University of Alberta

α-*Exo*-Alkylidene γ-Lactones and γ-Lactams via 2-Alkoxycarbonyl Allylboronates: Mechanistic Studies, Diversity-Oriented Synthesis and Target-Oriented Synthesis

by

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All for the glory of God

Abstract

Allylboration reactions have been thoroughly utilized in organic chemistry since it was discovered that they could add in a nucleophilic fashion to aldehydes and ketones in 1964. Modification of allylboronates and the substrates that they can react with has been the focus of many research groups over the past three decades. Recent works have made use of catalysis to promote the addition of allylboronates that are generally otherwise unreactive toward various electrophiles. Chapter 2 will discuss the discovery that Brønsted acids can catalyze the addition of unreactive 2-alkoxycarbonyl allylboronates to aldehydes and that the diastereoselectivity of the reaction is determined by the electronic nature of the aldehyde.

Ketones and imines are much less reactive than aldehydes towards allylboronates due to steric and electronic factors. As a result, new conditions are often required to promote the allylboration reaction of ketones and imines. Chapter 3 will briefly discuss the challenges that ketones present as substrates for allylboration reactions and show my attempts at achieving this transformation. Chapter 4 will describe imines and their associated challenges as substrates for allylboration reactions. However, once harnessed, these substrates provide easy access to α-methylene γ-lactones when a 2-alkoxycarbonyl allylboronate is used as the allylating reagent.

The modification of important or interesting molecules by making major or minor changes to a common core structure is the basis of diversity-oriented synthesis of combinatorial libraries. α-Alkylidene γ-lactones and α-alkylidene γ-lactams are biologically interesting compounds present in numerous natural products. Chapter 5 will discuss how the title compounds were modified by various metal-catalyzed coupling reactions to provide a diversity-oriented combinatorial library of γ-lactones and γ-lactams. Since γ-lactones are prevalent in many natural products, the application of 2-alkoxycarbonyl allylboronates to a target-oriented synthesis was intriguing. Unlike diversity-oriented synthesis, target oriented synthesis aims at synthesizing a single compound through any number of controlled steps, arriving at one specific product that is obtained as a pure isomer. Access to highly complex γ-lactones is often tedious, however, Chapter 6 will discuss how a simple, one-step allylboration reaction of a complex aldehyde with a 2-alkoxycarbonyl allylboronate can lead to a highly substituted γ-lactone. This γ-lactone can be further modified and transformed into chinensiolide B, a biologically active natural product isolated from a plant found in various locations in China.

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List of Abbreviations

Ac	Acetyl
acac	Acetylacetone
Ar	Aryl group
9-BBN	9-Borabicyclononane
B-CCB	B-Chlorocatecholborane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BQ	Benzoquinone
br	Broad
BRSM	Based on recovered starting material
Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
Calcd	Calculated
cm^{-1}	Wavenumbers
COD	Cyclooctadiene
dba	*trans*,*trans*-Dibenzylideneacetone
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dddd	Doublet of doublet of doublet of doublets
ddm	Doublet of doublet of multiplets
DIBALH	Diisobutylaluminum hydride
DCBQ	2,6-Dichlorobenzoquinone

dm	Doublet of multiplets
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron Impact
Elem. Anal.	Elemental Analysis
equiv	Equivalents
er	Enantiomeric ratio
ESI	Electrospray Ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
G-I	Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
G-II	1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene) (dichlorophenylmethylene)(tricyclohexylphosphine) ruthenium
HG-II	(1,3-Bis-(2,4,6-trimethylphenyl) -2-imidazolidinylidene)dichloro (o-isopropoxyphenylmethylene) ruthenium
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry

IR	Infrared Spectroscopy
LA	Lewis Acid
m	Multiplet
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeOH	Methanol
Nu	Nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
p	Pentet
PDC	Pyridinium dichlorochromate
Ph	Phenyl
pin	Pinacolato
PMA	Phosphomolybdic Acid
Pr	*n*-Propyl
^{i}Pr	*iso*-Propyl
PTAB	Phenyltrimethylammonium perbromide
PTSA	*para*-Toluenesulfonic acid
q	Quartet
qt	Quartet of triplets
R	Generic alkyl group
RCM	Ring-closing metathesis
rt	Room temperature
t	Triplet

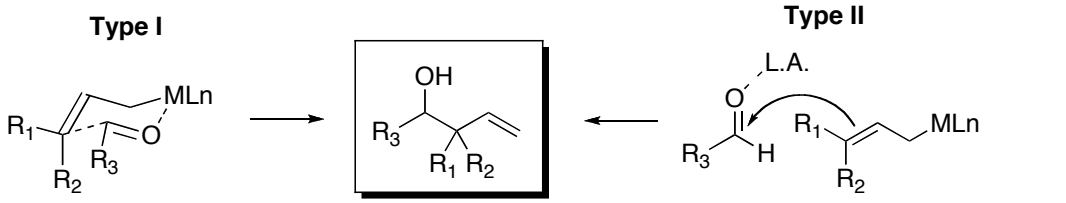
TBAF	Tetra-*n*-Butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	Tetrahydrofuran
TfOH	Trifluoromethane sulfonic acid
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl
μw	Microwave heating
xylyl	3-Methyltoluene

Chapter 1

Allylboration Chemistry: Associated Deficiencies With Unreactive Allylic boronates and Unreactive Substrates

1.1 Allylboration chemistry

Over the past three decades, the use of allylboronates for the stereocontrolled formation of carbon–carbon bonds in organic synthesis has increased vastly and has become an invaluable tool to synthetic chemists.[1,2] The popularity and use of allylation chemistry in the context of total synthesis is rivaled only by the use of modern asymmetric aldol methodologies. There are several excellent methodologies present in the literature that make use of a variety of allyl reagents based on boron, silicon, tin and titanium for carbonyl allylation reactions. In the early 1980's, Denmark and Weber developed a classification system for allylation reagents that takes into account their proposed mechanism of addition to the carbonyl moiety (Figure 1.1).[3]



- No added Lewis acid necessary
- Proceed via rigid chairlike T.S.
- Diastereospecific and diastereoselective

- Require Lewis acid activation (L.A.)
- Proceed via open T.S.
- Not diastereospecific, usually diastereoconvergent

Figure 1.1: Classification system for Type I and Type II allylation reagents[3]

Allylic boronates belong to the Type I class of reagents and are involved in closed, Zimmerman–Traxler chair-like transition states whereby activation of the carbonyl group is achieved by the boron atom in the allylic boronate reagent.[4,5] The stereochemistry present in the final propionate unit is dictated by the stereochemistry of the crotylation reagent: *Z*-crotyl leads to products with *cis* stereochemistry while *E*-crotyl provides products with *trans* stereochemistry. Allylic trialkyl tin reagents have also been shown to behave like Type I reagents, but only at high temperatures.[6] In contrast, most other allylation reagents based on silicon, titanium, chromium and other metals fall into the Type II class of reagents. These allylation reagents actually require that an additional Lewis acid be added to the reaction mixture in order for useful reaction times to be obtained. Due to the compact transition state observed for Type I reagents, carbonyl allylation proceeds with a level of diastereoselectivity that is generally far superior to that of the Type II silicon and tin reagents.

Organotitanium, organochromium and organozirconium reagents exemplify the lesser-known Type III reagents.[1] They are *anti* selective regardless of the geometry of the crotyl metal unit due to extremely rapid equilibration of the crotyl metal species to the more stable *E* isomer. Open-chain and chair-like transition structures have been invoked to rationalize the stereochemical outcome of aldehyde additions with these reagents.

Many carbonyl allylation reactions have also been shown to proceed in the presence of various organic and metallic catalysts in stoichiometric and substoichiometric amounts.[7] However, there have been significantly fewer reports of allylboration reactions that make use of any type of catalysts. The main use of allylboronates to date has been in the context of aldehyde allylation, whereby homoallylic secondary alcohols are formed via an allyl transfer reaction with aldehydes (Figure 1.2).[1,2,8-11] The synthesis of allylboronates has been studied in great depth, as the substitution pattern on the allylboronate dictates the type of reactions that can be used in the preparation of these important reagents.[12] Even though 2-alkoxycarbonyl allylboronates were crucial to the research carried out in

this thesis, the synthesis of these allylboronates will not be discussed in great detail.

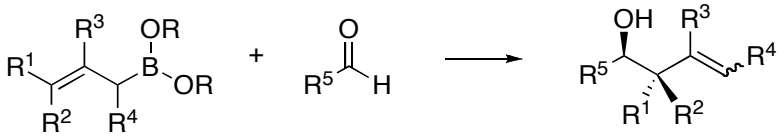


Figure 1.2: General structure of allylboronates and their stereoselective addition to aldehydes

1.2 α-Methylene γ-lactones and α-methylene γ-lactams

1.2.1 Importance and abundance in nature

The α-methylene γ-lactone ring is a key structural motif in many natural products, most notably the sesquiterpene lactones (Figure 1.3). In 1985, it was estimated that approximately 10% of the known 30,000 natural products contained this α-methylene γ-lactone functionality.[13] As the number of natural products that contain a α-methylene γ-lactone group has increased, more and more interest is being shown in these compounds due to their unique biological properties. In many cases, the high bioactivity of these compounds is due to the presence of the electrophilic exocyclic enoate moiety, which can trap nucleophilic residues present in the active site of the target enzyme. These natural products have shown to be quite useful as DNA polymerase inhibitors, nuclear vitamin D receptor inhibitors, cellular steroidal inhibitors, blockers of tumor necrosis factor-α production, as well as many other uses.[14] The wide inhibitory action of these natural products makes them potential drug candidates due to their cytotoxic, antiallergenic, anti-inflammatory, phytotoxic, and antimicrobial properties.[15] In fact, arglabin (Figure 1.3) has been used successfully in Kazakhstan for the treatment of breast, colon, ovarian, and lung cancers.[16]

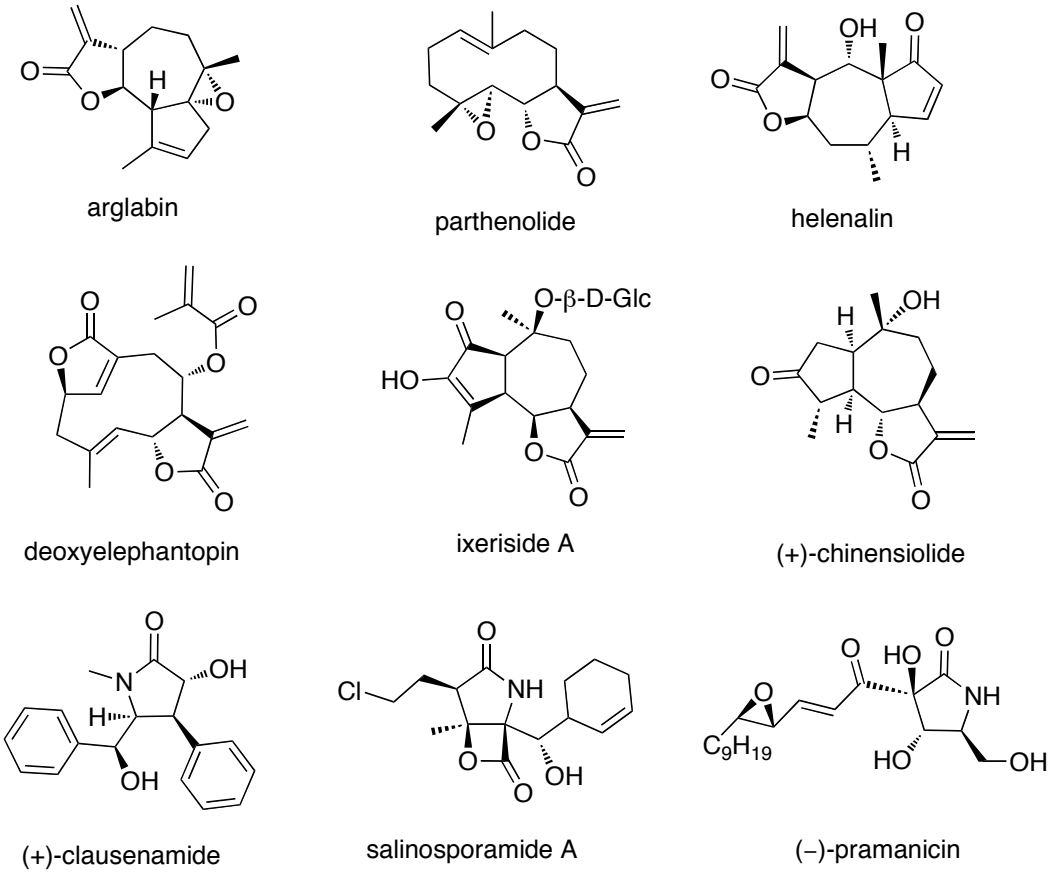


Figure 1.3: Selected natural products containing an α-methylene γ-lactone or γ-lactam ring

One closely related type of compound to the γ-lactones is the α-methylene γ-lactam scaffold (Figure 1.3). Even though there are significantly fewer reports compared to the γ-lactones, several natural products containing a γ-lactam ring are also known,[17] and these compounds also exhibit interesting biological properties in their own right.[18]

1.2.2 Traditional methods for the synthesis of α-methylene γ-lactones

As a result of the biological importance of these natural products, the synthesis of polysubstituted α-methylene γ-lactones has been of interest to synthetic chemists for several years. Several routes have been devised to access

the α-methylene γ-lactone ring, however, they tend to be lengthy and cumbersome if the lactone contains any sort of substitution.[19] A review by Hoffmann and Rabe in 1985 discussed some of the methods developed up to that day regarding the synthesis of α-methylene γ-lactones (Figure 1.4).[13]

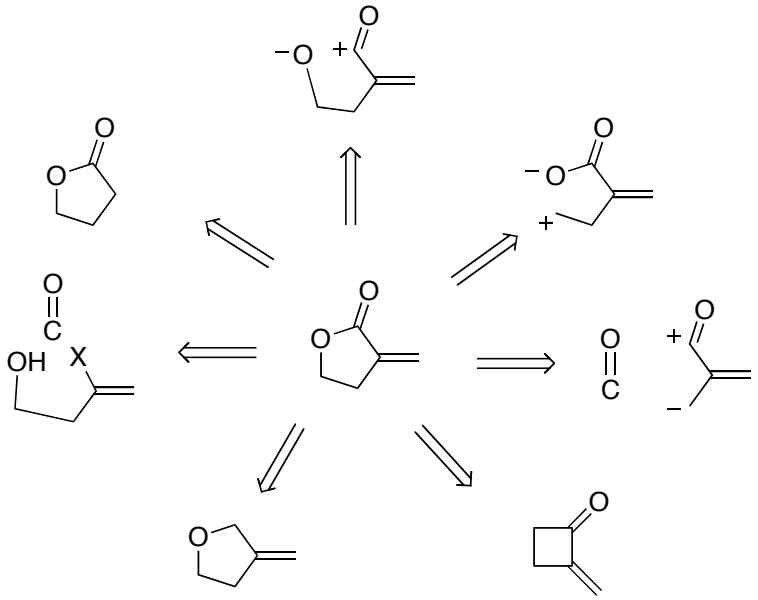
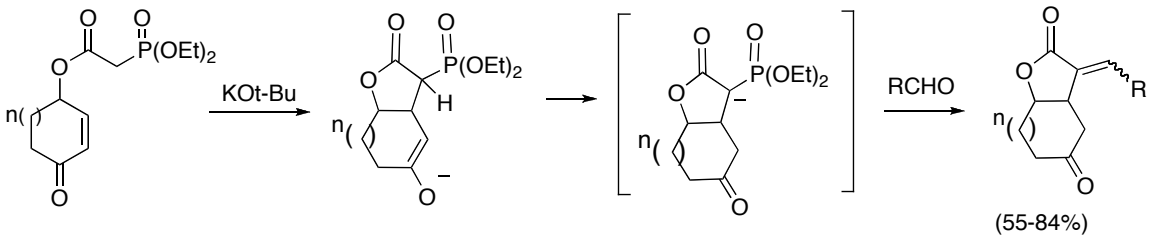


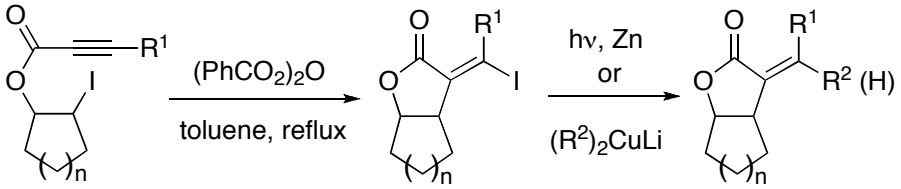
Figure 1.4: Various retrosynthetic routes to α-methylene γ-lactones discussed by Hoffmann and Rabe

Since that time, there have been other direct and indirect methods developed for the synthesis of these key structures.[20] Wittig–Horner–Emmons–Wadsworth olefinations utilizing cyclic phosphonate precursors can lead to both α-methylene and α-alkylidene γ-lactone products.[21] Using a similar approach to access bicyclic α-alkylidene γ-lactones, Taylor and co-workers developed a "one-pot" process initiated by the conjugate addition of tethered phosphonate stabilized anions (Equation 1.1).[22] The resulting enolate product undergoes a proton transfer to provide a second phosphonate substituted carbanion that can condense with various aldehydes.



Equation 1.1: One-pot conjugate addition/ HEW reaction to access α-alkylidene γ-lactones

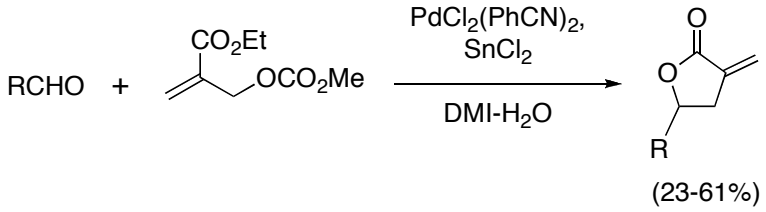
Another approach to bicyclic α-alkylidene γ-lactones requires the preparation of iodinated alkynoate precursors that can undergo a radical cyclization (Scheme 1.1).[23] The resulting alkenyl iodide can be reduced with zinc to provide the trisubstituted alkene or can be further substituted with organocopper reagents to give the desired γ-lactones with a tetrasubstituted alkene.



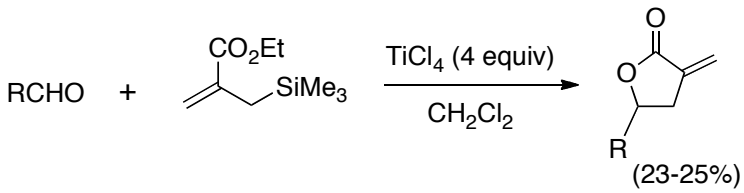
Scheme 1.1: Radical cyclization route to α-alkylidene γ-lactones

Other more direct methods make use of reagents that already have the methylene pre-installed or established during the cyclization process. Traditional carbonyl allylation chemistry based on silicon and tin reagents has long been used to access α-methylene γ-lactones. Tin-based reagents add to aldehydes readily at low temperatures but require an excess amount of strong Lewis acid.[24] Masuyama and co-workers developed an indirect, in-situ method to prepare allylic tin reagents from the corresponding allylic carbonates, as shown in Equation 1.2.[25] Under palladium catalysis, the transient allylic palladium complex that is generated transmetallates to tin to make a new allylic tin reagent, which subsequently adds to the aldehyde to provide γ-lactones in modest yields. Not surprisingly, the analogous silicon reagents are much less reactive and require

higher reaction temperatures (Equation 1.3).[26] Even under these conditions, reactions with aldehydes provide low yields.

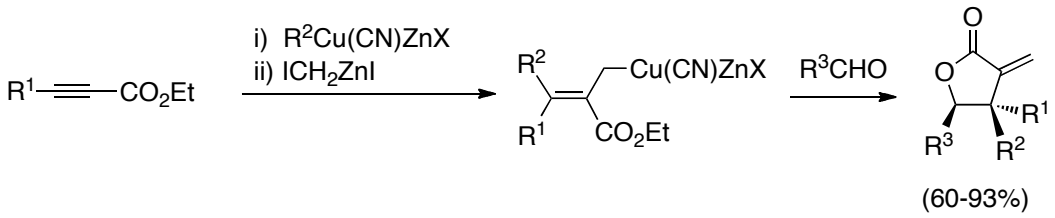


Equation 1.2: Palladium-mediated allylation reaction using *in situ* prepared allyl tin reagents to access α-methylene γ-lactones



Equation 1.3: Titanium-catalyzed allylsilation reaction to form α-methylene γ-lactones

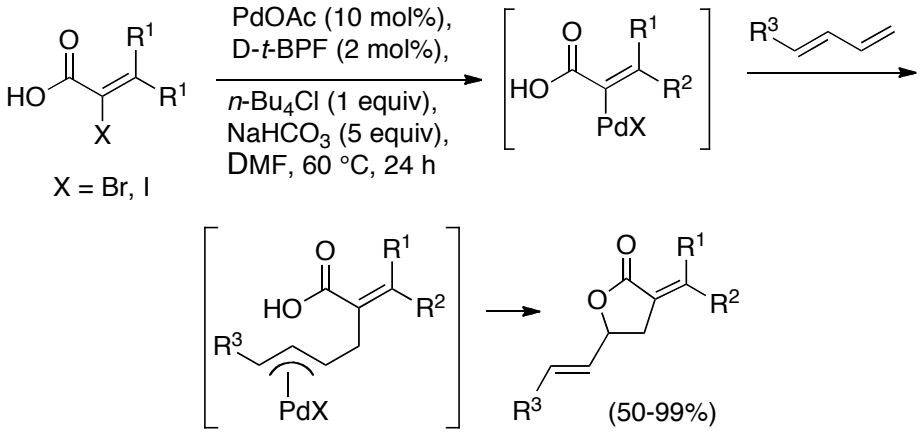
Sidduri and Knochel have utilized a mixed zinc–copper reagent that has allowed for the one-pot preparation of α-methylene γ-lactones (Scheme 1.2).[27] The desired allylation reagents are formed with high selectivity in the *cis*-carbocupration, and the diastereoselectivity of aldehyde additions is high, which suggests a Type I chair-like transition state similar to allylboration reactions.



Scheme 1.2: Preparation of mixed allylcopper-tin reagent and its addition to aldehydes to form α-methylene γ-lactones

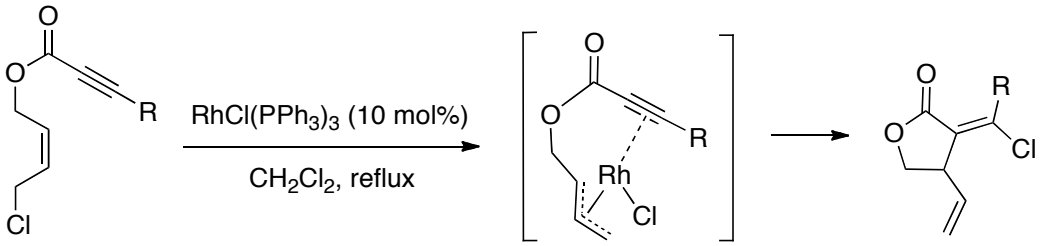
Barbier-type additions are attractive methods because the required allylic halide precursors are often commercially available, and are more stable than a pre-formed organometallic reagent. Zinc reagents can be prepared from zinc powder.[28] The cyclization occurs under the reaction conditions, however, the diastereoselectivity of the reactions tends to be poor with 3-substituted reagents. Zinc-mediated Barbier-type allylations are mild enough for use with functionalized substrates. For example, Yang and co-workers have made use of a zinc-mediated Barbier reaction with either aldehydes or methyl ketones to form α-methylene γ-lactones containing novel indole substituents that were tested as inhibitors of kinase enzymes.[29] Indium has also been used in Barbier-type additions and it has the advantage of being compatible with aqueous conditions and the reactions occur readily at room temperature.[30]

With the rise of cross-coupling chemistry mediated by various transition metals, new methods of α-alkylidene γ-lactone formation are appearing. Gagnier and Larock developed a heteroannulation method mediated by palladium utilizing α-halo alkenoic acids and substituted butadienes (Equation 1.4).[31] Under palladium catalysis in the presence of a bulky phosphine, (di-*t*-butylphosphino) ferrocene, a cascade process leads to α-alkylidene γ-lactones in moderate to high yields.



Equation 1.4: Palladium-mediated cyclization reaction to access α-alkylidene γ-lactones

In a similar fashion, Zhang and co-workers have made use of a rhodium-catalyzed cycloisomerization protocol utilizing tethered 1,6-enynes as an efficient route to α-alkylidene γ-lactones containing a β-vinyl group and various substituents on the exo-alkene as shown in Equation 1.5.[32] In the presence of a cationic rhodium catalyst, a rhodium π-allyl species is formed that coordinates to the pendant alkyne. Subsequent carborhodation forms the γ-lactone ring of the final product and this is followed by reductive elimination to generate the vinyl chloride. Various alkyl and aryl substituents are tolerated on the end of the alkyne; however, bulky groups on the alkyne or substrates with another carbonyl group in conjugation to the alkyne are not tolerated. Zhang and co-workers have also made use of similar substrates with allylic alcohols instead of allylic chlorides and subjected them to an intramolecular rhodium-catalyzed Alder ene reaction, thus accessing α-alkylidene γ-lactones containing an aldehyde substituent in the β-position.[33]

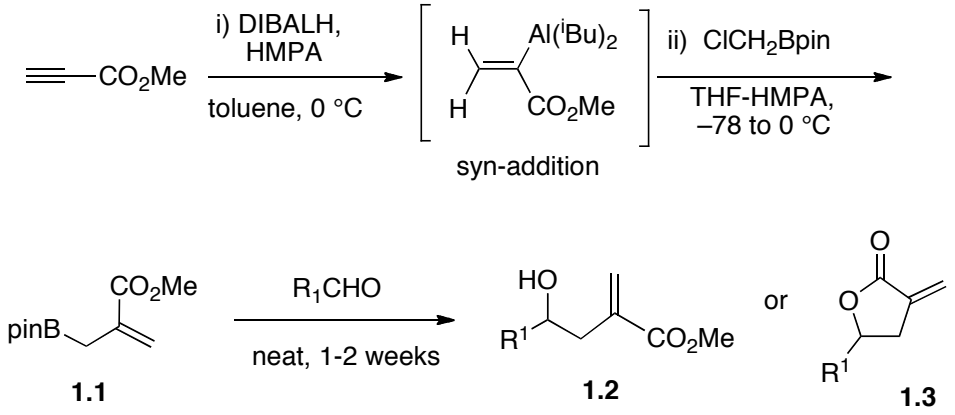


Equation 1.5: Rhodium-mediated cyclization to form α- alkylidene γ-lactones

1.2.3 Use of 2-alkoxycarbonyl allylboronates to form α-methylene γ- lactones

Allylic boronates containing a carboxyl group in the two-position are known as 2-alkoxycarbonyl (or 2-carboalkoxy) allylboronates. The first report describing the preparation of unsubstituted 2-alkoxycarbonyl allylboronate reagents, and their subsequent addition to aldehydes to form α-methylene γ-lactones, was disclosed by Villiéras and co-workers in 1993.[34] The desired 2-alkoxycarbonyl allylboronate **1.1** was prepared in a stereoselective fashion via a

regioselective hydroalumination of methyl propiolate followed by trapping of the resulting alkenyl aluminum species with highly electrophilic halomethylboronic esters (Scheme 1.3). The resulting 2-alkoxycarbonyl allylboronate reagent **1.1** was combined with various aldehydes to provide the expected alcohols **1.2** after a long reaction time of almost two weeks at room temperature. When the reactions were performed in toluene at reflux, the reaction time was slightly decreased and a significant proportion of lactonized product **1.3** was isolated.



Scheme 1.3: Synthesis and reactivity of 2-alkoxycarbonyl allylboronate **1.1** with aldehydes

1.3 Reactivity of 2-alkoxycarbonyl allylboronates towards aldehydes

In the past, the reactivity of allylic boronates has typically been modulated by varying the two substituents on the boron atom, thus achieving the desired reaction rate. This has been met with success in the context of various allylboranes and boronates and their additions to aldehydes.[34-44] The same cannot be said about 2-alkoxycarbonyl allylboronates, as these allylboronates have completely different reactivity profiles. Their reactivity is highly attenuated due to the electron withdrawing nature of the ester group at the 2-position. This

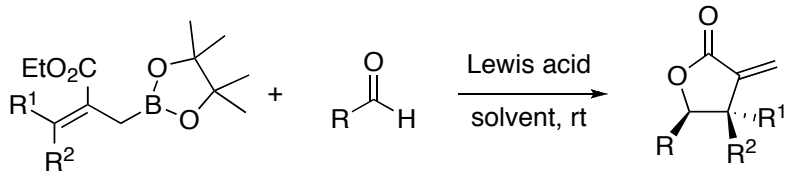
conjugation creates a less nucleophilic γ-carbon and results in very unreactive allylboronates. The issue of reactivity cannot simply be modulated by varying the boron substituents like other allylboronates and allylboranes. If one desires to increase their reactivity, then one must envisage the use of a catalyst. Other allylation reagents are used in combination with external catalysts, so the concept of catalyzing an allylboration reaction through the use of external Lewis or Brønsted acids is an option. However, until very recently, the notion of catalyzing an allylboration reaction through the use of an external activator seemed preposterous based on its classification as a Type I allylation reagent.

1.4 Lewis acid-catalyzed additions of allylic boronates to aldehydes

The idea to catalyze an allylboration reaction would seem to be counterintuitive when one considers the mechanism and transition state of an allylboration reaction. Again, allylboronates are Type I reagents, and hence, the boron atom acts as the carbonyl activator in the six-membered transition state. Adding anything that might disrupt this highly organized, compact transition state might prove to be disastrous for the diastereoselectivity of the allylboration reaction. An added activating group might induce a change from a Type I mechanism to a Type II mechanism, which proceeds through an open transition state. One of the main advantages of allylboronates is this Type I mechanism and its associated diastereospecificity, and to possibly lose control of this benefit would be a significant step backward for allylboration chemistry. Be that as it may, two research groups went against the prevailing perception of the times and attempted to catalyze an allylation reaction between an allylboronate and an aldehyde.[46]

The first[47] report in 2002 by Kennedy and Hall showed that both scandium (III) triflate and copper (II) triflate were capable of acting as Lewis acid catalysts

in the allylation reaction between 2-alkoxycarbonyl allylboronates and various aldehydes (Equation 1.6).[48] The uncatalyzed allylboration reaction of benzaldehyde is very slow. To form the desired γ-lactone takes almost two weeks when the reaction is carried out at room temperature. However, in the presence of 10 mol% of $Sc(OTf)_3$, the reaction requires only 12 hours to reach completion.



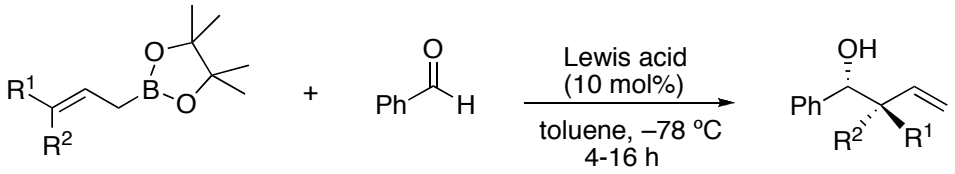
Equation 1.6: Lewis acid-catalyzed addition of 2-alkoxycarbonyl allylboronates to aldehydes

It was also noted that the initially formed homoallylic alcohol underwent *in situ* lactonization to form the γ-lactone product. Previously, it had been necessary to treat the homoallylic alcohol product with a solution of *para*-toluenesulfonic acid in order to induce lactonization. Various 2-alkoxycarbonyl allylboronates and aldehydes were tested as substrates for this new catalytic allylboration reaction, and the reaction proved to be quite general. Both electron deficient and electron rich aromatic aldehydes were suitable substrates, along with linear and branched aliphatic aldehydes.

The stereospecificity of this new catalytic allylboration manifold was also investigated, as that was the most important and possibly limiting factor in this new reaction. However, it was found that the diastereoselectivity of the allylboration reaction catalyzed by the Lewis acids was identical to the selectivity observed for the corresponding thermal reaction. This key result provided compelling evidence against the notion that additional activating compounds would disrupt the expected transition state in an allylboration reaction between allylic boronates and aldehydes.

The report by Kennedy and Hall was closely followed by a report by Miyaura and co-workers in which they also described the ability of Lewis acids to

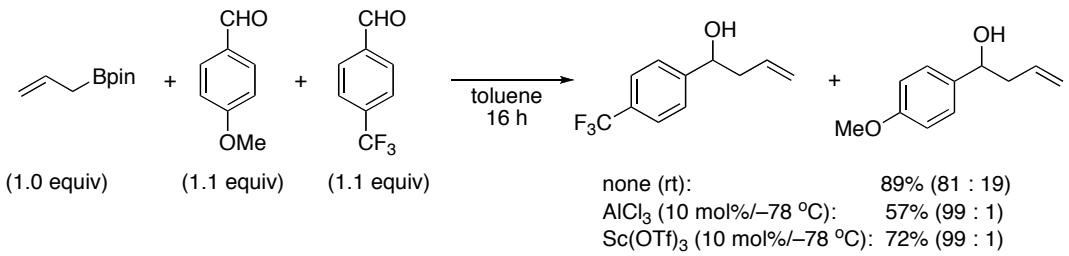
catalyze allylic boronate addition reactions to aldehydes in a diastereospecific manner.[49] Even though this report did not make use of the unreactive 2-alkoxycarbonyl allylboronates, the concept of catalyzing a slow allylboration reaction is still the predominant factor and thus worth discussing. Various Lewis acids were screened for their ability to catalyze the addition of pinacol allylboronate with benzaldehyde (Table 1.1).



Entry	Boronate	Lewis Acid	Yield (%)	Anti/Syn
1	$R^1 = H, R^2 = H$	$TiCl_4$	63	-
2	$R^1 = H, R^2 = H$	$BF_3 \bullet OEt_2$	56	-
3	$R^1 = H, R^2 = H$	$SnCl_4$	30	-
4	$R^1 = H, R^2 = H$	$AlCl_3$	88	-
5	$R^1 = H, R^2 = H$	$Sc(OTf)_3$	80	-
6	$R^1 = Me, R^2 = H$	$AlCl_3$	92	99/1
7	$R^1 = H, R^2 = Me$	$AlCl_3$	87	2/98

Table 1.1: Addition of allyl- and crotylboronates to benzaldehyde catalyzed by Lewis acids[49]

The reaction did not proceed in the absence of a Lewis acid, and several Lewis acids did show an ability to catalyze the allylboration reaction. It was noted that $Sc(OTf)_3$ and $AlCl_3$ showed the highest catalytic activity and provided the desired homoallylic alcohol in 16 h when the reaction was performed at –78 °C. Again, either aromatic or aliphatic aldehydes proved to be suitable substrates for this catalytic allylboration reaction, as well as α,β-unsaturated aldehydes. An investigation into the selective allylation of one aldehyde over another showed that in the presence of a Lewis acid, a more electron poor aldehyde could be allylated in the presence of a more electron rich aldehyde with complete selectivity (Equation 1.7). This selectivity is better than that observed in the thermal case, whereby a mixture of allylboration products is obtained.



Equation 1.7: Selective allylboration of aldehydes in the presence of a Lewis acid

The diastereoselectivity of the Lewis acid-catalyzed allylboration reaction was investigated for the reasons mentioned earlier. As observed by Miyaura and co-workers, the addition of either the *E*- or *Z*-crotyl allylboronate provided the isomerically pure *anti*- and *syn*-homoallylic alcohols, respectively (entries 6 and 7, Table 1.1). These results were in agreement with those of Hall and co-workers and further confirmed that Lewis acid activation of allylboronates occurred without disrupting the chair-like six-membered transition state typical of Type I allylation reagents.

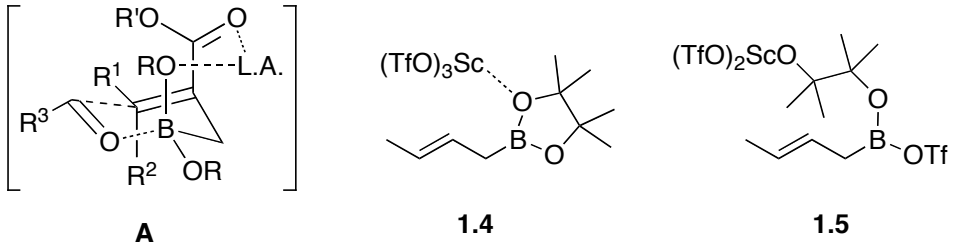
1.5 Mechanistic investigations of Lewis acid-catalyzed allylboration reactions

1.5.1 Control experiments and NMR studies

In the initial report by Kennedy and Hall, various control experiments were performed to investigate the exact nature of the Lewis acid activation in the allylboration reaction and to rule out the possibility that trace amounts of triflate ion or adventitious TfOH were acting as the catalyst for this reaction.[48] Furthermore, it turned out that the 2-alkoxycarbonyl substituent on the allylboronate was not necessary for this catalytic action to occur. Allylboronates that did not have the carbonyl-containing group at the 2-position also showed increased reaction rates with aldehydes, however, this rate enhancement was smaller.[48] NMR studies were performed that supported binding of the Lewis acid

to one of the oxygens on the allylboronate. This led to the proposition that the metal ion was coordinating to both the 2-alkoxycarbonyl ester and a boronate oxygen through a seven-membered complex **A** (Figure 1.5) within the usual Zimmerman–Traxler chair-like transition state for Type I allylation reagents. The rationale for this was that the metal ion would increase the acidity of boron, thus strengthening the interaction between the boron atom and the aldehyde oxygen.

A few years after these initial reports by the groups of Hall and Miyaura, more mechanistic work was described that helped to explain fully the observed catalysis. Allylboronates with chiral diols that were subjected to Lewis acid catalysis provided enantioenriched products,[50] thereby making transmetallation from boron to the Lewis acid improbable. ^{11}B and ^{1}H NMR spectroscopic studies indicated no complex between *E*-crotyl pinacol boronate and $Sc(OTf)_3$, thereby undermining the possibility of a Lewis acid-allylboronate complex **1.4** in the rate-limiting step (Figure 1.5).[51] This also rules out the notion of dioxaborolane opening to form highly electrophilic boron triflate species **1.5**.



A **1.4** **1.5**

Figure 1.5: Possible Lewis acid-allylboronate complexes and transition state to explain the catalytic activity

The rate order for the $Sc(OTf)_3$-catalyzed addition of *E*-crotyl pinacol boronate to *p*-tolualdehyde was first order for both the allylboronate and the aldehyde, thereby eliminating the possibility of a unisubstrate-scandium complex in the rate-determining step.[51] All of this data tentatively points to two possible modes of activation: coordination to one of the lone pairs of electrons on the allylboronate (**A**, Figure 1.6) or double coordination of the aldehyde to the Lewis acid and to the boron atom of the allylboronate reagent (**B**, Figure 1.6).

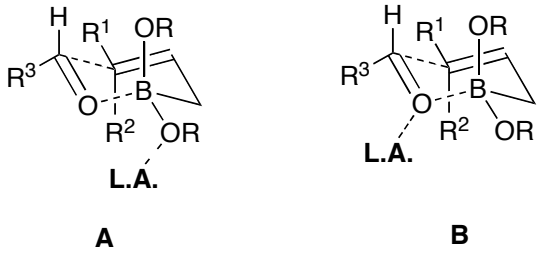
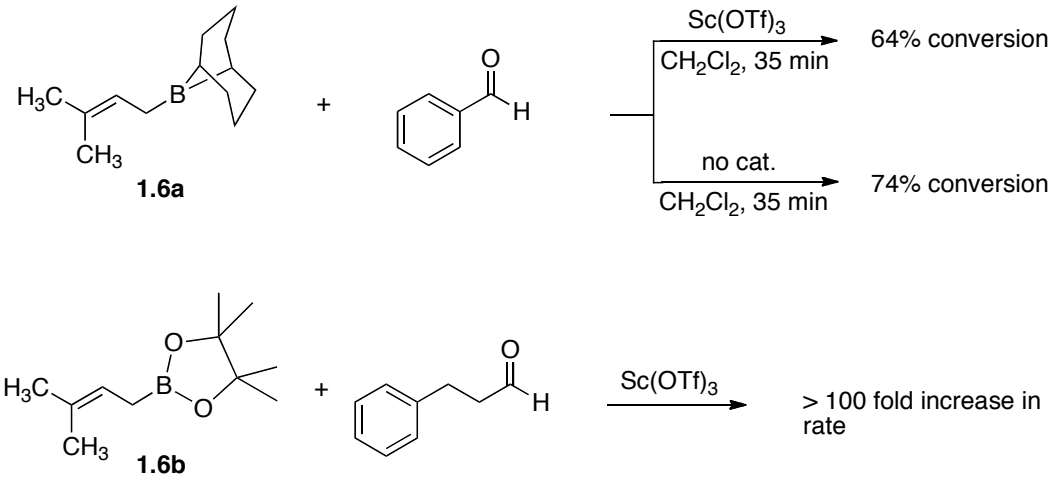


Figure 1.6: Possible transition states with Lewis acid activation

At a glance, both of these possibilities appear equally reasonable. To distinguish between the two, prenyl-BBN **1.6a** was used in a reaction with hydrocinnamaldehyde at −78 °C in the presence and absence of $Sc(OTf)_3$.[51] No appreciable rate acceleration was observed when the Lewis acid was present (Scheme 1.4). This is in stark contract with the >100 rate enhancement observed when prenyl pinacol boronate **1.6b** is used as the allylation reagent. Thus, it is clear that the boronate oxygens are required for the Lewis acid activation.



Scheme 1.4: Control experiment to determine site of Lewis acid binding

1.5.2 Rationale for rate enhancement

The hypothesis that coordination of the scandium to one of the boronate oxygen atoms increases the rate of reaction follows theoretical studies by Omoto

and Fujimoto, who showed that the strength of coordination between boron and the aldehyde carbonyl in the transition state of an allylboration reaction is the most important rate-determining factor.[4] In other words, coordination of the Lewis acid to the boronate oxygens would decrease the amount of electron delocalization from the oxygen atoms on the allylboronate to the empty p-orbital of the boron atom. As a result, the boron atom would become electron deficient and would compensate for this by creating a tighter complex with the aldehyde carbonyl oxygen. The strengthening of this key interaction would lower the activation energy of the desired allylboration reaction. This hypothesis comes out of the work of Brown and co-workers who described how the rate for a given allylboration reaction can "be rationalized in terms of the relative availability of lone pairs of electrons on the oxygen atoms attached to the boron" atom.[52]

1.5.3 Computational analysis to confirm method of activation

High-level DFT calculations have recently been carried out (*Gaussian03* and *GAMESS* programs packages were utilized, while the geometry optimization and analytical vibrational frequency analysis were performed by the B3LYP Kohn–Sham DFT method with the 6-311G** basis sets) and the calculated values of the transition states for the various activation methods support the experimental results.[53] For the reaction between allyl pinacol boronate and benzaldehyde catalyzed by $AlCl_3$, the reaction pathway that goes through a transition state in which the Lewis acid is coordinated to the oxygen atom of the allylboronate has a significantly lower overall energy of activation as compared to the reaction pathway where the Lewis acid is coordinated to the carbonyl oxygen of the aldehyde (17.5 kcal/mol vs. 40.9 kcal/mol). These calculations support the previous hypothesis set out by Hall and co-workers that the Lewis acid undergoes boronate activation rather than aldehyde activation. However, it then becomes a matter of which oxygen does the coordination occur with. Since it is unlikely that both of the oxygen atoms are coordinated to two molecules of Lewis acid, it could be either the more accessible pseudoequatorial one or the more basic (anomeric)

pseudoaxial one. Hypotheses have been made to try and suggest one over the other,[51] however, the quantum chemical calculations shed more light on this mechanistic question.[53] Coordination of the Lewis acid to the oxygen that is further away from the allyl group (i.e. the pseudoequatorial one) provides a transition state that is 6.2 kcal/mol lower in free energy compared to the transition state corresponding to Lewis acid coordination to the oxygen closer to the allyl group (pseudoaxial one), as shown in Figure 1.7. This difference in energy is due to distortion of the allyl group and the dioxoborolane ring, which is caused by repulsive forces between the allyl group and the coordinated Lewis acid.

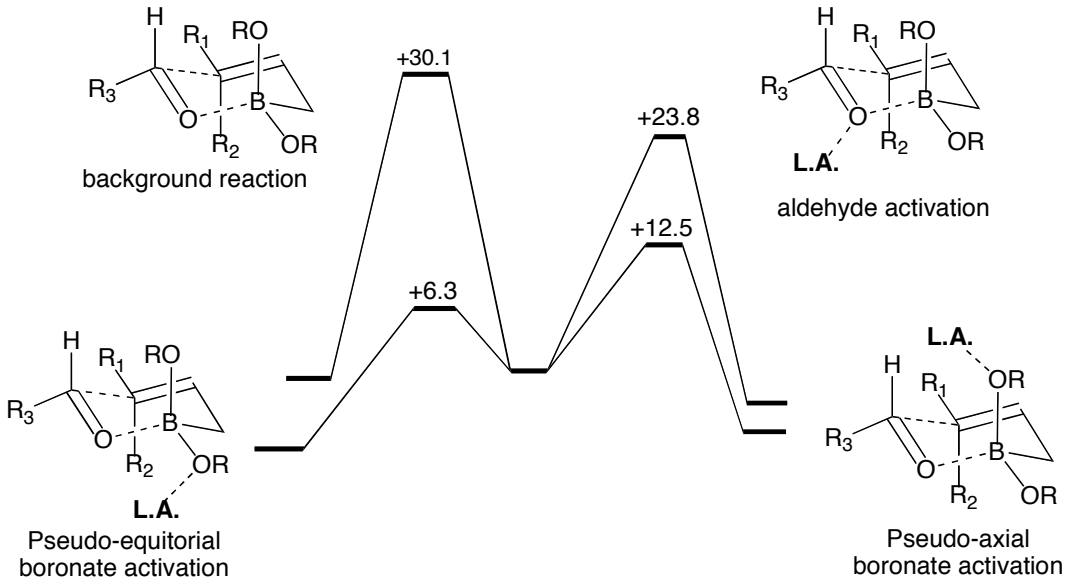
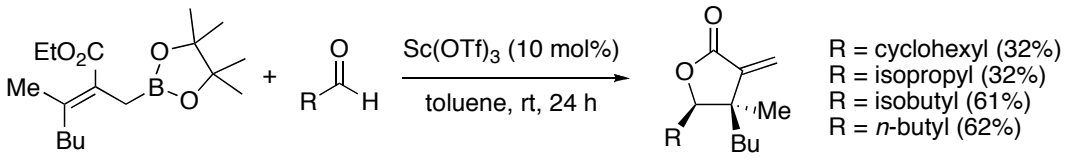


Figure 1.7: Calculated free energies (kcal/mol) for different catalyzed and uncatalyzed allylboration reaction transition states

1.5.4 Further advantages to Lewis acid catalysis

Since these initial forays into Lewis acid catalysis of allylboronate additions, further work as been done to exploit these new catalytic systems. Aliphatic aldehydes are notoriously slow when reacting with hindered and deactivated 2-alkoxycarbonyl allylboronates. Through the use of Lewis acids, these reactions can reach completion in less than 24 h (Equation 1.8).[54] Even

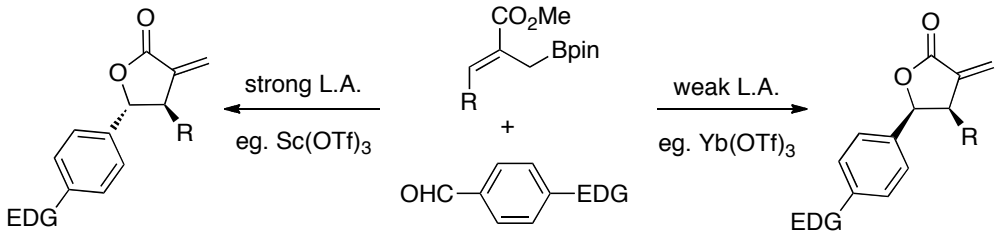
aldehydes that had previously failed to react under the thermal conditions can now be used as substrates to provide the desired γ-lactone products in moderate yields.



Equation 1.8: Lewis acid-catalyzed allylboration reaction of difficult aliphatic substrates

1.5.5 Effects of Lewis acid strength

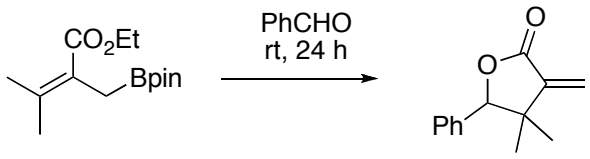
The difference in Lewis acidity has also been investigated and was shown to cause a reversal in the diastereoselectivity of certain allylboration reactions.[55] Allylboration reactions using electron rich aldehydes and strong Lewis acids led to the opposite diastereomer being observed as compared to the thermal allylboration reaction. Those reactions that made use of electron rich aldehydes and weak Lewis acids provided the expected diastereomer (Scheme 1.5). It was proposed that the strong Lewis acids allowed for the formation of an intermediate carbocation that could then reorganize itself to a more stable conformer before forming the observed *trans* diastereomer.



Scheme 1.5: Effect of Lewis acid strength on diastereoselectivity

1.6 Brønsted acid-catalyzed additions of allylic boronates to aldehydes

Many reports have disclosed the use of simple Brønsted acids as efficient catalysts that can facilitate challenging organic transformations and expand the substrate scope of other known catalyzed and uncatalyzed reactions.[56] The smaller size of the proton in a simple Brønsted acid as compared to the metal cation in Lewis acids can allow for the catalysis of more sterically demanding reactions. As well, the acidity difference also plays a major role in the observed catalytic activities of Brønsted and Lewis acids. Since Brønsted acids have been used as catalysts for a variety of organic transformations,[57] it was proposed that they might also be suitable catalysts for increasing the addition rate of deactivated allylic boronates to aldehydes. Indeed, the first report in 2005 by Hall and co-workers highlighted the superiority of small Brønsted acids in catalyzing the addition of deactivated allylboronates to aldehydes.[58] When scandium (III) triflate was used as a catalyst, only a trace amount of the desired product was obtained after 16 hours at a temperature of 0 ºC (Table 1.2). However, when triflic acid was used as the catalyst, the desired lactone product was obtained in a 99% yield.

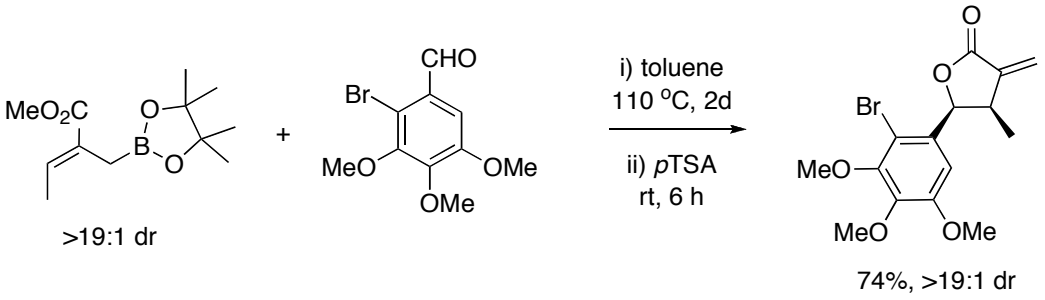


Entry	Catalyst	Yield (%)
1	none	0
2	$Sc(OTf)_3$	<5
3	CF_3CO_2H	77
4	CF_3SO_3H	99

Table 1.2: Comparison of Lewis acid and Brønsted acid catalytic systems

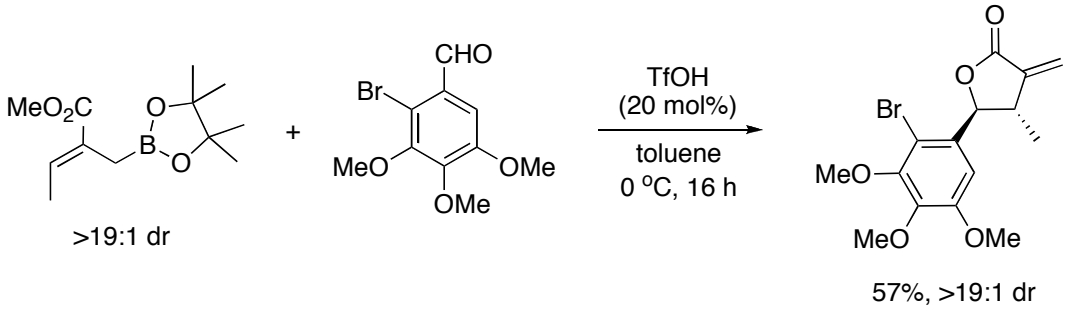
An interesting observation was made when it was noticed that in some cases of aldehyde allylboration under Brønsted acid catalysis, the opposite diastereomer was obtained as the major product. When the *E*-crotylboronate was

used with an electron rich aldehyde under thermal conditions, the expected *cis* γ-lactone was obtained as the major diastereomer (Equation 1.9).



Equation 1.9: Thermal addition of *E*-crotylboronate to electron rich aldehyde

However, under these new Brønsted acid-catalyzed conditions, the same *E*-crotylboronate and aldehyde led to the unexpected formation of the *trans* γ-lactone as the major product (Equation 1.10).



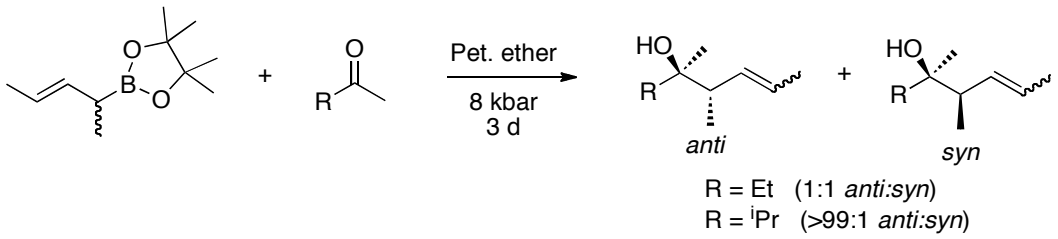
Equation 1.10: Brønsted acid-catalyzed addition of *E*-crotylboronate to electron rich aldehyde

This result was completely complementary to the standard thermal conditions of the allylboration reaction and allowed for a divergent synthesis of *cis* and *trans* γ-lactones from the same allylboronate. Utilizing this novel Brønsted acid-catalyzed allylboration reaction led to the unambiguous assignment of the relative and absolute stereochemistry in all four diastereomers of eupomatilone-6,[58] a member of a class of lignans isolated from the indigenous Australian shrub *Eupomatia bennettii*.[59] However, the role of the Brønsted acid and what guided the

diastereoselectivity of the reaction was completely unknown. This phenomenon had not been seen when using Lewis acids as catalysts, and so it was unclear as to how the Brønsted acid was catalyzing this allylboration reaction and how this new mechanism was resulting in the observed reversal of diastereoselectivity.

1.7 Addition of allylic boronates to ketones

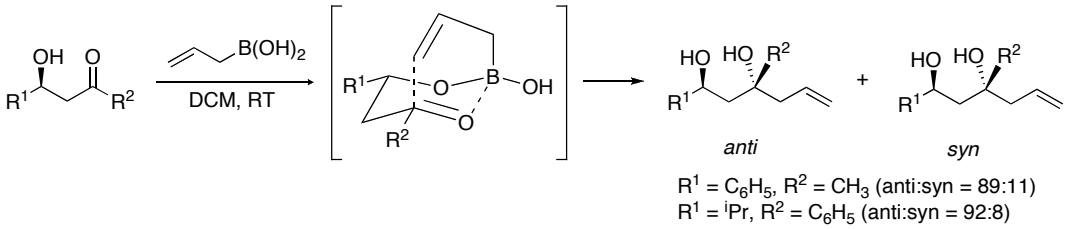
Although most examples of allylborations in the literature involve aldehydes as the electrophile, there have been an increasing number of examples where electrophilic partners other than aldehydes are being used. As shown in Equation 1.11, ketones can react with allylboronates to provide tertiary homoallylic alcohols.[60]



Equation 1.11: Thermal addition of crotyl boronates to ketones

Due to both steric and electronic factors, the addition of allylboronates to ketones is significantly slower than their addition to aldehydes. Electronically, ketone carbonyl groups are less electrophilic due to both substituents being more electron donating than in the case of aldehydes, which are substituted only on one side, and the other substituent, a hydrogen atom, is a poor electron donor. Sterically, since the allylboration reaction proceeds through a closed, six-membered transition state, one of the ketone groups must orient itself in an axial position in the transition state, thereby creating 1,3-diaxial interactions with the axial group on the boron atom and also the substituent in the 2-position on the allylboronate. Furthermore, the stereoselectivity of ketone allylboration reactions

is also more varied with ketones as compared to aldehydes. The difference in size between the two substituents on the ketone is usually the dominating factor for this: in general, the larger the size difference, the better the stereoselectivity. This observation was made in one of the early examples of stereoselective ketone allylborations, where high levels of enantioselectivity (>92% ee) were seen in the reaction of 3,3'-$(CF_3)_2$-BINOL allylboronate and several aromatic methyl ketones.[61] However, for ketones where both substituents were aliphatic, the enantioselectivity of the allylboration reaction dropped off to levels as low as 50% ee. Methods have been developed to help overcome this limitation. The addition of the allylboronate can be enhanced if the ketone also contains a chelating group elsewhere in the molecule (e.g. a nearby hydroxyl or carboxylic acid group).[61-66] The rationale for the increased selectivity is that the formation of a cyclic boronic ester rigidifies the transition state and allows for moderate levels of diastereoselectivity to be obtained when achiral allylboronates react with stereogenic β-hydroxyketones (Equation 1.12).[68]



Equation 1.12: Effect of substrate co-ordination in ketone allylboration reactions

Again, the use of 2-alkoxycarbonyl allylboronates and their additions to ketones has been completely ignored in the literature. No examples exist where these much less reactive allylic boronates have successfully been reacted with ketones. However, this would be a nice transformation to achieve as it would allow access to α-methylene γ-lactones that contain a quaternary center at the γ-position, which would be difficult or impossible to achieve by any other method.

1.8 Addition of allylic boronates to imines

The reactions of allylboronates with imines, oximes, acylhydrazones, hydrazono esters and ketoimines have been investigated over the past several years. These addition reactions are attractive in that they provide a route to homoallylic amines, which are useful synthetic intermediates for natural product synthesis and drug discovery. The use of 2-alkoxycarbonyl allylboronates is also attractive in that it provides α-methylene γ-lactams, a structural unit found in many natural products. The addition of allylic boronates to imines is much slower than the corresponding aldehyde additions. This is due to the difference in polarization of the imine C=N bond versus a C=O bond. The C=N bond is less polarized based on electronegativity differences (ΔEN = 0.49 for carbon and nitrogen compared to ΔEN = 0.89 for carbon and oxygen). This also means that coordination of the boron atom in the allylic boronate to the lone pair of electrons on the nitrogen atom of the imine is also less favorable.

1.8.1 Stereochemistry and activation geometry in imine allylboration reactions

The stereochemical outcome of imine allylation reactions is also complicated due to competing boat-like transition states that may be more favorable than the traditional chair-like transition states favored by aldehyde allylboration reactions. In aldehyde allylboration reactions, the boron atom coordinates to the lone pair of electrons that are *anti* to the R group of the aldehyde. In imine allylboration and crotylboration reactions, however, the boron atom has different possibilities (Figure 1.8).[69]

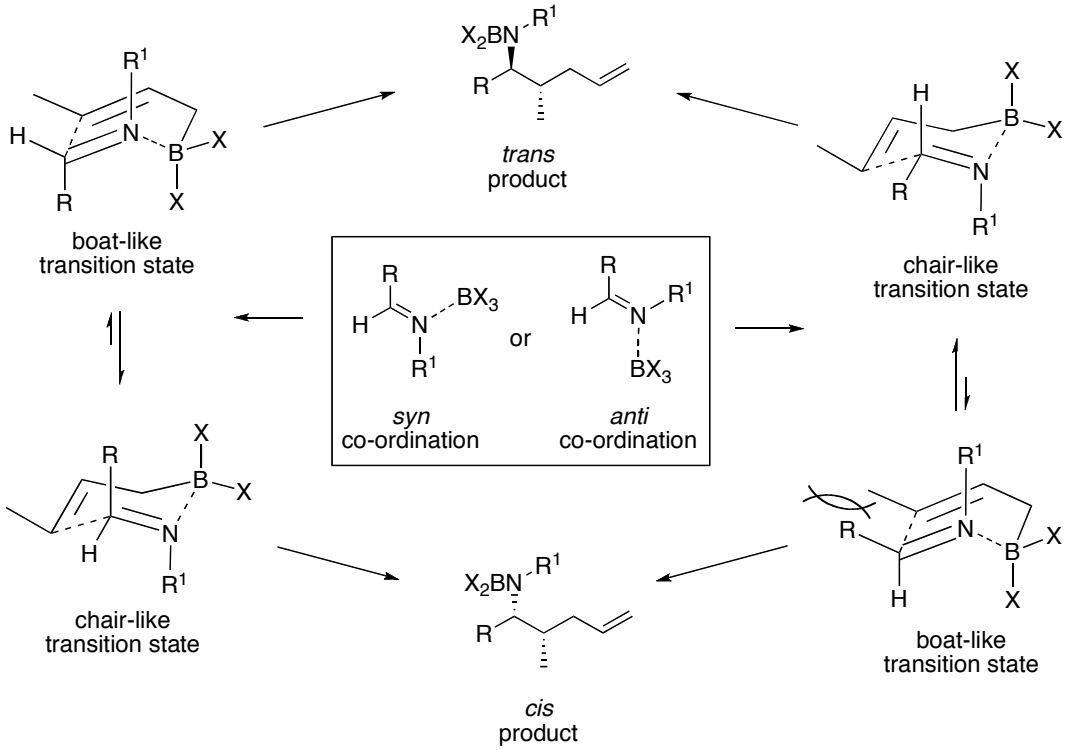


Figure 1.8: Possible coordination structures and transition states for imine allylboration and crotylboration reactions

For the more stable *trans* imines, the boron atom necessarily coordinates *syn* to the R group and the reaction typically proceeds through a chair-like transition state to provide the *cis* product. However, if the R group is aromatic or bulky, then the 1,3-diaxial interaction between this group and the X group on the boron atom becomes significant. At this point, there are two choices. The reaction can still proceed from the *syn*-coordinated imine and progress through a boat-like transition state to arrive at the *trans* product. Alternatively, if the imine can isomerize to its higher energy *cis* conformation, then the boron atom can coordinate to the electron pair that is *anti* to the R group and the reaction can proceed through a chair-like transition state and also lead to the *trans* product.

1.8.2 History of imine allylboration reactions

The racemic, thermal addition of allylboronates to imines and other similar derivatives has been studied as far back as the early 1980's. Hoffmann and co-workers originally described the addition of allylboronates to oximes to provide, after reduction, primary homoallylic amines.[70] They also described the use of oxime allylation products as intermediates towards oxazanorbornanes and piperidines.[71] However, in all cases, the ethanediol allylboronate utilized was more reactive than the pinacol derivative but also more susceptible to hydrolysis. Furthermore, reaction times were long and harsh (10 d in CCl_4 at reflux or 4 d at room temperature under 2 kbar pressure). Crotylboronates were investigated in their reactions with oximes, but again, reactive allylboronates were required at high temperatures or pressures to bring about useful conversions.[72] The crotylboronates did undergo addition to oximes, however, the diastereoselectivity was poor due to competing chair and boat-like transition states (Table 1.3). The geometry of the oxime played no role in the diastereoselectivity of the reaction, again indicating the delicate balance of competing transition states and the ease with which oxime isomerization can occur under the reaction conditions.

1.7 $R^1 = CH_3$, $R^2 = H$
1.8 $R^1 = H$, $R^2 = CH_3$

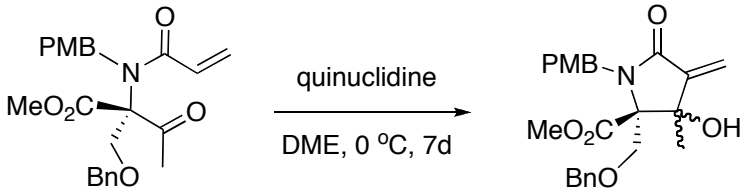
1.9 **1.10**

Crotylboronate	Oxime	Pressure (kbar)	Temp (°C)	Time (h)	Yield (%)	Ratio **1.9** : **1.10**
1.7 (E)	$R = C_6H_5$	9	46	23	64	95:5
1.7 (E)	$R = (CH_3)_2CH$	9	46	23	81	81:19
1.7 (E)	$R = CH_3(CH_2)_3$	4	25	100	84	75:25
1.8 (Z)	$R = C_6H_5$	9	46	23	38	12:88
1.8 (Z)	$R = (CH_3)_2CH$	9	46	23	65	20:80
1.8 (Z)	$R = (CH_3)_2CH$	3.6	88	48	50	3:97
1.8 (Z)	$R = CH_3(CH_2)_3$	9	46	23	60	30:70
1.8 (Z)	$R = CH_3(CH_2)_3$	3.6	88	48	25	6:94

Table 1.3: Diastereoselectivity of additions of crotylboronates to oximes

1.8.3 Common methods for the synthesis of α-methylene γ-lactams

The synthesis of α-methylene γ-lactams has been the focus of several reports in the literature;[73] however, several known routes are tedious in accessing this core structure. In their synthesis of salinosporamide, Corey and co-workers made use of an intramolecular Baylis–Hillman reaction to form the desired γ-lactam unit (Equation 1.13). This synthesis is not ideal, however, as it required seven steps to reach the precursor and the resulting alcohol that is generated would need to be removed if not present in the desired γ-lactam. Furthermore, Baylis–Hillman reactions are notorious for their long reaction times, although research in this area has helped to reduce the required reaction time.[74]



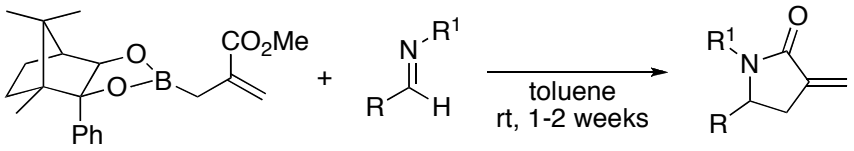
Equation 1.13: Example of α-methylene γ-lactam synthesis using an intramolecular Baylis–Hillman reaction

Other methods already discussed in the context of γ-lactone synthesis also apply to γ-lactam synthesis, including Barbier–type allylation reactions of imine derivatives mediated by tin or zinc[75] and Horner–Emmons–Wadsworth reactions utilizing acyclic amino phosphonate precursors.[76] The use of 2-alkoxycarbonyl allylboronates in imine addition reactions allows for a simple, one-step sequence that would allow for the formation of substituted γ-lactams. However, this route has not been explored in much detail and is discussed in the following section.

1.8.4 Imine allylboration reactions with 2-alkoxycarbonyl allylboronates

For the 2-alkoxycarbonyl allylboronates described in previous sections, their reactivity with imines has been essentially ignored. In 1998, Villiéras and

co-workers displayed the first example of imine allylation with a 2-alkoxycarbonyl allylboronate leading to α-methylene γ-lactams (Equation 1.14).[77] This approach made use of a chiral allylboronate based on Hoffmann's diol and the imines were specifically chosen due to their high reactivity. Substrates with electron donating groups on the nitrogen and electron withdrawing groups on the carbon of the imine were the only examples shown. Furthermore, the imines containing a silyl-protecting group are extremely sensitive to work with, however, could furnish the unprotected γ-lactams via deprotection under the reaction conditions. The other imines provided γ-lactams that were protected, and additional steps would be required to remove these groups. Another problem with this protocol was the reaction times, which were as long as 1-2 weeks. Additionally, no examples of crotylations were given in this report. Until my investigation into this area of research, this was the only example of 2-alkoxycarbonyl allylboronates reacting with imines to form either the acyclic allylboration product or the cyclized α-methylene γ-lactams.



Equation 1.14: Imine addition reactions with a 2-alkoxycarbonyl allylboronate

1.9 Thesis objectives

The discovery that Lewis acids could be used to catalyze the addition of allylboronates to aldehydes without disrupting the Zimmerman–Traxler transition state while preserving the diastereoselectivity of the reaction was a significant breakthrough and has led to many other discoveries in the area of allylation catalysis. Brønsted acids were also observed to accelerate the addition of 2-alkoxycarbonyl allylboronates to aldehydes; however, their stereochemical course

of addition was not as expected. Chapter 2 discusses the observed reversal of stereoselectivity and how it was substrate dependant. The mechanism of this reaction was investigated and this will also be presented in Chapter 2.

The use of ketones and imines as substrates in the context of allylation chemistry is interesting in that it provides complex products that can be used as intermediates to more interesting compounds. However, these reagents also provide interesting challenges in that they are less reactive and less predictable in their stereochemical outcome. The expansion of the uses of 2-alkoxycarbonyl allylboronates to both ketone allylation and imine allylation will be discussed in Chapters 3 and 4, respectively.

The synthesis of α-methylene and α-alkylidene γ-lactones and γ-lactams is a growing field in organic chemistry due to their key structural motif in many biologically important natural products. The use of 2-alkoxycarbonyl allylboronates provides facile access to these γ-lactones and γ-lactams. In the world of medicinal chemistry, drugs are often developed after several rounds of optimization and further functionalization of compounds. With this in mind, Chapter 5 will present a variety of methods that were developed to further functionalize α-methylene γ-lactones and γ-lactams in such a manner that would be suitable to large-scale combinatorial chemistry. A demonstration library was synthesized using combinatorial chemistry techniques and this library was screened in collaboration with colleagues at McMaster University. The outcome of this collaboration will also be described in Chapter 5.

The total synthesis of natural products is one approach employed in organic chemistry to test methodology and reactions that have been developed by applying them in more difficult cases and thus expand on substrate scope and utility of these reactions. Until this point, 2-alkoxycarbonyl allylboronates had been used in conjunction with relatively simple aldehydes and imine substrates. To push the scope of this methodology, the total synthesis of chinensiolide B was undertaken. Issues of chemoselectivity were encountered in this endeavor and the synthetic solutions to these problems will be described in Chapter 6. These findings did lead to the total synthesis of chinensiolide B, which utilizes a highly

selective allylboration reaction between a substituted 2-alkoxycarbonyl allyboronate and a highly functionalized and sensitive aldehyde.

1.10 References

[1] Denmark, S.E.; Almstead, N.G. in *Modern Carbonyl Chemistry*; J. Otera (Ed); Wiley-VCH: Weinheim, **2000**, Chap. 10, 299–402.

[2] Chemler, S.R.; Roush, W.R. in *Modern Carbonyl Chemistry*; J. Otera (Ed); Wiley-VCH: Weinheim, **2000**, Chap. 11, 403–490.

[3] Denmark, S.E.; Weber, E.J. *Helv. Chim. Acta*. **1983**, *66*, 1655-1660.

[4] Omoto, K.; Fujimoto, J. *J. Org. Chem*. **1989**, *63*, 8331-8336.

[5] Li, Y.; Houk, K.N. *J. Am. Chem. Soc*. **1989**, *111*, 1236-1240.

[6] Pratt, A.J.; Thomas, E.J. *J. Chem. Soc. Chem. Commun*. **1982**, 1115-1117.

[7] Denmark, S.E.; Fu, J. *Chem. Rev*. **2003**, *103*, 2763-2794.

[8] Matteson, D.S. in *Stereodirected Synthesis with Organoboranes*, Springer-Verlag, Berlin, Heidelberg, **1995**, Chapter 7.

[9] Roush, W.R. Houben-Weyl, *Stereoselective Synthesis*, 4th ed, Thieme, Stuttgart, **1995**, Vol. E21b, Chapter 1.3.3.3.3.

[10] Yamamoto, Y.; Asao, N. *Chem. Rev*. **1993**, *93*, 2207-2293.

[11] Hoffmann, R.W. *Pure Appl. Chem*. **1988**, *60*, 123-130.

[12] Kennedy, J.W.J.; Hall, D.G. in *Boronic Acids*; D. G. Hall (Ed); Wiley-VCH: Weinheim, **2005**, Chap. 6, 241-277.

[13] Hoffmann, H.M.R.; Rabe, J. *Angew. Chem. Int. Ed. Engl*. **1985**, *24*, 94-110.

[14] Konaklieva, M.I.; Plotkin, B.J. *Mini Rev. Med. Chem*. **2005**, *5*, 73-95.

[15] Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem*. **2005**, *48*, 3516-3521.

[16] Zhangabylov, N.S.; Dederer, L.Y.; Gorbacheva, L.B.; Vasil'eva, S.V., Terekhov, A.S.; Adekenov, S.M. *Pharm. Chem. J*. **2004**, *38*, 651-653.

[17] For example, see: (a) Feling, R.H.; Buchanan, G.O.; Mincer, T.J.; Kauffman, C.A.; Jensen, P.R.; Fenical, W. *Angew. Chem., Int. Ed*. **2003**, *42*, 355-357. (b) Zhu, X.Z.; Li, X.-Y.; Liu, J. *Eur. J. Pharmacol*. **2004**, *500*, 221-230. (c) Schwartz, R.E.; Helms, G.L.; Bolessa, E.A.; Wilson, K.E.; Giacobbe, R.A.;

Tkacz, J.S.; Bills, G.F.; Liesch, J.M.; Zink, D.L.; Curotto, J.E.; Pramanik, B.; Onishi, J.C. *Tetrahedron* **1994**, *50*, 1675-1686.

