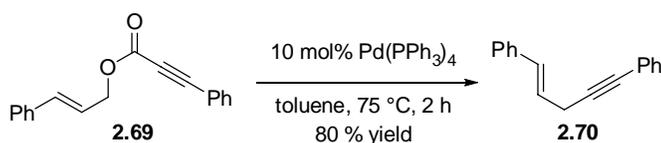
The Pd-catalyzed allyl-allyl coupling was also noteworthy, as high yields were obtained under mild reaction conditions, but the reaction was limited by poor regioselectivity and/or diallylation. Also, aryl (or quaternary carbon) substitution was necessary to afford regioselective deprotonation. Since we knew that Pd-catalyzed

decarboxylation generates anions regioselectively, it seemed that this type of method might allow for more diverse substrates.

## 2.6 Tandem Palladium-Catalyzed Decarboxylative Allyl-Allyl Coupling/Cope Rearrangement

### *Pd-Catalyzed Decarboxylative Metalation – Allyl-Acetylide Coupling*

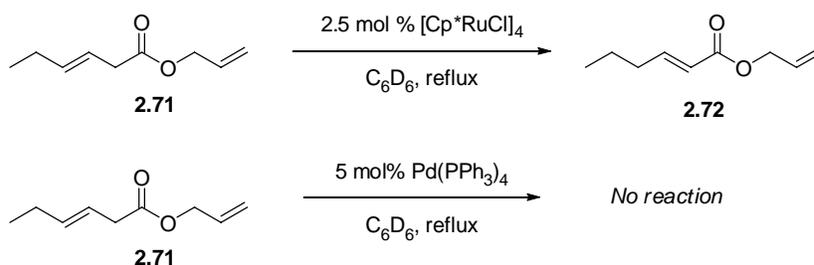
Prior to our studies in this area, a member of our group, Dinesh Rayabarapu, had developed a method for the Pd-catalyzed decarboxylative sp-sp<sup>3</sup> coupling of allyl electrophiles with acetylides (Scheme 2.45).<sup>78</sup> One of the remarkable features of this reaction was the ability to circumvent transmetalation of organometallic reagents, which are generally necessary to effect this type of coupling.<sup>79</sup> Alkyl-substituted allyls could even be employed in this reaction without competing β-hydride elimination.



### Scheme 2.45

After discovering the feasibility of this reaction, we thought it would also be desirable to extend the decarboxylative metalation method to other types of coupling which require a transmetalation step. We were initially curious as to whether simple allyl butenoates would be compatible reactants for the transition metal mediated decarboxylative coupling. Initially, **2.71** was subjected to catalytic amounts of

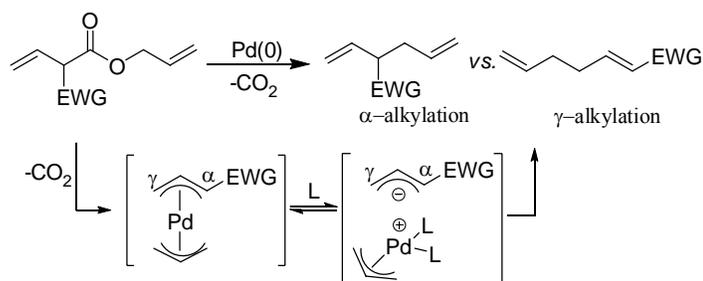
[RuCp\*Cl]<sub>4</sub> or Pd(PPh<sub>3</sub>)<sub>4</sub> in C<sub>6</sub>D<sub>6</sub> and heated to reflux (Scheme 2.46). Isomerization to the thermodynamically stable  $\alpha,\beta$ -unsaturated ester (**2.72**) in the presence of the ruthenium catalyst was observed, but decarboxylative coupling was not observed with either catalyst. Moreover, heating the reactions in a microwave reactor at 180 °C using polar solvents (CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>) was not effective.



**Scheme 2.46**

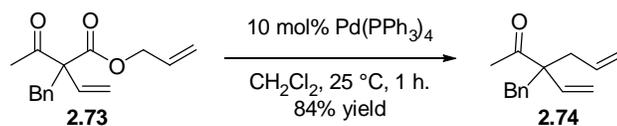
#### *Electron-Withdrawing Substitution for Decarboxylative Allyl-Allyl Coupling*

Based on this and prior experience in our group, we reasoned that rate of decarboxylation is dependent upon the  $pK_b$  of the anion generated following loss of CO<sub>2</sub>. Therefore, we reasoned that an electron-withdrawing group (EWG) strategically placed on the nucleophilic allyl fragment could aid in stabilization of the allylic anion (Scheme 2.47). Similar to Yamamoto's work, the allylation has potential to occur at either the  $\alpha$ - or  $\gamma$ -positions to the EWG of the receptor, although we were hopeful that multiple allylations would not be as prominent since only one equivalent of the nucleophilic allyl would be present.



**Scheme 2.47**

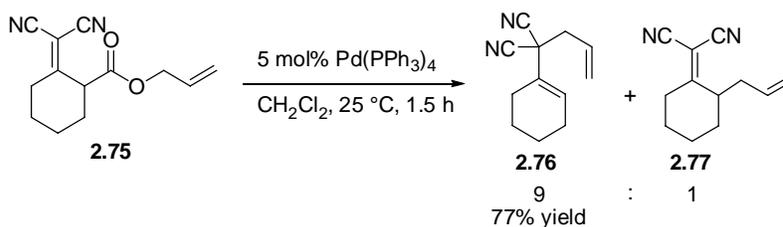
The first electron-withdrawing group tested was a simple ketone.<sup>80</sup> Since the synthesis of allyl  $\beta$ -ketoesters had been widely used in our group, this was a natural extension of our prior work and was examined by Dinesh Rayabarapu.  $\text{In}(\text{OTf})_3$ -catalyzed vinylation of the allyl  $\beta$ -ketoesters with acetylenes is a known procedure which allowed for the synthesis of **2.73** and its derivatives.<sup>81</sup> When treated with 10 mol%  $\text{Pd}(\text{PPh}_3)_4$ , decarboxylation proceeded smoothly at room temperature affording only the  $\alpha$ -allylated product (**2.74**) in good yield (Scheme 2.48). Overall, the procedure was effective for a variety of substrates, with good isolated yields and completely selective for  $\alpha$ -allylation.



**Scheme 2.48**

We were also interested in the effects of an EWG on the allyl terminus, such as a nitrile, and thus the vinylogous dicyano derivative was synthesized. This was possible through simple condensation of malononitrile onto the allyl  $\beta$ -ketoester to afford the alkylidene malononitrile (**2.75**). These substrates resembled the

dicyanosubstituted olefins which Yamamoto was also able to allylate. When **2.75** was tested with catalytic Pd(PPh<sub>3</sub>)<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub>, the reaction swiftly converted to a 9:1 mixture of regioisomers **2.76** and **2.77** (Scheme 2.49). These products could be easily separated *via* purification on silica gel and the product of α-allylation was isolated in 77% yield.



**Scheme 2.49**

#### *Extensions of Allyl-Allyl Coupling from Alkylidene Malononitriles*

The facile decarboxylation and high regioselectivity of **2.75** prompted us to test other alkylidene malononitriles (Table 2.7). It should be noted that these substrates were stable in the absence of catalyst even at elevated temperatures, although mono-α-substitution was necessary to prevent decomposition of the starting material. Primary, substituted, cyclic, and acyclic allyl esters were incorporated with no deleterious effect. In some cases, a decrease of regioselectivity was observed, but reaction was still robust as good yields were obtained. Since the thermodynamically more stable product is that of γ-allylation forming the α,β-unsaturated system, the α-allylation must be a result of kinetic allylation. The data also show that γ-allylation can be avoided if a sufficiently large allyl group is used. The major α-allylated

products for substrates (**2.78d-j**) were determined to have the *E*-configured olefin by nOe enhancement studies. Two substrates (**2.78d** and **2.78e**) afforded a mixture of *E/Z* isomers upon reacting, although the *E*-isomer was still highly favored.

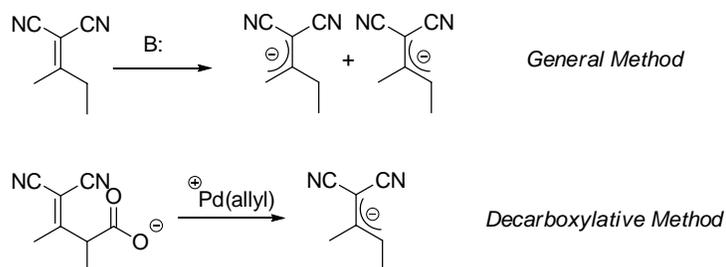
**Table 2.7** Pd-Catalyzed Decarboxylative Coupling of Alkylidene Malononitriles

Substrate	2.79:2.80	Yield(%)	Substrate	2.79:2.80	Yield(%)
 <b>2.78a</b>	78:22	71	 <b>2.78f</b>	79:21	58 <sup>c</sup>
 <b>2.78b</b>	>97:3	97	 <b>2.78g</b>	62:38	76 <sup>c</sup>
 <b>2.78c</b>	93:7	84	 <b>2.78h</b>	86:14	97 <sup>c</sup>
 <b>2.78d</b>	>95:5 <sup>a</sup>	84	 <b>2.78i</b>	84:16	91 <sup>c</sup>
 <b>2.78e</b>	>95:5 <sup>b</sup>	92	 <b>2.78j</b>	>95:5	93

<sup>a</sup> *E:Z* = 15:1 <sup>b</sup> *E:Z* = 8.3:1 <sup>c</sup> Combined yield of two isomers

As mentioned, one of the inherent advantages of the decarboxylative method was the regioselective generation of carbanions (Scheme 2.50). Thus, other aliphatic  $\alpha$ -substituents can be present with no deleterious effects on the regioselectivity. This is in stark contrast to  $\alpha$ -deprotonation using a strong base which is less capable of

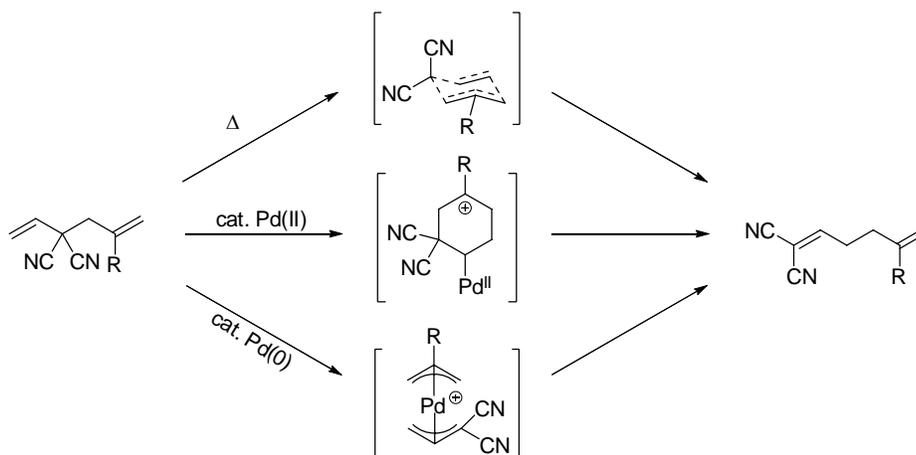
differentiating between the two positions and represents a common problem in organic synthesis.



**Scheme 2.50**

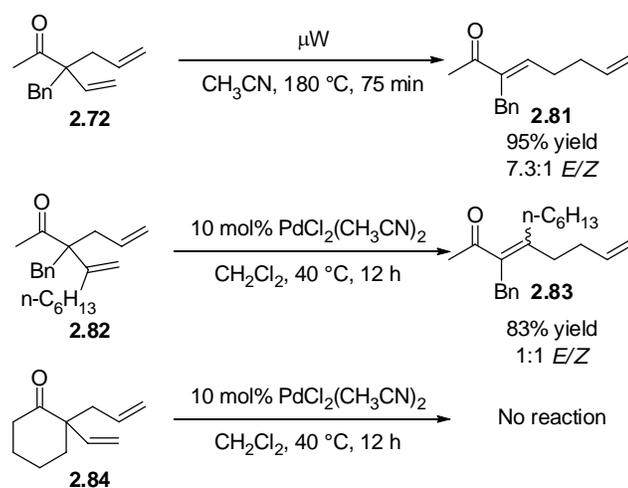
#### *Cope Rearrangement of 1,5-Hexadiene Products*

The formation of the less stable hexadiene product led to the possibility of equilibrating to the thermodynamic product by means of a Cope rearrangement, which can be facilitated by thermal means, palladium(II), or palladium(0) catalysis (Scheme 2.51). It has generally been accepted that the thermal Cope rearrangement proceeds through a “chair-like” transition state, which is capable of transferring chirality from the starting hexadiene to the product.<sup>82</sup> The palladium(II)-catalyzed reaction is less well understood, but is proposed to proceed through a cationic intermediate. Only one example is known for the palladium(0)-catalyzed Cope rearrangement and it is by far the least well understood in terms of stereochemical control and mechanism. Keeping this in mind, we thought it would be useful to be investigate each of these conditions as a means for producing the thermodynamically stable  $\alpha,\beta$ -unsaturated product.



**Scheme 2.51**

With this in mind, unsaturated ketone **2.72** was placed in a microwave reactor at 180 °C for 75 minutes and the desired  $\alpha,\beta$ -unsaturated ketone (**2.81**) was isolated in excellent yield (Scheme 2.52). When employing the conditions of Pd(II) catalysis for ketone **2.82**, the thermodynamic product was realized in a good yield, albeit as a 1:1 mixture of *E/Z* isomers. Hexadiene **2.84** was also tested under identical conditions, however no reaction was observed. This is due to the lack of substitution at the 2- or 5-position of the hexadiene which is required to stabilize the cationic intermediate. Thus, the thermal rearrangement was preferred over the Pd(II)-catalyzed conditions which required longer reaction times and afforded lower yields.

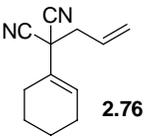
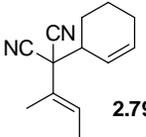
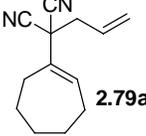
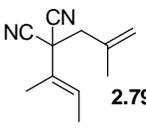
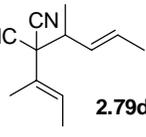
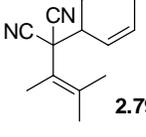


**Scheme 2.52**

The addition of electron-withdrawing substituents on the carbon skeleton of the hexadiene has been shown to have a pronounced effect on the rate of the Cope rearrangement by facilitating bond breakage in the transition state. This enhancement was also observed when heating the kinetic products of the decarboxylative coupling of the alkylidene malononitriles. The thermal rearrangements could be run at lower temperatures for shorter reaction times than their ketone substituted counterparts. For example, the rearrangement of **2.76** was complete in only 30 minutes at  $150\text{ }^\circ\text{C}$  (Table 2.8), while ketone **2.72** required 75 minutes at  $180\text{ }^\circ\text{C}$  to reach complete conversion (Scheme 2.52). One exception was tetrasubstituted olefin **2.79j** which required much longer reaction times to reach complete conversion (200 minutes). Generally, the yields for the thermal rearrangement were near quantitative and the products were obtained with high diastereoselectivity. When subjected to the conditions of Pd(II)-catalysis, the product was obtained with similar

diastereoselectivity as the thermal reaction, albeit in decreased yield and reduced reaction rate.

**Table 2.8** Cope Rearrangement of Substituted 3,3-Dicyanohexa-1,5-dienes

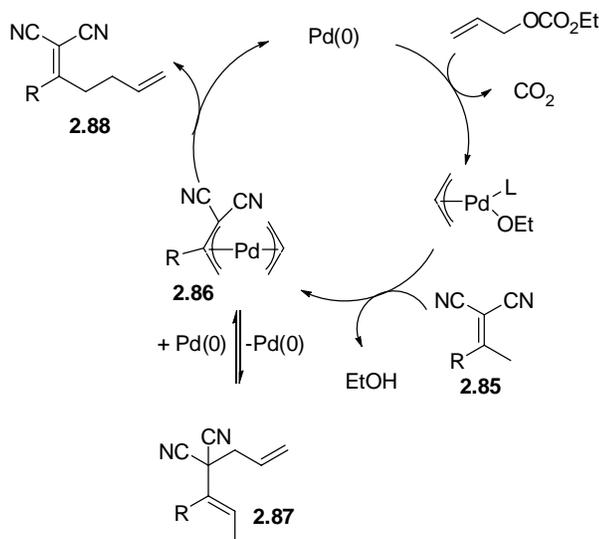
Substrate	Conditions	% Yield (dr)	Substrate	Conditions	% Yield (dr)
	A	94		A	98 (9.3:1)
	A	99		A	96
	A B	99 (12.4:1) 71 (11.2:1)		C	76

Conditions: A:  $\mu$ W, 150 °C, 30 min.; B: 10 mol% PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, 40 °C, 12 h.; C:  $\mu$ W, 150 °C, 200 min.

### *Pd(0)-Catalyzed Cope Rearrangement*

Overall, the thermal rearrangement afforded clean reaction products and excellent yields. When substituted allyls were used, the sigmatropic rearrangement gave rise to products with contiguous stereocenters in high diastereoselectivity. However, we had not yet addressed the Pd(0)-catalyzed Cope rearrangement, and we were curious as to whether this system would be amenable to this reaction. In their report, Yamamoto proposed a mechanism where bis(allyl)Pd intermediate **2.87** was formed upon oxidative addition of  $\alpha$ -allylated product **2.88** (Scheme 2.53). The breaking of a carbon-carbon bond can be facilitated because of the anion stabilization

provided by the nitrile groups. Since this is a reversible process, the cycle continues until complete equilibration to the thermodynamic product (**2.89**) is achieved.



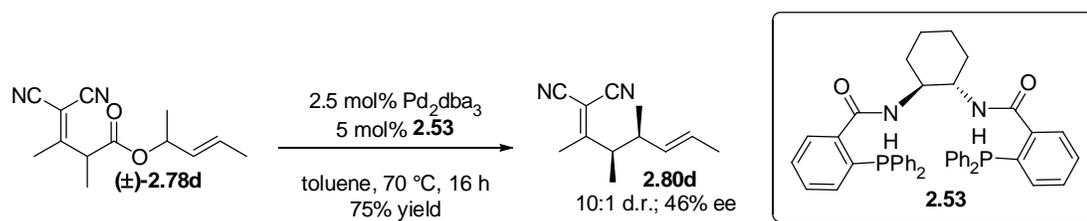
### Scheme 2.53

As shown, Yamamoto chooses to depict **2.86** as the bis( $\eta^3$ -allyl)Pd(II) species. However, the formation of the bis(allyl)Pd complex could also be represented as an ( $\eta^3$ -allyl)( $\eta^1$ -allyl)PdPPh<sub>3</sub> species (**2.90**) as this has been shown to be a contributing intermediate in the presence of phosphine ligands. The idea that both allyl groups were bound to palladium seemed debatable as a rather stable anion may exist as a freely diffusing species (**2.91**) in solution. This hypothesis is based on the observations of previous systems similar to this type where freely diffusing ions lead to a mixture of crossover products.



### *Asymmetric Extensions of Tandem Decarboxylative Coupling/Cope Rearrangement*

After discovering the ability to run the reactions in tandem, we began to explore the possibility of an asymmetric variant as a way of accessing enantioenriched substituted 1,5-hexadienes. To begin, **2.78d** was treated with 2.5 mol% Pd<sub>2</sub>dba<sub>3</sub> and 5 mol% of Trost ligand (**2.53**) in toluene at 70 °C (Scheme 2.56). After 16 hours, the reaction was complete to the  $\gamma$ -allylated product (**2.80d**) and a good yield was obtained. The enantiomers were separated *via* chiral gas chromatography and upon comparing the results to a racemic sample, it was determined that the reaction afforded 46% ee and a diastereoselectivity of 10:1 in favor of the *cis*-substituted isomer. The relative stereochemistry was postulated by employing a standard chair conformation for the transition state of the Cope rearrangement.

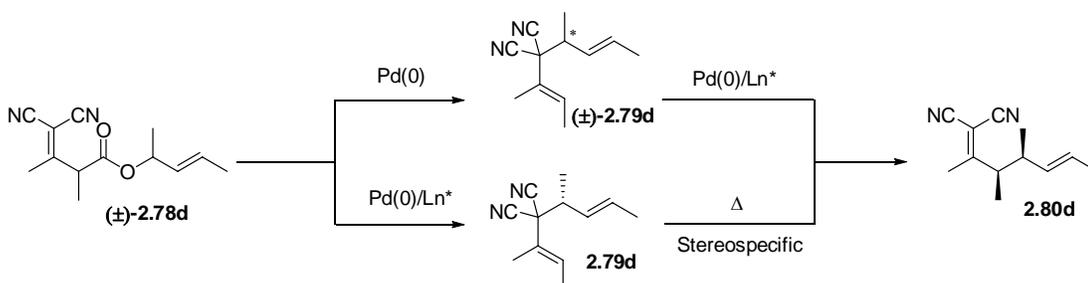


### **Scheme 2.56**

#### *Studies on the Stereochemistry Determining Step*

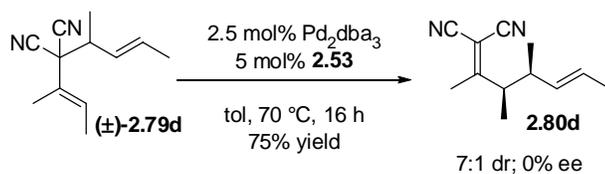
These results showed promise and we became curious as to the nature of asymmetric induction. Since palladium can catalyze both the decarboxylative allylation and the Cope rearrangement, the enantioselectivity of a chiral kinetic

allylation product was unclear, as the stereochemistry could be scrambled after the first step and reset in the palladium-catalyzed Cope rearrangement. Despite the tandem process, only one transformation could be defined as the stereochemistry determining step (Scheme 2.57). In the top pathway, even if a chiral palladium source were used for the decarboxylative allylation, the palladium-catalyzed Cope rearrangement would racemize **2.79d** upon oxidative addition to form the bis(allyl)Pd(II) intermediate. Thus, the stereochemistry determining step would be formation of the  $\gamma$ -allylated product. In the lower pathway, the stereochemistry of the kinetic  $\alpha$ -allylation product is first defined by the chiral palladium catalyst and then is stereospecifically converted to the thermodynamic product (**2.80d**) through a thermal Cope rearrangement.



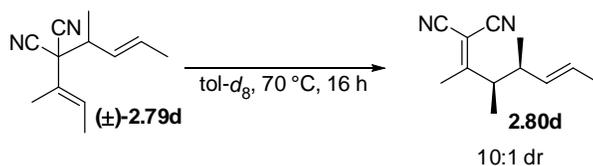
### Scheme 2.57

To distinguish these pathways, a racemic mixture of **2.79d** was heated in the presence of 2.5 mol% Pd<sub>2</sub>dba<sub>3</sub> and 5 mol% Trost ligand (**2.53**) (Scheme 2.58). As expected **2.80d** was isolated in 75% yield with a diastereomeric ratio of 7:1, but the product was completely racemic.



### Scheme 2.58

At this point, we were suspicious that palladium was not catalyzing this rearrangement, so **2.79d** was heated in tol-*d*<sub>8</sub> at 70 °C in the absence of palladium. Monitoring the reaction by <sup>1</sup>H NMR spectroscopy showed that after 16 hours, only the γ-allylated product (**2.80d**) was present in the solution. This was evidence that palladium was indeed not catalyzing this reaction, and the thermal Cope rearrangement was responsible for the thermodynamic product formation.



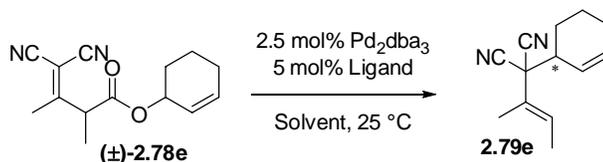
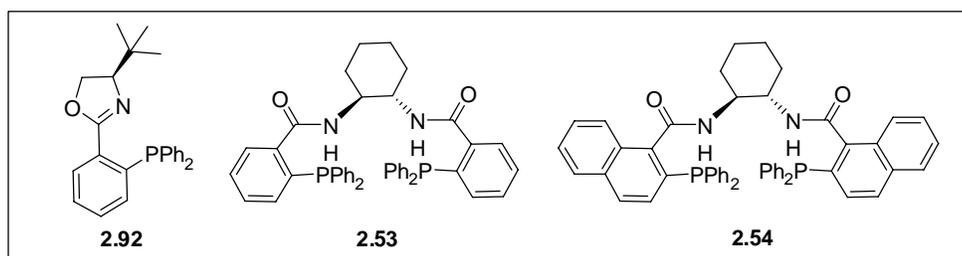
### Scheme 2.59

The combined information from these experiments led us to believe that only the rearrangement of the kinetic product **2.79i** to **2.80i** was catalyzed by palladium(0). We reasoned that the lack of allylic substituents allowed for nucleophilic attack to occur more readily than in the cases where more sterically congested allyl groups were present (**2.79d**). It was also concluded that the stereoselectivity must be determined in the first allylation step and then rely on the thermal Cope rearrangement to transfer the chirality to the γ-allylated product.

### Chiral Ligand Screening

Initial attempts in chiral ligand screening were performed to favor formation of the kinetic product of allylation, so the reaction mixtures were run at ambient temperature. As Table 2.9 displays, the reactions were considerably slower using the chiral ligand/palladium combinations than when using Pd(PPh<sub>3</sub>)<sub>4</sub>. In terms of enantioselective induction, the reaction with the naphthyl-Trost ligand (**2.54**) was the most effective, providing a moderate 76% ee, although the reaction suffered from incomplete conversion.

**Table 2.9** Chiral Ligand Screening for Synthesis of **2.79e**



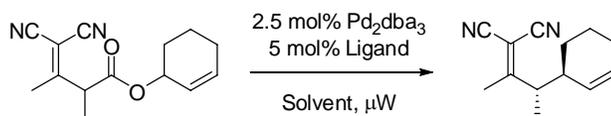
Ligand	Solvent	Time(h)	Conversion	%ee
<b>2.92</b>	C <sub>6</sub> D <sub>6</sub>	16	NR	--
<b>2.53</b>	tol- <i>d</i> <sub>8</sub>	2	100%	36
<b>2.54</b>	tol- <i>d</i> <sub>8</sub>	16	50%	76
PPh <sub>3</sub>	CD <sub>2</sub> Cl <sub>2</sub>	1.5	100%	N/A

Heating the reactions aided in driving them toward completion, but at higher temperatures the rate of the Cope rearrangement was competitive with the rate of allylation. We then decided to take advantage of the “one pot” tandem reaction as to

isolate only the thermodynamic product. First, the reactions were heated in an oil bath at reflux in *tol-d*<sub>8</sub> and dioxane (Table 2.10, entries 1,2). The rearrangements were rather slow at these temperatures, so we switched to a microwave reactor. This allowed for the screening process to be faster as the reactions were usually done within 2-3 hours, rather than the 16 hours required when an oil bath was used. Reaction optimization was approached from many angles, including varying the ligand, solvent and temperature. The results obtained demonstrated that solvent choice played a large role in effectiveness in terms of enantioselectivity (entries 3-7), with ClCH<sub>2</sub>CH<sub>2</sub>Cl affording the highest enantioselectivity. The naphthyl-Trost ligand (2.54) produced the highest enantiomeric ratios, as well as generally good diastereoselectivities. Decreasing the reaction concentration displayed a negative effect on diastereoselectivity, but increased the enantioselectivity slightly (entry 9). Lowering the catalyst loading to 1.25 mol% did not have a positive effect on the enantioselectivity, although high levels of diastereoselectivity were maintained (entry 10). Reducing the reaction time to 1.5 hours provided the optimal conditions as the reaction was still complete, while still achieving high enantiomeric excess and good diastereocontrol (entry 12). Lastly, it should be mentioned that toluene is generally a poor solvent for microwave conditions, but the addition of a small amount of ionic liquid allows it to reach temperatures much higher than it normally can attain. This combination was also tried, but the reaction gave poor enantio- and diastereoselectivities and was not pursued further (entry 14). More work on this

system is necessary to understand the influencing factors on enantioselectivity and particularly on the diastereoselectivity.

**Table 2.10** Optimization of the Enantioselective Tandem Decarboxylation/Cope Rearrangement



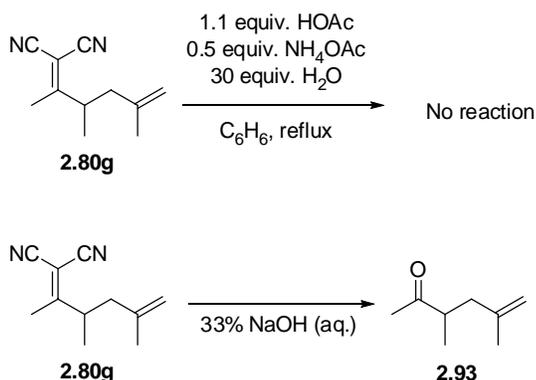
Entry <sup>a</sup>	Ligand	Solvent	Temp. (°C)	Time (h)	dr	%ee
1 <sup>b</sup>	2	tol- <i>d</i> <sub>8</sub>	110	48	4.8:1	73
2 <sup>b</sup>	2	Dioxane	100	48	13.3:1	70
3	2	THF	140	3	7.3:1	64
4 <sup>c</sup>	2	CH <sub>2</sub> Cl <sub>2</sub>	120	3	6.4:1	87
5	2	CH <sub>3</sub> CN	150	2	5.5:1	80
6	2	C <sub>6</sub> H <sub>5</sub> Cl	150	2	6.3:1	74
7 <sup>d</sup>	2	CICH <sub>2</sub> CH <sub>2</sub> Cl	150	3	1.8:1	93
8	1	CICH <sub>2</sub> CH <sub>2</sub> Cl	150	2	6.8:1	63
9	3	CICH <sub>2</sub> CH <sub>2</sub> Cl	150	2	5.3:1	79
10 <sup>e</sup>	2	CICH <sub>2</sub> CH <sub>2</sub> Cl	150	3	8.1:1	82
11	2	CICH <sub>2</sub> CH <sub>2</sub> Cl	150	1.5	5.4:1	90
12	2	CICH <sub>2</sub> CH <sub>2</sub> Cl	180	0.5	4.9:1	89
13 <sup>g</sup>	2	toluene/ IL	150	1.5	3:1	57

<sup>a</sup> All reactions heated in microwave reactor at 8 mM unless otherwise noted <sup>b</sup> Heated using an oil bath  
<sup>c</sup> Ratio of products  $\alpha:\gamma$  (1:1.5) <sup>d</sup> Reaction run at 2 mM <sup>e</sup> Used 1.25 mol% Pd<sub>2</sub>dba<sub>3</sub>  
<sup>f</sup> IL = 1-ethyl-3-methylimidazolium chloride

### Synthetic Applications via Functional Group Interconversion

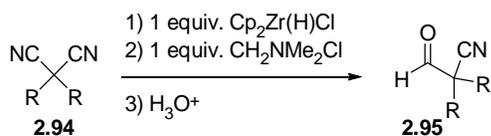
We were pleased with successful optimization of the asymmetric variant, but other substrates had not been tested. At the outset of the project, we were anticipating using the nitriles as a handle for further functionalization since they can be transformed into a variety of other functional groups, such as carboxylic acids, amides, amines, and ketones. Attempts to facilitate the transformation of the dicyano group back to the ketone from whence it came were made by using a similar procedure to the original Knoevenagel conditions. NH<sub>4</sub>OAc, HOAc, and H<sub>2</sub>O were

added to a solution of **2.80g** in  $C_6D_6$  and heated to reflux overnight, after which time no reaction was observed and only starting material was recovered (Scheme 2.60). Since acidic conditions were unsuccessful, we tried hydrolysis using basic conditions. To this end, **2.80g** was stirred in a solution of 33% NaOH and heated to 50 °C for 1 hour. This reaction cleanly hydrolyzed the malononitrile to afford ketone **2.93**.



### Scheme 2.60

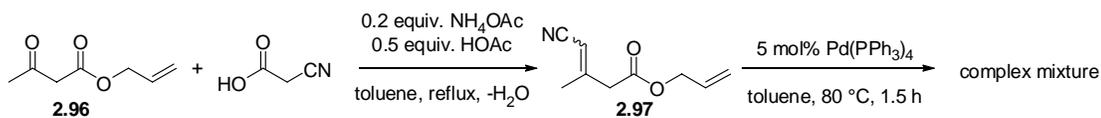
Although the reaction provided a route to convert the nitrile groups into a more synthetically useful functional group, the strongly basic were not ideal as substrates with  $\alpha$ -stereocenters could be easily racemized, but we have not yet found a solution to this problem. The importance of this step should not be overlooked as further functionalization will be necessary for synthetic utility. However, we remained optimistic upon finding a report that describes the use of Schwartz's reagent as a method for the hydrozirconation of geminal dinitrile compounds (**2.94**).<sup>83</sup> Following the addition of an equivalent of Schwartz's reagent, an iminium salt [CH<sub>2</sub>NMe<sub>2</sub>]Cl was then added to form the imine which could then be hydrolyzed to the aldehyde on silica gel (Scheme 2.61).



### Scheme 2.61

#### *Decarboxylative Coupling of Mononitrile Substrates*

The strong electron-withdrawing nature of two nitriles was an important factor in the rate of decarboxylation as the incipient anion was well-stabilized by these groups. However, we were curious as to whether decarboxylation of substrates with a single nitrile would be possible. In pursuit of this answer, the vinylogous nitrile **2.97** was synthesized via a condensation between the allyl β-ketoester and cyanoacetic acid, which was isolated as a mixture of *E/Z* isomers (Scheme 2.62). Upon reaction with 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in toluene at 80 °C, it was apparent that decarboxylation was occurring and that some sort of allylation was taking place, but even upon purification the complex mixture of products could not be separated.



### Scheme 2.62

This reaction was not as clean as the alkylidene malononitrile substrates, but it was still evident that the lone cyano group was capable of facilitating decarboxylation. This was not surprising as Saegusa has previously reported the

decarboxylation of cyanoacetic ester, of which our substrates were vinylogous analogues.

### *Summary*

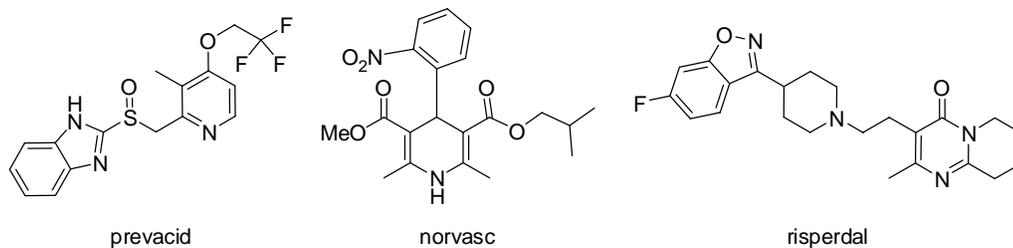
Overall, we have broadened our Pd-catalyzed decarboxylative coupling methodology to include the coupling of two  $sp^3$ -hybridized carbon through the cross-coupling of allyl groups. The addition of electron-withdrawing substituents, such as ketones and nitriles, onto the nucleophilic allyl fragment was capable of stabilizing the negative charge buildup following decarboxylation. Interestingly, this substituent could be placed on either terminus of the allylic moiety and still provide a productive reaction pathway. The decarboxylative allyl coupling provided the  $\alpha$ -allylated product which could be converted to the thermodynamic  $\gamma$ -allylated hexadiene *via* a Cope rearrangement, providing access to either regioisomer of the 1,5-hexadiene products. Further we have confirmed that when unsubstituted allyl esters are used, the Cope rearrangement can be catalyzed by Pd(0), but this is not applicable for substituted allyl groups as the additional steric hindrance disfavors reinsertion of the palladium catalyst into the newly formed C—C bond. We have also applied the use of chiral ligands in combination with catalytic Pd<sub>2</sub>dba<sub>3</sub> to afford high enantioselectivities and good diastereoselectivities for allyl—allyl coupling reactions. Here, the chirality is determined in the allylation step and transferred to the product with the thermal Cope rearrangement. Therefore, we have developed a tandem, asymmetric decarboxylative  $sp^3$ - $sp^3$  coupling/Cope rearrangement strategy, and we

believe this is the first enantioselective rearrangement of this type. Functional group interconversion of the hexadiene products will allow for further synthetic manipulations, perhaps in the synthesis of complex molecules or natural products.

## 2.7 Background of Heteroaromatic Functionalization

### *Biological and Synthetic Applications of Nitrogen-Containing Heterocycles*

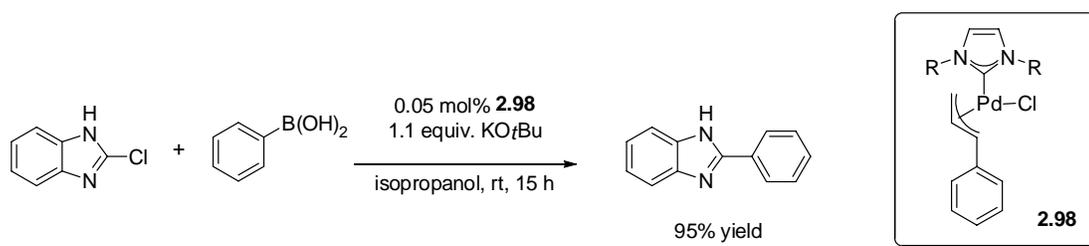
Heterocycles represent a large class of pharmaceutical targets. Currently, greater than 65% of drugs in late development stages, including those in clinical trials or on the market, are heterocyclic compounds.<sup>84</sup> Scheme 2.63 exhibits some of the structures of the top ten selling pharmaceutical drugs, of which seven are nitrogen-containing heterocycles.<sup>85</sup> It is clear that efficient functionalization of these heterocycles is important for the swift production of these targets, their derivatives, and other biologically or agriculturally relevant compounds.



### **Scheme 2.63**

A growing interest in synthetic organic chemistry has been centered on the catalytic coupling of aryl groups. One standard method for this type of  $sp^2$ - $sp^2$  carbon bond formation is the palladium-catalyzed reaction of an aryl halide with a nucleophilic aryl moiety (arylstannanes, arylboronic acids, etc.).<sup>86</sup> This reaction has

been adapted to incorporate heteroaryl groups, however these couplings are generally more difficult.<sup>87</sup> The inherent problem with these processes is that heteroaryl boronic acids are generally unstable at elevated temperatures, which are necessary for oxidative addition of palladium into the Ar—X bond.<sup>88</sup> Nitrogen- and sulfur-containing heteroaromatics can also be difficult to use in the presence of palladium catalysts, as they can “poison” the catalyst making it inefficient in the desired reaction. However, Nolan and coworkers have recently disclosed the use of *N*-heterocyclic carbene ligands on palladium (**2.98**) which allow the coupling of heteroaryl halides and heteroaryl boronic acids at ambient temperature affording the cross-coupled products in high yields (Scheme 2.64).<sup>89</sup> Organostannanes have also been successful for this type of coupling, but these reactions introduce a stoichiometric amount of a toxic metal, which is somewhat unattractive in synthesis.<sup>90</sup>

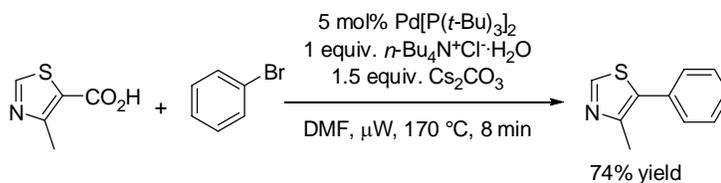


**Scheme 2.64**

#### *Heteroaryl-Aryl Cross-Coupling via Decarboxylation*

While other methods have been utilized as a means of cross-coupling heteroaryl groups,<sup>91</sup> one of particular interest was the seminal work by Gooßen in

2006 on the palladium/copper-catalyzed decarboxylative biaryl coupling.<sup>92</sup> In this report, boronic acids and tin reagents were replaced by carboxylic acids as a means for promoting the coupling of heteroaromatics with aryl halides. The report focused mostly on substituted phenyl rings, but briefly showed that heteroaryl functional groups were also compatible. One week later, Bilodeau disclosed the palladium-catalyzed decarboxylative coupling of heteroaryl groups using microwave irradiation (Scheme 2.65).<sup>93</sup> This system did not require the copper cocatalyst, but it was found that the addition of an equivalent of  $n\text{-Bu}_4\text{N}^+\text{Cl}^-\cdot\text{H}_2\text{O}$  was necessary to prevent over-arylation. Both of the decarboxylation methods required high temperatures, but use of the microwave reactor cut reaction times from 24 h (Gooßen) to 8 minutes (Bilodeau).

