

THE DEVELOPMENT OF NOVEL ORGANOCATALYTIC  
ENANTIOSELECTIVE PERICYCLIC REACTIONS

By

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**ABSTRACT OF THE DISSERTATION**

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Dissertation Director:

Professor Stacey Brenner-Moyer

Organocatalysis has played a role in the development of enantioselective catalytic reactions, specifically pericyclic reactions, including cycloadditions and sigmatropic rearrangements, especially in the past two decades. This dissertation presents a comprehensive review and background on the development of new organocatalytic pericyclic reactions methods, specifically cycloadditions and sigmatropic rearrangements, leading to asymmetric small molecules. Herein, the research that was conducted and lead to two successful new discoveries are described. The topics specifically discussed in this dissertation are: 1.) Cycloaddition reactions catalyzed by primary and secondary chiral amine catalysts since 2011. 2.) Sigmatropic rearrangements that have been catalyzed by organocatalysts in general. 3.) A novel [5 + 2] cycloaddition reaction catalyzed by a diphenyl prolinol silyl ether. 4.) A Claisen rearrangement kinetic resolution of  $\gamma$ -substituted *O*-allyl  $\alpha,\beta$ -unsaturated aldehydes catalyzed by 2,5-diphenyl pyrrolidine. The methodologies reviewed are all groundbreaking achievements improving the scope of pericyclic reactions that

achieve optically active products, that can potentially act as precursors to even larger chiral building blocks as a part of molecular architectures.



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*In loving memory of Marlene Bush and Essanna Gray*

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## LIST OF SYMBOLS AND ABBREVIATIONS

2°	secondary
2D NMR	two-dimensional nuclear magnetic resonance
Å	angstrom
[α] <sub>D</sub>	optical rotation
Ac	acetyl
AcO	acetate
AcOH	acetic acid
Ar	aryl
BHT	dibutylhydroxytoluene
BINAM	2,2'-diamino-1,1'-binaphthalenes
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
BnNH <sub>2</sub>	benzylamine
Boc	<i>tert</i> -butoxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
BzOH	benzoic acid
°C	degrees Celsius
<sup>13</sup> C NMR	carbon-13 nuclear magnetic resonance
calc	calculated
calcd.	calculated
cat	catalyst

CBS	Corey-Bakshi-Shibata
Cbz	carboxylbenzyl
CDCl <sub>3</sub>	deuterated chloroform
CD <sub>3</sub> CN	deuterated acetonitrile
cod	1,5-cyclooctadiene
conc	concentrated
Cy	tricyclohexylphosphine
δ	nuclear magnetic shift
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DHDQ	dihydroquinone
DIBAL-H	diisobutylaluminum hydride
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DKR	dynamic kinetic resolution
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide

DPP	diphenylphosphine
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DYKAT	dynamic kinetic asymmetric transformation
E <sup>+</sup>	electrophile
EDG	electron-donating group
ee	enantiomeric excess
enal	$\alpha,\beta$ -unsaturated aldehyde
<i>epi</i>	epimer
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et <sub>2</sub> O	diethyl ether
Et <sub>3</sub> N	triethylamine
EWG	electron-withdrawing group
FCC	flash-column chromatography
FT-IR	Fourier transform infrared spectroscopy
g	gram
h	hour
<sup>1</sup> H NMR	proton nuclear magnetic resonance
HFIP	hexafluoroisopropanol



HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resonance mass spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
IEDHDA	inverse-electron-demand hetero Diels–Alder
inc	incomplete
<i>i</i> PA	<i>iso</i> -propyl alcohol
<i>i</i> Pr <sub>2</sub> NPh	di- <i>iso</i> -propyl aniline
<i>i</i> Pr	<i>iso</i> -propyl
<i>i</i> PrOH	<i>iso</i> -propyl alcohol
IR	infrared
<i>J</i>	coupling constant
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar
M <sup>+</sup>	positively charged mass
M <sup>-</sup>	negatively charged mass
μM	micromolar
mM	millimolar
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeO-	methoxy

MeOH	methanol
Me <sub>2</sub> S	dimethylsulfide
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mol	mole
mol %	mole percent
MsCl	methanesulfonyl chloride
ms	molecular sieves
NaOAc	sodium acetate
Nap	naphthyl
NBS	<i>N</i> -bromosuccinimide
nd	not determined
NEt <sub>3</sub>	triethylamine
<i>n</i> BuLi	<i>n</i> -butyl lithium
NFSI	N-fluorobenzenesulfonimide
NMO	N-Methylmorpholine-N-oxide
<i>n</i> Pr	<i>n</i> -propyl
nr	no reaction
Nu <sup>-</sup>	nucleophile
[O]	oxidant
obs	observed

OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
pds	products
PE	petroleum ethers
pH	phenyl
pH	potential of hydrogen
PhCF <sub>3</sub>	trifluorotoluene
pK <sub>a</sub>	ionization constant
PMP	<i>para</i> -methoxyphenyl
<i>p</i> NBA	<i>para</i> -nitrobenzoic acid
PNP	<i>para</i> -nitrophenol
psi	pounds per square inch
<i>p</i> TSA	<i>para</i> -toluenesulfonic acid
Q-TOF	quadrupole time-of-flight
rac	racemic
R <sub>f</sub>	retention factor
rt	room temperature
rxn	reaction
s	singlet
SA	salicylic acid
sm	starting material
t	triplet
T	temperature
TBS	<i>tert</i> -butyldimethylsilyl

TBSCl	<i>tert</i> -butyldimethylsilyl chloride
<i>t</i> Bu	<i>tert</i> -butyl
TBME	<i>tert</i> -butyl methylether
<i>t</i> BuOH	<i>tert</i> -butyl alcohol
<i>t</i> BuOK	potassium <i>tert</i> -butoxide
TCA	trichloroacetic acid
temp	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
TFA	2,2,2-trifluoroacetic acid aka triflic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TS	transition state
TsNH <sub>2</sub>	tosylamine
UV	ultraviolet
μL	microliter
wt. %	weight percent

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## CHAPTER 1

### ORGANOCATALYTIC PERICYCLIC REACTIONS

#### 1.1 Brief Introduction to Organocatalysis

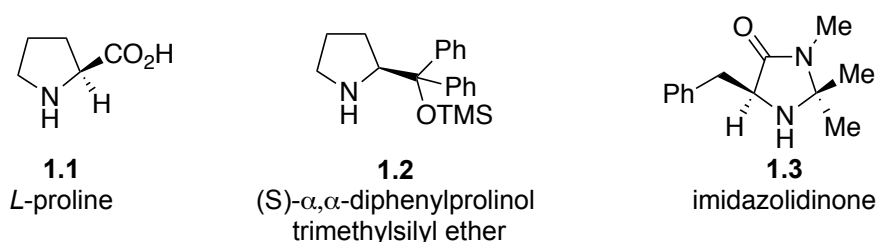
Catalysis provides a way for reactions to take place by lowering the activation energy for the reaction. Likewise, asymmetric catalysis can be used to control stereochemical outcomes of products by activating the substrate while providing a chiral environment. The field of organocatalysis enables access to optically active molecules by using chiral organic molecules as catalysts in organic synthesis.<sup>1</sup> While metal catalysts are commonly used, they can be costly, toxic, and difficult to handle since they often require inert reaction conditions (i.e., exclusion of air and water).<sup>2</sup>

Chiral organocatalysts are often prepared from naturally occurring single enantiomer precursors (i.e., amino acids, alkaloids, ureas, hydroxy acids) that are readily available. For example, the amino acid *L*-proline (**1.1**, **Figure 1.1**), proline derivatives like diarylprolinol silyl ether **1.2**, and imidazolidinone catalyst **1.3** derived from *L*-phenylalanine are commonly employed catalysts in organocatalytic reactions. Essentially, the secondary amine contains chiral information that will ultimately induce/assist the desired stereoselective transformation. This approach enables new ways to make molecules that traditional transition metal and enzyme-based catalysis cannot access, thus complementing an organic chemist's proverbial synthetic toolbox.<sup>3</sup>

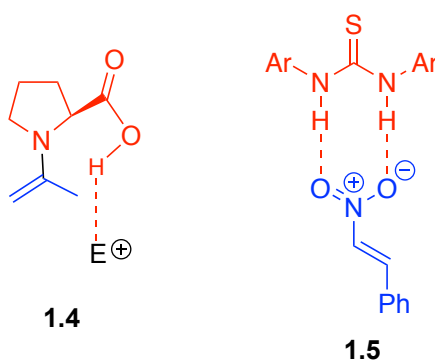
The field of aminocatalysis relies on two main modes of activation by utilizing chiral primary or secondary amines to activate the carbonyl functional group of aldehydes and ketones. Non-covalent interactions or covalent interactions can form depending on the catalyst and substrate.<sup>4</sup> Hydrogen bonding interactions can also occur from *L*-proline

through interaction of the carboxylic acid proton and the incoming electrophile (**1.4**, **Figure 1.2**).<sup>5</sup> This not only activates the electrophile, but directs it to one face of the nucleophile. Weak attractive bonding interactions include hydrogen bonding, electrostatic effects, hydrophobic,  $\pi$ - $\pi$ ,  $\pi$ -cation,<sup>6</sup> and Van der Waals forces.<sup>7</sup> Example of catalysts that participate in hydrogen bonding are thioureas, which can donate two hydrogen bonds to the substrate, thereby activating the molecule for subsequent nucleophilic attack (**1.5**).

**Figure 1.1** Some common chiral secondary catalysts.



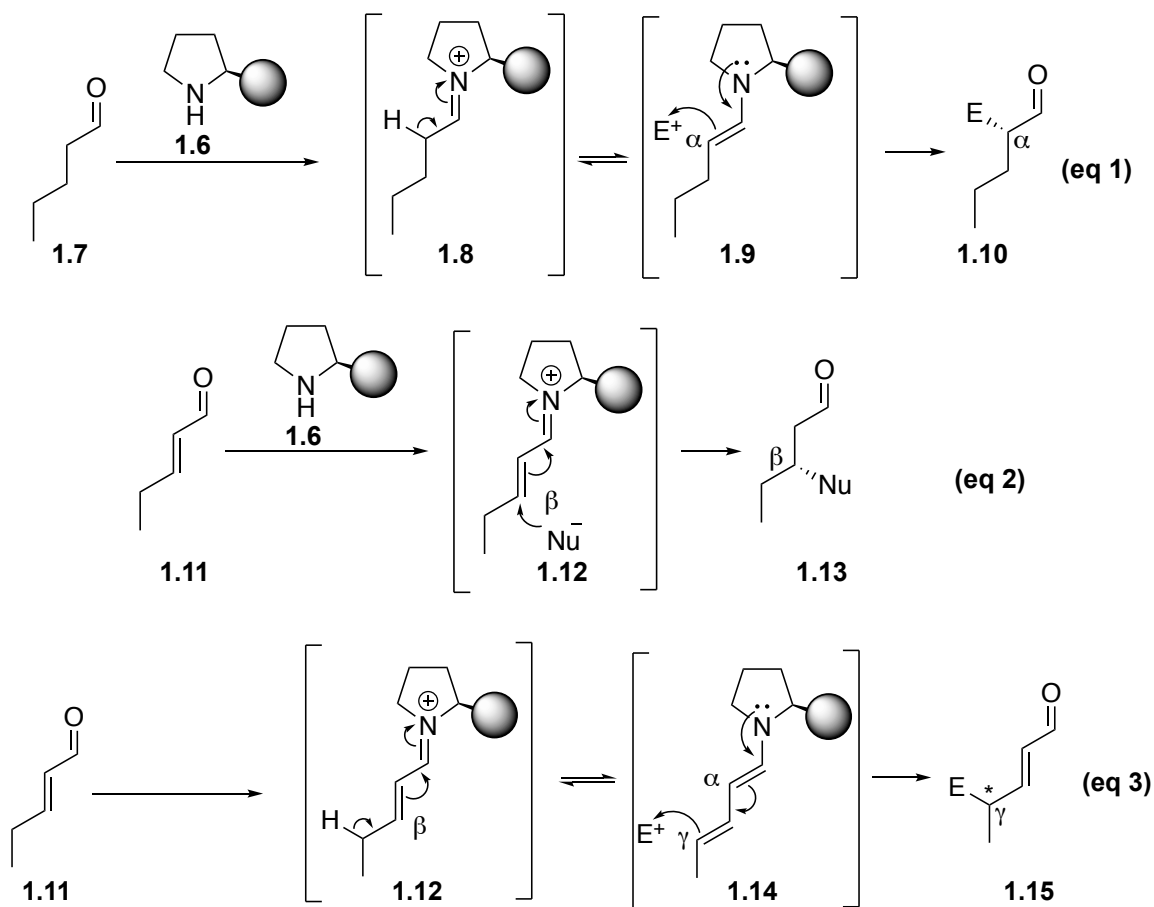
**Figure 1.2** Substrate activation via hydrogen bonding interactions.

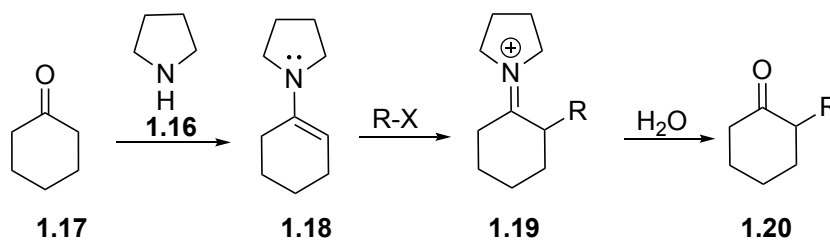


Saturated aldehydes can condense with a secondary chiral amine catalyst **1.6** to form iminium **1.8** (eq 1, **Scheme 1.1**). Dienamines **1.14** which have two nucleophilic sites at the  $\gamma$ - and  $\alpha$ -positions, form from condensation of **1.6** with an  $\alpha,\beta$ -unsaturated aldehyde **1.11** that offer a  $\gamma$ -enolizable proton (eq 3, **Scheme 1.1**). If regioselective, nucleophilic attack by the  $\gamma$ -carbon will produce a  $\gamma$ -functionalized  $\alpha,\beta$ -unsaturated aldehyde **1.15** after hydrolysis.

Early use of a secondary amine organocatalysis to promote organic transformations was done by Gilbert Stork in 1954; this reaction is dubbed the “Stork enamine alkylation” (**Scheme 1.2**).<sup>8</sup> Here, the use of pyrrolidine **1.16** and cyclohexanone **1.17** pre-form enamine **1.18**, that underwent alkylation at the alpha-position to form **1.19**, which after was hydrolyzed to form **1.20**. Later in the 1970’s, (*L*)-proline **1.1** was used to catalyze the Hajos-Parrish-Eder-Sauer-Wiechert reaction, a chiral intramolecular aldol reaction.<sup>9-10</sup> In 1997, Danishefsky and Barbas published an example of a Robinson annulation catalyzed by natural class I aldolase enzyme, that was known to have a participating lysine residue at the reactive site.<sup>11</sup>

**Scheme 1.1** Substrate activation of aldehydes by secondary chiral amine catalyst.



Scheme 1.2 Stork enamine reaction.<sup>8</sup>

The field of organocatalysis was revived in the early 2000's in two reports. An enamine-mediated intermolecular aldol reaction using *L*-proline **1.1** was reported by Benjamin List.<sup>5</sup> First use of diphenyl prolinol silyl ether **1.2** as an organocatalyst was reported independently by the groups of Hayashi<sup>12</sup> and Jorgenson<sup>13</sup> in 2005. David MacMillan reported the design and utility of the 1<sup>st</sup> generation imidazolidinone **1.3** developed in his group to form an iminium ion intermediate as the dienophile in a Diels–Alder cycloaddition.<sup>14</sup>

*“As organic molecules readily react with each other, why did we disregard these compounds as catalysts and rather relied on the assistance of biologists and inorganic chemists to provide enzymes or explain the foreign world of d-orbitals to us? Why did we not expect catalytic competence from organic molecules exactly those compounds we can truly design, make, and know most about?”*<sup>15</sup>

—Benjamin List

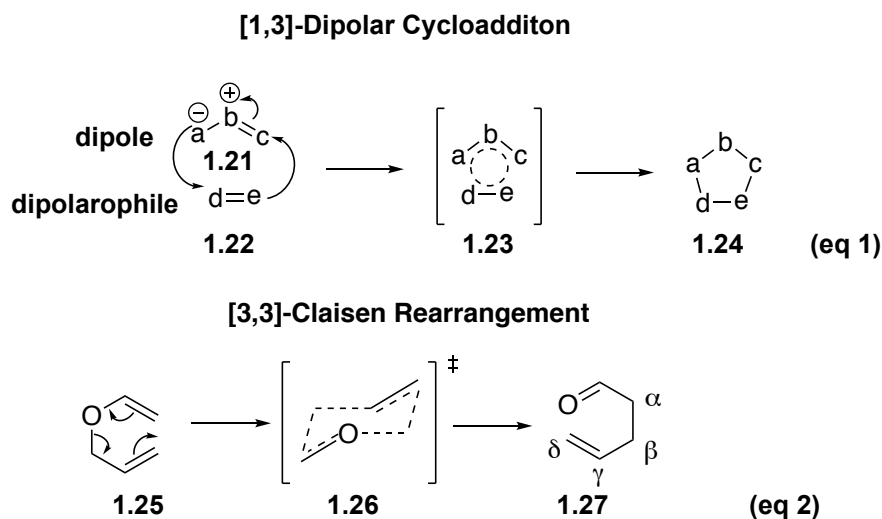
## 1.2 Pericyclic Processes: Cycloaddition and Sigmatropic

Concerted reactions that proceed via cyclic transition state are called pericyclic reactions.<sup>16</sup> Both cycloaddition reactions (i.e., Diels–Alder) and sigmatropic rearrangements are types of pericyclic reactions (**Scheme 1.3**). Other classes of pericyclic reactions include group transfer (i.e., ene reaction) and electrocyclic ring opening/closing reactions.

In a cycloaddition reaction, two unsaturated molecules undergo a concerted reaction to form a ring. The  $\pi$ -electrons reorganize, forming two new  $\sigma$ -bonds.<sup>17</sup> In a 1,3-dipolar cycloaddition, dipole **1.21** will react with dipolarophile **1.22** in a concerted mechanism to form a cyclic transition state **1.23** to produce **1.24** (eq 1, Scheme 1.3).

In Greek, the word *tropos* means “change”, thus sigmatropic literally translates to “change of sigma bonds”.<sup>18</sup> Sigmatropic rearrangement reactions involve the breaking of a  $\sigma$ -bond in a  $\pi$ -electron system, to form a new  $\sigma$ -bond with concomitant reorganization of the adjacent  $\pi$ -electrons in a concerted manner. The order of the reaction is indicated by the numbered position of the atom from which the  $\sigma$ -bond is breaking, followed by the numbered position of the atom where the new  $\sigma$ -bond is formed, in square brackets. One useful sigmatropic rearrangement is the Claisen reaction, a type of [3,3]-sigmatropic rearrangement (eq 2, Scheme 1.3). The mechanism occurs in a concerted fashion to form carbonyl compound **1.27** through cyclic transition state **1.26**.

**Scheme 1.3** Examples of cycloaddition reaction and sigmatropic rearrangement.



Both cycloaddition reactions<sup>19-27</sup> and sigmatropic rearrangements<sup>26,28-29</sup> are valuable synthetic tools that enable the rapid construction of complex molecular frameworks. Organocatalytic methodologies have rapidly expanded to include asymmetric



catalytic variants of cycloaddition and sigmatropic rearrangement reactions by different chiral aminocatalysts.<sup>1</sup> Numerous reports of asymmetric cycloadditions catalyzed by primary or secondary aminocatalysts have been reported in the literature. All reports up until 2011 were covered in a review by Moyano and Rios.<sup>26</sup> A review discussing [2 + 2], [3 + 3], and [4 + 2] cycloadditions specifically using diarylprolinol silyl ethers since September 2016 was published by Jørgensen.<sup>30</sup>

There has been less development in the case of organocatalyzed asymmetric sigmatropic rearrangements, as a result one of the few reviews on this topic was published in 2010.<sup>31</sup> Steglich rearrangements will not be included, although there has been development of asymmetric catalytic examples with use of: NHC's,<sup>32-33</sup> chiral ammonium betaine,<sup>34</sup> and isothiurea catalysts.<sup>35</sup> One example is by Seidel and coworkers, in which they demonstrated a dual catalytic approach using a chiral thiourea with DMAP.<sup>36</sup>

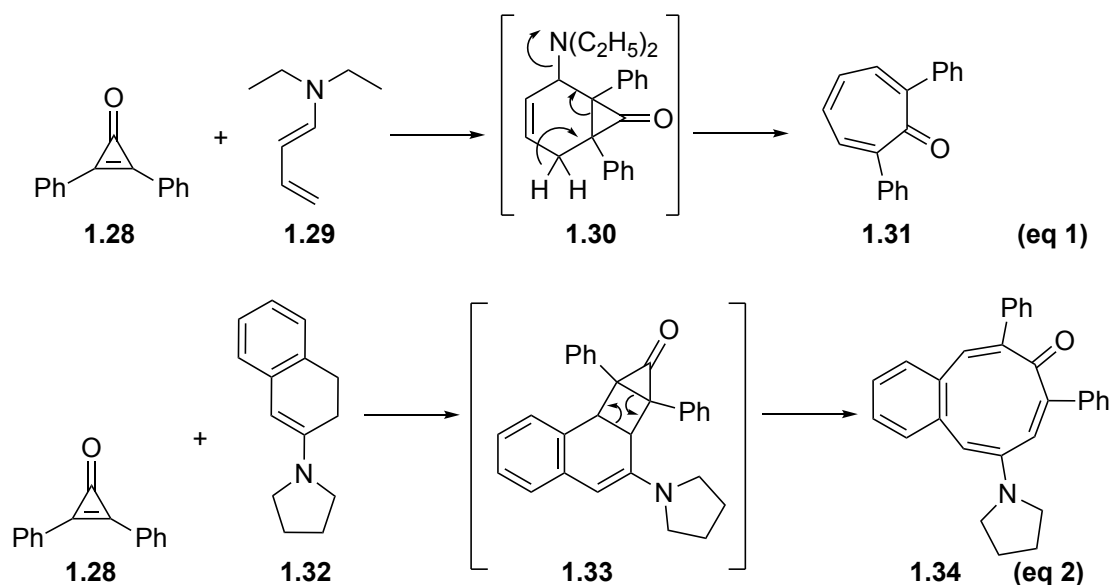
Pericyclic processes, specifically asymmetric catalytic cycloaddition reactions by primary or secondary aminocatalysts since 2011, all organocatalytic enantioselective sigmatropic rearrangements, and a few non-catalytic, stereospecific sigmatropic rearrangements will be covered in this review chapter. Both concerted (pericyclic) and stepwise (formal) cycloaddition and sigmatropic rearrangements will be included. The cycloaddition reactions discussed are: [4 + 2] (Section **1.3.1**), [3 + 2] and 1,3-dipolar (Section **1.3.2**), [2 + 2] (Section **1.3.3**), [5 + 2] (Section **1.3.4**), [5 + 3] and [3 + 3] (Section **1.3.1**). Although there has been interesting development on other cycloadditions that focus on larger frameworks, these reactions will not be discussed ([8+2], [6+4], and [6+2] cycloaddition reactions).<sup>37-38</sup> While there has been much noteworthy development on reactions utilizing synergistic catalytic systems (i.e. iminium-catalysis and transition

metal),<sup>39,40,41,42</sup> these reports that feature the participation of a metal catalyst will not be discussed in this review.

### 1.3 Cycloaddition Reactions Catalyzed by Chiral 1° and 2° Amines

The pioneering works of Ciabattini and Berchtold in 1965 and 1966, showcased the use of an enamine and dienamine in a symmetric cycloaddition reaction (**Scheme 1.4**).<sup>43-44</sup> When diphenylcyclopropenone **1.28** was reacted with enamine **1.29**, formation of product **1.31** was observed (**eq 1**), whereas reaction between **1.28** and enamine **1.32** led to the isolation of product **1.34** (**eq 2**). It was postulated that products **1.31** and **1.34** arise from cycloadducts **1.30** and **1.33** via 1,4 and 1,2-cycloaddition of the enamine to the cyclopropenone, respectively. It was not confirmed whether the mechanism proceeded by a concerted cycloaddition, or, by a Michael-type addition followed by ring closure of dipolar intermediate. These early examples established precedence for enamine and dienamines as reactants in these pericyclic transformations.

**Scheme 1.4** Early use of enamine and dienamine in cycloaddition reaction.<sup>43-44</sup>



### 1.3.1 [4 + 2] Cycloadditions

#### 1.3.1.1 Iminium Activation

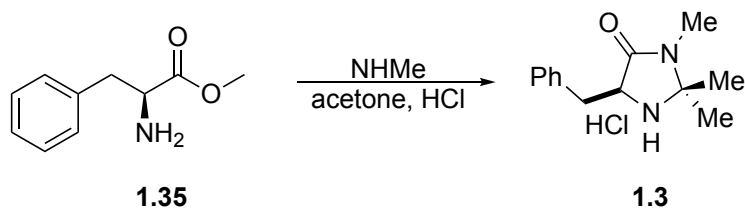
As mentioned previously, it was not until 2000 that organocatalysis reemerged in the literature. David MacMillan's group introduced the preparation and use of 1<sup>st</sup> generation imidazolidinone catalysts for asymmetric transformations.<sup>14</sup> Imidazolidinone **1.3** is synthesized in one step from the naturally occurring amino acid *L*-phenylalanine methyl ester **1.35** to afford bench-stable imidazolidinone catalyst **1.3** (**Scheme 1.5**). Use of this catalyst was demonstrated in a highly enantioselective organocatalytic Diels–Alder reaction by LUMO-lowering activation of cinnamaldehyde **1.36** to react with diene **1.37** (**Scheme 1.6**).

Polar solvent and mild reaction conditions (i.e., aerobic atmosphere and wet solvents) were used to form the product *exo* diastereomer **1.39b** in 99% yield and 93% ee. Based on DFT calculations of the iminium ion model, when using catalyst **1.3**, the *re* face of the (*E*)–iminium isomer **1.38** was shielded by the benzyl group of catalyst **1.3** exposing the *si* face of the dienophile for cycloaddition.<sup>45</sup> Later in 2002, this reaction was applied to  $\alpha,\beta$ -unsaturated ketones by employment of catalyst **1.40** (**Scheme 1.7**).<sup>46</sup> Use of **1.40** improved enantioselectivities (except for when R<sup>2</sup> = methyl).

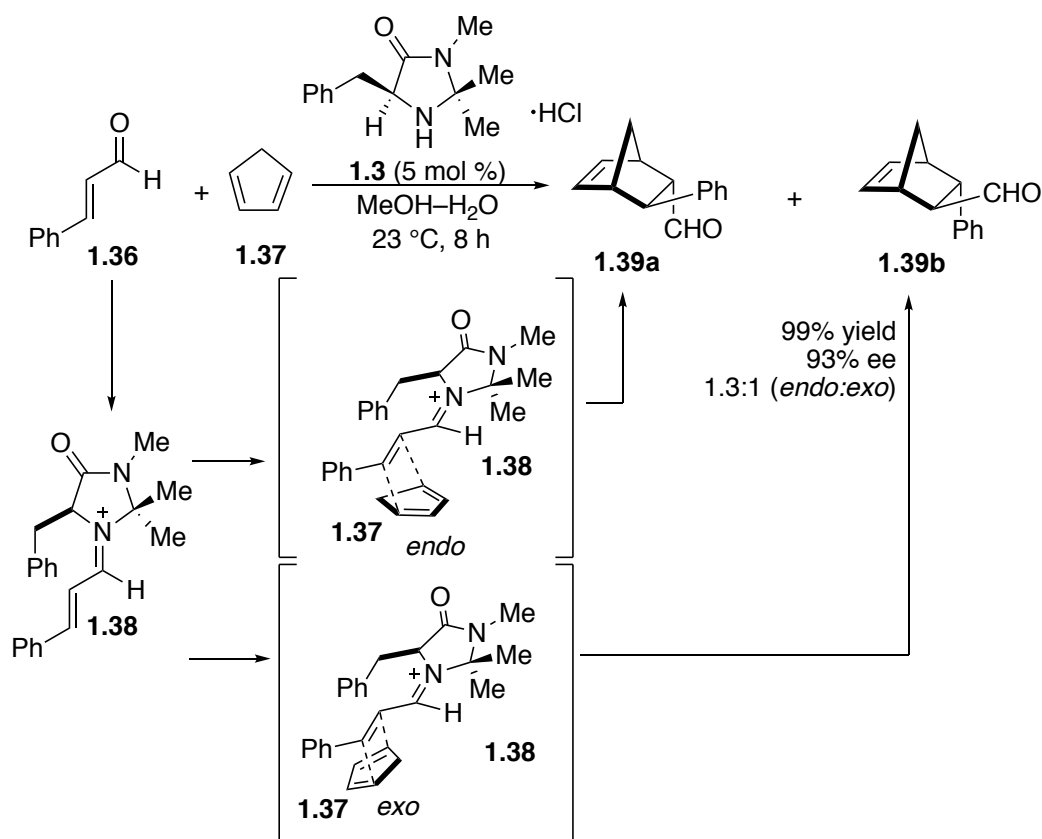
In 2007, Hayashi and group was first to demonstrate use of diarylprolinol silyl ether in an iminium-activated [4 + 2] cycloaddition (**eq 1**, **Scheme 1.8**).<sup>47</sup> In 2006, they published an asymmetric ene reaction using TBS-protected catalyst **1.44** with cinnamaldehyde **1.36** and cyclopentadiene **1.37** to form **1.45** and **1.46** (**eq 2**).<sup>48</sup> Subsequently, they found that slight changes of the reaction conditions could tune the reaction pathway to provide the Diels–Alder adduct **1.39**. In this cycloaddition reaction, cyclopentadiene **1.37** reacted with  $\alpha,\beta$ -unsaturated aldehyde **1.36**, in the presence of catalyst **1.43** and TFA as co-catalyst.

Selective formation of the *exo* diastereomer **1.39b** occurred in combined yields of 65-99% with excellent enantioselectivities of 84-97% ee. Further studies of this reaction expanded its use in aqueous conditions by employing a diarylprolinol silyl ether salt to afford purely the *exo* isomer **1.39b**.<sup>49</sup>

**Scheme 1.5** Preparation of imidazolidinone catalyst by MacMillan.



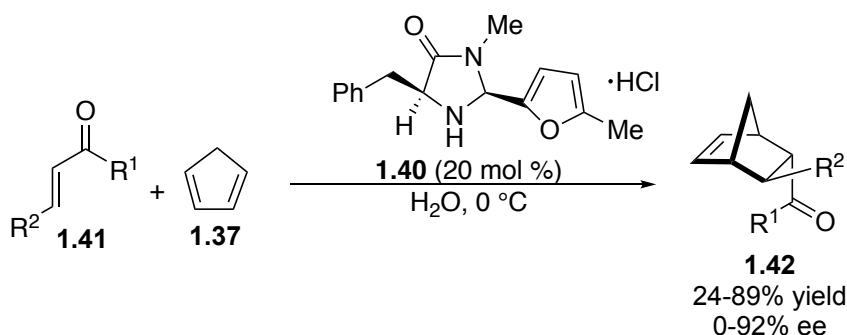
**Scheme 1.6** Iminium-activated Diels–Alder reaction by MacMillan.<sup>14</sup>



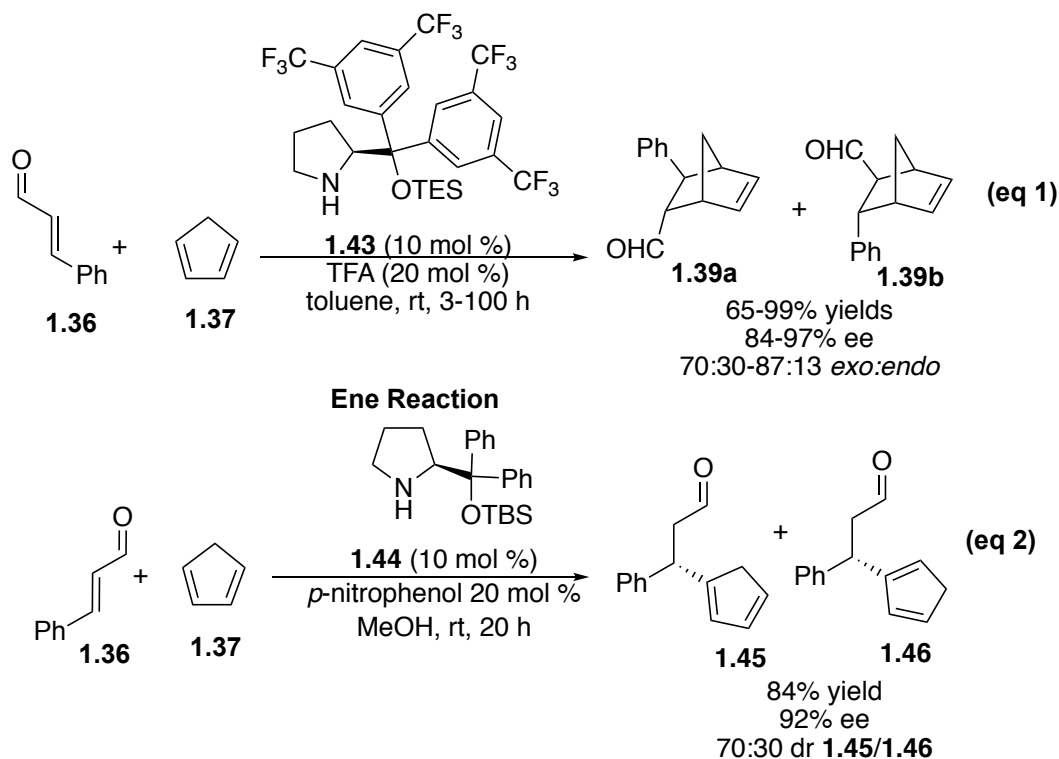
Like Ciabattini and Berchtold thought, Hayashi and group suspected and explored the possibility that not all cycloaddition reactions go through a concerted mechanism, but a stepwise one. In this case, the cyclization proceeds via nucleophilic addition to the

iminium cation intermediate.<sup>50-51</sup> Stepwise processes as such are referred to as formal cycloadditions. In 2015, nine years after publishing the ene reaction, Hayashi and group revised their postulated mechanism to: formation of iminium ion **1.49** from catalyst **1.44** and **1.36**, and of cyclopentadienyl anion **1.51** from cyclopentadiene **1.37** and **1.44** (Scheme 1.9).<sup>51</sup> The cyclopentadienyl anion **1.51** attacks the iminium in a 1,4-conjugate addition to form enamine **1.52**, and hydrolysis of the catalyst provides **1.45** and **1.46**.<sup>51</sup>

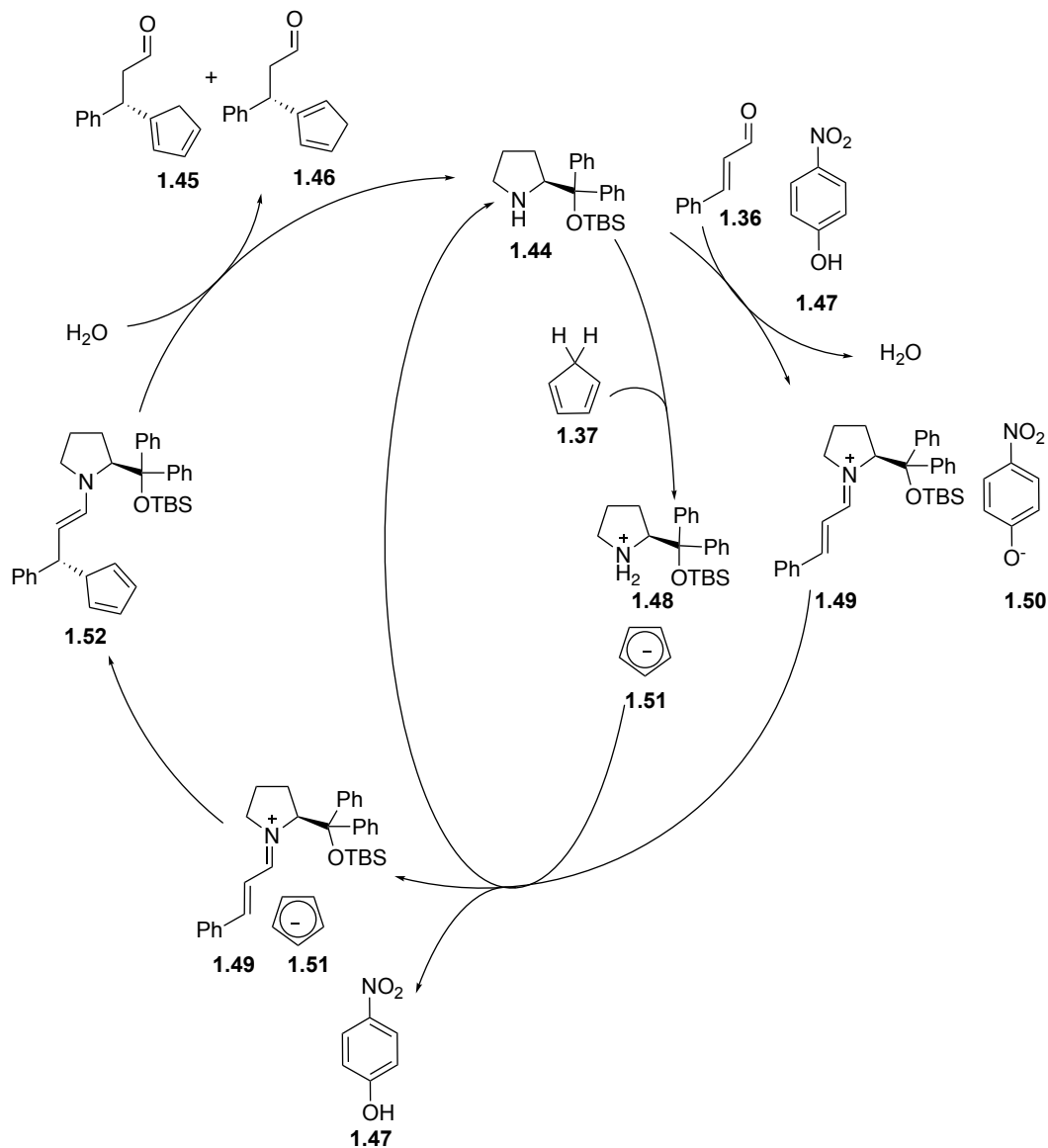
**Scheme 1.7** Organocatalyzed Diels–Alder reaction of unsaturated ketones.<sup>52</sup>



**Scheme 1.8** Iminium activation in [4 + 2] cycloaddition<sup>47</sup> and ene reaction<sup>48</sup>.



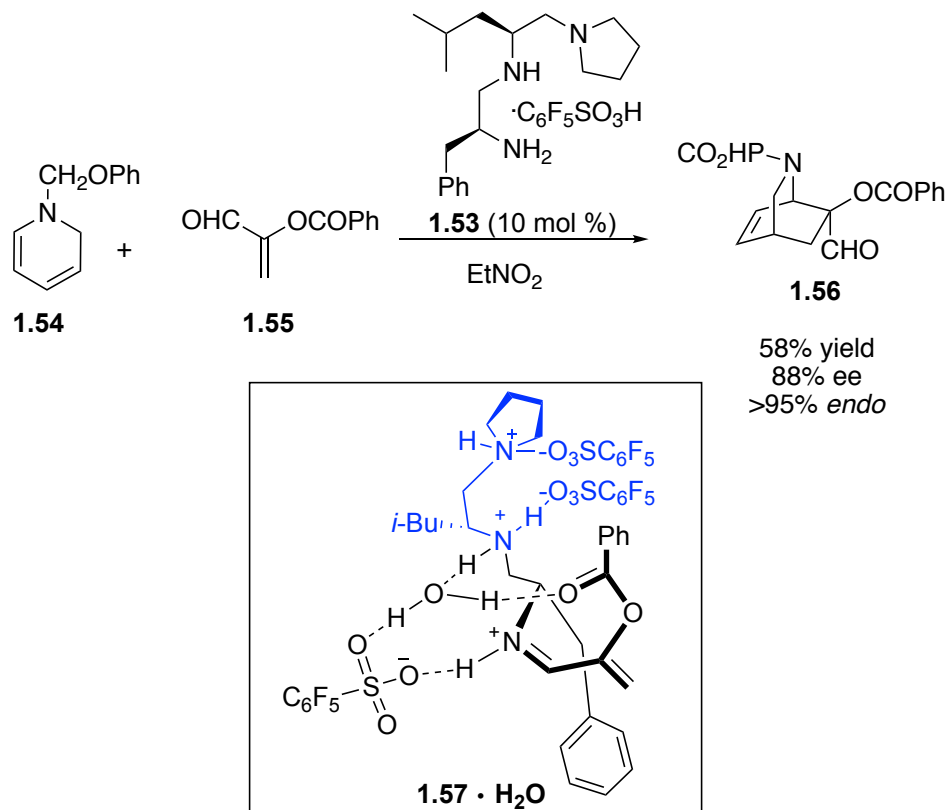
Scheme 1.9 Mechanism of ene reaction.



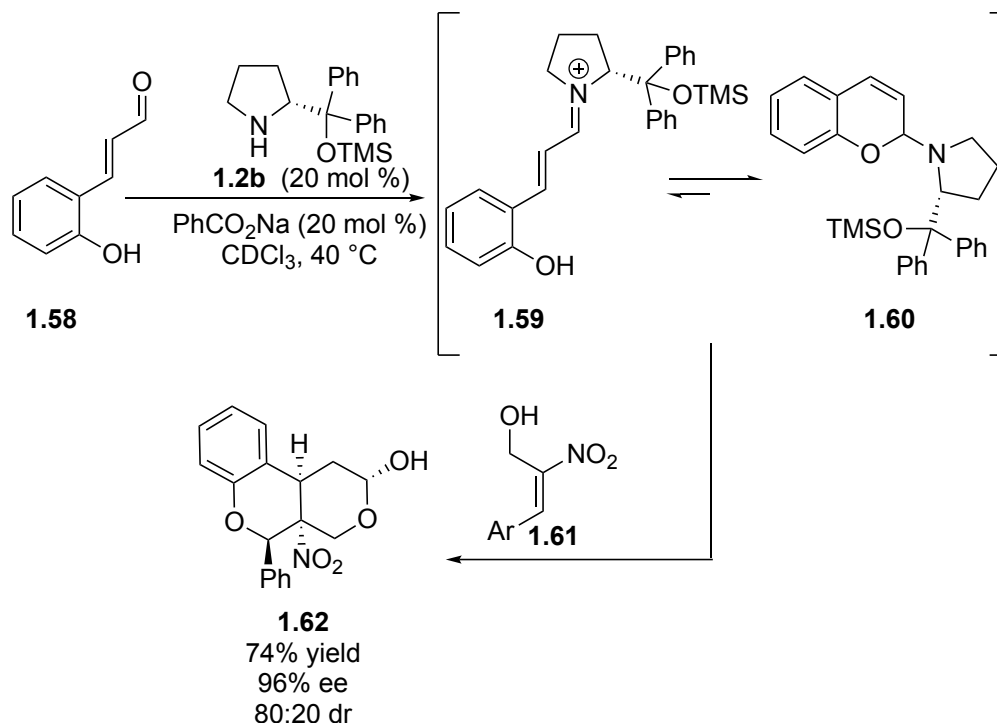
In 2014, Ishihara reported the first example of a catalytic enantioselective route to form isoquinuclidine derivatives by a Diels–Alder reaction of 1,2-dihydropyridines **1.54** with  $\alpha$ -acyloxyacroleins **1.55** catalyzed by chiral primary ammonium salt **1.53** (Scheme 1.10).<sup>53</sup> The model for asymmetric induction was formulated from DFT calculations performed to optimize the structure of the hydrate complex of the iminium salt **1.57**. They found that the (*Z*)-isomer of the iminium ion is stabilized via three bonds to one mole of

water (**1.57**), effectively shielding the *re*-face, allowing 1,2-dihydropyridine to attack the *si*-face to afford the *endo* product.

**Scheme 1.10** Ishihara's Diels–Alder reaction.<sup>53</sup>



In 2014, Jørgenson disclosed an organocatalytic enantioselective cascade reaction to form functionalized chromenes via iminium ion mediated oxa-Michael/Michael/intramolecular hemiacetalization with a tethered 2-nitroallylic alcohol **1.61** (Scheme 1.11).<sup>54</sup> Tricyclic and tetracyclic products **1.62** could be formed with excellent enantioselectivities, with good diastereoselectivities and in good yields.

**Scheme 1.11** Oxa-Michael/Michael/intramolecular hemiacetalization ring-closing.<sup>54</sup>

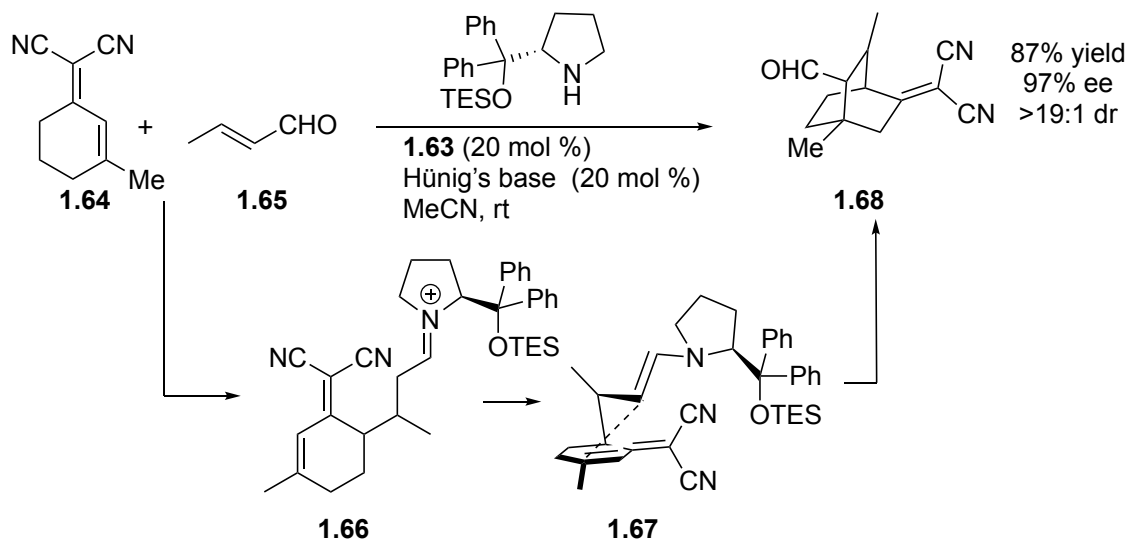
In 2014, Chen developed a highly regio- and stereoselective [4 + 2] formal cycloaddition process of cyclohexenylidenemalononitriles **1.64** and diverse  $\alpha,\beta$ -unsaturated aldehydes **1.65** by catalysis with **1.63** (Scheme 1.12).<sup>55</sup> Prior works inspired the reaction,<sup>56-57</sup> which proceeds by a  $\gamma$ -selective vinylogous Michael addition to form iminium ion intermediate **1.66** followed by a subsequent intramolecular 1,6-addition after conversion to the enamine **1.67** to afford a range of bridged bicyclo[2.2.2]octane architectures **1.68** with high molecular complexity in up to 98% ee, and in >19:1 dr.

In a 2015 report by Vicario and Carillo, 4-alkenyl-5H-1,2,3-oxathiazole 2,2-dioxide **1.69** was employed as a useful type of reagent to generate an electron-rich diene intermediate *in situ* which underwent a formal [4 + 2] cycloaddition with  $\alpha,\beta$ -unsaturated aldehydes of type **1.70** through iminium/enamine activation to form various fused products **1.71** (Scheme 1.13).<sup>58</sup> The iminium ion served as an electron-poor dienophile in this

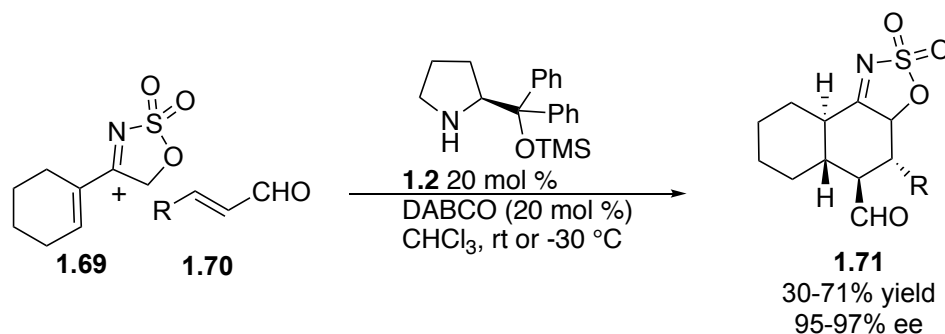


stepwise double Michael cascade process. Aliphatic enals and a variety of electronically diverse aryl substituted enals generated products in moderate yields with excellent enantioselectivities, and as a single diastereomer for the latter substrate class.

**Scheme 1.12** Chen's [4 + 2] formal cycloaddition.<sup>55</sup>



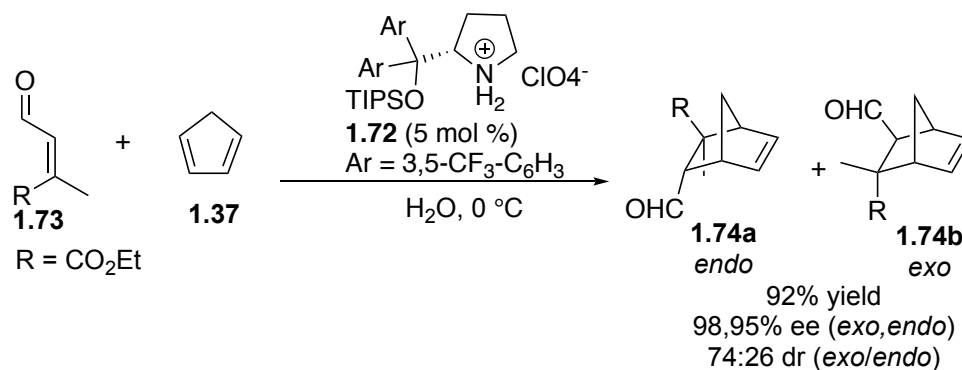
**Scheme 1.13** Vicario and Carillo's formal [4 + 2] cycloaddition of 4-(cyclohexenyl)-5H-1,2,3-oxathiazole 2,2-dioxide with enals via iminium/enamine activation.<sup>58</sup>



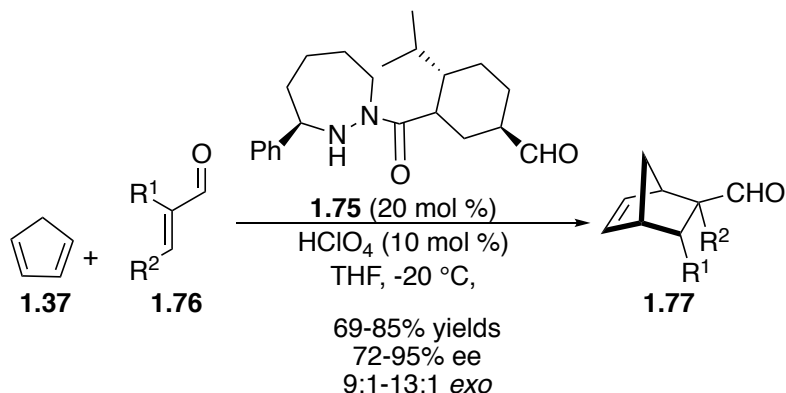
In 2016, Hayashi performed an asymmetric Diels–Alder reaction of **1.73** and cyclopentadiene **1.37** in the presence of the perchloric acid salt of diarylprolinol triisopropylsilyl ether **1.72** to form products **1.74a** and **1.74b** containing a quaternary stereocenter (**Scheme 1.14**).<sup>59</sup> When the reaction was done under anhydrous conditions, the *exo* Diels–Alder product **1.74b** was formed with both high enantioselectivity and diastereoselectivity. However, when water was the reaction solvent, the *exo* isomer was

formed in only moderate diastereoselectivity. Consequentially, the enantioselectivity suffered when water was used as the solvent, although it still is significant for future reaction conditions reaction since it is less detrimental to the environment and allows for mild reactions conditions.<sup>60</sup>

**Scheme 1.14** Hayashi's construction of quaternary center.<sup>59</sup>

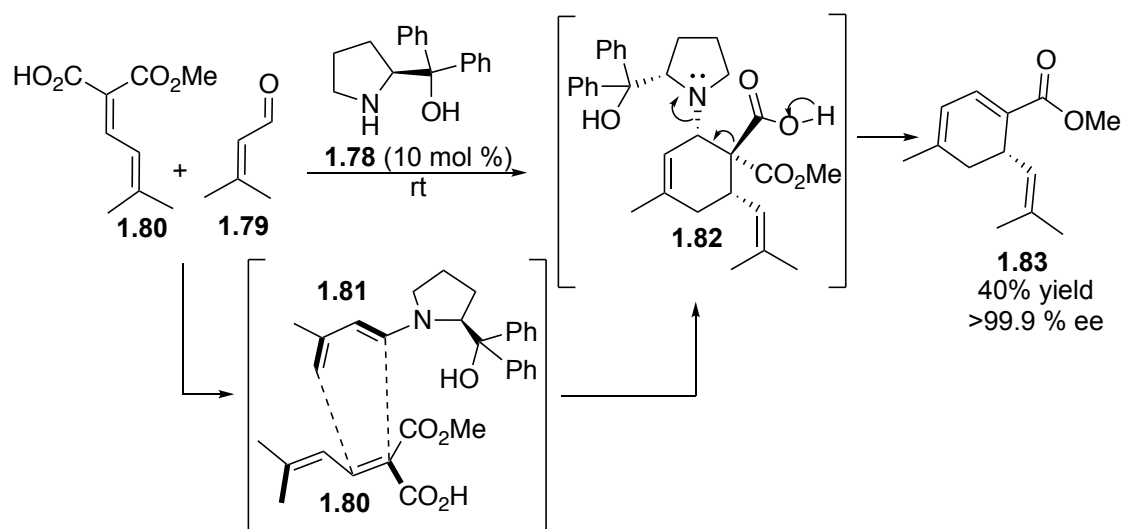


In 2018, Gleason et al. uncovered an alternative use of diazepane carboxylates as a catalyst for a [4 + 2] cycloaddition reaction during their work on developing an asymmetric Cope rearrangement (**Scheme 1.15**).<sup>61</sup> It was discovered that a diazepane carboxylate could efficiently catalyze the Diels–Alder cycloaddition of  $\alpha$ -substituted enals **1.76** via iminium ion organocatalysis.<sup>62</sup> The optimization revealed that electron withdrawing groups on the catalyst affected the ee drastically, which led to exploration of chiral carbamates. Ultimately, a catalyst bearing a (–)-menthyl carbamate **1.75** appeared to promote electrostatic stabilization of the transition state based on the minimum dipole moment calculated for the preferred *s-trans* (*Z*)–geometry iminium ion.

**Scheme 1.15** Gleason's diazepane carboxylate as catalyst in Diels–Alder.<sup>62</sup>

### 1.3.1.2 Dienamine Activation

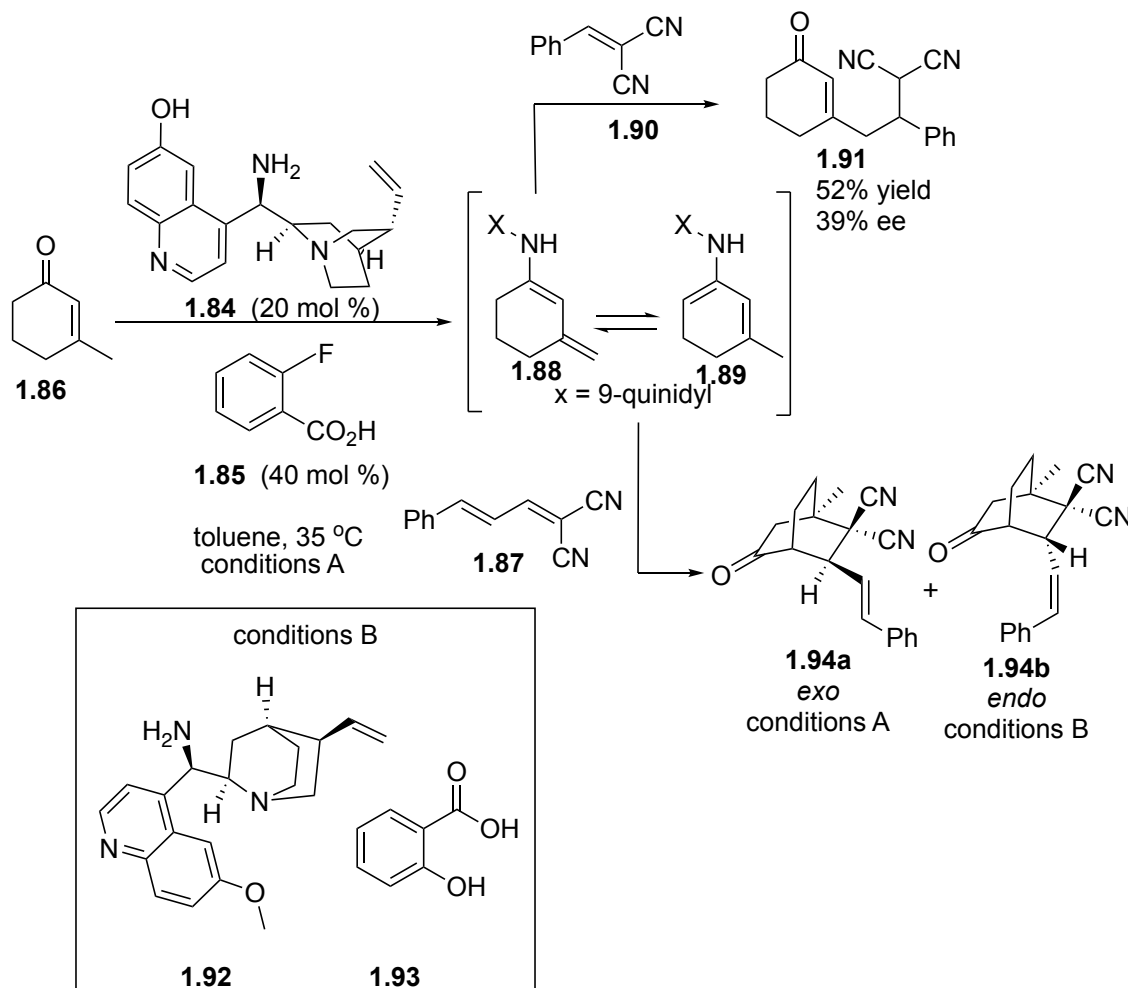
Although the boom of organocatalysis is most often associated with the works of MacMillan and List, in the 1990's Serebryakov utilized a dienamine intermediate formed by condensation of diaryl prolinol **1.78** with an  $\alpha,\beta$ -unsaturated aldehyde **1.79** in a Diels–Alder reaction (**Scheme 1.16**).<sup>63-65</sup> Dienamine intermediate **1.81** in the presence of dienophile **1.80** formed **1.82**, which after decarboxylation and catalyst elimination, formed polysubstituted cyclohexadiene **1.83** in 40% yield. The reaction exhibited an outstanding degree of stereocontrol.

**Scheme 1.16** Serebryakov's asymmetric Diels–Alder reaction via dienamine activation.<sup>63</sup>

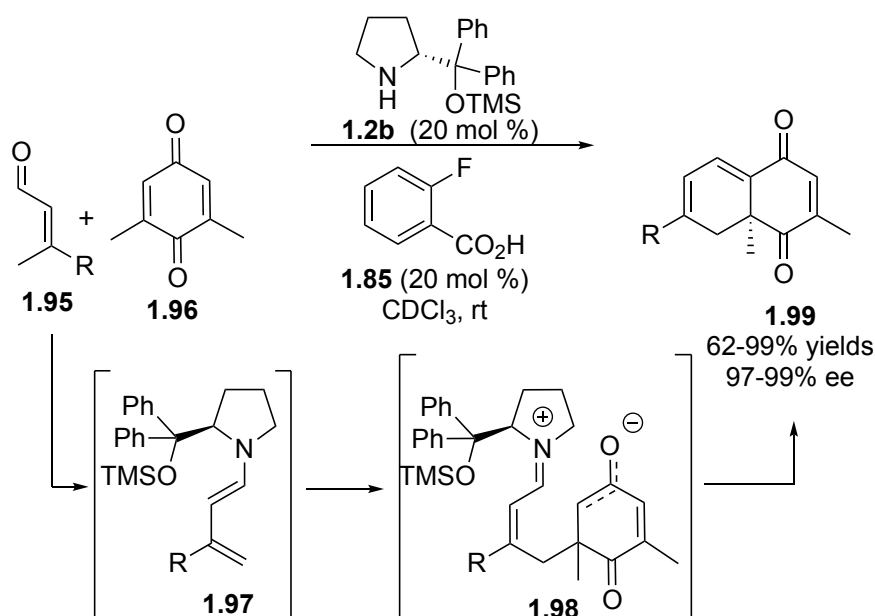
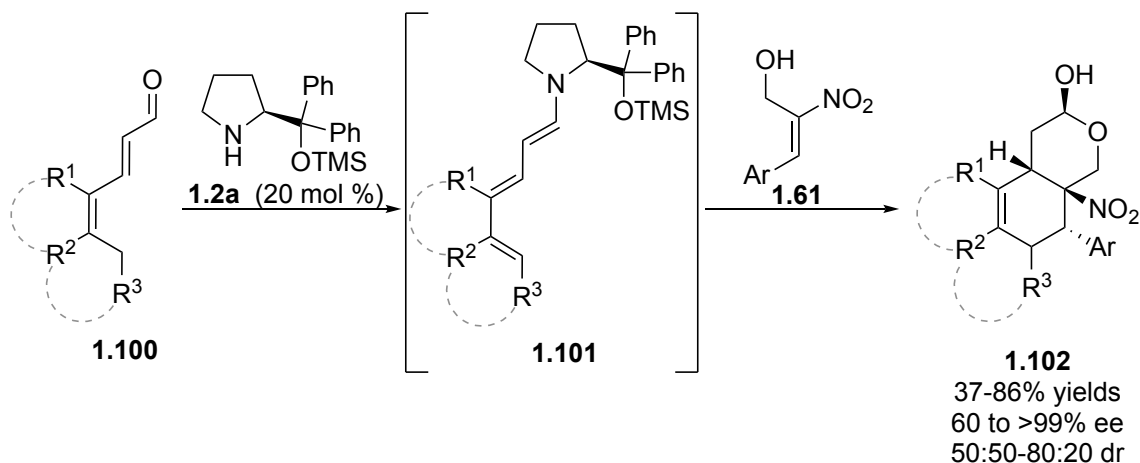
A report by the Chen group in 2012 featured “switchable” reaction patterns of  $\beta$ -substituted cyclic enone **1.86** via dienamine catalysis activated by **1.84** or **1.92** to afford *exo* **1.94a** (conditions A) or *endo* product **1.94b** respectively (conditions B, **Scheme 1.17**).<sup>66</sup> Furthermore, the regioselectivity can be tuned by the electrophile, albeit with low enantioselectivity (i.e., **1.91** in 39% ee). The [4 + 2] cycloadduct **1.94** was solely formed when 3-phenylallylidene malonitrile **1.87** was added via cycloaddition with dienamine **1.89**, while the formation of product **1.91** was observed when benzylidenemalonitrile **1.90** was employed as the electrophile to react with dienamine **1.88**. The reaction mechanism was reportedly a stepwise pathway rather than a concerted one, since the Michael addition adducts were isolated.

In 2013, Jørgensen’s group demonstrated that 1,4-benzo- and 1,4-naphthoquinones can be used as dienophiles in [4 + 2] cycloaddition reactions with dienamines.<sup>67</sup> In **Scheme 1.18**, **1.97**, which was generated *in situ* from  $\alpha,\beta$ -unsaturated aldehyde **1.95** and diphenyl prolinol silyl ether catalyst **1.2b**, reacts with 2,6-dimethylbenzoquinone **1.96** to form **1.98**. The cycloadducts **1.99** were formed in moderate yields but with high regio- and enantioselectivity. DFT calculations indicate that the reaction proceeds through a stepwise mechanism, with 1,4-conjugate addition of the dienamine **1.97** to the quinone forming a zwitterionic intermediate **1.98** that undergoes an intramolecular aldol reaction.

**Scheme 1.17** Chen's formal [4 + 2] cycloaddition with "switchable" reaction patterns.<sup>66</sup>



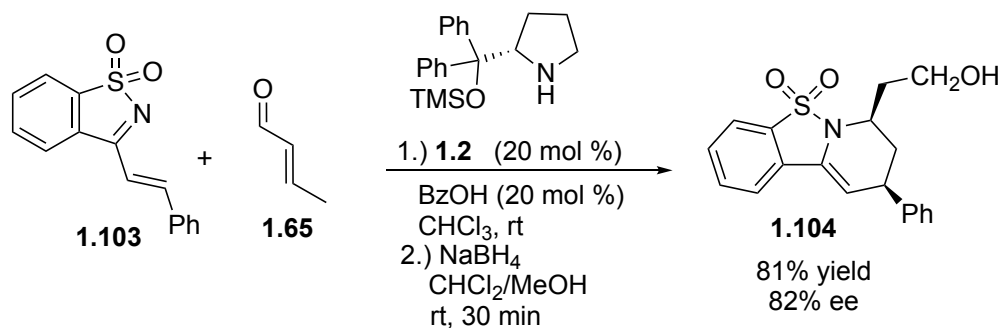
As part of an enantioselective cascade reaction along with the work from **Scheme 1.11**, in 2014, Jørgenson showed an enantioselective [4 + 2] cycloaddition/intramolecular hemiacetalization sequence to form functionalized hydroisochromenes like **1.102** via trienamine **1.101** (**Scheme 1.19**).<sup>54</sup> Using this methodology, aldehydes with alkyl and aryl substituents at R<sup>1</sup> and R<sup>2</sup> and could be used to form the product with high enantioselectivities and diastereoselectivities, in 37-86% yield. A tetracyclic indole product was obtained with a high yield of 85% in 93% ee. However, a decrease in diastereoselectivity, yield, and enantioselectivity was observed when the product was tricyclic (R<sup>2</sup> and R<sup>3</sup> as the bridgehead atoms).

**Scheme 1.18** Jørgensen's [4 + 2] cycloaddition of dienamines and quinone.<sup>67</sup>**Scheme 1.19** Trienamine mediated [4 + 2] cycloaddition/nucleophilic ring-closing.<sup>54</sup>

Two further reports of dienamine catalysis in [4 + 2] cycloaddition reactions by Chen and coworkers were published in 2014.<sup>68</sup> They reported a stereoselective inverse electron-demand aza-Diels-Alder cycloaddition between 1-aza-1,3-butadienes **1.103** and  $\alpha,\beta$ -unsaturated aldehydes **1.65** via dienamine catalysis (**Scheme 1.20**).<sup>69</sup> Also demonstrated was the use of 1-azadiene partners as electron deficient dienophiles in a [4 +

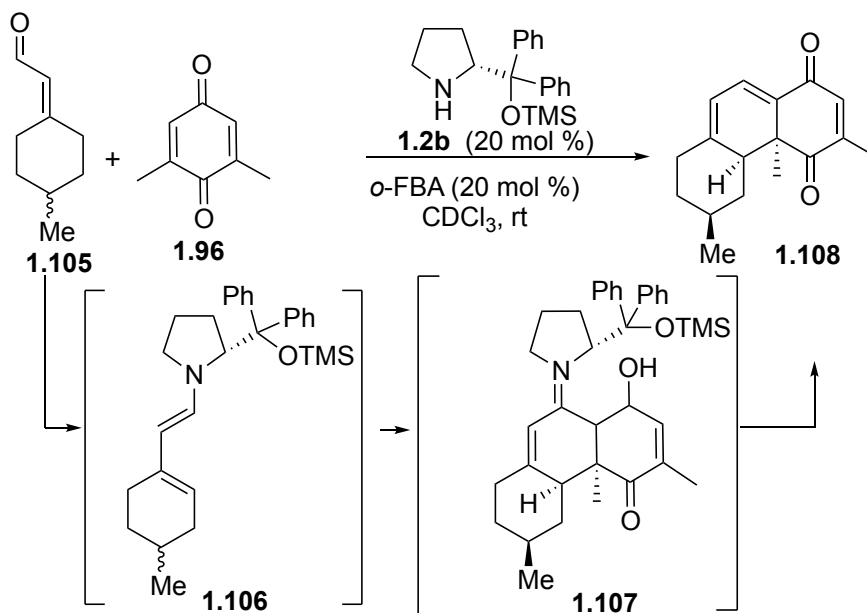
2] cycloaddition with 2-cyclohexenone via a cross-conjugated dienamine intermediate, providing cycloadducts of type **1.104**.

**Scheme 1.20** Chen's inverse-electron-demand aza-Diels–Alder reaction of dienamines.<sup>69</sup>



Dienamines were also shown to be involved in dynamic resolution of 2-cyclohexylidene acetaldehydes **1.105** in a 2016 report by Jørgensen (**Scheme 1.21**).<sup>70</sup> The reaction of racemic **1.105** with benzoquinone **1.96** in the presence of diarylprolinol-silyl ether catalyst **1.2b** produced tricyclic products **1.108** in good to high yields, and in excellent ee. However, the diastereoselectivity depended on the substituent on the 2-cyclohexylidene acetaldehydes.

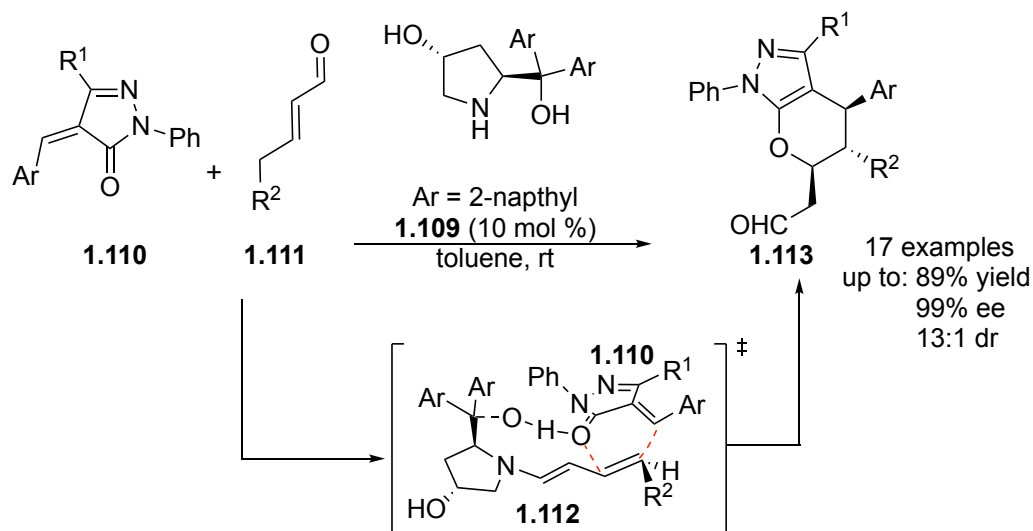
**Scheme 1.21** Dynamic thermodynamic directed resolution by Jørgensen.<sup>70</sup>



Also in 2016, Pericàs et al. reported that alkylidene pyrazolones **1.110** and  $\alpha,\beta$ -unsaturated aldehydes **1.111** activated by **1.109**, could form **1.113** in an efficient, highly regio- and stereoselective [4 + 2] cycloaddition reaction (**Scheme 1.22**).<sup>71</sup> The corresponding chiral tetrahydropyranopyrazoles derived from a variety of electronically diverse  $\alpha,\beta$ -unsaturated enals were obtained with high enantioselectivities (84–88%), diastereomeric ratios of 8:1 dr, and yields ranging from 72 to 83%. One aliphatic enal, crotonaldehyde, was tried in the reaction and gave the corresponding product in good ee but in decreased diastereoselectivity.

The absolute configuration was confirmed through X-ray crystallography, thus supporting the proposed mode of asymmetric induction involving *exo* approach of the more stable (*E,s-trans,E*)-dienamine **1.112** to (*Z*)-heterodiene **1.110**. This outcome was rationalized by: (a) stabilizing H-bond interactions between the hydroxyl group of the diarylprolinol and the carbonyl of **1.110** and (b) steric repulsion between the pyrazolonic aromatic group and dienamine moiety of **1.112**.

**Scheme 1.22** Pericàs' [4 + 2] cycloaddition.<sup>71</sup>

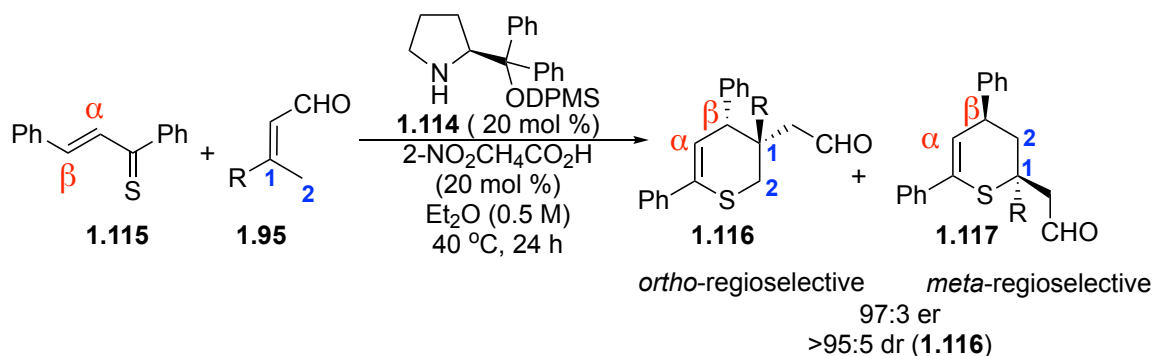




In 2017, the Albrecht and group reported an IEDHDA reaction with thiochalcones **1.115** as electron-poor heterodienes and enals **1.95** that proceeded with unprecedented *ortho*-regioselectivity yielding **1.116** and **1.117** (Scheme 1.23).<sup>72</sup> In the literature, *meta*-regioselectivity had been reported, which is when new bonds are formed at the C2 atom of the dienophile **1.95** to the  $\beta$ -carbon of the  $\alpha,\beta$ -unsaturated heterodiene **1.115**, and between the C1 atom of the dienophile and the heteroatom of the heterodiene. This was the first report forming the *ortho*-product **1.116** via IEDHDA, where the inverse connectivity is observed in bond formation during the reaction course (i.e., bond between C1 of the dienophile to the  $\beta$ -carbon of the heterodiene, and the heteroatom is bound to C2).

