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RHODIUM ALKENYLCARBENES: NOVEL REACTIVITY AND PRECURSORS

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RHODIUM ALKENYLCARBENES: NOVEL REACTIVITY AND PRECURSORS

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Abstract

RHODIUM ALKENYLCARBENES: NOVEL REACTIVITY AND PRECURSORS

By Brendan Thomas Parr

The stability imparted to a rhodium-bound carbene intermediate by an electron donating substituent is obviated by the broad range of efficient and enantioselective transformations these intermediates undergo. Indeed, the overlap of a π–orbital orthogonal to the metal–carbon bond aides in tempering reactivity of the metal carbene by donating electron density to the cationic resonance structure. Introduction of an olefinic π–donor group has enabled the development of new reactions in which this non-innocent moiety participates directly in the rhodium-catalyzed reaction.

Alkenyl substituted diazoacetates are particularly efficient substrates for tandem ylide formation/[2,3]-sigmatropic rearrangement between allyl alcohols and rhodium carbenes. The reaction has been studied with appropriately functionalized secondary alcohols for the synthesis of products containing vicinal stereogenic centers in exceptional stereoselectivity. In addition, modification of reaction conditions has enabled the implementation of primary alcohols, previously deemed incompatible, as competent partners.

The tandem ylide formation/[2,3]-sigmatropic rearrangement of allyl alcohols and alkenyldiazoacetates generates functionalized products capable of participating in a cascade of reactions. Due to the efficiency and limited byproducts associated with the rhodium carbene transformation, the domino sequence can be conducted as a one-pot process for the direct synthesis of cyclopentanes or cyclohexanes, depending upon the substitution of the starting alcohol. The individual reactions and intermediates have been studied in detail to understand various chirality transfer processes involved, in an effort to diagnose the limitations.

The 4-substituted-1,2,3-triazole nucleus has been identified as a viable precursor for a range of classical and novel carbene transformations. A unified strategy for the synthesis of triazole-based alkenylcarbene precursors for rhodium-catalyzed transformation has been developed. These substrates have been applied to classical, enantioselective transformations of alkenyldiazoacetates, including a detailed study of the tandem cyclopropanation/Cope rearrangement. These rhodium carbene precursors exhibit improved stability and ease of handling compared with their alkenyldiazoacetate counterparts.

Triazole-based carbene precursors have been found to exhibit an array of orthogonal reactivity compared with their diazo equivalents, due to an apparent propensity for the formation of zwitterionic intermediates upon addition of electron rich π–nucleophiles. Many of these reactions involve cyclization of the zwitterion through the imine moiety, resulting in the synthesis of nitrogenous heterocycles. In addition, formal C–H functionalization of aromatic heterocycles and arenes via electrophilic aromatic substitution reactions to generate diaryl enamines has been developed.

RHODIUM ALKENYLCARBENES: NOVEL REACTIVITY AND PRECURSORS

By

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B.Sc., University of Richmond, 2009

Advisor: Huw M. L. Davies, Ph.D.

Dedicated to my parents

Table of Contents

List of Abbreviations

1,2-DCE	1,2-dichloroethane
2,2-DMB	2,2-dimethylbutane
Ac	acetyl
AK	acetyl kinase
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Bn	benzyl
Boc	*tert*-butoxycarbonyl
c-Hex	*cyclo*-hexyl
$CaCl_2$	calcium chloride
cat.	catalyst
Cbz	benzyloxycarbonyl
CHCR	combined C–H functionalization/Cope rearrangement
cm	centimeter
$Co(acac)_3$	cobalt(III) acetylacetonate

$Cu(MeCN)_4PF_6$	tetrakis(acetonitrile)copper(I) hexafluorophosphate
CuAAC	copper-catalyzed azide/alkyne cycloaddition
CuTC	copper(I) thiophene-2-carboxylate
DBU	1,8-diazabicycloundec-7-ene
DFT	density functional theory
DMAP	4-dimethylaminopyridine
ΔG_{sol}	Gibbs free energy of solution
DIPT	di-*iso*-propyl tartrate
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EAS	electrophilic aromatic substitution
EDA	ethylenediamine
EDG	electron-donating group
ee	enantiomeric excess
ent	enantiomer
epi	epimer
ESI	electrospray ionization

Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron-withdrawing group
$FeSO_4$	iron(II) sulfate (ferrous sulfate)
FT	Fourier transform
GC	gas chromatography
HOMO	highest occupied molecular orbital
HPLC	high performance/pressure liquid chromatography
HRMS	high resolution mass spectrometry
i-Bu	*iso*-butyl
i-Pr	*iso*-propyl
IR	infrared
k_{rel}	relative rate constant
K_2CO_3	potassium carbonate
KCl_2	potassium chloride
KOH	potassium hydroxide

KO*t*Bu	potassium *tert*-butoxide
$LiAlH_4$	lithium aluminum hydride
$LiBH_4$	lithium borohydride
LiCl	lithium chloride
LUMO	lowest unoccupied molecular orbital
Me	methyl
$MgCl_2$	magnesium chloride
$MgSO_4$	magnesium sulfate
MOM	methoxymethyl ether
MP	melting point
Ms	methanesulfonyl
MsN_3	methanesulfonyl azide
n-Bu	*n*-butyl
n-Hex	*n*-hexyl
n-Pr	*n*-propyl
$NaBH_4$	sodium borohydride
NaCl	sodium chloride

$NaIO_4$	sodium periodate
NaOH	sodium hydroxide
NaOMe	sodium methoxide
NH_4Cl	ammonium chloride
nm	nanometer
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NSI	nanostructured silicon ionization
p-ABSA	4-acetamidobenzenesulfonyl azide
Pd/C	palladium on carbon
$Pd_2dba_3 \bullet CHCl_3$	tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct
$[Pd(PPh_3)_2]Cl_2$	bis(triphenylphosphine)palladium(II) dichloride
Ph	phenyl
$PhCH_3$	toluene
PhH	benzene
PKC	Protein Kinase C
$POCl_3$	phosphoryl chloride

rac	racemic
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
$[Rh_2(esp)_2]$	bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
$[Rh_2(hex)_4]$	dirhodium(II) tetrakis(hexanoate)
$[Rh_2(oct)_4]$	dirhodium(II) tetrakis(octanoate)
$[Rh_2(pfb)_4]$	dirhodium(II) tetrakis(perfluorobutyrate)
$[Rh_2(piv)_4]$	dirhodium(II) tetrakis(pivaloate)
$\{Rh_2[(R)\text{-dosp}]_4\}$	dirhodium(II) tetrakis{1-[(4-dodecylphenyl)sulfonyl]-(2*R*)-prolinate}
$\{Rh_2[(S)\text{-bitisp}]_2\}$	dirhodium(II) bis-1,3-[*N,N′*-di(4-dodecyl-benzenesulfonyl)-(2*S*,2′*S*),(5*R*,5′*R*)-5,5′-prolinate]benzene
$\{Rh_2[(S)\text{-btpcp}]_4\}$	dirhodium(II) tetrakis[(*S*)-1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylate]
$\{Rh_2[(S)\text{-dosp}]_4\}$	dirhodium(II) tetrakis{1-[(4-dodecylphenyl)sulfonyl]-(2S)-prolinate}
$\{Rh_2[(S)\text{-nttl}]_4\}$	dirhodium(II) tetrakis[*N*-naphthoyl-(*S*)-*tert*-leucinate]/Müller's catalyst
$\{Rh_2[(S)\text{-pta}]_4\}$	dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-alaninate]
$\{Rh_2[(S)\text{-ptad}]_4\}$	dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-adamantylglycinate]

{Rh_2[(*S*)-ptpa]$_4$}	dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate]
{Rh_2[(*S*)-pttl]$_4$}	dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate]
{Rh_2[(*S*)-ptv]$_4$}	dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-valinate]
{Rh_2[(*S*)-tbpttl]$_4$}	dirhodium(II) tetrakis[*N*-tetrabromophthaloyl-(*S*)-*tert*-leucinate]
{Rh_2[(*S*)-tcptad]$_4$}	dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-adamantylglycinate]
{Rh_2[(*S*)-tcpttl]$_4$}	dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate]
{Rh_2[(*S*)-tfpttl]$_4$}	dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate]
{Rh_2[(*S*)-tpcp]$_4$}	dirhodium(II) tetrakis[(*S*)-1,2,2-triphenylcyclopropanecarboxylate]
[Rh_2(TFA)$_4$]	dirhodium(II) tetrakis(trifluoroacetate)
[Rh_2(OAc)$_4$]	dirhodium(II) tetrakis(acetate)
[Rh_2(tpa)$_4$]	dirhodium(II) tetrakis(triphenylacetate)
$Sc(OTf)_3$	scandium triflate
$SrCl_2$	strontium chloride
t-Am	*tert*-amyl
t-Bu	*tert*-butyl
TBHP	*tert*-butyl hydrogen peroxide
TBS	*tert*-butyldimethylsilyl

temp.	temperature
Tf	trifluoromethanesulfonyl
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
Ti(O*i*-Pr)$_4$	titanium(IV) *iso*-propoxide
TIPS	tri*iso*propylsilyl
TMS	trimethylsilyl
TS	transition state
Ts	4-toluenesulfonyl
UV	ultraviolet
$Zn(OTf)_2$	zinc triflluoromethanesulfonate

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– Chapter 1 –

Overview of Donor/Acceptor Rhodium(II) Carbene Intermediates

1.1 Introduction

The field of rhodium carbene chemistry was revitalized by the unveiling of dirhodium tetracarboxylate catalysts as efficient promoters of denitrogenative decomposition of diazocarbonyl compounds. The metal-bound carbene intermediates are capable of a plethora of asymmetric reactions with a range of "nucleophilic" partners, including: cyclopropanation,[1–11] cyclopropenation,[12–15] C–H insertion,[16–22] and vinylogous addition[23–26] reactions. Further, pairing with prefunctionalized nucleophiles has broadened the scope of transformations to include a number of tandem reactions, such as: cyclopropanation/Cope rearrangement,[27–31] combined C–H functionalization/Cope rearrangement,[32–34] ylide formation/sigmatropic rearrangement,[35–40] and ylide formation/(1,3)-dipolar cycloaddition.[41–54]