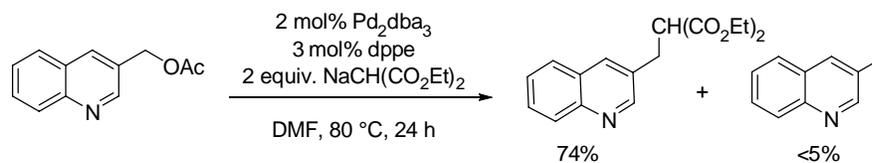


**Scheme 2.65**

#### *Pd-Catalyzed Benzylic Substitution*

The  $\text{sp}^2\text{-sp}^2$  coupling of heteroaryl groups has been an important advancement for the inclusion of these structures into complex syntheses. However, other methods of coupling are necessary for further diversification of these molecules. Benzylic substitution has been a formidable challenge in the realm of palladium catalysis, but this type of  $\text{sp}^3\text{-sp}^3$  coupling represents a powerful way to construct new

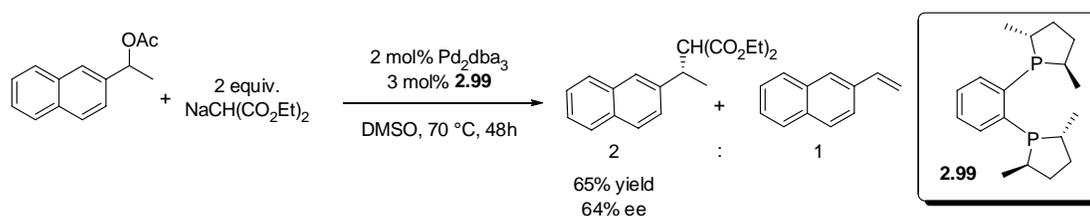
carbon—carbon or carbon—heteroatom bonds. Pioneering work by Legros and Fiaud on palladium-catalyzed benzylic-type substitution demonstrated that formation of the ( $\eta^3$ -benzyl)Pd(II) species was possible when a Pd(0) source was reacted in the presence of naphthyl acetates or carbonates.<sup>94</sup> Nucleophilic attack by sodiomalonate was then achieved producing the new benzylic substituted product. Benzyl acetates were unreactive, and thus the scope was limited to benzylic carbonates on naphthyl rings. Modifications to the reaction have been made to include the reactions of benzyl carbonates, as these were more reactive than the acetates.<sup>95</sup> Nitrogen-containing heteroaromatic<sup>96</sup> acetates, such as quinolyl acetates are now effective reaction partners in this process as well as protonation products are very limited (Scheme 2.66). The appropriate substitution of the quinoline ring is important as 2-quinolyl acetates are unreactive under these same conditions. Overall, the scope of benzylic coupling is still rather limited and requires further exploration to make the reaction more generally applicable.



### Scheme 2.66

With the relatively recent developments in this methodology, it is not surprising that few examples of enantioselective benzylic alkylation have been reported. The reaction of chiral, nonracemic naphthyl acetates has been demonstrated to maintain high levels of enantiomeric excess under optimized conditions.<sup>97</sup> This

scope has also been expanded to include heteroaromatics, such as benzofuran, benzothiophene, and indole.<sup>98</sup> However, the formation of new chiral centers has been more challenging and less well precedented. Legros and Fiaud have tested the efficiency of chiral ligands and found that ligand **2.99** gave the best result in the asymmetric palladium-catalyzed benzylic substitution (Scheme 2.67).<sup>99</sup> They were able to obtain enantioselectivities as high as 64%, but under these conditions, competing  $\beta$ -hydride elimination was prevalent.



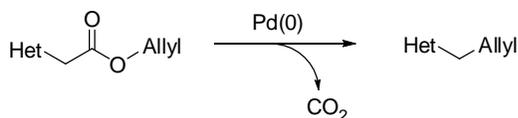
### Scheme 2.67

This newly developed area of benzylic substitution has the potential to make a large impact on the field of heteroarene chemistry. The reaction has been demonstrated on heteroaromatics as well, but it has been limited by strict use of malonate nucleophiles. Incorporation of other nucleophiles and heteroaromatic species would be a useful exercise in the expansion of this methodology. Overall, further exploration is essential to making this reaction synthetically useful, particularly in terms of enantioselectivity.

## 2.8 Palladium-Catalyzed Decarboxylative Synthesis of Heteroaromatic Alkanes

### *Allylic Anion Stabilization with Nitrogen-Containing Heteroaromatics*

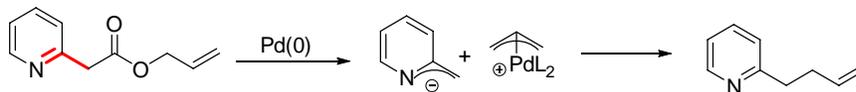
Since the introduction of palladium-catalyzed benzylic substitution, these methods have relied on the ability to form the *electrophilic* ( $\eta^3$ -benzyl)Pd(II) species. In contrast, our previous work focuses on the ability to stabilize the incipient anion generated following decarboxylation. As a means of expanding our generic decarboxylative coupling scheme, we sought to couple heteroaromatic nucleophiles to with ally electrophiles.<sup>100</sup>



### **Scheme 2.68**

In our previous work, decarboxylative cross-coupling of allyl groups was possible through allylic anion stabilization by electron-withdrawing groups. This led us to believe that other types of allylic anions could also be generated if provided with a sufficient amount of resonance stabilization. Therefore, we were curious whether nitrogen-containing heteroaromatic substrates would be provide enough stabilization of an allylic anion to make this type of reaction possible. If the reaction were feasible, it would be a reversed approach to previous Pd-catalyzed benzylic substitutions which utilize the benzyl group as the electrophilic moiety. Therefore, we thought that allyl-2-pyridinyl acetates would be appropriate substrates to begin the research (Scheme 2.69). This type of substrate would require dearomatization of the

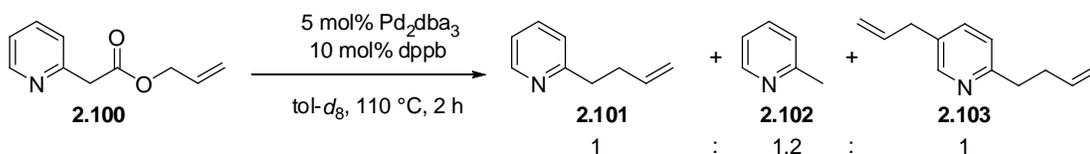
heteroaromatic ring to provide resonance stabilization of the incipient anion generated upon decarboxylation.



**Scheme 2.69**

*Decarboxylative Coupling of allyl 2-pyridinyl acetates*

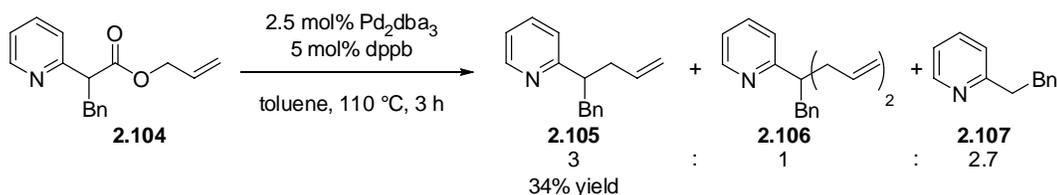
Initial tests were run on the simple allyl 2-pyridinyl acetate **2.100** in the presence of catalytic palladium(0). The first catalyst tested was Pd(PPh<sub>3</sub>)<sub>4</sub> in CD<sub>2</sub>Cl<sub>2</sub> at room temperature. Upon monitoring the reaction, it was clear that decarboxylation was occurring, but the reaction provided mostly 2-methyl pyridine which was a result of protonation of the anion generated. When the reactions were heated to higher temperatures in less polar solvents (toluene, benzene) for 20 hours, the reaction mixtures favored allylation, but multiple allylation products were present. Upon changing the catalyst to Pd<sub>2</sub>dba<sub>3</sub> with dppe as the ligand (Scheme 2.70), the reactions were faster (< 3 h), but this did not aid in suppressing over-allylation or protonation.



**Scheme 2.70**

Another attempt to prevent overallylation involved adding a benzyl at the  $\alpha$ -position to the ester. The reaction of benzylated substrate **2.104** did not proceed at

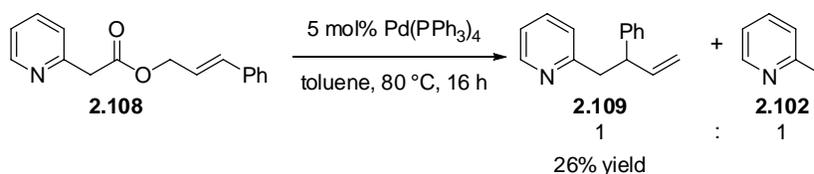
room temperature and required heating to at least 80 °C to proceed at acceptable rates (Scheme 2.71). It was determined that when **2.104** was treated with 2.5 mol% Pd<sub>2</sub>dba<sub>3</sub> and 5 mol% dppb at 110 °C in toluene, the crude reaction contained a mixture of **2.105**, **2.106**, and **2.107** in a 3:1:2.7 ratio, respectively. Upon chromatographic separation, only the monoallylated product **2.105** was isolated and a 34% yield was obtained. Hoping for an increase in selectivity and yield, the catalyst was changed to 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, but diallylation (**2.106**) became the major product over monoallylation (3:1) and the reaction took over 16 hours to reach complete conversion. Other attempts to improve overallylation by modifying the ligand to *o*-tol-PPh<sub>3</sub>, dppe, and dppf were also unsuccessful.



### Scheme 2.71

Additional substitution at the  $\alpha$ -position to afford the dibenzylated substrate eliminated the possibility of multiple allylations and was therefore included in the screening process. Reaction rates plummeted with this substrate as only 23% conversion was reached after 16 hours when treated with catalytic Pd<sub>2</sub>dba<sub>3</sub> and dppb in toluene at 110 °C. Given the rather slow rates, it did not appear that further substitution was the answer to the problem of over-allylation. The allyl fragment was also exchanged for 2-methylallyl, but the diallylated product was still prevalent upon reaction completion.

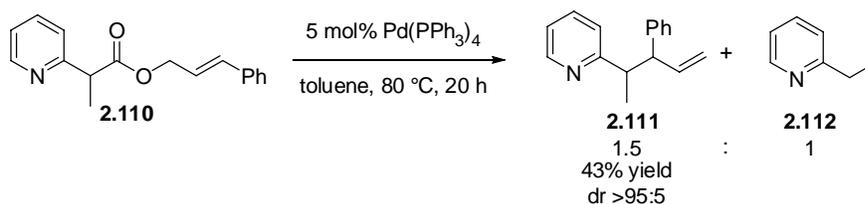
Additionally, a terminal substituent was placed on the allyl group to see if this had any effect on the reaction. Therefore, cinnamyl 2-pyridinyl acetate (**2.108**) was synthesized and subjected to the conditions of catalysis. No reaction was observed at room temperature in CD<sub>2</sub>Cl<sub>2</sub>, but when the reaction was run at elevated temperatures (80 °C or 110 °C) in toluene the reaction afforded a 1:1 mixture of the monoallylated and protonation products (Scheme 2.72). However, a surprising observation was made upon isolation of the allylated product. Apparently, allylation had occurred at the substituted allylic site providing the branched product (**2.109**), rather than the linear product. Palladium is known for its preference for alkylation at the least hindered allylic position, and although deviations from this trend have been seen, they are uncommon.<sup>101</sup>



### Scheme 2.72

In light of the notable regioselectivity, we were re-inspired to explore the reaction further. Again,  $\alpha$ -substitution was tried as a means of reducing protonation and overallylation that might have contributed to the low yield. Methylation of **2.108** provided cinnamyl 2-pyridinyl propanoate **2.110**. Next, a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to **2.110** in toluene, heated to 80 °C and monitored by <sup>1</sup>H NMR spectroscopy (Scheme 2.73). After 20 hours, the reaction had converted to the allylated product. We were pleased to see that the products of overallylation were not

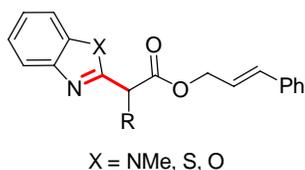
observed, although the product protonation was still present in a 1.5:1 ratio (**2.111**:**2.112**), demonstrating that  $\alpha$ -substitution was slightly effective in reducing the side reactions in favor of monoallylation over protonation. Perhaps more exciting was the high diastereoselectivity in a product with two contiguous stereogenic centers. The same substrate was also tested with catalytic Pd<sub>2</sub>dba<sub>3</sub> and dppe, and the same products were also observed albeit with a slight increase of product ratios (2:1) in favor of the allylated product (**2.111**). However, Pd(PPh<sub>3</sub>)<sub>4</sub> afforded a cleaner reaction mixture with shorter reaction times, and thus was the catalyst of choice for further investigations. Upon scaling up the reaction, a moderate 43% yield of **2.111** was isolated.



### Scheme 2.73

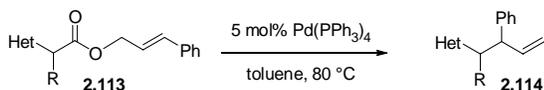
#### *Method Development for Other Heteroaromatic Substrates*

This result led us to search for other nitrogen-containing heteroaromatic substrates to examine. Common heteroaromatics such as benzoxazole, benzothiazole and benzimidazole were selected for further testing as they could stabilize the anionic allyl moiety following decarboxylation similar to the pyridyl examples (Scheme 2.74).



### Scheme 2.74

The respective cinnamyl 2-heteroaryl acetates were synthesized and subjected to the standard conditions of catalysis (Table 2.11). In all cases, the reactions were highly regioselective for the branched product (**2.114**). High diastereoselectivities were also obtained for most heteroaromatic groups, although the benzimidazole substrates (**2.113e,f**) displayed a decrease in diastereoselectivity. Nonetheless, chromatographic separation afforded the products with high diastereomeric ratios. The  $\alpha$ -methyl substituent was replaced by an  $\alpha$ -benzyl group with no adverse effects on reaction time, yield or diastereoselectivity. Benzothiazole **2.113d** achieved a very good yield upon reacting with the palladium catalyst. The most notable observation in the reactions among the different heteroaromatics was reaction rate. Benzothiazole and benzoxazole substrates were complete in four hours or less, while the benzimidazole and pyridyl substrates took substantially longer to reach complete conversion. These reaction rates loosely follow the trend for decarboxylation of the parent heteroaryl acetic acids.<sup>102</sup> Next, oxazole **2.113h** was examined, and it was observed that this substrate fit nicely with the trend of reaction rates, albeit with slightly lowered yields.

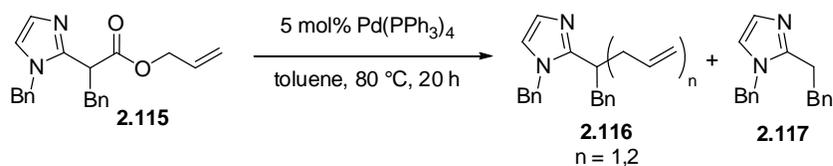
**Table 2.11** Pd-Catalyzed Decarboxylation of Heteroaromatic Cinnamyl Esters

Substrate	Product	Time (h)	Yield (dr)
		4	71 (>97:3)
		4	66 (>95:5)
		2	75 (>95:5)
		2	95
		16	43 (>95:5) <sup>a</sup>
		16	52 (>95:5) <sup>b</sup>
		20	53 (>95:5)
		2	47 (>95:5)

<sup>a</sup> Crude dr = 2.2:1 <sup>b</sup> Crude dr = 2.9:1

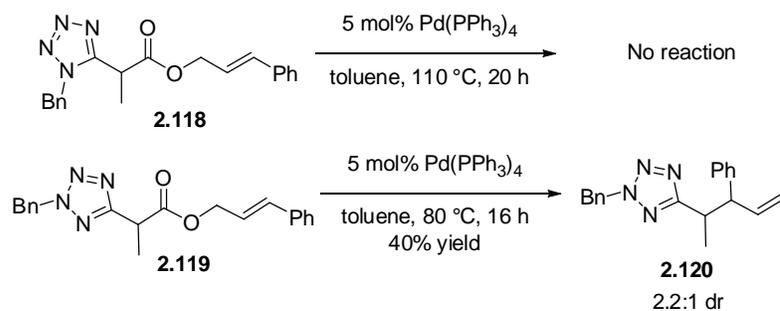
The ability to couple a nonbenzenoid heteroaromatic, such as oxazole, was also advantageous and so we pursued the allylation of similar nitrogen-containing heteroaromatic groups. Allyl 2-imidazolyl propanoate **2.115** was synthesized and subjected to the standard conditions of catalysis. Although previous reactions with unsubstituted allyl groups lacked selectivity for monoallylation (Scheme 2.71), we tried this substrate anyway because synthesis of this substrate was much more facile. The reaction of **2.115** afforded a mixture of allylation (**2.116**) and protonation products (**2.117**), although the ratios were undetermined (Scheme 2.75).

Cinnamyl esters previously were shown to produce fewer side products, so we attempted a cross metathesis of **2.115** with styrene to generate this product. This reaction was unsuccessful and the cinnamyl ester was not isolated. Further attempts to synthesize this substrate *via* other methods have not yet been made. However, the results of this reaction show that decarboxylation of this substrate was not a limiting step toward product formation, and we remain hopeful that the substituted allyl group might afford a more selective reaction.



#### Scheme 2.75

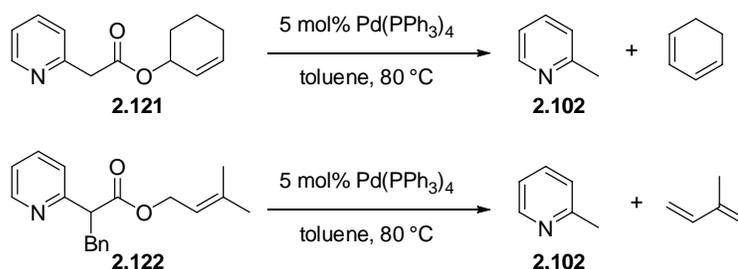
Tetrazolyl acetic acid is also commercially available and an interesting substrate to examine because of the increased number of nitrogens in the ring. After esterification of the acid, protection of the free nitrogen was accomplished *via* benzylation. This reaction gave a mixture of *N*-1- and *N*-2-benzylated products (**2.118** and **2.119**, respectively). These isomers were separated, substituted at the  $\alpha$ -position and treated with the palladium catalyst. Interestingly, **2.118** was inert under the reaction conditions (Scheme 2.76). However, the **2.119** did react and gave the desired product in 40% yield as a 2.2:1 mixture of diastereomers. We cannot explain the difference in reactivity of these two substrates at this time. However, the ability to perform this reaction on **2.119** showed that this method is rather general and could be used in the synthetic applications of a number of different heteroaromatic rings.



**Scheme 2.76**

*Reaction Optimization of Alkyl-Substituted Allyl Substrates*

The cinnamyl esters were ideal substrates because the allyl group lacks  $\beta$ -hydrogens, preventing the elimination pathway from competing with allylation. To verify whether alkyl-substituted allyl groups could also be integrated, two different allyl 2-pyridyl acetates (**2.121** and **2.122**) were examined (Scheme 2.77). The substrates were treated with catalytic Pd(0) and heated, but only 2-methyl pyridine and the substituted butadienes were observed.

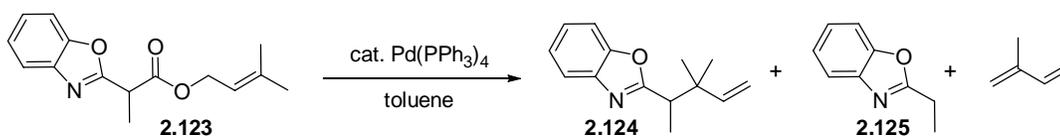


**Scheme 2.77**

Benzoxazole is less basic than pyridine, so it seemed better suited to tolerate alkyl-substituted allyls. Therefore, a similar substrate, **2.123**, was subjected to the

standard conditions of catalysis and monitored by  $^1\text{H}$  NMR spectroscopy (Table 2.12). We were pleased to discover that the reaction had proceeded quite well, giving only 42% elimination and 58% of the desired allylated product (entry 1). This was an impressive improvement from the 100% elimination obtained in the cases of the pyridyl substrates. High regioselectivity for the branched product was also observed for this substrate. With this result in hand, **2.123** was subjected to a variety of reaction conditions to further optimize the reaction for the desired product. As shown in Table 2.12, moderate changes in the amount of elimination were seen when substrate concentration was changed. Increased allylation was observed at lower concentrations, while more elimination was prevalent at higher concentrations (entries 1-3). Modifications in the reaction temperature had the most significant effect on the reaction, as room temperature conditions provided only elimination products (entries 4-6). Lastly, catalyst concentration was altered to determine its role in the reaction (entries 7-10). No significant changes could be seen at normal catalyst concentrations. Decreasing the  $\text{Pd}(\text{PPh}_3)_4$  to 0.5 mol% severely slowed the reaction, and other deviations from 5 mol%  $\text{Pd}(\text{PPh}_3)_4$  were not beneficial. A final reaction was run which combined the best of all scenarios; 5 mol%  $\text{Pd}(\text{PPh}_3)_4$  in toluene at 100 °C with concentration of **2.123** at 0.025M (entry 11). Gratifyingly, this reaction gave the best overall result with 75% of **2.124** and only 25% of **2.125**.

**Table 2.12** Effect of Concentration, Temperature and Catalyst Loading on Elimination



Entry	[2.123]	mol % cat.	Temp. °C	2.124	2.125
1	0.025	5	80	66	34
2	0.05	5	80	58	42
3	0.10	5	80	53	47
4	0.05	5	25	0	100
5	0.05	5	60	40	60
6	0.05	5	100	59	41
7	0.05	0.5 <sup>a</sup>	80	11	89
8	0.05	1	80	49	51
9	0.05	5	80	58	42
10	0.05	10	80	59	41
11	0.025	5	100	75	25

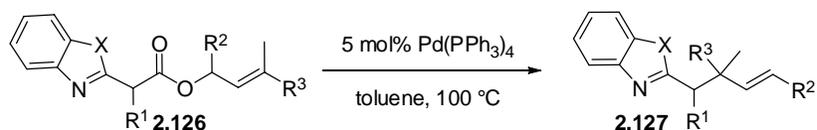
<sup>a</sup> Reaction only went to 42% completion after 16 h.

### *Coupling of Other Heteroaromatic Alkyl-Substituted Allylic Esters*

Once it was determined that alkyl-substituted allylic esters would be feasible with the less basic heterocycles (benzoxazole and benzothiazole), a variety of prenyl and crotyl esters were tested using the optimal conditions found for **2.123**. In general, the benzothiazole substrates gave higher yields and higher diastereoselectivities than the more basic benzoxazoles (Table 2.13). The isolated yields were moderately higher with the crotyl allyls, which can be explained best by the number of available hydrogens for elimination. The decreased number of  $\beta$ -hydrogens available disfavored elimination and made the allylation pathway more favorable than in the cases of prenyl olefins. When the symmetrically substituted allyl was employed with the benzothiazole (**2.126i**), the reaction still afforded a good

yield, albeit in slightly lower diastereoselectivity. The ability to avoid extensive elimination products in forming new C—C bonds between tertiary and/or quaternary carbon is also quite remarkable.

**Table 2.13** Decarboxylative Coupling of Heteroaromatic Alkyl-Allyl Esters



Substrate	Product	Time (h)	Yield (dr) <sup>a</sup>
		2	57
		2	30 <sup>c</sup>
		2	64 (2.5:1) <sup>b,c</sup>
		2	61 (2.8:1) <sup>d</sup>
		1	74
		1	50
		1	74 <sup>b</sup>
		1	72 (10:1) <sup>e</sup>
		1	59 (1.6:1)

<sup>a</sup> Isolated yields are mixtures of diastereomers where applicable. <sup>b</sup> Reaction run at 80 °C. <sup>c</sup> branched:linear (b:l) = 93:7

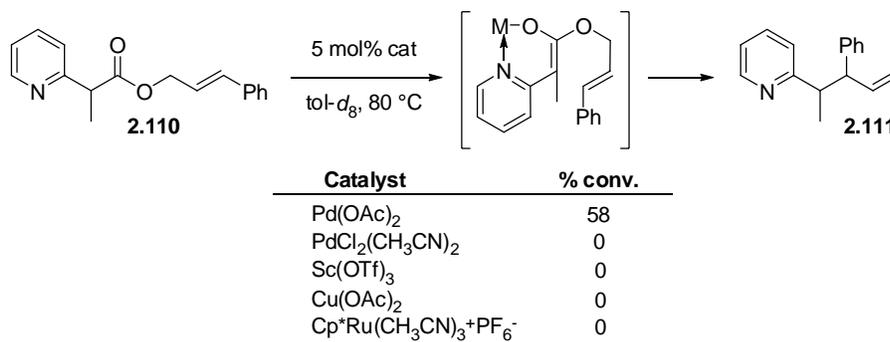
<sup>d</sup> b:l = 94:6 <sup>e</sup> b:l = 95:5

### *Screening for Other Potential Catalysts*

After having successfully coupled a broad range of heteroaromatic alkyl groups and allyl fragments, mechanistic studies were warranted to explain the unusual regioselectivity. To begin, it was possible that the formation of the branched product could be explained by a Carroll-type rearrangement catalyzed by trace amounts of Pd(II) in solution, which can act as a Lewis acid. To this end, **2.110** was treated with 5 mol% Pd(OAc)<sub>2</sub> in toluene at 80 °C and after 9 hours the reaction had reached 58% conversion to product **2.111** (Table 2.14). To discriminate between the Pd(II) catalyst and a Pd(0) catalyst generated *in situ*, another Pd(II) catalyst was tested. To this end, 5 mol% PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> was added to **2.110** and the reaction was run with similar reaction conditions. In this case, no reaction was observed. Furthermore, other Lewis acids [ScOTf<sub>3</sub>, Cu(OAc)<sub>2</sub>] were tested for their ability to afford the decarboxylatively coupled product but the reactions remained unchanged after heating for 16 hours. In light of these observations it was determined that Pd(0) was the active catalyst, rather than Pd(II). Heating a solution of **2.110** in the absence of any catalyst source was completely unproductive as only starting material was observed, proving that palladium was necessary to promote the reaction. As mentioned, palladium-catalyzed processes generally promote linear product formation, but ruthenium catalysts are known to favor production of the branched allylated products.<sup>14</sup> Therefore, we tested **2.110** with catalytic Cp<sup>\*</sup>Ru(CH<sub>3</sub>CN)<sub>3</sub><sup>+</sup>PF<sub>6</sub><sup>-</sup> to see if changing the metal affected the regioselectivity. To our dismay, the catalyst

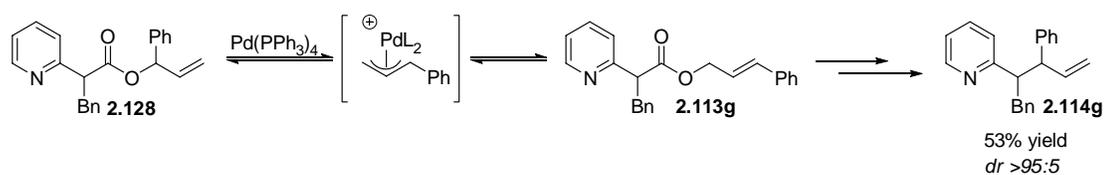
was completely inert under these conditions so we were unable to determine the effect based on this ruthenium catalyst.

**Table 2.14** Catalyst Screening



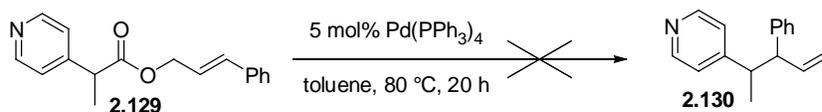
### *Mechanistic Studies*

Confident that our system was catalyzed by Pd(0), rather than Pd(II), but still lacking answers to many mechanistic questions, we tried a different substitution on the allyl fragment. It was a worthwhile exercise to observe if the regioselectivity would change if a substrate like **2.128** were used. We then added 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> to **2.128** in toluene-*d*<sub>8</sub> and the solution was heated to 80 °C. Monitoring by <sup>1</sup>H NMR spectroscopy showed that vinyl benzyl ester **2.128** quickly isomerized (< 3h) to linear cinnamyl ester **2.113g** before the product of decarboxylative coupling was observed. It was not surprising that upon allowing the reaction to stand for 20 hours, the same branched product was isolated in identical yield and diastereoselectivity as when starting with **2.113g**. The isomerization led us to believe that Pd- $\pi$ -allyl formation was occurring and that this happens much faster than decarboxylation.



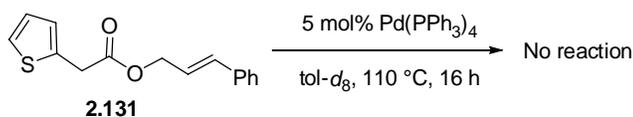
### Scheme 2.78

Continued efforts were made to identify mechanistic details by understanding the role of nitrogen in these systems. Therefore, cinnamyl 4-pyridyl propanoate **2.129** was synthesized and reacted under the conditions of catalysis. Decarboxylation of this substrate was not a problem as the starting material was entirely consumed after 20 hours, but the reaction provided an intractable mixture of products and the desired product (**2.130**) was not observed by  $^1\text{H}$  NMR spectroscopy. The absence of terminal olefin resonances suggests that the position of nitrogen relative to the substituent is crucial to the regioselectivity product formation.



### Scheme 2.79

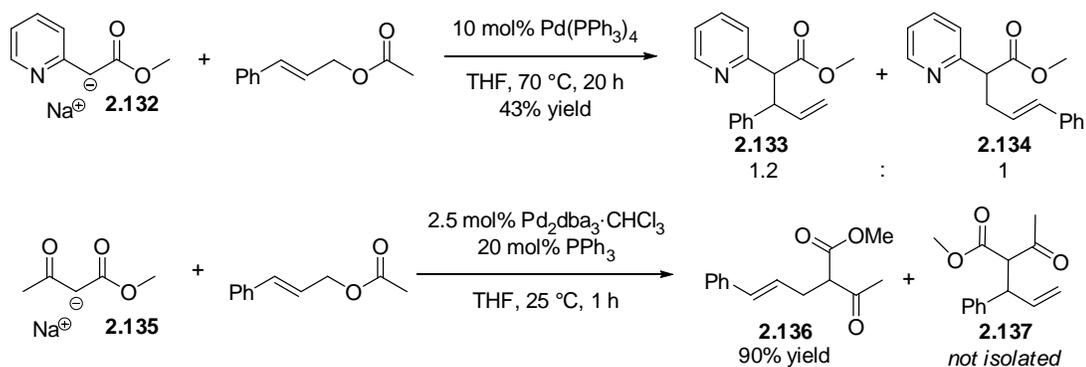
Since we did not want to overlook the possibility that other heteroatoms could also be playing a role in the reaction, we examined a thiophene substrate. Ester **2.131** was synthesized and treated with catalytic  $\text{Pd(PPh}_3)_4$  and heated to  $110^\circ\text{C}$  overnight (Scheme 2.80). In the morning, less than 5% reaction had occurred, demonstrating that the incorporated sulfur atom was not effective in promoting the reaction.



## Scheme 2.80

### *Efforts Toward Understanding Regioselectivity*

An intermolecular approach was then taken to determine nitrogen's role in the formation of the branched product. Methyl 2-pyridyl acetate **2.132** was synthesized to resemble the malonate nucleophile often used for palladium-catalyzed allylic substitution. Deprotonation by sodium hydride afforded the  $\alpha$ -anion, similar to that of the sodiomalonate, and the resulting nucleophile was added to a solution of cinnamyl acetate and 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in THF (Scheme 2.81). Interestingly, upon completion of the reaction, a mixture of regioisomers (**2.133** and **2.134**) was isolated. Although this system did reproduce the unusual regioselectivity observed previously with the standard pyridyl substrates, decarboxylation is not involved in this process so we cannot compare these reactions mechanistically. However, it does show that the presence of the pyridine ring has a pronounced effect on the regioselectivity of allylation. The “standard” preference of attack for stabilized nucleophiles (**2.135**) onto substituted allyl groups gives the linear product of allylation (**2.136**) with high regioselectivity.<sup>15</sup>



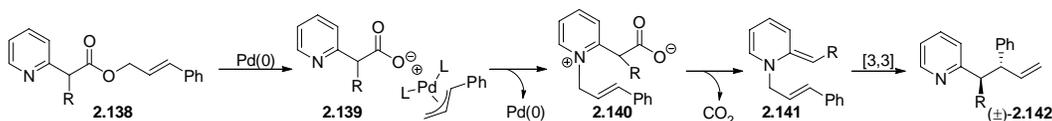
### Scheme 2.81

#### *Proposed Mechanisms*

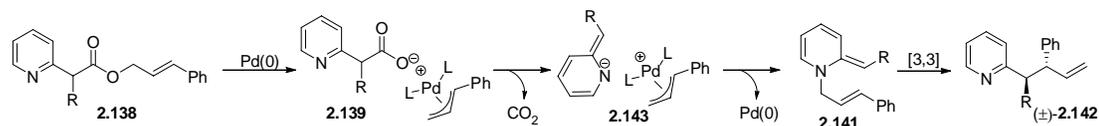
Based on the conclusions of our preliminary mechanistic investigations, we propose two mechanisms which account for the high regio- and diastereoselectivities observed. The allyl isomerization of the **2.128** (Scheme 2.78) prior to decarboxylation demonstrated that Pd- $\pi$ -allyl formation is the first step of the mechanism. Next, it is possible that nucleophilic attack on the Pd- $\pi$ -allyl group can occur on the heteroaromatic nitrogen, giving zwitterionic intermediate **2.140** and loss of the Pd(0) catalyst. It should be noted that this allylation occurs with “standard” preference for nucleophilic attack at the least hindered carbon. The zwitterionic pyridinium **2.140** is then activated, which promotes decarboxylation and effects dearomatization of the pyridine ring to give intermediate **2.141**. This hexadiene is conveniently arranged to undergo a [3,3]-sigmatropic rearrangement which is driven by rearomatization of the pyridine ring to afford **2.142**. Standard aza-Cope rearrangements require very high temperatures,  $\sim 200 \text{ }^\circ\text{C}$ , but given the driving force

of rearomatization, we propose that it is capable of occurring at much lower temperatures.<sup>103</sup> The timing of decarboxylation is what distinguishes the two mechanisms. Mechanism B shows that decarboxylation to form the amide nucleophile **2.143** occurs prior to allylation of the heteroaromatic amine. Following allylation, the aza-Cope rearrangement is facilitated in the same manner as mechanism A. It could be possible that the two allyl fragments of **2.143** could directly couple to afford the products, however this would be a result of allylation at the most sterically encumbered carbon of the allyl group which is unusual when palladium catalysts are employed. Also, this type of mechanism would not account for the high diastereoselectivities observed.

**Mechanism A:**



**Mechanism B:**



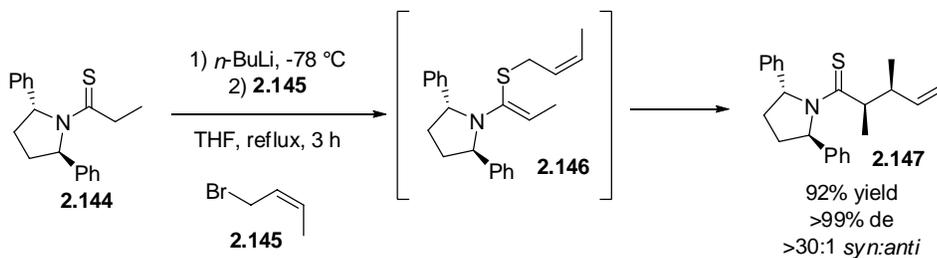
**Scheme 2.82**

To the best of our knowledge, a mechanism such as this has not yet been proposed, but we believe that it is a reasonable explanation for the unusual regiochemistry observed. It is important to note that several individual steps of the proposed mechanism can be supported by previous examples in the literature. First, pyridines are good nucleophiles and are alkylated in the presence of alkyl halides to

form pyridinium salts.<sup>104</sup> Although nucleophilic attack by pyridine onto Pd- $\pi$ -allyl electrophiles has not been reported, other methods of *N*-allylation of pyridines have been disclosed.<sup>105</sup> Next, extensive studies on the decarboxylation of heteroaromatic acetic acids have been carried out by Taylor. These results show that this type of decarboxylation proceeds through a zwitterionic intermediate, where the heteroaromatic ring is activated *via* protonation of the nitrogen rather than alkylation, although these two are conceptually similar. Finally, the aza-Cope rearrangement to rearomatize the heteroaromatic ring is the least well preceded. Although, a stepwise *N*-allylation of a non-aromatic enamine, followed by a Lewis acid-catalyzed aza-Cope rearrangement has been disclosed.<sup>106</sup> In this example, the addition of stoichiometric ZnCl<sub>2</sub> to *N*-allylated enamines allows for the 3-aza-Cope rearrangement at 140 °C, which is lower than temperatures required for standard aza-Cope conditions (~200°C). The authors propose that the increased reaction rate is due to a charge-accelerated mechanism. Our mechanism does not invoke any intermediate charges during the [3,3]-sigmatropic rearrangement, but does account for the rearomatization process which could have a drastic effect on the reaction rate as well.

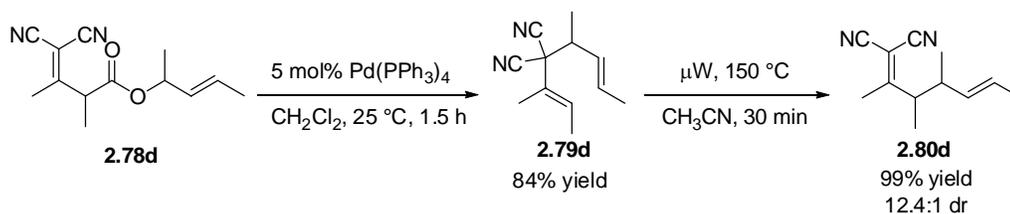
In addition, the mechanism in Scheme 2.82 also accounts for the high diastereoselectivities obtained for the products. Previous examples of tandem allylation/sigmatropic rearrangement processes have also been shown to proceed with high diastereoselectivity. Rawal and coworkers have demonstrated the *S*-allylation of a thioamide, followed by a subsequent thio-Claisen rearrangement (Scheme 2.83).<sup>107</sup>

The use of a chiral  $C_2$ -symmetric amine backbone (**2.144**) afforded high diastereoselectivities with various substituted allyl groups (**2.146**). Through this methodology, they were able to construct products containing contiguous stereocenters with high *syn:anti* ratios.



**Scheme 2.83**

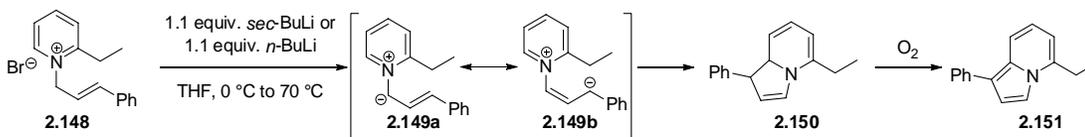
Our group has also shown a tandem allylation/rearrangement strategy in the decarboxylative allyl—allyl coupling (See Section 2.3). The Pd-catalyzed decarboxylation of alkylidene malononitriles provides a kinetic 1,5-hexadiene product, and upon treating under thermal conditions, undergoes a Cope rearrangement to afford the thermodynamic hexadiene product (Scheme 2.84). High diastereoselectivities were observed in this reaction. Therefore, the allylation/rearrangement strategy appears to have a fairly general ability to induce good diastereoselectivities, which can be attributed to the cyclic transition state of the Cope rearrangement.



## Scheme 2.84

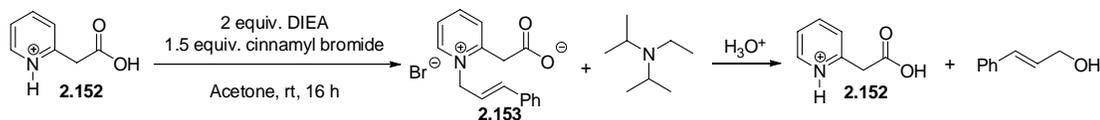
### *Mechanistic Support Studies*

In an effort to test our proposed mechanistic hypothesis, the task of synthesizing potential intermediates was undertaken as a way to replicate portions of the catalytic cycle. To this end, ethyl pyridine was allylated with cinnamyl bromide and pyridinium **2.148** was isolated. If treated with a strong enough base, we thought it might be possible to deprotonate the benzylic position in order to alleviate the charge on nitrogen, which would reproduce hexadiene **2.141** in the proposed mechanism. However, upon treatment with *n*-BuLi or *sec*-BuLi, the allylic proton was abstracted, giving allylic anions **2.149a/b**. The formation of cyclized intermediate **2.150** was observed by <sup>1</sup>H NMR spectroscopy and could be explained by anion attack onto the iminium carbon of **2.149b**. Isolation of this product resulted in oxidation to the aromatic bicyclic system. Similar types of indolizine product formation have been previously documented.<sup>104</sup>



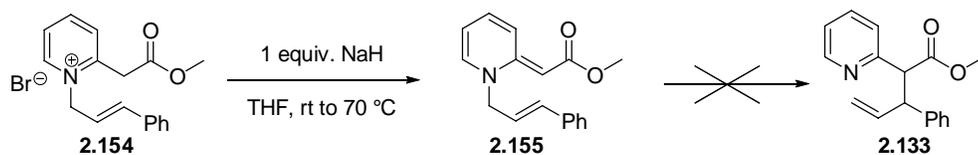
## Scheme 2.85

Since this result was not mechanistically beneficial we modified the substrate by changing to the 2-pyridyl acetic acid carboxylate (**2.152**) to lower the  $pK_a$  of the benzylic hydrogens. The 2-pyridyl acetic acid hydrochloride is commercially available and was used to try to synthesize pyridinium *N*-allylide **2.153** (Scheme 2.86). The allylation was partially successful as the desired product **2.153** constituted 13% of the crude reaction mixture. An attempt to isolate the small amount of product present was made by protonating the excess DIEA that remained in the mixture, however this resulted in hydrolysis of the pyridium *N*-allylide to cinnamyl alcohol and the acid **2.152**.



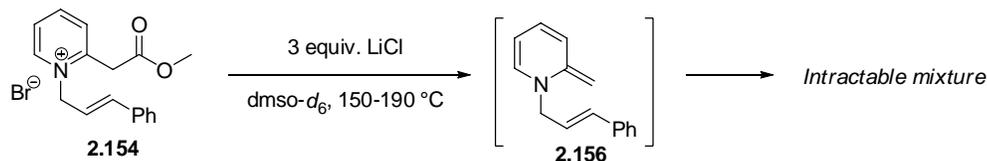
### Scheme 2.86

Instead, the methyl ester **2.154**, was synthesized, treated with one equivalent of NaH and stirred at room temperature (Scheme 2.87). Upon isolation of the product, we were pleased to discover the addition of the ester had favored deprotonation at the  $\alpha$ -position and had formed the desired intermediate (**2.155**). Unfortunately, this product proved to be stable to the rearrangement as heating to 70 °C did not effect any change in the product. We believe the conjugation of the  $\alpha,\beta$ -unsaturated ester provided additional stabilization and caused the lack of reactivity.