The absolute stereochemistry was confirmed through x-ray analysis, leading to the proposal that the cycloaddition step is *endo* selective with the dienophilic dienamine reacting in its (*S*)-*cis* geometry, which as a result increased the efficiency of secondary orbital interactions. The thiochalcone approaches the double bond of the dienamine distal to the catalyst, and from the opposite face of the bulky substituent on the pyrrolidine ring of the catalyst.

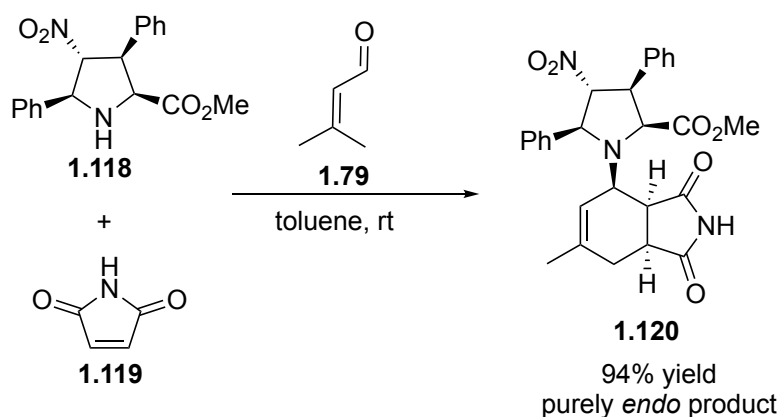
**Scheme 1.23** Albrecht's IEDHDA with thiochalcones.<sup>72</sup>



Although not catalytic, it was reported in 2017 that  $\alpha,\beta$ -unsaturated aldehyde **1.79** and maleimide **1.119** could react to form enantioenriched *exo* 4-nitroprolinate **1.120** in the presence of a chiral 4-nitroproline **1.118** in an amine-aldehyde-dienophile [4 + 2]

cycloaddition reaction (**Scheme 1.24**).<sup>73</sup> Only enals that contain a  $\gamma$ -enolizable proton form the required dienamine intermediate for the  $[4 + 2]$  cycloaddition to occur, otherwise a 1,3-dipolar cycloaddition reaction would proceed thus providing total periselectivity. Additionally, it was observed that the  $[4 + 2]$  cycloadduct would only form when a nitro group was bound to the 4-position of the chiral pyrrolidine ring.

**Scheme 1.24** Periselective reaction by C3zar.<sup>73</sup>

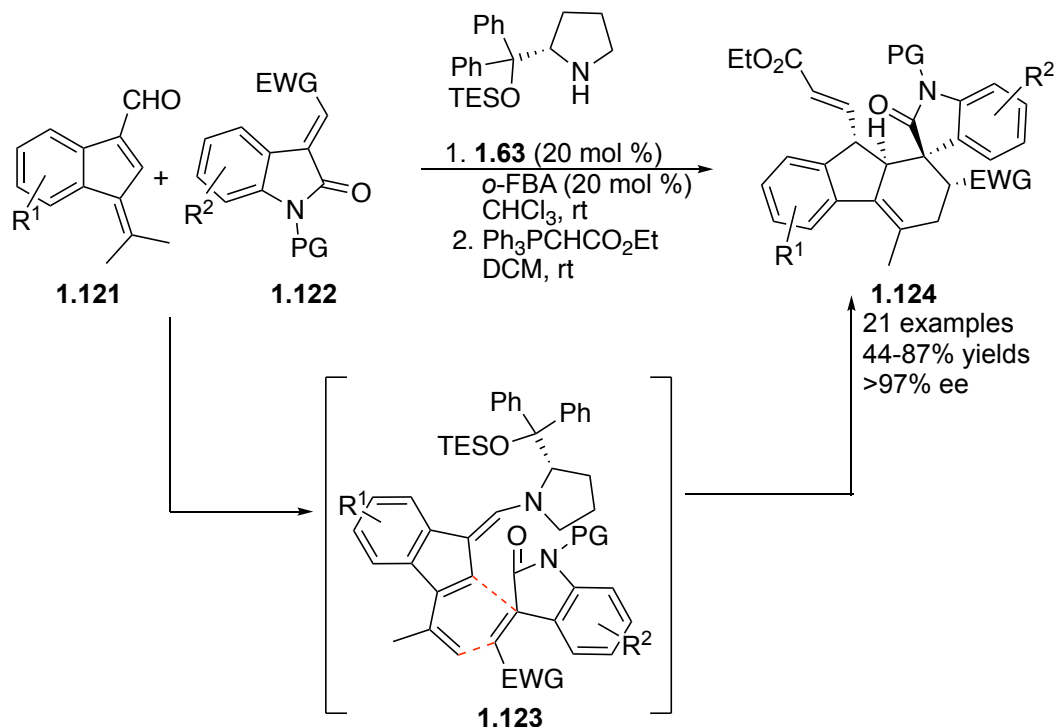


In 2018, Chen et al. published an asymmetric Diels–Alder reaction via trienamine catalysis by a chiral secondary amine **1.63** (**Scheme 1.25**).<sup>74</sup> This report featured the design and application of novel 2,4-dienal substrates in the form of 3-benzofulvene-based aldehydes **1.121**, which reacted with 3-olefinic oxindoles **1.122**, followed by a Wittig reaction to form the ethyl ester of polyhydrofluorene architectures of type **1.124**. The substrate scope included 3-olefinic oxindoles substituted with various benzoyl groups.

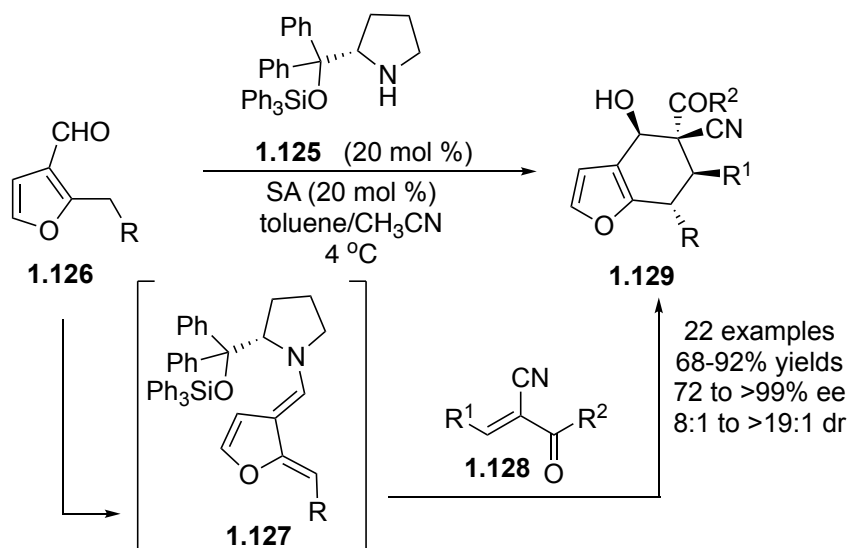
In the same year, the Chen group also published a  $[4 + 2]$  cycloaddition reaction between 3-furfurals **1.126** and  $\alpha$ -cyano-chalcone **1.128** using a diphenylprolinol triphenylsilylether catalyst **1.125** to afford fused tetrahydrobenzofurans **1.129** having four contiguous stereocenters (**Scheme 1.26**).<sup>75</sup> The mechanism begins with *in situ* generation of a dearomatizative dienamine species after the condensation of **1.126** and **1.125**, which then undergoes a  $\gamma$ -regioselective Michael addition followed by an intramolecular aldol

reaction. The substrate scope consisted of 22 examples that included olefins with various aryl groups or 2-furyl groups, generating products in yields of 68-92%, 72-99% ee and 8:1 to >19:1 dr.

**Scheme 1.25** Chen's trienamine mediated Diels–Alder reaction.<sup>74</sup>



**Scheme 1.26** Chen's [4 + 2] cycloaddition of furfural and  $\alpha,\beta$ -cyanochalcone.<sup>75</sup>

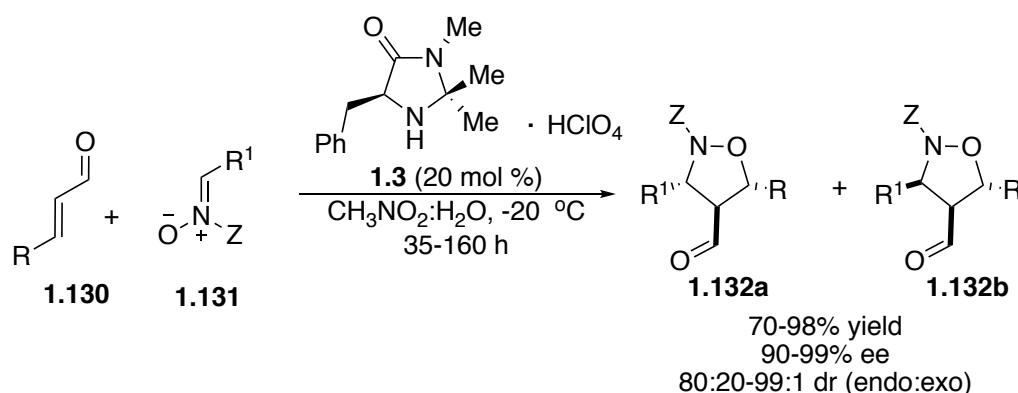


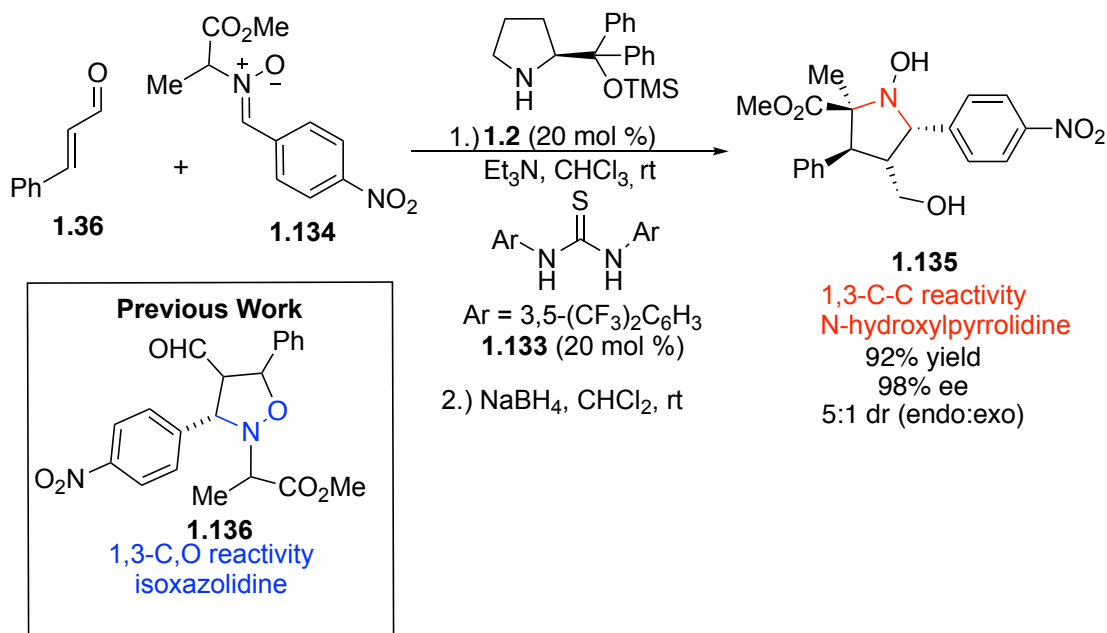
### 1.3.2 [3 + 2] and 1,3-Dipolar Cycloadditions

MacMillan and group revealed their second report of an organocatalytic enantioselective cycloaddition reaction in 2000 (**Scheme 1.27**).<sup>76</sup> This reaction was a 1,3-dipolar cycloaddition between  $\alpha,\beta$ -unsaturated aldehydes **1.130** and nitrones **1.131** in the presence of second generation MacMillan imidazolidinone catalyst **1.3** to form isoxazolidinines **1.132**. *Endo*-**1.132a** products were selectively formed in high yields and enantioselectivities.

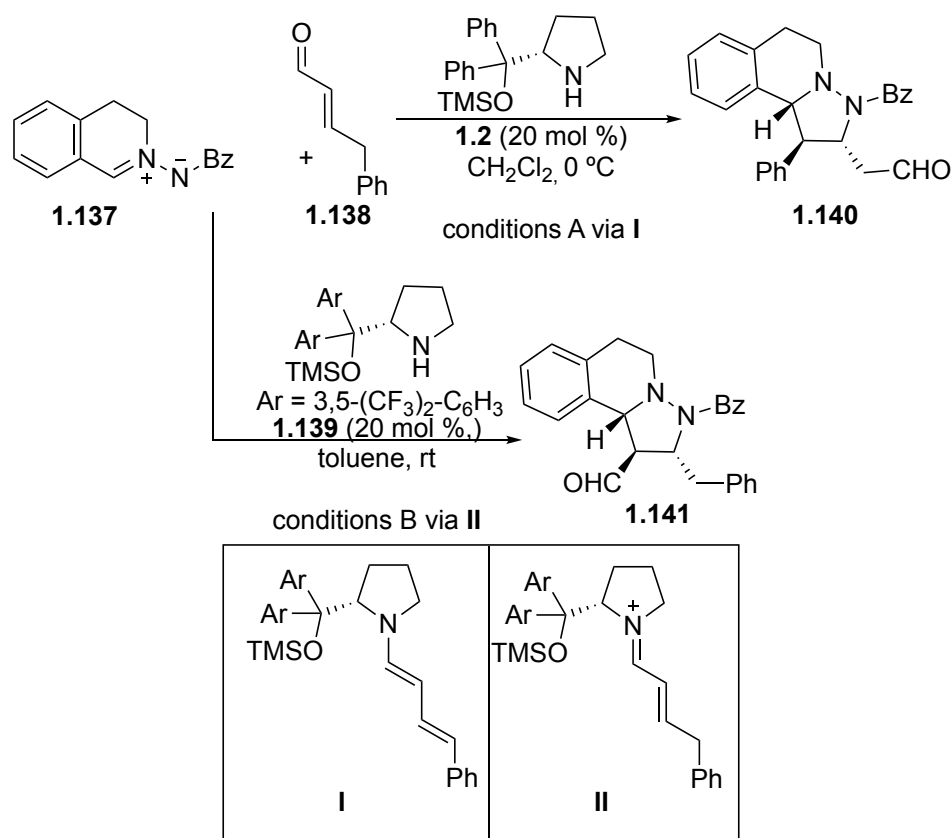
In 2017, Vicario and Merino expanded on MacMillan's previous work using nitrones as 1,3-dipoles (**Scheme 1.28**).<sup>77</sup> The reaction of nitrones of type **1.134** with enals **1.136** through iminium activation by **1.2** could be modulated, by using **1.133** to promote cooperative hydrogen bonding catalysis to induce the participation of a nitron ylide (C-N-C). This led to formation of product **1.135** instead of the product **1.136** arising from the classical C-N-O dipole. Later mechanistic studies revealed favorable evidence of a stepwise mechanism.<sup>78</sup>

**Scheme 1.27** MacMillan's 1,3-dipolar cycloaddition to form isoxazolidinines.<sup>76</sup>

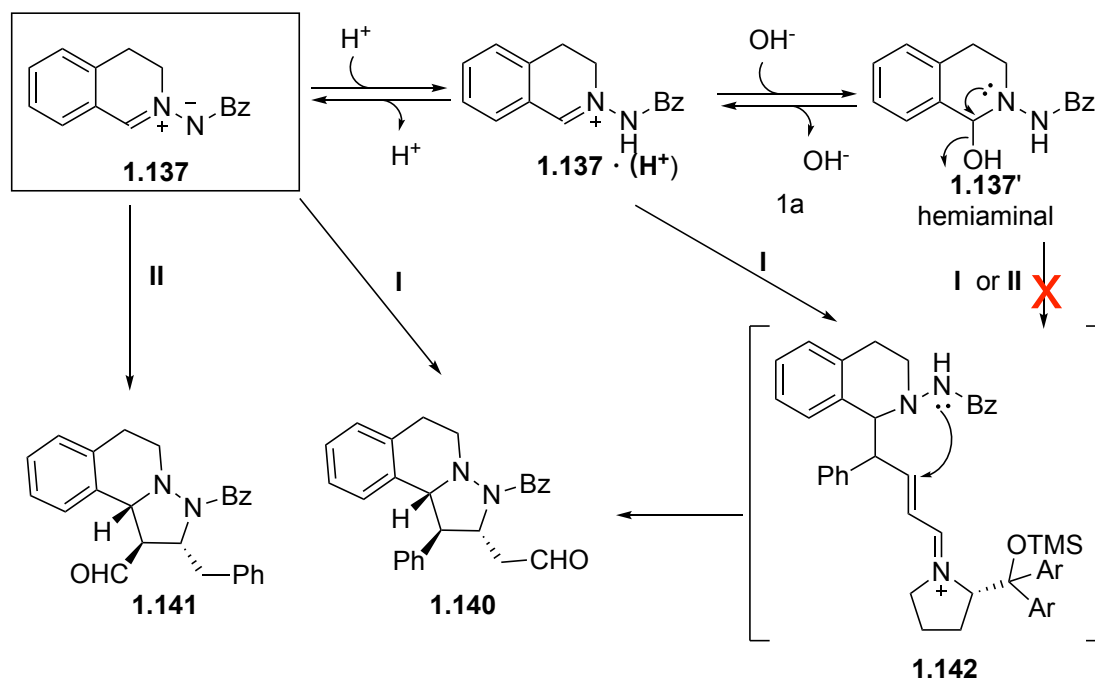
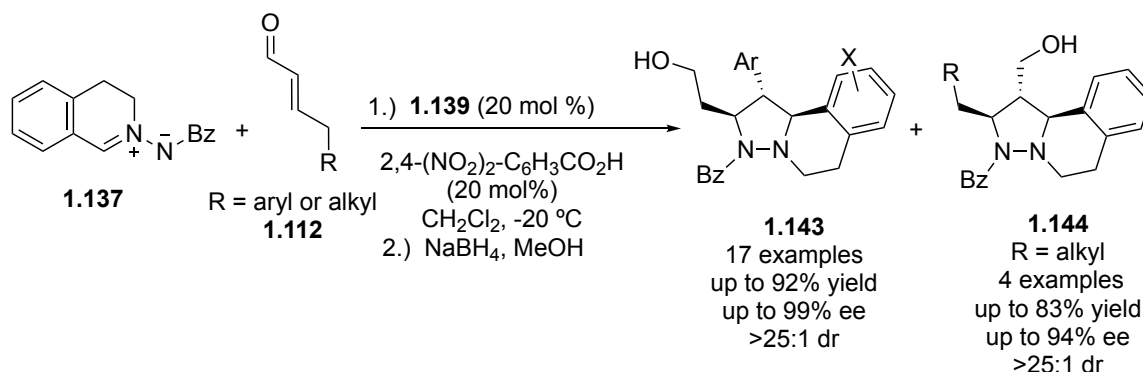


**Scheme 1.28** [3 + 2] cycloaddition with nitrones by Merino and Vicario.<sup>77</sup>

In 2014, Alemán and Fraile reported a 1,3-dipolar cycloaddition of C,N-cyclic azomethine imine dipole **1.137** with  $\alpha,\beta$ -unsaturated aldehyde **1.138** to form optically active tetrahydroisoquinolines **1.140** and **1.141** (Scheme 1.29).<sup>79</sup> The formation of the dienamine intermediate **I** or iminium ion **II** is dependent on conditions A and B respectively. This tunability allows for control of the regio-, diastereo-, and enantioselectivity. The chemoselectivity arising from conditions **I** is postulated to arise from the reactive dipole, that forms in two steps by: (1) protonation to form **1.137** • (H<sup>+</sup>), and (2) subsequent attack by the hydroxy to form the reversible hemiaminal **1.137'** species, which itself cannot go on to form any product (Scheme 1.30). The reversibility of the hemiaminal allows for the formation of the iminium ion **1.142**, ultimately leading to formation of **1.140**.

**Scheme 1.29** Alemán and Fraile's 1,3-dipolar cycloaddition.<sup>79</sup>

During the preparation of Alemán and Fraile's manuscript, a dienamine-mediated enantioselective 1,3-dipolar cycloaddition catalyzed by a chiral prolinol silyl ether catalyst was also developed by Du and Wang (**Scheme 1.31**).<sup>80</sup> When **1.137** was reacted with various enals of type **1.112** in the presence of catalyst **1.139** followed by reduction, alcohol products **1.143** (R = aryl, 82-92% yield, 90-99% ee) and **1.144** (R = alkyl, 79-83% yield, 80-94% ee) were afforded with high diastereoselectivity. Normal-electron demand [3 + 2] cycloadducts formed when alkyl substituted enals were used. This is due to the HOMO of the dipole interacting with the LUMO of the dienophile, which is lowered by initial formation of the  $\alpha,\beta$ -unsaturated iminium ion. Aryl substituted  $\alpha,\beta$ -unsaturated enals provided the inverse-demand cycloadducts.

**Scheme 1.30** Chemoselectivity arising from dipole.<sup>79</sup>**Scheme 1.31** Du and Wang's 1,3-dipolar cycloaddition.<sup>80</sup>

### 1.3.3 [2 + 2] Cycloadditions

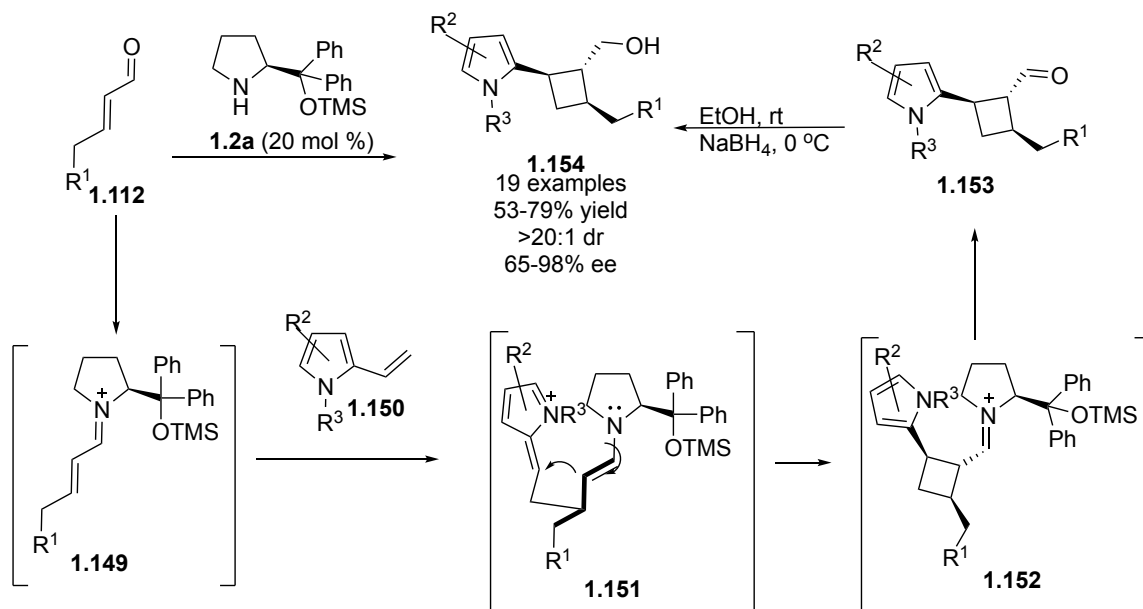
In 2012, a novel enantioselective formal [2 + 2] cycloaddition of  $\gamma$ -enolizable  $\alpha,\beta$ -unsaturated aldehydes **1.112** with nitroalkenes **1.145** to access cyclobutanes **1.148** was disclosed (**Scheme 1.32**).<sup>81</sup> In the dual-catalytic cycle, the enal is activated by the chiral amine catalyst **1.2a** leading to a dienamine intermediate **1.146**, which reacts at the  $\gamma$ -carbon with the nitroalkene **1.145**, which is activated through hydrogen bonding by thiourea **1.133**. Subsequent intramolecular conjugate addition of the nitronate intermediate to the iminium



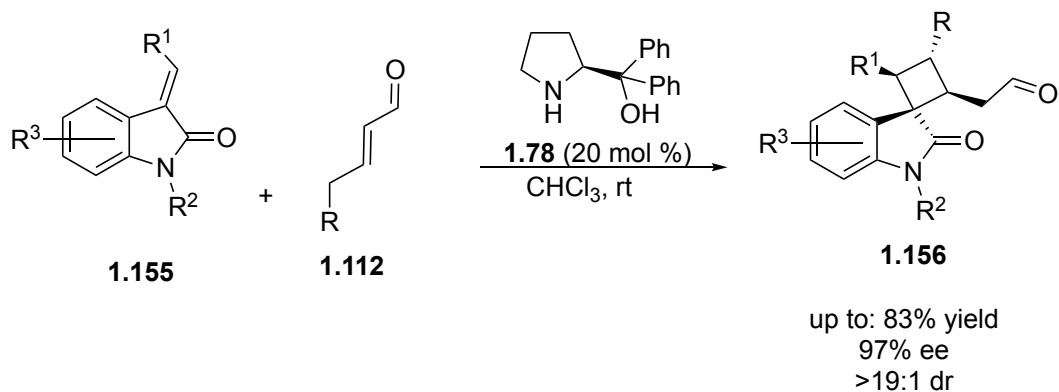


spirooxindoles **1.156** bearing a cyclobutane moiety, using H-bond-directing dienamine activation (**Scheme 1.34**).<sup>84</sup>

**Scheme 1.33** Xu's asymmetric formal [4 + 2] cycloaddition of 2-vinyl pyrroles.<sup>83</sup>



**Scheme 1.34** Wang's [2 + 2] cycloaddition between methyleneindoline and enals.<sup>84</sup>

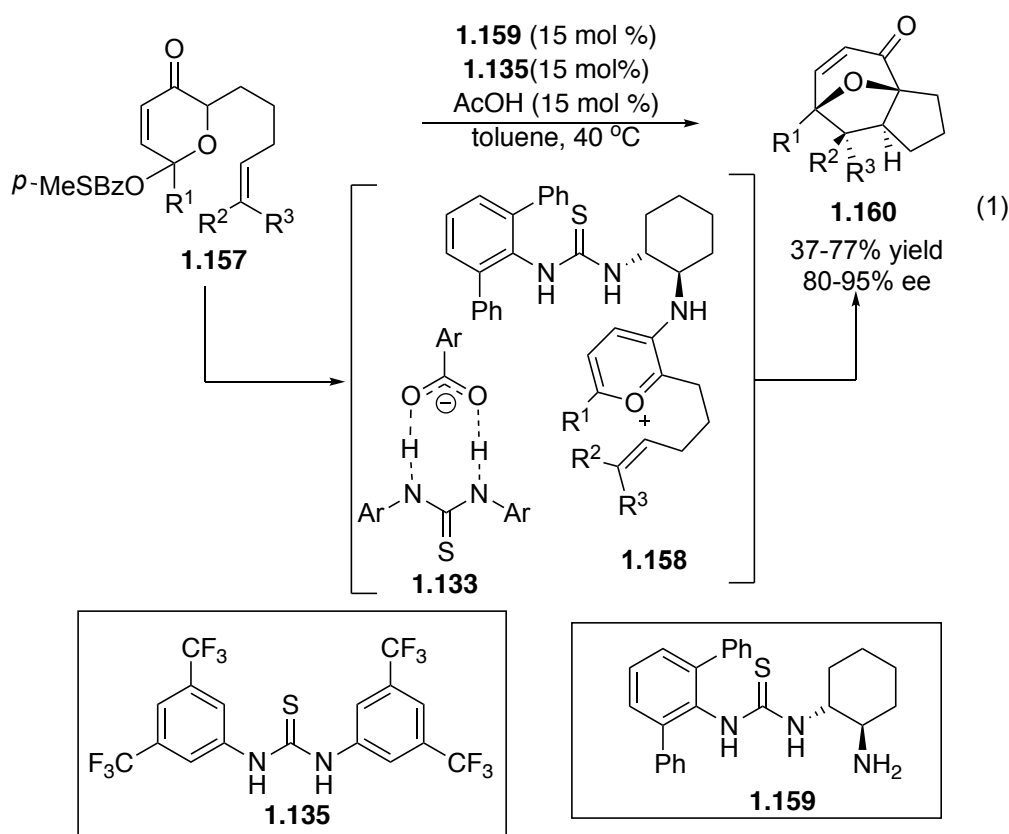


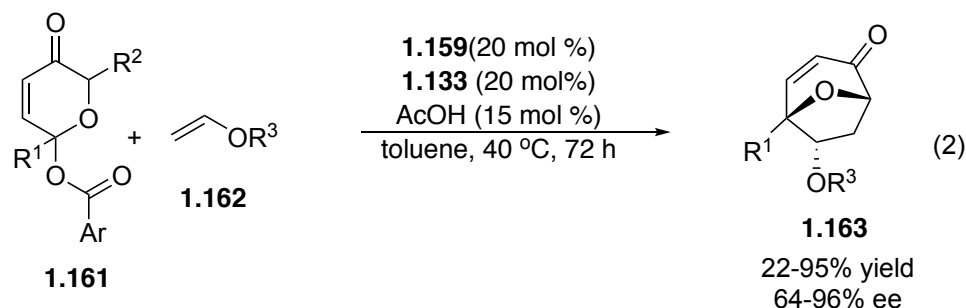
### 1.3.4 [5 + 2] Cycloadditions

The synthesis of 8-oxabicyclo[3.2.1]octane building blocks were achieved through [5 + 2] cycloadditions between oxidopyrylium ylides and olefins (**Scheme 1.35**).<sup>85-86</sup> The first example of a catalytic enantioselective [5 + 2] cycloaddition between an oxidopyrylium ylide and a tethered alkene (i.e., **1.158**) was in fact organocatalytic, and developed by

Jacobsen in 2011 (**eq 1**).<sup>85</sup> Up until their report, only chiral auxiliaries had been employed to achieve enantioselective oxidopyrylium cycloadditions. A dual catalyst of chiral primary aminothiurea **1.159** and achiral thiurea **1.133** participated in a novel mechanism involving cooperative catalysis. In the intramolecular reaction, **1.133** binds to the carboxylate leaving group of **1.157** to activate it, while the amine moiety of the chiral aminothiurea **1.159** covalently bonds to the pyranone carbonyl assisting ylide formation (i.e., **1.158**), while creating a chiral environment for the substrate during the reaction. The oxabicyclo[3.2.1]octane product **1.160** was formed with excellent enantioselectivity. The intermolecular version of this reaction between **1.161** and **1.162** was published in 2011 (**eq 2**).<sup>86</sup> Product **1.163** was formed in up to 95% yield and up to 96% ee, albeit with long reaction times.

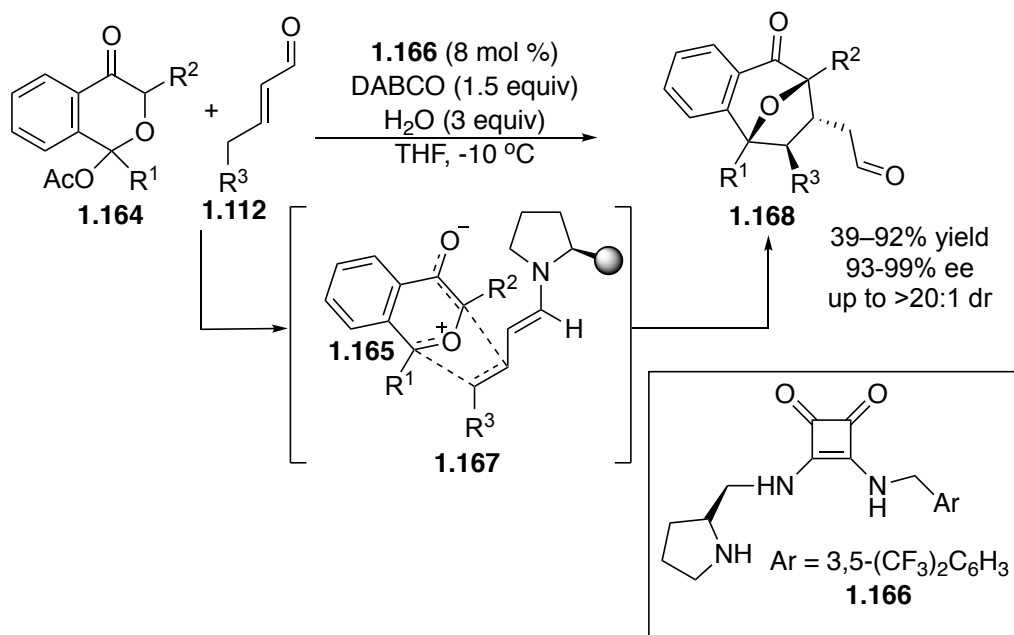
**Scheme 1.35** Dually-catalyzed [5 + 2] cycloaddition with oxidopyrylium ylides.<sup>85-86</sup>





In 2015, Reyes and Vicario *et al.* developed another enantioselective catalytic [5 + 2] cycloaddition reaction (**Scheme 1.36**).<sup>87</sup> In the presence of Bronsted base, *in situ* formation of oxidopyrylium ylide occurs from benzopyranone **1.164**, to react with  $\alpha,\beta$ -unsaturated enal **1.112** in the presence of hydrogen bond-directing pyrrolidine-squaramide bifunctional catalyst **1.166** via dienamine intermediate **1.167**. The product **1.168** was formed with four contiguous stereocenters and excellent enantioselectivity. Like the [5 + 2] cycloaddition reaction published by Jacobsen, this example also requires the use of electron-rich olefins as dipolarophiles.

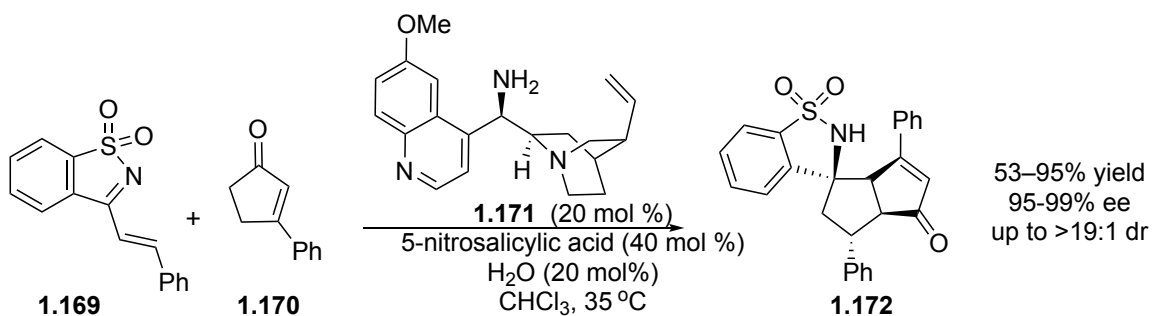
**Scheme 1.36** Vicario's [5 + 2] cycloaddition of  $\alpha,\beta$ -unsaturated aldehydes and oxidopyrylium ylides via dienamine activation.<sup>87</sup>

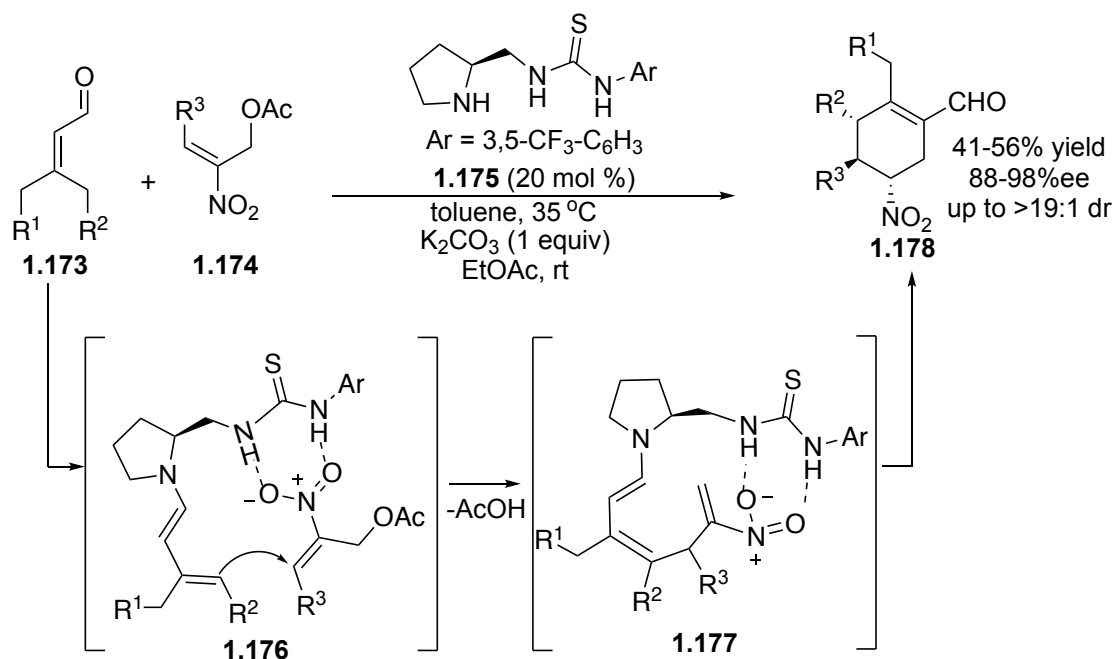


### 1.3.5 [5 + 3] and [3 + 3] Cycloadditions

In 2014, Chen and co-workers reported a novel cross-conjugated dienamine/*endo* dienamine catalytic pathway of 3-substituted 2-cyclopentenones **1.170** activated by chiral primary amine **1.171**, with **1.169**, in a formal,  $\alpha,\gamma$ -regioselective, asymmetric [5 + 3] formal cycloaddition (**Scheme 1.37**).<sup>88</sup> In 2016, Chen and co-workers expanded on the dienamine-dienamine cascade sequence they had employed in their [5 + 3] work. They reported a formal asymmetric,  $\alpha,\gamma$ -regioselective [3 + 3] cycloaddition of  $\alpha,\beta$ -unsaturated aldehydes **1.173** activated by a chiral bifunctional secondary amine-thiourea **1.175** with 2-nitroallylic acetates (**1.174**, **Scheme 1.38**).<sup>89</sup> After condensation of the amino catalyst with the enal, 2-nitroallylic acylate undergoes the initial Michael addition, elimination of a molecule of acid generates the second Michael acceptor, which reacts intramolecularly, followed by catalyst release via hydrolysis to furnish the cyclohexene product **1.178**.

**Scheme 1.37** [5 + 3] cycloaddition reaction by Chen.<sup>88</sup>



**Scheme 1.38** Formal [3 + 3] cycloaddition by Chen.<sup>89</sup>

## 1.4 Sigmatropic Rearrangements

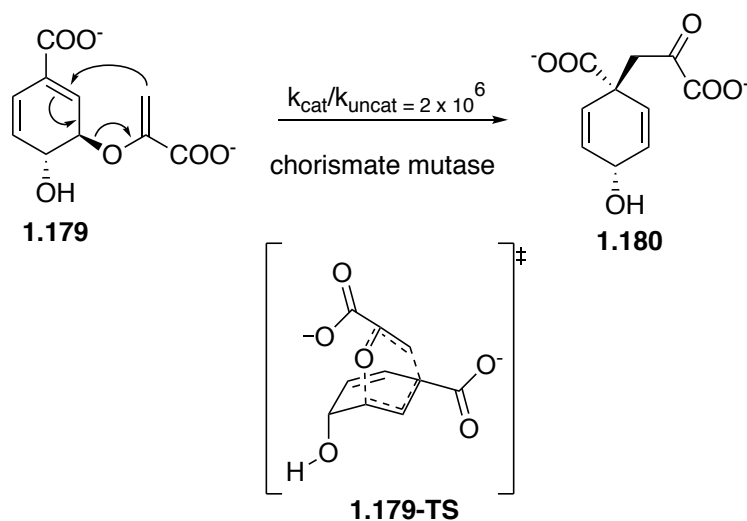
### 1.4.1 [3,3]-Sigmatropic Rearrangements

Since its discovery in 1973, extensive investigation has been done on the mechanism of the biosynthetic pathway of chorismate **1.179** to form prephenate **1.180** (Scheme 1.39), which occurs by a Claisen rearrangement catalyzed by the enzyme chorismate mutase.<sup>90-91</sup> Compared to the uncatalyzed reaction, the rate is increased by  $2 \times 10^6$  at 37 °C at pH 7.5.<sup>90,92-94</sup>

In 1987, the Carpenter group reported their study of this reaction in aqueous solution.<sup>91</sup> They observed that the rearrangement of allyl enol pyruvate analogues of chorismic acid were not accelerated by the enzyme, yet aqueous polar media increased the rate of the rearrangement of chorismic acid and the derivatives. The rate of rearrangement of chorismic acid **1.179** was accelerated 18 times faster than allyl vinyl ether **1.25** (Scheme 1.3, eq 2) in 2:1 MeOH:H<sub>2</sub>O at 75 °C, which is attributed to the stabilization of the

transition state **1.179-TS** in polar medium. It was later found that the chorismic acid intermediate is covalently bound to the enzyme through amide linkage.<sup>90,92-95</sup>

**Scheme 1.39** Chorismate mutase-catalyzed [3,3]-sigmatropic rearrangement of chorismic acid to form prephenate.<sup>90-91</sup>



Shortly after, Peter Schultz and group developed the first example of this reaction catalyzed by monoclonal antibodies.<sup>95</sup> The antibodies accelerated the reaction by a factor of  $1 \times 10^4$  at 10 °C under neutral conditions relative to the uncatalyzed thermal Claisen reaction. Rate experiments were conducted by Curran and Kuo in 1995; they discovered that the Claisen rearrangement of 6-phenylallyl vinyl ether can be accelerated by a stoichiometric amount of thioureas and ureas through *bis*-hydrogen bonding of the transition state.<sup>96</sup> Acidic conditions and water were also found to accelerate the reaction of electron-rich allyl vinyl ethers by 20-70 times.<sup>97,98</sup>

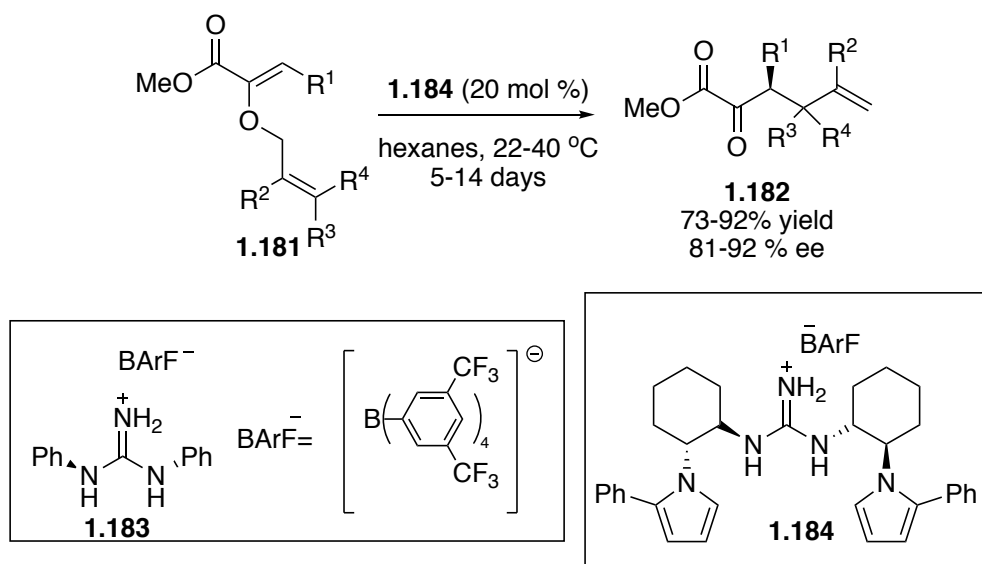
In 1992, Severance and Jorgenson proposed a transition state model based on theoretical work, which suggested hydrogen bonding facilitated the Claisen rearrangement by charge reorganization of the transition state and by exposure of the oxygen surface area to the surrounding solvent.<sup>99</sup> In addition, thioureas are on the order of  $10^6$  times more acidic

than ureas yet have a weaker accelerating effect. This observation refuted the earlier speculation that acidic media is responsible for accelerating the reaction.<sup>97</sup>

### 1.4.2 Asymmetric [3,3]-Sigmatropic Rearrangements

The first enantioselective organocatalytic Claisen rearrangement was published by Jacobsen and Uyeda in 2008 (**Scheme 1.40**).<sup>85</sup> They developed a  $C_2$  symmetric diphenylguanidinium ion salt **1.184** to catalyze a Claisen rearrangement for a variety of substituted allyl vinyl ethers **1.181**.<sup>100</sup> There were eight examples of products of type **1.182**, ranging in yield from 73-92% and with ee's between 81-92%. In 2009, Kozlowski and group designed a bisamidinium catalyst that featured a dual hydrogen bonding mode of activation.<sup>101</sup>

**Scheme 1.40** Enantioselective Claisen rearrangement catalyzed by chiral guanidinium salts.<sup>85</sup>



Jacobsen's Claisen rearrangement catalyzed by guanidinium salt induced excellent enantioselectivity but suffered from sluggish reaction rates as a result of poor catalyst turnover. In 2010, the Bode group reported a variation of a Claisen rearrangement that could circumvent this slow catalyst turnover (**Scheme 1.41**).<sup>102</sup> Use of a chiral *N*-

heterocyclic carbene **1.187** and ynal **1.186** led to formation of an  $\alpha,\beta$ -unsaturated acylazolium **1.189**. The 1,4-addition product between pyranone **1.185** and acylazolium **1.189** is **1.191**. Alternatively, **1.191** can be formed by a Coates-Claisen rearrangement of hemiacetal **1.190** arising from 1,2-addition of **1.185** to **1.189**. After tautomerization and acetalization of **1.191** forms **1.192**, lactonization promotes catalyst turnover yielding dihydropyranone **1.193** in yields of up to 78-98% and in 92-99% ee. An investigation of the substrate scope proved the reaction to be applicable to ynals containing both aliphatic and aryl groups, as well as aliphatic-substituted kojic acid partners.

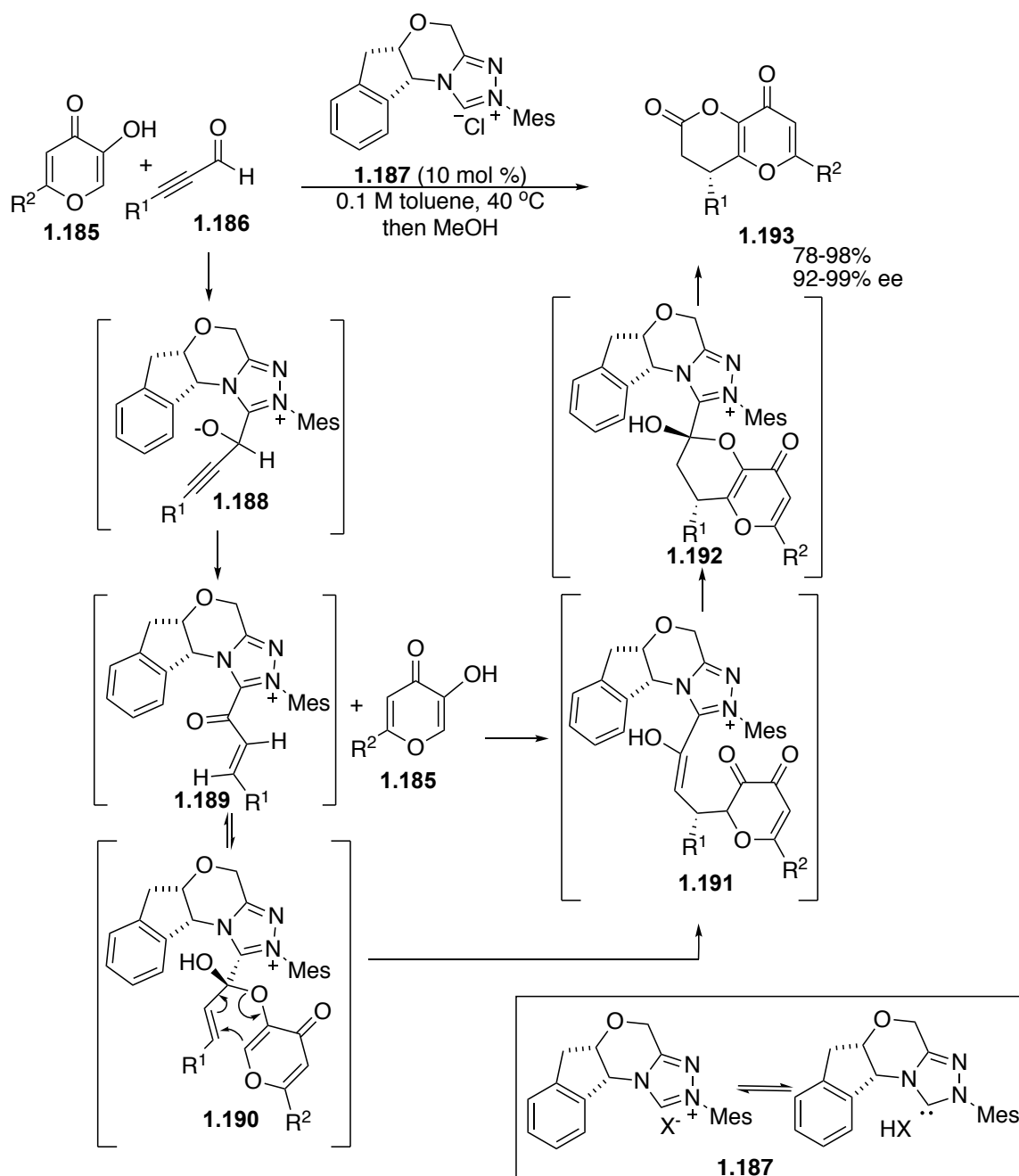
During the preparation of Bode's manuscript, the Lupton group reported a racemic dihydropyranone-forming annulation from enolates and an  $\alpha,\beta$ -unsaturated acylazolium under basic conditions.<sup>103</sup> All prior work on use of azolium salts as catalysts required a base additive in order to form the reactive carbene, however, Bode's reaction proceeded efficiently in lieu of added base. Monitoring the reaction by  $^1\text{H}$  NMR eluded that in the mechanism, the carbene counterion ( $\text{Cl}^-$  or  $\text{AcO}^-$ ) can sufficiently perform the role of a base additive to generate an ample amount of free carbene aiding the catalytic cycle.

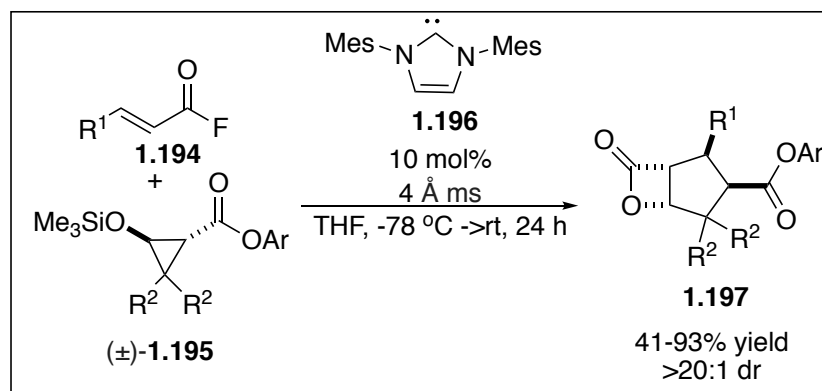
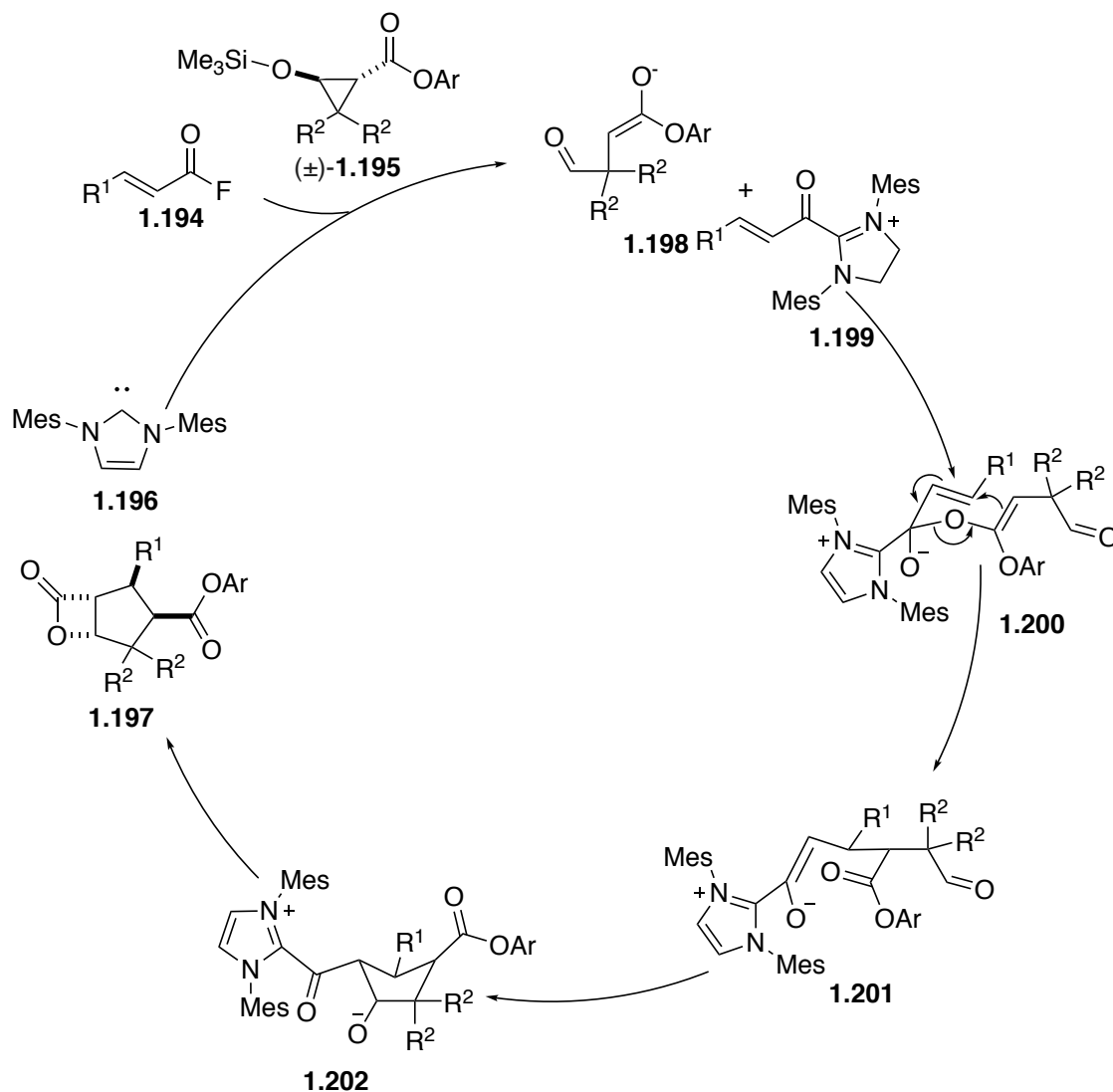
In 2012, Lupton reported the stereoselective NHC-catalyzed Ireland-Coates Claisen rearrangement of  $\alpha,\beta$ -unsaturated acyl fluorides **1.194** and silylated push-pull cyclopropanes **1.195** to form  $\beta$ -lactone fused cyclopentanes **1.197** (Scheme 1.42).<sup>104</sup> A secondary kinetic isotope effect observed at the  $\beta$ -position of **1.194** led to the postulated the reaction pathway. Addition of the carbene **1.196** to the  $\alpha,\beta$ -unsaturated acyl fluoride **1.194** resulted in  $\alpha,\beta$ -unsaturated acylazolium **1.199**. The enolate **1.198** formed by desilylation by liberated  $\text{F}^-$  and retro-aldol reaction traps **1.199** to form hemiacetal **1.200**, which undergoes the turnover-limiting Ireland-Coates-Claisen rearrangement to generate alkoxide **1.201**.

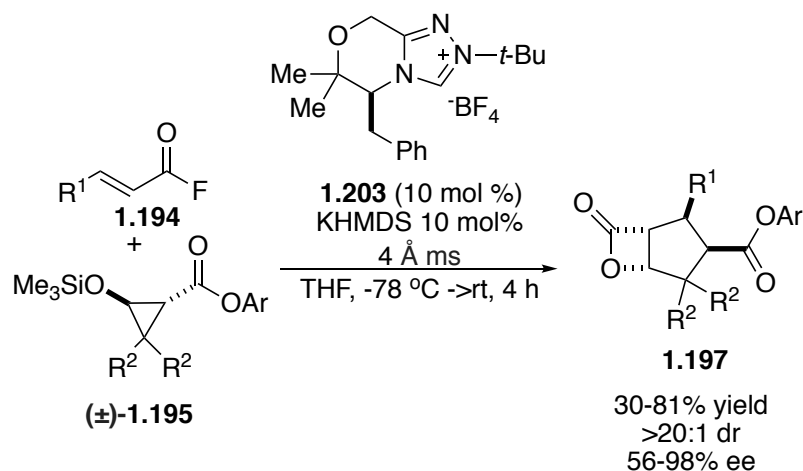


The scope of the reaction was examined using different  $\alpha,\beta$ -unsaturated acyl fluorides **1.194**. Excellent diastereoselectivities of >20:1 were obtained for electron-rich and electron-poor  $\alpha,\beta$ -unsaturated acyl fluorides, in yields of 41-93%. Heteroaromatics were tolerated in the scope, while aliphatic examples decreased in enantioselectivity. One year later, they successfully adapted this into an asymmetric reaction using chiral triazolium **1.203** affording enantioenriched **1.197** (Scheme 1.43).<sup>105</sup>

**Scheme 1.41** NHC-Catalyzed asymmetric Claisen rearrangement of ynals and kojic acid

by Bode.<sup>102</sup>

**Scheme 1.42** Stereoselective Ireland-Coates Claisen rearrangement reaction.<sup>104</sup>**Postulated mechanism**

**Scheme 1.43** NHC-Catalyzed enantioselective Ireland-Coates Claisen rearrangement.<sup>105</sup>

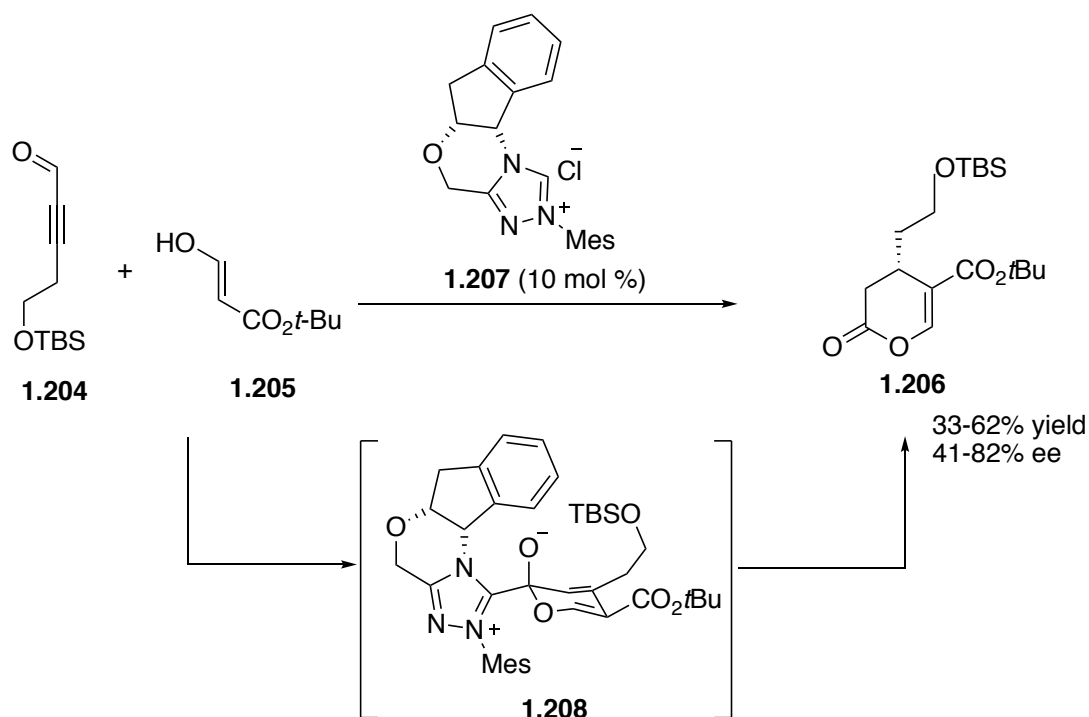
The development of the enantioselective routes employing NHC catalysts were promising for synthesis of potential entreeés into complex oxygen-containing molecular scaffolds with enantio- and diastereo-selective control. In 2018, Liu and Vedachalam published their novel organocatalytic approach for synthesis of oleuropein based secoiridoid, a monoterpenoid based natural product that exhibits potent therapeutic biological activities (i.e., antioxidant, anti-inflammatory, and anti-cancer) shown in **Scheme 1.44**.<sup>106</sup> This was accomplished through employment of the NHC-catalyzed Coates-Claisen rearrangement to form **1.206**, precursor of the dihydropyran core of the oleuropein secoiridoid. Solvents such as *o*-xylene, *p*-xylene, and trifluorotoluene afforded modest yields and good stereoselectivity, while toluene improved the yield without detriment to the selectivity.

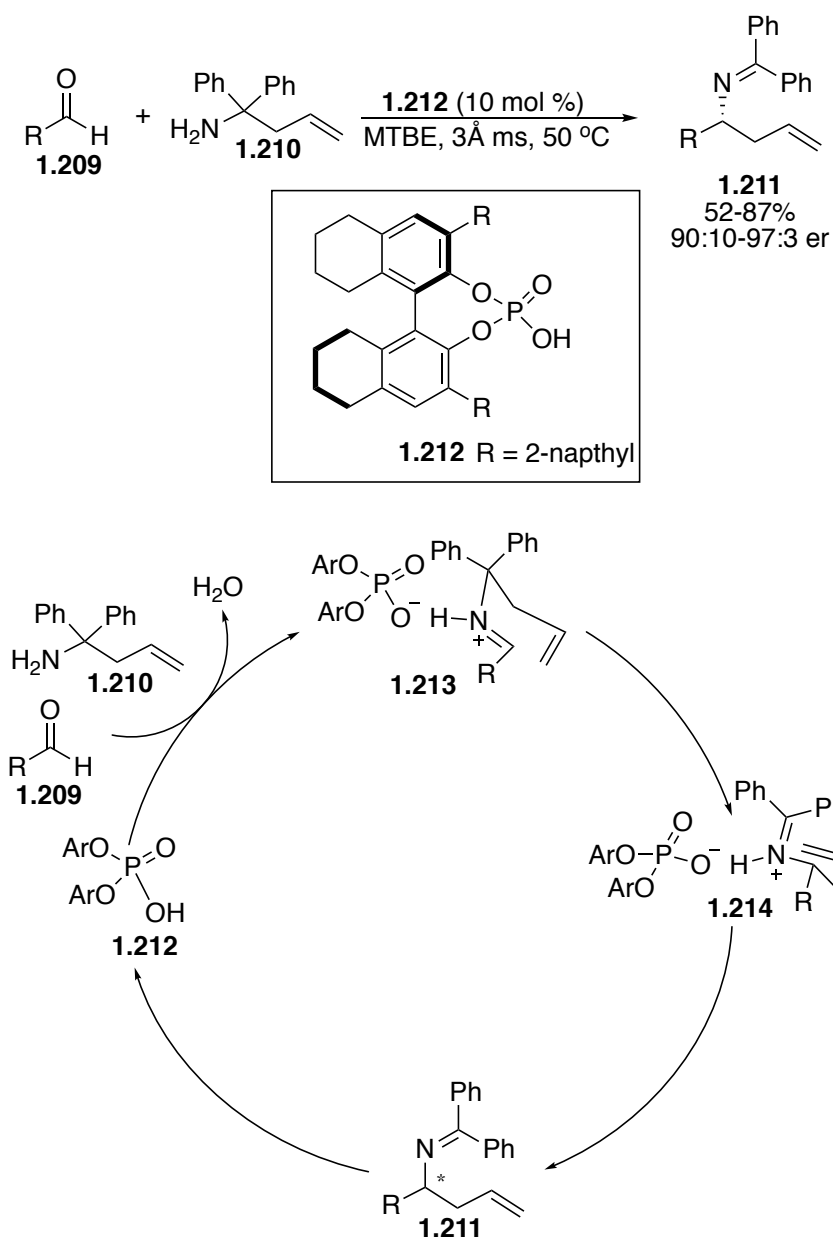
In 2008, Rueping and Antonchick revealed an asymmetric [3,3]-sigmatropic rearrangement (**Scheme 1.45**).<sup>107</sup> By reacting achiral homoallylic amine **1.210** with aldehyde **1.209** in the presence of a catalytic amount of phosphoric acid **1.212**, iminium ion formation results in a chiral ion pair **1.213**, which could undergo an aza-Cope

rearrangement to form adduct **1.214**. Deprotonation would produce the enantioenriched homoallylic amine product **1.211** and regenerate the chiral phosphoric acid catalyst **1.212**.

Initial studies identified (*R*)-3,3-bis-(naphthyl)octahydrobinol **1.212** as the best catalyst with respect to enantioselectivity, then other reaction variables including solvent, concentration, temperature, and catalyst loading were further optimized. A diverse scope of aldehydes were evaluated using the reaction conditions established, including the optimal electron-rich and electron-poor cinnamaldehydes, and a polyaromatic aldehyde, which generated products in yields of 52-77% having high enantioselectivities of 80-94%.

**Scheme 1.44** Liu and Vedachalam's use of a derivatized NHC-catalyzed Coates-Claisen rearrangement product.<sup>106</sup>



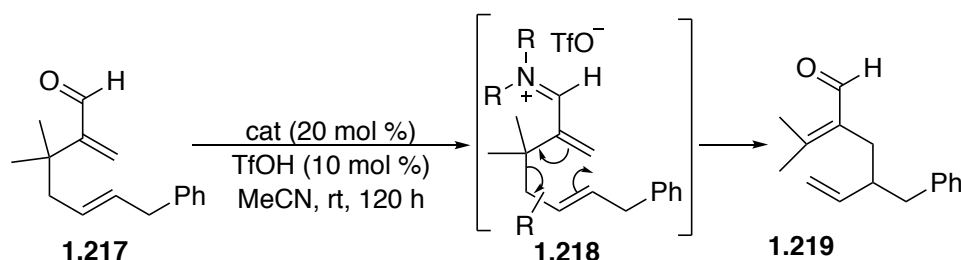
**Scheme 1.45** Aza-Cope and catalytic cycle.<sup>107</sup>

Recently, an organocatalytic Cope rearrangement was developed as a preliminary proof of concept for asymmetric catalysis by Gleason and Kaldre (**Scheme 1.46**).<sup>61</sup> A catalyst from this class was seen earlier in section **1.3.1.1** of this chapter, employed in an iminium ion catalyzed Diels–Alder reaction (**Scheme 1.15**). In 2016, they discovered a new class of seven-membered hydrazide catalyst, (diazepane carboxylates **1.215** and **1.216**) that could form product **1.219** through iminium-ion **1.218** from  $\alpha$ -substituted enals

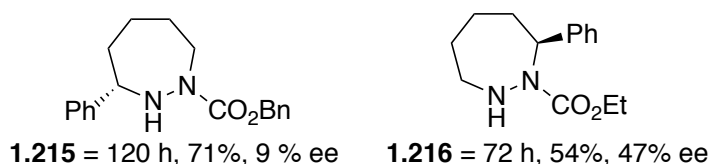
such as **1.217**. During the catalyst screening, no iminium ion formation was observed when using pyrrolidine, proline methyl ester, or second-generation MacMillan imidazolidinone catalysts. The addition of proline **1.1** at 50 mol % loading, did however, slightly increase the conversion.

Precedence for employing *N*-acyl hydrazides as catalysts in Diels–Alder reactions inspired the addition of another nitrogen into the ring, which increased the nucleophilicity of the catalyst due to the  $\alpha$ -effect.<sup>108</sup> Cyclic hydrazides gave the most conversion. Acetonitrile as solvent alleviated formation of side products, and the addition of 10 mol % triflic acid as co-catalyst improved the yield to 95%. The seminal asymmetric examples reported up to 47% ee through use of catalyst **1.216**.

**Scheme 1.46** Asymmetric Cope rearrangement by Gleason.<sup>61</sup>



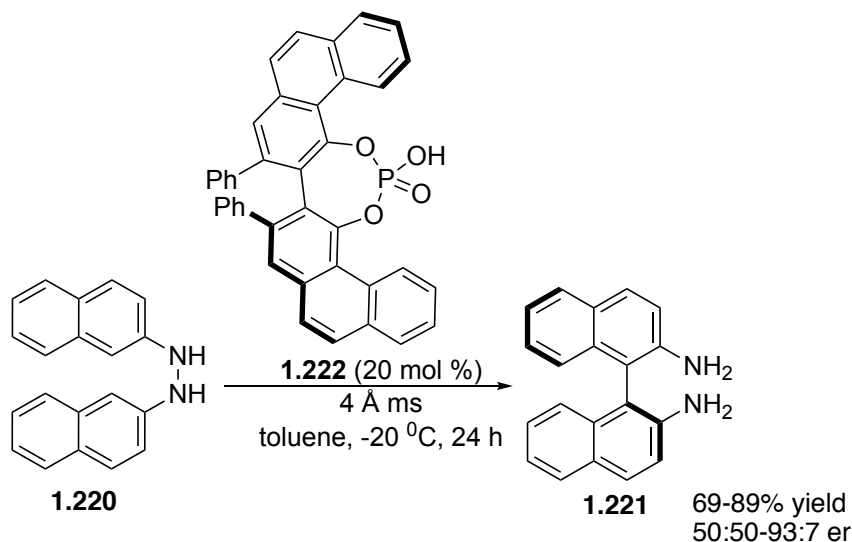
#### Catalysts



In 2013, the Kürti group disclosed an organocatalytic [3,3]-sigmatropic rearrangement (**Scheme 1.47**).<sup>109</sup> This aryl-aryl bond-forming process for the regio- and atroposelective synthesis of 2,2'-diamino-1,1'-binaphthalenes (BINAMs) **1.221** was done in the presence of an axially chiral phosphoric acid catalyst **1.222** with *N,N'*-binaphthyl hydrazines **1.220**. Symmetrical *N,N'*-binaphthyl hydrazines having 3,3'-, 5,5'-, 6,6'-, and 7,7'-substitution were investigated. When methoxy groups were present in the 3,3'-

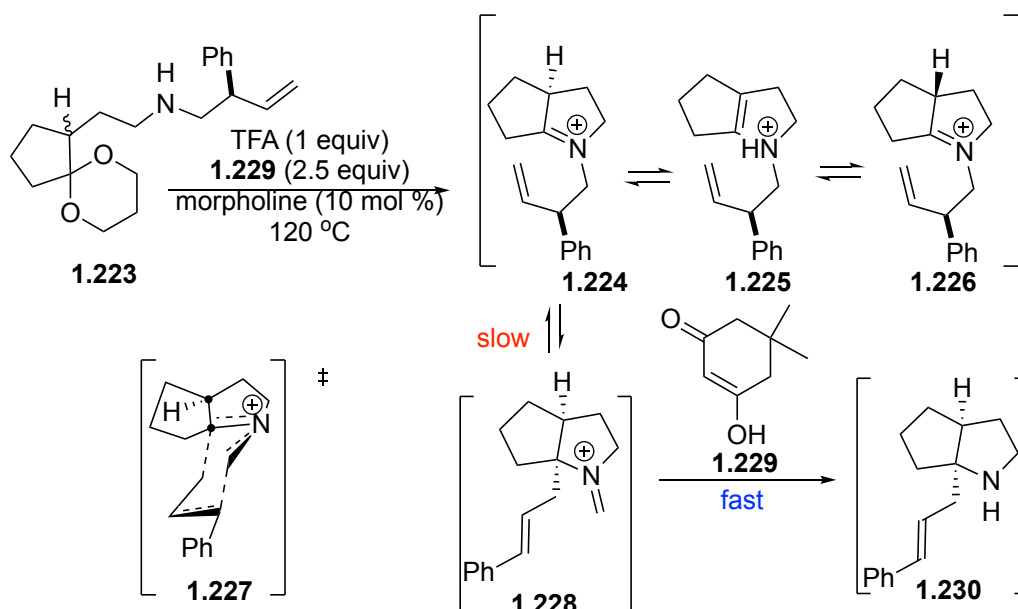
position, the enantioselectivity decreased, however this detrimental effect was not observed when methoxy groups were in 5,5'- and 7,7'- positions.