Central to the growth of rhodium carbene chemistry over the past several decades has been establishing the correlation between the substitution of the diazocarbonyl, and ensuing metallocarbene intermediate, and the chemo- and stereoselectivity of the transformations in which it participates. The metal carbene transient is generated through the general mechanism shown in Figure 1.1. Coordination of the nucleophilic diazo-substituted carbon to a mildly Lewis acidic rhodium(II) complex generates a tetrahedral intermediate. Back-donation of electrons from the

metal to the carbene carbon results in extrusion of diatomic nitrogen to provide the metallocarbene.[55] Rhodium-bound carbene intermediates have become popularly classified into three disctinct categories: acceptor carbenes (**4**), acceptor/acceptor carbenes (**5**), and donor/acceptor carbenes (**6**) (Figure 1.1).[20] Once again, upon denitrogenative decomposition of the diazocarbonyl (**1–3**) by a dirhodium tetracarboxylate catalyst, the corresponding rhodium bound carbene can be represented as a neutral intermediate (**4–6**) or charged canonical form (**4´–6´**). In accord, it is reasonable to assume that the presence of an electron donating π–network adjacent (**3** and **6**) would provide an additional element of stabilization to the carbene, thereby attenuating the electrophilicity. Subsequent Hammett studies by Davies and co-workers have confirmed the hypothesis that stabilization of cationic character of the carbene is appreciable for aryldiazoacetates in the cyclopropanation of styrenes.[56] Thus, the acceptor diazoacetates (**1**), such as that derived from ethyl diazoacetate, which have historically been routinely studied, have given way to investigations of various donor/acceptor substituted diazoacetates (**3**).

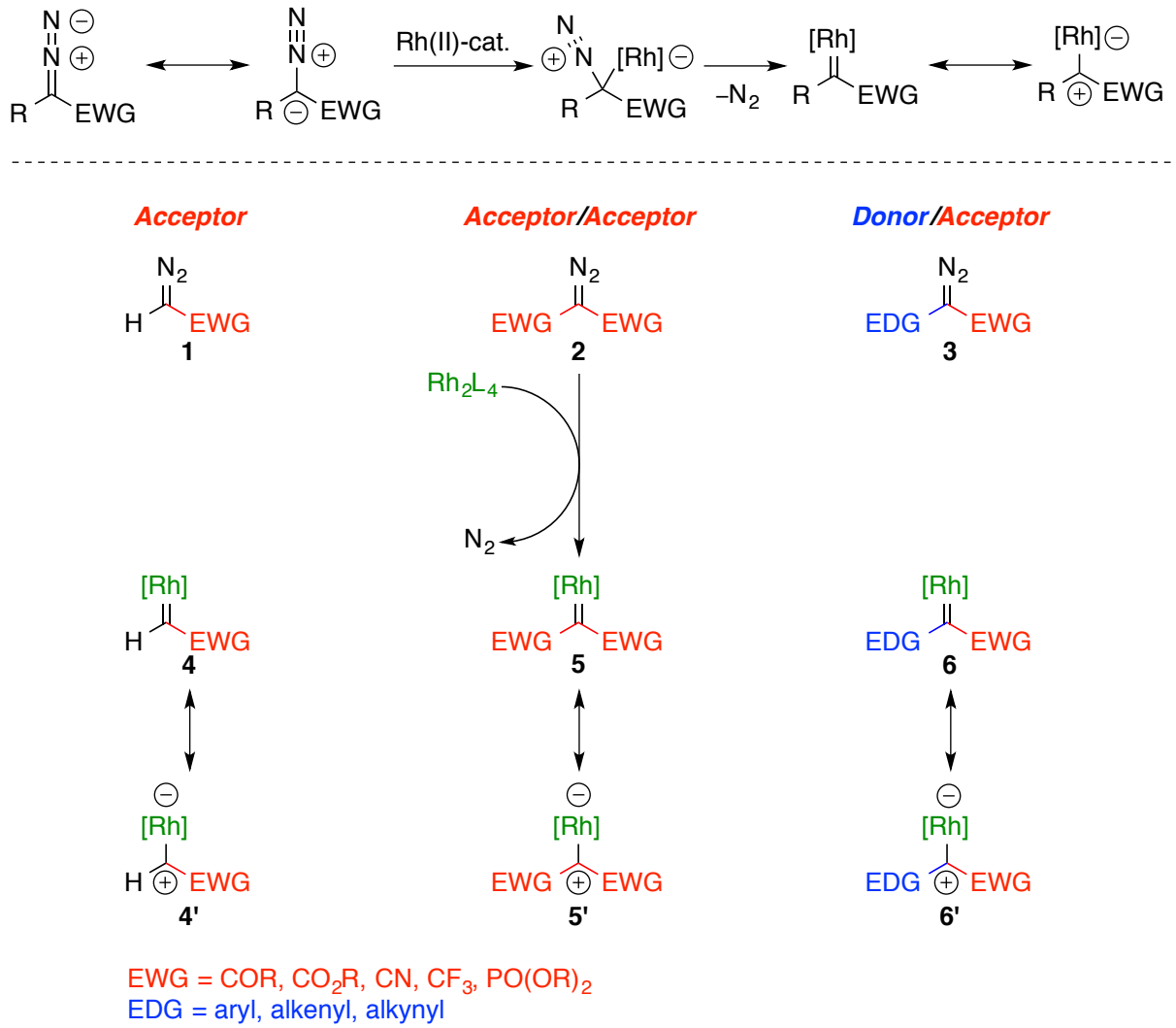


Figure 1.1 Overview of rhodium carbene formation and relevant resonance structures

Accompanying the appreciation for carbene substitution in rhodium carbene chemistry has been the development of chiral dirhodium tetracarboxylate catalysts, which have rendered a range of transformations stereoselective. The phthalimidyl (**7–12**) and naphthalimidyl (**13**) protected amino acid catalysts developed by Hashimoto,[15,57–59] Davies,[4] Charette,[9] and Müller[60] have proven effective for both stereoselective cyclopropanation and C–H insertion reactions of

donor/acceptor-substituted diazoacetates, as well as cyclopropanation and ylide formation/(1,3)-dipolar cycloadditions of acceptor/acceptor-substituted diazo compounds. The *N*-arylsulfonylprolinate-derived dirhodium tetracarboxylates (**14** and **15**), popularized by Davies and co-workers, have proven reliable in a broad range of donor/acceptor carbene transformations.[61–63] The most popular member of the family, {Rh_2[(*S*)-dosp]$_4$} (**14**), is particularly robust and has proven capable of achieving in excess of one million turnover numbers under solvent free reaction conditions.[61,64] The newest generation of chiral dirhodium tetracarboxylate catalysts are the triarylcyclopropane carboxylates {Rh_2[(*R*)-btpcp]$_4$} (**16**) and {Rh_2[(*R*)-tpcp]$_4$} (**17**).[26,65] Like the *N*-sulfonylprolinate catalysts, these sterically encumbered complexes are particularly effective for reactions of donor/acceptor substituted diazoacetates containing styryl donor groups, but are compatible with a broader range of esters. In addition, the cyclopropanecarboxylates have been uniquely effective in promoting enantioselective vinylogous additions/cyclizations of soft nucleophiles.[26]

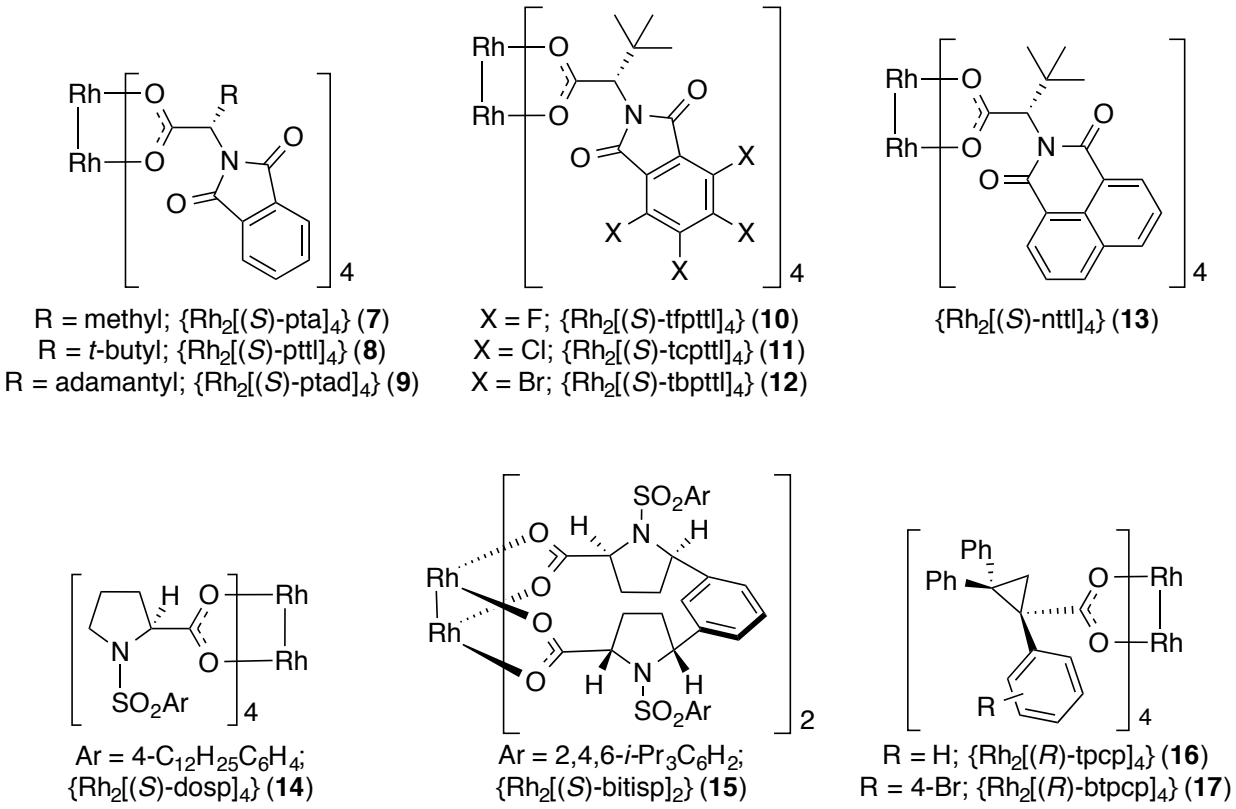


Figure 1.2 Representative chiral dirhodium tetracarboxylate catalysts

A distinguishing characteristic of these so-called "paddlewheel" dirhodium tetracarboxylate complexes is the element of axial symmetry.[66] In and of themselves, the individual ligands are generally lacking any elements of symmetry, whereas a simple achiral dirhodium tetracarboxylate, such as $[Rh_2(OAc)_4]$, possess a high order of symmetry. Substitution of the acetate groups on a highly symmetric dirhodium core with asymmetric, chiral ligands results in a complex of discrete axial symmetry.[61,62,66] Despite the conformational mobility of the carboxylate ligands, the phthalimide catalysts, specifically **8–12**, on the basis of X-ray crystallographic and computational studies, have been postulated to exist in an $\alpha\alpha\alpha\alpha$ C_4–symmetric "chiral crown." During