[18] For example, see: (a) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117-118. (b) Macherla, V.R.; Mitchell, S.S.; Manam, R.R.; Reed, K.A.; Chao, T.-H.; Nicholson, B.; Deyanat-Yazdi, G.; Mai, B.; Jensen, P.R. Fenical, W.F.; Neuteboom, S.T.C.; Lam, K.S.; Palladino, M.A.; Potts B.C.M. *J. Med. Chem.* **2005**, *48*, 3684-3687. (c) Xu, L.; Liu, S.-L.; Zhang, J.-T. *Chirality* **2005**, *17*, 239-244.

[19] (a) Hughes, M. A.; McFadden, J. M.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3857-3859. (b) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601-7607. (c) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198-8199. (d) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967-5971.

[20] For a review on this topic, see Elford, T.G., Hall, D.G. *Synthesis* **2009**, *42*, *in press*.

[21] Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U. Rózalski, M. *J. Med. Chem.* **2005**, *48*, 3216-3521.

[22] Edwards, M.G.; Kenworthy, M.N.; Kitson, R.R.A.; Scott, M.S.; Taylor, R.J.K. *Angew. Chem. Int. Ed.* **2008**, *47*, 1935-1937.

[23] (a) Haaima, G.; Weavers, R.T. *Tetrahedron Lett.* **1988**, *29*, 1085-1088. (b) Haaima, G.; Lynch, M.-J.; Routledge, A.; Weavers, R.T. *Tetrahedron* **1991**, *47*, 5203-5214.

[24] Baldwin, J.E.; Adlington, R.M.; Sweeney, J.B. *Tetrahedron Lett.* **1986**, *27*, 5423-5424.

[25] Masuyama, Y.; Nimura, Y.; Kurusu, Y. *Tetrahedron Lett.* **1991**, *32*, 225-228.

[26] Hosomi, A.; Hashimoto, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 951-954.

[27] Sidduri, A.R.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 7579-7581.

[28] (a) Lambert, F.; Kirschleger, B.; Villiéras, J. *J. Organomet. Chem.* **1991**, *406*, 71-86. (b) Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1985**, *26*, 5697-5698. (c)

Lee, A. S.-Y.; Chang, Y.-T.; Wang, S.-H.; Chu, S.-F. *Tetrahedron Lett*. **2002**, *43*, 8489-8492.

[29] Ding, H.; Zhang, C.; Wu, X.; Yang, C.; Zhang, X.; Ding, J.; Xie, Y. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4799-4802.

[30] Choudhury, P.K.; Foubelo, F.; Yus, M. *Tetrahedron Lett*. **1998**, *39*, 3581-3584.

[31] Gagnier, S.V.; Larock, R.C. *J. Org. Chem*. **2000**, *65*, 1525-1529.

[32] Yong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc*. **2004**, *126*, 7601-7607.

[33] Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc*. **2002**, *124*, 8198-81997.

[34] Nyzam, V.; Belaud, C.; Villiéras, J. *Tetrahedron Lett*. **1993**, *34*, 6899-6902.

[35] Hoffmann, R.W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 306-307.

[36] Hoffmann, R.W.; Zeiss, H.-J. *J. Org. Chem*. **1981**, *46*, 1309-1314.

[37] Brown, H.C.; Jadhav, P.K. *J. Am. Chem. Soc*. **1983**, *105*, 2092-2093.

[38] Brown, H.C.; Bhat, K.S. *J. Am. Chem. Soc*.**1986**, *108*, 293-294.

[39] Ramachandran, P.V. *Aldrichim. Acta* **2002**, *35*, 23-35.

[40] Garcia, J.; Kim, B.; Masamune, S. *J. Org. Chem*. **1987**, *52*, 4831-4832.

[41] Short, R.P.; Masamune, S. *J. Am. Chem. Soc*. **1989**, *111*, 1892-1894.

[42] Corey, E.J.; Yu, C.-M.; Kim, S.S. *J. Am. Chem. Soc*. **1989**, *111*, 5495-5496.

[43] Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem. Soc*. **1990**, *112*, 6339-6347.

[44] Burgos, C.-H.; Canales, E.; Matos, K.; Soderquist, J.A. *J. Am. Chem. Soc*. **2005**, *127*, 8044-8049.

[45] For a comprehensive review, see: Lachance, H.; Hall, D.G. in *Organic Reactions, Vol. 73*; S.E Denmark (Ed); John Wiley & Sons, **2008**, Chap. 1.

[46] Related allyltrifluoroborate salts add to aldehydes using a strong Lewis acid catalyst, however, this is outside this area of research: Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* **2000**, 990-998.

[47] Hoffmann and co-workers showed that Lewis acid-mediated acetal hydrolysis to their corresponding aldehydes can be followed by intramolecular allylboration reactions. However, the effect of the Lewis acid on the

allylboration step was not discussed: Hoffmann, R.W.; Kruger, J.; Bruckner, D. *New J. Chem.* **2001**, **25**, 102-107 and references cited therein.

[48] Kennedy, J.W.J.; Hall, D.G. *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587.

[49] Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415.

[50] Lachance, H.; Xu, M.; Gravel, M.; Hall, D.G. *J. Am. Chem. Soc.* **2003**, *125*, 10160-10161.

[51] Rauniyar, V.; Hall, D.G. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519.

[52] Brown, H.C.; Racherla, U.S.; Pelechia, P.J. *J. Org. Chem.* **1990**, *55*, 1868-1874.

[53] Sakata, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12519-12526.

[54] Kennedy, J.W.J.; Hall, D.G. *J. Org. Chem.* **2004**, *69*, 4412-4428.

[55] Ramachandran, P.V.; Pratihar, D.; Biswas, D. *Org. Lett.* **2006**, *8*, 3877-3879.

[56] For early examples in the field of Brønsted acid catalysis: (a) Williams, A.L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612-1613. (b) Zhang, L.; Kozmin, S.A. *J. Am. Chem. Soc.* **2004**, *126*, 10204-10205. (c) Mahoney, J.M.; Smith, C.R.; Johnston, J.N. *J. Am. Chem. Soc.* **2005**, *127*, 354-1355. (d) Zhang, Y.; Hsung, R.P.; Zhang, X.; Huang, J.; Slafer, B.W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047-1050. (e) Nakashima, D.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1251-1253.

[57] For reviews, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999-1010. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744-5758.

[58] Yu, S.H.; Ferguson, M.J.; McDonald, R.; Hall, D.G. *J. Am. Chem. Soc.* **2005**, *127*, 12808-12809.

[59] Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* **1991**, *44*, 1615-1626.

[60] (a) Hoffmann, R.W.; Dresely, S. *Tetrahedron Lett.* **1987**, *28*, 5303-5306. (b) Hoffmann, R.W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903-909.

[61] Wu, T.R.; Shen, L.; Chong, J.M. *Org. Lett.* **2004**, *6*, 2701-2704.

[62] Metternich, R.; Hoffmann, R.W. *Tetrahedron Lett.* **1984**, *37*, 4095-4096.

[63] Wang, Z.; Meng, X.-J.; Kabalka, G.W. *Tetrahedron Lett.* **1991**, *32*, 4619-4622.

[64] Wang, Z.; Meng, X.-J.; Kabalka, G.W. *Tetrahedron Lett.* **1991**, *32*, 5677-5680.

[65] Pace, R.D.; Kabalka, G.W. *J. Org Chem.* **1995**, *60*, 4838-4844.

[66] Kabalka, G.W.; Yang, K.; Wang, Z. *Synth. Commun.* **2001**, *31*, 511-517.

[67] Wang, Z.; Meng, X.-J.; Kabalka, G.W. *Tetrahedron Lett.* **1991**, *32*, 1945-1948.

[68] Kabalka, G.W.; Narayana, C.; Reddy, N.K. *Tetrahedron Lett.* **1996**, *37*, 2181-2184.

[69] Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115-3121.

[70] Hoffmann, R.W.; Eichler, G.; Endesfelder, A. *Liebigs Ann.Chem.* **1983**, 2000-2007.

[71] Hoffmann, R.W.; Endesfelder, A. *Liebigs Ann.Chem.* **1986**, 1823-1836.

[72] Hoffmann, R.W.; Endesfelder, A. *Liebigs Ann.Chem.* **1987**, 215-219.

[73] (a) Reddy, L.R.; Saravanan, P.; Corey, E.J. *J. Am. Chem. Soc.* **2004**, 126, 6230-6231. (b) Reddy, L.R.; Fournier, J.-F.; Subba Reddy, B.V.; Corey, E.J. *J. Am. Chem. Soc.* **2005**, *127*, 8974-8976. (c) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765-7768. (d) Lettan, R.B. *II*.; Woodward, C.C.; Scheidt, K.A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2294-2297.

[74] Robiette, R.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* **2007**, *129*, 15513-15525.

[75] El Alami, N.; Delaud, C.; Villiéras, J. *Synth. Commun.* **1988**, *18*, 2073-2081.

[76] Blaszczyk, E.; Krawczyk, H.; Janecki, T. *Synlett.* **2004**, *15*, 2685-2688.

[77] Chataigner, I.; Zammattio, F.; Lebreton, J.; Villiéras, J. *Synlett* **1998**, 275-276.

Chapter 2

Investigation of the Triflic Acid-Catalyzed Addition of 2-Alkoxycarbonyl Allylboronates to Aldehydes

2.1 Introduction

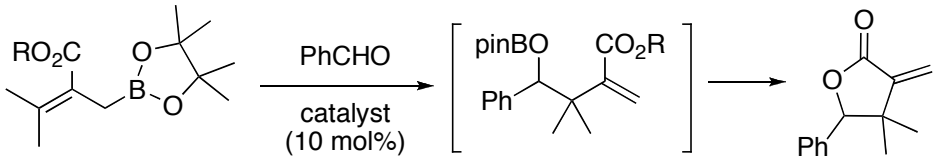
As mentioned in Chapter 1, several reports have recently highlighted the efficiency of simple Brønsted acids as catalysts that can facilitate difficult organic reactions and expand their substrate scope.[1] Strong organic acids like triflic acid and triflimide are remarkably effective in promoting various polar additions and cycloadditions, and are very convenient to use. These strong Brønsted acids are soluble in a wide range of organic solvents, and they can be prepared and employed in anhydrous form. The Hall group has recently described the use of strong Brønsted acids to catalyze the additions of 2-alkoxycarbonyl allylboronates to aldehydes.[2] Although strong Lewis acids had previously been reported to catalyze these additions,[3-5] it is quite surprising that allylic boronates can tolerate strong protic conditions susceptible to promoting undesired processes such as oligomerization or protodeboronation.[6]

The application of protic acid catalysis to the use of 2-alkoxycarbonyl allylboronates further facilitates the synthesis of α-methylene γ-lactones. These compounds are of interest because they could be used as building blocks for the construction of several natural products. Stereoselective synthesis of such compounds is quite significant[7,8] and could lead to a wide variety of natural product derivatives that could be screened for their biological activities. Natural products containing the α-methylene γ-lactones core are known to display a wide range of biological properties.[7] As well, derivatives of α-methylene γ-lactones have shown significant antitumor properties.[9] The biological importance of this class of compounds is well documented due to their cytotoxic, antiallergenic, anti-

inflammatory, phytotoxic, and antimicrobial properties.[10] Hence, there is a great need for a stereospecific route to this class of compounds that allows for diversity to be easily introduced along the synthetic pathway. Development of new methodologies for the synthesis of substituted γ-lactones would have applications in the areas of diversity-oriented synthesis and the generation of combinatorial libraries.

2.1.1 Development of optimal protic acid-catalyzed conditions[2]

The allylation of aldehydes with 2-alkoxycarbonyl allylboronates leads to α-methylene γ-lactones.[4,5,11-14] These deactivated allylic boronates, however, add very slowly under thermal conditions and require reaction temperatures over 100 °C. Optimization of the product yield in the addition of a prototypical 3,3-disubstituted 2-alkoxycarbonyl allylboronates to benzaldehyde (Table 2.1) was performed by Siu Hong Yu, a previous graduate student in the Hall group. He investigated the use of Lewis acids and strong Brønsted acids, and he found that $Sc(OTf)_3$ (entry 6), which had previously been a very good catalyst for allylboration reactions with 2-alkoxycarbonyl allylboronates, gave a slower reaction. However, Yu found that bis(trifluoromethylsulfonyl)imide and triflic acid were superior catalysts and provided higher conversions than Lewis acids. Also noteworthy is the concomitant lactonization of the intermediate hydroxy-ester, which is most likely promoted by the acid catalyst. Due to the easier handling and measurement of liquid reagents, triflic acid was chosen for further optimization. The TfOH-catalyzed reaction was investigated at a lower temperature in view of using sensitive aldehydes. Further fine-tuning of reaction parameters and substrate stoichiometry led to the conditions of entry 8. Indeed, it was found that triflic acid was very efficient at catalyzing the addition of very deactivated 2-alkoxycarbonyl allylboronates to aldehydes. This new variant proceeds with ease at a temperature more than 100 °C lower than the corresponding uncatalyzed reaction.[2]



Entry	PhCHO (equiv)	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	0.9	none	toluene	25	24	< 5
2	0.9	CF_3CO_2H	toluene	25	24	77
3	0.9	Tf_2NH	toluene	25	24	99
4	0.9	TfOH	toluene	25	24	99
5	0.9	TfOH	toluene	0	16	78
6	0.9	$Sc(OTf)_3$	toluene	0	16	< 5
7	1.5	TfOH	toluene	0	16	96
8	2.0	TfOH	toluene	0	16	99

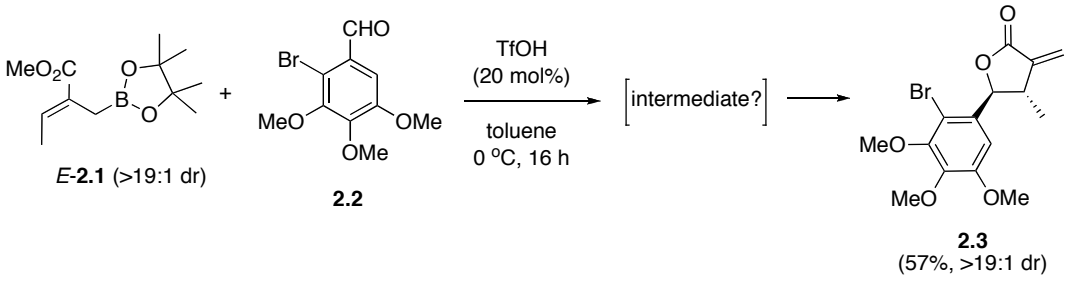
[a] Standard conditions: reaction scale: approx. 0.4 mmol of allylic boronate, 1.0 M solution. Entries 1-4: R = Et, entries 5-8: R = menthyl. [b] Isolated yields

Table 2.1: Yu's optimization of Brønsted acid-catalyzed allylboration reaction[2]

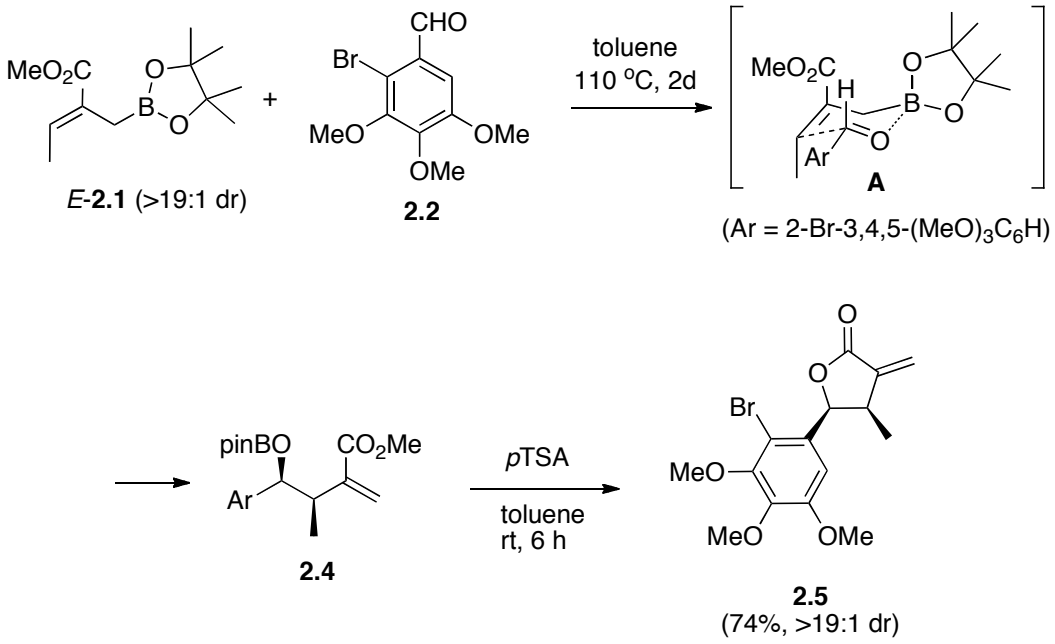
2.1.2 Application of triflic acid-catalyzed reaction conditions to the synthesis of all four diastereomers of eupomatilone-6[2]

The novel triflic acid-catalyzed procedure was applied to the synthesis of all four diastereomers of eupomatilone-6, a new natural product member of a structurally intriguing class of lignans isolated from the indigenous Australian shrub *Eupomatia bennettii*.[15] In this synthesis, Yu observed that the *E*-configured 2-alkoxycarbonyl allylboronate *E*-**2.1** provides the *trans* γ-lactone product **2.3** upon addition to aldehyde **2.2** (Equation 2.1). According to the expected six-membered transition structure **A** (Scheme 2.1), the *trans* stereochemistry of product **2.3** is opposite to that expected from the allylic boronate's *E* geometry. Indeed, the thermal, uncatalyzed addition between *E*-**2.1** and **2.2** (Scheme 2.1) afforded the expected *cis* configured γ-lactone **2.5** (after an acid-promoted lactonization on open intermediate **2.4**). The fact that *Z*-**2.6** also provided the *trans* γ-lactone **2.3** (which is expected based upon the Zimmerman–Traxler chair-like transition state) under triflic acid catalysis (Equation 2.2) suggested that

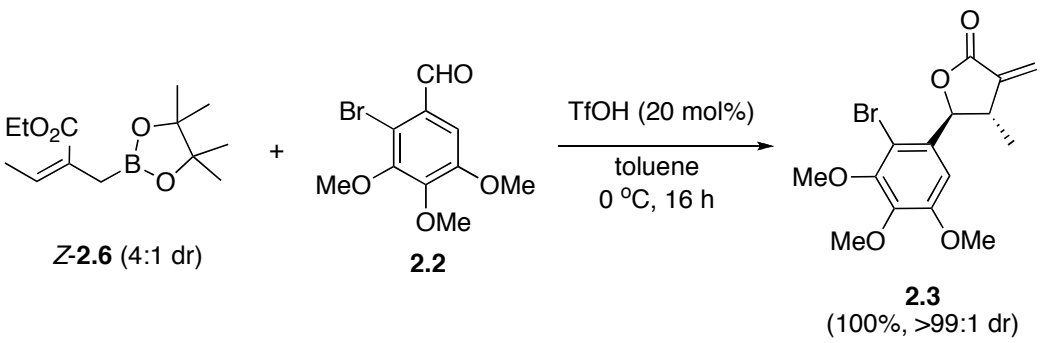
isomerization had occurred somewhere along the reaction pathway between 2-alkoxycarbonyl allylboronate *E*-**2.1** and γ-lactone product **2.3** in Equation 2.1.



Equation 2.1: Yu's triflic acid-catalyzed addition of *E*-**2.1** to aldehyde **2.2**



Scheme 2.1: Yu's thermal addition of *E*-**2.1** to aldehyde **2.2** followed by lactonization with PTSA



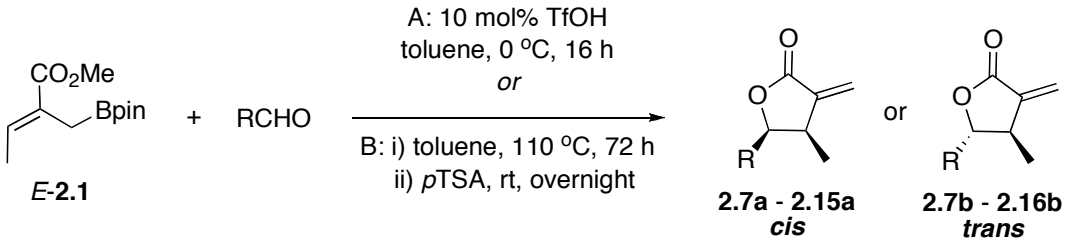
Equation 2.2: Yu's triflic acid-catalyzed addition of *Z*-**2.6** to aldehyde **2.2**

2.2 Questions regarding the acid-catalyzed allylboration reaction[16]

Due to the unexpected results obtained by Siu Hong Yu in his synthesis of all four diastereomers of Eupomatilone-6,[2] an investigation into the origin of the unexpected stereochemistry in the triflic acid-catalyzed additions of 2-alkoxycarbonyl allylboronates was needed. Allylboronate isomerization under the reaction conditions had already been ruled out by Yu,[2] thus, there were several questions about this new catalytic system that needed to be answered. First of all, do all aldehydes display the reversal of *cis*/*trans* selectivity that was observed in the synthesis of **2.3** (Equation 2.1) or is there some governing factor that allows for only certain *trans* γ-lactones to be formed? Secondly, what types of aldehydes are amenable as substrates for this reaction so as to provide a general reaction? Thirdly, how do triflic acid-catalyzed reactions compare with the corresponding thermal (uncatalyzed) variant? Fourthly, how is triflic acid catalyzing the reaction and what is the catalytic cycle?

2.3 Investigation of aldehyde substrate scope[16]

Since the conditions for the triflic acid-catalyzed allylboration reaction had been optimized by Siu Hong Yu, my first role in this project was to determine the substrate scope in terms of the aldehyde. Could all types of aldehydes be used under these strongly acidic conditions? Did all aldehydes result in the reversal of diastereoselectivity or was it substrate dependant? To address this issue, various model aldehydes were chosen and reacted with both *E*-**2.1** and *Z*-**2.1** under thermal and TfOH-catalytic conditions. The results from these reactions are summarized in Table 2.2 and Table 2.3, respectively.



E-**2.1**

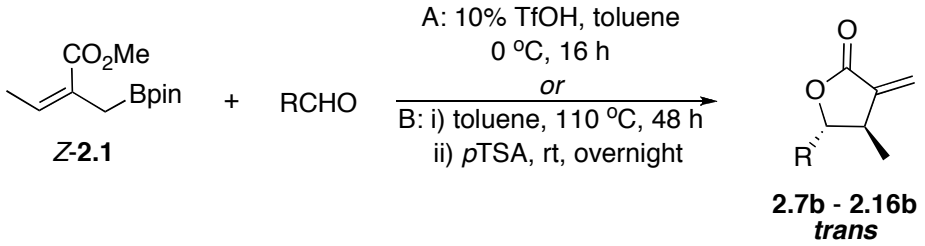
2.7a - 2.15a ***cis***

2.7b - 2.16b ***trans***

Entry	Aldehyde	Conditions [a]	Product [b]	D.r.	Yield (%)[c]
1	*p*-$NO_2C_6H_4CHO$	A	**2.7a**	>19:1	53
2	*p*-$NO_2C_6H_4CHO$	B	**2.7a**	>19:1	90
3	*p*-BrC_6H_4CHO	A	**2.8b**	>19:1	62
4	*p*-BrC_6H_4CHO	B	**2.8a**	>19:1	79
5	*p*-$MeOC_6H_4CHO$	A	**2.9b**	>19:1	62
6	*p*-$MeOC_6H_4CHO$	B	**2.9a/2.9b**	1:1	62
7	*o*-MeC_6H_4CHO	A	**2.10b**	>19:1	49
8	*o*-MeC_6H_4CHO	B	**2.10a**	>19:1	80
9	*p*-MeC_6H_4CHO	A	**2.11b**	>19:1	59
10	*p*-MeC_6H_4CHO	B	**2.11a**	>19:1	48
11	C_6H_5CHO	A	**2.12b**	>19:1	58
12	C_6H_5CHO	B	**2.12a**	>19:1	67
13	*E*-$CH_3CH{=}CHCHO$	A	**2.13b**	>19:1	79
14	*E*-$CH_3CH{=}CHCHO$	B	**2.13a**	>19:1	92
15	$H_{11}C_5C{\equiv}CCHO$	A	**2.14a**	>19:1	63
16	$H_{11}C_5C{\equiv}CCHO$	B	**2.14a**	>19:1	51
17	$PhCH_2CH_2CHO$	A	**2.15a**	>19:1	46
18	$PhCH_2CH_2CHO$	B	**2.15a**	>19:1	59
19	*c*-$C_6H_{11}CHO$	A	**2.16a**	>19:1	11
20	*c*-$C_6H_{11}CHO$	B	**2.16a**	>19:1	66
21	*E*-PhCH=CHCHO	A	**---**	n/a	0

[a] A) TfOH, 0 °C for 16 h or B) 110 °C for 48 h, then PTSA at rt for overnight. [b] Relative configuration determined by cycle NOE. See Section 2.4.2 for more details [c] Isolated yield after chromatography.

Table 2.2: Reaction of *E*-**2.1** with various aldehydes under thermal or TfOH-catalyzed conditions



Entry	Aldehyde	Conditions [a]	Product [b]	D.r.	Yield (%)[c]
1	*p*-$NO_2C_6H_4CHO$	A	**2.7b**	>19:1	52
2[d]	*p*-$NO_2C_6H_4CHO$	B	**2.7b**	3.6:1	61
3	*p*-BrC_6H_4CHO	A	**2.8b**	>19:1	59
4[d]	*p*-BrC_6H_4CHO	B	**2.8b**	3.1:1	53
5	*p*-$MeOC_6H_4CHO$	A	**2.9b**	>19:1	40
6[d]	*p*-$MeOC_6H_4CHO$	B	**2.9b**	5.7:1	57
7	*o*-MeC_6H_4CHO	A	**2.10b**	>19:1	49
8[d]	*o*-MeC_6H_4CHO	B	**2.10b**	6.1:1	49
9	*p*-MeC_6H_4CHO	A	**2.11b**	>19:1	91
10	*p*-MeC_6H_4CHO	B	**2.11b**	>19:1	71
11	C_6H_5CHO	A	**2.12b**	>19:1	78
12	C_6H_5CHO	B	**2.12b**	>19:1	66
13	*E*-$CH_3CH{=}CHCHO$	A	**2.13b**	>19:1	26
14[d]	*E*-$CH_3CH{=}CHCHO$	B	**2.13b**	5.3:1	58
15[d]	$H_{11}C_5C{\equiv}CCHO$	A	**2.14b**	2.7:1	46
16[d]	$H_{11}C_5C{\equiv}CCHO$	B	**2.14b**	5.2:1	62
17	$PhCH_2CH_2CHO$	A	**2.15b**	>19:1	44
18[d]	$PhCH_2CH_2CHO$	B	**2.15b**	2.5:1	40
19	*c*-$C_6H_{11}CHO$	A	**2.16b**	>19:1	71
20[d]	*c*-$C_6H_{11}CHO$	B	**2.16b**	2.9:1	47

[a] A) TfOH, 0 °C for 16 h or B) 110 °C for 48 h, then PTSA at rt for overnight. [b] Relative configuration determined by cycle NOE. See Section 2.4.2 for more details [c] Isolated yield after chromatography. [d] The allylboronate used was a 6:1 mixture of *Z*-**2.1** to *E*-**2.1**.

Table 2.3: Reaction of *Z*-**2.1** with various aldehydes under thermal or TfOH-catalyzed conditions

From these results, a comparison between the isomeric allylic boronates *E*-**2.1** and *Z*-**2.1** can be made. For both of these allylic boronates, there was no clear trend as to which one gave better yields for a given aldehyde. While some reactions gave high yields of lactones from *E*-**2.1** (entries 2, 8 and 14 in Table 2.2), others were not nearly as successful and gave lower yields. However, the same situation occurred with *Z*-**2.1**, where some aldehydes gave significantly

higher yields than others. This could be a matter of variability and experimental error, as the results shown are based on one reaction run. Repeat experiments may shed more light in this area and reveal whether there is a trend of one of the allylic boronates consistently providing the γ-lactone products in higher yields than the other. It is also useful to note that, while most of the aldehydes used were aromatic or straight-chain aliphatic ones, branched aldehydes are also suitable substrates for this reaction. Specifically, the use of cyclohexane carboxaldehyde (entries 19 and 20 in Table 2.2 and Table 2.3) as well as *o*-tolualdehyde (entries 7 and 8 in Table 2.2 and Table 2.3) demonstrated that more sterically hindered aldehydes are suitable for use in the triflic acid-catalyzed allylboration reaction. α,β-Unsaturated aldehydes are also suitable substrates as evidenced by the successful addition of both *E*-**2.1** and *Z*-**2.1** onto crotonaldehyde and 2-octynal (entries 13 - 16 in Table 2.2 and Table 2.3). One reaction was attempted using *E*-**2.1** with cinnamaldehyde under triflic acid-catalyzed conditions (entry 21, Table 2.2). No product was isolated, and a nearly quantitative amount of starting materials (*E*-**2.1** and aldehyde) was recovered. However, previous experience with cinnamaldehyde as a substrate in allylboration reactions has been negative, so this result was not surprising.

2.4 Observations resulting from the aldehyde substrate scope[16]

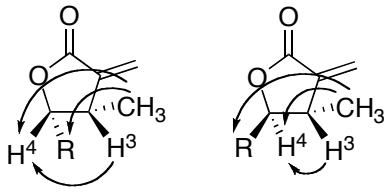
2.4.1 Aldehyde effect on diastereoselectivity

An interesting trend is observed when one looks at the relative stereochemistry of these γ-lactone products. While all reactions with *Z*-**2.1** led to the corresponding *trans* γ-lactones, some of the allylborations using *E*-**2.1** did in fact give the opposite selectivity and produced the *trans* γ-lactone as well. However, this is not always the case. Some of the aldehydes did produce the initially expected *cis* γ-lactone when reacted with *E*-**2.1**. Thus, it is apparent that not all aldehydes are prone to give the reverse selectivity as previously observed

when using *E*-**2.1** and aldehyde **2.2** in the synthesis of **2.3** (Equation 2.1). From the electronic nature of these aldehydes, it would seem that aldehydes with a substituent capable of stabilizing a carbocation at the 5-position in the resulting γ-lactones (entries 3, 5, 7, 9, 11 and 13 in Table 2.2) give the unexpected outcome (i.e. *trans* γ-lactones), while others that are less effective at stabilizing a carbocation (entries 1, 15, 17 and 19 in Table 2.2) lead to the expected *cis* γ-lactones when subjected to the triflic acid-catalyzed allylboration conditions. For example, the *p*-nitrophenyl group (entry 1 in Table 2.2) would destabilize any carbocation formed at the α-position (previously the carbonyl carbon of the aldehyde) and this leads to the observed *cis* γ-lactone being formed exclusively.

2.4.2 NOE correlations for *cis* and *trans* α-methylene γ-lactones

For all γ-lactones that were synthesized, cycle NOE experiments were used to determine the relative stereochemistry between the methyl group at the β-position and the R group at the γ-position. Due to the puckering of the five-member lactones, the same correlations could sometimes be seen in both isomers. When this was the case, the size of the correlation had to be compared. These correlations were very different in magnitude and allowed for definitive assignments of the relative stereochemistry. Typical correlations can be seen in Table 2.4. As one can see, protons present on the R group of the lactone (i.e. the substituent originating from the aldehyde) were also useful in obtaining NOE data to allow for assignment of stereochemistry.



cis lactones *trans* lactones

γ-Lactone	Stereochemistry	CH_3 - R correlation[a]	CH_3 - H^4 correlation[a]	H^3 - H^4 correlation[a]
2.7a	*cis*	---	0.70	---
2.7b	*trans*	---	1.85	---
2.8a	*cis*	0.76	0.16	---
2.8b	*trans*	0.32	1.13	---
2.10a	*cis*	---	0.28	---
2.10b	*trans*	---	1.13	---
2.11a	*cis*	0.61	0.78	---
2.11b	*trans*	0.14	1.02	---
2.13a	*cis*	0.89	0.22	---
2.13b	*trans*	0.00	0.90	---
2.14a	*cis*	---	---	4.11
2.14b	*trans*	---	---	0.87
2.15a	*cis*	1.66	0.24	---
2.15b	*trans*	0.61	1.40	---
2.16a	*cis*	---	---	4.73
2.16b	*trans*	---	---	0.71

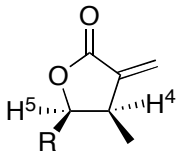
[a] Correlation values are obtained from cycle NOE spectrum that have been normalized to the irradiated peak intensity.

Table 2.4: Cycle NOE values for α-methylene γ-lactones

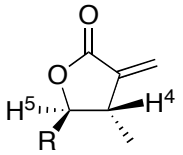
2.4.3 Trends in the ^{1}H NMR chemical shift for *cis* and *trans* α-methylene γ-lactones

Some interesting observations can be made when looking at the ^{1}H NMR data for these γ-lactones and comparing some of the chemical shifts between the different *cis* and *trans* isomers. The proton at the 4-position (H^4) was, in all cases studied, further upfield in the *trans* γ-lactone than the corresponding proton in the *cis* γ-lactone. The difference between the two was usually on the order of 0.7 ppm. Similarly, the proton at the 5-position (H^5) was also further upfield in the *trans* γ-lactone that the corresponding proton in the *cis* γ-lactone. These results,

summarized in Table 2.5, provide an established pattern that can allow for the relative stereochemistry of subsequently formed γ-lactones to be assigned based on the relative position of these peaks in the ^{1}H NMR spectrum. This chemical shift pattern may prove useful as a method of assigning relative stereochemistry in substituted α-methylene γ-lactones without the need to run time-consuming NOE experiments.



2.7a - 2.16a



2.7b - 2.16b

γ-Lactone	Stereochemistry	H^4 chemical shift[a] (ppm)	H^5 chemical shift[a] (ppm)
2.7a	*cis*	3.57 – 3.47	5.70
2.7b	*trans*	2.96 – 2.86	5.02
2.8a	*cis*	3.50 – 3.40	5.59
2.8b	*trans*	2.94 – 2.86	4.87
2.9a	*cis*	3.44 – 3.35	5.57
2.9b	*trans*	2.97 – 2.91	4.84
2.10a	*cis*	3.56 – 3.46	5.83
2.10b	*trans*	3.10 – 3.02	5.23
2.11a	*cis*	3.46 – 3.38	5.59
2.11b	*trans*	2.99 – 2.90	4.87
2.12a	*cis*	3.46 – 3.40	5.60
2.12b	*trans*	2.85 – 2.90	4.84
2.13a	*cis*	3.26 – 3.15	4.95
2.13b	*trans*	2.78 – 2.68	4.30
2.14a	*cis*	3.22 – 3.15	5.23
2.14b	*trans*	3.08 – 3.02	4.57
2.15a	*cis*	3.23 – 3.12	4.57 – 4.51
2.15b	*trans*	2.80 – 2.60	3.99
2.16a	*cis*	3.13	4.14
2.16b	*trans*	2.99 – 2.81	3.83

[a] Chemical shift is reported based on ppm downfield of tetramethylsilane. All ^{1}H NMR experiments were performed using $CDCl_3$ as solvent.

Table 2.5: Comparison of chemical shifts in ^{1}H NMR spectra for *cis* and *trans* γ-lactones

2.5 Mechanistic investigation into the origin of isomerization[16]

Several questions remained in our quest to understand the mechanism of the triflic acid-catalyzed allylboration reaction: was a carbocation being formed or not, how was the triflic acid turning over as a catalyst and what was the intermediate leading to the observed reversal of stereoselectivity? As first reported by the Hall group,[2] and further suggested by others,[17] we initially suspected that the open borate intermediate **A** (Figure 2.1) must be forming a carbocation, which would then be trapped by the nearby ester group to form the observed five-membered lactones.

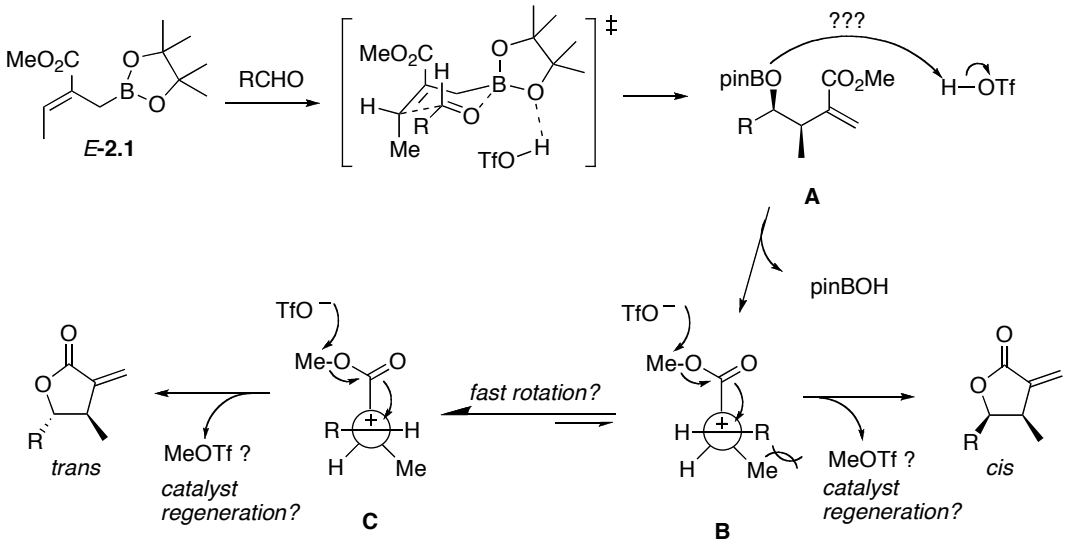


Figure 2.1: Early mechanistic hypotheses and questions that required investigation

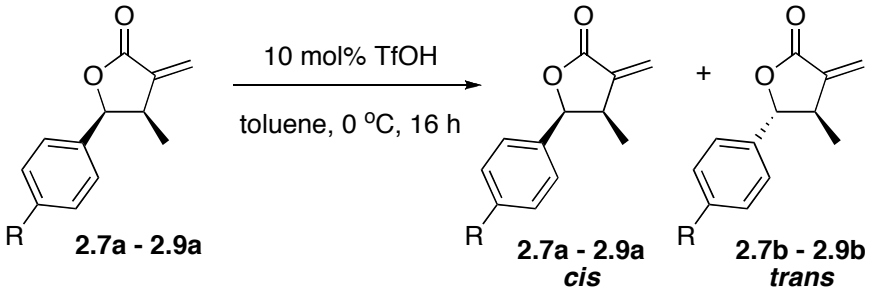
From my investigation on the substrate scope (Tables 2.2 and 2.3), it was immediately noticed that only allylic boronate *E*-**2.1** gave an inversion of the expected stereochemistry in the γ-lactone products while products obtained using *Z*-**2.1** did not show this reversal. Thus, there must be an intermediate, possibly carbocation **B** in Figure 2.1, which, when *E*-**2.1** is used, allows for a conformational change in the molecule (**B** to **C**, Figure 2.1) and subsequent formation of the *trans* γ-lactones. With the reasonable assumption that the *trans* γ-

lactone is the kinetically favored product, the same intermediate could also be present when *Z*-**2.1** is used, but still lead to the expected product stereochemistry. Circumstantial evidence for this comes from the substrate scope investigation (Table 2.2 and Table 2.3), where if one takes a close look at the electronic nature of the aldehydes used, those with a group (R) that could stabilize a carbocation on the resulting adduct are the ones that are observed to give the unexpected stereochemistry. Any aldehydes that contained electron-withdrawing groups and could not stabilize a nearby carbocation (e.g. alkyl, propargyl) did not display the reversal of stereochemistry. From these observations, it is not unreasonable to believe that the lactonization must be going through a carbocation (i.e. S_N1) mechanism, but conclusive proof was desired. A follow-up of the original report[2] by another group[17] also alluded to an S_N1 mechanism for the lactonization step under strong Lewis acid conditions, but it offered no evidence for it nor addressed several key issues.

2.5.1 Control experiments to address the possibility of lactone isomerization[16]

Based upon the acidic conditions used in this allylboration reaction, I was initially aware that it could be the *cis* lactones themselves that were isomerizing via a reversible S_N1 mechanism to the more stable *trans* form. Due to the eclipsing bulky substituents in the *cis* γ-lactones, the *trans* γ-lactones are likely to be thermodynamically favorable. Thus, in the presence of triflic acid, it might be possible that the initially formed *cis* γ-lactone product was opening up to form a carbocation, which then underwent a rearrangement to a different conformation via C–C bond rotation (i.e., **B** to **C** in Figure 2.1) to alleviate the steric strain of the nearby bulky groups. This would be followed by subsequent relactonization to form the observed *trans* γ-lactones. Under this hypothesis, aldehydes with a group that could stabilize the carbocation would undergo this inversion of stereoselectivity preferentially. To assess whether isomerization of the γ-lactone products is playing a role in the reversal of diastereoselectivity instead of an open borate intermediate forming a carbocation (Figure 2.1), I studied three different

cis γ-lactones. I started with the *cis* γ-lactones that had the *p*-nitro phenyl group (**2.7a**), the *p*-bromo phenyl group (**2.8a**) and the *p*-methoxy phenyl group (**2.9a**). Each of these *cis* γ-lactones were subjected to the same conditions used in the catalyzed allylboration reaction; 0 °C for sixteen hours with 10 mol% triflic acid. ^{1}H NMR spectra of crude products were obtained after the typical work-up, and the ratio of *cis*:*trans* isomers were measured (Table 2.6).



Entry	Initial lactone	Ratio of lactone products (**a**:**b**) [a]
1	**2.7a** (R = NO_2)	100:0
2	**2.8a** (R = Br)	74:26
3	**2.9a** (R = OMe)	5:95

[a] Ratio of products determined by ^{1}H NMR of crude reaction mixture.

Table 2.6: Attempts to isomerize c*is* γ-lactones to *trans* γ-lactones

When **2.7a** was subjected to these conditions, there was no isomerization observed. This can be rationalized because of the strong electron-withdrawing nature of the *p*-nitrophenyl group. The resulting benzylic carbocation would be highly destabilized by any buildup of charge and the lactone would immediately reform before any rotation/isomerization could occur. Thus, none of *trans* γ-lactone **2.7b** was observed. The complete opposite is true for **2.9a**. Here, the *p*-methoxyphenyl group stabilizes a benzylic carbocation and this allows for the *cis* isomer to completely isomerize to the more stable *trans* γ-lactone. These two results are consistent to those obtained in Table 2.2. However, the result from entry 2 in Table 2.6 provides us with new information. Even though there is isomerization of lactone **2.8a** to **2.8b** under the reaction conditions, it is only partial. This is significant in that during the substrate scope, **2.8b** was obtained as

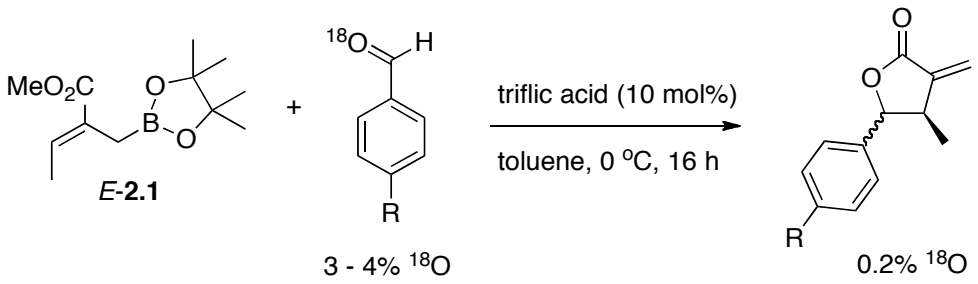
the sole product (entry 3, Table 2.2). Thus, the isomerization seen here is clearly not fast enough to explain the full isomerization observed previously for the allylboration/lactonization leading to **2.8b.** Hence, γ-lactone isomerization from the *cis* isomer to the *trans* isomer cannot be the sole mechanism affording this observed reversal of stereochemistry. Thus, the main origin of this isomerization phenomenon must occur prior to γ-lactone formation.

2.5.2 Isotopic labeling for tracking the aldehyde oxygen[16]

I decided to use oxygen-18 labelling of aldehydes to probe the location of the aldehyde oxygen throughout the reaction with respect to the suspected intermediacy of a carbocation in the isomerization event. If the aldehydes were labeled with oxygen-18 and then reacted with *E*-**2.1**, it would be possible to determine if the oxygen from the aldehyde ended up being incorporated into the γ-lactones. If the aldehyde oxygen atom is not incorporated into the final γ-lactone product, this would prove that the process must be proceeding through a carbocation intermediate. A mechanism incorporating an S_N2 attack on that carbon center leading to the loss of the aldehyde oxygen atom would result in an inversion (*trans* γ-lactone product) for all aldehydes, which is not observed and has therefore been ruled out.

I chose 4-nitrobenzaldehyde and 4-bromobenzaldehyde so as to make a good comparison between extremes of electronic properties. These two different oxygen-18 labeled aldehydes were made according to previously reported literature procedures[18] using 10% ^{18}O-enriched water. The oxygen-18 labeled aldehydes were confirmed by high-resolution mass spectrometry (3 - 4% ^{18}O incorporation). These aldehydes were subjected to the triflic acid-catalyzed allylboration reaction conditions, and the γ-lactones were purified in the typical fashion. Once isolated, they were analyzed by mass spectrometry in order to determine if there were elevated levels of oxygen-18. The normal isotopic distribution of oxygen includes 0.20% of naturally occurring oxygen-18. Based on the results from the mass spectrometry analysis, the two γ-lactones synthesized

from 4-nitrobenzaldehyde and 4-bromobenzaldehyde showed a level of oxygen-18 that was not distinguishable from the naturally occurring level (Equation 2.3).



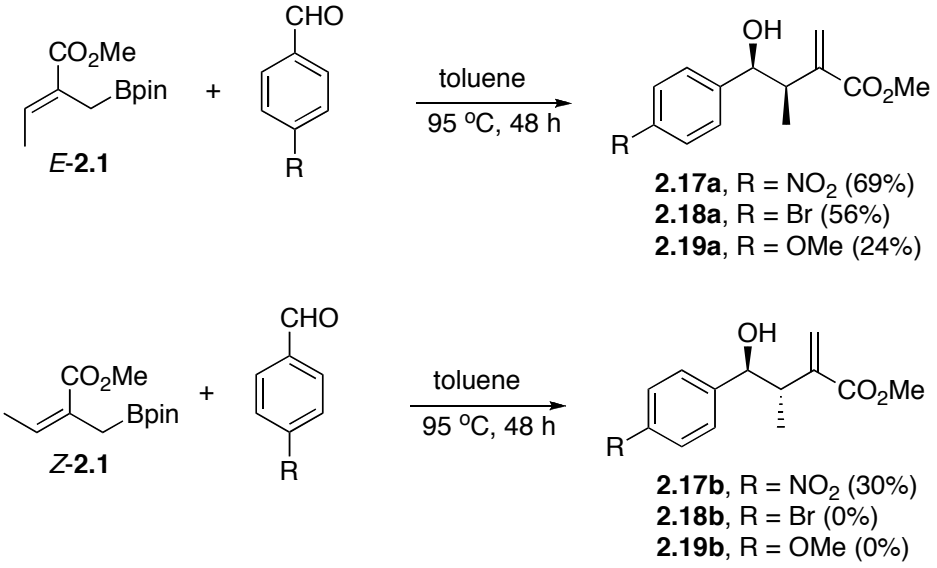
Equation 2.3: Oxygen-18 labeled aldehydes under Brønsted acid conditions

This experiment was performed twice, with the same conclusion that the oxygen from the aldehyde was not present in the final isolated lactone in each case. These results further support the hypothesis that the triflic acid-catalyzed allylboration reaction proceeds through a carbocation intermediate, leading to the loss of the aldehyde oxygen during the ionization process.

2.5.3 Isolation of open intermediates and investigations of their isomerization[16]

To further confirm the suspected carbocation isomerization process, I next turned our investigation toward the exact nature of the open intermediate that would lead to the suspected carbocation. To this end, I set out to isolate the open form of the allylboration product. Previous work in our group had found that a decrease in the temperature for the thermal allylboration reaction could prevent lactonization from occurring.[5] Using this information, I synthesized the corresponding acyclic methyl esters using three different aldehydes: 4-nitrobenzaldehyde, 4-bromobenzaldehyde, and 4-methoxybenzaldehyde. The three aldehyde substrates were reacted under thermal allylboration conditions with both *E*-**2.1** and *Z*-**2.1** in an attempt to obtain both the *cis* and *trans* acyclic methyl esters. Three of the *cis* methyl esters (**2.17a** – **2.19a**) and one of the *trans*

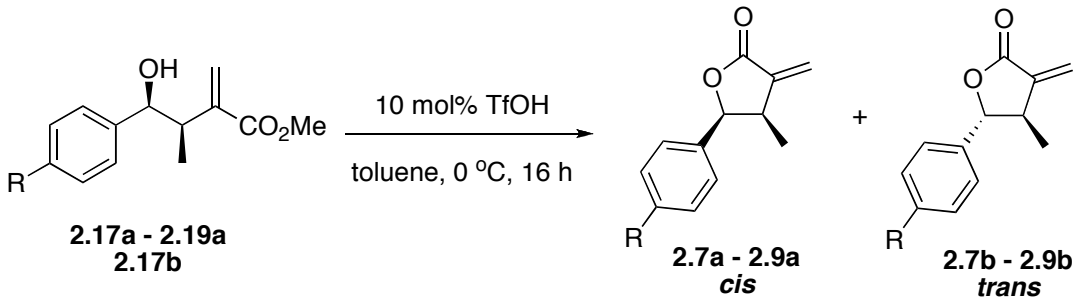
methyl esters (**2.17b**) were isolated after aqueous workup and purified by flash chromatography (Scheme 2.2).



Scheme 2.2: Synthesis of *cis* and *trans* acyclic methyl hydroxy-esters

All three aldehydes were reacted with *E*-**2.1** to give the corresponding *cis* methyl ester products **2.17a** – **2.19a**. The assignments of stereochemistry were done on the basis of coupling constants and comparison of chemical shifts in the H NMR spectrum between the methyl esters and their corresponding γ-lactones. This stereochemical outcome is consistent with standard allylboration chemistry based on a closed six-member transition state (as discussed in Chapter 1). When the same three aldehydes were reacted with *Z*-**2.1** under thermal conditions, only the reaction using 4-nitrobenzaldehyde resulted in any acyclic methyl ester product being isolated. For the other two cases, only the corresponding γ-lactones **2.8b** and **2.9b** were isolated after work-up. Interestingly, after **2.17b** was left on the benchtop for two weeks, an ^{1}H NMR experiment was performed and considerable conversion of **2.17b** to γ-lactone **2.7b** was observed. Therefore, it can be assumed that **2.18b** and **2.19b** were not isolable due to the fact that they were probably lactonizing spontaneously under the reaction conditions or at room temperature during work-up to their corresponding γ-lactones. The isolated

acyclic methyl esters were subjected to triflic acid catalysis at 0 °C for 16 hours (standard catalyzed conditions). All underwent lactonization to their corresponding γ-lactones, and these results are summarized in Table 2.7.



2.17a - 2.19a
2.17b

2.7a - 2.9a
cis

2.7b - 2.9b
trans

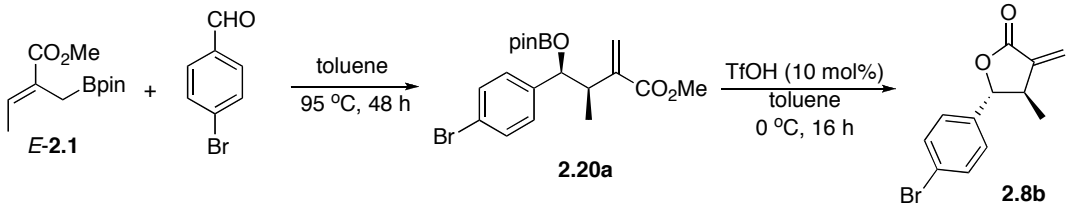
Entry	Methyl Ester	Product	Ratio of Products[a]
1	**2.17a** (R= NO_2)	**2.7a/2.7b**	90:1
2	**2.18a** (R= Br)	**2.8a/2.8b**	66:1
3	**2.19a** (R= OMe)	**2.9a/2.9b**	16:84
4	**2.17b** (R= NO_2)	**2.7a/2.7b**	0:100

[a] Ratio was determined by ^{1}H NMR analysis of crude reaction mixture

Table 2.7: Lactonization of acyclic methyl esters under triflic acid conditions

Upon investigation of these results, **2.17a** cyclizes to give mainly the *cis* γ-lactone **2.7a**, and **2.17b** cyclizes to give *trans* γ-lactone **2.7b**, which is consistent with our previous results obtained during the substrate scope investigation (entry 1, Table 2.2 and Table 2.3). As well, **2.19a** cyclizes to give mainly the *trans* γ-lactone **2.9b**, again consistent with our substrate scope investigation (entry 5, Table 2.2). Returning to the carbocation hypothesis, if a carbocation can be stabilized, it will give the *trans* γ-lactone as the major product. If no appreciable stabilization is possible, then the *cis* γ-lactone will be observed as the major product. These first three results discussed (entries 1, 2 and 4, Table 2.7) were quite reassuring. It was noted that the result in entry 2, however, was completely opposite to what was expected. One would expect that the *p*-bromophenyl group could stabilize a carbocation through resonance, so the *trans* γ-lactone would be expected as the major product based on our previous result using allylic boronate *E*-**2.1** and *p*-bromobenzaldehyde under triflic acid catalysis (entry 3, Table 2.2).

Instead, the *cis* γ-lactone isomer **2.8a** was observed as the major product from **2.18a**! A critical examination of this experiment can help to clarify these seemingly contradictory results. It should be realized that the free alcohols that were isolated and then subjected to the catalyzed allylboration conditions are not the true intermediates that would be present in the typical allylboration/lactonization reactions. The free alcohols may form in a serendipitous manner depending on the reaction conditions, but the anticipated intermediate would contain a pinacol borate unit at the benzylic position, not a free hydroxyl group. These borate intermediates may be more prone to acid-catalyzed isomerization. At this point, the borate analogue of **2.18a** was synthesized via a standard thermal allylboration procedure (Scheme 2.3). ^{1}H NMR spectroscopic analysis was performed on the crude reaction mixture before any work-up was done to confirm the presence of the borate group on intermediate **2.20a**. Once this had been confirmed, the borate intermediate **2.20a** was subjected to the triflic acid-catalyzed conditions. To my satisfaction, ^{1}H NMR spectroscopic analysis of the crude product after work-up showed the presence of *trans* γ-lactone **2.8b** as the major product with only a trace amount of *cis* γ-lactone **2.8a** present.



Scheme 2.3: Synthesis and cyclization of *cis* borate **2.20a** intermediate to provide *trans* α-methylene γ-lactone **2.8b**

As a side note, this surprising observation that the free alcohol intermediate **2.18a** leads to one isomer while the corresponding borate intermediate **2.20a** leads to the other isomer brings to light a selectivity issue with triflic acid activation. As discussed earlier, in the triflic acid-catalyzed allylboration reaction, the triflic acid activates the borate and causes carbocation

formation, which then allows for intramolecular trapping via the ester either before any bond rotation can occur (**B**, Figure 2.1, leading to the expected *cis* γ-lactones) or after bond rotation (**C**, Figure 2.1, leading to the observed reversal of stereochemical outcome in the form of the *trans* γ-lactone). However, if the borate intermediate is trapped and hydrolyzed to the corresponding alcohol, and then subjected to the triflic acid conditions, a different stereochemical outcome is observed. To explain this dichotomy, a mechanism that does not include carbocation formation may be considered to explain the competing lactonization pathways that provide retention of stereochemistry. In these instances, the triflic acid may be preferentially activating the carboxyester in the presence of the free alcohol (Figure 2.2). The activated ester is then attacked intramolecularly by the nearby alcohol, which leads to the eventual elimination of a molecule of methanol. This substitution-type mechanism would explain the retention of stereochemistry with certain aldehyde substrates. However, this proposal is inconsistent with the results of the oxygen-18 labelling studies (see section 2.5.2).

Another alternative, which is more consistent with the absence of O^{18} labeling when using *p*-nitrobenzaldehyde, suggests that a carbocation is still formed in these cases (thereby losing the oxygen originating from the aldehyde), but the carbocation's extreme reactivity (in aldehyde-specific cases) precludes bond rotation prior to attack by the ester. This hypothesis is discussed in the following section along with a complete analysis of the mechanistic experiments that were performed and a proposed mechanistic cycle.

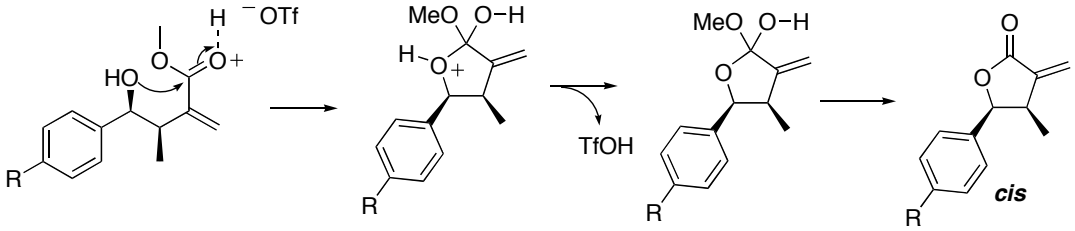


Figure 2.2: Possible cyclization mechanism of open methyl ester intermediates containing a free alcohol

2.6 Mechanistic cycle and triflic acid catalyst turnover[16]

2.6.1 Proposal of a mechanistic cycle

With all of the mechanistic results in hand, the reaction stereochemistry has been clarified. The reaction proceeds through the expected Zimmerman–Traxler transition state to provide borate intermediate **A** (Figure 2.3). The reversal of observed stereochemistry begins when the initial borate intermediate **A** is subsequently transformed into carbocation **B**. This is followed by bond rotation to a more favorable conformer **C** and subsequent trapping by the nearby ester group to give the *trans* γ-lactone. For aldehydes that do not stabilize a carbocation, this catalytic cycle is still valid. The difference for these aldehydes is that once the very reactive intermediate carbocation **B** forms, it is attacked immediately by the nearby ester to form the *cis* γ-lactone before any bond rotation can occur. As protonation/ionization could require a conformation where both the borate and the carboxyester are held in close proximity to allow for effective proton transfer, the carbocation would be generated while the molecule sits in an unfavorable conformation (with *syn* R and Me groups). However, lactonization is rapid and leads to the *cis* γ-lactone instead of the *trans* γ-lactone, as outlined in Figure 2.3.

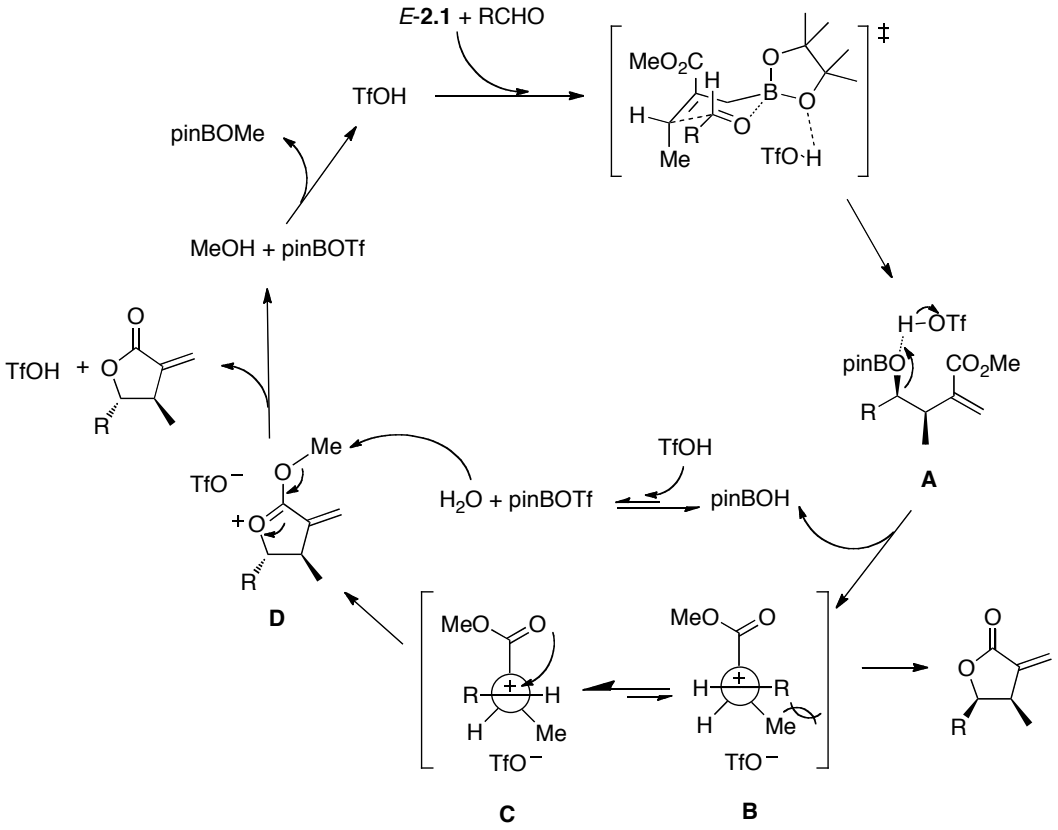
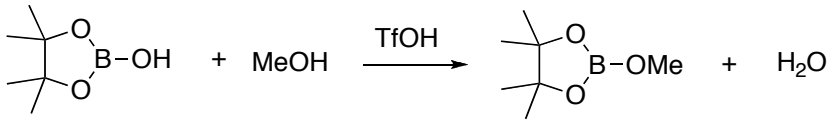


Figure 2.3: Proposed triflic acid-catalyzed allylboration/lactonization mechanism

2.6.2 Role of triflic acid in the allylboration/lactonization mechanism

Triflic acid plays numerous functions in the postulated multistep mechanism of Figure 2.3. First, it is expected to catalyze the allylboration reaction by the same electrophilic boronate activation mechanism demonstrated before for the Lewis acid-catalyzed variant.[19] As seen from this mechanistic cycle, the possible catalyst turnover requires the formation of one molecule of water from pinBOH and another equivalent of triflic acid. This water molecule would then act as a nucleophile on the methoxy moiety of the alkoxyoxonium intermediate **D**, leading to the lactone product and a molecule of methanol. One full equivalent of the triflic acid is also regenerated at this point via elimination of pinBOMe, making the entire cycle catalytic in TfOH. The overall reaction for these by-products is shown in Equation 2.4. As already mentioned, the molecule of water

produced is consumed in the reaction, and the only by-product of the reaction would be pinBOMe. It should be noted that the attack of water on the oxonium carbon of **D** in Figure 2.4 (as opposed to attacking the methoxy carbon) would lead to the same outcome, but this is not consistent with the absence of oxygen-18 labeling in the experiments described in Section 2.5.2. The oxygen atom in the H_2O by-product is the oxygen atom originally in the aldehyde carbonyl, thus, it is not reincorporated into the final γ-lactone products.

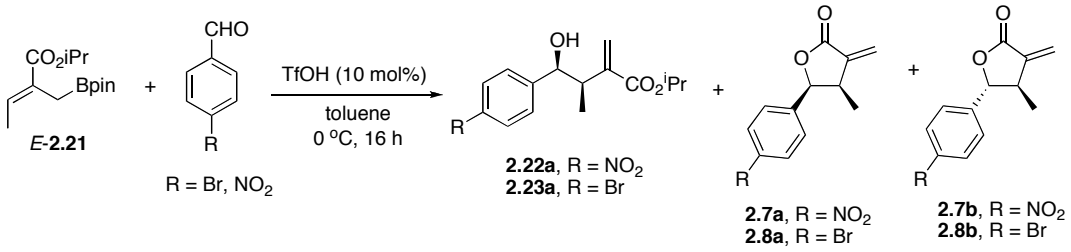


Equation 2.4: Overall reaction of by-products during triflic acid-catalyzed allylboration reaction

2.6.3 Other mechanistic considerations and alternative mechanisms

It is important to note that the issue of catalyst turnover remains uncertain, and there are other options for this catalytic cycle. Instead of a molecule of water, it could be the triflate anion itself that attacks the oxonium's methoxy group in **D** to form the final lactone products. This mechanism would lead to formation of MeOTf, which would be a dead end as it would likely cause irreversible consumption of the triflic acid. The initial catalyst, triflic acid, would not be regenerated and the reaction would require another species to perpetuate the cycle. In this regard, it is possible that pinBOTf could take over in the catalytic cycle and act as a Lewis acid to promote further allylboration/lactonization reactions to occur. At this point, it is not immediately evident what catalytic cycle is occurring. The triflate anion is a very poor nucleophile, but still might be capable of undergoing attack on the oxonium's methoxy group. A borate can be observed in the crude ^{11}B NMR spectrum at ~22 ppm, but this could correspond to either pinBOTf or pinBOMe. High-resolution mass spectrometry could have shed light on this issue but was not possible to carry out due to the extremely corrosive

nature of TfOH. To gain more information about this proposed catalytic cycle, we went one step further and synthesized the isopropyl 2-alkoxycarbonyl allylboronate *E*-**2.21** analogue of *E*-**2.1** and subjected it to the triflic acid allylboration conditions with two different aldehydes (Equation 2.5). This allylic boronate could provide more insight into the breakdown and cyclization process, as the isopropyl group in *E*-**2.21** is less prone to nucleophilic attack as compared to the methyl group in *E*-**2.1**. Two different aldehydes were reacted with *E*-**2.21** to give the expected corresponding γ-lactones **2.7a** (for R = NO_2) and **2.8b** (for R = Br) as products.



Equation 2.5: Reaction of *E*-**2.21** with two different aldehydes to provide insight into the cyclization process and catalyst turnover

From the crude ^{1}H NMR spectra, however, there were considerable amounts of the open allylboration products that had failed to undergo lactonization. For the reaction between *E*-**2.21** and *p*-nitrobenzaldehyde, **2.22a**, **2.7a** and **2.7b** were obtained in a ratio of 3.2 : 1 : 0. It is not surprising that none of **2.7b** was observed, as any carbocation formed from this aldehyde would be highly destabilized and would undergo lactonization prior to a conformational change (*cf*. Figure 2.3). The fact that **2.22a** was obtained as the major product is surprising. To explain this, one needs to consider the electronic and steric nature of the isopropyl group as compared to the methyl group. The oxonium intermediate **D** in Figure 2.3 would be slightly more stable when the ester group is an isopropyl versus a methyl. However, the steric bulk of the isopropyl group prevents the oxonium intermediate from breaking down by nucleophilic attack as shown for the case of the methyl ester in Figure 2.3. Instead, this intermediate

could be quenched by water in the reaction mixture or during the aqueous work-up. Either way, this break down of the oxonium in the presence of water leads to **2.22a** or **2.7a**, both of which were observed. For the reaction between *E*-**2.21** and *p*-bromobenzaldehyde, **2.23a**, **2.8a** and **2.8b** were obtained in a ratio of 1.3 : 1 : 2.8. *Trans* γ-lactone **2.8b** was still the major product (consistent with substrate scope results) and the presence of **2.23a** can be rationalized by the intermediate oxonium being much slower to break down to generate the γ-lactone as compared to the methyl ester analogue (Figure 2.3). The presence of **2.8a** could be due to direct attack of the hydroxyborate intermediate on the ester. This process would be slow, but would explain how some of *cis* γ-lactone **2.8a** is formed. Regardless of the obtained mixtures, the presence of **2.8a** provides some interesting insight into the process of lactonization. The S_N2 attack of a nucleophile (either H_2O or TfO–) on the isopropoxy group is much slower compared to the methoxy group, and this would allow for the previously slower process of hydroxyborate attack on the ester to become much more important and lead to the presence of the *cis* γ-lactone **2.8a** to be present. The same rationale holds true for the *p*-nitrobenzaldehyde example; however, it is inconsequential because the *cis* product is the expected one regardless of which process is faster. In both cases, lactonization is slower, which is in agreement with a mechanism involving nucleophilic attack on the oxonium's alkoxy substituent by either water or the triflate anion. Regardless, triflic acid is essential to initiate this allylboration/lactonization methodology, however, the issue of detailed catalyst turnover remains speculative.

2.7 Conclusions[16]

For the triflic acid-catalyzed allylboration/lactonization reaction, the substrate scope was investigated and then mechanistic studies provided insight into the role of the aldehyde in the diastereoselectivity of the reaction and identified the presence of a unique reversal in observed stereochemistry in many

of the α-methylene γ-lactone products. The nature of the aldehyde substrate is the determinant for the stereochemistry of the γ-lactone products. Investigation into the mechanism of this reaction process confirmed our previous suspicion that the lactonization was proceeding via a carbocation mechanism. It was shown that γ-lactone epimerization does occur in some cases of lactones, however, not in substantially large enough amounts to account for the observed diastereomeric ratios in the triflic acid-catalyzed allylboration reaction. Furthermore, oxygen-18 labeling was used to track the aldehyde oxygen throughout the reaction sequence and indicated that none of the aldehyde oxygen was present in the final γ-lactone products. In light of these observations, the main mechanism of this triflic acid-catalyzed allylboration reaction is thought to involve formation of a carbocation intermediate from the initially formed open borate product. This event is followed by trapping of the carbocation by the neighbouring ester, either before or after bond rotation occurs, which leads to the observed diastereoselectivities in the γ-lactone products.

Mechanistic possibilities to explain catalyst turnover were discussed, and control experiments support a cycle involving a nucleophilic attack on the ester's alkoxy substituent. This knowledge regarding a stereocontrolled reaction that proceeds through a carbocation should help in designing and developing other reactions that can make use of this phenomenon. Furthermore, predictions on the stereochemical outcome of a reaction are a common practice in organic chemistry. However, as shown in this chapter, even the most reliable reactions (e.g. the allylboration reaction) can sometimes be altered by novel reaction conditions to give unexpected stereochemical outcomes.

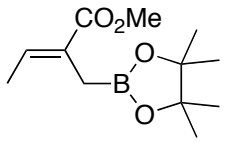
2.8 Experimental

2.8.1 General information

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, HMPA and CH_2Cl_2 were distilled over CaH_2. THF was distilled over sodium/benzophenone ketyl. NH_4Cl(aq) and $NaHCO_3$(aq) refer to saturated aqueous solutions. All aldehydes were purified by Kugelrohr distillation prior to use. Methyllithium was titrated according to the Gilman double titration method.[20] Iodomethaneboronate[21] and chloromethaneboronate[22] were prepared according to literature procedures. TfOH was stored under argon in a pear-shaped flask with a glass stopper and placed in a jar filled with anhydrous calcium sulfate which was then stored at 0 °C. All other chemicals were used as received from commercial sources. Thin layer chromatography (TLC) was performed on silica gel plates and was visualized with UV light or potassium permanganate stain. NMR spectra were recorded on 400 or 500 MHz instruments. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards ^{1}H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were recorded by the University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab.

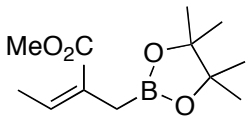
2.8.2 Synthesis of allylic boronates

Methyl (2*E*)-2-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-but-2-enoate (*E*-2.1)



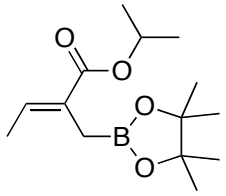
This compound was synthesized using known literature procedures and the product possessed identical spectroscopic characteristics to those reported in the literature.[2]

Methyl (2*Z*)-2-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-but-2-enoate (*Z*-2.1)



This compound was synthesized using known literature procedures and possessed identical spectroscopic characteristics to those reported in the literature.[2] This compound could be isolated as a 20:1 mixture of *Z*:*E* isomers, with the desired compound being the major component.

Isopropyl (2*E*)-2-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-but-2-enoate (*E*-2.21)



This compound was prepared using the identical procedure as that used to synthesize *E*-**2.1** except that isopropyl propiolate was used instead of methyl

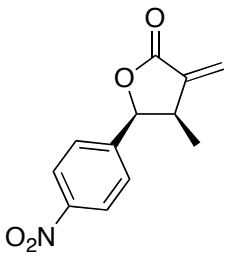
propiolate as the alkyne source. Isopropyl propiolate was made using a known literature procedure.[23]

Flash chromatography (15 % ethyl ether in hexanes) yielded the product as a pale yellow oil in 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 – 6.76 (m, 1H), 5.03 (sept, 1H, *J* = 6.2 Hz), 1.85 (br s, 2H), 1.77 (br dt, 3H, *J* = 7.0, 0.9 Hz), 1.26 (d, 6H, *J* = 6.2 Hz), 1.24 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 134.9, 130.9, 83.3, 67.7, 24.8, 24.5, 22.0, 14.5; ^{11}B NMR (128 MHz, $CDCl_3$): δ 31.7; IR (CH_2Cl_2 microscope, cm^{-1}): 2979, 2935, 1704, 1348, 1325, 1273, 1146; HRMS (EI, m/z) Calcd for $C_{14}H_{25}{}^{11}BO_4$: 268.1846. Found: 268.1843.