**Scheme 1.47** Atroposelective BINAM by Kürti.<sup>109</sup>



In 2010, Overman reported an enantioselective method to form substituted 1-azabicyclic ring systems via dynamic kinetic resolution (**Scheme 1.48**).<sup>110</sup> Previous work on cationic aza-Cope rearrangement,<sup>111</sup> led them to the discovery of chirality transfer. Iminium cation **1.224** is in equilibrium with the enammonium isomer **1.225**, and iminium cation **1.226**. The homoallylic side chain of **1.224** is preferentially transferred to the adjacent carbon in an aza-Cope rearrangement at a very slow rate via chair like transition state **1.227**. Iminium ion product **1.228** is thermodynamically less stable and can be trapped with dimedone **1.229** before it reverts into a racemate via equilibrium mixture of **1.224** and **1.226**. Although this example is not catalytic this finding was impactful to new strategies for developing enantioselective methods. These preliminary findings were applied to a novel enantioselective synthesis of 1-azacyclic rings via dynamic kinetic equilibration of an iminium ion, in which a [3,3]-sigmatropic rearrangement is the resolving step to achieve excellent enantioselectivity.<sup>112</sup>

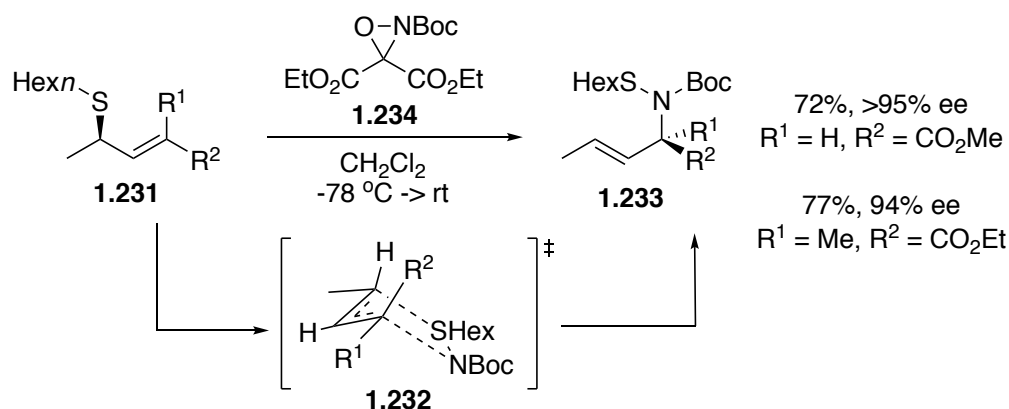


Scheme 1.48 Overman Aza-Cope DKR.<sup>110</sup>

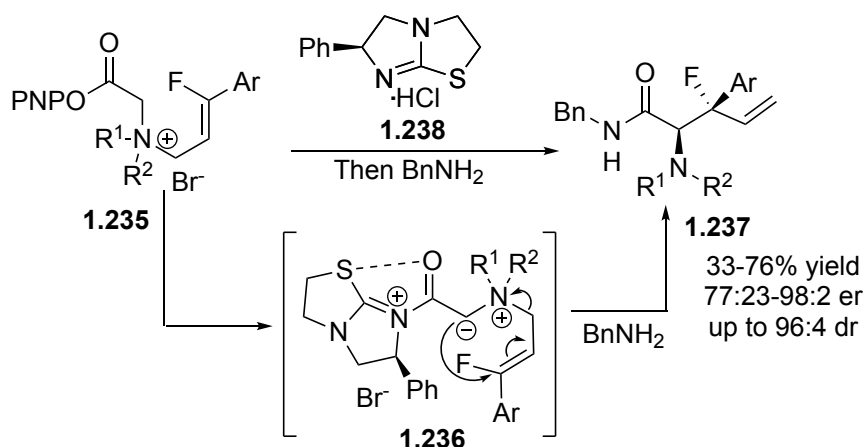
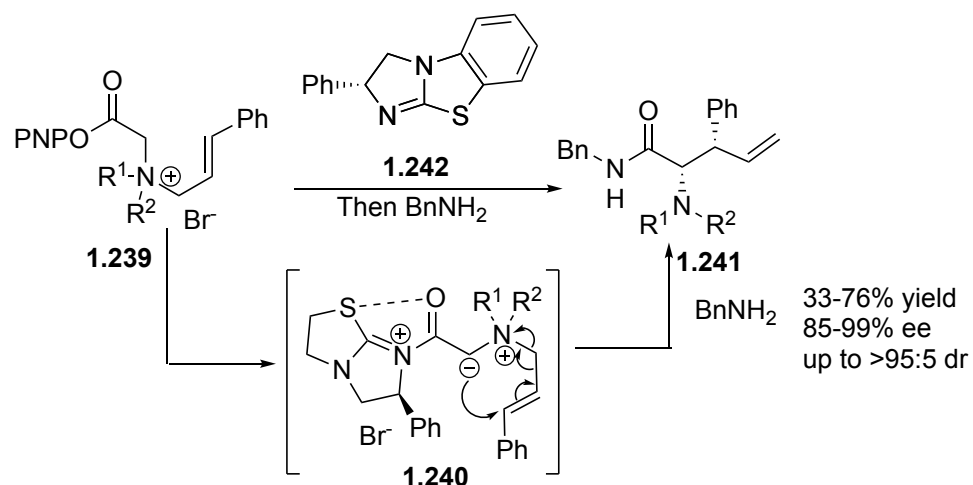
### 1.4.3 [2,3]-Sigmatropic Rearrangements

A class of amino acids,  $\beta,\gamma$ -unsaturated amino acids (vinyl glycines) were synthesized by chirality transfer in an stereospecific [2,3]-sigmatropic rearrangement (**Scheme 1.49**).<sup>113-</sup>

<sup>114</sup> Using chiral allylic sulfides **1.231** in the presence of *N*-Boc-oxaziridine **1.234**, the intermediate allylic *N*-Boc sulfimide undergoes the rearrangement, forming allylic amines with good enantioselectivity.<sup>113</sup> Formation of an unprecedented quaternary stereocenter could be achieved using this transformation. The sole formation of the *E* isomer of product **1.233** was observed, leading to the proposed transition state **1.232**.

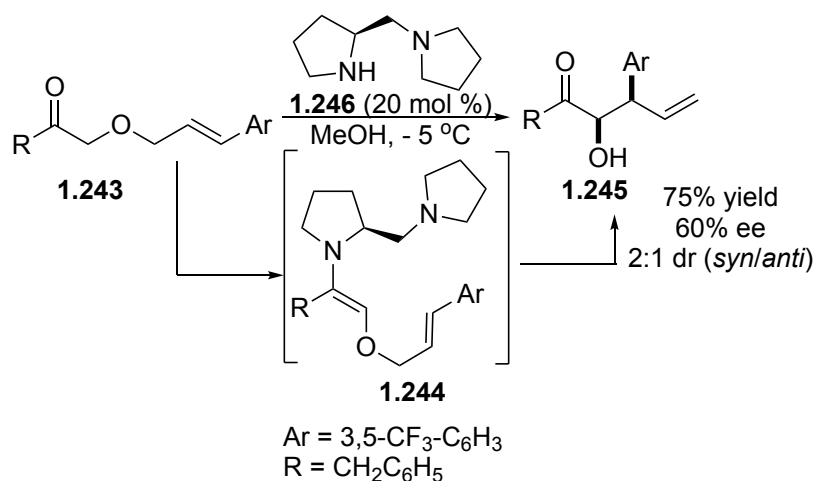
**Scheme 1.49** Stereospecific of vinyl glycines.<sup>114</sup>

In 2017, Smith reported a catalytic enantioselective [2,3]-sigmatropic rearrangement of quaternary ammonium salts bearing a (*Z*)-3-fluoro-3-arylprop-2-ene group, followed by addition of benzylamine (**Scheme 1.50**).<sup>115</sup> The  $\beta$ -fluoro- $\beta$ -aryl- $\alpha$ -aminopentenamide products **1.237** contain a stereogenic tetrasubstituted center with a fluorine substituent. Addition of tetramisole hydrochloride **1.238** was needed to achieve high enantio- and diastereoselectivity. Investigation into a substrate scope demonstrated tolerance for both cyclic and acyclic nitrogen substituents and different aromatic substituents, achieving up to 76% yield, 96:4 dr, and 98:2 er. Earlier work by the Smith group in 2014 demonstrated the [2,3]-sigmatropic rearrangement of **1.239** promoted by benztetramisole **1.242** to produce syn- $\alpha$ -amino acid derivatives **1.241** in up to 99% ee and >95:5 dr (**Scheme 1.51**).<sup>116</sup>

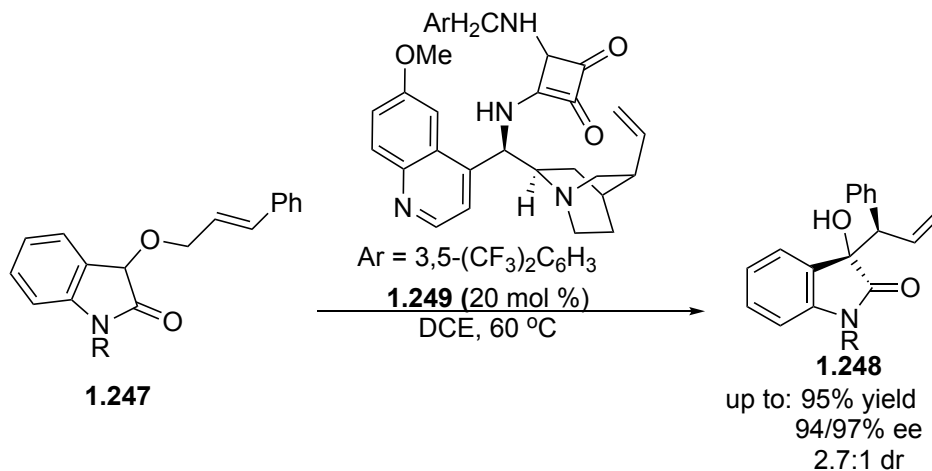
**Scheme 1.50** Smith's enantioselective [2,3]-sigmatropic rearrangement.<sup>115</sup>**Scheme 1.51** Isothiourea catalyzed [2,3]-sigmatropic rearrangement.<sup>116</sup>

#### 1.4.4 Wittig [2,3]-Rearrangements

In 2006, the Gaunt group presented the first organocatalytic enantioselective [2,3] Wittig rearrangement via chirality transfer process with use of an enamine **1.244** generated by catalyst **1.246** and allyloxyketone **1.243** (Scheme 1.52).<sup>117</sup> The reaction rate was slow and the product **1.245** was formed with modest ee. The substrate scope was broad, as this reaction was versatile for use with simple ketones to give excellent yields, as well as electronically diverse aromatic groups and trisubstituted alkenes, which could form products with good diastereoselectivity.

**Scheme 1.52** [2,3]-Wittig rearrangement by Gaunt group.<sup>117</sup>

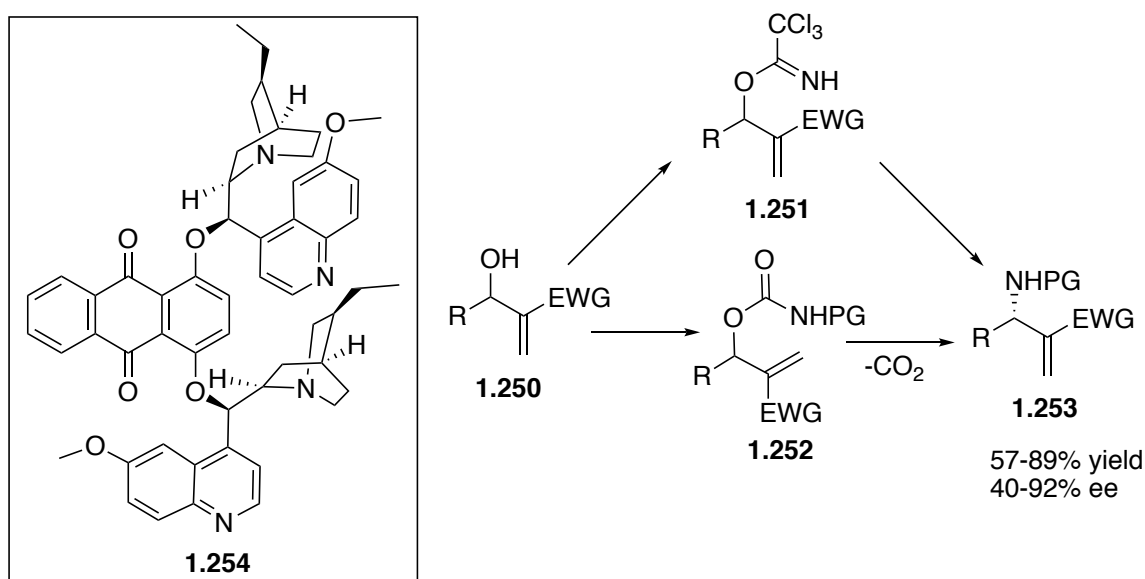
In 2016, stemming from the work by Gaunt, Kanger reported an enantioselective catalytic [2,3]-Wittig rearrangement of oxindole derivatives. The reaction was catalyzed by **1.249**, to provide optically active 3-hydroxy 3-substituted oxindoles **1.248** in yields of up to 95% and high enantioselectivities, but with low diastereoselectivity (**Scheme 1.53**).<sup>118</sup> The Denmark group also developed a version of this reaction under phase-transfer catalysis.<sup>119</sup>

**Scheme 1.53** Kanger's [2,3]-Wittig rearrangement.<sup>118</sup>

### 1.4.5 [1,3]-Sigmatropic Rearrangements

In 2008, Jørgensen and group reported the first formal organocatalytic catalyzed enantioselective [1,3]-sigmatropic O- to N-rearrangement (**Scheme 1.54**).<sup>120</sup> The transformation is of carbamate **1.252**, which in the presence of catalyst DHDQ **1.254**, undergoes decarboxylation to produce amine product **1.253**. Formation of **1.253** can also occur through **1.251**. The reaction proceeded with good regio and enantioselective control. Up to 92% ee of the product was achieved.

**Scheme 1.54** Sigmatropic decarboxylative.<sup>120</sup>



## 1.5 Conclusions

Organocatalysis has enabled numerous reactions and expanded the possibilities for transforming  $\alpha,\beta$ -unsaturated carbonyl compounds. Cycloadditions have been vigorously explored in the field of asymmetric organocatalysis, yet chiral catalysis of sigmatropic rearrangements are far less established in this area. Reactions that have been developed, such as Jacobsen's guanidinium catalyzed Claisen rearrangement, Gaunt's 2,3-Wittig rearrangement, and chirality transfer methods all provide a solid foundation for expansion

of this field, which can potentially lead to precursors for natural products and complex organic molecules. Tuning the reaction conditions have also been a clever tool for enabling specific processes to transform starting materials into cycloadducts with different regioselectivities and stereoselectivities.

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## CHAPTER 2

### A CATALYTIC ENANTIOSELECTIVE INTERMOLECULAR [5 + 2] DIPOLAR CYCLOADDITION OF A 3-HYDROXY-4-PYRONE-DERIVED OXIDOPYRYLIUM YLIDE

#### 2.1 Types and Formation of Oxidopyrylium Ylides from Pyrones

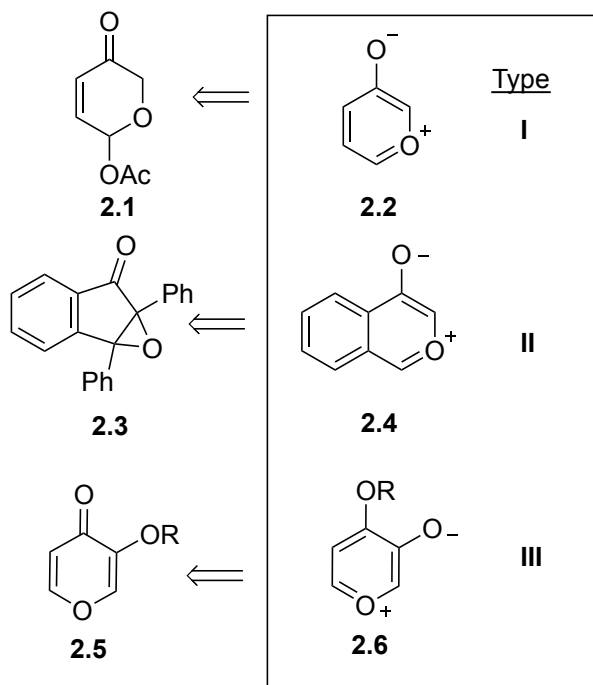
The oxidopyrylium ylide species consists of three different types<sup>1-2</sup> and can be formed in two different ways for use as the dipole in [5 + 2] dipolar cycloadditions (**Figure 2.1**).<sup>2-3</sup> Type **I**, 3-oxidopyrylium ylide **2.2**, forms when the acetoxy group undergoes elimination upon exposure to heat, acid, or a tertiary amine base.<sup>1,3-6</sup> Type **II**, benzopyrylium oxide ylide **2.4** is created from epoxyindanone **2.3**, upon exposure to heat or light.<sup>1</sup> Type **III** oxidopyrylium species is formed by group transfer and is less studied.

Traditionally, type **III** 4-alkoxy-3-oxidopyrylium ylide **2.6** is generated *in situ* by group transfer, a thermal process wherein R group of O-3 of **2.5** is attacked by O-4. For example, 3-hydroxy-4-pyrone **2.7** would form ylide **2.8a** in the presence of a tethered alkene or alkyne (**eq 1**, **Scheme 2.1**). Later, a milder stepwise group transfer process was developed by which methylation of O-4 of 3-hydroxy-4-pyrone **2.7** is done by addition of MeOTf, to form 3-hydroxy-4-methoxypyrylium monomer triflate salt **2.9** as ylide source.<sup>7</sup> Deprotonation of this species at the proton bound to O-3 by dimethylaniline or TMP, forms the cycloadduct **2.12b** from monomer ylide **2.8b** and an external dipolarophile **2.11** (**eq 2**).

Furthermore, it was recently discovered that oxidopyrylium dimer **2.10**, which was previously optimized against,<sup>8</sup> can be leveraged as the source of ylide in the reaction.<sup>9</sup> It was also found that bulkier amine bases could suppress demethylation inhibiting the ylide

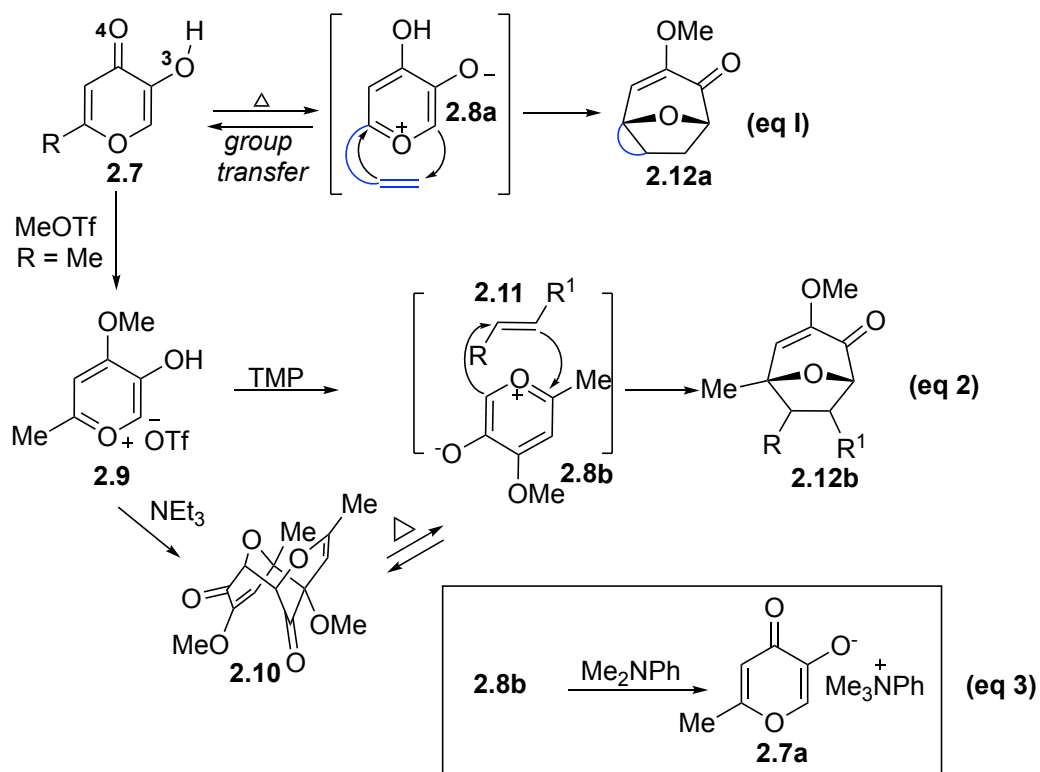
by formation of the pyrone **2.7a** (eq 3). Unlike types **I** and **II** oxidopyrylium, the type **III** ylide is electron-rich due to the extra oxygen from the alkoxy group that can donate its electrons across the dipole.<sup>8-9,16,18</sup>

**Figure 2.1** Types of oxidopyrylium ylides.



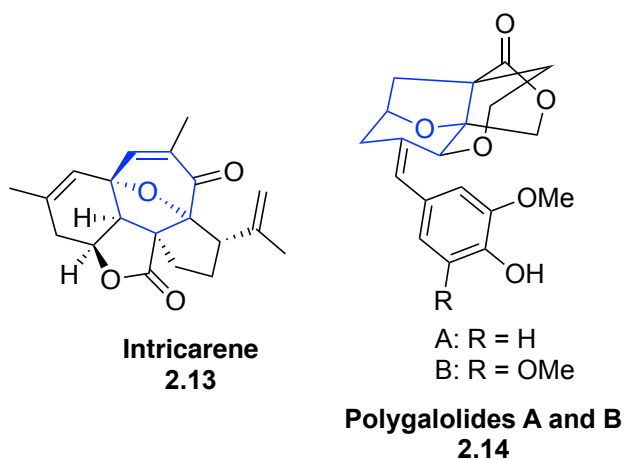
## 2.2 Catalytic Enantioselective [5 + 2] Cycloaddition Reactions of Oxidopyrylium Ylides

Cycloaddition reactions are useful for construction of complex cyclic molecular scaffolds with atom economy. The 8-oxabicyclo[3.2.1]octane motif occurs in natural products that have biological activity. In general, this 7-membered ring can be accessed by the [5 + 2] dipolar cycloaddition reaction between an oxidopyrylium ylide **2.9** and an olefin.

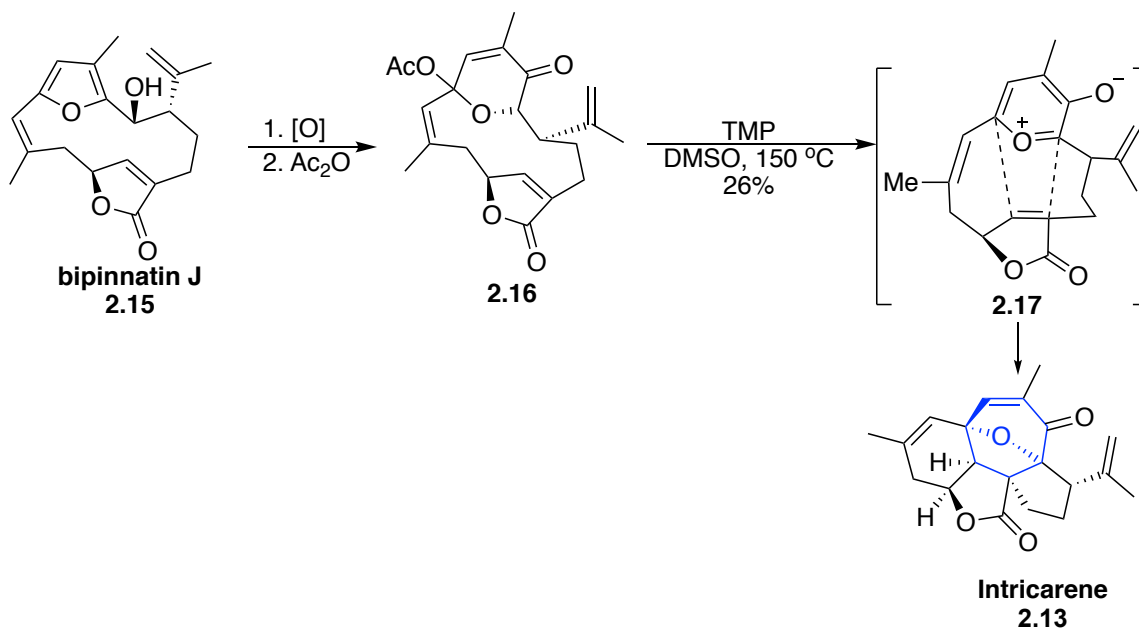
**Scheme 2.1** Methods to form type III oxidopyrylium ylide.

Some natural products containing the 8-oxabicyclo[3.2.1]octane motif offer medicinal value. Intricarene **2.13** has been found to exhibit mild cytotoxic activity (**Figure 2.2**), and polygalolides A and B **2.14** both have anti-cancer properties.<sup>10-11</sup> The Trauner group designed a biomimetic synthesis of intricarene from bipinnatin J **2.15** as the source of the oxidopyrylium ylide (**Scheme 2.2**).<sup>12</sup> In 2007, Snider employed this reaction in a stereo- and regiospecific [5 + 2] cycloaddition of bisacetoxypyranone **2.19** with **2.18** in a formal synthesis of polygalolides A and B (**Scheme 2.3**).

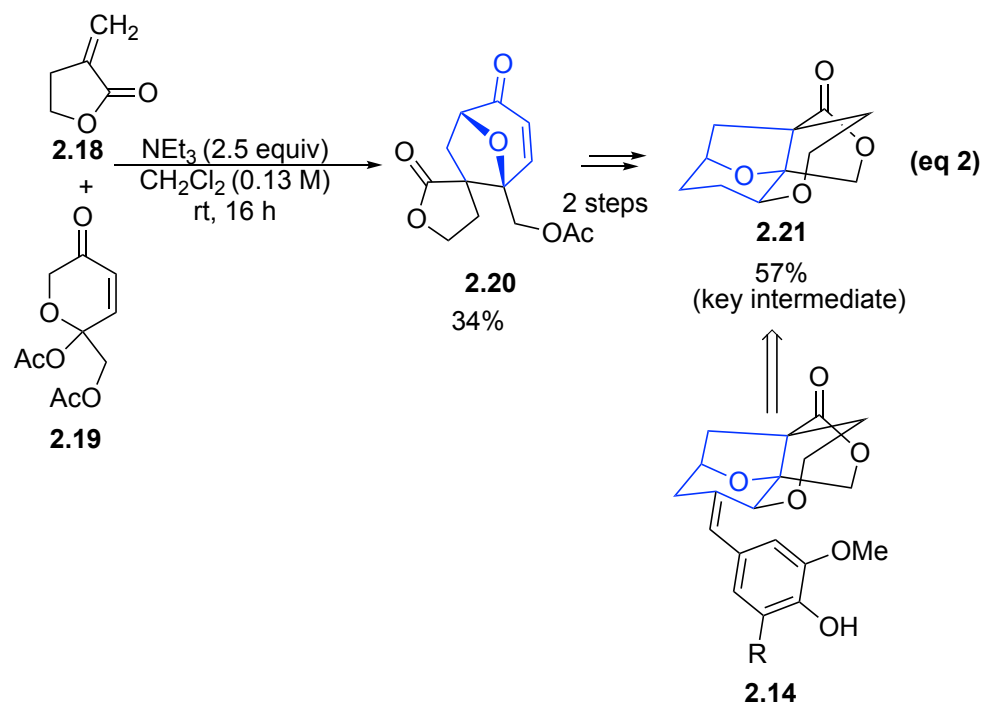
**Figure 2.2** Biologically active compounds containing 8-oxabicyclo[3.2.1]octane.



**Scheme 2.2** Synthesis of intricarene.<sup>12</sup>



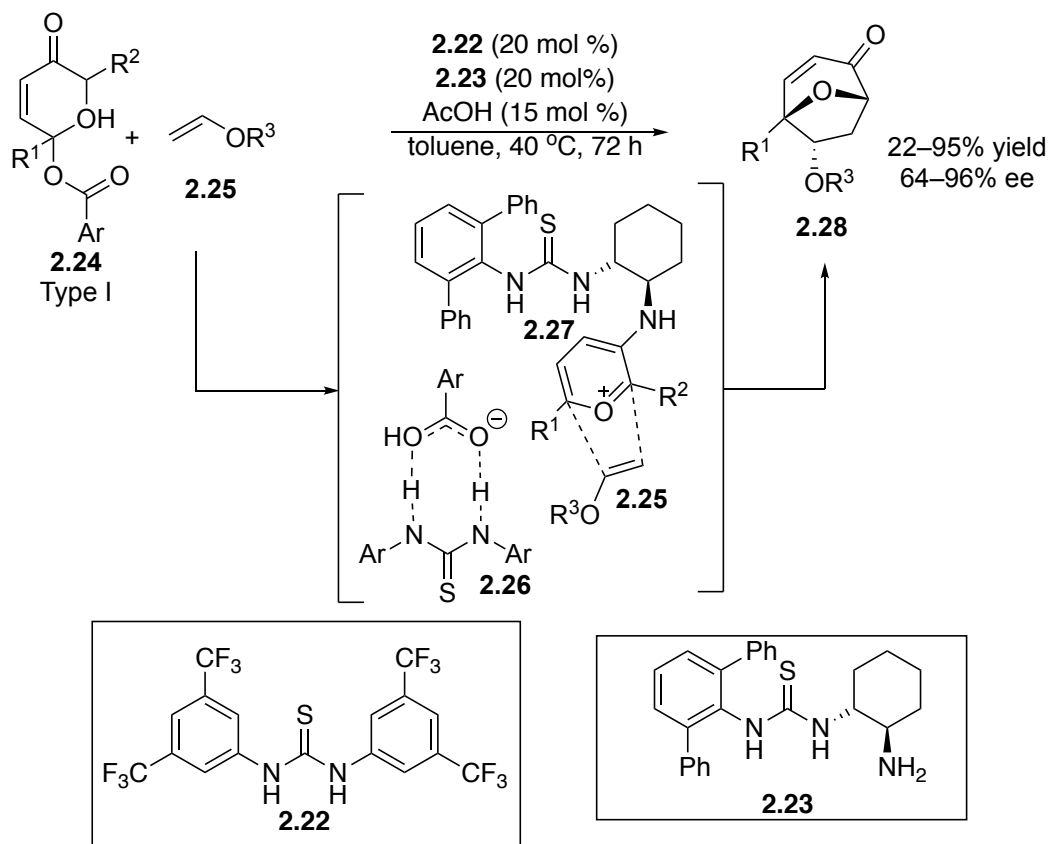
The first catalytic enantioselective [5 + 2] cycloaddition of an oxidopyrylium ylide was published by Jacobsen et al. in 2011 (**Scheme 2.4**).<sup>13,20</sup> They developed an intramolecular reaction that used enamine catalysis by a chiral primary aminothiurea **2.23** coupled with hydrogen bonding achiral thiurea catalyst **2.22**, to render asymmetric product **2.28**. In 2014, the reaction was adapted into an intermolecular process.<sup>14</sup>

**Scheme 2.3** Synthesis of polygalolides A and B.<sup>11</sup>

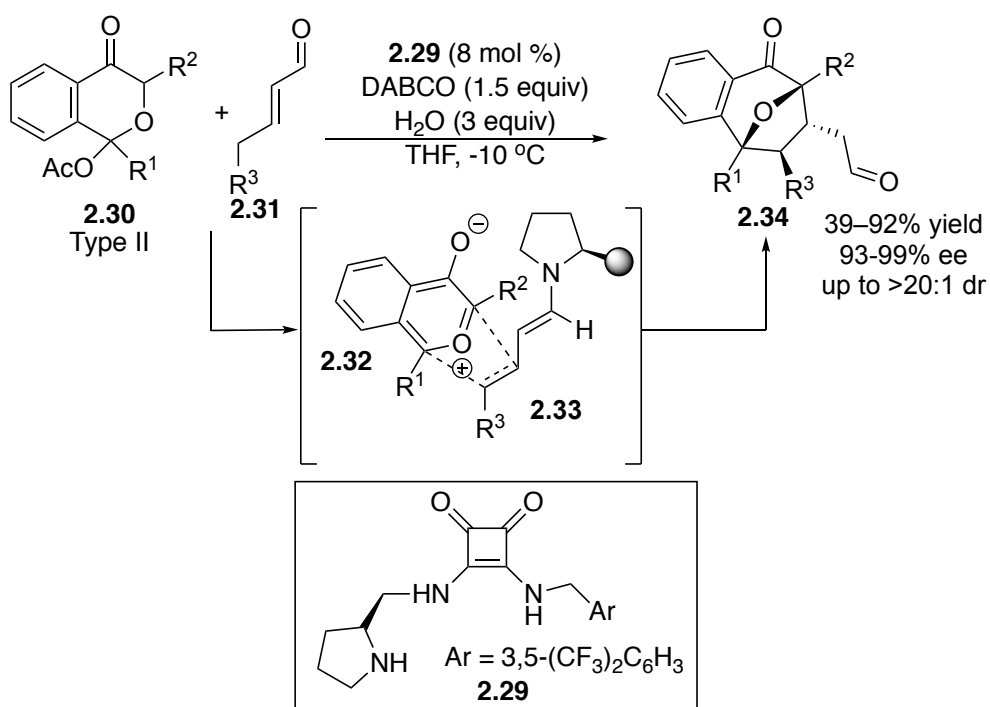
The second catalytic enantioselective [5 + 2] cycloaddition reaction, of benzopyrylium oxide **2.30** and an  $\alpha,\beta$ -unsaturated aldehyde **2.31**, was developed by Vicario and Reyes in 2015 (Scheme 2.5).<sup>15,22</sup> Enal **2.31** was condensed with pyrrolidine-squaramide bifunctional catalyst **2.29** to form an electron-rich dienamine intermediate **2.33**, while the squaramide tether could direct the approach of the ylide dipole through hydrogen bonding interactions. The cycloadduct **2.34** was afforded in good yields and in excellent enantioselectivities.

Whereas the two prior reports demonstrated enantioselective catalytic cycloaddition reactions of types **I** and **II** oxidopyrylium ylides with an electron-rich olefin, the type **III** ylide could be used to develop a reaction with an electron-deficient alkene. Moreover, it was envisaged that this reaction could be achieved using a type **III** oxidopyrylium ylide with an  $\alpha,\beta$ -unsaturated aldehyde, by employing a chiral secondary amine catalyst.

**Scheme 2.4** Jacobsen's enantioselective dually-catalyzed enamine and hydrogen bonding [5 + 2] dipolar cycloaddition.<sup>13-14</sup>



**Scheme 2.5** Vicario's enantioselective dienamine catalyzed [5 + 2] cycloaddition.<sup>15</sup>



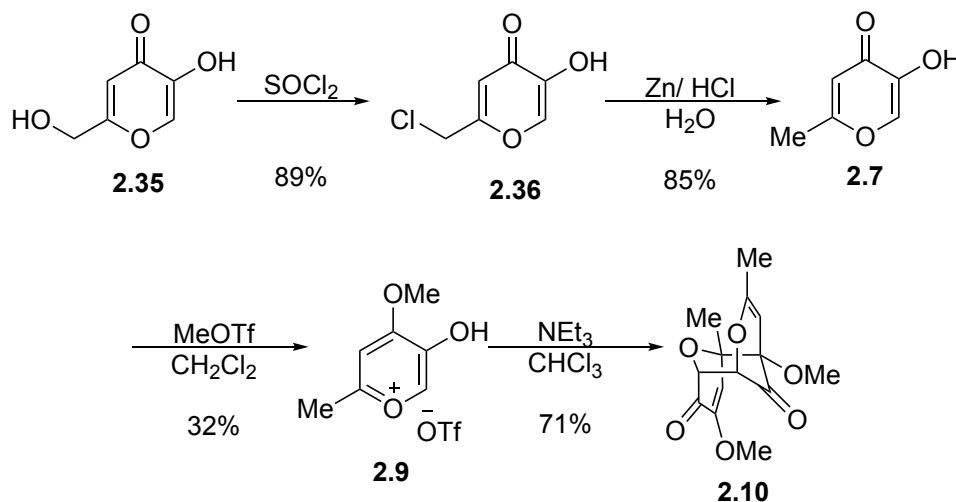


## 2.3 Results and Discussion

### 2.3.1 Preparation of Oxidopyrylium Ylides

Towards this goal, the starting material monomer **2.9** or dimer **2.10** was prepared in three steps starting from kojic acid **2.35** (**Scheme 2.6**).<sup>8,16</sup> Addition of thionyl chloride produces chlorokojic acid **2.36**. Reduction by Zn and HCl generates allomaltol **2.7**, followed by methylation of the pyrone carbonyl oxygen via addition of MeOTf, to yield oxidopyrylium in monomer form **2.9**, which requires a stoichiometric amount of *i*-Pr<sub>2</sub>NPh to generate the reactive ylide species **2.8b** *in situ*. Addition of NEt<sub>3</sub> to **2.9** forms dimer **2.10**, which can regenerate a reactive ylide *in situ* without any additives.

**Scheme 2.6** Preparation of monomer and formation of dimer.<sup>8,16</sup>



### 2.3.2 Reaction Development

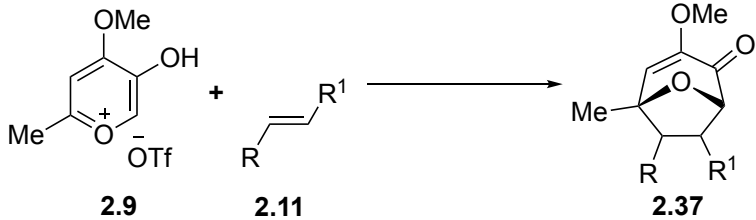
In collaboration with the Murelli group, initial investigations began by reacting monomer **2.9** with an electron deficient olefin source (**Table 2.1**). Initially, pentenal was tried at 50 °C, but no product formation was observed (entry 1). Cinnamaldehyde was then selected for further optimization because of its UV-visibility properties, and a lack of vinylogous enolizable  $\gamma$ -protons to prevent unwanted side reactions from occurring. Excess

cinnamaldehyde (20 equiv) in the presence of monomer **2.9** with *i*-Pr<sub>2</sub>NPh (1.2 equiv) in CHCl<sub>3</sub> (0.48 M) at 100 °C was used (entry 2) to replicate as much as possible the conditions reported by Murelli and group in general procedure B of their experimental work.<sup>9</sup>

This reaction was difficult to monitor by <sup>1</sup>H NMR due to the excess cinnamaldehyde, thus the loading of cinnamaldehyde was decreased to 6 equiv at 100 °C (entry 3). After 5 hours, the dipole was completely consumed as observed by <sup>1</sup>H NMR. The product **2.37a** was obtained with 2:1 dr (entry 3 and **Figure 2.3**) and in one regioisomeric form (**Figure 2.4**). In addition to trying enals in the reaction, β-nitrostyrene was also tried (entry 4). After 19 h, the product was collected with 76% yield.

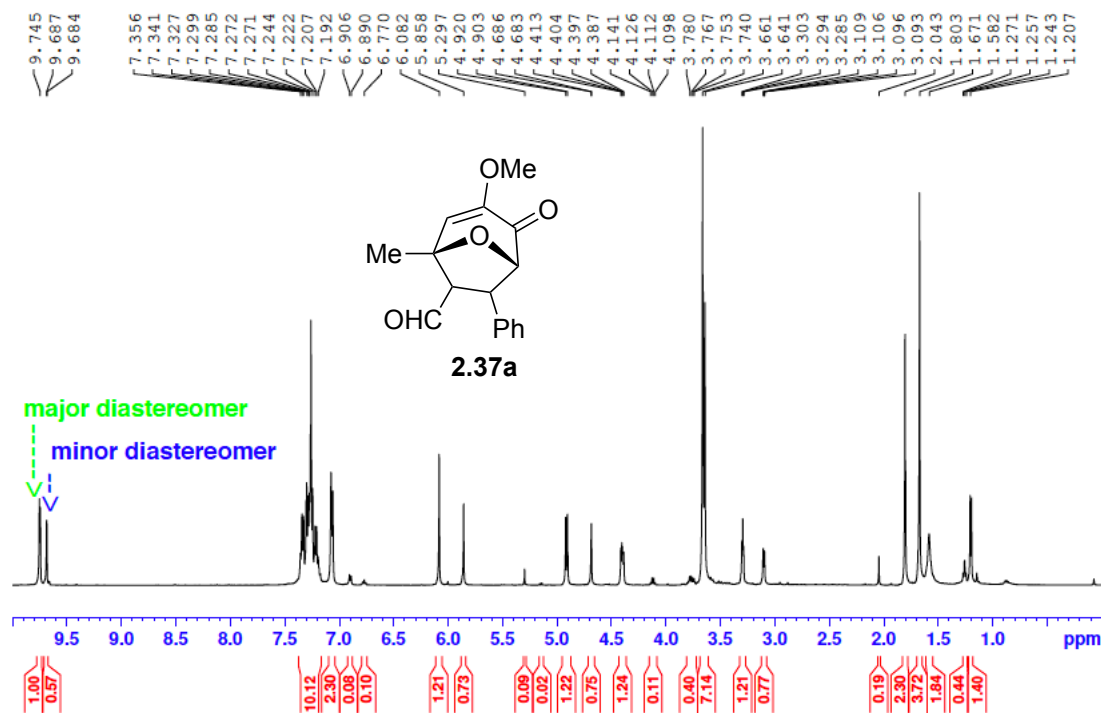
Similarly, dimer **2.10** was evaluated with various olefins (**Table 2.2**). The reaction was unsuccessful in dichloromethane (entry 1). The product was observed using cinnamaldehyde at 100 °C after 2 hours, a 3:1 dr (entry 5). The reaction with β-nitrostyrene also generated product at this temperature (entry 6), which was necessary for the reaction to proceed (entry 7).

**Table 2.1** Initial reactions with monomer.<sup>a</sup>

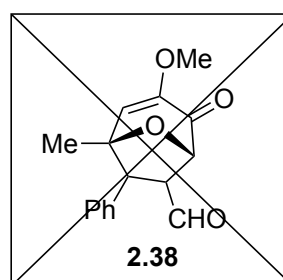
							
entry		R	R <sup>1</sup>	temp (°C)	<i>t</i> (h) <sup>b</sup>	yield <sup>c</sup> (%)	dr <sup>d</sup>
1	pentenal	CHO	C <sub>2</sub> H <sub>5</sub>	50	36	-	-
2 <sup>c</sup>	cinnamaldehyde	CHO	Ph	100	-	-	-
3	cinnamaldehyde	CHO	Ph	100	5	nd	2:1
4	β-nitrostyrene	NO <sub>2</sub>	Ph	100	19	76	-

<sup>a</sup> Reaction conditions: **2.11** (6 equiv), **2.9** (1 equiv), *i*-Pr<sub>2</sub>NPh (1.2 equiv), CHCl<sub>3</sub> (0.48 M). <sup>b</sup> Reactions were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield. <sup>d</sup> Determined by <sup>1</sup>H NMR. <sup>e</sup> alkene (20 equiv) used.

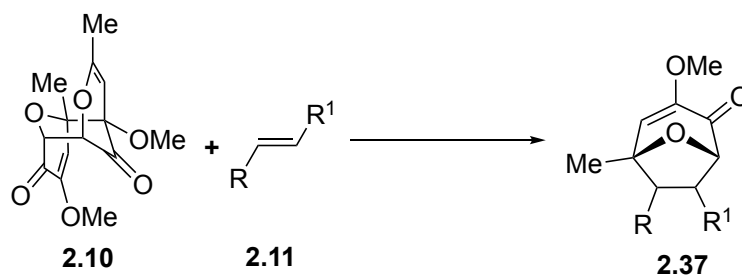
**Figure 2.3** Diastereomeric ratio determination of product.



**Figure 2.4** Other regioisomer not observed.



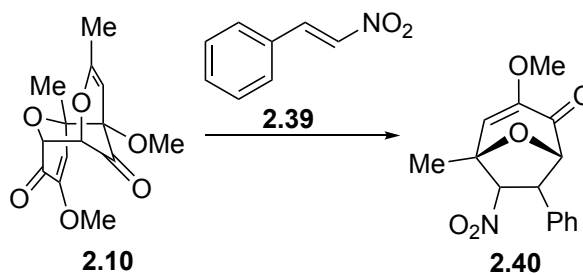
**Table 2.2** Initial reactions with dimer.<sup>a,b</sup>



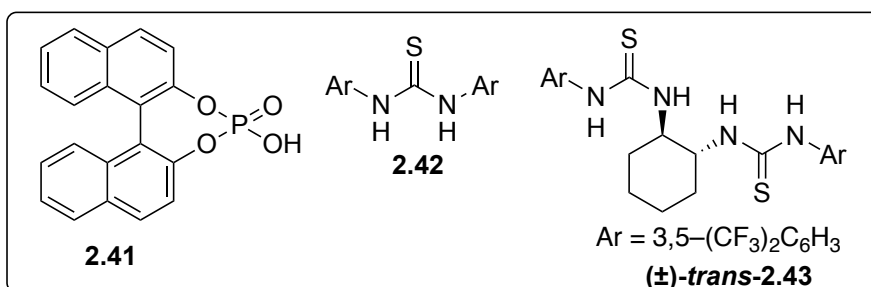
entry		R	R <sup>1</sup>	temp (°C)	<i>t</i> (h) <sup>c</sup>	yield (%) <sup>d</sup>	dr <sup>e</sup>
1 <sup>f</sup>	pentenal	CHO	C <sub>2</sub> H <sub>5</sub>	rt	36	-	-
2	cinnamaldehyde	CHO	Ph	rt	36	nr	-
3	cinnamaldehyde	CHO	Ph	50	36	-	-
4	pentenal	CHO	C <sub>2</sub> H <sub>5</sub>	50	24	nd	-
5	cinnamaldehyde	CHO	Ph	100	2	nd	3:1
6	β-nitrostyrene	NO <sub>2</sub>	Ph	100	19	89%	-
7	β-nitrostyrene	NO <sub>2</sub>	Ph	rt	19	nd	-

<sup>a</sup> Reaction conditions: **2.11** (6 equiv), **2.10** (1 equiv), CHCl<sub>3</sub> (0.48 M). <sup>b</sup> Equivalents and concentrations reported relative to monomeric ylide for consistency. <sup>c</sup> Reactions were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR. <sup>d</sup> Isolated yield. <sup>e</sup> Determined by <sup>1</sup>H NMR. <sup>f</sup> Reaction done in CH<sub>2</sub>Cl<sub>2</sub>.

Since a substantial background reaction was observed at 100 °C (entries 5-6, **Table 2.2**), the reaction was evaluated at lower temperatures and in the presence of different catalysts to potentially achieve asymmetric induction (**Tables 2.3** and **2.4**). The reactions were performed using dimer **2.10** as dipole and β-nitrostyrene **2.39** in the presence of various catalysts (**Table 2.3**). Only thiourea compounds **2.42** and **2.43** led to product formation, while phosphoric acid **2.41** did not. Enantiopure thioureas were not pursued. Instead, reactions using cinnamaldehyde **2.45a** in the presence of the (*S*)-diphenylprolinol trimethylsilyl ether catalyst **2.44** (20 mol %) in CHCl<sub>3</sub> (0.48 M) at 50 °C, or at room temperature, were simultaneously investigated while aforementioned experiments were ongoing (**Table 2.4**).

**Table 2.3** Initial catalytic reactions.<sup>a,b</sup>

entry	cat	temp (°C)	<i>t</i> (d) <sup>c</sup>	yield (%) <sup>d</sup>
1	<b>2.41</b>	rt	5	-
2	<b>2.42</b>	rt	1	58
3	<b>2.43</b>	rt	3	81



<sup>a</sup> Reaction conditions: **2.39** (6 equiv), cat (6 equiv), *i*-Pr<sub>2</sub>NPh (1.2 equiv), CHCl<sub>3</sub> (0.48 M). <sup>b</sup> Equivalents and concentrations reported relative to monomeric ylide for consistency. <sup>c</sup> Reactions were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR. <sup>d</sup> Isolated yield.

To our delight, reacting the monomer **2.9** with **2.45a** at rt and with catalyst **2.44**, formed the product **2.37a** in 92% ee and in a 12.5:1 dr, albeit in a low yield of 12% after an extended reaction time of 7 days (entry 1, **Table 2.4**). Heating the reaction improved the yield to 47%, but the dr and ee were negatively affected (entry 2). When the reaction was attempted using the dimeric oxidopyrylium **2.10**, no reaction occurred over the course of 7 days (entry 3). A catalytic amount of acid can promote formation of an iminium ion from an aldehyde and secondary amine, but benzoic acid as an additive gave little to no product (entry 4). Additionally, the dimer **2.10** without and with benzoic acid as an additive gave no to trace conversion, respectively at 50 °C (entries 5 and 6).

**Table 2.4** Initial optimizations using chiral catalyst.<sup>a,b</sup>

**Dipole**

**2.9**

**Dipole**

**2.10**

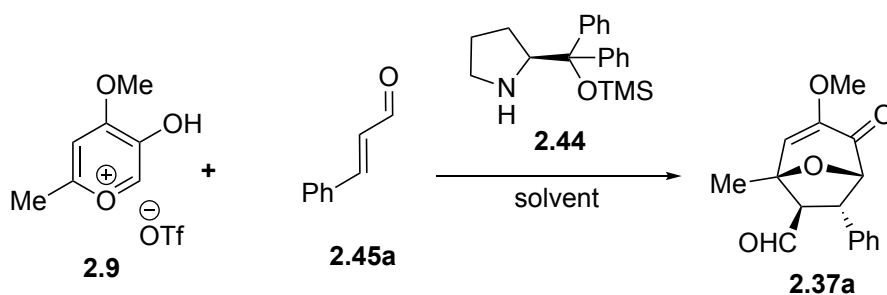
entry	dipole	additive (equiv)	temp (°C)	<i>t</i> (d) <sup>c</sup>	yield (%) <sup>d</sup>	ee (%) <sup>e</sup>	dr <sup>f</sup>
1	<b>2.9</b>	<i>i</i> -Pr <sub>2</sub> NPh (1.2)	rt	7	12	92	12.5:1
2	<b>2.9</b>	<i>i</i> -Pr <sub>2</sub> NPh (1.2)	50	0.1	47	67	5:1
3	<b>2.10</b>	-	rt	7	-	-	-
4	<b>2.10</b>	BzOH (0.2)	rt	7	-	-	-
5	<b>2.10</b>	-	50	7	-	-	-
6	<b>2.10</b>	BzOH (0.2)	50	7	trace	-	-

<sup>a</sup> Reaction conditions: **2.45a** (6 equiv), dipole (1 equiv), **2.44** (0.2 equiv), CHCl<sub>3</sub> (0.48 M). <sup>b</sup> Equivalents and concentrations reported relative to monomeric ylide for consistency. <sup>c</sup> Reactions were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR. <sup>d</sup> Isolated yield. <sup>e</sup> Determined by chiral phase HPLC. <sup>f</sup> Determined by <sup>1</sup>H NMR.

Since it appeared the use of dimer **2.10** as the dipole would not be productive, further investigations focused on monomer **2.9**. Solvents, including neat conditions, were evaluated using monomer **2.9**, cinnamaldehyde **2.45a** (6 equiv), catalyst **2.44** (20 mol %), and 1.2 equivalents of *i*-Pr<sub>2</sub>NPh at rt (**Table 2.5**). Acetonitrile was the only solvent that improved the yield, ee, and dr (entry 5). The neat conditions gave results that were like the original solvent choice of CHCl<sub>3</sub> (entry 2 vs. entry 1). In toluene, product formation was

observed by  $^1\text{H}$  NMR, but not in enough conversion to pursue this solvent choice (entry 3). No product formation occurred in MeOH (entry 4). Therefore, acetonitrile was selected as the solvent for further optimization. While the product ee and dr were both excellent, the reaction yield was still low. The reaction was thus further optimized to improve the yield.

**Table 2.5** Solvent screening.<sup>a</sup>



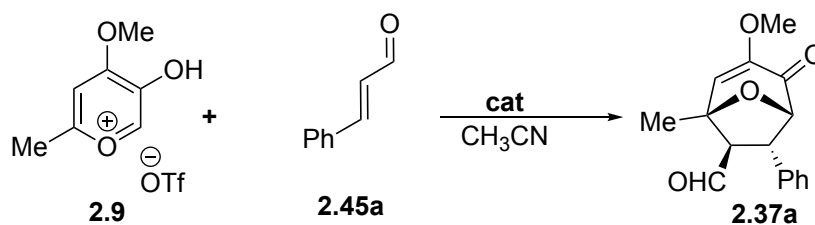
entry	solvent	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	dr <sup>d</sup>
1	$\text{CHCl}_3$	6	88	20:1
2	-	11	87	20:1
3 <sup>e</sup>	toluene	4	-	-
4	MeOH	-	-	-
5	$\text{CH}_3\text{CN}$	27	94	25:1

<sup>a</sup> Reaction conditions: **2.45a** (6 equiv), **2.9** (1 equiv), *i*-Pr<sub>2</sub>NPh (1.2 equiv), solvent (0.48 M), 7 d. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral phase HPLC. <sup>d</sup> Determined by  $^1\text{H}$  NMR. <sup>e</sup>  $^1\text{H}$  NMR yield using cyclohexene as internal standard.

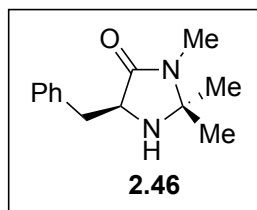
Towards this end, different reaction variables in acetonitrile were evaluated (**Table 2.6**). Doubling the loading of catalyst **2.44** improved the yield of **2.37a** from 27 to 45% and gave an excellent dr of 33:1 and an ee of 97% (entry 1, **Table 2.6** vs. entry 5, **Table 2.5**). However, in both cases, the catalyst loading was approximately equal to the yield of the reaction. It was suspected that there could be an issue with the catalyst turnover. The addition of H<sub>2</sub>O (0.2 equiv) was added to promote catalyst turnover but did not improve

the yield (entry 2). Increasing the reaction concentration ten-fold or trying a different catalyst, imidazolidinone **2.46**, also were not effective at improving reaction yield (entries 3 and 4). Lastly, slightly elevated temperature maintained the ee and dr while decreasing the reaction time, but the yields were still only moderate (entry 5). From earlier efforts (entry 2, **Table 2.4**), it was known that higher temperatures would improve the yield, although caused an unacceptable drop in enantioselectivity. Thus, the use of dimer **2.10** as reaction dipole was revisited.

**Table 2.6** Further optimizations in acetonitrile with monomer **2.9**.<sup>a</sup>



entry	additive (equiv)	cat (mol %)	<i>t</i> (d) <sup>b</sup>	yield (%) <sup>c</sup>	ee (%) <sup>d</sup>	dr <sup>e</sup>
1	<i>i</i> -Pr <sub>2</sub> NPh (1.2)	<b>2.44</b> (40)	7	45	97	33:1
2 <sup>f</sup>	<i>i</i> -Pr <sub>2</sub> NPh (1.2), H <sub>2</sub> O (0.2)	<b>2.44</b> (20)	7	22	-	-
3 <sup>f,g</sup>	<i>i</i> -Pr <sub>2</sub> NPh (1.2)	<b>2.44</b> (20)	7	16	-	0
4	<i>i</i> -Pr <sub>2</sub> NPh (1.2)	<b>2.46</b> (20)	-	-	-	-
5 <sup>h</sup>	<i>i</i> -Pr <sub>2</sub> NPh (1.2)	<b>2.44</b> (20)	0.4	39	95	10:1



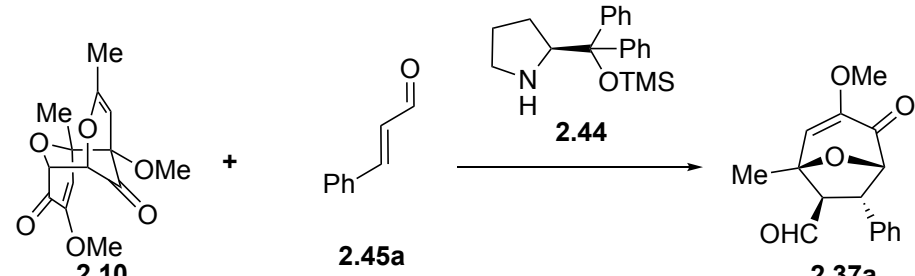
<sup>a</sup> Reaction conditions: **2.45a** (6 equiv), **2.9** (1 equiv), cat (0.2 equiv), CH<sub>3</sub>CN (0.48 M), rt. <sup>b</sup> Reactions were run for 7 d or were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR, whichever was sooner. <sup>c</sup> Isolated yield. <sup>d</sup> Determined by chiral phase HPLC. <sup>e</sup> Determined by <sup>1</sup>H NMR. <sup>f</sup> <sup>1</sup>H NMR yield using cyclohexene as internal standard. <sup>g</sup> Reaction concentration (4.8 M). <sup>h</sup> Reaction run at 35–40 °C.

Earlier attempts at trying the dimer **2.10** in the asymmetric catalytic cycloaddition reaction were unsuccessful (entries 3–6, **Table 2.4**), however product **2.37a** had formed



when the dimer **2.10** was heated with **2.45a** without catalyst present (entry 5, **Table 2.2**). The reaction of dimer **2.10** with **2.45a** without catalyst at 50 °C and room temperature was unsuccessful, which proved that there was no background reaction (entries 2 and 3, **Table 2.2**). At these temperatures, background reactions could be detrimental to the ee in the reactions using a chiral catalyst, so there was potential for achieving a high enantioselectivity if dimer **2.10** could successfully be employed as the ylide source. The reactivity of monomer salt **2.9** might be due to the presence of the *i*-Pr<sub>2</sub>HN<sup>+</sup>Ph • <sup>-</sup>OTf salt that formed as byproduct and was perhaps promoting iminium ion formation. Hence, optimization commenced with an exploration of these additives with the dimer salt **2.10** (**Table 2.7**).

The stoichiometry of the entry giving the best result with monomer **2.9** was mimicked by reacting the dimer **2.10** in the presence of 1 equivalent of triflic acid and 1.2 equivalents of *i*-Pr<sub>2</sub>NPh (entry 5, **Table 2.5** vs. entry 1, **Table 2.7**). The product was obtained in 28% yield, 97% ee, and 10:1 dr, supporting the hypothesis that the conjugate acid of *i*-Pr<sub>2</sub>NPh is needed to catalyze iminium ion formation. The reaction employing the dimer **2.10** had a comparable yield to the monomeric version, but merely increased ee by 3%. When monitoring the reactions done using monomer **2.9** (with added *i*-Pr<sub>2</sub>NPh) via <sup>1</sup>H NMR, immediate formation of dimer **2.10** from monomer **2.9** was always observed.

**Table 2.7** Optimization with dimer in the presence of stoichiometric amounts of acid and base.<sup>a,b</sup>


entry	TfOH (equiv) <sup>b</sup>	<i>i</i> -Pr <sub>2</sub> NPh (equiv) <sup>b</sup>	temp (°C)	<i>t</i> (d) <sup>c</sup>	yield (%) <sup>d</sup>	ee (%) <sup>e</sup>	dr <sup>f</sup>
1	1.0	1.2	rt	7	28	97	10:1
2	1.0	1.0	rt	7	32	95	10:1
3	1.0	1.0	35	2	42	93	6:1
4	1.0	1.0	40	2	86	93	7:1
5	1.0	1.0	45	2	91	89	6:1
6 <sup>g</sup>	1.0	1.0	40	4	8	-	1.5:1

<sup>a</sup> Reaction conditions: **2.45a** (6 equiv), **2.10** (1 equiv), **2.44** (0.2 equiv), CH<sub>3</sub>CN (0.48 M). <sup>b</sup> Concentration and equivalents reported relative to monomeric ylide for consistency. <sup>c</sup> Reactions were run for 7 d or were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR, whichever was sooner. <sup>d</sup> Isolated yield. <sup>e</sup> Determined by chiral phase HPLC. <sup>f</sup> Determined by <sup>1</sup>H NMR. <sup>g</sup> In the absence of **2.44**

Continuing reaction optimization using exactly 1 equiv of both acid and base at room temperature (entry 2 of **Table 2.7**) improved the yield slightly (32%) but the ee was compromised (decreased by 2%) and the dr was maintained. This transformation is highly sensitive to temperature and by trying various temperatures (entries 3–5), the yield was improved substantially in a significantly shorter reaction time, while maintaining the enantioselectivity. As some background reaction occurred in absence of catalyst **2.44** (entry 6); finer tuning of the equivalents was necessary to completely suppress the racemic reaction.

The optimization using dimer salt **2.10** continued by decreasing the loading of the acid and base additives (**Table 2.8**). While the presence of TfOH without *i*-Pr<sub>2</sub>NPh can

entry	TfOH (equiv) <sup>b</sup>	<i>i</i> -Pr <sub>2</sub> NPh (equiv) <sup>b</sup>	<i>t</i> (d) <sup>c</sup>	yield (%) <sup>d</sup>	ee (%) <sup>e</sup>	dr <sup>f</sup>
1	1.0	0	4	5	-	-
2	0.4	0	2	41	98	9:1
3	0.2	0	2	60	95	7:1
4	0.2	0.2	2	57	97	7:1
5	0.4	0.2	2	54	97	7:1
6	0.4	0.4	2	78	99	9:1

<sup>a</sup> Reaction conditions: **2.45a** (6 equiv), **2.10** (1 equiv), **2.44** (0.2 equiv), CH<sub>3</sub>CN (0.48 M), 40 °C. <sup>b</sup> Concentration and equivalents reported relative to monomeric ylide for consistency. <sup>c</sup> Reactions were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR. <sup>d</sup> Isolated yield. <sup>e</sup> Determined by chiral phase HPLC. <sup>f</sup> Determined by <sup>1</sup>H NMR.

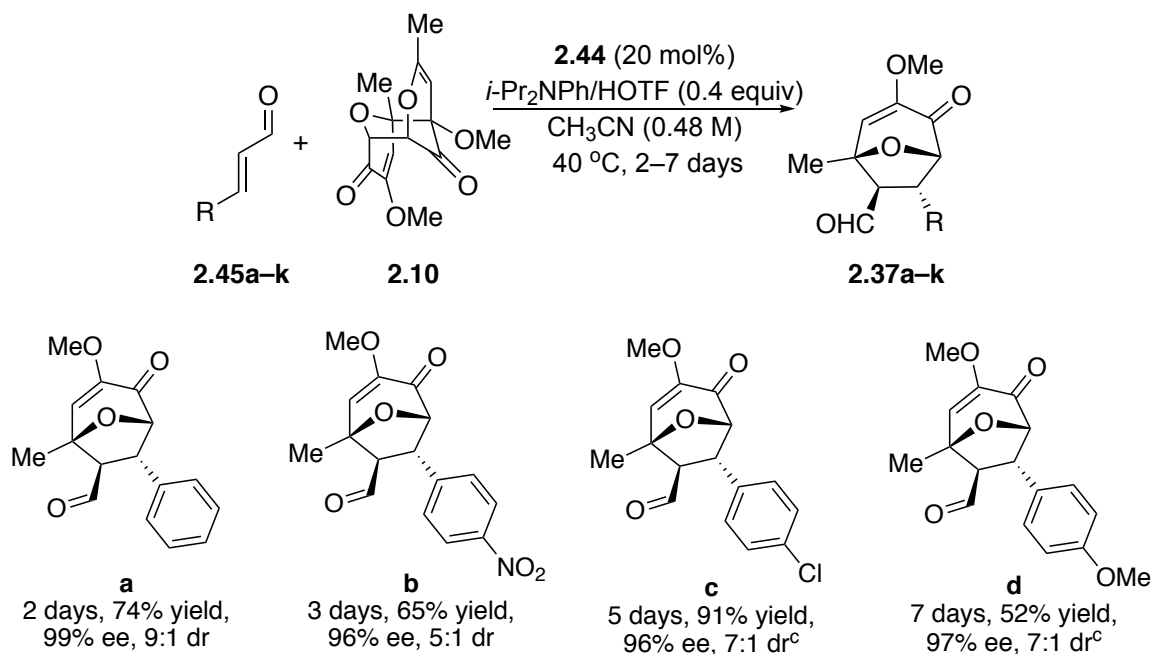
### 2.3.3 Substrate Scope

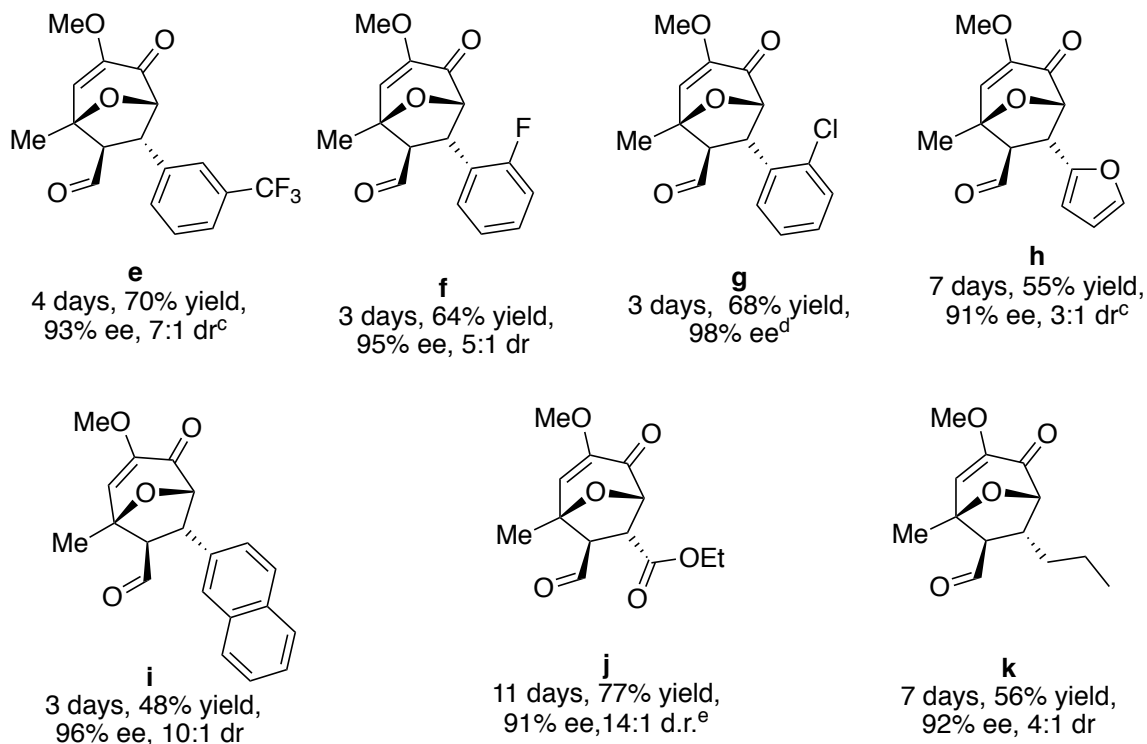
After identifying optimal reaction conditions (entry 6, **Table 2.8**), the scope of substrates was surveyed, as shown in **Table 2.9**. Products **2.37a-k** were afforded in fair to high yields (48–91%) and dr, (3:1 up to as a single diastereomer), and excellent ee (91–99%). These results demonstrate the broad applicability of enals that can be used in this cycloaddition. An array of aromatic enals were demonstrated in the cycloaddition reaction, including electron-rich and poor cinnamaldehydes. Heteroaromatic and polyaromatic R-groups on the enal were also tolerated (**2.37h–i**). It is, however, not a requirement to have an aromatic R group for the reaction to proceed. Aliphatic (**2.37k**) and non-aromatic  $sp^2$ -hybridized (**2.37j**) R groups were reacted successfully. The reaction of *meta*-chloro substituted cinnamaldehyde produced a single diastereomer which also had excellent ee and moderate yield, despite the hindered  $\beta$ -position of the aldehyde (**2.37g**).

Substrates **2.37c**, **2.37d**, **2.37e**, and **2.37f** required minor re-optimization due to the decrease in ee that occurred when subjected to the reaction conditions (entries 1-4b, **Table 2.10**). The re-optimization was achieved by trying different reaction temperatures and loadings of the acid and base additive, as these were all shown to have a pronounced effect on yield and selectivity. Maintaining equimolar amounts of acid (0.4 equiv) and base (0.4 equiv) while decreasing the temperature from 40 to 35 °C improved the product yield and enantioselectivity (entries 1–4a). However, this change of temperature negatively impacted the product's diastereoselectivities (entries 1b vs. 1a, 3b vs. 3a). In addition to changing the temperature, a higher loading of TfOH/*i*-Pr<sub>2</sub>NPh was tried (entries 1c-3c, 1d, and 4d). While this condition helped the yield increase, the ee stayed in the high 80's to low 90's. This could be due to the background reaction that can occur as a result of having a slight excess of these additives in the mixture.

The best results from re-optimization was the use of 0.4 equiv TfOH/*i*-Pr<sub>2</sub>NPh at 35 °C, since the ee was boosted. There was no distinct trend amongst substrates that required re-optimization. The ester substrate **2.37j** had a persistent background reaction, so lower temperatures were tried to find the conditions to prevent this from occurring. At rt and at 0 °C, 30–40% conversion of starting material to product was observed when no catalyst was used in the reaction. Finally, at –25 °C, the uncatalyzed background reaction was suppressed completely. The final reaction conditions were –25 °C for 11 days with 0.4 equivalents of acid and base additive, to provide the product in 77% yield, 14:1 dr, and 91% ee (**2.37j**, Table 2.9). We also attempted the cycloaddition reaction using *trans*-cinnamaldehyde and phenyl propargyl aldehyde, however no reaction took place after 3 days.

**Table 2.9** Substrate scope of **2.37**.<sup>a,b</sup>

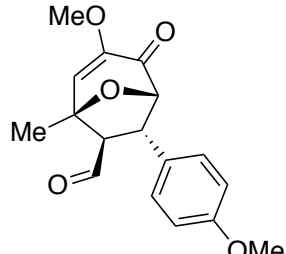
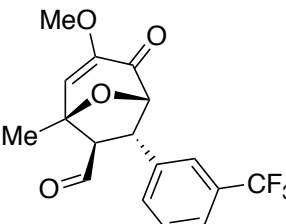
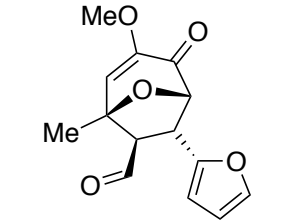




<sup>a</sup> Yields reflect isolated yields, with dr determined by <sup>1</sup>H NMR, and ee determined by chiral phase HPLC. <sup>b</sup> Concentration and equivalents reported relative to monomeric ylide. <sup>c</sup> Reaction run at 35 °C. <sup>d</sup> Single diastereomer. <sup>e</sup> Reaction run at -25 °C.

**Table 2.10** Re-optimization of substrates **2.37c–e**, and **h**.<sup>a,b</sup>

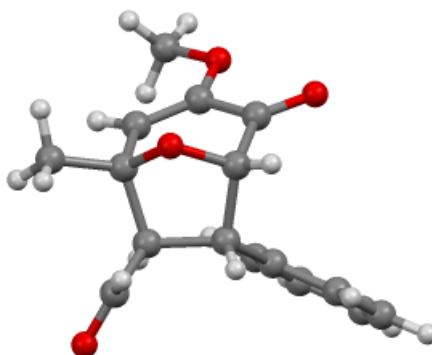
entry	substrate	TfOH + <i>i</i> -Pr <sub>2</sub> NPh (equiv) <sup>b</sup>	temp (°C)	<i>t</i> (d) <sup>c</sup>	yield (%) <sup>d</sup>	ee (%) <sup>e</sup>	dr <sup>f</sup>
1a	<p><b>2.37c</b></p>	0.4	35	5	91	96	7:1
1b		0.4	40	3	86	85	13:1
1c		1.0	35	4	99	93	7:1
1d		1.0	40	4	88	80	8:1
2a	<p><b>2.37c</b></p>	0.4	35	7	52	97	7:1
2b		0.4	40	2	41	84	8:1

2c		1.0	35	7	51	89	5:1
<b>2.37d</b>							
3a		0.4	35	4	70	93	7:1
3b		0.4	40	3	65	85	13:1
3c		1.0	35	3	76	91	6:1
<b>2.37e</b>							
4a		0.4	35	7	55	91	3:1
4b		0.4	40	6	46	85	10:1
4c		1.0	35	7	85	-	8:1
4d		1.0	40	7	52	90	3:1
<b>2.37h</b>							

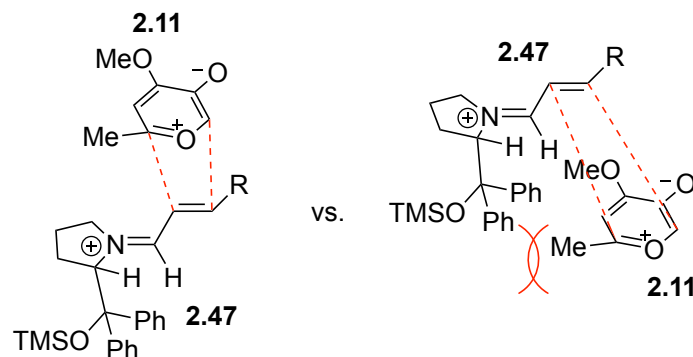
<sup>a</sup> Reaction conditions: **2.45** (6 equiv), **2.44** (0.2 equiv) **2.10** (1 equiv), CH<sub>3</sub>CN (0.48 M). <sup>b</sup> Concentration and equivalents reported relative to monomeric ylide for consistency. <sup>c</sup> Reactions were stopped when complete consumption of dipole was observed by <sup>1</sup>H NMR. <sup>d</sup> Isolated yield. <sup>e</sup> Determined by chiral phase HPLC. <sup>f</sup> Determined by <sup>1</sup>H NMR.

### 2.3.4 Synthetic Application and Determination of Configurations

Delightfully, the pure major diastereomer and minor diastereomers were separable during flash column chromatography (40% EtOAc/PE). Racemic product formed from reactions done using the corresponding racemic catalyst *rac*-**2.44** was used as a standard against crystalline fractions of **2.37a**, collected post-FCC, to determine the ee. X-ray crystallography confirmed the relative configurations of **2.37a** by assigning the stereochemistry of benzylic carbon as the (*S*)-stereocenter (**Figure 2.5**), which is set by the catalyst during the reaction.