the course of a reaction, however, a distortion in symmetry is believed to occur to enable carbene formation, rendering the complex C_2–symmetric.[9] By constrast, the *N*-sulfonylprolinate catalysts (**14** and **15**) and the triarylcyclopropanecarboxylate catalysts (**16** and **17**) are suggested to exist in a net-dipole minimized, $\alpha\beta\alpha\beta$ D_2–symmetric conformation.[61,63] As with the **8–12**, complexes **16** and **17** are sterically encumbered catalysts, and computational studies have similarly predicted a distortion in the catalyst symmetry during binding of a diazoacetate to allow sufficient physical space for the donor/acceptor carbene.[65] Although the high symmetry models of complexes provide elegant rationales for inducing asymmetry, high levels of enantioinduction in various [2 + 1]-cycloadditions with dirhodium tetracarboxylates containing three chiral and one achiral ligands have been achieved in the laboratories of Corey,[13] Charette,[67] and Fox.[68]

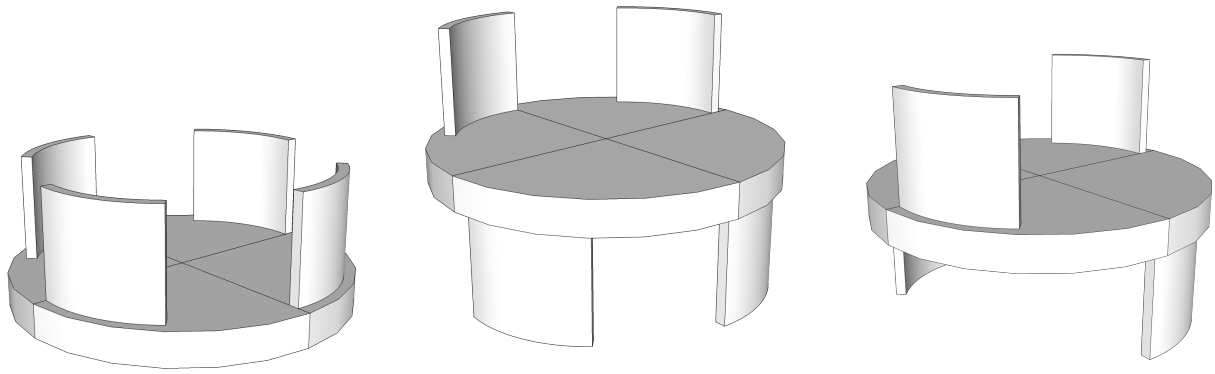
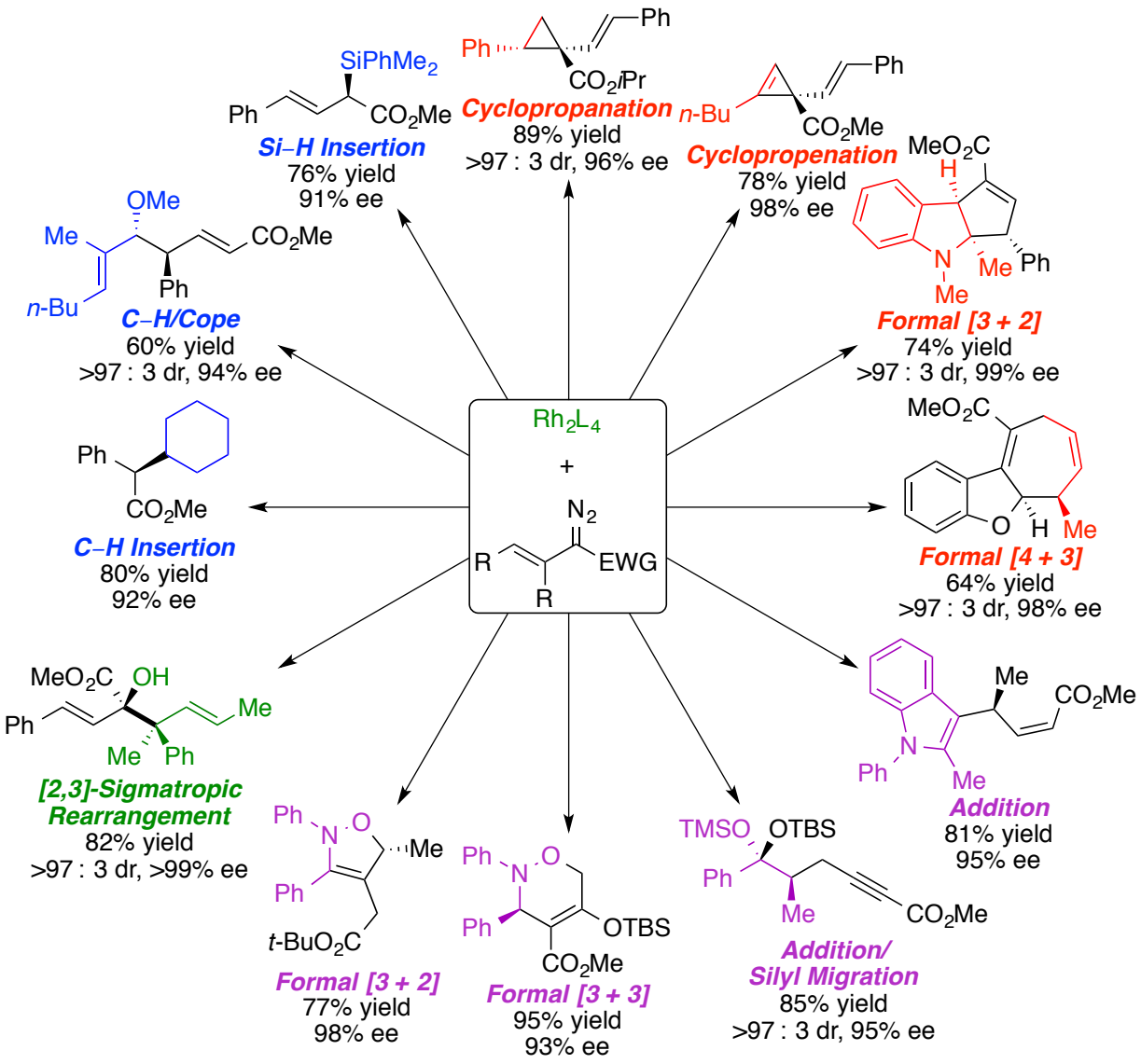


Figure 1.3 Relevant point group symmetries of chiral dirhodium tetracarboxylates

Indeed, the marriage of donor/acceptor-substituted diazocarbonyl compounds with chiral dirhodium tetracarboxylates has catalyzed a growth in achievable asymmetric transformations. A general, non-comprehensive overview, including representative examples of the stereoselective reactions known to date, is summarized in Scheme 1.1. Broad families of reactivity are color-coded along with the nucleophilic portion of the product. Thus, some of the reactions known to date are: insertion reactions into C–H[32,69] and Si–H[70] bonds (blue); formal cycloaddition reactions with electron rich π–bonds (red);[14,31,65,71] additions into the vinylogous position of a vinylcarbene (purple);[24–26,72,73] and tandem ylide formation/sigmatropic rearrangement (green).[36,37]



Scheme 1.1 Overview of asymmetric intermolecular transformations of donor/acceptor-substituted rhodium carbene intermediates

The following chapters will discuss advances made in some of these families of reactivity. The thematic focus will be on tandem and domino reactions involving rhodium carbene intermediates with alkenyl donor groups.

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– Chapter 2 –

Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement of Rhodium(II) Carbenes and Allyl Alcohols

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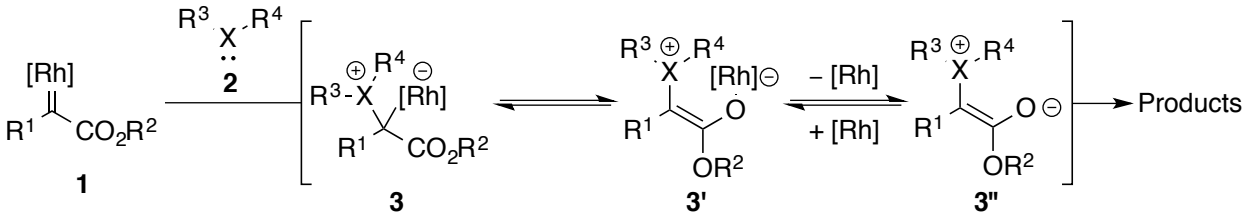
2.1 Introduction

Metal-catalyzed decomposition of diazoacetates to access transient metal-bound carbene intermediates, which undergo nucleophilic addition by a heteroatom to generate the corresponding ylide, have been studied in detail.[1–4] Metallated ylide intermediates are capable of a range of reactions, including: (1,3)-dipolar cycloaddition of carbonyl ylides with activated alkenes,[5–18] [2,3]-sigmatropic rearrangement of allyl-substituted ammonium/oxonium/thionium ylides,[19–25] [1,2]-Stevens-type rearrangement of alkyl and aryl substituted ammonium/oxonium/thionium ylides,[22–24,26–29] and formal [1,2]-hydrogen shift (formal O–H insertion) of protonated heteroatom ylides.[25,30,31]