2.8.3 General procedure for the synthesis of γ-lactones under TfOH-catalyzed conditions using *E*-2.1

A solution of *E*-**1** (100 mg, 0.42 mmol) and aldehyde (0.83 mmol) in toluene (1 mL) at 0 °C was treated with TfOH (4 μL, 0.04 mmol) and stirred at 0 °C under an argon atmosphere for 16 h. The mixture was then diluted with NH_4Cl(aq)/NH_4OH (9:1 v/v, 10 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated. Crude products were then purified by flash chromatography to yield the corresponding γ-lactone.

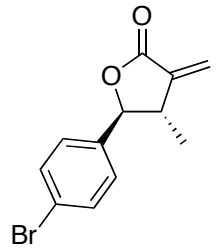
cis-4-Methyl-3-methylene-5-(4-nitro-phenyl)-dihydro-furan-2-one (2.7a)



Flash chromatography (20% EtOAc/hexanes) yielded the product as a yellow solid in 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 – 8.25 (m, 2H), 7.41 –

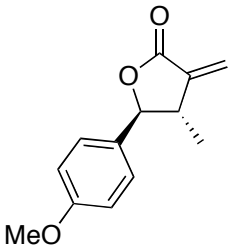
7.38 (m, 2H), 6.38 (d, 1H, *J* = 2.5 Hz), 5.70 (d, 1H, *J* = 8.1 Hz), 5.66 (d, 1H, *J* = 2.4 Hz), 3.57 – 3.47 (m, 1H), 0.80 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 147.9, 143.6, 135.2, 126.9, 123.8, 122.9, 80.7, 38.7, 15.8; IR (CH_2Cl_2 cast film, cm^{-1}): 3082, 2973, 2933, 1770, 1521, 1349; HRMS (EI, m/z) Calcd for $C_{12}H_{11}NO_4$: 233.0688. Found: 233.0685. Elem. Anal. (%) Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.99; H, 4.97; N, 5.74.

***trans*-5-(4-Bromo-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.8b)**



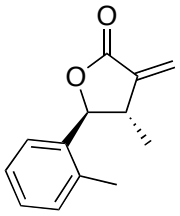
Flash chromatography (20% EtOAc/hexanes) yielded the product as a white solid in 62% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.52 (m, 2H), 7.25 – 7.21 (m, 2H), 6.33 (d, 1H, *J* = 3.3 Hz), 5.60 (d, 1H, *J* = 2.9 Hz), 4.87 (d, 1H, *J* = 7.7 Hz), 2.94 – 2.86 (m, 1H), 1.33 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 139.9, 137.3, 131.9, 127.4, 122.7, 121.2, 85.0, 43.3, 15.7; IR (CH_2Cl_2 cast film, cm^{-1}): 2968, 2931, 1769, 1490, 1254, 1039; HRMS (EI, m/z) Calcd for $C_{12}H_{11}O_2{}^{81}Br$: 267.9922. Found: 267.9925. Elem. Anal. (%) Calcd for $C_{12}H_{11}O_2{}^{81}Br$: C, 53.96; H, 4.15. Found: C, 53.85; H, 4.48.

***trans*-5-(4-Methoxy-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.9b)**



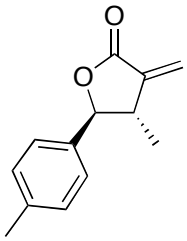
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow solid in 62% yield. Spectral data for **2.9b** was identical to that found in literature.[24]

***trans*-4-Methyl-3-methylene-5-*o*-tolyl-dihydro-furan-2-one (2.10b)**



Flash chromatography (10% EtOAc/hexanes) yielded the product as a pale yellow oil in 49% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.18 (m, 4H), 6.33 (d, 1H, *J* = 3.0 Hz), 5.60 (d, 1H, *J* = 2.7 Hz), 5.23 (d, 1H, *J* = 7.1 Hz), 3.10 – 3.02 (m, 1H), 2.37 (s, 3H), 1.32 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 140.6, 136.5, 135.5, 130.9, 128.6, 126.6, 125.7, 121.3, 83.1, 42.6, 19.5, 17.2; IR (microscope, cm^{-1}): 2968, 1768, 1312, 1255, 1140, 986; HRMS (EI, m/z) Calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0991.

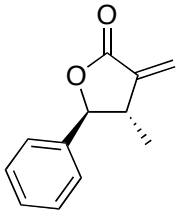
***trans*-4-Methyl-3-methylene-5-*p*-tolyl-dihydro-furan-2-one (2.11b)**



Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow oil in 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.19 (m, 4H), 6.31 (d, 1H, *J* = 3.2 Hz), 5.58 (d, 1H, *J* = 2.9 Hz), 4.87 (d, 1H, *J* = 7.8 Hz), 2.99 – 2.90 (m, 1H), 2.37 (s, 3H), 1.31 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2,

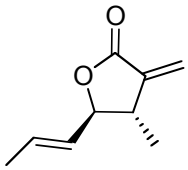
140.8, 138.8, 135.4, 129.5, 126.0, 120.8, 86.0, 43.4, 21.2, 15.8; IR (CH_2Cl_2 cast film, cm^{-1}): 2968, 2925, 1769, 1256, 1138, 983; HRMS (EI, m/z) Calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0996.

***trans*-4-methyl-3-methylene-5-phenyl-dihydro-furan-2-one (2.12b)**



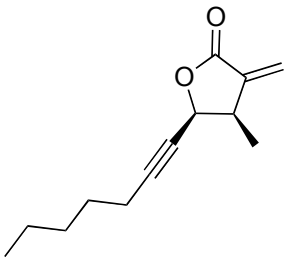
Flash chromatography (15% EtOAc/hexanes) yielded the product as a pale yellow solid in 58% yield. Spectral data for **2.12b** was identical to that found in literature.[25]

***trans*-4-Methyl-3-methylene-5-propenyl-dihydro-furan-2-one (2.13b)**



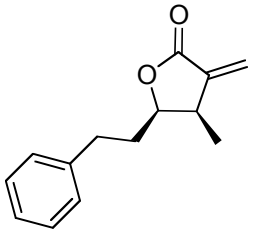
Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 79% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 6.23 (d, 1H, J = 3.3 Hz), 5.88 (dqd, 1H, J = 15.2, 6.7, 0.9 Hz), 5.52 (d, 1H, J = 3.0 Hz), 5.51 (ddq, 1H, J = 15.3, 7.9, 1.5 Hz), 4.30 (t, 1H, J = 7.9 Hz), 2.78 – 2.68 (m, 1H), 1.77 (ddd, 3H, J = 6.6, 1.7, 0.6 Hz), 1.23 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 140.6, 131.9, 127.9, 120.4, 85.6, 40.9, 17.9, 15.5; IR (CH_2Cl_2 cast film, cm^{-1}): 3096, 2969, 2920, 1766, 1248, 1143, 966; HRMS (EI, m/z) Calcd for $C_9H_{12}O_2$: 152.0837. Found: 152.0839.

***cis*-5-Hept-1-ynyl-4-methyl-3-methylene-dihydro-furan-2-one (2.14a)**



Flash chromatography (20% EtOAc/hexanes) yielded the product as an orange oil in 63% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.27 (d, 1H, *J* = 2.9 Hz), 5.57 (d, 1H, *J* = 2.7 Hz), 5.23 (dt, 1H, *J* = 8.0, 2.1 Hz), 3.22 – 3.15 (m, 1H), 2.23 (td, 2H, *J* = 7.2, 2.1 Hz), 1.54 – 1.48 (m, 2H), 1.38 – 1.27 (m, 4H), 1.31 (d, 3H, *J* = 7.0 Hz), 0.89 (app t, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 139.3, 121.6, 91.4, 73.8, 72.2, 37.9, 31.0, 28.0, 22.1, 18.7, 15.1, 14.0; IR (CH_2Cl_2 cast film, cm^{-1}): 2957, 2933, 2861, 2233, 1771, 1244, 1116, 969; HRMS (EI, m/z) Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1305. Elem. Anal. (%) Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.26; H, 8.99.

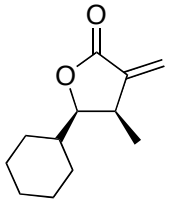
***cis*-4-Methyl-3-methylene-5-phenethyl-dihydro-furan-2-one (2.15a)**



Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 46% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.30 (m, 2H), 7.26 – 7.21 (m, 3H), 6.25 (d, 1H, *J* = 2.9 Hz), 5.56 (d, 1H, *J* = 2.6 Hz), 4.57 – 4.51 (m, 1H), 3.23 – 3.12 (m, 1H), 2.94 (ddd, 1H, *J* = 19.7, 8.7, 5.8 Hz), 2.74 (ddd, 1H, *J* = 16.7, 8.5, 8.5 Hz), 1.89 – 1.78 (m, 2H), 1.18 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 141.0, 140.8, 128.6, 128.6, 126.2, 120.9, 80.0, 37.5, 32.8, 31.9, 13.9; IR (CH_2Cl_2 cast film, cm^{-1}): 3506, 3062, 3027, 2968, 1762, 1267,

1245, 1124; HRMS (EI, m/z) Calcd for $C_{14}H_{16}O_2$: 216.1150. Found: 216.1153. Elem. Anal. (%) Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.99; H, 7.56.

***cis*-5-Cyclohexyl-4-methyl-3-methylene-dihydro-furan-2-one (2.16a)**

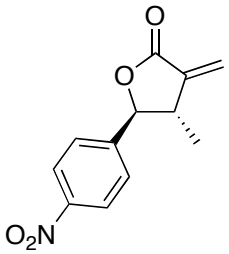


Flash chromatography (10% EtOAc/hexanes) yielded the product as a clear oil in 11% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.13 (d, 1H, *J* = 2.3 Hz), 5.53 (d, 1H, *J* = 2.0 Hz), 4.14 (t, 1H, *J* = 7.0 Hz), 3.13 (pt, 1H, *J* = 7.2, 2.2 Hz), 1.93 – 1.85 (m, 1H), 1.82 – 1.72 (m, 2H), 1.71 – 1.65 (m, 1H), 1.65 – 1.58 (m, 2H), 1.33 – 1.00 (m, 5H), 1.16 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 142.1, 119.7, 85.0, 38.2, 37.4, 29.3, 28.8, 26.2, 25.8, 25.5, 14.5; IR (microscope, cm^{-1}): 2930, 2854, 1765, 1268, 1151, 963; HRMS (EI, m/z) Calcd for $C_{12}H_{18}O_2$: 194.1307. Found: 194.1304.

2.8.4 General procedure for the synthesis of γ-lactones under TfOH-catalyzed conditions using *Z*-2.1

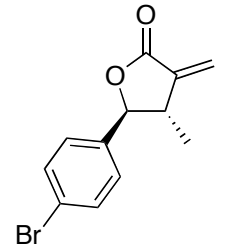
The procedure for the TfOH catalyzed allylboration reaction using *Z*-**2.1** was identical to that utilized in the reactions using *E*-**2.1**.

***trans*-4-Methyl-3-methylene-5-(4-nitro-phenyl)-dihydro-furan-2-one (2.7b)**



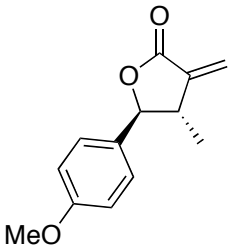
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow solid in 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 – 8.26 (m, 2H), 7.57 – 7.52 (m, 2H), 6.38 (d, 1H, *J* = 3.3 Hz), 5.65 (d, 1H, *J* = 2.7 Hz), 5.02 (d, 1H, *J* = 7.6 Hz), 2.96 – 2.86 (m, 1H), 1.40 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 145.7, 139.3, 126.5, 124.2, 122.2, 94.4, 84.3, 43.5, 16.2; IR (microscope, cm^{-1}): 3510, 3114, 2974, 2936, 1773, 1519, 1352, 1266, 1145; HRMS (EI, m/z) Calcd for $C_{12}H_{11}NO_4$: 233.0688. Found: 233.0689. Elem. Anal. (%) Calcd for $C_{12}H_{11}NO_4$: C, 61.84; H, 4.76; N, 6.01. Found: C, 61.91; H, 4.83; N, 5.99.

***trans*-5-(4-Bromo-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.8b)**



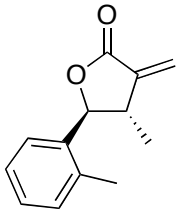
Flash chromatography (20% EtOAc/hexanes) yielded the product as a white solid in 59% yield. Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-5-(4-Methoxy-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.9b)**



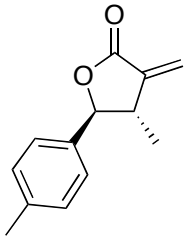
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow solid in 40% yield. Spectral data for **2.9b** was identical to that found in literature.[23]

***trans*-4-Methyl-3-methylene-5-*o*-tolyl-dihydro-furan-2-one (2.10b)**



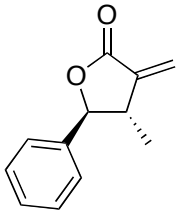
Flash chromatography (15% EtOAc/hexanes) yielded the product as a pale yellow oil in 49% yield. Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-4-Methyl-3-methylene-5-*p*-tolyl-dihydro-furan-2-one (2.11b)**



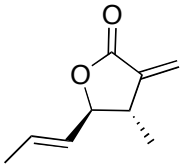
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow oil in 91% yield. Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-4-methyl-3-methylene-5-phenyl-dihydro-furan-2-one (2.12b)**



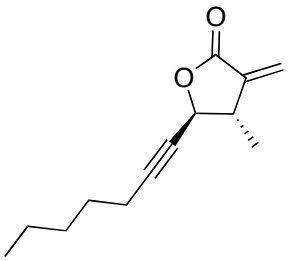
Flash chromatography (15% EtOAc/hexanes) yielded the product as a pale yellow solid in 78% yield. Spectral data for **2.12b** was identical to that found in literature.[25]

***trans*-4-Methyl-3-methylene-5-propenyl-dihydro-furan-2-one (2.13b)**



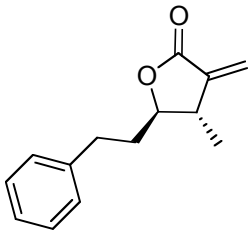
Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 26% yield. (Note: The compound is relatively volatile, and some product was lost during solvent removal. This can be reduced by keep the temperature on the rotovap at a temperature less than 30 ºC.) Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-5-Hept-1-ynyl-4-methyl-3-methylene-dihydro-furan-2-one (2.14b)**



Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow oil in 46% yield. (Note: The *cis* diastereomer was also isolated in 17% yield.) ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.25 (d, 1H, *J* = 3.0 Hz), 5.56 (d, 1H, *J* = 2.8 Hz), 4.57 (dt, 1H, *J* = 7.2, 1.9 Hz), 3.08 – 3.02 (m, 1H), 2.24 (td, 2H, *J* = 7.2, 2.1 Hz), 1.56 – 1.50 (m, 2H), 1.40 - 1.32 (m, 4H), 1.31 (d, 3H, *J* = 6.6 Hz), 0.91 (app t, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 139.5, 121.3, 89.5, 75.9, 74.0, 42.7, 31.0, 28.0, 22.2, 18.8, 16.2, 14.0; IR (CH_2Cl_2 cast film, cm^{-1}): 2933, 2861, 2241, 1772, 1304, 1254, 1132, 977; HRMS (EI, m/z) Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1313.

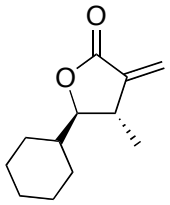
***trans*-4-Methyl-3-methylene-5-phenethyl-dihydro-furan-2-one (2.15b)**



Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.18 (m, 5H), 6.24 (d, 1H, *J* = 3.1 Hz), 5.54 (d, 1H, *J* = 2.9 Hz), 3.99 (ddd, 1H, *J* = 10.9, 6.8, 4.1 Hz), 2.91 (ddd, 1H, *J* = 13.9, 9.3, 5.3 Hz), 2.80 – 2.66 (m, 2H), 2.08 - 1.91 (m, 2H), 1.22 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 140.9, 128.6, 128.5, 126.2, 121.1, 84.1, 40.1, 36.8, 32.0, 31.7, 17.0; IR (CH_2Cl_2 cast film, cm^{-1}): 3506,

3062, 3027, 2932, 1766, 1250, 1134, 701; HRMS (EI, m/z) Calcd for $C_{14}H_{16}O_2$: 216.1150. Found: 216.1148.

***trans*-5-Cyclohexyl-4-methyl-3-methylene-dihydro-furan-2-one (2.16b)**

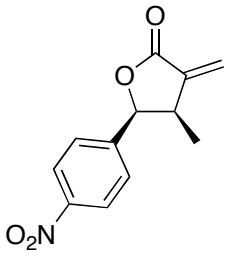


Flash chromatography (20% EtOAc/hexanes followed by a second column using 100% dichloromethane) yielded the product as a colorless oil in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (d, 1H, *J* = 3.1 Hz), 5.55 (d, 1H, *J* = 2.7 Hz), 3.83 (t, 1H, *J* = 5.6 Hz), 2.99 – 2.81 (m, 1H), 1.90 – 1.66 (m, 5H), 1.60 – 1.50 (m, 1H), 1.30 – 1.10 (m, 5H), 1.25 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 141.2, 121.0, 89.0, 42.4, 36.8, 28.6, 28.0, 26.4, 26.0, 25.8, 19.4; IR (neat film, cm^{-1}): 2928, 2854, 1765, 1663, 1451, 1255, 1134, 991; HRMS (EI, m/z) Calcd for $C_{12}H_{18}O_2$: 194.1307. Found: 194.1308.

2.8.5 General procedure for the synthesis of lactones under thermal conditions using *E*-2.1 followed by treatment with PTSA

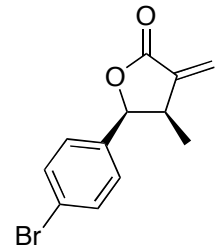
A solution of *E*-**2.1** (100 mg, 0.42 mmol) and aldehyde (0.46 mmol) in toluene (0.5 mL) was heated to 110°C in a high pressure vessel under an argon atmosphere for 72 h. *p*-TSA•H_2O (230 mg, 1.2 mmol) was then added and the mixture was stirred overnight at rt. The reaction was quenched with $NaHCO_3$ (aq) (20 mL) and extracted with Et_2O (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography gave the corresponding lactone.

***cis*-4-Methyl-3-methylene-5-(4-nitro-phenyl)-dihydro-furan-2-one (2.7a)**



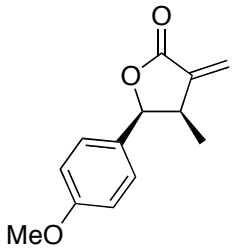
Flash chromatography (20% EtOAc/hexanes) yielded the product as a yellow solid in 90% yield. Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***cis*-5-(4-Bromo-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.8a)**



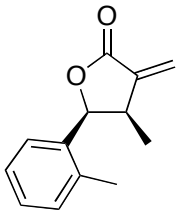
Flash chromatography (20% EtOAc/hexanes) yielded the product as a white solid in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.50 (m, 2H), 7.09 – 7.05 (m, 2H), 6.35 (d, 1H, *J* = 2.9 Hz), 5.61 (d, 1H, *J* = 2.5 Hz), 5.59 (d, 1H, *J* = 8.0 Hz), 3.50 – 3.40 (m, 1H), 0.82 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 139.7, 135.4, 131.8, 127.7, 122.5, 122.2, 81.4, 38.8, 15.5; IR (microscope, cm^{-1}): 3096, 2973, 2933, 1768, 1491, 1247, 1148, 996; HRMS (EI, m/z) Calcd for $C_{12}H_{11}O_2{}^{81}Br$: 267.9922. Found: 267.9926. Elem. Anal. (%) Calcd for $C_{12}H_{11}O_2{}^{81}Br$: C, 53.96; H, 4.15. Found: C, 54.32; H, 4.26.

***cis*-5-(4-Methoxy-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.9a)**



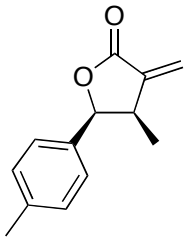
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow solid in 31% yield. (Note: The *trans* γ-lactone was also isolated in 31% yield.) Spectral data for **2.9a** was identical to that found in literature.[23]

***cis*-4-Methyl-3-methylene-5-*o*-tolyl-dihydro-furan-2-one (2.10a)**



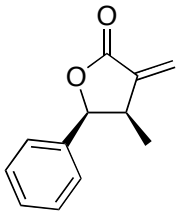
Flash chromatography (15% EtOAc/hexanes) yielded the product as a yellow solid in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.17 (m, 4H), 6.36 (d, 1H, J = 2.4 Hz), 5.83 (d, 1H, J = 7.7 Hz), 5.65 (d, 1H, J = 2.2 Hz), 3.56 – 3.46 (m, 1H), 2.32 (s, 3H), 0.76 (d, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 140.8, 134.6, 134.0, 130.4, 128.0, 126.2, 125.4, 122.3, 79.3, 37.6, 19.3, 16.5; IR (microscope, cm^{-1}): 3032, 2981, 2935, 1755, 1478, 1185, 981; HRMS (EI, m/z) Calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0993.

***cis*-4-Methyl-3-methylene-5-*p*-tolyl-dihydro-furan-2-one (2.11a)**



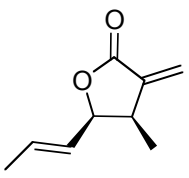
Flash chromatography (20% EtOAc/hexanes) yielded the product as a white solid in 48% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 – 7.15 (m, 2H), 7.07 – 7.03 (m, 2H), 6.32 (d, 1H, *J* = 2.9 Hz), 5.59 (d, 1H, *J* = 8.1 Hz), 5.56 (d, 1H, *J* = 2.6 Hz), 3.46 – 3.38 (m, 1H), 2.35 (s, 3H), 0.81 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 140.2, 138.1, 133.2, 129.1, 125.9, 121.5, 82.3, 39.1, 21.2, 15.4; IR ($CDCl_3$ cast film microscope, cm^{-1}): 2973, 1767, 1247, 1149, 1123, 984; HRMS (EI, m/z) Calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0996

***cis*-4-methyl-3-methylene-5-phenyl-dihydro-furan-2-one (2.12a)**



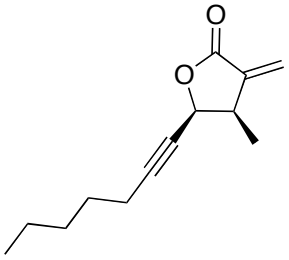
Flash chromatography (15% EtOAc/hexanes) yielded the product as a pale yellow solid in 67% yield. Spectral data for **2.12a** was identical to that found in literature.[25]

***cis*-4-Methyl-3-methylene-5-propenyl-dihydro-furan-2-one (2.13a)**



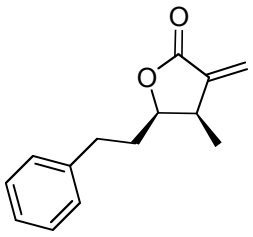
Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (d, 1H, *J* = 2.9 Hz), 5.82 (dqd, 1H, *J* = 15.1, 6.5, 0.9 Hz), 5.52 (d, 1H, *J* = 2.7 Hz), 5.37 (ddq, 1H, *J* = 15.2, 8.1, 1.7 Hz), 4.95 (t, 1H, *J* = 8.0 Hz), 3.26 – 3.15 (m, 1H), 1.76 (ddd, 3H, *J* = 6.6, 1.7, 0.5 Hz), 1.13 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 140.4, 132.0, 125.5, 120.9, 82.1, 38.1, 17.8, 14.4; IR (cast film, cm^{-1}): 2970, 2934, 1763, 1451, 1156, 963; HRMS (EI, m/z) Calcd for $C_9H_{12}O_2$: 152.0837. Found: 152.0836.

cis-5-Hept-1-ynyl-4-methyl-3-methylene-dihydro-furan-2-one (2.14a)



Flash chromatography (10% EtOAc/hexanes) yielded the product as a pale yellow oil in 51% yield. Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

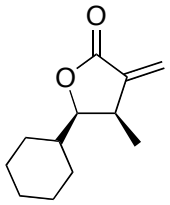
cis-4-Methyl-3-methylene-5-phenethyl-dihydro-furan-2-one (2.15a)



Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 59% yield. Spectral data for this compound was identical to that reported

when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***cis*-5-Cyclohexyl-4-methyl-3-methylene-dihydro-furan-2-one (2.16a)**

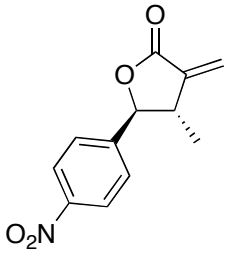


Flash chromatography (20% EtOAc/hexanes followed by a second column using 100% dichloromethane) yielded the product as a colorless oil in 66% yield. Spectral data for this compound was identical to that reported when *E*-**2.1** and corresponding aldehyde were reacted under TfOH acid conditions.

2.8.6 General procedure for the synthesis of γ-lactones using *Z*-2.1 under thermal conditions followed by treatment with PTSA

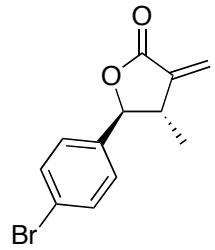
The procedure for the thermal allylboration using *Z*-**2.1** was identical to the thermal allylboration using *E*-**2.1**.

***trans*-4-Methyl-3-methylene-5-(4-nitro-phenyl)-dihydro-furan-2-one (2.7b)**



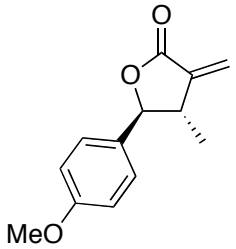
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow solid in 61% yield. (Note: The *cis* diastereomer was also isolated in 17% yield). Spectral data for this compound was identical to that reported when *Z*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-5-(4-Bromo-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.8b)**



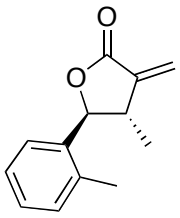
Flash chromatography (20% EtOAc/hexanes) yielded the product as a white solid in 53% yield. (Note: The *cis* diastereomer was also isolated in 17% yield) Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-5-(4-Methoxy-phenyl)-4-methyl-3-methylene-dihydro-furan-2-one (2.9b)**



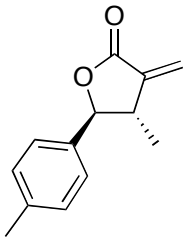
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow solid in 57% yield. (Note: The *cis* diastereomer was also isolated in 10% yield.) Spectral data for **2.9b** was identical to that found in literature.[23]

***trans*-4-Methyl-3-methylene-5-*o*-tolyl-dihydro-furan-2-one (2.10b)**



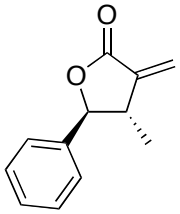
Flash chromatography (15% EtOAc/hexanes) yielded the product as a pale yellow oil in 49% yield. (Note: The *cis* diastereomer was also isolated in 8% yield.) Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-4-Methyl-3-methylene-5-*p*-tolyl-dihydro-furan-2-one (2.11b)**



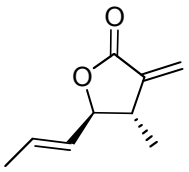
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow oil in 71% yield. (Note: The *cis* diastereomer was also isolated in 3% yield.) Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-4-Methyl-3-methylene-5-phenyl-dihydro-furan-2-one (2.12b)**



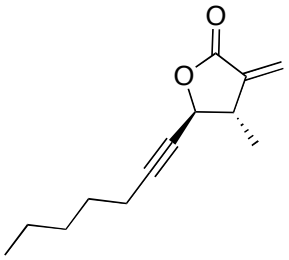
Flash chromatography (15% EtOAc/hexanes) yielded the product as a pale yellow solid in 66% yield. Spectral data for **2.12b** was identical to that found in the literature.[25]

***trans*-4-Methyl-3-methylene-5-propenyl-dihydro-furan-2-one (2.13b)**



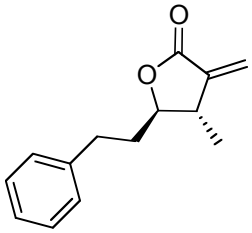
Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 58% yield. (Note: The *cis* diastereomer was also isolated in 11% yield. Compound is relatively volatile, and some product was lost during solvent removal.) Spectral data for this compound was identical to that reported when *E*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-5-Hept-1-ynyl-4-methyl-3-methylene-dihydro-furan-2-one (2.14b)**



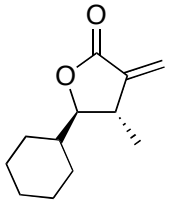
Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow oil in 62% yield. (Note: The *cis* diastereomer was also isolated in 12%.) Spectral data for this compound was identical to that reported when *Z*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-4-Methyl-3-methylene-5-phenethyl-dihydro-furan-2-one (2.15b)**



Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 40% yield. (Note: The *cis* diastereomer was also isolated in 16% yield) Spectral data for this compound was identical to that reported when *Z*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

***trans*-5-Cyclohexyl-4-methyl-3-methylene-dihydro-furan-2-one (2.16b)**

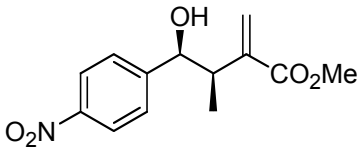


Flash chromatography (20% EtOAc/hexanes) yielded the product as a colorless oil in 47% yield. (Note: The *cis* diastereomer was also isolated in 16% yield) Spectral data for this compound was identical to that reported when *Z*-**2.1** and the corresponding aldehyde were reacted under TfOH acid conditions.

2.8.7 General procedure for the synthesis of butyric acid methyl esters and their subsequent cyclization under TfOH conditions

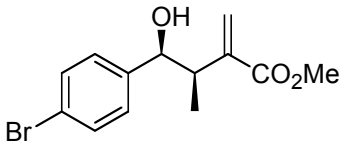
A solution of the corresponding *E*- or *Z*-**2.1** (100 mg, 0.42 mmol) and aldehyde (0.46 mmol) in toluene (0.5 mL) was heated at 95 °C under an argon atmosphere for 42 h. The reaction was allowed to cool to rt and the solvent was removed. Flash chromatography of the crude reaction mixture gave the corresponding methyl ester. The butyric acid methyl esters were then dissolved in 1 mL of toluene under argon and cooled to 0 ºC. TfOH (10 mol%) was added and the reactions were left to stir at 0 ºC for 16 h. The reactions were quenched with 10 mL of 9:1 NH_4Cl:NH_4OH (aq) and extracted with ether (x3). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. A crude ^1H NMR was taken for each sample in order to determine the ratio of γ-lactone products present. The γ-lactones obtained from this experiment were identical to those synthesized by previous routes (**2.7a/b**, **2.8a/b**, **2.9a/b**).

***cis*-4-Hydroxy-3-methyl-2-methylene-4-(4-nitro-phenyl)-butyric acid methyl ester (2.17a)**



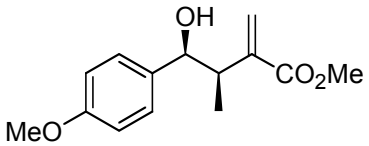
Flash chromatography (20 % EtOAc/hexanes) yielded the product as a yellow oil in 69% yield. (Note: The corresponding *trans* lactone was isolated in 6% yield.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 – 8.16 (m, 2H), 7.56 – 7.51 (m, 2H), 6.31 (d, 1H, *J* = 0.8 Hz), 5.59 (t, 1H, *J* = 0.9 Hz), 5.00 (t, 1H, *J* = 3.4 Hz), 3.80 (s, 3H), 3.13 (m, 1H), 2.75, (d, 1H, *J* = 1.0 Hz), 0.98 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 150.1, 147.2, 141.8, 127.1, 127.0, 123.3, 74.6, 52.3, 42.9, 12.0; IR (cast film microscope, cm^{-1}): 3508, 2952, 1712, 1520, 1348; HRMS (EI, m/z) Calcd for $C_{12}H_{12}NO_4$ [M – OCH_3]$^{+}$: 234.0766. Found: 234.0761.

***cis*-4-(4-Bromo-phenyl)-4-hydroxy-3-methyl-2-methylene-butyric acid methyl ester (2.18a)**



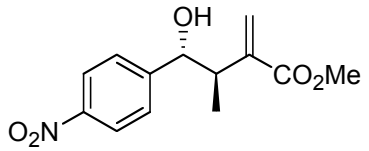
Flash chromatography (20 % EtOAc/hexanes) yielded the product as a colorless oil in 56% yield. (Note: The corresponding *cis* lactone was isolated in 11% yield.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.42 (m, 2H), 7.24 – 7.20 (m, 2H), 6.26 (d, 1H, *J* = 0.8 Hz), 5.55 – 5.53 (m, 1H), 4.84 (t, 1H, *J* = 3.6 Hz), 3.77 (s, 3H), 3.08 (m, 1H), 2.49, (d, 1H, *J* = 3.1 Hz), 1.00 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 142.2, 141.6, 131.1, 128.0, 126.5, 121.0, 75.1, 52.2, 42.7, 12.6; IR (cast film microscope, cm^{-1}): 3492, 2975, 2950, 1767, 1713; HRMS (EI, m/z) Calcd for $C_{13}H_{15}O_2{}^{81}Br$: 300.0184. Found: 300.0180.

***cis*-4-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-2-methylene-butyric acid methyl ester (2.19a)**



Flash chromatography (20 % EtOAc/hexanes) yielded the product as a colorless oil in 24% yield. (Note: The corresponding *trans* lactone was isolated in 13% yield and the corresponding *cis* lactone in 10% yield.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.24 (m, 2H), 6.88 – 6.84 (m, 2H), 6.24 (d, 1H, *J* = 1.0 Hz), 5.53 (br t, 1H, *J* = 1.0 Hz), 4.84 – 4.81 (m, 1H), 3.80 (s, 3H), 3.76, (s, 3H), 3.12 (m, 1H), 2.34, (br s, 1H), 1.06 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 158.8, 142.7, 134.7, 127.4, 126.1, 113.4, 75.6, 55.3, 52.1, 42.7, 13.3; IR (cast film microscope, cm^{-1}): 3496, 2952, 2838, 1766, 1715, 1513, 1248; HRMS (EI, m/z) Calcd for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1204.

***trans*-4-Hydroxy-3-methyl-2-methylene-4-(4-nitro-phenyl)-butyric acid methyl ester (2.17b)**



Flash chromatography (20 % EtOAc/hexanes) yielded the product as a yellow oil in 30% yield. (Note: The corresponding *trans* γ-lactone was isolated in 54% yield and could not be completely removed from the sample by chromatography. Hence, all spectra contain some contamination of this γ-lactone.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 – 8.16 (m, 2H), 7.50 – 7.45 (m, 2H), 6.20 (d, 1H, *J* = 0.8 Hz), 5.54 (br s, 1H), 4.86 – 4.81 (m, 1H), 3.77 (s, 3H), 3.42, (d, 1H, *J* = 5.5 Hz), 3.08 – 3.00 (m, 1H), 1.08 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 150.5, 147.4, 141.3, 127.4, 127.3, 123.4, 76.9, 52.4, 44.2, 16.3; IR (CH_2Cl_2

cast film, cm^{-1}): 3488, 3079, 2927, 1716, 1521, 1384; HRMS (EI, m/z) Calcd for $C_{12}H_{12}NO_4$ $[M - OCH_3]^+$: 234.0766. Found: 234.0759

2.8.8 Synthesis of acyclic borate intermediate 2.20a and its cyclization under TfOH conditions

A solution of *E*-**2.1** (100 mg, 0.42 mmol) and 4-bromobenzaldehyde (0.46 mmol) in toluene (0.5 mL) was heated at 95°C under an argon atmosphere for 48 h. The reaction was allowed to cool to rt and the solvent was removed. A crude ^1H NMR spectrum was recorded and a comparison of the peak integration for the pinacol peak against other peaks confirmed that the pinacol boronate was present on the molecule. Thus, **2.20a** had been formed. The crude boronate was then dissolved in 1 mL of toluene under argon and cooled to 0 ºC. TfOH (10 mol%) was added and the reactions were left to stir at 0 ºC for 16 h. The reactions were quenched with 10 mL of 9:1 NH_4Cl:NH_4OH (aq) and extracted with ether (x3). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. A crude ^1H NMR was taken and showed that the only product present was *trans* γ-lactone **2.8b**.

2.8.9 Synthesis of ^{18}O-labelled aldehydes

The synthesis of ^{18}O-*p*-nitrobenzaldehyde and ^{18}O-*p*-bromobenzaldehyde was done according to literature procedures.[26] Both oxygen-18 labelled aldehydes displayed identical spectroscopic characteristics when compared the corresponding unlabeled aldehyde. The percentage of labeled to unlabeled aldehyde was determined by comparing the peak intensities for the different molecular ions in the HRMS.

For ^{18}O-*p*-nitrobenzaldehyde, the peak heights were 3.38% for $[C_7H_5O_2{}^{18}ON]^+$ and 95.57% for $[C_7H_5O_3N]^+$. This corresponds to an oxygen-18 labeling of 3.54%.

For ^{18}O-*p*-bromobenzaldehyde, the peak heights were 2.96% for $[C_7H_5{}^{81}Br{}^{18}O]^+$ and 83.89% for $[C_7H_5O^{79}Br]^+$. This corresponds to an oxygen-18 labeling of 3.53%. The peaks corresponding to $[C_7H_5O^{81}Br]^+$ and $[C_7H_5{}^{18}O^{79}Br]^+$ were overlapping in the HRMS and gave a peak height of 85.61%. Due to the essentially 1:1 isotopic ratio of ^{79}Br and ^{81}Br in nature, the peaks were compared as above.

2.9 References

[1] Recent examples: (a) Williams, A.L.; Johnston, J.N. *J. Am. Chem. Soc.* **2004**, *126*, 1612-1613. (b) Zhang, L.; Kozmin, S.A. *J. Am. Chem. Soc.* **2004**, *126*, 10204-10205. (c) Mahoney, J.M.; Smith, C.R.; Johnston, J.N. *J. Am. Chem. Soc.* **2005**, *127*, 1354-1355. (d) Zhang, Y.; Hsung, R.P.; Zhang, X.; Huang, J.; Slafer, B.W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047-1050. (e) Nakashima, D.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1251-1253.

[2] Yu, S.H.; Ferguson, M.J.; McDonald, R.; Hall, D.G. *J. Am. Chem. Soc.* **2005**, *127*, 12808-1280.

[3] Hall, D.G., Chapter 1 in Boronic Acids – Preparation, Applications in Organic Synthesis and Medicine (Ed.: Hall, D.G.), Wiley-VCH, Weinheim, **2005**.

[4] Kennedy, J.W.J.; Hall, D.G. *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587.

[5] Kennedy, J.W.J.; Hall, D.G. *J. Org. Chem.* **2004**, *69*, 4412-4428.

[6] Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415.

[7] Hoffmann, H.M.R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 110.

[8] Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243* (*Natural Product Synthesis I*), 43-72.

[9] Matsuda, F.; Ohsaki, M.; Yamada, K.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2123-2131.

[10] Janecki, T.; Blaszcyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem.* **2005**, *48*, 3516-3521.

[11] Chataigner, I.; Lebreton, J.; Zammatio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719-3722.

[12] Kennedy, J.W.J.; Hall, D.G. *J. Am. Chem. Soc.* **2002**, *124*, 898-899.

[13] Ramachandran, P.V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M.V.R. *Org. Lett.* **2004**, *6*, 481-484.

[14] Kabalka, G.W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807-5809.

[15] (a) Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* **1991**, *44*, 1615-1626. (b) Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* **1991**, *44*, 1705-1714.

[16] A version of this chapter has been published: Elford, T.G.; Arimura, Y.; Yu, S.H.; Hall, D.G. *J. Org. Chem.* **2007**, *72*, 1276-1284.

[17] Ramachandran, P.V.; Pratihar, D.; Biswas, D. *Org. Lett*, **2006**, *8*, 3877-3879.

[18] Baraniak, J.; Wojciech, J. S. *J. Chem. Soc. Perkin Trans. 1* **1987**, *8*, 1645-1656.

[19] Rauniyar, V.; Hall, D.G. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519.

[20] Taylor, R. K.; Casy, G. In Organocopper Reagents: A Practical Approach; Taylor, R. K., Ed.; Oxford University Press: New York, **1994**, pp 53-72.

[21] Phillion, D. P.; Neubauer, R.; Andrew, S. S. *J. Org. Chem.* **1986**, *51*, 1610-1612.

[22] Whiting, A. *Tetrahedron Lett.* **1991**, *32*, 1503-1506.

[23] Jung, M.E.; Buszek, K.R. *J. Am. Chem. Soc.* **1988**, *110*, 3965-3969

[24] Csuk, R.; Schroder, C.; Hutter, S.; Mohr, K. *Tetrahedron: Asymmetry*, **1997**, *8*, 1411-1429.

[25] Lin, S.H.; Chen, C.C.; Vong, W.J.; Liu, R.S.; *Organometallics*, **1995**, *14*, 1619-1625.

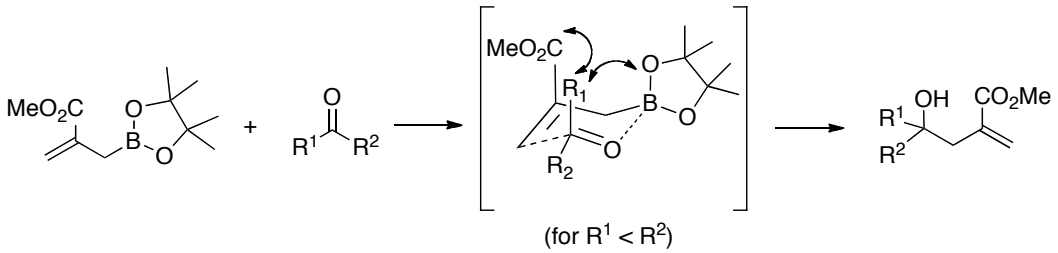
[26] Baraniak, J and Wojciech, J. S. *J. Chem. Soc. Perkin Trans. 1* **1987**, *8*, 1645-1656.

Chapter 3

Catalyzed Additions of 2-Alkoxycarbonyl Allylboronates to Ketones

3.1 Introduction

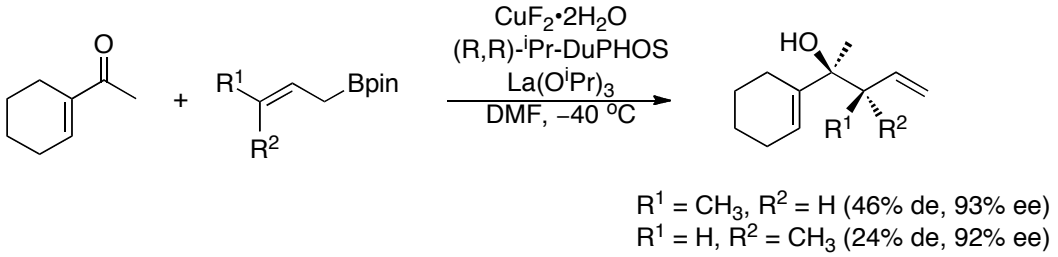
Although the majority of methods in the literature that use allylic boronates deal with their addition to aldehydes, there has been an increasing number of examples where electrophilic partners other than aldehydes are being used. Ketones are possible substrates that can react with allylic boronates to provide tertiary homoallylic alcohols. As discussed in Section 1.7, the addition of allylic boronates to ketones is significantly slower than their addition to aldehydes. The reason for this reduced reactivity lies in both electronic and steric arguments. Electronically, ketone carbonyl groups are less electrophilic due to the electron donating ability of carbon-based groups as compared to aldehydes, which are carbon substituted only on one side, and the other substituent, a hydrogen atom, is a poor electron donor. For steric arguments, because the allylboration reaction proceeds through a closed, six-member transition state, one of the ketone groups must orient itself in an axial position in the transition state, thereby creating 1,3-diaxial interactions with the axial group on the boron atom and with the substituent in the 2-position on the 2-alkoxycarbonyl allylboronate (Equation 3.1).



Equation 3.1: Steric interactions present for ketone allylboration reactions

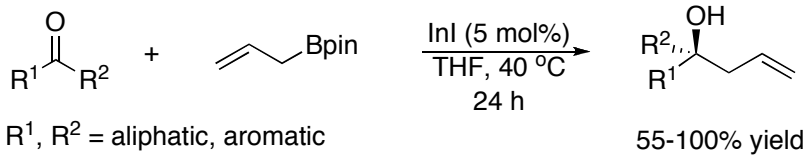
3.1.1 Development of catalytic methods for ketone allylboration reactions

As discussed previously in the context of aldehyde allylborations (*cf.* Chapter 2), the discovery that Lewis acids and Brønsted acids are capable of catalyzing allylboration reactions was a significant achievement. These methods allowed for much shorter reaction times and lower temperatures to be used. To extrapolate the concept of catalyzing aldehyde allylboration reactions to the field of ketone allylboration chemistry is not too difficult. As such, the development of catalytic methods for performing ketone allylation reactions was a topic of various highlights[1] and reviews.[2] In the past, only allylstannanes have been used as the allylating reagent for ketones, along with 10 to 30 mol% of metal catalyst.[3] However, these methods are neither green nor useful for ketone crotylation reactions. It was not until 2004 when Shibasaki and co-workers described a truly catalytic and enantioselective method for the allylboration and crotylation of ketones.[4] Using 3 mol% of a copper catalyst and 6 mol% of a chiral diphosphine ligand (DuPHOS) along with 4.5 mol% of a lanthanide additive, both aromatic and aliphatic ketones could be allylated in high yields (83-99%) and good to excellent enantioselectivities (67-91%). Furthermore, crotylborations could be performed using these reaction conditions (Equation 3.2). Although the enantioselectivity in the crotylborations was substrate dependant, this was the first example of a catalytic crotylboration of a ketone. Based on ^{11}B NMR spectroscopic experiments and on the lack of diastereoselectivity seen in the crotylation reactions, it is believed that the mechanism of allylation involves transmetallation from boron to copper to produce a reactive allylcopper species.



Equation 3.2: Copper-catalyzed crotylboration of ketones

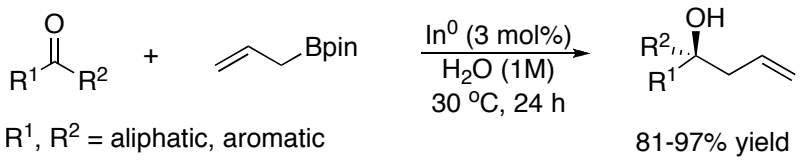
More recently, other metal catalysts have also proven to be very efficient at catalyzing the addition of allylic boronates to ketones. In 2007, Kobayashi and coworkers demonstrated that indium (I) species are capable of catalyzing the addition of allyl pinacol boronate to a wide variety of aliphatic and aromatic ketones.[5] Using 5 mol% of InI in THF, a large selection of tertiary homoallylic alcohols could be formed (Equation 3.3). Several functionalities (e.g. hydroxy, methoxy, amino, amide, chloro, bromo, nitro) also proved to be compatible under these reaction conditions.



Equation 3.3: Indium-catalyzed addition of allylic boronates to ketones

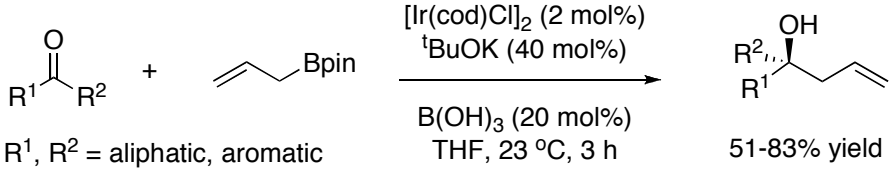
It has been shown that indium is also capable of catalyzing the addition of allylic boronates to ketones in an aqueous environment.[6] Since indium (I) species are unstable in aqueous environments, the use of indium (0) metal was investigated and found to efficiently catalyze the addition of allylic boronates to ketones in an aqueous reaction mixture (Equation 3.4). A variety of ketones were suitable as substrates, however, the allylic boronate was limited to the use of allyl pinacol boronate. This limitation is probably due to the instability of most allylic boronates to water. Crotyl boronates were also ineffective allylating reagents under this procedure. The use of α-methyl allyl pinacol boronate was investigated, but unlike traditional catalyzed protocols where the allylic boronate adds to give the γ-adduct, under indium (0) catalysis in water, the addition went through a formal α-addition to the ketone with high *syn* diastereoselectivity. This result is quite unusual in that it provides the same product as would be obtained through the use of crotyl boronates. Nonetheless, this observation provides clues to the mechanism and points to a transmetallation from boron to indium. Indeed,

it is proposed that the reaction occurs at the surface of the indium metal, but the exact nature of the transmetallation/allylboration is still unknown.



Equation 3.4: Indium-catalyzed ketone allylboration reactions performed in water

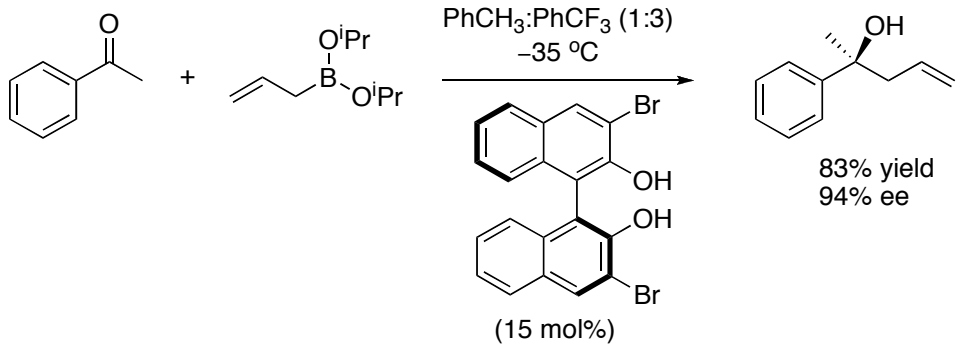
In addition to copper and indium, iridium catalysts have also been shown to facilitate the addition of allylic boronates to ketones (Equation 3.5).[7] Using labeling studies, it was shown that in the case of iridium, transmetallation is probably occurring under the reaction conditions to form a new allyliridium species, which is the active allylation reagent that adds to the ketone substrate. The iridium catalyst system does appear to be faster than the indium protocol, as the reactions are complete after 3 hours as compared to the 24 h reaction time required for the indium (I) catalyst system.



Equation 3.5: Iridium-catalyzed ketone allylboration reaction performed at room temperature

Besides metals, chiral diols have also been shown to catalyze the addition of allylic boronates to ketones.[8] The rationale behind using chiral diols as catalysts lies in their ability to exchange rapidly with the substituents on acyclic dialkoxyallylic boronates and in their Brønsted acidic characteristics. After screening of various chiral diols, it was found that Br-substituted derivatives of BINOL served as the best catalysts in the addition of diisopropoxyallylboronate to

acetophenone (Equation 3.6). Various aromatic, aliphatic and unsaturated ketones were shown to be suitable substrates for this protocol and provided the desired tertiary homoallylic products with high yields (81-93% yield) and high enantioselectivities (90-99% ee). Furthermore, crotylborations were also highly successful and provided the corresponding *syn* and *anti* products with good yields, high diastereoselectivity (>98:2 dr), and high enantioselectivity (>98:2 er). The *syn* and *anti* products arise from the *cis* and *trans* crotylboronates, respectively, as expected from a closed, six-membered transition state that is typical for crotylboronates (*cf.* Chapter 1).



Equation 3.6: Diol-catalyzed addition of allylic boronates to ketones

Preliminary mechanistic experiments were performed and indicated a catalyst-associated boronate complex had formed. Rapid exchange of one isopropoxy ligand was observed by ^{1}H NMR spectroscopy. It was also noted that the reaction was first order in catalyst. On this basis it was proposed that catalysis and selectivity both arise via a diol-allylic boronate complex that activates the remaining alkoxy ligand via hydrogen bonding[9] leading to preferential *si* facial attack on the ketone via a chair-like transition state **A** (Figure 3.1).[8] However, subsequent DFT calculation performed by Goodman and co-workers seem to suggest that the chiral diol displaces both of the alkoxy ligands on the boronate to form a highly reactive species.[10] This intermediate, albeit present in low amounts, then acts as a Lewis acid to activate the ketone (transition state B, Figure 3.1) and subsequently transfers an allyl group to form the tertiary homoallylic alcohol

product. This proposition is based on the high reactivity of catechol allylboronate compared to other alkoxy derivatives.[11] However, recent mechanistic experiments looking at rate order and inhibition studies seem to favor the originally proposed mechanism proceeding through transition state **A**.[12]

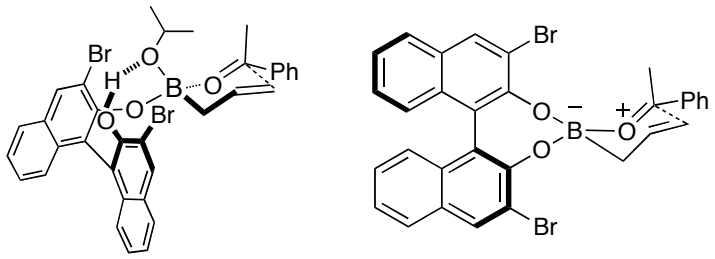
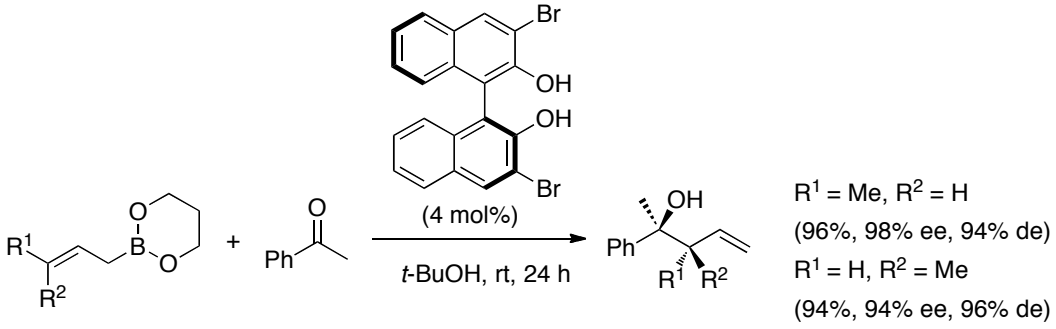


Figure 3.1: Proposed transition states for diol-catalyzed allylboration of ketones

Further optimization of the reaction conditions led to the development of a second-generation system, whereby ketone allylboration reactions catalyzed by the chiral diol occur at room temperature while still retaining high enantioselectivities.[12] This new system also allows for ketone crotylation reactions to be performed with excellent enantioselectivity and diastereoselectivity (Equation 3.7).



Equation 3.7: Ketone crotylboration reactions catalyzed by a BINOL derivative

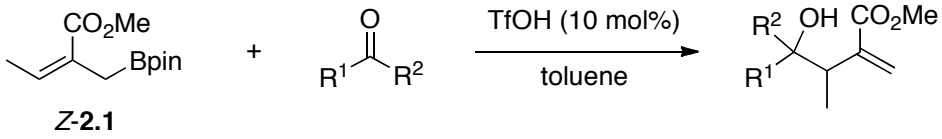
3.1.2 Use of 2-alkoxycarbonyl allylboronates for ketone allylboration reactions

In all of the examples shown in the previous section, the allylic boronates that are utilized are very reactive if compared to 2-alkoxycarbonyl allylboronates. To date, no examples have been shown in the literature where ketones have been used as substrates in an allylation reaction with 2-alkoxycarbonyl allylboronates. Whether this is due to the reactivity issue or otherwise is unclear. However, this clearly indicates that an investigation into the reactivity of 2-alkoxycarbonyl allylboronates needs to be performed. There are a few different possibilities that could be probed. Because the thermal reaction of 2-alkoxycarbonyl allylboronates with aldehydes is extremely slow (*cf*. Section 2.1), extrapolation to ketones would suggest that ketones simply would not react under thermal conditions. However, the use of either Lewis acids or Brønsted acids might help in lowering the activation barrier and allow for ketones to react with 2-alkoxycarbonyl allylboronates. Another alternative would be to test some of the conditions used for more reactive allylic boronates to see if they would apply to 2-alkoxycarbonyl allylboronates. The rest of this chapter will discuss our brief foray into a few of these possibilities.

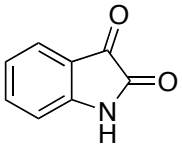
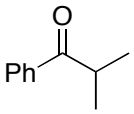
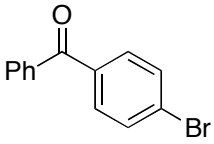
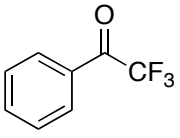
3.2 Brønsted acid-catalyzed additions of 2-alkoxycarbonyl allylboronates to ketones

The use of Brønsted acids greatly facilitated the addition of 2-alkoxycarbonyl allylboronates to aldehydes and allowed the reactions to be carried out at temperatures more than 100 ºC below the standard thermal conditions while also allowing reaction times to be significantly shortened[13] (see Chapter 2). With this precedent in mind, it was rationalized that these same catalysts might be capable of facilitating the more difficult additions to ketones. To test this theory, five different ketones were chosen and subjected to Brønsted

acid conditions in the presence of 2-alkoxycarbonyl allylboronate *Z*-**2.1**. The reactions were performed with 10 mol% TfOH in toluene at both 0 °C and at room temperature. The findings are summarized in Table 3.1. In all cases, both at 0 °C and at room temperature, no reaction was ever observed. The crude ^{1}H NMR spectra showed only starting materials in all cases. Because none of these reactions provided a trace of the desired allylation product, it was determined that TfOH was not capable of acting as a sufficiently active Brønsted acid catalyst for the addition of *Z*-**2.1** to ketones.



Z-**2.1**

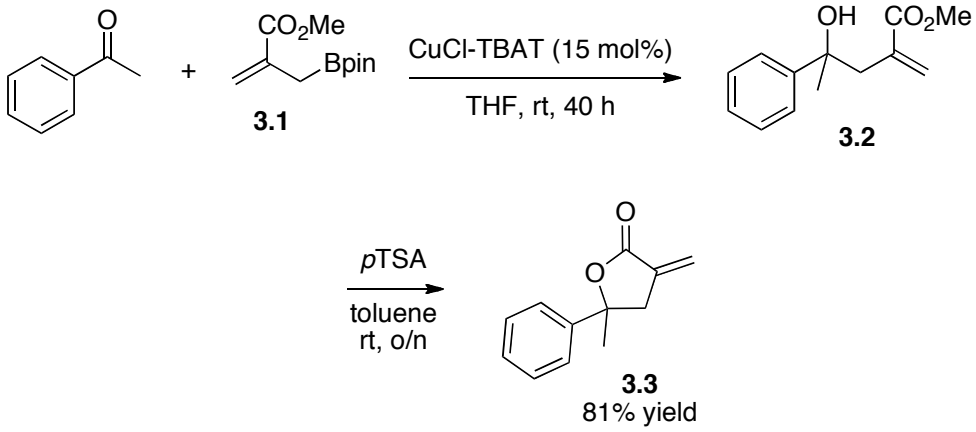
Entry	Aldehyde	Temperature (°C)	Reaction Time (h)	Conversion[a]
1		0	16	0
2		23	72	0
3		0	16	0
4		23	72	0
5		0	16	0
6		23	72	0
7		0	16	0
8		23	72	0
9		0	16	0
10		23	72	0

[a] Conversions were measured by ^{1}H NMR spectroscopy of the crude reaction mixture

Table 3.1: Brønsted acid-catalyzed addition of *Z*-**2.1** to ketones

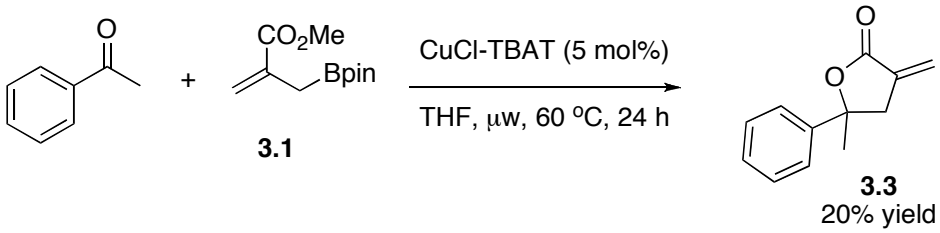
3.3 Copper-catalyzed addition of 2-alkoxycarbonyl allylboronates to ketones

Because Brønsted acids proved to be unsuitable as catalysts for the addition of 2-alkoxycarbonyl allylboronates to ketones, I next turned my attention to applying known catalyst systems to these less active allylboronates. The protocol developed by Shibasaki was interesting as they utilized simple copper salts as a catalyst. (At the time this project was initiated, this was the only report of catalytic ketone allylborations.) The Shikasaki group had discovered that catalytic allylation of various ketones, including aromatic, heteroaromatic, α,β-unsaturated, and aliphatic ketones, could be performed at ambient temperature in THF, using 1-3 mol% of CuCl–Tetrabutylammonium triphenydifluorosilicate (TBAT) catalyst.[4] They had also discovered that ketones could react with allylic boronates in an enantioselective fashion using a copper–chiral phosphine system (see Section 3.1.1). I initially tried the racemic protocol to determine whether the 2-alkoxycarbonyl allylboronates would show any activity towards ketones in the presence of a copper catalyst. The first attempt using the CuCl-TBAT catalyst system with 2-alkoxycarbonyl allylboronate **3.1** proved to be successful and provided the acyclic allylation product **3.2** (Scheme 3.1). This acyclic product was not isolated, as the crude reaction mixture was subjected to PTSA in toluene in order to induce lactonization to provide γ-lactone **3.3**.



Scheme 3.1: CuCl-TBAT catalyzed addition of **3.1** to acetophenone

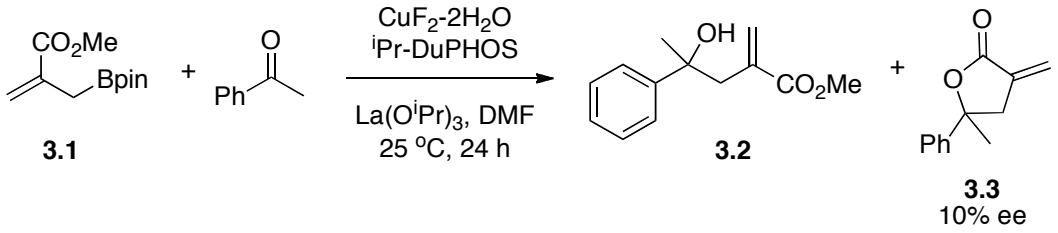
In an attempt to speed up this reaction and possibly induce *in situ* lactonization, the reaction was also attempted under microwave conditions. Using the same two substrates, acetophenone and 2-alkoxycarbonyl allylboronate **3.1**, the reaction was performed at 60 °C for 24 h under microwave irradiation (Equation 3.8). However, this led to only a 20% yield of the desired γ-lactone product, with the rest of the reaction mixture being a complex mix of indiscernible products.



Equation 3.8: CuCl-TBAT catalyzed addition of **3.1** to acetophenone under microwave irradiation

Shibasaki and co-workers had also reported a chiral variant of their ketone allylboration methodology that made use of a chiral phosphine ligand and an added lanthanide salt (refer to Section 3.1.1). Since the racemic variant had provided the desired γ-lactone **3.3** in an acceptable yield (Scheme 3.1), and since the asymmetric synthesis of these compounds would be much more interesting, I set out to test these conditions with 2-alkoxycarbonyl allylboronate **3.1**. Again, using acetophenone as our model ketone, I attempted to catalyze the asymmetric addition of 2-alkoxycarbonyl allylboronate **3.1** (Equation 3.9). Shibasaki and co-workers had managed to obtain high levels of enantioselectivity when their reactions were performed at -40 °C. However, when 2-alkoxycarbonyl allylboronate **3.1** was utilized in the asymmetric variant with acetophenone, no reaction was observed. Therefore, in my case, the reaction was carried out at room temperature for 24 h, leading to a mix of acyclic product **3.2** and γ-lactone **3.3**. I was not able to separate and obtain **3.2** in pure form; however, γ-lactone **3.3** could be obtained as a pure sample. The pure γ-lactone **3.3** was analyzed by chiral

HPLC to determine if any enantioselectivity had been achieved. (The sample of **3.3** obtained via the CuCl-TBAT method was used as the racemic control.) Though I hoped to achieve some enantiocontrol, these attempts were essentially unsuccessful. The reaction performed at room temperature provided γ-lactone **3.3** with an enantiomeric excess of only 10%. Thus, no practical levels of enantioselectivity were achieved using Shibasaki's conditions with 2-alkoxycarbonyl allylboronate **3.1**.



Equation 3.9: Attempted catalytic, asymmetric addition of **3.1** to acetophenone

3.4 Conclusions

Although there are no examples in the literature that utilize 2-alkoxycarbonyl allylboronates in ketone allylation reactions, I attempted to find conditions that would successfully allow for their union to form tertiary homoallylic alcohols. Because Brønsted acids had proven capable of catalyzing the addition of deactivated allylboronates to aldehydes, TfOH was first investigated for its ability to catalyze the addition of a 2-alkoxycarbonyl allylboronate to ketones. This system proved to be unsuccessful with a variety of ketones and only returned starting materials. In no case was any of the desired γ-lactone product observed. I next turned to two sets of conditions reported by Shibasaki and co-workers[4] and attempted to apply them to reactions utilizing 2-alkoxycarbonyl allylboronates. The racemic variant using CuCl-TBAT as the catalyst system did prove to be useful and allowed for the formation of the γ-

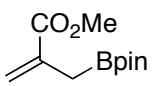
lactone product in an acceptable yield after a lactonization step utilizing PTSA. The asymmetric variant was then attempted to see if γ-lactone products could be accessed in an enantioenriched form. However, despite being able to form the desired γ-lactone under the asymmetric reaction conditions, it was obtained in essentially racemic form. Thus, the enantiocontrolled formation of γ-lactone products using Shibasaki's conditions was unsuccessful in providing enantioenriched products. At this point, further investigation of this project was suspended due to other projects taking a priority. However, the promising results achieved with the CuCl-TBAT system in allowing for the successful addition of 2-alkoxycarbonyl allylboronates to ketones should be further investigated as far as substrate scope (ketones and allylboronates) and to determine if any of the newer systems since developed in the literature[5-8] would allow for the asymmetric addition of 2-alkoxycarbonyl allylboronates to ketones.

3.5 Experimental

3.5.1 General information

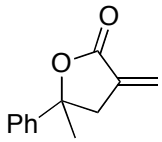
Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene was distilled over CaH_2. THF was distilled over sodium/benzophenone ketyl. NH_4Cl(aq) and $NaHCO_3$(aq) refer to saturated aqueous solutions. TfOH was stored under argon in a pear-shaped flask with a glass stopper and placed in a jar filled with anhydrous calcium sulfate which was then stored at 0 °C. All other chemicals were used as received from commercial sources.

3.5.2 Synthesis of 2-alkoxycarbonyl allylboronate 3.1



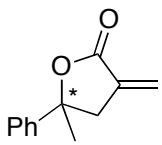
2-Alkoxycarbonyl allylboronate **3.1** was made according to literature procedure.[14] It was obtained in a yield of 82% and spectral properties were identical to those reported in the literature.

3.5.3 Racemic synthesis of γ-lactone 3.3 using CuCl-TBAT catalyst system



CuCl (3.7 mg, 0.15 equiv) and TBAT (20.0 mg, 0.15 equiv) were dissolved in 0.25 mL THF under argon and stirred at rt for 1 h. Allylboronate **3.1** (339 mg, 2.0 equiv) was dissolved in 0.25 mL and added to the reaction mixture, followed by acetophenone (88 μL, 1.0 equiv). The reaction was stirred at rt for 40 h, where upon it was quenched with saturated $NaHCO_3$ (aq) and extracted with EtOAc (x3). The organic layer was combined and removed *in vacuo* to provide crude acyclic product **3.2**. This crude mixture was put under argon and dissolved in 10 mL DCM and to this was added PTSA (285 mg, 2.0 equiv). The mixture stirred overnight at rt. The reaction was quenched with saturated $NaHCO_3$ (aq) and extracted with Et_2O (x3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide crude γ-lactone **3.3**. The mixture was purified by flash chromatography (20% EtOAc/hexanes) to provide pure γ-lactone **3.3** with a yield of 88%. Spectral properties of γ-lactone **3.3** matched those reported in the literature.[15]

3.5.4 Attempted enantiocontrolled synthesis of γ-lactone 3.3 using Cu-DuPHOS catalyst system



$CuF_2 \bullet 2H_2O$ (0.3 mg, 0.03 equiv) and (R,R)-^{i}Pr-DuPHOS (2.8 mg, 0.06 mmol) were added to a small microwave vessel and were subsequently dissolved in 0.3 mL methanol and put under argon. The vessel was capped and heated to 80 ºC for 2 h. The solvent was removed *in vacuo*, then toluene (0.3 mL) was added and the mixture was evaporated. After the toluene had been removed, this was repeated. $La(O^{i}Pr)_3$ (1.4 mg, 0.04 equiv) was added to the vessel, along with 0.3 mL THF. The mixture was stirred at rt until everything had dissolved. The THF was then removed *in vacuo*. Allylboronate **3.1** (30 mg, 1.2 equiv) was dissolved in 0.2 mL DMF and added to the microwave vessel, followed by acetophenone (11 μL, 1.0 equiv). The reaction was stirred at rt for 24 h at which time the reaction mixture was quenched with 10% citric acid and extracted with EtOAc (x3). The organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide a mixture of crude γ-lactone **3.3** along with the acyclic precursor **3.2**. The mixture was purified by flash chromatography (20% EtOAc/hexanes) to provide pure γ-lactone **3.3**. The spectral properties of γ-lactone **3.3** obtained from this reaction matched those reported in the literature.[15]

3.5.5 Determination of enantioselectivity by chiral HPLC analysis

The γ-lactone **3.3** obtained from the racemic synthesis (Section 3.5.3) and the chiral variant (Section 3.5.4) was analyzed by chiral HPLC analysis using an OD column with 3 μL volume injections. The flow rate was 1 mL/min, the temperature was 5 ºC and the solvent was hexanes: EtOAc (97:3). I was not able to achieve baseline resolution of the two peaks, but there was enough separation to see individual peaks. The racemic synthesis provided the enantiomers in a ratio of 46:54 (8% ee) and the enantiocontrolled synthesis provided the enantiomers in a ratio of 59:41 (18% ee). This led to an adjusted value for the enantiomeric excess of 10%.

3.6 References

[1] Yoo, W.-J.; Li, C.-J. *ChemSusChem* **2009**, *2*, 205-206.

[2] a) Kennedy, J.W.J.; Hall, D.G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4732-4739. b) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853-2873. c) Hatano, M.; Ishihara, K.; *Synthesis* **2008**, *11*, 1647-1675. d) Hall, D.G. *Synlett* **2007**, *11*, 1644-1655.

[3] (a) Casolari, S.; D'Addario, D.; Tagliavini, E.; *Org. Lett.* **1999**, *1*, 1061-1063. (b) Cunningham, A.; Woodward, S. *Synthesis* **2002**, 43-44. (c) Waltz, K.M.; Gavenonis, J.; Walsh, P.J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3697-3699. (d) Kii, S.; Maruoka, K.; *Chirality* **2003**, *15*, 68-70.

[4] Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910-8911.

[5] Schneider, U.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 5909-5912.

[6] Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13824-13825.

[7] Barker, T.J.; Jarvo, E.R. *Org. Lett.* **2009**, *11*, 1047-1049.

[8] Lou, S.; Moquist, P.N.; Schaus, S.E. *J. Am. Chem. Soc.* **2006**, *128*, 12660-12661.

[9] Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.***1988**, *110*, 6254-6255.

[10] Paton, R.S.; Goodman, J.M.; Pellegrinet, S.C. *Org. Lett.* **2009**, *11*, 37-40.

[11] Brown, H.C., Racherla, U.S., Pelechia, P.J. *J. Org. Chem.* **1990**, *55*, 1868-1874.

[12] Barnett, D.S., Moquist, P.N., Schaus, S.E. *Angew. Chem. Int. Ed.* **2009**, *48*, 8679-8682.

[13] Yu, S.H.; Ferguson, M.J.; McDonald, R.; Hall, D.G. *J. Am. Chem. Soc.* **2005**, *127*, 12808-1280.

[14] Nyzam, V.; Belaud, C.; Villieras, J. *Tetrahedron Lett.* **1993**, *34*, 6899-6902.

[15] Okabe, M.; Abe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 1775-1777.