**Scheme 2.87**

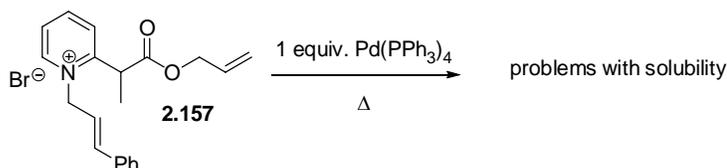
We then attempted to induce dealkoxycarbonylation *via* the Krapcho conditions (Scheme 2.88).<sup>108</sup> This allows for the formal decarboxylation of esters upon treatment with LiCl in DMSO at extremely high temperatures (150-190 °C). However, these conditions on **2.154** were too harsh as the crude reaction mixture was very messy with no distinguishable resonances for the linear or branched products (by <sup>1</sup>H NMR spectroscopy).



**Scheme 2.88**

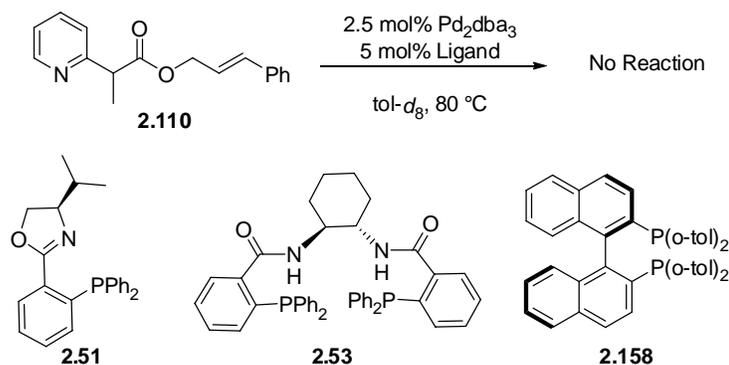
Lastly, we conceived it might be possible to synthesize a reactant such as **2.157** (Scheme 2.89). The goal was to have two different allyl groups present which must be differentiated by palladium. If Pd- $\pi$ -allyl formation occurs on the allylic acetate as usual, then decarboxylation onto the preformed pyridinium should occur and the [3,3]-rearrangement should provide the branched product. However, if the Pd- $\pi$ -allyl complex were formed from nucleophilic attack onto the cinnamyl allyl (where reaction occurred in basic conditions), then other potential routes could be imagined, but formation of the desired product would not be expected.

Unfortunately, attempts to dissolve this substrate into a variety of solvents (dms-*d*<sub>6</sub>, CD<sub>2</sub>Cl<sub>2</sub>, tol-*d*<sub>8</sub>, acetone-*d*<sub>6</sub>, CD<sub>3</sub>OD) were unsuccessful even after heating. A stoichiometric amount of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to these reactions, but the lack of solubility was detrimental to the reaction, such that any reaction progress could not easily be monitored.



### Scheme 2.89

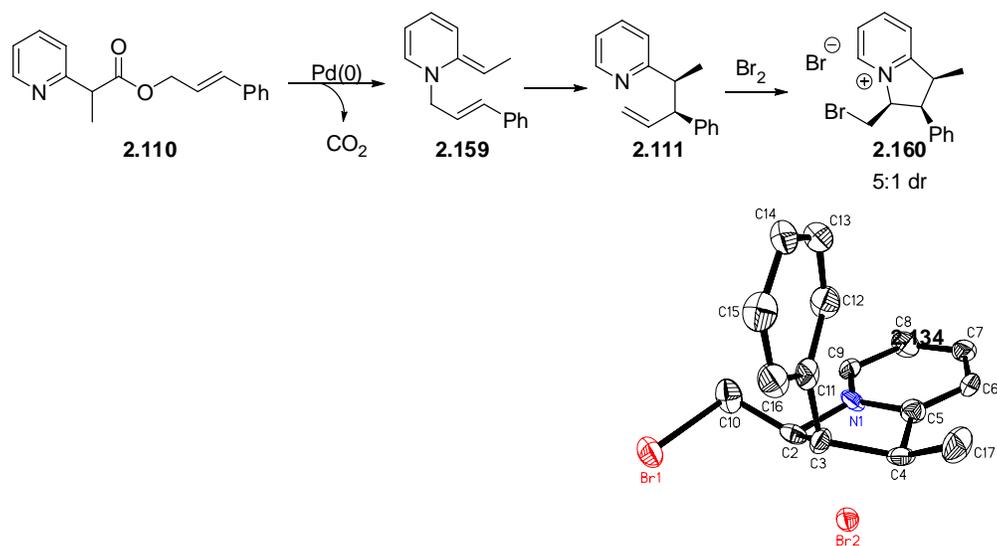
The inability to reproduce the reactive intermediates was somewhat disappointing, but we tried to approach the mechanistic questions from another angle. In the proposed mechanism (Scheme 2.82), nitrogen is first allylated with “standard” preference of attack. This affords the unbranched *N*-pyridinium allylide, an intermediate that is achiral. The aza-Cope rearrangement cannot promote chiral product formation from this intermediate. Therefore, if a chiral ligand was used, and enantioselectivity was observed in the product, then it would demonstrate that another mechanism must be operative. To examine this possibility, various chiral ligands were screened for reactivity with **2.110**. Unfortunately, none of the ligands provided any of the desired reaction even upon heating at 80 °C for 20 hours. In fact, only ligand **2.158** showed a slight amount of reactivity, but the product was not identified.



### Scheme 2.90

#### *Assignment of Relative Stereochemistry*

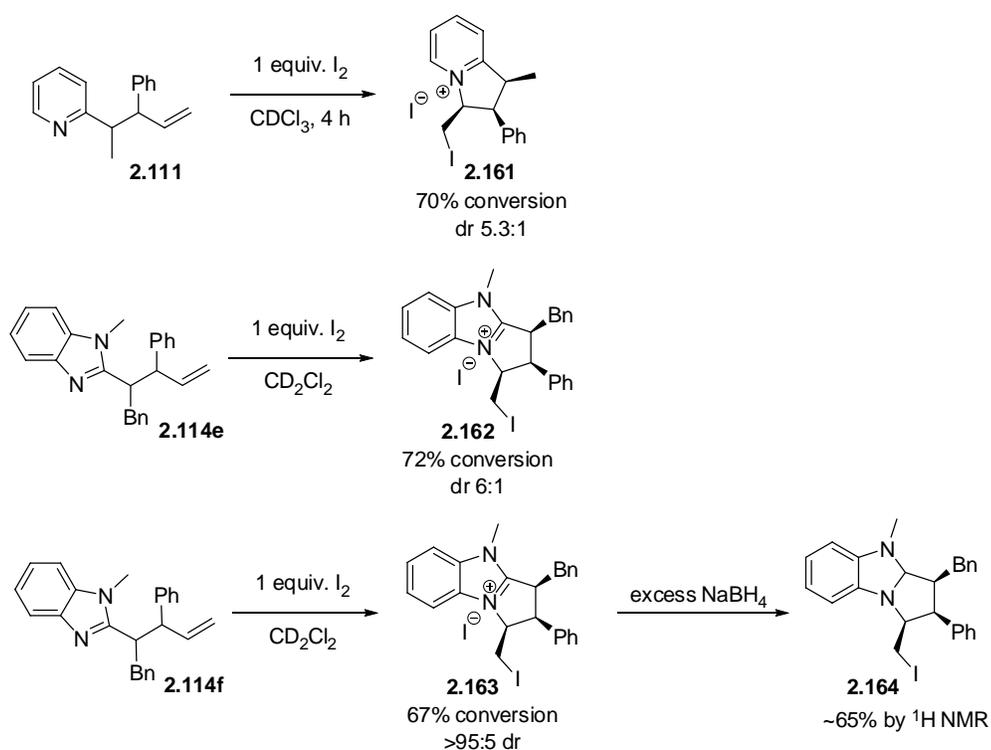
One question that needed to be addressed was in relation to the relative stereochemistry of the product. Since the product was acyclic,  $^1\text{H}$  NMR coupling constants would not be a reliable tool to determine the relative configuration, but cyclization of the product would allow for a more definite analysis of the product. Therefore, **2.111** was treated under conditions similar to those reported for the bromocyclization (Scheme 2.91).<sup>109</sup> Isolation and crystallization allowed for stereochemical assignment *via* single crystal X-ray diffraction. The crystal structure revealed an all *cis*-configuration on the newly formed ring which must come from the *trans*-configuration of the acyclic precursor. This stereochemistry suggests a boat-like transition state utilizing the *E,E*-geometry of intermediate **2.159**. Extensive studies on related asymmetric Claisen rearrangements have shown that cyclic substrates generally assume the boat transition state as a means of alleviating excess strain imposed by the chair conformation.<sup>110</sup>



### Scheme 2.91

Other cyclizations of this nature have also been probed with the heterocyclic products. I<sub>2</sub> acts similarly with the products of allylation to form the iodocyclized products. The addition of one equivalent of I<sub>2</sub> to **2.111** in CDCl<sub>3</sub> at room temperature afforded the desired cyclized pyridinium species. However, all of the starting material was not consumed as the reaction only progressed to 70% conversion as shown by <sup>1</sup>H NMR spectroscopy. The incomplete reaction could be attributed to the presence of the complexed I<sub>3</sub><sup>-</sup> counterion, from I<sub>2</sub> and I<sup>-</sup>. Products **2.114e** and **2.114f** was also treated to the same conditions, where it was found that this cyclization proceeded to 72% and 67% conversion, respectively. The cyclic products presented the potential for further synthetic manipulations if nucleophiles could be added into the electrophilic iminium species. Consequently, NaBH<sub>4</sub>, a common reagent for reductive amination, was added to the reaction mixture. By <sup>1</sup>H NMR spectroscopy, it

appears that the desired product was actually formed. Terminal olefin resonances were also observed in the spectrum, but the structures of these compounds were not determined. Overall, these impurities only accounted for 35% of the product mixture, as compared to the reduced heterocycle **2.164** (65%). The ability to further functionalize these heterocycles makes the decarboxylative coupling products useful synthons.

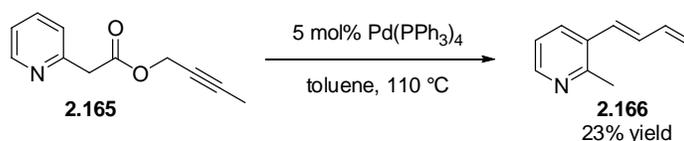


**Scheme 2.92**

### *Pd-Catalyzed Decarboxylation Using Propargylic Esters*

Previously, we have used the allylic alcohol derived esters as substrates, due to the numerous reports on Pd- $\pi$ -allyl formation. However, we thought it would be

worthwhile to test if this reaction would be feasible with propargylic derived esters. Reactions of this type are known, but less common than their allylic counterparts.<sup>111</sup> Therefore, we first treated **2.165** with 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in toluene at 80 °C. This temperature was not sufficient to effect the reaction at a reasonable rate, and so it was increased to 110 °C, at which point, the reaction started progressing as determined by the loss of starting material in the <sup>1</sup>H NMR spectrum. After 18 hours, the reaction was complete, and it appeared as though methyl pyridine was present, although a significant number olefin resonances were also present. Although we were unable to determine the products formed, we ran the reaction on a large scale so as to isolate the major product of the reaction. Upon doing so, we isolated diene **2.166** as the major product. Despite the low yield, this result was significant as the diene functionality can be used for further synthetic manipulations, such as the Diels-Alder reaction. The optimization of this reaction and mechanistic investigations are warranted to better understand the scope and utility of the reaction.



### Scheme 2.93

#### Summary

In conclusion, we have developed a method for the palladium-catalyzed decarboxylative coupling of heteroaromatic alkanes. This new methodology will

allow for incorporation and further functionalization of these heteroaryl groups in more complex syntheses. Moreover, this transformation is unique as unusual regioselectivity and high diastereoselectivities were observed. The proposed mechanism involves *N*-allylation followed by decarboxylative dearomatization. This is followed by a [3,3]-sigmatropic aza-Cope rearrangement driven by rearomatization of the heteroaromatic ring. Further mechanistic work is warranted, though the data presented supports the mechanism shown. Remarkably, alkyl-substituted allyl groups could also be employed without substantial elimination. The construction of new carbon—carbon bonds between tertiary and quaternary centers is a particularly salient feature of this reaction. Altogether, this catalytic allylation/aza-Cope rearrangement strategy is the first of its kind to be reported. Efforts toward enantioselective catalysis of this nature will be also explored in the future. In light of the progress that has been made with the Pd-catalyzed decarboxylative coupling it is clear that newly developed reactions can provide alternate solutions to seemingly old synthetic problems.

## 2.9 General Methods and Compound Characterization

### *Materials*

All air and moisture sensitive reactions were carried out in flame-dried glassware under argon using standard Schlenk techniques. Methylene Chloride, toluene, and THF were dried over activated alumina columns on an Innovative Technology Solvent System.<sup>112</sup> Benzene was distilled over sodium prior to use. Acetonitrile was stored over activated 4Å molecular sieves. Commercially available

reagents were used without additional purification unless otherwise stated. All chiral ligands were purchased from Strem Chemicals, except ligand **2.54**, which was synthesized in our laboratory.<sup>113</sup> Flash column chromatography was performed with 230x400 mesh, 60 Å porosity, silica obtained from Sorbent Technologies. Thin layer chromatography was performed on silica gel 60F<sub>254</sub> plates (EM-5715-7, EMD chemicals). Visualization of the plates was accomplished with a UV lamp (254 nm) or KMnO<sub>4</sub> stain. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 DRX spectrometer using the designated frequencies and referenced to residual protio solvent signals (some spectra were taken using a QNP Cryoprobe). <sup>77</sup>Se NMR spectra were obtained on a Bruker Avance 500 DRX spectrometer at 95.4 MHz and were externally referenced to PhSeSePh at 449 ppm. Variable temperature NMR (vtNMR) spectra were acquired on a Bruker Avance 400 DRX spectrometer. Structural assignments are based on <sup>1</sup>H, <sup>13</sup>C, DEPT-135, COSY, sEI-nOe and HMQC spectroscopies. FTIR spectra were recorded using either a ATI Mattson Genesis Series FTIR or Shimadzu 8400-S FTIR spectrometers. High Resolution Mass Spectrometry (HRMS) were performed using EI, ESI, and FAB techniques. EI MS spectra were obtained on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). ESI MS spectra were acquired either on a LCT Premier (Waters Corp., Milford, MA) or Q-ToF-2 (Microsmass Ltd, Manchester UK) spectrometers. FAB MS spectra were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd, Manchester UK). Elemental Analyses were performed by Desert Analytics Laboratory (Tucson, AZ). All microwave reactions

were performed using an Emerys Creator Microwave Reactor. Chiral gas phase chromatography was performed on a Shimadzu GC-17A instrument with an AOC-20i autoinjector using Chiraldex TA or Chiraldex B-DM columns (Astec, Whippany, NJ). Chiral high pressure liquid chromatography was performed on a Shimadzu SCL-10AVP instrument using Daicel Chiralpak AD and OD-H columns.

### *General Procedures and Spectral Characterization*

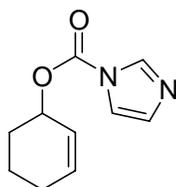
#### **General procedure for preparation of 1,1'-carbonyldipyrazole.**

1,1'-Carbonyldipyrazole was prepared by stirring a solution of pyrazole (11.0 mmol), Et<sub>3</sub>N (11.0 mmol), and tetrabutylammonium chloride (.09 mmol) in diethyl ether (100mL) in a dry Schlenk flask under Ar atmosphere.<sup>114</sup> To another Schlenk flask was added triphosgene (1.83 mmol) and diethyl ether (15 mL). The triphosgene was allowed to dissolve and then transferred via cannula into the flask containing the pyrazole. Upon addition of the triphosgene, the solution became cloudy and a white precipitate formed. The reaction was allowed to stir for 2 hours to ensure complete reaction. The solution was then filtered and the mother liquor was concentrated to afford a white solid. The product was prepared for immediate use with no purification needed, as prolonged exposure to air led to decomposition of the product.

#### **General procedure for coupling of alcohols and amines.**

The alcohol (1.78 mmol), prepared from simple reduction of the corresponding ketone,<sup>115</sup> was dissolved in dichloroethane (30mL). To the solution was added 1,1'-

carbonyldiimidazole (or 1,1'-carbonyldipyrzazole) (3.78 mmol) and was heated at reflux for 5 hours while stirring. The solution was allowed to cool to room temperature, at which time 20 mL of diethyl ether was added. The solution was washed with brine (3 × 10mL), and the organic layers were combined, dried over MgSO<sub>4</sub> and concentrated. The products were purified on silica gel via flash column chromatography using 90:10 hexane:ethyl acetate as the solvent system.



cyclohex-2-enyl 1*H*-imidazole-1-carboxylate

**2.39a** (srm3126)

white solid

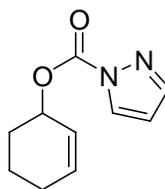
Yield: 68%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.69-1.87 (m, 2H: CHOCH<sub>2</sub>CH<sub>2</sub>), 1.95-2.01 (m, 2H: CH<sub>2</sub>CHO), 2.03-2.11 (m, 1H: CH=CHCHH), 2.14-2.22 (m, 1H: CH=CHCHH), 5.48 (d, 1H: *J* = 3.9 Hz, CHO), 5.85 (m, 1H: CHOCH=CH), 6.10 (dt, 1H: *J* = 3.7, 9.9 Hz, CHOCH=CH), 7.08 (d, 1H: *J* = 0.7 Hz, CON-CH=CH), 7.44 (s, 1H: CON-CH=CH), 8.16 (d, 1H: *J* = 0.7 Hz, CON-CH=N).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 18.7 (CH<sub>2</sub>CH<sub>2</sub>CHO), 24.9 (CH<sub>2</sub>CH=CH), 28.2 (OCHCH<sub>2</sub>), 72.9 (CHO), 117.3 (CON-CH=CH), 124.0 (OCHCH=CH), 130.7 (CON-CH=CH), 135.0 (OCHCH=CH), 137.3 (N-CH=N), 148.6 (C=O).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3087, 2950, 1755, 1471, 1385, 1003.

**HRMS** calcd for [M+H] 193.0977, found 193.0977



cyclohex-2-enyl 1*H*-pyrazole-1-carboxylate

**2.39b** (srm3146)

colorless oil

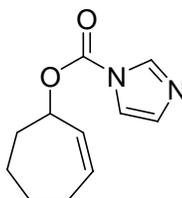
Yield: 97%

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.68-1.75 (m, H: OCHCH<sub>2</sub>CHH), 1.82-1.89 (m, 1H: OCHCH<sub>2</sub>CHH), 2.00-2.04 (m, 2H: OCHCH<sub>2</sub>), 2.05-2.09 (m, 1H: CH=CHCHH), 2.12-2.18 (m, 1H: CH=CHCHH), 5.52 (s, 1H: CHO), 5.88 (d, 1H: *J* = 10.7 Hz, CHOCH=CH), 6.07 (dt, 1H: *J* = 4.4, 9.8 Hz, CHOCH=CH), 6.43 (dd, 1H: *J* = 1.6, 2.8 Hz, CON-CH=CH), 7.75 (s, 1H: N-N=CH), 8.15 (d, 1H: *J* = 2.8 Hz, CON-CH=CH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 18.8 (CH<sub>2</sub>CH<sub>2</sub>CHO), 25.0 (CH<sub>2</sub>CH=CH), 28.3 (CHOCH<sub>2</sub>), 73.1 (CHO), 109.1 (CON-CH=CH), 124.4 (OCHCH=CH), 131.0 (CON-CH=CH), 134.6 (OCHCH=CH), 144.5 (N-N=CH), 149.3 (C=O).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3037, 2948, 1762, 1533, 1425, 1213, 1182, 1004.

**HRMS** calcd for [M+Na] 215.0796, found 215.0782



(*Z*)-cyclohept-2-enyl 1*H*-imidazole-1-carboxylate

**2.39e** (srm3278)

colorless oil

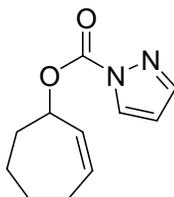
Yield: 73%

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.49-1.55 (m, 1H: CH=CHCH<sub>2</sub>CHH), 1.69-1.77 (m, 2H: CH=CHCH<sub>2</sub>CHH and OCHCH<sub>2</sub>CHH), 1.87-1.93 (m, 1H: OCHCHH), 1.98-2.06 (m, 2H: OCHCHH and OCHCH<sub>2</sub>CHH), 2.11-2.18 (m, 1H: CH=CHCHH), 2.24-2.31 (m, 1H: CH=CHCHH), 5.62 (d, 1H: *J* = 10.1 Hz, 1H: CHO), 5.78 (d, 1H: *J* = 11.4 Hz, OCHCH=CH), 5.95 (m, 1H: CHOCH=CH), 7.07 (q, 1H: *J* = 0.6 Hz, CON-CH=CH), 7.44 (t, 1H: *J* = 1.3 Hz, CON-CH=CH), 8.15 (s, 1H: CON-CH=N).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 26.2 (cycloheptyl CH<sub>2</sub>), 26.6 (cycloheptyl CH<sub>2</sub>), 28.6 (CH=CHCH<sub>2</sub>), 32.8 (OCHCH<sub>2</sub>), 80.5 (CHO), 117.3 (CON-CH=CH), 130.8 (CON-CH=CH), 131.4 (OCHCH=CH), 133.7 (OCHCH=CH), 137.3 (N-CH=N), 148.4 (C=O).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3033, 2933, 1759, 1471, 1388, 1280, 1178, 1003.

**HRMS** calcd for [M+H] 217.1134, found 207.1142



(Z)-cyclohept-2-enyl 1H-pyrazole-1-carboxylate

**2.39f** (srm3253)

colorless oil

Yield: 86%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.43-1.52 (m, 1H: CH=CHCH<sub>2</sub>CHH), 1.68-1.77 (m, 2H: CH=CHCH<sub>2</sub>CHH and OCHCH<sub>2</sub>CHH), 1.92-1.99 (m, 1H: OCHCH<sub>2</sub>CHH), 2.00-2.18 (m, 3H: OCHCH<sub>2</sub> and CH=CHCHH), 2.23-2.30 (m, 1H: CH=CHCHH), 5.67 (d, 1H: *J* = 10.1 Hz, CHO), 5.84 (dt, 1H: *J* = 1.8, 11.5 Hz, CHOCH=CH), 5.92 (m, 1H: OCHCH=CH), 6.43 (dd, 1H: *J* = 1.5, 2.9 Hz, CON-CH=CH), 7.75 (t, 1H: *J* = 0.9 Hz, N-N=CH), 8.16 (d, 1H: *J* = 2.77 Hz, CON-CH=CH).

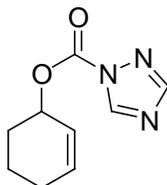
**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 26.4 (cycloheptyl CH<sub>2</sub>), 26.7 (cycloheptyl CH<sub>2</sub>), 28.6 (CH=CHCH<sub>2</sub>), 32.8 (OCHCH<sub>2</sub>), 79.2 (CHO), 109.2 (CON-CH=CH), 131.0 (CON-CH=CH), 132.1 (one of cycloheptyl CH=CH), 132.9 (one of cycloheptyl CH=CH), 144.6 (N-N=CH-CH), 149.0 (C=O).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3037, 2933, 1766, 1425, 1390, 1265, 1184.

**HRMS** calcd for [M+Na] 229.0953, found 229.0956.

### Procedure for the carbonylative coupling of alcohols with triazole derivatives.

The triazole derivatives were synthesized using a modified procedure. To a dried Schlenk flask under Ar was added the triazole derivative (1.34 mmol), alcohol (1.34 mmol), Et<sub>3</sub>N (2.68 mmol), and tetrabutylammonium chloride (0.02 mmol) dissolved in diethyl ether (75 mL). To another dried Schlenk flask under Ar was added triphosgene (0.447 mmol) dissolved in diethyl ether (20 mL). This solution was transferred via cannula to the flask containing the triazole derivative and a white solid precipitated from the solution upon addition. After 2 hours, the solution was filtered and the mother liquor was concentrated. The product was purified on silica gel via flash column chromatography.



cyclohex-2-enyl 1H-1,2,4-triazole-1-carboxylate

**2.39c** (srm3281)

white solid

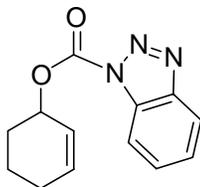
Yield: 45%

**Purification:** flash chromatography (80:20 hexane: ethyl acetate); cyclohexenol impurity removed via vacuum evaporation

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.69-1.78 (m, 1H: OCHCH<sub>2</sub>CHH), 1.80-1.90 (m, 1H: OCHCH<sub>2</sub>CHH), 2.04 (q, 2H: *J* = 2.0 Hz, OCHCH<sub>2</sub>), 2.07-2.13 (m, 1H: CH=CHCHH), 2.14-2.24 (m, 1H: CH=CHCHH), 5.57 (s, 1H: CHO), 5.88 (d, 1H: *J* = 10.1 Hz, CHOCH=CH), 6.13 (dt, 1H: *J* = 3.5, 10.1 Hz, OCHCH=CH), 8.07 (s, 1H: triazole C-H), 8.82 (s, 1H: triazole C-H).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 18.7 (CH<sub>2</sub>CH<sub>2</sub>CHO), 25.0 (CH<sub>2</sub>CH=CH), 28.2 (OCHCH<sub>2</sub>), 74.5 (CHO), 123.6 (OCCH=CH), 135.7 (OCCH=CH), 145.8 (triazole C-H), 147.4 (C=O), 153.8 (triazole C-H).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3100, 2950, 1764, 1510, 1404, 1375, 1203, 1112.



cyclohex-2-enyl 1*H*-benzo[1,2,3]triazole-1-carboxylate

**2.39d** (srm3152)

white solid

yield: 57%

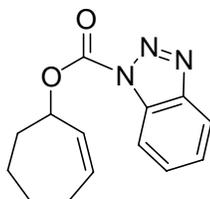
**Purification:** flash chromatography (95:5 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.76-1.83 (m, 1H: CHHCH<sub>2</sub>CHO), 1.88-1.98 (m, 1H: CHHCH<sub>2</sub>CHO), 2.06-2.26 (m, 4H: CH<sub>2</sub>CHO and C=CHCH<sub>2</sub>); 5.70 (d, 1H: *J* = 4.53 Hz, CHO), 5.99 (m, 1H: CHOCH=C), 6.16 (dt, 1H: *J* = 3.5, 9.9 Hz, CHOCH=CH), 7.50 (app. t, 1H: *J* = 7.2 Hz, one of NC=CH), 7.66 (app t, 1H: *J* = 7.2 Hz, one of NC=CH), 8.11 (dd, 1H: *J* = 0.7, 8.3 Hz, one of NC=CHCH), 8.15 (dd, 1H: *J* = 0.9, 8.3 Hz, one of NC=CHCH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>)  $\delta$  18.8 (CH<sub>2</sub>CH<sub>2</sub>CHO), 25.0 (CH<sub>2</sub>CHO), 28.4 (C=CCH<sub>2</sub>), 73.9 (CHO), 113.8 (one of NC=CHCH), 120.6 (one of NC=CHCH), 123.9 (CHOCH=CH), 125.9 (one of NC=CH), 130.3 (one of NC=CH), 132.0 (C=ONC), 135.4 (CHOCH=CH), 146.2 (N=NC), 148.9 (C=O).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3037, 2950, 1755, 1487, 1452, 1209, 1039.

**HRMS** calcd for [M+Na] 266.0905, found 266.0903.



cyclohept-2-enyl 1*H*-benzo[1,2,3]triazole-1-carboxylate

**2.39g** (srm3279)

colorless oil

Yield: 20%

**Purification:** flash chromatography (95:5 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.54-1.59 (m, 1H: CH=CHCH<sub>2</sub>CHH), 1.74-1.84 (m, 2H: CH=CHCH<sub>2</sub>CHH and OCHCH<sub>2</sub>CHH), 2.05-2.12 (m, 2H: OCHCH<sub>2</sub>CHH and OCHCHH); 2.16-2.22 (m, 2H: OCHCHH and CH=CHCHH), 2.30-2.37 (m, 1H: OCHCHH), 5.84 (d, 1H: *J* = 9.8 Hz, CHO), 5.95 (d, 1H: *J* = 12.6 Hz, CHOCH=CH), 6.00 (m, 1H: CHOCH=CH), 7.51 (t, 1H: *J* = 7.6 Hz, one of NC=CH), 7.67 (app t, 1H: *J* = 7.3 Hz, one of NC=CH), 8.14 (dd, 2H: *J* = 9.1, 10.1 Hz, NC=CHCH).

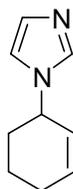
**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 26.4 (cycloheptyl CH<sub>2</sub>), 26.7 (cycloheptyl CH<sub>2</sub>), 28.7 (cycloheptyl CH<sub>2</sub>), 32.9 (OCHCH<sub>2</sub>), 79.9 (CHO), 113.8 (one of NC=CHCH), 120.7 (one of NC=CHCH), 125.9 (one of NC=CH), 130.3 (one of NC=CH), 131.6 (CHOCH=CH), 132.1 (C=ONC), 133.7 (CHOCH=CH), 146.2 (N=NC), 148.8 (C=O)

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3031, 2933, 1755, 1487, 1452, 1392, 1255, 1039.

**HRMS** calcd for [M+Na] 279.0984, found 279.0956.

#### **Procedure for Pd-catalyzed decarboxylative amination.**

To a dry, air-free 25mL Schlenk flask was added substrate (0.780 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%, 0.039 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) to form a colorless solution. Reactions were allowed to stir at room temperature for reaction times as noted in Table 2.2; reaction completion was indicated by the solution turning to a bright yellow color. The solution was then concentrated and the residue was directly purified by flash column chromatography with the eluent system noted for each compound. Due to the polarity of the imidazole products, these were first triturated with hexanes, filtered and then subjected to chromatography.



1-(cyclohex-2-enyl)-1*H*-imidazole

**2.40a** (srm3118)

colorless oil

Yield: 90%

**Purification:** flash chromatography (100% hexane, then 60:40 hexane: ethyl acetate)

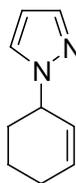
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.66-1.73 (m, 2H: CH<sub>2</sub>CH<sub>2</sub>CHN), 1.77-1.85 (m, 1H: CHHCHN), 2.05-2.22 (m, 3H: CHHCHN and CH=CHCH<sub>2</sub>); 4.71 (s, 1H: CHN), 5.74 (dq, 1H: *J* = 2.3, 9.9 Hz, CHNCH=CH), 6.08 (m, 1H: CHNCH=CH), 6.96 (s, 1H: NCH=CH), 7.06 (s, 1H: NCH=CH), 7.55 (s, 1H: NCH=N).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 19.5 (CH<sub>2</sub>CH<sub>2</sub>CHN), 24.7 (CH<sub>2</sub>CH=CH), 31.9 (NCHCH<sub>2</sub>), 52.7 (CHN), 118.0 (NCH=CH), 125.5 (NCHCH=CH), 129.3 (NCH=CH), 133.0 (NCHCH=CH), 136.4 (NCH=N).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3114, 3033, 2947, 1652, 1604, 1496, 1218, 1109, 1065.

**HRMS** calcd for [M+H] 149.1079, found 149.1087

**Chiral HPLC Column:** Chiralpak OD-H column **Eluent:** 95:5 hexane:isopropanol  
**Flow rate:** 1 mL/min **Wavelength:** 210nm. **Retention times:** 23.1 and 26.5 minutes.



1-(cyclohex-2-enyl)-1*H*-pyrazole

**2.40b** (srm3147)

colorless oil

Yield: 77%

**Purification:** flash chromatography (90:10 hexane : ethyl acetate)

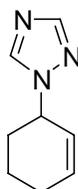
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.68 (p, 2H: *J* = 6.13 Hz, CH<sub>2</sub>CH<sub>2</sub>CHN), 1.94-2.01 (m, 1H: CHHCHN), 2.05-2.21 (m, 3H: CHHCHN and C=CHCH<sub>2</sub>); 4.94 (m, 1H:

CHN), 5.82 (dq, 1H:  $J = 2.2, 10.1$  Hz, NCHCH=CH), 6.09 (m, 1H: CHNCH=CH), 6.24 (t, 1H:  $J = 2.2$  Hz, NCH=CH), 7.46 (d, 1H:  $J = 2.3$  Hz, NN=CH), 7.54 (d, 1H:  $J = 1.3$  Hz, NCH=CH).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  19.5 ( $\text{CH}_2\text{CH}_2\text{CHN}$ ), 25.0 ( $\text{CH}_2\text{CH}=\text{CH}$ ), 30.7 ( $\text{CH}=\text{CHCH}_2$ ), 57.2 (CHN), 105.0 (N=CHCH), 125.6 (NCHCH=CH), 127.8 (NN=CH), 132.8 (NCHCH=CH), 139.3 (NCH=CH)

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3031, 2947, 2933, 1652, 1510, 1436, 1396, 1267, 1089, 1043;

HRMS calcd for  $[\text{M}+\text{H}]$  149.1079, found 149.1077



1-(cyclohex-2-enyl)-1H-1,2,4-triazole

**2.40c** (srm3283)

yellow oil

Yield: 88%

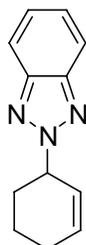
**Purification:** flash chromatography (80:20 hexane : ethyl acetate)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.57-1.65 (m, 1H: CHHCH<sub>2</sub>CHN), 1.65-1.75 (m, 1H: CHHCH<sub>2</sub>CHN), 1.99-2.11 (m, 2H: CH<sub>2</sub>CHN), 2.15-2.21 (m, 1H: CH=CHCHH), 2.21-2.25 (m, 1H: CH=CHCHH), 4.95 (s, 1H: CHN), 5.84 (d, 1H:  $J = 9.5$  Hz, NCHCH=CH), 6.18 (d, 1H:  $J = 9.4$  Hz, NCHCH=CH), 7.96 (s, 1H: triazole C-H), 8.10 (s, 1H: triazole C-H).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  18.8 ( $\text{CH}_2\text{CH}_2\text{CHN}$ ), 24.9 ( $\text{CH}_2\text{CH}=\text{CH}$ ), 30.0 (NCHCH<sub>2</sub>), 55.4 (CHN), 123.7 (NCHCH=CH), 134.6 (NCHCH=CH), 142.3 (triazole C-H), 152.13 (triazole C-H).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3035, 2948, 2933, 1498, 1433, 1346, 1274, 1243, 1197, 1137, 1010.

HRMS calcd for  $[\text{M}+\text{H}]$  150.1031, found 150.1028.



2-(cyclohex-2-enyl)-2*H*-benzo[1,2,3]triazole

**2.40d-1** (srm3153)

colorless oil

Yield: 81% (combined isomers)

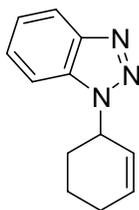
**Purification:** flash chromatography (90:10 hexane : ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.74-1.84 (m, 1H: *CHHCH*<sub>2</sub>CHN), 1.93-2.01 (m, 1H: *CHHCH*<sub>2</sub>CHN), 2.13-2.21 (m, 1H: *CHHCH=CH*), 2.22-2.35 (m, 3H: *CHHCH=CH* and *NCHCH*<sub>2</sub>), 5.55 (m, 1H: CHN), 6.00 (dq, 1H: *J* = 2.3, 9.9 Hz, *CHNCH=CH*), 6.19 (dq, 1H: *J* = 3.8, 10.1 Hz, *CHNCH=CH*), 7.38 (dd, 2H: *J* = 3.1, 6.6 Hz, *N=CCH=CH*), 7.89 (dd, 2H: *J* = 3.1, 6.6 Hz, *N=CCH*).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 20.0 (*CH*<sub>2</sub>*CH*<sub>2</sub>CHN), 24.8 (*CH*<sub>2</sub>*CH=CH*), 30.5 (*NCHCH*<sub>2</sub>), 62.5 (CHN), 118.3 (*N=CCH*), 124.8 (*NCHCH=CH*), 126.3 (*N=CCHCH*), 132.8 (*NCHCH=CH*), 144.4 (*N=C*)

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3037, 2948, 1691, 1566, 1452, 1317, 1267, 1209.

**HRMS** calcd for [M+H] 200.1188, found 200.1203



1-(cyclohex-2-enyl)-1*H*-benzo[1,2,3]triazole

**2.40d-2** (srm3165)

colorless oil

Yield: 81% (combined isomers)

**Purification:** flash chromatography (90:10 hexane : ethyl acetate)

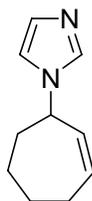
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.78-1.89 (m, 1H: *CHHCH*<sub>2</sub>CHN), 1.93-2.00 (m, 1H: *CHHCH*<sub>2</sub>CHN), 2.10-2.19 (m, 1H: *NCHCHH*), 2.24-2.36 (m, 3H: *NCHCHH* and

CH=CHCH<sub>2</sub>), 5.63 (m, 1H: CHN), 5.90 (d, 1H: *J* = 9.5 Hz, CHNCH=C), 6.20 (m, 1H: CHNCH=CH), 7.36 (app. t, 1H: *J* = 8.3 Hz, one of N-C=CHCH), 7.45 (app t, 1H: *J* = 7.0 Hz, one of N-C=CHCH), 7.62 (d, 1H: *J* = 8.3 Hz, one of N-C=CH), 8.07 (d, 1H: *J* = 8.5 Hz, one of N-C=CH).

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 20.7 (CH<sub>2</sub>CH<sub>2</sub>CHN), 24.8 (CH<sub>2</sub>CHN), 29.9 (C=CCH<sub>2</sub>), 56.4 (CHN), 110.8 (one of NC=CH), 120.3 (one of NC=CH), 123.9 (one of N-C=CHCH), 125.2 (NCHCH=CH), 127.0 (one of N-C=CHCH), 132.4 (quat. arom. C), 133.0 (NCHCH=CH), 146.7 (quat arom. C).

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3065, 2948, 2935, 1653, 1614, 1493, 1452, 1274.

HRMS calcd for [M+H] 200.1188, found 200.1191



(*Z*)-1-(cyclohept-2-enyl)-1*H*-imidazole

**2.40e** (3270a)

white solid

Yield: 71%

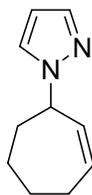
**Purification:** flash chromatography (90:10 hexane : ethyl acetate)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.47-1.55 (m, 1H: CH=CHCH<sub>2</sub>CHH), 1.67-1.74 (m, 1H: CHHCH<sub>2</sub>CHN), 1.76-1.83 (m, 1H: CH=CHCH<sub>2</sub>CHH), 1.96-2.04 (m, 3H: CH<sub>2</sub>CHN and NCH<sub>2</sub>CHCHH), 2.16-2.23 (m, 1H: CH=CHCHH), 2.29-2.35 (m, 1H: CH=CHCHH), 4.85 (s, 1H: CHN), 5.72 (dt, 1H: *J* = 3.3, 12.1 Hz, CHNCH=CH), 5.92 (m, 1H: CHNCH=CH), 6.98 (s, 1H: NCH=CH), 7.09 (s, 1H: NCH=CH), 7.57 (s, 1H: NCH=N);

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 27.0 (CH=CHCH<sub>2</sub>CH<sub>2</sub>), 28.4 (NCHCH<sub>2</sub>CH<sub>2</sub>), 29.1 (CH=CHCH<sub>2</sub>), 36.4 (NCHCH<sub>2</sub>), 59.2 (CHN), 117.9 (NCH=CH), 130.0 (NCH=CH), 132.7 (one of cycloheptyl CH=CH), 132.8 (one of cycloheptyl CH=CH), 133.9 (NCH=N).

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3029, 2972, 2933, 1498, 1260, 1108, 1076.

HRMS calcd for [M+H] 163.1235, found 163.1227



(*Z*)-1-(cyclohept-2-enyl)-1*H*-pyrazole  
**2.40f** (srm3261)  
colorless oil  
Yield: 65%

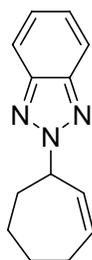
**Purification:** flash chromatography (100% hexane, then 60:40 hexane : ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.46-1.55 (m, 1H: CH=CHCH<sub>2</sub>CHH), 1.65-1.81 (m, 2H: one of CH=CHCH<sub>2</sub>CHH and one of CHNCH<sub>2</sub>CHH), 1.92-1.98 (m, 1H: one of CHNCH<sub>2</sub>CHH); 2.03-2.06 (m, 2H: CHNCH<sub>2</sub>), 2.14-2.22 (m, 1H: CH=CHCHH), 2.26-2.33 (m, 1H: CH=CHCHH), 5.06 (d, 1H: *J* = 9.4 Hz, 1H: CHN), 5.82 (dt, 1H: *J* = 2.1, 11.4 Hz, NCHCH=CH), 5.93 (m, 1H: NCHCH=CH), 6.26 (t, 1H: *J* = 1.3 Hz, NCH=CH), 7.45 (d, 1H: *J* = 2.2 Hz, NN=CH), 7.52 (d, 1H: *J* = 2.1 Hz, NCH=CH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 26.7 (CH=CHCH<sub>2</sub>CH<sub>2</sub>), 27.9 (cycloheptyl CH<sub>2</sub>), 28.7 (cycloheptyl CH<sub>2</sub>), 35.2 (NCHCH<sub>2</sub>), 63.3 (CHN), 105.4 (NCH=CH), 127.3 (N=N=CH), 132.8 (NCHCH=CH), 133.3 (NCHCH=CH) 139.1 (N-CH=CH).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3028, 2931, 1510, 1446, 1396, 1089, 1047.