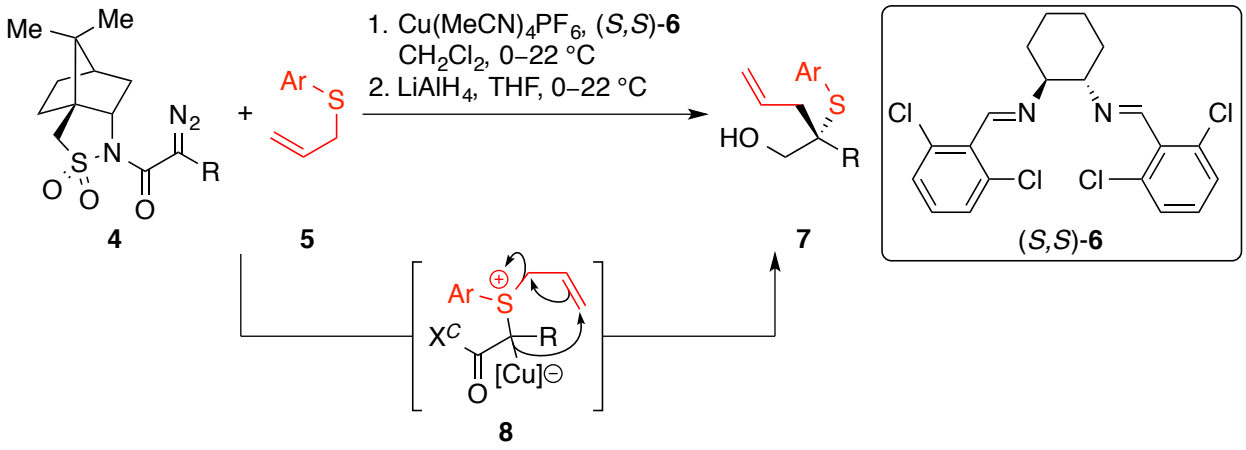
Until the past decade, scant examples of rhodium carbene-derived ylides participating in enantioselective intermolecular transformations were known.[19] Ylide formation can generally be thought of as the association of a generic rhodium carbene intermediate **1** with a Lewis basic heteroatom nucleophile **2**, which generates the three equilibrating metal-bound intermediates **3**–**3´´** (Scheme 2.1).[23] The commonly accepted rationale for the challenge of achieving asymmetric induction in rhodium-catalyzed reactions is that the mild Lewis acidity of the divalent rhodium

results in a rapid, barrierless liberation of the ylide intermediate to provide **3´´**. The process of demetallation is significantly faster than subsequent reaction or rearrangement, such that the rhodium complex cannot impart its chiral influence during the construction of new bonds and stereocenters.[32] Indeed, the only chiral transition metal catalysts capable of inducing enantioselective O–H and N–H insertion reactions are all copper-based.[33–36]



Scheme 2.1 Rhodium-catalyzed ylide formation

A few examples of the intermolecular formation of heteroatom ylides participating in tandem ylide formation/[2,3]-sigmatropic rearrangement, involving allyl and propargyl sulfides and donor/acceptor metallocarbene intermediates had been reported prior to investigations by the Davies group.[37–40] In these studies, achieving synthetically useful levels of asymmetric induction during formation of the 1,2-hydroxysulfide (**7**) was dependent upon both a chiral camphor sultam auxiliary on the carbene precursor (**4**) and a chiral copper-salen [(*S,S*)-**6**] complex.[40] Though a copper(I)-nuclear catalyst was necessary for achieving high levels of enantioselectivity (≥90% ee), rhodium(II)-based complexes would provide rearrangement products from the reaction of achiral aryldiazoesters and sulfides **5** in moderate stereoselectivity (79% ee).[37]



Scheme 2.2 Tandem ylide formation/[2,3]-sigmatropic rearrangement of donor/acceptor diazocarbonyls **4** and allyl thioethers **5**

Stereoselective, intermolecular reactions with protonated Lewis bases as ylide sources are, for the most part, absent from the rhodium carbene literature. In contemporaneous efforts, Zhu, Zhou, and Hu pioneered investigations to render both the formal X–H insertion process as well as 1,2- and 1,4-additions of rhodium carbene-derived ylides enantioselective transformations. Zhu and Zhou recognized that the proteodemetallation of an amine-derived ylide would conceivably by catalyzed by a Brønsted acid. Although unavailable to them at the time of their study, the computational investigations by Yu and co-workers suggest the general possiblity.[32] The theoretical study found that direct [1,2]-hydrogen shift of the oxonium ylide **10** is an energetically inaccessible pathway (ΔG_{sol} = 38.6 kcal mol^{-1}). Rather, the ylide (**10**) is intercepted by a second molecule of water (highlighted in red) to generate a new three component ylidic complex **11** (Figure 2.1). Isomerization to a metal-free enolic transient (**12-F**) is favored over the rhodium-enolate equivalent (**12-O**) by >6 kcal mol^{-1}, and thus, ensuing rhodium-associated intermediates are excluded for clarity. A second transition state (**TS-2**) arises along the reaction

landscape as partial protonation of the enol(ate) by a hydrogen (highlighted in red) with concomitant deprotonation of the first water molecule (highlighted in blue). Ejection of a water molecule from **TS-2** generates formal O–H insertion product **13**.

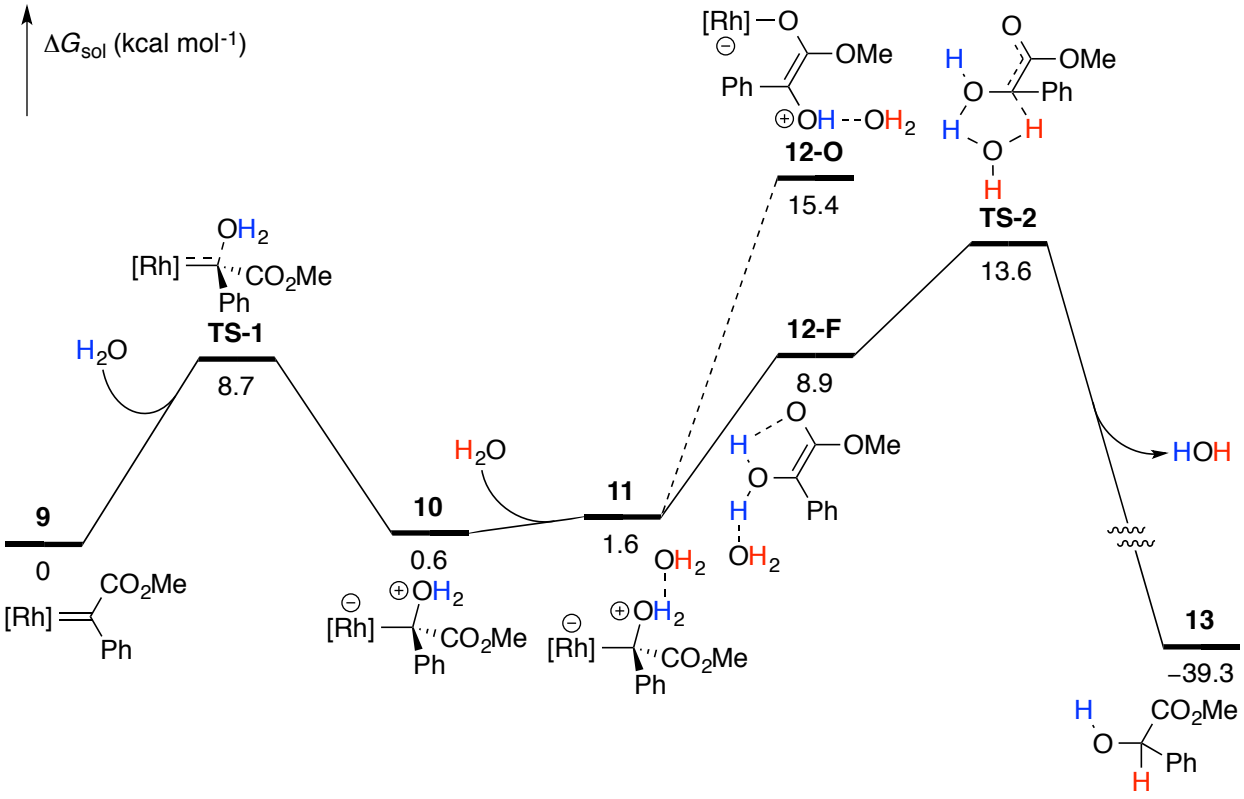
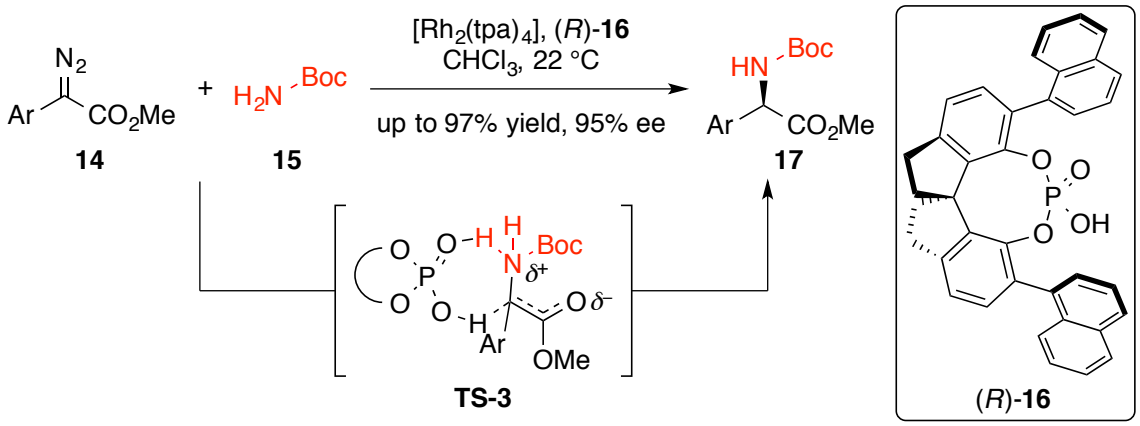


Figure 2.1 DFT computed free energy surface for Rh(II) carbene insertion into the O–H bond of water

Since formation of **TS-2** involves an exogenous Brønsted acid (the second molecule of water in Figure 2.1) and is a process with a significant energy barrier, it stands to reason that a more acidic proton source than water would be able to catalyze the process **12-F** → **TS-2**. Indeed, the

work by Zhu and Zhou in chiral phosphonate catalyzed enantioselective N–H insertion with rhodium carbene-derived ylides demonstrates the feasibility of tapping into these intermediates. Implementing the *t*-butoxycarbamate (**15**) as a N–H source and the spirocyclic C_2–symmetric phosphoric acid (*R*)-**16**, they found that the α-amino esters (**17**) were forged in excellent yield and enantioselectivity (Scheme 2.3).[41] A phosphonate moiety, like a water (or alcohol) molecule, is able to act in tandem as a Brønsted acid/base pair in close proximity. Thus, kinetic protonation of the enol(ate) and simultaneous deprotonation of the ammonium group, as represented by **TS-3**, provides the product in exceptional levels of enantioinduction.