Chapter 4

Catalyzed Additions of 2-Alkoxycarbonyl Allylboronates to Imines

4.1 Introduction

The α-methylene γ-lactone ring is a key structural motif in many natural products, most notably the sesquiterpene lactones (Figure 4.1).[1-6] These natural products have proven to be quite useful as DNA polymerase inhibitors, nuclear vitamin D receptor inhibitors, cellular steroidal inhibitors, blockers of tumor necrosis factor-α production, as well as many other uses.[7] The wide inhibitory action of these natural products makes them potential drug candidates due to their cytotoxic, antiallergenic, anti-inflammatory, phytotoxic, and antimicrobial properties.[8] However, many of these α-methylene γ-lactone natural products display toxic side effects when tested in vitro and are thus not suitable for pharmaceutical purposes.[8,9] One closely related class of molecules to the γ-lactones is the corresponding α-methylene γ-lactam scaffold. Even though there are significantly fewer reports compared to the γ-lactones, there are still a considerable number of natural products that contain a γ-lactam moiety as part of their structures (Figure 4.1). Furthermore, because the α-methylene γ-lactones are often too toxic to be used for pharmaceutical purposes, it has been suggested that the use of substituted α-methylene γ-lactams in place of the γ-lactone moiety might help to mitigate their intrinsic biological toxicity.[9] Synthetic routes to access γ-lactams have been the focus of several reports in the literature;[8,10,11] however, many of the reported routes are tedious in accessing the γ-lactam core structure. A few of these routes were outlined in Chapter 1. To satisfy the demands of parallel synthesis, more efficient routes to *N*-unsubstituted α-methylene γ-lactams are greatly needed.[11a]

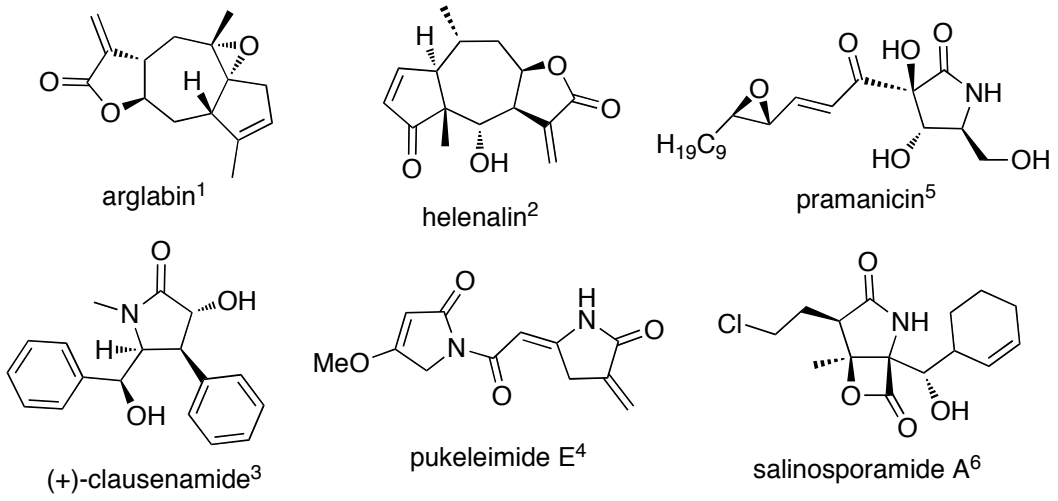
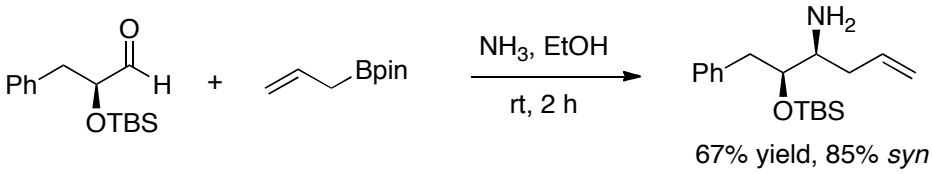


Figure 4.1: Natural products containing γ-lactone and γ-lactam rings

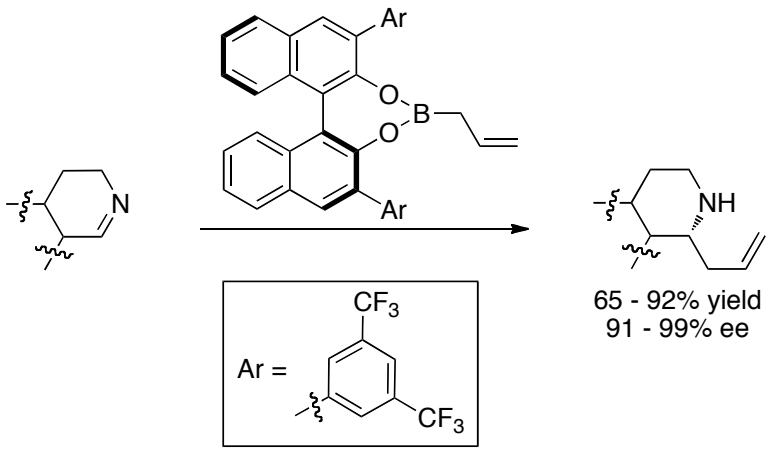
4.1.1 Recent examples of allylboronate additions to imine derivatives

Some of the more recent examples of allylboronate additions to imines made use of chiral imines in an attempt to access enantioenriched imine allylation products. In 1991, Wutz and co-workers were the first to describe an allylboration reaction using chiral imines.[12] The addition reaction between allylboronates and chiral *N*-benzyl imine derivatives occurred with excellent diastereoselectivity (>50:1 dr). Kobayashi and co-workers have also made use of chiral imines to afford enantioenriched homoallylic amines.[13] Using a solution of ethanolic ammonia, chiral α-substituted aldehydes are converted to unprotected imines *in situ* and subsequently react with allylpinacol boronate to provide the desired homoallylic amine with quite good selectivity (Equation 4.1).



Equation 4.1: Allylboronate addition to imines generated *in situ* from ammonia and aldehydes

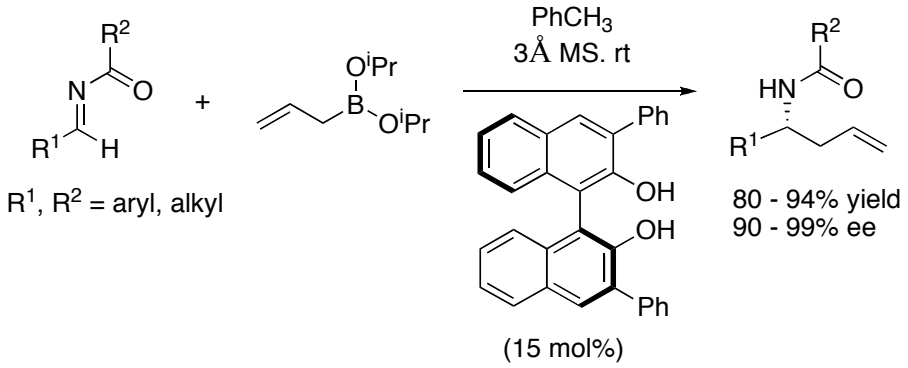
Another approach to chiral homoallylic amines involves the addition of chiral allylboronates to imines. Chong and co-workers have shown that chiral allylboronates with auxiliaries based on BINOL can provide excellent results in the enantioselective allylboration of imines.[14] Screening of various chiral auxiliaries for the allylboronate provided a suitable method in which cyclic imines could be allylated enantioselectively (Equation 4.2). These cyclic allylation products are useful intermediates and examples of their conversion to natural products can be found.[14]



Equation 4.2: Chiral allylboronate addition to cyclic imines

Schaus and co-workers have also utilized their diol catalyst system that had previously been used in a ketone-allylation to also work for acyl-substituted imines. Using (*S*)-3,3'-Ph_2-BINOL, it was shown that this diol catalyzed the addition of allyl diisopropoxyborane to various acyl imines (Equation 4.3).[15] This methodology is suitable to both aromatic and aliphatic imines, providing the desired homoallylic amides with good yields (80-94%) and excellent enantioselectivities (90-99% ee). Various protecting groups on the imine were investigated to determine their influence on the enantioselectivity of the reaction. Carbamate proved to be poor substrates (low yields due to decomposition of the imine and low enantioselectivities). Electron-deficient benzoyl groups proved to react slowly under the reaction conditions, but still provide the desired products

with high enantioselectivity. Electron-rich benzoyl groups along with cinnamoyl imine and cyclohexyl carboxamide imine were the best substrates and provided the desired allylation products in high yields and excellent enantioselectivity.

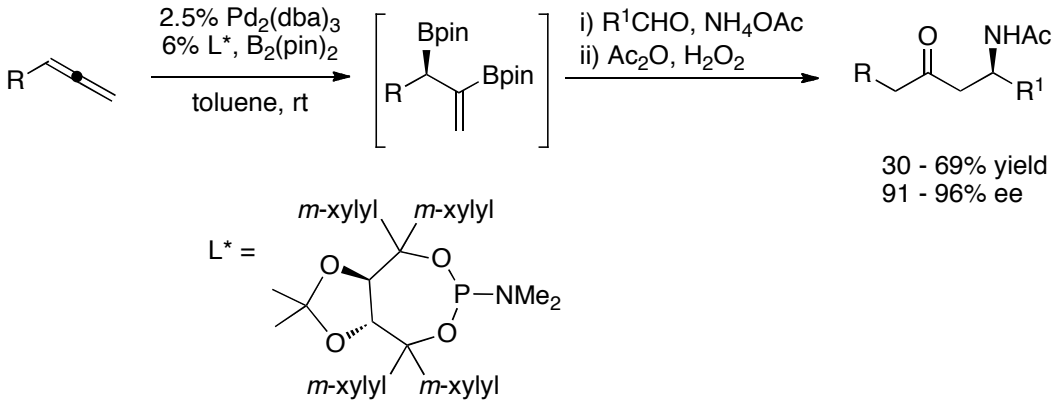


Equation 4.3: BINOL-derived ligand exchange system for the asymmetric allylboration of imine derivatives

Crotylation of imines catalyzed by this system are also highly stereoselective, but unfortunately, convergent as both the *E* and *Z*-crotylboronates lead to the *anti*-addition product. This indicates that the *Z*-crotylboronate may be proceeding through a boat-like transition state instead of the expected chair-like transition state. This alternative boat-like transition state may be favorable for the *Z*-crotylboronate due to diaxial interactions between the methyl group of the allylboronate and the acyl substituent of the imine.[15] This catalyst system is proposed to proceed via first ligand exchange between the diol and the allylboronate, producing a new allylboronate that can then activate the imine through hydrogen bonding between the remaining OH group of the diol and the carbonyl of the acyl protecting group. Allyl transfer and ligand exchange then leads to the observed allylation product and regenerates the diol catalyst.

Another approach to accessing homoallylic amines in an enantioselective fashion involves the use of chiral α-substituted allylboronates. Using a palladium-catalyzed diboration reaction, Morken and co-workers have shown that chiral α-substituted allylboronates can be formed *in situ* and subsequently reacted with preformed imines or imines that have also been prepared *in situ* (Equation 4.4).[16]

The products of this reaction were protected as the *N*-acyl derivatives and oxidized to the corresponding ketones. This is a nice example of a one-pot synthesis of β-ketoamides from allenes, and the allylboration reaction occurred with very high levels of stereocontrol. Very little erosion of the stereochemistry was observed in this imine allylboration reaction, except for the examples utilizing α,β-unsaturated imines.



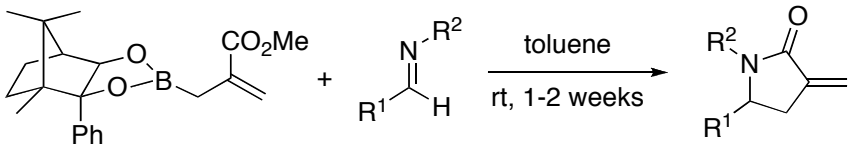
Equation 4.4: One-pot diboration-imine allylation protocol

These routes outlined above are excellent examples of addition of allylic boronates to imines that are preformed or formed *in situ*. However, in comparing these methods, they all make use of relatively reactive allylic boronates. The reactivity of these compounds, as discussed in previous chapters, is in stark contrast to the reactivity that is typical of the 2-alkoxycarbonyl allylboronates. Thus, it is unclear as to how these types of systems would behave if the allylation reagent was changed to something that was significantly less reactive.

4.1.2 Use of 2-alkoxycarbonyl allylboronates in imine allylation reactions

As a solution to the synthetic problem of accessing γ-lactams in a short and efficient manner, it was envisioned that one could simply add 2-alkoxycarbonyl allylboronates to imines and thus form α-methylene γ-lactams in a single step via a tandem allylation/lactamization reaction. Villiéras and co-

workers have demonstrated that this chemistry is indeed possible.[17] Their work described the use of highly activated, preformed imines reacting with 2-alkoxycarbonyl allylboronates to form γ-lactams through the same allylation/cyclization process described with aldehydes. (Equation 4.5) It should also be noted that this approach was made enantioselective by utilizing a chiral allylboronate based on Hoffmann's camphor-derived diol. The imines were specifically chosen due to their high reactivity, but the reactions were quite successful in that they provided the chiral homoallylic amine products with excellent enantioselectivity (>95% ee). The facial selectivity for allylboronate attack[17b] is similar to models already discussed in Chapter 1. Despite the fact that this route provided facile access to the γ-lactam core structure, the imines utilized in this protocol are severely limiting, not to mention the need to first pre-form the imines before carrying out the allylboration reactions. Furthermore, the reaction times are long (14 days at room temperature).



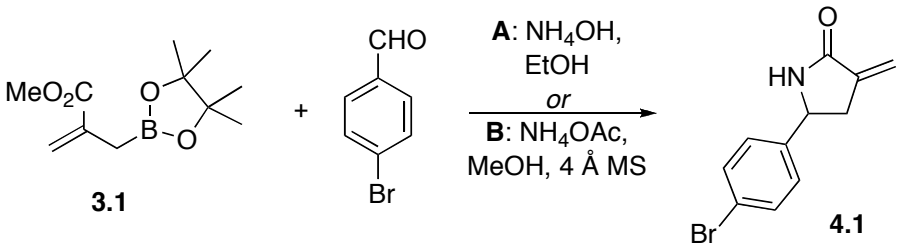
Equation 4.5: Thermal addition of 2-alkoxycarbonyl allylboronates to imines

4.2 Application of recent imine allylation protocols to 2-alkoxycarbonyl allylboronates

4.2.1 Initial investigation to adapt known protocols to 2-alkoxycarbonyl allylboronates[18]

As discussed above, Villiéras has made use of 2-alkoxycarbonyl allylboronates in imine addition reactions. However, the imines that can be utilized are limiting and the reaction times are long. It is more desirable to find

conditions that utilize imines formed *in situ*. In this regard, the Kobayashi[13] and Morken[16] groups have recently shown that imines formed *in situ* from aldehydes can be allylated to form homoallylic amines. However, both of these reports take advantage of significantly more reactive allylboronates as compared to the less reactive 2-alkoxycarbonyl allylboronates required to access γ-lactams. I wondered whether either of these reported conditions would also be suitable with less reactive allylboronates, such as 2-alkoxycarbonyl allylboronate **3.1**. Initially, both sets of conditions were attempted on a typical aromatic aldehyde, 4-bromobenzaldehyde (Table 4.1).



Entry	Method	Temperature (°C)	Time (h)	Yield[a] (%)
1	A	20	4	0
2	B	20	16	0
3	A	70	4	48
4	B	70	16	36

[a]Isolated yield after flash chromatography

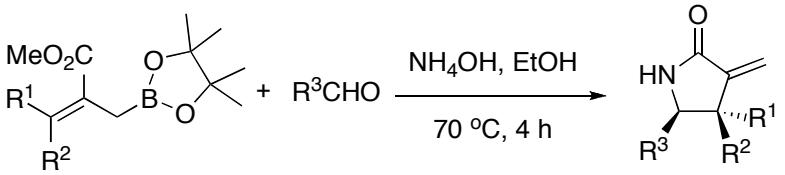
Table 4.1: Imine allylation using 2-alkoxycarbonyl allylboronate **3.1**

Not surprisingly, under both Kobayashi's conditions (entry 1, Table 4.1) and Morken's conditions (entry 2, Table 4.1), none of the desired γ-lactam product **4.1** was obtained. The reactions were then repeated, but with a higher reaction temperature of 70 °C. Gratifyingly, this time both method A[13] and method B[16] provided the desired lactam product **4.1**. Because the yields of **4.1** were similar for these two different sets of reaction conditions, the modified Kobayashi conditions (Method A) were chosen for further investigation of α-methylene γ-lactam formation. This choice was based on the fact that method A is

experimentally easier to perform, the reaction time is shorter and the purification steps are more straightforward.

4.2.2 Aldehyde substrate scope[18]

Various aldehydes were selected and then subjected to the imine allylation conditions, forming a wide variety of γ-substituted α-methylene γ-lactams (Table 4.2). Not only allylboronate **3.1**, but also the corresponding *Z*- and *E*-crotylboronates *Z*-**2.1** and *E*-**2.1** were used in the investigation of these imine allylation conditions. Initially, unsubstituted allylboronate **3.1** was used with a number of electron poor aromatic aldehydes (entries 1-3, Table 4.2), an electron rich aromatic aldehyde (entry 4) and even a number of aliphatic aldehydes (entries 7 and 8). The yields were typically good to excellent; however, a few entries displayed less satisfactory results. The lower yield observed for entry 4 can most likely be attributed to poor imine formation. *p*-Anisaldehyde is less reactive towards imine formation, and under the standard reaction conditions, would be slow in forming the required imine intermediate. Longer reaction times may help to increase the yield for similarly less reactive aldehydes. Lower yields were also observed for the aldehydes containing an enolizable proton (entries 7 and 8). However, this result could be predicted due to the strongly basic conditions the reactions are performed under. Enamine formation is expected to be a competing side reaction, and would result in a lower observed yield. Kobayashi and co-workers have shown that modifying the order of reagent addition is advantageous for obtaining the desired products with aliphatic aldehydes.[13] In the typical reaction procedure, the aldehyde is dissolved in a mixture of NH_4OH and ethanol, and the allylboronate is added to this reaction solution and subsequently heated. However, the order of addition was switched for aldehydes containing an enolizable proton (entries 7 and 8), whereby allylboronate **3.1** was added first. The aldehyde was then added to the reaction mixture, which was subsequently heated to provide the desired α-methylene γ-lactams **4.7** and **4.8**. (see Section 4.4.3 for a more detailed description).



Entry	Allylboronate	R^1	R^2	Aldehyde (R^3CHO)	Product	Yield (%)[a]
1	**3.1**	H	H	4-Br-C_6H_4CHO	**4.1**	48
2	**3.1**	H	H	4-NO_2-C_6H_4CHO	**4.2**	76
3	**3.1**	H	H	4-F-C_6H_4CHO	**4.3**	62
4	**3.1**	H	H	4-MeO-C_6H_4CHO	**4.4**	39
5	**3.1**	H	H	4-Me-C_6H_4CHO	**4.5**	90
6	**3.1**	H	H	PhCHO	**4.6**	53
7 [b]	**3.1**	H	H	$PhCH_2CH_2CHO$	**4.7**	39
8 [b]	**3.1**	H	H	n-$C_{10}H_{21}CHO$	**4.8**	35
9	*Z*-**2.1**	CH_3	H	4-Br-C_6H_4CHO	**4.9**	63
10	*Z*-**2.1**	CH_3	H	4-NO_2-C_6H_4CHO	**4.10**	52
11	*Z*-**2.1**	CH_3	H	4-CH_3-C_6H_4CHO	**4.11**	56
12	*Z*-**2.1**	CH_3	H	2-Br-C_6H_4CHO	**4.12**	98
13	*E*-**2.1**	H	CH_3	4-Br-C_6H_4CHO	**4.13**	73
14	*E*-**2.1**	H	CH_3	4-NO_2-C_6H_4CHO	**4.14**	66
15	*E*-**2.1**	H	CH_3	4-CH_3-C_6H_4CHO	**4.15**	95
16	*E*-**2.1**	H	CH_3	2-Br-C_6H_4CHO	**4.16**	74

[a]Isolated yields after flash chromatography and are the result of only one run for each reaction.
[b]Reverse order of addition used in reaction procedure (see Section 4.4.3 for more information).

Table 4.2: Substrate scope using boronates **3.1**, *Z*-**2.1** and *E*-**2.1** and various aldehydes

4.2.3 Diastereoselectivity of 2-alkoxycarbonyl crotylboronate addition to imines[18]

I was also interested in the diastereoselectivity of these imine allylboration reactions. According to the rules set out by Hoffman,[19] allylborations with *E*- and *Z*-crotylboronates and aldehydes provide distinct diastereomers depending on the initial geometry of the crotylboronate. 2-Alkoxycarbonyl crotylboronates have already been shown in Chapters 1 and 2 of this thesis to react with the same diastereospecificity, either under thermal conditions, with Lewis acid catalysts and Brønsted acid catalysts. Villiéras and co-workers have also shown that imine allylboration reactions carried out at room temperature also proceed in a

diastereospecific manner.[17] Although I suspected that the diastereospecific nature of the allylboration reaction would still manifest itself under these new imine allylation conditions, it needed to be verified. Thus, both *Z*-crotylboronate (*Z*-**2.1**) and *E*-crotylboronate (*E*-**2.1**) were utilized under the same imine allylboration conditions to test the diastereoselectivity of the reaction under these strongly basic conditions. *Z*-Crotylboronate *Z*-**2.1** was reacted with four different aromatic aldehydes and, in each case, the desired *trans* γ-lactam product was obtained as the sole product in moderate to excellent yields after flash chromatography purification (entries 9-12, Table 4.2). The X-ray crystallographic structure of **4.9** was obtained and allowed us to conclusively assign the relative stereochemistry for this product as being *trans* with respect to the aldehyde substituent and the methyl group (Figure 4.2).[20]

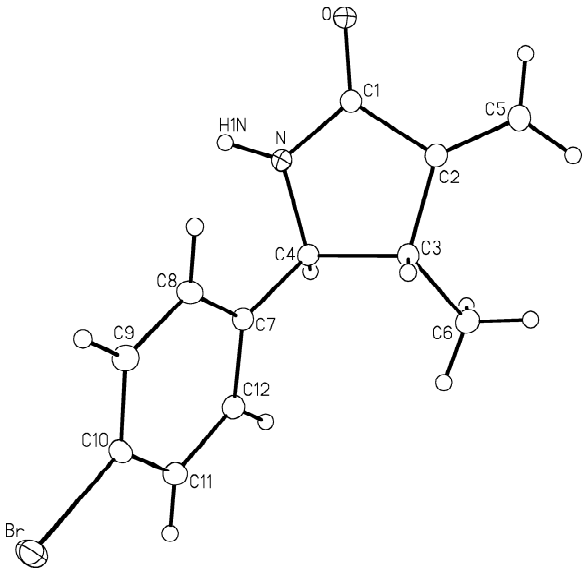
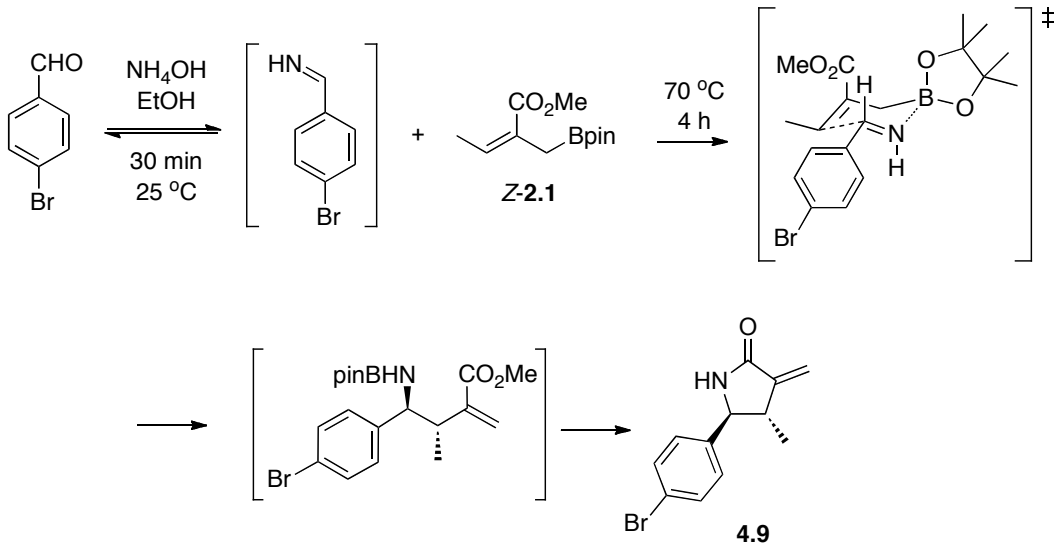


Figure 4.2: ORTEP diagram of crystal structure for **4.9**

The relative stereochemistry of all γ-lactams containing substituents in the β- and γ-positions were thus assigned as *trans* or *cis* based on this result. Similarly, *E*-crotylboronate *E*-**2.1** (19:1 dr) was reacted with the same four aldehydes and provided the desired *cis* γ-lactam products as the major

diastereomers in moderate to excellent yields (entries 13-16, Table 4.2). The diastereomeric ratio for the γ-lactam products in these four examples was 19:1, which was identical to the diastereomeric ratio of *E*-**2.1**. The complete transfer of stereochemistry from starting material to products further demonstrated that the imine allylboration reaction is indeed diastereospecific, even under these harsh, basic reaction conditions. The reaction described thus proceeds in a manner that can be considered to be a three-component reaction. Imines are formed *in situ* from ammonia and aldehydes, and are subsequently allylated using 2-alkoxycarbonyl allylboronates. As exemplified for **4.9** in Scheme 4.1, the initial allylboration step is followed by *in situ* lactamization of the intermediate homoallylic amine to form the observed γ-lactam products.



Scheme 4.1: Proposed mechanism for three-component imine allylation/lactamization reaction

4.3 Conclusions[18]

In conclusion, I have developed and optimized a new procedure for accessing highly substituted α-methylene γ-lactams through the use of a

diastereospecific, three-component reaction. The reaction is quite general in that a wide variety of aromatic aldehydes and aliphatic aldehydes are suitable substrates, providing the corresponding α-methylene γ-lactams in moderate to excellent yields. One should note that this protocol furnishes polysubstituted α-methylene γ-lactams that lack any activating or protecting groups on the nitrogen, which allows for immediate functionalization of the γ-lactam nitrogen without an extra deprotection step. Very few examples are found in the literature where this is the case.[11a,21] Further studies to expand this work to include other types of aldehydes, as well as investigations into the functionalization of these substituted α-methylene γ-lactams, were performed and will be discussed in Chapter 5. As mentioned earlier, the lactam sub-unit is a key component in a wide variety of bioactive natural products and synthetic drugs. Additional modifications of the α-methylene γ-lactam sub-unit would allow for facile access to these natural products as well as allow for analogues to be made in a convergent fashion. This would be one area where further investigations could be performed. By using more complex aldehydes and more elaborate boronates, it may be possible to expand this methodology to difficult substrates and allow for quick and direct access to many different natural products.

4.4 Experimental[18]

4.4.1 General information

Unless otherwise noted, all reactions were performed under an argon atmosphere. Methanol was distilled over CaH_2. NH_4Cl(aq) refers to a saturated aqueous solution. All aldehydes were purified by Kugelrohr distillation prior to their use. Allylboronate **3.1** was synthesized according to a literature procedure.[17] All other chemicals were used as received from commercial sources. Thin layer chromatography (TLC) was performed on silica gel plates and was visualized with UV light or potassium permanganate stain. NMR spectra were recorded on

400 or 500 MHz instruments. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards. ^{1}H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were recorded by the University of Alberta Spectral Services.

4.4.2 Procedures for the synthesis of α-methylene γ-lactam 4.1

Method A:

4-Bromobenzaldehyde (92 mg, 0.50 mmol) was dissolved in 1 mL ethanol in a high pressure vessel under argon. Ammonium hydroxide (30%, 0.75 mL) was added and the mixture was stirred at rt for 30 min. Allylboronate **3.1** (113 mg, 0.50 mmol) was diluted in 0.5 mL ethanol and added to the reaction mixture. An additional 0.5 mL ethanol was used as rinse and added to the reaction mixture. The mixture was heated to 70 ºC for 4 h. The reaction mixture was then cooled to rt, and 1N HCl was added to quench the reaction and bring the pH of the solution to ~1. The mixture was extracted four times with Et_2O, and the organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash chromatography (50% EtOAc/hexanes) to provide the desired α-methylene γ-lactam **4.1** in a yield of 48%.

Method B:

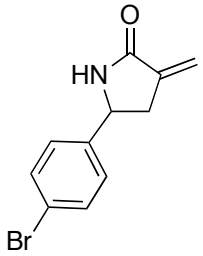
In a flame dried high pressure vessel, ammonium acetate (128 mg, 1.7 mmol) was added to 4Å activated molecular sieves in 1.5 mL methanol under argon. 4-Bromobenzaldehyde (61 mg, 0.33 mmol) was added to the mixture and stirred for 2 h at rt. Allylboronate **3.1** (0.22 mmol) was dissolved in 0.5 mL methanol and added to the reaction, which was subsequently heated to 70 ºC for

16 h. The reaction was quenched with saturated NH_4Cl and 1N HCl to bring the pH to ~5. The mixture was extracted three times with Et_2O and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (50% EtOAc/hexanes) to provide the desired α-methylene γ-lactam **4.1** in a yield of 36%.

4.4.3 General procedure for the synthesis of α-methylene γ-lactams:

The appropriate aldehyde (0.50 mmol) was dissolved in 1 mL ethanol in a high pressure vessel under argon. NH_4OH (30%, 0.75 mL) was added and the mixture was stirred at rt for 30 min. Allylboronate **3.1** (0.50 mmol) was diluted in 0.5 mL ethanol and added to the reaction mixture. An additional 0.5 mL ethanol was used as rinse and added to the reaction mixture. The mixture was heated to 70 ºC for 4 h. The reaction mixture was then cooled to rt, and 1N HCl was added to quench the reaction and bring the pH of the solution to ~1. The mixture was extracted four times with Et_2O, and the organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash chromatography (50-70% EtOAc/hexanes) to provide the desired α-methylene γ-lactam.

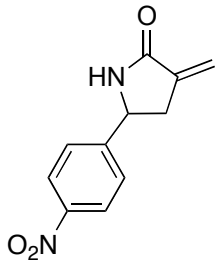
5-(4-Bromo-phenyl)-3-methylene-pyrrolidin-2-one (4.1)



Obtained as a white solid in a yield of 48% (method A) or 36% (method B). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 2H), 7.17 – 7.12 (m, 2H), 6.09 – 6.04 (m, 1H), 6.00 – 5.92 (br s, 1H), 5.43 – 5.38 (m, 1H), 4.73 (dd, 1H, *J* = 8.4, 4.7 Hz), 3.31 (app ddt, 1H, *J* = 17.2, 8.2, 2.3 Hz), 2.63 (ddd, 1H, *J* = 17.2, 4.5, 2.5

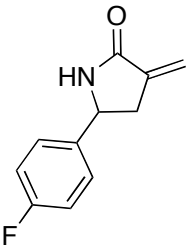
Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 141.9, 138.3, 132.4, 127.7, 122.2, 117.3, 54.5, 37.0. IR (CH_2Cl_2, microscope, cm^{-1}): 3177, 1697. HRMS (EI, m/z) Calcd for $C_{11}H_{10}ON^{81}Br$: 252.9925. Found: 252.9927.

3-Methylene-5-(4-nitro-phenyl)-pyrrolidin-2-one (4.2)



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 – 8.21 (m, 2H), 7.51 – 7.45 (m, 3H), 6.08 (t, 1H, *J* = 2.8 Hz), 5.44 – 5.42 (m, 1H), 4.90 (dd, 1H, *J* = 8.5, 4.5 Hz), 3.39 (ddt, 1H, *J* = 17.2, 8.5, 2.6 Hz), 2.69 – 2.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 149.8, 147.6, 137.4, 126.5, 124.2, 117.5, 54.2, 36.3. IR (CH_2Cl_2, cast film, cm^{-1}): 3187, 1698, 1519. HRMS (EI, m/z) Calcd for $C_{11}H_{10}O_3N_2$: 218.0691. Found: 218.0692.

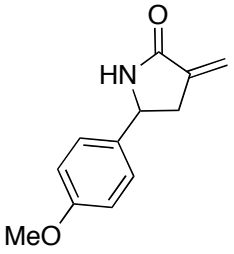
5-(4-Fluoro-phenyl)-3-methylene-pyrrolidin-2-one (4.3)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H), 7.09 – 7.03 (m, 2H), 6.12 – 6.09 (m, 1H), 6.10 – 5.95 (br s, 1H), 5.43 – 5.40 (m, 1H), 4.75 (dd, 1H, *J* = 8.2, 4.9 Hz), 3.39 (dddd, 1H, *J* = 17.2, 8.1, 2.5, 2.5 Hz), 2.67 (dddd, 1H, *J* = 17.3, 5.4, 2.9, 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 163.8, 161.3, 138.4, 138.2, 127.5, 127.4, 117.1, 116.1, 115.9, 54.2, 37.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -

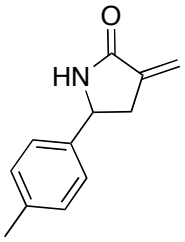
114.3 to -114.4 (m). IR ($CDCl_3$, microscope, cm^{-1}): 3173, 1694. HRMS (EI, m/z) Calcd for $C_{11}H_{10}NOF$: 191.0746. Found: 191.0745.

5-(4-Methoxy-phenyl)-3-methylene-pyrrolidin-2-one (4.4)



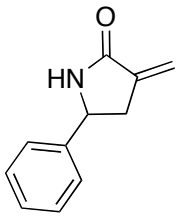
^1H NMR (500 MHz, $CDCl_3$): δ 7.23 – 7.19 (m, 2H), 6.92 – 6.88 (m, 2H), 6.08 (dd, 1H, *J* = 3.0, 3.0 Hz), 5.99 (br s, 1H), 5.40 (br s, 1H), 4.71 (dd, 1H, *J* = 8.0, 4.8 Hz), 3.82 (s, 3H), 3.29 (dddd, 1H, *J* = 17.1, 8.2, 2.4, 2.4 Hz), 2.68 (dddd, 1H, *J* = 17.2, 5.1, 2.9, 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 159.6, 138.8, 134.6, 127.0, 116.7, 114.4, 55.4, 54.4, 37.2. IR ($CDCl_3$, microscope, cm^{-1}): 3220, 1698, 1659. HRMS (EI, m/z) Calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0940.

3-Methylene-5-*p*-tolyl-pyrrolidin-2-one (4.5)



^1H NMR (400 MHz, $CDCl_3$): δ 8.26 – 8.21 (m, 2H), 7.51 – 7.45 (m, 3H), 6.08 (t, 1H, *J* = 2.8 Hz), 5.44 – 5.42 (m, 1H), 4.90 (dd, 1H, *J* = 8.5, 4.5 Hz), 3.39 (ddt, 1H, *J* = 17.2, 8.5, 2.6 Hz), 2.69 – 2.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 149.8, 147.6, 137.4, 126.5, 124.2, 117.5, 54.2, 36.3. IR (CH_2Cl_2, cast film, cm^{-1}): 3187, 1698, 1519. HRMS (EI, m/z) Calcd for $C_{11}H_{10}O_3N_2$: 218.06914. Found: 218.06918.

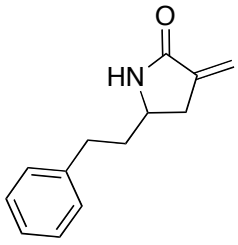
3-Methylene-5-phenyl-pyrrolidin-2-one (4.6)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 2H), 7.32 – 7.26 (m, 3H), 7.03 (br s, 1H), 6.03 (dd, 1H, *J* = 2.8, 2.8 Hz), 5.36 (br s, 1H), 4.75 (dd, 1H, *J* = 8.3, 4.7 Hz), 3.30 (dddd, 1H, *J* = 17.2, 8.2, 2.5, 2.5 Hz), 2.67 (dddd, 1H, *J* = 17.2, 5.0, 2.5, 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 142.7, 138.8, 129.0, 128.0, 125.7, 116.5, 54.9, 36.9. IR ($CDCl_3$, cast film microscope, cm^{-1}): 3172, 3067, 1696. HRMS (EI, m/z) Calcd for $C_{11}H_{11}ON$: 173.0841. Found: 173.0838.

For the synthesis of **4.7** and **4.8**, the order of addition was changed as follows. Allylboronate **3.1** was added to the ethanol and ammonium hydroxide first, and this reaction solution was stirred at rt for 30 min. At that point, the corresponding aldehyde was added and the reaction was heated to 70 ºC for 4 h. The work-up of the reaction remained the same.

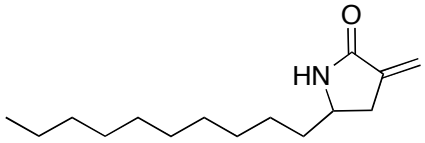
3-Methylene-5-phenethyl-pyrrolidin-2-one (4.7)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (br s, 1H), 7.31 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 5.99 (dd, 1H, *J* = 2.7, 2.7 Hz), 5.35 (br s, 1H), 3.70 – 3.63 (m, 1H), 2.99 (dddd, 1H, *J* = 17.0, 7.4, 2.4, 2.4 Hz), 2.69 (t, 2H, *J* = 8.1 Hz), 2.52 – 2.44 (m, 1H), 1.94 – 1.78 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 140.9, 139.3, 128.6, 128.3, 126.2, 116.6, 50.8, 38.9, 33.1, 32.0. IR (CH_2Cl_2, cast film

microscope, cm^{-1}): 3211, 2926, 1698, 1660. HRMS (EI, m/z) Calcd for $C_{13}H_{15}ON$: 201.1154. Found: 201.1154.

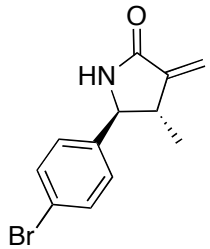
5-Decyl-3-methylene-pyrrolidin-2-one (4.8)



^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (br s, 1H), 5.97 (br t, 1H, *J* = 2.5 Hz), 5.32 (br s, 1H), 3.66 – 3.59 (m, 1H), 2.96 (dddd, 1H, *J* = 17.0, 7.4, 2.4, 2.4 Hz), 2.47 – 2.39 (m, 1H), 1.58 – 1.42 (m, 2H), 1.36 – 1.20 (m, 16H), 0.88 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 139.4, 115.9, 51.4, 37.3, 33.2, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 25.5, 22.7, 14.1. IR (microscope, cm^{-1}): 3182, 2917, 1706, 1662. HRMS (EI, m/z) Calcd for $C_{15}H_{27}ON$: 237.2093. Found: 237.2094.

α-Methylene γ-lactams **4.9** to **4.12** were synthesized using method A as described above, with the exception of using crotylboronate *Z*-**2.1** as the allylation reagent. This allylboronate was prepared according to a literature procedure.[22]

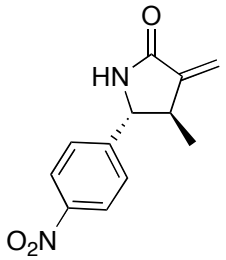
***trans*-5-(4-Bromo-phenyl)-4-methyl-3-methylene-pyrrolidin-2-one (4.9)**



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.49 (m, 2H), 7.23 – 7.12 (m, 2H), 6.09 (d, 1H, *J* = 3.1 Hz), 6.07 (br s, 1H), 5.35 (dd, 1H, *J* = 2.7, 0.9 Hz), 4.16 (d, 1H, *J* = 6.0 Hz), 2.79 – 2.67 (m, 1H), 1.29 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 148.7, 148.0, 143.5, 127.0, 124.4, 116.7, 63.0, 44.2, 17.3. IR

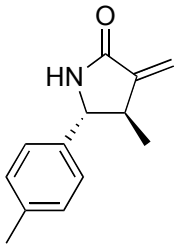
($CDCl_3$, cast film microscope, cm^{-1}): 3223, 1703. HRMS (EI, m/z) Calcd for $C_{12}H_{12}ON^{79}Br$: 265.0102. Found: 265.0102.

***trans*-4-Methyl-3-methylene-5-(4-nitro-phenyl)-pyrrolidin-2-one (4.10)**



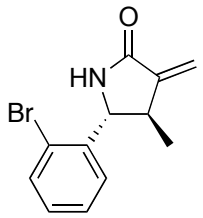
^1H NMR (500 MHz, $CDCl_3$): δ 8.28 – 8.24 (m, 2H), 7.53 – 7.49 (m, 2H), 6.15 (d, 1H, *J* = 3.0 Hz), 5.96 (br s, 1H), 5.40 (dd, 1H, *J* = 2.7, 1.0 Hz), 4.33 (d, 1H, *J* = 5.9 Hz), 2.80-2.73 (m, 1H), 1.35 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 148.7, 148.0, 143.5, 127.0, 124.4, 116.7, 63.0, 44.2, 17.3. IR (CH_2Cl_2, microscope, cm^{-1}): 1704. HRMS (EI, m/z) Calcd for $C_{12}H_{12}O_3N_2$: 232.0848. Found: 232.0852.

***trans*-4-Methyl-3-methylene-5-*p*-tolyl-pyrrolidin-2-one (4.11)**



^1H NMR (500 MHz, $CDCl_3$): δ 7.23 – 7.16 (m, 4H), 6.63 – 6.55 (m, 1H), 6.04 (d, 1H, *J* = 3.0 Hz), 5.30 (br d, 1H, J = 2.5 Hz), 4.15 (d, 1H, *J* = 6.0 Hz), 2.78 – 2.69 (m, 1H), 2.35 (s, 3H), 1.27 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 145.1, 138.2, 138.0, 129.6, 126.1, 115.2, 63.5, 44.4, 21.1, 16.7. IR (CH_2Cl_2, cast film, cm^{-1}): 3204, 1702, 1659. HRMS (EI, m/z) Calcd for $C_{13}H_{15}ON$: 201.1154. Found: 201.1152.

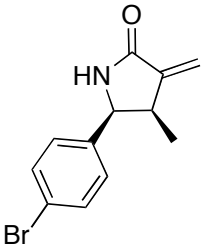
***trans*-5-(2-Bromo-phenyl)-4-methyl-3-methylene-pyrrolidin-2-one (4.12)**



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.56 (m, 1H), 7.37 – 7.30 (m, 2H), 7.20 – 7.13 (m, 1H), 6.43 (br s, 1H), 6.07 (d, 1H, *J* = 2.9 Hz), 5.35 – 5.33 (m, 1H), 4.78 (dd, 1H, *J* = 3.8, 1.0 Hz), 2.88 – 2.77 (m, 1H), 1.44 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 144.2, 141.0, 133.2, 129.4, 128.1, 127.0, 122.8, 166.6, 61.3, 43.7, 20.0. IR ($CDCl_3$, cast film microscope, cm^{-1}): 3197, 1696, 1660. HRMS (EI, m/z) Calcd for $C_{12}H_{12}ON^{81}Br$: 267.0082. Found: 267.0083.

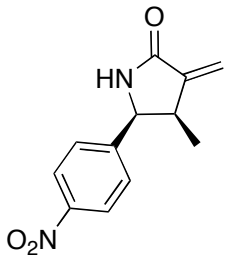
α-Methylene γ-lactams **4.13** to **4.16** were synthesized using method A as described above, with the exception of using crotylboronate *E*-**2.1** as the allylating reagent. This allylboronate was prepared according to a literature procedure.[22]

***cis*-5-(4-Bromo-phenyl)-4-methyl-3-methylene-pyrrolidin-2-one (4.13)**



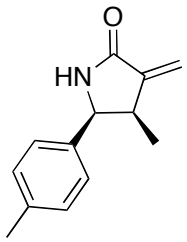
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 2H), 7.05 – 6.99 (m, 2H), 6.12 (d, 1H, *J* = 6.7), 6.10 (br s, 1H), 5.31 (dd, 1H, *J* = 2.8, 1.0 Hz), 4.75 (d, 1H, *J* = 8.1 Hz), 3.44 – 3.30 (m, 1H), 0.76 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 143.6, 138.1, 131.7, 128.5, 122.1, 116.5, 59.0, 38.3, 15.2. IR ($CDCl_3$, cast film microscope, cm^{-1}): 3218, 1699. HRMS (EI, m/z) Calcd for $C_{12}H_{12}ON^{79}Br$: 265.0102. Found: 265.0101.

***cis*-4-Methyl-3-methylene-5-(4-nitro-phenyl)-pyrrolidin-2-one (4.14)**



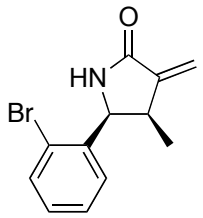
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 – 8.19 (m, 2H), 7.36 – 7.32 (m, 2H), 6.94 (br s, 1H), 6.13 (d, 1H, *J* = 3.1 Hz), 5.34 (dd, 1H, *J* = 2.7, 1.0 Hz), 4.92 (d, 1H, *J* = 8.4 Hz), 3.50 – 3.40 (m, 1H), 0.76 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 147.8, 146.5, 143.2, 127.8, 123.8, 117.0, 59.0, 38.3, 15.2. IR ($CDCl_3$, cast film microscope, cm^{-1}): 3210, 1703. HRMS (EI, m/z) Calcd for $C_{12}H_{12}O_3N_2$: 232.0848. Found: 232.0851.

***cis*-4-Methyl-3-methylene-5-*p*-tolyl-pyrrolidin-2-one (4.15)**



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 – 7.11 (m, 2H), 7.04 – 6.98 (m, 2H), 6.44 (br s, 1H), 6.08 (d, 1H, *J* = 3.4 Hz), 5.27 (br d, 1H, J = 2.9 Hz), 4.75 (d, 1H, *J* = 8.3 Hz), 3.40 – 3.27 (m, 1H), 2.33 (s, 3H), 0.75 (d, 3H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 144.4, 137.8, 136.0, 129.2, 126.9, 115.9, 59.4, 38.5, 21.1, 15.2. IR (CH_2Cl_2, cast film, cm^{-1}): 3221, 1698, 1659. HRMS (EI, m/z) Calcd for $C_{13}H_{15}ON$: 201.1154. Found: 201.1152.

***cis*-5-(2-Bromo-phenyl)-4-methyl-3-methylene-pyrrolidin-2-one (4.16)**



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 – 7.56 (m, 1H), 7.36 – 7.29 (m, 1H), 7.23 – 7.14 (m, 2H), 6.14 (d, 1H, *J* = 2.8 Hz), 5.88 (br s, 1H), 5.36 (dd, 1H, *J* = 2.5, 0.9 Hz), 5.31 (d, 1H, *J* = 8.2 Hz), 3.60 – 3.48 (m, 1H), 0.79 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 144.2, 138.0, 133.0, 129.3, 127.7, 123.3, 117.0, 58.0, 37.1, 15.9. IR (microscope, cm^{-1}): 3177, 1708. HRMS (EI, m/z) Calcd for $C_{12}H_{12}ON^{81}Br$: 267.0082. Found: 267.0081.

4.5 References

[1] (a) Adekenov, S.M.; Mukhametshanov, M.N., Kupriyanov, A.N. *Khim. Prir. Soedin.* **1982**, 565. (b) Shaikenov, T.E.; Adekenov, S.; Williams, R.M.; Prashad, N.; Baker, F.; Madden, T.L.; Newman, R. *Oncol. Rep.* **2001**, *8*, 173-179. (c) Zhangabylov, N.S.; Dederer, L.Y.; Gorbacheva, L.B.; Vasil'eva, S.V.; Terekhov, A.S.; Adekenov, S.M. *Pharm. Chem. J.* **2004**, *38*, 651.

[2] (a) Lyss, G.; Knorre, A.; Schmidt, T.J.; Pahl, H.L.; Merfort, I. *J. Biol. Chem.* **1998**, *273*, 33508-33516. (b) Huang, P.R.; Yeh, Y.M.; Wang, T.C. *Cancer Lett.* **2005**, *227*, 169-174. (c) Jimenez-Ortiz, V.; Brengio, S.D.; Giordano, O.; Tonn, C.; Sánchez, M.; Burgos, M.H.; Sosa, M.A. *J. Parasitol.* **2005**, *91*, 170-174. (d) Schmidt, T.J.; Brun, R.; Willuhn, G.; Khalid, S.A. *Planta. Med.* **2002**, *68*, 750-751. (e) François, G.; Passreiter, C.M. *Phytother. Res.* **2004**, *18*, 184-186. (f) Boulanger, D.; Brouillette, E.; Jaspar, F.; Malouinc, F.; Mainil, J.; Bureau, F.; Lekeux, P. *Vet. Microbiol.* **2007**, *119*, 330-388.

[3] (a) Yang, M.H.; Cao, Y.H.; Li, W.X.; Yang, Y.Q.; Huang, L. *Acta. Pharm. Sinica* **1987**, *22*, 33-40. (b) Yang, M.H.; Chen, Y.Y.; Huang, L. *Acta. Chim. Sinica (English Ed.)*, **1987**, 267-270. (c) Zhang, J.T. *Acta. Pharm. Sinica* **1986**, *21*, 636-640. d) Duan, W.Z.; Zhang, J.T. *Acta. Chim. Sinica* **1997**, *32*, 259-263.

[4] Cardellina, J.H.; Moore, R.E. *Tetrahedron Lett.* **1979**, *22*, 2007-2010.

[5] Schwartz, R.E.; Helms, G.L.; Bolessa, E.A.; Wilson, K.E.; Giacobbe, R.A.; Tkacz, J.S.; Bills, G.F.; Liesch, J.M.; Zink, D.L.; Curotto, J.E.; Pramanik, B.; Onishi, J.C. *Tetrahedron* **1994**, *50*, 1675-1686.

[6] (a) Feling, R.H.; Buchanan, G.O.; Mincer, T.J.; Kauffman, C.A.; Jensen, P.R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355-357. (b) Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T.H.; Neuteboom, S.T.; Richardson, P.; Palladino, M.A.; Anderson, K.C. *Cancer Cell* **2005**, *8*, 407-419.

[7] Konaklieva, M.I.; Plotkin, B.J. *Mini Rev. Med. Chem.* **2005**, *5*, 73-95.

[8] Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem.* **2005**, *48*, 3516-3521.

[9] Belaud, C.; Roussakis, C.; Letourneux, Y.; El Alami, N.; Villiéras, J. *Syn. Commun.* **1985**, *15*, 1233-1243.

[10] (a) Reddy, L.R.; Saravanan, P.; Corey, E.J. *J. Am. Chem. Soc.* **2004**, *126*, 6230-6231. (b) Reddy, L.R.; Fournier, J.-F.; Subba Reddy, B.V.; Corey, E.J. *J. Am. Chem. Soc.* **2005**, *127*, 8974-8976. (c) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765-7768. (d) Lettan, R.B. *II*.; Woodward, C.C.; Scheidt, K.A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2294-2297.

[11] (a) Krawczyk, H.; Albrecht, L.; Wojciechowski, J.; Wolf, W.M., Krajewska, U.; Rozalski, M. *Tetrahedron*, **2008**, *42*, 6307-6314. (b) Alami, N.E.; Belaud, C.; Villiéras, J. *Tetrahedron Lett.* **1987**, *28*, 59-60. (c) Dembele, Y.A.; Belaud, C.; Hitchcock, P.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 351-354. (d) Dembele, Y.A.; Belaud, C.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511-514. (e) Nyzam, V.; Belaud, C.; Zammattio, F.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *7*, 1835-1843. (f) Choudhury, P.K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376-3378. (g) Tanaka, K.; Yoda, H.; Kaji, A. *Synthesis* **1985**, 84-86. (h) Beji, F.; Lebreton, J.; Villiéras, J.; Amri, H. *Tetrahedron* **2001**, *57*, 9959-9962. (i) Lee, K.Y.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 2007-2011.

[12] Wutz, P.G.M.; Jung, Y.-W. *J. Org. Chem.* **1991**, *56*, 365-372.

[13] Suigiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182-7183.

[14] Wu, T.R.; Chong, J.M. *J. Am. Chem. Soc.* **2006**, *128*, 9646-9647.

[15] S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, *129*, 15398-15404.

[16] Sieber, J.D.; Morken, J.P. *J. Am. Chem. Soc.* **2006**, *128*, 74-75.

[17] (a) Chataigner, I.; Zammattio, F.; Lebreton, J.; Villiéras, J. *Synlett*. **1998**, 275-276. (b) Chataigner, I.; Zammattio, F.; Lebreton, J.; Villiéras, J. *Tetrahedron* **2008**, *64*, 2441-2455.

[18] A version of this chapter has been published: Elford, T.G., Hall, D.G. *Tetrahedron Lett*. **2008**, *49*, 6995-6998.

[19] (a) Hoffmann, R.W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 306. (b) Hoffmann, R.W.; Zeiss, H.-J. *J. Org. Chem*. **1981**, *46*, 1309-1314.

[20] Crystallographic data (excluding structure factors) for the structure of compound **4.9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-695506. Copies of these data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif).

[21] Basavaiah, D.; Rao, S.J. *Tetrahedron Lett*. **2004**, *45*, 1621-1625.

[22] Elford, T.G.; Arimura, Y.; Yu, S.H.; Hall, D.G. *J. Org. Chem*. **2007**, *72*, 1276-1284.

Chapter 5

Diversity-Oriented Synthesis and Preliminary Biological Screening of Highly Substituted γ-Lactones and γ-Lactams via Allylboration of Aldehydes and Imines

5.1 Introduction

5.1.1 Combinatorial chemistry and drug discovery

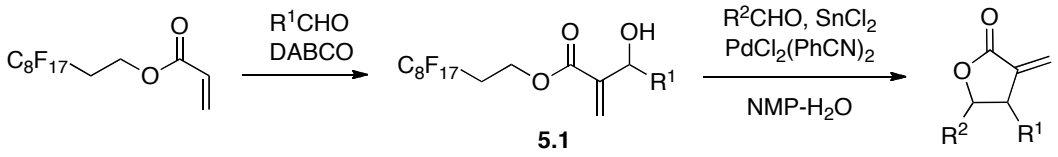
The modern pharmaceutical industry is built on the premise of developing new and more effective drugs. Typically, two methods have been used in this endeavor. In the first, natural products and their derivatives have been relied upon heavily and a majority of the drugs in use today are a result of this exploitation of nature's pharmacy. Penicillin, morphine and paclitaxel are three well-known examples of this. The second method involves the synthesis of novel compounds and their screening for activity against various biological targets. This approach can be approached from either a purely random molecular scaffold or a designed structure that is based on some other experiment or concept. While the use of rational design of compounds for drug discovery has experienced recent growth due to increased computational power and the advancement of knowledge in computational techniques for enzymatic docking and crystal structures, there still remains the need to actually synthesize many different compounds that are closely related. Structure activity relationship (SAR) studies rely upon the testing of these closely related compounds to determine the optimal candidate or the best substitution pattern. One tool that has been developed for facilitating the synthesis of many closely related compounds efficiently in a short period of time is combinatorial chemistry.

Combinatorial chemistry is a technique that can trace its origins back to the solid-phase peptide chemistry work of Merrifield[1] in the 1960's and the concept of tagging solid supports that was developed by Geysen in the 1980's. The area of combinatorial chemistry has changed greatly over the past 25 years and now allows for collections of different compounds to be rapidly synthesized to make what is called a "library of compounds". Synthesis of molecules in a combinatorial fashion can quickly lead to large numbers of molecules. For example, a molecule with three points of diversity (R^1, R^2, and R^3) can generate N_{R1} x N_{R2} x N_{R3} possible structures, where N_{R1}, N_{R2}, and N_{R3} are the number of different substituents utilized. This technique also makes use of common reaction conditions for a given transformation. In the past, chemists have made one compound at a time, one reaction at a time. Reaction conditions are optimized for an individual substrate and the reaction is then performed, followed by product purification and characterization. Combinatorial chemistry does away with these time-consuming steps. By performing robust chemical reactions that are general (thereby foregoing the step of optimizing reaction conditions) and by using little to no purification except for the final desired compound, the time consuming steps of organic synthesis are avoided and a large number of compounds can be generated in a short period of time. The use of customized equipment that can hold several reaction vessels and the implementation of robotics have further helped in the acceptance and utilization of combinatorial chemistry.

5.1.2 Library of γ-lactones and γ-lactams through diversity-oriented synthesis

As mentioned in many of the previous chapters, the α-methylene γ-lactone ring is a key structural motif in many natural products, most notably the sesquiterpene lactones (Figure 1.3). As a result of the biological importance of these natural products, the synthesis of polysubstituted α-methylene γ-lactones has been of interest to synthetic chemists for several years. Several routes have been devised to access the α-methylene γ-lactone ring, however, they tend to be

lengthy and cumbersome if the lactone contains any sort of substitution (*cf.* Chapter 2).[2,3] Libraries of γ-lactones containing various substituents at the β- and γ-positions have been synthesized via a Baylis-Hillman reaction to form β-hydroxy ketones **5.1** (Scheme 5.1).[4] These are further subjected to a palladium mediated carbonyl allylation protocol to furnish the desired library of substituted γ-lactones. This library was purified by fluorous phase extraction techniques.



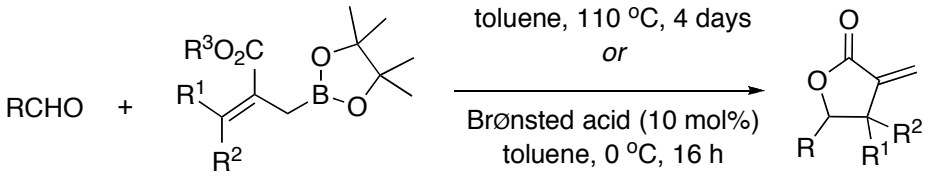
Scheme 5.1: Library of γ-lactones purified by fluorous phase purification techniques[4]

Studies in the Hall group[5] and others[6] have shown that the allylboration of aldehydes using thermal or Brønsted acidic conditions is an expedient and very convenient approach to access a wide range of highly substituted α-methylene γ-lactones. With my experience in forming many different γ-lactones, I undertook a project that utilized the allylboration/cyclization chemistry to synthesize numerous α-methylene γ-lactones containing a wide variety of substituents. Furthermore, it was found that I could also access α-methylene γ-lactams through the allylboration of imines (*cf.* Chapter 4). Several natural products containing a γ-lactam ring are also known (Figure 1.3),[7] and many of these molecules exhibit interesting biological properties in their own right.[8] Therefore, it was decided to include α-methylene γ-lactams as part of this diverse library. Various routes to further functionalize these γ-lactones and γ-lactams were investigated and led to the formation of α-alkylidene and α-alkylated γ-lactones as well as α-alkylidene and α-alkylated γ-lactams.

5.2 Scaffold optimization and synthesis of γ-lactone sub-libraries

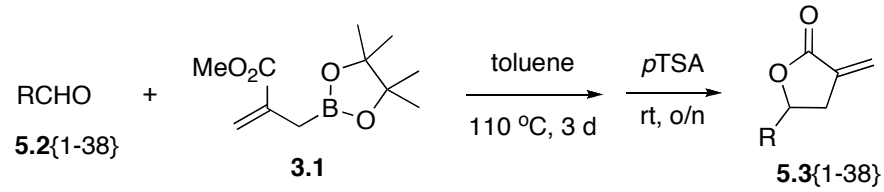
5.2.1 α-Methylene γ-lactones[9]

Based upon previous work in the Hall group[5] revolving around the allylboration reaction of aldehydes with 2-alkoxycarbonyl allylboronates, I have shown that α-methylene γ-lactones can be easily accessed using either thermal or Brønsted acid-catalyzed conditions (Equation 5.1).



Equation 5.1: General addition of 2-alkoxycarbonyl allylboronates to aldehydes

This previous work and expertise in allylboration reactions meant that no optimization was required for this sub-library. The thermal allylboration reaction requires significantly longer reaction times and substantially elevated temperatures as compared to the Brønsted acid-catalyzed allylboration conditions.[5] However, because of the technological challenge of carrying out a large number of reactions at 0 °C, it was decided that the preparation of the α-methylene γ-lactone scaffold would be carried out under thermal allylboration conditions. Towards this end, allylboronate **3.1** was reacted with a wide variety of aldehydes **5.2**{1-38} (Figure 5.1) to provide the desired γ-lactone products **5.3**{1-38} (Table 5.1). The numbering system used in this chapter is based on the numbering system used by the *Journal of Combinatorial Chemistry*. The numbers in the braces indicate what building block of a given category or type was used. This allows for easy tracing of products back to reactants over one or more steps. For example, γ-lactone product **5.3**{3} indicates that in the allylboration reaction, aldehyde **5.2**{3} was used.



5.2{1-38}

3.1

5.3{1-38}

Entry	Aldehyde (RCHO)	Product	Yield (%)[a]
1	**5.2**{1}	**5.3**{1}	73
2	**5.2**{2}	**5.3**{2}	46
3	**5.2**{3}	**5.3**{3}	9
4	**5.2**{4}	**5.3**{4}	59
5	**5.2**{5}	**5.3**{5}	1
6	**5.2**{6}	**5.3**{6}	1
7	**5.2**{7}	**5.3**{7}	22
8	**5.2**{8}	**5.3**{8}	19
9	**5.2**{9}	**5.3**{9}	49
10	**5.2**{10}	**5.3**{10}	3
11	**5.2**{11}	**5.3**{11}	60
12	**5.2**{12}	**5.3**{12}	45
13	**5.2**{13}	**5.3**{13}	19
14	**5.2**{14}	**5.3**{14}	49
15	**5.2**{15}	**5.3**{15}	14
16	**5.2**{16}	**5.3**{16}	10
17	**5.2**{17}	**5.3**{17}	1
18	**5.2**{18}	**5.3**{18}	18
19	**5.2**{19}	**5.3**{19}	0.4
20	**5.2**{20}	**5.3**{20}	37
21	**5.2**{21}	**5.3**{21}	6
22	**5.2**{22}	**5.3**{22}	36
23	**5.2**{23}	**5.3**{23}	27
24	**5.2**{24}	**5.3**{24}	6
25	**5.2**{25}	**5.3**{25}	5
26	**5.2**{26}	**5.3**{26}	4
27	**5.2**{27}	**5.3**{27}	6
28	**5.2**{28}	**5.3**{28}	9
29	**5.2**{29}	**5.3**{29}	28
30	**5.2**{30}	**5.3**{30}	7
31	**5.2**{31}	**5.3**{31}	14
32	**5.2**{32}	**5.3**{32}	23
33	**5.2**{33}	**5.3**{33}	21

34	**5.2**{34}	**5.3**{34}	4
35	**5.2**{35}	**5.3**{35}	6
36	**5.2**{36}	**5.3**{36}	20
37	**5.2**{37}	**5.3**{37}	3
38	**5.2**{38}	**5.3**{38}	18

[a] Isolated yield after preparatory HPLC. See purity table in Section 5.6.17.

Table 5.1: Synthesis of α-methylene γ-lactones **5.3**{1-38} from allylboronate **3.1** and aldehydes **5.2**{1-38}

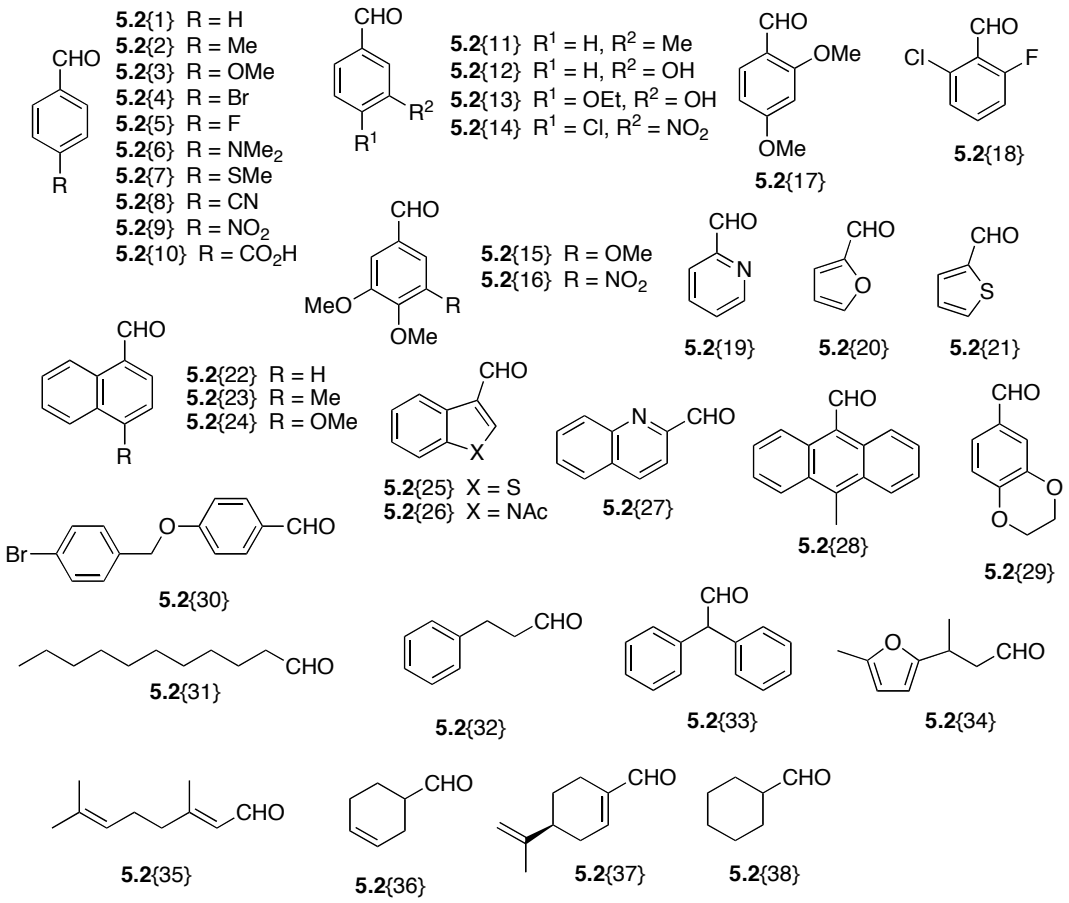


Figure 5.1: Aldehyde diversity reagents **5.2**{1-38}

One will note the generality of aldehydes that can be utilized in the allylboration reaction. A variety of substituted aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes are all suitable substrates for this reaction. All reactions were performed simultaneously in solution phase using a parallel synthesizer, quenched with aqueous $NaHCO_3$ and extracted with EtOAc. Crude reaction mixtures were purified by semi-preparative HPLC by Mr. Eric Pelletier. To focus on product purity rather that recovered yields, a very conservative fraction collection threshold was employed for this sub-library as well as all other sub-libraries reported in this chapter. While conventional purification using flash chromatography provided reaction products with typically >50% recovered yields on a larger scale, careful purification using preparatory HPLC afforded the library members with lower reported yields but in >90% purity for 80% of the library members according to a random analysis. This careful purification protocol explains the lower yields compared to the individual examples involving flash-chromatographic purification on normal silica gel. For example, **5.3**{3} and **5.3**{5} were isolated in yields of 32% and 70%, respectively, when purified by flash chromatography as compared to only 9% and 1%, respectively, when purified by preparatory HPLC. For this analysis of purity, two or three members of each sub-library were chosen at random and analyzed by HPLC-ESMS and NMR spectroscopy to further confirm their identity and purity. As shown in Section 5.6, 20 randomly selected compounds from the complete library (~10% of the library) were analyzed and characterized.

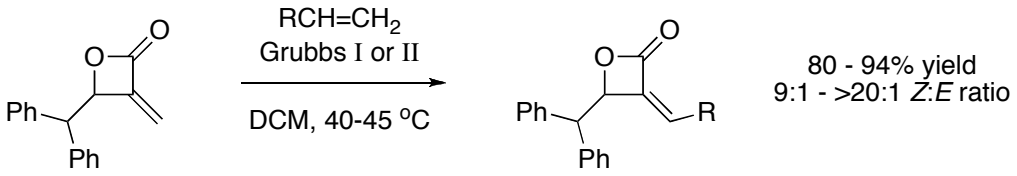
5.2.2 α-Alkylidene γ-lactones[9]

I then turned my attention to the modification of these simple γ-lactones **5.3**, since many of the bioactive natural products containing this ring moiety are also further functionalized. When looking at the structure of the α-methylene γ-lactones, it was obvious to us that the most suitable modification would be to further modify the *exo*-methylene group. Moreover, substrates containing a less electrophilic α-methylene γ-lactone moiety might help to mitigate the

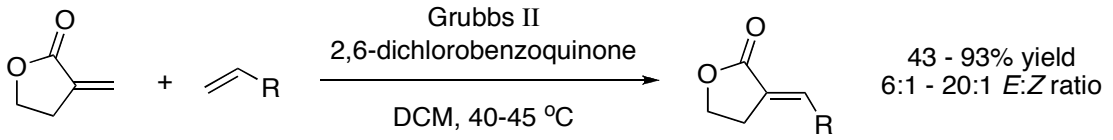
promiscuous reactivity of these compounds in biological systems and allow for more selective targeting. Alkenes can be commonly modified through many different types of reactions. Heck coupling reactions, conjugate additions, cross-metathesis, Morita–Baylis–Hillman reactions, cycloadditions and various other oxidation or reduction reactions are just a few of the possibilities that are available to functionalize this methylene group.[10]

5.2.2.1 Alkene functionalization utilizing cross-metathesis

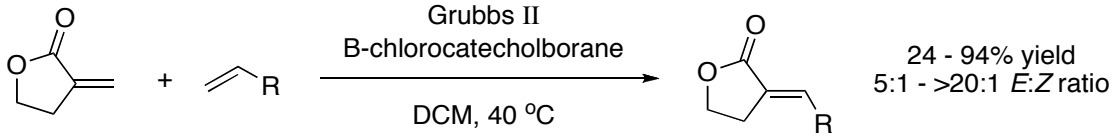
Initially, I had hoped to be able to modify γ-lactones **5.3** via ruthenium-mediated cross-metathesis. Cross-metathesis would make use of the vast number of commercially available terminal alkenes and allow for a sizeable sub-library to be generated. The required cross-metathesis catalysts are, however, relatively expensive. On the other hand, the reactions are executed on small scale and I should be able to perform the reactions with low catalyst loadings. One report by Howell and co-workers (Equation 5.2)[11a] makes use of α-methylene β-lactones as substrates for cross-metathesis. They have shown in a follow-up report that α-methylene γ-lactones are also suitable substrates as long as a suitable additive, namely 2,6-dichlorobenzoquinone, was used in the reaction mixture (Equation 5.3).[11b] Likewise, Cossy and co-workers have utilized similar α-methylene γ-lactones in performing cross-metathesis reactions with terminal alkenes.[12] Similarly, they also found that an additive, B-chlorocatecholborane, was necessary to bring about useful conversions (Equation 5.4).



Equation 5.2: Cross-metathesis of α-methylene β-lactones with terminal alkenes[11a]



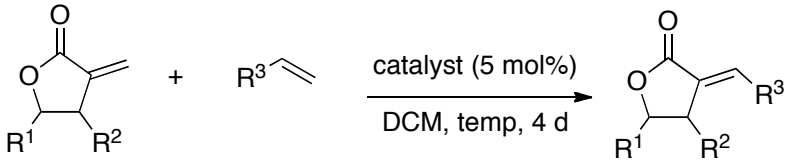
Equation 5.3: Cross-metathesis of α-methylene γ-lactones with 2,6-dichlorobenzoquinone additive[11b]



Equation 5.4: Cross-metathesis of α-methylene γ-lactones with B-chlorocatecholborane additive[12]

With this precedent in mind, initial trials were conducted to investigate the feasibility of utilizing cross-metathesis in our library synthesis, as shown in Table 5.2. Despite my initial enthusiasm regarding cross-metathesis, the reaction proved to be rather sporadic in its ability to functionalize α-methylene γ-lactones. Both Grubbs II (G-II) and Hoveyda–Grubbs II (HG-II) were examined as cross-metathesis catalysts. α-Methylene γ-lactones containing a β-methyl substituent were completely unreactive to the reaction conditions (entries 1-5, Table 5.2). Some cross-metathesis reactions did proceed smoothly and provided reasonable yields when HG-II was used in conjunction with benzoquinone as an additive (entries 6, 8, 9, 13, Table 5.2), while others provided low to negligible yields (entries 7, 10-12, 14-19, Table 5.2). All attempts to bring about further conversion and higher yields for these reactions failed, including adding more catalyst and utilizing other additives (entries 20 and 21, Table 5.2). Because our desire was to build a library using standard conditions that would apply to all reactions carried out, it was deemed that cross-metathesis was unsuitable for functionalization of α-methylene γ-lactones to form α-alkylidene γ-lactones. This was a rather

unfortunate setback, as cross-metathesis would have been an almost ideal reaction for library generation.



5.4a-m

Entry	γ-Lactone substrate	R^3	Catalyst/ additive[a]	Temp (°C)	Product	Yield[b] (%)
1	**2.9b**	Ph	G-II	40	---	0
2	**2.9b**	Ph	HG-II	40	---	0
3	**2.11b**	Ph	G-II	40	---	0
4	**2.7b**	Ph	HG-II	40	---	0
5[c]	**2.7b**	Ph	HG-II	110	---	0
6	**5.3**{4}	$TBSO(CH_2)_8$-	HG-II/ BQ	40	**5.4a**	78
7	**5.3**{4}	Ph	HG-II/ BQ	40	---	0
8	**5.3**{9}	$AcO(CH_2)_4$-	HG-II/ BQ	40	**5.4b**	44
9	**5.3**{9}	$TBSO(CH_2)_8$-	HG-II/ BQ	40	**5.4c**	68
10	**5.3**{9}	Ph	HG-II/ BQ	40	**5.4d**	24
11	**5.3**{1}	Ph	HG-II/ BQ	40	**5.4e**	28
12	**5.3**{1}	$AcO(CH_2)_4$-	HG-II/ BQ	40	---	0
13	**5.3**{1}	$TBSO(CH_2)_8$-	HG-II/ BQ	40	**5.4f**	43
14[d]	**5.3**{1}	$TBSO(CH_2)_8$-	HG-II/ BQ	140	---	0
15[e,f]	**5.3**{1}	$AcO(CH_2)_4$-	HG-II/ BQ	100	**5.4g**	5
16[f]	**5.3**{32}	$AcO(CH_2)_4$-	HG-II/ BQ	60	**5.4h**	6
17[f]	**5.3**{32}	$TBSO(CH_2)_8$-	HG-II/ BQ	60	**5.4i**	10
18[f]	**5.3**{32}	Ph	HG-II/ BQ	60	**5.4j**	18
19[f]	**5.3**{32}	$CH_3(CH_2)_3$-	HG-II/ BQ	60	**5.4k**	6
20	**5.3**{1}	$Ph(CH_2)_2$-	HG-II/ DCBQ	40	**5.4l**	6
21	**5.3**{1}	$Ph(CH_2)_2$-	HG-II/ B-CCB	40	**5.4l**	21

[a] Additive was used in an amount of 10 mL% compared to the starting lactone. [b] Yield refers to isolated yield after flash chromatography. [c] Reaction was carried out in a sealed vessel. [d] Reaction was carried out with microwave heating for 4 h. [e] Reaction was carried out with microwave heating for 1 h. [f] Solvent used was toluene.