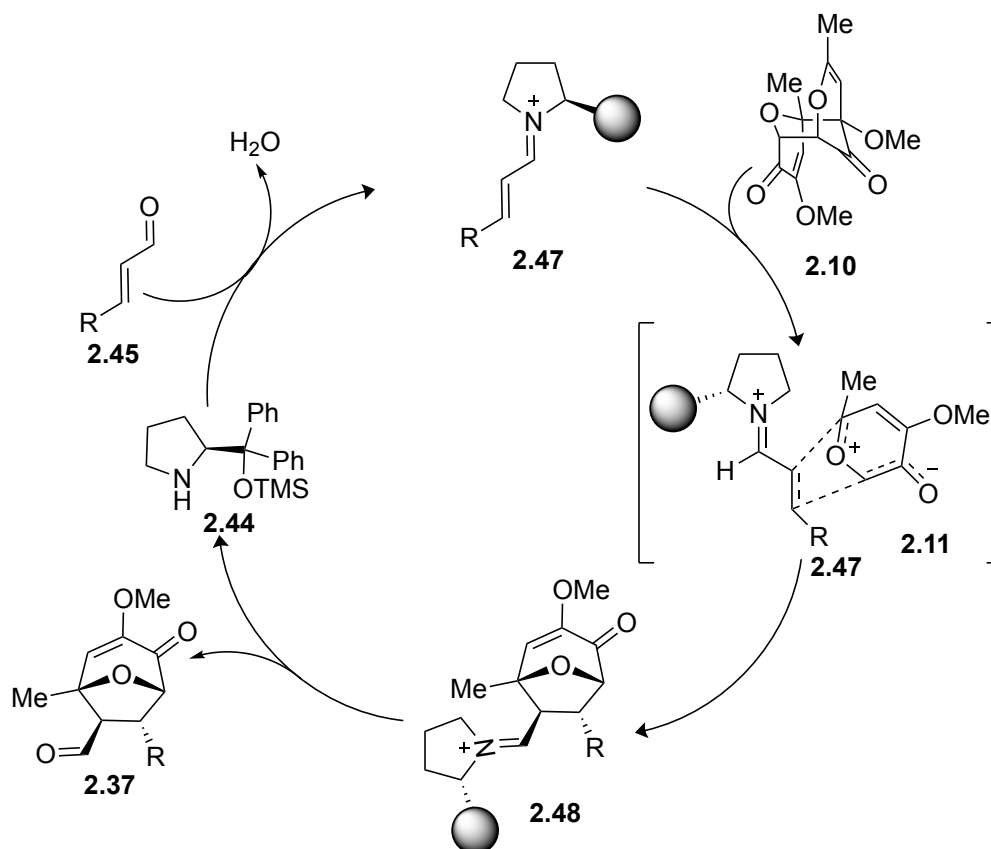
**Figure 2.5** X-ray structure of **2.37a-exo**.**2.37a-exo**

From this data, the proposed mode for asymmetric induction is depicted in **Figure 2.6**. The diarylprolinol silyl ether activates the enal for iminium catalysis while oxidopyrylium ylide must approach the reactive olefin in an *exo* manner and from the opposite face of the bulky silyl group on the catalyst. It cannot be ruled out that the iminium ion reacts with other sources of ylide in the reaction. This data also led to the proposed catalytic cycle of **Scheme 2.7**. It is still unclear what the iminium ion is reacting directly with, **2.10** or **2.9**, although **2.10** was solely observed via  $^1\text{H}$  NMR at any time point during the reaction.

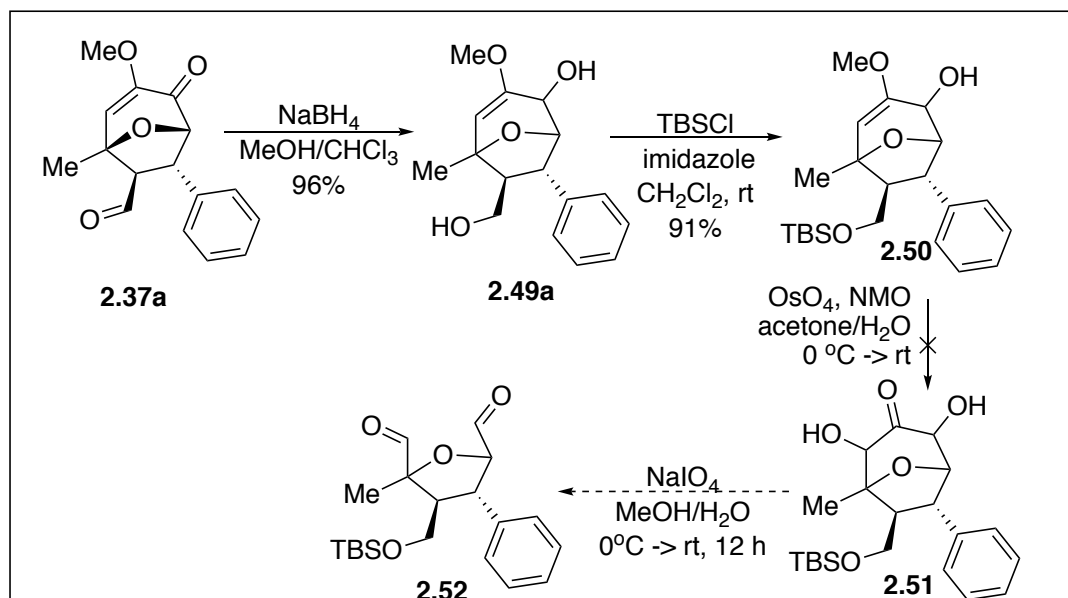
**Figure 2.6** Proposed model of asymmetric induction.



Scheme 2.7 Catalytic cycle.



The product **2.37a-exo** was subjected to further transformations demonstrating the utility of this reaction as a synthetic tool for generation of, and modification of, chiral oxabicyclic scaffolds. Initially, efforts were focused on the proposed synthetic route shown in **Scheme 2.8**, starting with transformation of the oxa[3.2.1]bicyclooctane structure into a five-membered ring. Global reduction of the ketone and aldehyde by sodium borohydride unveiled the fifth stereocenter in diol **2.49a**, which was collected as a foam in 96% yield. Selective protection of primary alcohol with TBSCl gave **2.50** in 91%. When **2.50** was subjected to dihydroxylation, no reaction occurred (**Scheme 2.8**).

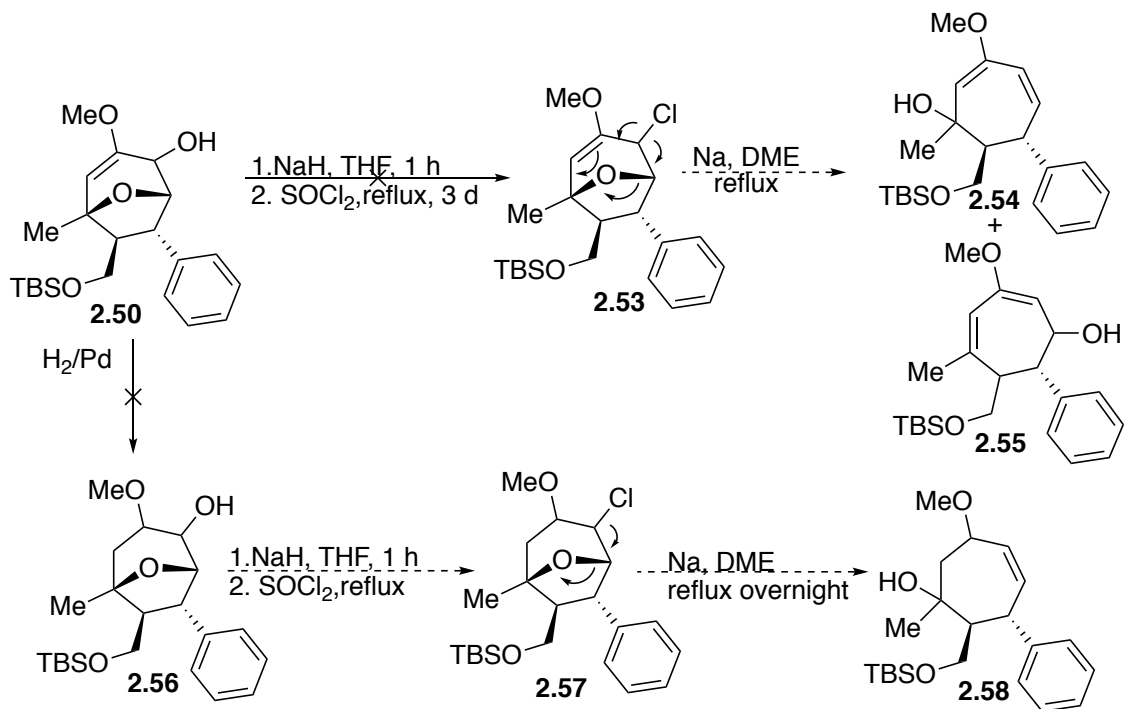
**Scheme 2.8** Initial proposed route to five-membered ring.

Formation of seven-membered rings, such as **2.56** and **2.57**, became the next synthetic pursuit, from the proposed route of **Scheme 2.9**. This approach would utilize **2.50** of **Scheme 2.8** for creating a seven-membered ring via ethereal cleavage of halogenated compounds **2.53** or **2.57**. Unfortunately, the desired chlorinated intermediate was never formed from **2.50**. Since chlorination of the unsaturated system had been unsuccessful, hydrogenation of the **2.50** to form saturated diol **2.56** was tried, since it might be a more suitable intermediate for the transformation (**Scheme 2.9**) This also led to no product, and pursuit of a better protecting group.

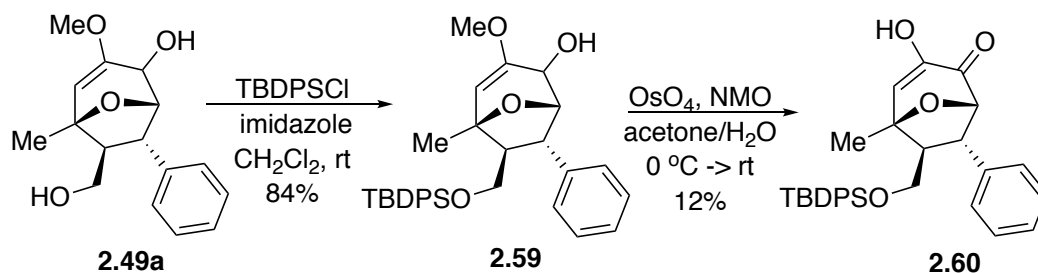
It was found that using a bulkier protecting group was critical for these reactions to occur (**2.59** of **Scheme 2.10**). Dihydroxylation of **2.59** afforded product **2.60**, unexpectedly. Deprotonation of the secondary alcohol **2.60** was attempted with  $\text{NaH}$ , followed by addition of thionyl chloride (**eq 1**, **Scheme 2.11**). Product **2.61** was yet again obtained even when the alcohol was converted into a mesylate **2.62** and allowed to react with  $n\text{-Bu}_4\text{NCl}$  (**eq 2**). Ketone **2.61** was formed as the product. The second chlorination

approach tried utilized triphenyl phosphine and NCS but only the saturated ketone **2.63** formed (eq 3).

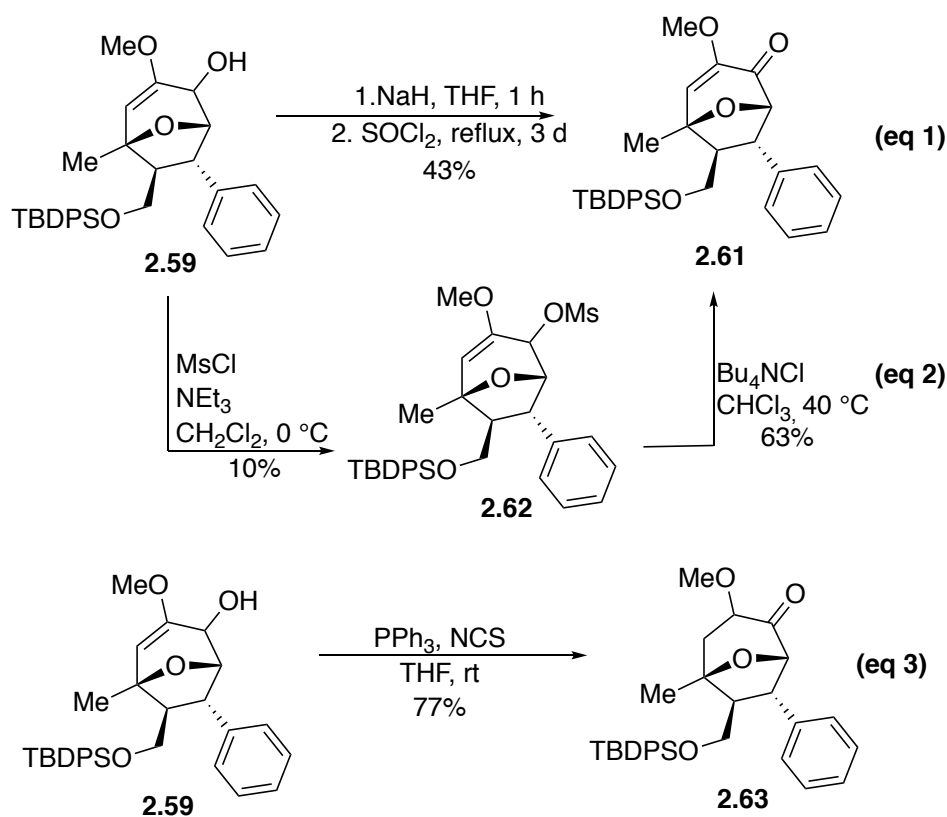
**Scheme 2.9** Design of ethereal bridge cleavage.



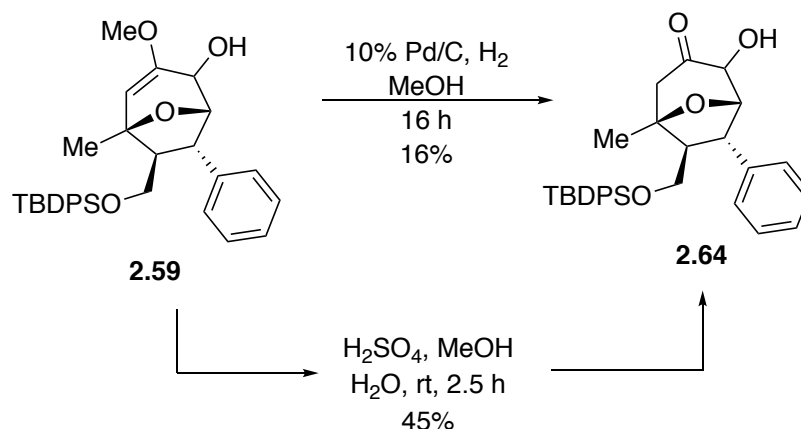
**Scheme 2.10** Product from osmium tetroxide.



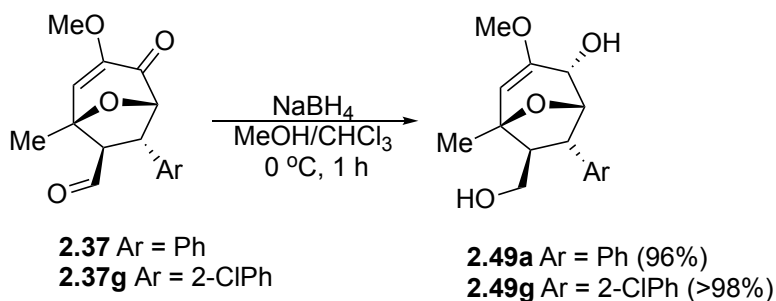
Scheme 2.11 Attempts at chlorination.

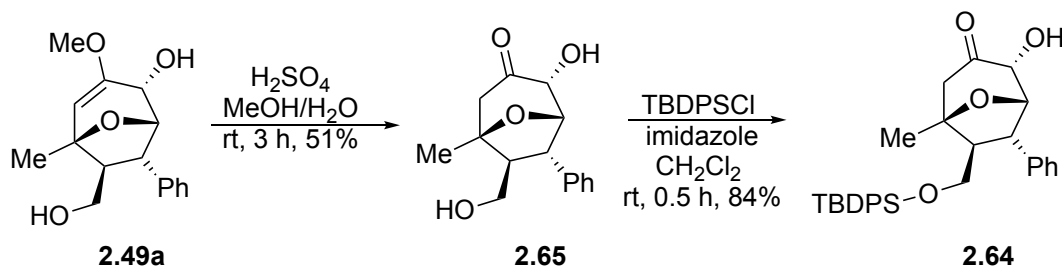


Hydrogenation of **2.59** resulted in formation and collection of **2.64** in 16% yield, the result of a methyl enol ether hydrolysis, which may have formed if trace amounts of acid were present in the starting material (Scheme 2.12). Originally, it was suspected that this transformation was occurring, and its discovery led to the final synthetic plan. Indeed, hydrolysis of the methyl enol ether of **2.59** with  $\text{H}_2\text{SO}_4$  in aqueous conditions at rt afforded **2.64** in 45% yield.

**Scheme 2.12** Hydrolysis product.

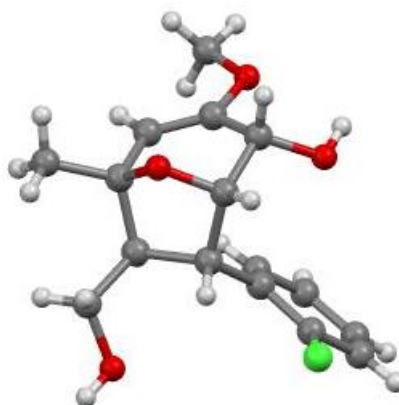
The final transformation synthetic transformations that were ultimately demonstrated are shown in **Scheme 2.13**. Beginning with reduction of the ketone and aldehyde of **2.37** by sodium borohydride unveiled the fifth stereocenter in the form of the diol **2.49a**, collected as a colorless oil in 96% yield. The acidic hydrolysis product of the unprotected diol formed ketone **2.65** in with a slightly improved yield of 51% relative to the monoprotected **2.59** (**Scheme 2.12**). The primary alcohol was selectively protected with TBDPSCl to form **2.64** in 84% after only 0.5 h. The preference for protection of the primary versus secondary hydroxyl groups enables orthogonal synthetic elaboration, which is a useful method often leveraged in many formal and total syntheses. For example, orthogonal protection can be seen in some of the formal and total syntheses of Taxol.<sup>17-18</sup>

**Scheme 2.13** Actual synthetic transformations of oxa[3.2.1]bicyclooctane scaffold.



The configuration of the diol needed to be determined. Initially, derivatization of diol **2.49a** with *p*-nitrobenzoyl was tried in hopes of forming crystalline product for X-ray crystallography. NOESY experiments had lacked sufficient evidence to unambiguously determine the configuration. Looking back over the scope of substrates, we recalled that **2.37g** (Table 2.9) formed as a single diastereomer and in crystalline phase. Upon global reduction conditions of **2.37g**, the 2-chloro diol **2.49g** was successfully collected as a crystalline solid in quantitative yield (Scheme 2.13). The presence of the heavy chlorine atom allowed for absolute configuration of the five contiguous stereocenters in diol **2.49g** to be determined (Figure 2.7).<sup>10,11</sup>

**Figure 2.7** Crystal structure of **2.49g-*exo***.



## 2.4 Conclusions

The development of the first catalytic enantioselective [5 + 2] dipolar cycloaddition between an oxidopyrylium ylide and an electron-poor alkene in the form of an iminium

ion was described. The reaction gave access to a chiral 8-oxabicyclo[3.2.1]octane scaffold, which is a common substructure motif that is found in some natural products exhibiting anti-cancer properties. The major diastereomer of the products was the *exo* isomer, which was maintained after global reduction. Transformation of the product introduced a fifth stereocenter, and selective protection of a primary over secondary alcohol proved this scaffold to be a worthy candidate for orthogonal protection strategies in further syntheses.

## 2.5 References

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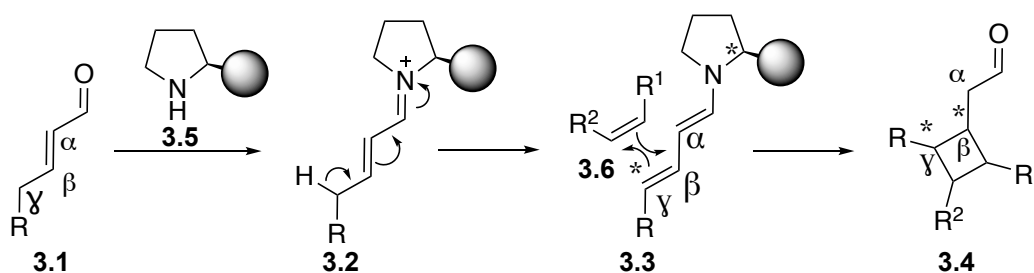
## CHAPTER 3

## CLAISEN REARRANGEMENT

## 3.1 Introduction

Iminium, enamine, and dienamine intermediates have been used in a wide variety of cycloaddition reactions as seen in **Chapter 1**. There are two significant issues with reactivity of dienamines of type **3.3** (**Scheme 3.1**) in reactions: 1.) regioselectivity, due to two reactive,  $\alpha$ - and  $\gamma$ - nucleophilic centers, and 2.) stereocontrol of the position remote to the catalyst chiral center. To circumvent the latter, cycloaddition reactions are often utilized because the concerted mechanism through which they go, has a reactive center with increased proximity to the stereocenter of the catalyst, whilst synchronized bond formation allows for a higher degree of stereocontrol, as illustrated in **Scheme 3.1**. Mechanistic studies have shed insight on the dienamine intermediate reacting in stepwise cycloaddition reactions.<sup>1-10</sup>

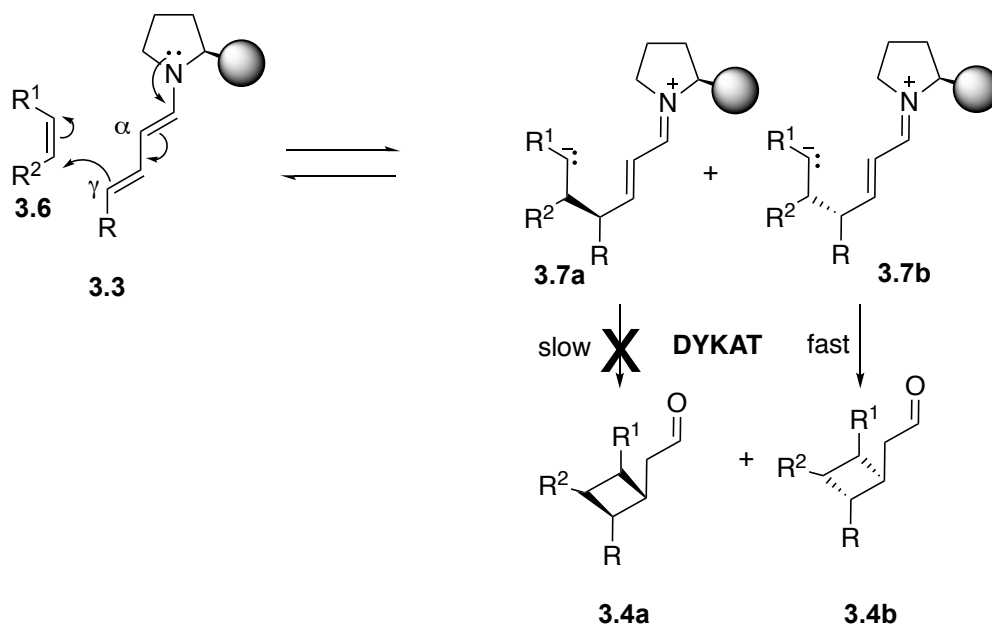
**Scheme 3.1** Concerted cycloaddition of a dienamine.



It was postulated that these cycloadditions could generate products in high ee even if a nonstereoselective  $\gamma$ -functionalization was occurring in a stepwise cycloaddition. In theory, iminium ion **3.7** can exist as an epimeric mixture (**Scheme 3.2**). Subsequent intramolecular reactions could resolve the epimeric mixture if there was a preference for

one enantiomer to react faster with the catalyst and the  $\gamma$ -epimers can interconvert, resulting in a DYKAT that leads to a single enantiomer of **3.4**.

**Scheme 3.2** Stepwise mechanism of dienamine in cycloaddition.

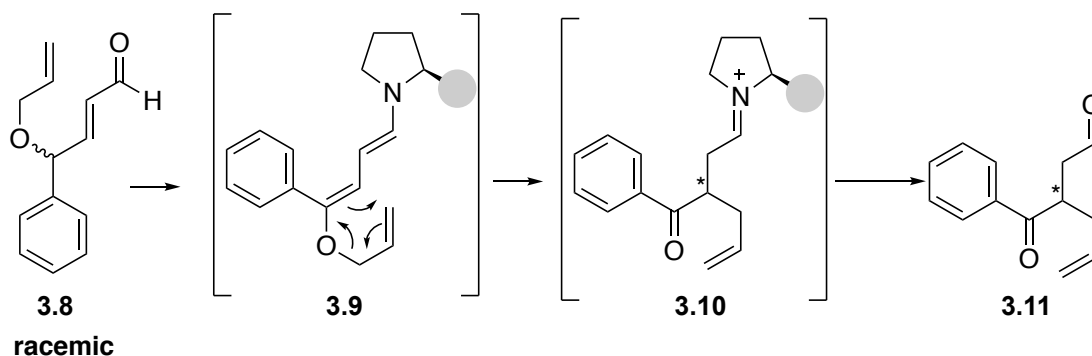


To date, there are only a few examples of enantioselective [3,3]-sigmatropic rearrangements catalyzed by amine organocatalysts published in the literature.<sup>11-21</sup> In 2008, a report from the Jacobsen group was published featuring a guanidinium salt-catalyzed enantioselective Claisen rearrangement.<sup>22</sup> Later in 2016, Gleason and co-workers reported an organocatalytic Cope rearrangement as proof of principle for chiral catalyst development.<sup>22-23</sup> These, and other examples, were discussed in Chapter 1.

This idea prompted the design of enal **3.8** to be used as a starting material (**Scheme 3.3**). This  $\gamma$ -racemate represents the product of a hypothetical nonstereoselective  $\gamma$ -functionalization of a dienamine intermediate. Formation of dienamine intermediate **3.9** by addition of chiral amine catalyst **3.5** (**Scheme 3.1**), could facilitate a [3,3]-sigmatropic rearrangement, transposing the allyl group from the  $\gamma$ -oxygen to the  $\beta$ -position. In the same manner as a stepwise cycloaddition, resolution should consequentially occur in this

intramolecular step, leading to enantiomerically enriched enamine **3.10** from either enantiomer of **3.8**. Upon hydrolysis, the catalyst release could provide enantiopure **3.11** in a stereoselective, organocatalyzed Claisen rearrangement reaction. With the objective of testing this hypothesis, exploration of synthetic routes to this type of starting material commenced.

**Scheme 3.3** Proposed dienamine-catalyzed enantioselective Claisen rearrangement via DYKAT.

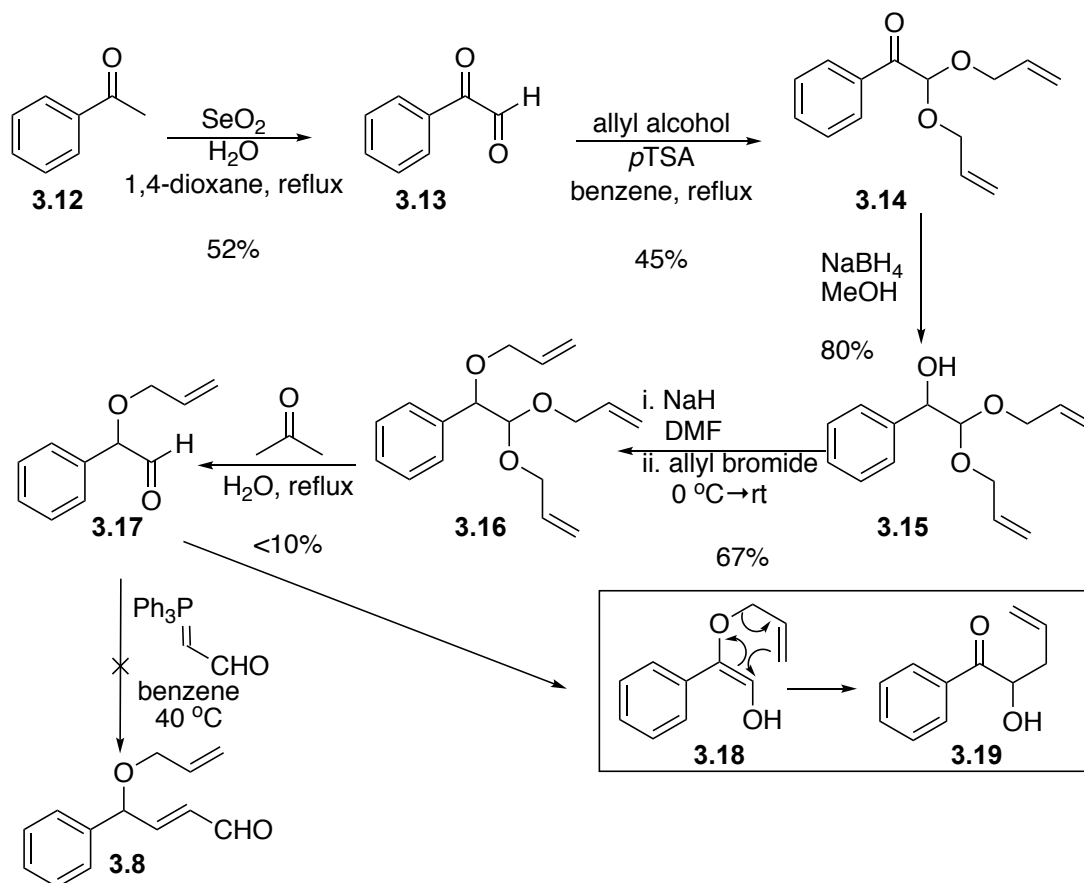


## 3.2 Results and Discussion

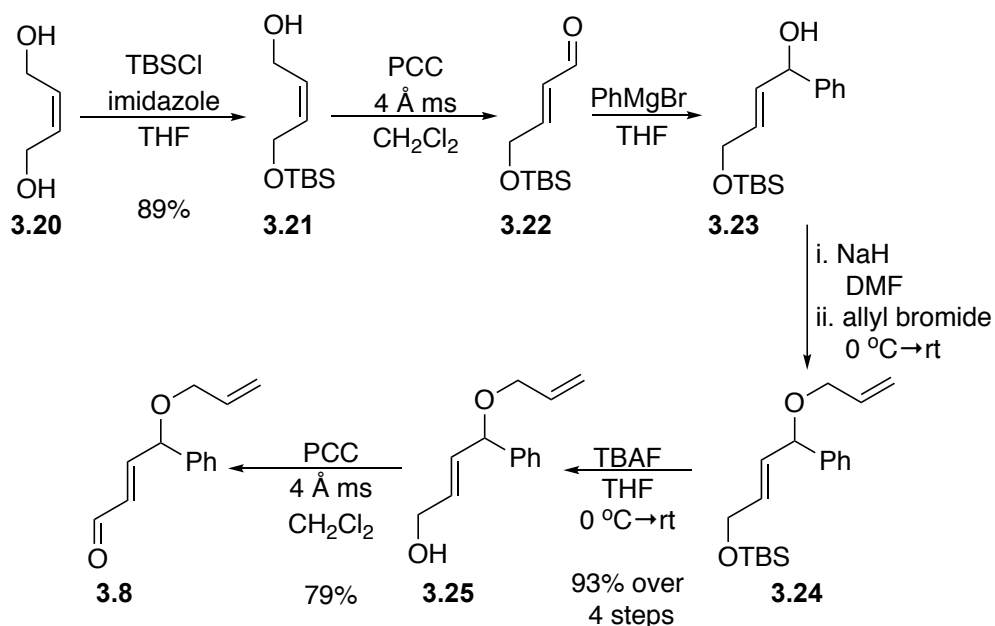
### 3.2.1 Starting Material Synthesis

The initial synthetic route used to prepare starting material **3.8** began with Riley oxidation of acetophenone **3.12** to form **3.13** in 52% yield (**Scheme 3.4**). Protection to form acetal **3.14** in 45% yield, was accomplished via addition of allyl alcohol and refluxing in benzene with *p*TSA. Reduction of the ketone led to alcohol **3.15** in good yield, which was subjected to allyl bromide to form **3.16**. The deprotection of **3.16** required heat and aqueous conditions to form aldehyde **3.17**. However, evidently the enol form, **3.18**, was undergoing a detrimental Claisen rearrangement to form **3.19**, leaving less than 10% of the desired product (**3.17**) for the final Wittig reaction. The undesired product had a similar  $^1\text{H}$  NMR spectrum to **3.17**. The Wittig reaction could not proceed in high yields due to this lack of penultimate material.

Scheme 3.4 Initial starting material synthesis.

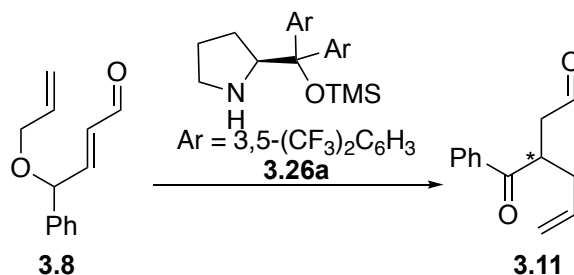


I conceived and established a new synthetic route shown in **Scheme 3.5**, that generated an abundance of starting material **3.8**. Mono-protection of 1,4-*cis*-diol **3.20** led to **3.21**, followed by oxidation to the *trans*-enal **3.22** carried out according to literature procedure.<sup>24</sup> Grignard addition with PhMgBr provided alcohol **3.23**, which was then protected with allyl bromide after deprotonation with NaH in DMF. Desilylation of **3.24** with TBAF produced the penultimate product **3.25** in 93% yield over four steps. Lastly, **3.25** was oxidized by using PCC to provide the desired enal **3.8** in 79% yield. This method proved to be a reliable process for producing generous amounts of the starting material, with the penultimate alcohol being very stable in the freezer for storage over extended periods of time.

**Scheme 3.5** New synthetic route to make starting material.

### 3.2.2 Optimizations

With the starting material for the proposed Claisen rearrangement in hand, the optimization began, by subjecting **3.8** to catalyst **3.26a** in the presence of co-catalytic BzOH in toluene (**Table 3.1**). After 4 days at rt, product **3.11** was obtained in a mere 5% yield, however with a promising ee of 64% (entry 1). Heating the reaction to 40 °C decreased the reaction time to 3 days and increased the yield significantly; however, the heat was detrimental to the stereoselectivity of the reaction (entry 2). Next, other catalysts were screened to find one better suited to increase both the yield and ee of the reaction product.

**Table 3.1** Initial studies.<sup>a</sup>

entry	t <sup>b</sup> (d)	temp (°C)	yield <sup>c</sup> (%)	ee <sup>d</sup> (%)
1	4	rt	5	64
2	3	40	29	46

<sup>a</sup> Reaction conditions: **3.8** (1 equiv), **3.26a** (0.2 equiv), BzOH (0.2 equiv), toluene (0.2 M). <sup>b</sup> Reactions were stopped when complete consumption of sm was observed by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield. <sup>d</sup> Determined by chiral phase HPLC.

Other secondary amine catalysts were tried, including diphenylprolinol **3.26b**, diphenylprolinol silyl ether **3.26c**, 2,5-(*S,S*)-diphenylpyrrolidine **3.27a**, bifunctional secondary amine/squaramide catalyst **3.28**, imidazolidinone catalysts **3.29a** and **3.30**, and pyrrolidine/thiourea catalyst **3.31** (Table 3.2). When **3.26a** or **3.27a** was used in the reaction with benzoic acid as additive, formation of allyl benzoate as the side product was observed by <sup>1</sup>H NMR (entries 1 and 4). It was postulated that the BzOH was somehow reacting with the allyl group of the reactant or product, although a mechanism for its formation was uncertain. BzOH is known to assist the catalytic turnover, this side reaction could explain the low yield of the reaction with **3.27a** (entry 4), which gave the product in 14% yield and in 80% ee.

Diphenyl prolinol **3.26b** was the only other catalyst, in addition to **3.26a** and **3.27a**, to form the product, but yield of this reaction was low despite no formation of the allyl benzoate side product (entry 2). It was determined that incorporation of a hydrogen bonding moiety into the catalyst structure was not fruitful since use of bifunctional secondary amine/squaramide **3.28** and secondary amine/thiourea **3.31** did not form any product (entries 5 and 11). Trace amounts of other aldehydes were observed by <sup>1</sup>H NMR when using **3.26c** or **3.28** (entries 3 and 5).

Imidazolidinones **3.29a** and **3.30** were not successful at catalyzing the reaction as the starting material remained, even when other acid additives were employed (entries 6-10). Catalytic amounts of DBU did not produce any product which suggests that the

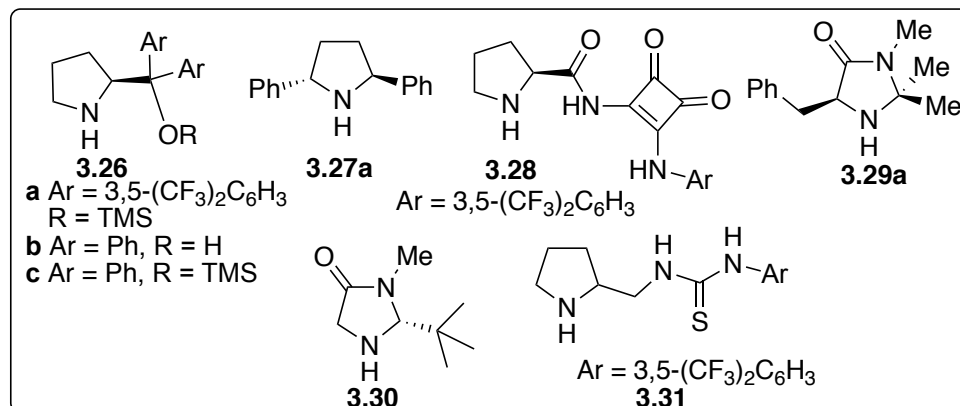
mechanism does not proceed through a dienol or dienolate intermediate (entries 12-13).

The optimization was continued with use of **3.27a**.

**Table 3.2** Initial catalyst screen.<sup>a</sup>



entry	cat.	additive	t (d)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>3.26a</b>	BzOH	4	5	64
2	<b>3.26b</b>	BzOH	5	11	20
3	<b>3.26c</b>	BzOH	5	-	-
4	<b>3.27a</b>	BzOH	4	14	80
5	<b>3.28</b>	-	5	-	-
6	<b>3.29a</b>	BzOH	4	-	-
7	<b>3.29a</b>	HCl	4	nr	-
8	<b>3.29a</b>	DCA	-	-	-
9	<b>3.30</b>	CF <sub>3</sub> CO <sub>2</sub> H	2	-	-
10	<b>3.30</b>	BzOH	2	nr	-
11	<b>3.31</b>	-	2	nr	-
12	DBU	BzOH	4	-	-
13	DBU	-	1	-	-



<sup>a</sup> Reaction conditions: **3.8** (1 equiv), catalyst (0.2 equiv), additive (0.2 equiv), toluene (0.2 M), rt. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral phase HPLC.

In addition to assisting turnover of secondary amine organocatalysts, hydrogen bonding interactions have been attributed to rate enhancement of the Claisen rearrangement.<sup>25</sup> Employing benzoic acid in the reaction gave the product, but was possibly detrimental to the yield. Therefore, other hydrogen bond donor additives were screened for the reaction catalyzed by diphenylpyrrolidine in toluene including: Brønsted-Lowry acids (other than benzoic acid), thioureas, and phenols (**Table 3.3**). Using substituted benzoic acids **3.32** as additive did not lead to product formation, but a side product was not observed by <sup>1</sup>H NMR (entries 1-3). Inorganic acid, HCl, was revisited as a potential additive, however product formation did not occur, and trace amounts of other aldehydes started to form after a couple of days (entry 4).

The hydrogen bond donors gave auspicious results; electron-deficient phenols, **3.36a** and **3.36b** provided the product with a slightly better yield than BzOH, and slightly increased the enantioselectivity as well (entry 6 and 8). Conversely, electron-rich **3.36c** yielded very little product, but this result afforded the prime selectivity of this study (entry 10). For the reactions with electron-deficient phenols **3.36a** and **3.36b**, the temperature was lowered to 0 °C. This caused a drop in the yield and a slight increase in ee (entries 7 and 9). When using **3.36c**, heat was advantageous to increase the yield while not too



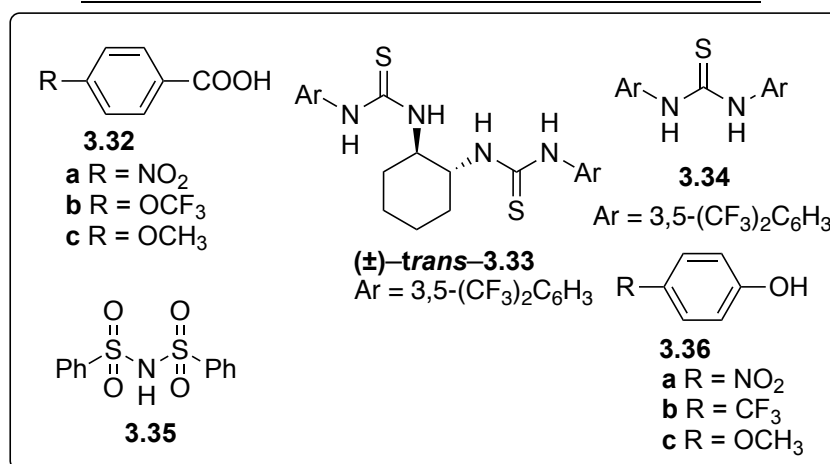
disruptive to the high selectivity, but other aldehydes began forming (entry 11). Additionally, despite numerous purification efforts, the product was inseparable from phenol additives **3.36a-c** despite having different  $R_f$  values. This could be due to hydrogen bonding interactions between the phenol and the product that caused them to coelute.

Thiourea additives were also conducive to this reaction. C<sub>2</sub>-symmetric thiourea **3.34** slightly facilitated the product formation in low yield and moderate ee, while employment of ( $\pm$ )-*trans*-**3.33** thiourea significantly boosted the yield while improving the ee of the product (entries 12 versus 13). Water is known to facilitate catalytic turnover of 2° amine catalysts,<sup>26</sup> so it was evaluated (entry 14). Despite the enhancement of selectivity by use of hydrogen bond donor additives, the yield was stagnant.

**Table 3.3** Additive screen.<sup>a</sup>

entry	additive	$t$ (h)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>3.32a</b>	46	nr	-
2	<b>3.32b</b>	42	nr	-
3	<b>3.32c</b>	40	nr	-
4	HCl	52	-	-
5	<b>3.35</b>	18	nr	-
6 <sup>d</sup>	<b>3.36a</b>	100	23	83
7 <sup>e</sup>	<b>3.36a</b>	120	12	85
8 <sup>d</sup>	<b>3.36b</b>	100	20	85

9 <sup>e</sup>	<b>3.36b</b>	192	9	88
10	<b>3.36c</b>	90	5	89
11 <sup>f</sup>	<b>3.36c</b>	90	31	83
12	<b>3.34</b>	208	16	62
13	<b>(±)-trans-3.33</b>	90	29	75
14	H <sub>2</sub> O	89	15	84



<sup>a</sup> Reaction conditions: **3.8** (1 equiv), **3.27a** (0.2 equiv), additive (0.2 equiv), toluene (0.2 M), rt. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral phase HPLC. <sup>d</sup> Average of three experiments. <sup>e</sup> Reaction run at 0 °C. <sup>f</sup> Reaction run at 30 °C.

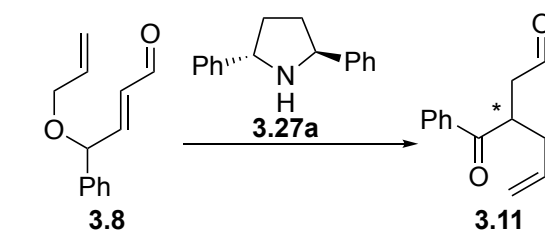
Next, solvent screens began (**Table 3.4**). Polar protic solvents were chosen for their ability to potentially promote favorable H-bonding interactions for product formation. The reactions were tried with and without thiourea **(±)-trans-3.33**, since hydrogen bond donating solvents may be activating enough without the need for an additional additive. With hydrogen bond donating solvents methanol and HFIP, the starting material remained unreacted (entries 3-4).

Powerful hydrogen bond donating solvent, TFE, resulted in product formation and drastically improved the yields when compared to toluene (entries 1 and 2 vs **Table 3.3**, entry 13).<sup>27</sup> In TFE, removing the **(±)-trans-3.33** additive substantially improved the yield, however the selectivity was slightly compromised compared to when it was employed in

the reaction (entry 1 versus entry 2). In polar aprotic solvents DMSO and DMF, no conversion of the starting material was observed by  $^1\text{H}$  NMR (entries 5–8). Only trace product formed in acetonitrile (entries 9–10).

TFE improved the reaction yield substantially and preserved selectivity. This could be due to the fact that TFE has a low self-association,<sup>28</sup> however it is a strong hydrogen bond donor. The optimization of our Claisen rearrangement therefore continued in this solvent.

**Table 3.4** Solvent screen.<sup>a</sup>



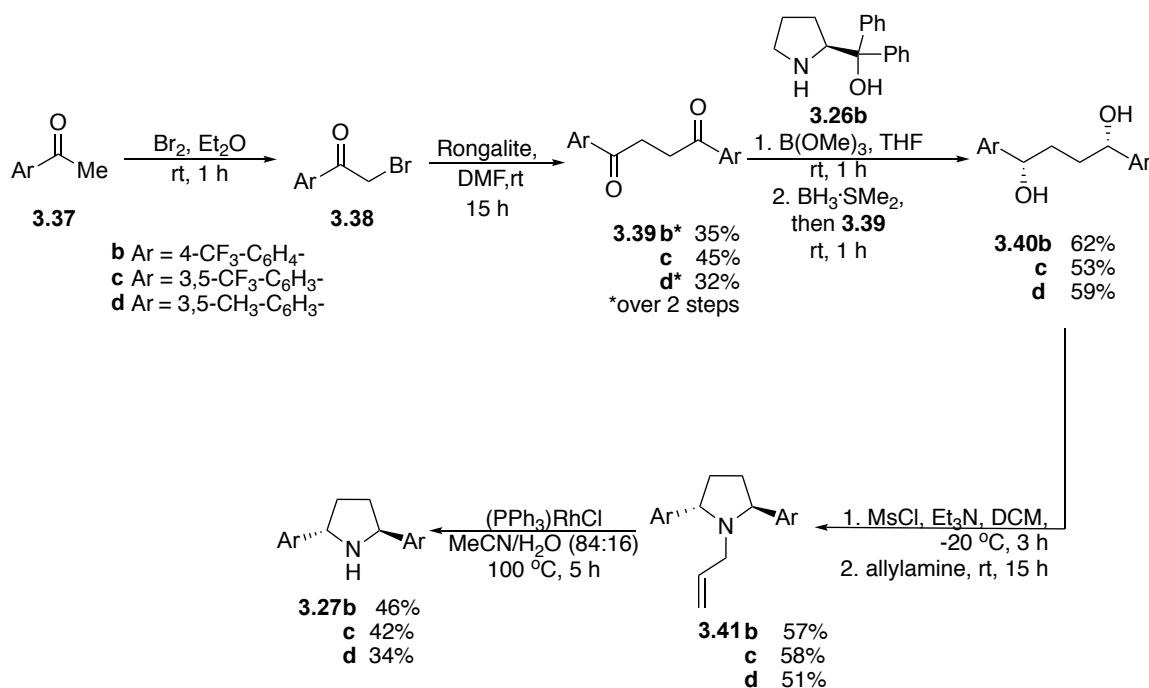
entry	solvent	<i>t</i> (h)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	TFE	48	50	70
2 <sup>d</sup>	TFE	48	62	68
3	MeOH	46	nr	-
4 <sup>d</sup>	HFIP	22	nr	-
5	DMSO	36	nr	-
6 <sup>d</sup>	DMSO	36	nr	-
7	DMF	36	trace	-
8 <sup>d</sup>	DMF	36	nr	-
9	MeCN	36	trace	-
10 <sup>d</sup>	MeCN	36	trace	-

<sup>a</sup> Reaction conditions: **3.8** (1 equiv), **3.27a** (0.2 equiv), ( $\pm$ )-**trans-3.33** (0.2 equiv), solvent (0.2 M), rt. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral phase HPLC. <sup>d</sup> Reaction run without ( $\pm$ )-**trans-3.33**.

The success of 2,5-diphenylpyrrolidine **3.27a** piqued the interest of exploring other diaryl groups to potentially improve the yield of the Claisen rearrangement at this point. Catalysts (*S,S*)-**3.27b**, (*S,S*)-**3.27c**, and (*S,S*)-**3.27d** are known in the literature (Scheme 3.6).<sup>29-31</sup> These different 2,5-diarylpyrrolidines (*S,S*)-**3.27b-d** were prepared in accord with characterization data.

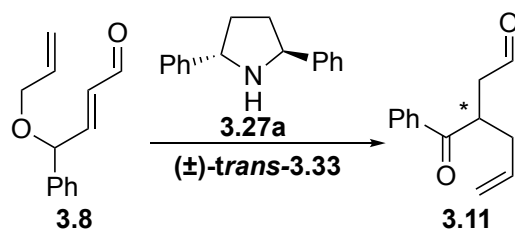
The synthesis began by subjecting corresponding ketones **3.37b** and **3.37d** to bromination. The  $\alpha$ -bromo product **3.38b** and **d**, and commercially available **3.38c**, were each mixed with Rongalite ( $\text{Na}^+\text{HOCH}_2\text{SO}_2^-$ ) in DMF to obtain diones **3.39b-d**. Next, CBS reduction afforded chiral 1,4-diol, of which cyclization by allyl amine afforded **3.41b-d**. Deprotection with Wilkinson's catalyst yielded **3.27b-d**, which were subjected to reaction conditions in Table 3.5 for investigation. Relative to **3.27a**, neither  $-\text{CF}_3$  substituted **3.27b** or **3.27c** improved the yield or ee (entries 7–8 and 9–10). Electronically rich **3.27d** inhibited the reaction (entries 11–12).

Scheme 3.6 Synthesis of 3.27b-d.



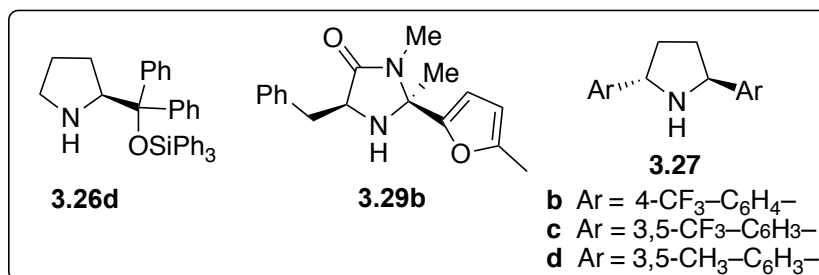
Commercially available imidazolidinone **3.29b** was also examined because of its 2,5-disubstitution. However, the reaction formed only a small amount of product with degraded enantioselectivity when thiourea was present (entries 5–6). Resubjecting the reaction to Jørgenson catalyst **3.26a** in TFE lowered the amount and selectivity of the formation of **3.11** (entry 2 vs. entry 1). Catalyst **3.26c** only led to decomposition of the starting material (entry 3). Racemic product formed from employment of **3.26d** (entry 4). The best result thus far, was from **Table 3.5** (entry 1), using ( $\pm$ )-*trans*-**3.33** additive in TFE at rt.

**Table 3.5** Catalyst screen in TFE.<sup>a</sup>



entry	catalyst	<i>t</i> (h)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>3.27a</b>	48	50	70
2 <sup>d</sup>	<b>3.26a</b>	66	39	40
3 <sup>d</sup>	<b>3.26c</b>	22	-	-
4 <sup>d</sup>	<b>3.26d</b>	42	20	3
5	<b>3.29b</b>	120	13	45
6 <sup>d</sup>	<b>3.29b</b>	120	-	-
7	<b>3.27b</b>	120	52	65
8 <sup>d</sup>	<b>3. 27b</b>	120	21	62
9	<b>3. 27c</b>	120	47	57
10 <sup>d</sup>	<b>3. 27c</b>	120	48	59

11	<b>3. 27d</b>	120	nr	-
12 <sup>d</sup>	<b>3. 27d</b>	120	nr	-



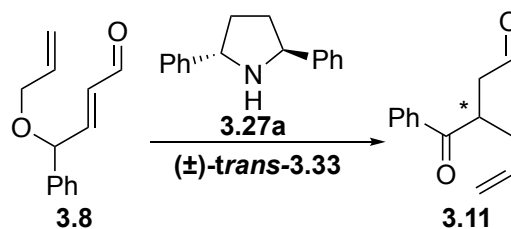
<sup>a</sup> Reaction conditions: **3.8** (1 equiv), catalyst (0.2 equiv), (±)-**trans-3.33** (0.2 equiv), TFE (0.2 M), rt. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral phase HPLC. <sup>d</sup> Reaction run without (±)-**trans-3.33**.

Further optimizations were done in TFE (**Table 3.6**). An attempt at boosting the ee was made by running this reaction at 0 °C. While the yield of product **3.11** stayed the same, the ee was slightly improved (entry 1 versus entry 2). Increasing the loading of the catalyst and additive up to 30 mol % was a bit detrimental to the product yield (entry 3). Doubling the reaction concentration decreased the reaction yield as it never went to completion (entry 4), while halving the concentration made the reaction too dilute for product formation to occur (entry 5). Reactions with the addition of 5 Å ms (entry 7) and added water (entry 8) prevented reactivity, and decomposition after prolonged reaction times occurred at -20 °C (entry 6).

As discussed previously in **Table 3.3**, *p*-nitrophenol (**3.36a**) increased the rate and ee of the reaction in toluene (entries 6 and 7 of **Table 3.3** versus entry 4 of **Table 3.2**), therefore it was re-examined in TFE (**Table 3.6**). With **3.36a** both at rt and lower temperature, the starting material **3.8** was consumed sooner in TFE than in toluene but at the expense of selectivity, which became comparable to the result with (±)-**trans-3.33** at 0 °C (entries 9-10). Although the selectivity was comparable to the result using additive

(±)-*trans*-**3.33** in TFE at 0 °C, the low yield was not a significant result to pursue any further.

**Table 3.6** Further optimizations in TFE.<sup>a</sup>



entry	temp (°C)	additive	<i>t</i> (d)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	rt	(±)- <i>trans</i> - <b>3.33</b>	2	50	70
2	0	(±)- <i>trans</i> - <b>3.33</b>	3	50	77
3 <sup>d</sup>	rt	(±)- <i>trans</i> - <b>3.33</b>	3	41	77
4 <sup>e</sup>	0	(±)- <i>trans</i> - <b>3.33</b>	15	14	79
5 <sup>f</sup>	0	(±)- <i>trans</i> - <b>3.33</b>	5	trace	nd
6	-20	(±)- <i>trans</i> - <b>3.33</b>	6	-	-
7	0	5 Å ms	6	nr	-
8	0	H <sub>2</sub> O	6	nr	-
9	0	<b>3.36a</b>	3	12	75
10	rt	<b>3.36a</b>	3	25	75
11	0	-	2	12	72

<sup>a</sup> Reaction conditions: **3.8** (1 equiv), **3.27a** (0.2 equiv), additive (0.2 equiv), TFE (0.2 M). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral phase HPLC.

<sup>d</sup> **3.27a** (30 mol %) and additive (30 mol %) was used. <sup>e</sup> Reaction concentration = (0.4 M). <sup>f</sup> Reaction concentration = (0.1 M).

As a control, the reaction was run without any additive at 0 °C (entry 11). At rt, this same reaction had a slightly lower ee but a much more substantial amount of product

formation (entry 2, **Table 3.4**). This is expected since the rate is faster at warmer temperatures and selectivity is often impeded.

At this point in the study, yields had been persistently at or below 50%. Different proportions of TFE and toluene were examined to maximize yield, while maintaining or improving the enantioselectivity of the reaction (**Table 3.7**). A 9:1 mixture of toluene and TFE resulted in collection of the product in a lower yield, but slightly higher selectivity after only 1 day (entry 1). Using a 1:1 solvent mixture gave the product with a slightly deteriorated yield (entry 2). Unexpectedly, using less toluene to TFE resulted in only trace conversion (entry 3).

**Table 3.7** Optimization in toluene and TFE.<sup>a</sup>

Reaction scheme: **3.8** + **3.27a** + **(±)-trans-3.33** → **3.11**

entry	toluene:TFE	<i>t</i> (h)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1 <sup>d</sup>	9:1	22	38	79
2	1:1	119	21	78
3	1:9	119	trace	nd
4	0:1	72	50	77

<sup>a</sup> Reaction conditions: **3.8** (1 equiv), **3.27a** (0.2 equiv), **(±)-trans-3.33** (0.2 equiv), solvent (0.2 M), 0 °C.

<sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral phase HPLC. <sup>d</sup> Average of 3 experiments.

### 3.2.3. Mechanistic Studies

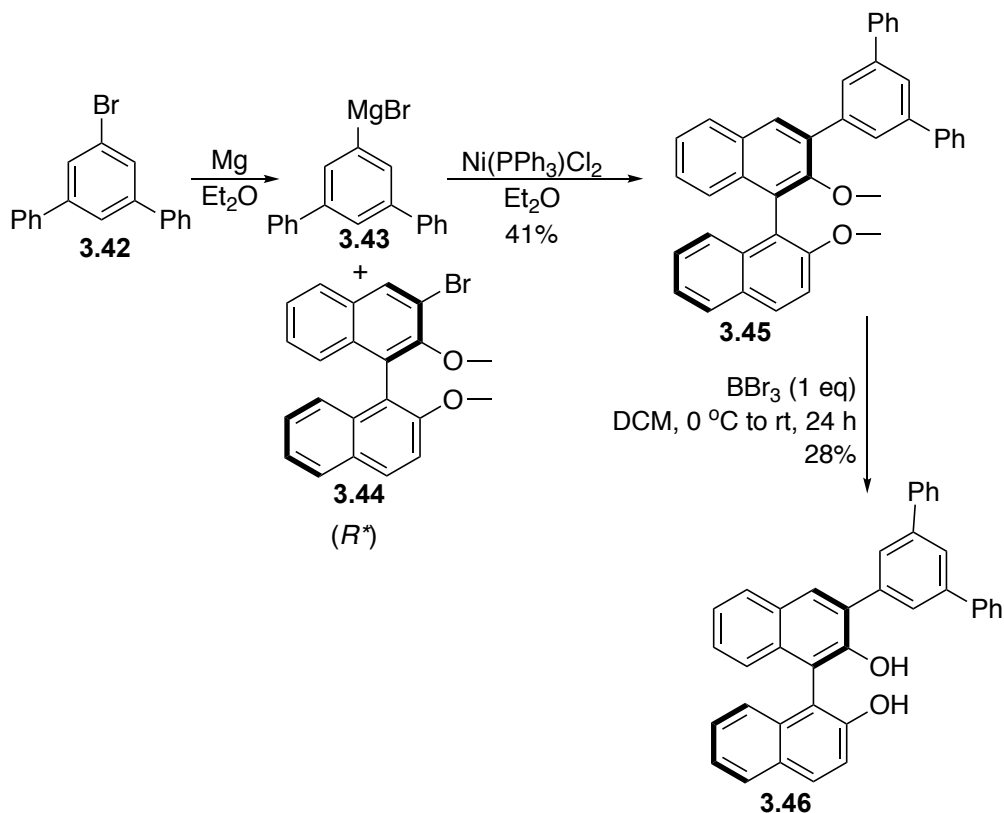
During initial experiments, recovered starting material **3.8** from reactions with **3.26a** was determined to have 85% ee. There was evidence in support of a DKR: 1.) the starting material was completely consumed in the reaction, and 2.) the recovery of starting material



with ee. However, at rt and at the lower temperature the yields did not reach above 50%. Only the conditions with TFE, no additive, and at rt (entry 2, **Table 3.4**) had a yield above 50%. These results were the initial evidence that the reaction may not be a DKR, but rather a kinetic resolution. A more concrete experiment was done to evaluate this possibility.

Using an established procedure, ligand (**R**)-**3.46** was synthesized by the route shown in **Scheme 3.7**.<sup>32-33</sup> In the first step, Grignard reagent **3.43** is prepared, and reacted with **3.44**, which had been prepared by another Brenner-Moyer lab member for his own project.<sup>34</sup> Ligand (**R**)-**3.46** was used to prepare starting material (**R**)-**3.8** in an asymmetric Grignard reaction illustrated in **Scheme 3.8**.<sup>35</sup>

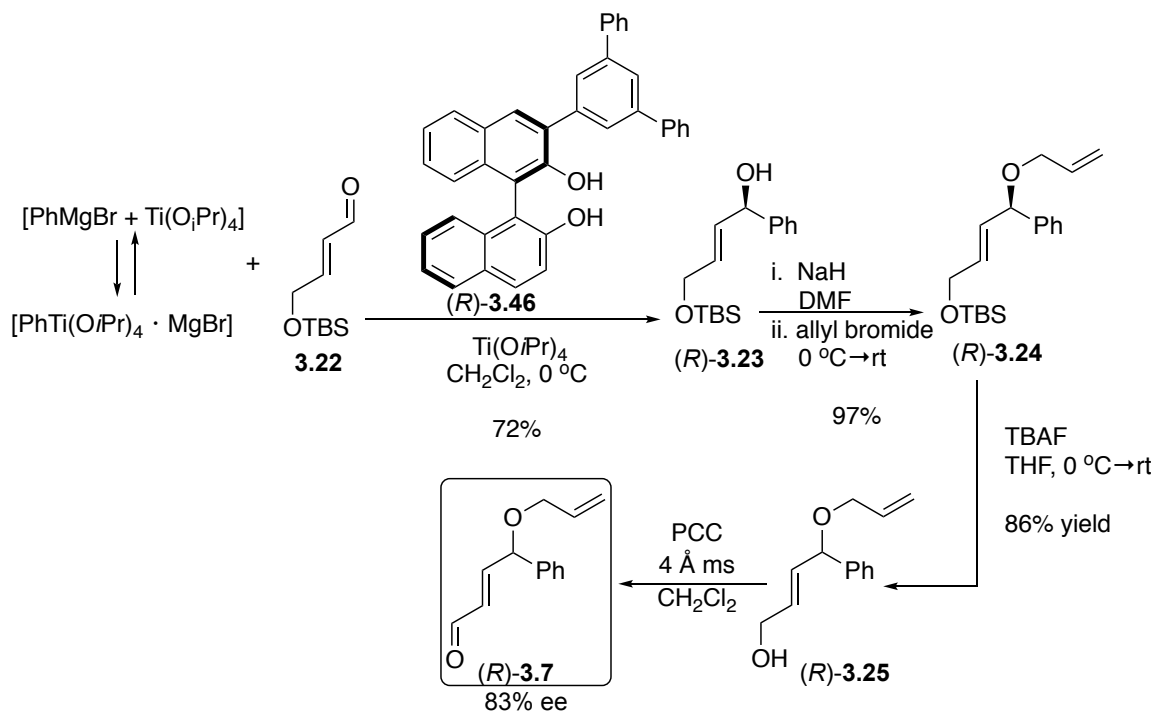
**Scheme 3.7** Preparation of catalyst for asymmetric Grignard reaction.



Arylation of aldehyde **3.22** was achieved with organotitanate reagent **3.48** formed *in situ* from phenylmagnesium bromide treated with titanium tetraisopropoxide, and titanium(IV) complex **3.47** derived from mixing (**R**)-**3.46** with titanium tetraisopropoxide

(**Scheme 3.9**). The asymmetric alcohol (**R**)-**3.23** was subjected to the next 3 steps from the starting material synthesis (**Scheme 3.5**). Allylation, deprotection, and then oxidation to the aldehyde provided the enal (**R**)-**3.8** in 83% ee.

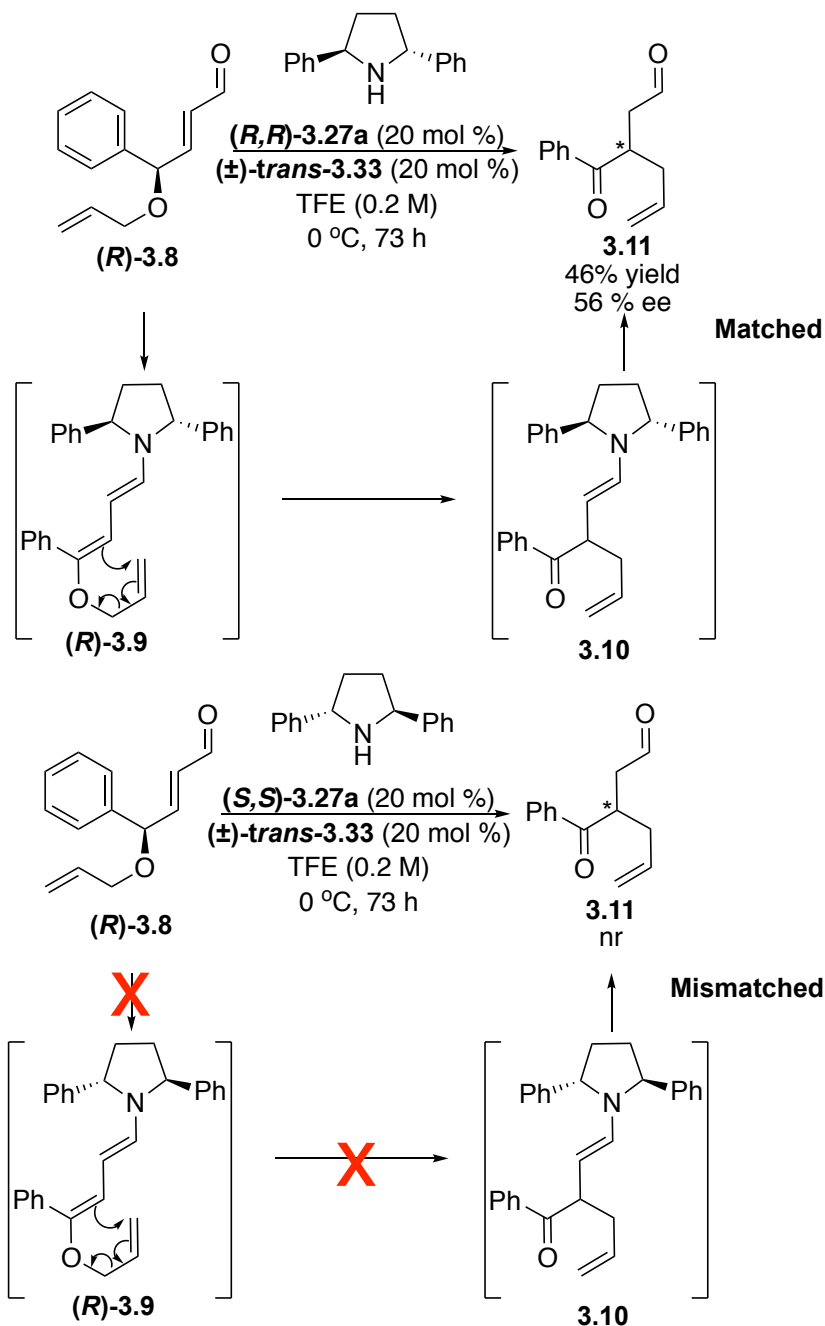
**Scheme 3.8** Asymmetric Grignard reaction.



**Scheme 3.9** Role of titanium complex in Grignard.



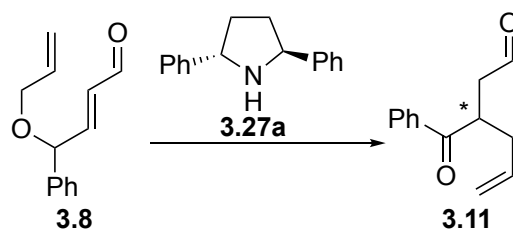
Scheme 3.10 Match/mismatch substrate and catalyst.



Since thiourea **3.33** being used is the racemic *trans*-isomer, **(R,R)-3.33** and **(S,S)-3.33** were each evaluated in the reaction to determine if they had any affect on product enantioselectivity. Compounds **(R,R)-3.33** and **(S,S)-3.33** were synthesized by coupling the corresponding enantiopure diaminocyclohexane (commercially available) with 3,5-

bis(trifluoromethyl)phenyl isothiocyanate according to a precedent procedure.<sup>39</sup> The racemic starting material was evaluated in reactions with **3.27a** and each enantiomer of thiourea **3.33**, and the products were isolated when the ratio of product to starting material was approximately 1.0 : 1.0, and also when the starting material was completely consumed according to <sup>1</sup>H NMR (**Table 3.8**). It was determined that the configuration of additive **3.33** does not impact the ee of the product, since all reactions of **Table 3.8** resulted in similar enantioselectivities. More importantly, the major product enantiomer was the same using either enantiomer of **3.33**.

**Table 3.8** Chiral thiourea additives.<sup>a</sup>



entry	<b>3.33</b>	<i>t</i> (h)	yield <sup>c</sup> (%)	(pdt:sm) <sup>b</sup>	ee <sup>d</sup> (%)
1	( <i>R,R</i> )	89	23	1:1	84
2	( <i>R,R</i> )	110	33	1:0	80
3	( <i>S,S</i> )	15	25	1:1	80
4	( <i>S,S</i> )	30	6	1:0	-
5	(±)- <i>trans</i>	89	30	1:1	84

<sup>a</sup> Reaction conditions: **3.8** (1 equiv), **3.27a** (0.2 equiv), additive (0.2 equiv), TFE (0.2 M), 0 °C. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield. <sup>d</sup> Determined by chiral phase HPLC.

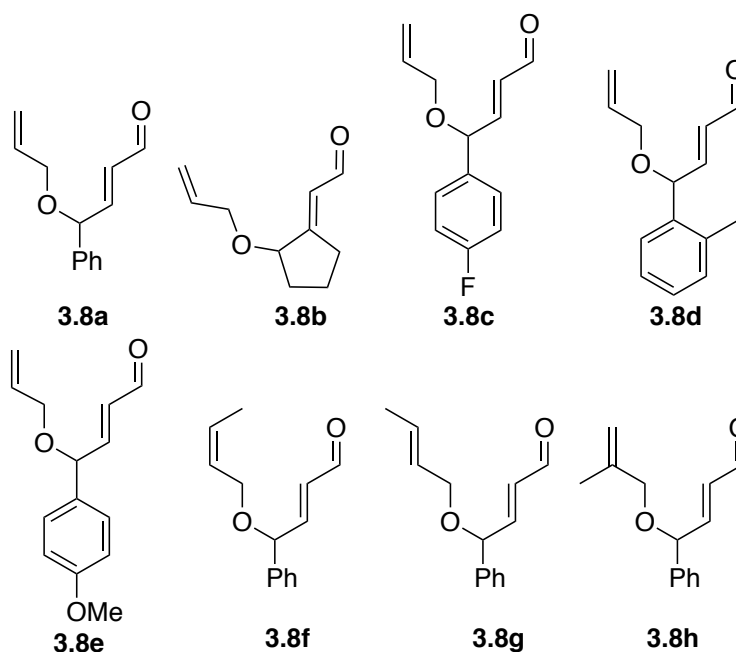
### 3.2.4 Substrate Scope

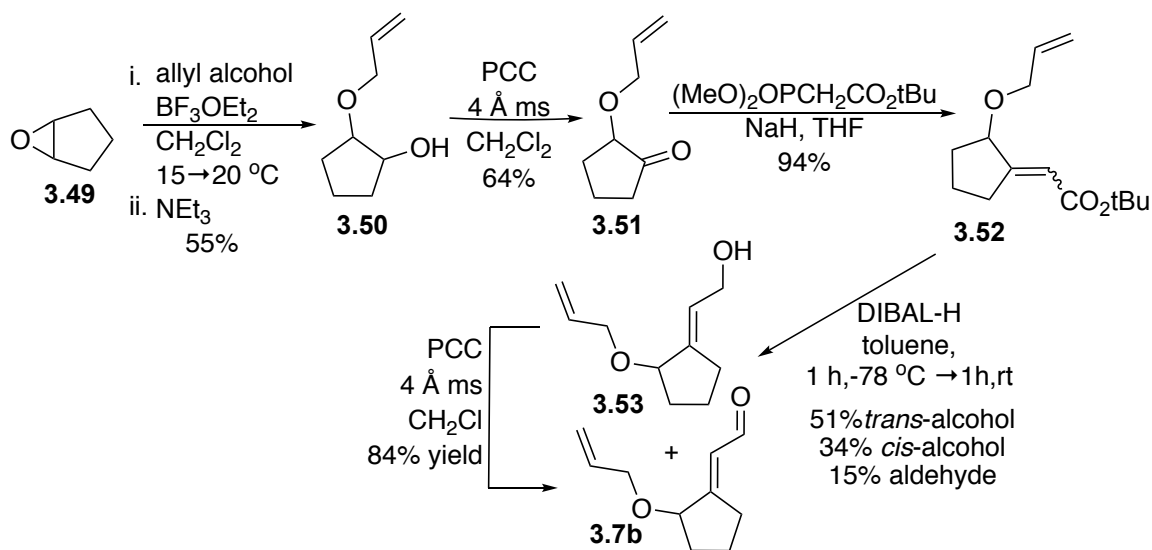
An investigation of substrate scope began after identifying the optimal reaction conditions. Substrates with different aryl R groups (**3.8c-e**), various allyl groups (**3.8f-h**), and an aliphatic cyclic example **3.8b** were envisaged (**Figure 3.1**). Approached first was the

aliphatic example since the five-membered ring could potentially be applied to a formal synthesis of alkaloid (-)-isochizogamine,<sup>40</sup> while also confirming the configuration of the quaternary stereocenter formed in the product (**Scheme 3.11**).