**HRMS** calcd for [M+H] 163.1235, found 163.1237



(*Z*)-2-(cyclohept-2-enyl)-2*H*-benzo[1,2,3]triazole  
**2.40g-1** (srm3267\_1)  
colorless oil  
Yield: 79% (combined isomers)

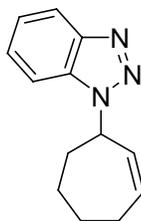
**Purification:** flash chromatography (95:5 hexane : ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.53-1.61 (m, 1H: NCHCH<sub>2</sub>CH<sub>2</sub>CHH), 1.78-1.88 (m, 2H: NCHCH<sub>2</sub>CH<sub>2</sub>CHH and CH=CH=CH<sub>2</sub>CHH), 2.06-2.13 (m, 1H: NCHCH<sub>2</sub>CHH), 2.21-2.33 (m, 3H: CH=CHCHH and NCHCH<sub>2</sub>), 2.35-2.42 (CH=CHCHH), 5.70 (m, 1H: NCH), 6.06 (m, 2H: NCHCH=CH and NCHCH=CH), 6.62 (dd, 2H: *J* = 3.2, 6.6 Hz, Ar CH's), 7.38 (dd, 2H: *J* = 2.8, 6.3 Hz, Ar CH's).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 26.6 (CH=CHCH<sub>2</sub>CH<sub>2</sub>), 28.3 (cycloheptyl CH<sub>2</sub>), 28.7 (cycloheptyl CH<sub>2</sub>), 35.4 (NCHCH<sub>2</sub>), 68.3 (CHN), 118.3 (arom CH), 126.4 (arom CH), 131.6 (one of cycloheptyl CH=CH), 133.1 (one of cycloheptyl CH=CH), 144.3 (N=C);

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3004, 2933, 1446, 1274, 1255.

**HRMS** calcd for [M+H] 214.1344, found 214.1341



(*Z*)-1-(cyclohept-2-enyl)-1*H*-benzo[1,2,3]triazole  
**2.40g-2** (srm3267\_2)  
white solid  
Yield: 79% (combined isomers)

**Purification:** flash chromatography (95:5 hexane : ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.53-1.62 (m, 1H: CH=CHCH<sub>2</sub>CHH), 1.77-1.86 (m, 2H: CH<sub>2</sub>CH<sub>2</sub>CHN), 1.88-1.94 (m, 1H: CH=CHCH<sub>2</sub>CHH), 2.09-2.13 (m, 2H: NCHCHH and NCHCH<sub>2</sub>CHH), 2.25-2.37 (m, 2H: NCHCHH and CH=CHCH<sub>2</sub>), 2.41-2.47 (m, 1H: CH=CHCHH), 5.73 (d, 1H: *J* = 11.7 Hz, CHN), 5.95 (d, 1H: *J* = 11.35 Hz, NCHCH=C), 6.05 (m, 1H: CHNCH=CH), 7.38 (t, 1H: *J* = 6.9 Hz, one of N-C=CHCH), 7.47 (app t, 1H: *J* = 7.4 Hz, one of N-C=CHCH), 7.61 (d, 1H: *J* = 8.5 Hz, one of N-C=CH), 8.08 (d, 1H: *J* = 8.5 Hz, one of N-C=CH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 26.6 (CH=CHCH<sub>2</sub>CH<sub>2</sub>), 28.5 (NCHCH<sub>2</sub>CH<sub>2</sub>), 28.9 (CH=CHCH<sub>2</sub>), 34.6 (NCHCH<sub>2</sub>), 61.6 (CHN), 110.6 (one of NC=CH), 120.3 (one of NC=CH), 124.0 (one of N-C=CHCH), 127.1 (one of N-C=CHCH), 131.9 (two overlapping peaks, NCHCH=CH and quat. arom. C), 133.7 (NCHCH=CH), 146.6 (quat arom. C).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\text{max}}$ : 3065, 2933, 1452, 1265.

**HRMS** calcd for [M+H] 214.1344, found 214.1331

**Procedure for the crossover experiments of carbamates.**

To a dried NMR tube was added a solution of **2.39e** (21 mg, 0.10 mmol) and **2.39b** (20 mg, 0.10 mmol) in CD<sub>2</sub>Cl<sub>2</sub> (600  $\mu$ L). This mixture was observed by <sup>1</sup>H NMR spectroscopy prior to adding Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol%, 0.10 mmol). The colorless reaction was allowed to react for 1.5 hours after which time the solution turned a bright yellow color, signifying reaction completion. Gas chromatographic analysis of the resulting solution showed that the four products **2.40a**, **2.40b**, **2.40e**, and **2.40f** were formed in an 1.3:1:1.7:1.1 ratio. A similar procedure was used for the crossover experiment between **2.39a** and **2.39f**, where the ratio of the same four products were determined (1.3:1:1.4:1.6).

**Rate enhancement studies for 2.39f.**

To a dried NMR tube was added **2.39f** (20 mg, 0.10 mmol) dissolved in CD<sub>2</sub>Cl<sub>2</sub> (600  $\mu$ L). Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%, 0.005 mmol) was added to the solution and the reaction was monitored by <sup>1</sup>H NMR spectroscopy. After 1.5 hours, the reaction was spiked with **2.39a** (3.3 mg, 0.017 mmol). After 1 hour, the reaction was again monitored by <sup>1</sup>H NMR spectroscopy. At this point, the reaction was spiked again with **2.39a** (5 mg, 0.026 mmol) and allowed to react for 1.5 hours. The reaction was again monitored for conversion. The results of these experiments were compared to a standard

reaction run simultaneously using the same conditions as this procedure, but the reaction was not spiked with **2.39a**.

**Procedure for the palladium-catalyzed amination of cyclohexenyl acetate 2.48.**

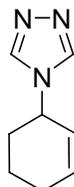
To a solution of **2.48** (21 mg, 0.15 mmol) and pyrazole (10 mg, 0.15 mmol) in CD<sub>2</sub>Cl<sub>2</sub> (600 μL) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (8.4 mg, 0.007 mmol). The reaction was monitored by <sup>1</sup>H NMR spectroscopy and after 19 hours, it was observed that reaction had reached 84% conversion to product **2.40b**. A reaction was also run using this procedure with 4-methyl imidazole (rather than the pyrazole) and a 1.6:1 mixture of **2.46** and **2.47** were isolated in a 52% yield, respectively.

**General procedure for the non-racemic synthesis of 2.40a.**

To a solution of Pd<sub>2</sub>dba<sub>3</sub> (4.8 mg, 0.005 mmol) and a chiral ligand (0.010 mmol) in the specified solvent (600 μL) (as listed in Table 2.3) was added carbamate **2.39a** (20 mg, 0.10 mmol). The reactions were allowed to react, and confirmation of reaction completion after 18 hours was obtained by <sup>1</sup>H NMR spectroscopy. The resulting product, **2.40a**, was triturated with hexane and purified using a silica plug with 80:20 hexane:ethyl acetate. The pure product was subject to chiral HPLC using the method determined for this compound.

### General procedure for the synthesis of 2.41.

The triazole carbamate **2.39c** was synthesized and allowed to stand on the benchtop for 6 days. The decomposition of the carbamate resulted in the formation of **2.41** and it was identified by  $^1\text{H}$  NMR spectroscopy.



4-(cyclohex-2-enyl)-4H-1,2,4-triazole

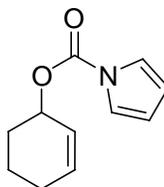
**2.41** (srm3254)

yield: >90% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.57-2.28 (m, 6H, cyclohexyl CH's), 5.14 (br. s, 1H, CHN), 5.82 (d, 1H:  $J = 2.0$  Hz,  $\text{CHOCN}=\text{CH}$ ), 5.97 (br. s., 1H:  $\text{CHNCH}=\text{CH}$ ), 8.24 (s, 2H:  $\text{N-CH}=\text{N}$ )

### Procedure for the preparation of 2.44.

Pyrrole carbamate **2.44** was synthesized by means of a previously reported procedure.<sup>116</sup>



cyclohex-2-enyl 1H-pyrrole-1-carboxylate

**2.44** (srm4011)

Yield: 38%

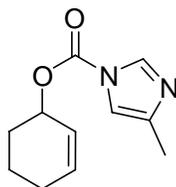
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.55-1.68 (m, 1H: cyclohexyl CH), 1.68-1.78 (m, 1H: cyclohexyl CH), 1.80-1.91 (m, 2H: cyclohexyl CH's), 1.92-2.02 (m, 1H: cyclohexyl CH), 2.02-2.12 (m, 1H: cyclohexyl CH), 5.35 (ddd, 1H,  $J = 3.5, 1.7,$

1.4 Hz, CHO), 5.73-5.81 (m, 1H: CHOCH=CH), 5.97 (dt, 1H:  $J = 10.2, 3.4$  Hz, CHOCH=CH), 6.17 (t, 2H:  $J = 2.4$  Hz, N-CH=CH), 7.21 (t, 2H:  $J = 2.2$  Hz, N-CH=CH).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  18.67 (cyclohexyl  $\text{CH}_2$ ), 24.90 (cyclohexyl  $\text{CH}_2$ ), 28.27 (cyclohexyl  $\text{CH}_2$ ), 71.43 (CHO), 112.2 (N-CH=CH), 120.08 (N-CH=CH), 124.73 (CHOCH=CH) 133.85 (CHOCH=CH), 150.13 (C=O).

### Procedure for the synthesis of 2.45.

Carbamate **2.45** was synthesized using a modified procedure reported by Byers and coworkers.<sup>114</sup>



cyclohex-2-enyl 4-methyl-1*H*-imidazole-1-carboxylate  
**2.45** (srm4060)  
colorless oil  
Yield: 65%

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.68-1.84 (m, 2H: CHOCH<sub>2</sub>CH<sub>2</sub>), 1.90-2.00 (m, 2H: CH<sub>2</sub>CHO), 2.01-2.10 (m, 1H: CH=CHCHH), 2.12-2.20 (m, 1H: CH=CHCHH), 5.44 (d, 1H:  $J = 4.1$  Hz, CHO), 5.82 (m, 1H: CHOCH=CH), 6.08 (dt, 1H:  $J = 3.5, 10.1$  Hz, CHOCH=CH), 7.13 (s, 1H: CON-CH=CH), 8.04 (s, 1H: CON-CH=N).

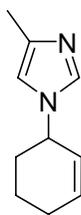
$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  13.8 (CH<sub>3</sub>), 18.7 (CH<sub>2</sub>CH<sub>2</sub>CHO), 25.0 (CH<sub>2</sub>CH=CH), 28.3 (OCHCH<sub>2</sub>), 72.6 (CHO), 113.3 (CON-CH=CH), 124.2 (OCHCH=CH), 134.8 (OCHCH=CH), 136.8 (OCNCH=N), 140.0 (N-CH=CCH<sub>3</sub>), 148.6 (C=O)

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3053, 2985, 2956, 1753, 1421, 1402, 1257.

HRMS calcd for [M+H] 207.1134, found 207.1121

### Procedure for Pd-catalyzed decarboxylative amination of **2.45**.

To a dry, air-free 25 mL Schlenk flask was added **2.45** (0.78 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %, 0.039 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) to form a colorless solution. The solution was allowed to stir at room temperature for 40 minutes; reaction completion was indicated by the solution turning to a bright yellow color. The solution was then concentrated and directly purified by flash column chromatography with 80:20 hexane:ethyl acetate as the eluent. A mixture of **2.46** and **2.47** (1.3:1) was isolated as an inseparable mixture in 57% yield



1-(cyclohex-2-enyl)-4-methyl-1*H*-imidazole (major isomer)

**2.46** (srm4074<sup>117</sup>)

isolated as mixture of *N*-allylated isomers

pale yellow oil

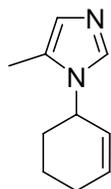
Yield: 52% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.63-1.83 (m, 3H: CH<sub>2</sub>CH<sub>2</sub>CHN and CHHCHN), 1.99-2.17 (m, 3H: CHHCHN and CH<sub>2</sub>CH=CH), 2.22 (s, 3H, CH<sub>3</sub>) 4.61 (m, 1H: CHN), 5.72 (m, 1H: NCHCH=CH), 6.05 (dq, 1H: *J* = 3.5, 10.1 Hz, CHNCH=CH), 6.65 (s, 1H: NCH=CCH<sub>3</sub>), 7.42 (s, 1H: NCH=N).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 14.0 (CH<sub>3</sub>), 19.6 (CH<sub>2</sub>CH<sub>2</sub>CHN), 24.89 (CH<sub>2</sub>CH=CH), 31.9 (NCHCH<sub>2</sub>), 52.7 (CHN), 114.6 (NCH=CCH<sub>3</sub>), 125.8 (NCHCH=CH), 132.8 (NCHCH=CH), 135.5 (NCH=N), 138 (NCH=CCH<sub>3</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3053, 2985, 2950, 1421, 1271, 1259.

**HRMS** calcd for [M+H] 163.1235, found 163.1230.



1-(cyclohex-2-enyl)-5-methyl-1*H*-imidazole (minor isomer)

**2.47** (srm4074)

isolated as mixture of *N*-allylated isomers

pale yellow oil

Yield: 52% (combined isomers)

**Purification:** flash chromatography (80:20 hexane : ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.63-1.83 (m, 3H: CH<sub>2</sub>CH<sub>2</sub>CHN and CHHCHN), 1.99-2.17 (m, 3H: CHHCHN and CH<sub>2</sub>CH=CH), 2.22 (s, 3H, CH<sub>3</sub>) 4.61 (m, 1H: CHN), 5.72 (m, 1H: NCHCH=CH), 6.10 (dq, 1H: *J* = 3.6, 10.1 Hz, CHNCH=CH), 6.79 (s, 1H: NCH=CCH<sub>3</sub>), 7.46 (s, 1H: NCH=N).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 9.7 (CH<sub>3</sub>), 19.2 (CH<sub>2</sub>CH<sub>2</sub>CHN), 24.86 (CH<sub>2</sub>CH=CH), 30.9 (NCHCH<sub>2</sub>), 50.5 (CHN), 125.6 (NCHCH=CH), 126.9 (NCH=CCH<sub>3</sub>, broad peak: line width = 24 Hz), 133.1 (NCHCH=CH), 140.0 (NCH=N, broad peak: line width = 34 Hz), quat. carbon not seen due to significant line broadening of minor isomer due to restricted rotation.

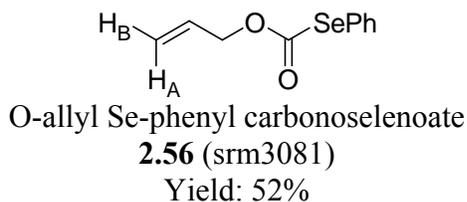
**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3053, 2985, 2950, 1421, 1271, 1259.

**HRMS** calcd for [M+H] 163.1235, found 163.1230.

### **Procedure for the synthesis of selenoformate 2.56.**

PhSeSePh (129 mg, 0.41 mmol) was dissolved in EtOH (5 mL) and NaBH<sub>4</sub> (31 mg, 0.83 mmol) was added until the color of the solution changed from orange to white. Then allyl chloroformate (88 μL, 0.83 mmol) was added *via* syringe to the reaction and allowed to stir until the reaction was complete as monitored by TLC, about 4 hours. The reaction was then quenched with H<sub>2</sub>O (5 mL) and extracted with Et<sub>2</sub>O (10 mL). The organic phase was dried over MgSO<sub>4</sub> and concentrated. The crude product

mixture was purified *via* flash chromatography with 95:5 hexane:ethyl acetate as the eluent. **2.56** was isolated in 50% yield.

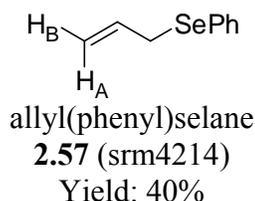


<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.75 (d, 2 H: *J* = 5.9 Hz, CH<sub>2</sub>O), 5.29 (dq, 1 H: *J* = 1.5, 10.3 Hz, H<sub>A</sub>), 5.35 (dq, 1H: *J* = 1.5, 17.1 Hz, H<sub>B</sub>), 5.94 (dddd, 1H: *J* = 5.9, 5.9, 11.7, 16.6 Hz, CH<sub>2</sub>=CH) 7.33-7.45 (m, 3H) 7.60-7.67 (m, 2H)

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 69.1 (CH<sub>2</sub>O), 120.0 (CH=CH<sub>2</sub>), 126.3 (quat. Ar C), 129.62 (CH=CH<sub>2</sub>), 129.75 (Ar CH's), 131.67 (Ar CH), 136.25 (Ar CH's), 167.2 (C=O)

#### Procedure for the Pd-catalyzed decarboxylative selenation.

To a dried Schlenk flask was added selenoformate **2.56** (100 mg, 0.41 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Pd(PPh<sub>3</sub>)<sub>4</sub> (24 mg, 0.02 mmol) was then added to the reaction and the mixture was stirred for 1 hour. Upon reaction completion, as determined by TLC, the reaction was concentrated and directly subjected to flash column chromatography using 100% hexane. The pure allyl selenide **2.57** was isolated in 40% yield.



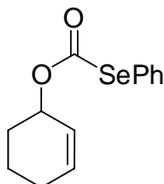
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.57 (d, 1H: *J* = 7.2 Hz, CH<sub>2</sub>SePh), 4.97 (dt, 1H: *J* = 9.9, 0.9 Hz, H<sub>B</sub>), 5.02 (dq, 1H: *J* = 1.4, 16.7 Hz, H<sub>A</sub>), 5.93-6.06 (m, 1H: CH=CH<sub>2</sub>), 7.27-7.33 (m, 2H: Ar CH's), 7.50-7.55 (m, 2H: Ar CH's)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 31.1 (CH<sub>2</sub>SePh), 117.3 (CH=CH<sub>2</sub>), 127.6 (Ar CH), 129.4 (Ar CH), 129.4 (quat. Ar C), 133.8 (Ar CH), 134.8 (CH=CH<sub>2</sub>).

### General procedure for the synthesis of selenoformates **2.58**

The selenoformates were synthesized using a modified procedure from Tian and coworkers.<sup>118</sup> The appropriate allylic alcohol (1.5 mmol) was dissolved in dichloroethane (10 mL). Then 1,1'-carbonyl diimidazole (2.23 mmol) was added to the solution and the reaction was heated to reflux for 3 hours. The solution was allowed to cool to room temperature, after which time it was diluted with Et<sub>2</sub>O (20 mL) and washed with brine solution (2 × 3 mL). The organic layer was dried over MgSO<sub>4</sub> and concentrated. The crude imidazolyl carbamate was then subjected to flash column chromatography using 90:10 hexane:ethyl acetate. The resulting carbamate (1.2 mmol) was then dissolved in dichloroethane (5 mL). To this mixture was added 4Å mol sieves (4 beads, ~ 0.15 g) and benzeneselenol (2.4 mmol) and the reaction was heated to reflux for 6 hours. Then the solution was cooled to room temperature and concentrated. Purification of the crude residue was then

accomplished *via* flash column chromatography using 95:5 hexane:ethyl acetate as the eluent.

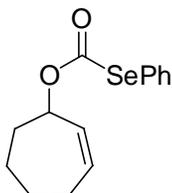


O-cyclohex-2-enyl Se-phenyl carbonoselenoate

**2.58a** (srm4163)

Yield: 71%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.59-1.69 (m, 1H: cyclohexyl CH), 1.73 (m, 1H: cyclohexyl CH), 1.87 (m, 2H: cyclohexyl CH's), 2.02 (m, 1H: cyclohexyl CH), 2.10 (m, 1H: cyclohexyl CH), 5.41 (app. d, 1H: *J* = 4.8 Hz, CHSePh), 5.79 (dddd, 1H: *J* = 2.1, 2.1, 4.1, 9.9 Hz, PhSeCHCH=CH), 6.00 (dt, 1H: *J* = 4.1, 9.9 Hz, PhSeCHCH=CH), 7.39 (m, 3H: Ar CH's), 7.64 (m, 2H: Ar CH's)

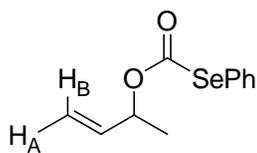


(*Z*)-O-cyclohept-2-enyl Se-phenyl carbonoselenoate

**2.58b** (srm4145)

Yield: 42%

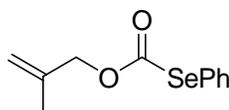
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.44 (m, 1 H: cycloheptyl CH), 1.63 (m, 2H: cycloheptyl CH's), 1.79 (m, 1H: cycloheptyl CH), 1.85-1.99 (m, 2H: cycloheptyl CH's), 2.06 (m, 1H: cycloheptyl CH), 2.18 (m, 1H: cycloheptyl CH), 5.56 (app. d, 1H: *J* = 9.6 Hz, CHO), 5.73 (app. d, 1H: *J* = 9.6 Hz, CHOCH=CH), 5.87 (m, 1H: CHOCH=CH), 7.33-7.42 (m, 3H: Ar CH's), 7.64 (dd, 2H: *J* = 2.0, 7.5 Hz, Ar CH's)



O-but-3-en-2-yl Se-phenyl carbonoselenoate  
**2.58c** (srm4154a)  
 Yield: 65%

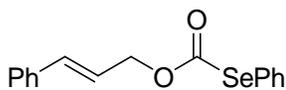
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.41 (dd, 2H: *J* = 1.3, 6.3 Hz, CH<sub>3</sub>), 5.21 (dq, 1H: *J* = 1.3, 10.4 Hz, H<sub>A</sub>), 5.31 (dq, 1H: *J* = 1.3, 17.3 Hz, H<sub>B</sub>), 5.49 (m, 1H: CHO), 5.88 (dddd, 1H: *J* = 1.3, 6.3, 10.4, 17.3 Hz, CH=CH<sub>2</sub>), 7.35-7.45 (m, 3H: Ar CH's), 7.65 (m, 2H: Ar CH's).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 20.1 (CH<sub>3</sub>), 117.1 (CH=CH<sub>2</sub>), 126.2 (quat. Ar C), 129.1 (Ar CH), 129.3 (Ar CH), 135.79 (Ar CH), 136.73 (CH=CH<sub>2</sub>), 166.1 (C=O).



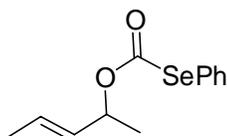
O-2-methylallyl Se-phenyl carbonoselenoate  
**2.58d** (srm4232)  
 Yield: 78%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.76 (s, 3H: CH<sub>3</sub>), 4.67 (s, 2H: CHO), 4.98 (d, 2H: *J* = 10.9 Hz, R<sub>2</sub>C=CH<sub>2</sub>), 7.39 (m, 3H: Ar CH's), 7.65 (dd, 2H: *J* = 1.4, 7.5 Hz, Ar CH's).



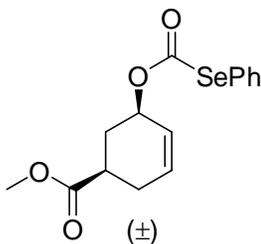
O-cinnamyl Se-phenyl carbonoselenoate  
**2.58e** (srm4159)  
 Yield: 81% (74% pure by <sup>1</sup>H NMR)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.91 (dd, 2H: *J* = 1.2, 6.7 Hz, CH<sub>2</sub>O), 6.31 (dt, 1H: *J* = 6.5, 15.7 Hz, PhCH=CH), 6.67 (d, 1H: *J* = 15.7 Hz, PhCH=CH), 7.29 (m, 1H: Ar CH), 7.34 (m, 3H: Ar CH's), 7.40 (m, 3H: Ar CH's), 7.65 (dd, 2H: *J* = 1.7, 7.9 Hz, Ar CH's).



(E)-O-pent-3-en-2-yl Se-phenyl carbonoselenoate  
**2.58f** (srm4246)  
 Yield: 9%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.39 (d, 3H: *J* = 6.3 Hz, OCHCH<sub>3</sub>), 1.72 (dd, 3H: *J* = 1.8, 6.3 Hz, CH=CHCH<sub>3</sub>), 5.46 (m, 1H: CHO), 5.51 (m, 1H: CH=CHCH<sub>3</sub>), 5.78 (dq, 1H: *J* = 6.3, 14.5 Hz, CH=CHCHO), 7.38 (m, 3H: Ar CH's), 7.65 (m, 2H: Ar CH).



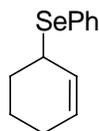
methyl 5-(phenylselanylcarbonyloxy)cyclohex-3-enecarboxylate  
**2.58g**<sup>119</sup> (srm5053)  
 Yield: 79%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.92 (dt, 1H: *J* = 8.8, 12.2 Hz, cyclohexyl CH), 2.34 (m, 2H: cyclohexyl CH's), 2.46 (m, 1H: cyclohexyl CH), 2.74 (dddd, 1H: *J* = 3.1, 6.0, 8.9, 11.8 Hz, CHCO<sub>2</sub>CH<sub>3</sub>), 3.74 (s, 3H: OCH<sub>3</sub>), 5.54 (br. s, 1H: CHO), 5.73 (app. d, 1H: *J* = 10.2 Hz, CHOCH=CH), 5.95 (m, 1H: CHOCH=CH), 7.40 (m, 3H: Ar CH's), 7.64 (m, 2H: Ar CH's).

#### General procedure for the Pd-catalyzed decarboxylative selenation.

To a dried Schlenk flask was added the selenoformate (0.41 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Pd(PPh<sub>3</sub>)<sub>4</sub> (24 mg, 0.02 mmol) was then added to the reaction and the mixture was stirred for 1 hour. Upon reaction completion, as determined by TLC, the solution was concentrated and directly subjected to flash column chromatography using 100%

hexane affording the pure allylic selenides. The isolated yields are reported in Table 2.4



cyclohex-2-enyl(phenyl)selane

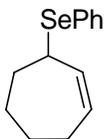
**2.59a** (srm4219)

Yield: 82%

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.58 (m, 1H: cyclohexyl CH), 1.78-1.90 (m, 2H: cyclohexyl CH's), 1.90-1.96 (m, 1H: cyclohexyl CH), 1.97-2.02 (m, 2H: cyclohexyl CH's), 3.91 (br. s, 1H: CHSePh), 5.67-5.72 (dt, 1H: *J* = 3.8, 6.0 Hz, PhSeCHCH=CH), 5.79 (dddd, 1H: *J* = 1.9, 1.9, 4.1, 9.8 Hz, PhSeCHCH=CH), 7.20 (m, 3H: Ar CH's), 7.50 (m, 2H: Ar CH's)

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 18.6 (cyclohexyl CH<sub>2</sub>), 23.9 (cyclohexyl CH<sub>2</sub>), 28.4 (cyclohexyl CH<sub>2</sub>), 40.2 (CHSePh), 126.2 (Ar CH's), 126.7 (Ar CH), 128.0 (PhSeCHCH=CH), 128.75 (PhSeCHCH=CH), 129.67 (quat. Ar C), 130.50 (O C, s), 133.09 (Ar CH's).

**Chiral HPLC Column:** Chiralpak AD **Eluent:** 99.8:0.2 hexane:isopropanol **Flow rate:** 0.5 mL/min **Wavelength:** 210 nm **Retention times:** 9.6 and 10.0 minutes.



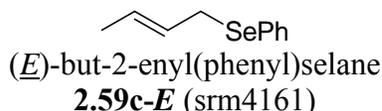
(Z)-cyclohept-2-enyl(phenyl)selane

**2.59b** (srm4151)

Yield: 66%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.43-1.52 (m, 1H: cycloheptyl CH), 1.73-1.81 (m, 2H: cycloheptyl CH's), 1.92 (m, 2H: cycloheptyl CH's), 2.03 (m, 1H: cycloheptyl CH), 2.20 (app. q, 2H: *J* = 5.8 Hz, cycloheptyl CH), 4.15 (ddd, 1H: *J* = 3.4, 4.1, 5.8 Hz, CHSePh), 5.80 (dd, 1H: *J* = 5.8, 11.3 Hz, PhSeCHCH=CH), 5.87 (ddt, 1H: *J* = 1.0, 6.5, 11.3 Hz, PhSeCHCH=CH), 7.25-7.30 (m, 3H: Ar CH's), 7.55-7.60 (m, 2H: Ar CH's).

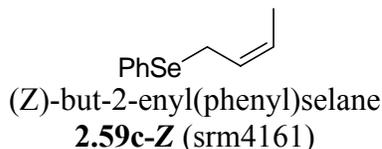
**Chiral HPLC Column:** Chiralpak AD **Eluent:** 99.8:0.2 hexane:isopropanol **Flow rate:** 0.5 mL/min **Wavelength:** 210 nm **Retention times:** 9.6 and 10.0 minutes.



isolated as 3.9:1 mixture of *E*:*Z* isomers  
Yield: 95% (combined isomers)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) *E*-isomer δ 1.64 (ddt, 3H: *J* = 1.0, 1.6, 6.6 Hz, CH<sub>3</sub>), 3.51 (dp, 2H: *J* = 1.3, 7.3 Hz, CH<sub>2</sub>SePh), 5.44 (m, 1H: CH=CHCH<sub>3</sub>), 5.59 (ddq, 1H: *J* = 1.6, 7.6, 15.1 Hz, CH=CHCH<sub>3</sub>), 7.26 (m, 3H: Ar CH's), 7.48 (m, 2H: Ar CH's).

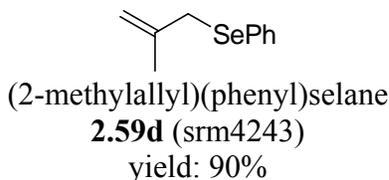
**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) *E*-isomer δ 16.7 (CH<sub>3</sub>), 29.1 (CH<sub>2</sub>SePh), 125.9 (CH=CHCH<sub>3</sub>), 125.98 (CH=CHCH<sub>3</sub>), 127.8 (Ar CH's), 127.9 (Ar CH), 129.4. (quat. Ar C), 132.3 (Ar CH's).



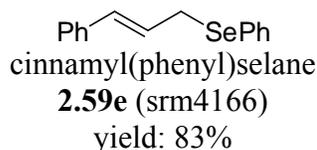
isolated as 3.9:1 mixture of *E*:*Z* isomers  
Yield: 95% (combined isomers)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) *Z*-isomer δ 1.50 (app. dd, 3H: *J* = 1.6, 6.9 Hz, CH<sub>3</sub>), 3.59 (app. d, 2H: *J* = 8.2 Hz, CH<sub>2</sub>SePh), 5.52 (m, 1H: CH=CHCH<sub>3</sub>), 5.63 (m, 1H: CH=CHCH<sub>3</sub>), 7.26 (m, 3H: Ar CH's), 7.54 (m, 2H: Ar CH's).

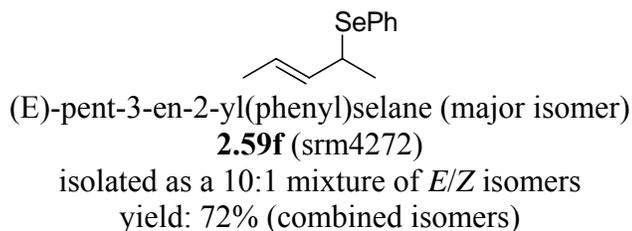
**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) *Z*-isomer δ 11.4 (CH<sub>3</sub>), 23.40 (PhSeCH<sub>2</sub>), 126.03 (CH=CHCH<sub>3</sub>), 126.10 (CH=CHCH<sub>3</sub>), 127.4 (Ar CH's), 128.2 (Ar CH), 132.63 (Ar CH's), quat. Ar C not observed.



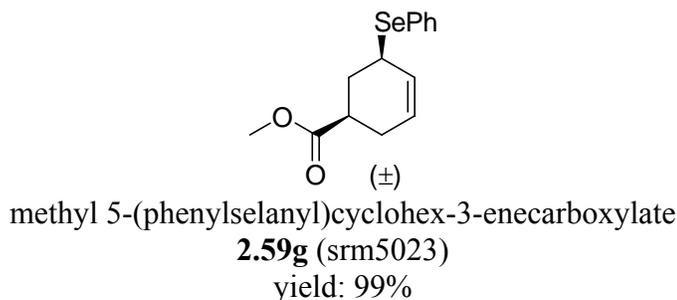
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.88 (m, 3H: CH<sub>3</sub>), 3.54 (app. d, 2H: CH<sub>2</sub>SePh), 4.73 (app. d, 2H: R<sub>2</sub>C=CH<sub>2</sub>), 7.26 (m, 3H: Ar CH's), 7.51 (m, 2H: Ar CH's).



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.70 (d, 2H: *J* = 7.5 Hz, CH<sub>2</sub>SePh), 6.27 (app. t, 1H: *J* = 15.7 Hz, PhCH=CH), 6.35 (dd, 1H: *J* = 7.5, 15.7 Hz, PhCH=CH), 7.22 (m, 1H: Ar CH), 7.28 (m, 7H; Ar CH's), 7.54 (m, 2H: Ar CH's).



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) *E*-isomer δ 1.48 (d, 2H: *J* = 6.7 Hz, PhSeCHCH<sub>3</sub>), 1.63 (dd, 3H: *J* = 1.7, 6.5 Hz, CH=CHCH<sub>3</sub>), 3.88 (p, 1 H: *J* = 7.2 Hz, CHSePh), 5.29 (ddd, 1 H: *J* = 1.7, 6.5, 15.3 Hz, CH=CHSePh), 5.55 (ddq, 1H: *J* = 1.7, 8.6, 15.3 Hz, CH<sub>3</sub>CH=CH), 7.30 (m, 3H: Ar CH's), 7.53 (m, 2H: Ar CH's).



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.89 (ddd, 1H: *J* = 10.6, 12.1, 13.2 Hz, PhSeCHCHH), 2.25 (m, 2H: CH=CHCH<sub>2</sub>), 2.49 (ddd, 1H: *J* = 2.7, 6.0, 13.2 Hz, PhSeCHCHH), 2.61 (dddd, 1H: *J* = 2.7, 6.4, 9.2, 12.2, Hz, CHCO<sub>2</sub>CH<sub>3</sub>), 3.70 (s, 3H: OCH<sub>3</sub>), 3.93 (m, 1H: CHSePh), 5.75 (m, 1H: PhSeCHCH=CH), 5.85 (app. d, 1H: *J* = 10.2 Hz, PhSeCHCH=CH), 7.31 (m, 3H: Ar CH's), 7.60 (m, 2H: Ar CH's).

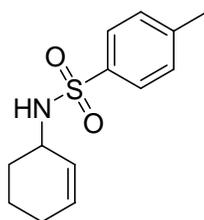
**Chiral HPLC Column:** Chiralpak AD **Eluent:** 99.5:0.5 hexane:isopropanol **Flow rate:** 0.5 mL/min **Wavelength:** 210 nm **Retention times:** 21.7 and 22.3 minutes.

**General procedure for the synthesis of chiral allylic selenides.**

To a dried NMR tube was added a solution of Pd<sub>2</sub>dba<sub>3</sub> (0.8 mg, 0.0008 mmol) and a chiral ligand (0.0017 mmol) in the designated solvent (600 μL) (as listed in Table 2.5). The selenoformate (0.035 mmol) was then added to the NMR tube and the reaction was allowed to stand at room temperature for 24 hours. The reactions were monitored by <sup>1</sup>H NMR spectroscopy to determine reaction conversion. Once the reaction had stopped, even if complete conversion had not been reached, the solution was concentrated. The residue was purified on a silica plug with 100% hexane and subjected to chiral high pressure liquid chromatography to determine enantioselectivity.

**General procedure for the synthesis of 2.62 via [2,3]-sigmatropic rearrangement.**

To a dried NMR tube was added allyl selenide **2.59a** (5 mg, 0.021 mmol) and CD<sub>2</sub>Cl<sub>2</sub> (600 μL). Then, anhydrous Chloramine-T (12 mg, 0.052 mmol) was added to the solution and the reaction was monitored by <sup>1</sup>H NMR spectroscopy. After 1 hour, the starting material had been consumed, but the reaction was allowed to stir for an additional 2 hours. Then, the solution was concentrated and directly purified *via* flash column chromatography (90:10 hexane:ethyl acetate), where **2.62** was isolated, although it was contaminated with tosylamine. An enantioenriched sample of **2.59a** was subjected to the same reaction conditions and isolated.



N-(cyclohex-2-enyl)-4-methylbenzenesulfonamide

**2.62** (srm4194)

~28% contamination with TsNH<sub>2</sub>

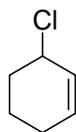
yield: 33% by <sup>1</sup>H NMR

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.57 (m, 3H: cyclohexyl CH's), 1.78 (m, 1H: cyclohexyl CH), 1.94 (m, 2H: cyclohexyl CH's), 2.44 (s, 3H: Ar CH<sub>3</sub>), 3.83 (br. s, 1H: NHTs), 4.38 (app. d, 1H: *J* = 8.2 Hz, CHNHTs), 5.35 (m, 1H: NHCHCH=CH), 5.77 (m, 1H: NHCHCH=CH), 7.31 (d, 2H: *J* = 7.9 Hz, Ar CH's), 7.78 (d, 2H: *J* = 8.2 Hz, Ar CH's).

**Chiral HPLC Column:** Chiralpak AD **Eluent:** 95:5 hexane:isopropanol **Flow rate:** 0.5 mL/min **Wavelength:** 210 nm **Retention times:** 27.3 and 29.8 minutes.

### **General procedure for the synthesis of allyl chlorides via [2,3]-sigmatropic rearrangement.**

The allylic chlorination was achieved using a procedure by Sharpless.<sup>120</sup> To a dried NMR tube was added the appropriate allyl selenide **2.59** (0.05 mmol) dissolved in CD<sub>2</sub>Cl<sub>2</sub> (600 μL). Then NCS (0.045 mmol) was added to the mixture and the reaction was monitored for conversion by <sup>1</sup>H NMR spectroscopy, and the clean formation of the allylic chloride **2.63** was observed.



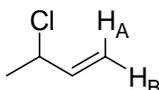
3-chlorocyclohex-1-ene

**2.63a** (srm4220)

yield: 95% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.67 (m, 1H: cyclohexyl CH), 1.88 (m, 1H: cyclohexyl CH), 1.95 - 2.20 (m, 4H: cyclohexyl CH's), 4.65 (s, 1H:  $\text{CHCl}$ ), 5.81 (m, 1H:  $\text{ClCHCH}=\text{CH}$ ), 5.90 (m, 1H:  $\text{ClCHCH}=\text{CH}$ ).

**Chiral GC Column:** Chiraldex B-TA **Program:** Initial Hold Temp. 30 °C for 5 minutes, ramp 1 °C/minute to 50 °C, hold at 50 °C 80 minutes **Retention times:** 41.0 and 45.0 minutes.

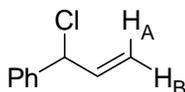


3-chlorobut-1-ene

**2.63c** (srm4172)

yield: 95% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.61 (dd, 3H:  $J = 0.7, 6.5$  Hz,  $\text{CHClCH}_3$ ), 4.57 (p, 1H:  $J = 6.8$  Hz,  $\text{CHCl}$ ), 5.13 (dq, 1H:  $J = 1.0, 10.2$  Hz,  $\text{H}_\text{B}$ ), 5.28 (dq, 1H:  $J = 1.0, 17.1$  Hz,  $\text{H}_\text{A}$ ), 5.99 (dddd, 1H:  $J = 0.7, 7.5, 10.2, 17.1$  Hz).



(1-chloroallyl)benzene

**2.63e** (srm4204)

yield: 75% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  5.27 (d, 1H:  $J = 9.9$  Hz,  $\text{H}_\text{B}$ ), 5.36 (app. d, 1H:  $J = 17.1$  Hz,  $\text{H}_\text{A}$ ), 5.51 (d, 1H:  $J = 7.5$  Hz,  $\text{PhCHCl}$ ), 6.24 (dddd, 1H:  $J = 0.7, 7.5, 10.2, 16.7$  Hz), 7.40 (m, 3H: Ar CH's), 7.75 (m, 2H: Ar CH).

**Procedure for the synthesis of chiral allyl chloride 2.63a.**

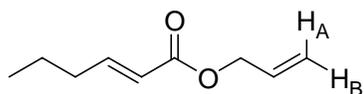
To a dried NMR tube was added chiral allyl selenide **2.59a** (0.004 mmol) and the appropriate solvent (600  $\mu$ L). Then NCS (0.0037 mmol) was added to the reaction mixture and the reaction was stopped after 1 hour. The enantiomeric excess was determined using chiral stationary phase GC.

**Procedure for the “one-pot” reaction of selenoformate 2.58a to allyl chloride 2.63a.**

To a dried NMR tube was added Pd<sub>2</sub>dba<sub>3</sub> (0.8 mg, 0.0008 mmol) and Naphthyl-Trost ligand **2.54** (1.5 mg, 0.0018 mmol) and dissolved in tol-*d*<sub>8</sub> (600  $\mu$ L). The selenoformate **2.58a** (10 mg, 0.035 mmol) was added to the mixture and allowed to react for 2 hours. Then, NCS (4.8 mg, 0.04 mmol) was added to the solution and was allowed to react for another 4 hours. The reaction was monitored by <sup>1</sup>H NMR spectroscopy during the reaction for conversion, and the enantioselectivity was determined using chiral stationary phase GC.

**Procedure for the synthesis of allylic ester 2.72.**

To a solution of ester **2.171** (10 mg, 0.065 mmol) was added [Cp\**Ru*Cl]<sub>4</sub> (1.8 mg, 0.0016 mmol) in C<sub>6</sub>D<sub>6</sub> (600  $\mu$ L). The solution was allowed to react at room temperature and it was monitored by <sup>1</sup>H NMR spectroscopy for completion. After 5 hours, the reaction had reached 80% conversion to the isomerized allylic ester **2.172**.