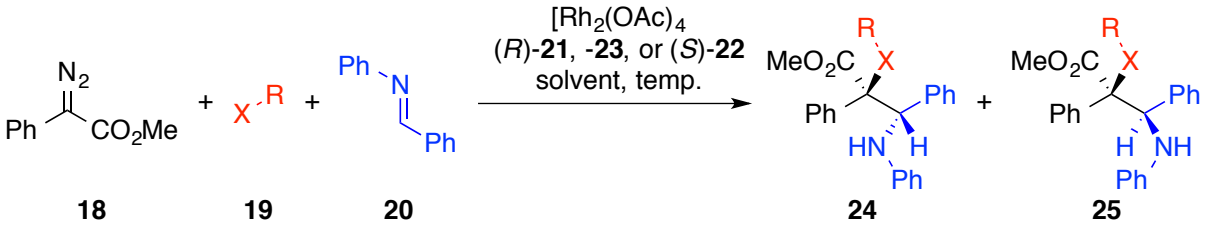


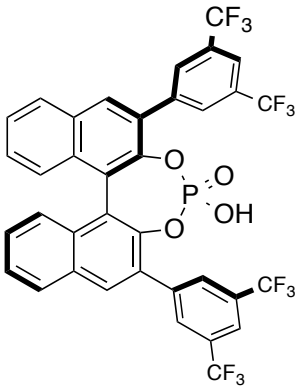
Scheme 2.3 Chiral phosphonate-catalyzed enantioselective N–H insertion

Rather than trapping the free enolic intermediate directly with a chiral proton source, Hu and co-workers implemented chiral Brønsted and Lewis acids for the activation of the carbonyl electrophile. A number of seminal investigations by Hu and Doyle demonstrated that oxonium and ammonium ylides from donor/acceptor-substituted rhodium carbenes could be intercepted by *N*-

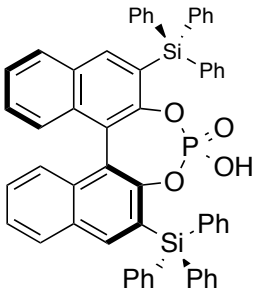
aryl imines,[42,43] aldehydes,[43,44] and α-ketocarbonyls[45,46] in high yield and diastereoselectivity. By extension, activated α,β-unsaturated carbonyls were found to be competent Michael acceptors for the electrophilic trap of the rhodium-generated ylide intermedaites.[47] Incorporating a chiral Brønsted or Lewis acid into the reaction mixture, stereoselective activation of the carbonyl electrophile was envisioned.

In subsequent studies, Hu demonstrated that both diastereomeric series of addition products (**24** and **25**) were accessible by tuning of the chiral phosphonate (Scheme 2.4); thus, implementing (*R*)-**21** provided smooth entry to **24** (90% yield, 10 : 90 dr, 96% ee) whereas phosphoric acid (*S*)-**22** provided the C(3)-epimeric amino ester **25** as the major product (93% yield, 97 : 3 dr, 93% ee).[48] Intriguingly, addition of catalytic (L)-tartaric acid proved beneficial from the standpoint of enantioselectivity in these reactions; however, the authors did not provide an explicit rationale for the cooperative effect of the two chiral catalysts. The oxonium ylides derived from arenols, specifically 9-phenanthyl alcohol, were also compatible partners for chiral phosphonate-catalyzed addition to imines.[49,50] In this study, the 3,3′-(9-phenanthryl)-binaphthylphosponate (*R*)-**23** was ideally suited for generating the α-alkoxy ester products in good yield and excellent stereoselectivity (86% yield, >99 : 1 dr, 93% ee).

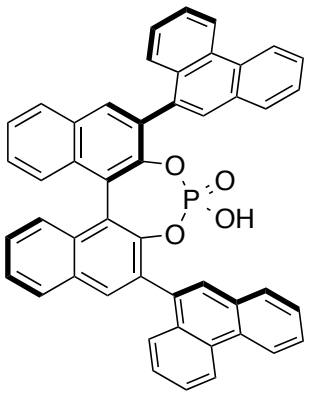




(*R*)-**21**
XR = H_2NCbz
90% yield
10 : 90 dr
96% ee



(*S*)-**22**
XR = H_2NCbz
93% yield
97 : 3 dr
93% ee

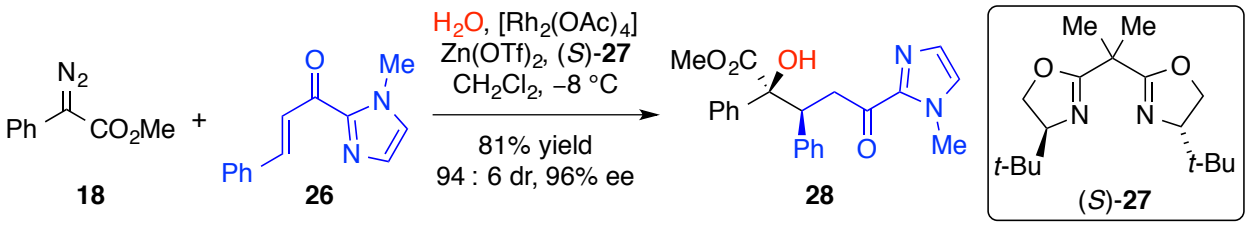


(*R*)-**23**
XR = 9-anthryl-OH
86% yield
>99 : 1 dr
93% ee

Scheme 2.4 Chiral phosphonate-catalyzed 1,2-addition of rhodium carbene-derived ylides

The diastereo- and enantioselective addition was also extended to include Michael acceptor electrophiles under modified conditions. As with the preliminary diastereoselective studies, achieving desired reactivity and stereoselection in these reactions was provisory to the presence of an electron deficient cinnamyl ketone moiety.[51,52] In the enantioselective variant of the transformation, a *N*-methylimidazole moiety was identified as a competent provider of both the withdrawing effect for requisite reactivity and a basic imine moiety to facilitate bidentate coordination of the chiral Lewis acid catalyst (Scheme 2.5, **26**).[52] Thus oxononium ylide generation from

water and rhodium acetate-catalyzed decomposition of phenyldiazoacetate **18**, with concomitant trap by the Zn-bisoxazoline [(*S*)-**27**] complex, afforded the product **28** in excellent yield and stereoselectivity (81% yield, 94 : 6 dr, 96% ee).

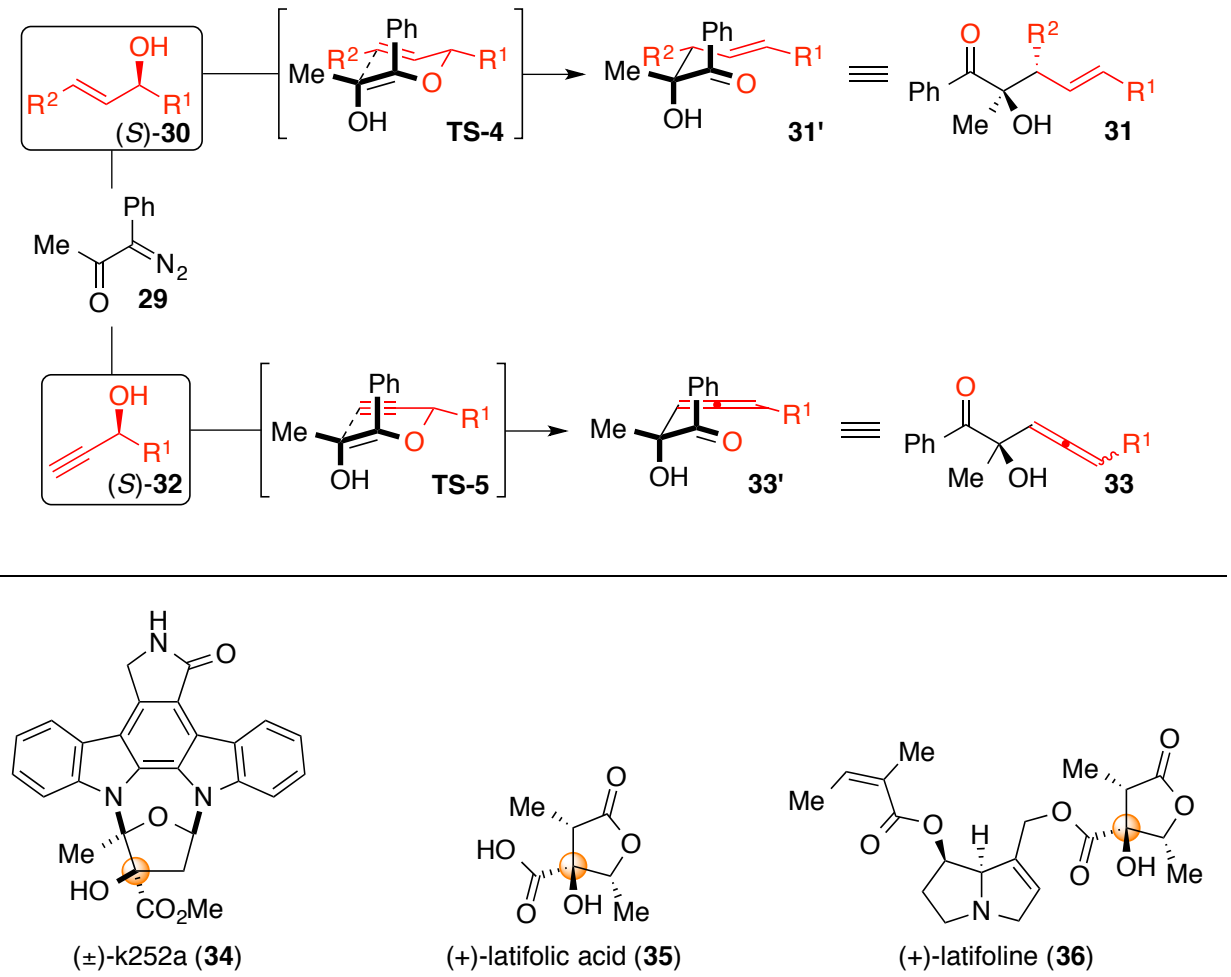


Scheme 2.5 Chiral Lewis acid-catalyzed 1,4-addition of rhodium carbene-derived ylides