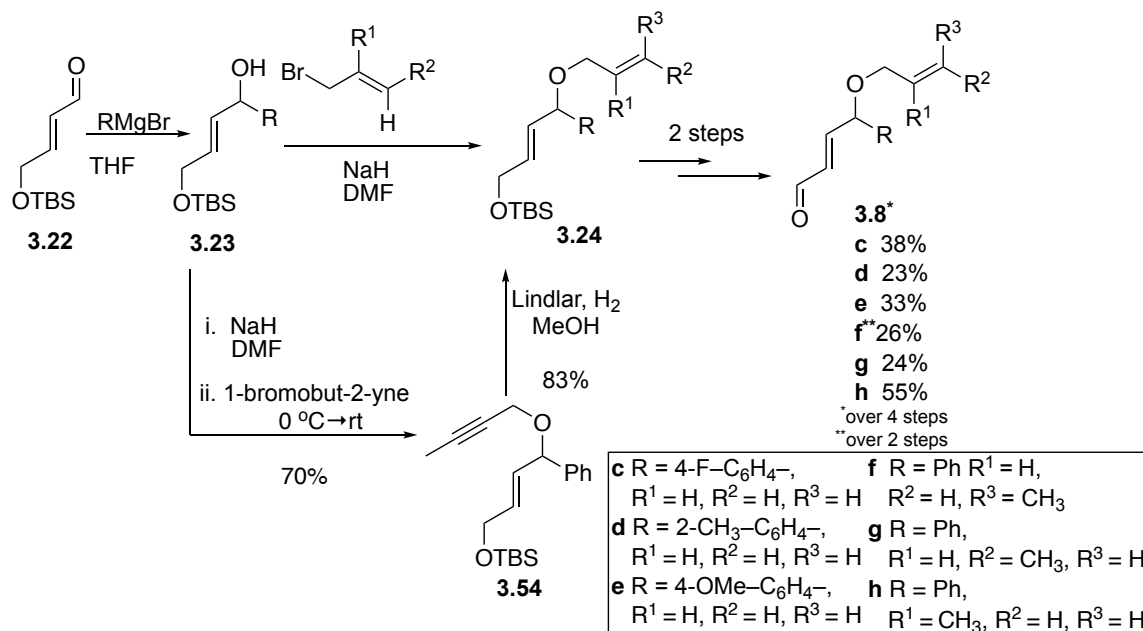
The synthesis of the five-membered ring began by opening epoxide **3.49** in the presence of  $\text{BF}_3\text{OEt}_2$ , allyl alcohol, and  $\text{NEt}_3$  to provide cyclopentanol derivative **3.50** in 55% yield (**Scheme 3.11**).<sup>41-42</sup> After distillation, **3.50** was oxidized via PCC to afford the ketone **3.51** in 64% yield, followed by a Horner–Wadsworth–Emmons homologation to afford *t*-butyl ester **3.52**.<sup>43</sup> After reduction with excess DIBAL-H, the reaction was chromatographed immediately to separate out enal from the alcohol to prevent them from reacting with each other. The alcohol **3.53** underwent a final oxidation to the substrate of interest **3.8b**.

**Figure 3.1** Proposed substrates for chiral Claisen reaction.



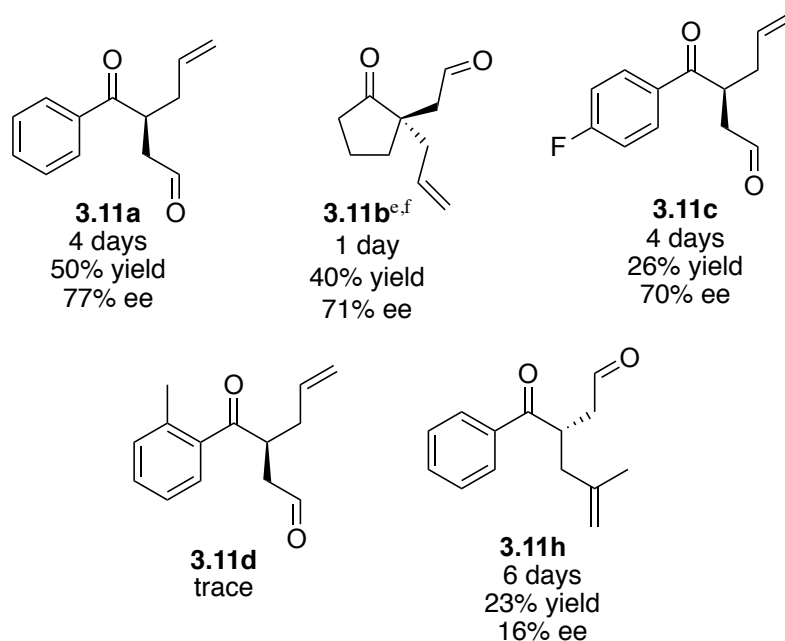
**Scheme 3.11** Synthesis of five-membered ring substrate **3.8b**.

Incorporation of different aromatic groups was achieved in the Grignard step of the synthesis, and different allyl groups were introduced in the allylation step (**Scheme 3.12**). Substrate **3.8f** required an additional step, as the *cis*-alkene was formed by hydrogenation of the corresponding alkyne **3.54** using Lindlar catalyst. Attempts were made at synthesizing a substrate with a heteroaromatic R group, using 2-bromopyridine, however significant decomposition was observed in the allylation and desilylation steps. This substrate was not pursued further.

Scheme 3.12 Synthesis of substrates **3.8c-h**.

The reaction worked well when substrates with electron-poor (**3.11c**) aromatic groups were tried in the reaction (Scheme 3.13). When the Claisen rearrangement was tried on substrate **3.8d** with an *ortho* methyl group, **3.11d** formed in trace amounts and with decomposition. One example of an enal with a substituted allyl group **3.11h** formed in low yield, with a low ee. A quaternary center was generated in product **3.11b** in good enantioselectivity, the configuration of which was determined in experiments discussed in section 3.2.5.



**Scheme 3.13** Substrate scope products from kinetic resolution Claisen rearrangement.<sup>a-d</sup>

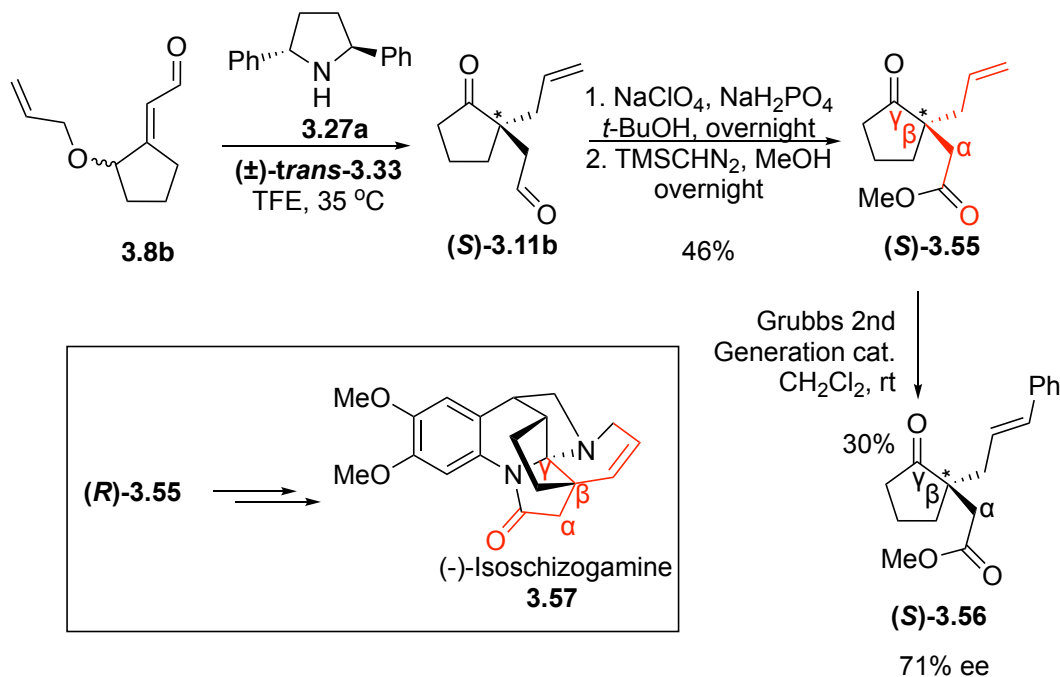
<sup>a</sup> Reaction conditions: **3.8** (1 equiv), **3.27a** (0.2 equiv), ( $\pm$ )-**trans-3.33** (0.2 equiv), TFE (0.2 M), 0 °C <sup>b</sup> Reaction times determined by monitoring the disappearance of sm by <sup>1</sup>H NMR. <sup>c</sup> Isolated yields reported. <sup>d</sup> Determined all reported ee's by chiral phase HPLC. <sup>e</sup> Reaction was run at 35 °C. <sup>f</sup> ee determined by derivation to **3.56**.

### 3.2.5 Determination of Configuration

Product **3.11b** was inseparable from ( $\pm$ )-**trans-3.33** most likely due to hydrogen bonding interactions. Accurate chiral phase HPLC data could therefore not be gathered. Instead, Pinnick oxidation of the aldehyde, followed by methyl ester formation with diazomethane was carried out. After this stage, the thiourea was separable from the product mixture, leaving the freshly purified ester **3.55** free of impurities (**Scheme 3.14**). To determine the ee and absolute configuration of **3.55**, as per the literature protocol,<sup>40</sup> derivatization of **3.55** was done by metathesis with styrene using Grubbs 2<sup>nd</sup> generation catalyst, and the enantiomer peaks were resolved with the AD-H chiralpak column. Comparing our results to the literature, it was concluded that our reaction conditions were leading to the (*S*)-enantiomer of the product. If **3.8b** had been reacted in the presence of (*R,R*)-**3.27a**, the

configuration of enantiomer formed would be suitable for a formal synthesis of (-)-isoschizogamine **3.57**.

**Scheme 3.14** Determination of configuration.<sup>40</sup>

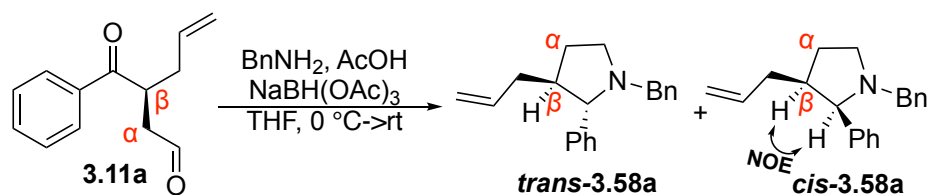


### 3.2.6 Reductive Amination of Claisen Product

Product **3.11a** was transformed into chiral pyrrolidines via reductive amination reaction, shown in **Scheme 3.15**. The reaction produced the product **3.58a** in 2.5:1 dr with a 60% yield of the major *trans*-**3.58a** diastereomer and 24% yield of the minor diastereomer *cis*-**3.58a**. The major diastereomer had a slightly higher R<sub>f</sub> than the minor diastereomer and were separated by FCC. The relative configuration of *trans*-**3.58** and *cis*-**3.58a** were determined by NOE NMR. The minor diastereomer displayed NOE signals between the protons attached to the tertiary centers of the cyclic amine. However, the major diastereomer lacked NOE signals between these proton peaks. Based on this data and assigning the absolute configuration of the stereocenter of the carbon containing the allylic

group based on the catalyst, the major diastereomer has an (*S,S*)-configuration the minor diastereomer is the (*S,R*)-enantiomer.

**Scheme 3.15** Reductive amination.<sup>44</sup>



### 3.3 Conclusions

A full investigation of conditions were done in order to optimize this catalytic enantioselective Claisen rearrangement reaction. It was hypothesized that using enal **3.8**, which resembles the product of a non-stereoselective dienamine-catalyzed  $\gamma$ -functionalization, in a Claisen rearrangement would emulate the reactivity in a stepwise process by going through a subsequent intramolecular reaction that allows only one enantiomer to form. The reaction was determined to be a kinetic resolution (not DYKAT), that provides  $\beta$ -functionalized aldehydes with yields of up to 50% and enantioselectivity in up to 77% ee. Much optimization was done, which led to finding conditions in which an achiral *trans*-thiourea **3.33** is used as an additive. The reaction proceeds robustly in hydrogen bonding solvent TFE, yet no other alcohol solvent worked in the reaction.

The reaction scope was tolerant of substrates with various aromatic groups, but enals with an *ortho*-substituted aromatic group did not form any product. Substitution on the allyl group decreased the enantioselectivity and yield of product. The configuration of the stereocenter generated was determined using aliphatic cyclic substrate **3.11b** by transforming it into a known precursor to the natural product (-)-isoschizogamine. In the process, a quaternary center was formed. Since there are not as many literature reports on

organocatalyzed asymmetric sigmatropic rearrangements when compared to cycloaddition reactions, these results offer promising merits that may be harnessed to develop other reactions and methodologies.

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## CHAPTER 4

### EXPERIMENTAL AND CHARACTERIZATION

#### 4.1 General Information

All chemicals and solvents were purchased from Sigma-Aldrich, Fisher Scientific, or TCI America.  $^1\text{H}$  and  $^{13}\text{C}$  NMR data were acquired on Bruker 400 MHz and 500 MHz NMR spectrometers and use the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, brm = broad multiplet, brs = broad singlet. HRMS spectra were acquired using an MS spectrometer with Q-TOF mass analyzer. Flash chromatography was carried out with F60, 40–63 mm, 60 Å silica gel and EMD silica 60 F254 glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit and were evaporated using a standard rotovapor and high vacuum. All reactions were carried out in oven-dried glassware, under an Ar atmosphere. All enals were distilled freshly before use. Reactions were cooled to  $-25\text{ }^{\circ}\text{C}$  and below using a ThermoFisher Scientific EK90 cryocooler. Crystallographic data were obtained by William W. Brennessel of the University of Rochester Department of Chemistry X-ray Crystallographic Facility.

#### 4.2 Experimental and Characterization for Chapter 2

##### Determination of Enantiomeric Excesses

Enantiomeric excesses were determined by comparison to a racemic sample (prepared with the corresponding racemic catalyst *rac*-2.44).

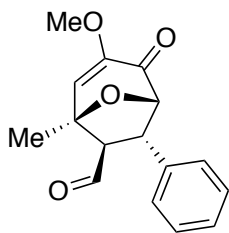
##### Preparation of oxidopyrylium salts (2.9 and 2.10)

Oxidopyrylium salts were prepared using known procedures.<sup>1-2</sup>

##### Representative procedure for the synthesis of oxabicyclo[3.2.1]octanes (2.37a-2.37k)

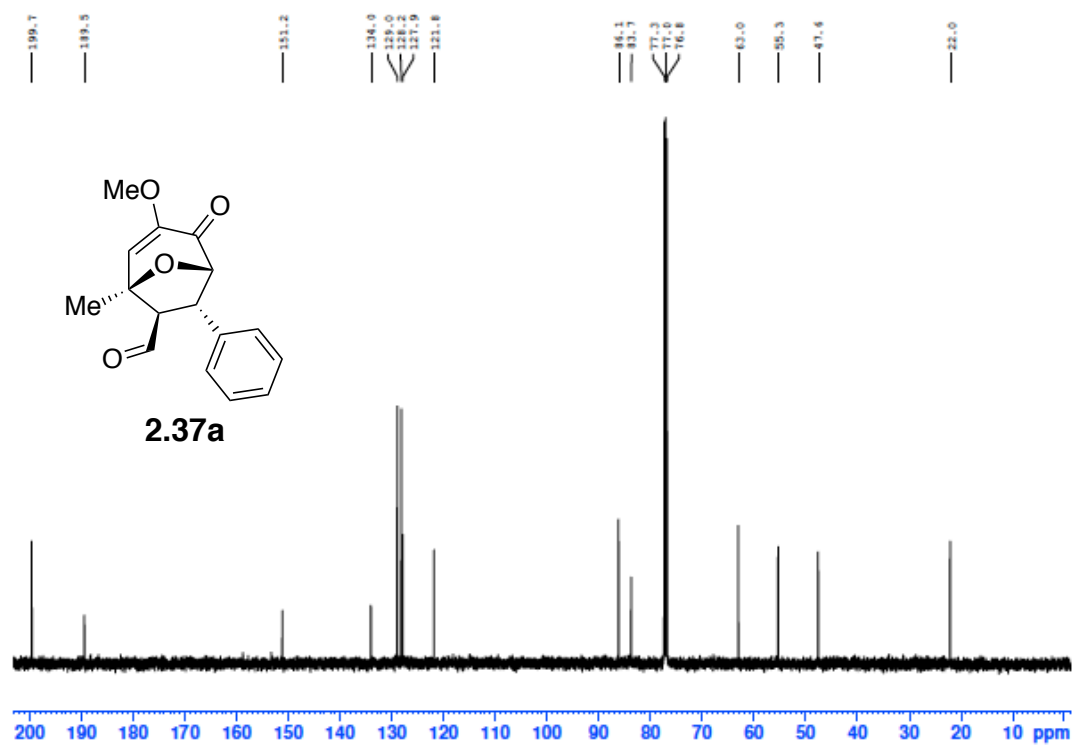
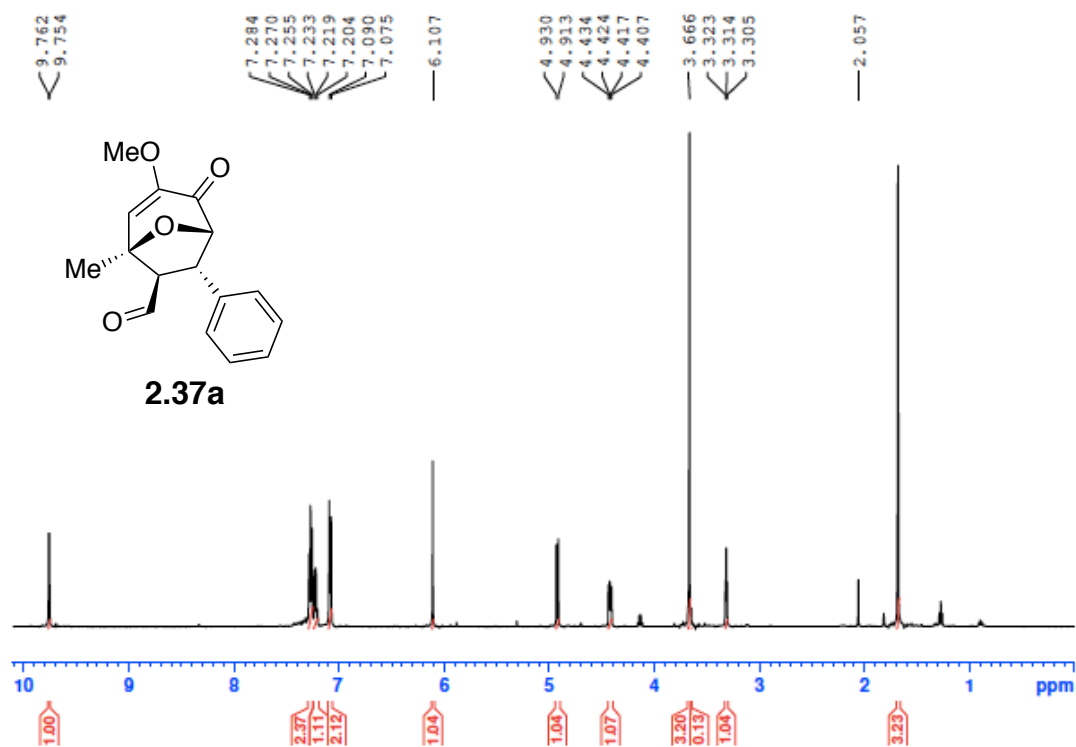
To a 4-mL pressure tube containing freshly distilled cinnamaldehyde **2.45a** (144.7  $\mu$ L, 1.15 mmol), was added oxidopyrylium salt **2.10** (26.8 mg, 0.0955 mmol) and catalyst **2.44** (12.4 mg, 20 mol %). Triflic acid (6.7  $\mu$ L, 40 mol %) and N,N-diisopropylaniline (14.9  $\mu$ L, 40 mol %) in CH<sub>3</sub>CN (0.4 mL) to the reaction mixture and the pressure tube was sealed. This reaction mixture was stirred for 5 minutes at rt and then stirred at 40 °C until complete consumption of oxidopyrylium salt **2.10** as observed by <sup>1</sup>H NMR. The crude reaction mixture was immediately loaded onto silica gel and purified by flash column chromatography (40% EtOAc/PE). The pure fractions were collected and reduced under pressure to yield product **2.37a** (38.1 mg, 74% yield).

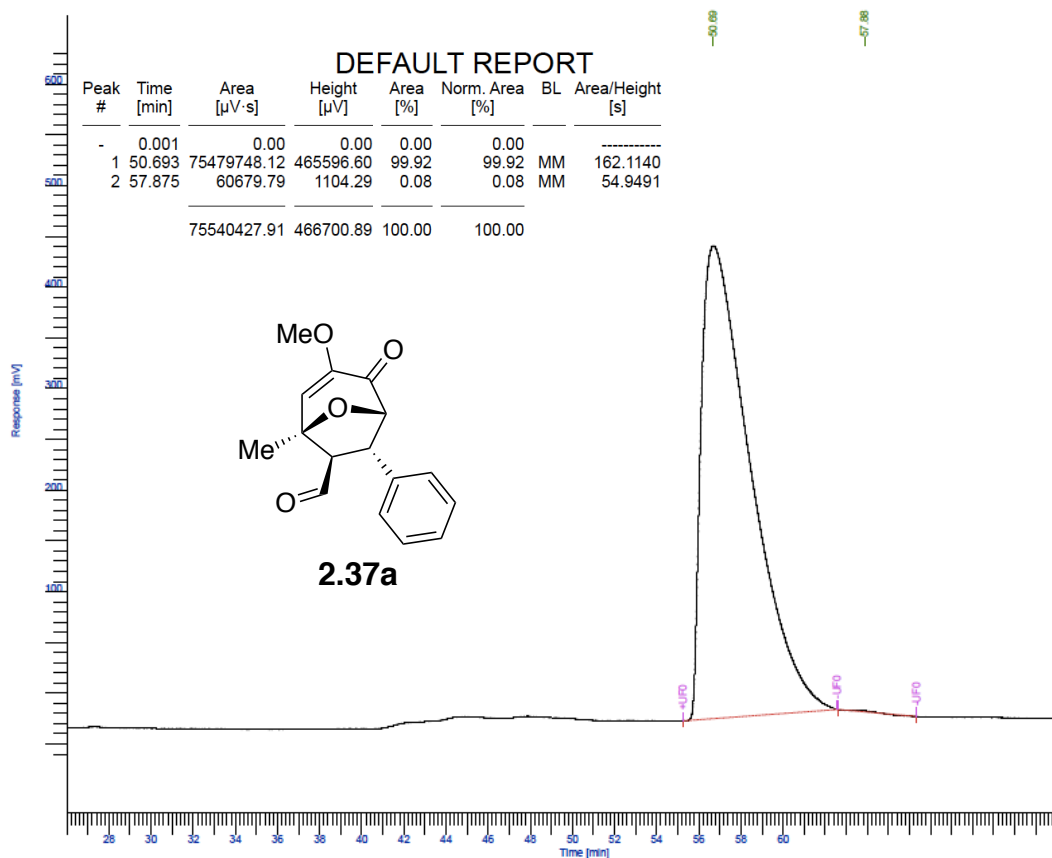
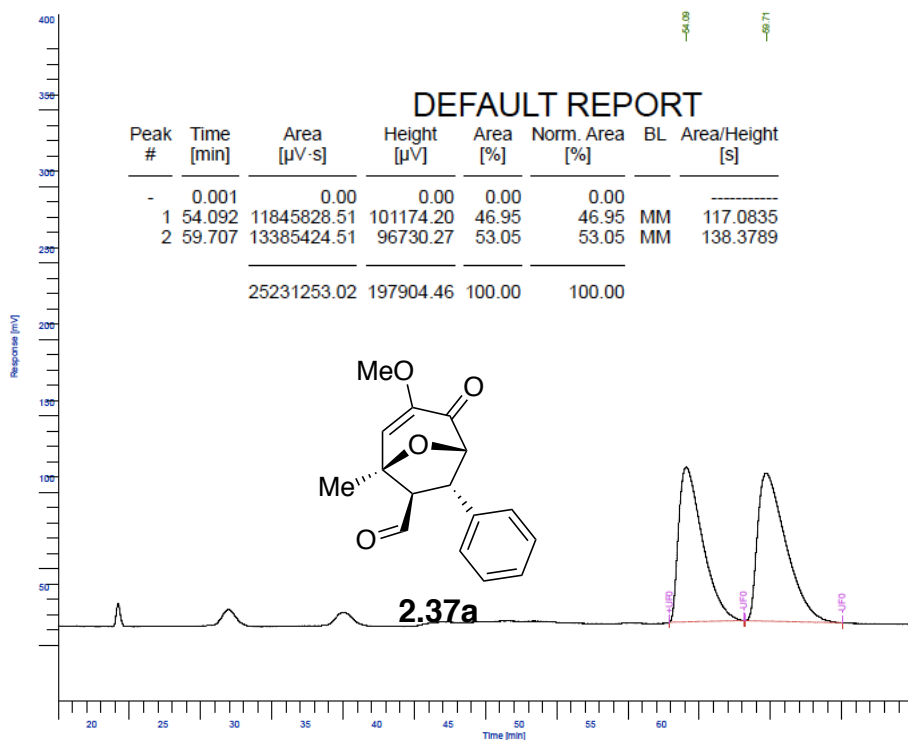
**3-methoxy-5-methyl-2-oxo-7-phenyl-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde**  
(**2.37a**)



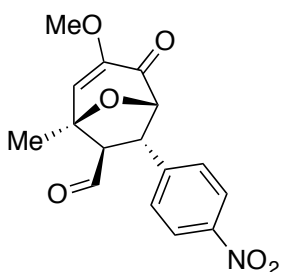
White solid (38.1 mg, 74% yield); m.p. 179-181 °C; dr 9:1;  $[\alpha]_D^{22} = +31.3$  ( $c = 1.0$  in CH<sub>2</sub>Cl<sub>2</sub>, 99% ee); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.76 (d,  $J = 4.0$  Hz, 1H), 7.28-7.20 (m, 3H), 7.08 (d,  $J = 7.4$  Hz, 2H), 6.11 (s, 1H), 4.92 (d,  $J = 8.4$  Hz, 1H), 4.42 (dd,  $J = 8.4, 5.0$  Hz, 1H), 3.67 (s, 3H), 3.31 (t,  $J = 4.4$  Hz, 1 H), 1.68 (s, 1H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  199.7, 189.5, 151.2, 134.0, 129.0, 128.2, 127.9, 121.8, 86.1, 83.7, 63.0, 55.3, 47.6, 22.0 ppm. HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 90:10 at 1.0 mL/min for 30 minutes then *n*-hexane/*i*-PrOH = 80:20 at 1.0 mL/min for 80 minutes); major enantiomer  $t_R = 50.69$  min, minor enantiomer  $t_R = 57.91$  min; HRMS (ESI)  $[M+Na]^+$  calcd. for [C<sub>16</sub>H<sub>16</sub>O<sub>4</sub>Na] 295.0946, found 295.0951.



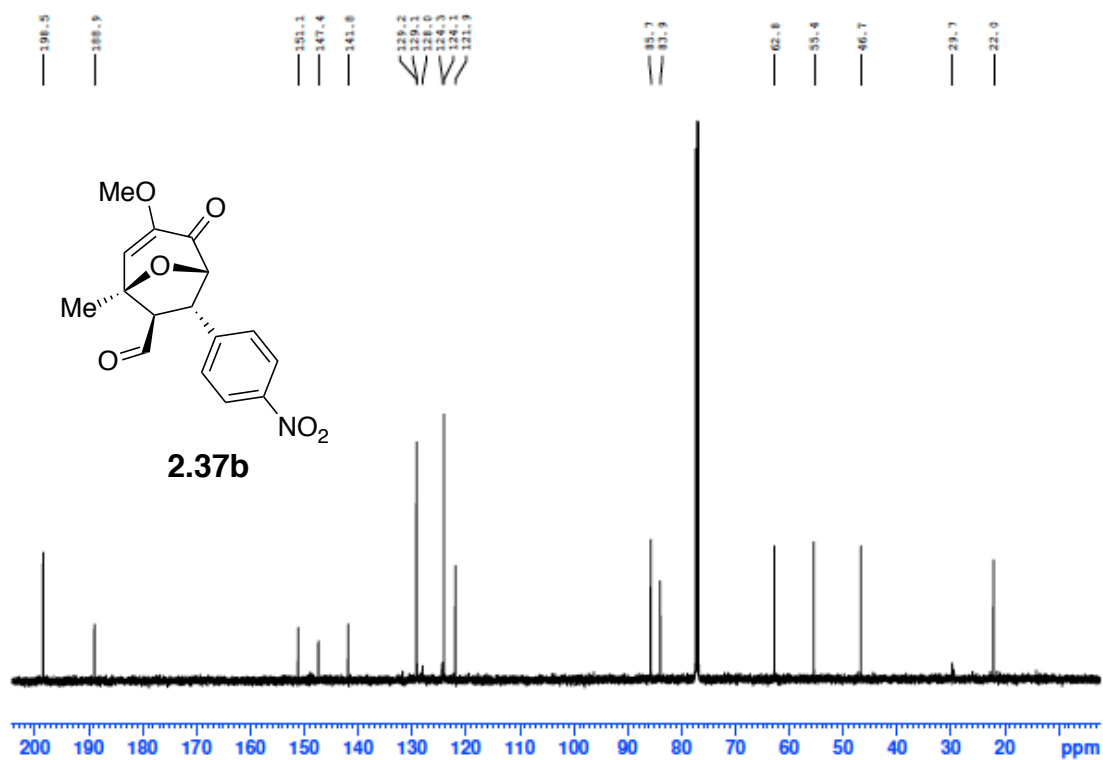
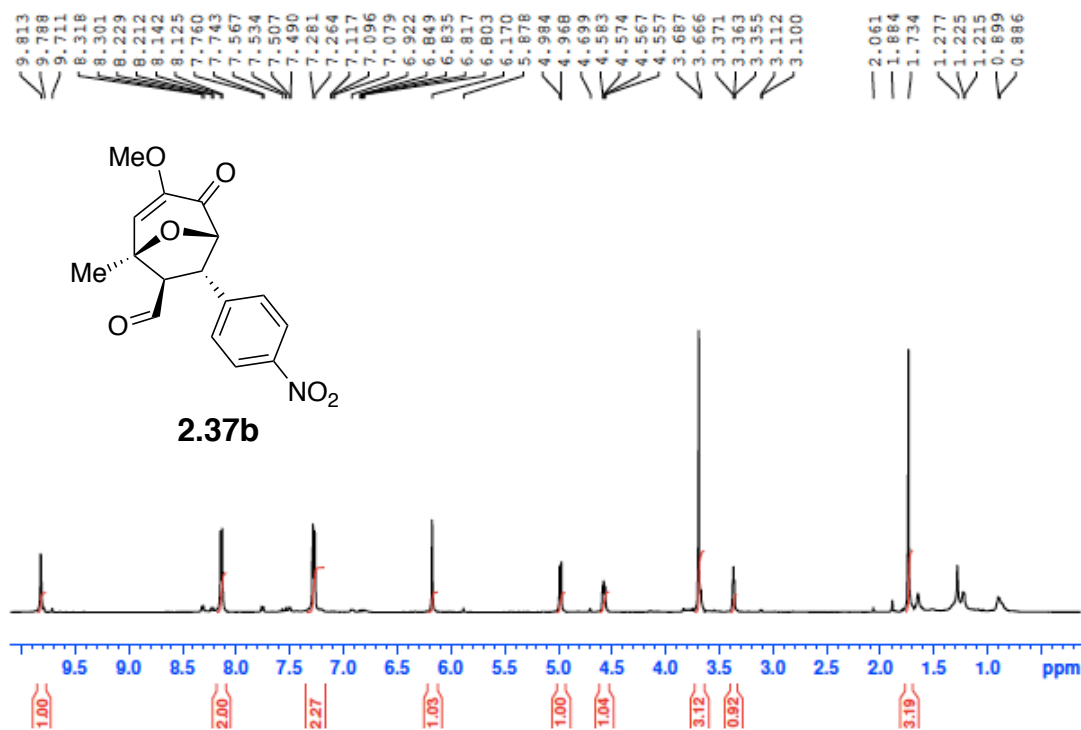


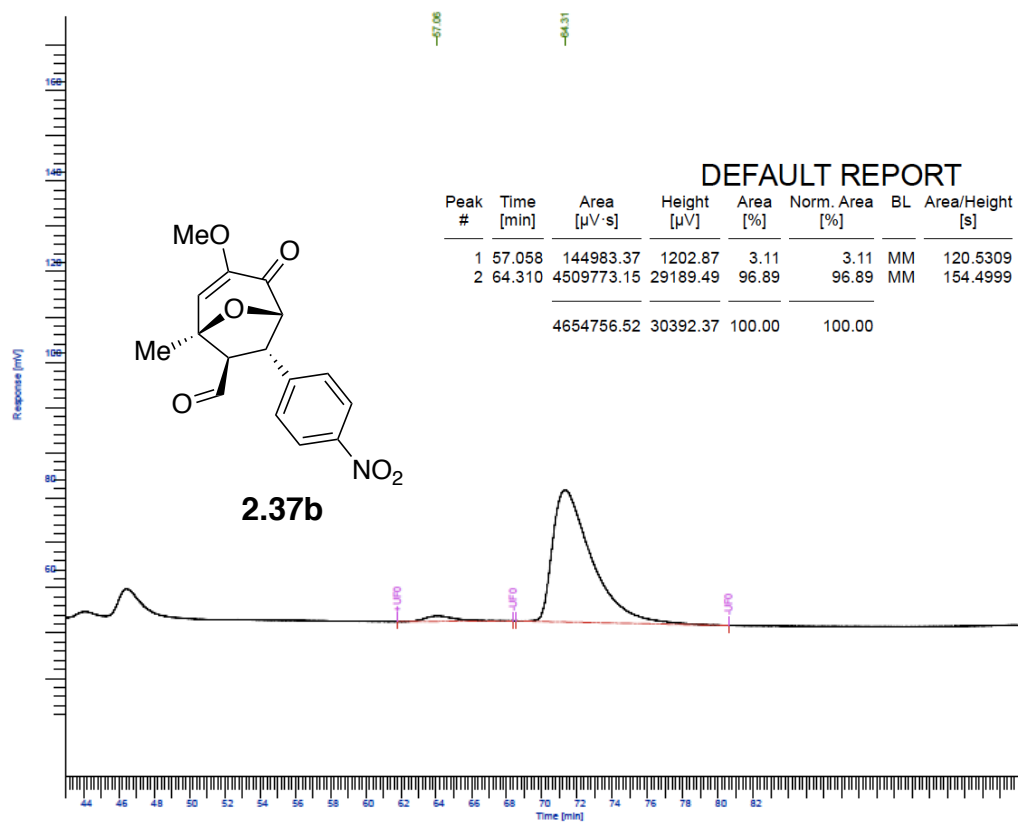
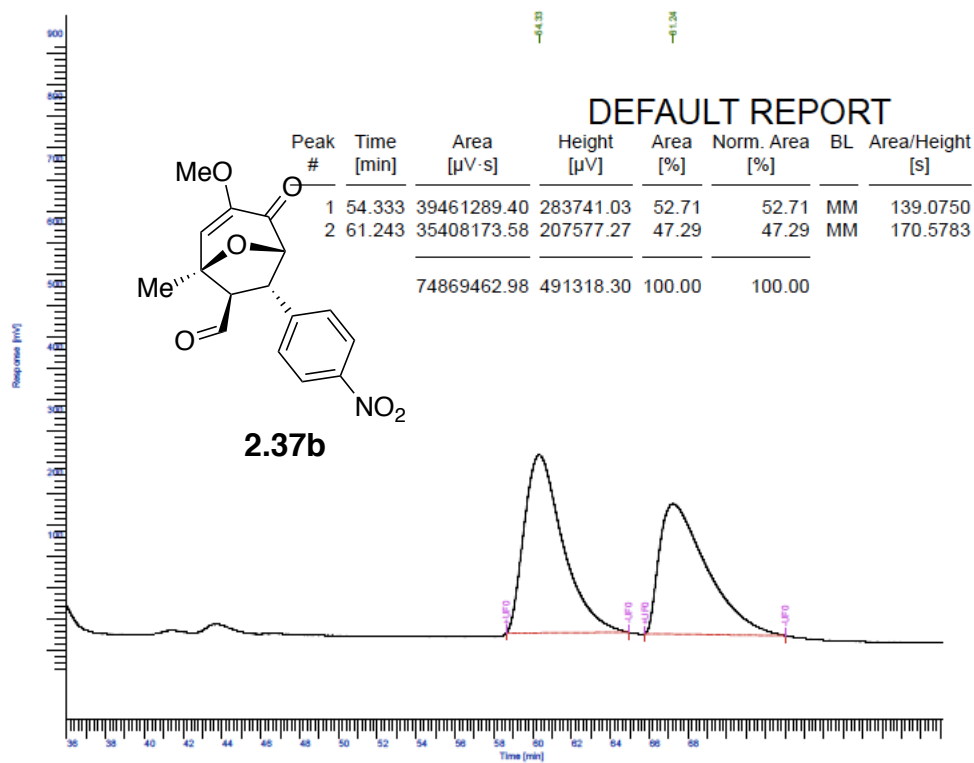


**3-methoxy-5-methyl-7-(4-nitrophenyl)-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37b)**

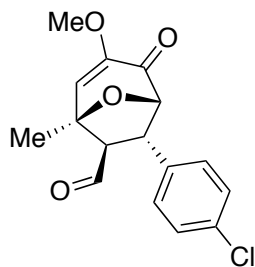


Pale yellow oil (39.3 mg, 65% yield); dr: 5:1;  $[\alpha]_{\text{D}}^{22} = +59.6$  ( $c = 1.3$  in  $\text{CH}_2\text{Cl}_2$ , 94% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.81 (d,  $J = 3.4$  Hz, 1H), 8.14 (d,  $J = 8.7$  Hz, 2H), 7.28 (s, 2H), 6.16 (s, 1H), 4.98 (d,  $J = 8.5$  Hz, 1H), 4.56 (dd,  $J = 8.5, 5.0$  Hz, 1H), 3.69 (s, 3H), 3.35 (dd,  $J = 4.0, 1.0$  Hz, 1H), 1.57 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  198.4, 188.9, 151.1, 147.4, 141.8, 129.1, 124.1, 121.9, 85.7, 83.9, 62.8, 55.4, 46.7, 22.0 ppm. HPLC with an AD-H column ( $n$ -hexane/ $i$ -PrOH = 88:12 at 1.0 mL/min for 90 minutes); major enantiomer  $t_{\text{R}} = 61.82$  min, minor enantiomer  $t_{\text{R}} = 56.15$  min; HRMS (ESI)  $[\text{M}]^+$  calcd. for  $[\text{C}_{16}\text{H}_{16}\text{NO}_6]$  318.0978, found 318.0981.

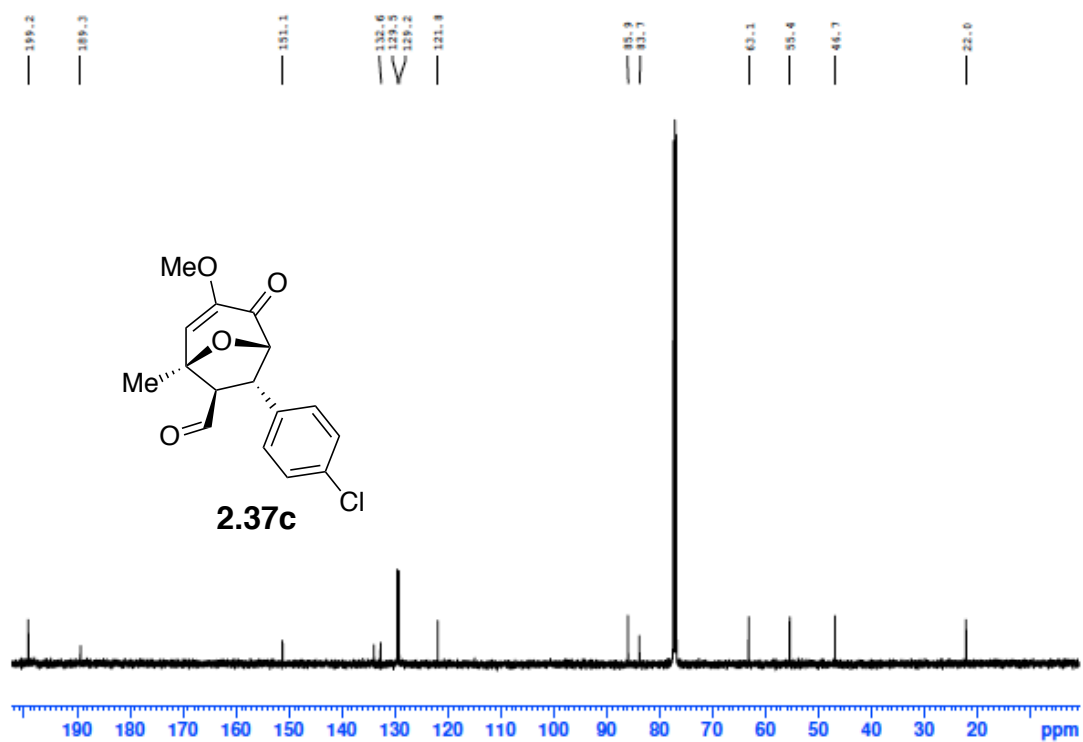
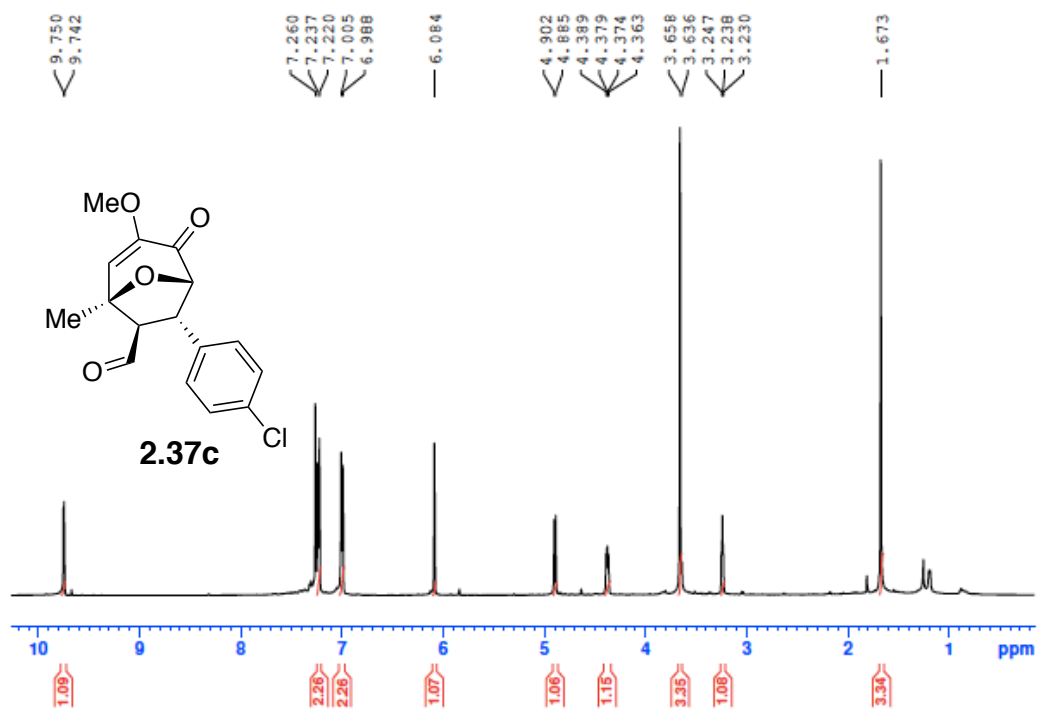


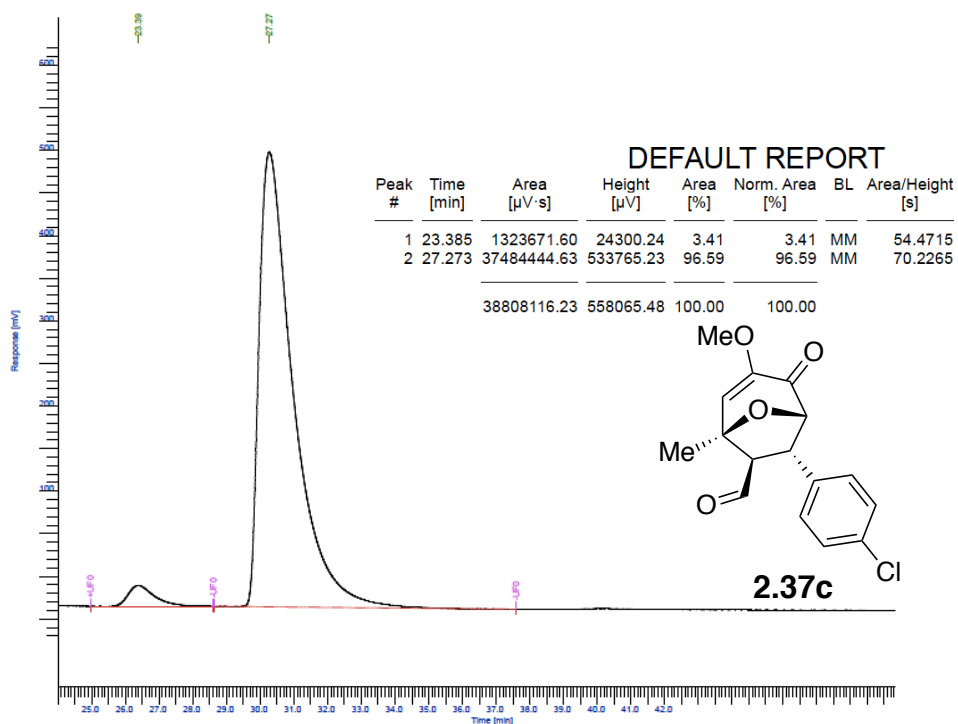
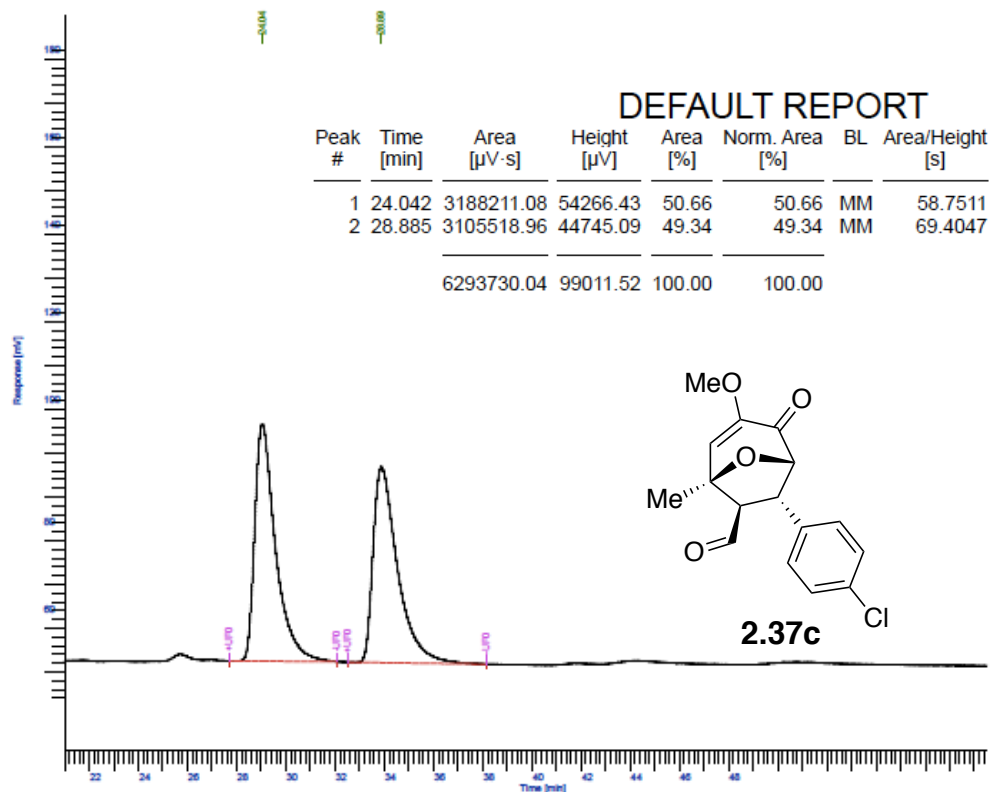


**7-(4-chlorophenyl)-3-methoxy-5-methyl-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37c)**



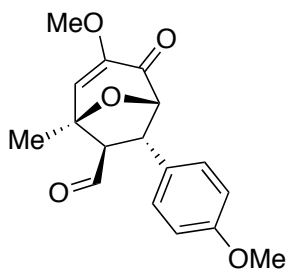
Pale yellow oil (53.3 mg, 91% yield); dr: 7:1;  $[\alpha]_{\text{D}}^{22} = +43.5$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ , 93% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.75 (d,  $J = 4$  Hz, 1H), 7.23 (d,  $J = 8.2$  Hz, 2H), 7.00 (d,  $J = 8.2$ , 2H) 6.08 (s, 1H), 4.89 (d,  $J = 8.4$  Hz, 1H), 4.38 (dd,  $J = 7.8, 4.9$  Hz, 1H), 3.66 (s, 1H), 3.24 (t,  $J = 4.1$  Hz, 1H), 1.67 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.2, 189.3, 151.1, 132.6, 129.5, 129.2, 121.8, 85.9, 83.7, 63.1, 55.4, 46.7, 22.0. HPLC with an AD-H column ( $n$ -hexane/ $i$ -PrOH = 90:10 at 1.0 mL/min for 60 minutes); major enantiomer  $t_{\text{R}} = 27.27$  min, minor enantiomer  $t_{\text{R}} = 23.37$  min; HRMS (ESI)  $[\text{M}]^+$  calcd. for  $[\text{C}_{16}\text{H}_{15}\text{O}_4\text{Cl}]$  306.0659, found 306.0665.



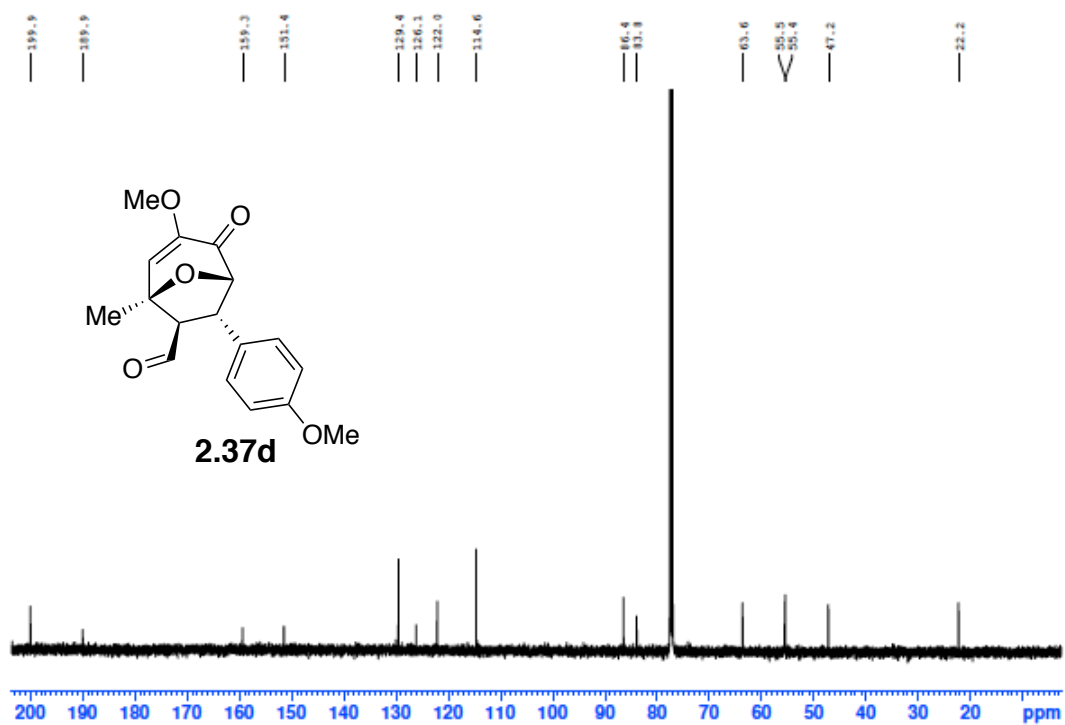
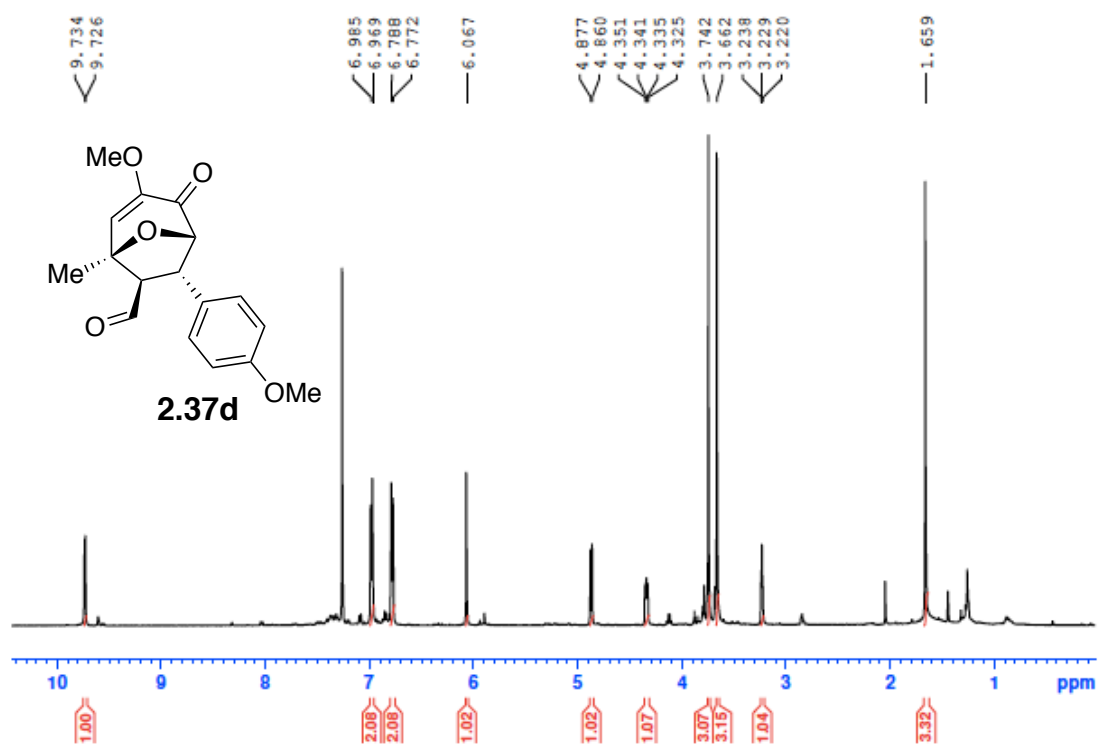


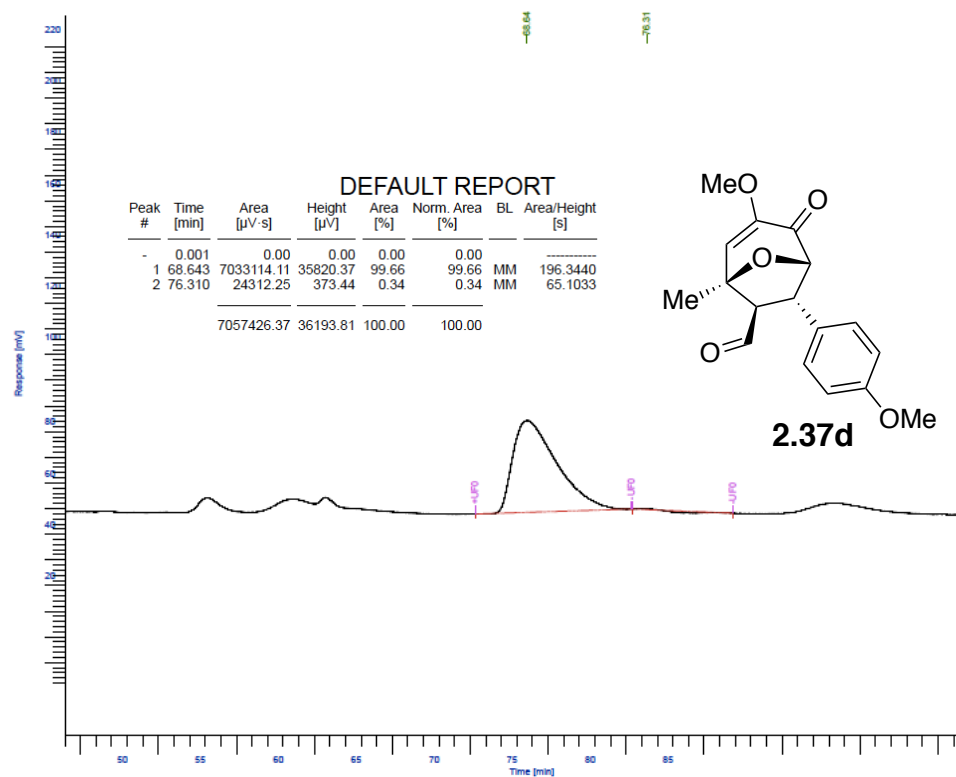
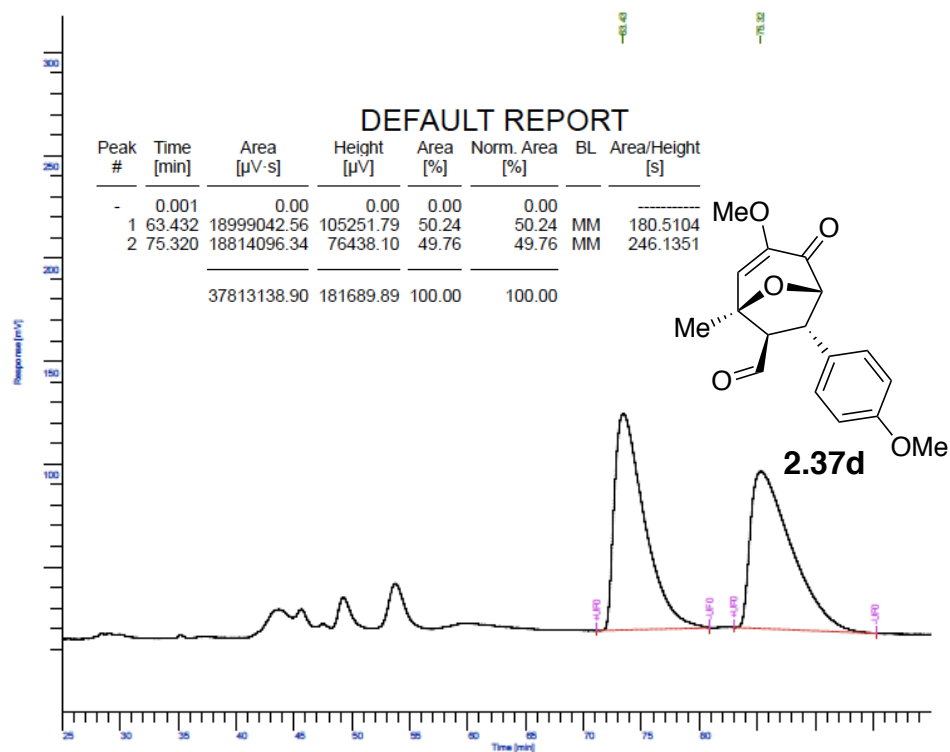
**3-methoxy-7-(4-methoxyphenyl)-5-methyl-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37d)**



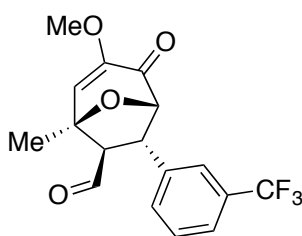


Pale viscous yellow oil (30.2 mg, 52% yield); dr: 7:1;  $[\alpha]_D^{22} = +23.9$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ , 99% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.73 (d,  $J = 4\text{ Hz}$ , 1H), 6.98 (d,  $J = 8.3\text{ Hz}$ , 2H), 6.78 (d,  $J = 8.4\text{ Hz}$ , 2H), 6.07 (s, 1H), 4.87 (d,  $J = 8.4$ , 1H), 4.34 (dd,  $J = 8.0$ , 4.9 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 3.23 (t,  $J = 4.3\text{ Hz}$ , 1H), 1.66 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.9, 189.9, 159.3, 151.4, 129.4, 126.1, 122.0, 114.6, 86.4, 83.8, 63.6, 55.5, 55.4, 47.2, 22.2 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH = 90:10 at 1.0 mL/min for 30 minutes then  $n$ -hexane/ $i$ -PrOH = 80:20 at 1.0 mL/min for 80 minutes); major enantiomer  $t_R = 67.81\text{ min}$ , minor enantiomer  $t_R = 79.88\text{ min}$ ; HRMS (ESI)  $[\text{M}]^+$  calcd. for  $[\text{C}_{17}\text{H}_{18}\text{O}_5]$  302.1154, found 302.1153.

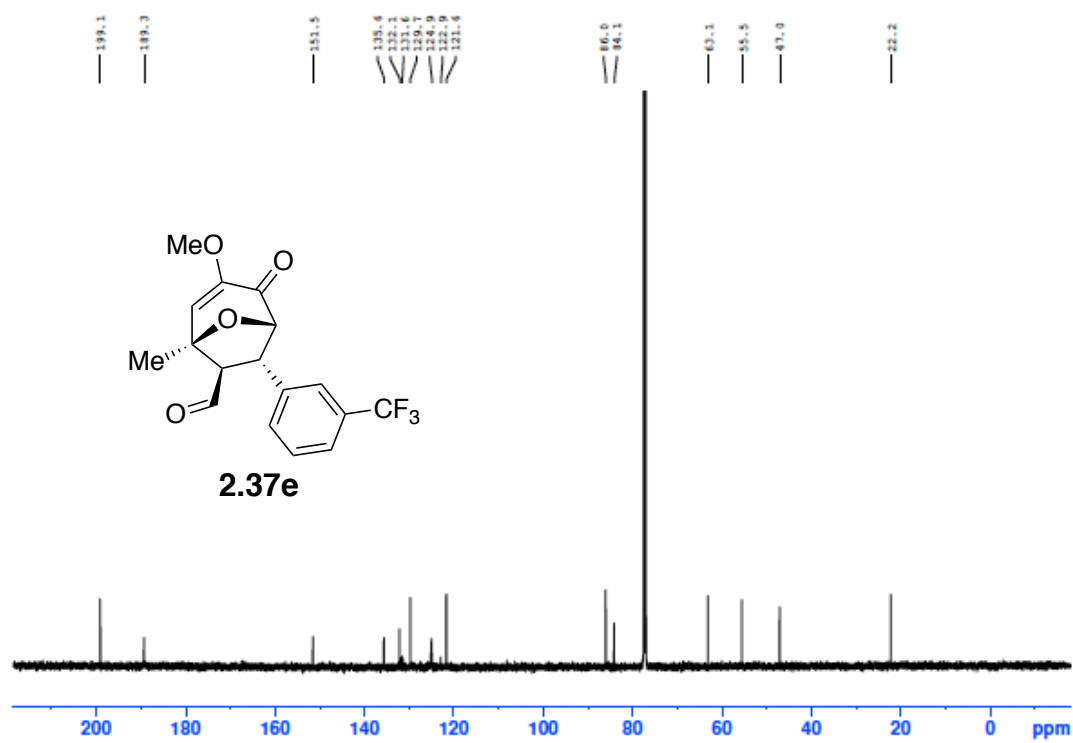
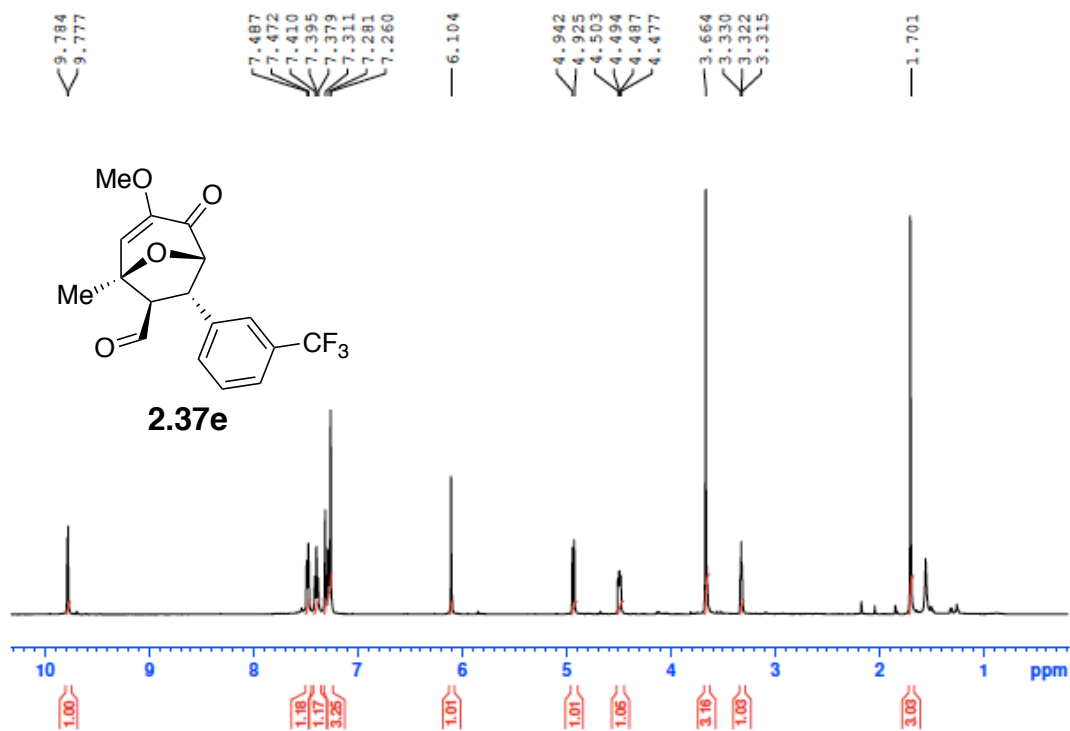


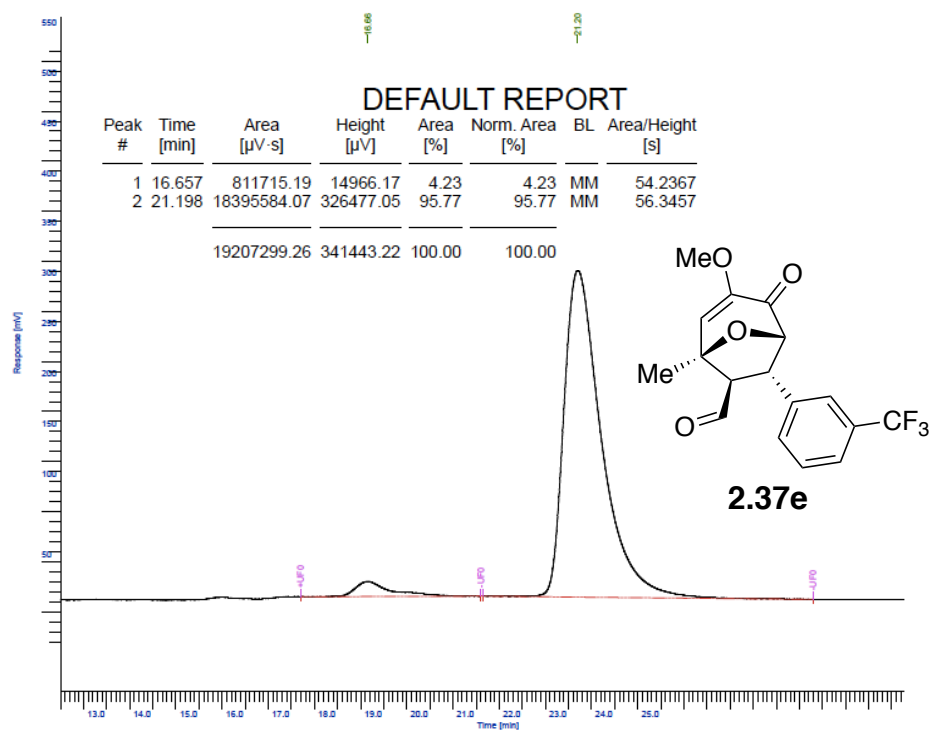
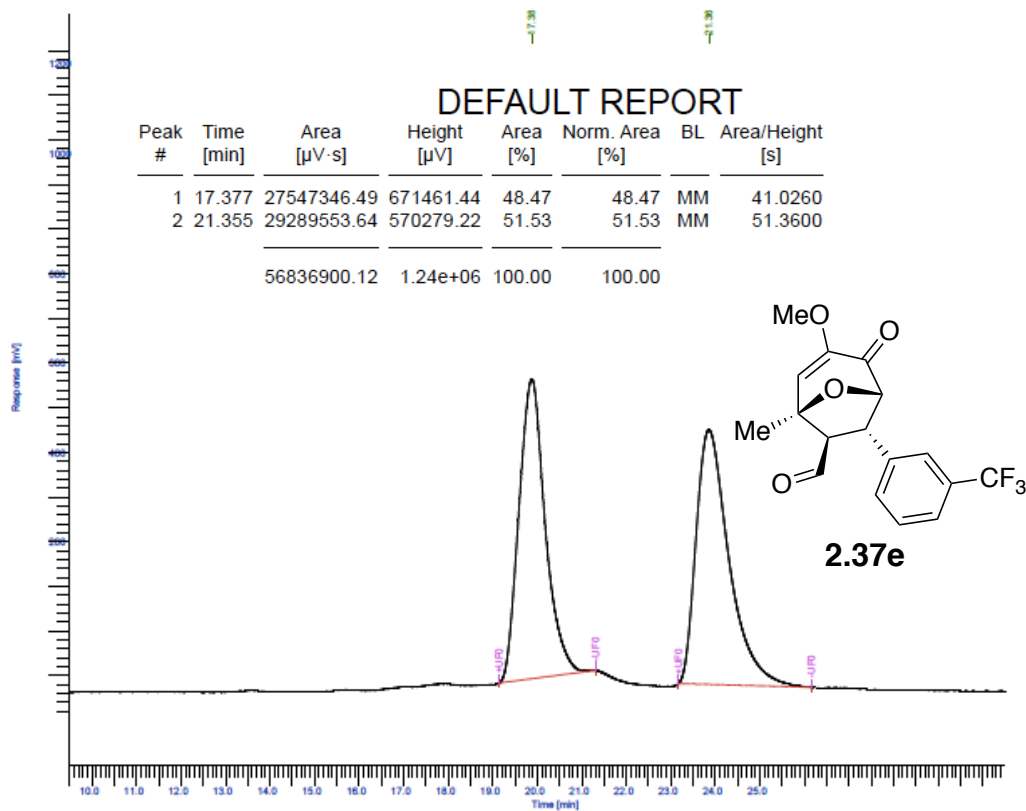


**3-methoxy-5-methyl-2-oxo-7-(3-(trifluoromethyl)phenyl)-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37e)**

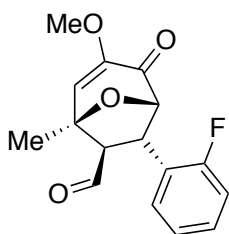


Pale yellow oil (43.4 mg, 70% yield); dr: 7:1;  $[\alpha]_{\text{D}}^{22} = +40.6$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ , 92% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.78 (d,  $J = 3.2$  Hz, 1H), 7.48 (d,  $J = 87.6$  Hz, 1H), 7.39 (t,  $J = 7.7$  Hz, 1H), 7.28 (t,  $J = 12.6$  Hz, 2H), 6.10 (s, 1H), 4.93 (d,  $J = 8.5$  Hz, 1H), 4.49 (dd,  $J = 7.8, 4.6$  Hz, 1H), 3.66 (s, 3H), 3.32 (t,  $J = 5.5$  Hz, 1H), 1.70 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.1, 189.3, 151.5, 135.6, 132.1, 131.6, 129.7, 124.9, 122.9, 121.6, 86.0, 84.1, 63.1, 55.5, 47.0, 22.2 ppm. HPLC with an AD-H column ( $n$ -hexane/ $i$ -PrOH = 90:10 at 1.0 mL/min for 60 minutes); major enantiomer  $t_{\text{R}} = 21.20$  min, minor enantiomer  $t_{\text{R}} = 16.54$  min; HRMS (ESI)  $[\text{M}^+]$  calcd. for  $[\text{C}_{17}\text{H}_{15}\text{O}_4\text{F}_3]$  340.0923, found 340.0913.