(E)-allyl hex-2-enoate

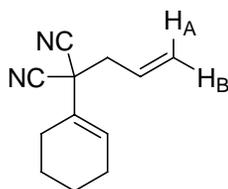
**2.72** (srm3161)

yield: 75% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  0.76 (td, 3H:  $J = 1.0, 7.4$  Hz,  $\text{CH}_3$ ), 1.19 (m, 2H:  $\text{CH}_3\text{CH}_2\text{R}$ ), 1.83 (m, 2H:  $\text{CH}_3\text{CH}_2\text{CH}_2\text{R}$ ), 4.65 (dq, 2H:  $J = 1.3, 5.7$  Hz,  $\text{OCH}_2$ ), 5.07 (dp, 1H:  $J = 1.4, 10.3$  Hz,  $\text{H}_\text{B}$ ), 5.24 (dp, 1H:  $J = 1.5, 18.7$  Hz,  $\text{H}_\text{A}$ ), 5.86 (m, 1H:  $\text{CH}=\text{CH}_2$ ), 5.95 (dq, 1H:  $J = 1.5, 15.8$  Hz,  $\text{CH}=\text{CHCO}_2\text{R}$ ), 7.12 (dddd, 1H:  $J = 1.0, 7.0, 15.6$  Hz,  $\text{CH}=\text{CHCO}_2\text{R}$ ).

### General procedure for the palladium-catalyzed decarboxylation of alkylidene malononitriles.

The alkylidene malononitriles were synthesized first by preparing the linear  $\beta$ -ketoesters *via* a DMAP-catalyzed addition of diketene to the corresponding allylic alcohols.<sup>121</sup> Cyclic  $\beta$ -ketoesters were prepared *via* a DMAP-catalyzed condensation of  $\beta$ -ketomethylesters and allylic alcohols.<sup>122</sup> Alkylation of linear  $\beta$ -ketoesters was achieved using  $^t\text{BuOK}$  and the corresponding alkylating agent.<sup>123</sup> Alkylidene malononitrile substrates were prepared *via* a Knoevenagel condensation of malononitrile with  $\beta$ -ketoesters.<sup>124</sup> Then, in a dried Schlenk flask under argon,  $\text{Pd}(\text{PPh}_3)_4$  (29 mg, 0.025 mmol) was added to substrates (0.5 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL). The resulting solutions were stirred at room temperature for 1-2 hours. The reaction mixture was then concentrated and directly purified via flash chromatography ( $\text{SiO}_2$ , 5% EtOAc:hexane). In some cases, mixtures of  $\alpha$ -alkylated and  $\gamma$ -alkylated products were obtained. The regioselectivities and isolated yields are reported in Table 2.7.



2-allyl-2-cyclohexenylmalononitrile

**2.76** (srm5075)

colorless oil

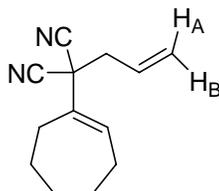
yield: 77%

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.61 (m, 2H: cyclohexyl CH's), 1.73 (pd, 2H: *J* = 1.9, 6.1 Hz, cyclohexyl CH's), 2.14 (m, 4H: cyclohexyl CH's), 2.75 (d, 2H: *J* = 7.2 Hz, allylic CH<sub>2</sub>), 5.36 (d, 1H: *J* = 11.2 Hz, H<sub>A</sub>), 5.39 (d, 1H: *J* = 4.16 Hz, H<sub>B</sub>), 5.80 (m, 1H: CH=CH<sub>2</sub>), 6.21 (app. d, 1H: *J* = 1.6 Hz, CH=CRC(CN)<sub>2</sub>).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 21.6 (cyclohexyl CH<sub>2</sub>), 22.5 (cyclohexyl CH<sub>2</sub>), 24.8 (cyclohexyl CH<sub>2</sub>), 25.5 (cyclohexyl CH<sub>2</sub>), 41.5 (allylic CH<sub>2</sub>), 43.9 (C(CN)<sub>2</sub>), 114.5 (CN), 123.1 (CH=CH<sub>2</sub>), 127.7 (CH=CRC(CN)<sub>2</sub>), 128.4 (CH=CH<sub>2</sub>), 130.1 (CH=CRC(CN)<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 2933, 2249, 1643, 1448, 1436.

**HRMS** calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub> [M<sup>+</sup>]: 186.1157, found: 185.9901.



(*E*)-2-allyl-2-cycloheptenylmalononitrile

**2.79a** (srm5190)

colorless oil

yield: 80%

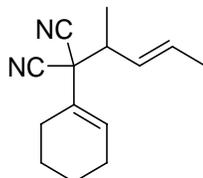
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.53 (m, 2H: cycloheptyl CH<sub>2</sub>), 1.61 (m, 2H: cycloheptyl CH<sub>2</sub>), 1.81 (m, 2H: cycloheptyl CH<sub>2</sub>), 2.26 (m, 2H: cycloheptyl CH<sub>2</sub>), 2.34 (m, 2H: cycloheptyl CH<sub>2</sub>), 2.74 (d, 2H: *J* = 7.3 Hz, (CN)<sub>2</sub>CCH<sub>2</sub>), 5.38 (dq, 1H: *J* = 1.4, 16.8 Hz, H<sub>A</sub>), 5.41 (dd, 1H: *J* = 0.8, 9.5 Hz, H<sub>B</sub>), 5.83 (dddd, 1H: *J* = 7.2, 7.2, 10.2, 14.3 Hz, CH=CH<sub>2</sub>), 6.37 (t, 1H: *J* = 6.7 Hz, CH=CR<sub>2</sub>).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 26.0 (cycloheptyl CH<sub>2</sub>), 26.6 (cycloheptyl CH<sub>2</sub>), 28.4 (cycloheptyl CH<sub>2</sub>), 29.7 (cycloheptyl CH<sub>2</sub>), 32.2 (cycloheptyl CH<sub>2</sub>), 41.6

$((\text{CN})_2\text{CCH}_2)$ , 45.1 ( $\text{C}(\text{CN})_2$ ), 114.6 (CN), 123.1 ( $\text{CH}=\text{CH}_2$ ), 129.0 ( $\text{CH}=\text{CH}_2$ ), 133.6 ( $\text{CH}=\text{CR}_2$ ), 134.5 ( $\text{CH}=\text{CR}_2$ ).

**FTIR** ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 2929, 2247, 1643, 1448.

**HRMS** calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2$  [ $\text{M}^+$ ]: 200.1313, found: 200.1310.



(*E*)-2-cyclohexenyl-2-(pent-3-en-2-yl)malononitrile

**2.79b** (srm5028)

colorless oil

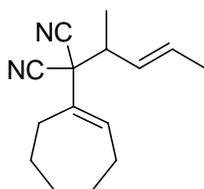
yield 97%

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.22 (d, 3H:  $J = 6.9$  Hz,  $\text{CH}_3\text{CHR}_2$ ), 1.59 (m, 2H: cyclohexyl CH's), 1.72 (m, 2H: cyclohexyl CH's), 1.74 (dd, 3H:  $J = 1.5, 6.5$  Hz,  $\text{CH}_3\text{CH}=\text{CHR}$ ), 2.07 (m, 2H: cyclohexyl CH's), 2.17 (m, 2H: cyclohexyl CH's), 2.76 (p, 1H:  $J = 7.1$  Hz,  $\text{CH}_3\text{CHR}_2$ ), 5.40 (ddq, 1H:  $J = 1.7, 8.4, 15.0$  Hz,  $\text{CH}=\text{CHCH}_3$ ), 5.73 (dq, 1H:  $J = 6.4, 15.2$  Hz,  $\text{CH}_3\text{CH}=\text{CH}$ ), 6.20 (app. s, 1H:  $\text{CH}=\text{C}(\text{CN})_2$ ).

**$^{13}\text{C}$  NMR** (75 Hz,  $\text{CDCl}_3$ )  $\delta$  16.2 ( $\text{CH}_3\text{CHR}_2$ ), 18.2 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 21.7 (cyclohexyl  $\text{CH}_2$ ), 22.3 (cyclohexyl  $\text{CH}_2$ ), 24.9 (cyclohexyl  $\text{CH}_2$ ), 25.6 (cyclohexyl  $\text{CH}_2$ ), 43.0 ( $\text{CH}_3\text{CHR}_2$ ), 50.2 ( $\text{C}(\text{CN})_2$ ), 114.2 (CN), 114.4 (CN), 127.6 ( $\text{CH}=\text{CR}_2$ ), 128.0 ( $\text{CH}=\text{CHCH}_3$ ), 130.7 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 131.2 ( $\text{CH}=\text{C}(\text{CN})_2$ ).

**FTIR** ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3053, 2986, 2231.

**HRMS** calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_2$  [ $\text{M}^+$ ]: 214.1470, found: 214.1473.



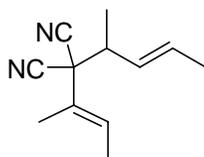
(*E*)-2-cycloheptenyl-2-((*E*) pent-3-en-2-yl)malononitrile  
**2.79c** (srm5125)  
 colorless oil  
 yield: 84%

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.22 (d, 3H: *J* = 6.8 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 1.53 (m, 2H: cycloheptyl CH<sub>2</sub>), 1.59 (sext, 2H: *J* = 6.2 Hz, cycloheptyl CH's), 1.75 (dd, 3H: *J* = 1.4, 6.5 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 1.80 (m, 2H: cycloheptyl CH's), 2.27 (m, 4H: cycloheptyl CH's), 2.73 (p, 1H: *J* = 7.2 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 5.40 (ddq, 1H: *J* = 1.7, 8.3, 15.1 Hz, CH=CHCH<sub>3</sub>), 5.72 (ddq, 1H: *J* = 0.8, 6.5, 15.1 Hz, CH<sub>3</sub>CH=CHR), 6.33 (t, 1H: *J* = 6.6 Hz, CH=CR<sub>2</sub>).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 16.4 (CH<sub>3</sub>CHR<sub>2</sub>), 18.2 (CH<sub>3</sub>CH=CHR), 26.0 (cycloheptyl CH<sub>2</sub>), 26.4 (cycloheptyl CH<sub>2</sub>), 28.5 (cycloheptyl CH<sub>2</sub>), 29.7 (cycloheptyl CH<sub>2</sub>), 32.2 (cycloheptyl CH<sub>2</sub>), 42.8 (CH<sub>3</sub>CHR<sub>2</sub>), 51.3 (C(CN)<sub>2</sub>), 114.3 (CN), 114.5 (CN), 128.2 (CH<sub>3</sub>CH=CHR), 131.2 (CH<sub>3</sub>CH=CHR), 133.3 (CH=CR<sub>2</sub>), 135.3 (CH=CR<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3053, 2986, 2229.

**HRMS** calcd for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub> [M<sup>+</sup>]: 228.1626, found: 228.1624.



2-((*E*)-but-2-en-2-yl)-2-((*E*)-pent-3-en-2-yl)malononitrile  
**2.79d** (srm5189)  
 isolated as a 15:1 of diastereomers  
 colorless oil  
 yield: 84% (combined diastereomers)

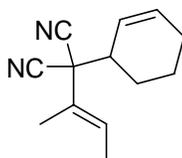
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 1.20 (d, 3H: *J* = 6.9 Hz, CH<sub>3</sub>CH=CHR), 1.74 (m, 6H: CH<sub>3</sub>CH=CHR and CH<sub>3</sub>CR=CHR), 1.79 (t, 3H: *J* = 1.0 Hz, CH<sub>3</sub>CH=CR<sub>2</sub>), 2.78 (p, 1H: *J* = 7.4 Hz, CH<sub>3</sub>CHCH=CHR), 5.40 (ddq, 1H: *J* = 1.5, 8.4, 15.1 Hz, RCH=CHCH<sub>3</sub>), 5.73 (ddd, 1H: *J* = 6.7, 13.4, 15.1 Hz,

$\text{CH}_3\text{CH}=\text{CHR}$ ), 6.05 (dq, 1H:  $J = 1.2, 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{CR}_2$ ). selective nOe irr 6.05 ppm, no significant enhancements observed

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  12.9 ( $\text{CH}_3\text{CH}=\text{CR}_2$ ), 14.0 ( $\text{CH}_3\text{CR}=\text{CHR}$ ), 16.1 ( $\text{CH}_3\text{CHR}_2$ ), 18.2 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 42.9 ( $\text{CH}_3\text{CHR}_2$ ), 51.0 ( $\text{C}(\text{CN})_2$ ), 114.2 (CN), 114.5 (CN), 125.4 ( $\text{CH}_3\text{CR}=\text{CHR}$ ), 127.9 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 128.2 ( $\text{CH}_3\text{CH}=\text{CR}_2$ ), 131.2 ( $\text{CH}_3\text{CH}=\text{CHR}$ ).

**FTIR** ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 2979, 2252, 1645.

**HRMS** calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_2$  [ $\text{M}^+$ ] 188.1313, found: 188.1324.



(E)-2-(but-2-en-2-yl)-2-(cyclohex-2-enyl)malononitrile

**2.79e** (srm5069)

colorless oil

isolated as an 8.3:1 mixture of diastereomers

yield: 92% (combined diastereomers)

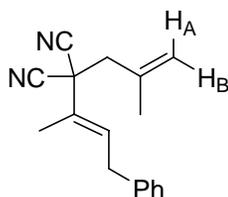
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) major diastereomer:  $\delta$  1.55 (m, 3H: cyclohexyl CH's), 1.79 (dd, 3H:  $J = 1.0, 6.9$  Hz,  $\text{CH}_3\text{CH}$ ), 1.83 (t, 3H:  $J = 1.1$  Hz,  $\text{CH}_3\text{CR}_2$ ), 1.95 (m, 2H: cyclohexyl CH's), 2.10 (m, 1H: cyclohexyl CH), 2.80 (app. s, 1H:  $\text{CH}=\text{CHCHR}_2$ ), 5.60 (dp, 1H:  $J = 2.1, 10.2$  Hz,  $\text{CH}=\text{CHCHR}_2$ ), 6.08 (m, 1H:  $\text{CH}=\text{CHCHR}_2$ ), 6.12 (qq, 1H:  $J = 1.2, 6.7$  Hz,  $\text{CH}_3\text{CH}=\text{CR}_2$ ). selective nOe irr @ 6.12 ppm, large enhancement observed at 1.79 ppm

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  12.9 ( $\text{CH}_3\text{CR}_2$ ), 14.1 ( $\text{CH}_3\text{CHR}$ ), 21.4 (cyclohexyl  $\text{CH}_2$ ), 24.9 (cyclohexyl  $\text{CH}_2$ ), 25.7 (cyclohexyl  $\text{CH}_2$ ), 41.1 ( $\text{CH}=\text{CHCHR}_2$ ), 50.2 ( $\text{C}(\text{CN})_2$ ), 114.2 (CN), 114.5 (CN), 122.7 ( $\text{CH}=\text{CHCHR}_2$ ), 124.9 ( $\text{CH}_3\text{CR}=\text{CHR}$ ), 128.5 ( $\text{CH}_3\text{CH}=\text{CR}_2$ ), 134.1 ( $\text{CH}=\text{CHCHR}_2$ ).

**FTIR** ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3029, 2947, 2247, 1652.

**Elemental Analysis** Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2$ : C, 77.96; H, 8.05; N, 13.99. Found: C, 78.21; H, 8.25; N, 13.82.

**Chiral HPLC Column:** Chiralcel OD-H **Eluent:** 99.8:0.8 hexane:isopropanol **Flow rate:** 0.5 mL/min **Wavelength:** 210 nm **Retention Times:** 15.9 and 17.5 minutes.



(E)-2-(2-methylallyl)-2-(4-phenylbut-2-en-2-yl)malononitrile

**2.79f** (srm5060)

colorless oil

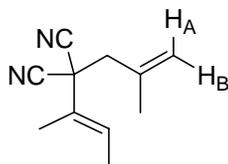
yield: 58% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.92 (s, 3H: CH<sub>3</sub>CR=CH<sub>2</sub>), 1.97 (s, 3H: CH<sub>3</sub>CR=CHR), 2.74 (s, 2H: allylic CH<sub>2</sub>), 3.46 (d, 2H: *J* = 7.3 Hz, RCH<sub>2</sub>Ph), 5.03 (s, 1H: H<sub>A</sub>), 5.11 (app. t, 1H: *J* = 1.3 Hz, H<sub>B</sub>), 6.19 (tq, 1H: *J* = 1.3, 7.2 Hz, PhCH<sub>2</sub>CH=CR<sub>2</sub>), 7.13 (d, 2H: *J* = 8.0 Hz, Ph-H), 7.22 (m, 1H: Ph-H) 7.29 (app. t, 2H: *J* = 1.7 Hz, Ph-H).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 13.6 (CH<sub>3</sub>CRC(CN)<sub>2</sub>), 23.2 (CH<sub>3</sub>CR=CH<sub>2</sub>), 34.6 (CH<sub>2</sub>Ph), 44.2 (C(CN)<sub>2</sub>), 45.2 (CH<sub>2</sub>CR=CH<sub>2</sub>), 114.8 (CN), 119.1 (R<sub>2</sub>C=CH<sub>2</sub>), 126.6 (CH<sub>3</sub>CR=CHR), 126.8 (Ph-CH), 128.5 (Ar-CH), 128.9 (Ar-CH), 131.3 (CH=CRC(CN)<sub>2</sub>), 137.3 (R<sub>2</sub>C=CH<sub>2</sub>), 138.7 (quat. Ar-C)

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3053, 2985, 2253.

**HRMS** calcd for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub> [M<sup>+</sup>] 250.1470, found: 250.1457.



(E)-2-(but-2-en-2-yl)-2-(2-methylallyl)malononitrile

**2.79g** (srm5136)

colorless oil

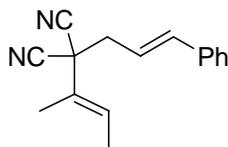
yield: 76% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.72 (dd, 3H: *J* = 1.0, 6.7 Hz, CH<sub>3</sub>CH=CR<sub>2</sub>), 1.84 (app. t, 3H: *J* = 0.90 Hz, CH<sub>3</sub>CR=C(CN)<sub>2</sub>), 1.89 (s, 3H: CH<sub>3</sub>CR=CH<sub>2</sub>), 2.69 (s, 2H: allylic CH<sub>2</sub>), 5.03 (app. s, 1H: H<sub>A</sub>), 5.12 (p, 1H: *J* = 1.4 Hz, H<sub>B</sub>), 6.07 (qq, 1H: *J* = 1.2, 6.8 Hz, CH<sub>3</sub>CH=CR<sub>2</sub>).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 13.1 (CH<sub>3</sub>CR=CHR), 14.1 (CH<sub>3</sub>CH=CR<sub>2</sub>), 23.2 (CH<sub>3</sub>CR=CH<sub>2</sub>), 44.3 (C(CN)<sub>2</sub>), 45.1 (allylic CH<sub>2</sub>), 114.9 (CN), 119.0 (R<sub>2</sub>C=CH<sub>2</sub>), 126.3 (CH<sub>3</sub>CR=CHR), 127.2 (CH<sub>3</sub>CH=CR<sub>2</sub>), 137.5 (CR<sub>2</sub>=CH<sub>2</sub>);.

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3082, 2995, 2231, 1649.

**HRMS** calcd for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub> [M<sup>+</sup>] 174.1157, found: 174.1149.



2-((E)-but-2-en-2-yl)-2-cinnamylmalononitrile

**2.79h** (srm5183)

white solid

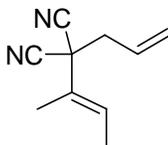
yield: 97%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.76 (dd, 3H:  $J$  = 1.1, 6.9 Hz, CH<sub>3</sub>CH=CR<sub>2</sub>), 1.89 (t, 3H:  $J$  = 1.1 Hz, CH<sub>3</sub>CR=CHR), 2.93 (dd, 2H:  $J$  = 1.3, 2.6 Hz, allylic CH<sub>2</sub>), 6.10 (qq, 1H:  $J$  = 1.3, 6.9 Hz, CH<sub>3</sub>CH=CR<sub>2</sub>), 6.14 (dt, 1H:  $J$  = 6.7, 15.6 Hz, CH=CHPh), 7.30 (d, 1H:  $J$  = 7.4 Hz, Ph-H), 7.35 (t, 2H:  $J$  = 7.4 Hz, Ph-H), 7.40 (d, 2H:  $J$  = 7.2 Hz, Ph-H).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>)  $\delta$  13.0 (CH<sub>3</sub>CR=CHR), 14.1 (CH<sub>3</sub>CHR), 41.3 (CH<sub>2</sub>CH=CHPh), 45.1 (C(CN)<sub>2</sub>), 114.7 (CN), 119.5 (CH=CHPh), 125.6 (quat Ar-C), 126.9 (Ph-CH), 127.8 (CH<sub>3</sub>CHR), 128.6 (Ph-CH), 128.9 (Ph-CH), 136.1 (R<sub>2</sub>C=CH<sub>2</sub>), 137.7 (CH=CHPh)

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3083, 3062, 2975, 2925, 2249, 1708, 1654, 1598, 1496, 1450, 1436.

**HRMS** calcd for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub> [M<sup>+</sup>] 236.1313, found: 236.1312.



(E)-2-allyl-2-(but-2-en-2-yl)malononitrile

**2.79i** (srm5162\_1)

colorless oil

yield: 91% (combined isomers)

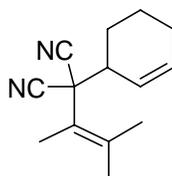
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.75 (app. d, 3H:  $J$  = 6.9 Hz, CH<sub>3</sub>CR=CHR), 1.85 (app. d, 3H:  $J$  = 1.2 Hz, CH<sub>3</sub>CH=CR<sub>2</sub>), 2.77 (dd, 2H:  $J$  = 0.9, 7.2 Hz, allylic CH<sub>2</sub>),

5.39 (m, 2H: CH=CH<sub>2</sub>), 5.81 (m, 1H: CH=CH<sub>2</sub>), 6.07 (app. q, 1H: *J* = 6.7 Hz, CH<sub>3</sub>CH=CR<sub>2</sub>).

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 13.1 (CH<sub>3</sub>CH=CR<sub>2</sub>), 14.1 (CH<sub>3</sub>CR=CHR), 41.7 (allylic CH<sub>2</sub>), 44.8 (C(CN)<sub>2</sub>), 114.6 (CN), 123.1 (R<sub>2</sub>C=CH<sub>2</sub>), 125.6 (CHR=CR<sub>2</sub>), 127.7 (CH<sub>3</sub>CH=CR<sub>2</sub>), 128.8 (CH=CH<sub>2</sub>).

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3064, 2993, 2248, 1643.

HRMS calcd for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub> [M<sup>+</sup>] 160.1000, found: 160.0996.



2-(cyclohex-2-enyl)-2-(3-methylbut-2-en-2-yl)malononitrile  
**2.79j** (srm5191)

6:1 ratio of dimethylated : monomethylated product, inseparable mixture  
colorless oil  
yield: 93%

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.56 (m, 1H: cyclohexyl CH), 1.65 (m, 1H: cyclohexyl CH<sub>2</sub>), 1.82 (d, 3H: *J* = 0.8 Hz, one of (CH<sub>3</sub>)<sub>2</sub>C=CR<sub>2</sub>), 1.96 (app. t, 3H: *J* = 1.2 Hz, one of (CH<sub>3</sub>)<sub>2</sub>C=CR<sub>2</sub>), 1.99 (app. d, 1H: *J* = 1.5 Hz, cyclohexyl CH), 2.01 (m, 1H: cyclohexyl CH), 2.09 (m, 2H: cyclohexyl CH<sub>2</sub>), 3.00 (m, 1H: CHCH=CH), 5.62 (dp, 1H: *J* = 2.2, 10.2 Hz, CH=CHCHR<sub>2</sub>), 6.08 (m, 1H: CH=CHCHR<sub>2</sub>).

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 20.0 (one of CH<sub>3</sub>), 21.5 (cyclohexyl CH<sub>2</sub>), 22.7 (one of CH<sub>3</sub>), 23.7 (one of CH<sub>3</sub>), 24.9 (cyclohexyl CH<sub>2</sub>), 25.8 (cyclohexyl CH<sub>2</sub>), 43.8 (CH=CHCHR<sub>2</sub>), 46.5 (CR<sub>2</sub>(CN)<sub>2</sub>), 115.0 (CN), 115.3 (CN), 117.8 (RC(CH<sub>3</sub>)<sub>2</sub>), 123.3 (CHCH=CH), 134.1 (CHCH=CH), 135.3 (R<sub>2</sub>C=C(CH<sub>3</sub>)<sub>2</sub>).

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3029, 3012, 2947, 2929, 2245, 1650, 1448, 1433.

HRMS calcd for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub> [M<sup>+</sup>] 214.1470, found: 214.1470.

**General procedure for the Cope rearrangement using a microwave reactor.**

To a microwave safe vial was added a solution of the substrate (0.15 mmol) dissolved into CH<sub>3</sub>CN (1.5 mL). The vial was then appropriately sealed and placed in the microwave reactor. The solution was then heated to 150 °C for 30 minutes. Upon reaction completion, the solution was concentrated and the product **2.80** was purified *via* flash column chromatography if necessary. Substrate **2.80j** required 180 °C for 200 minutes to reach reaction completion. Isolated yields are reported in Table 2.8.

**Procedure for the Pd(II)-catalyzed synthesis of 2.80d.**

To a dried NMR tube was added **2.79d** (14 mg, 0.074 mmol) and CD<sub>2</sub>Cl<sub>2</sub> (600 μL). Then, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (1.9 mg, 0.0074 mmol) was added to the mixture and the solution was heated to 80 °C. The conversion of the reaction was monitored by <sup>1</sup>H NMR spectroscopy. Once the reaction was 90% complete, the reaction was concentrated and the residue was purified *via* flash column chromatography (98:2 hexane:ethyl acetate). The product **2.80d** was isolated in 71% yield as an 11.2:1 mixture of diastereomers.

**Procedure for the synthesis of 2.80i *via* the Pd(0)-catalyzed Cope rearrangement.**

To a dried NMR tube was added **2.79i** (30 mg, 0.18 mmol) dissolved in tol-*d*<sub>8</sub> (800 μL). Then, Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mg, 0.009 mmol) was added to the solution and the reaction was heated to 70 °C for 16 hours. Reaction completion was verified by <sup>1</sup>H NMR spectroscopy at which time the reaction was concentrated and purified *via* flash

column chromatography (95:5 hexane:ethyl acetate). Product **2.80i** was isolated in 95% yield.

**Procedure for the tandem decarboxylation/Cope rearrangement reaction.**

To a Schlenk flask was added **2.78i** (102 mg, 0.5 mmol) dissolved in toluene (5 mL). Then, Pd(PPh<sub>3</sub>)<sub>4</sub> (29 mg, 0.025 mmol) was added to the solution and it was heated to 70 °C for 16 hours. The reaction was allowed to cool to room temperature and concentrated. The crude mixture was directly purified *via* flash column chromatography (95:5 hexane: ethyl acetate). Hexadiene **2.80i** was isolated in 55% yield.

**Procedure for the synthesis of chiral hexadiene 2.80d from 2.78d.**

To a Schlenk flask was added Pd<sub>2</sub>dba<sub>3</sub> (9.9 mg, 0.01 mmol) and Trost ligand **2.53** (15 mg, 0.22 mmol) dissolved in toluene (5 mL). Then, **2.78d** (100 mg, 0.43 mmol) was added to the solution and the reaction was heated to 70 °C for 16 hours. The solution was allowed to cool to room temperature and was concentrated. The crude mixture was purified *via* flash column chromatography (95:5 hexane: ethyl acetate). The enantiomeric excess was determined using chiral stationary phase GC. **2.80d** was isolated in 75% yield as a 10:1 mixture of diastereomers with a 46% ee.

**Procedure for the treatment of 2.79d with Pd(0) and Trost ligand.**

To a Schlenk flask was added Pd<sub>2</sub>dba<sub>3</sub> (10.7 mg, 0.012 mmol) and Trost ligand (16 mg, 0.23 mmol) dissolved in toluene (5 mL). Then, **2.79d** (88 mg, 0.47 mmol) was added to the solution and the solution was heated to 70 °C for 16 hours. The solution was allowed to cool to room temperature and was concentrated. The crude mixture was purified *via* flash column chromatography (95:5 hexane: ethyl acetate). The enantiomeric excess was determined using chiral stationary phase GC. Hexadiene **2.80d** was isolated in 75% yield, as a 7:1 mixture of diastereomers with no enantiomeric excess.

**Procedure for the thermal Cope rearrangement of 2.79d to 2.80d.**

To a dried NMR tube was added **2.79d** (3.5 mg, 0.019 mmol) in tol-*d*<sub>8</sub> (600 μL). The reaction mixture was heated to 70 °C for 16 hours, after which point the reaction was monitored by <sup>1</sup>H NMR spectroscopy. It was observed that the reaction had completely converted to **2.80d** with a 10:1 diastereomeric ratio.

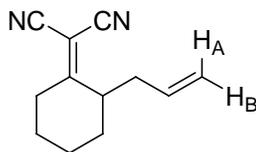
**General procedure for the enantioselective synthesis of 2.79e.**

To a dried NMR tube was added Pd<sub>2</sub>dba<sub>3</sub> (0.92 mg, 0.001 mmol) and chiral ligand (0.002 mmol) in the designated solvent (600 μL) (as listed in Table 2.9). Then, **2.78e** (10 mg, 0.04 mmol) was added to the solution and the reaction was stirred at room temperature unless otherwise noted. The reactions were monitored by <sup>1</sup>H NMR

spectroscopy. After the appropriate time, the solution was concentrated and the enantioselectivity was determined using chiral stationary phase HPLC.

### General procedure for the enantioselective synthesis of **2.80e**.

To a dried NMR tube was added Pd<sub>2</sub>dba<sub>3</sub> (0.92 mg, 0.001 mmol) and chiral ligand (0.002 mmol) in the designated solvent (600 μL) (as listed in Table 2.10). Then, **2.78e** (10 mg, 0.04 mmol) was added to the solution and it was heated to the specified temperature using a microwave reactor unless otherwise noted. After the appropriate time, the reaction was concentrated and the enantioselectivity was determined using a chiral stationary phase GC.



2-(2-allylcyclohexylidene)malononitrile

**2.77** (srm5094)

colorless oil

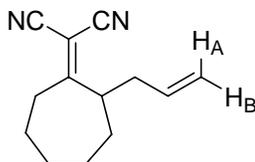
yield: 94%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.49 (m, 1H: cyclohexyl CH), 1.67 (m, 3H: cyclohexyl CH's), 1.99 (m, 1H: cyclohexyl CH), 2.09 (m, 1H: cyclohexyl CH), 2.37 (m, 3H: one of cyclohexyl CH and allylic CH<sub>2</sub>), 2.93 (d, 1H: *J* = 14.13 Hz, cyclohexyl CH), 3.21 (app. s, 1H: (CN)<sub>2</sub>C=C-CHR<sub>2</sub>), 5.08 (dq, 1H: *J* = 1.6, 17.1 Hz, H<sub>A</sub>), 5.12 (d, 1H: *J* = 10.1 Hz, H<sub>B</sub>), 5.70 (dddd, 1H: *J* = 7.5, 7.5, 10.3, 17.5 Hz, RCH=CH<sub>2</sub>).

<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 19.9 (cyclohexyl CH<sub>2</sub>), 28.1 (cyclohexyl CH<sub>2</sub>), 31.2 (cyclohexyl CH<sub>2</sub>), 31.5 (cyclohexyl CH<sub>2</sub>), 37.3 (allylic CH<sub>2</sub>), 42.7 ((CN)<sub>2</sub>C=CRCHR<sub>2</sub>), 83.5 ((CN)<sub>2</sub>C=C), 111.9 (CN), 118.5 (C=CH<sub>2</sub>), 134.2 (CH=CH<sub>2</sub>), 187.5 (R<sub>2</sub>C=C(CN)<sub>2</sub>);

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 2252, 1641, 1267, 1263.

HRMS calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub> [M<sup>+</sup>] 186.1157, found: 186.1166.



2-(2-allylcycloheptylidene)malononitrile

**2.80a** (srm5195)

colorless oil

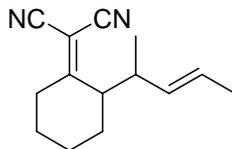
yield: 99%

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.02 (app. q, 1H: *J* = 12.2 Hz, cycloheptyl CH), 1.36 (m, 3H: cycloheptyl CH's), 1.86 (m, 2H: cycloheptyl CH's), 2.09 (m, 1H: cycloheptyl CH), 2.17 (m, 2H: one of cycloheptyl CH and one of allylic CH<sub>2</sub>), 2.32 (m, 2H: one of cycloheptyl CH and one of allylic CH<sub>2</sub>), 2.90 (ddd, 1H: *J* = 1.4, 6.4, 12.2 Hz, cycloheptyl CH), 3.17 (m, 1H: (CN)<sub>2</sub>C=CRCHR<sub>2</sub>), 5.05 (dq, 1H: *J* = 1.5, 16.9 Hz, H<sub>A</sub>), 5.12 (app. d, 1H: *J* = 9.0 Hz, H<sub>B</sub>), 5.74 (dddd, 1H: *J* = 7.3, 7.3, 10.0, 16.9 Hz, RCH=CH<sub>2</sub>).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 25.8 (cycloheptyl CH<sub>2</sub>), 29.4 (cycloheptyl CH<sub>2</sub>), 30.5 (cycloheptyl CH<sub>2</sub>), 31.4 (cycloheptyl CH<sub>2</sub>), 32.9 (cycloheptyl CH<sub>2</sub>), 40.7 (allylic CH<sub>2</sub>), 47.1 ((CN)<sub>2</sub>C=CRCHR<sub>2</sub>), 86.6 ((CN)<sub>2</sub>C=C), 112.1 (CN), 112.3 (CN), 118.8 (C=CH<sub>2</sub>), 133.9 (CH=CH<sub>2</sub>), 191.1 (R<sub>2</sub>C=C(CN)<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 2931, 2231, 1641, 1579, 1448.

HRMS calcd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub> [M<sup>+</sup>] 200.1313, found 200.1322.



(E)-2-(2-(pent-3-en-2-yl)cyclohexylidene)malononitrile

**2.80b** (srm5042)

colorless oil

yield: 82% (93% pure)

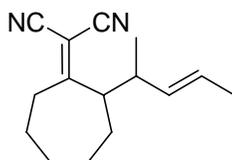
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.12 (d, 3H: *J* = 6.5 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 1.55 (m, 4H: cyclohexyl CH<sub>2</sub>'s), 1.66 (dd, 3H: *J* = 1.4, 6.3 Hz, CH<sub>3</sub>CH=CHR), 2.11 (m, 2H: cyclohexyl CH<sub>2</sub>), 2.31 (td, 1H: *J* = 5.6, 13.6 Hz, cyclohexyl CH), 2.49 (m, 1H: R<sub>2</sub>CHCH<sub>3</sub>), 2.71 (d, 1H: *J* = 10.5 Hz, (CN)<sub>2</sub>C=CRCH), 2.90 (d, 1H: *J* = 14.3 Hz,

cyclohexyl CH), 5.18 (ddd, 1H:  $J = 1.5, 9.2, 15.2$  Hz,  $\text{CH}_3\text{CH}=\text{CHR}$ ), 5.39 (dq, 1H:  $J = 6.4, 15.0$  Hz,  $\text{CH}_3\text{CH}=\text{CHR}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  17.9 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 19.3 ( $\text{CH}_3\text{CHR}_2$ ), 19.9 (cyclohexyl  $\text{CH}_2$ ), 28.4 (cyclohexyl  $\text{CH}_2$ ), 29.5 (cyclohexyl  $\text{CH}_2$ ), 31.8 (cyclohexyl  $\text{CH}_2$ ), 38.5 ( $\text{CH}_3\text{CHR}_2$ ), 49.0 ( $(\text{CN})_2\text{C}=\text{CRCH}$ ), 83.3 ( $\text{C}=\text{C}(\text{CN})_2$ ), 112.1 (CN), 112.2 (CN), 126.0 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 133.1 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 188.7 ( $\text{R}_2\text{C}=\text{C}(\text{CN})_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3053, 2986, 2231, 1589.

Elemental Analysis Calcd For  $\text{C}_{14}\text{H}_{18}\text{N}_2$ : C, 78.46; H, 8.47; N, 13.07. Found: C, 78.52; H, 8.68; N, 12.78.



(E)-2-(2-(pent-3-en-2-yl)cycloheptylidene)malononitrile

**2.80c** (srm5123)

colorless oil

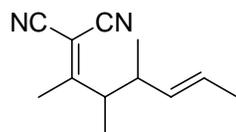
yield: 89%

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.00 (m, 1H: cycloheptyl CH), 1.08 (d, 3H:  $J = 6.7$  Hz,  $\text{CH}_3\text{CHR}_2$ ), 1.36 (m, 3H: cycloheptyl CH's), 1.67 (dd, 3H:  $J = 1.5, 6.2$  Hz,  $\text{CH}_3\text{CH}=\text{CHR}$ ), 1.87 (m, 2H: cycloheptyl CH's), 2.14 (m, 2H: cycloheptyl CH's), 2.19 (q, 1H:  $J = 7.7$  Hz, cycloheptyl CH's), 2.28 (td, 1H:  $J = 2.2, 12.0$  Hz, cycloheptyl CH), 2.86 (ddd, 1H:  $J = 1.7, 5.9, 12.3$  Hz, cycloheptyl CH), 2.92 (m, 1H:  $\text{CH}_3\text{CHRCHR}_2$ ) 5.24 (ddq, 1H;  $J = 1.1, 8.6, 15.0$  Hz,  $\text{CH}_3\text{CH}=\text{CH}$ ), 5.35 (dq, 1H:  $J = 6.3, 15.3$  Hz,  $\text{CH}_3\text{CH}=\text{CH}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  18.0 ( $\text{CH}_3\text{CH}=\text{CH}$ ), 18.3 ( $\text{CH}_3\text{CHR}_2$ ), 25.6 (cycloheptyl  $\text{CH}_2$ ), 29.5 (cycloheptyl  $\text{CH}_2$ ), 29.5 (cycloheptyl  $\text{CH}_2$ ), 30.6 (cycloheptyl  $\text{CH}_2$ ), 33.5 (cycloheptyl  $\text{CH}_2$ ), 43.9 ( $\text{CH}_3\text{CHR}_2$ ), 52.8 ( $\text{CH}_3\text{CHRCHR}_2$ ), 87.1 ( $\text{C}(\text{CN})_2$ ), 112.2 (CN), 112.7 (CN), 126.5 ( $\text{CH}=\text{CHCH}_3$ ), 133.5 ( $\text{CH}_3\text{CH}=\text{CHR}$ ), 191.4 ( $\text{C}=\text{C}(\text{CN})_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3053, 2984, 2231, 1651, 1581.

HRMS calcd for  $\text{C}_{15}\text{H}_{20}\text{N}_2$   $[\text{M}^+]$  228.1626, found: 228.1630.



(E)-2-(3,4-dimethylhept-5-en-2-ylidene)malononitrile

**2.80d** (srm5188)

isolated as a 12.4:1 mixture of diastereomers

colorless oil

yield: 99% (combined diastereomers)

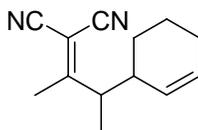
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.09 (d, 3H: *J* = 6.6 Hz, CH<sub>3</sub>CHRCH=CHR), 1.15 (d, 3H: *J* = 6.9 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 1.65 (dd, 3H: *J* = 1.4, 6.3 Hz, CH<sub>3</sub>CH=CHR), 2.14 (m, 4H: CH<sub>3</sub>CR=C(CN)<sub>2</sub> and CH<sub>3</sub>CHRCH=CHR), 2.86 (m, 1H: CH<sub>3</sub>CHR<sub>2</sub>), 5.18 (ddd, 1H: *J* = 1.4, 9.1, 15.2 Hz, RCH=CHCH<sub>3</sub>), 5.40 (dq, 1H: *J* = 6.4, 15.1 Hz, CH<sub>3</sub>CH=CHR).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 16.6 (CH<sub>3</sub>CHR<sub>2</sub>), 18.0 (CH<sub>3</sub>CH=CHR), 18.5 (CH<sub>3</sub>CR=C(CN)<sub>2</sub>), 19.2 (CH<sub>3</sub>CHRCH=CHR), 42.8 (CH<sub>3</sub>CHRCH=CHR), 47.3 (CH<sub>3</sub>CHR<sub>2</sub>), 85.78 (C(CN)<sub>2</sub>), 112.0 (CN), 112.3 (CN), 126.3 (CH<sub>3</sub>CH=CHR), 133.4 (CH<sub>3</sub>CH=CHR), 186.4 (R<sub>2</sub>C=C(CN)<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 2977, 2253.

**HRMS** calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub> [M<sup>+</sup>] 188.1313, found: 188.1311.

**Chiral GC Column:** Chiraldex B-DM **Program:** Initial Hold Temp. 50 °C for 5 minutes, ramp 10 °C/minute to 120 °C, hold at 120 °C 35 minutes **Retention times:** 30.6 and 31.3 minutes for major diastereomer, and 35.9 and 37.3 minutes for minor diastereomer.



2-(3-(cyclohex-2-enyl)butan-2-ylidene)malononitrile

**2.80e** (srm5187)

isolated as 9.1:1 mixture of diastereomers

colorless oil

yield: 98% (combined diastereomers)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.10 (m, 1H: cyclohexyl CH), 1.22 (d, 3H: *J* = 6.8 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 1.55 (m, 2H: cyclohexyl CH's), 1.73 (m, 1H: cyclohexyl CH), 2.02 (m, 2H: cyclohexyl CH<sub>2</sub>), 2.15 (m, 1H: R<sub>2</sub>CHCH=CHR), 2.20 (s, 3H:

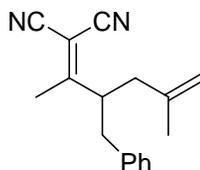
$\text{CH}_3\text{CR}=\text{C}(\text{CN})_2$ , 2.95 (dd, 1H:  $J = 6.7, 10.14$  Hz,  $\text{CH}_3\text{CHR}_2$ ), 5.71 (dq, 1H:  $J = 2.4, 10.3$  Hz,  $\text{RCH}=\text{CHCHR}_2$ ), 5.85 (dddd, 1H:  $J = 2.2, 3.5, 3.5, 7.3$  Hz,  $\text{RCHCH}=\text{CHR}$ ).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  16.6 ( $\text{CH}_3\text{CHR}_2$ ), 18.0 ( $\text{CH}_3\text{CR}=\text{C}(\text{CN})_2$ ), 20.6 (cyclohexyl  $\text{CH}_2$ ), 25.2 (cyclohexyl  $\text{CH}_2$ ), 27.5 (cyclohexyl  $\text{CH}_2$ ), 38.6 ( $\text{R}_2\text{CHCH}=\text{CHR}$ ), 46.5 ( $\text{CH}_3\text{CHR}_2$ ), 86.1 ( $(\text{CN})_2\text{C}$ ), 112.0 (CN), 112.2 (CN), 126.5 ( $\text{R}_2\text{CHCH}=\text{CHR}$ ), 130.6 ( $\text{R}_2\text{CHCH}=\text{CHR}$ ), 186.0 ( $\text{R}_2\text{C}=\text{C}(\text{CN})_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3053, 2977, 2231, 1647, 1591.