The Davies group approached the field of rhodium carbene induced ylide formation anticipating that the discrete stabilization and selectivity afforded to donor/acceptor rhodium carbenes might present an opportunity to assert novel chemoselectivity over ylidic intermediates. The value of many of the aforementioned ylide-mediated reactions is the ability to construct quaternary, heteroatom-substituted stereocenters, and oftentimes a second, vicinal stereocenter, in a catalytic asymmetric fashion. The chiral-acid activated reactions take advantage of the significant energy barrier for the loss of the dirhodium catalyst and formal X–H insertion event of the ylidic intermediate (Figure 2.1), which involves an "intermolecular" component in the entry of a second equivalent of X–H (*e.g.* **10** → **11** → **12F**). Presumably intermediates **10** and **11**, being relatively isoergonic, exist in equilibrium prior to reacting. Thus, developing "intramolecular" manifolds for reactivity from the rhodium-bound ylide intermediate would offer the best opportunity for inducing chirality transfer from a dirhodium tetracarboxylate to the products. In addi-

tion to expanding the scope of existing asymmetric intermolecular rhodium-catalyzed reactions, avoiding the use of a dual catalyst system would be a more economically sound practice.

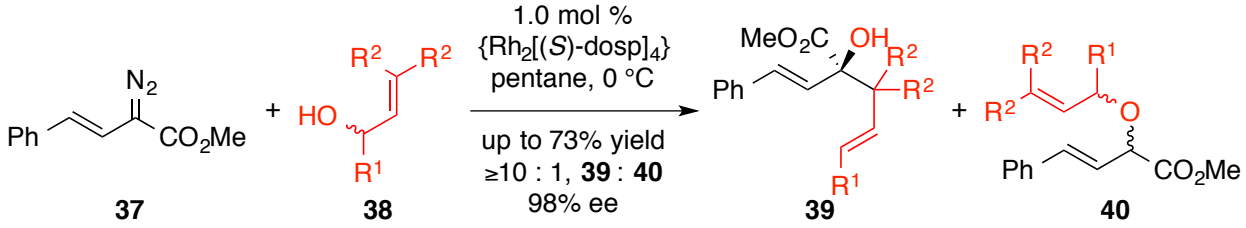
Although examples of intramolecular tandem ylide formation/[2,3]-sigmatropic rearrangement are extensive, the intermolecular variants involving rhodium carbene intermediates are much less investigated. Wood and co-workers had discerningly studied the chirality transfer process involved in tandem O–H insertion/Claisen rearrangements of diazoketone **29** derived rhodium carbenes and chiral secondary allyl[53,54] [(*S*)-**30**] and propargyl[55] [(*S*)-**32**] alcohols (Scheme 2.6). Transient formation of a so-called allyloxy (**TS-4**) or propargyloxy enol (**TS-5**), which undergoes [3,3]-sigmatropic rearrangement *via* a chair-like transition state, furnishes the hydroxy ketone products **31** or **33**, respectively. The chiral center of the alcohols dictate a favorable geometry for the chair-like transition state, which renders smooth chirality transfer to the products. The tandem reaction developed by Wood was subsequently utilized in construction of challenging hydroxy ester/acid stereocenters embedded in the structures of a potent PKC inhibitor (±)-K252a[56] (**34**) and the pyrrolizidine alkaloids (+)-latifolic acid (**35**) and (+)-latifoline (**36**).[57]



Scheme 2.6 Tandem O–H insertion/Claisen rearrangement and target applications

Since the intramolecular [2,3]-sigmatropic rearrangement of a rhodium-bound ylide intermediate would be expected to occur more rapidly than competing intermolecular processes, and the energy for dissociation of the rhodium complex from an oxonium ylide is calculated to be >7 kcal mol^{-1}, Davies and co-workers identified the corresponding allyl alcohols as promising candidates for methodology development. Indeed, the reaction of the racemic secondary 3,3′-disubstituted alcohol **38** (R^1 = R^2 = Me) with styryldiazoacetate **37** provided the rearrangement

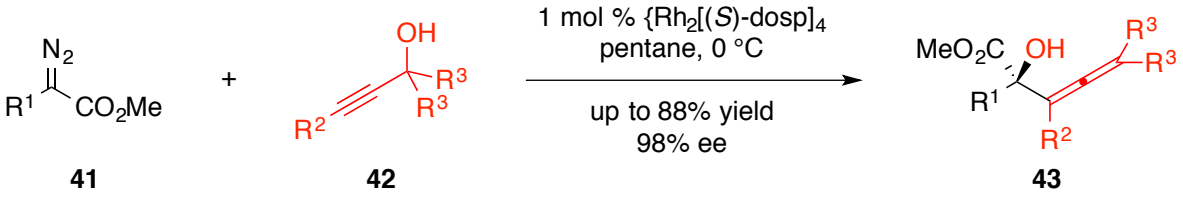
product (**39**) in excellent yield and stereoselection.[19] Noteably, the corresponding O–H insertion product (**40**) was formed in only trace quantities, if at all, under the prescribed reaction conditions; though, it became a competitive process in non-hydrocarbon solvents and with other dirhodium tetracarboxylate catalysts. The reaction was tolerant for a range of alkyl-carbinol substituents; however, primary and 3,3′-unsubstituted alcohols (**38**; R^1 = H or R^2 = H) led in general, to formation of the racemic O–H insertion product. The poor performance of these substrates was attributed to their hampered ability to stabilize positive charge accumulation across the allylic bond network. Aryldiazoacetates such as **18** were also competent carbene precursors; however, a measurable decrease in enantioselectivity was observed (*e.g.* **18**; 88% ee). The subtle differences in reaction conditions and use of diazoacetates rather than diazoketones is a testament to the sensitivity of the rhodium-bound ylide intermediate.



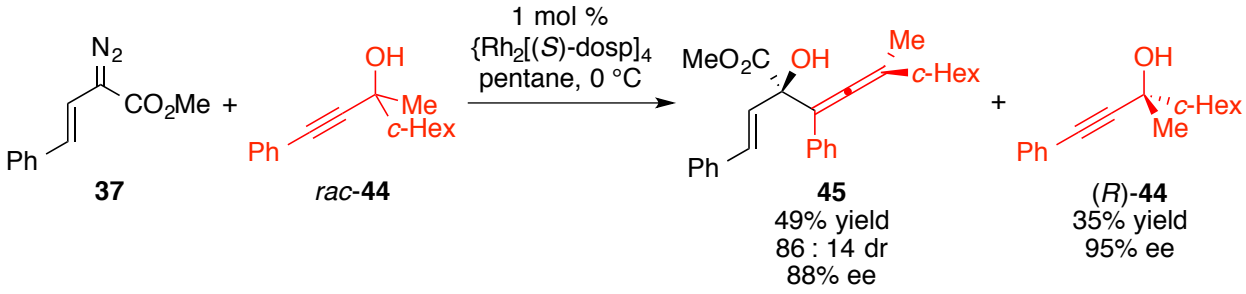
Scheme 2.7 Tandem ylide formation/[2,3]-sigmatropic rearrangement of rhodium carbenes and allyl alcohols

In an ensuing study from the Davies group, tertiary propargyl alcohols (**42**) were also proven competent sources for ylides formation/[2,3]-sigmatropic rearrangement (Scheme 2.8).[21] The rearrangement products (**43**) bearing a fully substituted allene were formed in excellent enanti-

oselectivity. As with the seminal investigation, styryl donor groups (**41**; R^1 = -HCCHAr) afforded products in higher stereoselectivity than their aryl counterparts. Moreover, acceptor-substituted diazo compounds (**41**, R^1 = H) were incompatible with the [2,3]-sigmatropic rearrangement chemistry, furnishing only the corresponding O–H insertion product in low yield. When a chiral, racemic tertiary propargyl alcohol such as *rac*-**44** was implemented, a kinetic resolution was observed through apparent match/mismatch of substrate and catalyst chirality. Thus, {Rh_2[(*S*)-dosp]$_4$}-catalyzed reaction with 1 equivalent of styryldiazoacetate **37** and *rac*-**44** led to stereoselective formation of axially chiral allene **45** and enantioenriched tertiary propargyl alcohol (*R*)-**44** (Scheme 2.8b). The minor diastereomer of **45** was inverted about the axial stereocenter, and the formation was attributed to reaction with (*S*)-**44**.



(a) Generic [2,3]-sigmatropic rearrangement of tertiary propargyl alcohols **42**



(b) Kinetic resolution of tertiary propargyl alcohol *rac*-**44**

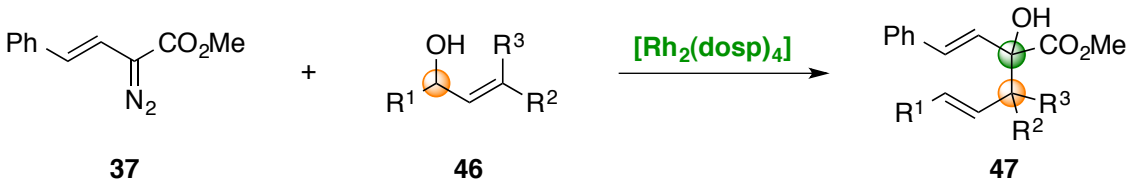
Scheme 2.8 Tandem ylide formation/[2,3]-sigmatropic rearrangement of rhodium carbenes and propargyl alcohols

We were encouraged by the immediate success with which we were met in reactions of allyl and propargyl alcohols. Thus, subsequent studies to expand the scope of the tandem ylide formation/[2,3]-sigmatropic rearrangement with additional classes of allyl alcohols, with a particular emphasis on attaining understanding of broader mechanistic aspects, were pursued.