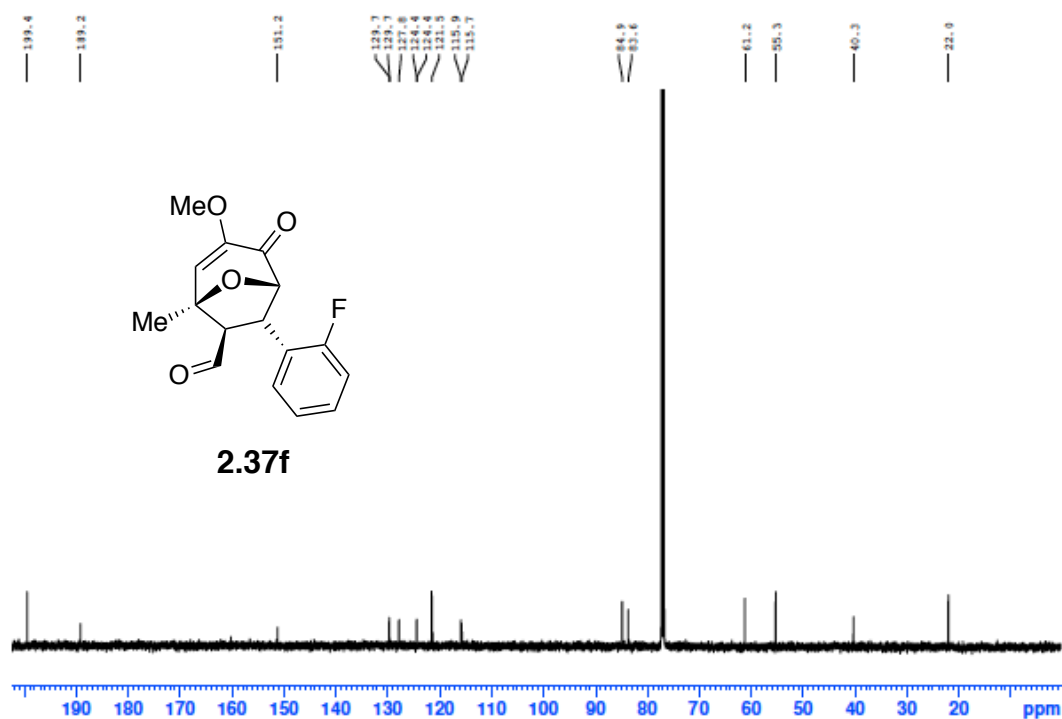
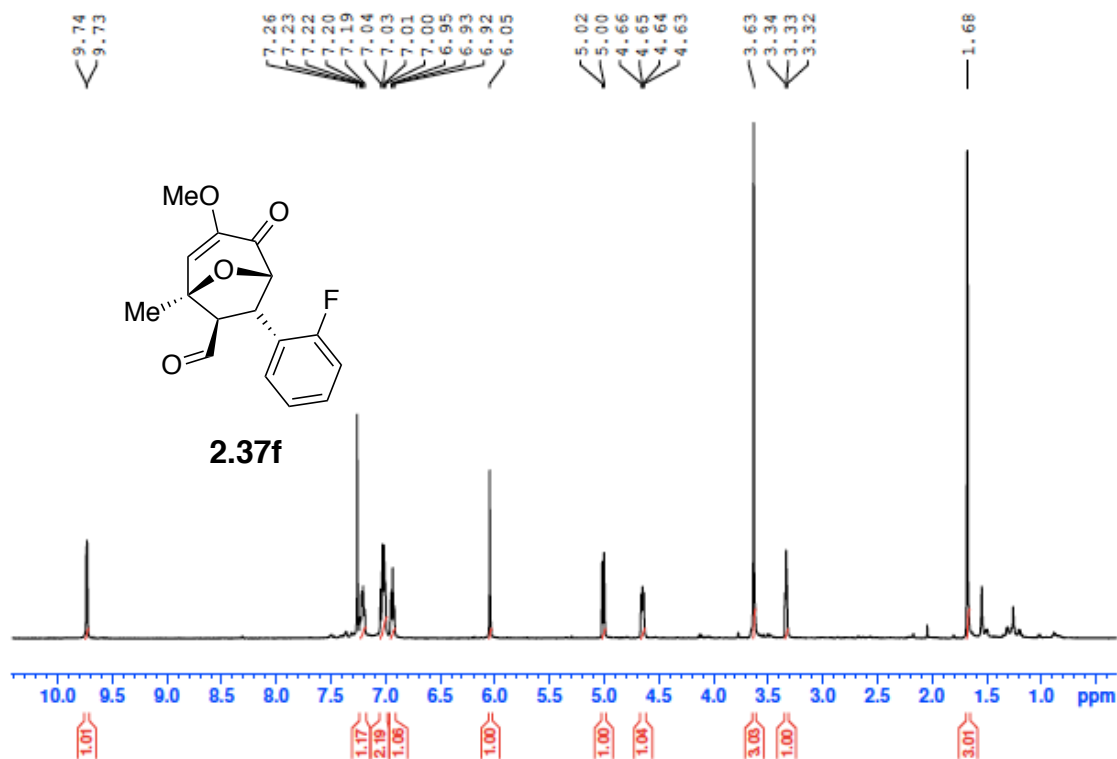




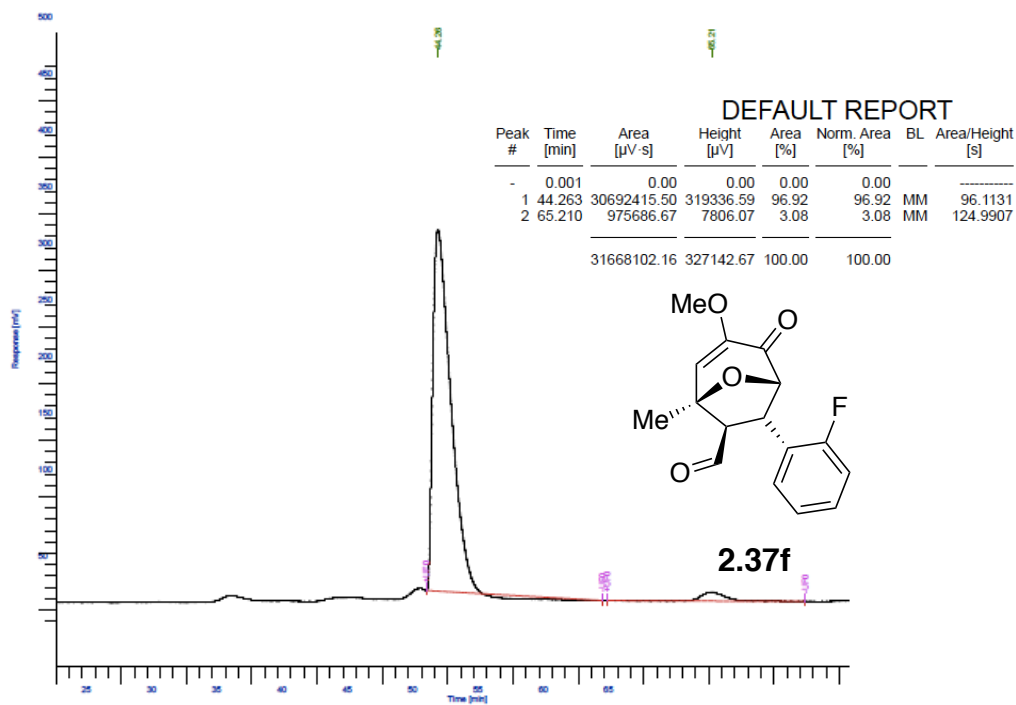
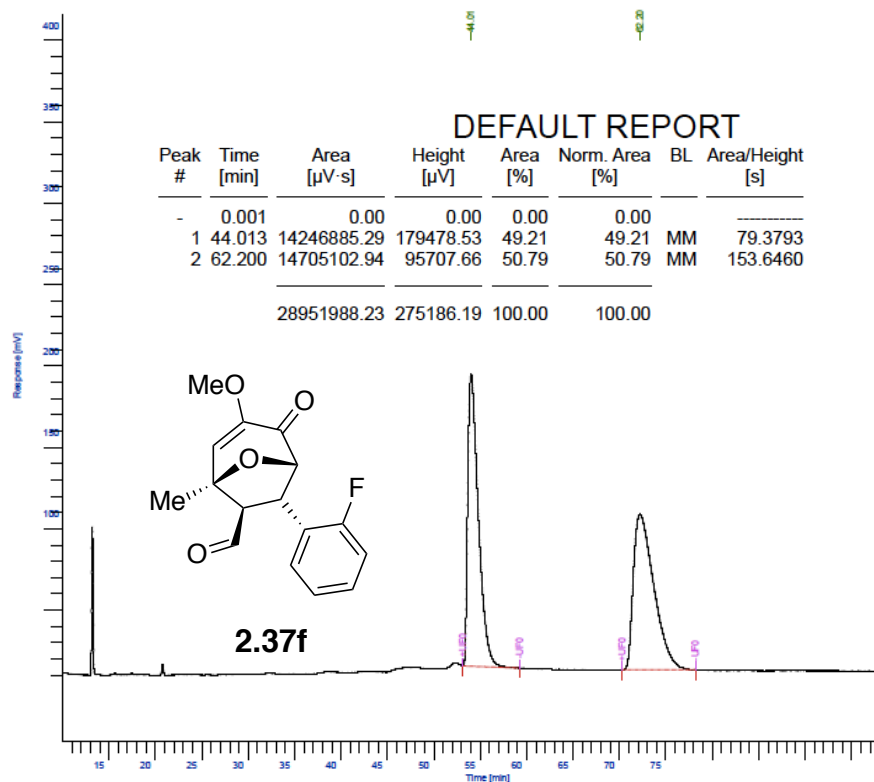
**7-(2-fluorophenyl)-3-methoxy-5-methyl-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37f)**



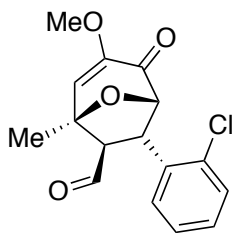
Pale yellow oil (35.4 mg, 64% yield); dr: 5:1;  $[\alpha]_{\text{D}}^{22} = +52.3$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ , 94% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.74 (d,  $J = 4.1$  Hz, 1H), 7.21 (dd,  $J = 13.5, 6.0$  Hz, 1H), 7.02 (dd,  $J = 15.5, 8.9$  Hz, 2H), 6.93 (t,  $J = 7.5$  Hz, 1H), 6.05 (s, 1H), 5.01 (d,  $J = 8.3$  Hz, 1H), 4.65 (dd,  $J = 7.9, 4.9$  Hz, 1H), 3.63 (s, 3H), 3.33 (t,  $J = 4.2$  Hz, 1H), 1.68 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.4, 189.2, 151.2, 129.8, 129.7, 127.8, 124.5, 124.4, 121.5, 115.9, 115.7, 84.9, 83.6, 61.2, 55.3, 40.3, 22.0 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH = 90:10 at 1.0 mL/min for 30 minutes then  $n$ -hexane/ $i$ -PrOH = 80:20 at 1.0 mL/min for 80 minutes); major enantiomer  $t_{\text{R}} = 44.26$  min, minor enantiomer  $t_{\text{R}} = 65.21$  min; HRMS (ESI)  $[\text{M}]^+$  calcd. for  $[\text{C}_{16}\text{H}_{15}\text{O}_4\text{F}]$  290.0954, found 290.0952.



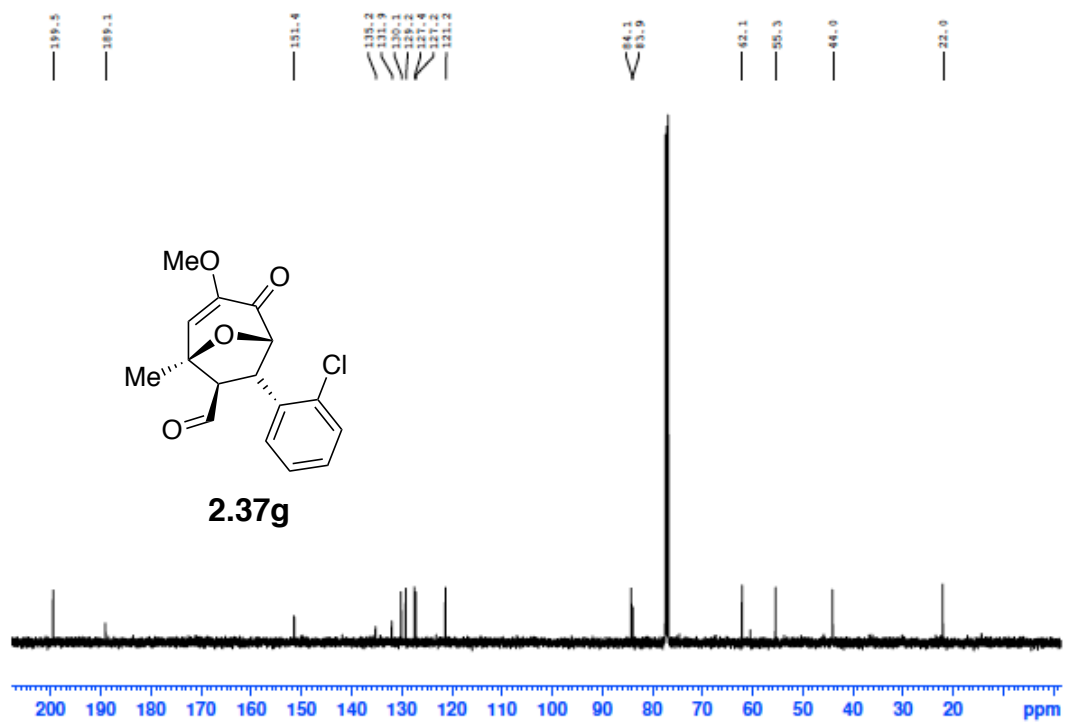
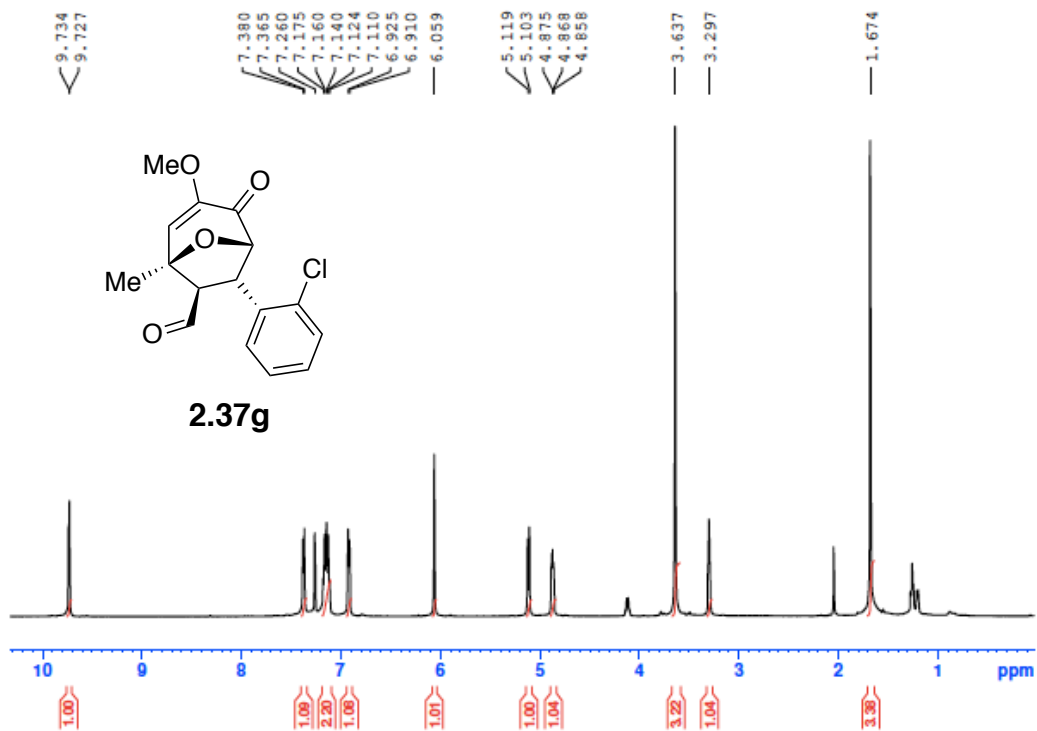


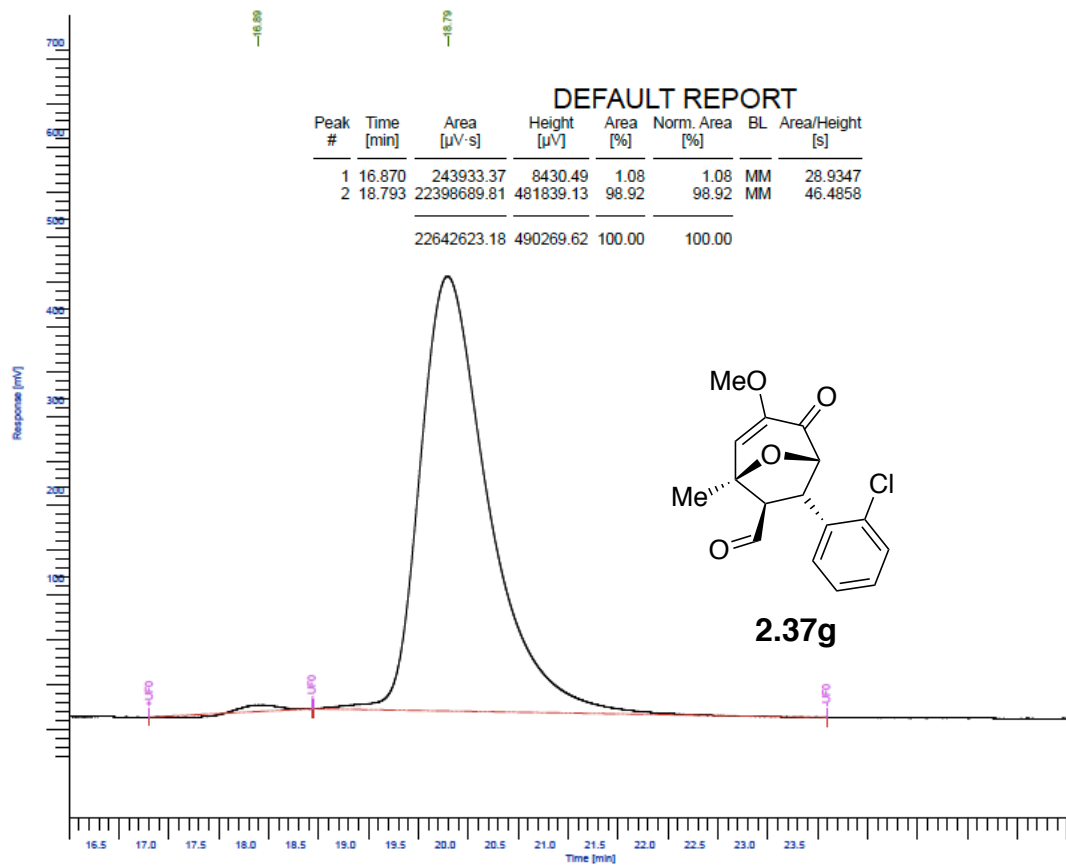
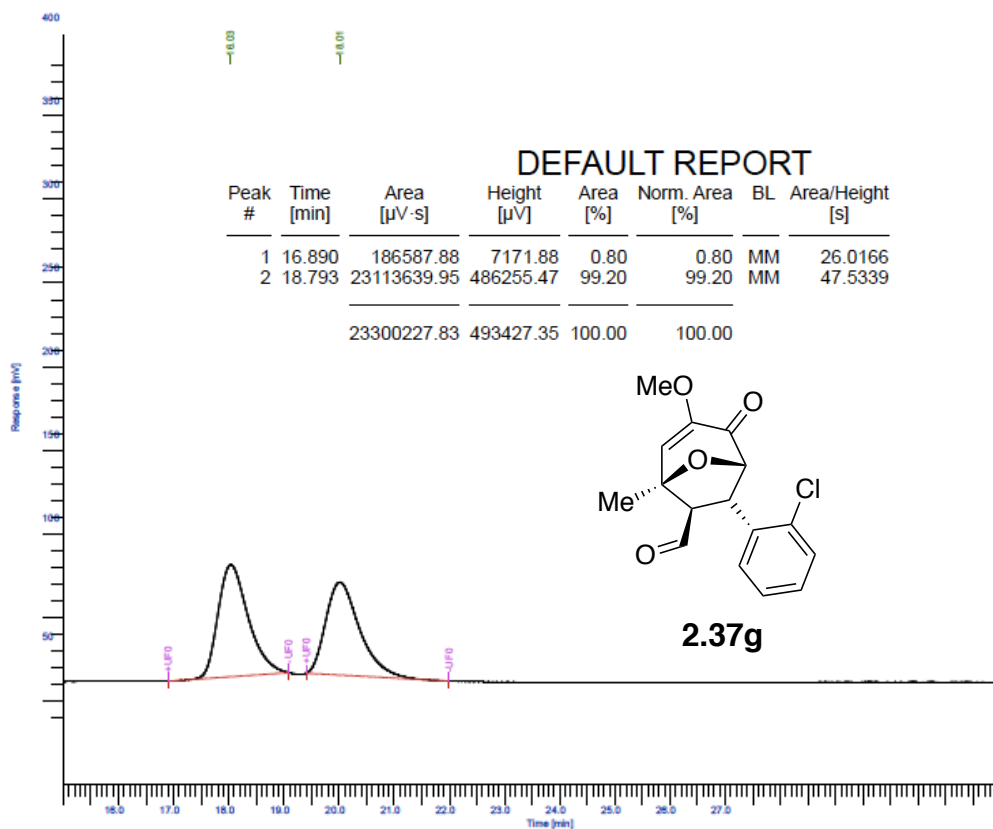


**7-(2-chlorophenyl)-3-methoxy-5-methyl-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37g)**

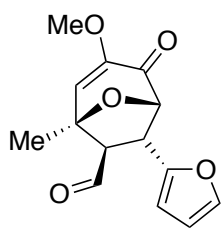


White solid (39.8 mg, 68% yield); m.p. 146-148 °C;  $[\alpha]_D^{22} = +68.5$  ( $c = 0.7$  in  $\text{CH}_2\text{Cl}_2$ , 98% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.73 (d,  $J = 3.4$  Hz, 1H), 7.37 (d,  $J = 7.6$  Hz, 1H), 7.18-7.11 (m, 2H), 6.92 (d,  $J = 7.3$  Hz, 1H), 6.06 (s, 1H), 5.11 (d,  $J = 7.3$  Hz, 1H), 4.87 (t,  $J = 4.1$  Hz, 1H), 3.64 (s, 3H), 3.30 (s, 1H), 1.67 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.5, 189.1, 151.4, 135.2, 131.9, 130.1, 129.2, 127.4, 127.2, 121.2, 84.1, 83.9, 62.1, 55.3, 44.0, 22.0 ppm. HPLC with an AD-H column ( $n$ -hexane/ $i$ -PrOH = 90:10 at 1.0 mL/min for 30 minutes); major enantiomer  $t_R = 18.79$  min, minor enantiomer  $t_R = 16.87$  min; HRMS (ESI)  $[M^+]$  calcd. for  $[\text{C}_{16}\text{H}_{15}\text{O}_4\text{Cl}]$  306.0659, found 306.0668.

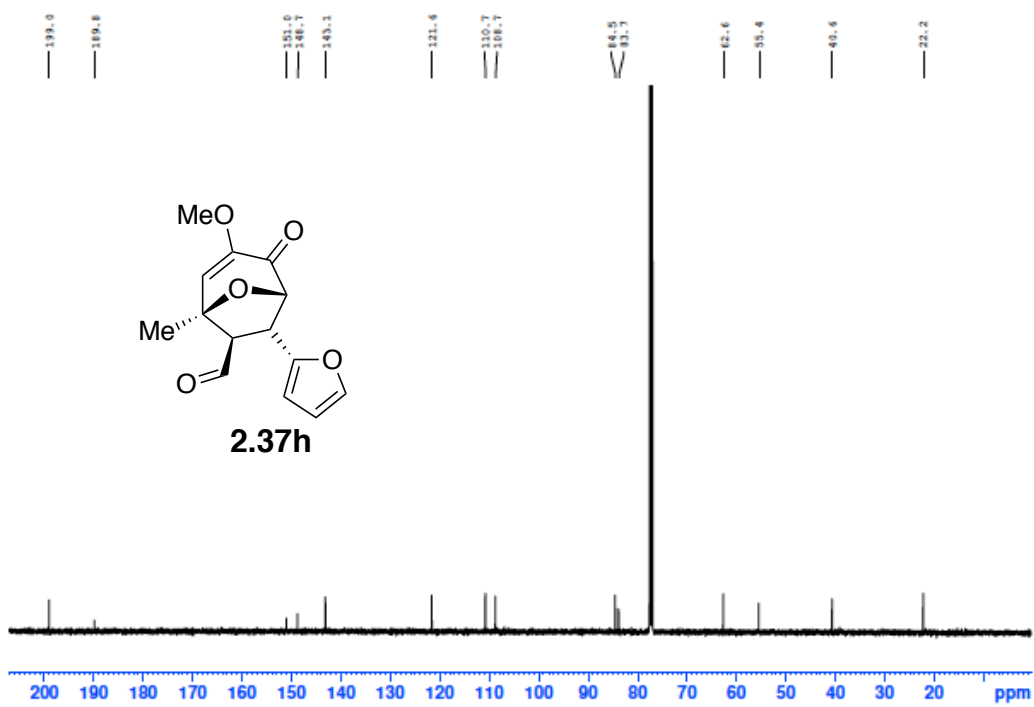
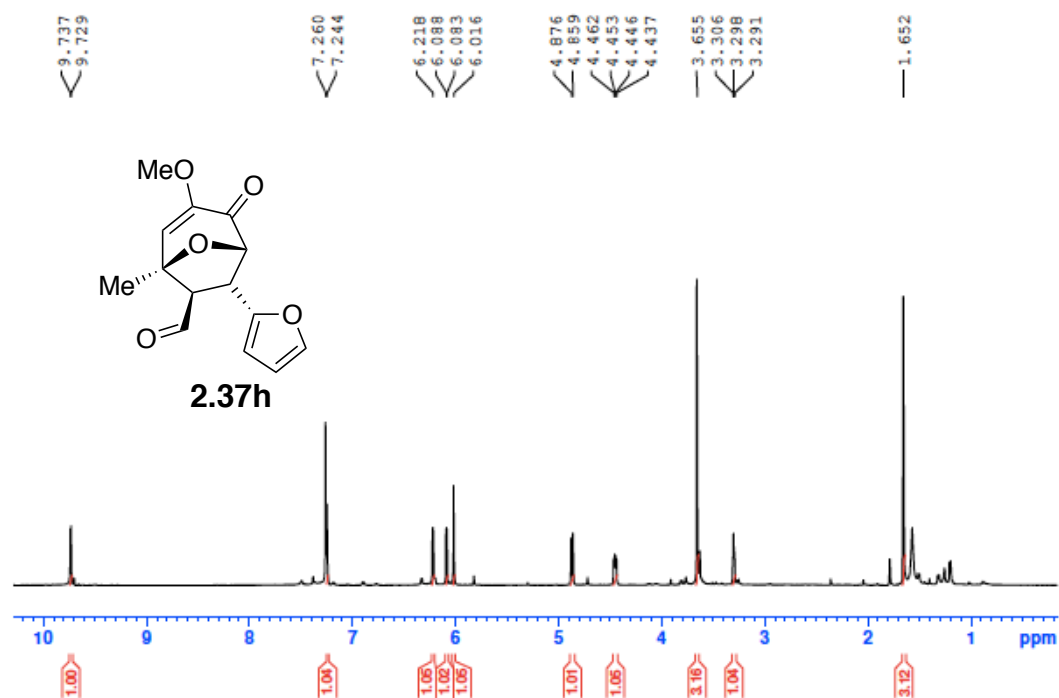


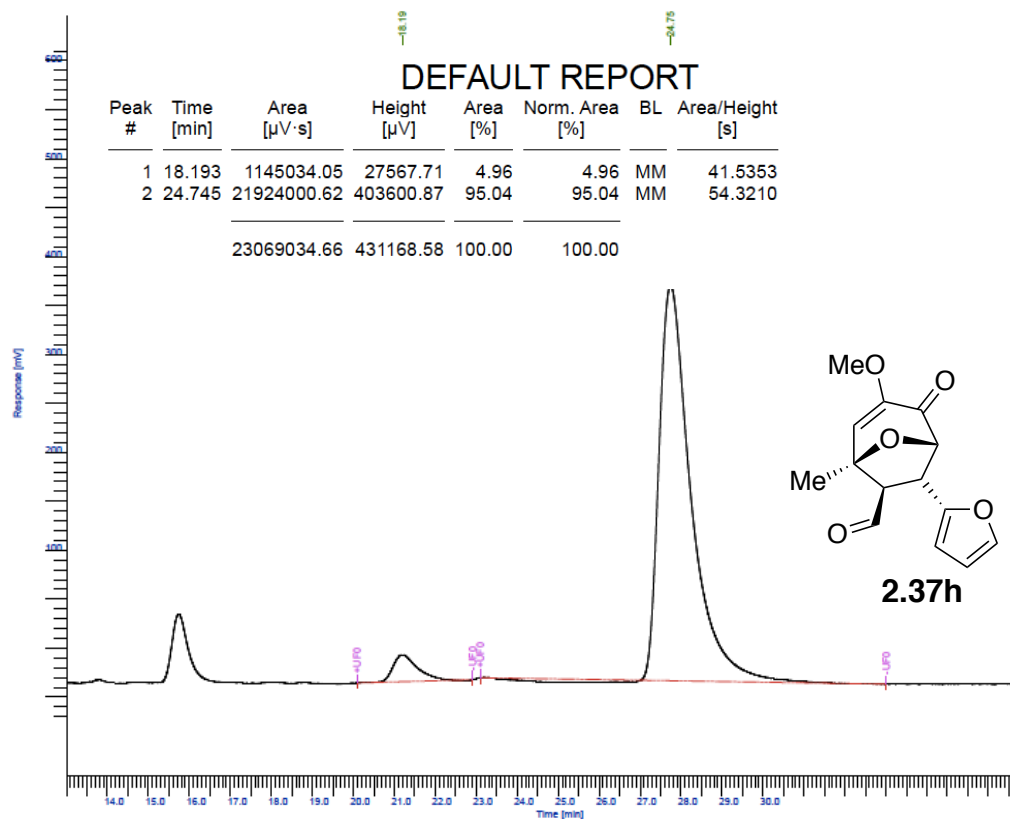
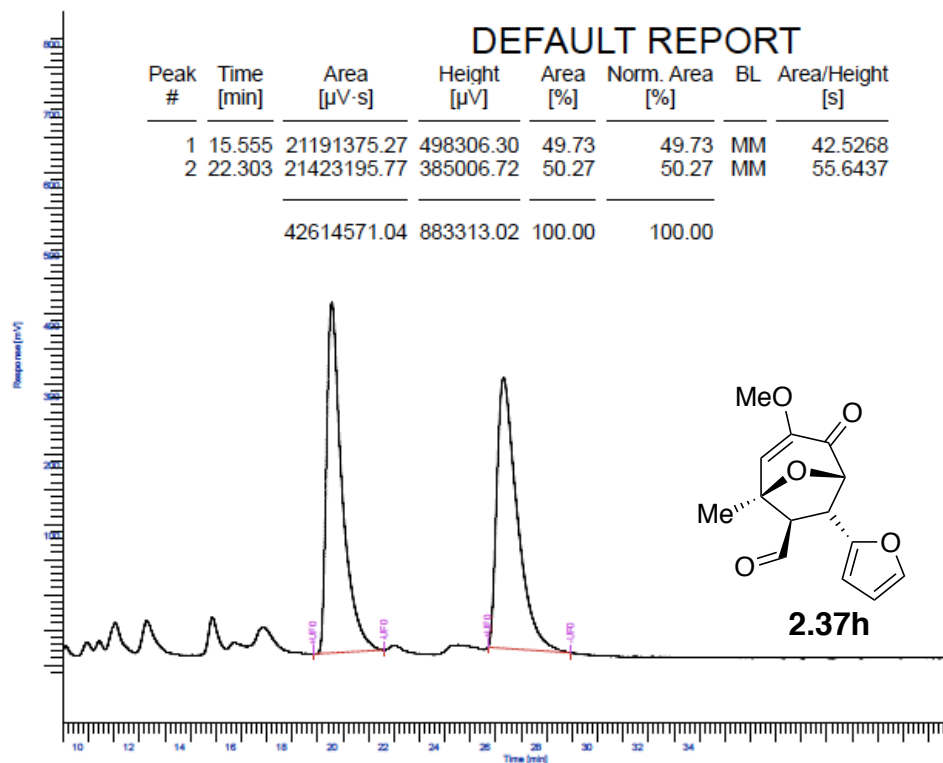


**7-(furan-2-yl)-3-methoxy-5-methyl-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37h)**

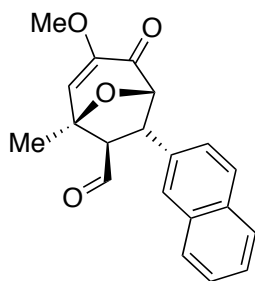


Yellow oil (27.6 mg, 55% yield); dr: 3:1;  $[\alpha]_D^{22} = +20.0$  ( $c = 0.3$  in  $\text{CH}_2\text{Cl}_2$ , 90% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.73 (d, 1H), 7.24 (s, 1H), 6.22 (s, 1H), 6.09 (d,  $J = 2.5$  Hz, 1H), 6.02 (s, 1H), 4.87 (d,  $J = 8.3$  Hz, 1H), 4.45 (dd,  $J = 8.0, 4.6$  Hz, 1 H), 3.66 (s, 3H), 3.30 (t,  $J = 3.9$  Hz, 1H), 1.65 (s, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.0, 189.8, 151.0, 148.7, 143.1, 121.6, 110.7, 108.7, 84.5, 83.7, 62.6, 55.4, 40.6, 22.2 ppm. HPLC with an AD-H column ( $n$ -hexane/ $i$ -PrOH = 90:10 at 1.0 mL/min for 60 minutes); major enantiomer  $t_R = 24.75$  min, minor enantiomer  $t_R = 18.19$  min; HRMS (ESI)  $[M^+]$  calcd. for  $[\text{C}_{14}\text{H}_{14}\text{O}_5]$  262.0841, found 262.0834.



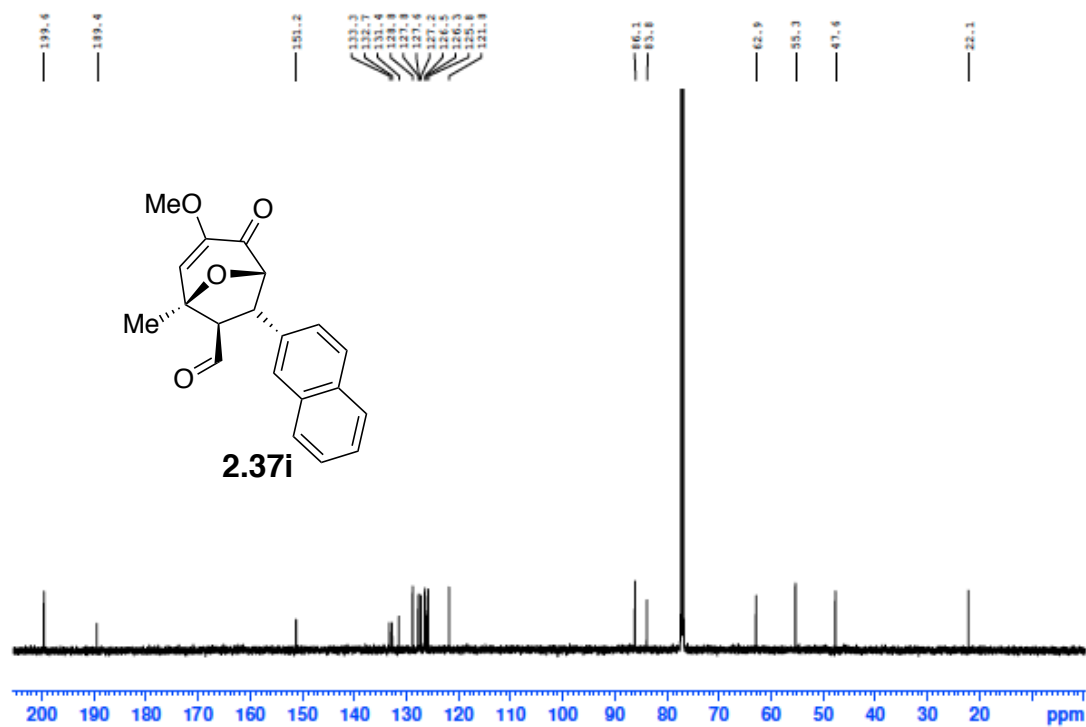
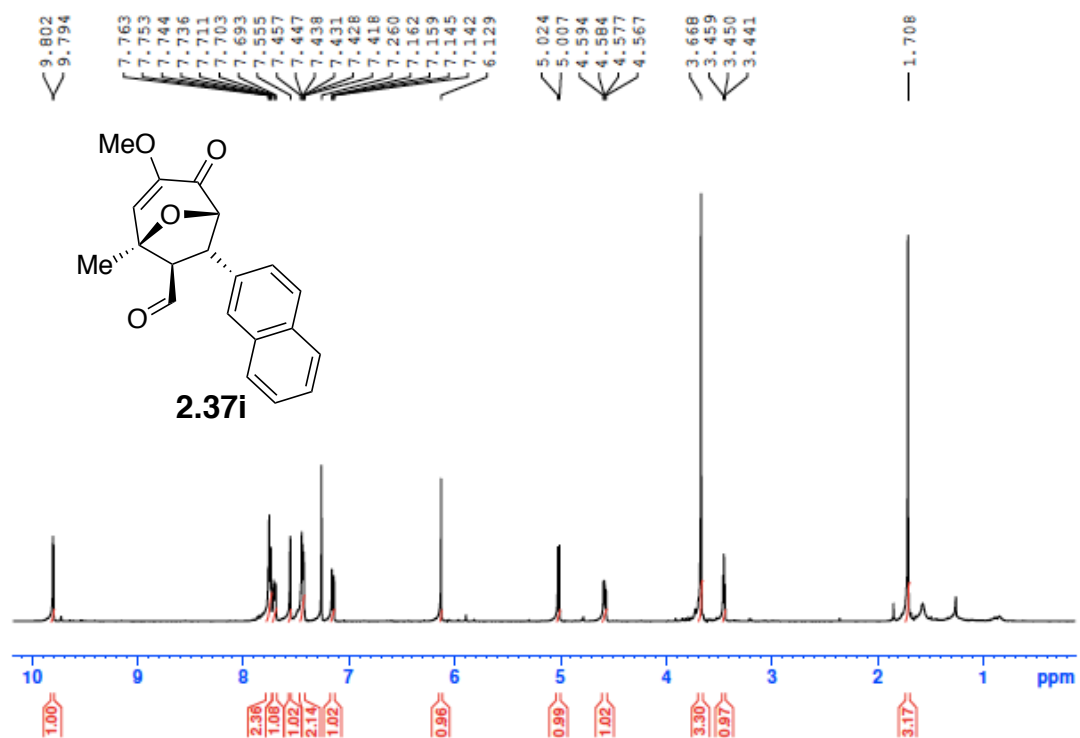


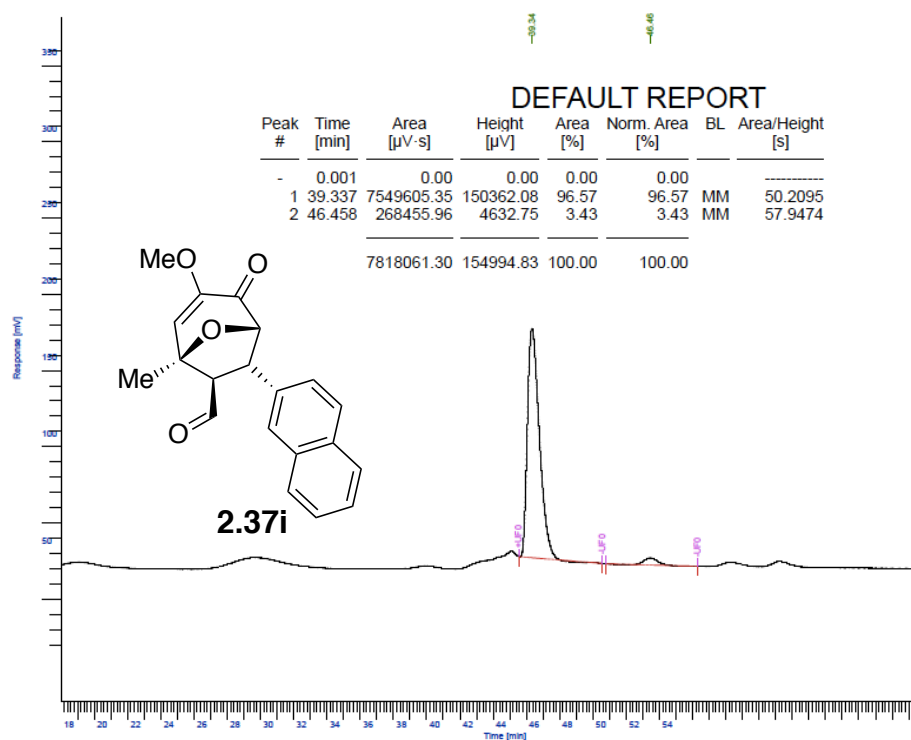
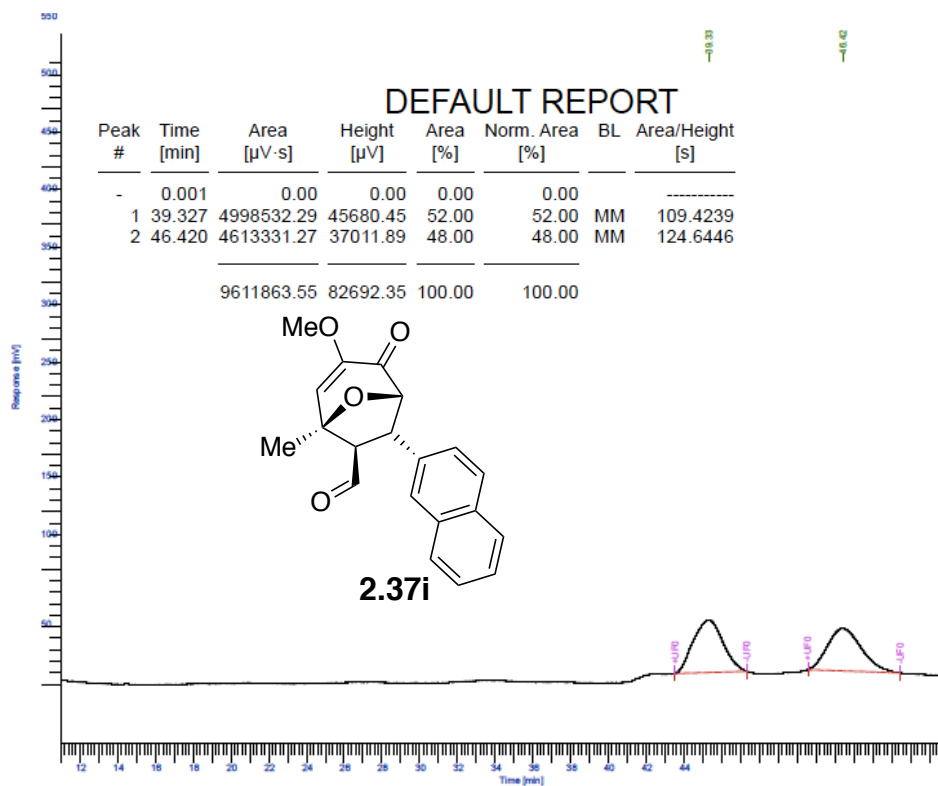
**3-methoxy-5-methyl-7-(naphthalen-2-yl)-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde (2.37i)**



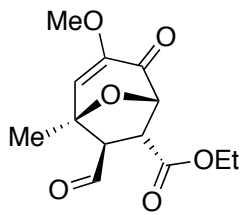
Pale yellow oil (29.6 mg, 48% yield); dr: 10:1;  $[\alpha]_{\text{D}}^{22} = +69.3$  ( $c = 0.7$  in  $\text{CH}_2\text{Cl}_2$ , 93% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.80 (d,  $J = 4.0$  Hz, 1H), 7.76-7.74 (m, 2H), 7.70 (t,  $J = 4.7$  Hz, 1H), 7.56 (s, 1H), 7.46-7.42 (m, 2H), 7.15 (dd,  $J = 8.5, 1.7$  Hz, 1H), 6.13 (s, 1H), 5.02 (d,  $J = 8.5$  Hz, 1H), 4.58 (dd,  $J = 8.4, 5.0$  Hz, 1H), 3.67 (s, 3H), 3.45 (t,  $J = 4.5$  Hz, 1H), 1.71 (s, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.6, 189.4, 151.2, 133.3, 132.7, 131.4, 128.8, 127.8, 127.6, 127.2, 126.5, 126.3, 125.8, 121.8, 86.1, 83.8, 62.9, 55.3, 47.6, 22.1 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH= 90:10 at 1.0 mL/min for 30 minutes then  $n$ -hexane/ $i$ -PrOH= 80:20 at 1.0 mL/min for 80 minutes); major enantiomer  $t_{\text{R}} = 39.34$  min, minor enantiomer  $t_{\text{R}} = 49.46$  min; HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd. for  $[\text{C}_{20}\text{H}_{18}\text{O}_4\text{Na}]$  345.1103, found 345.1105.



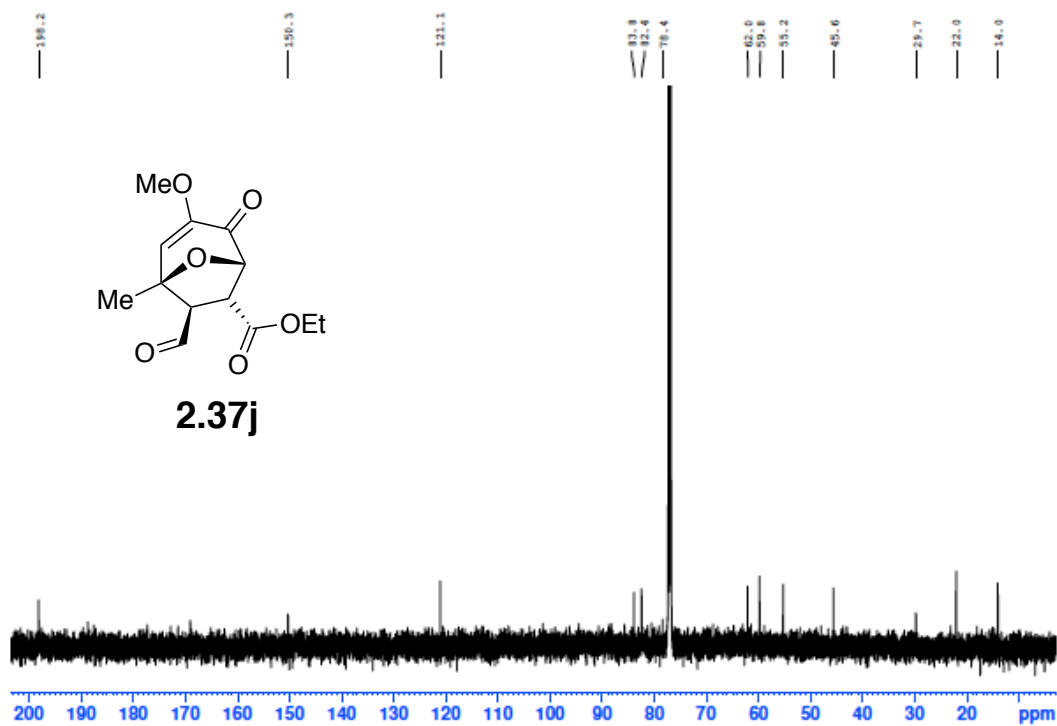
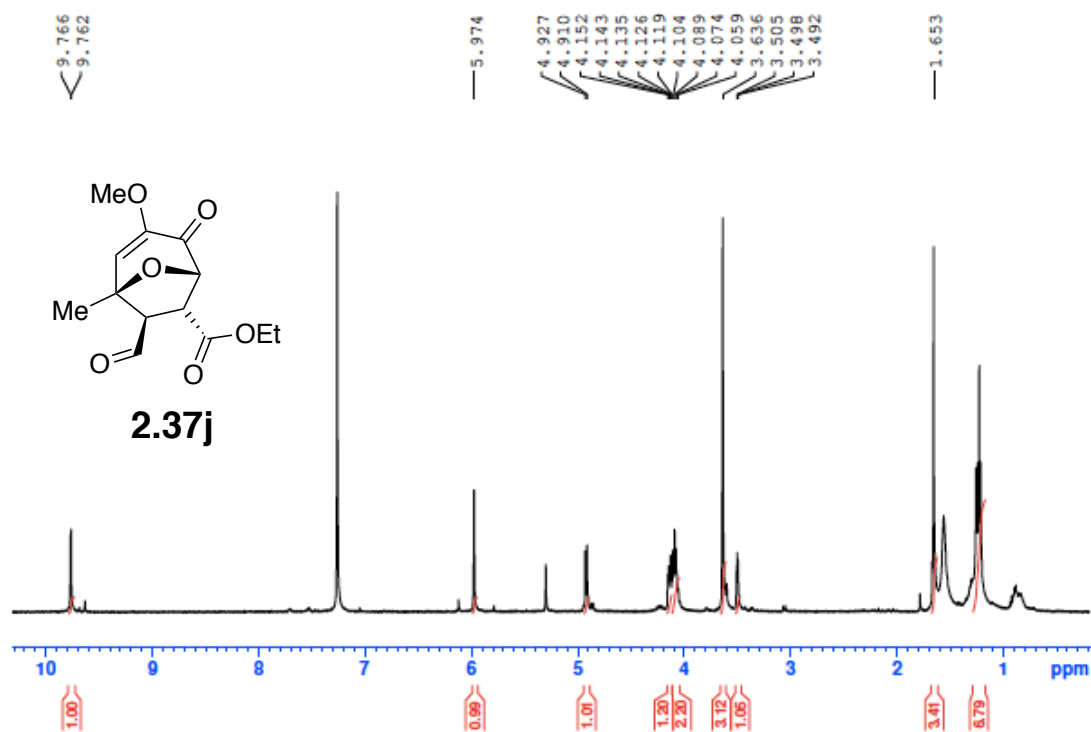


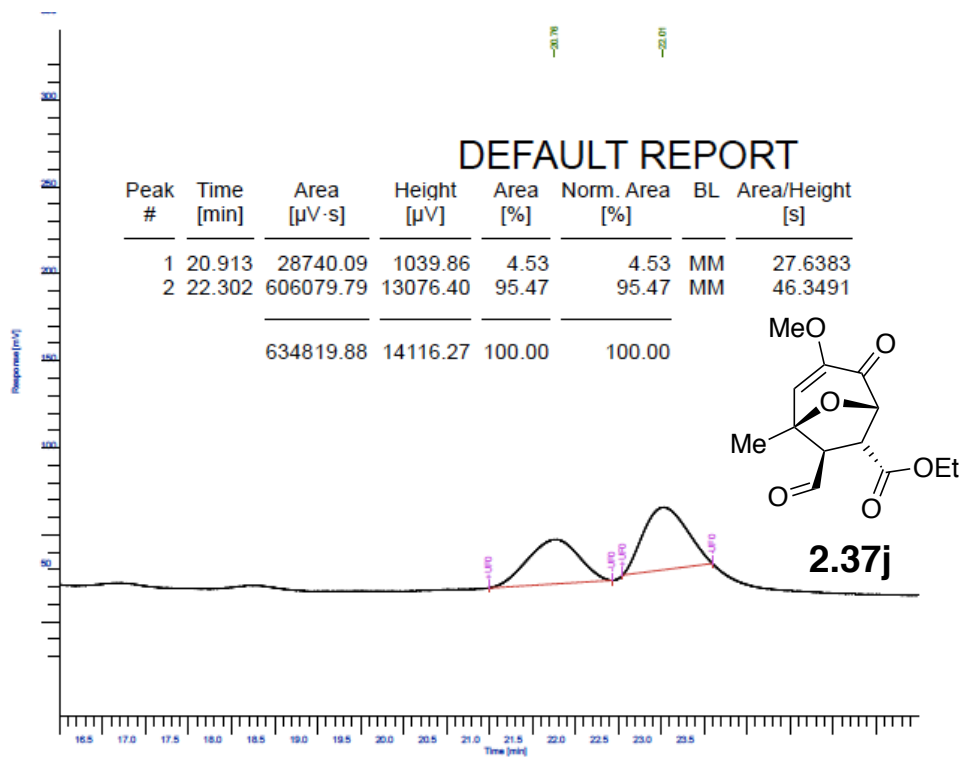
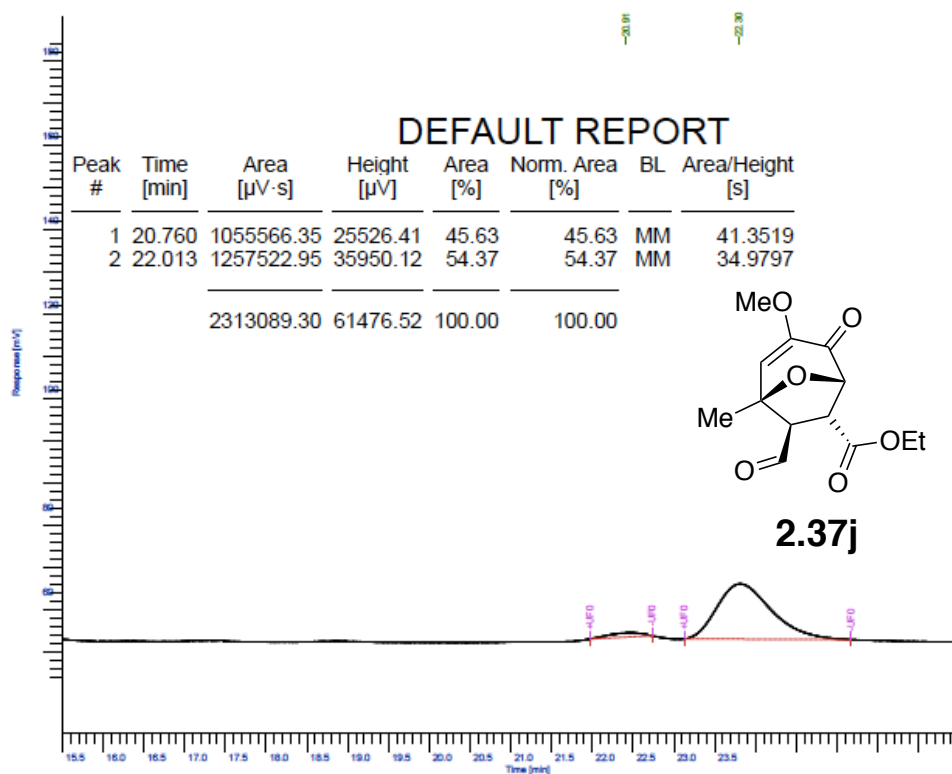


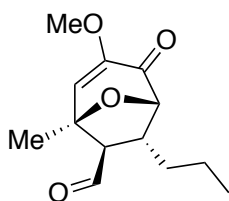
**Ethyl-7-formyl-3-methoxy-1-methyl-4-oxo-8-oxabicyclo[3.2.1]oct-2-ene-6-carboxylate (2.37j)**



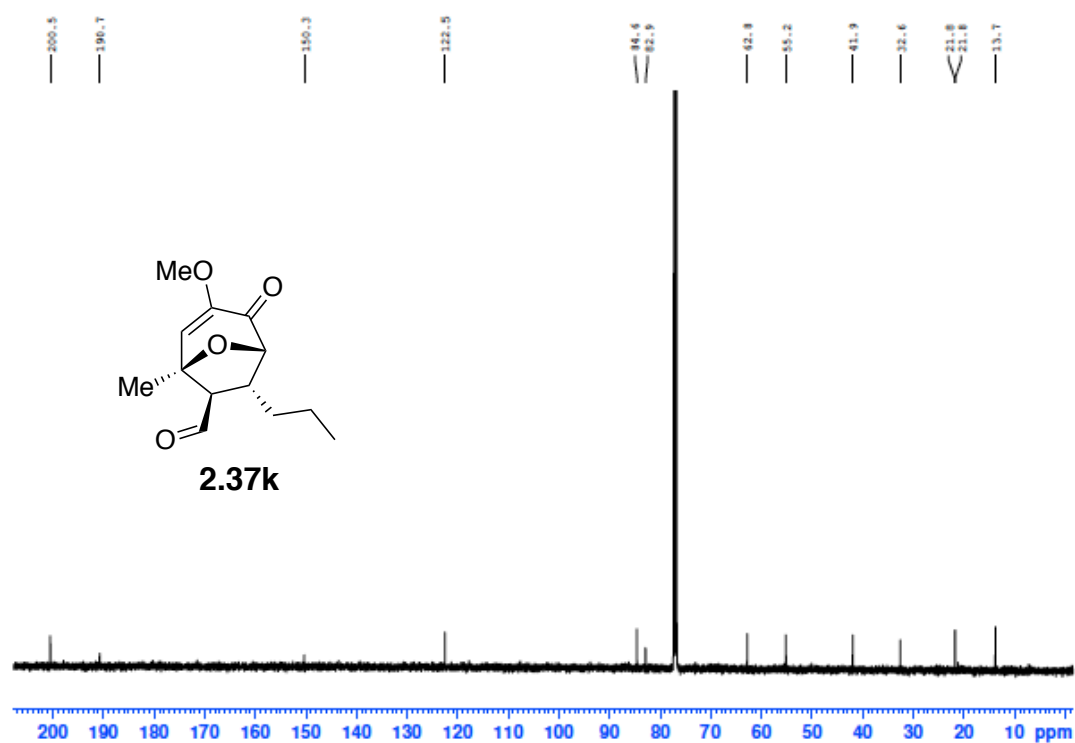
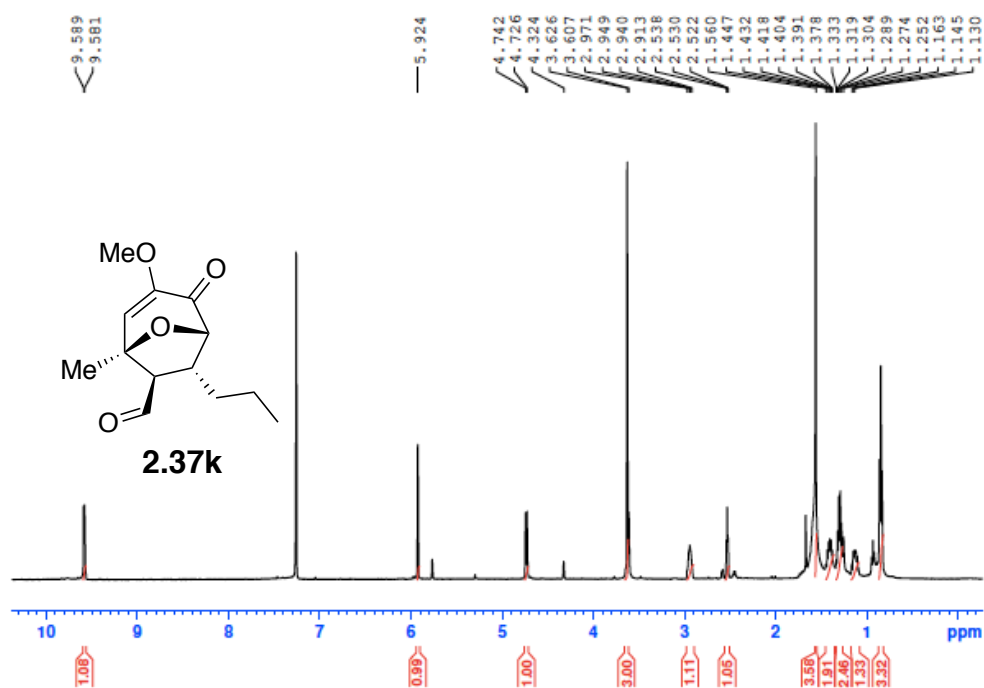
Pale yellow oil (37.3 mg, 77% yield); dr: 10:1;  $[\alpha]_{\text{D}}^{22} = -25.0$  ( $c = 0.4$  in  $\text{CH}_2\text{Cl}_2$ , 91% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.76 (d,  $J = 2.3$  Hz, 1H), 5.97 (s, 1H), 4.92 (d,  $J = 8.6$  Hz, 1H), 4.15-4.12 (m, 1H), 4.10-4.06 (m, 2H), 3.64 (s, 3H), 3.50 (t,  $J = 3.1$  Hz, 1H), 1.65 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  198.4, 188.9, 169.3, 150.5, 121.3, 84.0, 82.6, 62.2, 59.9, 55.4, 45.8, 22.2, 14.2 ppm. HPLC with an AD-H column ( $n$ -hexane/ $i$ -PrOH = 88:12 at 1.0 mL/min for 90 minutes); major enantiomer  $t_{\text{R}} = 22.30$  min, minor enantiomer  $t_{\text{R}} = 20.91$  min; HRMS (ESI)  $[\text{M}^+]$  calcd. for  $[\text{C}_{13}\text{H}_{17}\text{O}_6]$  268.0947, found 269.1033.

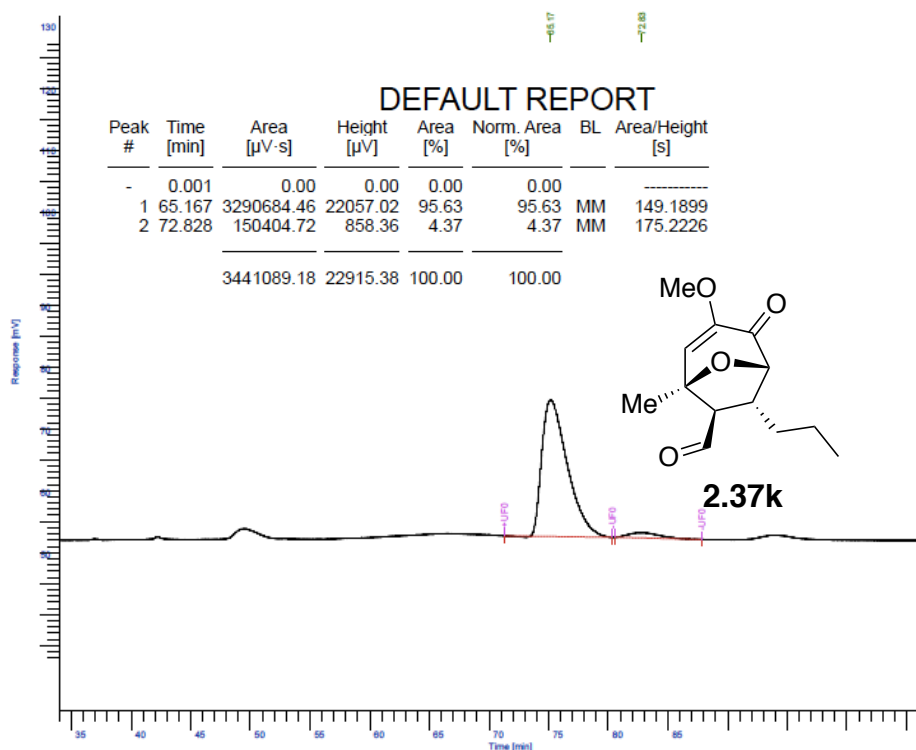
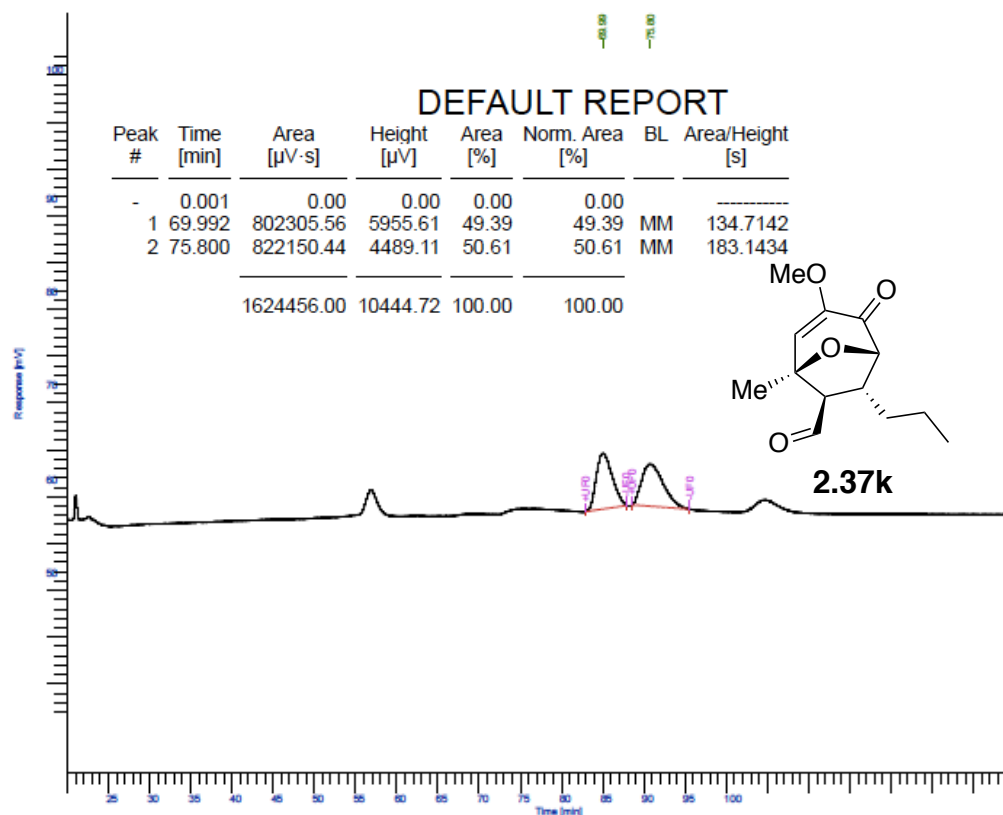




**3-methoxy-5-methyl-2-oxo-7-propyl-8-oxabicyclo[3.2.1]oct-3-ene-6-carbaldehyde****(2.37k)**

Pale yellow oil (25.4 mg, 56%), dr: 4:1;  $[\alpha]_{\text{D}}^{22} = -36.0$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ , 91% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.59 (d,  $J = 4.3$  Hz, 1H), 5.92 (s, 1H), 4.73 (d,  $J = 8.2$  Hz, 1H), 3.63 (s, 3H), 2.97–2.91 (m, 1H), 2.53 (t,  $J = 4.1$  Hz, 1H), 1.56 (s, 3H), 1.45–1.38 (m, 2H), 1.33–1.25 (m, 2H), 1.16–1.09 (m, 1H), 0.83 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.5, 190.7, 150.3, 122.5, 84.6, 82.9, 62.8, 55.2, 41.9, 32.6, 21.8, 21.8, 13.7 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH = 98:02 at 1.0 mL/min for 120 minutes); major enantiomer  $t_{\text{R}} = 65.17$  min, minor enantiomer  $t_{\text{R}} = 72.83$  min; HRMS (ESI)  $[\text{M}^+]$  calcd. for  $[\text{C}_{13}\text{H}_{18}\text{O}_4]$  238.1205, found 238.1208.





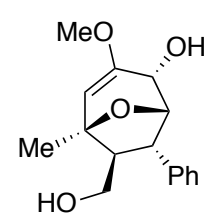
**Procedure for synthesis of protected ketone (2.64)**

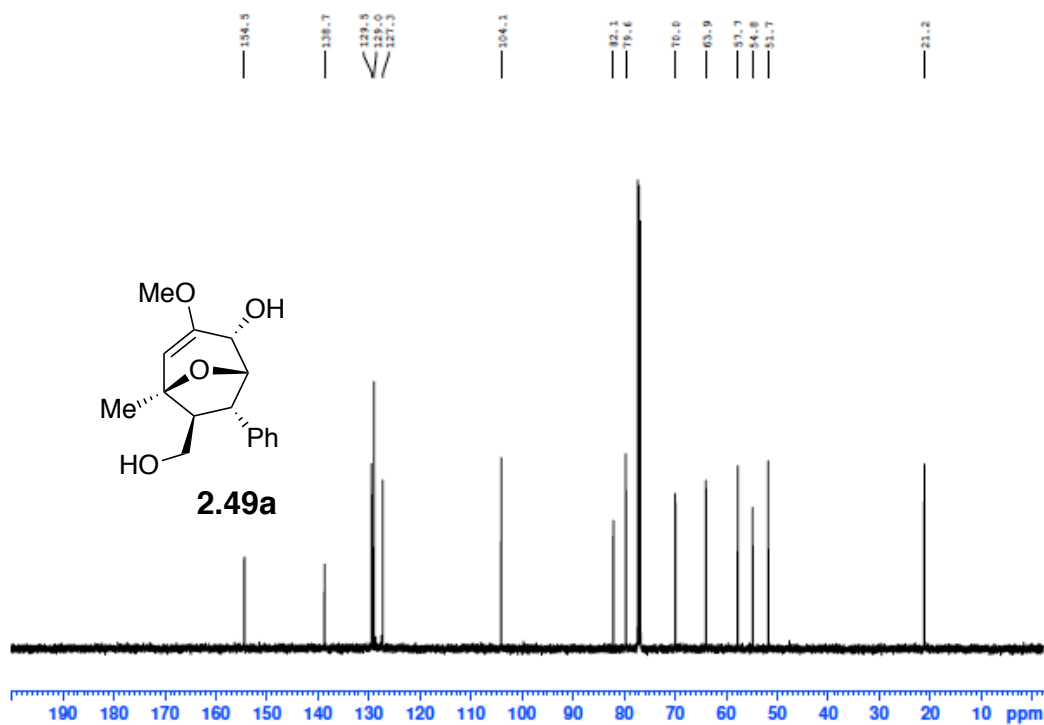
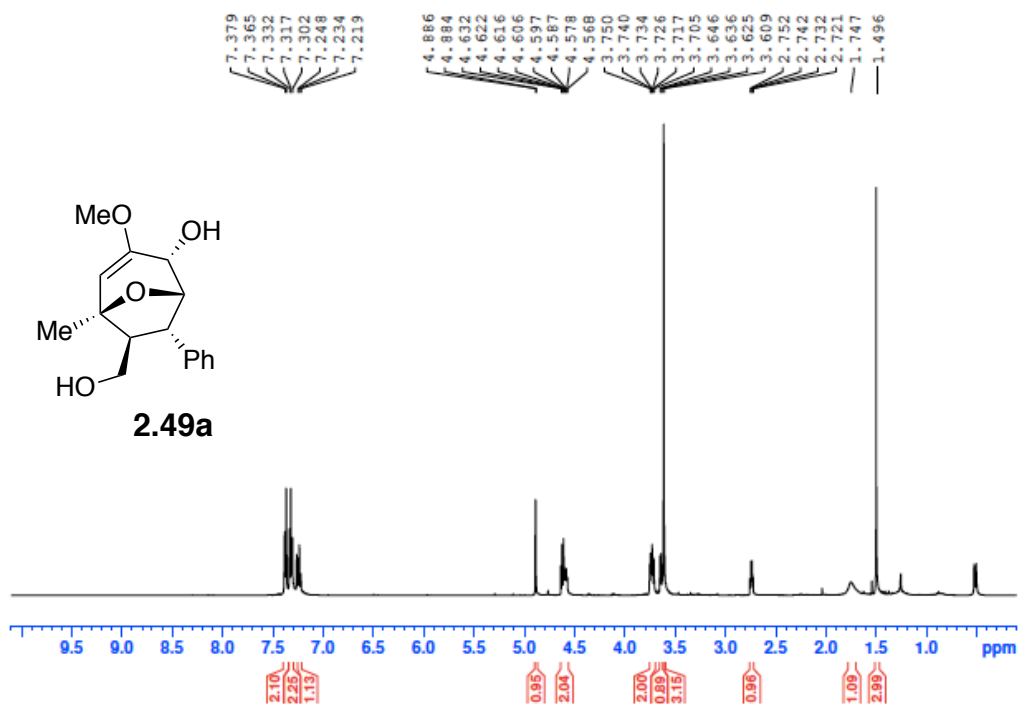


### Reduction of 2.37

To a solution of **2.37a** (99 mg, 0.36 mmol) in  $\text{CHCl}_3$  (3 mL) and MeOH (2.5 mL) in an ice bath,  $\text{NaBH}_4$  (82.5 mg, 2.18 mmol) was added in portions. The mixture was stirred at 0 °C for 30 minutes, then let warm up to rt., stirred for 30 minutes, then extracted with EtOAc (3 x 15 mL), washed with  $\text{H}_2\text{O}$  and brine, and dried over  $\text{MgSO}_4$ . The mixture was filtered and concentrated under pressure to yield the crude alcohol. The residue was purified by flash column chromatography with silica gel (20% EtOAc: P.E.) to yield compound **2.49a** as a foam (96 mg, 96% yield).

### 6-(hydroxymethyl)-3-methoxy-5-methyl-7-phenyl-8-oxabicyclo[3.2.1]oct-3-en-2-ol (2.49a)

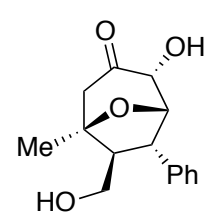
 White foam (96 mg, 96% yield);  $[\alpha]_{\text{D}}^{22} = +57.5$  ( $c = 1.8$  in  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37 (d,  $J = 7.4$  Hz, 2H), 7.32 (t,  $J = 7.6$  Hz, 2H), 7.23 (t,  $J = 7.2$  Hz, 1H), 4.88 (d,  $J = 1.0$  Hz, 1H), 4.63-4.57 (m, 2H), 3.75-3.71 (m, 2H), 3.64 (t,  $J = 5.4$  Hz, 1H), 3.61 (s, 1H), 2.74 (dd,  $J = 10.2, 5.1$  Hz, 1H), 1.75 (brs, 1H), 1.50 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.5, 138.7, 129.5, 129.0, 127.3, 104.1, 82.1, 79.6, 70.0, 63.9, 57.7, 54.8, 51.7, 21.2 ppm. HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd. for  $[\text{C}_{16}\text{H}_{20}\text{O}_4\text{Na}]$  299.1259, found 299.1253.