Table 5.2: Examination of cross-metathesis for forming α-alkylidene γ-lactones

5.2.2.2 Alkene functionalization utilizing the Heck reaction[9]

Because cross-metathesis failed for the purposes of generating γ-lactone libraries, I decided to examine other transformations that would result in similar products. The reaction that seemed to fit the criteria was the Heck reaction. There is a vast amount of literature available that makes use of Heck or Heck-type reactions to couple alkenes to aryl or alkyl halides or pseudo-halides.[13] The coupling of α,β-unsaturated enoates (present in our substrate γ-lactones **5.3**) to aryl halides, however, is much less investigated. Moreover, alkenes that are *gem*-disubstituted have a tendency to be problematic in Heck reactions due to steric hindrance and competing β-hydrogen eliminations.[13c] With these limiting factors in mind, a search of the literature did provide some insight into utilizing the α-methylene γ-lactones as coupling partners in Heck or Heck-type reactions.[14] I began by screening a wide variety of standard conditions and protocols that are typically used for Heck reactions (Table 5.3). γ-Lactones **5.5**{1-2} were used in these initial experiments and are shown in Figure 5.2. It is necessary to note that γ-lactones **5.5**{1-2} have been discussed in Chapter 2. However, due to the complex numbering system used for libraries, it was necessary to assign new numbers for their use in Chapter 5. This will be the case for other compounds throughout this chapter. To help minimize confusion, compounds that have already been assigned a number in previous chapters will be shown with both the old number along with the newly assigned number in the corresponding figures.

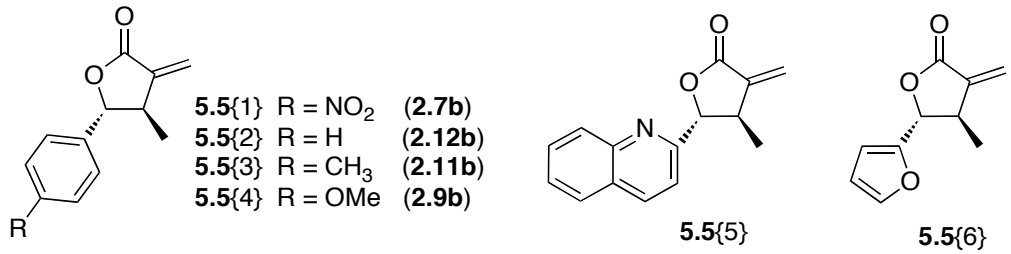
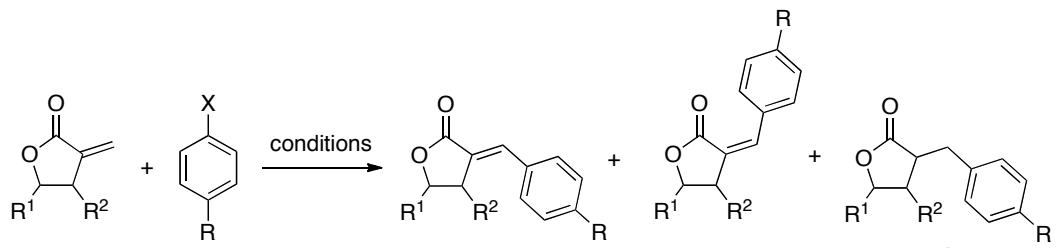


Figure 5.2: α-Methylene β-methyl γ-lactone substrates **5.5**{1-6}



Entry	γ-lactone[a]	(R, X)	Catalyst/ ligand/ additive[b]	Base[b]	Solvent	Temp (°C)/ time (h)	Yield (%)[c]	Product ratio (*E*-**5.6** : *Z*-**5.6** : **5.7**)[d]
1	**5.3**{1}	R = NO_2 X = I	$Pd(OAc)_2$/ none/ none	KOAc	DMF	80/ 24	0	N/A
2	**5.3**{1}	R = H X = I	$Pd(OAc)_2$/ DABCO/ none	K_2CO_3	DMF	120/ 48	0	N/A
3[e]	**5.3**{38}	R = Me X = $B(OH)_2$	$Pd(OAc)_2$/ none/ $Cu(OAc)_2$	LiOAc	DMF	100/ 4	16[f]	5.6 : 7.2 : 1[g]
4[e]	**5.5**{2}	R = Me X = $B(OH)_2$	$Pd(OAc)_2$/ none/ $Cu(OAc)_2$	LiOAc	DMF	100/ 4	7	1 : 0 : 0
5	**5.5**{2}	R = H X = I	$Pd(OAc)_2$/ PPh_3 / Bu_4NBr	K_2CO_3	MeCN	90/ 24	64	22 : 1 : 3[g]
6	**5.5**{2}	R = H X = I	$Pd(OAc)_2$/ PPh_3 / none	Cs_2CO_3	MeCN	90/ 48	23	1 : 0 : 0
7	**5.3**{1}	R = Ph X = I	$Pd(OAc)_2$/ PPh_3 / none	Cs_2CO_3	MeCN	90/ 6	53	1 : 0 : 0
8	**5.5**{2}	R = Ph X = Br	$Pd(OAc)_2$/ PPh_3 / none	Cs_2CO_3	MeCN	90/ 12	0	N/A
9	**5.3**{1}	R = Ph X = Br	$Pd(OAc)_2$/ PPh_3 / none	Cs_2CO_3	MeCN	90/ 48	0	N/A

[a] Refer to Section 5.6 for the synthesis of the lactones used as substrates. [b] Refer to Section 5.6 for stoichiometry of all reagents and catalyst. [c] Yields are reported after flash chromatography, unless otherwise specified. [d] Ratio of products was determined based on the yield of each component. [e] Reaction done under microwave conditions. [f] Yield is after preparatory HPLC purification. [g] Ratio determined by integration of crude ^{1}H NMR spectra.

Table 5.3: Screening of conditions for Heck and Heck-type reactions on γ-lactones

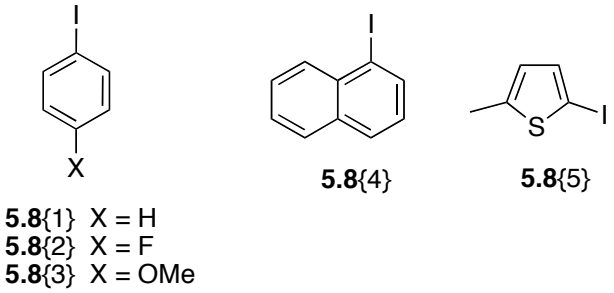
Phosphine-containing compounds are sometimes problematic during product purification, so I initially tried a few sets of Heck reactions that avoid the

use of phosphine-containing ligands (entries 1-4, Table 5.3). These efforts proved futile, and all of these reactions resulted in minimal to none of the desired products being obtained. I then switched to the Jeffery conditions[15] in hopes of bringing about further conversion. This procedure proved to be successful, as the desired coupling product was obtained as the major product in a moderate yield (entry 5). However, the presence of two side products *Z*-**5.6c** and **5.7c** caused significant problems with the purification and the desired product could not be isolated in pure form. These two cross-coupling byproducts co-eluted with the desired product *E*-**5.6c**, both during flash chromatography and also during preparatory scale HPLC. This purification issue would be a serious problem should these conditions be utilized during library synthesis.

Heck reaction conditions without the phase transfer catalyst were then attempted using the same lactone substrate **5.5**{2} (entry 6). Longer reaction times were required, and the reaction never reached completion even after heating at reflux for 48 hours. However, neither of the previously observed byproducts was detected under these reaction conditions. Since this result could be a scenario where steric hindrance between the methyl group in the β-position and the palladium catalyst was playing a role in reduced reactivity of the γ-lactone substrate, a similar but less sterically demanding lactone substrate was used as the alkene coupling partner. Thus, with lactone **5.3**{1}, which lacks the methyl group in the β-position, the desired product *E*-**5.6d** was obtained as the sole product in a decent yield (entry 7). Aryl bromides were also attempted as substrates for this reaction (entries 8 and 9), as they would be useful in library preparation due to the large number of commercially available ones as compared to aryl iodides. However, even with longer reaction times, none of the desired coupling products were obtained when aryl bromides were used as substrates.

With conditions in hand that would provide the desired α-alkylidene γ-lactone products and would also be amenable to library synthesis, a subset of γ-lactone substrates was selected for the synthesis of this sub-library with the α-alkylidene scaffold. Towards this end, four different α-methylene γ-lactones that contained differing functionality in the γ-position and contained only hydrogens

in the β-position were chosen due to the problems already discussed. These γ-lactones were coupled with aryl iodides **5.8**{1-5} shown in Figure 5.3.



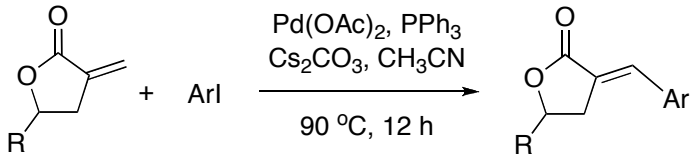
5.8{1} X = H
5.8{2} X = F
5.8{3} X = OMe

5.8{4}

5.8{5}

Figure 5.3: Aryl iodides **5.7**{1-5} used as coupling partners

Aryl iodides **5.8**{1-5} were chosen to be used as a diverse set of coupling partners in the Heck reactions based on commercial availability, price and possible biological relevance. The Heck reactions were realized according to Table 5.4 to provide the desired cross-coupling products in the form of α-alkylidene γ-lactones **5.9**. All 20 reactions were performed simultaneously using a parallel synthesizer and the resulting α-alkylidene γ-lactones **5.9** were purified by preparatory HPLC. It should be noted that some of the isolated products did contain trace amounts (~5% by ^{1}H NMR spectroscopy) of the undesired coupling byproduct with opposite (*Z*) alkene geometry.



5.3{2-3}
5.3{5}
5.3{20}

5.8{1-5}

5.9{2-3,1-5}
5.9{5,1-5}
5.9{20,1-5}

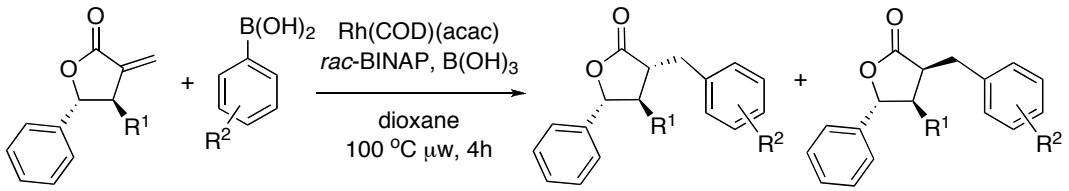
Entry	γ-Lactone	ArI	Product	R, Ar	Yield (%)[a]
1	**5.3**{2}	**5.8**{1}	**5.9**{2,1}	R = 4-MeC_6H_4, Ar = C_6H_5	13
2	**5.3**{2}	**5.8**{2}	**5.9**{2,2}	R = 4-MeC_6H_4, Ar = 4-FC_6H_4	21
3	**5.3**{2}	**5.8**{3}	**5.9**{2,3}	R = 4-MeC_6H_4, Ar = 4-$MeOC_6H_4$	19
4	**5.3**{2}	**5.8**{4}	**5.9**{2,4}	R = 4-MeC_6H_4, Ar = 1-naphthyl	12
5	**5.3**{2}	**5.8**{5}	**5.9**{2,5}	R = 4-MeC_6H_4, Ar = 5-methyl-2-thiophenyl	8
6	**5.3**{3}	**5.8**{1}	**5.9**{3,1}	R = 4-$MeOC_6H_4$, Ar = C_6H_5	7
7	**5.3**{3}	**5.8**{2}	**5.9**{3,2}	R = 4-$MeOC_6H_4$, Ar = 4-FC_6H_4	6
8	**5.3**{3}	**5.8**{3}	**5.9**{3,3}	R = 4-$MeOC_6H_4$, Ar = 4-$MeOC_6H_4$	16
9	**5.3**{3}	**5.8**{4}	**5.9**{3,4}	R = 4-$MeOC_6H_4$, Ar = 1-naphthyl	18
10	**5.3**{3}	**5.8**{5}	**5.9**{3,5}	R = 4-$MeOC_6H_4$, Ar = 5-methyl-2-thiophenyl	2
11	**5.3**{5}	**5.8**{1}	**5.9**{5,1}	R = 4-FC_6H_4, Ar = C_6H_5	12
12	**5.3**{5}	**5.8**{2}	**5.9**{5,2}	R = 4-FC_6H_4, Ar = 4-FC_6H_4	7
13	**5.3**{5}	**5.8**{3}	**5.9**{5,3}	R = 4-FC_6H_4, Ar = 4-$MeOC_6H_4$	17
14	**5.3**{5}	**5.8**{4}	**5.9**{5,4}	R = 4-FC_6H_4, Ar = 1-naphthyl	5
15	**5.3**{5}	**5.8**{5}	**5.9**{5,5}	R = 4-FC_6H_4, Ar = 5-methyl-2-thiophenyl	2
16	**5.3**{20}	**5.8**{1}	**5.9**{20,1}	R = 2-furanyl, Ar = C_6H_5	17
17	**5.3**{20}	**5.8**{2}	**5.9**{20,2}	R = 2-furanyl, Ar = 4-FC_6H_4	13
18	**5.3**{20}	**5.8**{3}	**5.9**{20,3}	R = 2-furanyl, Ar = 4-$MeOC_6H_4$	31
19	**5.3**{20}	**5.8**{4}	**5.9**{20,4}	R = 2-furanyl, Ar = 1-naphthyl	11
20	**5.3**{20}	**5.8**{5}	**5.9**{20,5}	R = 2-furanyl, Ar = 5-methyl-2-thiophenyl	3

[a] Isolated yields after preparatory HPLC. See purity table in Section 5.6.17.

Table 5.4: Synthesis of α-alkylidene γ-lactones **5.9** by a Pd-catalyzed Heck reaction

5.2.3 α-Alkylated γ-lactones[9]

My attention next turned to another sub-library scaffold by modifying α-methylene γ-lactones **5.3** in such a way as to obtain the saturated form of the lactone, that is, α-alkylated γ-lactones. One could simply hydrogenate the *exo*-methylene group to obtain α-methyl γ-lactones, and there is precedent in achieving this transformation in a stereoselective fashion.[5b] However, it would be ideal if one could go directly from an α-methylene γ-lactones **5.3** to an α-alkylated γ-lactone, and in doing such, introduce additional chemical functionality. Some of the methods mentioned in the previous section would be applicable here, such as conjugate additions or oxidations. Instead, I was more interested in metal-catalyzed reductive alkylations for carrying out this transformation from α-methylene γ-lactones **5.3** to α-alkylated γ-lactones. There are many reports in the literature where aryl halides or aryl boronic acids are added to α,β-unsaturated ketones and esters through the use of palladium or rhodium catalysts,[16] but most of these examples involve unsubstituted or 1,2-disubstituted α,β-unsaturated ketones and esters and not the *gem*-disubstituted α,β-unsaturated substrates related to γ-lactones **5.3**. On the other hand, a promising report was recently disclosed where hindered *gem*-disubstituted α,β-unsaturated esters were utilized in rhodium-catalyzed conjugate addition reactions to form the saturated products.[17] This reaction, published by Frost and co-workers, utilizes rhodium to catalyze the 1,4-addition of arylboronic acids to α-benzyl acrylates under microwave heating, and the rhodium enolates that are subsequently formed are then protonated by the boric acid present in the reaction mixture to provide α,α'-dibenzyl esters. With this report in hand, I investigated these conditions with α-methylene γ-lactones **5.3**{1} and **5.5**{2} as substrates (Table 5.5).



5.3{1} R^1 = H
5.5{2} R^1 = Me

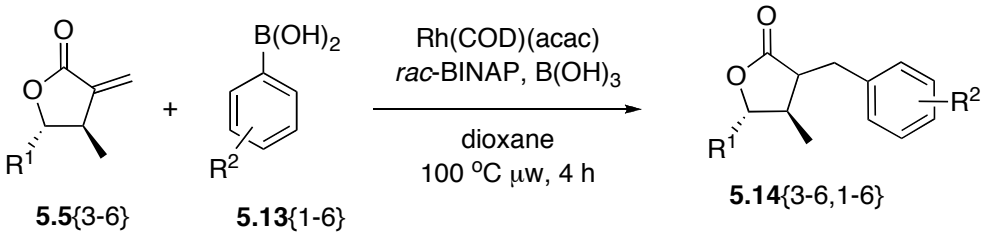
5.10a-5.12a **5.10b-5.12b**

Entry	Substrate	R^1	R^2	Yield[a] (%)	Product	Product ratio[b] (**a**:**b**)
1	**5.3**{1}	H	4-Me	66	**5.10**	1.2 : 1
2	**5.5**{2}	Me	4-Me	74	**5.11**	1 : 10
3	**5.3**{1}	H	2-Me	86	**5.12**	2.8 : 1

[a] Isolated yield after flash chromatography. [b] Product ratio was determined by comparison of peak height in the ^{1}H NMR spectra. Relative stereochemistry of products was determined by TROESY experiments.

Table 5.5: Rh-catalyzed conjugate addition of arylboronic acids to γ-lactones **5.3**{1} and **5.5**{2}

It was satisfying to see that α-methylene γ-lactones **5.3** and **5.5** are suitable substrates for this rhodium-catalyzed conjugate addition/protonation reaction. γ-Lactone **5.5**{2} containing a methyl group in the β-position gave a better selectivity in terms of the *cis*/*trans* ratio of the α-alkylated lactones, which seems intuitive based on the fact that protonation by $B(OH)_3$ would occur from the least hindered face. Even though this observation is based on only one example and may not be generally applicable, I chose α-methylene γ-lactones containing a methyl in the β-position as substrates for the synthesis of the sub-library of α-alkylated-γ-lactones (Table 5.6). The four α-methylene γ-lactones **5.5**{3-6} (Figure 5.2) were subjected to rhodium-catalyzed conjugate 1,4-addition/protonation reaction conditions with boronic acids **5.13**{1-6} (Figure 5.4) under microwave heating to provide the desired α-alkylated γ-lactones **5.14** (Table 5.6).



5.5{3-6} **5.13**{1-6} **5.14**{3-6,1-6}

Entry	γ-Lactone substrate	Coupling partner	Product	R^1, R^2	Yield (%)[a]
1	**5.5**{3}	**5.13**{1}	**5.14**{3,1}	R = 4-MeC_6H_5, R^1 = H	92
2	**5.5**{3}	**5.13**{2}	**5.14**{3,2}	R = 4-MeC_6H_5, R^1 = 4-OCH_3	64
3	**5.5**{3}	**5.13**{3}	**5.14**{3,3}	R = 4-MeC_6H_5, R^1 = 2-CH_3	86
4	**5.5**{3}	**5.13**{4}	**5.14**{3,4}	R = 4-MeC_6H_5, R^1 = 4-Br	88
5	**5.5**{3}	**5.13**{5}	**5.14**{3,5}	R = 4-MeC_6H_5, R^1 = 4-OC_6H_5	58
6	**5.5**{3}	**5.13**{6}	**5.14**{3,6}	R = 4-MeC_6H_5, R^1 = 3,5-$(CF_3)_2$	25
7	**5.5**{4}	**5.13**{1}	**5.14**{4,1}	R = 4-$MeOC_6H_5$, R^1 = H	84
8	**5.5**{4}	**5.13**{2}	**5.14**{4,2}	R = 4-$MeOC_6H_5$, R^1 = 4-OCH_3	76
9	**5.5**{4}	**5.13**{3}	**5.14**{4,3}	R = 4-$MeOC_6H_5$, R^1 = 2-CH_3	82
10	**5.5**{4}	**5.13**{4}	**5.14**{4,4}	R = 4-$MeOC_6H_5$, R^1 = 4-Br	41
11	**5.5**{4}	**5.13**{5}	**5.14**{4,5}	R = 4-$MeOC_6H_5$, R^1 = 4-OC_6H_5	15
12	**5.5**{4}	**5.13**{6}	**5.14**{4,6}	R = 4-$MeOC_6H_5$, R^1 = 3,5-$(CF_3)_2$	63
13	**5.5**{5}	**5.13**{1}	**5.14**{5,1}	R = 2-quinolinyl, R^1 = H	78
14	**5.5**{5}	**5.13**{2}	**5.14**{5,2}	R = 2-quinolinyl, R^1 = 4-OCH_3	50
15	**5.5**{5}	**5.13**{3}	**5.14**{5,3}	R = 2-quinolinyl, R^1 = 2-CH_3	62
16	**5.5**{5}	**5.13**{4}	**5.14**{5,4}	R = 2-quinolinyl, R^1 = 4-Br	51
17	**5.5**{5}	**5.13**{5}	**5.14**{5,5}	R = 2-quinolinyl, R^1 = 4-OC_6H_5	53
18	**5.5**{5}	**5.13**{6}	**5.14**{5,6}	R = 2-quinolinyl, R^1 = 3,5-$(CF_3)_2$	61
19	**5.5**{6}	**5.13**{1}	**5.14**{6,1}	R = 2-furanyl, R^1 = H	75
20	**5.5**{6}	**5.13**{2}	**5.14**{6,2}	R = 2-furanyl, R^1 = 4-OCH_3	83

21	**5.5**{6}	**5.13**{3}	**5.14**{6,3}	R = 2-furanyl, R^1 = 2-CH_3	82
22	**5.5**{6}	**5.13**{4}	**5.14**{6,4}	R = 2-furanyl, R^1 = 4-Br	76
23	**5.5**{6}	**5.13**{5}	**5.14**{6,5}	R = 2-furanyl, R^1 = 4-OC_6H_5	51
24	**5.5**{6}	**5.13**{6}	**5.14**{6,6}	R = 2-furanyl, R^1 = 3,5-$(CF_3)_2$	9

[a] Isolated yield after preparatory HPLC. See purity table in Section 5.6.17.

Table 5.6: Rh-catalyzed conjugate addition reaction to form α-alkylated-γ-lactones **5.14**

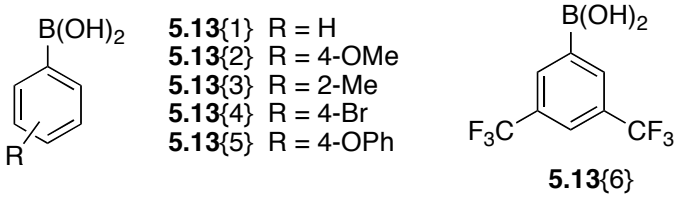


Figure 5.4: Boronic acids **5.13**{1-6} for Rh-catalyzed conjugate addition reaction

The reactions were run sequentially in the microwave reactor and once all 24 reaction combinations were completed, they were filtered through a small pad of celite with EtOAc, concentrated and purified via preparatory HPLC to provide the desired α-alkylated-γ-lactones **5.14**{3-6,1-6}. These compounds were obtained as mixtures of 3,4-*cis* and 3,4-*trans* isomers (usually >10:1 dr), and further separation was not attempted.

5.3 Scaffold optimization and synthesis of γ-lactam sub-libraries

As discussed earlier in Chapter 1, there is an abundance of literature containing interesting α-methylene γ-lactones, both in the form of natural products and as parts of synthetic analogues. One closely related type of compound to the γ-lactones is the α-methylene γ-lactam scaffold. Even though

there are significantly fewer reports compared to the γ-lactones, a considerable number of natural products contain a γ-lactam as part of their structures (Figure 1.3 and Figure 4.1). The synthesis of γ-lactams has been the focus of several reports in the literature;[18] however, several known routes are tedious in accessing this core structure. I have discussed in Chapter 4 how I optimized an expeditious route to accessing these α-methylene γ-lactam core structures. With this new protocol, imines are formed *in situ* from ammonia and aldehydes, and subsequently allylated using 2-alkoxycarbonyl allylboronates.[19] Due to the ester functionality present in the reagent, the homoallylic amine intermediate formed from the allylation reaction undergoes *in situ* lactamization to afford substituted β-methyl α-methylene γ-lactams in a single step (*cf*. Scheme 4.1).

5.3.1 Synthesis of α-methylene γ-lactams[9]

Utilizing this key imine allylboration reaction, a small sub-library of α-methylene γ-lactams **5.15** was synthesized utilizing aldehydes **5.2**{1-9, 15, 18, 20-23, 25, 27, 30-33} (Figure 5.1) and **5.2**{39-42} (Figure 5.5) together with allylboronate **3.1** (Table 5.7).

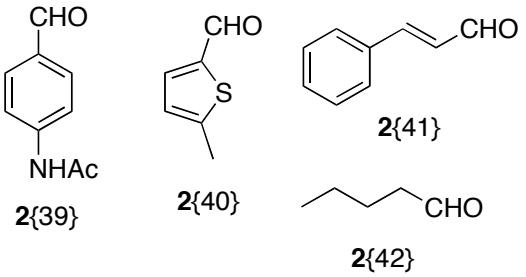
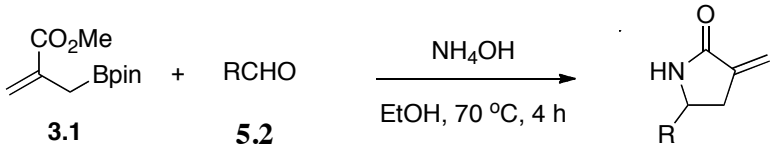


Figure 5.5: Additional aldehyde substrates **5.2**{39-42} for sub-library of β-unsubstituted α-methylene γ-lactams **5.15**

The α-methylene γ-lactams were synthesized by this route using a parallel synthesizer and subsequently worked up using the standard extraction protocol and purified by preparatory HPLC. Typical yields for this reaction are in the range

of 45-90%,[19] so it is uncertain at this point why significantly lower yields were observed in a few cases. Neither electronic nor steric factors seem to be responsible. Larger scale reactions were performed with a subset of aldehydes **5.2,** using typical bench-scale techniques to obtain α-methylene γ-lactams **5.15** in sufficient quantities so as to carry out further investigations on the functionalization of this α-methylene γ-lactam scaffold. These studies are described in the sections to follow.



3.1 **5.2** {1-9, 15, 18, 20-23, 25, 27, 30-33, 39-42} **5.15** {1-9, 15, 18, 20-23, 25, 27, 30-33, 39-42}

Entry	Aldehyde	Product	Previous compound number	Yield (%)[a]
1	**5.2**{1}	**5.15**{1}	**4.6**	53
2	**5.2**{2}	**5.15**{2}	**4.5**	61
3	**5.2**{3}	**5.15**{3}	**4.4**	14
4	**5.2**{4}	**5.15**{4}	**4.1**	36
5	**5.2**{5}	**5.15**{5}	**4.3**	37
6	**5.2**{6}	**5.15**{6}	--	3
7	**5.2**{7}	**5.15**{7}	--	9
8	**5.2**{8}	**5.15**{8}	--	12
9	**5.2**{9}	**5.15**{9}	**4.2**	76
10	**5.2**{15}	**5.15**{15}	--	18
11	**5.2**{18}	**5.15**{18}	--	10
12	**5.2**{20}	**5.15**{20}	--	38
13	**5.2**{21}	**5.15**{21}	--	34
14	**5.2**{22}	**5.15**{22}	--	11
15	**5.2**{23}	**5.15**{23}	--	5
16	**5.2**{25}	**5.15**{25}	--	45
17	**5.2**{27}	**5.15**{27}	--	30
18	**5.2**{30}	**5.15**{30}	--	2
19	**5.2**{31}	**5.15**{31}	**4.8**	35
20	**5.2**{32}	**5.15**{32}	**4.7**	13
21	**5.2**{33}	**5.15**{33}	--	12
22	**5.2**{39}	**5.15**{39}	--	4
23	**5.2**{40}	**5.15**{40}	--	39
24	**5.2**{41}	**5.15**{41}	--	48
25	**5.2**{42}	**5.15**{42}	--	45

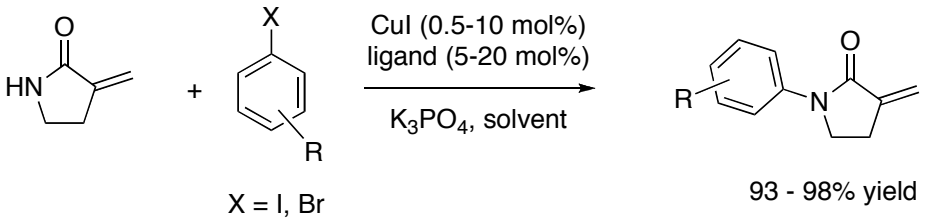
[a] Isolated yield after preparatory HPLC. See purity table in Section 5.6.17.

Table 5.7: Formation of α-methylene γ-lactams **5.15** from **3.1** and aldehydes **5.2**

5.3.2 *N*-Arylated α-methylene γ-lactams[9]

As with the γ-lactones, I aimed to determine the extent to which the α-methylene γ-lactam scaffold could be functionalized. With the nitrogen in the γ-

lactam ring, these γ-lactams have one additional degree of diversity that can be exploited as compared to the γ-lactones. Several types of reactions could be envisaged in order to functionalize this nitrogen atom, including alkylation, acylation and arylation reactions. My initial interests lay in modulating the γ-lactams via the use of metal catalyzed *N*-arylation reactions. Over the past few years, Buchwald and co-workers have reported noteworthy new methodologies in the area of copper-catalyzed amidation reactions using aryl halides.[20] In particular, one report[20d] makes use of secondary amides, and more specifically, a γ-lactam as the coupling partner with aryl iodides and aryl bromides (Equation 5.5).



Equation 5.5: *N*-Arylation reaction of γ-lactams using Buchwald conditions[20d]

With the reaction conditions from this report in hand, I set out to investigate whether this coupling chemistry could be applied successfully to our more functionalized α-methylene γ-lactams. To this end, we chose a few representative α-methylene γ-lactams **4.2**, **4.10** and **4.11** (Figure 5.6) and attempted to couple them with various aryl iodides and bromides (Table 5.8).

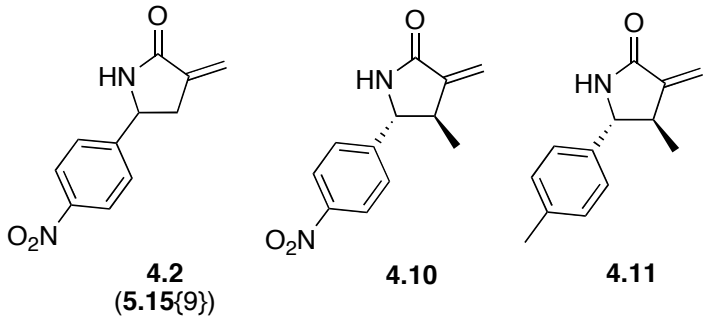
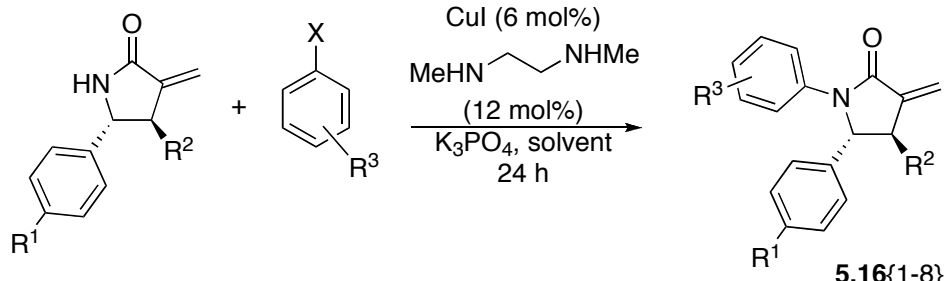


Figure 5.6: Selected α-methylene γ-lactams used to test conditions for *N*-functionalization



4.2, **4.10**, or **4.11**

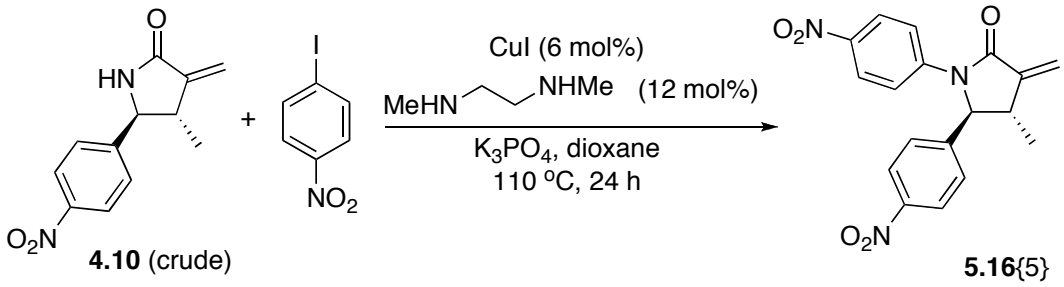
5.16{1-8}

Entry	γ-Lactam	R^3, X	Solvent, Temp. (°C)	Product	Yield (%)[a]
1	**4.10**	R^2 = H, X = I	toluene, 80	**5.16**{1}	44
2	**4.11**	R^2 = H, X = I	toluene, 80	**5.16**{2}	80
3	**4.11**	R^2 = 4-NO_2, X = I	toluene, 80	**5.16**{3}	74
4	**4.2**	R^2 = 4-NO_2, X = I	toluene, 80	**5.16**{4}	59
5	**4.10**	R^2 = 4-NO_2, X = I	dioxane, 110	**5.16**{5}	31[b]
6	**4.10**	R^2 = 4-Ph, X = I	dioxane, 110	**5.16**{6}	29[b]
7	**4.10**	R^2 = 4-OMe, X = Br	dioxane, 110	**5.16**{7}	17[b]
8	**4.10**	R^2 = 4-F, X = Br	dioxane, 110	**5.16**{8}	24[b]

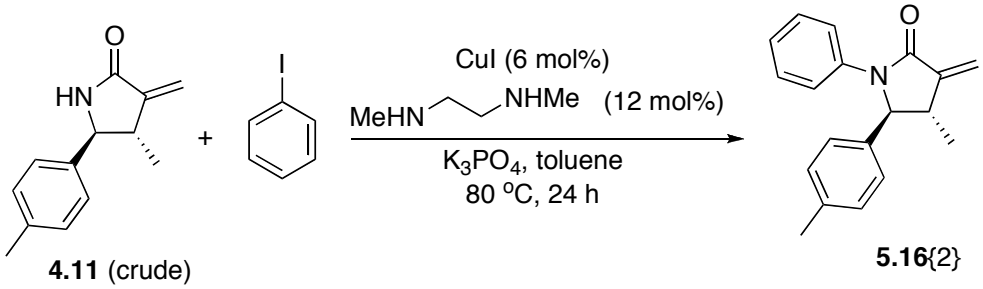
[a] Yields reported are isolated yields after flash chromatography, unless otherwise specified. [b] Product was purified by preparatory HPLC. See purity table in Section 5.6.17.

Table 5.8: Copper-catalyzed *N*-arylation of functionalized α-methylene γ-lactams

From our sampling of the *N*-arylation reaction conditions, it is apparent that both aryl iodides and aryl bromides are suitable coupling partners with the α-methylene γ-lactams, but since aryl iodides provided the desired products with significantly better yields, they were chosen as components for this sub-library. Extensive purification of library intermediates is generally avoided, if at all possible. Extra purification steps in the preparation of a library causes longer sequences and leads to large amounts of solvent waste. With this in mind, I investigated the possibility of utilizing the α-methylene γ-lactams **4.10** and **4.11** in crude form following the allylation/cyclization reaction for subsequent functionalization reactions. I attempted this strategy with the copper-catalyzed *N*-arylation of a few selected α-methylene γ-lactams (Equations 5.6 and 5.7).



Equation 5.6: *N*-Arylation of crude γ-lactam **4.10** with 4-iodonitrobenzene



Equation 5.7: *N*-Arylation of crude γ-lactam **4.11** with iodobenzene

Thus, after acidic extraction and solvent removal, the crude γ-lactams **4.10** and **4.11** were immediately subjected to the *N*-arylation reaction conditions. I was pleased to find that the *N*-arylation reactions could proceed smoothly when using crude γ-lactams **4.10** and **4.11** as substrates. With this chemistry functioning well, various γ-lactams **5.15** (Figure 8) and aryl iodides **5.8** (Figures 5.3 and 5.7) were selected for the preparation of a sub-library of *N*-arylated α-methylene γ-lactams **5.17** (Table 5.9). All *N*-arylation reactions for this sub-library were done using crude samples of α-methylene γ-lactams **5.15** employing a parallel synthesizer and were subsequently filtered through a short plug of Celite and concentrated. The crude mixtures were purified by preparatory HPLC to provide the desired sub-library members *N*-arylated α-methylene γ-lactams **5.17**.

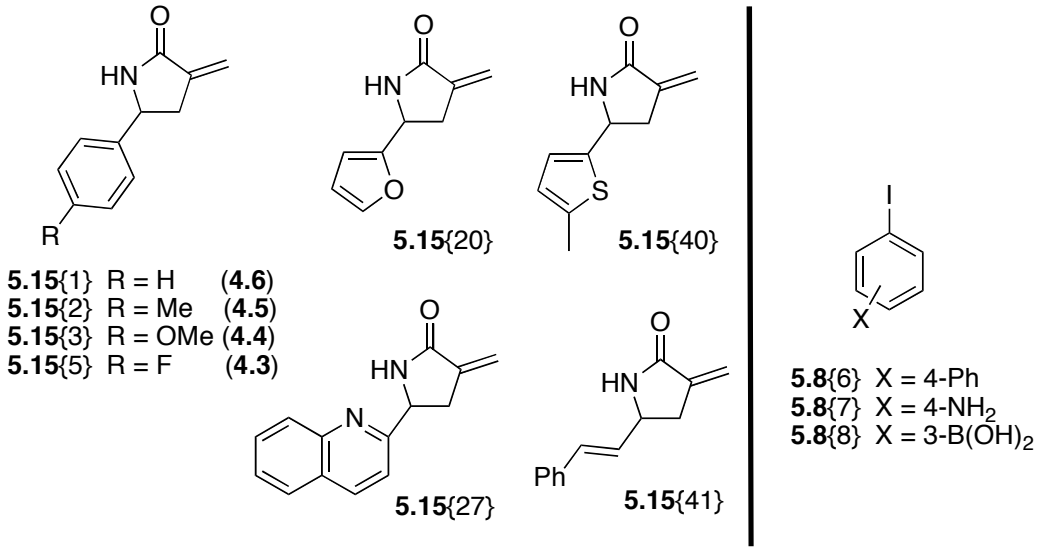
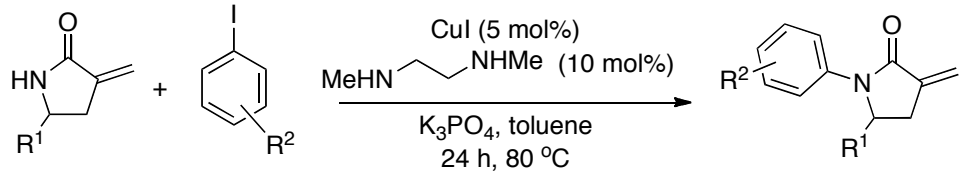


Figure 5.7: Diversity reagents **5.15** and **5.8**{6-8} to produce *N*-arylated α-methylene γ-lactams **5.17**



5.15{1-3}
5.15{5}
5.15{20}
5.15{27}
5.15{40-41}

5.8{1-3}
5.8{6-8}

5.17{1-3,1-3}, **5.17**{1-3,6-8}
5.17{5,1-3}, **5.17**{5,6-8}
5.17{20,1-3}, **5.17**{20,6-8}
5.17{27,1-3}, **5.17**{27,6-8}
5.17{40-41,1-3}, **5.17**{40-41,6-8}

Entry	γ-Lactam	Coupling partner	Product	R^1, R^2	yield (%)[a]
1	**5.15**{1}	**5.8**{1}	**5.17**{1,1}	R = C_6H_5, R^1 = H	2
2	**5.15**{1}	**5.8**{2}	**5.17**{1,2}	R = C_6H_5, R^1 = 4-F	1
3	**5.15**{1}	**5.8**{3}	**5.17**{1,3}	R = C_6H_5, R^1 = 4-OCH_3	45
4	**5.15**{1}	**5.8**{6}	**5.17**{1,6}	R = C_6H_5, R^1 = 4-C_6H_5	11
5	**5.15**{1}	**5.8**{7}	**5.17**{1,7}	R = C_6H_5, R^1 = 4-NH_2	41
6	**5.15**{1}	**5.8**{8}	**5.17**{1,8}	R = C_6H_5, R^1 = 3-$B(OH)_2$	46
7	**5.15**{2}	**5.8**{1}	**5.17**{2,1}	R = 4-MeC_6H_4, R^1 = H	1
8	**5.15**{2}	**5.8**{2}	**5.17**{2,2}	R = 4-MeC_6H_4, R^1 = 4-F	4
9	**5.15**{2}	**5.8**{3}	**5.17**{2,3}	R = 4-MeC_6H_4, R^1 = 4-OCH_3	1
10	**5.15**{2}	**5.8**{6}	**5.17**{2,6}	R = 4-MeC_6H_4, R^1 = 4-C_6H_5	2
11	**5.15**{2}	**5.8**{7}	**5.17**{2,7}	R = 4-MeC_6H_4, R^1 = 4-NH_2	61

12	**5.15**{2}	**5.8**{8}	**5.17**{2,8}	R = 4-MeC_6H_4, R^1 = 3-$B(OH)_2$	42
13	**5.15**{3}	**5.8**{1}	**5.17**{3,1}	R = 4-$MeOC_6H_4$, R^1 = H	6
14	**5.15**{3}	**5.8**{2}	**5.17**{3,2}	R = 4-$MeOC_6H_4$, R^1 = 4-F	70
15	**5.15**{3}	**5.8**{3}	**5.17**{3,3}	R = 4-$MeOC_6H_4$, R^1 = 4-OCH_3	2
16	**5.15**{3}	**5.8**{6}	**5.17**{3,6}	R = 4-$MeOC_6H_4$, R^1 = 4-C_6H_5	5
17	**5.15**{3}	**5.8**{7}	**5.17**{3,7}	R = 4-$MeOC_6H_4$, R^1 = 4-NH_2	68
18	**5.15**{3}	**5.8**{8}	**5.17**{3,8}	R = 4-$MeOC_6H_4$, R^1 = 3-$B(OH)_2$	17
19	**5.15**{5}	**5.8**{1}	**5.17**{5,1}	R = 4-FC_6H_4, R^1 = H	6
20	**5.15**{5}	**5.8**{2}	**5.17**{5,2}	R = 4-FC_6H_4, R^1 = 4-F	38
21	**5.15**{5}	**5.8**{3}	**5.17**{5,3}	R = 4-FC_6H_4, R^1 = 4-OCH_3	50
22	**5.15**{5}	**5.8**{6}	**5.17**{5,6}	R = 4-FC_6H_4, R^1 = 4-C_6H_5	27
23	**5.15**{5}	**5.8**{7}	**5.17**{5,7}	R = 4-FC_6H_4, R^1 = 4-NH_2	27
24	**5.15**{5}	**5.8**{8}	**5.17**{5,8}	R = 4-FC_6H_4, R^1 = 3-$B(OH)_2$	36
25	**5.15**{20}	**5.8**{1}	**5.17**{20,1}	R = 2-furanyl, R^1 = H	31
26	**5.15**{20}	**5.8**{2}	**5.17**{20,2}	R = 2-furanyl, R^1 = 4-F	45
27	**5.15**{20}	**5.8**{3}	**5.17**{20,3}	R = 2-furanyl, R^1 = 4-OCH_3	67
28	**5.15**{20}	**5.8**{6}	**5.17**{20,6}	R = 2-furanyl, R^1 = 4-C_6H_5	4
29	**5.15**{20}	**5.8**{7}	**5.17**{20,7}	R = 2-furanyl, R^1 = 4-NH_2	10
30	**5.15**{20}	**5.8**{8}	**5.17**{20,8}	R = 2-furanyl, R^1 = 3-$B(OH)_2$	29
31	**5.15**{27}	**5.8**{1}	**5.17**{27,1}	R = 2-quinolinyl, R^1 = H	5
32	**5.15**{27}	**5.8**{2}	**5.17**{27,2}	R = C_6H_5, R^1 = 4-F	8
33	**5.15**{27}	**5.8**{3}	**5.17**{27,3}	R = 2-quinolinyl, R^1 = 4-OCH_3	9
34	**5.15**{27}	**5.8**{6}	**5.17**{27,6}	R = 2-quinolinyl, R^1 = 4-C_6H_5	1
35	**5.15**{27}	**5.8**{7}	**5.17**{27,7}	R = 2-quinolinyl, R^1 = 4-NH_2	31
36	**5.15**{27}	**5.8**{8}	**5.17**{27,8}	R = 2-quinolinyl, R^1 = 3-$B(OH)_2$	9
37	**5.15**{40}	**5.8**{1}	**5.17**{40,1}	R = 5-methyl-2-thiophenyl, R^1 = H	2
38	**5.15**{40}	**5.8**{2}	**5.17**{40,2}	R = 5-methyl-2-thiophenyl, R^1 = 4-F	4
39	**5.15**{40}	**5.8**{3}	**5.17**{40,3}	R = 5-methyl-2-thiophenyl, R^1 = 4-OCH_3	1
40	**5.15**{40}	**5.8**{6}	**5.17**{40,6}	R = 5-methyl-2-thiophenyl, R^1 = 4-C_6H_5	1
41	**5.15**{40}	**5.8**{7}	**5.17**{40,7}	R = 5-methyl-2-thiophenyl, R^1 = 4-NH_2	9

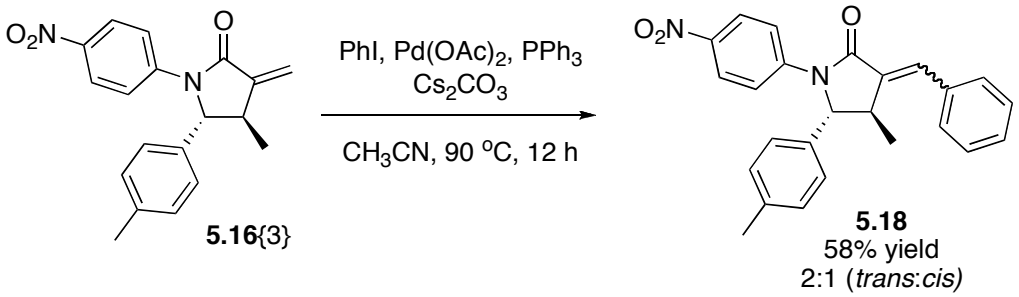
42	**5.15**{40}	**5.8**{8}	**5.17**{40,8}	R = 5-methyl-2-thiophenyl, R^1 = 3-$B(OH)_2$	24
43	**5.15**{41}	**5.8**{1}	**5.17**{41,1}	R = β-styryl, R^1 = H	32
44	**5.15**{41}	**5.8**{2}	**5.17**{41,2}	R = β-styryl, R^1 = 4-F	47
45	**5.15**{41}	**5.8**{3}	**5.17**{41,3}	R = β-styryl, R^1 = 4-OCH_3	28
46	**5.15**{41}	**5.8**{6}	**5.17**{41,6}	R = β-styryl, R^1 = 4-C_6H_5	9
47	**5.15**{41}	**5.8**{7}	**5.17**{41,7}	R = β-styryl, R^1 = 4-NH_2	43
48	**5.15**{41}	**5.8**{8}	**5.17**{41,8}	R = β-styryl, R^1 = 3-$B(OH)_2$	2

[a] Isolated yield after preparatory HPLC purification. See purity table in Section 5.6.17.

Table 5.9: Preparation of *N*-arylated α-methylene γ-lactams **5.17**

5.3.3 *N*-Arylated α-alkylidene γ-lactams[9]

Just as with the α-methylene γ-lactones discussed earlier, I next turned my attention to functionalizing the *exo*-methylene unit of γ-lactams **5.16** and **5.17**. The Heck reaction had proved efficient with the γ-lactones (see Section 5.2.2.2), so I decided to apply the same approach. One test reaction was performed using γ-lactam **5.16**{3}, where it was successfully functionalized using iodobenzene as the coupling partner to form fully functionalized γ-lactam **5.18** (Equation 5.8).



Equation 5.8: N-Arylated α-methylene γ-lactams as substrates Heck reaction

Using these reaction conditions, the *N*-phenyl α-methylene γ-lactams **5.17** (Figure 5.8) were cross-coupled under palladium catalysis with aryl iodides **5.8**{1-4} (Figure 5.3) and **5.8**{9-10} (Figure 5.8) to form the desired *N*-phenyl α-alkylidene γ-lactams **5.19** (Table 5.10).

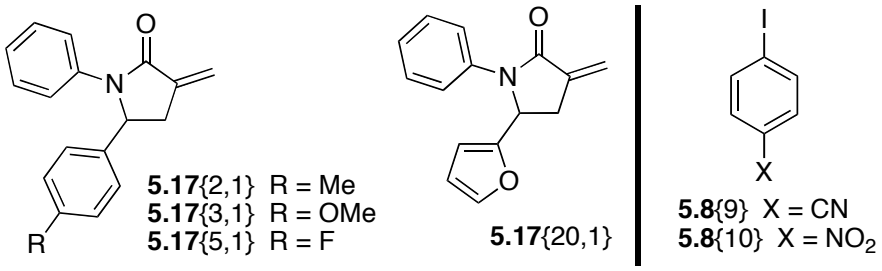
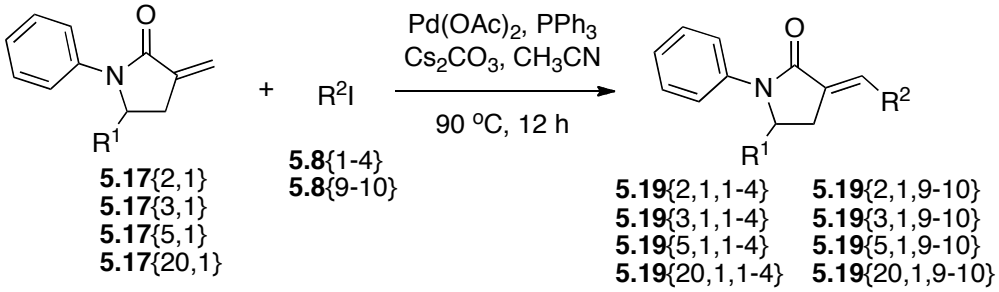


Figure 5.8: Diversity reagents **5.17** and **5.8**{9-10} for producing *N*-phenyl α-alkylidene γ-lactams **5.19**



Entry	γ-Lactam	R^2I	Product	R^1, R^2	Yield (%)[a]
1	**5.17**{2,1}	**5.8**{1}	**5.19**{2,1,1}	R^1 = 4-MeC_6H_4, R^2 = C_6H_5	16
2	**5.17**{2,1}	**5.8**{2}	**5.19**{2,1,2}	R^1 = 4-MeC_6H_4, R^2 = 4-F-C_6H_4	14
3	**5.17**{2,1}	**5.8**{3}	**5.19**{2,1,3}	R^1 = 4-MeC_6H_4, R^2 = 4-MeO-C_6H_4	27
4	**5.17**{2,1}	**5.8**{4}	**5.19**{2,1,4}	R^1 = 4-MeC_6H_4, R^2 = 1-naphthyl	10
5	**5.17**{2,1}	**5.8**{9}	**5.19**{2,1,9}	R^1 = 4-MeC_6H_4, R^2 = 4-CN	1
6	**5.17**{2,1}	**5.8**{10}	**5.19**{2,1,10}	R^1 = 4-MeC_6H_4, R^2 = 4-NO_2	0
7	**5.17**{3,1}	**5.8**{1}	**5.19**{3,1,1}	R^1 = 4-$MeOC_6H_4$, R^2 = C_6H_5	20
8	**5.17**{3,1}	**5.8**{2}	**5.19**{3,1,2}	R^1 = 4-$MeOC_6H_4$, R^2 = 4-F-C_6H_4	20
9	**5.17**{3,1}	**5.8**{3}	**5.19**{3,1,3}	R^1 = 4-$MeOC_6H_4$, R^2 = 4-MeO-C_6H_4	21
10	**5.17**{3,1}	**5.8**{4}	**5.19**{3,1,4}	R^1 = 4-$MeOC_6H_4$, R^2 = 1-naphthyl	4
11	**5.17**{3,1}	**5.8**{9}	**5.19**{3,1,9}	R^1 = 4-$MeOC_6H_4$, R^2 =	6

				4-CN	
12	**5.17**{3,1}	**5.8**{10}	**5.19**{3,1,10}	R^1 = 4-$MeOC_6H_4$, R^2 = 4-NO_2	3
13	**5.17**{5,1}	**5.8**{1}	**5.19**{5,1,1}	R = 4-FC_6H_4, R^2 = C_6H_5	33
14	**5.17**{5,1}	**5.8**{2}	**5.19**{5,1,2}	R^1 = 4-FC_6H_4, R^2 = 4-FC_6H_4	20
15	**5.17**{5,1}	**5.8**{3}	**5.19**{5,1,3}	R^1 = 4-FC_6H_4, R^2 = 4-MeO-C_6H_4	16
16	**5.17**{5,1}	**5.8**{4}	**5.19**{5,1,4}	R^1 = 4-FC_6H_4, R^2 = 1-naphthyl	16
17	**5.17**{5,1}	**5.8**{9}	**5.19**{5,1,9}	R^1 = 4-FC_6H_4, R^2 = 4-CN	5
18	**5.17**{5,1}	**5.8**{10}	**5.19**{5,1,10}	R^1 = 4-FC_6H_4, R^2 = 4-NO_2	0
19	**5.17**{20,1}	**5.8**{1}	**5.19**{20,1,1}	R^1 = 2-furanyl, R^2 = C_6H_5	6
20	**5.17**{20,1}	**5.8**{2}	**5.19**{20,1,2}	R^1 = 2-furanyl, R^2 = 4-F-C_6H_4	25
21	**5.17**{20,1}	**5.8**{3}	**5.19**{20,1,3}	R^1 = 2-furanyl, R^2 = 4-$MeOC_6H_4$	19
22	**5.17**{20,1}	**5.8**{4}	**5.19**{20,1,4}	R^1 = 2-furanyl, R^2 = 1-naphthyl	38
23	**5.17**{20,1}	**5.8**{9}	**5.19**{20,1,9}	R^1 = 2-furanyl, R^2 = 4-CN	1
24	**5.17**{20,1}	**5.8**{10}	**5.19**{20,1,10}	R^1 = 2-furanyl, R^2 = 4-NO_2	5

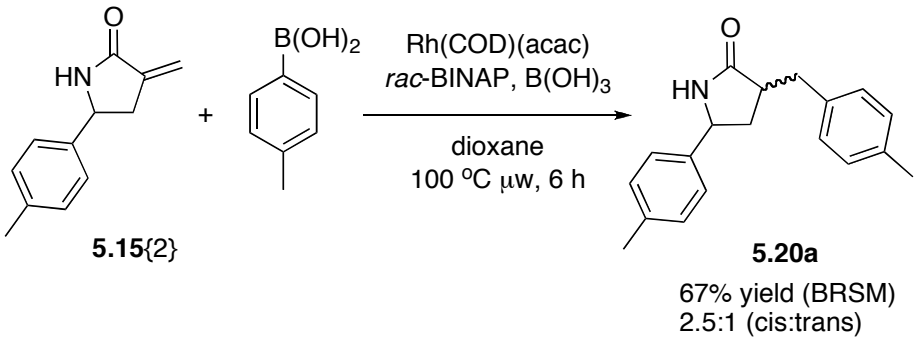
[a] Isolated yield after preparatory HPLC purification. See purity table in Section 5.6.17.

Table 5.10: Preparation of *N*-phenyl α-alkylidene γ-lactams **5.19**

These reactions were not quite as efficient as was observed with the corresponding γ-lactones, and in a few cases, the desired product was not obtained. As well, some of the reactions produced a mixture of the desired product and a related by-product where the double bond had isomerized to yield an internal alkene instead of the desired *exo*-alkene. Nonetheless, the desired γ-lactam products **5.19** were obtained in modest to good yields under these reaction conditions. The crude reaction mixtures were filtered through a short plug of celite, concentrated and purified by preparatory HPLC to provide the product as a mixture containing the desired product and minor amounts of the by-product with the internal double bond.

5.3.4 α-Alkylated γ-lactams[9]

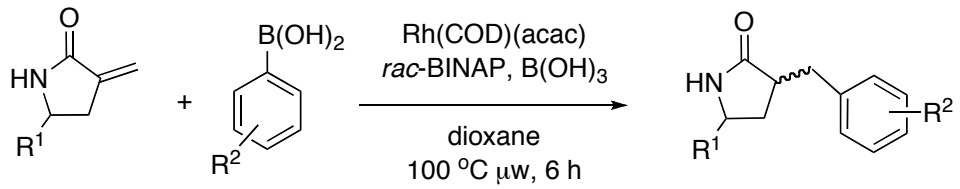
In a similar fashion as with the corresponding γ-lactones **5.5** (Section 5.2.3), I applied the conditions for the rhodium-catalyzed conjugate addition reaction to α-methylene γ-lactam **5.15**{2}. Because Miyaura and co-workers had shown that 1,2-disubstituted α,β-unsaturated amides were suitable substrates for Rh-catalyzed 1,4-addition reactions,[21] I was optimistic that the α-methylene γ-lactam **5.15**{2} would also prove to be a suitable substrate for this reaction. The test reaction was carried out, and I was delighted that it proceeded smoothly to provide desired α-alkylated γ-lactam **5.20a** (Equation 5.9).



Equation 5.9: α-Methylene γ-lactam **5.15**{2} as a model substrate for rhodium-catalyzed conjugate addition of aryl boronic acids

If the reaction was left for a longer period of time, no further conversion was observed, so these reaction conditions were chosen for the synthesis of the sub-library. The same boronic acids **5.13**{1-6} (Figure 5.4) utilized in making the α-alkylated γ-lactones were also used for this sub-library. α-Methylene γ-lactams **5.15**{2-4} and **5.15**{20} (Figure 5.7) were utilized and, under rhodium catalysis, formed the desired α-alkylated γ-lactams **5.20**{2-4,1-6} and **5.20**{20,1-6} (Table 5.11). The crude reaction mixtures were worked up in an identical fashion to the reactions performed on γ-lactones **5.5**, and the desired products **5.20** were isolated through preparatory HPLC. The *cis* and *trans* isomers of products **5.20** were not

separated by preparatory HPLC and the diastereomeric ratio (typically >5:1) was determined by ^{1}H NMR.



5.15{2-3}
5.15{5}
5.15{20}

5.13{1-6}

5.20{2-3,1-6}
5.20{5,1-6}
5.20{20,1-6}

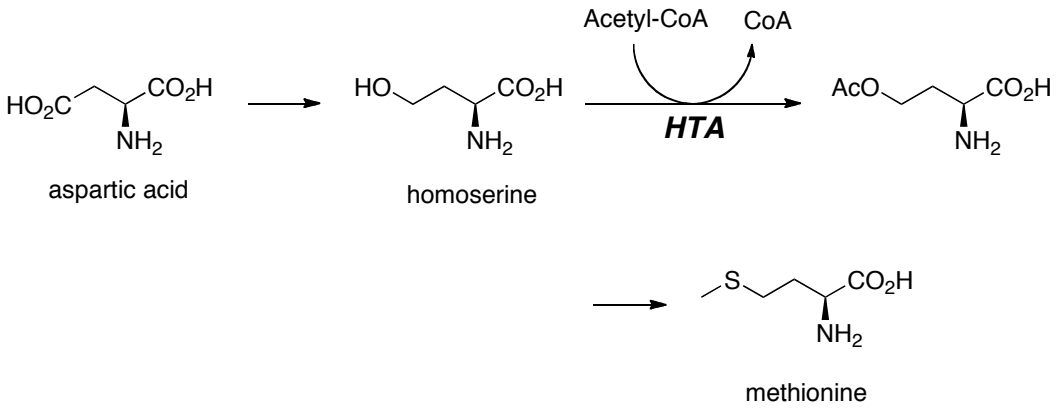
Entry	γ-Lactam	Coupling partner	Product	R^1, R^2	Yield (%)[a]
1	**5.15**{2}	**5.13**{1}	**5.20**{2,1}	R^1 = 4-MeC_6H_4, R^2 = H	28
2	**5.15**{2}	**5.13**{2}	**5.20**{2,2}	R^1 = 4-MeC_6H_4, R^2 = 4-OCH_3	25
3	**5.15**{2}	**5.13**{3}	**5.20**{2,3}	R^1 = 4-MeC_6H_4, R^2 = 2-CH_3	37
4	**5.15**{2}	**5.13**{4}	**5.20**{2,4}	R^1 = 4-MeC_6H_4, R^2 = 4-Br	32
5	**5.15**{2}	**5.13**{5}	**5.20**{2,5}	R^1 = 4-MeC_6H_4, R^2 = 4-OPh	11
6	**5.15**{2}	**5.13**{6}	**5.20**{2,6}	R^1 = 4-MeC_6H_4, R^2 = 3,5-$(CF_3)_2$	12
7	**5.15**{3}	**5.13**{1}	**5.20**{3,1}	R^1 = 4-MeOC_6H_4, R^2 = H	14
8	**5.15**{3}	**5.13**{2}	**5.20**{3,2}	R^1 = 4-MeOC_6H_4, R^2 = 4-OCH_3	18
9	**5.15**{3}	**5.13**{3}	**5.20**{3,3}	R^1 = 4-MeOC_6H_4, R^2 = 2-CH_3	30
10	**5.15**{3}	**5.13**{4}	**5.20**{3,4}	R^1 = 4-MeOC_6H_4, R^2 = 4-Br	26
11	**5.15**{3}	**5.13**{5}	**5.20**{3,5}	R^1 = 4-MeOC_6H_4, R^2 = 4-OPh	21
12	**5.15**{3}	**5.13**{6}	**5.20**{3,6}	R^1 = 4-MeOC_6H_4, R^2 = 3,5-$(CF_3)_2$	32
13	**5.15**{5}	**5.13**{1}	**5.20**{5,1}	R^1 = 4-FC_6H_4, R^2 = H	33
14	**5.15**{5}	**5.13**{2}	**5.20**{5,2}	R^1 = 4-FC_6H_4, R^2 = 4-OCH_3	15
15	**5.15**{5}	**5.13**{3}	**5.20**{5,3}	R^1 = 4-FC_6H_4, R^2 = 2-CH_3	26
16	**5.15**{5}	**5.13**{4}	**5.20**{5,4}	R^1 = 4-FC_6H_4, R^2 = 4-Br	26
17	**5.15**{5}	**5.13**{5}	**5.20**{5,5}	R^1 = 4-FC_6H_4, R^2 = 4-OPh	22
18	**5.15**{5}	**5.13**{6}	**5.20**{5,6}	R^1 = 4-FC_6H_4, R^2 = 3,5-$(CF_3)_2$	33
19	**5.15**{20}	**5.13**{1}	**5.20**{20,1}	R^1 = 2-furanyl, R^2 = H	26
20	**5.15**{20}	**5.13**{2}	**5.20**{20,2}	R^1 = 2-furanyl, R^2 = 4-OCH_3	30
21	**5.15**{20}	**5.13**{3}	**5.20**{20,3}	R^1 = 2-furanyl, R^2 = 2-CH_3	16
22	**5.15**{20}	**5.13**{4}	**5.20**{20,4}	R^1 = 2-furanyl, R^2 = 4-Br	15
23	**5.15**{20}	**5.13**{5}	**5.20**{20,5}	R^1 = 2-furanyl, R^2 = 4-OPh	7
24	**5.15**{20}	**5.13**{6}	**5.20**{20,6}	R^1 = 2-furanyl, R^2 = 3,5-$(CF_3)_2$	17

[a] Isolated yield after preparatory HPLC purification. See purity table in Section 5.6.17.

Table 5.11: Formation of α-alkylated γ-lactams **5.20**{2-4,1-6} and **5.20**{20,1-6}

5.4 Preliminary screening of a library subset[9]

The HPLC-purified library of substituted γ-lactones and γ-lactams were evaporated and stored as solids or films in small glass vials. A representative subset consisting of 111 members of the compound collection was selected and sent to the laboratory of Professor Gerald Wright at McMaster University, where the compounds were evaluated in high-throughput assays for their ability to inhibit homoserine transacetylase (HTA). Homoserine transacetylase from *Haemophilus influenzae* catalyzes the transfer of an acetyl group from acetyl-CoA to the hydroxyl group of homoserine (Scheme 5.2).[22]

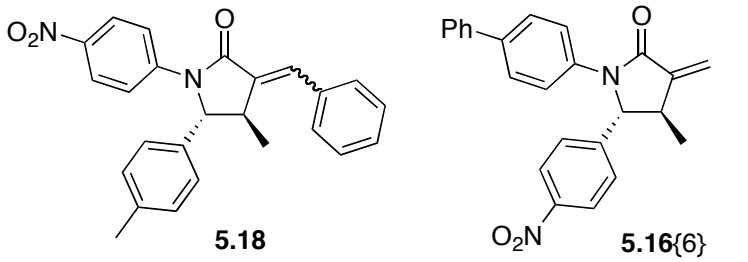


Scheme 5.2: HTA-mediated acylation of homoserine during conversion of aspartic acid to methionine

This enzyme is the first committed step in the biosynthesis of methionine from aspartic acid.[23,24] HTA is found in fungi, gram positive bacteria and some gram negative bacteria; however, it is absent in higher eukaryotes. This is an important enzyme for organisms in methionine poor environments such as blood serum. Therefore, inhibition of this enzyme could be deleterious to the organism since methionine is involved in several biochemical processes. The enzyme catalyzes the transfer mechanism via a ping-pong or double displacement mechanism facilitated by a catalytic triad of Ser-His-Asp. The Ser hydroxyl is activated for nucleophilic attack on the carbonyl center of acetyl-CoA by the His

residue. This leads to the modification of the enzyme and the release of CoA. The second step of the mechanism involves another nucleophilic attack by the hydroxyl group of homoserine on the labile ester bond formed between the enzyme and the acetyl group. Finally, the acetylated amino acid is released and the enzyme is reconstituted for another round of catalysis.[22,25] Based on the role of lactams, lactones, and cephalosporins in the inactivation of enzymes by acylation of the nucleophilic serinyl residue at the active site,[26,27] HTA is a good target for this library of compounds.

To this end, the selection of 111 compounds from the library was screened against HTA at three different incubation times (15, 70 and 200 minutes) and 100 μM final concentration. HTA has proven to be insensitive to a panel of beta-lactam antibiotics (penicillins and cephalosporins), but was inhibited by several members of the 111 compound library that were tested. From the primary assay, ten compounds (9%) showed inactivation of HTA and were subsequently retested for confirmation. After re-assay, five out of ten compounds confirmed their inhibitory activity versus HTA. Four of these five compounds have been resynthesized for further enzymatic characterizations. For two of them, **5.18** and **5.16**{6} (Figure 5.9), it was possible to determine IC_{50} values of 144 ± 22.5 μM and 140 ± 17.9 μM respectively; they also showed a time dependent inhibition, therefore consistent with the predicted mechanism of covalent modification of an enzyme nucleophile. These values are in the same range as the best inhibitor of HTA reported to date. 6-Carbamoyl-3a,4,5,9b-tetrahydro-3H-cyclo-penta[c] quinoline-4-carboxylic acid (CTCQC) has an IC_{50} of 4.50 μM with *Cryptococcus neoformans* HTA and acts as a reversible inhibitor. One must be aware that this stated value for CTCQC is for a different enzyme and, therefore, a direct comparison cannot be made. However, it provides insight as a qualitative measure of ability to inhibit the target class of enzymes. Although only two compounds (**5.18** and **5.16**{6}) showed moderate *in vitro* inhibition of HTA from *Haemophilus influenzae*, these results validate the potential of polysubstituted α-alkylidene γ-lactams as inhibitors of serine nucleophile dependent enzymes.



5.18 IC_{50} = 144 ± 22.5 μM

5.16{6} IC_{50} = 140 ± 17.9 μM

Figure 5.9: Structures and IC_{50} values for **5.18** and **5.16**{6}

5.5 Conclusions[9]

Through a protocol involving a tandem allylboration/cyclization reaction of aldehydes or imines, I have successfully formed a diverse library of α-methylene γ-lactones and α-methylene γ-lactams. This reaction sequence uses a wide variety of aldehydes containing a high degree of diversity and allows for the generation of highly substituted γ-lactone and γ-lactam systems in a single step.

Furthermore, I have shown that these γ-lactones and γ-lactams can be further modified to increase the degree of substitution and complexity of these small molecules. Attempts were made to functionalize the double bond through the use of cross-metathesis; however, this chemistry proved to be too unreliable for library synthesis. Suitable conditions could not be found to achieve consistent conversions, despite trying different catalysts and different additives. Through the use of the Heck reaction, the *exo*-methylene unit could be modified and thus allow for incorporation of various benzylidene groups at the α position. Functionalization of the double bond may allow for selective modulation in the reactivity of these γ-lactones and γ-lactams with biological nucleophiles, thus allowing for more specific interactions and better selectivity as drug candidates. Modification of the γ-lactones and γ-lactams was achieved through the use of a rhodium-catalyzed conjugate addition reaction of aryl boronic acids to the *exo*-methylene, thus providing highly substituted α-alkyl γ-lactones and α-alkyl γ-

lactams. Again, this type of modification could help in tuning the reactivity of these compounds towards biological targets. Because the α-methylene γ-lactams contain a nitrogen atom that could be modified, I turned to a copper-catalyzed *N*-arylation reaction that allowed for the facile arylation of the amide nitrogen atom. This reaction proved to be quite general and various substituted aryl iodides were coupled successfully with the α-methylene γ-lactams.

Preliminary biological screening was carried out with a subset of the compounds synthesized in this library, and a few of the γ-lactams displayed inhibitory activity against homoserine transacetylase from *Haemophilus influenzae*. Because only a subset of these compounds were screened against only one family of enzymes, many opportunities remain to be considered for these γ-lactone and γ-lactam libraries. Further collaboration with other research groups and additional screening of these library members would allow for further exploration into the biological properties of these γ-lactones and γ-lactams and their possible use to treat a wide variety of medical issues.

5.6 Experimental[9]

5.6.1 General information

Unless otherwise noted, all reactions were performed under an argon atmosphere. Toluene, CH_3CN and CH_2Cl_2 were distilled over CaH_2. THF was distilled over sodium/ benzophenone ketyl. NH_4Cl(aq) and $NaHCO_3$(aq) refer to saturated aqueous solutions. All other chemicals were used as received from commercial sources. Thin layer chromatography (TLC) was performed on Macherey-Nagel Polygram Sil G/UV_{254} plates and was visualized with UV light or potassium permanganate stain. NMR spectra were recorded on 300, 400, 500 or 600 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, integration,

coupling constant). HPLC-grade solvents were obtained from commercial suppliers and used without further purification. HPLC-grade deionized water was employed. LCMS analyses were performed on a Hewlett-Packard/Agilent 1100 MSD using an electron spray ionization detector. Many parts of the library were synthesized using a Trident Synthesizer External-Thermal agitation unit (Biotage). Those that were synthesized under microwave conditions utilized a Biotage Initiator Sixty EXP microwave synthesis system with fixed hold times. Microwave reactions were performed with constant temperature settings and variable power. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were obtained by the University of Alberta Spectral Services Laboratory. The *Journal of Combinatorial Chemistry* requires 5% of library members or 20 compounds (whichever is greater) to be further characterized for proof of concept and confirmation of purity. Furthermore, they require that 80% of these compounds have purity of 80% or greater. Both of these requirements were met for this project, and as a result, not all compounds were fully characterized.

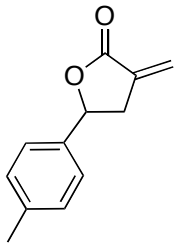
5.6.2 HPLC method for analysis and preparative purification

After the reaction workup, solvents were removed using a Genevac rapid evaporator. The crude library members were dissolved in HPLC grade THF (150 μL per 30 mg of crude product); the solutions were centrifuged to precipitate particular solids, and the supernatants were transferred into HPLC conical vial inserts (300 μL). Next, the compounds were injected into the LCMS instrument equipped with a semi-preparative Zorbax Rx-C8 column (9.4 × 250 mm, 5 μm). The solvent system was H_2O/CH_3CN (50% B at 0 min to 95% B at 25 min), both containing HCO_2H (0.05%); the flow rate was 3.00 mL/min, and the column temperature was 40 °C. The splitter ratio was 999:1 with a make-up pump using a mobile phase H_2O/CH_3CN (60:40) containing HCO_2H (0.1%). The compounds were monitored by UV at 254 nm and by ESI-MS (scan range: 100 to 1500 m/z).