HRMS calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_2$  [M+] 200.1313, found: 200.1324.

**Chiral GC Column:** Chiraldex B-DM **Program:** Isocratic Hold at 120 °C **Retention times:** 132.2 and 139.9 minutes for the major diastereomer 136.6 and 138.3 for the minor diastereomer.



2-(3-benzyl-5-methylhex-5-en-2-ylidene)malononitrile

**2.80f** (srm5061)

colorless oil

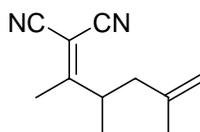
yield: 58% (combined isomers)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.68 (s, 3H:  $\text{CH}_3\text{CR}=\text{CH}_2$ ), 2.10 (s, 3H:  $\text{CH}_3\text{CR}=\text{C}(\text{CN})_2$ ), 2.19 (dd, 1H:  $J = 9.6, 14.1$  Hz,  $\text{CHHCR}=\text{CH}_2$ ), 2.28 (dd, 2H:  $J = 5.3, 13.9$  Hz,  $\text{CHHCR}=\text{CH}_2$ ), 2.61 (dd, 1H:  $J = 9.1, 13.9$  Hz,  $\text{CHHPh}$ ), 2.87 (dd, 1H:  $J = 6.4, 14.1$  Hz,  $\text{CHHPh}$ ), 3.51 (dddd, 1H:  $J = 5.9, 5.9, 9.3, 15.4$  Hz,  $\text{CHCH}_2\text{Ph}$ ), 4.62 (s, 1H:  $\text{CR}_2=\text{CHH}$ ), 4.77 (s, 1H:  $\text{CR}_2=\text{CHH}$ ), 7.06 (d, 2H:  $J = 7.5$  Hz, Ph-H), 7.19 (app. t, 1H:  $J = 7.5$  Hz, Ph-H), 7.15 (app. t, 2H:  $J = 7.2$  Hz, Ph-H).

$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  18.0 ( $\text{CH}_3\text{CR}=\text{C}(\text{CN})_2$ ), 22.2 ( $\text{CH}_3\text{CR}=\text{CH}_2$ ), 39.8 ( $\text{CH}_2\text{Ph}$ ), 41.3 ( $\text{CH}_2\text{CR}=\text{CH}_2$ ), 47.1 ( $\text{R}_2\text{CHCH}_2\text{Ph}$ ), 87.5 ( $\text{R}_2\text{C}=\text{C}(\text{CN})_2$ ), 111.7 (CN), 111.9 (CN), 114.1 ( $\text{R}_2\text{C}=\text{CH}_2$ ), 127.4 (Ph-CH), 128.8 (Ph-CH), 129.1 (Ph-CH), 137.2 (quat. Ph-C), 141.5 ( $\text{R}_2\text{C}=\text{CH}_2$ ), 183.6 ( $\text{R}_2\text{C}=\text{C}(\text{CN})_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3078, 3029, 2941, 2233, 1652, 1591.

HRMS calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_2$  [M+] 250.1470, found: 250.1472.



2-(3,5-dimethylhex-5-en-2-ylidene)malononitrile

**2.80g** (srm5084)

colorless oil

yield: 76% (combined isomers)

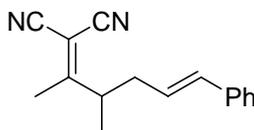
yield: 96% (Cope rearrangement)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.16 (dd, 3H: *J* = 1.7, 6.9 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 1.76 (s, 3H: CH<sub>3</sub>CR=CH<sub>2</sub>), 2.18 (d, 3H: *J* = 1.5 Hz, CH<sub>3</sub>CR=C(CN)<sub>2</sub>), 2.20 (d, 2H: *J* = 7.9 Hz, CH<sub>2</sub>=CHRCH<sub>2</sub>), 3.35 (dsxt., 1H: *J* = 1.2, 6.9 Hz, CH<sub>3</sub>CHRCH<sub>2</sub>), 4.67 (s, 1H: R<sub>2</sub>C=CHH), 4.84 (s, 1H: R<sub>2</sub>C=CHH).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 17.8 (CH<sub>3</sub>CR=C(CN)<sub>2</sub>), 18.7 (CH<sub>3</sub>CHRCH<sub>2</sub>), 22.2 (CH<sub>3</sub>CR=CH<sub>2</sub>), 29.9 (CHCH<sub>3</sub>), 39.5 (CH<sub>2</sub>=CHRCH<sub>2</sub>), 85.9 (R<sub>2</sub>C=C(CN)<sub>2</sub>), 111.8 (CN), 112.1 (CN), 113.9 (R<sub>2</sub>C=CH<sub>2</sub>), 141.7 (CH<sub>2</sub>=CR<sub>2</sub>), 186.0 (R<sub>2</sub>C=C(CN)<sub>2</sub>).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3076, 2975, 2231, 1650.

**Elemental Analysis** Calcd for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.43; H, 8.11; N, 15.79.



(E)-2-(3-methyl-6-phenylhex-5-en-2-ylidene)malononitrile

**2.80h** (srm5183\_2)

pale yellow oil

yield: 97% (combined isomers)

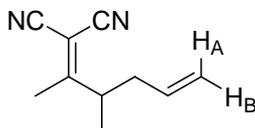
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.23 (dd, 3H: *J* = 1.5, 6.8 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 2.22 (d, 3H: *J* = 1.6 Hz, CH<sub>3</sub>CR=C(CN)<sub>2</sub>), 2.38 (m, 1H: CHHCH=CHPh), 2.46 (m, 1H: CHHCH=CHPh), 3.31 (dsxt., 1H: *J* = 1.3, 6.8 Hz, CHCH<sub>3</sub>), 6.06 (m, 1H: CH=CHPh), 6.43 (d, 1H: *J* = 15.7 Hz, CH=CHPh), 7.34 (m, 5 H: Ph-H).

**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 18.2 (CH<sub>3</sub>CR=C(CN)<sub>2</sub>), 18.4 (CH<sub>3</sub>CH), 38.5 (CH<sub>2</sub>CH=CHPh), 41.6 (CHCH=CHPh), 86.1 (R<sub>2</sub>C=C(CN)), 111.8 (CN), 112.1

(CN), 125.3 (CH=CHPh), 126.4 (Ph-CH), 128.0 (Ph-CH), 128.9 (Ph-CH), 133.5 (CH=CHPh), 136.7 (quat. Ph-C), 185.5 ( $R_2C=C(CN)_2$ ).

**FTIR** ( $CH_2Cl_2$ )  $\nu_{max}$ : 3051, 2985, 2253.

**HRMS** calcd for  $C_{16}H_{16}N_2$  [M+] 236.1313, found: 236.1300.



2-(3-methylhex-5-en-2-ylidene)malononitrile

**2.80i** (srm5162\_2)

colorless oil

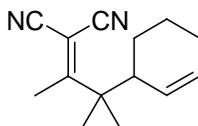
yield: 91% (combined isomers)

**$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  1.18 (d, 3H:  $J = 6.6$  Hz,  $CH_3CH$ ), 2.18 (s, 3H:  $CH_3CR=C(CN)_2$ ), 2.22 (m, 1H:  $CH_2=CHCHH$ ), 2.31 (m, 1H:  $CH_2=CHCHH$ ), 5.07 (d, 1H:  $J = 18.4$  Hz,  $H_A$ ), 5.11 (d, 1H:  $J = 10.8$  Hz,  $H_B$ ), 5.67 (m, 1H:  $CH=CH_2$ ).

**$^{13}C$  NMR** (75 Hz,  $CDCl_3$ )  $\delta$  18.0 ( $CH_3CR=C(CN)_2$ ), 18.4 ( $CH_3CH$ ), 39.2 (allylic  $CH_2$ ), 41.2 ( $CH_3CHR_2$ ), 86.04 ( $C(CN)_2$ ), 111.7 (CN), 112.1 (CN), 118.4 ( $CH=CH_2$ ), 134.1 ( $CH=CH_2$ ), 185.47 ( $C=C(CN)_2$ ).

**FTIR** ( $CH_2Cl_2$ )  $\nu_{max}$ : 3083, 2982, 2233, 1643, 1591.

**HRMS** calcd for  $C_{10}H_{12}N_2$  [M+] 160.1000, found: 160.0993.



2-(3-(cyclohex-2-enyl)-3-methylbutan-2-ylidene)malononitrile

**2.80j** (srm5193)

6:1 ratio of dimethylated : monomethylated product, inseparable mixture

colorless oil

yield: 76%

**$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  1.27 (s, 3H: one of  $R_2C(CH_3)_2$ ), 1.35 (s, 3H: one of  $R_2C(CH_3)_2$ ), 1.55 (m, 1H: cyclohexyl CH), 1.63 (m, 2H: cyclohexyl CH's), 1.83 (m, 1H: cyclohexyl CH), 1.99 (m, 2H: cyclohexyl  $CH_2$ ), 2.32 (s, 3H:

$\text{CH}_3\text{CR}=\text{C}(\text{CN})_2$ , 2.77 (m, 1H:  $\text{RCH}=\text{CHCHR}_2$ ), 5.41 (dp, 1H:  $J = 1.9, 10.3$  Hz,  $\text{RCH}=\text{CHCHR}_2$ ), 5.86 (m, 1H:  $\text{RCHCH}=\text{CHR}$ ).

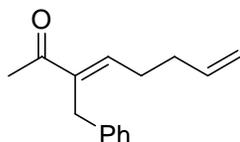
$^{13}\text{C}$  NMR (75 Hz,  $\text{CDCl}_3$ )  $\delta$  22.4 (cyclohexyl  $\text{CH}_2$ ), 23.2 (one of  $(\text{CH}_3)_2\text{CR}_2$ ), 23.6 ( $\text{CH}_3\text{CR}=\text{C}(\text{CN})_2$ ), 24.4 (one of  $(\text{CH}_3)_2\text{CR}_2$ ), 24.6 (cyclohexyl  $\text{CH}_2$ ), 25.1 (cyclohexyl  $\text{CH}_2$ ), 44.2 (cyclohexyl CH), 46.1 ( $\text{R}_2\text{C}(\text{CH}_3)_2$ ), 85.7 ( $(\text{CN})_2\text{C}$ ), 113.3 (CN), 113.7 (CN), 126.2 ( $\text{R}_2\text{CHCH}=\text{CHR}$ ), 131.1 ( $\text{R}_2\text{CHCH}=\text{CHR}$ ), 189.6 ( $\text{R}_2\text{C}=\text{C}(\text{CN})_2$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3028, 2981, 2937, 2230, 1569, 1471, 1448, 1433.

HRMS calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_2$  [M+] 214.1470, found: 214.1476.

### Procedure for the synthesis of **2.81** via microwave assisted Cope rearrangement.

To a microwave safe vial was added **2.72** (21 mg, 0.097 mmol) in  $\text{CH}_3\text{CN}$  (1.5 mL). The vial was then appropriately sealed and placed in the microwave reactor. The solution was then heated to 180 °C for 75 minutes. Upon reaction completion, the reaction was concentrated and the pure product **2.81** was obtained in 95% yield as a 7.3:1 mixture of *E/Z* isomers.



(*E*)-3-benzyl-octa-3,7-dien-2-one (major isomer)

**2.81** (srm5076)

isolated as a 7.3:1 mixture of *E/Z* isomers

pale yellow oil

yield: 95% (combined isomers)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.33 (q, 2H:  $J = 7.4$  Hz,  $\text{CH}_2=\text{CHCH}_2$ ), 2.44 (d, 3H:  $J = 1.6$  Hz,  $\text{CH}_3\text{COR}$ ), 2.55 (q, 2H:  $J = 7.3$  Hz,  $\text{R}_2\text{C}=\text{CHCH}_2$ ), 3.81 (s, 1H:  $\text{PhCH}_2\text{R}$ ), 5.15 (m, 2H:  $\text{CH}_2=\text{CHR}$ ), 5.92 (m, 1H:  $\text{CH}_2=\text{CHR}$ ), 6.89 (dt, 1H:  $J = 1.6, 6.9$  Hz,  $\text{R}_2\text{C}=\text{CHR}$ ), 7.26 (m, 2H: Ph-H), 7.36 (m, 3H: Ph-H). selective nOe irr @ 3.81 ppm, large enhancement observed at 2.55 ppm

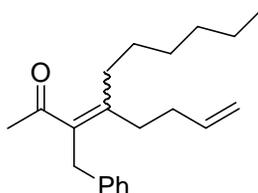
<sup>13</sup>C NMR (75 Hz, CDCl<sub>3</sub>) δ 26.0 (CH<sub>3</sub>COR), 28.8 (CH<sub>2</sub>CH=CR<sub>2</sub>), 31.3 (RCH<sub>2</sub>Ph), 32.8 (RCHCH=CH<sub>2</sub>), 115.9 (CH<sub>2</sub>=CHR), 126.1 (Ph-CH), 128.5 (Ph-CH), 128.5 (Ph-CH), 137.4 (CH<sub>2</sub>=CHR), 140.1 (quat. C), 141.3 (quat. C), 144.5 (R<sub>2</sub>C=CHR), 199.4 (C=O).

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 2923, 1666, 1501.

HRMS calcd for [M+H] 215.1436, found 215.1443.

**Procedure for the synthesis of 2.83 via the Pd(II)-catalyzed Cope rearrangement.**

To a dried NMR tube was added **2.82** (24 mg, 0.08 mmol) dissolved in CD<sub>2</sub>Cl<sub>2</sub> (600 μL). Then, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (2.1 mg, 0.008 mmol) was added to the mixture and the solution was heated to 40 °C for 12 hours. After this time the solution was concentrated and directly purified *via* flash column chromatography (95:5 hexane:ethyl acetate). Ketone **2.83** was isolated in 83% yield as a 1:1 mixture of *E/Z* isomers.



3-benzyl-4-(but-3-enyl)dec-3-en-2-one

**2.83** (srm5112)

~1:1 mixture of cis:trans isomers

pale yellow oil

yield: 83% (combined isomers)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.89 (m, 3H: CH<sub>3</sub>CH<sub>2</sub>R), 1.29 (m, 6H: n-hexyl CH<sub>2</sub>'s), 1.42 (m, 1H: n-hexyl CH), 1.49 (m, 1H: n-hexyl CH), 2.06 (d, 3H: *J* = 1.3 Hz, CH<sub>3</sub>COR), 2.18-2.35 (m, 6H: allylic CH<sub>2</sub>'s), 3.68 (d, 2H: *J* = 5.0 Hz, RCH<sub>2</sub>Ph), 5.03 (m, 2H: RCH=CH<sub>2</sub>), 5.84 (m, 1H: RCH=CH<sub>2</sub>), 7.15 (m, 2H: Ph-H), 7.19 (m, 1H: Ph-H), 7.78 (m, 1H: Ph-H).

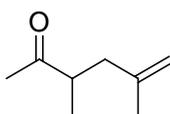
**<sup>13</sup>C NMR** (75 Hz, CDCl<sub>3</sub>) δ 14.26, 14.29 (CH<sub>3</sub>-n-hexyl), 22.78, 22.85 (n-hexyl CH<sub>2</sub>), 28.60, 29.33 (n-hexyl CH<sub>2</sub>), 29.81, 29.84 (n-hexyl CH<sub>2</sub>), 30.97, 31.08 (CH<sub>3</sub>COR), 31.87, 31.89 (n-hexyl CH<sub>2</sub>), 32.01, 32.66 (allylic CH<sub>2</sub>), 32.86, 33.14 (allylic CH<sub>2</sub>), 33.50, 33.79 (allylic CH<sub>2</sub>), 35.34 (RCH<sub>2</sub>Ph), 115.02, 115.23 (RCH=CH<sub>2</sub>), 126.46, (Ph-CH), 128.37, 128.39 (Ph-CH), 128.76 (Ph-CH), 135.87, 136.06 (RCH=CH<sub>2</sub>), 138.01, 138.42 (quat. C), 139.16, 139.17 (quat. C), 145.22, 146.02 (quat. C), 205.64, 205.98 (C=O).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3053, 2956, 1684.

**HRMS** calcd for [M+H] 299.2375, found 299.2379.

### Procedure for the hydrolysis of **2.80g**.

The synthesis of **2.93** was modified from a previous report.<sup>125</sup> To a flask was added **2.80g** (48 mg, 0.24 mmol) and 33% aqueous NaOH solution (3 mL). The solution was heated to 50 °C for 1 hour, then it was cooled to room temperature and diluted with Et<sub>2</sub>O (10 mL). The organic phase was extracted with H<sub>2</sub>O (2 × 3 mL) and dried over MgSO<sub>4</sub>. The product solution was concentrated and the crude product **2.93** was isolated.

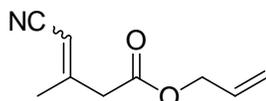


3,5-dimethylhex-5-en-2-one  
**2.93** (srm5175)  
yield: >95% by crude <sup>1</sup>H NMR

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.10 (d, 3H, *J* = 7.0 Hz, CHCH<sub>3</sub>), 1.74 (s, 3H: CH<sub>2</sub>CRCH<sub>3</sub>), 2.03 (dd, 1H: *J* = 7.8, 14.5 Hz, CH<sub>2</sub>CRCHH), 2.17 (s, 3H: CH<sub>3</sub>COR), 2.41 (dd, 1H: *J* = 6.7, 14.5 Hz, CH<sub>2</sub>CRCHH), 2.75 (m, 1H: CHCH<sub>3</sub>), 4.70 (s, 1H, R<sub>2</sub>C=CHH), 4.80 (s, 1H: R<sub>2</sub>C=CHH).

### Procedure for the synthesis of **2.97**.

The starting  $\beta$ -ketoester was synthesized by a DMAP-catalyzed reaction of diketene and allyl alcohol. The synthesis of **2.97** was accomplished via a Knoevenagel condensation using a previously reported procedure.<sup>126</sup>

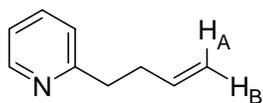


allyl 4-cyano-3-methylbut-3-enoate  
**2.97** (srm4253)  
isolated as 1.4:1 mixture of isomers  
yield: 55%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.05 (d, 3H:  $J = 1.6$  Hz, CH<sub>3</sub>, minor isomer), 2.17 (d, 3H:  $J = 1.2$  Hz, CH<sub>3</sub>, major isomer), 3.24 (s, 1H: CH<sub>2</sub>CO<sub>2</sub>R, major isomer), 3.49 (s, 1H: CH<sub>2</sub>CO<sub>2</sub>R, major isomer), 4.65 (tt, 2H:  $J = 1.2, 6.3$  Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.35 (m, 3H: CH=CH<sub>2</sub> and CHCN), 5.93 (m, 1H: RCH=CH<sub>2</sub>).

### Procedure for the synthesis of **2.101** and **2.103**.

Ester **2.100** was synthesized by the DCC/DMAP catalyzed coupling of 2-pyridyl acetic acid hydrochloride with the appropriate allylic alcohol. To a dried Schlenk flask was added a solution of **2.100** (100 mg, 0.56 mmol) in C<sub>6</sub>D<sub>6</sub> (5 mL). Then, Pd(PPh<sub>3</sub>)<sub>4</sub> (33 mg, 0.03 mmol) was added to the solution and the reaction was heated to 80 °C. The reaction was run for four hours and then cooled to room temperature. Following concentration of the solution, direct purification *via* flash column chromatography was achieved using 85:15 hexane:ethyl acetate as the eluent. .

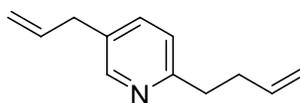


2-(but-3-enyl)pyridine

**2.101** (srm4165)

yield: 32%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.52 (m, 2H: CH<sub>2</sub>CH=CH<sub>2</sub>), 2.90 (t, 2H: *J* = 8.2 Hz, HetCH<sub>2</sub>), 4.98 (dq, 1H: *J* = 1.4, 10.2 Hz, H<sub>B</sub>), 5.07 (dq, 1H: *J* = 1.7, 17.1 Hz, H<sub>A</sub>), 5.87 (m, 1H: CH=CH<sub>2</sub>), 7.16 (m, 2H: Het. Ar CH's), 7.60 (td, 1H: *J* = 1.9, 7.7 Hz, Het Ar CH), 8.54 (m, 1H: Het Ar CH).



5-allyl-2-(but-3-enyl)pyridine

**2.103** (srm4165)

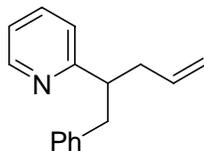
yield: 5%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.50 (m, 2H: HetCH<sub>2</sub>CH<sub>2</sub>), 2.87 (t, 2H: *J* = 7.5 Hz, HetCH<sub>2</sub>CH<sub>2</sub>), 3.37 (d, 2H: *J* = 6.8 Hz, HetCH<sub>2</sub>CH=CH<sub>2</sub>), 4.98 (m, 1H: one of CH=CHH), 5.04 (m, 1H: one of CH=CHH), 5.08 (m, 1H: one of CH=CHH), 5.12 (m, 2H: two of CH=CHH), 5.93 (m, 2H: two CH=CH<sub>2</sub>), 7.10 (d, 1H: *J* = 8.2 Hz, Het Ar CH), 7.44 (dd, 1H: *J* = 2.2, 8.2 Hz, Het Ar CH), 8.37 (d, 1H: *J* = 2.2 Hz, Het Ar CH).

#### Procedure for the synthesis of 2.105 and 2.106.

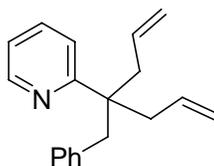
Ester **2.100** was synthesized by the DCC/DMAP catalyzed coupling of 2-pyridyl acetic acid hydrochloride with the appropriate allylic alcohol. Alkylation was achieved with <sup>t</sup>BuOK and the benzyl bromide. To a dried Schlenk flask was added Pd<sub>2</sub>dba<sub>3</sub> (13.6 mg, 0.001 mmol) and dppb (12.8 mg, 0.029 mmol) in toluene (5 mL). Then, **2.104** (80 mg, 0.30 mmol) was added and the resulting solution was heated to 110 °C for 3 hours. At that time, the solution was cooled to room temperature and concentrated under vacuum. Direct purification of the residue *via* flash column

chromatography (90:10 hexane:ethyl acetate) afforded products **2.105** (34% yield) and **2.106**.



2-(1-phenylpent-4-en-2-yl)pyridine  
**2.105** (srm5231)  
yield: 34%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.49 (m, 1H: PhCHH), 2.58 (m, 1H: PhCHH), 3.01-3.15 (m, 3H: HetCHBn and RCH<sub>2</sub>CH=CH<sub>2</sub>), 4.90-5.01 (m, 2H: CH=CH<sub>2</sub>), 5.70 (m, 1H: CH=CH<sub>2</sub>), 6.92 (d, 1H: *J* = 7.8 Hz, Het Ar CH), 7.04 (d, 1H: *J* = 6.7 Hz, Het Ar CH), 7.14 (m, 2H: Ar CH's), 7.19 (m, 3H: Ar CH's), 7.51 (td, 1H: *J* = 2.0, 7.6 Hz, Het Ar CH), 8.61 (app. d, 1H: *J* = 4.7 Hz, Het Ar CH).



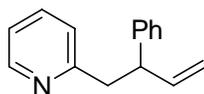
2-(4-benzylhepta-1,6-dien-4-yl)pyridine  
**2.106** (srm5277)  
yield: 92% by <sup>1</sup>H NMR

<sup>1</sup>H NMR (400 MHz, tol-*d*<sub>8</sub>) δ 2.01 (m, 6H: PhCH<sub>2</sub> and CH<sub>2</sub>CH=CH<sub>2</sub>), 4.91 (m, 4H: CH=CH<sub>2</sub>), 5.72 (m, 2H: CH=CH<sub>2</sub>), 6.66 (t, 1H: Het Ar CH), 6.85 - 7.24 (m, 5H: Ar CH's), 7.39 (t, 1H: *J* = 7.6 Hz, Het Ar CH), 7.72 (m, 1H: Het Ar CH), 8.45 (m, 1H: Het Ar CH), 8.51 (m, 1H: Het Ar CH).

#### Procedure for the synthesis of **2.109**.

Ester **2.108** was synthesized by the DCC/DMAP catalyzed coupling of 2-pyridyl acetic acid hydrochloride with the cinnamyl alcohol. To a dried Schlenk flask was added a solution of **2.108** (106 mg, 0.41 mmol) in toluene (5 mL). Then, Pd(PPh<sub>3</sub>)<sub>4</sub>

(24 mg, 0.02 mmol) was added to the solution and the reaction was heated to 80 °C. The reaction was run for 18 hours and then cooled to room temperature. Following concentration of the solution, direct purification *via* flash column chromatography was achieved using 90:10 hexane:ethyl acetate as the eluent. **2.109** was isolated in 26% yield.



2-(2-phenylbut-3-enyl)pyridine

**2.109** (srm7018)

yield: 26%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.20 (dddd, 2H: *J* = 8.1, 13.4, 13.4, 13.4 Hz, HetCH<sub>2</sub>), 3.91 (q, 1H: *J* = 8.1 Hz, PhCHR<sub>2</sub>), 5.00 (m, 2H: CH=CH<sub>2</sub>), 6.05 (ddd, 1H: *J* = 7.2, 10.2, 17.2 Hz, RCH=CH<sub>2</sub>), 6.94 (dt, 1H: *J* = 1.0, 7.8 Hz, Het Ar CH), 7.06 (m, 1H: Het Ar CH), 7.15-7.22 (m, 3H: Ar CH's), 7.23 - 7.30 (m, 2H: Ar CH's), 7.49 (td, 1H: *J* = 1.9, 7.6 Hz, Het Ar CH), 8.54 (ddd, 1H: dd, *J* = 1.0, 1.8, 5.0 Hz, Het Ar CH).

#### Procedure for the synthesis of allyl-2-benzoxazole propanoates.

This was prepared using a modification of a procedure by Cherney.<sup>127</sup> Dimethyl malonate (13.8 mmol) was added to 2-aminophenol (4.6 mmol). The mixture was heated to 160° C for 5 hours, at which time *p*-TsOH (0.46 mmol) was added to the reaction. This solution was stirred at 160° C for 12 hours. The mixture was cooled to room temperature and directly purified on silica gel using 95:5 hexane/ethyl acetate as the eluent. The resulting methyl-2-benzoxazol-2-yl acetate was then treated with LiOH according to the procedure by Cherney and let stir at room temperature overnight. The crude acid was treated with 1.1 equivalents of the appropriate allylic

alcohol, 1.0 equivalents of DCC, and 0.10 equivalents of DMAP in CH<sub>2</sub>Cl<sub>2</sub>.<sup>128</sup> The solutions were stirred at room temperature overnight. The reactions were filtered and washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, and concentrated. The allyl-2-benzoxazol-2-yl acetates were purified on silica gel using 90:10 hexane/ethyl acetate. Alkylation of the  $\alpha$ -position was accomplished using <sup>t</sup>BuOK and the corresponding alkylating agent.<sup>129</sup>

**Procedure for the synthesis of allyl-2-benzothiazole propanoates.**

A mixture of the appropriate allyl cyanoacetate<sup>130</sup> was mixed with 2-aminothiophenol<sup>131</sup> and heated at 120° C overnight.<sup>132</sup> The crude reaction mixture was purified directly on silica gel. The resulting ester was alkylated with <sup>t</sup>BuOK and the appropriate alkylating agent.<sup>3</sup>

**Procedure for the synthesis of allyl-2-benzimidazole propanoates.**

Benzimidazolyl acetonitrile was hydrolyzed to the corresponding acid according to Copeland and Day.<sup>133</sup> Coupling of the acid was achieved using cinnamyl alcohol, DCC, Et<sub>3</sub>N and cat. DMAP after heating at reflux in CH<sub>2</sub>Cl<sub>2</sub> overnight. The benzimidazole nitrogen was then alkylated with MeI according to Das and coworkers.<sup>134</sup> Alkylation was achieved with <sup>t</sup>BuOK and the appropriate alkylating agent.

**Procedure for the synthesis of cinnamyl 2-(4,5-diphenyloxazol-2-yl)-3-phenylpropanoate.**

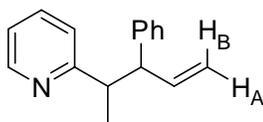
The methyl 2-(4,5-diphenyloxazol-2-yl)acetate was synthesized in a procedure described by Davies.<sup>135</sup> The ester was hydrolyzed using LiOH. The crude acid was coupled with cinnamyl alcohol using DCC/DMAP catalyzed reaction. Alkylation was achieved using <sup>t</sup>BuOK and benzyl bromide.<sup>129</sup>

**General procedure for Pd-catalyzed decarboxylation of heteroaromatic esters.**

In a dried Schlenk tube under argon, Pd(PPh<sub>3</sub>)<sub>4</sub> (15 mg, 0.013 mmol) was added to substrate **2.113** (0.25 mmol) in toluene (5 mL). The reactions of the cinnamyl esters were run at 0.05 M substrate concentration and 80 °C for the specified time. After such time, the solutions were cooled to room temperature, concentrated *in vacuo* and directly purified via flash chromatography on silica gel using the specified elution system. Isolated yields are reported in Table 2.11.

**Procedure for the screening of Lewis acid catalysts with 2.110.**

To a dried NMR tube was added the catalyst (0.0009 mmol) in tol-*d*<sub>8</sub>. Then, **2.110** (5 mg, 0.002 mmol) was added to the solution and the reaction was heated to 80 °C for 18 hours. The reaction conversions were monitored by <sup>1</sup>H NMR spectroscopy.



2-(2-phenylpent-4-en-2-yl)pyridine  
**2.111** (srm6045)  
 pale orange oil  
 yield: 43%

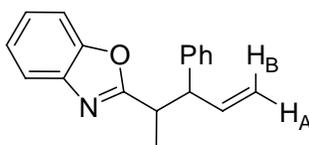
**Purification:** flash chromatography (95:5 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.39 (d, 3H: *J* = 7.0 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.24 (dq, 1H: *J* = 7.0, 9.7 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.68 (t, 1H: *J* = 9.7 Hz, R<sub>2</sub>CHPh), 5.10 (dd, 1H: *J* = 1.4, 10.1 Hz, H<sub>A</sub>), 5.16 (app. d, 1H: *J* = 17.0 Hz, H<sub>B</sub>), 6.10 (dt, 1H: *J* = 9.7, 17.0 Hz, RCH=CH<sub>2</sub>), 6.82 (d, 1H: *J* = 7.7 Hz, R(C=N)CH), 6.96 (dd, 1H: *J* = 4.4 Hz, NCH=CH), 7.04 (m, 3H: Ar CH's), 7.12 (m, 2H: Ar CH's), 7.37 (t, 1H: *J* = 7.5 Hz, NCH=CHCH), 8.48 (d, 1H: *J* = 4.4 Hz, NCH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 19.4 (R<sub>2</sub>CHCH<sub>3</sub>), 47.0 (R<sub>2</sub>CHCH<sub>3</sub>), 56.9 (R<sub>2</sub>CHPh), 116.3 (RCH=CH<sub>2</sub>), 121.2 (NCH=CH), 123.3 (N=CRCH), 126.1 (Ar CH), 128.1 (Ar CH), 128.7 (Ar CH), 136.2 (NCH=CHCH), 140.4 (RCH=CH<sub>2</sub>), 143.7 (quat. Ar C), 149.1 (NCH), 164.6 (N=CR).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2987, 1637, 1591, 1569, 1550, 1474, 1422, 1263, 1150, 992, 896.

**HRMS** calcd for [M+H] 224.1439, found 224.1426.



2-(3-phenylpent-4-en-2-yl)benzoxazole  
**2.114a** (srm6168)  
 white solid  
 yield: 71%

**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

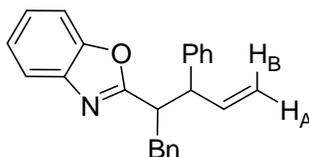
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.49 (d, 3H: *J* = 7.0 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.53 (dq, 1H: *J* = 7.0, 9.1 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.86 (t, 1H: *J* = 9.1 Hz, R<sub>2</sub>CHPh), 5.15 (dd, 1H: *J* = 1.5, 10.1 Hz, H<sub>A</sub>), 5.19 (dd, 1H: *J* = 1.5, 17.0 Hz, H<sub>B</sub>), 6.10 (ddd, 1H: *J* = 9.1, 10.0, 17.0 Hz, RCH=CH<sub>2</sub>), 7.11 (m, 1H: Ar CH), 7.13 (s, 2H: overlapping Ar

CH's), 7.19 (d, 1H:  $J = 1.5$  Hz, Ar CH), 7.24 (m, 2H: overlapping Het Ar CH's), 7.41 (m, 1H: Het Ar CH's), 7.60 (m, 1H: Het Ar CH).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  16.9 ( $\text{R}_2\text{CHCH}_3$ ), 40.0 ( $\text{R}_2\text{CHCH}_3$ ), 55.3 ( $\text{R}_2\text{CHPh}$ ), 111.1 (Het Ar CH), 118.1 ( $\text{RCH}=\text{CH}_2$ ), 120.5 (Het Ar CH), 124.9 (Het Ar CH), 125.2 (Het Ar CH), 127.5 (Ar CH), 128.6 (Ar CH), 129.4 (Ar CH), 139.3 ( $\text{RCH}=\text{CH}_2$ ), 142.1 (quat. Ar C), 142.9 (quat. Ar C), 151.5 (quat. Ar C), 170.3 ( $\text{N}=\text{CO}$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3054, 2986, 1638, 1613, 1569, 1456, 1421, 1263, 1152, 994, 926, 896.

HRMS calcd for  $[\text{M}+\text{H}]$  264.1388, found 264.1382.



2-(1,3-diphenylpent-4-en-2-yl)benzoxazole

**2.114b** (srm6149)

white solid

yield: 66%

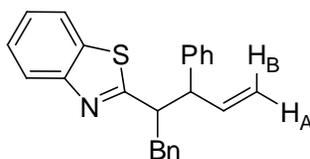
**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.21 (dd, 1H:  $J = 10.9, 13.9$  Hz,  $\text{CHHPh}$ ), 3.34 (dd, 1H:  $J = 4.0, 13.9$  Hz,  $\text{CHHPH}$ ), 3.72 (ddd, 1H:  $J = 4.0, 9.6, 10.9$  Hz,  $\text{R}_2\text{CHCH}_2\text{Ph}$ ), 3.92 (t, 1H:  $J = 9.6$  Hz,  $\text{R}_2\text{CHPh}$ ), 5.25 (app. d, 1H:  $J = 10.0$  Hz,  $\text{H}_A$ ), 5.29 (app. d, 1H:  $J = 17.0$  Hz,  $\text{H}_B$ ), 6.22 (ddd, 1H:  $J = 1.3, 10.0, 17.0$  Hz,  $\text{RCH}=\text{CH}_2$ ), 7.03-7.21 (m, 12H: overlapping Ar CH's), 7.31 (m, 1H: Het Ar CH), 7.55 (m, 1H: Het Ar CH).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  38.3 ( $\text{PhCH}_2\text{R}$ ), 48.3 ( $\text{R}_2\text{CHCH}_2\text{Ph}$ ), 55.2 ( $\text{R}_2\text{CHPh}$ ), 111.0 (Het Ar CH), 118.3 ( $\text{RCH}=\text{CH}_2$ ), 120.5 (Het Ar CH), 124.8 (Het Ar CH), 125.2 (Het Ar CH), 127.3 (Ar CH), 127.7 (Ar CH), 128.6 (Ar CH), 129.4 (Ar CH), 129.5 (Ar CH), 129.7 (Ar CH), 140.0 ( $\text{RCH}=\text{CH}_2$ ), 140.1 (quat. Ar C), 141.9 (quat. Ar C), 142.4 (quat. Ar C), 151.3 (quat. Ar C), 168.5 ( $\text{OC}=\text{N}$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3054, 2985, 1637, 1612, 1570, 1495, 1455, 1421, 1263, 1144, 992, 926, 896.

HRMS calcd for  $[\text{M}+\text{H}]$  340.1701, found 340.1712.



2-(1,3-diphenylpent-4-en-2-yl)benzothiazole

**2.114c** (srm7133)

yellow oil

yield: 75%

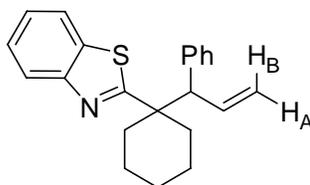
**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 3.20 (dd, 1H: *J* = 11.0, 14.0 Hz, CHHPh), 3.45 (dd, 1H: *J* = 3.8, 14.0 Hz, CHHPh), 3.77 (ddd, 1H: *J* = 3.8, 9.9, 11.0 Hz, R<sub>2</sub>CHCH<sub>2</sub>Ph), 3.95 (t, 1H: *J* = 9.9 Hz, R<sub>2</sub>CHPh), 5.25 (dd, 1H: *J* = 1.3, 9.9 Hz, H<sub>A</sub>), 5.31 (app. d, 1H: *J* = 17.0 Hz, H<sub>B</sub>), 6.23 (dt, 1H: *J* = 9.9, 17.0 Hz, RCH=CH<sub>2</sub>), 7.03-7.21 (m, 10H: overlapping Ar CH's), 7.24 (ddd, 1H: *J* = 1.0, 7.3, 8.0 Hz, Het Ar CH), 7.38 (ddd, 1H: *J* = 1.0, 7.3, 8.0 Hz, Het Ar CH), 7.63 (d, 1H: *J* = 8.0 Hz, Het Ar CH), 7.92 (d, 1H: *J* = 8.0 Hz, Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 40.2 (PhCH<sub>2</sub>R), 52.3 (R<sub>2</sub>CHCH<sub>2</sub>Ph), 56.6 (R<sub>2</sub>CHPh), 117.5 (RCH=CH<sub>2</sub>), 121.5 (Het Ar CH), 122.8 (Het Ar CH), 124.6 (Het Ar CH), 125.7 (Het Ar CH), 126.3 (Ar CH), 126.7 (Ar CH), 128.0 (Ar CH), 128.5 (Ar CH), 128.6 (Ar CH), 129.1 (Ar CH), 134.8 (quat. Ar C), 138.4 (quat. Ar C), 139.7 (RCH=CH<sub>2</sub>), 142.1 (quat. Ar C), 147.0 (quat. Ar C), 173.4 (SC=N)

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3053, 2986, 1637, 1601, 1550, 1496, 1454, 1436, 1422, 1264, 924, 896.

**HRMS** calcd for [M+H] 356.1473, found 356.1482.



2-(1-(1-phenylallyl)cyclohexyl)benzothiazole

**2.114d** (srm7078)

pale yellow oil

yield: 95%

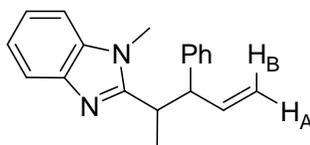
**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.15-1.40 (m, 2H: overlapping cyclohexyl CH's), 1.44-1.56 (m, 2H: overlapping cyclohexyl CH's), 1.63-1.79 (m, 4H: overlapping cyclohexyl CH's), 2.34 (app. d, 1H: *J* = 12.5 Hz, cyclohexyl CH), 2.42 (app. d, 1H: *J* = 13.2 Hz, cyclohexyl CH), 3.52 (d, 1H: *J* = 9.9 Hz, R<sub>2</sub>CHPh), 5.03 (app. dd, 1H: *J* = 1.7, 16.7 Hz, H<sub>B</sub>), 5.09 (dd, 1H: *J* = 1.7, 10.1 Hz, H<sub>A</sub>), 6.36 (dt, 1H: *J* = 10.1, 16.7 Hz, RCH=CH<sub>2</sub>) 6.84 (dd, 2H: *J* = 1.8, 7.7 Hz, overlapping Ar CH's), 7.13 (m, 3H: overlapping Ar CH's), 7.35 (app. t, 1H: *J* = 7.8 Hz, Het Ar CH), 7.45 (app. t, 1H: *J* = 7.8 Hz, Het Ar CH) 7.84 (d, 1H: *J* = 7.8 Hz, Het Ar CH), 8.01 (d, 1H: *J* = 7.8 Hz, Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 22.9 (overlapping cyclohexyl CH<sub>2</sub>'s), 25.9 (cyclohexyl CH<sub>2</sub>), 24.9 (cyclohexyl CH<sub>2</sub>), 35.9 (cyclohexyl CH<sub>2</sub>), 49.3 (quat. cyclohexyl C), 63.1 (R<sub>2</sub>CHPh), 117.5 (RCH=CH<sub>2</sub>), 121.6 (Het Ar CH), 123.1 (Het Ar CH), 124.7 (Het Ar CH), 125.7 (Het Ar CH), 126.7 (Ar CH), 127.9 (Ar CH), 129.5 (Ar CH), 135.5 (Ar CH), 137.4 (RCH=CH<sub>2</sub>), 140.6 (quat. Ar C), 153.2 (quat. Ar C), 177.2 (SC=N).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2986, 2933, 2857, 1633, 1600, 1492, 1451, 1421, 1313, 1264, 1047, 1013, 919, 896.