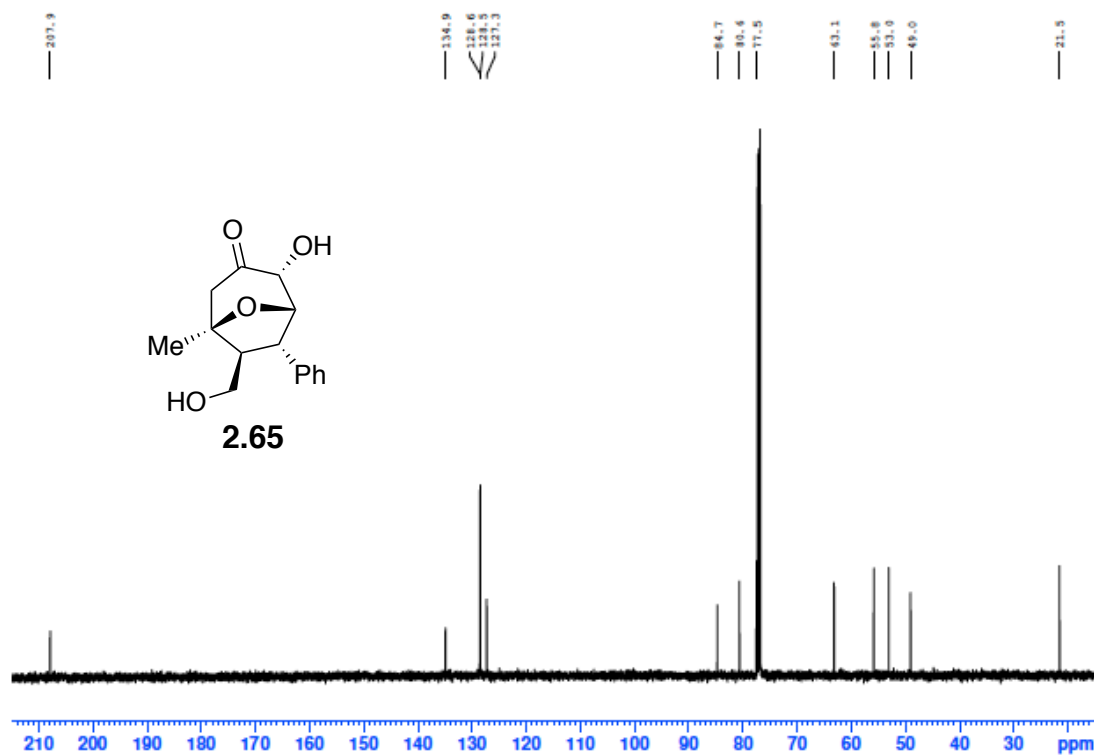
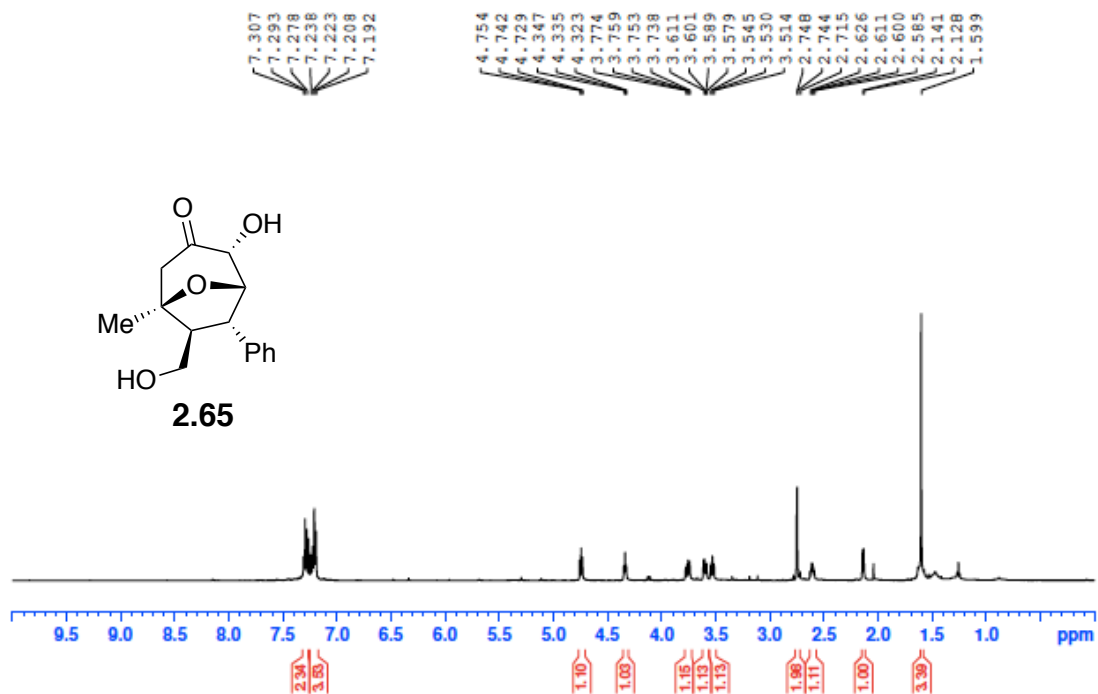


### Preparation of 2.65

Diol **2.49a** (25 mg, 0.09 mmol) was dissolved in MeOH (8 mL) and H<sub>2</sub>O (2 mL) and stirred at rt for 5 minutes. Concentrated H<sub>2</sub>SO<sub>4</sub> (1.5 mL) was added drop-wise over about five minutes. After stirring for 2.5 hours at rt, the crude mixture was extracted with EtOAc (3 x 15 mL), washed with H<sub>2</sub>O, saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, and then with brine. The collected organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> filtered and reduced under pressure. The residue was purified by flash column chromatography with silica gel (50% EtOAc: P.E.) to yield compound **2.65** (12 mg, 51% yield).

### 4-hydroxy-7-(hydroxymethyl)-1-methyl-6-phenyl-8-oxabicyclo[3.2.1]octan-3-one (2.65)

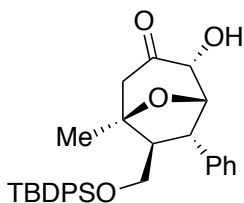
 Colorless oil (12 mg, 51% yield);  $[\alpha]_D^{22} = +13.8$  ( $c = 1.7$  in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.30 (t,  $J = 7.5$  Hz, 2H), 7.21 (t,  $J = 7.4$  Hz, 3H), 4.75 (t,  $J = 6.2$  Hz, 1H), 4.34 (t,  $J = 5.6$  Hz, 1H), 3.77 (s, 1H), 3.62 (d,  $J = 9.8$  Hz, 1H), 3.54 (t,  $J = 7.9$  Hz, 1H), 2.75 (s, 2H), 2.62 (dd,  $J = 13.4, 7.4$  Hz, 1H), 2.13 (d, 1H), 1.61 (s, 3H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  207.9, 134.9, 128.6, 128.5, 127.3, 84.7, 80.6, 77.5, 63.2, 55.8, 53.1, 49.0, 21.5 ppm. HRMS (ESI)  $[M+Na]^+$  calcd. for [C<sub>15</sub>H<sub>18</sub>O<sub>4</sub>Na] 285.1103, found 285.1097.



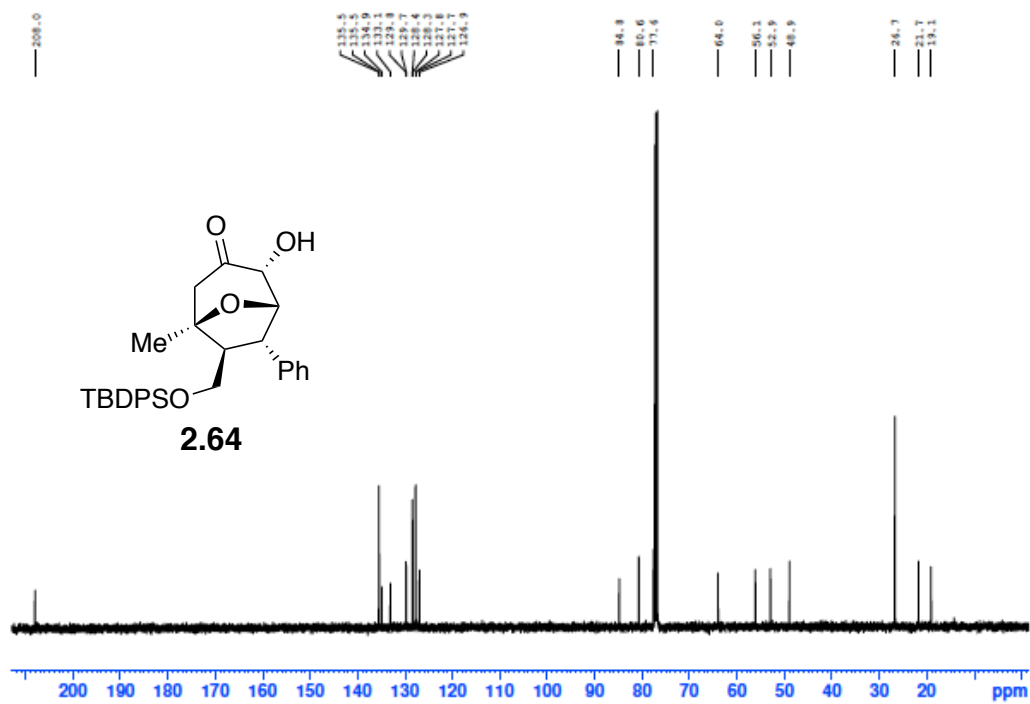
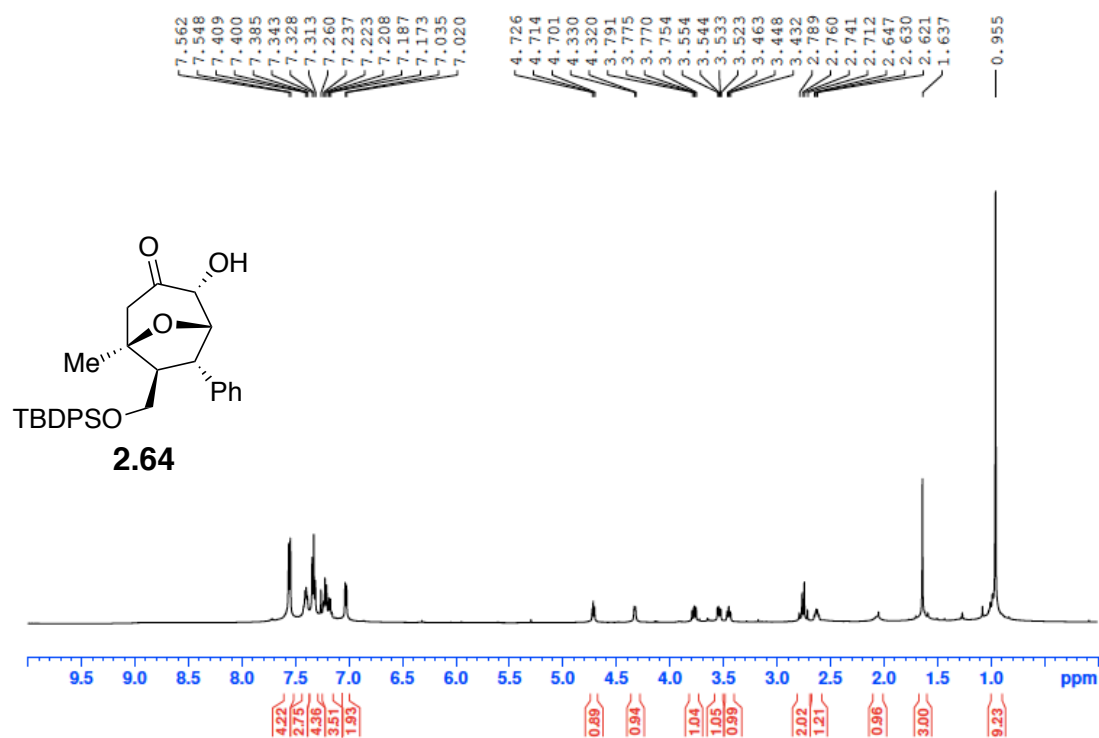
### Preparation of **2.64**

*tert*-Butylchlorodiphenylsilane (12.6 mg, 0.05 mmol) was added to a solution of **2.65** (12 mg, 0.05 mmol) and imidazole (6.2 mg, 0.09 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). The solution was stirred at rt for 30 minutes. MeOH (0.5 mL) was added, and after 10 minutes, then solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL) and washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and reduced under pressure. The residue was purified by flash column chromatography on silica gel (20% EtOAc: PE) to yield the protected ketone **2.64** (19.2 mg, 84% yield).

### 7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxy-1-methyl-6-phenyl-8-oxabicyclo[3.2.1]octan-3-one (**2.64**)



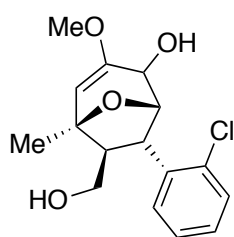
Pale yellow oil (19.2 mg, 84% yield);  $[\alpha]_D^{22} = +6.5$  ( $c = 0.3$  in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.55 (d,  $J = 6.8$  Hz, 3H), 7.42-7.39 (m, 2H), 7.33 (t,  $J = 7.4$  Hz, 4H), 7.24-7.16 (m, 4H), 7.03 (d,  $J = 7.3$  Hz, 2H), 4.71 (t,  $J = 6.2$  Hz, 1H), 3.77 (d,  $J = 10.7, 8.0$  Hz, 1H), 3.54 (dd,  $J = 10.7, 5.0$  Hz, 1H), 3.45 (t,  $J = 7.7$  Hz, 1H), 2.75 (dd,  $J = 23.9, 14.4$  Hz, 2H), 2.63 (dd,  $J = 13.3, 8.1$  Hz, 1H), 1.64 (s, 3H), 0.95 (s, 9H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  208.0, 135.5, 135.5, 134.9, 133.1, 129.8, 129.7, 128.4, 128.3, 127.8, 127.7, 126.9, 84.8, 80.6, 77.6, 64.0, 56.1, 52.9, 48.9, 26.7, 21.7, 19.1 ppm. HRMS (ESI)  $[M+Na]^+$  calcd. for [C<sub>31</sub>H<sub>36</sub>O<sub>4</sub>NaSi] 523.2281, found 523.2261.



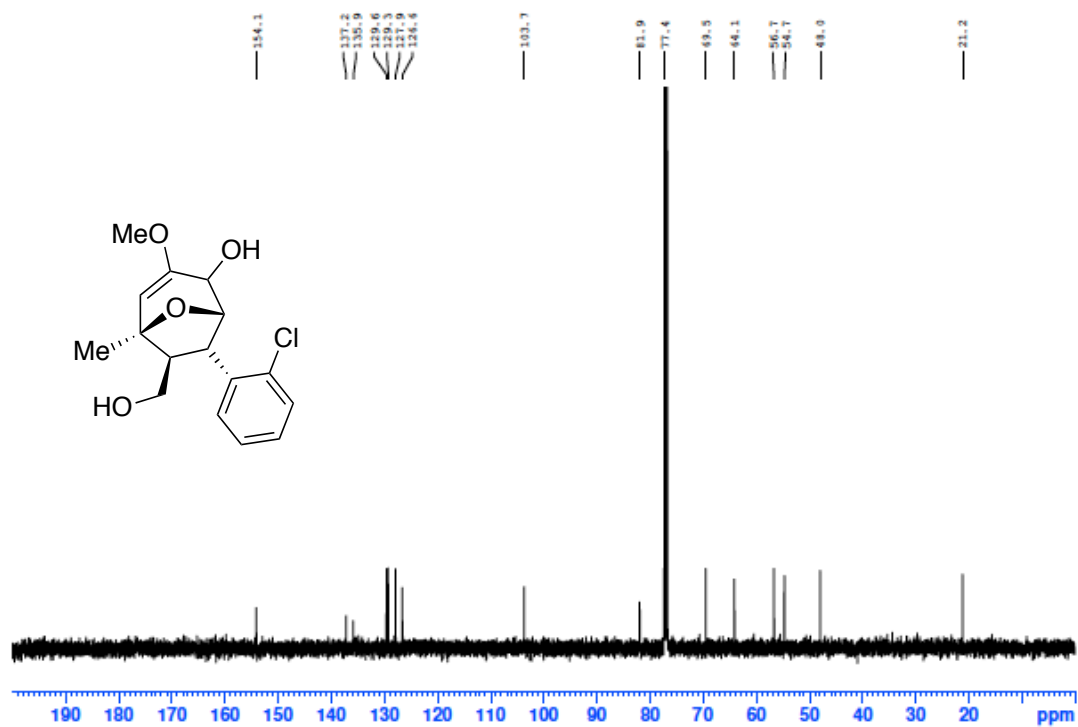
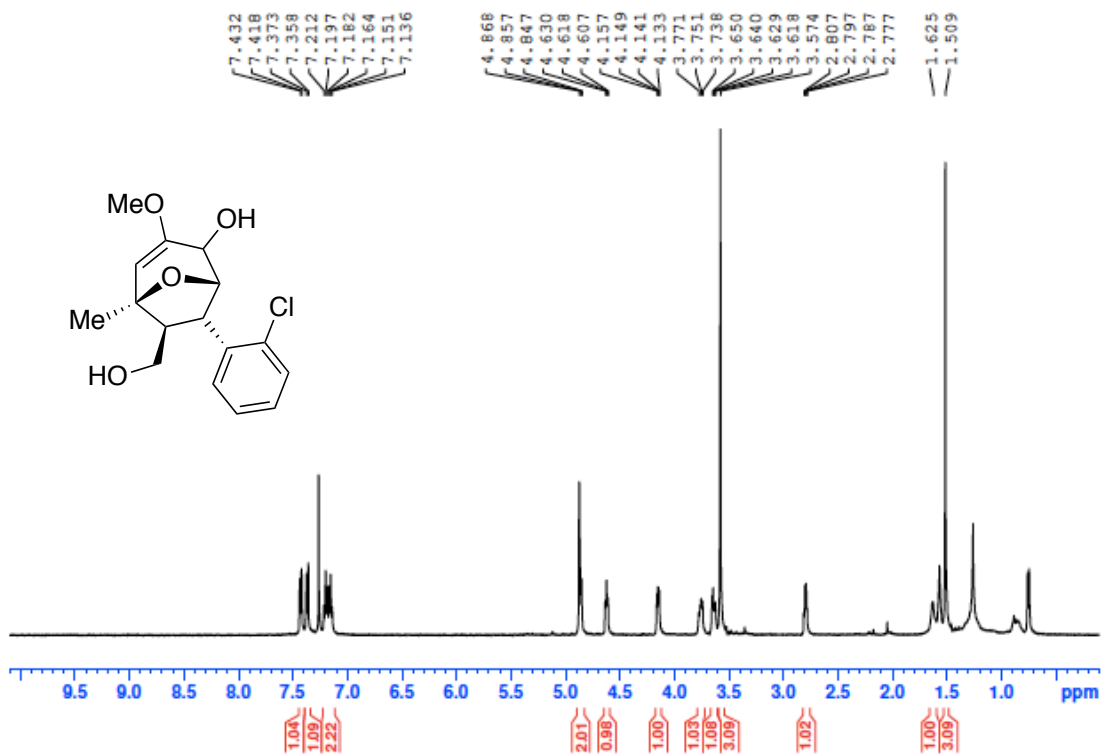
### Procedure for synthesis of diol (2.49g)

To a solution of **2.37g** (25 mg, 0.08 mmol) in  $\text{CHCl}_3$  (650  $\mu\text{L}$ ) and MeOH (500  $\mu\text{L}$ ) in an ice bath,  $\text{NaBH}_4$  (18.5 mg, 0.49 mmol) was added in portions. The mixture was stirred at 0 °C for 30 minutes, then let warm up to rt and stirred for another 30 minutes, then extracted with EtOAc (3 x 5 mL), washed with  $\text{H}_2\text{O}$  and brine, and dried over  $\text{MgSO}_4$ . The mixture was filtered and concentrated under pressure. The residue was purified by FCC with silica gel (20% EtOAc/PE) to yield compound **2.49g** as a white solid in quantitative yield.

### 7-(2-chlorophenyl)-6-(hydroxymethyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]oct-3-en-2-ol (2.49g)



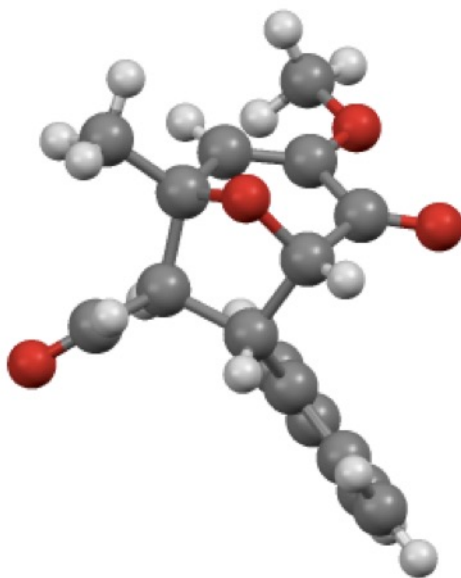
White solid (24.7 mg, 99.8% yield); m.p. 157-159 °C;  $[\alpha]_{\text{D}}^{22} = +119.9$  ( $c = 0.6$  in  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43 (d,  $J = 7.1$  Hz, 1H), 7.37 (d,  $J = 7.6$  Hz, 1H), 7.21-7.14 (m, 2H), 4.86 (t,  $J = 5.3$  Hz, 2H), 4.62 (t,  $J = 5.6$  Hz, 1H), 4.14 (dd,  $J = 7.7, 4.0$  Hz, 1H), 3.75 (t,  $J = 8.2$  Hz, 1H), 3.63 (dd,  $J = 10.6, 5.1$  Hz, 1H), 3.57 (s, 3H), 2.79 (dd,  $J = 10.1, 5.3$  Hz, 1H), 1.62 (brs, 1H), 1.51 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.1, 137.2, 135.9, 129.6, 129.3, 127.9, 126.6, 103.7, 81.9, 77.4, 69.5, 64.1, 56.7, 54.7, 48.0, 21.2 ppm. HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd. for  $[\text{C}_{16}\text{H}_{19}\text{ClO}_4\text{Na}]$  333.0870, found 333.0860.



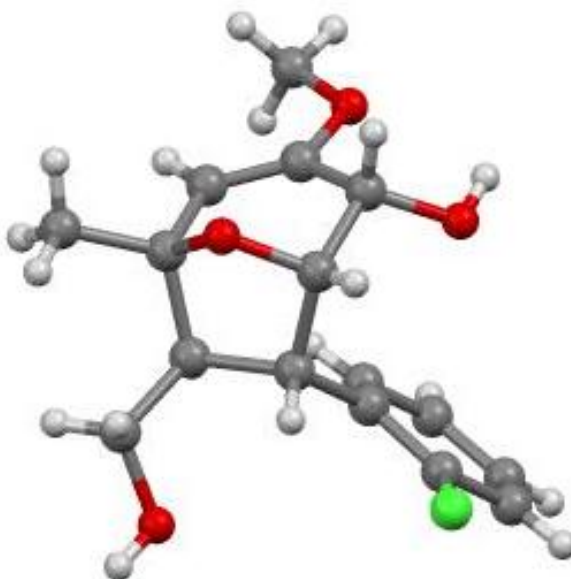


### Crystallography

The crystal structure of **2.37a** (CDC 1567374) and reduction product **2.49g** (CDC 1567375) to confirm the absolute configuration of the major isomer.



**2.37a** (CDC 1567374)

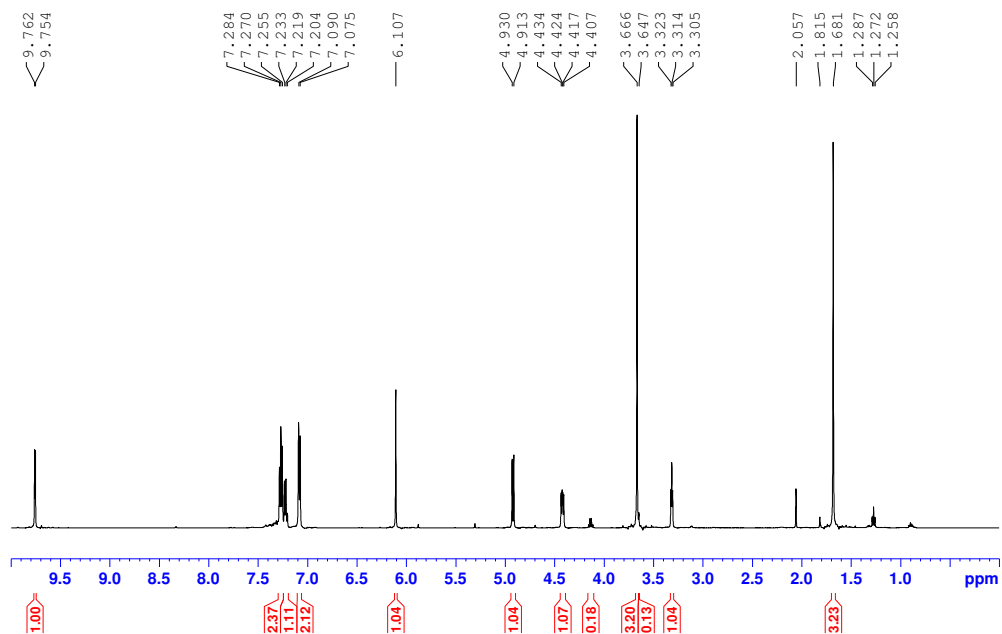


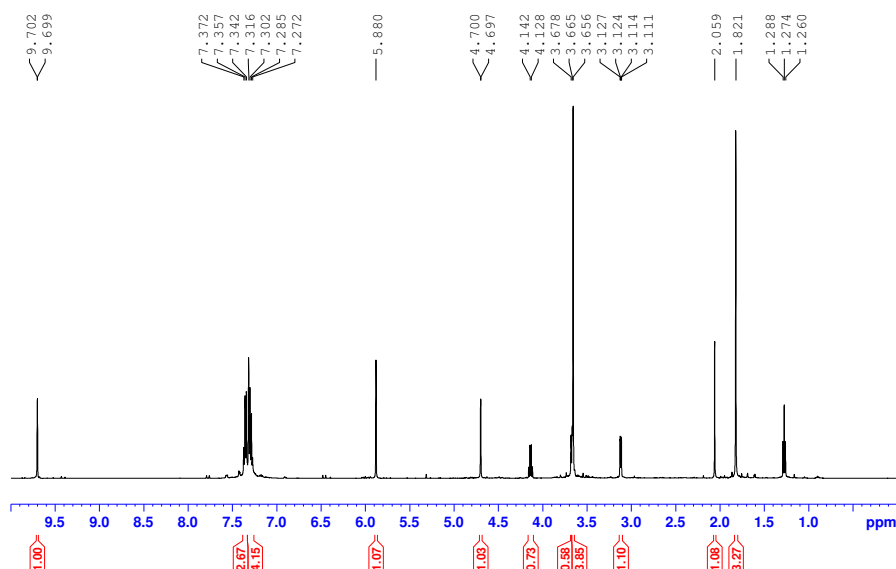
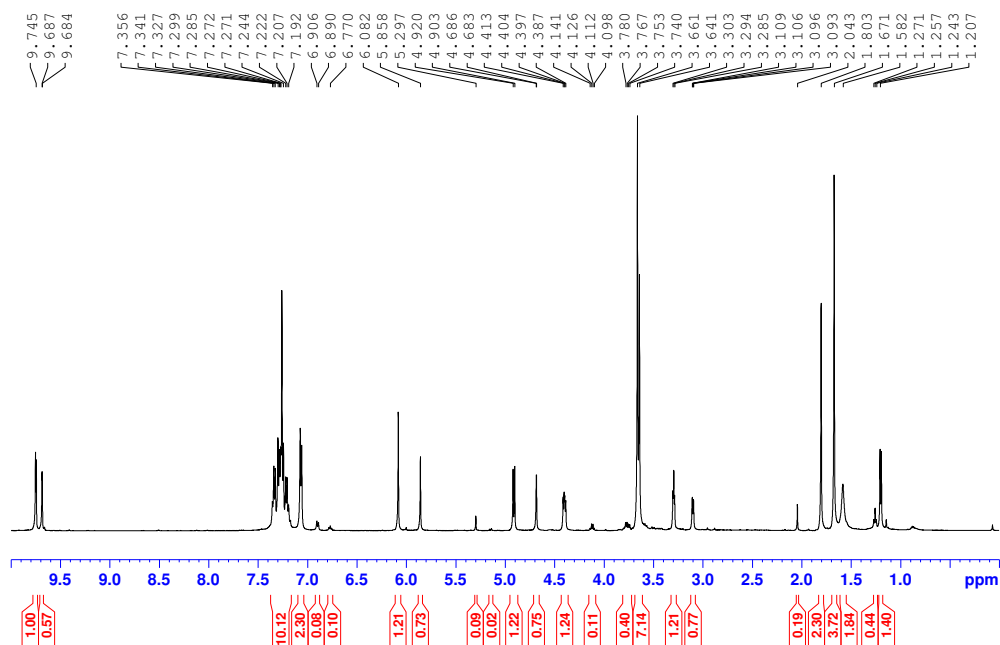
**2.49g** (CDC 1567375)

### Diastereomeric Ratio Determination

The dr was determined by using the  $^1\text{H}$  NMR integrations of the major and minor aldehyde peak after flash column chromatography. The major and minor diastereomer aldehyde peaks were distinguished by separation of the diastereomers.

Major diastereomer (**2.37a-exo**)



Minor diastomer (**2.37a-endo**)Mixture of diastereomers (**2.37a**)

### 4.3 Experimental and Characterization for Chapter 3

#### Preparation of catalysts

Catalysts **3.27b-c<sup>3</sup>** and **3.27d<sup>4-5</sup>** were prepared using known procedures and were in accordance with experimental data.

#### Preparation of thiourea **3.33**

Compound was prepared using known procedure and was in accordance with experimental data.<sup>6</sup>

#### Representative procedure for the synthesis of enals **3.8a,c-h**

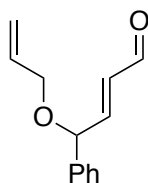
To a solution of phenylmagnesium bromide (1.0 M in THF, 27 mmol), or the corresponding arylmagnesium bromide, in THF (27 mL), was added **3.22** (3.6 g, 18 mmol) using a syringe pump over the course of one hour. The reaction was stirred for 16 hours at room temperature. The mixture was poured into a separatory funnel containing 1 M HCl (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, then neutralized with saturated aqueous NaHCO<sub>3</sub>, washed with brine, then dried over MgSO<sub>4</sub>, filtered, and evaporated *in vacuo*. The crude product **3.23** was used for the next step.

NaH (60% by weight in mineral oil, 1.5 equiv) was added portion wise to a solution of alcohol **3.23** in DMF (1 mL/mmol) under argon at 0 °C. After addition was complete, the suspension was stirred for one hour at 0 °C, then allyl bromide (1.5 equiv) was added and the reaction was warmed up to rt and stirred for two hours. The reaction was quenched with saturated NH<sub>4</sub>Cl solution, washed with brine, and extracted with EtOAc (10 mL/mmol x

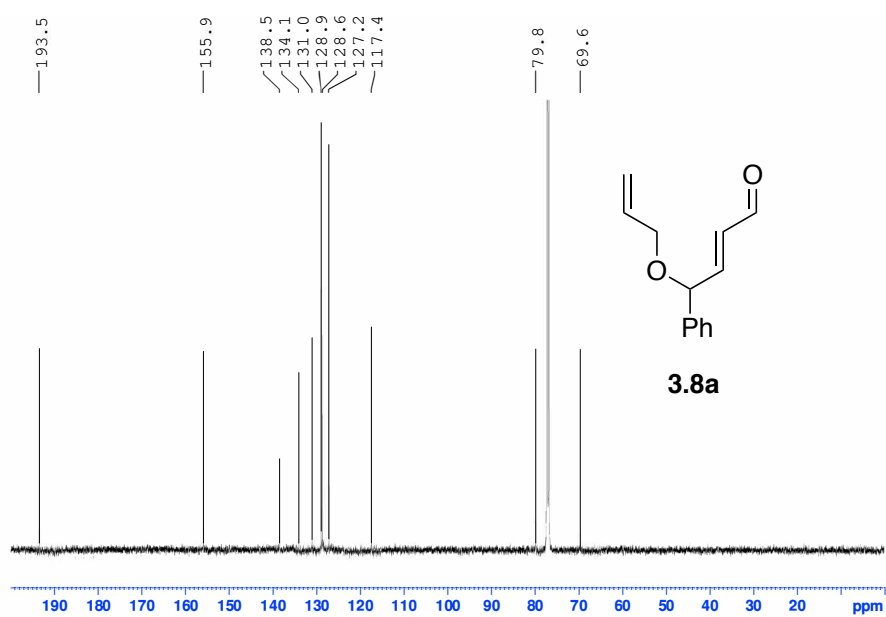
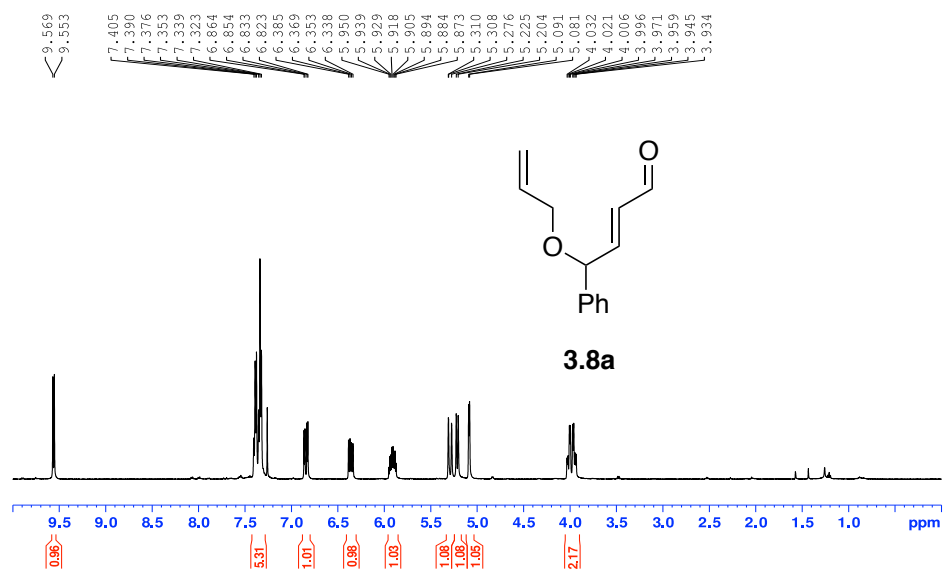
3). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* to afford the product **3.24**, which was used crude in the next step.

To a solution of **3.24** in THF (10 mL/mmol) at 0 °C under argon, was added TBAF (1.0 M solution in THF, 1.5 eq), dropwise over the course of an hour. The reaction was stirred for 16 hours, then quenched with saturated  $\text{NH}_4\text{Cl}$  solution. The mixture was extracted with EtOAc (10 mL/mmol x 3), washed with brine, and dried over  $\text{MgSO}_4$ . The crude reaction mixture was concentrated *in vacuo*. The crude mixture was chromatographed with 20% EtOAc/PE, to afford the product **3.25** (93% yield over 4 steps).

To a solution of **3.25** in  $\text{CH}_2\text{Cl}_2$  (1 mL/ 0.1 mmol), was added PCC (1.5 equiv), and 4 Å ms (equiv to mass of PCC). The reaction was stirred for two hours, then  $\text{Et}_2\text{O}$  (5 mL/mmol) was added. The reaction was filtered over florisil, then subjected to flash column chromatography with 10% EtOAc/PE to afford the product **3.8a** in 79% yield.

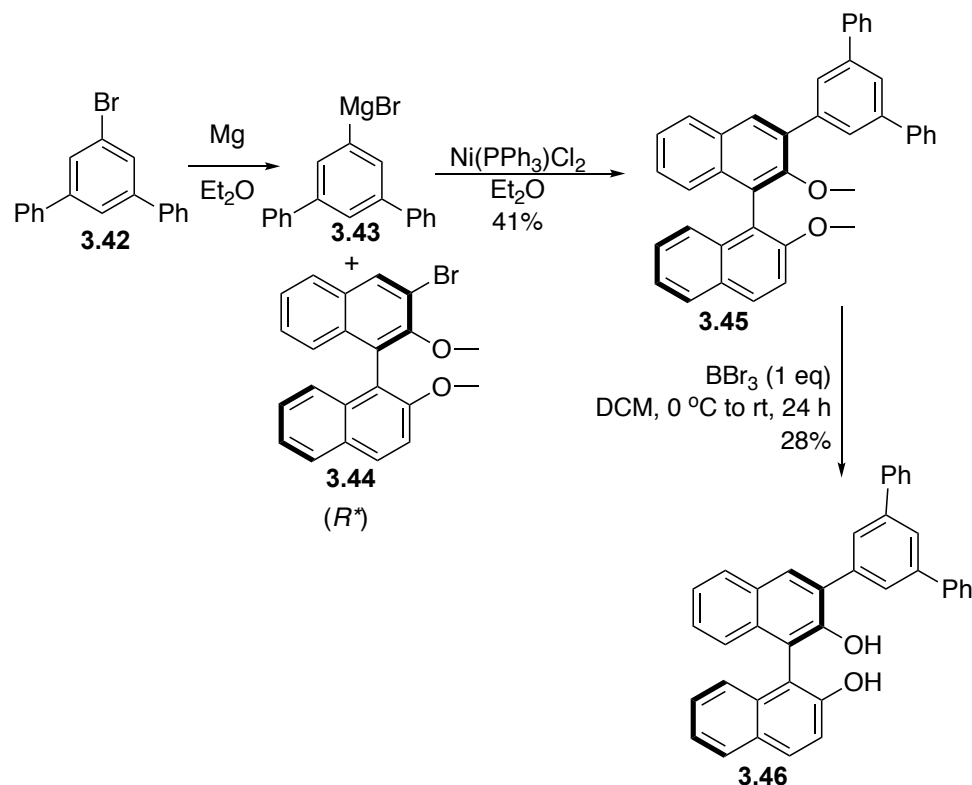
**(E)-4-(allyloxy)-4-phenylbut-2-enal (3.8a)**

Pale yellow oil (465.2 mg, 80% yield);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.56 (d,  $J = 8.0$  Hz, 1H), 7.40-7.32 (m, 5H), 6.84 (dd,  $J = 15.5, 5$  Hz, 1H), 6.36 (dd,  $J = 15.5, 8.0$  Hz, 1H), 5.95-5.87 (m, 1H), 5.29 (d,  $J = 16.0$  Hz, 1H), 5.22 (d,  $J = 10.5$  Hz, 1 H), 5.09 (d,  $J = 4.9$ , 1H), 4.03-3.93 (m, 2H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.5, 155.9, 138.5, 134.1, 131.0, 128.9, 128.6, 127.2, 117.4, 79.8, 69.6 ppm. HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{13}\text{H}_{15}\text{O}_2]$  203.1067, found 203.1072.



### Procedure for synthesis of enal (*R*)-3.8

#### Preparation of chiral catalyst 3.46 for asymmetric Grignard reaction



Dry ether (10.0 mL) was added to magnesium metal (352.9 mg, 14.52 mmol) in a 2-necked round bottom flask equipped with a reflux condenser in an argon atmosphere. Then 1-bromo-3,5-diphenylbenzene (1.73 mL, 7.26 mmol) was added dropwise. The reaction was stirred at reflux for 16 h and then cooled to room temperature.

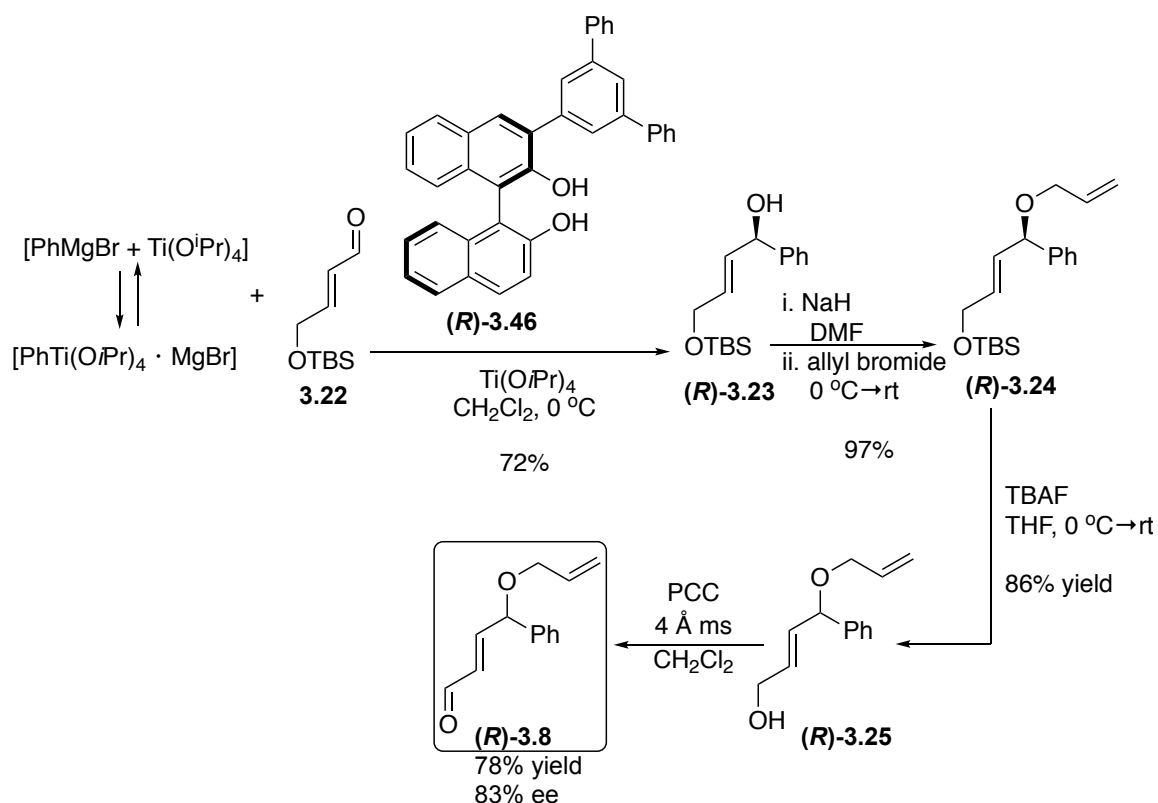
A solution of **3.43** (10 mL, 0.73 M, 0.1 equiv) was added dropwise via cannula to a suspension of Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (43.2 mg, 0.066 mmol), (*R*)-3-bromo-2,2''-dimethoxy-1,1''-binaphthyl **3.44** (260.0 mg, 0.66 mmol), and dry Et<sub>2</sub>O (10 mL) in a Schlenk flask at room temperature. The mixture was stirred at reflux for 24 hours and then cooled to room temperature and stirred for 1 h. The mixture cooled to 0 °C, quenched with an aqueous solution of HCl (2 mL, 1 M). The resulting mixture was separated, and the aqueous layer



was washed with Et<sub>2</sub>O (3 x 15 mL). The Et<sub>2</sub>O layers were combined, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to afford the product, which was purified via flash column chromatography (5% EtOAc/PE) to yield the product in 41% yield.

Dry dichloromethane (5.5 mL) and (*R*)-2,2'-bis(methoxy(methoxy))-3-(3,5-diphenylphenyl)-1,1'-binaphthyl **3.45** (0.66 mmol) were added to a Schlenk flask under argon atmosphere. The solution was cooled to 0 °C followed by a slow addition of a solution of BBr<sub>3</sub> (440 µL, 4.62 mmol, 7.0 equiv) in dichloromethane (5 mL). The resulting solution was warmed up to room temperature and stirred for 24 hours. The reaction was quenched with water (5 mL) at 0 °C. The resulting mixture was separated, and the aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to afford the product, which was subjected to flash column chromatography (EtOAc/DCM/PE, 20/30/50) to afford the (*R*)-3-(3,5-diphenylphenyl)-1,1'-bi-2-naphthol **3.46** in 28% yield and characterization agreed with literature.<sup>7</sup>

### Asymmetric Grignard reaction



To a solution of titanium tetraisopropoxide (1.2 mL, 4.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (16 mL) at  $-78^\circ\text{C}$  under argon atmosphere was added  $\text{PhMgBr}$  (1.0 M in THF, 2.2 mL, 2.2 mmol). After stirring for 15 minutes at this temperature, the resulting mixture was slowly added over a period of 2 h via syringe pump to a solution of **3.22** (400.7 mg, 2 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (8 mL), **(R)-3.46** (20.6 mg, 0.04 mmol), and titanium tetraisopropoxide (0.6 mL, 2.0 mmol) at  $0^\circ\text{C}$  under argon atmosphere. After 3.5 h, the reaction was quenched with an aqueous solution of  $\text{HCl}$  (5 mL, 1 N). The resulting mixture was separated, and the aqueous layer was washed with  $\text{CH}_2\text{Cl}_2$  (3 x 15 mL). After separation from the aqueous layer, the organic layers were combined, and stirred with a sat. aq. solution of  $\text{NaHCO}_3$  (5 mL) for 10 minutes. The layers were separated and the  $\text{CH}_2\text{Cl}_2$  layer was dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford the product which was subjected to flash column chromatography (12% EtOAc/PE) to afford **(R)-3.23** in 72% yield.

### Allylation of (*R*)-3.23

The asymmetric alcohol (*R*)-3.23 was subjected to allylation. NaH (60% by weight in mineral oil, 1.5 equiv) was added portion wise to a solution of (*R*)-3.23 (399.5 mg, 1.44 mmol) in DMF (1 mL/mmol) under argon at 0 °C. After addition was complete, the suspension was stirred for one hour at 0 °C, then allyl bromide (1.5 equiv) was added and the reaction was warmed up to rt and stirred for two hours. The reaction was quenched with saturated NH<sub>4</sub>Cl solution, washed with brine, and extracted with EtOAc (10 mL/mmol x 3). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to afford the product (*R*)-3.24 that was used crude in the next step.

### Deprotection of (*R*)-3.24

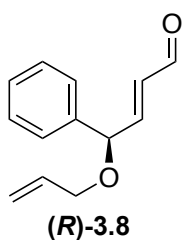
To a solution of (*R*)-3.24 (445.1 mg, 1.4 mmol) in THF (10 mL/mmol) at 0 °C under argon, was added TBAF (1.0 M in THF, 2.1 mL, 1.5 equiv) dropwise over the course of an hour. The reaction was stirred for 16 hours, then quenched with saturated NH<sub>4</sub>Cl solution. The mixture was extracted with EtOAc (3 x 10 mL/mmol), washed with brine, and dried over MgSO<sub>4</sub>. The crude reaction mixture was concentrated *in vacuo*. The crude mixture was chromatographed with 25-30% EtOAc/PE, to afford the product (*R*)-3.25 (86% yield over 2 steps).

### Oxidation of (*R*)-3.25 to form enal (*R*)-3.8

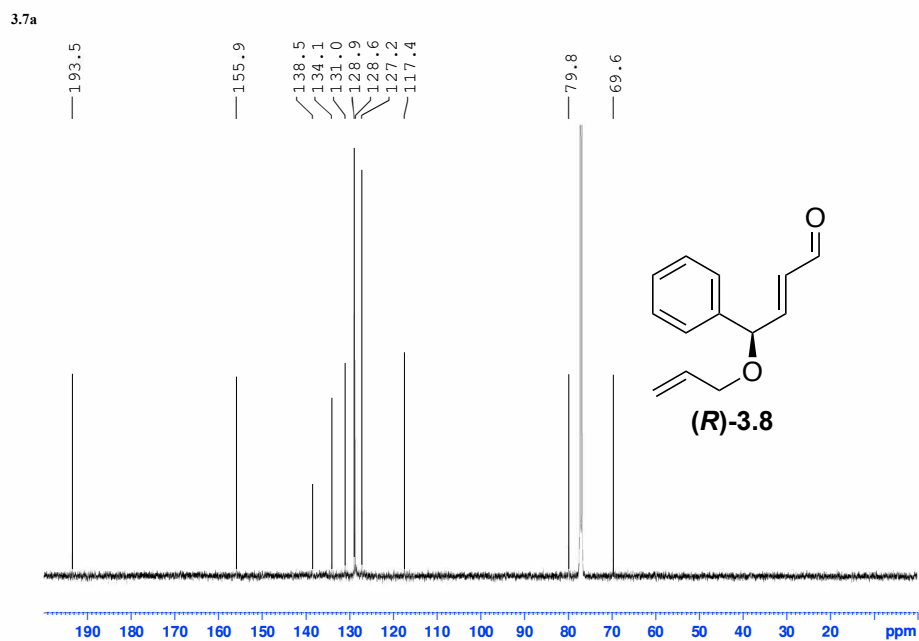
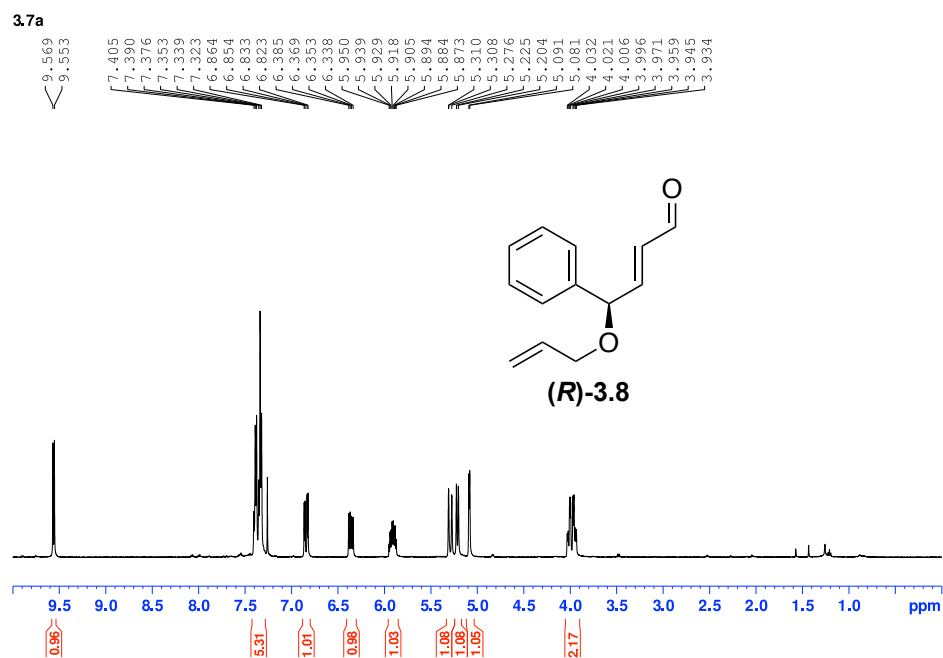
To a solution of (*R*)-3.25 (248.2 mg, 1.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6.2 mmol), was added PCC (392 mg, 1.8 mmol), and 4 Å ms (392 mg). The reaction was stirred for two hours, then Et<sub>2</sub>O (5 mL/mmol) was added. The reaction was filtered over florisil, then subjected to

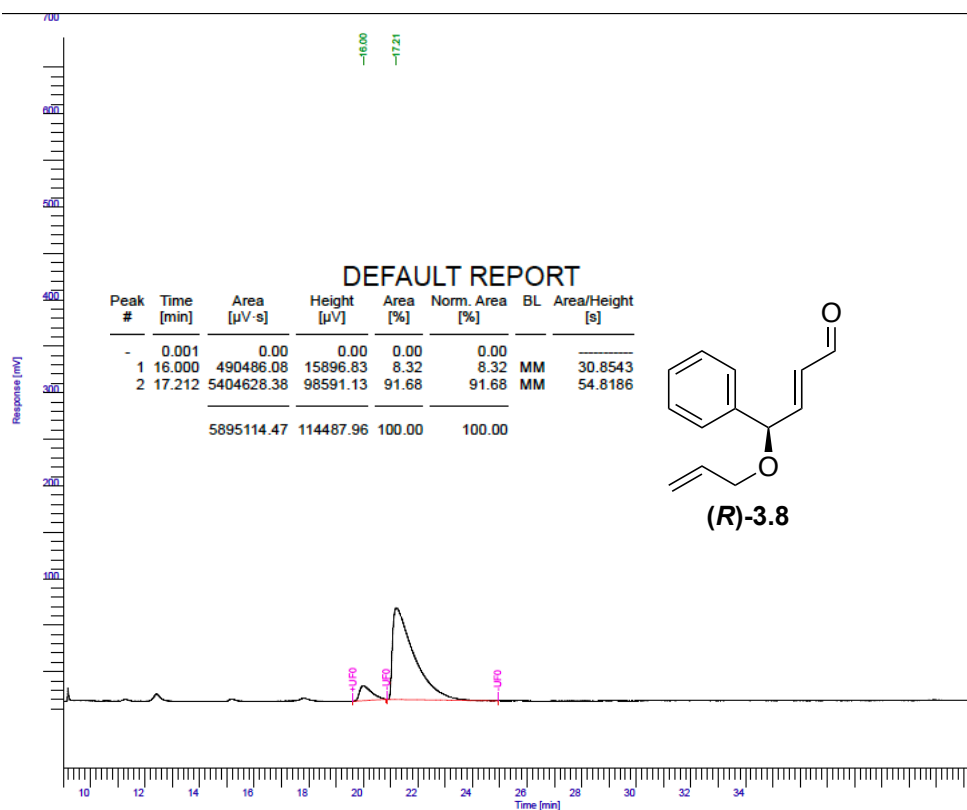
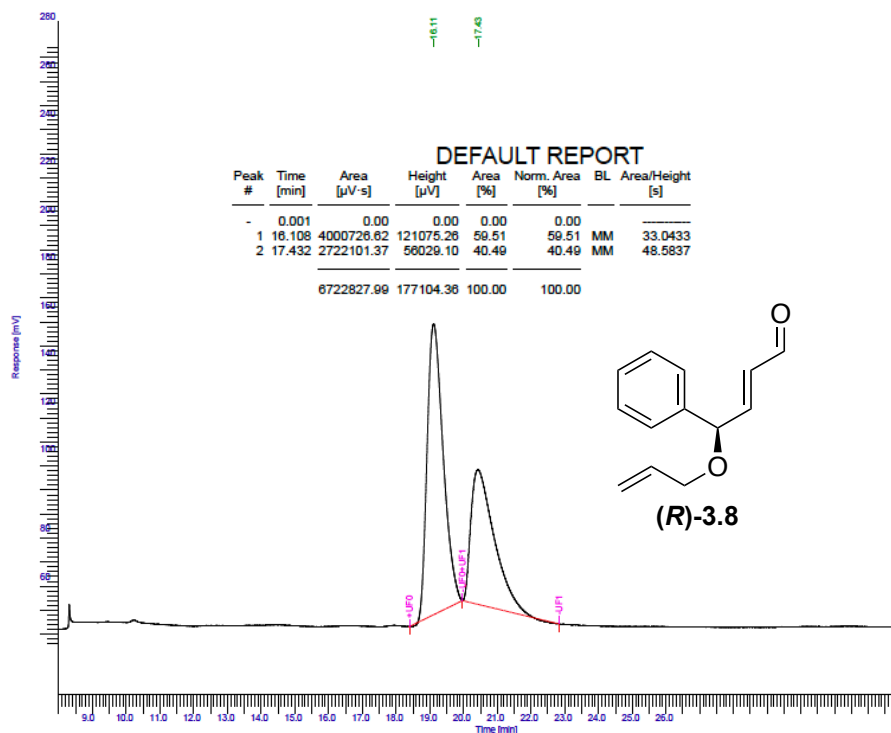
flash column chromatography with 10% EtOAc/PE to afford the product (**R**)-**3.8** in 79% yield with 83% ee.

**(R)-4-(allyloxy)-4-phenylbut-2-enal (R)-3.8**



Pale yellow oil (189.93 mg, 78% yield);  $[\alpha]_D^{22} = -73.09$  ( $c = 1.0$  in  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.56 (d,  $J = 8.0$  Hz, 1H), 7.40-7.32 (m, 5H), 6.84 (dd,  $J = 15.5, 5$  Hz, 1H), 6.36 (dd,  $J = 15.5, 8.0$  Hz, 1H), 5.95-5.87 (m, 1H), 5.29 (d,  $J = 16.0$  Hz, 1H), 5.22 (d,  $J = 10.5$  Hz, 1H), 5.09 (d,  $J = 4.9$ , 1H), 4.03-3.93 (m, 2H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.5, 155.9, 138.5, 134.1, 131.0, 128.9, 128.6, 127.2, 117.4, 79.8, 69.6 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH = 99:1 at 1.0 mL/min for 40 minutes); major enantiomer  $t_R = 17.21$  min, minor enantiomer  $t_R = 16.00$  min; HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{13}\text{H}_{15}\text{O}_2]$  203.1067, found 203.1072.





### Preparation of enal 3.8b

Ring-opening of 1,2-epoxycyclopentane **3.49** was done using known a procedure to afford a mixture of the *cis* and *trans* **3.50**.<sup>8</sup> PCC oxidation to generate **3.51** was performed using literature conditions, characterization was in accordance with the data.<sup>9</sup>

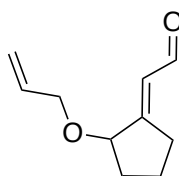
To a suspension of NaH (60% by weight in mineral oil, 143 mg, 3.58 mmol, washed with hexane) in THF (19 mL) was added at 0 °C under Ar-butyl (diethoxyphosphoryl)acetate (846 µL, 3.60 mmol) over 40 min. To the colorless solution was added a solution of **3.51** (500 mg, 3.57 mmol) in THF (5 mL). After 1 h at room temperature, the solvent was evaporated, and the residual gel was diluted EtOAc. The mixture was washed with water, brine and the organic layer was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and then evaporated. The ester **3.52** (802 mg, 94%, 1:1 inseparable diastereoisomeric mixture) was collected and used in the next step.

To a solution of **3.52** (417 mg, 1.75 mmol) toluene (20 mL) at -78 °C was added DIBAL-H (1 M in hexane, 7 mL, 7.0 mmol). The reaction was stirred at -78 °C for 1 h and then for 1 h at rt. The reaction was quenched with saturated NH<sub>4</sub>Cl solution at 0 °C The mixture was extracted with EtOAc, washed with 2 N HCl, water, and brine. The collected organic layers were dried over MgSO<sub>4</sub>, filtered, and evaporated. The crude oil was purified via column chromatography with EtOAc/PE (10-15%) and TLC analysis was done using EtOAc/PE (15%) as eluent then stained in aq. KMnO<sub>4</sub>. The *trans* alcohol **3.53** (151 mg, 0.89 mmol, 51% yield, 0.12 R<sub>f</sub>), *cis* alcohol **3.53** (64.0 mg 0.59 mmol, 34% yield, 0.2 R<sub>f</sub>), and aldehyde **3.8b** (43.0 mg, 0.26 mmol, 15%, 0.6 R<sub>f</sub>, 4:1 dr, visible by UV light).

To a solution of PCC (227.0 mg, 1.05 mmol) and 4 Å ms (226 mg) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (9 mL) was added *trans* alcohol **3.53** (117 mg, 91.0 mg). The reaction was stirred for 2 h,

then filtered over a plug of florisil, eluting with Et<sub>2</sub>O. Product **3.8b** (98 mg, 84% yield) was collected from the crude oil by column chromatography using EtOAc/PE (10%).

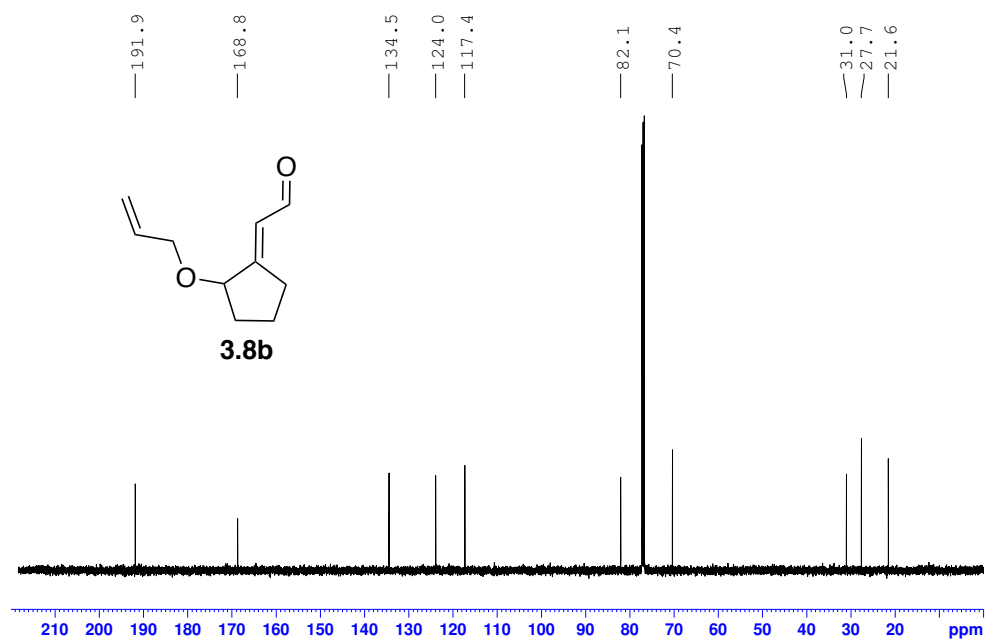
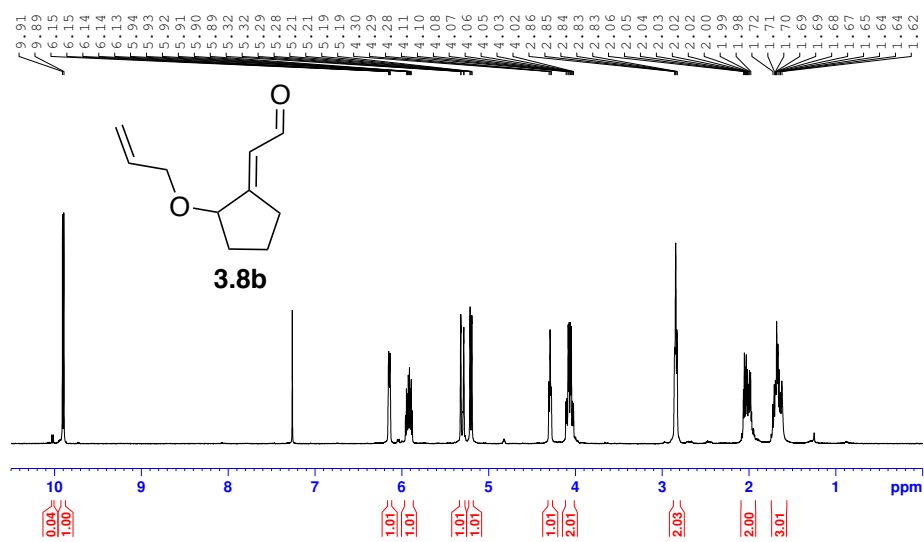
**(*E*)-2-(2-(allyloxy)cyclopentylidene)acetaldehyde (3.8b)**

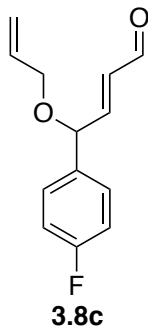


**3.8b**

Colorless oil (98 mg, 84% yield); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 9.90 (d, *J* = 10 Hz, 1H), 6.14 (dd, *J* = 7.7, 1.7 Hz, 1H), 5.91 (ddd, *J* = 15.9, 10.5, 5.3 Hz, 1H), 5.30 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 1H), 4.11–4.02 (m, 2H), 2.86–2.83 (m, 2H), 2.08–1.95 (m, 2H), 1.74–1.62 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 191.9, 168.8, 134.5, 124.0, 117.4, 82.1, 70.4, 31.0, 27.7, 21.6 ppm. HRMS (ESI) [M+H]<sup>+</sup> calcd. for [C<sub>10</sub>H<sub>15</sub>O<sub>2</sub>] 167.1072, found 167.1075.

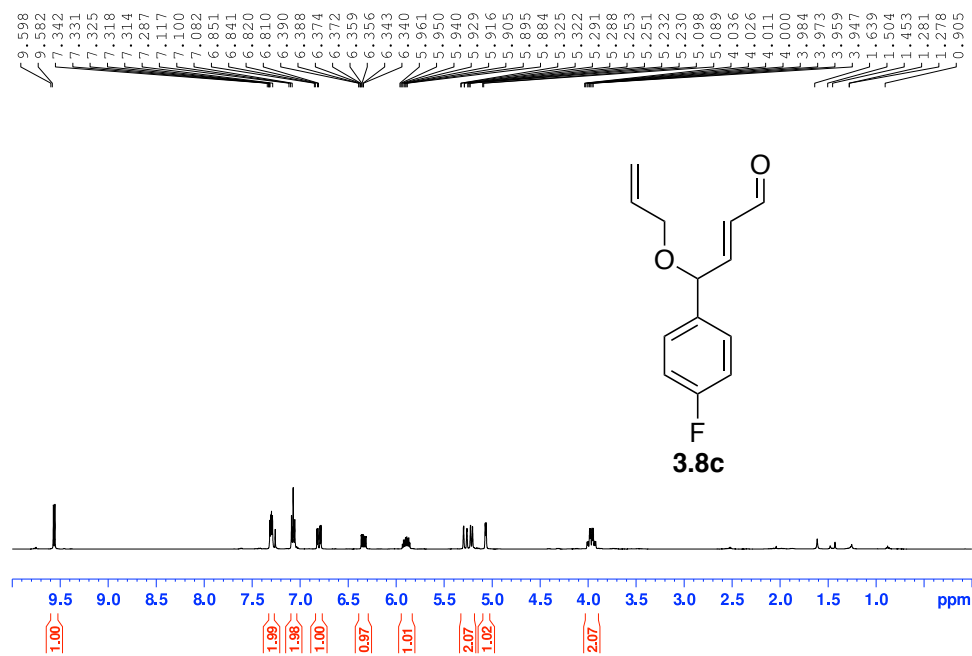




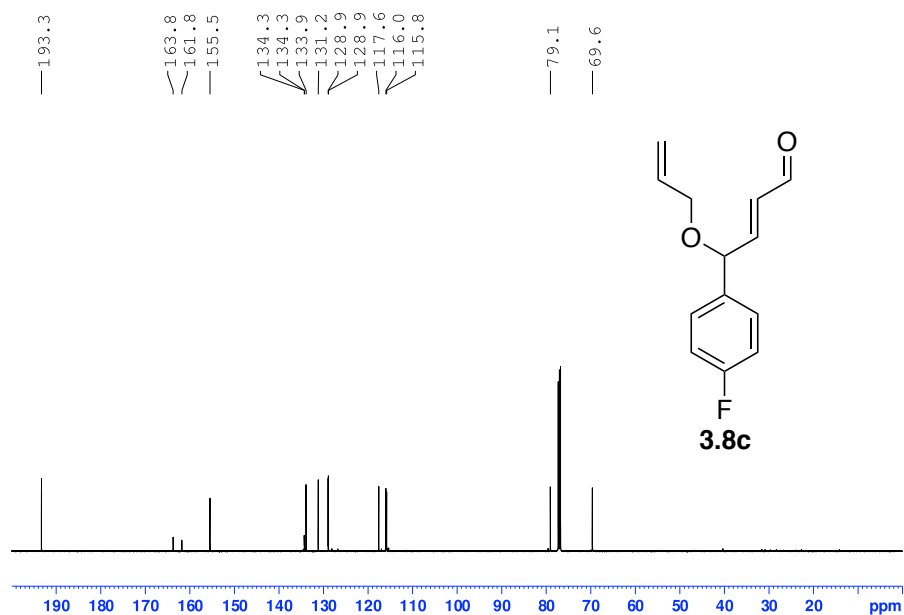
**(E)-4-(allyloxy)-4-(4-fluorophenyl)but-2-enal (3.8c)**

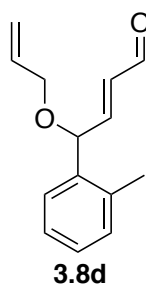
Colorless oil. Collected in 38% yield over 4 steps.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.59 (d,  $J = 1.5$  Hz, 1H), 7.34–7.29 (t,  $J = 5.3$  Hz, 2H), 7.10 (t,  $J = 8.2$  Hz, 2H), 6.83 (dd,  $J = 15.7, 4.6$  Hz, 1H), 6.37 (dd,  $J = 15.6, 7.8$  Hz, 1H), 5.95–5.89 (m, 1H), 5.30 (d,  $J = 17.1$  Hz, 1H), 5.24 (d,  $J = 10.4$  Hz, 1H), 5.09 (d,  $J = 4.0$  Hz, 1H), 4.02–3.96 (m, 2H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.4, 155.5, 134.2, 133.9, 131.2, 129.0, 128.9, 128.4, 117.6, 116.0, 115.8, 79.1, 69.6 ppm. HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{13}\text{H}_{14}\text{FO}_2]$  221.0978 for, found 221.0974.

3.8c

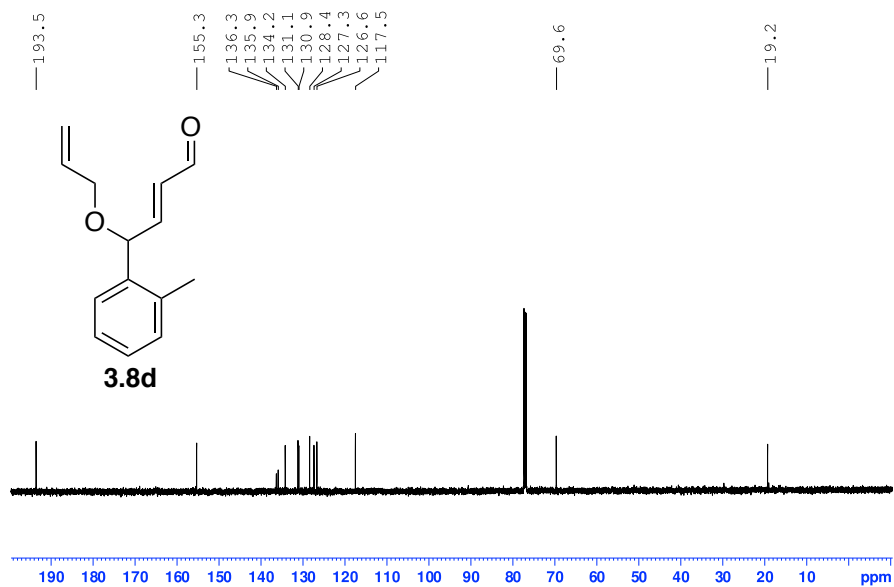
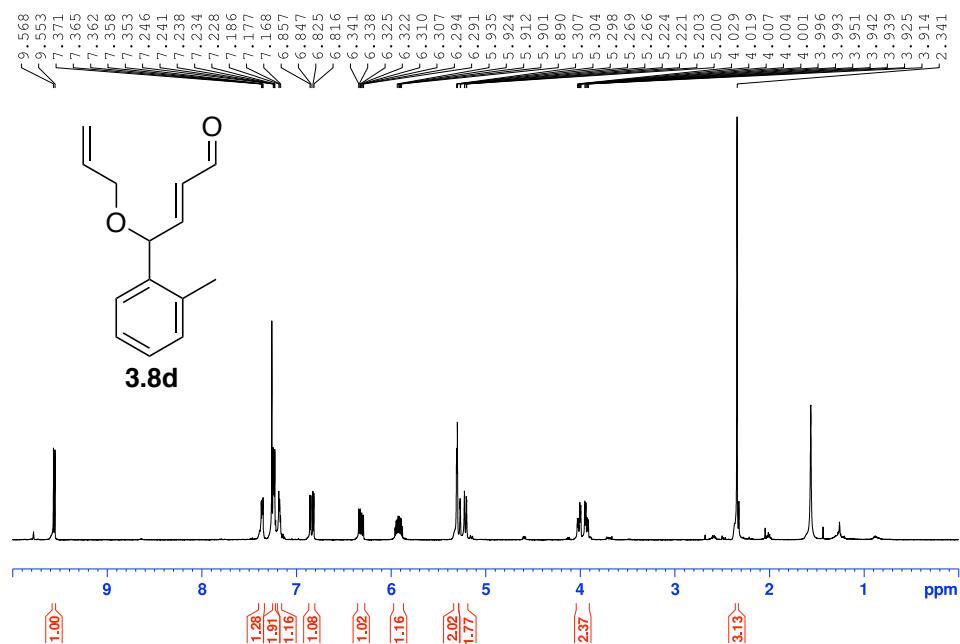


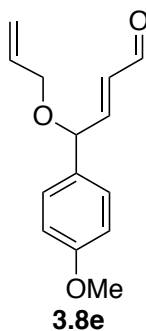
3.8c



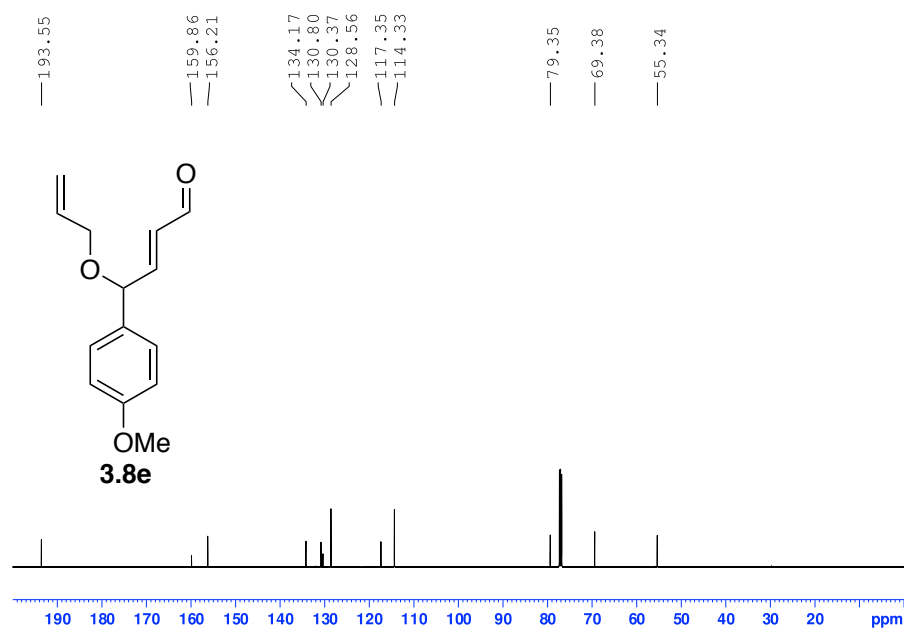
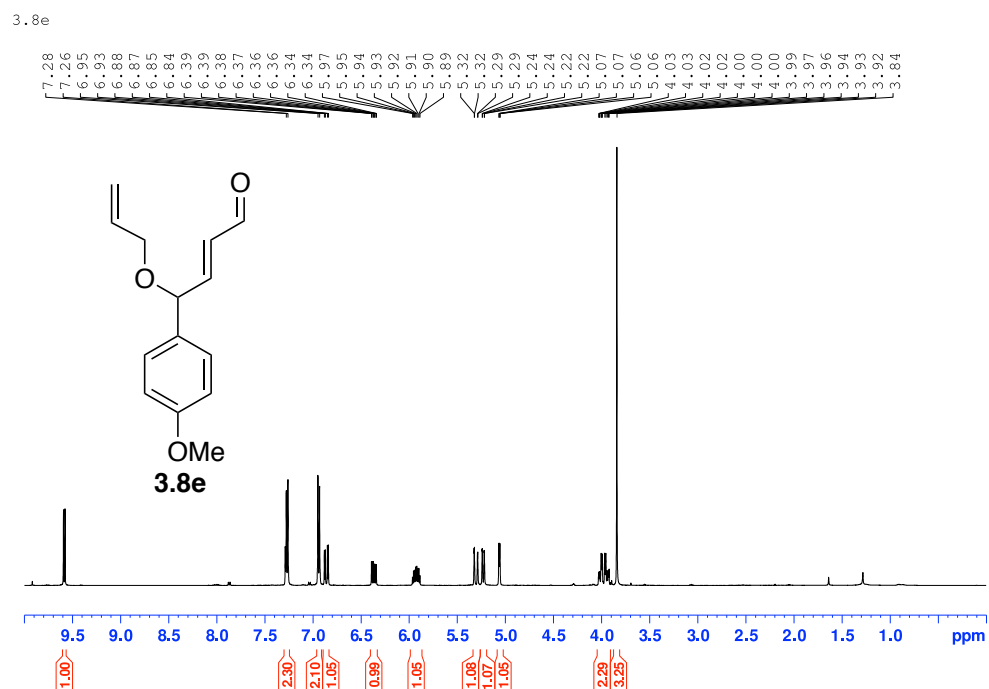
**(*E*)-4-(allyloxy)-4-(*o*-tolyl)but-2-enal (3.8d)**

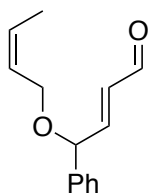
Pale yellow oil. Collected in 23% yield over 4 steps.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.56 (d,  $J = 7.9$  Hz, 1H), 7.37–7.35 (m, 1H), 7.24–7.23 (m, 2H), 7.19–7.17 (m, 1H), 6.84 (dd,  $J = 15.7, 4.9$  Hz, 1H), 6.33 (ddd,  $J = 15, 7.9, 1.5$  Hz, 1H), 5.96–5.88 (m, 1H), 5.31–5.26 (m, 2H), 5.21 (dd,  $J = 11.8, 9.1$  Hz, 1H), 4.03–3.91 (m, 2H), 2.34 (s, 3H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.5, 155.3, 136.3, 135.9, 134.2, 131.1, 130.9, 128.4, 127.3, 126.6, 117.5, 69.6, 19.3 ppm. HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{14}\text{H}_{17}\text{O}_2]$  217.1229, found 217.1222.