5.6.3 General procedure for the synthesis of α-methylene γ-lactones 5.3

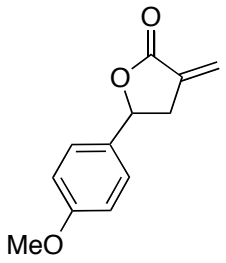
Allylboronate **3.1** (0.16 mmol, 36 mg) and aldehyde **5.2** (0.18 mmol) were dissolved in 2 mL of toluene in a parallel synthesizer vial under argon. The reaction mixture was agitated and heated at 110 ºC for 3 d. After this point, the reaction was cooled to rt and PTSA (0.48 mmol) was added. The reaction was agitated for 16 h, then quenched by the addition of $NaHCO_3$ (aq) and extracted three times with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was purified by semi-preparative HPLC using the method of Section 5.6.2.

3-Methylene-5-*p*-tolyl-dihydro-furan-2-one (5.3{2})



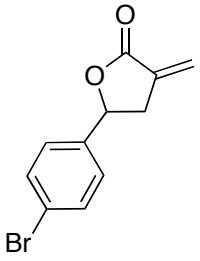
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.15 (m, 4H), 6.31 (t, 1H, *J* = 2.8 Hz), 5.68 (t, 1H, *J* = 2.8 Hz), 5.50 (dd, 1H, *J* = 8.1, 6.6 Hz), 3.38 (dddd, 1H, *J* = 17.1, 8.1, 2.4, 2.4 Hz), 2.91 (dddd, 1H, *J* = 17.1, 6.5, 2.8, 2.8 Hz), 2.36 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 170.2, 138.5, 136.9, 134.5, 129.5, 125.5, 122.3, 78.1, 36.4, 21.2. IR ($CDCl_3$, microscope, cm^{-1}): 1765. HRMS (EI, m/z) Calcd for $C_{12}H_{12}O_2$: 188.0837. Found: 188.0839.

3-Methylene-5-(4-methoxy-phenyl)-furan-2-one (5.3{3})



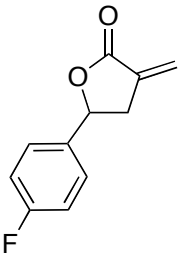
Spectral properties match those reported in the literature.[28]

5-(4-bromo-phenyl)-3-methylene-dihydro-furan-2-one (5.3{4})



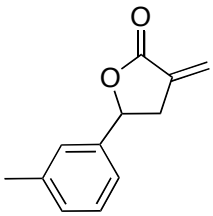
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.51 (m, 2H), 7.23 – 7.18 (m, 2H), 6.33 (t, 1H, J = 2.8 Hz), 5.71 (t, 1H, J = 2.6 Hz), 5.49 (dd, 1H, J = 7.6, 6.6 Hz), 3.41 (ddt, 1H, J = 17.1, 8.2, 2.5 Hz), 2.86 (dddd, 1H, J = 17.1, 6.4, 2.9, 2.9 Hz).

3-Methylene-5-(4-fluoro-phenyl)-furan-2-one (5.3{5})



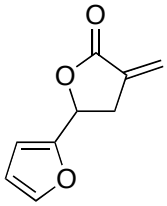
Spectral properties match those reported in the literature.[28]

5-(3-methyl-phenyl)-3-methylene-dihydro-furan-2-one (5.3{11})



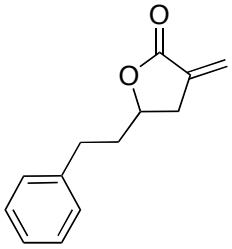
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.25 (m, 1H), 7.18 – 7.09 (m, 3H), 6.31 (ddd, 1H, *J* = 2.8, 2.8, 0.5 Hz), 5.69 (ddd, 1H, *J* = 2.3, 2.3, 0.5 Hz), 5.50 (dd, 1H, *J* = 8.0, 6.5 Hz), 3.39 (ddt, 1H, *J* = 17.1, 8.0, 2.5), 2.91 (ddt, 1H, *J* = 17.1, 6.4, 2.9 Hz), 2.37 (s, 3H).

4-Methylene-3,4-dihydro-2H-[2,2']bifuranyl-5-one (5.3{20})



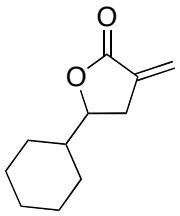
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 1H), 6.40 (m, 1H), 6.39 (m, 1H), 6.32 (t, 1H, *J* = 3.0 Hz), 5.74 (m, 1H), 5.53 (dd, 1H, *J* = 7.9, 6.6 Hz), 3.25 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$): δ169.5, 151.0, 143.7, 133.9, 122.5, 110.6, 109.5, 71.3, 32.1, 29.8. IR ($CDCl_3$, microscope, cm^{-1}): 1764. HRMS (EI, m/z) Calcd for $C_9H_8O_3$: 164.0474. Found: 164.0469.

3-methylene-5-phenethyl-dihydro-furan-2-one (5.3{32})



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 6.23 (t, 1H, *J* = 2.8 Hz), 5.63 (t, 1H, *J* = 2.6 Hz), 4.50 (dddd, 1H, *J* = 13.0, 13.0, 6.2, 5.0 Hz), 3.04 (dddd, 1H, *J* = 17.1, 7.8, 2.6, 2.6 Hz), 2.88 – 2.70 (m, 2H), 2.59 (dddd, 1H, *J* = 17.2, 6.0, 3.0,3.0 Hz), 2.09 – 1.99 (dddd, 1H, *J* = 14.2, 9.4, 7.2, 5.0 Hz).

5-Cyclohexyl-3-methylene-dihydro-furan-2-one (5.3{38})

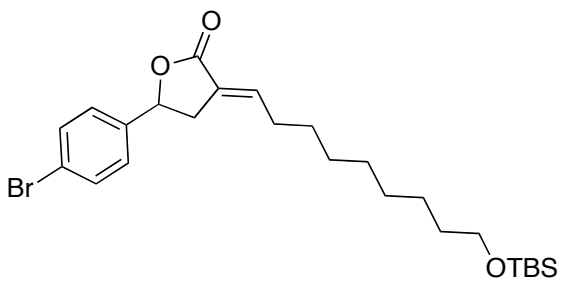


Spectral properties matched those reported in the literature.[29]

5.6.4 General procedure for functionalization of the α-methylene group via cross-metathesis

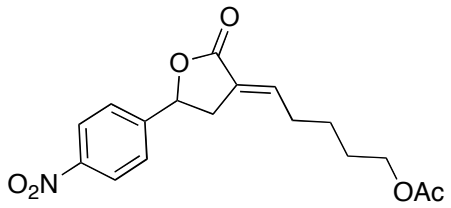
The appropriate γ-lactone (1.0 equiv) and terminal alkene (1.5 equiv) were dissolved in the appropriate solvent (DCM or toluene) and put under argon. The catalyst (0.05 equiv) and additive (0.1 equiv, if needed) were then added and the mixture was heated to the specified temperature (see Table 5.2) for 4 d. Once finished, the solvent was removed and the products were separated by flash chromatography.

(*E*)-5-(4-bromophenyl)-3-(9-((*tert*-butyldimethylsilyl)oxy)nonylidene) dihydrofuran-2(3*H*)-one (5.4a)



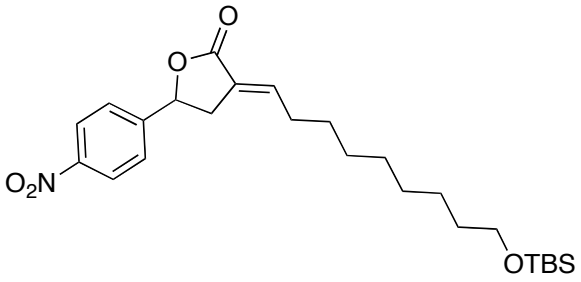
γ–Lactone **5.4a** was obtained via flash chromatography (0 to 20% EtOAc/hexanes) in a yield of 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 – 7.49 (m, 2H), 7.23 – 7.17 (m, 2H), 6.82 (dddd, 1H, *J* = 7.6, 7.6, 2.8, 2.8 Hz), 5.48 (dd, 1H, *J* = 8.3, 6.3 Hz), 3.60 (t, 2H, *J* = 6.5 Hz), 3.32 (ddddd, 1H, *J* = 16.9, 8.5, 3.0, 1.6, 1.6 Hz), 2.76 – 2.67 (m, 1H), 2.21 – 2.13 (m, 2H), 1.53 – 1.43 (m, 4H), 1.35 – 1.25 (m, 8H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 142.0, 139.6, 132.0, 127.0, 125.3, 122.4, 63.7, 63.3, 34.1, 32.9, 30.4, 29.4, 29.3, 29.3, 28.1, 26.0, 25.8, 18.4, 17.7, 10.5, –5.2. IR (microscope, cm^{-1}): 2929, 2856, 1762. HRMS (ESI, m/z) Calcd for $C_{25}H_{39}O_3SiBrNa$ $[M+Na]^+$: 517.1744. Found: 517.1743.

(*E*)-5-(5-(4-nitrophenyl)-2-oxodihydrofuran-3(2*H*)-ylidene)pentyl acetate (5.4b)



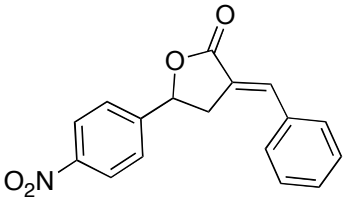
γ-Lactone **5.4b** was obtained via flash chromatography (20 to 50% EtOAc/hexanes) in a yield of 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 – 8.25 (m, 2H), 7.54 – 7.50 (m, 2H), 6.87 – 6.81 (m, 1H), 5.64 (dd, 1H, *J* = 8.1, 7.0 Hz), 4.10 (dd, 1H, *J* = 6.5, 6.5 Hz), 4.07 (t, 2H, *J* = 6.5 Hz), 3.47 – 3.39 (m, 1H), 2.79 – 2.70 (m, 1H), 2.33 – 2.20 (m, 2H), 2.04 (s, 3H), 1.85 (p, 2H, *J* = 7.2 Hz), 1.71 – 1.55 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 169.9, 147.4, 141.7, 130.6, 126.1, 125.2, 124.2, 76.5, 63.8, 34.0, 29.9, 28.3, 24.5, 21.0. IR (microscope, cm^{-1}): 3081, 2948, 1761, 1736. HRMS (EI, m/z) Calcd for $C_{17}H_{19}O_6N$: 333.1212. Found: 333.1213.

(*E*)-3-(9-((*tert*-butyldimethylsilyl)oxy)nonylidene)-5-(4-nitrophenyl) dihydrofuran-2(3*H*)-one (5.4c)



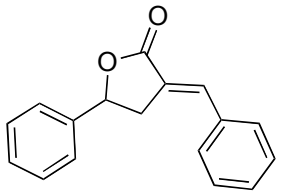
γ-Lactone **5.4c** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 68%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 – 8.24 (m, 2H), 7.54 – 7.50 (m, 2H), 6.86 (dddd, 1H, *J* = 7.7, 7.7, 2.9, 2.9 Hz), 5.62 (dd, 1H, *J* = 8.5, 6.4 Hz), 3.59 (t, 2H, *J* = 6.7 Hz), 3.46 – 3.38 (m, 1H), 2.77 – 2.69 (m, 1H), 2.23 – 2.15 (m, 2H), 1.55 – 1.44 (m, 4H), 1.36 – 1.26 (m, 8H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 147.6, 142.8, 126.1, 124.5, 124.2, 76.5, 63.3, 34.0, 32.9, 30.5, 29.4, 29.3, 28.1, 26.0, 25.8, 18.4, 14.3, –5.2. IR (microscope, cm^{-1}): 2930, 2856, 1764. HRMS (ESI, m/z) Calcd for $C_{25}H_{39}NO_5SiNa$ $[M+Na]^+$: 484.2490. Found: 484.2490.

(*E*)-3-benzylidene-5-(4-nitrophenyl)dihydrofuran-2(3*H*)-one (5.4d)



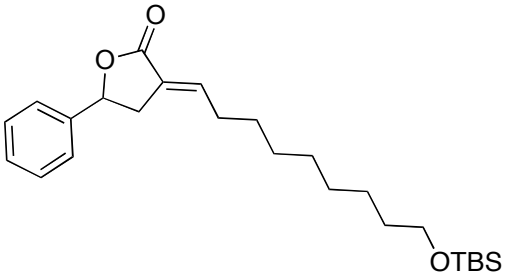
γ-Lactone **5.4d** was obtained via flash chromatography (25% EtOAc/hexanes) in a yield of 24%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 – 8.24 (m, 2H), 7.68 (dd, 1H, *J* = 2.9, 2.9 Hz), 7.59 – 7.54 (m, 2H), 7.52 – 7.42 (m, 5H), 5.72 (dd, 1H, *J* = 8.3, 6.1 Hz), 3.80 (ddd, 1H, *J* = 17.4, 8.6, 2.7 Hz), 3.12 (ddd, 1H, *J* = 17.4, 5.9, 3.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 147.9, 147.4, 138.2, 134.2, 130.4, 130.1, 129.1, 126.1, 124.3, 122.5, 76.7, 36.3. IR (microscope, cm^{-1}): 3112, 3081, 2925, 1756. HRMS (EI, m/z) Calcd for $C_{17}H_{13}NO_4$: 295.0845. Found: 295.0843.

(*E*)-3-benzylidene-5-phenyldihydrofuran-2(3*H*)-one (5.4e)



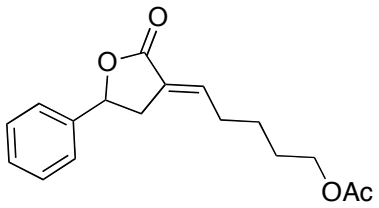
γ-Lactone **5.4e** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 28%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, 1H, *J* = 2.9, 2.9 Hz), 7.52 – 7.48 (m, 2H), 7.46 – 7.33 (m, 8H), 5.62 (dd, 1H, *J* = 8.3, 6.0 Hz), 3.71 (ddd, 1H, *J* = 17.6, 8.5, 2.8 Hz), 3.18 (ddd, 1H, *J* = 17.5, 6.0, 3.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0,140.4, 137.0, 134.6, 130.1, 130.0, 129.0, 128.9, 128.6, 125.4, 124.1, 78.2, 36.6. IR (microscope, cm^{-1}): 3090, 3059, 3027, 2927, 1730. HRMS (EI, m/z) Calcd for $C_{17}H_{14}O_2$: 250.0994. Found: 250.0993.

(*E*)-3-(9-((*tert*-butyldimethylsilyl)oxy)nonylidene)-5-phenyldihydrofuran-2(3*H*)-one (5.4f)



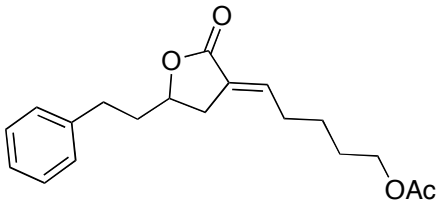
γ-Lactone **5.4f** was obtained via flash chromatography (5 to 15% EtOAc/hexanes) in a yield of 43%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.37 (m, 2H), 7.36 – 7.31 (m, 3H), 6.81 (dddd, 1H, *J* = 7.7, 7.7, 3.0, 3.0 Hz), 5.53 (dd, 1H, *J* = 8.4, 6.2 Hz), 3.59 (t, 2H, *J* = 6.6 Hz), 3.35 – 3.28 (m, 1H), 2.81 – 2.74 (m, 1H), 2.21 – 2.15 (m, 2H), 1.54 – 1.45 (m, 4H), 1.35 – 1.25 (m, 8H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 141.4, 140.5, 128.8, 128.4, 125.8, 125.3, 78.0, 63.2, 34.1, 32.8, 30.3, 29.4, 29.3, 29.3, 28.1, 26.0, 25.8, 18.4, –5.3.

(*E*)-5-(2-oxo-5-phenyldihydrofuran-3(2*H*)-ylidene)pentyl acetate (5.4g)



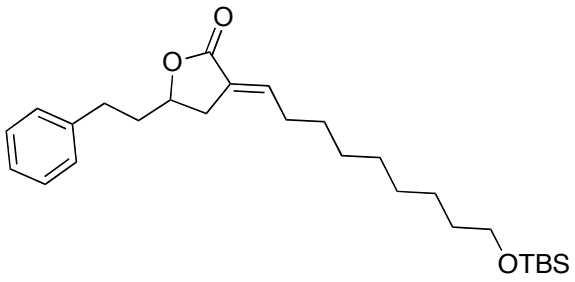
γ-Lactone **5.4g** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 5%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (m, 5H), 6.79 (dddd, 1H, *J* = 7.6, 7.6, 2.9, 2.9 Hz), 5.54 (dd, 1H, *J* = 8.3, 6.3 Hz), 4.07 (t, 2H, *J* = 6.3 Hz), 3.33 (ddddd, 1H, *J* = 16.8, 8.3, 3.0, 1.5, 1.5 Hz), 2.83 – 2.74 (m, 1H), 2.26 – 2.19 (m, 2H), 2.05 (s, 3H), 1.71 – 1.53 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 170.6, 140.4, 140.4, 128.9, 128.5, 126.5, 125.4, 78.1, 63.9, 34.2, 29.8, 28.3, 24.7, 21.0.

(*E*)-5-(2-oxo-5-phenethyldihydrofuran-3(2*H*)-ylidene)pentyl acetate (5.4h)



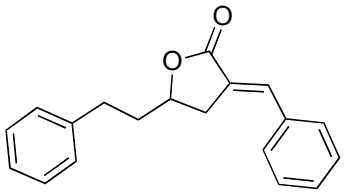
γ-Lactone **5.4h** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 6%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 6.72 (dddd, 1H, *J* = 7.5, 7.5, 2.9, 2.9 Hz), 4.52 (dddd, 1H, *J* = 14.0, 8.3, 6.0, 4.8 Hz), 4.07 (t, 2H, *J* = 6.5 Hz), 2.96 (ddddd, 1H, *J* = 16.8, 7.9, 2.8, 1.5, 1.5 Hz), 2.89 – 2.71 (m, 2H), 2.50 – 2.42 (m, 1H), 2.28 – 2.17 (m, 2H), 2.10 – 1.96 (m, 2H), 2.05 (s, 3H), 1.93 (dddd, 1H, *J* = 14.0, 7.3, 2.4, 2.4 Hz), 1.71 – 1.67 (m, 2H), 1.60 – 1.52 (m, 2H). HRMS (EI, m/z) Calcd for $C_{19}H_{24}O_4$: 316.1674. Found: 316.1674.

(*E*)-3-(9-((*tert*-butyldimethylsilyl)oxy)nonylidene)-5-phenethyldihydrofuran-2(3*H*)-one (5.4i)



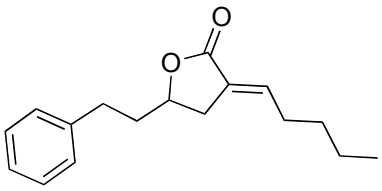
γ-Lactone **5.4i** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 10%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.17 (m, 5H), 6.74 (dddd, 1H, *J* = 7.6, 7.6, 2.9, 2.9 Hz), 4.51 (m, 1H), 3.60 (t, 2H, *J* = 6.5 Hz), 3.00 – 2.89 (m, 1H), 2.89 – 2.70 (m, 2H), 2.50 – 2.40 (m, 1H), 2.21 – 2.10 (m, 2H), 2.10 – 1.85 (m, 2H), 1.57 – 1.40 (m, 4H), 1.38 – 1.25 (m, 8H), 0.90 (s, 9H), 0.05 (s, 6H). HRMS (ESI, m/z) Calcd for $C_{27}H_{44}O_3Si$: 444.3060. Found: 444.3050.

(*E*)-3-benzylidene-5-phenethyldihydrofuran-2(3*H*)-one (5.4j)



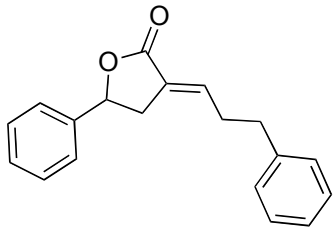
γ-Lactone **5.4j** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (t, 1H, *J* = 3.0 Hz), 7.50 – 7.40 (m, 5H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 4.61 (dddd, 1H, *J* = 8.3, 8.3, 5.5, 5.5 Hz), 3.34 (ddd, 1H, *J* = 17.6, 7.9, 3.0 Hz), 2.93 – 2.76 (m, 3H), 2.16 – 1.95 (m, 2H). HRMS (ESI, m/z) Calcd for $C_{19}H_{18}O_2$: 278.1307. Found: 278.1307.

(*E*)-3-pentylidene-5-phenethyldihydrofuran-2(3*H*)-one (5.4k)



γ-Lactone **5.4k** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 6%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 6.74 (dddd, 1H, *J* = 7.2, 7.2, 2.8, 2.8 Hz), 4.51 (dddd, 1H, *J* = 14.2, 8.2, 6.2, 4.9 Hz), 2.95 (ddddd, 1H, *J* = 16.8, 8.2, 3.1, 1.8, 1.8 Hz), 2.89 – 2.71 (m, 2H), 2.50 – 2.39 (m, 1H), 2.17 (app. qt, 2H, *J* = 7.2, 1.6 Hz), 2.10 – 1.99 (m, 1H), 1.93 (dddd, 1H, *J* = 14.0, 12.1, 7.2, 4.9 Hz), 1.51 – 1.42 (m, 2H), 1.40 – 1.30 (m, 2H), 0.92 (t, 3H, *J* = 7.2 Hz). HRMS (EI, m/z) Calcd for $C_{17}H_{22}O_2$: 258.1620. Found: 258.1620.

(*E*)-5-phenyl-3-(3-phenylpropylidene)dihydrofuran-2(3*H*)-one (5.4l)



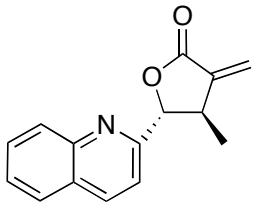
γ-Lactone **5.4l** was obtained via flash chromatography (20% EtOAc/hexanes) in a yield of 6% (2,6-dicholorbenzoquinone) or 21% (B-chlorocatechol borane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.14 (m, 10H), 6.87 – 6.81 (m, 1H), 5.42 (dd, 1H, *J* = 8.1, 6.2 Hz), 3.14 – 3.05 (m, 1H), 2.81 (dd, 2H, *J* = 7.4, 7.4 Hz), 2.63 – 2.55 (m, 1H), 2.55 – 2.47 (m, 2H).

5.6.5 Synthesis of α-methylene γ-lactones 5.5{5-6}

A solution of methyl (2*Z*)-2-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-but-2-enoate (100 mg, 0.42 mmol) and aldehyde (0.52 mmol) in

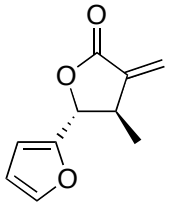
toluene (1 mL) was heated to 110 °C in a high pressure vessel under an argon atmosphere for 72 h. PTSA (230 mg, 1.2 mmol) was then added and the mixture was stirred overnight at rt. The reaction was quenched with $NaHCO_3$ (aq) (20 mL) and extracted with Et_2O (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography (5-30% EtOAc/hexanes) gave the corresponding lactone.

4-Methyl-3-methylene-5-quinolin-2-yl-dihydro-furan-2-one (5.5{5})



Obtained as a red oil in a yield of 51%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, 1H, *J* = 9.2 Hz), 8.08 (d, 1H, *J* = 8.4 Hz), 7.84 (d, 1H, *J* = 8.4 Hz), 7.75 (m, 1H), 7.57 (m, 2H), 6.36 (d, 1H, *J* = 3.2 Hz), 5.65 (d, 1H, *J* = 3.1 Hz), 3.34 (m, 1H), 1.52 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (125 Hz, $CDCl_3$): δ 170.0, 158.1, 147.5, 140.2, 137.4, 129.9, 129.4, 127.8, 127.7, 126.9, 121.6, 117.9, 86.0, 41.3, 17.3. IR (microscope, cm^{-1}): 1770. HRMS (EI, m/z) Calcd for $C_{15}H_{13}O_2N$: 239.0946. Found: 239.0944.

3-Methyl-4-methylene-3,4-dihydro-2H-[2,2']bifuranyl-5-one (5.5{6})



Obtained as a colorless oil in a yield of 45%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (m, 1H), 6.47 (m, 1H), 6.39 (m, 1H), 6.31 (m, 1H), 5.62 (m, 1H), 4.95 (d, 1H, *J* = 7.6 Hz), 3.35 (m, 1H), 1.30, (d, 1H, *J* = 6.9 Hz). ^{13}C NMR (125 Hz, $CDCl_3$): δ

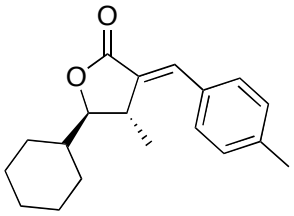
169.4, 149.8, 143.8, 140.1, 121.2, 110.6, 110.1, 78.7, 38.9, 16.4. IR ($CDCl_3$, microscope, cm^{-1}): 1767. HRMS (EI, m/z) Calcd for $C_{10}H_{10}O_3$: 178.0630. Found: 178.0629.

5.6.6 Screening of Heck coupling reaction conditions

5.6.6.1 Synthesis of *E*-5.6a, *Z*-5.6a, 5.7a mixture

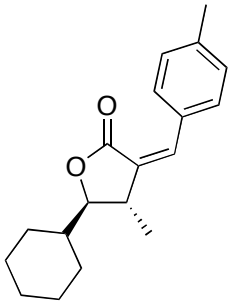
p–Tolylboronic acid (17 mg, 0.13 mmol), $Pd(OAc)_2$ (1.2 mg, 0.006 mmol), $Cu(OAc)_2$ (38 mg, 0.21 mmol) and LiOAc (21 mg, 0.32 mmol) were added to a microwave vial under argon. 1 mL of DMF was added and the reaction mixture was stirred to mix reagents. γ-Lactone **5.3**{38} (19 mg, 0.11 mmol) was added to the reaction mixture, along with an additional 2 mL of DMF. The microwave vial was capped and irradiated for 4 h at 100 °C, with 30 seconds of pre-stirring. The reaction mixture was quenched by the addition of saturated NH_4Cl (aq) and extracted with Et_2O three times. The organic extracts were concentrated and purified by preparatory HPLC. *E*-**5.6a** and **7a** were unable to be separated by HPLC.

_E_-5-Cyclohexyl-3-(4-methyl-benzylidene)-dihydro-furan-2-one (_E_-5.6a)



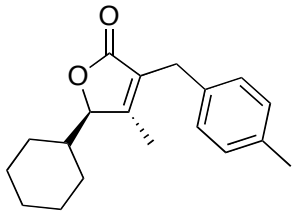
Obtained in a yield of 6%. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (t, 1H, J = 2.8 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.25 (d, 1H, J = 8.2 Hz), 4.38 – 4.33 (m, 1H), 3.22 (ddd, 1H, J = 17.7, 8.4, 2.9 Hz), 2.91 (ddd, 1H, J = 17.7, 6.1, 3.1 Hz), 2.40 (s, 3H), 1.97 – 1.90 (m, 1H), 1.83 – 1.52 (m, 5H), 1.34 – 1.02 (m, 4H). HRMS (EI, m/z) Calcd for $C_{18}H_{22}O_2$: 270.1620. Found: 170.1619.

***Z*-5-Cyclohexyl-3-(4-methyl-benzylidene)-dihydro-furan-2-one (*Z*-5.6a)**



Obtained in a yield of 9%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 8.3 Hz), 7.18 (d, 2H, *J* = 8.3 Hz), 6.91 (br s, 1H), 4.26 (q, 1H, *J* = 7.3 Hz), 3.10 – 3.03 (m, 1H), 2.90 – 2.82 (m, 1H), 2.36 (s, 3H), 2.02 – 1.94 (m, 1H), 1.82 – 1.75 (m, 2H), 1.74 – 1.65 (m, 2H), 1.62 – 1.50 (m, 1H), 1.32 – 1.01 (m, 5H). HRMS (EI, m/z) Calcd for $C_{18}H_{22}O_2$: 270.1620. Found: 170.1619.

5-Cyclohexyl-3-(4-methyl-benzyl)-5H-furan-2-one (5.7a)

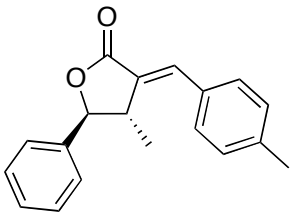


Obtained in a yield of 1%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 – 7.09 (m, 4H), 6.82 (br q, 1H, *J* = 1.6 Hz), 4.70 – 4.66 (m, 1H), 3.55 (br s, 2H), 2.34 (s, 3H), 1.83 – 1.52 (m, 6H), 1.34 – 1.02 (m, 4H). HRMS (EI, m/z) Calcd for $C_{18}H_{22}O_2$: 270.1620. Found: 170.1619.

5.6.6.2 Synthesis of *E*-5.6b and 5.7b

Procedure was identical to that used for **5.6a**/**7a**, except was purified by flash chromatography using dichloromethane as the eluant.

***E*-4-Methyl-3-(4-methyl-benzylidene)-5-phenyl-dihydro-furan-2-one (*E*-5.6b)**



Obtained in a yield of 7%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (br d, 1H, *J* = 2.3 Hz), 7.42 – 7.28 (m, 7H), 7.23 – 7.19 (m, 2H), 5.20 (br d, 1H, *J* = 2.6 Hz), 3.59 – 3.51 (m, 1H), 2.38 (s, 3H), 1.47 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 140.5, 140.5, 137.9, 131.1, 130.2, 129.7, 128.9, 128.5, 128.4, 125.2, 85.6, 41.9, 21.5, 18.5. HRMS (EI, m/z) Calcd for $C_{18}H_{22}O_2$: 278.1307. Found: 278.1286.

5.6.6.3 Synthesis of *E*-5.6c, *Z*-5.6c, 5.7c mixture

Method A (entry 5, Table 5.3**)**

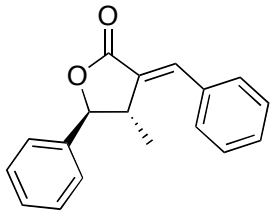
In a flame-dried flask, $Pd(OAc)_2$ (1.8 mg, 0.008 mmol) and PPh_3 (4.2 mg, 0.016 mmol) were dissolved in 7 mL of acetonitrile under argon. **5.5**{2} (30 mg, 0.16 mmol), iodobenzene (38 μL, 0.17 mmol), K_2CO_3 (55 mg, 0.40 mmol) and Bu_4NBr (53 mg, 0.16 mmol) were added to the reaction mixture. The reaction was heated to 90 ºC for 24 h, at which time none of **5.5**{2} was left, based upon TLC comparison. The crude reaction mixture was loaded onto a silica gel column and eluted with 10% EtOAc/hexanes to provide *E*-**5.6c** in a yield of 55%, *Z*-**5.6c** in a yield of 2% and **5.7c** in a yield of 7%.

Method B (entry 6, Table 5.3**)**

In a flame-dried flask, $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and PPh_3 (2.6 mg, 0.010 mmol) were dissolved in 5 mL of acetonitrile under argon. **5.5**{2} (19 mg, 0.10 mmol), iodobenzene (24 μL, 0.11 mmol) and Cs_2CO_3 (81 mg, 0.25 mmol)

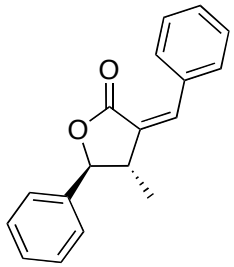
were added to the reaction mixture. The reaction was heated to 90 ºC for 48 h, at which time none of **5.5**{2} was left, based upon TLC comparison. The crude reaction mixture was loaded onto a silica gel column and eluted with 10% EtOAc/hexanes to provide *E*-**5.6c** in a yield of 23% and **5.7c** in only trace amounts (<1%).

_E_-3-Benzylidene-4-methyl-5-phenyl-dihydro-furan-2-one (_E_-5.6c)



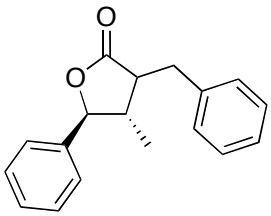
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, 1H, *J* = 2.1 Hz), 7.52 – 7.47 (m, 2H), 7.44 – 7.28 (m, 8H), 5.21 (d, 1H, *J* = 2.6 Hz), 3.57 (app qt, 1H, *J* = 7.0, 2.5 Hz), 1.47 (d, 3H, *J* = 7.0 Hz). HRMS (EI, m/z): Calcd for $C_{18}H_{16}O_2$: 246.1150. Found: 264.1150.

_Z_-3-Benzylidene-4-methyl-5-phenyl-dihydro-furan-2-one (_Z_-5.6c)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.86 (m, 2H), 7.44 – 7.35 (m, 8H), 6.85 (d, 1H, *J* = 2.7 Hz), 4.96 (d, 1H, *J* = 8.0 Hz), 3.16 – 3.09 (m, 1H), 1.39 (d, 3H, *J* = 6.7 Hz). HRMS (EI, m/z): Calcd for $C_{18}H_{16}O_2$: 246.1150. Found: 264.1158.

3-Benzyl-4-methyl-5-phenyl-5H-furan-2-one (5.7c)

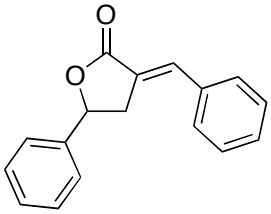


^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.70 (m, 2H), 7.37 – 7.28 (m, 3H), 7.11 – 7.02 (m, 3H), 6.49 – 6.45 (m, 2H), 3.38 (d, 1H, *J* = 15.7 Hz), 3.26 (d, 1H, *J* = 15.7 Hz), 2.33 (s, 3H). HRMS (EI, m/z): Calcd for $C_{18}H_{16}O_2$: 246.1150. Found: 264.1132.

5.6.6.4 Synthesis of *E*-5.6d

In a flame-dried flask, $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and PPh_3 (2.6 mg, 0.010 mmol) were dissolved in 5 mL of acetonitrile under argon. **5.3**{1} (17 mg, 0.10 mmol), iodobenzene (24 μL, 0.11 mmol) and Cs_2CO_3 (81 mg, 0.25 mmol) were added to the reaction mixture. The reaction was heated to 90 ºC for 6 h, at which time none of **5.3**{1} was left, based upon TLC comparison. The crude mixture was filtered through a short pad of Celite, rinsed with EtOAc and concentrated. The reaction mixture was purified by flash chromatography using 10% EtOAc/hexanes to provide the desired compound.

***E*-3-Benzylidene-5-phenyl-dihydro-furan-2-one (*E*-5.6d)**



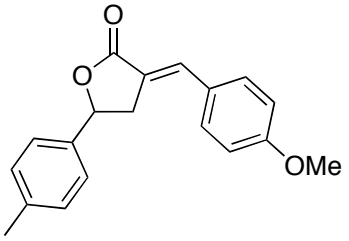
Obtained in a yield of 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (t, 1H, *J* = 3.2 Hz), 7.53 – 7.48 (m, 2H), 7.46 – 7.33 (m, 8H), 5.63 (dd, 1H, *J* = 8.4, 6.0 Hz), 3.71 (ddd, 1H, 17.5, 8.2, 2.8 Hz), 3.18 (ddd, 1H, *J* = 17.5, 5.9, 3.1 Hz). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 172.2, 140.6, 137.3, 134.9, 130.3, 130.2, 129.2, 129.1, 128.8, 125.6, 124.4, 78.4, 36.8. IR (CH_2Cl_2 cast film microscope, cm^{-1}): 1754, 1178. HRMS (EI, m/z): Calcd for $C_{17}H_{14}O_2$: 250.0994. Found: 250.0997.

5.6.7 General procedure for the synthesis of *exo*-alkylidene γ-lactones 5.9

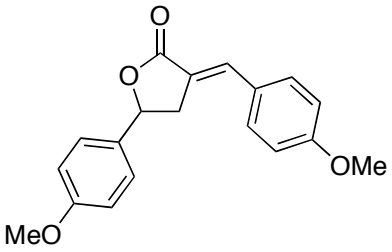
In a parallel synthesizer vial, α-methylene γ-lactone **5.3** (0.075 mmol), Cs_2CO_3 (61 mg, 0.19 mmol), palladium (II) acetate (1.1 mg, 0.005 mmol), triphenylphosphine (2.6 mg, 0.01 mmol) and aryl iodide **5.8** (0.083 mmol) were combined. Acetonitrile (2 mL) was added, and the reaction vessel was put under an argon atmosphere. The reaction was put into the parallel synthesizer and was heated for 6 h at 90 ºC with agitation. The crude reaction mixture was then filtered through a short pad of Celite and washed with EtOAc. The organic solvent was removed to provide the crude product, which was purified by preparatory HPLC.

***E*-3-(4-methyoxy-benzylidene)-5-*p*-tolyl-dihydro-furan-2-one (5.9{2,3})**



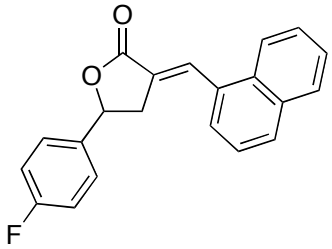
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (t, 1H, *J* = 2.8 Hz), 7.48 – 7.42 (m, 2H), 7.28 – 7.18 (m, 4H), 6.96 – 6.92 (m, 2H), 5.58 (dd, 1H, *J* = 8.7, 6.2 Hz), 3.85 (s, 3H), 3.65 (ddd, 1H, *J* = 17.4, 8.5, 2.8 Hz), 3.12 (ddd, 1H, *J* = 17.4, 6.0, 3.1 Hz), 2.36 (s, 1H).

***E*-3-(4-methyoxy-benzylidene)-5-(4-methoxy-phenyl)-dihydro-furan-2-one (5.9{3,3})**



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (t, 1H, *J* = 3.1 Hz), 7.49 – 7.44 (m, 2H), 7.32 – 7.27 (m, 2H), 6.97 – 6.94 (m, 2H), 6.94 – 6.90 (m, 2H), 5.56 (dd, 1H, *J* = 8.4, 6.1 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 3.63 (ddd, 1H, *J* = 17.3, 8.4, 2.6 Hz), 3.14 (ddd, 1H, *J* = 17.5, 6.0, 3.1 Hz).

***E*-5-(4-Fluoro-phenyl)-3-naphthalen-1-ylmethylene-dihydro-furan-2-one (5.9{5,4})**



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (t, 1H, *J* = 3.0 Hz), 8.15 (d, 1H, *J* = 8.3 Hz), 7.91 (d, 1H, *J* = 7.8 Hz), 7.64 – 7.47 (m, 4H), 7.38 – 7.33 (m, 2H), 7.11 – 7.06 (m, 2H), 5.59 (dd, 1H, *J* = 7.3, 7.3 Hz), 3.63 (ddd, 1H, *J* = 17.4, 8.0, 2.7 Hz), 3.13 (ddd, 1H, *J* = 17.6, 6.6, 3.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ –113.5.

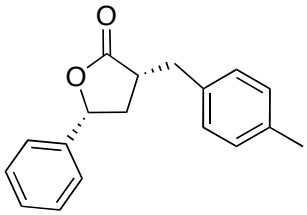
5.6.8 Rh-catalyzed conjugate addition reactions: synthesis of α-alkyl γ-lactones 5.10-5.12

γ-Lactone **5.3**{1} or **5.5**{2} (0.075 mmol), arylboronic acid (0.30 mmol), Rh(COD)(acac) (1.2 mg, 0.004 mmol), *rac*-BINAP (3.7 mg, 0.006 mmol), boric

acid (25 mg, 0.30 mmol) and 1 mL dioxane were added to a microwave vessel and then put under argon. The vessel was capped and then irradiated for 4 h at 100 °C. The crude reaction mixture was filtered through a short pad of celite, rinsed with EtOAc and concentrated. The crude reaction mixture was purified by flash chromatography using 10% EtOAc/hexanes to provide the desired products.

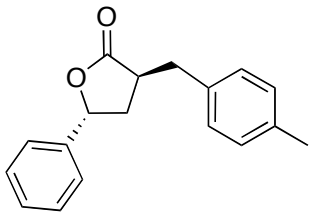
5.10a and **5.10b** were obtained in a total yield of 66% and in a ratio of 1.2:1.

***cis*-3-(4-Methyl-benzyl)-5-phenyl-dihydro-furan-2-one (5.10a)**



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.30 (m, 3H), 7.28 – 7.24 (m, 2H), 7.13 – 7.06 (m, 4H), 5.33 (dd, 1H, *J* = 10.4, 5.8 Hz), 3.32 (dd, 1H, *J* = 13.8, 4.0 Hz), 3.09 – 3.01 (m, 1H), 2.75 (dd, 1H, *J* = 13.8, 9.3 Hz), 2.61 (ddd, 1H, *J* = 12.8, 8.2, 5.8 Hz), 2.33 (s, 3H), 1.91 (ddd, 1H, *J* = 12.4, 12.4, 10.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 139.3, 136.5, 135.6, 129.6, 128.9, 128.7, 125.6, 94.6, 79.7, 43.7, 37.8, 35.9, 21.2. HRMS (EI, m/z): Calcd for $C_{18}H_{18}O_2$: 266.1307. Found: 266.1307.

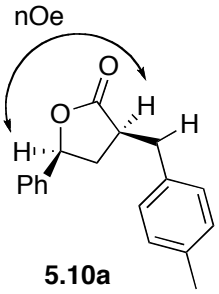
***trans*-3-(4-Methyl-benzyl)-5-phenyl-dihydro-furan-2-one (5.10b)**



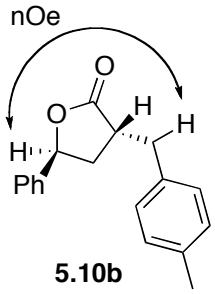
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.23 (m, 5H), 7.14 – 7.09 (m, 4H), 5.37 (dd, 1H, *J* = 8.2, 5.0 Hz), 3.19 (dd, 1H, *J* = 14.3, 4.5 Hz), 2.99 – 2.92 (m, 1H), 2.84 (dd, 1H, *J* = 14.0, 9.0 Hz), 2.45 (dt, 1H, *J* = 13.1, 8.1 Hz), 2.33 (s, 3H), 2.27

(ddd, 1H, J = 12.9, 8.8, 4.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 139.8, 136.5, 135.0, 129.5, 128.9, 128.8, 125.0, 94.6, 78.7, 40.7, 35.9, 35.6, 21.0. HRMS (EI, m/z): Calcd for $C_{18}H_{18}O_2$: 266.1307. Found: 266.1303.

TROESY experiment for 5.10a and 5.10b



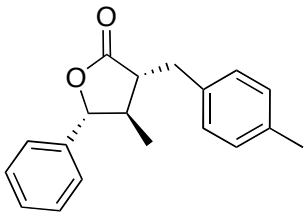
5.10a



5.10b

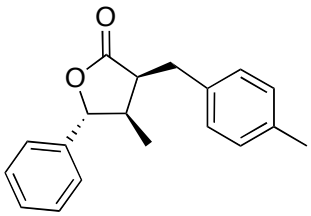
5.11a and **5.11b** were obtained as a mixture in a total yield of 74% and in a ratio of 1:10. Mixture of **5.11a** and **5.11b**: HRMS (EI, m/z) Calcd for $C_{19}H_{20}O_2$: 280.1463. Found: 280.1465.

(3,4-*trans*-3,5-*cis*)-4-Methyl-3-(4-methyl-benzyl)-5-phenyl-dihydro-furan-2-one (5.11a)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.30 (m, 3H), 7.29 – 7.27 (m, 2H), 7.13 – 7.08 (m, 4H), 5.14 (d, 1H, J = 2.6 Hz), 3.17 (dd, 1H, J = 14.7, 5.1 Hz), 3.01 (ddd, 1H, J = 12.7, 7.6, 5.3 Hz), 2.79 (dd, 1H, J = 15.1, 10.2 Hz), 2.58 (ddd, 1H, J = 7.2, 7.2, 3.3 Hz), 2.31 (s, 3H), 1.23 (d, 3H, J = 7.2 Hz).

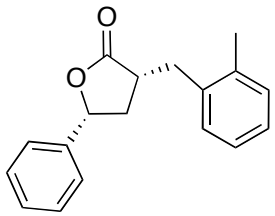
(3,4-*cis*-3,5-*trans*)-4-Methyl-3-(4-methyl-benzyl)-5-phenyl-dihydro-furan-2-one (5.11b)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.30 (m, 3H), 7.22 – 7.18 (m, 2H), 7.13 – 7.08 (m, 4H), 4.77 (d, 1H, *J* = 9.1 Hz), 3.18 (dd, 1H, *J* = 14.3, 5.3 Hz), 2.97 (dd, 1H, *J* = 14.3, 7.0 Hz), 2.65 (ddd, 1H, *J* = 11.3, 6.9, 5.2 Hz), 2.33 (s, 3H), 2.15 – 2.05 (m, 1H), 0.92 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 137.7, 136.3, 134.8, 129.3, 129.1, 128.7, 128.6, 126.3, 86.2, 49.7, 44.6, 34.3, 21.0, 15.1.

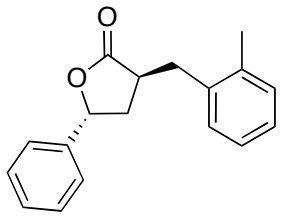
5.12a and **5.12b** were obtained as a mixture in a total yield of 86% and in a ratio of 2.8:1. Mixture of **5.12a** and **5.12b**: HRMS (EI, m/z) Calcd for $C_{18}H_{18}O_2$: 266.1307. Found: 266.1306.

***cis*-3-(2-Methyl-benzyl)-5-phenyl-dihydro-furan-2-one (5.12a)**



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.26 (m, 5H), 7.19 – 7.10 (m, 4H), 5.34 (dd, 1H, *J* = 10.4, 5.7 Hz), 3.47 (dd, 1H, *J* = 14.4, 4.2 Hz), 3.05 (dddd, 1H, *J* = 18.4, 10.3, 8.1, 4.0 Hz), 2.71 (dd, 1H, *J* = 14.3, 10.3 Hz), 2.63 (ddd, 1H, *J* = 12.8, 8.2, 5.7 Hz), 2.34 (s, 3H), 1.91 (ddd, 1H, *J* = 12.5, 12.5, 10.5 Hz).

***trans*-3-(2-Methyl-benzyl)-5-phenyl-dihydro-furan-2-one (5.12b)**

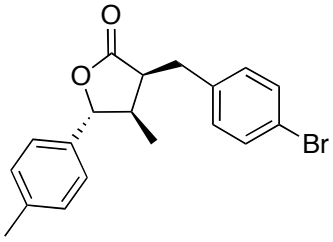


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.26 (m, 5H), 7.19 – 7.10 (m, 4H), 5.55 (dd, 1H, *J* = 7.6, 4.7 Hz), 3.35 (dd, 1H, *J* = 14.1, 4.2 Hz), 2.95 (dddd, 1H, *J* = 10.4, 8.5, 8.5, 4.4 Hz), 2.78 (dd, 1H, *J* = 14.3, 10.3 Hz), 2.46 (app dt, 1H, *J* = 12.8, 8.0 Hz), 2.35 (s, 3H), 2.29 (ddd, 1H, *J* = 12.9, 8.6, 4.5 Hz).

5.6.9 General procedure for the synthesis of α-alkylated-γ-lactones 5.14

γ-Lactone **5.5** (0.075 mmol), arylboronic acid **5.13** (0.30 mmol), Rh(COD)(acac) (1.2 mg, 0.004 mmol), *rac*-BINAP (3.7 mg, 0.006 mmol), boric acid (25 mg, 0.30 mmol) and 1 mL dioxane were added to a microwave vessel and put under argon. The vessel was capped and irradiated for 4 h at 100 ºC. The crude reaction mixture was filtered through a short pad of Celite, rinsed with EtOAc and concentrated. The crude mixture was purified by preparatory HPLC to provide the desired compounds.

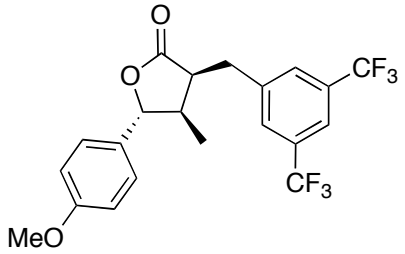
(3,4-*cis*-3,5-*trans*)-3-(4-Bromo-benzyl)-4-methyl-5-*p*-tolyl-dihydro-furan-2-one (5.14{3,4**})**



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.41 (m, 2H), 7.19 – 7.14 (m, 2H), 7.14 – 7.10 (m, 2H), 7.10 – 7.06 (m, 2H), 4.75 (d, 1H, *J* = 9.9 Hz), 3.14 (dd, 1H, *J* =

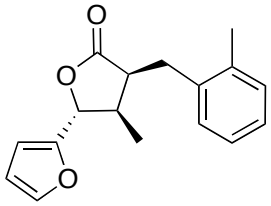
14.2, 5.4 Hz), 2.99 (dd, 1H, *J* = 14.2, 6.6 Hz), 2.64 (ddd, 1H, *J* = 11.7, 6.5, 5.4 Hz), 2.35 (s, 3H), 2.11 – 2.00 (m, 1H), 0.94 (d, 3H, *J* = 6.5 Hz). Ratio of isomers is 13.0:1 based on ^{1}H NMR integration.

(3,4-*cis*-3,5-*trans*)-3-(3,5-Bis-trifluoromethyl-benzyl)-5-(4-methoxy-phenyl)-4-methyl-dihydro-furan-2-one (5.14{4,6**})**



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.74 (br s, 2H), 7.19 – 7.15 (m, 2H), 6.92 – 6.87 (m, 2H), 4.79 (d, 1H, *J* = 9.8 Hz), 3.81 (s, 3H), 3.33 (dd, 1H, *J* = 14.9, 6.1 Hz), 3.12 (dd, 1H, *J* = 14.3, 6.1 Hz), 2.70 (ddd, 1H, *J* = 11.7, 6.3, 6.3 Hz), 2.15 – 2.04 (m, 1H), 0.97 (d, 3H, *J* = 6.5 Hz). Ratio of isomers is 10.6:1 based on ^{1}H NMR integration.

(3,4-*cis*-3,5-*trans*)-4-Methyl-3-(2-methyl-benzyl)-3,4-dihydro-2*H*-[2,2'] bifuranyl-5-one (5.14{6,3**})**

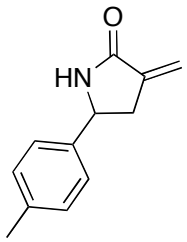


^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, 1H, *J* = 1.9, 0.8 Hz), 7.25 – 7.12 (m, 5H), 6.44 (dm, 1H), 6.39 (dd, 1H, *J* = 3.3, 1.8 Hz), 4.84 – 4.80 (m, 1H), 3.45 (dd, 1H, *J* = 14.3, 4.4 Hz), 2.86 – 2.78 (m, 1H), 2.66 – 2.53 (dm, 1H), 2.38 (s, 3H), 0.77 (d, 3H, *J* = 6.3 Hz). Ratio of isomers is 12.7:1 based on ^{1}H NMR integration.

5.6.10 General Procedure for the synthesis of α-methylene γ-lactams 5.15

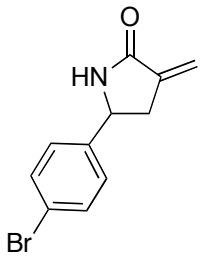
The corresponding aldehyde **5.2** (0.21 mmol) was dissolved in 1ml EtOH in a parallel synthesizer vessel under argon. NH_4OH (30%, 0.4 mL) was added and the mixture was stirred at rt for 30 min. Allylboronate **3.1** (45 mg, 0.2 mmol) was diluted in 0.5 mL EtOH and added to the reaction mixture. An additional 0.5 mL EtOH was used as rinse and added to the reaction mixture. The mixture was heated to 70 ºC for 4 h. The reaction mixture was then cooled to rt, and 1N HCl was added to quench the reaction and bring the pH of the solution to ~1. The mixture was extracted four times with Et_2O, and the organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The crude reaction mixtures were purified by preparatory HPLC to give the desired compounds.

3-Methylene-5-*p*-tolyl-pyrrolidin-2-one (5.15{2})



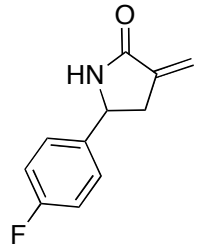
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 – 7.15 (m, 4H), 6.10 – 6.07 (m, 1H), 6.08 – 5.98 (br s, 1H), 5.41 – 5.38, (m, 1H), 3.30 (ddm, 1H, *J* = 17.2, 8.1 Hz), 2.69 (ddd, 1H, *J* = 17.3, 5.1, 5.1 Hz), 2.36 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 139.6, 138.7, 138.0, 129.7, 125.7, 116.7, 77.3, 54.6, 37.1, 21.1. IR ($CDCl_3$ microscope, cm^{-1}): 3168, 1695, 1658. HRMS (EI, m/z): Calcd for $C_{12}H_{13}NO$: 187.0997. Found: 187.0993.

5-(4-Bromo-phenyl)-3-methylene-pyrrolidin-2-one (5.15{4})



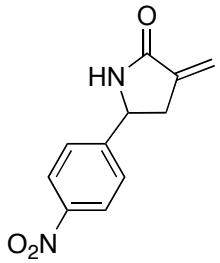
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 2H), 7.17 – 7.12 (m, 2H), 6.09 – 6.04 (m, 1H), 6.00 – 5.92 (br s, 1H), 5.43 – 5.38 (m, 1H), 4.73 (dd, 1H, *J* = 8.4, 4.7 Hz), 3.31 (app ddt, 1H, *J* = 17.2, 8.2, 2.3 Hz), 2.63 (ddd, 1H, *J* = 17.2, 4.5, 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 141.9, 138.3, 132.4, 127.7, 122.2, 117.3, 54.5, 37.0. IR (CH_2Cl_2, microscope, cm^{-1}): 3177, 1697. HRMS (EI, m/z) Calcd for $C_{11}H_{10}ON^{81}Br$: 252.9925. Found: 252.9927.

5-(4-Fluoro-phenyl)-3-methylene-pyrrolidin-2-one (5.15{5})



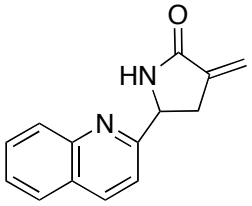
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H), 7.09 – 7.03 (m, 2H), 6.12 – 6.09 (m, 1H), 6.10 – 5.95 (br s, 1H), 5.43 – 5.40 (m, 1H), 4.75 (dd, 1H, *J* = 8.2, 4.9 Hz), 3.39 (dddd, 1H, *J* = 17.2, 8.1, 2.5, 2.5 Hz), 2.67 (dddd, 1H, *J* = 17.3, 5.4, 2.9, 2.9 Hz).

3-Methylene-5-(4-nitro-phenyl)-pyrrolidin-2-one (5.15{9})



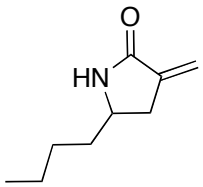
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 – 8.21 (m, 2H), 7.51 – 7.45 (m, 3H), 6.08 (t, 1H, *J* = 2.8 Hz), 5.44 – 5.42 (m, 1H), 4.90 (dd, 1H, *J* = 8.5, 4.5 Hz), 3.39 (ddt, 1H, *J* = 17.2, 8.5, 2.6 Hz), 2.69 – 2.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9,149.8, 147.6, 137.4, 126.5, 124.2, 117.5, 54.2, 36.3. IR (CH_2Cl_2, cast film, cm^{-1}): 3187, 1698, 1519. HRMS (EI, m/z) Calcd for $C_{11}H_{10}O_3N_2$: 218.0691. Found: 218.0692.

3-Methylene-5-quinolin-2-yl-pyrrolidin-2-one (5.15{27})



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 1H, *J* = 9.1 Hz), 8.05 (d, 1H, *J* = 8.7 Hz), 7.38 (d, 1H, *J* = 8.7 Hz), 7.74 (ddd, 1H, *J* = 8.4, 6.8, 1.4 Hz, 7.56 (ddd, 1H, *J* = 8.1, 7.0, 1.3 Hz), 7.42 (d, 1H, *J* = 8.5 Hz), 6.75 (br s, 1H), 6.12 (br t, 1H, *J* = 2.9 Hz), 5.45 – 5.43 (m, 1H), 5.07 (ddd, 1H, *J* = 8.6, 4.6, 0.9 Hz), 3.48 (ddt, 1H, *J* = 17.3, 8.8, 2.6 Hz), 2.93 (dddd, 1H, *J* = 17.4, 5.0, 2.7, 2.7 Hz).

5-Butyl-3-methylene-pyrrolidin-2-one (5.15{42})



^{1}H NMR (400 MHz, 90:10 $CDCl_3$: $(CD_3)_2CO$): δ 6.39 (br s, 1H), 5.86 (ddd, 1H, *J* = 2.9, 2.9, 0.9 Hz), 5.22 (ddd, 1H, *J* = 3.5, 2.4, 1.0 Hz), 3.58 – 3.51 (m, 1H), 2.88 (ddt, 1H, *J* = 17.1, 7.9, 2.6 Hz), 2.35 (ddt, 1H, *J* = 17.2, 4.5, 2.7 Hz), 1.51 – 1.35 (m, 2H), 1.29 – 1.17 (m, 4H), 0.81 (br t, 3H, *J* = 7.0 Hz).

5.6.11 Synthesis of α-methylene γ-lactams 5.15 for N-arylation reactions

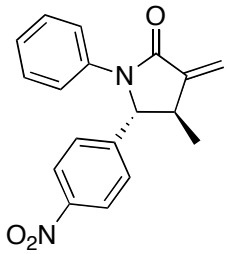
In a high-pressure vessel under argon, the desired aldehyde **5.2** (5.3 mmol) was dissolved in 4 mL ethanol. NH_4OH (5 mL) was added, and the reaction was stirred for 30 min. At this point, allylboronate **3.1** (600 mg, 2.7 mmol) was diluted in 1 mL ethanol and added to the reaction mixture. The reaction was heated for 5 h at 70 °C. The reaction was quenched by the addition of 1N HCl so as to bring the pH of the solution to ~1. The mixture was extracted four times with Et_2O, and the organic layer was dried over Na_2SO_4, filtered and concentrated. Note: For aldehydes containing an enolizable proton alpha to the carbonyl, the order of addition was modified as follows. Allylboronate **3.1** was combined first with the NH_4OH in ethanol, and the aldehyde was added after 30 min. Compounds **5.15**{1-3}, **5.15**{5}, **5.15**{20}, **5.15**{27} and **5.15**{40-41} were used as such without any further purification.

5.6.12 Synthesis of *N*-arylated α-methylene γ-lactams 5.16{1-8}

In a high-pressure vessel, CuI (1.0 mg, 0.005 mmol), γ-lactam **4.2**, **4.10** or **4.11** (0.10 mmol) and K_3PO_4 (35 mg, 0.17 mmol) were combined under argon. Toluene (1 mL) was added to the vessel and the mixture was stirred. Aryl halide

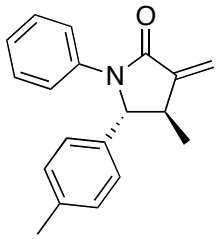
(0.08 mmol) and *N*,*N*'-dimethylethylenediamine (1.0 μL, 0.01 mmol) were added and the reaction mixture was heated to 80 ºC overnight. The resulting mixture was cooled, filtered through a short plug of Celite, washed with EtOAc and concentrated. The product was purified by flash chromatography (50% EtOAc/hexanes) to provide the desired compound.

trans-4-Methyl-3-methylene-5-(4-nitro-phenyl)-1-phenyl-pyrrolidin-2-one (5.16{1})



Obtained as a white solid in a yield of 44%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 – 8.14 (m, 2H), 7.42 – 7.38 (m, 4H), 7.29 – 7.24 (m, 2H), 7.12 – 7.07 (m, 1H), 6.27 (d, 1H, *J* = 2.8 Hz), 5.47 (d, 1H, *J* = 2.5 Hz), 4.85 (d, 1H, *J* = 4.9 Hz), 2.84 – 2.77 (m, 1H), 1.43 (d, 3H, *J* = 7.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ177.9, 148.1, 144.2, 137.7, 129.6, 127.4, 125.9, 124.6, 122.6, 117.7, 68.4, 42.4, 28.6, 18.6. IR (CH_2Cl_2 cast film microscope, cm^{-1}): 1702, 1523, 1349. HMRS (EI, m/z) Calcd for $C_{18}H_{16}N_2O_3$: 308.1161. Found: 308.1160.

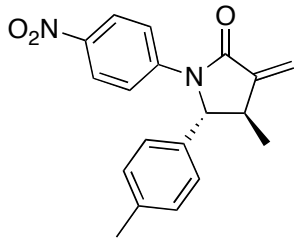
trans-4-Methyl-3-methylene-1-phenyl-5-_p_-tolyl-pyrrolidin-2-one (5.16{2})



Obtained as a white solid in a yield of 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.08 (m, 2H), 7.72 – 7.66 (m, 2H), 7.14 – 7.06 (m, 4H), 6.29 (d, 1H, *J* = 2.8 Hz),

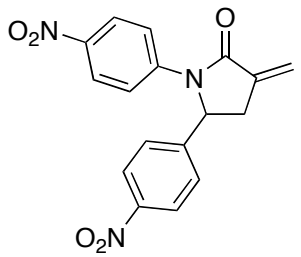
5.50 (d, 1H, J = 2.5 Hz), 4.72 (d, 1H, J = 5.0 Hz), 2.89 – 2.80 (m, 1H), 2.30 (s, 3H), 1.40 (d, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ167.5, 145.2, 138.2, 137.7, 137.5, 129.7, 128.6, 126.2, 125.1, 122.6, 116.3, 68.8, 42.5, 21.1, 18.4. IR (CH_2Cl_2 cast film microscope, cm^{-1}): 1698, 1371. HMRS (EI, m/z) Calcd for $C_{19}H_{19}NO$: 277.1467. Found: 277.1466.

***trans*-4-Methyl-3-methylene-1-(4-nitro-phenyl)-5-*p*-tolyl-pyrrolidin-2-one (5.16{3})**



Obtained as a yellow solid in a yield of 74%. ^{1}H NMR (500 MHz, $CDCl_3$): δ8.18 – 8.14 (m, 2H), 7.42 – 7.38 (m, 4H), 7.29 – 7.24 (m, 2H), 7.12 – 7.07 (m, 1H), 6.27 (d, 1H, J = 2.8 Hz), 5.47 (d, 1H, J = 2.5 Hz), 4.85 (d, 1H, J = 4.9 Hz), 2.84 – 2.77 (m, 1H), 1.43 (d, 3H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 144.1, 143.9, 143.7, 138.2, 136.5, 130.0, 125.8, 124.2, 121.5, 118.3, 68.4, 42.3, 21.0, 18.3. IR (CH_2Cl_2 microscope, cm^{-1}): 1706, 1333. HRMS (EI, m/z): Calcd for $C_{19}H_{18}O_3N_2$: 322.1317. Found: 322.1318.

***trans*-3-Methylene-1,5-bis-(4-nitro-phenyl)-pyrrolidin-2-one (5.16{4})**

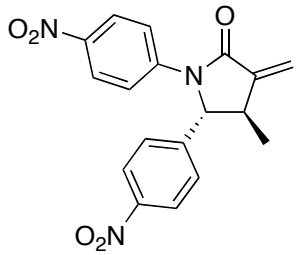


Obtained as an orange solid in a yield of 59%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 – 8.20 (m, 2H), 8.18 – 8.14 (m, 2H), 7.77 – 7.73 (m, 2H), 7.42 – 7.37 (m,

2H), 6.36 (app t, 1H, J = 2.7 Hz), 5.61 (app t, 1H, J = 2.4 Hz), 5.47 (dd, 1H, J = 9.2, 3.4 Hz), 3.51 (ddt, 1H, J = 16.8, 9.1, 2.8 Hz), 2.75 (ddt, 1H, J = 16.9, 3.3, 2.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 147.9, 147.8, 144.1, 143.4, 136.7, 126.4, 124.8, 124.7, 120.7, 120.6, 59.9, 34.5. IR (CH_2Cl_2 microscope, cm^{-1}): 1708, 1519, 1342. HRMS (EI, m/z): Calcd for $C_{17}H_{13}O_5N_3$: 339.0855. Found: 339.0856.

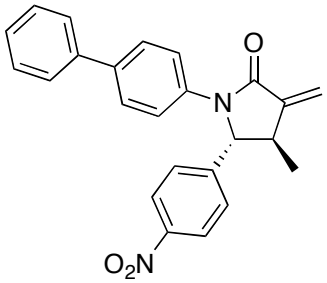
For the synthesis of compounds **5.16**{5} to 5.**16**{8}, γ-lactam **4.10** was used as a mixture of isomers (*cis* and *trans* in a ratio of ~1:2) and so the products exist as a ratio of isomers in a ~1:2 ratio. These isomers were not separable by HPLC, preparatory TLC or flash chromatography.

***trans*-4-Methyl-3-methylene-1,5-bis-(4-nitro-phenyl)-pyrrolidin-2-one (5.16{5})**



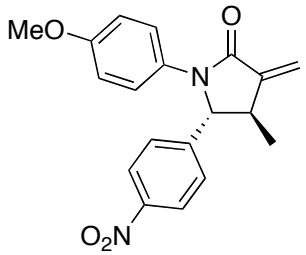
Obtained as an orange solid in a yield of 31% by HPLC purification. ^{1}H NMR (400 MHz, $CDCl_3$): (*trans* isomer) δ 8.24 – 8.18 (m, 2H), 8.17 – 8.12 (m, 2H), 7.69 – 7.64 (m, 2H), 7.43 – 7.38 (m, 2H), 6.35 (d, 1H, J = 2.7 Hz), 5.57 (d, 1H, J = 2.6 Hz), 4.90 (d, 1H, J = 5.0 Hz), 2.90 – 2.81 (m, 1H), 1.47 (d, 3H, J = 6.9 Hz). (*cis* isomer) δ 8.24 – 8.18 (m, 2H), 8.17 – 8.12 (m, 2H), 7.83 – 7.78 (m, 2H), 7.35 – 7.29 (m, 2H), 6.37 (d, 1H, J = 3.3 Hz), 5.48 (d, 1H, J = 3.1 Hz), 5.42 (d, 1H, J = 8.6 Hz), 3.58 – 3.50 (m, 1H), 0.87 (d, 3H, J = 7.1 Hz).

***trans*-1-Biphenyl-4-yl-4-methyl-3-methylene-5-(4-nitro-phenyl)-pyrrolidin-2-one (5.16{6})**



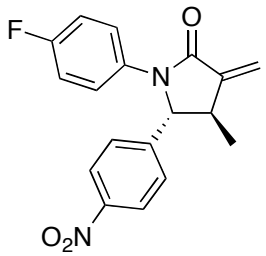
Obtained as a yellow solid in a yield of 29% by HPLC purification. ^{1}H NMR (400 MHz, $CDCl_3$): (*trans* isomer) δ 8.23 – 8.16 (m, 2H), 7.53 – 7.28 (m, 11H), 6.29 (d, 1H, *J* = 2.7 Hz), 5.49 (d, 1H, *J* = 2.3 Hz), 4.89 (d, 1H, *J* = 4.9 Hz), 2.87 – 2.79 (m, 1H), 1.45 (d, 3H, *J* = 7.2 Hz). (*cis* isomer) δ 7.65 – 7.60 (m, 2H), 7.53 – 7.28 (m, 11H), 6.31 (d, 1H, *J* = 3.3 Hz), 5.42 – 5.39 (m, 2H), 3.57 – 3.48 (m, 1H), 0.85 (d, 3H, *J* = 7.0 Hz).

***trans*-1-(4-Methoxy-phenyl)-4-methyl-3-methylene-5-(4-nitro-phenyl)-pyrrolidin-2-one (5.16{7})**



Obtained as a yellow solid in a yield of 17% by HPLC purification. ^{1}H NMR (400 MHz, $CDCl_3$): (*trans* isomer) δ 8.20 – 8.14 (m, 2H), 7.42 – 7.36 (m, 2H), 7.32 – 7.25 (m, 2H), 6.82 – 6.76 (m, 2H), 6.25 (d, 1H, *J* = 2.8 Hz), 5.45 (d, 1H, *J* = 2.6 Hz), 4.78 (d, 1H, *J* = 5.0 Hz), 3.73 (s, 3H), 2.85 – 2.76 (m, 1H), 1.42 (d, 3H, *J* = 7.0 Hz). (*cis* isomer) δ 8.20 – 8.14 (m, 2H), 7.42 – 7.36 (m, 2H), 7.32 – 7.25 (m, 2H), 6.82 – 6.76 (m, 2H), 6.26 (d, 1H, *J* = 3.2 Hz), 5.37 (d, 1H, *J* = 3.0 Hz), 5.30 (d, 1H, *J* = 8.4 Hz), 3.74 (s, 3H), 3.57 – 3.45 (m, 1H), 0.82 (d, 3H, *J* = 7.0 Hz).

***trans*-1-(4-Fluoro-phenyl)-4-methyl-3-methylene-5-(4-nitro-phenyl)-pyrrolidin-2-one (5.16{8})**

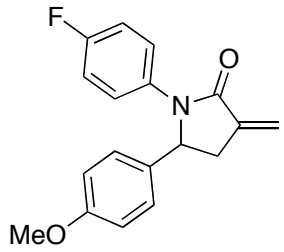


Obtained as a orange liquid in a yield of 24% by HPLC purification. ^{1}H NMR (400 MHz, $CDCl_3$): (*trans* isomer) δ 8.21 – 8.15 (m, 2H), 7.41 – 7.33 (m, 4H), 7.00 – 6.92 (m, 2H), 6.27 (d, 1H, *J* = 2.8 Hz), 5.48 (d, 1H, *J* = 2.5 Hz), 4.79 (d, 1H, *J* = 5.1 Hz), 2.86 – 2.77 (m, 1H), 1.43 (d, 3H, *J* = 7.1 Hz). (*cis* isomer) δ 8.21 – 8.15 (m, 2H), 7.52 – 7.46 (m, 2H), 7.32 – 7.28 (m, 2H), 7.00 – 6.92 (m, 2H), 6.29 (d, 1H, *J* = 3.3 Hz), 5.40 (d, 1H, *J* = 2.9 Hz), 5.31 (d, 1H, *J* = 8.3 Hz), 3.56 – 3.47 (m, 1H), 0.83 (d, 3H, *J* = 6.8 Hz).

5.6.13 General procedure for the synthesis of *N*-arylated α-methylene γ-lactams 5.17

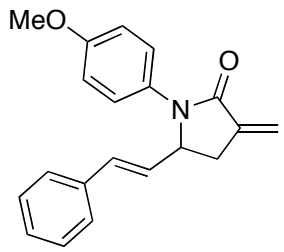
In a Trident synthesizer vessel, CuI (1.0 mg, 0.005 mmol), crude **5.15** (0.11 mmol) and K_3PO_4 (42 mg, 0.20 mmol) were combined under argon. Aryl iodide **5.7** (0.10 mmol) and *N*,*N*'-dimethylethylenediamine (1.1 μL, 0.01 mmol) were added, along with 1 mL toluene. The reaction mixture was heated to 80 ºC overnight with agitation on the parallel synthesizer. The resulting mixture was cooled, filtered through a short plug of Celite, washed with EtOAc and concentrated. The crude reaction mixture was purified by preparatory HPLC to give the desired compounds **5.17**.

1-(4-Fluoro-phenyl)-5-(4-methoxy-phenyl)-3-methylene-pyrrolidin-2-one (5.17{3,2})



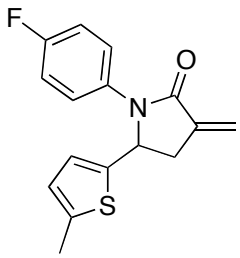
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 2H), 7.13 – 7.08 (m, 2H), 6.98 – 6.91 (m, 2H), 6.84 – 6.79 (m, 2H), 6.23 – 6.21 (m, 1H), 5.48 – 5.46 (m, 1H), 5.14 (dd, 1H, *J* = 8.6, 3.7 Hz), 3.76 (s, 3H), 3.36 (ddt, 1H, *J* = 17.0, 8.6, 2.8 Hz), 2.76 – 2.68 (m, 1H).

1-(4-Methoxy-phenyl)-3-methylene-5-styryl-pyrrolidin-2-one (5.17{20,3})



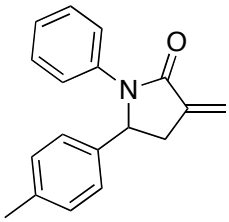
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.41 (m, 2H), 7.31 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 6.90 – 6.86 (m, 2H), 6.50 (d, 1H, *J* = 16.1 Hz), 6.16 (t, 1H, *J* = 2.6 Hz), 6.07 (dd, 1H, *J* = 16.1, 8.0 Hz), 4.77 (br td, 1H, *J* = 8.3, 4.0 Hz), 3.78 (s, 3H), 3.22 (ddt, 1H, *J* = 16.8, 8.3, 2.5 Hz), 2.72 (ddt, 1H, *J* = 16.8, 3.9, 2.4 Hz).