2.2 Results & Discussion

2.2.1 Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement of Chiral Secondary Allyl Alcohols

Chiral allyl alcohols are readily available and have been widely used as versatile building blocks in organic synthesis.[58–63] The recent discovery of the tandem ylide formation/[2,3]-sigmatropic rearrangement as a preferred reaction outlet for rhodium-bound oxonium ylides, rather than the typified O–H insertion pathway prompted further investigations into the substrate scope and generality of the reaction. In particular, we envisioned the possibility of generating products containing vicinal stereocenters in a stereoselective manner (Scheme 2.9). The previous studies on sigmatropic rearrangement of chiral tertiary propargyl alcohols demonstrated the plausibility of a tetrahedral-to-axial chirality transfer with regard to the alcohol. Due to the crowded steric environment of the alcohol and rhodium carbene intermediate, however, a non-negligible match and mismatch was observed. Thus, only two of the four possible diastereoisomers, being an enantiomeric pair, could be prepared in an efficient fashion. Since secondary allyl alcohols were already demonstrated to be competent substrates, but do not present the same potential issue of steric bulk, we anticipated a "tetrahedral-to-tetrahedral" chirality transfer process conjoined with the enantioselective ylide forming process catalyzed by $\{Rh_2[(S)\text{-dosp}]_4\}$ to enable synthesis of all four of the possible stereoisomers (Scheme 2.9). Moreover, we envisioned the chirality transfer processes to be reliable and predictable: the allylic stereocenter of the product **47** (orange sphere) is controlled by the chirality of the allylic alcohol and the alkene geometry (**46**), whereas the homoallylic stereocenter (green sphere) is dictated by the chirality of the catalyst.



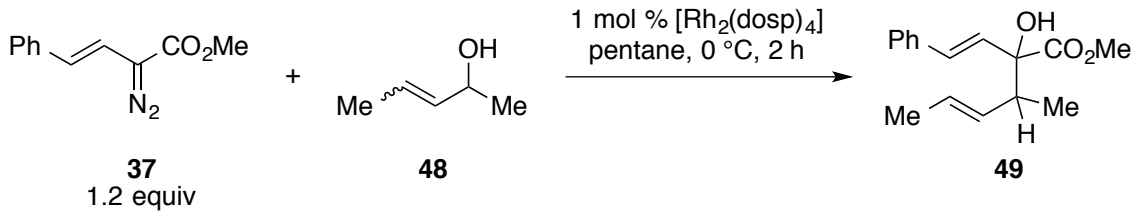
Scheme 2.9 Overview of ylide formation/[2,3]-sigmatropic rearrangement to form products bearing vicinal stereocenters

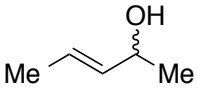
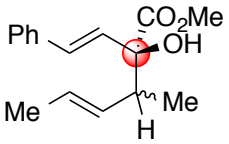
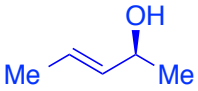
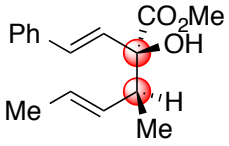
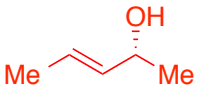
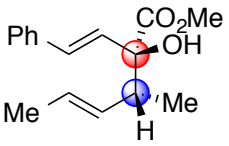
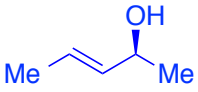
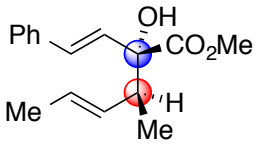
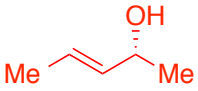
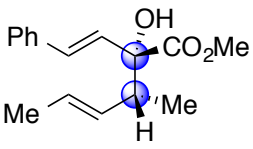
Chirality Transfer. We began our investigations by studying the reaction of the stereoisomers of 3-penten-2-ol (**48**) with 1.2 equiv of styryldiazoacetate **37**, catalyzed by 1 mole % of either {Rh_2[(*R*)-dosp]$_4$} or {Rh_2[(*S*)-dosp]$_4$} (Table 2.1). For purposes of clarity, a molecule of (*R*)-chirality or (*R*)-stereocenter is highlighted in red and a molecule of (*S*)-chirality or (*S*)-stereocenter is highlighted in blue. For each reaction, the diastereomeric ratio was determined from ^{1}H NMR analysis of the crude reaction residue and the ee of the major diastereomer isolated was determined by HPLC analysis upon comparison with a racemic sample. Reaction of *rac*-**48** with {Rh_2[(*S*)-dosp]$_4$} (entry 1) resulted in the indiscriminate formation of an equimolar mixture of C(3)-epimers of rearrangement product **49**. The diastereomers, which were readily separated by silica gel chromatography, were isolated in good combined yield. Comparison of the HPLC traces for each diastereomer with those of the reaction catalyzed by a racemic sample of rhodium catalyst, produced by mixing equal portions of {Rh_2[(*R*)-dosp]$_4$} and {Rh_2[(*S*)-dosp]$_4$}, revealed that both were formed in excellent levels of enantioselectivity, indicating both impecable stereocontrol by the rhodium catalyst and the absence of a chirality mismatch. Each C(3) diastereomer of **49** could be individually prepared in high yield and stereocontrol by reaction with enantiopure alcohols (entries 2 and 3). Thus, {Rh_2[(*S*)-dosp]$_4$}-catalyzed reaction of

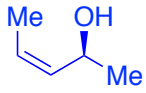
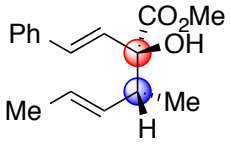
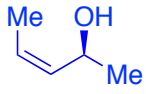
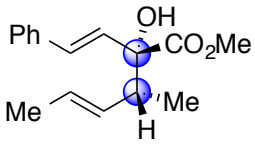
(*S*)- or (*R*)-**48** led to formation of the rearrangement products (2*R*,3*R*)- and (2*R*,3*S*)-**49**, respectively, in >10 : 1 dr and as single enantiomers. The remaining C(2) diastereomeric pair could be synthesized by substituting for the opposite enantiomer of the rhodium complex. And so, reaction of (*S*)- or (*R*)-**48** again provided smooth entry to **49** (entries 4 and 5). The (2*S*,3*R*) and (2*S*,3*S*) diastereomers were formed in marginally greater diastereoselectivity (92 : 8 and 95 : 5, respectively) and in exceptional enantioselectivity (>99% ee). The reactions of the four possible combinations of (*E*)-**48** and $[Rh_2(dosp)_4]$ reveal that all the stereoisomers of the product (**49**) can be obtained in good yields (54–78% yield) a stereoselective manner in (≥10 : 1 dr and >99% ee) (entries 2–5).

The reactions of (*S*,*Z*)-**48** with $\{Rh_2[(R)\text{-dosp}]_4\}$ and $\{Rh_2[(S)\text{-dosp}]_4\}$ were also examined (entries 6 and 7). As with the rhodium-catalyzed [2,3]-sigmatropic rearrangement of tertiary propargyl alcohols, matched and mismatched interactions between the chiral entities are evident. The $\{Rh_2[(R)\text{-dosp}]_4\}$-catalyzed reaction of (*S*,*Z*)-**48** with the styryldiazoacetate (**37**) is an efficient transformation, generating (2*S*,3*R*)-**49** in 69% yield and high stereoselectivity (entry 7, 94 : 6 dr and >99% ee). The stereochemical configuration of the product is the same as that of the product derived from the $\{Rh_2[(R)\text{-dosp}]_4\}$-catalyzed reaction of (*R*,*E*)-**48** in entry 4, as determined by comparison of HPLC traces. However, the $\{Rh_2[(S)\text{-dosp}]_4\}$-catalyzed reaction of (*S*,*Z*)-**48** with **37** is a mismatched reaction. A modest mixture of diastereoisomers (75 : 25 dr) is produced, and the major diastereomer of **49** shown is isolated in poor overall yield (entry 6, 33% yield). Notably, in this example, formal O–H insertion is the dominant reaction pathway, which could be deduced from ^{1}H NMR analysis of the crude reaction residue.

Table 2.1[a–c] Chirality transfer study for the ylide formation/[2,3]-sigmatropic rearrangement



entry	Rh(II)-cat.	alcohol	product	yield, %	dr	ee, %
1	***S***			72[d]	50 : 50	>99
2	***S***			70	92 : 8	>99
3	***S***			64	91 : 9	>99
4	***R***			54	92 : 8	>99
5	***R***			78	95 : 5	>99

6	***S***			35	75 : 25	>99
7	***R***			69	94 : 6	>99

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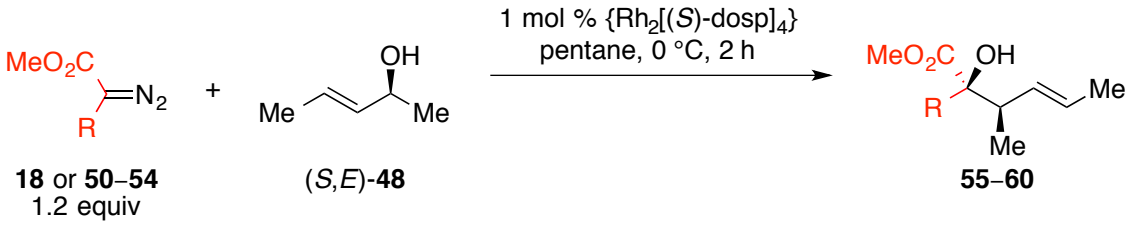
[a] Isolated yield of the major diastereomer of **49**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] Combined isolated yield of two diastereomers of **49**. (*R*)-chiral molecule or (*R*)-stereocenter. (*S*)-chiral molecule or (*S*)-stereocenter.