**(E)-4-(allyloxy)-4-(4-methoxyphenyl)but-2-enal (3.8e)**

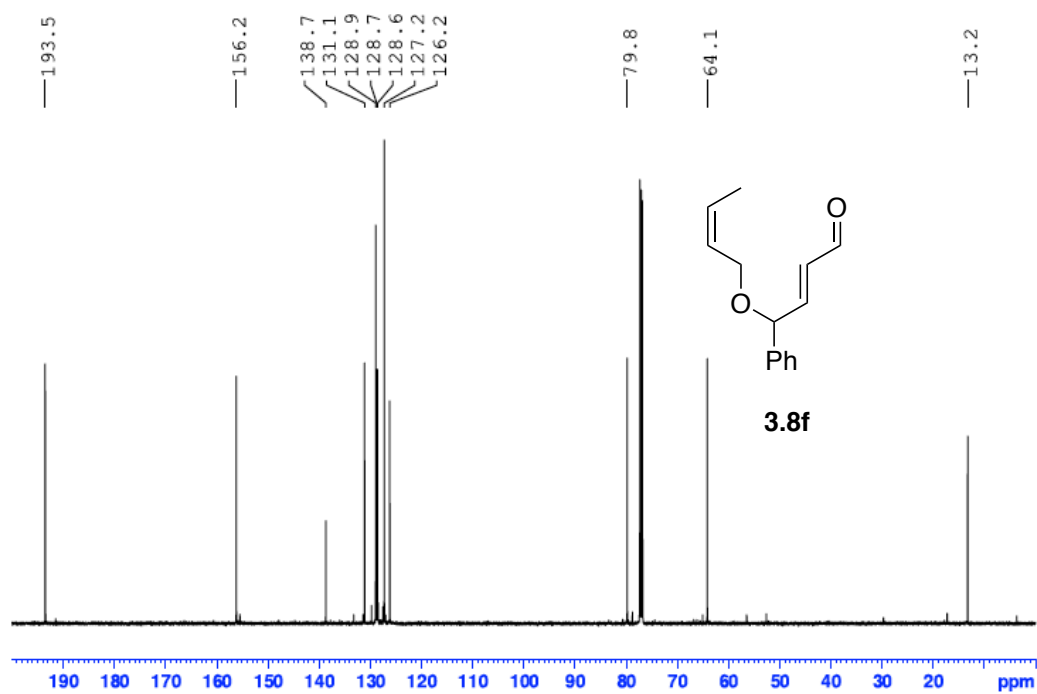
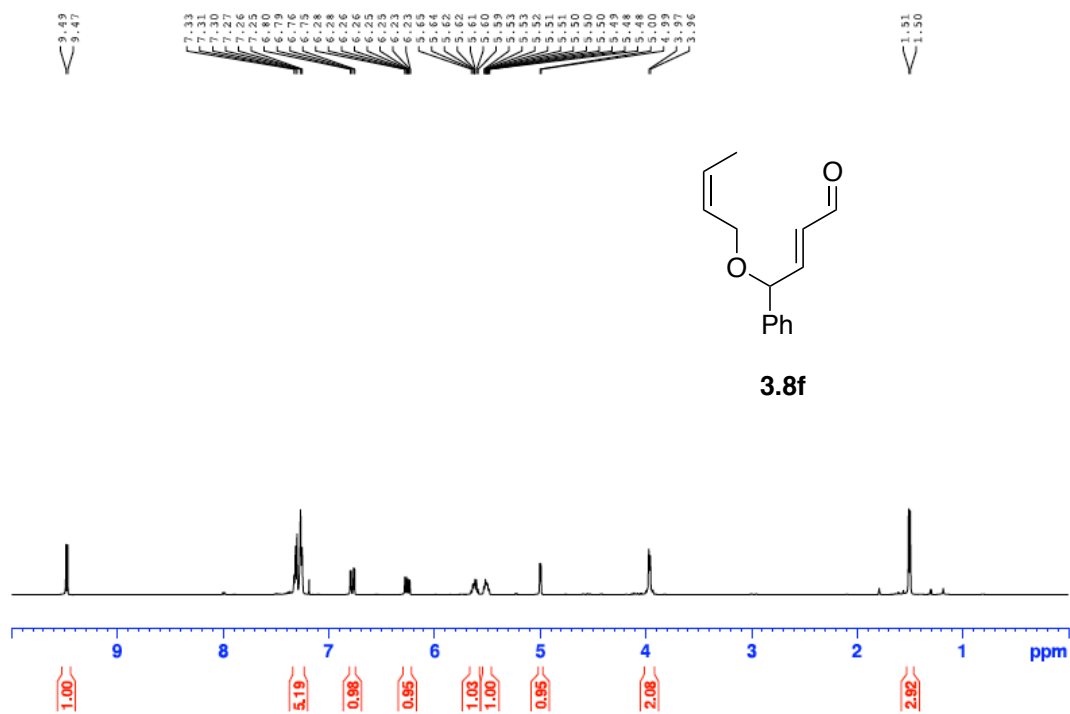
Pale yellow oil. Collected in 33% yield over 4 steps.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.56 (d,  $J = 7.9$  Hz, 1H), 7.25 (t,  $J = 7.0$  Hz, 2H), 6.91 (d,  $J = 8.7$  Hz, 2H), 6.83 (dd,  $J = 15.7, 5.1$  Hz, 1H), 6.34 (m, 1H), 5.90 (m, 1H), 5.28 (dd,  $J = 17.2, 1.6$  Hz, 1H), 5.20 (dd,  $J = 10.4, 1.3$  Hz, 1H), 5.03 (dd,  $J = 5.8, 4.1$  Hz, 1H), 3.95 (m, 2H), 3.81 (s, 3H) ppm.  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.5, 190.8, 159.9, 156.2, 134.2, 132.0, 130.8, 130.4, 128.6, 117.3, 114.3, 79.4, 77.3, 77.0, 76.8, 69.4, 55.6, 55.3 ppm. HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd. for  $[\text{C}_{14}\text{H}_{16}\text{O}_3\text{Na}]$  255.0997, found 255.0997

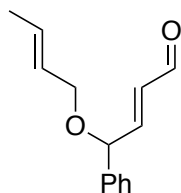


**(*E*)-4-(((*Z*)-but-2-en-1-yl)oxy)-4-phenylbut-2-enal (3.8f)****3.8f**

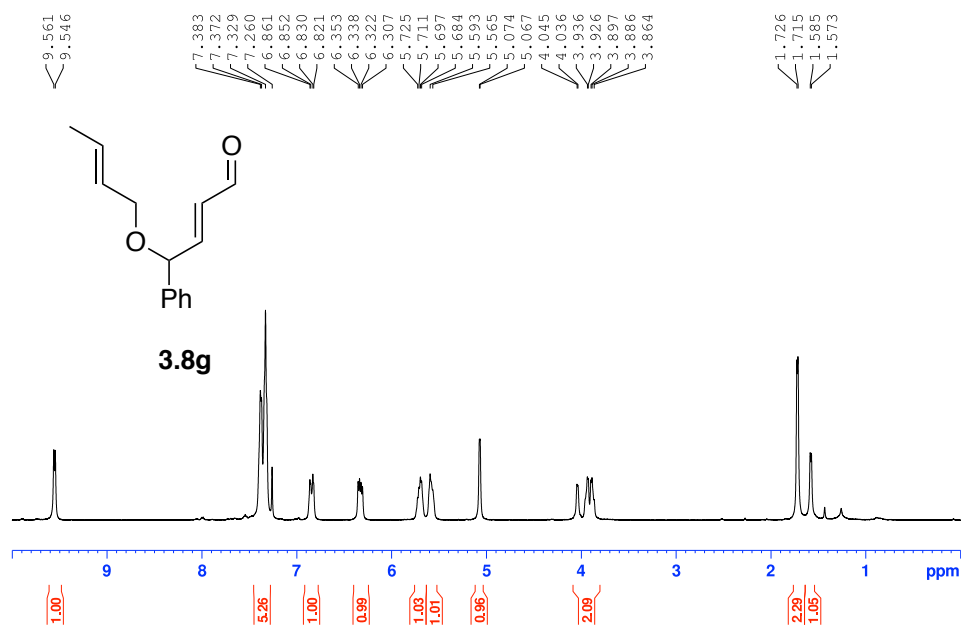
Pale yellow oil. Collected in 26% yield over 2 steps.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.48 (d,  $J = 7.9$  Hz, 1H), 7.29 (m,  $J = 7.7$  Hz, 5H), 6.78 (dd,  $J = 15.7, 5.2$  Hz, 1H), 6.25 (ddd,  $J = 15.7, 8.0, 1.3$  Hz, 1H), 5.62 (m, 1H), 5.51 (m, 1H), 5.00 (d,  $J = 5.1$  Hz, 1H), 3.96 (d,  $J = 6.6$  Hz, 2H), 1.50 (d,  $J = 6.9$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.5, 156.2, 138.7, 131.1, 128.9, 128.7, 128.6, 127.2, 126.2, 79.8, 64.1, 13.2 ppm. HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd. for  $[\text{C}_{14}\text{H}_{16}\text{O}_2\text{Na}]$  239.1048, found 239.1053.



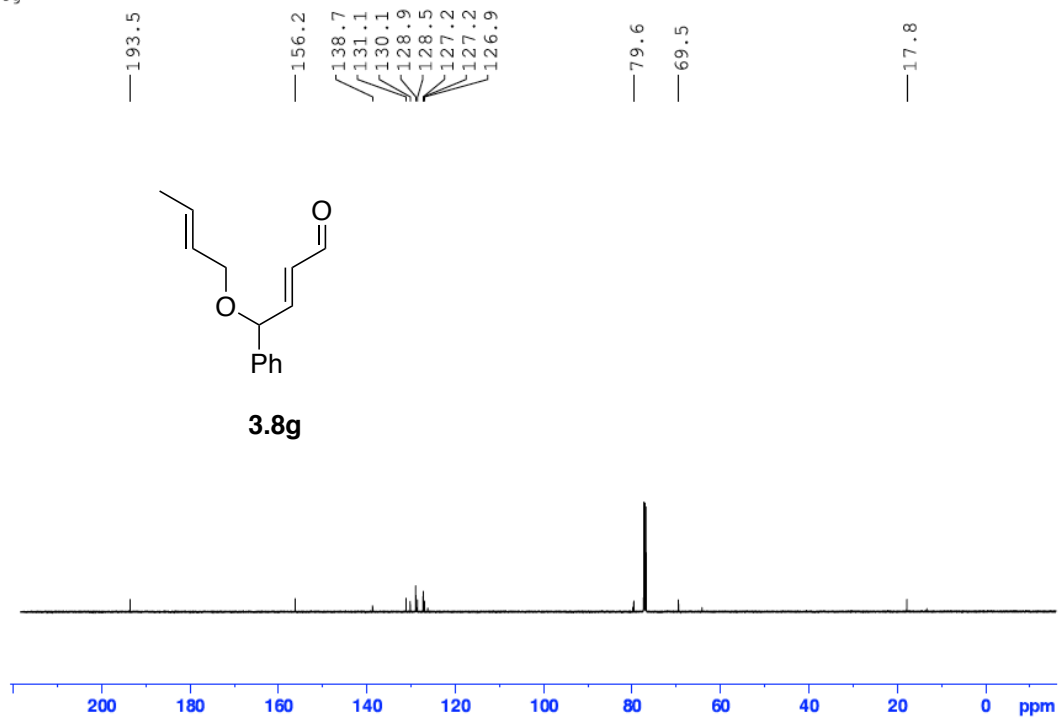


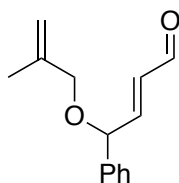
**(*E*)-4-(((*E*)-but-2-en-1-yl)oxy)-4-phenylbut-2-enal (3.8g)****3.8g**

Pale yellow oil. Collected in 24% yield over 4 steps.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.55 (d,  $J = 7.5$  Hz, 1H), 7.38–7.33 (m, 5H), 6.84 (dd,  $J = 15.5$ , 4.5 Hz, 1H) 6.33 (dd,  $J = 15.3$ , 7.4 Hz, 1H), 5.73–5.68 (m, 1H), 5.59–5.57 (m, 1H), 5.07 (d,  $J = 3.3$  Hz, 1H), 4.04–3.86 (m, 2H), 1.72 (d,  $J = 5.5$  Hz, 2H), 1.58 (d,  $J = 6.1$  Hz, 1H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.5, 156.2, 138.7, 131.1, 130.1, 128.9, 128.5, 127.2, 127.2, 79.6, 69.5, 17.8 ppm. HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{14}\text{H}_{17}\text{O}_2]$  217.1229, found 217.1221.

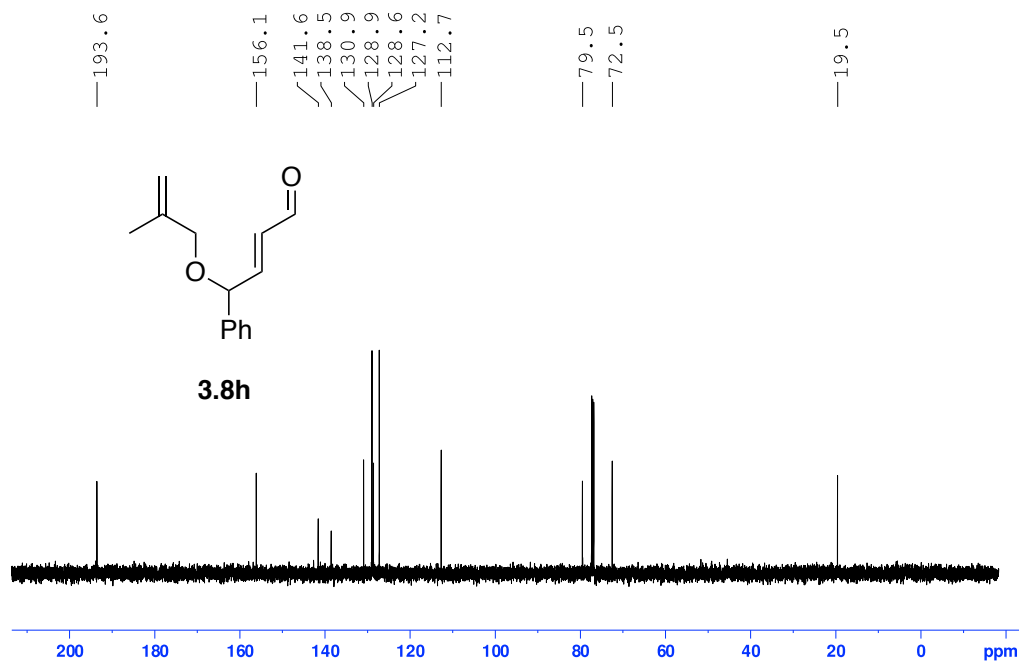
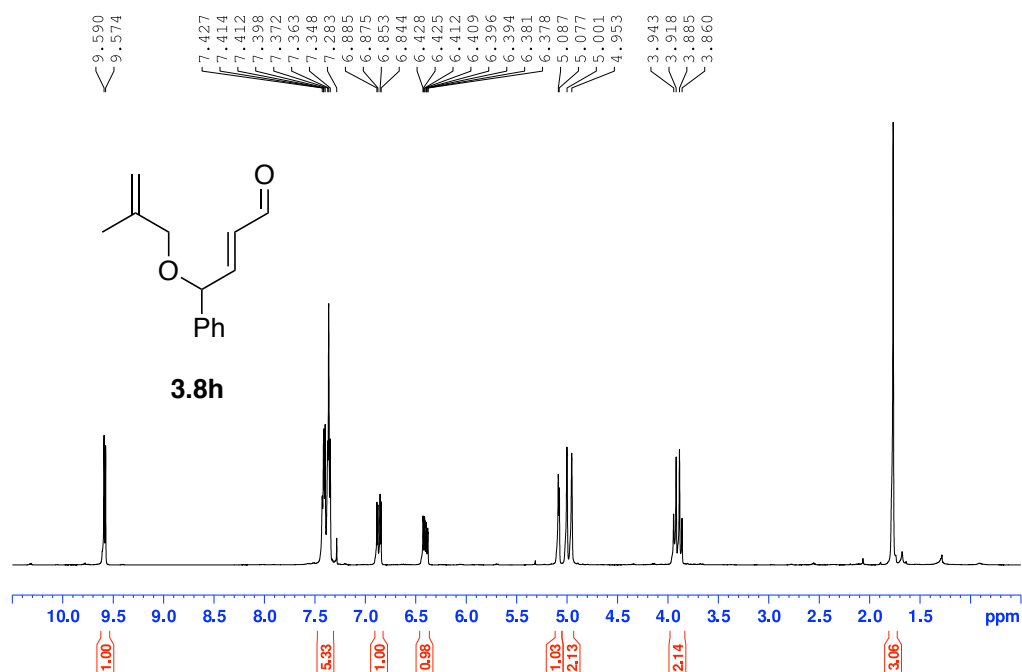


3.8g



**(E)-4-((2-methylallyl)oxy)-4-phenylbut-2-enal (3.8h)****3.8h**

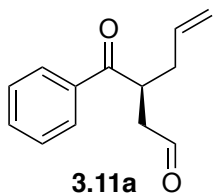
Pale yellow oil. Collected in 55% yield over 4 steps.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.58 (d,  $J = 7.9$  Hz, 1H), 7.45–7.33 (m, 5H), 6.86 (dd,  $J = 15.6$ , 5.0 Hz, 1H), 6.40 (ddd,  $J = 15.6$ , 7.9, 1.2 Hz, 1H), 5.08 (d,  $J = 4.8$  Hz, 1H), 4.98 (d,  $J = 23.8$  Hz, 2H), 3.90 (dd,  $J = 16.7$ , 12.5 Hz, 2H), 1.77 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.6, 156.1, 141.6, 138.5, 130.9, 128.9, 128.6, 127.2, 112.7, 79.5, 72.5, 19.6. HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{14}\text{H}_{17}\text{O}_2]$  217.1229, found 217.1225.



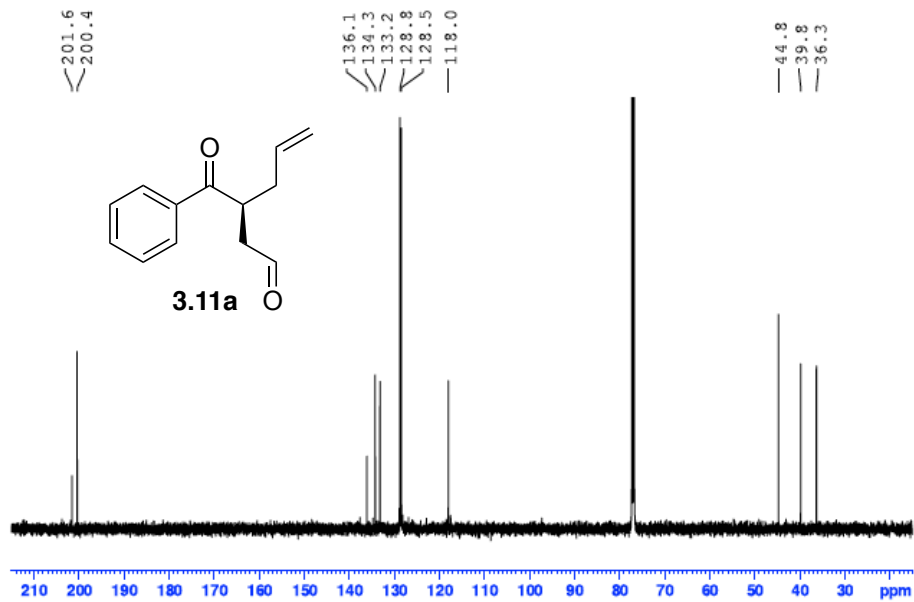
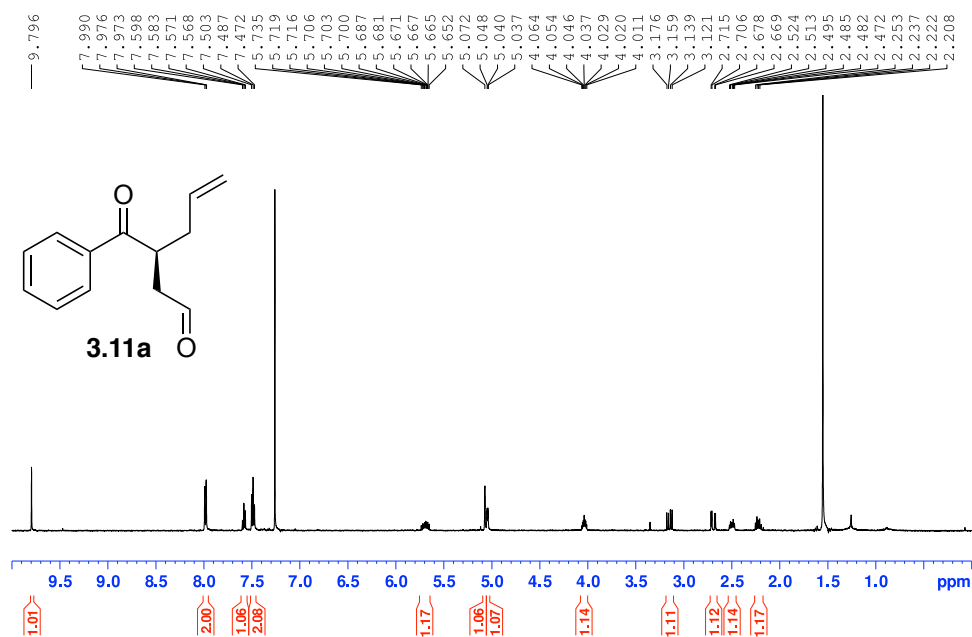
### Representative procedure for the synthesis of **3.11a-d, h**

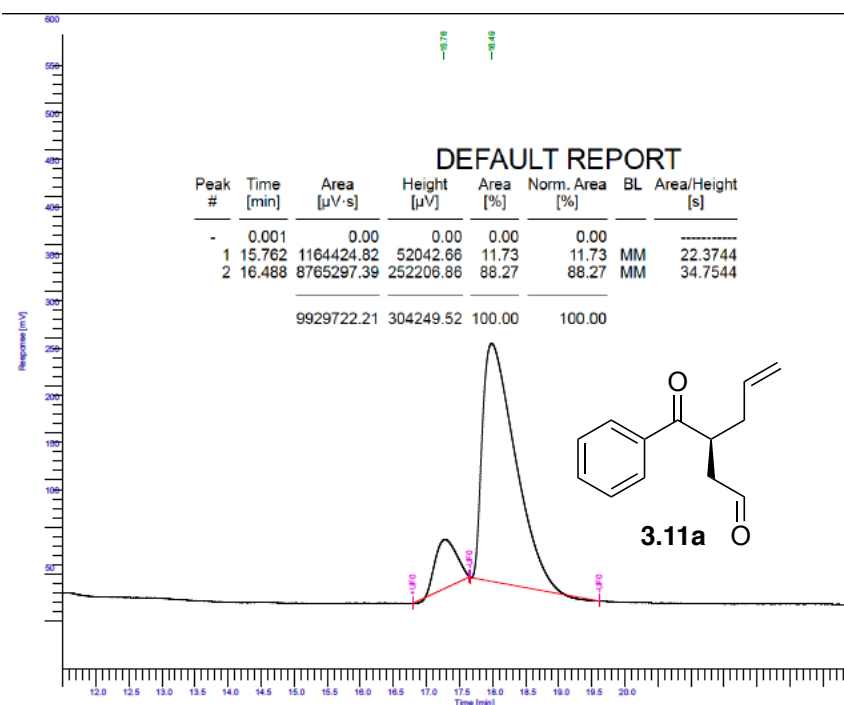
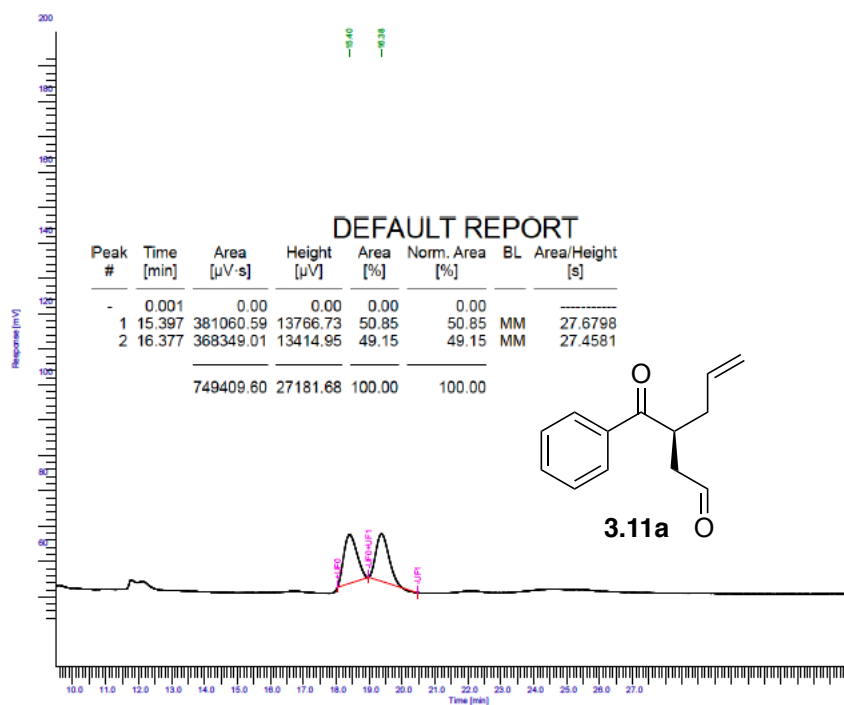
To a 5 mL round bottom flask equipped with a stir bar and septum containing enal **3.8a** (25 mg, 0.12 mmol), was added catalyst **3.27** (5.4 mg, 0.024 mmol), ( $\pm$ )-**trans-3.33** (15.8 mg, 0.024 mmol), and TFE (600  $\mu$ L). The reaction mixture was stirred at 0 °C until complete consumption of **3.8a**, as observed by  $^1\text{H}$  NMR. The crude reaction mixture was loaded on silica gel and purified by flash column chromatography (8.5% EtOAc:PE). The pure fractions were collected and reduced under pressure to yield product **3.11a** (12.1 mg, 50% yield).

#### (*S*)-3-benzoylhex-5-enal (**3.11a**)



Yellow oil (12.1 mg, 50% yield);  $[\alpha]_{\text{D}}^{22} = -23.9$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ , 77% ee)  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.80 (s, 1H), 7.98 (dd,  $J = 8.5$ , 1.23 Hz, 2H), 7.60-7.57 (m, 1H), 7.50-7.47 (m, 2H), 5.73-5.65 (m, 1H), 5.07 (s, 1H), 5.05-5.03 (m, 1 H), 4.03 (m, 1H), 3.14 (dd,  $J = 18.9$ , 8.8 Hz, 1H), 2.69 (dd,  $J = 18.8$ , 4.5 Hz, 1H), 2.52-2.47 (m, 1H), 2.22 (dt,  $J = 14.8$ , 10 Hz, 1H), ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  201.6, 200.4, 136.1, 134.3, 133.2, 128.8, 128.5, 118.0, 44.8, 39.8, 36.3 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH= 99:1 at 1.0 mL/min for 40 minutes); major enantiomer  $t_{\text{R}} = 16.49$  min, minor enantiomer  $t_{\text{R}} = 15.76$  min; HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{13}\text{H}_{15}\text{O}_2]$  203.1068, found 203.1072.







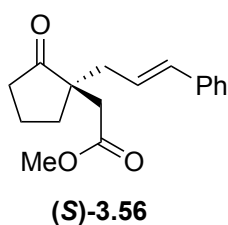
### Modification of **3.11b** for Chiral HPLC Analysis

Product **3.11b** was further modified according to the following procedure, in order to obtain ee and absolute configuration information through chiral HPLC analysis.

To a solution of **3.11b** (37.2 mg) in *t*-BuOH (5 mL) was added NaClO<sub>2</sub> (124 mg, 0.90 mmol) and NaHPO<sub>4</sub> (124 mg, 0.90 mmol), and H<sub>2</sub>O (2.5 mL). The reaction was stirred at rt overnight until complete consumption of **3.11b**, as observed by <sup>1</sup>H NMR. The reaction was diluted with brine (3.0 mL) and extracted with EtOAc (3 x 7.5 mL), then dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give the crude acid which was used in the next step.

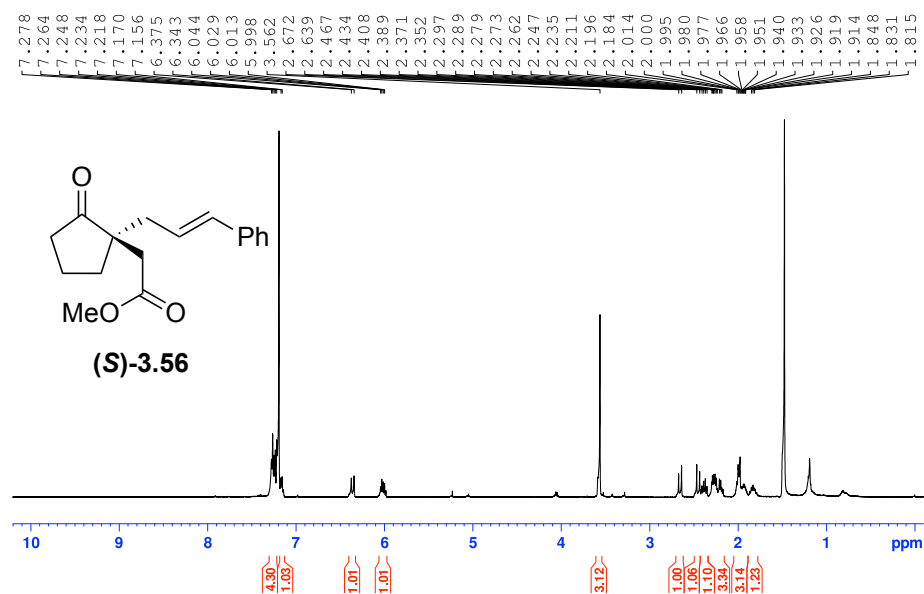
To a solution of the crude acid dissolved in anhydrous MeOH (1 mL), cooled to 0 °C was added TMSCHN<sub>2</sub> (460 µL, 0.92 mmol) dropwise, until a yellow color persisted. The reaction was warmed up to rt and stirred overnight. The crude reaction was poured into a separatory funnel containing brine, washed with water, and extracted with EtOAc (3 x 7.5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give the crude methyl ester **3.55**. The crude mixture was filtered over a silica plug with 10% EtOAc/PE gradient, to obtain impure ester **3.55** in a two-step yield of 46% (10.1 mg of colorless oil).

**3.56** was prepared from **3.55** using a known procedure and the characterization was in agreement with the experimental data.<sup>10</sup>

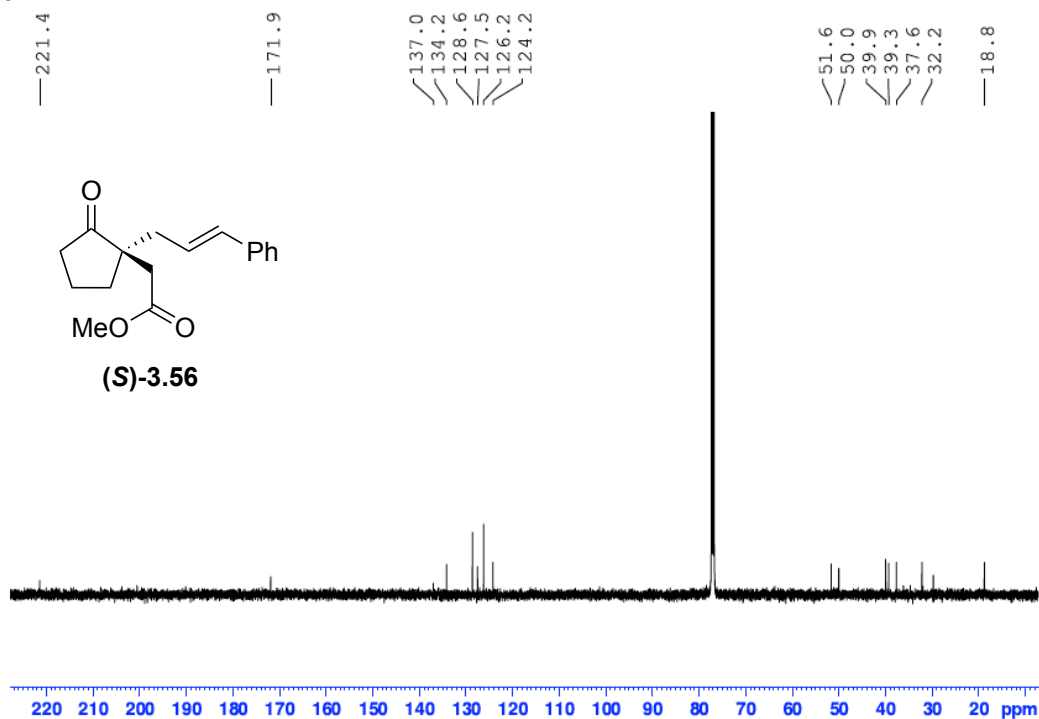
**(*S,E*)-methyl 2-(1-cinnamyl-2-oxocyclopentyl)acetate (3.56)<sup>10</sup>**

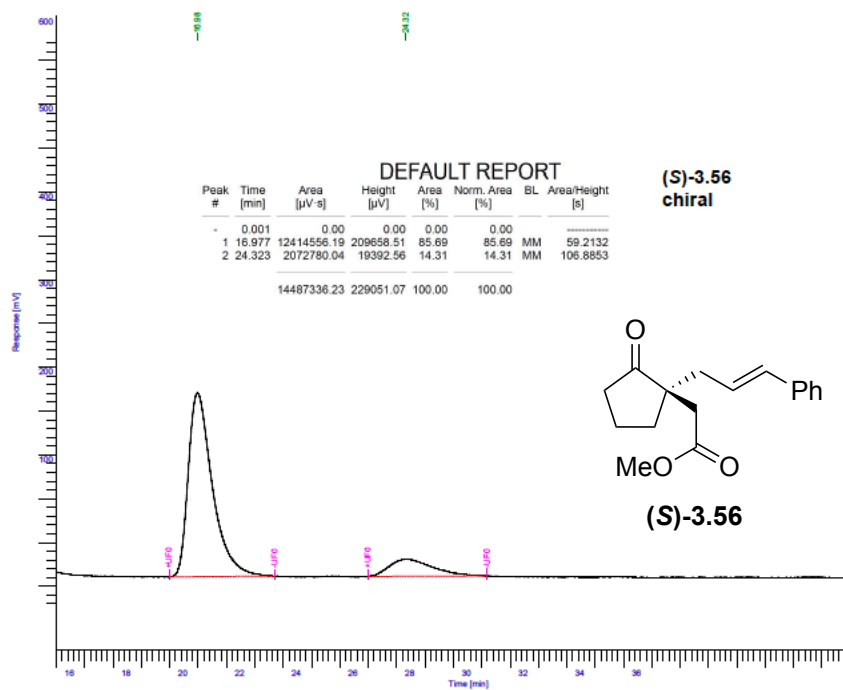
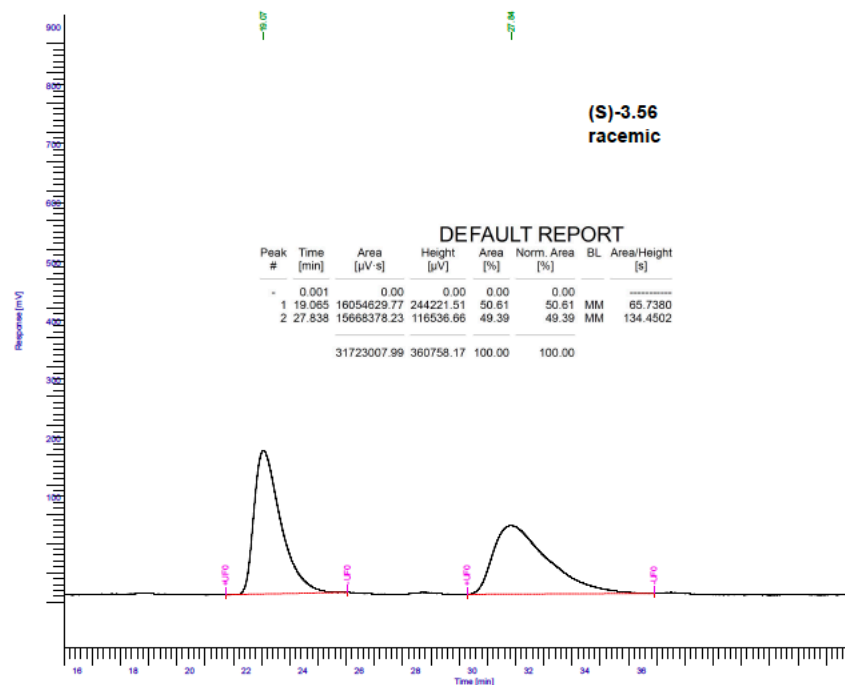
Colorless oil (4.9 mg, 30% yield);  $[\alpha]_{\text{D}}^{22} = -21.2$  ( $c = 0.11$  in  $\text{CH}_2\text{Cl}_2$ , 71% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.28–7.22 (m, 4H), 7.17–7.14 (m, 1H), 6.6 (d,  $J = 15.7$  Hz, 1H), 6.01 (dt,  $J = 15.5, 7.6$  Hz, 1H), 3.56 (s, 3H), 2.65, 2.45 (ABq,  $J = 16.4$  Hz, 1Hx2), 2.41–2.35 (m, 1H), 2.30–2.17 (m, 3H), 2.01–1.89 (m, 3H), 1.86–1.77 (m, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  221.4, 171.9, 137.0, 134.2, 128.6, 127.5, 126.2, 124.2, 51.6, 50.0, 39.9, 39.3, 37.6, 32.2, 18.8 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH = 99.5:0.5 at 1.0 mL/min for 40 minutes); major enantiomer  $t_{\text{R}} = 16.98$  min, minor enantiomer  $t_{\text{R}} = 24.32$  min; HRMS (ESI)  $[\text{M}+\text{Na}]^+$  calcd. for  $[\text{C}_{17}\text{H}_{20}\text{O}_3\text{Na}]$  295.1305, found 295.1302.

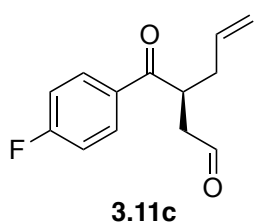
3.56



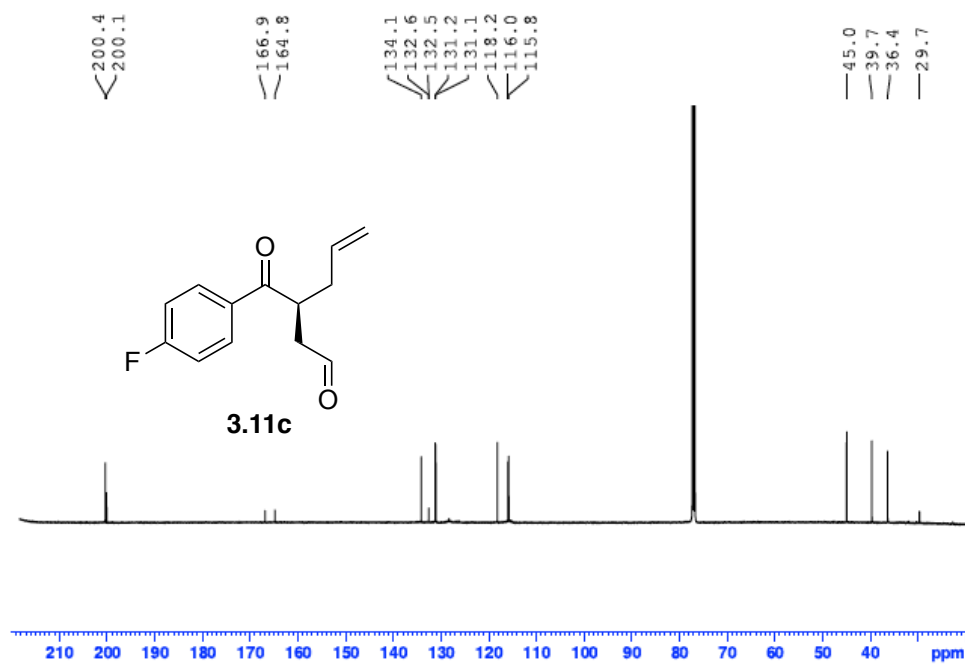
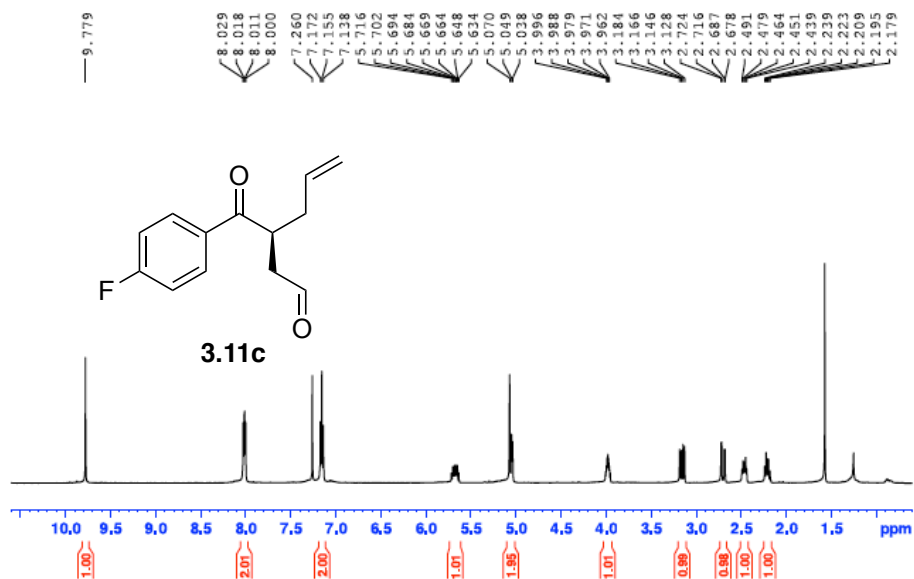
3.56

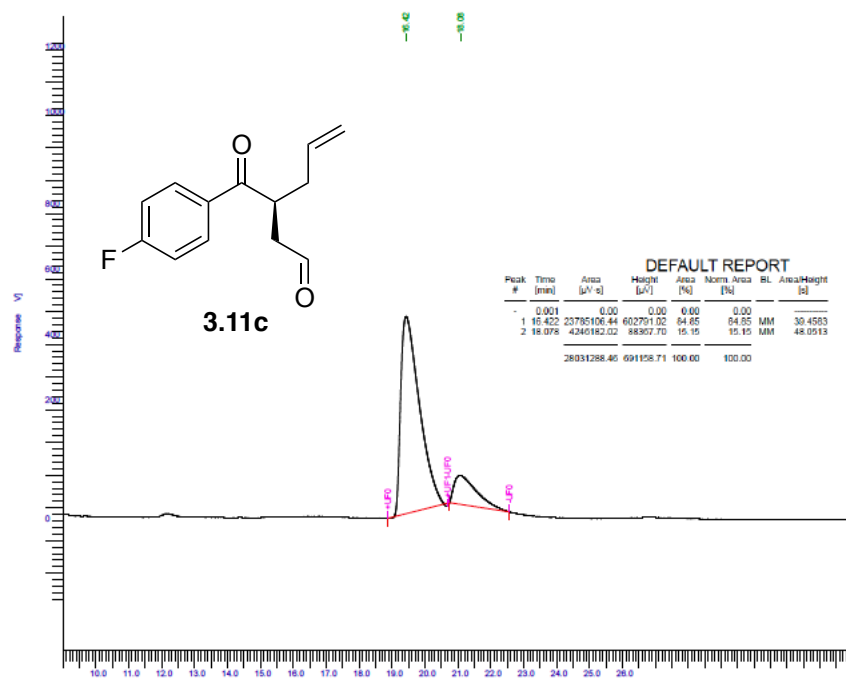
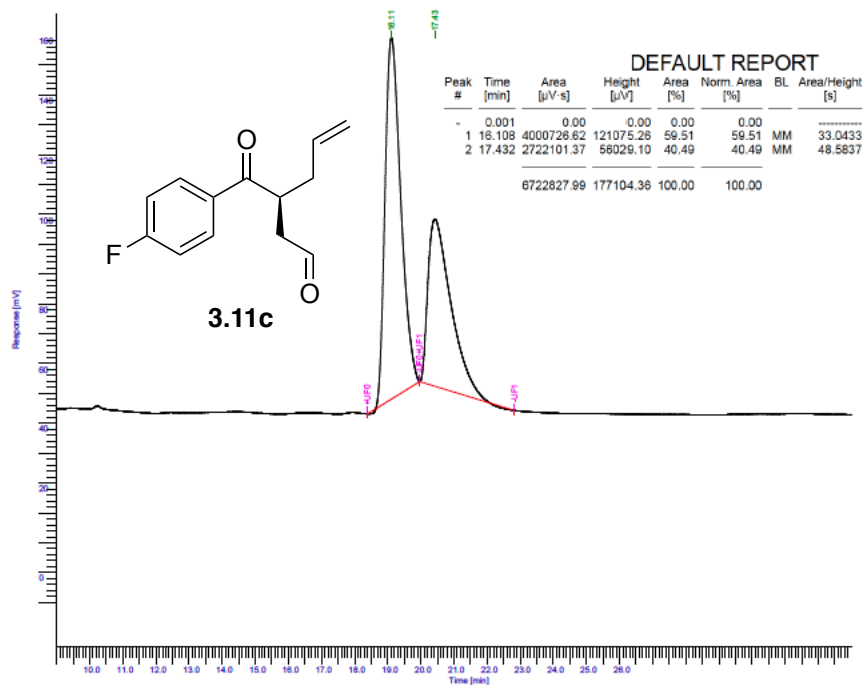


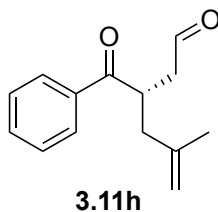


**(S)-3-(4-fluorobenzoyl)hex-5-enal (3.11c)**

Pale yellow oil (7 mg, 26% yield);  $[\alpha]_D^{22} = -19.0$  ( $c = 0.6$  in  $\text{CH}_2\text{Cl}_2$ , 70% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.78 (s, 1H), 8.01 (dd,  $J = 8.7, 5.5$  Hz, 2H), 7.17–7.14 (m, 2H), 5.72–5.64 (m, 1H), 5.07 (s, 1H), 5.04 (d,  $J = 5.8$  Hz, 1H), 4.01–3.96 (m, 1 H), 3.15 (dd,  $J = 18.8, 9.1$  Hz, 1H), 2.70 (dd,  $J = 18.9, 4.1$  Hz, 1H), 2.48–2.44 (m, 1H), 2.24–2.18 (m, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.4, 200.1, 166.9, 164.8, 134.1, 132.6, 132.5, 131.2, 131.1, 118.2, 116.0, 115.8, 45.0, 39.7, 36.4 ppm. HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH = 99:1 at 1.0 mL/min for 40 minutes); major enantiomer  $t_R = 16.42$  min, minor enantiomer  $t_R = 18.08$  min; HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{13}\text{H}_{14}\text{FO}_2]$  221.0975, found 221.0978.

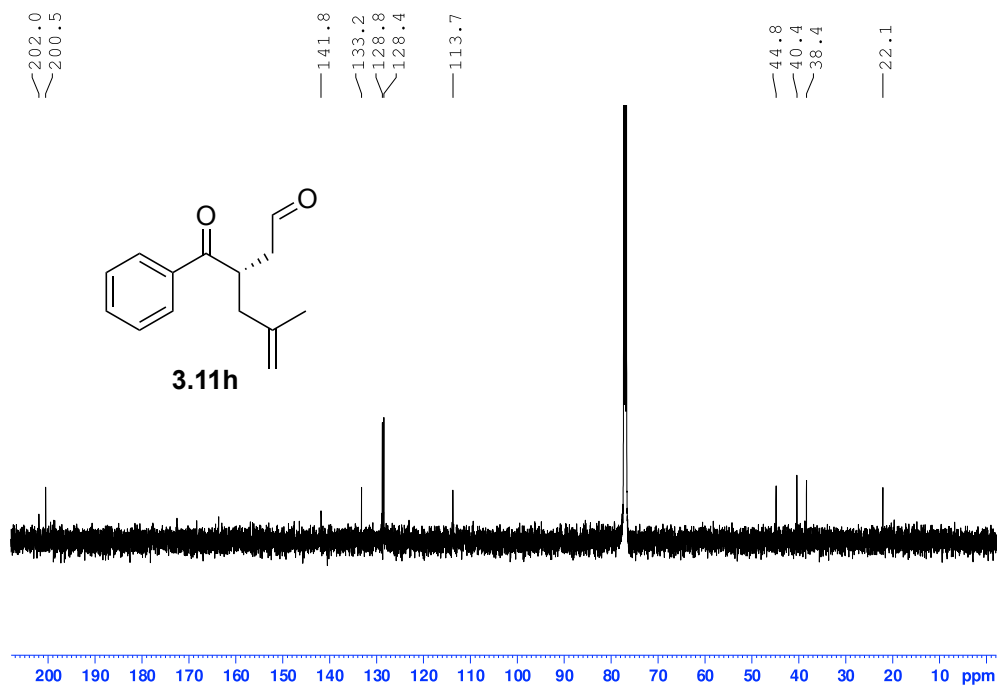
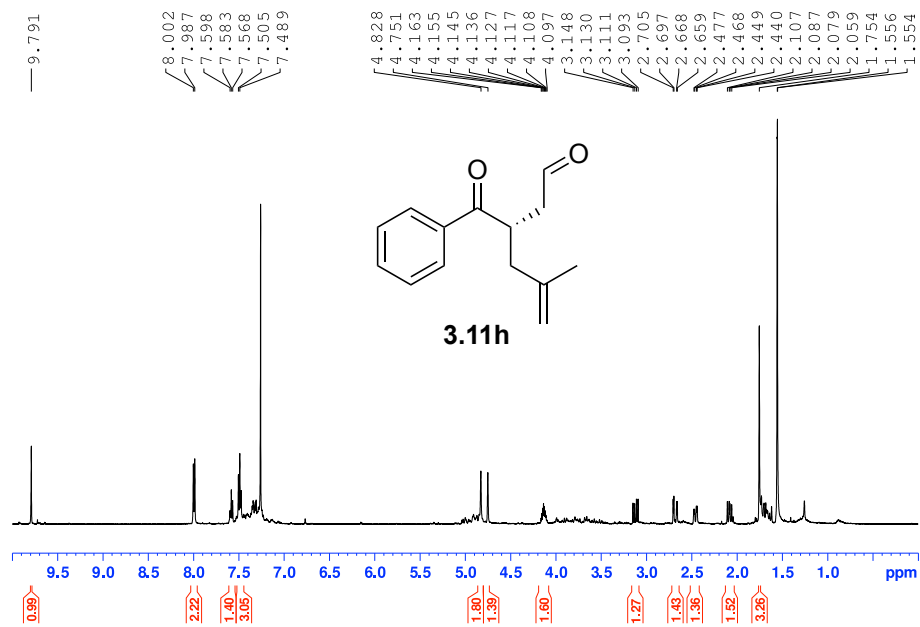


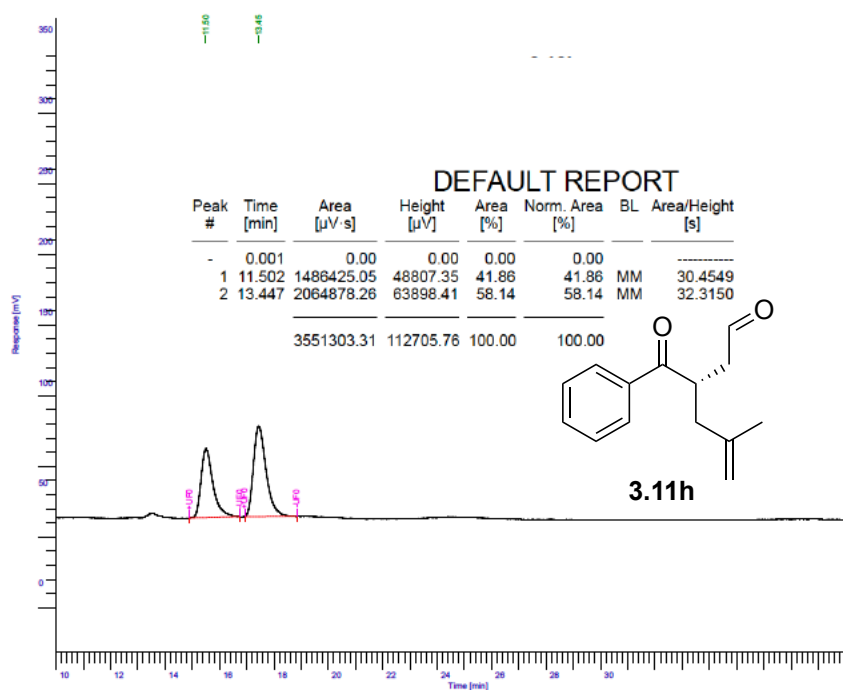
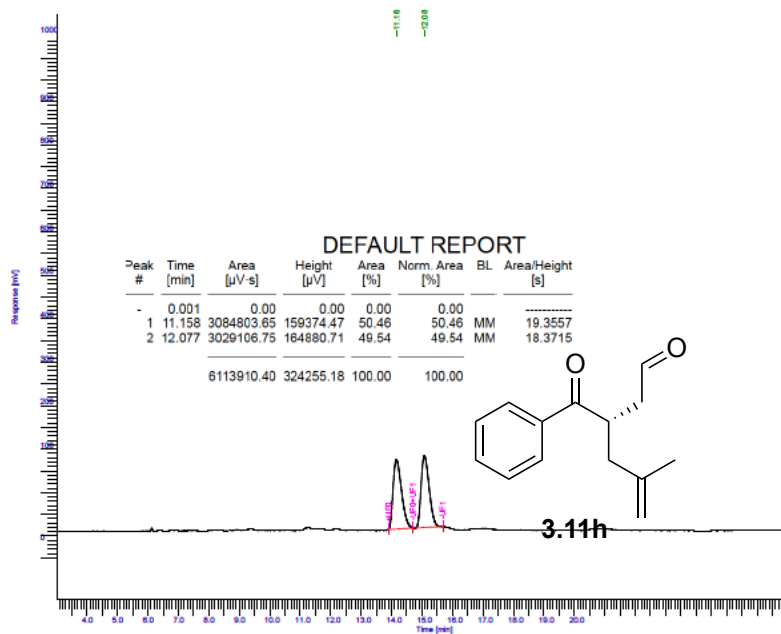


**(S)-3-benzoyl-5-methylhex-5-enal (3.11h)**

Colorless oil (18.4 mg, 23% yield);  $[\alpha]_{\text{D}}^{22} = -13.0$  ( $c = 0.1$  in  $\text{CH}_2\text{Cl}_2$ , 16% ee);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.79 (s, 1H), 7.99 (d,  $J = 8$  Hz, 2H), 7.58 (t,  $J = 7.4$  Hz, 1H), 7.48 (t,  $J = 7.8$  Hz, 3H), 4.83 (s, 1H), 4.75 (s, 1H), 4.16–4.10 (m, 1 H), 3.12 (dd,  $J = 18.7, 9.0$  Hz, 1H), 2.68 (dd,  $J = 18.7, 3.9$  Hz, 1H), 2.45 (dd,  $J = 14.1, 4.5$  Hz, 1H), 2.08 (dd,  $J = 14.0, 9.9$  Hz, 1H), 1.75 (s, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.0, 200.5, 198.6, 141.8, 133.2, 128.8, 128.4, 113.7, 44.8, 40.4, 38.4, 22.1; HPLC with an AS-H column ( $n$ -hexane/ $i$ -PrOH = 99:1 at 1.0 mL/min for 40 minutes); major enantiomer  $t_{\text{R}} = 13.45$  min, minor enantiomer  $t_{\text{R}} = 11.5$  min; HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{14}\text{H}_{17}\text{O}_2]$  217.1225, found 217.1229.



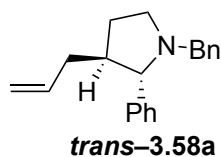




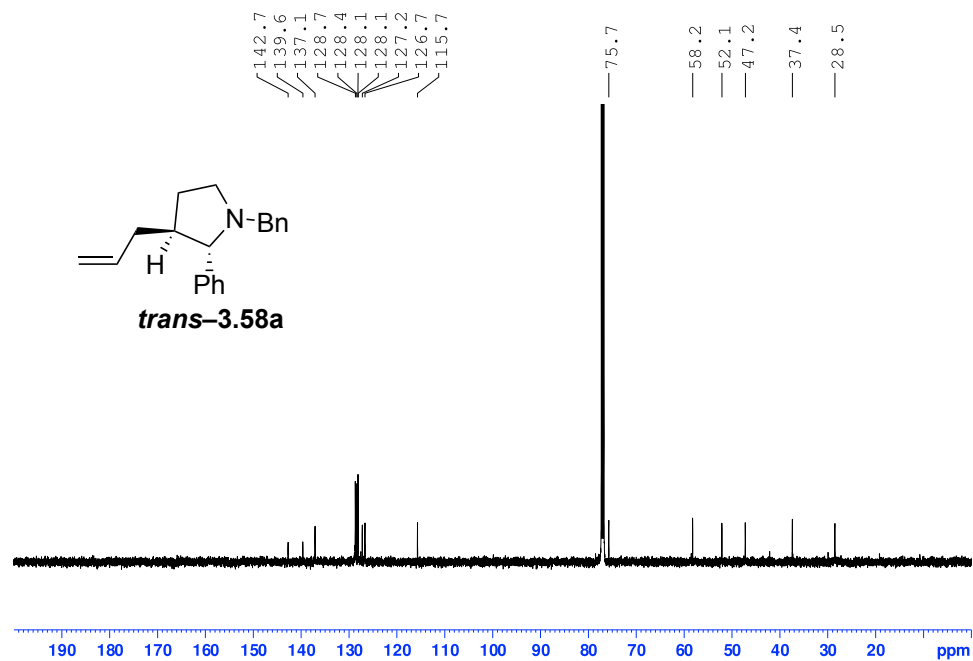
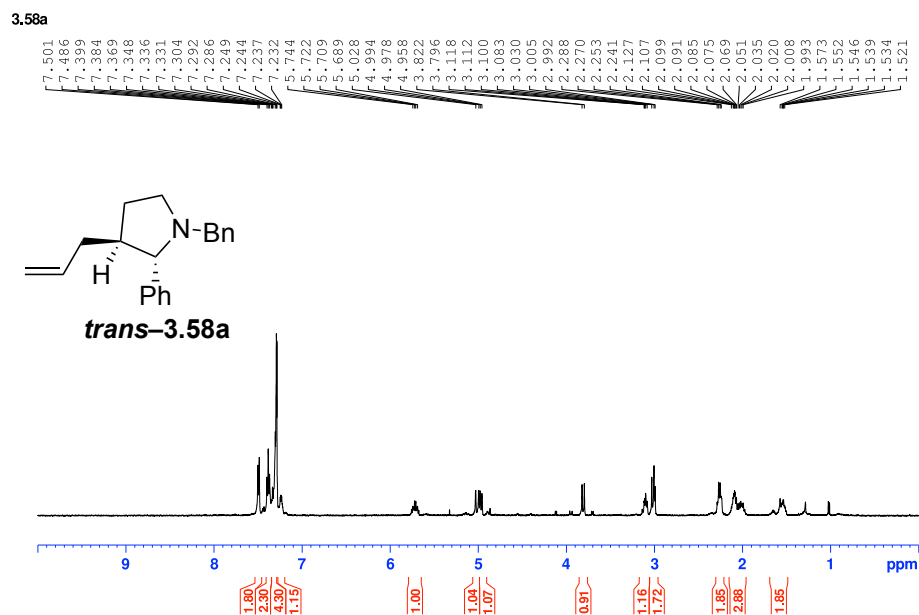
### Procedure for synthesis of 3.58

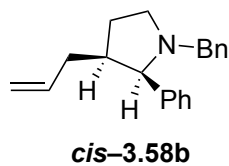
To a solution of **3.11a** (80 mg, 0.40 mmol in THF) at 0 °C was added NaBH(OAc)<sub>3</sub> (258 mg, 1.2 mmol), benzylamine (66.5  $\mu$ L, 0.61 mmol) and AcOH (22.61  $\mu$ L, 0.4 mmol). After stirring for 1 h at 0 °C and 16 h at rt, the reaction was quenched with aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give a residue, which was purified by preparative thin layer chromatography (15% EtOAc/hexane) to yield the compounds **trans-3.58a** and **cis-3.58a** as colorless oils (60% and 24% yields, respectively). The relative configurations of **trans-3.58a** and **cis-3.58a** were determined by NOE.

#### (2*S*,3*S*)-3-allyl-1-benzyl-2-phenylpyrrolidine (**trans-3.58a**)



Major diastereomer, colorless oil (77 mg, 60% yield);  $[\alpha]_D^{22} = 1.0$  ( $c = 0.1$  in CH<sub>2</sub>Cl<sub>2</sub>); NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.49 (d,  $J = 7.3$  Hz, 2H), 7.38 (t,  $J = 7.5$  Hz, 2H), 7.34–7.29 (m, 4H), 7.24 (dd,  $J = 5.9, 2.2$  Hz, 1H), 5.76–5.68 (m, 1H), 5.01 (d,  $J = 17.1$  Hz, 1H), 4.97 (d,  $J = 10.1$  Hz, 1H), 3.81 (d,  $J = 7.2$  Hz, 1H), 3.14–3.08 (m, 1H), 3.03–2.99 (m, 2H), 2.29–2.24 (m, 2H), 2.13–1.98 (m, 3H), 1.67–1.52 (m, 2H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  142.7, 139.7, 137.1, 128.7, 128.4, 128.1, 128.1, 127.2, 126.7, 115.7, 75.7, 58.2, 52.1, 47.2, 37.4, 28.5. HRMS (ESI)  $[M+H]^+$  calcd. for [C<sub>20</sub>H<sub>24</sub>N] 278.1909, found 278.1908.

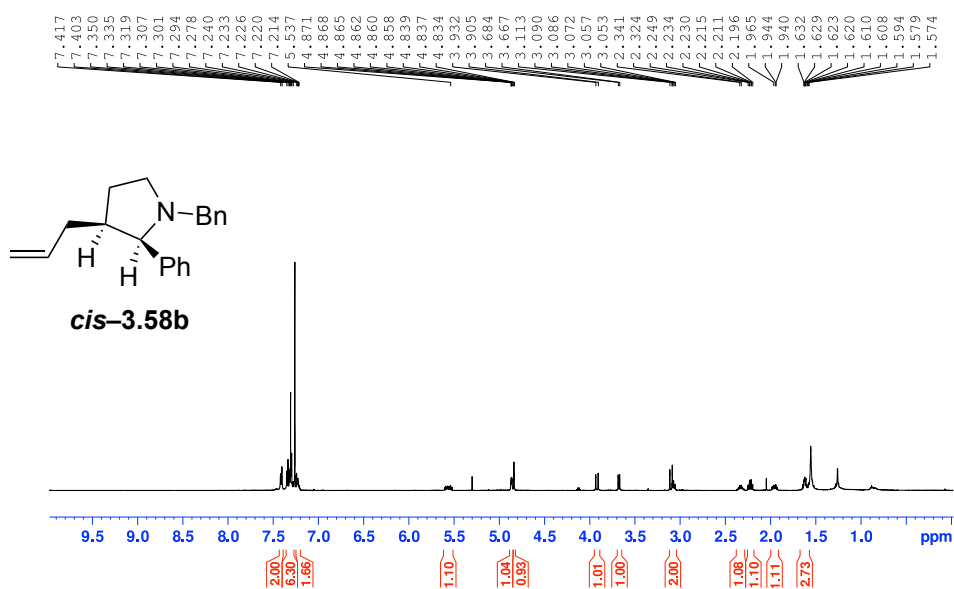


**(2*R*,3*S*)-3-allyl-1-benzyl-2-phenylpyrrolidine (*cis*-3.58b)**

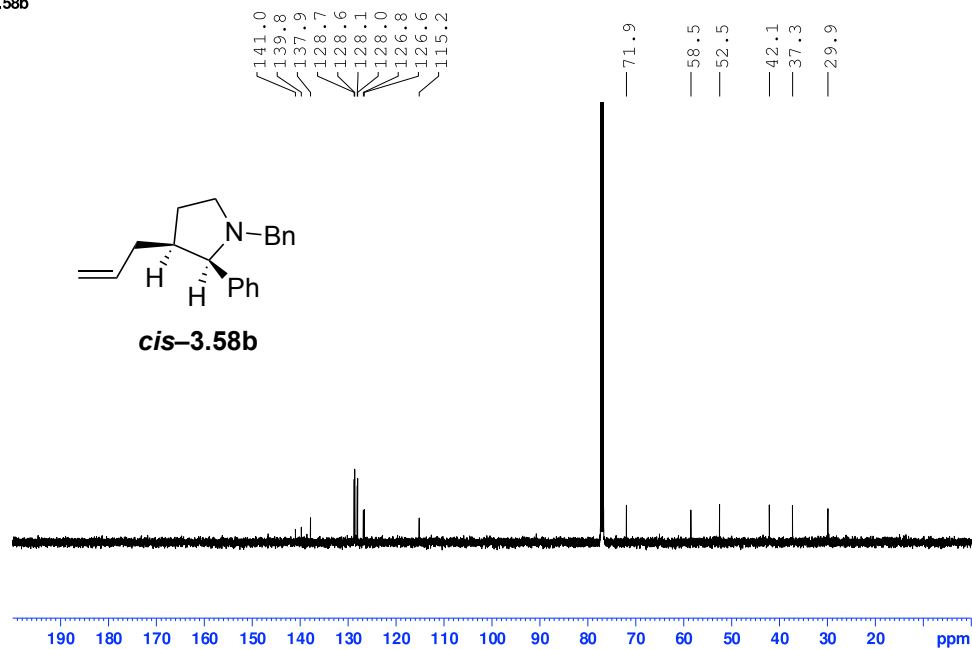
Obtained as a minor product in the synthesis of **3.58** described above.

Minor diastereomer, colorless oil (27 mg, 24% yield);  $[\alpha]_{\text{D}}^{22} = -1.0$  ( $c = 0.11$  in  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43 (d,  $J = 7.2$  Hz, 2H), 7.37–7.30 (m, 6H), 7.27–7.24 (m, 2H), 5.62–5.54 (m, 1H), 4.88 (ddd,  $J = 6.6, 4.0, 1.5$  Hz, 1H), 4.86 (t,  $J = 1.3$ , 1H), 3.94 (d,  $J = 13.3$  Hz, 1H), 3.70 (d,  $J = 8.5$  Hz, 1H), 3.13–3.07 (m, 2H), 2.39–2.31 (m, 1H), 2.24 (td,  $J = 9.4, 9.3$  Hz, 1H), 2.00–1.94 (m, 1H), 1.69–1.59 (m, 3H) ppm.  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.0, 137.9, 128.7, 128.6, 128.1, 128.0, 126.8, 126.6, 115.2, 71.9, 58.5, 52.5, 42.1, 37.3, 29.9 ppm. HRMS (ESI)  $[\text{M}+\text{H}]^+$  calcd. for  $[\text{C}_{20}\text{H}_{24}\text{N}]$  278.1909, found 278.1908.

3.58b



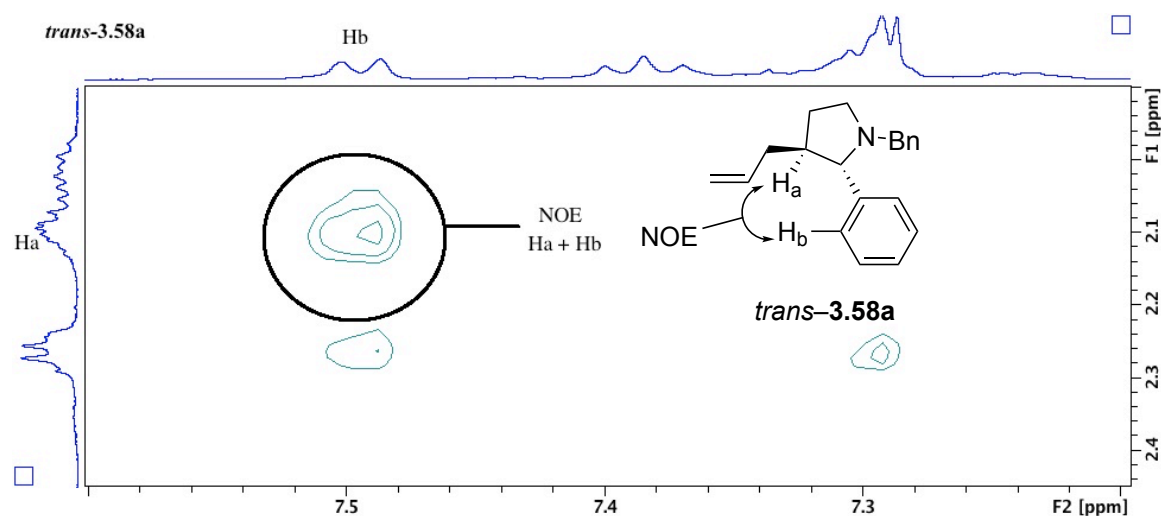
3.58b



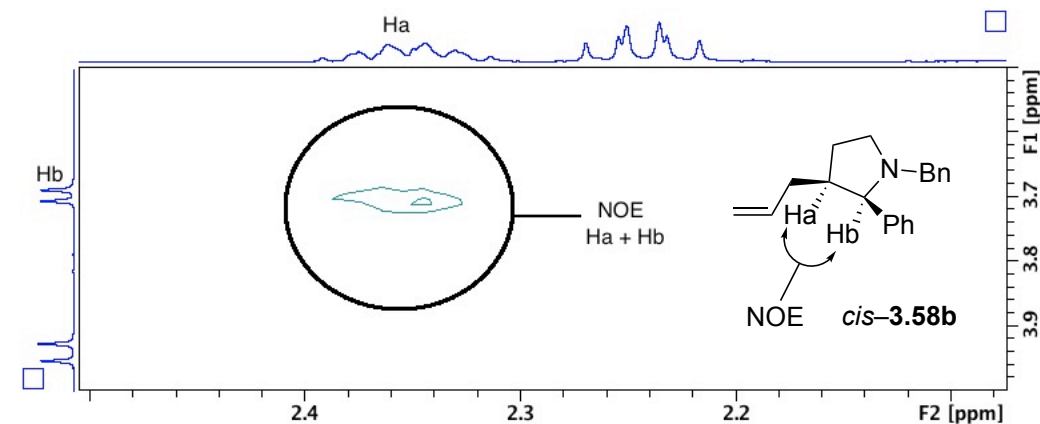
## NOE Experiments

The relative configurations of *trans*-**3.58a** and *cis*-**3.58a** (dr 2.5:1) were determined by NOE NMR experiments. The major diastereomer had a NOE signal between H<sub>a</sub> and H<sub>b</sub>, indicating that the phenyl group was *trans* to H<sub>a</sub>. The minor diastereomer was determined to have a *cis* configuration indicated by the observed NOE interaction between H<sub>a</sub> and H<sub>b</sub>.

### NOE NMR of *trans*-**3.58ab**



### NOE NMR of *cis*-**3.58a**



#### 4.4 References

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