1-(4-Fluoro-phenyl)-3-methylene-5-(5-methyl-thiophen-2-yl)-pyrrolidin-2-one (5.17{41,2})



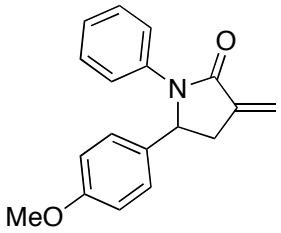
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 2H), 7.03 – 6.97 (m, 2H), 6.66 (d, 1H, *J* = 3.5 Hz), 6.49 (dq, 1H, *J* = 3.4, 1.1 Hz), 6.22 (br t, 1H, *J* = 2.8 Hz), 5.50 (br t, 1H, *J* = 4.9), 5.36 (dd, 1H, *J* = 8.5, 3.8 Hz), 3.37 (ddt, 1H, *J* = 17.0, 8.6, 2.8 Hz), 2.89 (ddt, 1H, *J* = 16.9, 3.7, 2.5 Hz), 2.39 (d, 1H, *J* = 1.1 Hz).

3-Methylene-1-phenyl-5-*p*-tolyl-pyrrolidin-2-one (5.17{2,1})



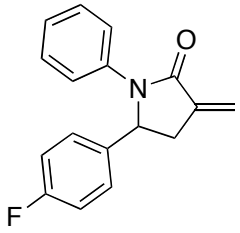
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 – 7.49 (m, 2H), 7.27 – 7.24 (m, 2H), 7.07 – 7.05 (m, 5H), 6.29 (t, 1H, *J* = 2.8 Hz), 5.45 (t, 1H, *J* = 2.5 Hz), 5.23 (dd, 1H, *J* = 8.5, 3.1 Hz), 3.41 – 3.32 (m, 1H), 2.74 – 2.67 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ167.6, 139.2, 138.7, 138.4, 137.6, 129.7, 128.7, 125.7, 125.1, 122.2, 117.4, 60.4, 35.6, 21.1. IR ($CDCl_3$ microscope, cm^{-1}): 3089, 1682, 1658. HRMS (EI, m/z): Calcd for $C_{18}H_{17}NO$: 263.13101. Found: 263.13094.

5-(4-Methoxy-phenyl)-3-methylene-1-phenyl-pyrrolidin-2-one (5.17{3,1})



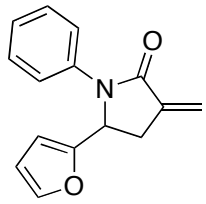
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 2H), 7.29 – 7.24 (m, 2H), 7.14 – 7.05 (m, 3H), 6.84 – 6.79 (m, 2H), 6.22 (t, 1H, *J* = 3.0 Hz), 5.46 (t, 1H, *J* = 2.2 Hz), 5.21 (dd, 1H, *J* = 8.6, 3.4 Hz), 3.76 (s, 3H), 3.36 (ddt, 1H, *J* = 16.6, 8.5, 2.6 Hz), 2.71 (dm, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 159.2, 139.2, 138.3, 133.7, 128.7, 127.0, 125.2, 122.3, 117.4, 114.4, 60.2, 55.2, 35.6. IR ($CDCl_3$ microscope, cm^{-1}): 1694, 1513. HRMS (EI, m/z): Calcd for $C_{18}H_{17}NO_2$: 279.1259. Found: 279.1258.

5-(4-Fluoro-phenyl)-3-methylene-1-phenyl-pyrrolidin-2-one (5.17{5,1})



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 2H), 7.30 – 7.24 (m, 2H), 7.21 – 7.15 (m, 2H), 7.12 – 7.07 (m, 1H), 7.01 – 6.94 (m, 2H), 6.24 (t, 1H, *J* = 2.9 Hz), 5.48 (t, 1H, *J* = 2.4 Hz), 5.26 (dd, 1H, *J* = 8.8, 3.5 Hz), 3.38 (ddt, 1H, *J* = 16.8, 8.9, 2.9 Hz), 2.70 (dm, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 161.0, 138.7, 138.1, 137.4, 128.8, 127.6, 127.5, 125.3, 122.3, 117.8, 116.2, 115.9, 115.0, 60.0, 35.5. IR ($CDCl_3$ microscope, cm^{-1}): 1697, 1509. HRMS (EI, m/z): Calcd for $C_{17}H_{14}NOF$: 267.1060. Found: 267.1057. ^{19}F NMR (100 MHz, $CDCl_3$): δ -114.5 ppm.

5-Furan-2-yl-3-methylene-1-phenyl-pyrrolidin-2-one (5.17{20,1})

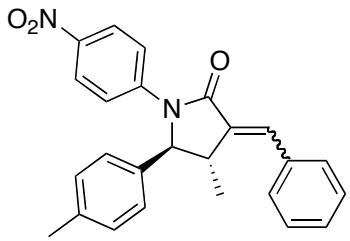


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 – 7.41 (m, 2H), 7.35 – 7.29 (m, 3H), 7.19 – 7.13 (m, 1H), 6.24 (dd, 1H, *J* = 3.3, 1.9 Hz), 6.22 (t, 1H, *J* = 2.5 Hz), 6.12 (d, 1H, *J* = 3.2 Hz), 5.50 (t, 1H, *J* = 2.6 Hz), 5.29 (dd, 1H, *J* = 8.8, 3.6 Hz), 3.27 (ddt, 1H, *J* = 16.8, 8.6, 2.7 Hz), 3.00 (dm, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 152.9, 142.5, 138.7, 138.0, 128.8, 125.8, 122.9, 117.5, 110.4, 107.9, 96.2, 54.7, 31.9. IR ($CDCl_3$ microscope, cm^{-1}): 1677, 1655, 1503. HRMS (EI, m/z): Calcd for $C_{15}H_{13}NO_2$: 239.0946. Found: 239.0944.

5.6.14 Synthesis of *N*-arylated α-alkylidene γ-lactam 5.18

In a parallel synthesizer vial, α-methylene γ-lactam **5.16**{3} (0.075 mmol), Cs_2CO_3 (61 mg, 0.19 mmol), palladium (II) acetate (1.1 mg, 0.005 mmol), triphenylphosphine (2.6 mg, 0.01 mmol) and iodobenzene (0.083 mmol) were combined. Acetonitrile (2 mL) was added, and the reaction vessel was put under an argon atmosphere. The reaction was put into the parallel synthesizer and heated for 12 h at 90 ºC with agitation. The crude reaction mixture was then filtered through a short pad of Celite and washed with EtOAc. The organic solvent was then removed to provide the crude product, which was purified by preparatory HPLC to provide **5.18** in a yield of 58% and a ratio of isomers of 2:1.

3-Benzylidene-4-methyl-1-(4-nitro-phenyl)-5-*p*-tolyl-pyrrolidin-2-one (5.18)

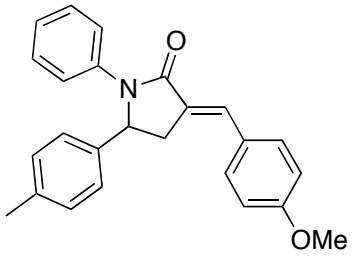


^{1}H NMR (400 MHz, $CDCl_3$): *trans* isomer: δ 8.19 – 8.73 (m, 2H), 7.94 – 7.88 (m, 2H), 7.63 (br s, 1H), 7.51 – 7.46 (m, 2H), 7.43 – 7.31 (m, 3H), 7.16 – 7.06 (m, 4H), 4.89 (s, 1H), 3.43 (br. q, 1H, *J* = 7.5 Hz), 2.30 (s, 3H), 1.51 (d, 3H, *J* = 7.1 Hz). *cis* isomer: δ 8.12 – 8.07 (m, 2H), 7.88 – 7.83 (m, 2H), 7.72 – 7.67 (m, 2H), 7.43 – 7.31 (m, 3H), 7.16 – 7.06 (m, 4H), 6.82 (d, 1H, *J* = 2.2 Hz), 4.78 (d, 1H, *J* = 4.5 Hz), 4.01 – 3.93 (m, 1H), 2.31 (s, 3H), 1.48 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): mixture of isomers: δ 169.0, 144.7, 144.3, 143.6, 143.4, 138.2, 137.5, 137.3, 136.6, 134.9, 134.6, 134.4, 134.1, 130.5, 130.1, 129.9, 129.4, 129.0, 128.9, 128.0, 125.8, 124.9, 124.5, 124.2, 121.5, 120.2, 119.6, 69.0, 68.0, 44.9, 41.3, 25.8, 21.2, 20.0, 19.6. IR ($CDCl_3$ microscope, cm^{-1}): mixture of isomers: 1698, 1514, 1327. HRMS (EI, m/z): Calcd for $C_{25}H_{22}N_2O_3$: 398.1631. Found: 398.1626.

5.6.15 General procedure for the synthesis of *N*-phenyl α-alkylidene γ-lactams 5.19

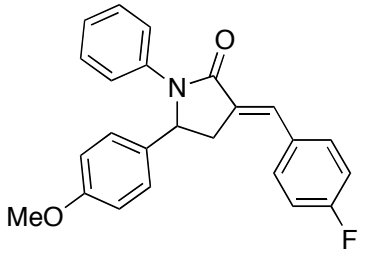
In a parallel synthesizer vial, *N*-phenyl α-methylene γ-lactams **5.17** (0.075 mmol), Cs_2CO_3 (61 mg, 0.19 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), PPh_3 (2.6 mg, 0.01 mmol) and aryl iodide **5.8** (0.083 mmol) were combined. Acetonitrile (2 mL) was added, and the reaction vessel was put under an argon atmosphere. The reaction was put into the parallel synthesizer and heated for 12 h at 90 ºC with agitation. The crude reaction mixture was then filtered through a short pad of celite and washed with EtOAc. The organics were then removed to provide the crude product, which was purified by preparatory HPLC.

3-(4-Methoxy-benzylidene)-1-phenyl-5-*p*-tolyl-pyrrolidin-2-one (5.19{2,1,3})



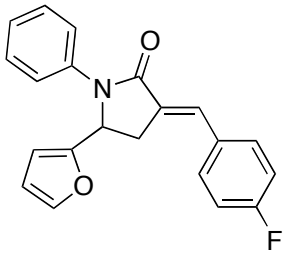
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.52 (m, 3H), 7.45 – 7.41 (m, 2H), 7.29 – 7.24 (m, 2H), 7.14 – 7.04 (m, 5H), 6.93 – 6.89 (m, 2H), 5.33 (dd, 1H, *J* = 8.9, 3.5 Hz), 3.83 (s, 3H), 3.65 (ddd, 1H, *J* = 17.2, 8.6, 2.9 Hz), 2.97 (dt, 1H, *J* = 17.1, 2.9 Hz), 2.28 (s, 3H). Ratio of desired product to by-product with internal alkene was 7:1 based on ^{1}H NMR integration of the methoxy peak.

3-(4-Fluoro-benzylidene)-5-(4-methoxy-phenyl)-1-phenyl-pyrrolidin-2-one (5.19{3,1,2})



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 – 7.50 (m, 3H), 7.49 – 7.44 (m, 2H), 7.30 – 7.22 (m, 2H), 7.17 – 7.13 (m, 2H), 7.11 – 7.05 (m, 2H), 6.83 – 6.78 (m, 2H), 5.32 (dd, 1H, *J* = 8.5, 3.4 Hz), 3.74 (s, 3H), 3.64 (ddd, 1H, *J* = 17.4, 8.7, 2.9 Hz), 2.97 (dt, 1H, *J* = 17.5, 3.3 Hz), 2.28 (s, 3H). Ratio of desired product to by-product with internal alkene was 6:1 based on ^{1}H NMR integration of the proton α to the nitrogen.

3-(4-Fluoro-benzylidene)-5-furan-2-yl-1-phenyl-pyrrolidin-2-one (5.19{20,1,2})



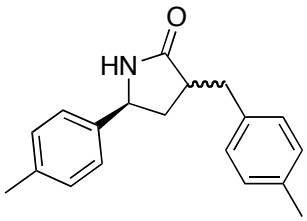
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (t, 1H, *J* = 2.7 Hz), 7.53 – 7.45 (m, 4H), 7.37 – 7.31 (m, 3H), 7.20 – 7.15 (m, 1H), 7.14 – 7.09 (m, 2H), 6.24 (dd, 1H, *J* = 3.4, 1.9 Hz), 6.14 (dm, 1H), 5.40 (dd, 1H, *J* = 8.8, 3.5 Hz), 3.55 (ddd, 1H, *J* = 17.0, 8.5, 2.8 Hz), 3.26 (dt, 1H, *J* = 17.3, 3.1 Hz). Ratio of desired product to by-product with internal alkene was 10:1 based on ^{1}H NMR integration of the proton α to the nitrogen.

5.6.16 Procedures for the synthesis of α-alkylated γ-lactams 5.20

5.6.16.1 α-Alkyl γ-lactam 5.20a

A microwave vessel was loaded with **5.15**{2} (19 mg, 0.1 mmol), *p*-tolylboronic acid (54 mg, 0.4 mmol), Rh(COD)(acac) (1.2 mg, 0.004 mmol), racemic BINAP (3.7 mg, 0.006 mmol), boric acid (25 mg, 0.4 mmol) and 1 mL 1,4-dioxane. The vessel was capped and irradiated at 100 ºC for 6 h. The crude reaction mixture was loaded onto a column and purified by flash chromatography with no work-up using 50% EtOAc/hexanes as the eluant. The *trans* product was isolated in a yield of 14% and the *cis* product in a yield of 36%. Also, 5 mg (26%) of **15**{2} was recovered.

3-(4-Methyl-benzyl)-5-*p*-tolyl-pyrrolidin-2-one (5.20a)



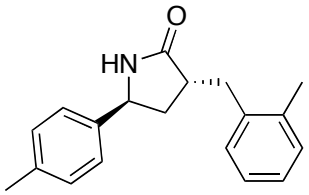
(*cis* isomer) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 – 7.12 (m, 2H), 7.10 – 7.05 (m, 6H), 5.73 (br s, 1H), 4.55 (dd, 1H, *J* = 9.2, 6.8 Hz), 3.28 (dd, 1H, *J* = 13.8, 4.0 Hz), 2.84 – 2.75 (m, 1H), 2.68 (dd, 1H, *J* = 13.8, 9.8 Hz), 2.52 – 2.45 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 1.66 (ddd, 1H, *J* = 13.0, 10.8, 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 139.0, 137.8, 136.3, 135.8, 129.5, 129.2, 128.8, 125.8, 56.1, 44.2, 38.4, 36.2, 21.1, 21.0. HRMS (EI, m/z): Calcd for $C_{19}H_{21}NO$: 279.1623. Found: 279.1625.

(*trans* isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 – 7.07 (m, 2H), 5.72 (br s, 1H), 4.49 (dd, 1H, *J* = 8.2, 4.3 Hz), 3.17 (dd, 1H, *J* = 14.1, 4.3 Hz), 2.87 – 2.80 (m, 1H), 2.73 (dd, 1H, *J* = 13.5, 9.3 Hz), 2.36 – 2.30 (m, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.17 (ddd, 1H, *J* = 13.0, 8.7, 4.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 139.6, 137.5, 135.9, 129.5, 129.2, 128.9, 125.3, 55.4, 41.7, 36.6, 36.2, 21.0. HRMS (EI, m/z): Calcd for $C_{19}H_{21}NO$: 279.1623. Found: 279.1623.

5.6.16.2 α-Alkyl γ-lactams 5.20

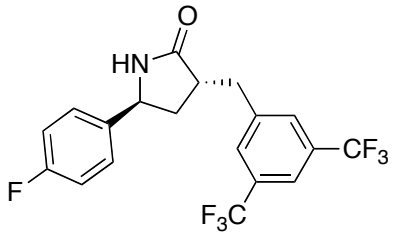
α-Methylene γ-lactam **5.15** (0.1 mmol), arylboronic acid **5.13** (0.40 mmol), Rh(COD)(acac) (1.2 mg, 0.004), *rac*-BINAP (3.7 mg, 0.006 mmol), boric acid (25 mg, 0.40 mmol) and 1 mL 1,4-dioxane were added to a microwave vessel, which was put under argon. The vessel was capped, then irradiated for 4 h at 100 °C. The crude reaction mixture was filtered through a short pad of celite, rinsed with EtOAc and concentrated. The crude mixture was purified by preparatory HPLC to provide the desired compounds as a mixture of *cis* and *trans* isomers, which were not separated.

3-(2-Methyl-benzyl)-5-*p*-tolyl-pyrrolidin-2-one (5.20{2,3})



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.09 (m, 8H), 5.86 (br s, 1H), 4.57 (dd, 1H, *J* = 9.2, 6.4 Hz), 3.45 (dd, 1H, *J* = 14.3, 3.9 Hz), 2.86 – 2.77 (m, 1H), 2.66 – 2.58 (m, 1H), 2.54 – 2.46 (m, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 1.65 (ddd, 1H, *J* = 12.7, 11.0, 9.2 Hz). Ratio of *cis* to *trans* diastereomers was 5.5:1 based on ^{1}H NMR integration of the proton α to the nitrogen.

3-(3,5-Bis-trifluoromethyl-benzyl)-5-(4-fluoro-phenyl)-pyrrolidin-2-one (5.20{5,6})



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (br s, 1H), 7.66 (br s, 2H), 7.20 – 7.13 (m, 2H), 7.08 – 6.99 (m, 2H), 6.04 (br s, 1H), 4.64 (dd, 1H, *J* = 9.1, 6.5 Hz), 3.45 – 3.36 (m, 1H), 2.95 – 2.82 (m, 2H), 2.61 – 2.52 (m, 1H), 1.67 – 1.54 (m, 1H). Ratio of *cis* to *trans* diastereomers was 6.7:1 based on ^{1}H NMR integration of the nitrogen proton.

5.6.17 Purity table for 20 library members and compounds 5.16{5-8}

Of the 20 library members chosen at random for additional analysis, 80% of the compounds tested had a purity >90%. These 20 library members represent approximately 10% of the complete library. As stated in Section 5.6.1, the *Journal of Combinatorial Chemistry* requires 5% of library members or 20 compounds (whichever is greater) to be further characterized for proof of concept and confirmation of purity. As a result, not all compounds were fully characterized.

Entry	Compound number	Percent purity by UV at 254 nm (%)
1	**5.3**{4}	97.7
2	**5.3**{11}	92.4
3	**5.3**{32}	96.5
4	**5.9**{2,3}	76.1
5	**5.9**{3,3}	92.6
6	**5.9**{5,4}	87.9
7	**5.14**{3,4}	23.3
8	**5.14**{4,6}	89.2
9	**5.14**{6,3}	84.4
10	**5.15**{5}	99.5
11	**5.15**{27}	95.2
12	**5.15**{42}	99.5
13	**5.17**{3,2}	99.5
14	**5.17**{20,3}	99.5
15	**5.17**{41,2}	98.9
16	**5.19**{2,1,3}	86.1
17	**5.19**{3,1,2}	96.9
18	**5.19**{20,1,2}	94.6
19	**5.20**{2,3}	91.4
20	**5.20**{5,6}	95.4
21	**5.16**{5}	97.6
22	**5.16**{6}	97.6
23	**5.16**{7}	98.9
24	**5.16**{8}	99.5

Table 5.12: Purity table for various library members

5.6.18 Biochemical screening for inhibition of homoserine transacetylase

The primary screening was performed in a Molecular Devices SpectraMAX Plus spectrophotometer using a 384-well flat-bottom polystyrene microtiter plates. The HTA activity was determined by monitoring the production of CoA because of the increase in absorbance at 324 nm upon the titration of 4,4′-dithiodipyridine (DTDP $\varepsilon_{324\ nm}$ = 19800 $M^{-1}cm^{-1}$). The reaction volume was 50 μL. Assays were performed in 50 mM HEPES (pH 8.0) containing 0.001% Tween 20, 200 μM *L*-Hse, 2 mM DTDP, and 300 μM acetylCoA. The reaction was started by the addition (5 μL) of enzyme that was preincubated with the compounds. The preincubation mix was in 50 mM HEPES (pH 8.0) containing 8 μg/mL HTA, 100 M inhibitor and 10% DMSO. Three different preincubation times (15, 70, and 200 min) with HTA were tested. The positive compounds were rescreened in the same way to confirm the inhibitory activity. For IC50 determination, a dilution series was performed starting with 500 μM as the highest concentration. The inhibitors were preincubated with HTA for 30 min. From this, IC50 values were calculated from linear extrapolation of reaction velocity as a function of the logarithmic of concentration.

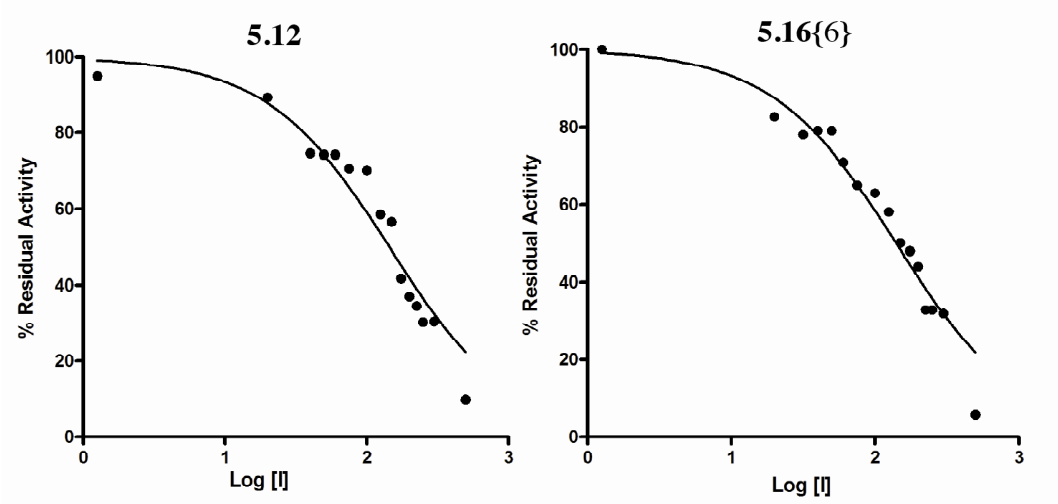


Figure 5.10: IC_{50} graphs for **5.18** and **5.16**{6}

5.7 References

[1] Merrifield, R.B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

[2] Hoffmann, H.M.R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94-110.

[3] (a) Hughes, M. A.; McFadden, J. M.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3857-3859. (b) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601-7607. (c) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198-8199. (d) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967-5971.

[4] Le Lamer, A.-C.; Gouault, N.; David, M.; Boustie, J. Uriac, P. *J. Comb. Chem.* **2006**, *8*, 643-645.

[5] a) Kennedy, J.W.J.; Hall, D.G. *J. Org. Chem.* **2004**, *69*, 4412-4428. b) Yu, S.H.; Ferguson, M.J.; McDonald, R.; Hall, D.G. *J. Am. Chem. Soc.* **2005**, *127*, 12808-1280. c) Elford, T.G.; Arimura, Y.; Yu, S.H.; Hall, D.G. *J. Org. Chem.* **2007**, *72*, 1276-1284.

[6] Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Org. Lett.* **2006**, *8*, 3877-3879.

[7] For example, see: a) Feling, R.H.; Buchanan, G.O.; Mincer, T.J.; Kauffman, C.A.; Jensen, P.R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355-357. b) Zhu, X.Z.; Li, X.-Y.; Liu, J. *Eur. J. Pharmacol.* **2004**, *500*, 221-230. c) Schwartz, R.E.; Helms, G.L.; Bolessa, E.A.; Wilson, K.E.; Giacobbe, R.A.; Tkacz, J.S.; Bills, G.F.; Liesch, J.M.; Zink, D.L.; Curotto, J.E.; Pramanik, B.; Onishi, J.C. *Tetrahedron* **1994**, *50*, 1675-1686.

[8] For example, see: a) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117-118. b) Macherla, V.R.; Mitchell, S.S.; Manam, R.R.; Reed, K.A.; Chao, T.-H.; Nicholson, B.; Deyanat-Yazdi, G.; Mai, B.; Jensen, P.R. Fenical, W.F.; Neuteboom, S.T.C.; Lam, K.S.; Palladino, M.A.; Potts B.C.M. *J. Med. Chem.* **2005**, *48*, 3684-3687. c) Xu, L.; Liu, S.-L.; Zhang, J.-T. *Chirality* **2005**, *17*, 239-244.

[9] A version of this chapter has been published: Elford, T.G.; Ulaczyk-Lesanko, A.; De Pascale, G.; Wright, G.D.; Hall, D.G. *J. Comb. Chem.* **2009**, *11*, 155-168.

[10] a) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320-2322. b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series 9; Pergamon: Oxford, **1992**. c) Gibson, S.E.; Keen, S.P. In *Alkene Metathesis in Organic Synthesis*; Furstner, A. Ed.; Springer Berlin/Heidelberg, **1999**. d) Mortia, K., Suzuki, Z., Hirose, H. *Bull. Chem. Soc. Jap.* **1968**, *41*, 2815.

[11] a) Raju, R. and Howell, A.R. *Org. Lett.* **2006**, *8*, 2139-2141. b) Raju, R.; Allen, L.J.; Le, T.; Taylor, C.D.; Howell, A.R. *Org. Lett.* **2007**, *9*, 1699-1701.

[12] Moise, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 1695-1698.

[13] For reviews, see: a) Heck, R.F. *Acc. Chem. Res.* **1979**, *12*, 146-151. b) Crisp, G.T. *Chem. Soc. Rev.* **1998**, *27*, 427-436. c) Beletskaya, I.P.; Cheprakov, A.V. *Chem. Rev.* **2000**, *100*, 3009-3066. d) Whitcombe, N.J.; Hii, K.K.; Gibson, S.E. *Tetrahedron* **2001**, *57*, 7449-7476. e) van der Boom, M.E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759-1792. f) Dounay, A.B. and Overman, L.E. *Chem. Rev.* **2003**, *103*, 2945-2963.

[14] a) Arcadi, A.; Chiarini, M.; Marinelli, F.; Berente, Z.; Kollar, L. *Eur. J. Org. Chem.* **2001**, 3165-3173. b) Li, J.-H.; Wang, D.-P.; Xie, Y.-X. *Synthesis* **2005**, *13*, 2193-2197. c) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett.* **2001**, *3*, 3313-3316. d) Farrington, E.J.; Brown, J.M.; Barnard, C.F.J.; Rowsell, E. *Angew. Chem.* **2002**, *114*, 177-179. e) Lindh, J.; Enquist, P.-A.; Pilotti, A.; Nilsson, P.; Larhed, M. J. *Org. Chem.* **2007**, *72*, 7957-7962. f) Li, L.-S.; Rader, C.; Matsushita, M.; Das, S.; Barbas, C.F. III; Lerner, R.A.; Sinha, S.C. *J. Med. Chem.* **2004**, *47*, 5630-5640. g) Li, H.J. and Wang, L. *Eur. J. Org. Chem.* **2006**, 5099-5102. h) Reetz, M.T.; de Vries, J.G. *Chem. Commun.* **2004**, 1559-1563. i) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron*, **2001**, *57*, 9711-9718.

[15] Jeffery, T. *Tetrahedron* **1996**, *52*, 10113-10130.

[16] a) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279-3281. b) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229-4231. c) Yoshida, K and Hayashi, T. In *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Hall, D.G. Ed.; Wiley-VCH: Weinheim, **2005** and references cited within. d) Tomioka, K. and Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Ed.; Springer-Verlag: New York, **1999** e) Krause, N. and Hoffmann-Roder, A. *Synthesis* **2001**, 171-196. f) Sibi, M.P. and Manyem, S. *Tetrahedron* **2000**, *56*, 8033-8061.

[17] Frost, C.G.; Penrose, S.D.; Lambshead, K.; Raithby, P.R; Warren, J.E.; Gleave, R. *Org. Lett.* **2007**, *9*, 2119-2122.

[18] a) Reddy, L. R.; Saravanan, P.; Corey, E. J. J. Am. Chem. Soc. **2004**, 126, 6230-6231. b) Reddy, L.R.; Fournier, J.-F.; Subba Reddy, B.V.; Corey, E.J. *J. Am. Chem. Soc.* **2005**, *127*, 8974-8976. c) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765-7768. d) Lettan, R.B. *II*.; Woodward, C.C.; Scheidt, K.A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2294-2297.

[19] Elford, T.G., Hall, D.G. *Tetrahedron Lett.* **2008**, *49*, 6995-6998.

[20] Selected examples: a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742-8743. b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120-4121. c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727-7729. d) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421-7428.

[21] Sakuma, S., Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944-8946

[22] Born, T. L.; Franklin, M.; Blanchard, J. S. *Biochemistry* **2000**, *39*, 8556-8564.

[23] Umbarger, H. E. *Annu. Rev. Biochem.* **1978**, *47*, 532-606.

[24] Nazi, I.; Wright, G. D. *Biochemistry* **2005**, *44*, 13560-13566.

[25] Mirza, I. A.; Nazi, I.; Korczynska, M.; Wright, G. D.; Berghuis, A. M. *Biochemistry* **2005**, *44*, 15768-15773.

[26] Frere, J. M.; Duez, C.; Ghuysen, J. M.; Vandekerkhove, J. *FEBS Lett*. **1976**, *70*, 257-260.

[27] Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D. W.; Aplin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J. *Biochemistry* **1999**, *38*, 7989-7998.

[28] Reid, C. S.; Zhang, Y.; Li, C.-J. *Org. Biomol. Chem*. **2007**, *5*, 3589-3591.

[29] Hon, Y.-S.; Liu, Y.-W.; Hsieh, C.-H. *Tetrahedron* **2004**, *60*, 4837-4860.

Chapter 6

Target-Oriented Synthesis: An Allyboration/ Lactonization Strategy for the Total Synthesis of Chinensiolide B

6.1 Introduction[1]

α-Methylene γ-lactones are highly privileged structures that are present in a large number of natural products (*cf*. Figure 1.1).[2] As the number of natural products that contain an α-methylene γ-lactone group continues to grow, more and more interest is being shown in these compounds due to their unique biological properties. One family of natural products that contain α-methylene γ-lactones as a part of their 5,7,5-ring structures is the chinensiolides. There are five members of this family of sesquiterpenes that have been isolated and characterized to date, and their structures are shown in Figure 6.1. The chinensiolide family of natural products are isolated from Rabbit Milkweed (*Ixeris chinensis Nakai),* a perennial plant that grows in various parts of China.[3,4] The plant is used in Chinese folk medicine for the treatment of bronchitis, pneumonia, pharyngitis, dysentery, and poisonous indigestion on the basis of its antifebrile, antidotal, and analgesic effects. Despite their interesting biological properties, there have been no total syntheses of any of the chinensiolides to date. As well, the absolute configuration for these natural products has not been confirmed.

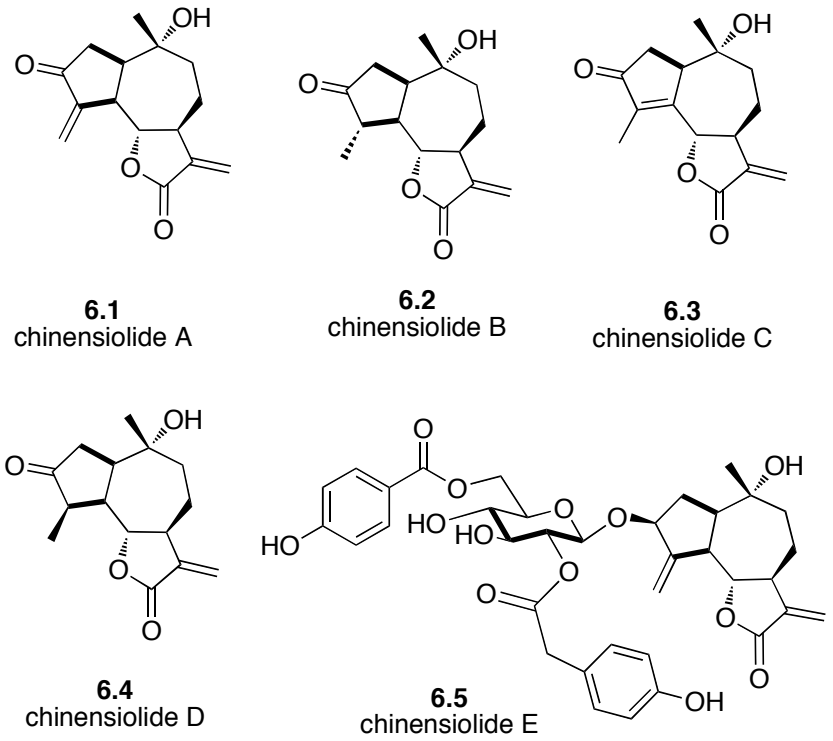


Figure 6.1: Family of chinensiolides

Very few studies have been reported that evaluate the biological importance of this family of natural products. It has been shown, however, that some of the chinensiolides, along with a few closely related analogues (Figure 6.2) display cytotoxic behavior against human primary liver cancer (HepG2) and two human lung fibroblasts (WI-38 and VA-13) cell lines (Table 6.1).[5] However, cytotoxic specificity of these compounds is yet to be explored.

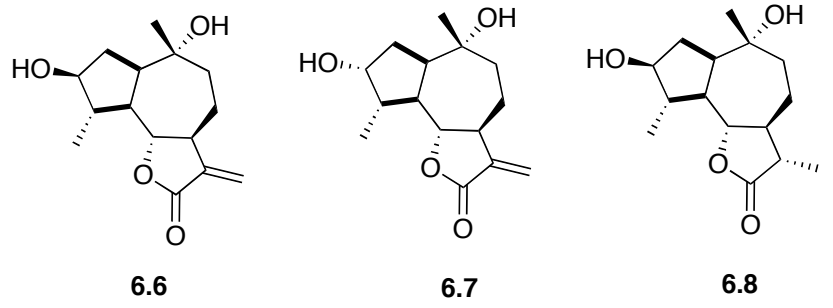


Figure 6.2: Analogues of chinensiolide B[5]

Compound	HepG2 (μM)	WI-38 (μM)	VA-13 (μM)
6.2	26.5	0.34	26.8
6.3	23.0	24.0	22.0
6.5	140	23.0	0.72
6.6	23.9	1.69	23.4
6.7	22.7	0.33	3.30
6.8	24.2	1.94	21.0
paclitaxel	8.09	0.005	0.040

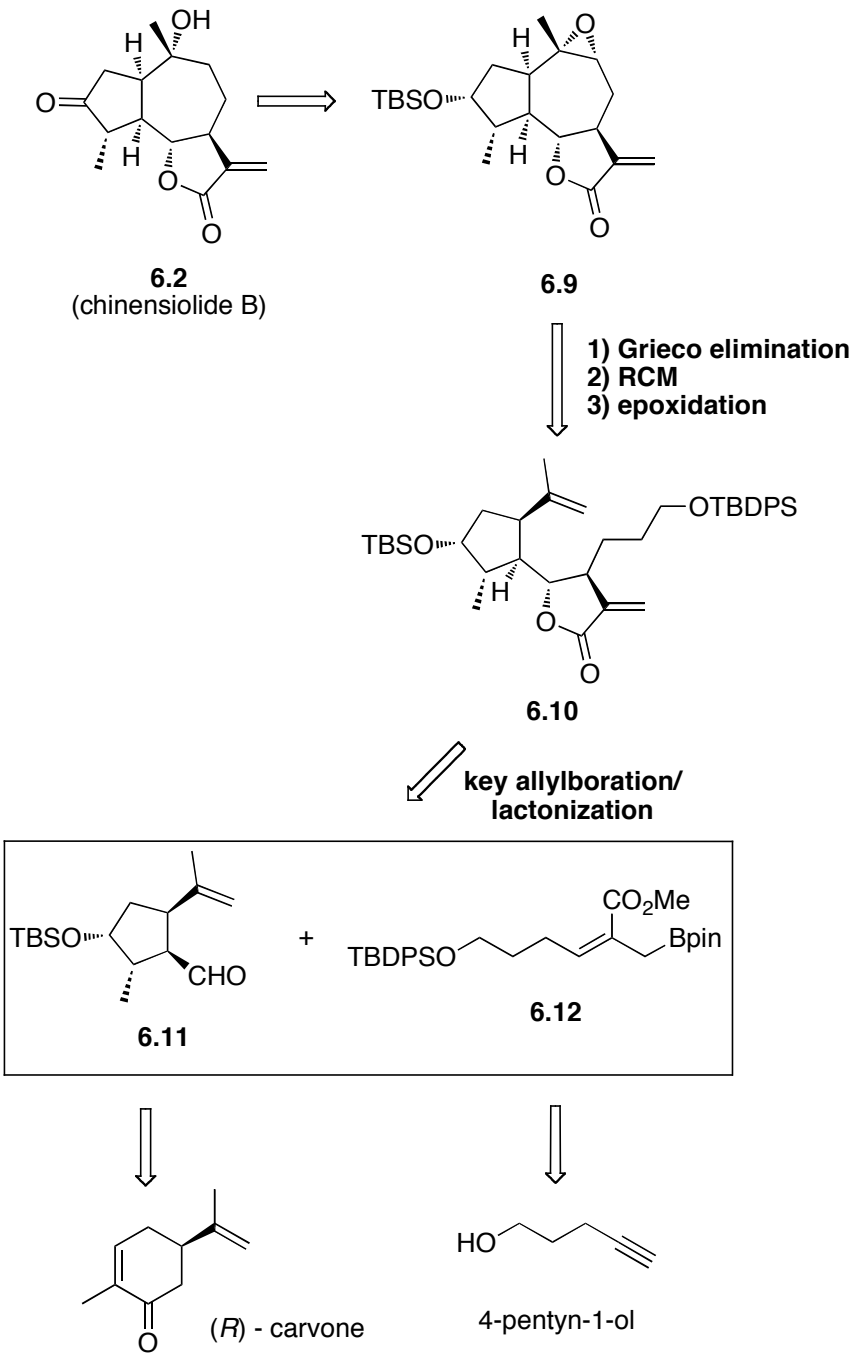
Table 6.1: IC_{50} values for various chinensiolides and analogues

These cytotoxicities are not as potent at the control (paclitaxel, Table 6.1); however, these results are promising in that other derivatives could possess better activity profiles. Futhermore, paclitaxel has various associated side effects, such as nausea and vomiting, loss of appetite, change in taste, thinned or brittle hair, pain in the joints of the arms or legs, changes in the color of the nails, and tingling in the hands or toes.[6] More serious side effects such as unusual bruising or bleeding, pain/redness/swelling, change in normal bowel habits, fever, chills, cough, sore throat, difficulty swallowing, dizziness, shortness of breath, severe exhaustion, skin rash, facial flushing and chest pain can also occur.[6] Any new drugs or compounds that display high potency but have limited side effects are always advantageous. Thus, the synthesis of natural products that show promising bioactivity allows for routes that can later be exploited to access analogues that may be more suitable as drugs.

My interest in α-methylene γ-lactone natural products results from my background studies on the Lewis and Brønsted acid-catalyzed addition of 2-alkoxycarbonyl allylboronates to aldehydes,[7] as discussed in Chapter 2. Through a tandem allylboration/lactonization protocol, highly substituted α-methylene γ-lactones can be synthesized in one step. To test the efficiency with which complex targets could be assembled through this protocol, I undertook the challenge of synthesizing chinensiolide B (**6.2**). Facile access to the core structure of chinensiolide B would allow for various analogues to be made in a future project with the potential to find more bioactive compounds through screening of these new molecules.

6.2 Retrosynthetic analysis of chinensiolide B

In performing a retrosynthetic analysis (Scheme 6.1) on chinensiolide B (**6.2**), there are a few key points that make this target a challenging prospect. First, **6.2** contains five contiguous stereocenters along a flexible seven-member ring. Second, the sixth stereocenter may be subject to epimerization due it being adjacent to a ketone. Third, the α-methylene γ-lactone itself is a very reactive center, and reactions carried out after installation of this moiety must be carefully chosen to avoid possible side reactions. Finally, installation of a tertiary alcohol in a diastereoselective fashion is not always straightforward. With these potential issues in mind, I envisioned that chinensiolide B could be accessed from advanced intermediate **6.9** via a regioselective reductive epoxide opening of the epoxide and oxidative cleavage of the TBS protecting group. This intermediate epoxide **6.9** would arise from a desilylation/elimination, followed by ring-closing metathesis and diastereoselective epoxidation of **6.10**, which in turn would arise directly from the tandem allylboration/lactonization methodology that has been discussed in previous chapters utilizing highly functionalized coupling partners: aldehyde **6.11** and allylboronate **6.12**. Introduction of the reactive α-methylene γ-lactone this early in the synthetic strategy allowed for the convergence of this strategy, however, it could be seen as unwise due to severe chemoselectivity issues later on in the synthetic sequence. Regardless of this apprehension, it could be imagined that aldehyde **6.11** could be accessed from (*R*)-carvone through a Favorskii rearrangement.[8] Allylboronate **6.12** could be synthesized in three steps from 4-pentyn-1-ol.

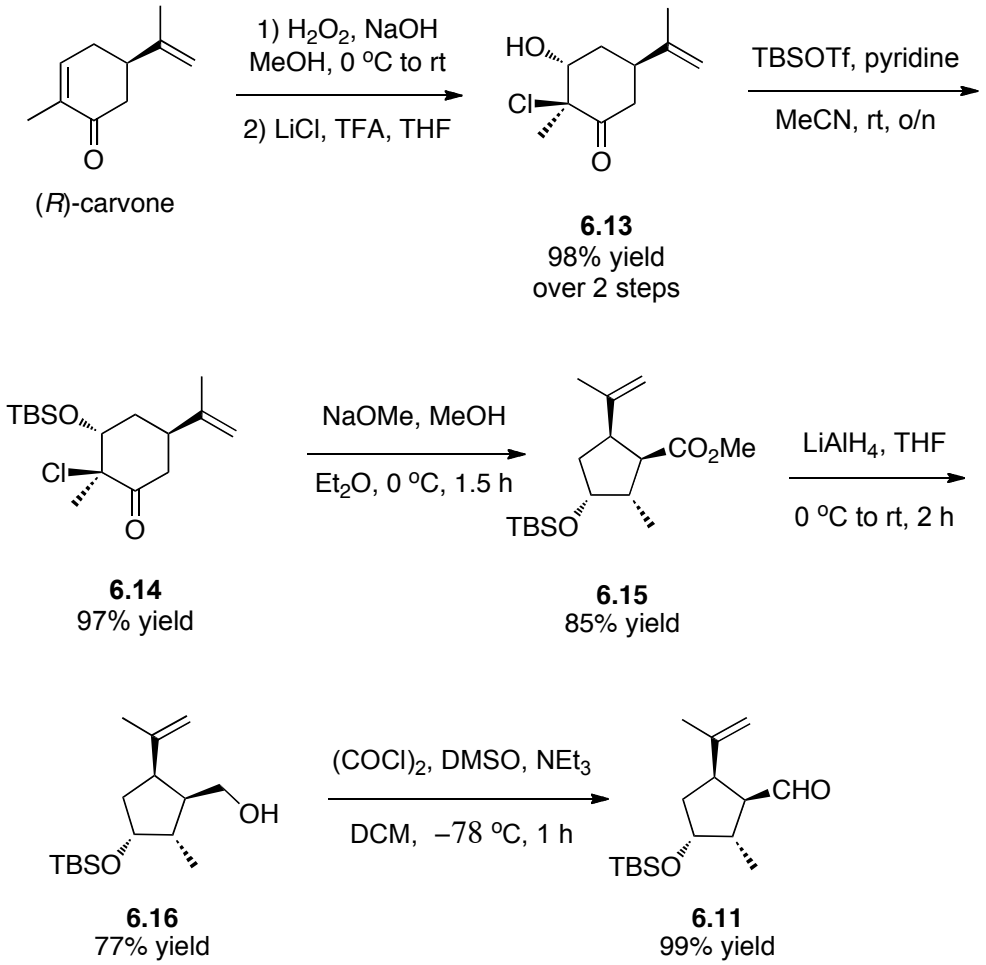


Scheme 6.1: Retrosynthetic analysis for chinensiolide B (**6.2**)

6.3 Total synthesis of chinensiolide B

6.3.1 Synthesis of aldehyde 6.11

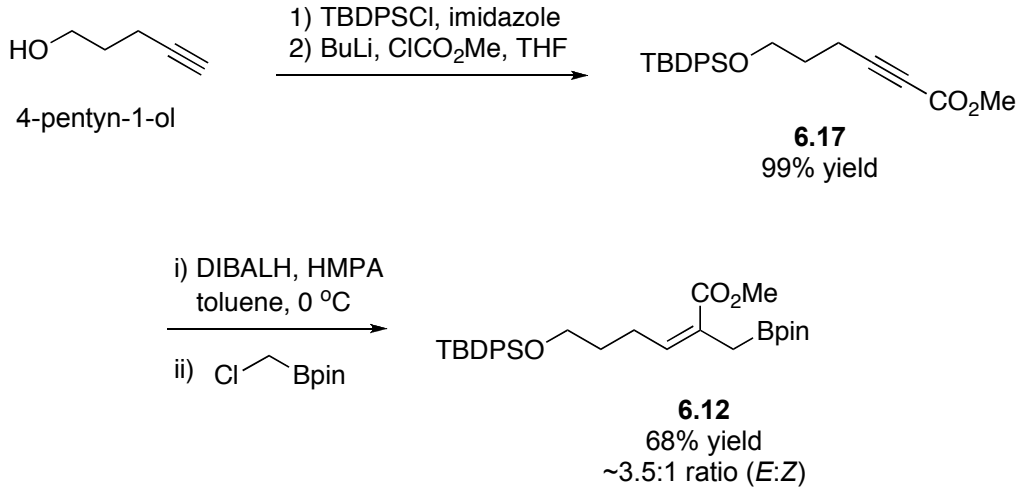
The synthesis of the required aldehyde **6.11** began by following a two-step protocol reported by Ley and co-workers to convert carvone into ketone **6.13**.[9] After obtaining ketone **6.13** from (*R*)-carvone, TBS protection of the secondary alcohol led to intermediate **6.14**. This reaction was followed by a Favorskii rearrangement to provide the desired tetrasubstituted cyclopentane **6.15** in an excellent yield of 85%. The ester functionality in **6.15** was reduced with $LiAlH_4$ to give product **6.16** and subsequently reoxidized under Swern conditions[10] to provide key aldehyde **6.11**.



Scheme 6.2: Synthesis of aldehyde **6.11** from (*R*)-carvone

6.3.2 Synthesis of allylboronate 6.12

The synthesis of allylboronate **6.12** began by following a two-step procedure[11] that provided propiolic ester **6.17** in 99% yield from 4-pentyn-1-ol after flash chromatography. Conversion of propiolic ester **6.17** to allylboronate **6.12** was achieved through a DIBALH-mediated reduction[12] of the triple bond followed by electrophilic quench with chloromethylpinacolboronate.[13] Unfortunately, allylboronate **6.12** could only be synthesized as a mixture of alkene isomers (*Z*:*E* ratio of ~3.5:1) and the isomers could not be easily separated on larger scale. As a result, the mixture of isomers was used in the allylboration step.

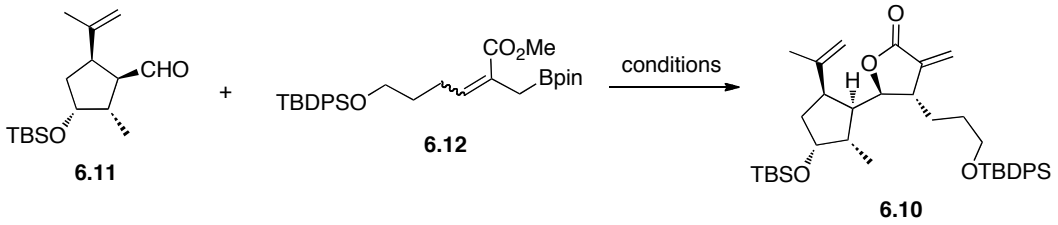


Scheme 6.3: Synthesis of allylboronate **6.12** from 4-pentyn-1-ol

6.3.3 Allylboration reaction between allylboronate 6.12 and aldehyde 6.11

Now that the two key fragments had been made, it was time to attempt the key allylboration/lactonization step. Initially, the thermal reaction was investigated and it was discovered that conversion was slow and after three and a half days, the reaction was only 66% completed (entry 1, Table 6.2). Triflic acid was investigated as a catalyst; however, only starting materials were isolated

when the reaction was performed at 0 ºC (entry 2), and the aldehyde decomposed when the reaction was performed at room temperature (entry 3). Scandium (III) triflate was also investigated with similarly poor results (entry 4). However, when BF_3•OEt_2 was used as the catalyst, the desired reaction occurred quite readily at room temperature (entry 5). Lowering the catalyst loading from 20 to 2.5 mol% and the reaction temperature from 23 ºC to 0 ºC provided the optimal conditions (entry 7).



Entry	Catalyst	Loading (mol%)	Temp (ºC)	Time (h)	Conversion[a] (%)
1	none	n/a	90	84	66
2	TfOH	20	0	16	0
3	TfOH	20	23	16	0
4	$Sc(OTf)_3$	10	23	48	10
5	BF_3•OEt_2	20	23	16	100
6	BF_3•OEt_2	5	0	24	100
7	BF_3•OEt_2	2.5	0	48	100

[a] Conversion was determined by ^{1}H NMR of the crude reaction mixture.

Table 6.2: Screening of conditions for allylboration/lactonization reaction

Using 2.5 mol% of BF_3•OEt_2 at 0 ºC for 48 hours provided the desired γ-lactone product **6.10** in an exceptional yield of 87% (based on the amount of *Z*-**6.12** used) and with complete diastereoselectivity. This observed selectivity (>95% dr) was completely unexpected, as a possible four isomers could be expected from this reaction mixture. However, allylboronate *Z*-**6.12** reacted in a completely diastereoselctive fashion with aldehyde **6.11** to provide only one diastereomer. Furthermore, allylboronate *E*-**6.12** proved to be essentially inert to the reaction conditions and could be isolated again after the reaction. Thus, of four possible products, only the desired *trans* γ-lactone was obtained and possessed the correct relative stereochemistry that is present in chinensiolide B

(see Section 6.3.4 for proof of stereochemistry). The *trans* diastereoselectivity in the allylboration step can be explained with the usual six-member chairlike transition state for this reaction (**A**, Figure 6.3). The chairlike transition state for this allylboration reaction also explains why *E*-**6.12** is drastically slower to react, since there are significant *syn*-pentane interactions in the corresponding Zimmerman–Traxler transition state (**B**, Figure 6.3). The remarkable diastereofacial selectivity in the reaction of *Z*-**6.12** with **6.11** can be rationalized according to Felkin model **C** depicted in Figure 6.3. These two results are quite surprising, but nonetheless, very satisfying.

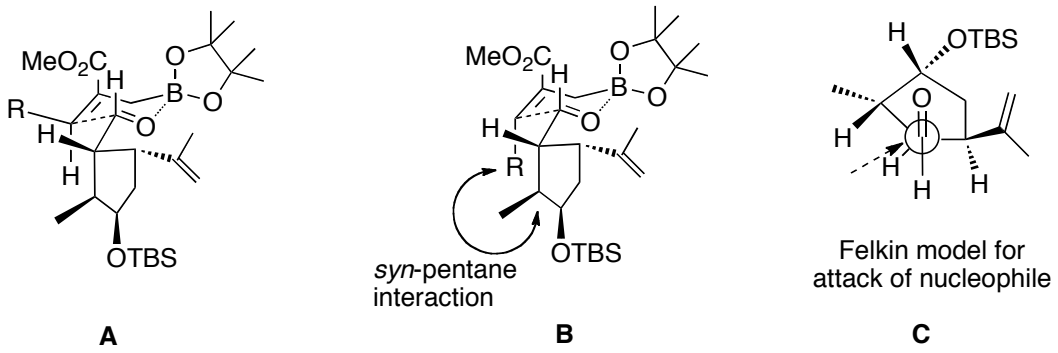
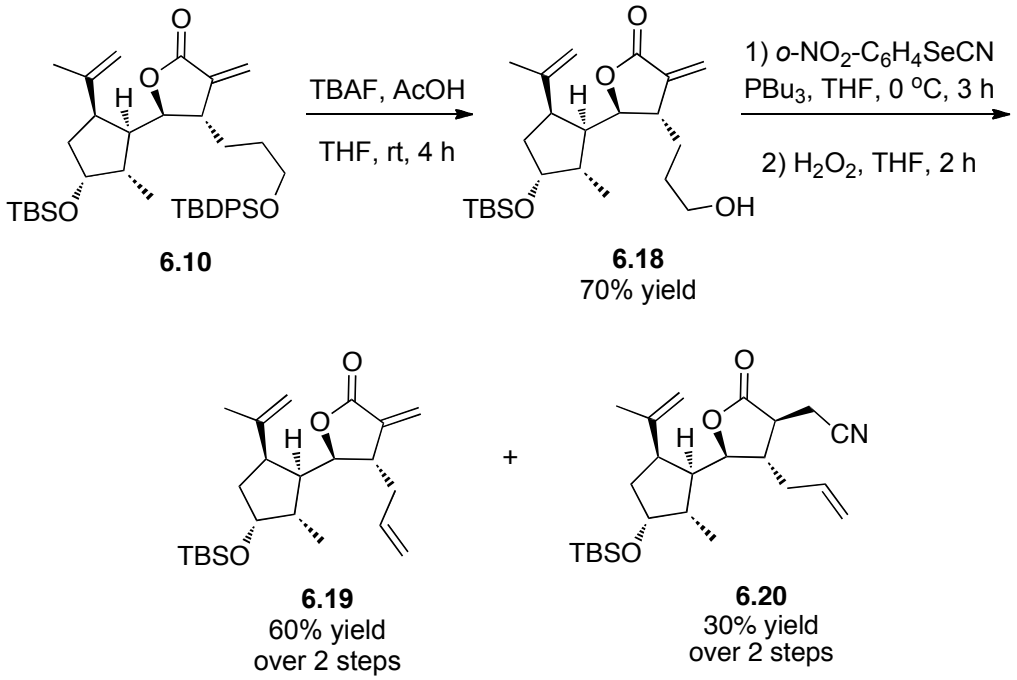


Figure 6.3: Rationale for observed stereoselectivity during the formation of **6.10**

6.3.4 Completion of the synthesis of chinensiolide B

Once allylboration product **6.10** had been synthesized, selective deprotection[14] of the primary TBDPS group in the presence of the secondary TBS protected alcohol was carried out using buffered TBAF to provide alcohol **6.18** in a yield of 70% (Scheme 6.4). A Grieco elimination[15] on the primary alcohol of **6.18** was performed to afford desired triene **6.19**, albeit with a moderate yield of 60% for the two steps.



Scheme 6.4: Selective deprotection and Grieco elimination to provide triene **6.19**

Careful control on the stoichiometry of the selenium reagent and tributylphosphine was important during the Grieco elimination. As mentioned earlier, the *exo*-methylene on the γ-lactone is a very reactive center for nucleophiles. If excess reagents are used, or if the reaction was performed at room temperature, conjugate addition of the cyanide anion or selenium reagent was rapid. This led to a considerable amount of by-product **6.20** (Scheme 6.4), where the cyanide anion had undergone conjugate addition to the enoate. Fortuitously, this by-product proved to be crystalline and allowed for an X-ray crystal structure to be obtained (Figure 6.4).[16]

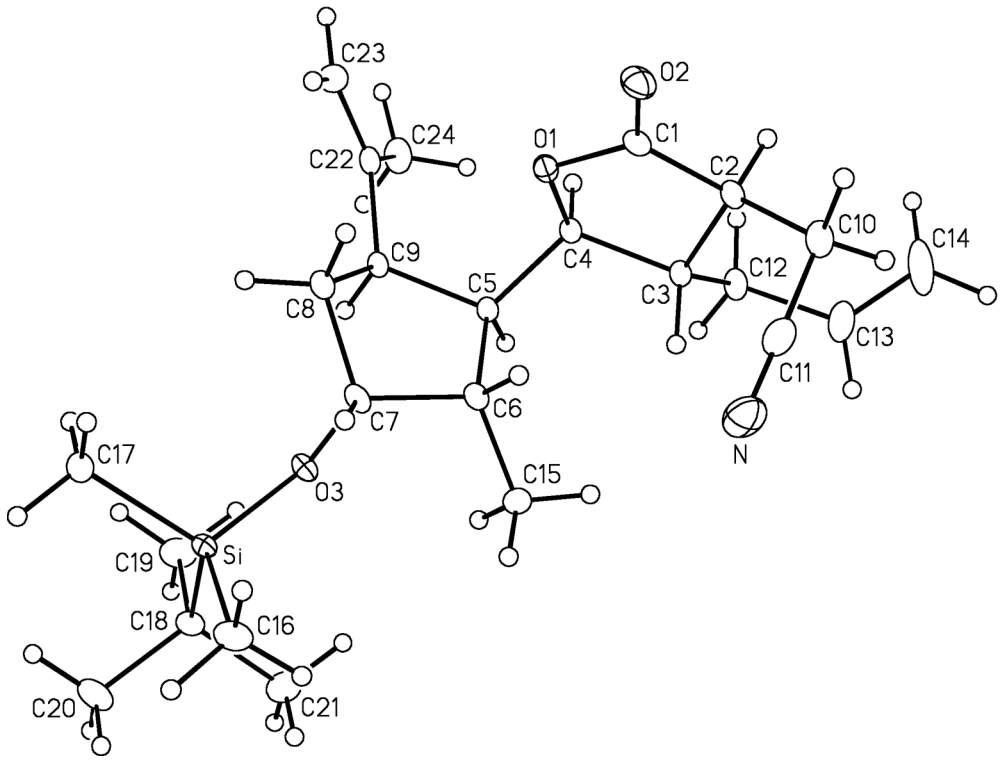
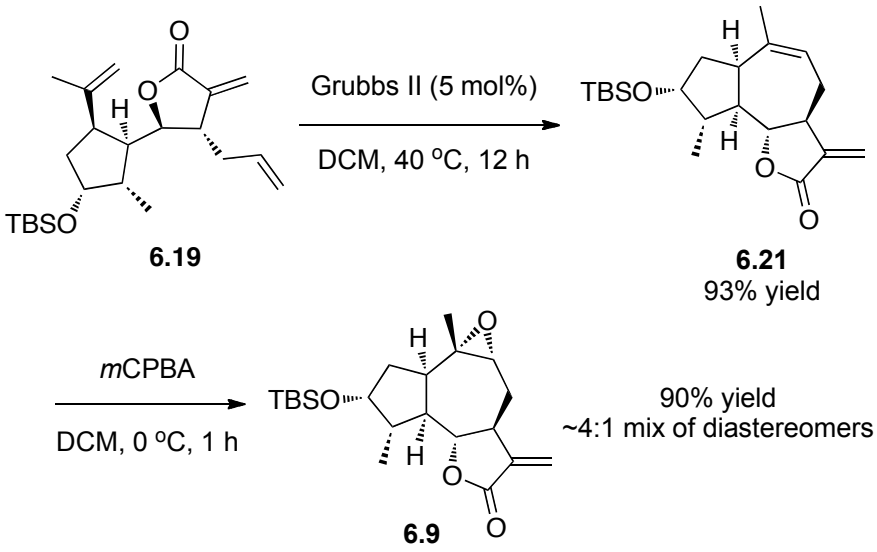


Figure 6.4: ORTEP diagram of crystal structure for **6.20**

Although this by-product was undesired and could not be avoided, it did allow for conclusive proof that the allylboration reaction did indeed provide the desired diastereomer that was required to complete the synthesis. Various NMR correlation experiments performed previously had been inconclusive in determining the relative stereochemistry of the allylboration/lactonization step.

In principle, the ring-closing metathesis of **6.19** would furnish the final seven-member ring of chinensiolide B. Formation of medium sized rings can be problematic, especially when the final product is tri- or tetrasubstituted,[17] however, there are several examples where cross-metathesis has been successful in achieving this feat.[18] One additional point of chemoselectivity that arises, though, is the coupling of two different alkenes in the presence of a third alkene. In other words, ring-closing metathesis to form the requisite seven-member ring must be chemoselective and avoid the reactivity of the α-methylene γ-lactone unit that could also participate to give four- or six-member rings. In spite of my apprehensions about this step, by using 10 mol% of Grubbs II catalyst, the desired

ring-closing metathesis was successfully achieved in 12 h. The ring-closing metathesis was then attempted with only 5 mol% of catalyst, and this also provided the desired product with an excellent yield of 93% and a reaction time of 12 h (Scheme 6.5). Most likely, the steric bulk around the α-methylene and formation of a bridgehead olefin suppressed cross-metathesis at this alkene and allowed for the desired ring-closing metathesis to proceed uncontested. This strategy proves to be quite effective for accessing the core structure of the chinensiolide family.

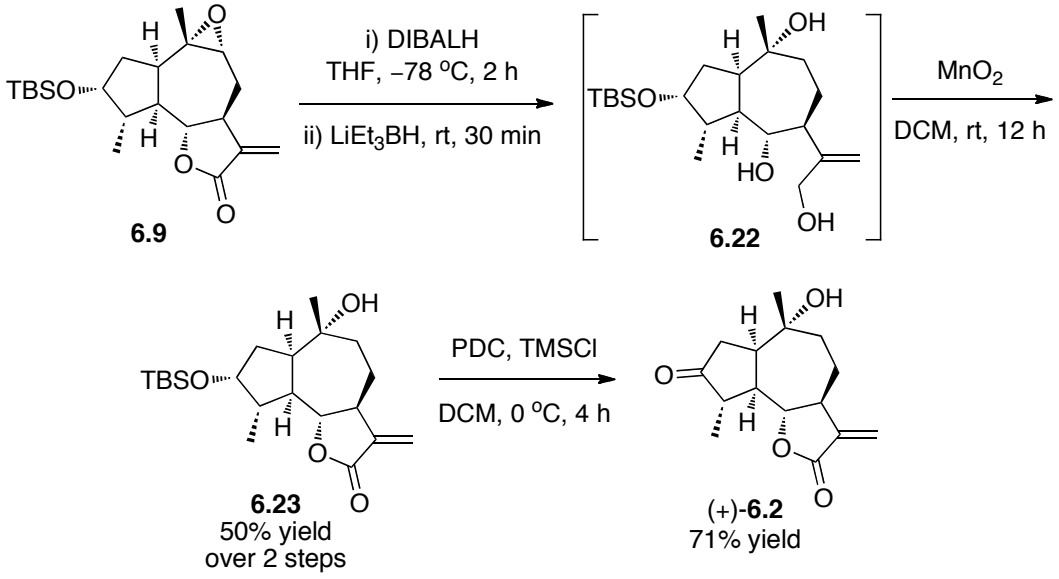


Scheme 6.5: Ring-closing metathesis and alkene epoxidation of γ-lactone **6.19**

The final stages of the synthesis involve the diastereoselective epoxidation of this newly formed alkene. Again, the issue of chemoselectivity arose due to the presence of the α-methylene γ-lactone. Nucleophilic epoxidation reagents or conditions could not be used due to the electrophilic nature of the γ-lactone. Similar substrates in the literature have been epoxidized in a chemo- and diastereoselectively fashion using either AcOOH or *m*CPBA. First attempts at the epoxidation with AcOOH proved to be futile, as none of the desired epoxide was obtained and only starting materials were isolated after work-up. However, with *m*CPBA as the epoxidizing agent, **6.21** could be successfully epoxidized to give

intermediate **6.9** as a mixture of diastereomers (~4:1 mixture) favoring the desired one (Scheme 6.5). Unfortunately, all attempts to separate the diastereomers were unsuccessful, and as such, were carried through to the next step as such.

Regioselective opening of epoxides to give Markovnikov products is typically achieved through the use of nucleophilic hydride reagents such as $LiAlH_4$ or $LiEt_3BH$.[19] However, as one would expect, over-reduction of the γ-lactone occurs with $LiAlH_4$ to give the fully saturated triol and conjugate reduction of the α-methylene group occurs preferentially to epoxide opening with $LiEt_3BH$. Many other reducing agents were also tested for their ability to open the epoxide selectively with no success. What proved ultimately successful, though, was a one-pot double reduction protocol whereby the γ-lactone of **6.9** was reduced with DIBALH *in situ*, then further reacted with $LiEt_3BH$ to regio- and chemoselectively open the epoxide (Scheme 6.6). Treatment of crude product **6.22** with MnO_2 allowed for reoxidation to occur, thus easily reforming the α-methylene γ-lactone unit. As well, the two diastereomers present at the end of this reduction/oxidation sequence (arising from the epoxidation step) could now be separated to provide the desired γ-lactone **6.23**. Although not ideal as far as step-count is concerned (two steps to reductively open an epoxide), it shows that the extreme reactivity of the α-methylene γ-lactone can be circumvented by temporarily altering its oxidation state. Finally, oxidative cleavage of the secondary TBS protecting group on **6.23** to reveal the desired ketone functionality in one step was achieved through the use of PDC in the presence of TMSCl,[20] thus completing the synthesis of (+)-chinensiolide B (**6.2**).



Scheme 6.6: Reductive epoxide-opening and oxidative TBS-cleavage to provide (+)-**6.2**

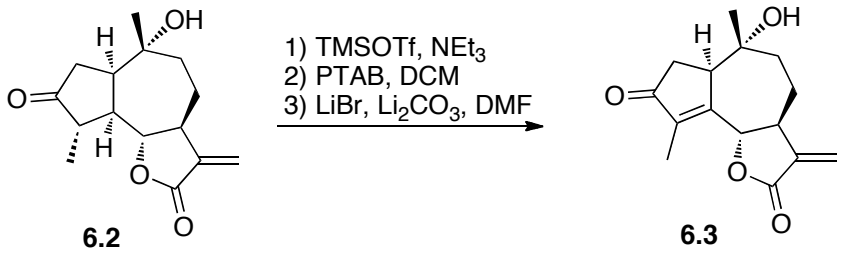
Once synthetic **6.2** was obtained, a comparison of the ^{1}H and ^{13}C NMR spectroscopic peak listings was performed. However, the spectral data for synthetic **6.2** did not match that reported in the original isolation paper.[3] The ^{1}H NMR data for synthetic **6.2** had some of the peaks that were close in chemical shift (within 0.1 ppm) to the reported values, however, others were quite different in chemical shift (0.5 ppm). The ^{13}C NMR spectrum also had some peaks that were identical in chemical shift and others that were different (>1 ppm difference). Chinensiolide B is known to be somewhat flexible due to the seven-member ring; however, on the time-scale of ^{1}H NMR spectroscopy, this was irrelevant.[3] The HRMS and IR data for synthetic **6.2** confirmed my compound as having the correct molecular formula and functional groups, so it was suggested that epimerization of one of the stereocenters had occurred to give a diastereomer of **6.2**. I was not convinced of this possibility. I contacted the corresponding author of the isolation paper (Professor Masayoshi Ando), and to my surprise, learned that the solvent listed for the NMR analysis in the isolation paper was wrong. Instead of the stated solvent ($CDCl_3$), according to Prof. Ando, the NMR analysis had actually been done using pyridine-d_5 as the solvent! After dissolving

synthetic **6.2** in pyridine-d_5 and repeating the NMR experiments, the ^{13}C NMR spectrum was now a match and the ^{1}H NMR spectrum was also a match except for one peak. The peak listed at 2.27 ppm in the isolation paper was not present in my ^{1}H NMR spectra for synthetic **6.2**. Instead, I had an extra peak at 2.76 ppm. However, upon looking at the actual copy of the ^{1}H NMR spectrum obtained from Prof. Ando for natural **6.2**, it was realized that the listing of peaks in the ^{1}H NMR description in the isolation paper was also wrong! The ^{1}H NMR spectrum showed a peak at 2.76 ppm and no peak at 2.27 ppm as well as a peak at 1.84 ppm and not two at 1.36 ppm. There were, in fact, two errors in the isolation paper with the listing the chemical shift for this proton. So, to my relief, the ^{1}H NMR spectra for natural **6.2** and synthetic **6.2** were an unambiguous match once the same solvents for the NMR analysis were used and the errors in chemical shift were noted.

All that was left to be done was confirmation of the optical rotation of synthetic **6.2**. At this point, it needs to be stated that in carrying out this total synthesis, I had been using an old bottle marked (*S*)-carvone as the starting material. Thus, I was intentionally preparing the antipode of natural **6.2**. This choice was justified by the convenience of having a large bottle of (*S*)-carvone on hand in the laboratory. When I submitted synthetic **6.2** for optical rotation, I was expecting to see a result that had a negative optical rotation. To my surprise, the optical rotation came back positive. This unexpected optical rotation result indicated one of two things. Either the isolation paper had the wrong absolute stereochemistry of natural **6.2** or my synthesis was actually of the natural enantiomer. This latter explanation seemed outrageous at first, since the bottle was labelled as (*S*)-carvone and the crystal structure of by-product **6.21** had confirmed the absolute stereochemistry. Again, a minor detail that had been omitted from the discussion until this point proved to be the guiding light. When the crystal structure of **6.21** was obtained, it had actually suggested that the absolute stereochemistry was opposite to what I had proposed. The crystal structure pointed to an absolute stereochemistry that would correspond to the postulated stereochemistry of natural **6.2** as stated in the isolation paper. However, because there were no “heavy atoms” in the molecule and the

stereochemistry of the (*S*)-carvone was known, then the crystal structure was fixed to correspond to what was expected. This minor detail, which had been previously rationalized due to large experimental error in the crystal structure data by Dr. Bob McDonald, proved to be significant in that it indicated there might be a problem in the synthesis and not in the isolation paper. In particular, the bottle that was labelled as (*S*)-carvone and was assumed to be (*S*)-carvone might not actually contain (*S*)-carvone. After smelling the contents of the bottle and obtaining an optical rotation for the contents of the bottle ($[\alpha]_D$ = –61 (neat)), it was realized that the bottle in fact contained (*R*)-carvone (literature value for $[\alpha]_D$ = –61 (neat)). Thus, the starting material for my total synthesis was indeed (*R*)-carvone, which corresponded to a synthesis of the natural enantiomer of **6.2**. Once this discovery was made, the sign of the observed optical rotation for synthetic **6.2** made sense and did indeed match the optical rotation for natural **6.2**. As a result, I did complete a total synthesis of the natural enantiomer of **6.2** and confirmed the absolute stereochemistry and structure of natural chinensiolide B (**6.2**).

This successfully completed total synthesis of chinensiolide B (**6.2**) was accomplished with a sequence of 15 steps for the longest linear sequence and had a total overall yield of 6.7% starting from cheap and readily available (*R*)-carvone. This work constitutes the first total synthesis of any of the chinensiolide family of natural products. Furthermore, it has been shown that chinensiolide B obtained from natural sources can be converted into chinensiolide C in three steps (Equation 6.1).[3] As a consequence, this total synthesis of chinensiolide B also constitutes the first formal total synthesis of chinensiolide C in a total of 18 steps for the longest linear sequence.



Equation 6.1: Conversion of **6.2** to **6.3** as reported by Ando and co-workers[3]

6.4 Conclusions

The disclosed route to (+)-chinensiolide B is the first total synthesis of any member of the chinensiolide family. It also confirms the absolute stereochemistry of chinensiolides B and C. The synthetic sequence makes use of a stereoselective and *E*/*Z*-selective allylboration reaction between two highly functionalized partners as a key step to form two of the required stereocenters in one step. This total synthesis also highlights the chemoselectivity issues that arise with such a reactive functional group as the α-methylene γ-lactone, and how milder reagents or alternative strategies were utilized to bring about the desired transformations. This synthetic route also employs a ring-closing metathesis step to form the requisite seven-member ring, again in a chemoselective fashion that avoids the reactivity of the α-methylene γ-lactone unit. This study also brings to light some of the issues that can arise when data that is reported in the literature is either misrepresented or wrong. Further studies towards the total synthesis of the remaining members of the chinensiolide family would be important in showing the utility of this route to access a wide range of substrates. The synthesis and biological testing of derivatives of this family of natural products would also be an important area to explore and might help in the ongoing search for new drugs with better performance and less side effects.

6.5 Experimental

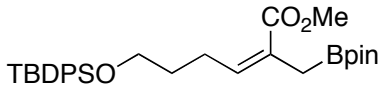
6.5.1 General information

Unless otherwise noted, all reactions were performed under an argon atmosphere. Toluene, HMPA, CH_3CN and CH_2Cl_2 were distilled over CaH_2. THF was distilled over sodium/ benzophenone ketyl. NH_4Cl(aq) and $NaHCO_3$(aq) refer to saturated aqueous solutions. All other chemicals were used as received from commercial sources. Thin layer chromatography (TLC) was performed on

Macherey–Nagel Polygram Sil G/UV_{254} plates and was visualized with UV light, potassium permanganate stain or Seebach's stain. NMR spectra were recorded on 300, 400, 500 or 600 MHz instruments as indicated in procedures. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards. ^{1}H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra and optical rotations were recorded by the University of Alberta Spectral Services Laboratory.