**HRMS** calcd for [M+H] 343.1630, found 343.1630.



1-methyl-2-(3-phenylpent-4-en-2-yl)-1*H*-benzimidazole  
**2.114e** (srm6137\_1)  
 yellow solid  
 yield: 43%

**Purification:** flash chromatography (95:5 to 90:10 hexane: ethyl acetate)

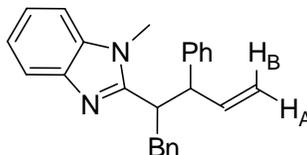
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.29 (d, 3H: *J* = 6.9 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.44 (dq, 1H: *J* = 6.9, 9.5 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.63 (s, 3H: NCH<sub>3</sub>), 3.90 (t, 1H: *J* = 9.5 Hz, R<sub>2</sub>CHPh), 4.84 (app. d, 1H: *J* = 17.0 Hz, H<sub>B</sub>), 4.88 (d, 1H: *J* = 0.7, 10.4 Hz, H<sub>A</sub>), 6.01 (ddd, 1H: *J* = 8.2, 10.4, 17.0 Hz, RCH=CH<sub>2</sub>), 7.24 (dd, 2H: *J* = 7.8, 9.0 Hz, Ar H's), 7.28 (m, 4H: Ar CH), 7.33 (overlapping dd, 3H: *J* = 7.8, 15.3 Hz, Ar CH's).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 19.1 (R<sub>2</sub>CHCH<sub>3</sub>), 29.9 (NCH<sub>3</sub>), 37.2 (R<sub>2</sub>CHCH<sub>3</sub>), 56.0 (R<sub>2</sub>CHPh), 109.4 (Ar CH), 116.8 (RCH=CH<sub>2</sub>), 119.4 (Ar CH), 122.3 (Ar

CH), 127.0 (Ar CH), 128.7 (2 Ar CH's), 128.9 (2 Ar CH's), 135.2 (quat Ar C), 139.2 (RCH=CH<sub>2</sub>), 142.3 (quat. Ar C), 157.8 (NC=N).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3054, 2987, 1599, 1550, 1422, 1265, 1153, 896.

**HRMS** calcd for [M+H] 277.1705, found 277.1698.



2-(1,3-diphenylpent-4-en-2-yl)-1-methyl-1H-benzimidazole  
**2.114f** (srm6245)  
pale yellow oil  
yield: 52%

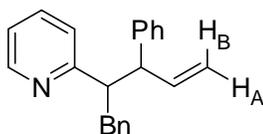
**Purification:** flash chromatography (95:5 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.90 (dd, 1H:  $J = 3.8, 13.1$  Hz, PhCHH), 3.02 (s, 3H: NCH<sub>3</sub>), 3.12 (dd, 1H:  $J = 11.2, 13.1$  Hz, PhCHH), 3.48 (dt, 1H:  $J = 4.1, 10.2$  Hz, R<sub>2</sub>CHBn), 4.12 (t, 1H:  $J = 8.5$  Hz, R<sub>2</sub>CHPh), 4.86 (app. d, 1H:  $J = 17.0$  Hz, H<sub>B</sub>), 4.89 (app. d, 1H:  $J = 10.3$  Hz, H<sub>A</sub>), 5.98 (ddd, 1H:  $J = 8.1, 10.3, 17.0$  Hz, RCH=CH<sub>2</sub>), 6.79 (m, 2H: overlapping Ar CH's), 7.06 (m, 3H: overlapping Ar CH's), 7.15 (d, 1H:  $J = 7.9$  Hz, Het Ar CH), 7.23 (dt, 1H: 1.1, 7.9 Hz, Het Ar CH), 7.26 (m, 1H: Het Ar CH), 7.30 (m, 3H: overlapping Ar CH's), 7.39 (m, 2H: overlapping Ar CH's), 7.85 (d, 1H:  $J = 7.9$  Hz, Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  29.0 (NCH<sub>3</sub>), 40.4 (CH<sub>2</sub>Ph), 46.2 (R<sub>2</sub>CHBn), 54.8 (R<sub>2</sub>CHPh), 109.4 (Ar CH), 116.9 (RCH=CH<sub>2</sub>), 119.4 (Ar CH), 122.0 (overlapping Ar CH's), 126.4 (Ar CH), 127.1 (Ar CH), 128.4 (Ar CH), 128.5 (Ar CH), 128.9 (Ar CH), 129.1 (Ar CH), 135.0 (quat. Ar C), 139.0 (RCH=CH<sub>2</sub>), 140.2 (quat. Ar C), 142.5 (quat. Ar CH), 143.0 (quat. Ar C), 156.3 (NC=N).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3054, 2987, 1601, 1551, 1493, 1466, 1440, 1422, 1267, 1154, 896;

**HRMS** calcd for [M+H] 353.2018, found 353.2015.



2-(1,3-diphenylpent-4-en-2-yl)pyridine

**2.114g** (srm7134)

yellow oil

yield: 53%

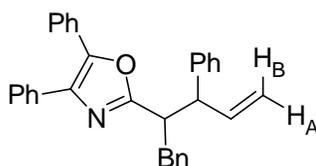
**Purification:** flash chromatography (100 CH<sub>2</sub>Cl<sub>2</sub>)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 3.12 (app. t, 1H: *J* = 11.5 Hz, PhCHHR), 3.32 (m, 2H: one of PhCHHR and BnCHR), 3.89 (t, 1H: *J* = 9.6 Hz, R<sub>2</sub>CHPh), 5.22 (dd, 1H: *J* = 1.4, 10.0 Hz, H<sub>A</sub>), 5.30 (d, 1H: *J* = 17.1 Hz, H<sub>B</sub>), 6.22 (dt, 1H: *J* = 10.0, 17.1 Hz, RCH=CH<sub>2</sub>), 6.38 (d, 1H: *J* = 7.6 Hz, Het Ar CH), 6.89 (d, 3H: *J* = 7.3 Hz, overlapping Het Ar CH and 2 Ar CH's), 6.98-7.12 (m, 9H: one Het Ar CH and 8 Ar CH's), 8.50 (dd, 1H: *J* = 0.9, 4.8 Hz, Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 39.9 (PhCH<sub>2</sub>R), 44.2 (R<sub>2</sub>CHBn), 56.2 (R<sub>2</sub>CHPh), 116.7 (RCH=CH<sub>2</sub>), 121.1 (Het Ar CH), 125.3 (Het Ar CH), 125.8 (Ar CH), 126.1 (Ar CH), 128.0 (Ar CH), 128.1 (Ar CH), 128.3 (Ar CH), 129.2 (Ar CH), 135.5 (Het Ar CH), 140.8 (RCH=CH<sub>2</sub>), 140.9 (quat. Ar C), 143.4 (quat. Ar C), 149.1 (Het Ar CH), 161.8 (N=CR);

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2987, 1637, 1600, 1570, 1551, 1490, 1470, 1435, 1422, 996, 920, 896.

**HRMS** calcd for [M+H] 300.1752, found 300.1765.



2-(1,3-diphenylpent-4-en-2-yl)-4,5-diphenyloxazole

**2.114h** (srm7059)

yellow oil

yield: 47%

**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

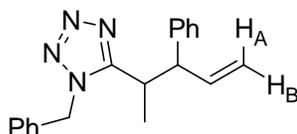
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.20 (dd, 1H: *J* = 10.8, 13.9 Hz, RCHHPh), 3.31 (dd, 1H: *J* = 4.2, 13.9 Hz, RCHHPh), 3.61 (ddd, 1H: *J* = 4.2, 10.8, 10.8 Hz, R<sub>2</sub>CHCH<sub>2</sub>Ph), 3.87 (t, 1H: *J* = 9.4 Hz, R<sub>2</sub>CHPh), 5.26 (dd, 1H: *J* = 1.3, 9.8 Hz,

H<sub>A</sub>), 5.29 (app. d, 1H: *J* = 17.0 Hz, H<sub>B</sub>), 6.25 (dt, 1H: *J* = 9.8, 17.0 Hz, RCH=CH<sub>2</sub>), 7.12-7.17 (m, 4H: Ar CH's), 7.19-7.25 (m, 8H: Ar CH's), 7.27-7.34 (m, 6H: Ar CH's), 7.46 (m, 2H: Ar CH's).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 38.4 (RCH<sub>2</sub>Ph), 48.0 (R<sub>2</sub>CHCH<sub>2</sub>Ph), 55.4 (R<sub>2</sub>CHPh), 118.1 (RCH=CH<sub>2</sub>), 127.2 (Ar CH), 127.4 (Ar CH), 127.6 (Ar CH), 128.8 (Ar CH), 128.9 (Ar CH), 128.9 (Ar CH), 129.1 (Ar CH), 129.3 (Ar CH), 129.4 (Ar CH), 129.6 (overlapping Ar CH's), 129.9 (Ar CH), 130.1 (quat. Ar C), 133.8 (quat. Ar C), 135.9 (quat. Ar C), 140.3 (RCH=CH<sub>2</sub>), 140.6 (quat. Ar C), 142.9 (quat. Ar C), 145.7 (quat. Ar C), 164.7 (N=CO).

FTIR (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2986, 1695, 1602, 1560, 1494, 1436, 1421, 1263, 1157, 1072, 1025, 992, 963, 896.

HRMS calcd for [M+H] 442.2171, found 442.2175.



1-benzyl-5-(3-phenylpent-4-en-2-yl)-1H-tetrazole (major diastereomer)

**2.120** (srm7118)

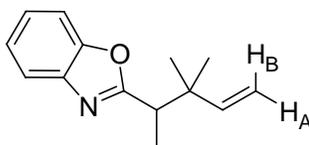
yield: 40% (combined diastereomers)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) major diastereomer δ 1.10 (d, 3H: *J* = 7.1 Hz, CH<sub>3</sub>), 3.22 (dq, 1H: *J* = 7.0, 8.9 Hz, HetCHR<sub>2</sub>), 3.70 (t, 1H: *J* = 9.1 Hz, PhCH), 4.86 (app. d, 1H: *J* = 8.8 Hz, H<sub>A</sub>), 4.90 (m, 1H: H<sub>B</sub>), 5.01 (d, 1H: *J* = 15.7 Hz, PhCHHN), 5.42 (d, 1H: *J* = 15.4 Hz, PhCHHN), 5.73 (ddd, 1H: *J* = 9.0, 10.4, 16.8 Hz, CH=CH<sub>2</sub>), 6.96 (td, 1H: *J* = 2.0, 7.6 Hz, Ar CH), 7.07 (m, 2H: Ar CH's), 7.11-7.18 (m, 3H: Ar CH's), 7.23-7.29 (m, 1H: Ar CH), 7.30-7.38 (m, 3H: Ar CH's)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) minor diastereomer δ 1.29 (d, 3H: *J* = 6.8 Hz, CH<sub>3</sub>), 3.11 (dq, 1H: *J* = 6.9, 10.6 Hz, HetCHR<sub>2</sub>), 3.69 (t, 1H: *J* = 10.1 Hz, PhCH), 4.64 (d, 1H: *J* = 15.7 Hz, PhCHHN), 4.86 (m, 1H: H<sub>A</sub>), 4.90 (m, 1H: H<sub>B</sub>), 5.23 (d, 1H: *J* = 6.8 Hz, PhCHHN), 6.05 (dt, 1H: *J* = 9.9, 16.6 Hz, CH=CH<sub>2</sub>), 6.96 (td, 1H: *J* = 2.0, 7.6 Hz, Ar CH), 7.07 (m, 2H: Ar CH's), 7.11-7.18 (m, 3H: Ar CH's), 7.23-7.29 (m, 1H: Ar CH), 7.30-7.38 (m, 3H: Ar CH's).

**General procedure for Pd-catalyzed decarboxylation of heteroaromatic esters.**

In a dried Schlenk tube under argon, Pd(PPh<sub>3</sub>)<sub>3</sub> (15 mg, 0.013 mmol) was added to substrate **2.113** (0.25 mmol) in toluene (5 mL). The reactions of the alkyl substituted allyl esters were run at 0.025 M substrate concentration at 100 °C (unless otherwise noted) for the specified time as noted in Table 2.13. After such time, the reactions were cooled to room temperature, concentrated *in vacuo* and directly purified via flash chromatography on silica gel using the specified eluent system. Isolated yields are reported in Table 2.13.



2-(3,3-dimethylpent-4-en-2-yl)benzoxazole  
**2.127a** (srm7148)  
pale orange oil  
yield: 57%

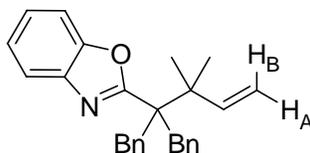
**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.12 (s, 3H: one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 1.13 (s, 3H: one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 1.38 (d, 3H: *J* = 7.2 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.08 (q, 1H: *J* = 7.2 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 5.01 (dd, 1H: *J* = 1.1, 17.5 Hz, H<sub>B</sub>), 5.04 (dd, 1H: *J* = 1.1, 10.8 Hz, H<sub>A</sub>), 5.94 (dd, 1H: *J* = 10.8, 17.5 Hz, RCH=CH<sub>2</sub>), 7.31 (m, 2H: Het Ar CH), 7.51 (m, 1H: Het Ar CH), 7.71 (m, 1H: Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 14.5 (R<sub>2</sub>CHCH<sub>3</sub>), 24.0 (one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 25.8 (one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 40.3 (R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 44.0 (R<sub>2</sub>CHCH<sub>3</sub>), 110.6 (Het Ar CH), 112.6 (RCH=CH<sub>2</sub>), 119.9 (Het Ar CH), 124.4 (Het Ar CH), 124.6 (Het Ar CH), 141.4 (quat. Het Ar C), 145.9 (RCH=CH<sub>2</sub>), 150.6 (quat. Het Ar C), 169.4 (N=CO).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2984, 1782, 1638, 1610, 1563, 1456, 1421, 1378, 1263, 1139, 1074, 1003, 922, 895.

**HRMS** calcd for [M+H] 216.1388, found 216.1390.



2-(2-benzyl-3,3-dimethyl-1-phenylpent-4-en-2-yl)benzoxazole  
**2.127b** (srm6248)  
pale yellow solid  
yield: 30%

**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.14 (s, 6H: R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 3.45 (d, 2H: *J* = 14.9 Hz, R<sub>2</sub>C(CHHPh)<sub>2</sub>), 3.60 (d, 2H: *J* = 14.9 Hz, R<sub>2</sub>C(CHHPh)<sub>2</sub>), 4.97 (dd, 1H: *J* = 1.0, 17.4 Hz, H<sub>B</sub>), 5.02 (dd, 1H: *J* = 1.0, 10.2 Hz, H<sub>A</sub>), 6.11 (dd, 1H: *J* = 10.2, 17.4 Hz, RCH=CH<sub>2</sub>), 7.02 (m, 4H: Ar CH's), 7.07 (m, 6H: Ar CH's), 7.36 (dp, 2H: *J* = 1.5, 7.3 Hz, Ar CH's), 7.50 (app. d, 1H: *J* = 7.3 Hz, Het Ar CH), 7.81 (app d., 1H: *J* = 7.3 Hz, Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 24.6 (R<sub>2</sub>C(CH<sub>2</sub>Ph)<sub>2</sub>), 40.0 (R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 45.4 (R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 52.0 (R<sub>2</sub>C(CH<sub>2</sub>Ph)<sub>2</sub>), 111.4 (Het Ar CH), 113.7 (RCH=CH<sub>2</sub>), 120.9 (Het Ar CH), 125.1 (Het Ar CH), 125.6 (Het Ar CH), 126.9 (Ar CH), 128.8 (Ar CH), 131.5 (Ar CH), 139.7 (quat. Ar C), 141.9 (quat. Ar C), 146.0 (RCH=CH<sub>2</sub>), 151.0 (quat. Ar C), 170.9 (N=CO).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2987, 1603, 1550, 1496, 1456, 1421, 1261, 1154, 896;

**HRMS** calcd for [M+H] 382.2171, found 382.2172.



2-(3-methyl-1-phenylpent-4-en-2-yl)benzoxazole  
**2.127c** (srm7068)

isolated as 2.5:1 mixture of diastereomers, and 12.5:1 branched to linear product  
colorless oil  
yield: 64% (combined diastereomers)

**Purification:** flash chromatography (99:1 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 1.02 (d, 3H: *J* = 7.1 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 2.73 (sext., 1H: *J* = 7.1 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 3.15-3.22 (m, 3H: overlapping PhCH<sub>2</sub> and PhCH<sub>2</sub>CHR<sub>2</sub>), 5.13 (dd, 1H: *J* = 1.1, 10.2 Hz, H<sub>A</sub>), 5.15 (dd, 1H: *J* = 1.1, 17.2 Hz, H<sub>B</sub>), 5.86 (ddd, 1H: *J* = 8.3, 10.2, 17.2 Hz, RCH=CH<sub>2</sub>), 7.07 (m, 2H: overlapping Ar CH's), 7.20 (m, 3H: overlapping Ar CH's), 7.29 (m, 2H: overlapping Het Ar CH's), 7.46 (m, 1H: Het Ar CH), 7.67 (m, 1H: Het Ar CH).

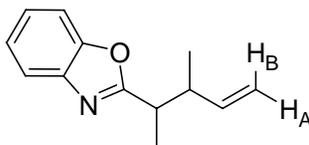
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) major diastereomer: δ 18.3 (R<sub>2</sub>CHCH<sub>3</sub>), 37.9 (PhCH<sub>2</sub>R), 42.3 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 48.1 (PhCH<sub>2</sub>CHR<sub>2</sub>), 110.6 (Het Ar CH), 115.8 (RCH=CH<sub>2</sub>), 120.0 (Het Ar CH), 124.3 (Het Ar CH), 124.6 (Het Ar CH), 126.4 (Ar CH), 128.6 (Ar CH), 128.9 (Ar CH), 139.6 (quat. Ar C), 141.4 (quat. Ar C), 141.7 (RCH=CH<sub>2</sub>), 150.8 (quat Ar C), 168.2 (N=CO).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) minor diastereomer: δ 1.16 (d, 3H: *J* = 7.1 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 2.73 (sext., 1H: *J* = 7.1 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 3.11 (m, 1H: PhCHHR), 3.25 (m, 1H: BnCHR<sub>2</sub>), 3.36 (dt, 1H: *J* = 5.6, 9.4 Hz, PhCHHR), 5.06 (m, 2H: RCH=CH<sub>2</sub>), 5.87 (ddd, 1H: 8.2, 10.4, 17.0 Hz, CH<sub>2</sub>=CHR), 7.12 (m, 2H: overlapping Ar CH's), 7.20 (m, 3H: overlapping Ar CH's), 7.29 (m, 2H: overlapping Het Ar CH's), 7.46 (m, 1H: Het Ar CH), 7.67 (m, 1H: Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) minor diastereomer: δ 18.4 (R<sub>2</sub>CHCH<sub>3</sub>), 36.8 (PhCH<sub>2</sub>R), 41.5 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 47.7 (PhCH<sub>2</sub>CHR<sub>2</sub>), 110.6 (Het Ar CH), 115.9 (RCH=CH<sub>2</sub>), 120.0 (Het Ar CH), 124.2 (Het Ar CH), 124.6 (Het Ar CH), 126.5 (Ar CH), 128.6 (Ar CH), 129.0 (Ar CH), 129.1 (quat. Ar C), 139.7 (quat. Ar C), 140.5 (RCH=CH<sub>2</sub>), 141.4 (quat. Ar C), 170.0 (N=CO).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2986, 1641, 1565, 1485, 1455, 1421, 1264, 1141, 1003, 923, 896.

**HRMS** calcd for [M+H] 278.1545, found 278.1544.



2-(3-methylpent-4-en-2-yl)benzoxazole  
**2.127d** (srm7156)

isolated as 2.9 : 1 mixture of diastereomers, and 15.9 : 1 branched to linear product  
 yellow oil

yield: 61% (combined diastereomers)

**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer: δ 1.03 (d, 3H: *J* = 6.8 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 1.40 (d, 3H: *J* = 7.1 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 2.70 (p, 1H: *J* = 7.1 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.03 (app. p, 1H: *J* = 7.1 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 5.06 (dd, 1H: *J* = 1.7, 10.4 Hz, H<sub>A</sub>), 5.08 (dd, 1H: *J* = 1.0, 17.2 Hz, H<sub>B</sub>), 5.76 (dd, 1H: *J* = 10.4, 17.2 Hz, RCH=CH<sub>2</sub>), 7.31 (m, 2H: overlapping Het Ar CH's), 7.50 (m, 1H: Het Ar CH's), 7.70 (m, 1H: Het Ar CH).

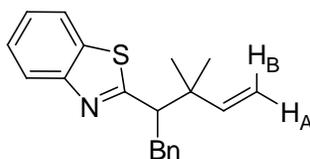
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) major diastereomer: δ 16.1 (R<sub>2</sub>CHCH<sub>3</sub>), 18.5 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 39.9 (R<sub>2</sub>CHCH<sub>3</sub>), 42.7 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 110.5 (Het Ar CH), 115.6 (RCH=CH<sub>2</sub>), 119.9 (Het Ar CH), 124.3 (Het Ar CH), 124.6 (Het Ar CH), 141.1 (RCH=CH<sub>2</sub>), 141.2 (quat. Ar C), 150.8 (quat Ar C), 170.0 (N=CO).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) minor diastereomer: δ 1.09 (d, 3H: *J* = 6.8 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 1.42 (d, 3H: *J* = 7.1 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 2.74 (p, 1H: *J* = 7.1 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.16 (app. p, 1H: *J* = 7.1 Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 4.99 (m, 2H: H<sub>B</sub> and H<sub>A</sub>), 5.80 (m, 1H: RCH=CH<sub>2</sub>), 7.31 (m, 2H: overlapping Het Ar CH's), 7.50 (m, 1H: Het Ar CH's), 7.70 (m, 1H: Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) minor diastereomer: δ 14.8 (R<sub>2</sub>CHCH<sub>3</sub>), 16.6 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 39.6 (R<sub>2</sub>CHCH<sub>3</sub>), 41.9 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 110.5 (Het Ar CH), 115.1 (RCH=CH<sub>2</sub>), 119.9 (Het Ar CH), 124.2 (Het Ar CH), 124.6 (Het Ar CH), 141.1 (RCH=CH<sub>2</sub>), 141.3 (quat. Ar C), 141.4 (quat. Ar C), 170.0 (N=CO).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3052, 2983, 1780, 1640, 1612, 1566, 1456, 1421, 1264, 1147, 1069, 1003, 922, 896.

**HRMS** calcd for [M+H] 202.1232, found 202.1226.



2-(3,3-dimethyl-1-phenylpent-4-en-2-yl)benzothiazole

**2.127e** (srm7158)

colorless oil

yield: 74%

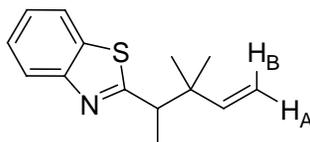
**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.16 (s, 3H: one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 1.25 (s, 3H: one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 3.17 (m, 2H: R<sub>2</sub>C(CH<sub>2</sub>Ph)<sub>2</sub>), 3.34 (dd, 1H: *J* = 3.4, 11.4 Hz, R<sub>2</sub>CHBn), 5.12 (dd, 1H: *J* = 1.0, 17.3 Hz, H<sub>B</sub>), 5.15 (dd, 1H: *J* = 1.0, 10.7 Hz, H<sub>A</sub>), 6.10 (dd, 1H: *J* = 10.7, 17.3 Hz, RCH=CH<sub>2</sub>), 7.01 (m, 2H: overlapping Ar CH's), 7.09 (m, 3H: overlapping Ar CH's), 7.33 (app. t, 1H: *J* = 8.1 Hz, Het Ar CH), 7.43 (app. t, 1H: *J* = 8.1 Hz, Het Ar CH), 7.78 (d, 1H: *J* = 8.1 Hz, Het Ar CH), 7.99 (d, 1H: *J* = 8.1 Hz, Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 23.6 (one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 27.0 (one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 37.7 (RCH<sub>2</sub>Ph), 40.9 (R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 57.1 (R<sub>2</sub>CHBn), 113.1 (RCH=CH<sub>2</sub>), 121.5 (Het Ar CH), 123.0 (Het Ar CH), 124.7 (Het Ar CH), 125.8 (Het Ar CH), 126.1 (Ar CH), 128.4 (Ar CH), 128.9 (Ar CH), 134.9 (quat. Ar C), 140.4 (quat. Ar C), 146.4 (RCH=CH<sub>2</sub>), 153.2 (quat. Ar C), 172.6 (N=CS).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>) ν<sub>max</sub>: 3054, 2986, 1603, 1550, 1501, 1437, 1421, 1265, 920, 896.

**HRMS** calcd for [M+H] 308.1473, found 308.1477.



2-(3,3-dimethylpent-4-en-2-yl)benzothiazole

**2.127f** (srm7122)

pale yellow oil

yield: 50%

**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

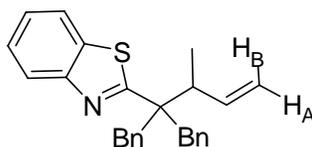
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.13 (s, 3H: one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 1.14 (s, 3H: one of diastereotopic R<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 1.40 (d, 3H: *J* = 7.1 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 3.27 (q, 1H: *J* = 7.1 Hz, R<sub>2</sub>CHCH<sub>3</sub>), 5.03 (dd, 1H: *J* = 1.3, 17.4 Hz, H<sub>B</sub>), 5.08 (dd,

$^1\text{H}$ :  $J = 1.3, 10.9$  Hz,  $\text{H}_\text{A}$ ), 5.99 (dd, 1H:  $J = 10.9, 17.4$  Hz,  $\text{RCH}=\text{CH}_2$ ), 7.36 (ddd, 1H:  $J = 1.2, 7.2, 8.1$  Hz, Het Ar CH), 7.46 (ddd, 1H:  $J = 1.2, 7.2, 8.1$  Hz, Het Ar CH), 7.85 (d, 1H:  $J = 8.1$  Hz, Het Ar CH), 8.01 (d, 1H:  $J = 8.1$  Hz, Het Ar CH).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  17.0 ( $\text{R}_2\text{CHCH}_3$ ), 24.2 (one of diastereotopic  $\text{R}_2\text{C}(\text{CH}_3)_2$ ), 26.2 (one of diastereotopic  $\text{R}_2\text{C}(\text{CH}_3)_2$ ), 40.2 ( $\text{R}_2\text{C}(\text{CH}_3)_2$ ), 49.2 ( $\text{R}_2\text{CHCH}_3$ ), 112.9 ( $\text{RCH}=\text{CH}_2$ ), 121.5 (Het Ar CH), 122.9 (Het Ar CH), 124.8 (Het Ar CH), 125.9 (Het Ar CH), 135.1 (quat. Het Ar C), 145.9 ( $\text{RCH}=\text{CH}_2$ ), 153.0 (quat. Het Ar C), 174.9 ( $\text{N}=\text{CS}$ ).

FTIR ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3054, 2979, 1637, 1506, 1455, 1437, 1421, 1265, 1048, 1004, 918, 896.

HRMS calcd for  $[\text{M}+\text{H}]$  232.1160, found 232.1158.



2-(2-benzyl-3-methyl-1-phenylpent-4-en-2-yl)benzothiazole

**2.127g** (srm6285)

pale yellow oil

yield: 74%

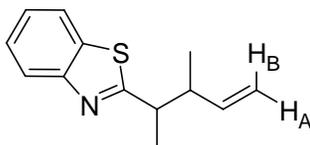
**Purification:** flash chromatography (99.5:0.5 hexane: ethyl acetate)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.06 (d, 3H:  $J = 6.8$  Hz,  $\text{R}_2\text{CHCH}_3$ ), 2.76 (dq, 1H:  $J = 6.8, 8.7$  Hz,  $\text{R}_2\text{CCHCH}_3$ ), 3.09 (d, 1H:  $J = 15.4$  Hz, one of diastereotopic  $\text{R}_2\text{C}(\text{CHHPh})_2$ ), 3.47 (app. q, 2H:  $J = 14.4$  Hz, diastereotopic  $\text{R}_2\text{C}(\text{CHHPh})_2$ ), 3.63 (d, 1H:  $J = 15.4$  Hz, one of diastereotopic  $\text{R}_2\text{C}(\text{CHHPh})_2$ ), 5.02 (dd, 1H:  $J = 1.7, 17.1$  Hz,  $\text{H}_\text{B}$ ), 5.07 (dd, 1H:  $J = 1.7, 10.2$  Hz,  $\text{H}_\text{A}$ ), 6.01 (ddd, 1H:  $J = 8.8, 10.2, 17.1$  Hz,  $\text{RCH}=\text{CH}_2$ ), 6.98 (m, 2H: overlapping Ar CH's), 7.01 (m, 2H: overlapping Ar CH's), 7.16 (m, 3H: overlapping Ar CH's), 7.20 (m, 3H: Ar CH's), 7.41 (ddd, 1H:  $J = 0.9, 7.4, 8.1$  Hz, Het Ar CH), 7.52 (ddd, 1H:  $J = 1.2, 7.4, 8.1$  Hz, Het Ar CH), 7.90 (d, 1H:  $J = 8.1$  Hz, Het Ar CH), 8.09 (d, 1H:  $J = 8.1$  Hz, Het Ar CH).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  16.8 ( $\text{R}_2\text{CHCH}_3$ ), 41.2 (diastereotopic  $\text{CH}_2\text{Ph}$ ), 43.2 (diastereotopic  $\text{CH}_2\text{Ph}$ ), 45.7 ( $\text{R}_2\text{CHCH}_3$ ), 52.1 ( $\text{R}_2\text{C}(\text{CH}_2\text{Ph})_2$ ), 117.2 ( $\text{RCH}=\text{CH}_2$ ), 122.3 (Het Ar CH), 124.1 (Het Ar CH), 125.7 (Het Ar CH), 126.7 (Het Ar CH), 127.1 (Ar CH), 127.4 (Ar CH), 128.9 (Ar CH), 129.0 (Ar CH), 131.3 (Ar CH), 131.7 (Ar CH), 136.1 (quat. Ar. C), 138.6 (quat. Ar. C), 139.3 (quat. Ar C), 141.3 ( $\text{RCH}=\text{CH}_2$ ), 153.8 (quat. Ar C), 178.5 ( $\text{N}=\text{CS}$ ).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3055, 2985, 1635, 1603, 1550, 1496, 1453, 1437, 1421, 1263, 1004, 951, 919, 896.

**HRMS** calcd for [M+H] 384.1786, found 384.1785.



2-(3-methylpent-4-en-2-yl)benzothiazole

**2.127h** (srm7152)

isolated as 10:1 mixture of diastereomers, and 18.5:1 branched to linear product  
yellow oil  
yield: 72% (combined diastereomers)

**Purification:** flash chromatography (98:2 hexane: ethyl acetate)

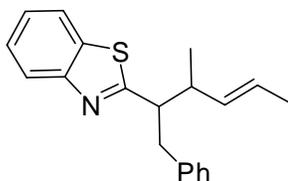
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) major diastereomer:  $\delta$  1.04 (d, 3H:  $J = 6.9$  Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 1.42 (d, 3H:  $J = 7.0$  Hz, R<sub>2</sub>CHCH<sub>3</sub>), 2.65 (sext., 1H:  $J = 6.9$  Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 3.17 (dq, 1H:  $J = 6.9, 7.8$  Hz, R<sub>2</sub>CHCH<sub>3</sub>), 5.06 (dd, 1H:  $J = 1.6, 10.3$  Hz, H<sub>A</sub>), 5.09 (dd, 1H:  $J = 1.6, 17.2$  Hz, H<sub>B</sub>), 5.77 (ddd, 1H:  $J = 8.3, 10.3, 17.2$  Hz, RCH=CH<sub>2</sub>), 7.36 (ddd, 1H:  $J = 1.3, 7.3, 8.2$  Hz, Het Ar CH), 7.46 (ddd, 1H:  $J = 1.3, 7.3, 8.2$  Hz, Het Ar CH), 7.86 (app. d, 1H:  $J = 8.2$  Hz, Het Ar CH), 8.00 (app. d, 1H:  $J = 8.2$  Hz, Het Ar CH).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) major diastereomer:  $\delta$  18.7 (R<sub>2</sub>CHCH<sub>3</sub>), 18.8 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 44.5 (R<sub>2</sub>CHCH<sub>3</sub>), 44.7 (CH<sub>2</sub>=CHCHCH<sub>3</sub>), 115.4 (RCH=CH<sub>2</sub>), 121.5 (Het Ar CH), 122.7 (Het Ar CH), 124.6 (Het Ar CH), 125.8 (Het Ar CH), 134.7 (quat. Het Ar C), 141.1 (RCH=CH<sub>2</sub>), 153.0 (quat. Het Ar C), 176.6 (N=CS);

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) minor diastereomer:  $\delta$  1.10 (d, 3H:  $J = 7.1$  Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 1.44 (d, 3H:  $J = 7.1$  Hz, R<sub>2</sub>CHCH<sub>3</sub>), 2.73 (sext., 1H:  $J = 7.1$  Hz, CH<sub>2</sub>=CHCHCH<sub>3</sub>), 3.32 (app. p, 1H:  $J = 7.1$  Hz, R<sub>2</sub>CHCH<sub>3</sub>), 4.99 (dt, 1H:  $J = 1.4, 10.2$  Hz, H<sub>B</sub>), 5.03 (dt, 1H: 1.4, 17.3 Hz, H<sub>B</sub>), 5.83 (ddd, 1H:  $J = 7.3, 10.2, 17.3$  Hz, RCH=CH<sub>2</sub>), 7.36 (ddd, 1H:  $J = 1.3, 7.3, 8.2$  Hz, Het Ar CH), 7.46 (ddd, 1H:  $J = 1.3, 7.3, 8.2$  Hz, Het Ar CH), 7.86 (app. d, 1H:  $J = 8.2$  Hz, Het Ar CH), 8.00 (app. d, 1H:  $J = 8.2$  Hz, Het Ar CH).

**FTIR** (CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3053, 2983, 2930, 1695, 1641, 1514, 1455, 1438, 1421, 1268, 1042, 999, 920, 896.

HRMS calcd for [M+H] 218.1003, found 218.0993.



(E)-2-(3-methyl-1-phenylhex-4-en-2-yl)benzothiazole  
**2.127i** (srm7175)

isolated as 1.6:1 mixture of diastereomers

colorless oil

yield: 59% (combined diastereomers)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) major diastereomer: δ 0.98 (d, 3H: *J* = 6.8 Hz, CH=CHCH<sub>3</sub>), 1.73 (dd, 3H: *J* = 1.4, 6.4 Hz, CH=CHCH<sub>3</sub>), 2.67 (sext. 1H: *J* = 7.6 Hz, CH=CHCHR<sub>2</sub>), 3.06 (m, 1H: HetCHR<sub>2</sub>), 3.25 (dd, 1H: *J* = 4.3, 8.3 Hz, RCHHPh), 3.29 (1 H, *J* = 4.0, 13.4 Hz), 5.46 (m, 1H: CH=CHCH<sub>3</sub>), 5.60 (m, 1H: RCH=CHCH<sub>3</sub>), 7.07 (m, 3H: Ar CH's), 7.14 (m, 2H: Ar CH's), 7.32 (app. t, 1H: *J* = 7.8 Hz, Het Ar CH), 7.43 (app. t, 1H: *J* = 7.1 Hz, Het Ar CH), 7.79 (app. d, 1H: *J* = 7.8 Hz, Het Ar CH), 7.98 (dt, 1H: *J* = 0.5, 8.1 Hz, Het Ar CH).

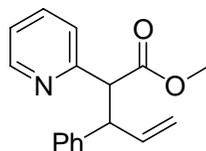
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) major diastereomer: δ 18.1 (CH=CHCH<sub>3</sub>), 19.0 (CH=CHCH<sub>3</sub>), 40.2 (RCH<sub>2</sub>Ph), 42.9 (CH=CHCHR<sub>2</sub>), 52.9 (HetCHR<sub>2</sub>), 121.5 (Ar CH), 122.6 (CH<sub>3</sub>CH=CHR), 124.5 (Het Ar CH), 125.7 (Het Ar CH), 126.0 (Het Ar CH), 126.40 (Het Ar CH), 128.2 (Ar CH), 128.84 (Ar CH), 134.6 (quat. Het Ar C), 134.7 (R<sub>2</sub>CH=CHCH<sub>3</sub>), 139.9 (quat. Ar C), 153.1 (quat. Het Ar C), 174.4 (N=C).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) minor diastereomer: δ 0.94 (d, 3H: *J* = 6.8 Hz, CH=CHCH<sub>3</sub>), 1.68 (dd, 3H: *J* = 1.9, 6.9 Hz, CH=CHCH<sub>3</sub>), 1.73 (2 H, dd, *J* = 6.4, 1.4 Hz), 3.06 (m, 1H: CH=CHCHR<sub>2</sub>), 3.25 (m, 2H: RCH<sub>2</sub>Ph), 5.46 (m, 1H: CH=CHCH<sub>3</sub>), 5.60 (m, 1H: RCH=CHCH<sub>3</sub>), 7.07 (m, 3H: Ar CH's), 7.14 (m, 2H: Ar CH's), 7.32 (app. t, 1H: *J* = 7.8 Hz, Het Ar CH), 7.43 (app. t, 1H: *J* = 7.1 Hz, Het Ar CH), 7.79 (app. d, 1H: *J* = 7.8 Hz, Het Ar CH), 7.98 (dt, 1H: *J* = 0.5, 8.1 Hz, Het Ar CH).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) minor diastereomer: δ 13.3 (CH=CHCH<sub>3</sub>), 19.1 (CH=CHCH<sub>3</sub>), 37.2 (CH=CHCHR<sub>2</sub>), 40.1 (RCH<sub>2</sub>Ph), 53.4 (HetCHR<sub>2</sub>), 121.5 (Ar CH), 122.7 (CH<sub>3</sub>CH=CHR), 124.5 (Het Ar CH), 125.0 (Het Ar CH), 125.7 (Het Ar CH), 126.0 (Het Ar CH s), 128.2 (Ar CH), 128.8 (Ar CH), 134.5 (R<sub>2</sub>CH=CHCH<sub>3</sub>), 134.6 (quat. Het Ar C), 139.8 (quat. Ar C), 153.2 (quat. Het Ar C), 174.3 (N=C)

### Procedure for the synthesis of **2.133** and **2.134**.

To a Schlenk flask was added **2.132** (45 mg, 0.29 mmol) in THF (2 mL). Then, NaH (12 mg, 0.50 mmol) was added to the solution portionwise and the reaction was stirred for 30 minutes. Meanwhile, cinnamyl acetate (52 mg, 0.29 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (34 mg, 0.03 mmol) were dissolved in toluene (2 mL). After the 30 minutes was complete, this solution was transferred via cannula into the solution containing **2.132** and the resulting solution was heated to 70 °C for 20 hours. Then the solution was cooled to room temperature and concentrated under vacuum. The residue was dissolved into Et<sub>2</sub>O (20 mL) and washed with H<sub>2</sub>O (2 × 3 mL). The organic phases were combined and dried over MgSO<sub>4</sub>. Concentration of the solution was followed by purification *via* flash column chromatography with 90:10 hexane:ethyl acetate as the elution system. A mixture of **2.133** and **2.134** were isolated in a 1.2:1 ratio, respectively in an overall 43% yield.

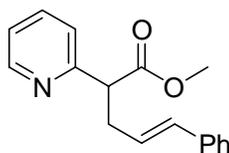


methyl 3-phenyl-2-(pyridin-2-yl)pent-4-enoate (major isomer)

**2.133** (srm6240)

yield: 43% (combined isomers)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.73 (s, 3H: OCH<sub>3</sub>), 4.30 (m, 2H: HetCHR<sub>2</sub> and PhCHR<sub>2</sub>), 5.14 (app. d, 1H: *J* = 10.9 Hz, CH=CHH<sub>cis</sub>), 5.25 (dd, 1H: *J* = 1.0, 17.2 Hz, CH=CH<sub>cis</sub>H), 6.14 (m, 1H: CH=CH<sub>2</sub>), 7.03 (ddd, 1H: *J* = 1.3, 4.9, 7.5 Hz, Het Ar CH), 7.09 (m, 2H: Ar CH's), 7.15 (m, 1H: Het Ar CH), 7.26 (m, 3H: Ar CH's), 7.46 (td, 1H: *J* = 2.0, 7.7 Hz, Het Ar CH), 8.47 (ddd, 1H: *J* = 1.0, 2.0, 5.0 Hz, Het Ar CH)



(E)-methyl 5-phenyl-2-(pyridin-2-yl)pent-4-enoate (minor isomer)

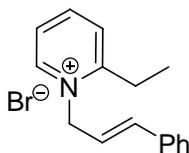
**2.134** (srm6240)

yield: 43% (combined isomers)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 2.87 (m, 1H: CHHCHHet), 3.06 (m, 1H: CHHCHHet), 3.72 (s, 3H: OCH<sub>3</sub>), 4.00 (t, 1H: *J* = 7.7 Hz, HetCHR<sub>2</sub>), 6.15 (m, 1H: PhCH=CH), 6.43 (dt, 1H: *J* = 1.3, 15.9 Hz, PhCH=CH), 7.09 (m, 2H: Ar CH's), 7.22 (m, 1H: Het Ar CH), 7.26 (m, 3H: Ar CH's), 7.34 (m, 1H: Het Ar CH), 7.68 (td, 1H: *J* = 1.9, 7.8 Hz, Het Ar CH), 8.61 (d, 1H: *J* = 0.8, 1.8, 4.8 Hz, Het Ar CH).

#### General Procedure for the synthesis of cinnamyl pyridinium salt **2.148**.

To a flask was added ethyl pyridine (500 mg, 4.67 mmol) and cinnamyl bromide (1.38 g, 7.0 mmol) in acetone (10 mL). The reaction was stirred at room temperature overnight, at which time the reaction was concentrated to < 1 mL. The residue was washed with Et<sub>2</sub>O (5 mL) to remove the residual cinnamyl alcohol and the solution was then decanted off the syrupy product **2.148** and isolated in 90% crude yield.