6.5.2 Experimental procedures

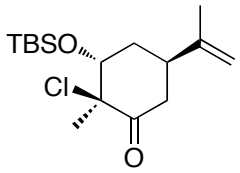
(*Z*)-Methyl 6-((tert-butyldiphenylsilyl)oxy)-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl)hex-2-enoate (*Z*-12)



To a solution of HMPA (10.0 mL, 6.0 equiv) in toluene (100 mL) under argon at 0 ºC was added DIBALH (10.0 mL, 1.5 M solution in toluene, 1.5 equiv). This mixture was left to stir for 1 h, at which point, known propiolic ester derivative **6.17**[11] (3.81 g, 1.0 equiv) was added. The mixture was stirred for 5 h at 0 ºC, then freshly distilled chloromethylpinacolboronate[13] was added. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with 1M HCl and extracted with Et_2O (x4). The combined organic extracts were washed with 1M HCl (x3), $NaHCO_3$(aq) (x2), water and brine. The organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (3% EtOAc/DCM) to provide allylboronate **6.12** as a mixture of alkene isomers (3.92 g, 68% yield). The major isomer was the desired one and was often obtained in a ratio >3.5:1. The mixture of isomers was used for the next step as separation on large scale was

difficult and the minor isomer does not react in the next step of the synthesis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 – 7.63 (m, 4H), 7.45 – 7.33 (m, 6H), 5.92 (t, 1H, *J* = 7.6 Hz), 3.69 (s, 3H), 3.68 (t, 2H, *J* = 6.5 Hz), 2.60 (q, 2H, *J* = 7.8 Hz), 1.82 (br s, 2H), 1.68 (app p, 2H, *J* = 7.3 Hz), 1.23 (s, 12H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 142.9, 135.6, 134.1, 129.5, 128.1, 127.6, 83.3, 63.6, 51.2, 32.5, 26.9, 26.4, 24.8, 19.3. ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.1. IR ($CDCl_3$, cast film, cm^{-1}): 3071, 2932, 1722. HRMS (EI, m/z) Calcd for $C_{26}H_{34}O_5Si^{35}B^{11}$ $[M-C_4H_9]^+$: 465.2269. Found: 465.2281.

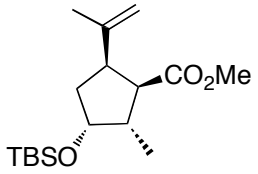
(2*S*,3*R*,5*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-2-methyl-5-(prop-1-en-2-yl) cyclohexanone (6.14)



Known alcohol **6.13**[21] (127.8 mmol, 1.00 equiv) was dissolved in 150 mL acetonitrile and cooled to 0 ºC under argon. To this stirred solution was added pyridine (12.4 mL, 1.20 equiv) followed by *tert*-butyldimethylsilyltrifluoro-methane sulfonate (32.3 mL, 1.10 equiv). The reaction solution was then warmed to rt and allowed to stir overnight. The reaction was then quenched by the addition of NH_4Cl(aq) and the mixture was extracted with EtOAc (x3). The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude product **6.14** was obtained as a colorless oil and was pure enough by ^{1}H NMR to be used without further purification (39.5 g, 97% yield). $[\alpha]_D$ = +60.5 (*c* 0.34, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 (br s, 1H), 4.76 (br s, 1H), 4.19 (dd, 1H, *J* = 3.5, 1.9 Hz), 3.04 (dd, 1H, *J* = 14.0, 14.0 Hz), 2.83 (app tt, 1H, *J* = 12.5, 3.4 Hz), 2.42 (ddd, 1H, *J* = 14.3, 12.6, 2.0 Hz), 2.35 (ddd, 1H, 13.5, 3.7, 2.2 Hz), 1.84 – 1.73 (m, 1H), 1.75 (s, 3H), 1.60 (s, 3H), 0.87 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 146.7, 110.4, 77.9, 68.2, 41.1, 39.2, 33.7, 25.7, 23.0, 20.4, 18.0, –4.5, –4.9. IR ($CDCl_3$,

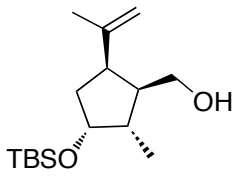
cast film, cm^{-1}): 2957, 2936, 1729. HRMS (EI, m/z) Calcd for $C_{12}H_{20}O_2Si^{35}Cl$ [M-C_4H_9]$^+$: 259.0921. Found: 259.0920.

(1*R*,2*S*,3*R*,5*R*)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentanecarboxylate (6.15)



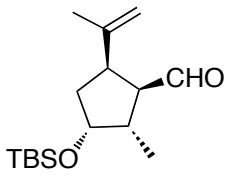
Sodium hydride (3.23 g, 1.5 equiv, 60 wt% in oil) was washed with pentane and then suspended in 60 mL dry methanol at 0 ºC under argon. Crude TBS-protected alcohol **6.14** (53.9 mmol) was dissolved in dry ether at 0 ºC under argon, and to this solution was added the sodium methoxide/methanol solution by cannula. The reaction was left to stir at 0 ºC for 1.5 h, then quenched with 30 mL NH_4Cl(aq) and 10 mL water. The reaction was warmed to rt and stirred vigorously for 1 h. The mixture was then extracted with Et_2O (x3) and the combined organics were washed with brine. The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. THF (100 mL) was added to help removed methanol during concentration. Product **6.15** was obtained as an orange oil and was essentially pure by ^{1}H NMR spectroscopy and could be used without further purification (14.34 g, 85% yield). $[\alpha]_D$ = –20.5 (*c* 1.00, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$): δ 4.78 (br s, 1H), 4.70 (br s, 1H), 4.17 (dd, 1H, *J* = 3.9, 3.9 Hz), 3.60 (s, 3H), 3.20 (ddd, 1H, *J* = 10.5, 10.5, 7.0 Hz), 2.82 (dd, 1H, *J* = 10.1, 9.3 Hz), 2.48 – 2.34 (m, 1H), 2.01 – 1.90 (m, 1H), 1.78 – 1.68 (m, 1H), 1.73 (s, 3H), 0.98 (d, 3H, *J* = 7.3 Hz), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2, 145.5, 111.2, 75.5, 53.3, 51.1, 46.5, 43.2, 40.1, 25.8, 22.5, 18.1, 14.3, –4.7, –5.0. IR ($CDCl_3$, cast film, cm^{-1}): 2956, 2931, 1738. HRMS (ESI, m/z) Calcd for $C_{17}H_{33}O_3Si$ [M+H]$^+$: 313.2194. Found: 313.2190.

((1*R*,2*S*,3*S*,5*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentyl) methanol (6.16)



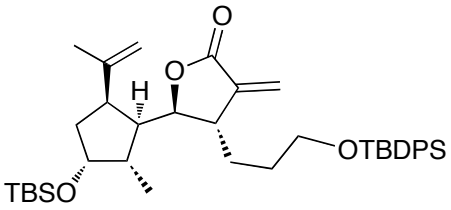
Crude ester **6.15** (45.9 mmol) was dissolved in 150 mL THF and cooled to 0 ºC under argon. $LiAlH_4$ (1.82 g, 1.00 equiv) was added slowly to the reaction mixture. The reaction was stirred at 0 ºC for 1 h, then warmed to rt and stirred for an additional 1 h. The reaction was quenched by slowly adding water and EtOAc until all the bubbling stopped. The reaction mixture was then filtered through a pad of Celite and concentrated *in vacuo*. THF was used to help co-evaporate the water in the mixture. This provided **6.16** as a white solid that was pure enough by ^{1}H NMR spectroscopy to be used without further purification (10.11 g, 77% yield). $[\alpha]_D$ = –17.5 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.90 (br s, 1H), 4.81 (br s, 1H), 4.12 (dd, 1H, *J* = 3.6, 3.6 Hz), 3.56 (dd, 1H, *J* = 11.6, 4.8), 3.49 (dd, 1H, *J* = 11.6, 5.9 Hz), 3.09 – 2.98 (m, 1H), 2.02 – 1.84 (m, 2H), 1.86 (s, 3H), 1.80 (dd, 1H, *J* = 11.9, 3.6 Hz), 1.66 (ddd, 1H, *J* = 12.7, 6.7, 1.3 Hz), 1.00 (d, 3H, *J* = 7.0 Hz), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.9, 110.4, 75.0, 63.9, 48.3, 44.8, 42.1, 39.7, 25.8, 24.0, 18.2, 14.6, –4.6, –5.0. IR ($CDCl_3$, cast film, cm^{-1}): 3353, 2957, 2929. HRMS (EI, m/z) Calcd for $C_{16}H_{32}O_2Si$: 284.2172. Found: 284.2173.

(1*R*,2*S*,3*R*,5*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-(prop-1-en-2-yl) cyclopentanecarbaldehyde (6.11)



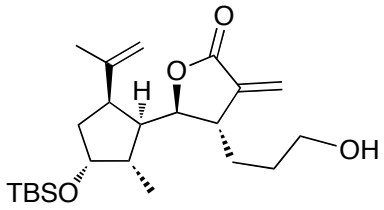
Oxalyl chloride (2.0 mL, 1.3 equiv) was dissolved in 30 mL DCM under argon at –78 ºC. To this stirred solution was slowly added a solution of DMSO (2.75 mL, 2.2 equiv) in 3 mL DCM. The reaction mixture was stirred for 15 minutes, then a solution of crude alcohol **6.16** (17.6 mmol) dissolved in 10 mL DCM was added. The reaction mixture was stirred for 15 min, and then NEt_3 (12.0 mL, 5.0 equiv) was added. The reaction was allowed to warm to rt over 1 h. The reaction was quenched with water and extracted with DCM (x3). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified via flash chromatography (5% EtOAc in hexanes) to provide **6.11** as a colorless oil (4.89 g, 99% yield). There was a trace amount of a contaminant in the final product that could not be removed despite several attempts. This contaminant was not characterized and did not affect subsequent reactions. $[\alpha]_D$ = –21.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.53 (d, 1H, *J* = 4.0 Hz), 4.86 (br s, 1H), 4.83 (br s, 1H), 4.19 (dd, 1H, *J* = 3.8, 3.8 Hz), 3.31 (ddd, 1H, *J* = 10.7, 10.7, 6.9), 2.62 (ddd, 1H, *J* = 10.7, 8.6, 3.9 Hz), 2.32-2.25 (m, 1H), 1.87 (ddd, 1H, *J* = 12.8, 12.8, 3.4 Hz), 1.80 (ddd, 1H, *J* = 12.8, 6.8, 1.0 Hz), 1.73 (s, 3H), 0.99 (d, 3H, *J* = 6.9 Hz), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 144.1, 111.8, 75.6, 58.1, 46.0, 40.6, 40.0, 25.9, 22.9, 18.2, 14.1, –4.6. IR ($CDCl_3$, cast film, cm^{-1}): 2957, 2930, 1721. HRMS (EI, m/z) Calcd for $C_{16}H_{30}O_2Si$: 282.2015. Found: 282.2013.

(4*S*,5*S*)-5-((1'*R*,2'*S*,3'*R*,5'*R*)-3'-((*tert*-Butyldimethylsilyl)oxy)-2'-methyl-5'-(prop-1-en-2-yl) cyclopentyl)-4-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-3-methylenedihydrofuran-2(3*H*)-one (6.10)



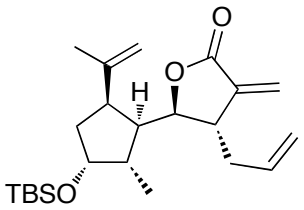
Allylboronate **6.12** (6.2 mmol, 1.0 equiv) and aldehyde **6.11** (6.2 mmol, 1.0 equiv) were dissolved in toluene under argon and cooled to 0 ºC. To this stirred solution was added BF_3•Et_2O (20 μL, 0.025 equiv) and the reaction was stirred for 48 h. Crude ^{1}H NMR spectroscopy at this point showed complete consumption of *Z*-**6.12**, a significant amount of *E*-**6.12** still remaining, and a small amount of unreacted aldehyde **6.11**. The reaction was quenched by the addition of 9:1 NH_4Cl(aq):NH_4OH and extracted with EtOAc (x3). The organic solvent was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (5% EtOAc in hexanes) to provide **6.10** as a colorless oil (3.49 g, 87% yield). $[\alpha]_D$ = +1.3 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 – 7.62 (m, 4H), 7.47 – 7.34 (m, 6H), 6.22 (d, 1H, *J* = 2.6 Hz), 5.51 (d, 1H, *J* = 2.4 Hz), 4.92 (br s, 1H), 4.85 (br s, 1H), 4.19 – 4.12 (m, 2H), 3.75 – 3.61 (m, 2H), 3.04 (ddd, 1H, *J* = 13.7, 8.9, 6.0 Hz), 2.77 – 2.67 (m, 1H), 2.07 – 1.88 (m, 3H), 1.77 (s, 3H), 1.73 – 1.54 (m, 5H), 1.06 (s, 9H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 144.3, 139.6, 135.8, 134.0, 129.9, 127.9, 121.7, 112.8, 83.6, 74.8, 63.6, 50.4, 46.2, 42.8, 40.0, 38.7, 30.0, 29.6, 27.1, 26.1, 23.7, 19.5, 18.4, 17.4, –4.4, –4.8. IR ($CDCl_3$, cast film, cm^{-1}): 3072, 2956, 2931, 1767. HRMS (ESI, m/z) Calcd for $C_{39}H_{58}O_4Si_2Na$ $[M+Na]^+$: 669.3766. Found: 669.3751.

(4*S*,5*S*)-5-((1'*R*,2'*S*,3'*R*,5'*R*)-3'-((*tert*-Butyldimethylsilyl)oxy)-2'-methyl-5'-(prop-1-en-2-yl) cyclopentyl)-4-(3-hydroxypropyl)-3-methylenedihydrofuran-2(3*H*)-one (6.18)



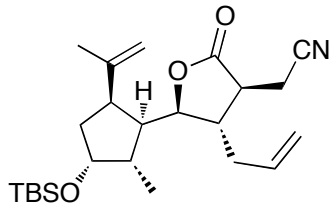
A solution of tetrabutylammonium fluoride (2.6 mL, 1.0 M solution in THF, 1.5 equiv) and glacial acetic acid (146 μL, 1.50 equiv) was stirred in 10 mL DMF for 30 min under argon. This mixture was then cannulated into a solution of **6.10** in 10 mL DMF at rt. The reaction mixture was stirred and monitored by TLC (20% EtOAc in hexanes) until consumption of **6.10** was complete (typically 3 to 4 h). The reaction was quenched by the addition of water and extracted with Et_2O (x3). The organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The mixture was purified by flash chromatography (20 to 30% EtOAc/hexanes) to provide alcohol **6.18** as a colorless oil (487 mg, 70% yield). $[\alpha]_D$ = +14.2 (*c* 0.84, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (d, 1H, *J* = 3.1 Hz), 5.58 (d, 1H, *J* = 2.4 Hz), 4.93 (br s, 1H), 4.85 (br s, 1H), 4.19 (dd, 1H, *J* = 5.3, 2.8 Hz), 4.14 (dd, 1H, *J* = 4.8, 4.8 Hz), 3.70 – 3.65 (m, 2H), 3.05 (ddd, 1H, *J* = 12.7, 9.0, 6.1 Hz), 2.80 – 2.73 (m, 1H), 2.05 – 1.91 (m, 3H), 1.79 (s, 3H), 1.70 – 1.51 (m, 6H), 1.03 (d, 3H, *J* = 6.5 Hz), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 144.1, 139.2, 121.7, 112.6, 83.4, 74.5, 62.4, 50.3, 45.9, 42.6, 39.8, 38.5, 29.8, 29.3, 25.8, 23.4, 18.1, 17.1, –4.7, –5.0. IR ($CDCl_3$, cast film, cm^{-1}): 3433, 2956, 2930, 1764. HRMS (ESI, m/z) Calcd for $C_{23}H_{44}O_4SiNa$ $[M+Na]^+$: 432.2588. Found: 431.2596.

(4*S*,5*S*)-4-allyl-5-((1'*R*,2'*S*,3'*S*,5'*R*)-3'-((*tert*-Butyldimethylsilyl)oxy)-2'-methyl-5'-(prop-1-en-2-yl)cyclopentyl)-3-methylenedihydrofuran-2(3*H*)-one (6.19)



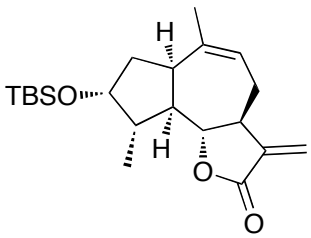
Alcohol **6.18** (1.05 g, 2.57 mmol) was dissolved in 24 mL THF under argon at rt. To this was added 2-nitrophenylselenium cyanate (583 mg, 2.57 mmol) and the dark red reaction mixture was cooled to 0 ºC. Once cooled, tributylphosphine (0.63 mL, 2.57 mmol) was added to create a black solution, which was stirred at 0 ºC for 3 h and eventually became a orange/brown, transparent solution. The reaction was quenched by adding NH_4Cl(aq) and was extracted with EtOAc (x3). The organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude mixture was redissolved in 24 mL THF, put under argon and cooled to 0 ºC. Hydrogen peroxide (2.6 mL, 1.0 mL/mmol substrate) was added and the mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched by addition of saturated $NaHSO_3$ (aq) and was extracted with EtOAc (x3). The organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (3-5% EtOAc/hexanes) provided **6.19** as a pale yellow oil (602 mg, 60% yield). $[\alpha]_D = -1.14$ (*c* 0.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (d, 1H, *J* = 3.0 Hz), 5.74 (dddd, 1H, *J* = 16.8, 10.8, 7.3, 7.3), 5.59 (d, 1H, *J* = 2.6 Hz), 5.15 (m, 1H), 5.12 (m, 1H), 4.92 (br s, 1H), 4.85 (br s, 1H), 4.19 (dd, 1H, *J* = 6.2, 2.7 Hz), 4.15 (dd, 1H, *J* = 4.6, 4.6 Hz), 3.02 (ddd, 1H, *J* = 13.8, 9.0, 5.9 Hz), 2.85 – 2.79 (m, 1H), 2.41-2.34 (m, 1H), 2.34 – 2.26 (m, 1H), 2.06 – 1.93 (m, 3H), 1.76 (s, 3H), 1.59 (dd, 1H, *J* = 12.7, 6.0 Hz), 1.03 (d, 3H, *J* = 6.9 Hz), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 144.0, 138.7, 134.0, 121.7, 118.3, 112.3, 82.8, 74.5, 49.6, 45.9, 42.0, 39.8, 38.3, 37.5, 25.9, 23.4, 18.2, 17.2, –4.7, –5.0. IR ($CDCl_3$, cast film, cm^{-1}): 2957, 2930, 1767. HRMS (EI, m/z) Calcd for $C_{19}H_{29}O_3Si$ $[M-C_4H_9]^+$: 333.1886. Found: 333.1899.

(3*S*,*4S*,5*S*)-*5*-((1'*R*,2'*S*,3'*S*,5'*R*)-3'-(*t*-Butyl(dimethyl)siloxy)-2'-methyl-5'-(prop-1-en-2-yl)cyclopentyl)-5-cyanomethyl-4-(prop-2-en-1-yl) tetrahydrofuran-2-one (6.20)



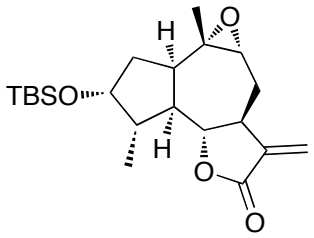
Obtained during the purification of **6.19** in an amount of 325 mg (30% yield) and was recrystallized from Et_2O. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 – 5.73 (m, 1H), 5.24 – 5.21 (m, 1H), 5.20 (br s, 1H), 4.91 (br s, 1H), 4.82 (br s, 1H), 3.10 – 3.03 (m, 1H), 4.17 (br dd, 1H, *J* = 4.9, 4.9 Hz), 4.14 (br d, 1H, *J* = 9.1 Hz), 3.10 – 3.03 (m, 1H), 2.81 (dd, 1H, *J* = 17.2, 5.4 Hz), 2.76 (dd, 1H, *J* = 17.1, 5.0 Hz), 2.53 (ddd, 1H, *J* = 11.0, 5.1, 5.1 Hz), 2.46 – 2.29 (m, 3H), 2.13 – 2.03 (m, 2H), 1.97 (ddd, 1H, *J* = 13.2, 13.2, 4.7 Hz), 1.75 (s, 3H), 1.58 (dd, 1H, *J* = 12.5, 5.4 Hz), 1.09 (d, 3H, *J* = 7.1 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 143.8, 133.3, 119.5, 116.7, 112.3, 82.8, 74.4, 46.9, 45.9, 42.9, 41.7, 39.6, 37.8, 34.5, 25.9, 23.5, 18.2, 17.7, 17.3, –4.6, –4.9. IR ($CDCl_3$ cast film, cm^{-1}): 3083, 2957, 2930, 2857, 2251, 1776. HRMS (EI, m/z) Calcd for $C_{20}H_{30}NO_3Si$ $[M-C_4H_9]^+$: 360.1995. Found: 360.1994. This product was also analyzed by X-ray analysis. See Appendix 2 for crystallographic data.

(3a*S*,6a*R*,8*R*,9*S*,9a*R*,9b*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-6,9-dimethyl-3-methylene-3a,4,6a,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (6.21)



γ-Lactone **6.19** (300 mg, 0.77 mmol, 1.0 equiv) was dissolved in 150 mL DCM under argon. Grubbs II catalyst (32 mg, 0.038 mmol, 0.05 equiv) was added and the reaction was heated to 40 ºC for 12 h. The solvent was removed and the crude mixture was purified by flash chromatography (10% EtOAc/hexanes) to provide **6.21** as a light beige solid (259 mg, 93% yield). $[\alpha]_D$ = –42.8 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (d, 1H, *J* = 3.5 Hz), 5.47 (d, 1H, *J* = 3.2 Hz), 5.44 (br s, 1H), 4.11 (br. t, 1H, *J* = 4.4 Hz), 3.92 (dd, 1H, *J* = 11.3, 8.9 Hz), 3.19 – 3.07 (m, 1H), 2.74 – 2.67 (m, 1H), 2.64 – 2.56 (m, 1H), 2.29 – 2.17 (m, 1H), 2.08 – 2.03 (m, 1H), 2.03 – 1.95 (m, 1H), 1.91, (ddd, 1H, *J* = 11.2, 8.6, 5.4 Hz), 1.78 (s, 3H), 1.54 (ddd, 1H, *J* = 12.5, 12.5, 3.9 Hz), 1.10 (d, 3H, *J* = 7.0 Hz), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 140.3, 137.0, 120.1, 119.9, 87.3, 73.6, 52.3, 45.3, 44.7, 42.7, 42.3, 30.7, 28.5, 25.9, 18.2, 15.8, –4.6, –4.9. IR (cast film microscope, cm^{-1}): 2957, 2930, 1771. HRMS (EI, m/z) Calcd for $C_{21}H_{34}O_3Si$: 362.2277. Found: 362.2280.

(1*S*,2*R*,3a*R*,3b*S*,4a*R*,5a*S*,8a*R*,8b*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1,3b-dimethyl-6-methylenedecahydrooxireno[2',3':7,8]azuleno[4,5-*b*]furan-7(2*H*)-one (6.9)



γ-Lactone **6.21** (90 mg, 0.25 mmol, 1.0 equiv) was dissolved in 5 mL DCM under argon and cooled to 0 ºC. *m*CPBA (111 mg, 0.50 mmol, 2.0 equiv) was added and the reaction was stirred at 0 ºC for 1 h. The reaction mixture was quenched by adding water and was diluted with DCM. The water layer was extracted with DCM (x3), then the organic extracts were washed with 1N NaOH (x2) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (20% EtOAc/hexanes) to provide **2**

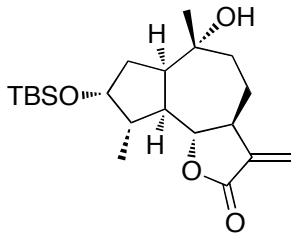
as an inseparable mixture of diastereomers (85 mg, 90% yield). The major diastereomer was the desired one and was obtained in a ratio ranging from 3.5:1 to 4.5:1, depending on the batch.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (d, 1H, *J* = 3.6 Hz), 5.48 (d, 1H, *J* = 3.2 Hz), 4.23 (td, 1H, *J* = 5.8, 2.4 Hz), 3.60 (dd, 1H, *J* = 11.7, 9.3 Hz), 3.11 (dt, 1H, *J* = 13.9, 7.5 Hz), 3.06 (d, 1H, *J* = 5.0 Hz), 2.89 – 2.76 (m, 1H), 2.67 (ddd, 1H, *J* = 15.4, 5.0, 3.6 Hz), 2.43 (pd, 1H, *J* = 7.2, 2.5 Hz), 1.98 (dd, 1H, *J* = 8.8, 2.9 Hz), 1.96 – 1.73 (m, 3H), 1.35 (s, 3H), 1.02 (d, 3H, *J* = 6.8 Hz), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (d, 1H, *J* = 3.6 Hz), 5.47 (d, 1H, *J* = 3.3 Hz), 4.42 (dd, 1H, *J* = 10.3, 8.9 Hz), 4.09 – 4.06 (m, 1H), 3.05 (d, 1H, *J* = 3.9), 3.01 – 2.93 (m, 1H), 2.89 – 2.76 (m, 1H), 2.57 (ddd, 1H, *J* = 15.4, 5.0, 5.0 Hz), 2.14 (dd, 1H, *J* = 16.0, 11.9 Hz), 2.09-2.02 (m, 1H), 1.96 – 1.73 (m, 3H), 1.29 (s, 3H), 1.09 (d, 3H, *J* = 6.8 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

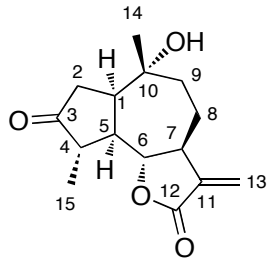
Mixture of diastereomers: ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 139.9, 139.6, 120.0, 119.5, 85.4, 83.5, 75.2, 72.1, 64.9, 64.7, 63.6, 62.3, 60.4, 51.8, 51.0, 45.7, 42.9, 41.9, 41.5, 40.5, 40.2, 40.1, 39.4, 29.3, 29.0, 27.2, 25.8, 25.8, 24.9, 18.1, 15.4, 14.9, 14.2, 11.9, –4.6, –4.8, –5.0. IR (microscope, cm^{-1}): 2957, 2929, 1769. HRMS (EI, m/z) Calcd for $C_{21}H_{34}O_4Si$: 378.2226. Found: 378.2225.

(3a*S*,6*R*,6a*R*,8*R*,9*S*,9a*S*,9b*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-6,9-dimethyl-3-methylenedecahydroazuleno[4,5-*b*]furan-2(9b*H*)-one (6.23)



Epoxide **6.9** (30 mg, 0.08 mmol, 1.0 equiv) was dissolved in THF under argon and cooled to –78 ºC. To this was added DIBALH (0.19 mL, 0.28 mmol, 3.5 equiv) as a 1.5 M solution in toluene. The reaction mixture was stirred for 2 h, then $LiEt_3BH$ (87 μL, 87 μmol, 1.1 equiv) was added and the reaction was allowed to warm to rt over 30 min. The reaction was quenched by adding a 30% solution of sodium potassium tartrate and was extracted with EtOAc (x4). The organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue containing **6.22** was dissolved in 15 mL DCM and to this was added powdered 90% MnO_2 (~20 equiv). The reaction was stirred overnight at rt, then filtered through Celite, washed with DCM and the solvent was removed. Flash chromatography (20 to 50% EtOAc/hexanes) provided **6.23** as a colorless oil (15 mg, 50% yield). $[\alpha]_D$ = –22.2 (*c* 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (d, 1H, *J* = 3.5 Hz), 5.47 (d, 1H, *J* = 3.2 Hz), 4.11 – 4.04 (m, 2H), 2.88 – 2.77 (m, 1H), 2.25 – 2.12 (m, 2H), 2.00 – 1.87 (m, 2H), 1.87 – 1.81 (m, 2H), 1.78 – 1.68 (m, 1H), 1.51 – 1.39 (m, 1H), 1.19 (s, 3H), 1.11 (d, 3H, *J* = 7.2 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 140.1, 119.5, 85.9, 75.5, 75.0, 49.8, 46.4, 45.6, 41.6, 37.8, 29.8, 25.9, 25.3, 18.2, 15.0, –4.6, –4.8. IR (microscope, cm^{-1}): 3474, 2955, 2928, 1762. HRMS (EI, m/z) Calcd for $C_{17}H_{27}O_4Si$ $[M-C_4H_9]^+$: 323.1679. Found: 323.1680.

(3a*S*,6*R*,6a*R*,9*S*,9a*R*,9b*R*)-6-Hydroxy-6,9-dimethyl-3-methyleneoctahydro azuleno[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (6.2)



To a suspension of PDC (15 mg, 1.5 equiv) in 0.5 mL DCM under argon at 0 ºC was added TMSCl (12 μL, 3.5 equiv). After stirring this mixture for 5 min, γ-lactone **6.23** (10 mg, 1.0 equiv) was dissolved in 0.5 mL DCM and added to the reaction mixture. This mixture was stirred at 0 ºC for 4 h, then quenched by the addition of moist silica gel. The resulting suspension was filtered through a short pad of silica with DCM and EtOAc. Purification of the reaction mixture was done via flash chromatography (20% EtOAc/hexanes) to provide pure **6.2** as a crystalline solid (5 mg, 71% yield). As already discussed in Section 6.3.4, the initial isolation[3] of chinensiolide B indicated that the NMR spectra were obtained using $CDCl_3$ as the solvent. However, upon consultation with the corresponding author (Professor Masayoshi Ando), it was found that the NMR spectra were actually recorded in deuterated pyridine. Upon running NMR analyses of the synthetic sample of **6.2** in pyridine-d[5], the spectral properties (^{1}H NMR and ^{13}C NMR) were identical to those provided by Professor Ando. Other analyses (IR, HRMS and $[\alpha]^{20}_D$) were consistent with that reported in the original isolation paper.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (d, 1H, *J* = 3.5 Hz), 5.52 (d, 1H, *J* = 3.1 Hz), 4.11 (dd, 1H, *J* = 9.9, 9.9 Hz), 3.12 – 3.02 (m, 1H), 2.66 – 2.57 (m, 2H), 2.51 – 2.34 (m, 3H), 2.32 – 2.22 (m, 1H), 1.99 (d, 1H, *J* = 14.5, 6.1, 6.1 Hz), 1.78 (ddd, 1H, *J* = 14.3, 8.3, 5.8 Hz), 1.57 – 1.47 (m, 1H), 1.25 (d, 3H, *J* = 7.2 Hz), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.0, 169.7, 139.8, 120.5, 85.0, 74.2, 50.5, 48.0, 46.0, 44.3, 39.8, 39.8, 28.0, 25.3, 15.9.

^{1}H NMR (400 MHz, Pyr-D_5): δ 6.24 (d, 1H, *J* = 3.7 Hz), 6.22 (br s, 1H), 5.44 (d, 1H, *J* = 3.2 Hz), 4.12 (dd, 1H, *J* = 9.9 Hz), 3.09 – 2.96 (m, 2H), 2.79 (m, 1H), 2.54 – 2.44 (m, 2H), 2.34 (ddd, 1H, *J* = 10.0, 8.4, 8.4 Hz), 2.18 – 2.03 (m, 2H), 1.88-1.81 (m, 1H), 1.39 – 1.29 (m, 1H), 1.27 (s, 3H), 1.24 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, Pyr-d_5): δ 219.7, 170.1, 141.2, 119.6, 86.0, 73.3, 50.5, 48.3, 46.4, 44.5, 40.4, 27.1, 25.8, 15.8.

IR (microscope, cm^{-1}): 3459, 2968, 2932, 1761, 1738. HRMS (EI, m/z) Calcd for $C_{15}H_{20}O_4$: 264.1362. Found: 264.1364. $[\alpha]_D$ = +4.8 (*c* 0.12, $CHCl_3$). Literature = +2.6 (*c* 0.469, $CHCl_3$).[3]

6.5.3 ^{13}C NMR spectroscopic data for natural and synthetic 6.2

Carbon	Natural product[4] in Pyr-d_5 (ppm)	Synthetic product in Pyr-d_5 (ppm)	Synthetic product in $CDCl_3$ (ppm)
1	46.5	46.4	46.0
2	40.3	40.4	39.8
3	219.3	219.7	219.0
4	48.3	48.3	48.0
5	50.5	50.5	50.5
6	85.8	86.0	85.0
7	44.5	44.5	44.3
8	25.9	25.8	25.3
9	40.6	--[a]	39.8
10	73.1	73.3	74.2
11	141.3	141.2	139.8
12	169.9	170.1	169.7
13	119.4	119.6	120.5
14	27.3	27.1	28.0
15	15.9	15.8	15.9

[a] Due to conformational flexibility in the seven-member ring, the carbon peaks for C9 and C14 appear as very broad peaks. The peak for C9 in the ^{13}C NMR is sometimes not observed due to overlap with the C2 peak. This issue was mentioned and discussed in the original isolation paper.[3]

6.6 References

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[1] A version of this chapter has been published: Elford, T.G.; Hall, D.G. *J. Am. Chem. Soc.* **2010**, *132*, 1488-1489.

[2] Hoffmann, H.M.R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94-110.

[3] Zhang, S.; Wang, J.; Xue, H.; Deng, Q.; Xing, F.; Ando, M. *J. Nat. Prod.* **2002**, *65*, 1927-1929.

[4] Zhang, S.; Zhao, M.; Bai, L.; Hasegawa, T.; Wang, J.; Wang, L.; Xue, H.; Deng, Q.; Xing, F.; Bai, Y.; Sakai, J.; Bai, J.; Koyanagi, R.; Tsukumo, Y.; Kataoka, T.; Nagai, K.; Hirose, K.; Ando, M. *J. Nat. Prod.* **2006**, *69*, 1425-1428.

[5] Dai, J.; Yang, L.; Sakai, J.; Ando, M. *J. Mol. Catal. B: Enzym.* **2005**, *33*, 87-91.

[6] http://www.cancer.org/docroot/CDG/content/CDG_paclitaxel.asp. Accessed on February 2, 2010.

[7] Elford, T.G.; Arimura, Y.; Yu, S.H.; Hall, D.G. *J. Org. Chem.* **2007**, *72*, 1276-1284 and references cited therein.

[8] a) Favorskii, A.E. *J. Russ. Phys. Chem. Soc.* **1894**, *26*, 590. b) Favorskii, A.E. *J. Russ. Phys. Chem. Soc.* **1905**, *37*, 643. c) Favorskii, A.E. *J. Prakt. Chem.* **1913**, *88*, 658.

[9] Oliver, S.F.; Hogenauer, K.; Simic, O.; Antonello, A.; Smith, M.D.; Ley, S.V. *Angew. Chem Int. Ed.* **2003**, *42*, 5996-6000.

[10] Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.

[11] Hall, D.G.; Deslongchamps, P. *J. Org. Chem.* **1995**, *60*, 7796-7814.

[12] a) Ramachandran, P.V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M.V.R. *Org. Lett.* **2004**, *6*, 481-484. b) Nyzam, V.; Belaud, C.; Villiéras, J. *Tetrahedron Lett.* **1993**, *34*, 6899-6902.

[13] Whiting, A. *Tetrahedron Lett.* **1991**, 32, 1503-1506.

[14] Crouch, R.D. *Tetrahedron*, **2004**, *60*, 5833-5871.

[15] Grieco, P.A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486.

[16] Crystallographic data (excluding structure factors) for the structure of **6.20** in have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-756958. Copies of the data can be

obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif).

[17] For example, see: a) Chatterjee, A.K.; Morgan, J.P.; Scholl, M.; Grubbs, R.H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784. b) Hekking, K.F.W.; van Delft, F.L.; Rutjes, F.P.J.T *Tetrahedron* **2003**, *59*, 6571-6758.

[18] For example, see: a) Paquette, L.A.; Arbit, R.M.; Funel, J.-A.; Bolshakov, S. *Synthesis* **2002**, *14*, 2105-2109. b) Kalidindi, S.; Jeong, W.B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 6361-6363.

[19] Brown, H.C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567-607.

[20] Cossio, F.P.Aizpura, J.M.; Palomo, C. *Can. J. Chem.* **1986**, *64*, 225-231.

[21] Andrews, S.P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Hogenauer, K.; Simic, O.; Antonello, A.; Hunger, U.; Smith, M.D.; Ley, S.V. *Chem. Eur. J.* **2007**, *13*, 5688-5712.

Chapter 7

Thesis Conclusions and Future Work

7.1 Thesis conclusions and future work

The research that has been discussed throughout the chapters of this thesis revolves around the use of a special class of allylic boronates, 2-alkoxycarbonyl allylboronates, and how they can be used in conjunction with various electrophiles to prepare α-methylene γ-lactones and α-methylene γ-lactams in a stereocontrolled fashion. Unlike the typical allylic boronates, these electronically deactivated derivatives are extremely slow to react, and thus, have often been avoided due to the long reaction times associated with their use.

The discovery that Lewis and Brønsted acids could catalyze the addition of 2-alkoxycarbonyl allylboronates to aldehydes was a significant find in the field of carbonyl allylation chemistry. Over the course of my research, I was able to investigate the Brønsted acid protocol and its substrate scope, and determine the mechanism by which the observed diastereoselectivity arose. The nature of the reversal of stereoselectivity observed with electron-rich aldehydes was attributed to the formation of an intermediate carbocation during the reaction. The exact nature of the catalyst and many of the reaction intermediates were also investigated. Questions still remain regarding what the true catalyst is and how it turns over.

An expansion on the use of 2-alkoxycarbonyl allylboronates to other electrophiles was also investigated over the course of my doctoral research. With ketones, it was determined that both Lewis and Brønsted acids failed to sufficiently activate the allylboronate for effective additions to occur. However, it was determined that a previously disclosed copper catalyst system was capable of promoting ketone allylboration with 2-alkoxycarbonyl allylboronates. The

substrate scope for this reaction remains to be investigated and a catalyst system that would allow this transformation to proceed in an enantioselective fashion is also desirable. Other catalyst systems have since been developed by other investigators and may be helpful in achieving this latter goal.

Since many γ-lactones and γ-lactams that are present in nature are more complex and contain various patterns of substitution, it was my goal to investigate various methods that would allow for further functionalization of these substrates for applications in diversity-oriented synthesis. By building a small representative library, I succeeded in demonstrating that many different γ-lactones and γ-lactams can be synthesized using allylboration chemistry and additionally, that these substrates can be further modified in a variety of ways. The nitrogen atom of the γ-lactams can be arylated using copper catalysis and the *exo*-methylene group can be modified either through the Heck reaction or by rhodium-catalyzed conjugate addition to provide α-alkylidene or α-alkylated γ-lactones and γ-lactams with varying degrees of saturation at the α-position. A subset of the library was screened against homoserine transacetylase from *Haemophilus influenzae* in collaboration with the research group of Dr. Wright from McMaster University. Two compounds from the library proved to be moderate inhibitors of HTA. More of these compounds could be synthesized in the future and, by entering into collaborative efforts with other researchers around the world, further biological screening of these compounds could prove useful in providing new lead compounds to treat disease or illness.

The research described in the thesis for the first five chapters involved relatively simple 2-alkoxycarbonyl allylboronates and commercially available electrophiles. In an effort to investigate how the allyboration reaction would fare with more sensitive and elaborate substrates, the total synthesis of a natural product was launched. Chinensiolide B is a natural product that is quite complex for its size due to five contiguous stereocenters along a flexible seven-member ring. The synthesis of chinensiolide B involved the use of both a functionalized 2-alkoxycarbonyl allylboronate and a chiral, highly complex aldehyde. The key allylboration reaction proved to be highly successful and allowed for a highly

advanced intermediate to be accessed in a short period of time. Chemoselectivity issues did arise throughout the synthesis due to the high reactivity of the α-methylene γ-lactone unit, but these were resolved either by careful control of reaction conditions or by unconventional methods.

To conclude, the research presented in my doctoral thesis outlines the many advantages of using 2-alkoxycarbonyl allylboronates in accessing γ-lactones and γ-lactams. The stability of these reagents is unmatched, and their associated stereoselectivity during reactions is undeniable. This work also highlights the wide range of applications, from diversity-oriented synthesis to target-oriented synthesis, which 2-alkoxycarbonyl allylboronates can play an integral role in. I believe that this thesis establishes that 2-alkoxycarbonyl allylboronates are arguably the most efficient and robust method for preparing highly functionalized γ-lactones and γ-lactams. The development of catalytic, asymmetric methods whereby 2-alkoxycarbonyl allylboronates add to carbonyl or imine groups in an enantioselective fashion is highly desirable. The application of these methods to more difficult allylboration reactions and thus access compounds in a stereoselective fashion without using stoichiometric chiral reagents is one area where progress could be made. Since α-methylene γ-lactones are so prevalent in nature, the enantioselective synthesis of these compounds is important. This thesis discusses my forays into these areas and sheds some light on the challenges that still exist and the synthetic utility that these 2-alkoxycarbonyl allylboronates possess.

Appendix 1: Crystallographic data for γ-lactam 4.9

Table 1: Crystallographic Experimental Details

A. Crystal Data

formula	$C_{12}H_{12}BrNO$
formula weight	266.14
crystal dimensions (mm)	0.32 x 0.30 x 0.26
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	8.1760 (6)
b (Å)	12.3583 (9)
c (Å)	11.2820 (8)
β (deg)	98.652 (1)
V (Å^3)	1126.98 (14)
Z	4
ρ_{calcd} (g cm^{-3})	1.569
μ (mm^{-1})	3.619

B. Data Collection and Refinement Conditions

diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Ka (0.71073)
temperature (°C)	–80
scan type	w scans (0.3°) (15 s exposures)
data collection 2θ limit (deg)	52.72
total data collected	8493 ($-10 \le h \le 10$, $-15 \le k \le 15$, $-14 \le l \le 14$)
independent reflections	2300 ($R_{int} = 0.0220$)
number of observed reflections (*NO*)	2027 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.3904–0.3366
data/restraints/parameters	2300 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 136
goodness-of-fit (S)[e]	1.047 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[f]	
$R1$ [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0246
$wR2$ [$F_o^2 \ge -3\sigma(F_o^2)$]	0.0647
largest difference peak and hole	0.450 and –0.344 e Å^{-3}

[a]Obtained from least-squares refinement of 6001 reflections with $4.92° < 2\theta < 52.70°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr*. **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0351P)^2 + 0.4713P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2: Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
Br	-0.37593(3)	0.394020(18)	0.603483(19)	0.04296(10)*
O	0.22958(15)	0.50644(11)	0.01715(12)	0.0326(3)*
N	0.06286(19)	0.41024(12)	0.12528(14)	0.0286(3)*
C1	0.2097(2)	0.44159(14)	0.09705(15)	0.0257(4)*
C2	0.3411(2)	0.38343(13)	0.17847(16)	0.0258(4)*
C3	0.2586(2)	0.32499(15)	0.27140(16)	0.0276(4)*
C4	0.0722(2)	0.32432(15)	0.21494(15)	0.0266(4)*
C5	0.4987(2)	0.38795(16)	0.16576(18)	0.0345(4)*
C6	0.3264(3)	0.21335(18)	0.3074(2)	0.0429(5)*
C7	-0.0442(2)	0.34223(15)	0.30518(16)	0.0260(4)*
C8	-0.0873(2)	0.44605(15)	0.33732(17)	0.0305(4)*
C9	-0.1880(2)	0.46208(15)	0.42426(17)	0.0320(4)*
C10	-0.2445(2)	0.37318(16)	0.48017(16)	0.0289(4)*
C11	-0.2059(2)	0.26874(15)	0.44948(16)	0.0307(4)*
C12	-0.1058(2)	0.25422(15)	0.36143(17)	0.0296(4)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3: Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
Br	C10	1.8988(18)	C4	C7	1.511(2)
O	C1	1.235(2)	C7	C8	1.393(3)
N	C1	1.344(2)	C7	C12	1.391(3)
N	C4	1.461(2)	C8	C9	1.386(3)
C1	C2	1.489(2)	C9	C10	1.381(3)
C2	C3	1.513(2)	C10	C11	1.385(3)
C2	C5	1.320(3)	C11	C12	1.390(3)
C3	C4	1.561(2)	H1N	O[a]	2.00[†]
C3	C6	1.519(3)			

[a]Located at $\overline{x}$, 1–y, $\overline{z}$.

[†]Nonbonded interaction.

Table 4: Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	N	C4	114.71(14)	C4	C7	C8	121.34(16)
O	C1	N	125.47(16)	C4	C7	C12	120.06(16)
O	C1	C2	126.96(16)	C8	C7	C12	118.56(17)
N	C1	C2	107.56(15)	C7	C8	C9	121.08(17)
C1	C2	C3	107.62(15)	C8	C9	C10	119.00(17)
C1	C2	C5	122.58(17)	Br	C10	C9	119.48(15)
C3	C2	C5	129.80(17)	Br	C10	C11	119.02(13)
C2	C3	C4	103.26(14)	C9	C10	C11	121.50(17)
C2	C3	C6	115.85(15)	C10	C11	C12	118.68(16)
C4	C3	C6	113.51(16)	C7	C12	C11	121.15(17)
N	C4	C3	102.99(14)	N	H1N	O[a]	167.0[†]
N	C4	C7	112.81(14)				
C3	C4	C7	113.55(14)				

[a]Located at $\overline{x}$, 1–y, $\overline{z}$.

[†]Includes nonbonded interaction.

Table 5: Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle
C4	N	C1	O	173.93(17)
C4	N	C1	C2	-5.6(2)
C1	N	C4	C3	16.1(2)
C1	N	C4	C7	138.87(16)
O	C1	C2	C3	172.56(17)
O	C1	C2	C5	-6.7(3)
N	C1	C2	C3	-7.91(19)
N	C1	C2	C5	172.87(18)
C1	C2	C3	C4	16.82(18)
C1	C2	C3	C6	141.54(16)
C5	C2	C3	C4	-164.04(19)
C5	C2	C3	C6	-39.3(3)
C2	C3	C4	N	-19.06(17)
C2	C3	C4	C7	-141.37(15)
C6	C3	C4	N	-145.29(16)
C6	C3	C4	C7	92.4(2)
N	C4	C7	C8	-30.3(2)
N	C4	C7	C12	152.13(16)
C3	C4	C7	C8	86.4(2)
C3	C4	C7	C12	-91.2(2)
C4	C7	C8	C9	-176.94(17)
C12	C7	C8	C9	0.7(3)
C4	C7	C12	C11	176.48(16)
C8	C7	C12	C11	-1.2(3)
C7	C8	C9	C10	0.6(3)
C8	C9	C10	Br	177.75(14)
C8	C9	C10	C11	-1.4(3)
Br	C10	C11	C12	-178.23(13)
C9	C10	C11	C12	0.9(3)
C10	C11	C12	C7	0.4(3)

Table 6: Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br	0.04850(15)	0.04381(14)	0.04147(14)	0.00545(9)	0.02269(10)	0.00358(9)
O	0.0293(6)	0.0338(7)	0.0361(7)	0.0110(6)	0.0095(5)	0.0035(5)
N	0.0225(7)	0.0348(8)	0.0284(8)	0.0082(6)	0.0031(6)	0.0017(6)
C1	0.0254(9)	0.0255(8)	0.0264(8)	-0.0007(7)	0.0052(7)	0.0020(7)
C2	0.0273(9)	0.0243(8)	0.0257(8)	-0.0022(7)	0.0037(7)	0.0015(7)
C3	0.0243(8)	0.0308(9)	0.0274(9)	0.0016(7)	0.0032(7)	0.0008(7)
C4	0.0254(8)	0.0263(9)	0.0278(9)	0.0022(7)	0.0030(7)	0.0000(7)
C5	0.0276(9)	0.0388(11)	0.0370(10)	0.0050(8)	0.0050(8)	0.0031(8)
C6	0.0340(10)	0.0414(12)	0.0534(13)	0.0193(10)	0.0069(9)	0.0045(9)
C7	0.0213(8)	0.0284(9)	0.0274(8)	0.0025(7)	0.0007(7)	0.0016(7)
C8	0.0310(9)	0.0271(9)	0.0342(10)	0.0054(8)	0.0075(7)	0.0036(8)
C9	0.0343(10)	0.0264(9)	0.0359(10)	0.0017(8)	0.0070(8)	-0.0008(8)
C10	0.0247(8)	0.0356(10)	0.0273(9)	0.0039(7)	0.0073(7)	-0.0001(7)
C11	0.0289(9)	0.0291(9)	0.0342(9)	0.0085(7)	0.0053(7)	-0.0024(7)
C12	0.0280(9)	0.0249(9)	0.0357(9)	0.0026(7)	0.0044(7)	0.0004(7)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 7: Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	x	y	z	U_{eq}, Å^2
H1N	-0.0314	0.4392	0.0923	0.034
H3	0.2704	0.3710	0.3451	0.033
H4	0.0454	0.2536	0.1735	0.032
H5A	0.5322	0.4295	0.1027	0.041
H5B	0.5788	0.3496	0.2196	0.041
H6A	0.4433	0.2194	0.3424	0.064
H6B	0.3160	0.1666	0.2364	0.064
H6C	0.2638	0.1820	0.3665	0.064
H8	-0.0471	0.5069	0.2990	0.037
H9	-0.2176	0.5332	0.4451	0.038
H11	-0.2469	0.2082	0.4878	0.037
H12	-0.0790	0.1829	0.3393	0.035

Appendix 2: Crystallographic data for γ-lactone 6.20

Table 1: Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{24}H_{39}NO_3Si$
formula weight	417.65
crystal dimensions (mm)	0.47 × 0.25 × 0.12
crystal system	monoclinic
space group	$P2_1$ (No. 4)
unit cell parameters[a]	
a (Å)	10.9585 (4)
b (Å)	7.9293 (3)
c (Å)	15.5064 (6)
β (deg)	107.7359 (4)
V (Å^3)	1283.36 (8)
Z	2
ρ_{calcd} (g cm^{-3})	1.081
μ (mm^{-1})	0.113
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	55.00
total data collected	11315 (-14 ≤ h ≤ 14, -10 ≤ k ≤ 10, -20 ≤ l ≤ 19)
independent reflections	5820 (R_{int} = 0.0160)
number of observed reflections (*NO*)	5554 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9867–0.9482
data/restraints/parameters	5820 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 263
Flack absolute structure parameter[e]	0.04(7)
goodness-of-fit (*S*)[f]	1.045 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0319
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.0868
largest difference peak and hole	0.388 and –0.159 e Å^{-3}

[a]Obtained from least-squares refinement of 9952 reflections with $5.42° < 2\theta < 54.90°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr*. **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112–122.

[e]Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr*. **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst*. **2000**, *33*, 1143–1148. Ideally, the Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. In this case, the relatively large standard uncertainty indicates that the structural data alone should not be used to confirm absolute stereochemistry. The conformation of the model presented herein is based upon the established stereochemistry of the precursor compound (specifically the configurations of the stereogenic centers of the 3-{*t*-butyl(dimethyl)siloxy}-2-methyl-5-(prop-1-en-2-yl)cyclopentyl group).

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0570P)^2 + 0.0794P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2: Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
Si	-0.17321(3)	0.52206(4)	0.04847(2)	0.02365(8)*
O1	0.34611(8)	0.55436(13)	0.38211(6)	0.0317(2)*
O2	0.47670(10)	0.76824(15)	0.44097(8)	0.0418(3)*
O3	-0.07215(8)	0.46586(12)	0.14665(6)	0.0287(2)*
N	0.14210(17)	0.9668(2)	0.46920(13)	0.0605(4)*
C1	0.40153(12)	0.66359(19)	0.44880(9)	0.0301(3)*
C2	0.35633(13)	0.63258(18)	0.53070(9)	0.0281(3)*
C3	0.23970(11)	0.51706(18)	0.49444(8)	0.0256(2)*
C4	0.26391(12)	0.43460(17)	0.41129(8)	0.0251(3)*
C5	0.14563(12)	0.39474(16)	0.33250(8)	0.0235(2)*
C6	0.05835(12)	0.55107(17)	0.29753(8)	0.0290(3)*
C7	0.03885(12)	0.56094(17)	0.19503(8)	0.0286(3)*
C8	0.15888(13)	0.47833(19)	0.18460(9)	0.0320(3)*
C9	0.17337(12)	0.32347(17)	0.24605(8)	0.0265(3)*
C10	0.33532(16)	0.80013(19)	0.57389(10)	0.0378(3)*
C11	0.22748(17)	0.8951(2)	0.51583(12)	0.0419(4)*
C12	0.22169(15)	0.38815(19)	0.56324(9)	0.0337(3)*
C13	0.2031(2)	0.4701(2)	0.64526(11)	0.0487(4)*
C14	0.2859(3)	0.4598(3)	0.72698(12)	0.0747(7)*
C15	-0.06660(14)	0.5473(3)	0.32158(10)	0.0450(4)*
C16	-0.22779(14)	0.74276(18)	0.05361(12)	0.0387(3)*
C17	-0.09707(13)	0.5053(2)	-0.04333(9)	0.0393(3)*
C18	-0.31049(13)	0.36902(17)	0.02907(10)	0.0295(3)*
C19	-0.26065(16)	0.18782(19)	0.03268(13)	0.0435(4)*
C20	-0.40858(15)	0.4003(2)	-0.06451(12)	0.0456(4)*
C21	-0.37666(16)	0.3914(2)	0.10211(12)	0.0459(4)*
C22	0.29202(14)	0.2170(2)	0.25999(9)	0.0361(3)*
C23	0.39190(15)	0.2661(3)	0.23399(11)	0.0494(4)*
C24	0.28853(19)	0.0474(2)	0.30016(11)	0.0520(4)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3: Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
Si	O3	1.6479(9)	C5	C6	1.5587(17)
Si	C16	1.8589(14)	C5	C9	1.5675(17)
Si	C17	1.8610(14)	C6	C7	1.5397(18)
Si	C18	1.8843(14)	C6	C15	1.5252(19)
O1	C1	1.3438(17)	C7	C8	1.5215(19)
O1	C4	1.4718(16)	C8	C9	1.5326(19)
O2	C1	1.2012(18)	C9	C22	1.5095(19)
O3	C7	1.4335(15)	C10	C11	1.458(2)
N	C11	1.144(2)	C12	C13	1.497(2)
C1	C2	1.517(2)	C13	C14	1.317(3)
C2	C3	1.5332(18)	C18	C19	1.532(2)
C2	C10	1.536(2)	C18	C20	1.540(2)
C3	C4	1.5391(16)	C18	C21	1.530(2)
C3	C12	1.5330(19)	C22	C23	1.335(2)
C4	C5	1.5191(16)	C22	C24	1.487(3)

Table 4: Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
O3	Si	C16	110.45(6)	C5	C6	C7	106.09(10)
O3	Si	C17	110.83(6)	C5	C6	C15	113.62(12)
O3	Si	C18	104.62(5)	C7	C6	C15	113.63(11)
C16	Si	C17	108.98(8)	O3	C7	C6	110.02(10)
C16	Si	C18	111.18(7)	O3	C7	C8	109.95(11)
C17	Si	C18	110.73(7)	C6	C7	C8	103.60(10)
C1	O1	C4	110.78(10)	C7	C8	C9	102.01(10)
Si	O3	C7	124.44(8)	C5	C9	C8	103.44(11)
O1	C1	O2	122.04(13)	C5	C9	C22	117.52(10)
O1	C1	C2	110.70(11)	C8	C9	C22	117.30(12)
O2	C1	C2	127.26(13)	C2	C10	C11	112.24(12)
C1	C2	C3	103.78(10)	N	C11	C10	178.59(19)
C1	C2	C10	110.81(12)	C3	C12	C13	112.43(13)
C3	C2	C10	117.23(12)	C12	C13	C14	123.9(2)
C2	C3	C4	102.94(10)	Si	C18	C19	109.86(10)
C2	C3	C12	114.38(10)	Si	C18	C20	109.92(10)
C4	C3	C12	113.03(12)	Si	C18	C21	110.03(10)
O1	C4	C3	105.14(10)	C19	C18	C20	108.92(14)
O1	C4	C5	109.82(10)	C19	C18	C21	109.01(14)
C3	C4	C5	116.08(10)	C20	C18	C21	109.06(13)
C4	C5	C6	113.40(10)	C9	C22	C23	122.92(16)
C4	C5	C9	115.00(10)	C9	C22	C24	115.76(14)
C6	C5	C9	104.33(10)	C23	C22	C24	121.23(16)

Table 5: Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle
C16	Si	O3	C7	-51.38(12)
C17	Si	O3	C7	69.50(12)
C18	Si	O3	C7	-171.11(10)
O3	Si	C18	C19	-56.30(13)
O3	Si	C18	C20	-176.15(10)
O3	Si	C18	C21	63.72(11)
C16	Si	C18	C19	-175.54(12)
C16	Si	C18	C20	64.62(13)
C16	Si	C18	C21	-55.51(13)
C17	Si	C18	C19	63.15(13)
C17	Si	C18	C20	-56.69(12)
C17	Si	C18	C21	-176.82(11)
C4	O1	C1	O2	176.92(13)
C4	O1	C1	C2	-2.61(15)
C1	O1	C4	C3	17.99(13)
C1	O1	C4	C5	143.56(11)
Si	O3	C7	C6	142.74(9)
Si	O3	C7	C8	-103.78(11)
O1	C1	C2	C3	-13.82(15)
O1	C1	C2	C10	-140.49(12)
O2	C1	C2	C3	166.68(14)
O2	C1	C2	C10	40.01(19)
C1	C2	C3	C4	23.33(13)
C1	C2	C3	C12	146.34(11)
C10	C2	C3	C4	145.84(12)
C10	C2	C3	C12	-91.14(15)
C1	C2	C10	C11	67.93(16)
C3	C2	C10	C11	-50.89(17)
C2	C3	C4	O1	-25.22(12)
C2	C3	C4	C5	-146.80(11)
C12	C3	C4	O1	-149.14(11)
C12	C3	C4	C5	89.29(14)
C2	C3	C12	C13	60.50(17)
C4	C3	C12	C13	177.88(13)
O1	C4	C5	C6	-63.40(13)
O1	C4	C5	C9	56.56(14)
C3	C4	C5	C6	55.65(15)
C3	C4	C5	C9	175.61(11)
C4	C5	C6	C7	126.60(11)
C4	C5	C6	C15	-107.86(13)
C9	C5	C6	C7	0.74(13)
C9	C5	C6	C15	126.28(12)

C4	C5	C9	C8	-98.91(12)
C4	C5	C9	C22	32.11(17)
C6	C5	C9	C8	25.94(12)
C6	C5	C9	C22	156.96(12)
C5	C6	C7	O3	90.12(12)
C5	C6	C7	C8	-27.38(13)
C15	C6	C7	O3	-35.42(17)
C15	C6	C7	C8	-152.92(13)
O3	C7	C8	C9	-73.81(12)
C6	C7	C8	C9	43.74(13)
C7	C8	C9	C5	-43.19(12)
C7	C8	C9	C22	-174.33(11)
C5	C9	C22	C23	-113.14(16)
C5	C9	C22	C24	70.28(16)
C8	C9	C22	C23	11.2(2)
C8	C9	C22	C24	-165.39(12)
C2	C10	C11	N	13(8)
C3	C12	C13	C14	-113.09(19)

Table 6: Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Si	0.02151(15)	0.02406(16)	0.02326(16)	0.00321(13)	0.00365(11)	0.00183(13)
O1	0.0272(4)	0.0439(6)	0.0235(4)	-0.0025(4)	0.0067(3)	-0.0050(4)
O2	0.0328(5)	0.0503(7)	0.0400(6)	0.0016(5)	0.0076(4)	-0.0128(5)
O3	0.0270(4)	0.0306(5)	0.0237(4)	0.0037(4)	0.0004(3)	-0.0017(4)
N	0.0679(10)	0.0501(9)	0.0678(10)	0.0031(8)	0.0269(9)	0.0196(8)
C1	0.0225(6)	0.0372(7)	0.0272(7)	0.0007(5)	0.0024(5)	-0.0003(5)
C2	0.0285(6)	0.0301(6)	0.0222(6)	-0.0024(5)	0.0025(5)	-0.0020(5)
C3	0.0271(5)	0.0281(5)	0.0201(5)	-0.0028(5)	0.0052(4)	-0.0005(5)
C4	0.0251(6)	0.0288(6)	0.0203(6)	-0.0007(5)	0.0053(5)	0.0005(5)
C5	0.0249(6)	0.0256(6)	0.0189(5)	0.0000(5)	0.0051(5)	-0.0001(5)
C6	0.0289(6)	0.0306(7)	0.0235(6)	-0.0009(5)	0.0021(5)	0.0042(5)
C7	0.0280(6)	0.0295(7)	0.0227(6)	0.0041(5)	-0.0004(5)	-0.0022(5)
C8	0.0294(6)	0.0434(8)	0.0216(6)	0.0050(5)	0.0053(5)	-0.0019(5)
C9	0.0273(6)	0.0321(7)	0.0182(5)	-0.0020(5)	0.0040(5)	0.0020(5)
C10	0.0469(8)	0.0329(7)	0.0331(7)	-0.0086(6)	0.0112(6)	-0.0077(6)
C11	0.0536(9)	0.0323(7)	0.0458(9)	-0.0058(7)	0.0237(8)	0.0010(7)
C12	0.0419(8)	0.0350(7)	0.0243(6)	-0.0019(6)	0.0104(6)	-0.0077(6)
C13	0.0693(11)	0.0501(10)	0.0345(8)	-0.0068(7)	0.0274(8)	-0.0183(8)
C14	0.1220(19)	0.0741(14)	0.0273(8)	-0.0092(9)	0.0215(10)	-0.0426(14)
C15	0.0335(7)	0.0681(12)	0.0329(7)	-0.0016(8)	0.0093(6)	0.0156(8)
C16	0.0342(7)	0.0240(6)	0.0530(9)	0.0041(6)	0.0062(7)	0.0045(6)
C17	0.0334(7)	0.0568(10)	0.0279(6)	0.0073(7)	0.0096(5)	0.0015(7)
C18	0.0246(6)	0.0272(6)	0.0345(7)	0.0021(5)	0.0058(5)	0.0006(5)
C19	0.0406(8)	0.0257(7)	0.0617(11)	-0.0015(7)	0.0116(8)	-0.0010(6)
C20	0.0307(7)	0.0481(9)	0.0467(9)	0.0045(8)	-0.0050(6)	-0.0068(7)
C21	0.0375(8)	0.0478(9)	0.0578(10)	-0.0014(8)	0.0227(8)	-0.0090(7)
C22	0.0353(7)	0.0490(9)	0.0198(6)	-0.0072(6)	0.0024(5)	0.0124(6)
C23	0.0346(8)	0.0721(12)	0.0398(8)	-0.0126(8)	0.0087(7)	0.0110(8)
C24	0.0664(10)	0.0505(10)	0.0348(8)	0.0023(7)	0.0090(7)	0.0247(9)

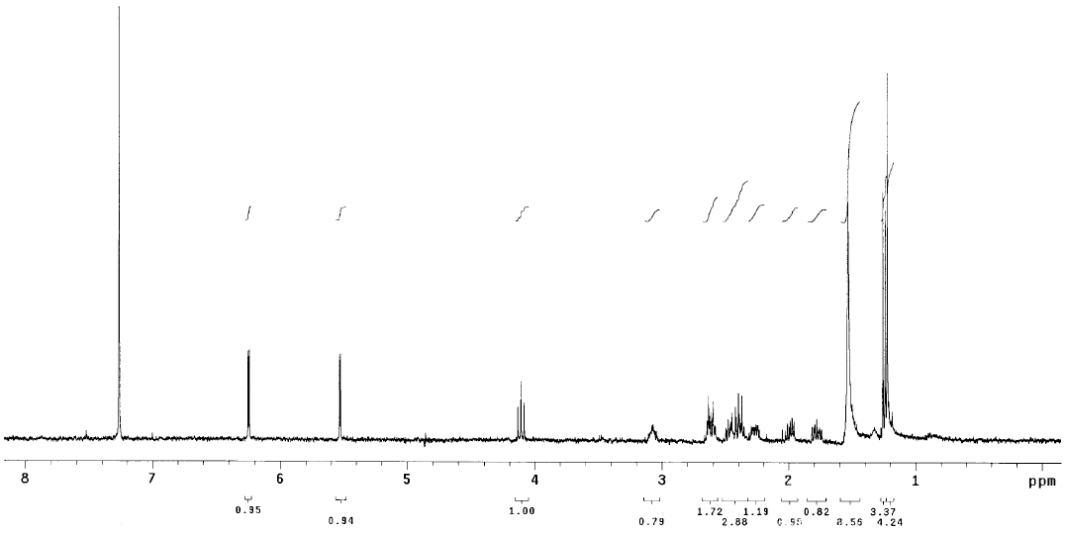
The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

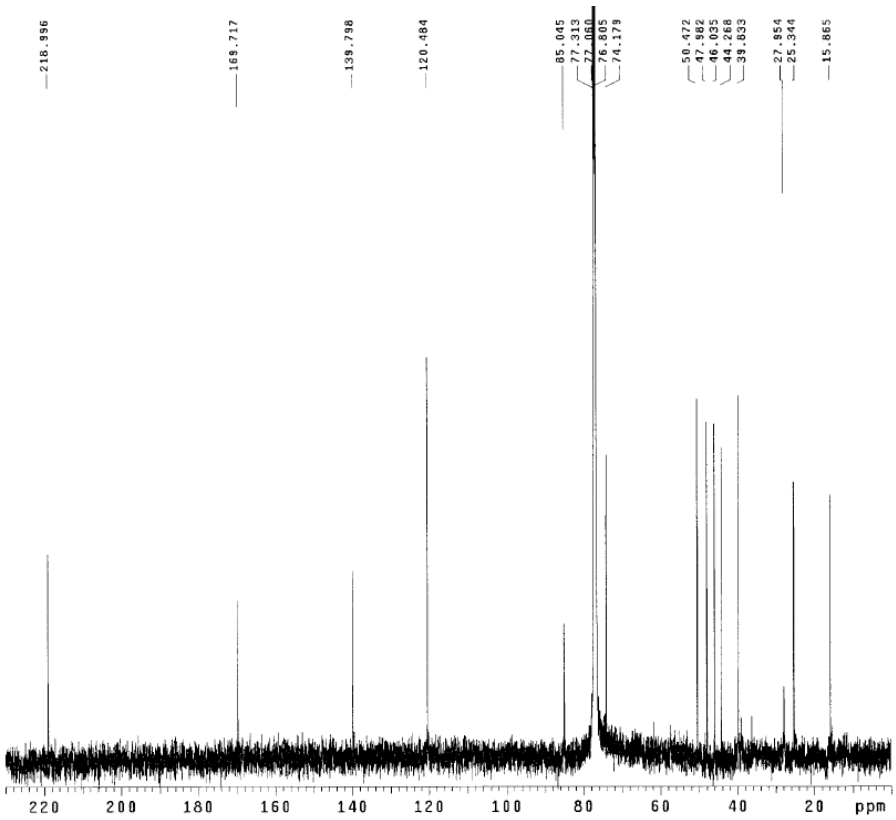
Table 7: Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2	0.4245	0.5680	0.5764	0.034
H3	0.1609	0.5885	0.4736	0.031
H4	0.3130	0.3278	0.4310	0.030
H5	0.0942	0.3088	0.3535	0.028
H6	0.1071	0.6537	0.3262	0.035
H7	0.0317	0.6807	0.1739	0.034
H8A	0.2340	0.5540	0.2054	0.038
H8B	0.1470	0.4453	0.1210	0.038
H9	0.0994	0.2482	0.2160	0.032
H10A	0.3197	0.7768	0.6324	0.045
H10B	0.4140	0.8694	0.5864	0.045
H12A	0.1463	0.3169	0.5339	0.040
H12B	0.2978	0.3138	0.5821	0.040
H13	0.1270	0.5334	0.6380	0.058
H14A	0.3629	0.3975	0.7364	0.090
H14B	0.2686	0.5148	0.7764	0.090
H15A	-0.1166	0.6488	0.2980	0.054
H15B	-0.0475	0.5434	0.3875	0.054
H15C	-0.1160	0.4471	0.2947	0.054
H16B	-0.2652	0.7536	0.1033	0.046
H16A	-0.2924	0.7716	-0.0037	0.046
H16C	-0.1546	0.8195	0.0640	0.046
H17A	-0.0263	0.5860	-0.0322	0.047
H17B	-0.1607	0.5303	-0.1017	0.047
H17C	-0.0642	0.3906	-0.0445	0.047
H19B	-0.1993	0.1661	0.0924	0.052
H19C	-0.2182	0.1725	-0.0140	0.052
H19A	-0.3326	0.1089	0.0219	0.052
H20A	-0.4793	0.3198	-0.0743	0.055
H20B	-0.3669	0.3857	-0.1117	0.055
H20C	-0.4420	0.5155	-0.0671	0.055
H21A	-0.4477	0.3111	0.0916	0.055
H21B	-0.4098	0.5066	0.0997	0.055
H21C	-0.3149	0.3708	0.1618	0.055
H23A	0.4625	0.1923	0.2410	0.059
H23B	0.3924	0.3749	0.2085	0.059
H24A	0.3640	-0.0172	0.2986	0.062
H24B	0.2108	-0.0121	0.2653	0.062
H24C	0.2885	0.0599	0.3630	0.062

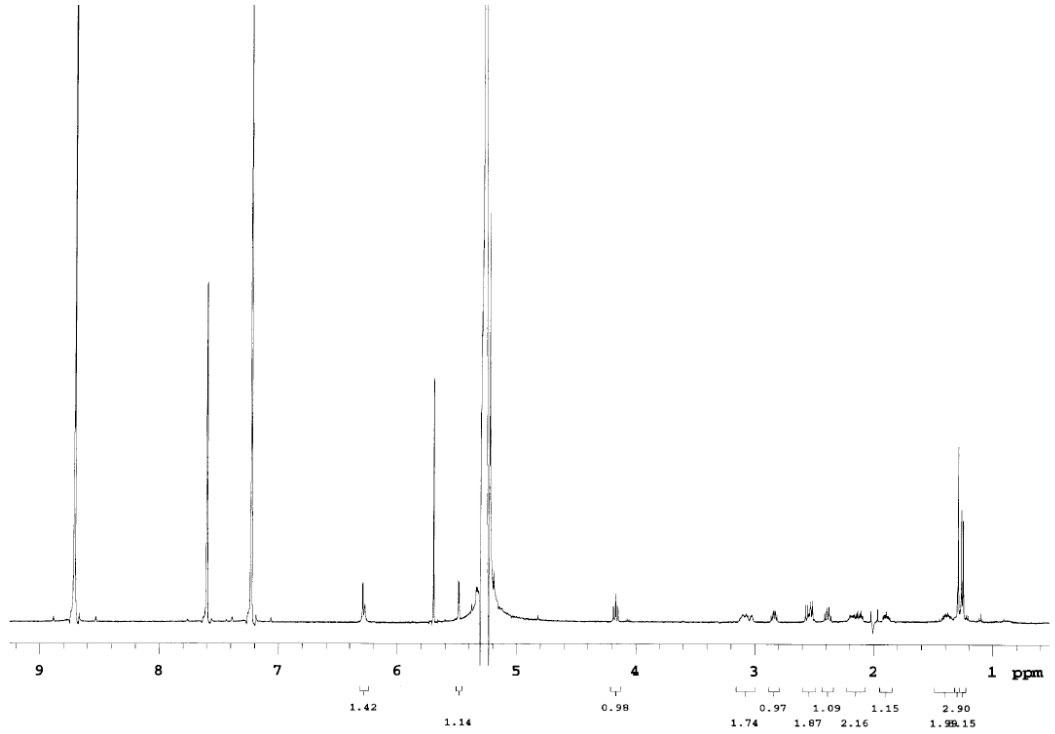
Appendix 3: Copies of NMR spectra for natural and synthetic 6.2

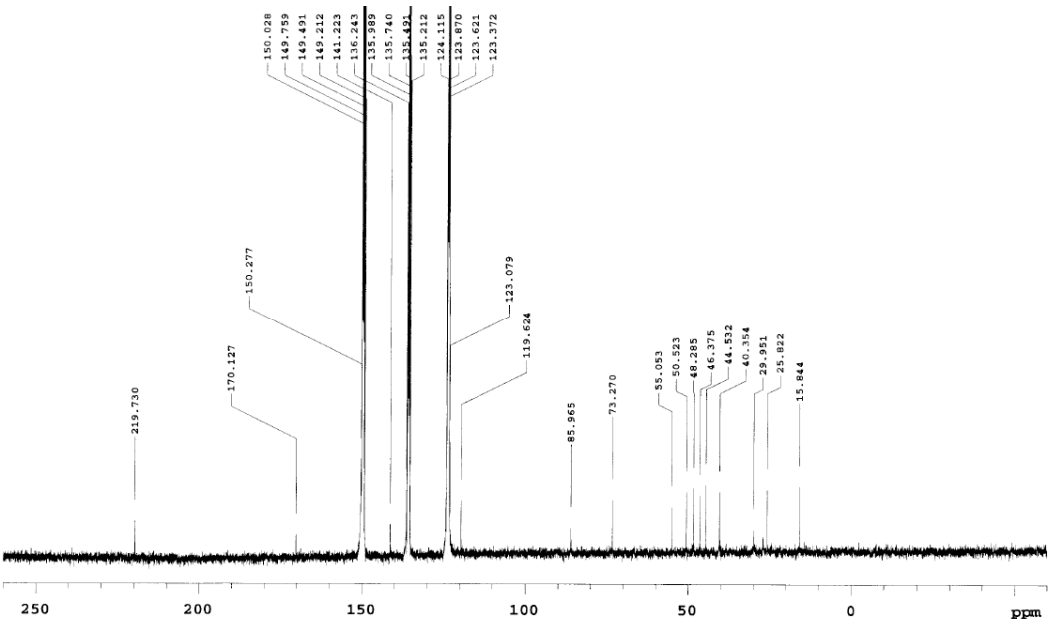
NMR spectra for synthetic **6.2** in $CDCl_3$:





NMR spectra for synthetic **6.2** in pyridine-d_5:





NMR spectra provided by Professor Ando for natural **6.2**[3] (in pyridine-d_5):