1-cinnamyl-2-ethylpyridinium

**2.148** (srm6161)

dark red oil

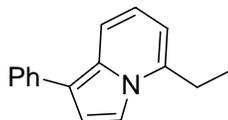
yield: 90%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 1.47 (t, 3H: *J* = 7.4 Hz, CH<sub>3</sub>), 3.33 (q, 2H: *J* = 7.4 Hz, HetCH<sub>2</sub>CH<sub>3</sub>), 5.82 (d, 2H: *J* = 6.7 Hz, NCH<sub>2</sub>CH=CHPh), 6.40 (ddd, 1H: *J* = 6.3, 6.5, 15.8 Hz, PhCH=CHR), 6.88 (d, 1H: *J* = 16.0 Hz, PhCH=CHR), 7.29 (m, 3H: *J* = 7.8 Hz, Ar CH's), 7.39 (dd, 2H: *J* = 2.0, 7.8 Hz, Ar CH's), 7.86 (d, 1H: *J* =

7.8 Hz, Het Ar CH), 7.98 (t, 1H:  $J = 6.5$  Hz, Het Ar CH), 8.43 (t, 1H:  $J = 7.2$  Hz, Het Ar CH), 9.72 (d, 1H:  $J = 5.5$  Hz, Het Ar CH).

#### Procedure for the synthesis of indolizine 2.151.

To a Schlenk flask was added **2.148** (173 mg, 0.77 mmol) in THF (9 mL). Then, *n*-BuLi (.53 mL of 1.6M solution in hexanes, 0.85 mmol) was added dropwise at 0 °C. Following this addition, the solution was heated at 70 °C for 18 hours. The resulting solution was cooled to room temperature and then quenched with NH<sub>4</sub>Cl (5 mL). The resulting mixture was diluted with Et<sub>2</sub>O (10 mL) and the organic phase was extracted with brine (2 × 3 mL). The organic layers were combined and dried over MgSO<sub>4</sub>. Purification of the resulting product was achieved *via* flash column chromatography (98:2 hexane:ethyl acetate) and **2.151** was isolated in 23% yield.



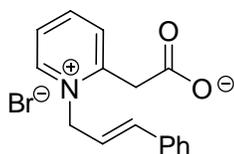
5-ethyl-1-phenylindolizine  
**2.151** (srm6220)  
yield: 23%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.48 (t, 3H:  $J = 7.5$  Hz, CH<sub>3</sub>), 2.89 (q, 2H:  $J = 7.4$  Hz, HetCH<sub>2</sub>CH<sub>3</sub>), 6.46 (app. d, 1H:  $J = 6.6$  Hz, Het Ar CH), 6.82 (dd, 1H:  $J = 6.6, 9.1$  Hz, Het Ar CH), 7.08 (br. s, 1H: Het Ar CH), 7.26 (m, 1H: Het Ar CH), 7.35 (br.s, 1H: Ar CH), 7.46 (t, 2H:  $J = 7.7$  Hz, Ar CH's), 7.65 (m, 2H: Ar CH's), 7.72 (d, 1H:  $J = 9.1$  Hz, Het Ar CH).

#### Procedure for the synthesis of pyridinium salt 2.153.

To a flask was added commercially available 2-pyridyl acetic acid hydrochloride (125 mg, 2.33 mmol), DIEA (301 mg, 4.7 mmol), and cinnamyl bromide (346 mg, 3.5

mmol) in acetone (2.5 mL). The reaction progress was checked by  $^1\text{H}$  NMR spectroscopy after stirring at room temperature for 7 hours, but the reaction had not completed, so the reaction was allowed to stir 18 more hours. After this time, the solution was concentrated to dryness and the residue was dissolved in  $\text{Et}_2\text{O}$  (5 mL) as an attempt to get rid of impurities. After decanting off the  $\text{Et}_2\text{O}$  solution, the product was again monitored by  $^1\text{H}$  NMR spectroscopy. The product **2.153** was present in this spectrum. The addition of 1M HCl (1 mL) and  $\text{Et}_2\text{O}$  (5 mL) was done to try to isolate the acid product, but hydrolysis of the pyridinium salt was observed.



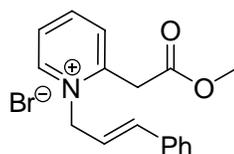
(*E*)-2-(1-cinnamylpyridinium-2-yl)acetate  
**2.153** (srm7105)  
 yield: 23% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.90 (s, 2H:  $\text{HetCH}_2\text{CO}_2$ ) 5.87 (d, 2H:  $J = 6.3$  Hz,  $\text{NCH}_2\text{R}$ ), 6.38 (m, 1H:  $\text{PhCH=CHR}$ ), 6.90 (d, 1H:  $J = 15.4$  Hz,  $\text{PhCH=CHR}$ ), 7.33 (m, 3H: Ar CH's), 7.39 (m, 2H: Ar CH's), 7.86 (d, 1H:  $J = 8.6$  Hz, Het Ar CH), 7.95 (t, 1H:  $J = 6.9$  Hz, Het Ar CH), 8.34 (t, 1H:  $J = 7.7$  Hz, Het Ar CH), 9.80 (d, 1H: 6.1 Hz, Het Ar CH).

#### General procedure for the synthesis of cinnamyl pyridinium salt **2.154**.

To a flask was added ester **2.153** (330 mg, 2.2 mmol) and cinnamyl bromide (645 mg, 3.3 mmol) in acetone (7 mL). The solution was stirred at room temperature overnight, at which time it was concentrated to  $< 1$  mL. The residue was washed with  $\text{Et}_2\text{O}$  (5 mL) but this did not get rid of the cinnamyl alcohol present.  $\text{CH}_2\text{Cl}_2$  (3 mL)

was then added, and **2.154** precipitated as a white solid and the product was filtered from the solution and isolated in 34% yield.



1-cinnamyl-2-(2-methoxy-2-oxoethyl)pyridinium

**2.154** (srm7116)

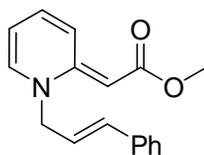
yield: 34%

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.66 (s, 3H: OCH<sub>3</sub>), 4.62 (s, 2H: HetCH<sub>2</sub>R), 5.87 (d, 2H: *J* = 6.8 Hz, NCH<sub>2</sub>CH=CHPh), 6.40 (ddd, 1H: *J* = 6.7, 6.8, 15.8 Hz, PhCH=CH), 6.98 (d, 1H: *J* = 15.9 Hz, PhCH=CHR), 7.34 (m, 3H: Ar CH's), 7.42 (dd, 2H: *J* = 1.8, 7.8 Hz, Ar CH's), 8.01 (d, 2H: *J* = 7.8 Hz, Het Ar CH's), 8.40 (td, 1H: *J* = 1.4, 7.9 Hz, Het Ar CH), 9.64 (d, 1H: *J* = 6.3 Hz, Het Ar CH).

#### **Procedure for the synthesis of the neutral species 2.155.**

To a flask was added **2.154** (100 mg, 0.37 mmol) in THF (5 mL). Then, NaH (15 mg, 0.38 mmol, 60% dispersion in mineral oil) was added portionwise to the solution and the reaction was allowed to stir at room temperature overnight. The solution was then diluted with Et<sub>2</sub>O (5 mL) and the extracted with H<sub>2</sub>O (2 × 3 mL). The organic phase was then dried over MgSO<sub>4</sub> and concentrated, which afforded the crude product,

**2.155.**



(*E*)-methyl 2-(1-cinnamylpyridin-2(1H)-ylidene)acetate

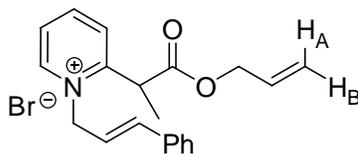
**2.155** (srm7120)

yield: 90% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.65 (s, 3H:  $\text{OCH}_3$ ), 4.40 (dd, 2H:  $J = 1.4, 5.7$  Hz,  $\text{NCH}_2\text{CH=CHPh}$ ), 4.56 (s, 1H: Het $\text{CHCO}_2\text{R}$ ), 6.01 (td, 1H:  $J = 1.3, 6.6$  Hz, Het Ar CH), 6.24 (dt, 1H:  $J = 5.7, 16.0$  Hz,  $\text{PhCH=CHR}$ ), 6.51 (d, 1H:  $J = 15.7$  Hz,  $\text{PhCH=CHR}$ ), 6.95 (m, 1H: Het Ar CH), 7.03 (d, 1H:  $J = 6.3$  Hz, Het Ar CH), 7.28 (m, 1H: Ar CH), 7.33 (t, 2H:  $J = 7.2$  Hz, Ar CH's), 7.39 (m, 2H: Ar CH's), 8.49 (d, 1H:  $J = 9.6$  Hz, Het Ar CH).

#### General Procedure for the synthesis of cinnamyl pyridinium salt **2.157**.

To a flask was added ester **2.110** (240 mg, 1.3 mmol) and cinnamyl bromide (371 mg, 1.9 mmol) in acetone (5 mL). The reaction was stirred at room temperature overnight, at which time the reaction was concentrated to < 1 mL. The residue was washed with  $\text{Et}_2\text{O}$  (5 mL) and  $\text{CH}_2\text{Cl}_2$  (3 mL). Upon addition of hexane to the crude product mixture, product **2.157** precipitated and was filtered from the solution.



2-(1-(allyloxy)-1-oxopropan-2-yl)-1-cinnamylpyridinium

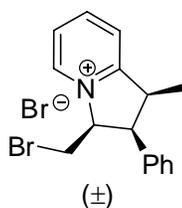
**2.157** (srm7192)

yield: 7%

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.18 (m, 3H:  $\text{CH}_3$ ), 4.62 (m, 1H: Het $\text{CHR}$ ), 5.27 (m, 2H:  $\text{CH=CH}_2$ ), 5.31 (m, 2H:  $\text{OCH}_2$ ), 5.98 (m, 2H:  $\text{NCH}_2\text{CH=CHPh}$ ), 6.04 (m, 1H:  $\text{CH=CH}_2$ ), 6.40 (m, 1H:  $\text{PhCH=CH}$ ), 6.98 (m, 1H:  $\text{PhCH=CHR}$ ), 7.34 (m, 5H: Ar CH's), 8.01 (m, 2H: Het Ar CH's), 8.42 (m, 1H: Het Ar CH), 10.0 (m, 1H: Het Ar CH).

### Procedure for the bromocyclization of 2.111.

**2.111** (5 mg, 0.02 mmol) was dissolved in C<sub>6</sub>D<sub>6</sub> (0.5 mL) and treated with bromine (0.22 mmol, 0.97 M solution in CH<sub>2</sub>Cl<sub>2</sub>) at 0 °C. The solution was stirred at room temperature for 15 min and then filtered. The filtrate was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/pentane.<sup>136</sup>



3-(bromomethyl)-1-methyl-2-phenyl-2,3-dihydro-1H-indolizinium

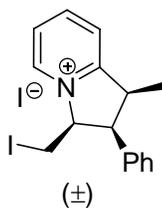
**2.160** (srm7057\_1)

yield: 25%

<sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 1.19 (d, 3H: *J* = 6.9 Hz, RCH<sub>3</sub>), 3.47 (dd, 1H: *J* = 6.6, 11.3 Hz, RCHHBr), 4.00 (dd, 1H: *J* = 6.6, 11.3 Hz, RCHHBr), 4.12 (app. t, 1H: *J* = 6.9 Hz, CH<sub>3</sub>CHR<sub>2</sub>), 4.32 (t, 1H: *J* = 6.6 Hz, PhCHR<sub>2</sub>), 5.60 (q, 1H: *J* = 6.6 Hz, NCHCH<sub>2</sub>Br), 6.67 (d, 2H: *J* = 7.3 Hz, Ar CH's), 7.23 (t, 2H: *J* = 7.7 Hz, Ar CH's), 7.30 (m, 1H: Ar CH), 7.98 (m, 1H: *J* = 6.6 Hz, Het Ar CH), 8.01 (d, 1H: *J* = 8.2 Hz, Het Ar CH), 8.55 (t, 1H: *J* = 7.9 Hz, Het Ar CH), 9.04 (d, 1H: *J* = 5.7 Hz, Het Ar CH).

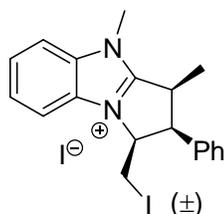
### Procedure for the iodocyclization of 2.111, 2.114e, and 2.114f.

To a dried NMR tube was added the substrate (0.02 mmol) and I<sub>2</sub> (17 mg, 0.04 mmol) in CDCl<sub>3</sub> (600 μL). The solution was allowed to stand at room temperature for four hours after which the reaction was monitored by <sup>1</sup>H NMR spectroscopy, and the products were identified in the reaction mixture.



3-(iodomethyl)-1-methyl-2-phenyl-2,3-dihydro-1H-indolizinium  
**2.161** (srm6207)  
 yield: 42% by  $^1\text{H}$  NMR

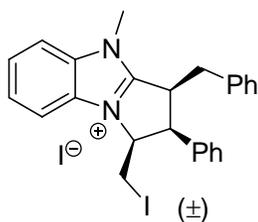
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d, 3H:  $J = 6.4$  Hz,  $\text{CH}_3$ ), 3.00 (t, 1H:  $J = 10.0$  Hz,  $\text{PhCHR}$ ), 4.12 (m, 1H:  $\text{CH}_3\text{CHR}_2$ ), 4.47 (m, 2H:  $\text{RCH}_2\text{I}$ ), 5.87 (m, 1H:  $\text{NCHR}_2$ ), 6.64 (d, 2H:  $J = 7.8$  Hz, Ar CH's), 7.23 (m, 2H: Ar CH's), 7.44 (m, 1H: Ar CH), 8.00 (d, 1H:  $J = 7.8$  Hz, Het Ar CH), 8.17 (t, 1H:  $J = 6.8$  Hz, Het Ar CH), 8.62 (t, 1H:  $J = 6.8$  Hz, Het Ar CH), 9.07 (br. s, 1H: Het Ar CH).



1-(iodomethyl)-3,4-dimethyl-2-phenyl-1,2,3,4-tetrahydrobenzopyrrolo[1,2-a]-imidazol-9-ium (major diastereomer)  
**2.162** (srm6241)  
 6:1 mixture of diastereomers  
 yield: 72% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.84 (d, 3H:  $J = 5.3$  Hz,  $\text{CR}_2\text{CHCH}_3$ ), 3.22 (dd, 1H:  $J = 4.0, 11.9$  Hz,  $\text{CHCHHI}$ ), 3.60 (dd, 1H:  $J = 4.3, 11.9$  Hz,  $\text{CHCHHI}$ ), 4.31 (s, 3H:  $\text{NCH}_3$ ), 4.77 (m, 2H:  $\text{CH}_3\text{CHR}_2$  and  $\text{PhCHR}_2$ ), 5.73 (m, 1H:  $\text{NCHR}_2$ ), 7.28 (m, 1H: Het Ar CH), 7.50 (m, 3H: Ar CH's), 7.62 (m, 1H: Het Ar CH), 7.70 (m, 2H: Ar CH's), 7.79 (m, 1H: Het Ar CH), 7.91 (m, 1H: Het Ar CH).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  2.9 ( $\text{RCH}_2\text{I}$ ), 15.1 ( $\text{R}_2\text{CHCH}_3$ ), 33.7 ( $\text{NCH}_3$ ), 35.7 ( $\text{R}_2\text{CHCH}_3$ ), 58.7 ( $\text{PhCHR}_2$ ), 62.5 ( $\text{NCHR}_2$ ), 113.4 (Het Ar CH), 114.2 (Het Ar CH), 127.2 (Ar CH), 127.3 (Ar CH), 127.9 (quat Ar C), 128.0 (Ar CH), 128.9 (Het Ar CH), 129.5 (Het Ar CH), 131.3 (quat Het Ar C), 136.2 (quat Het Ar C), 157.7 (N-CR=N).



3-benzyl-1-(iodomethyl)-4-methyl-2-phenyl-1,2,3,4-tetrahydrobenzopyrrolo[1,2-a]imidazol-9-ium

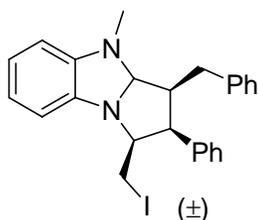
**2.163** (srm7014)

yield: 68% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.23 (dd, 1H:  $J = 3.8, 11.7$  Hz,  $\text{RCHHI}$ ), 3.41 (dd, 1H:  $J = 6.3, 14.5$  Hz,  $\text{RCHHPH}$ ), 3.48 (dd, 1H:  $J = 5.4, 11.7$  Hz,  $\text{RCHHI}$ ), 3.61 (dd, 1H:  $J = 7.7, 14.5$  Hz,  $\text{RCHHPH}$ ), 3.90 (s, 3H:  $\text{NCH}_3$ ), 4.81 (app. t, 1H:  $J = 8.5$  Hz,  $\text{R}_2\text{CHPh}$ ), 4.92 (m, 1H:  $\text{R}_2\text{CHBn}$ ), 5.64 (ddd, 1H:  $J = 3.5, 5.4, 8.5$  Hz,  $\text{NCHR}_2$ ), 7.18 (m, 1H: Ar CH) 7.25 (m, 1H: Ar CH's), 7.31 (m, 4H: Ar CH's), 7.37 (m, 3H: Ar CH's), 7.44 (m, 2H: Ar CH and Het Ar CH), 7.63 (dp, 2H:  $J = 1.6, 7.4$  Hz, Het Ar CH's), 7.71 (dd, 1H:  $J = 1.6, 7.3$  Hz, Het Ar CH).

#### Procedure for the synthesis of **2.164**.

The iodocyclization was performed *via* the described methods for these compounds. Then, an excess of  $\text{NaBH}_4$  was added to the reaction. After mixing, the reaction was monitored by  $^1\text{H}$  NMR spectroscopy where product **2.164** was tentatively identified in the reaction mixture.



3-benzyl-1-(iodomethyl)-4-methyl-2-phenyl-2,3,3a,4-tetrahydro-1H-benzopyrrolo[1,2-a]imidazole

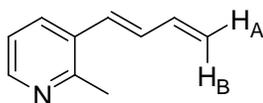
**2.164** (srm7014)

yield: 60% by  $^1\text{H}$  NMR

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.57 (m, 3H:  $\text{NCH}_3$ ), 2.95 (dd, 2H:  $J = 3.9, 10.0$  Hz,  $\text{CH}_2\text{Ph}$ ), 3.06 (m, 1H:  $\text{R}_2\text{CHBn}$ ) 3.19 (dd, 1H:  $J = 9.9, 11.4$  Hz,  $\text{R}_2\text{CHPh}$ ), 3.36 (m, 2H:  $\text{RCH}_2\text{I}$ ), 3.78 (m, 1H:  $\text{NCHRCH}_2\text{I}$ ), 5.22 (d, 1H:  $J = 5.1$  Hz,  $\text{N-CHR-N}$ ), 6.48 (dd, 1H:  $J = 1.1, 7.4$  Hz, Het Ar CH), 6.73 (dt, 1H:  $J = 1.3, 7.6$  Hz, Het Ar CH), 6.87 (dt, 1H:  $J = 1.3, 7.8$  Hz, Het Ar CH), 7.06 (dd, 1H:  $J = 1.3, 7.6$  Hz, Het Ar CH), 7.15 (m, 2H: Ar CH's), 7.20 (m, 2H: Ar CH's), 7.22 - 7.31 (m, 6H: Ar CH's).

#### Procedure for the synthesis of diene **2.166**.

Ester **2.165** was synthesized using the DCC/DMAP coupling of 2-pyridyl acetic acid hydrochloride with propargyl alcohol. To a Schlenk flask was added **2.165** (100 mg, 0.53 mmol) in toluene (5 mL). Then,  $\text{Pd}(\text{PPh}_3)_4$  (31 mg, 0.026 mmol) was added to the solution and the reaction was heated to 110 °C for 24 hours. The solution was cooled to room temperature, concentrated and directly purified *via* flash column chromatography (90:10 to 80:20 hexane:ethyl acetate). Diene **2.166** was isolated in 24% yield.



(E)-3-(buta-1,3-dienyl)-2-methylpyridine

**2.166** (srm7035)

yield: 24%

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.47 (s, 3H: Het $\text{CH}_3$ ), 5.14 (app. d, 1H:  $J = 9.5$  Hz,  $\text{H}_A$ ), 5.29 (dd, 1H:  $J = 1.7, 15.8$  Hz,  $\text{H}_B$ ), 6.43 (m, 2H:  $\text{CH}=\text{CHCH}_2$ ), 6.71 (m, 1H: Het $\text{CH}=\text{CH}$ ), 7.03 (d, 1H:  $J = 8.2$  Hz, Het Ar CH), 7.55 (dd, 1H:  $J = 2.4, 8.0$  Hz, Het Ar CH), 8.41 (d, 1H:  $J = 2.8$  Hz, Het Ar CH).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  24.2 ( $\text{CH}_3$ ), 118.4 ( $\text{CH}=\text{CH}_2$ ), 123.1 (Het Ar CH), 129.1 ( $\text{CH}=\text{CH}=\text{CH}_2$ ), 130.0 (quat. Het Ar C) 130.6 (Het $\text{CH}=\text{CH}$ ), 132.9 (Het Ar CH), 136.82 ( $\text{CH}=\text{CH}=\text{CH}_2$ ), 147.81 (Het Ar CH), 179.3 (quat. Het Ar C).

## 2.10 X-ray Crystallography Data for 2.160

### Comments

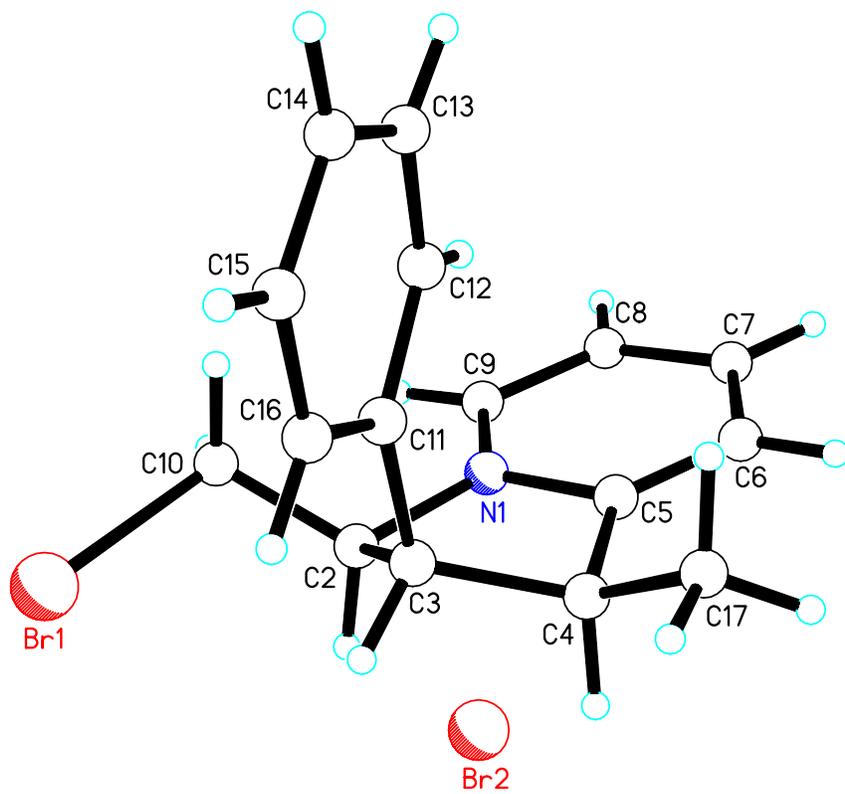
The asymmetric unit contains one  $[\text{C}_{16}\text{H}_{17}\text{BrN}]^+$  cation and one  $[\text{Br}]^-$  anion. All displacement ellipsoids are drawn at the 50% probability level. The authors thank the National Science Foundation (grant CHE-0079282) and the University of Kansas for funds to purchase the x-ray instrument and computers.

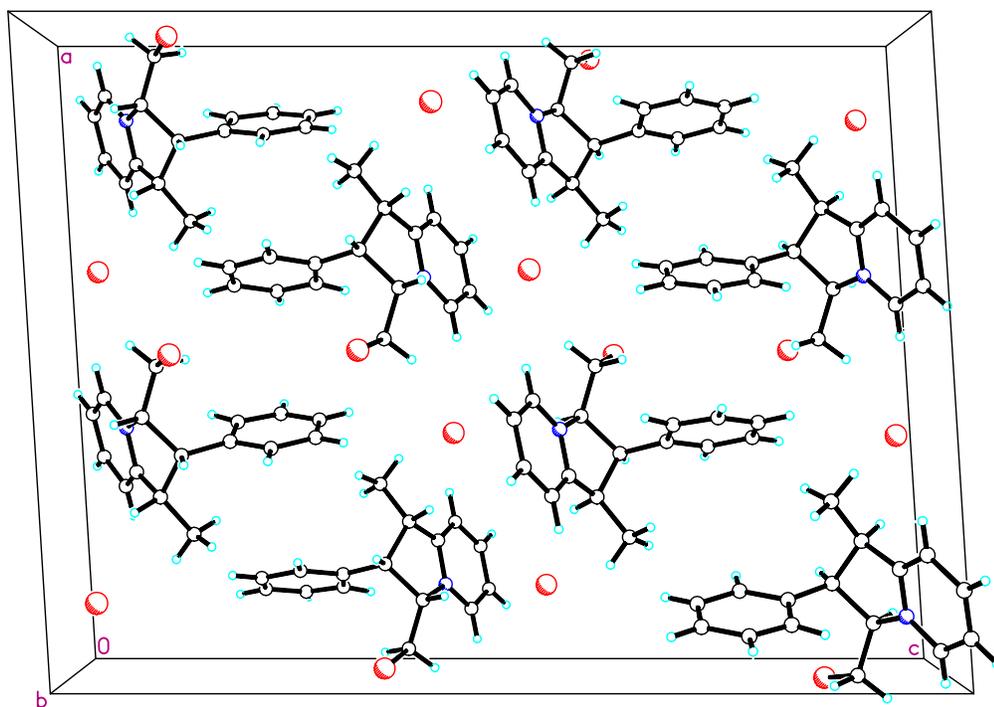
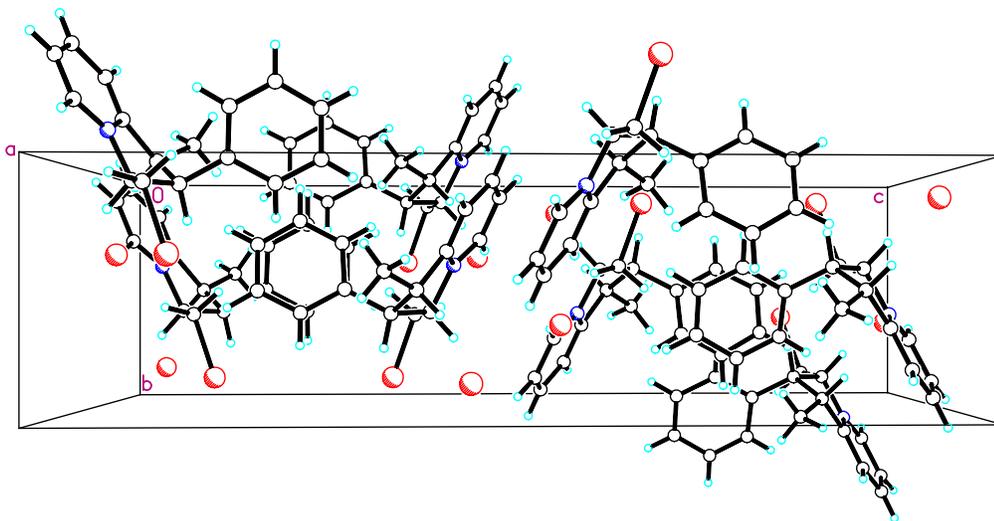
Colorless crystals of  $[\text{C}_{16}\text{H}_{17}\text{BrN}][\text{Br}]$  are, at 100(2) K, monoclinic, space group  $\text{C}2/c - \text{C}_{2h}^6$  (No. 15)(1) with  $\mathbf{a} = 18.373(5)$  Å,  $\mathbf{b} = 6.874(2)$  Å,  $\mathbf{c} = 24.778(6)$  Å,  $\beta = 93.551(5)^\circ$ ,  $V = 3123$  Å<sup>3</sup> and  $Z = 8$  anion/cation pairs  $\{\text{d}_{\text{calcd}} = 1.630$  g/cm<sup>3</sup>;  $\mu_a(\text{MoK}\alpha) = 5.178$  mm<sup>-1</sup>\}.<sup>137</sup> A full hemisphere of diffracted intensities (1850 40-second frames with a  $\omega$  scan width of  $0.30^\circ$ ) was measured for a single-domain specimen using graphite-monochromated MoK $\alpha$  radiation ( $\lambda = 0.71073$  Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System.<sup>138</sup> X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 1660 reflections. A total of 13202 integrated reflection intensities having  $2\theta(\text{MoK}\alpha) < 52.74^\circ$  were produced using the Bruker program SAINT;<sup>139</sup> 3205 of

these were unique and gave  $R_{\text{int}} = 0.118$  with a coverage which was 99.9% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.823 to 1.000. The Bruker software package SHELXTL was used to solve the structure using “direct methods” techniques. All stages of weighted full-matrix least-squares refinement were conducted using  $F_o^2$  data with the SHELXTL Version 6.10 software package.<sup>140</sup>

The single methyl group was incorporated into the structural model as a rigid group (using idealized  $sp^3$ -hybridized geometry and a C-H bond length of 0.98 Å) which was allowed to rotate about its C-C bond in least-squares refinement cycles. The remaining hydrogen atoms were included into the structural model as idealized atoms (assuming  $sp^2$ - or  $sp^3$ -hybridization of the carbon atoms and C-H bond lengths of 0.95 - 1.00 Å). The isotropic thermal parameters of all hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. A total of 173 parameters were refined using no restraints, 3205 data and weights of  $w = 1/[\sigma^2(F^2) + (0.0757 P)^2]$ , where  $P = [F_o^2 + 2F_c^2] / 3$ . Final agreement factors at convergence are:  $R_1$ (unweighted, based on F) = 0.068 for 1706 independent absorption-corrected “observed” reflections having  $2\theta(\text{MoK}\alpha) < 52.74^\circ$  and  $I > 2\sigma(I)$ ;  $R_1$ (unweighted, based on F) = 0.130 and  $wR_2$ (weighted, based on  $F^2$ ) = 0.168 for all 3205 independent absorption-corrected reflections having  $2\theta(\text{MoK}\alpha) < 52.74^\circ$ . The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference Fourier had maxima and minima of  $1.20 \text{ e}^-/\text{\AA}^3$  and  $-1.32 \text{ e}^-/\text{\AA}^3$ , respectively.





**Table 2.15.** Crystal data and structure refinement for [C<sub>16</sub>H<sub>17</sub>BrN][Br].

Empirical formula	C <sub>16</sub> H <sub>17</sub> Br <sub>2</sub> N	
Formula weight	383.13	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c – C <sub>2h</sub> <sup>6</sup> (No. 15)	
Unit cell dimensions	<b>a</b> = 18.373(5) Å	<b>α</b> = 90.000°
	<b>b</b> = 6.874(2) Å	<b>β</b> = 93.551(5)°
	<b>c</b> = 24.778(6) Å	<b>γ</b> = 90.000°
Volume	3123(1) Å <sup>3</sup>	
Z	8	
Density (calculated)	1.630 Mg/m <sup>3</sup>	
Absorption coefficient	5.178 mm <sup>-1</sup>	
F(000)	1520	
Crystal size	0.30 x 0.22 x 0.02 mm <sup>3</sup>	
Theta range for data collection	2.68° to 26.37°	
Index ranges	-22 ≤ h ≤ 22, -8 ≤ k ≤ 8, -30 ≤ l ≤ 30	
Reflections collected	13202	
Independent reflections	3205 [R <sub>int</sub> = 0.118]	
Completeness to theta = 26.37°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	1.000 and 0.823	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	3205 / 0 / 173	
Goodness-of-fit on F <sup>2</sup>	0.985	
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.068, wR <sub>2</sub> = 0.151	
R indices (all data)	R <sub>1</sub> = 0.130, wR <sub>2</sub> = 0.168	
Largest diff. peak and hole	1.20 and -1.32 e <sup>-</sup> /Å <sup>3</sup>	

$$R_1 = \frac{\sum ||F_O| - |F_C||}{\sum |F_O|}$$

$$wR_2 = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/2}$$

**Table 2.16** Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for  $[\text{C}_{16}\text{H}_{17}\text{BrN}][\text{Br}]$ . U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	U(eq)
Br(1)	4964(1)	8686(2)	1461(1)	41(1)
N(1)	3823(4)	3976(9)	727(3)	23(2)
C(2)	4005(5)	5890(12)	997(4)	29(2)
C(3)	3420(4)	5947(12)	1421(3)	22(2)
C(4)	2762(5)	4997(12)	1113(4)	27(2)
C(5)	3118(4)	3451(13)	791(3)	25(2)
C(6)	2858(5)	1764(12)	577(4)	29(2)
C(7)	3309(5)	585(13)	282(4)	31(2)
C(8)	4010(5)	1176(13)	209(4)	34(2)
C(9)	4272(5)	2915(12)	436(4)	26(2)
C(10)	4788(5)	6025(13)	1200(4)	34(2)
C(17)	2163(5)	4260(15)	1445(4)	40(3)
C(11)	3623(4)	4966(13)	1950(4)	26(2)
C(12)	3902(5)	3076(13)	1992(4)	33(2)
C(13)	4023(5)	2164(14)	2477(4)	34(2)
C(14)	3936(5)	3141(13)	2948(4)	31(2)
C(15)	3683(5)	5026(14)	2933(4)	35(2)
C(16)	3529(5)	5924(13)	2439(4)	33(2)
Br(2)	3736(1)	6429(1)	-490(1)	28(1)

**Table 2.17.** Bond lengths [Å] for [C<sub>16</sub>H<sub>17</sub>BrN][Br].

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Br(1)-C(10)	1.960(9)
N(1)-C(9)	1.345(10)
N(1)-C(5)	1.363(10)
N(1)-C(2)	1.505(10)
C(2)-C(10)	1.496(12)
C(2)-C(3)	1.549(12)
C(3)-C(11)	1.500(12)
C(3)-C(4)	1.535(11)
C(4)-C(17)	1.501(12)
C(4)-C(5)	1.503(12)
C(5)-C(6)	1.350(12)
C(6)-C(7)	1.398(12)
C(7)-C(8)	1.373(13)
C(8)-C(9)	1.394(12)
C(11)-C(12)	1.398(12)
C(11)-C(16)	1.401(12)
C(12)-C(13)	1.361(13)
C(13)-C(14)	1.365(13)
C(14)-C(15)	1.376(13)
C(15)-C(16)	1.384(13)

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**Table 2.18.** Bond angles [°] for [C<sub>16</sub>H<sub>17</sub>BrN][Br].

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C(9)-N(1)-C(5)	122.6(7)	N(1)-C(5)-C(4)	108.8(7)
C(9)-N(1)-C(2)	125.9(7)	C(5)-C(6)-C(7)	119.7(8)
C(5)-N(1)-C(2)	111.5(7)	C(8)-C(7)-C(6)	119.3(8)
C(10)-C(2)-N(1)	112.7(7)	C(7)-C(8)-C(9)	120.3(8)
C(10)-C(2)-C(3)	117.6(7)	N(1)-C(9)-C(8)	118.2(8)
N(1)-C(2)-C(3)	100.3(6)	C(2)-C(10)-Br(1)	107.7(6)
C(11)-C(3)-C(4)	112.8(7)	C(12)-C(11)-C(16)	115.8(9)
C(11)-C(3)-C(2)	115.9(7)	C(12)-C(11)-C(3)	123.6(8)
C(4)-C(3)-C(2)	102.2(7)	C(16)-C(11)-C(3)	120.6(8)
C(17)-C(4)-C(5)	114.2(8)	C(13)-C(12)-C(11)	122.3(9)
C(17)-C(4)-C(3)	117.0(8)	C(12)-C(13)-C(14)	120.4(9)
C(5)-C(4)-C(3)	102.1(7)	C(13)-C(14)-C(15)	119.8(9)
C(6)-C(5)-N(1)	119.9(8)	C(14)-C(15)-C(16)	119.6(9)
C(6)-C(5)-C(4)	131.3(8)	C(15)-C(16)-C(11)	121.8(9)

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**Table 2.19** Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for  $[\text{C}_{16}\text{H}_{17}\text{BrN}][\text{Br}]$ .  
 The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	$U_{11}$	$U_{22}$	$U_{33}$	$U_{23}$	$U_{13}$	$U_{12}$
Br(1)	35(1)	23(1)	64(1)	-10(1)	-6(1)	-2(1)
N(1)	24(4)	12(4)	33(4)	5(3)	8(3)	-1(3)
C(2)	32(5)	13(4)	41(6)	-1(4)	0(4)	6(4)
C(3)	15(4)	23(5)	29(5)	-6(4)	-3(4)	1(3)
C(4)	21(5)	20(4)	39(6)	13(4)	3(4)	6(4)
C(5)	23(4)	24(5)	27(5)	2(4)	3(4)	2(4)
C(6)	15(4)	28(5)	42(6)	8(4)	-7(4)	-2(4)
C(7)	34(5)	19(4)	36(6)	-2(4)	-11(4)	1(4)
C(8)	40(5)	21(5)	40(6)	-10(4)	2(4)	5(4)
C(9)	17(5)	22(5)	39(6)	-1(4)	-4(4)	4(4)
C(10)	31(5)	32(6)	39(6)	-16(4)	12(4)	-3(4)
C(17)	18(5)	48(6)	53(7)	-1(5)	5(4)	2(4)
C(11)	11(4)	31(5)	37(6)	0(4)	8(4)	-4(4)
C(12)	30(5)	28(5)	40(6)	-11(4)	1(4)	4(4)
C(13)	31(5)	26(5)	44(6)	5(5)	-2(5)	-3(4)
C(14)	27(5)	27(5)	39(6)	1(4)	0(4)	-7(4)
C(15)	35(6)	42(6)	28(6)	-3(5)	4(4)	-3(5)
C(16)	24(5)	28(5)	49(6)	-4(5)	8(4)	0(4)
Br(2)	25(1)	25(1)	34(1)	-1(1)	3(1)	-1(1)

**Table 2.20.** Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for  $[\text{C}_{16}\text{H}_{17}\text{BrN}][\text{Br}]$ .

	x	y	z	U(eq)
H(2)	3901	6958	729	34
H(3)	3299	7337	1494	27
H(4)	2545	5980	853	32
H(6)	2370	1379	627	34
H(7)	3132	-612	133	37
H(8)	4317	396	3	41
H(9)	4756	3338	386	32
H(10A)	5110	5724	905	40
H(10B)	4891	5083	1497	40
H(17A)	1753	3818	1204	59
H(17B)	2000	5309	1676	59
H(17C)	2345	3172	1670	59
H(12)	4011	2406	1672	39
H(13)	4169	838	2488	41
H(14)	4049	2522	3286	37
H(15)	3615	5707	3260	42
H(16)	3356	7227	2433	40

**Table 2.21.** Torsion angles [°] for [C<sub>16</sub>H<sub>17</sub>BrN][Br].

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C(9)-N(1)-C(2)-C(10)	-33.7(12)
C(5)-N(1)-C(2)-C(10)	149.0(8)
C(9)-N(1)-C(2)-C(3)	-159.6(8)
C(5)-N(1)-C(2)-C(3)	23.1(8)
C(10)-C(2)-C(3)-C(11)	-35.6(11)
N(1)-C(2)-C(3)-C(11)	87.0(8)
C(10)-C(2)-C(3)-C(4)	-158.6(7)
N(1)-C(2)-C(3)-C(4)	-36.0(7)
C(11)-C(3)-C(4)-C(17)	37.1(10)
C(2)-C(3)-C(4)-C(17)	162.2(7)
C(11)-C(3)-C(4)-C(5)	-88.3(8)
C(2)-C(3)-C(4)-C(5)	36.8(8)
C(9)-N(1)-C(5)-C(6)	2.9(13)
C(2)-N(1)-C(5)-C(6)	-179.7(8)
C(9)-N(1)-C(5)-C(4)	-177.2(7)
C(2)-N(1)-C(5)-C(4)	0.2(9)
C(17)-C(4)-C(5)-C(6)	28.9(14)
C(3)-C(4)-C(5)-C(6)	156.1(9)
C(17)-C(4)-C(5)-N(1)	-151.0(8)
C(3)-C(4)-C(5)-N(1)	-23.8(9)
N(1)-C(5)-C(6)-C(7)	-1.3(13)
C(4)-C(5)-C(6)-C(7)	178.9(9)
C(5)-C(6)-C(7)-C(8)	-0.7(14)
C(6)-C(7)-C(8)-C(9)	1.2(14)
C(5)-N(1)-C(9)-C(8)	-2.4(12)
C(2)-N(1)-C(9)-C(8)	-179.4(8)
C(7)-C(8)-C(9)-N(1)	0.3(13)
N(1)-C(2)-C(10)-Br(1)	173.4(6)
C(3)-C(2)-C(10)-Br(1)	-70.6(9)
C(4)-C(3)-C(11)-C(12)	67.2(10)
C(2)-C(3)-C(11)-C(12)	-50.1(11)
C(4)-C(3)-C(11)-C(16)	-112.1(9)

C(2)-C(3)-C(11)-C(16)	130.6(8)
C(16)-C(11)-C(12)-C(13)	4.9(13)
C(3)-C(11)-C(12)-C(13)	-174.4(8)
C(11)-C(12)-C(13)-C(14)	-5.9(15)
C(12)-C(13)-C(14)-C(15)	3.7(14)
C(13)-C(14)-C(15)-C(16)	-0.9(14)
C(14)-C(15)-C(16)-C(11)	0.1(14)
C(12)-C(11)-C(16)-C(15)	-2.0(13)
C(3)-C(11)-C(16)-C(15)	177.3(8)

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