Diazoacetate Scope. The tandem ylide formation/[2,3]-sigmatropic rearrangement was then examined for a series of donor/acceptor-substituted diazoacetates (**18** and **50**–**54**) to determine the robustness over a variety of aryl and alkenyl substituents (Table 2.2). In all cases, the yields refer to the isolated yield of the major diastereomer of rearrangement product. The ee of the major diastereomer was determined by comparison of HPLC traces with the reaction of *racemic* **48** catalyzed by {Rh_2[(*R*)-dosp]$_4$} and {Rh_2[(*S*)-dosp]$_4$} mixtures. Across all substrates, the major diastereomer was produced with very high levels of enantioselectivity (>99% ee), but the diastereoselectivity was variable (79 : 21 – >95 : 5 dr). In the case of the aryldiazoacetates (**18**, R^1 = Ph and **50**, R^1 = 4-BrC_6H_4) the hydroxy esters **55** and **56** were forged in moderate yields (56% and 66% yield, respectively) and diastereoselectivity (≥9 : 1 dr). The 4-bromostyryl derivative (entry 3, **51** → **57**, R^1 = 4-BrC_6H_4HC=CH) was comparable to the unsubstituted phenyl analogue

(Table 1, entry 2). The butenyl- and propenyl-substituted diazo compounds (**52**, R^1 = EtHC=CH and **53**, R^1 = MeHC=CH, respectively) participated in the rhodium-catalyzed transformation to afford the corresponding products with high levels of asymmetric induction (**58** and **59**, respectively). In the case of an unsubstituted vinyldiazoacetate (**54**, R^1 = H_2C=CH), rearrangement product **60** was obtained in modest yield (43%) and with poor diastereoselectivity (79 : 21 dr), although the enantiopurity of the major diastereomer was again high (>99% ee). It is well established that {Rh_2[(*S*)-dosp]$_4$}–catalyzed cyclopropanations with vinyldiazoacetate **54** proceed with moderate enantiocontrol,[64–68] and so, the disappointing diastereoselectivity observed in formation of **60** is consistent with an inability of {Rh_2[(*S*)-dosp]$_4$} to exert high stereocontrol in the ylide-forming process in this case. The relative and absolute configuration of compound **57** was determined by X-ray crystallographic analysis and was tentatively assigned to the series of products by analogy.

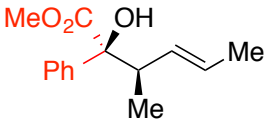
Table 2.2[a–c] Scope of the donor group for the tandem ylide formation/[2,3]-sigmatropic rearrangement



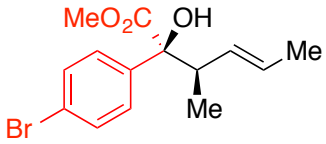
18 or **50**–**54**
1.2 equiv

(*S*,*E*)-**48**

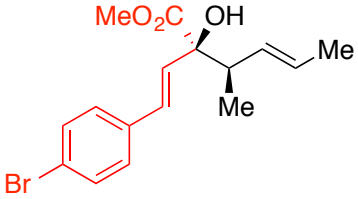
55–**60**



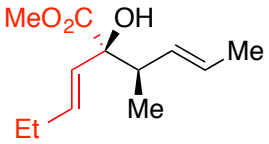
55
56% yield
94 : 6 dr
>99% ee



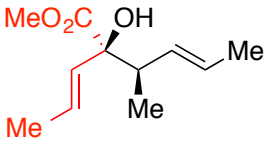
56
66% yield
90 : 10 dr
>99% ee



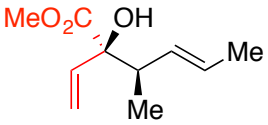
57
69% yield
>95 :5 dr
>99% ee



58
60% yield
>95 : 5 dr
>99% ee



59
65% yield
>95 : 5 dr
>99% ee



60
43% yield
79 : 21 dr
>99% ee

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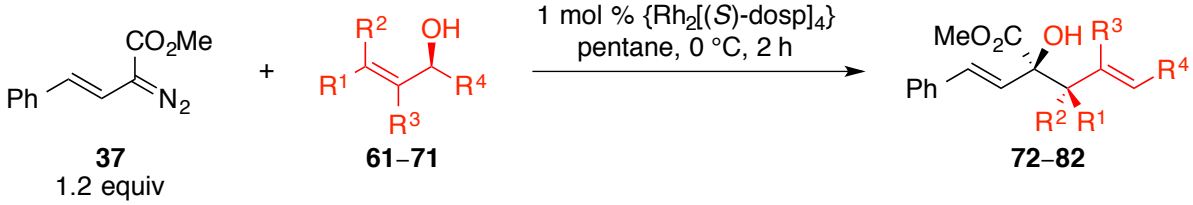
[a] Isolated yields of the major diastereomer of **55**–**60**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Alcohol Scope. The tolerance of the reaction to various substituents on the alcohol (**61**–**71**) was then studied, and the results of these investigations are summarized in Table 2.3. Noteably, the enantiopure (*S*)-alcohols bearing a methyl substituent at the carbinol position (R^4 = Me) were readily resolved from their racemates *via* Amano AK Lipase-catalyzed (*R*)-selective acetylation. For alcohols with more encumbered carbinol groups, resolution of racemic alcohol was accomplished by Sharpless asymmetric epoxidation. In general, extended aliphatic and aryl substituents at the C(3) position of the alcohol were well tolerated (entries 1 and 2, **61** and **62**). Alcohols with secondary or tertiary substituents at R^1 (entries 3 and 4, **63** and **64**) afforded the corresponding rearrangement products in excellent asymmetric induction, but the yields were attenuated (60% and 42%, respectively), presumably due to unfavorable steric interactions with the catalyst at the site of C–C bond formation. The effect of various functional groups at the carbinol position was explored in entries 5–7, and in all cases the desired products (**76–78**, respectively) are formed in excellent yield. Thus, mismatch between alcohol and catalyst is unlikely to be present, even for more hindered secondary allyl alcohols. Of particular significance is the reaction of the mono-benzyl-protected 1,2-diol (**67**), which is capable of selective reaction at the allylic alcohol over the nucelophilic benzyl ether functionality. An array of alcohols bearing C(2)-substitution (entries 8–10, **69**–**70**) were also evaluated, and proved amenable to the tandem ylide formation/[2,3]-sigmatropic rearrangement. It is expected that in the oxonium-ylide intermediate formed any functionality at C(2) would be oriented away from the catalyst, and thus, have minimal consequence on reactivity. The products **79**–**81** bearing a trisubstituted olefin were formed in generally good yields (61–77%) and as single stereoisomers. Moreover, a 3,3′-disubstituted alcohol (**71**) enabled the synthesis of [2,3]-rearrangement product **82**, bearing vicinal quaternary stereocenters in excellent yield and stereoselection (82% yield, >95 : 5 dr, 99% ee).

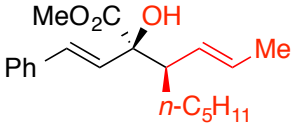
Table 2.3[a–c] Scope of the allyl alcohol for the tandem ylide formation/[2,3]-sigmatropic rearrangement



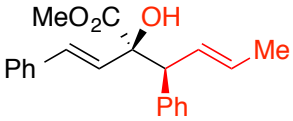
37
1.2 equiv

61–71

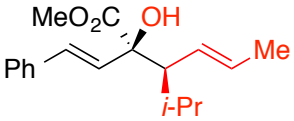
72–82



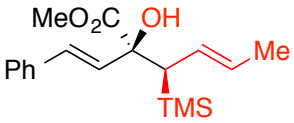
72
83% yield
>95 : 5 dr
99% ee



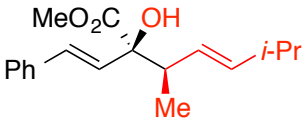
73
71% yield
>95 : 5 dr
99% ee



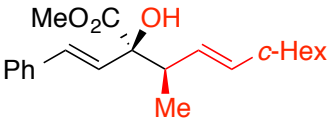
74
60% yield
>95 : 5 dr
99% ee



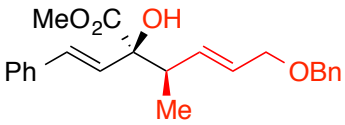
75
42% yield
>95 : 5 dr
99% ee



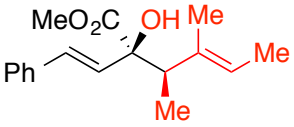
76
75% yield
>95 : 5 dr
99% ee



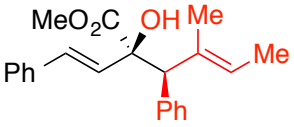
77
86% yield
>95 : 5 dr
99% ee



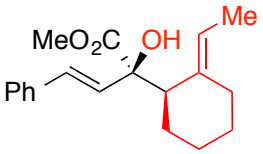
78
70% yield
>95 : 5 dr
99% ee



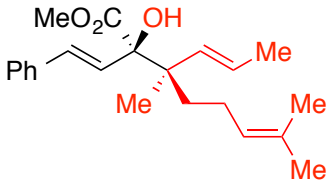
79
61% yield
>95 : 5 dr
99% ee



80
68% yield
>95 : 5 dr
99% ee



81
77% yield
>95 : 5 dr
99% ee



82
82% yield
>95 : 5 dr
99% ee

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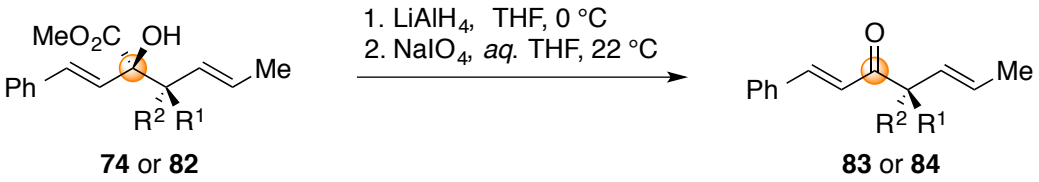
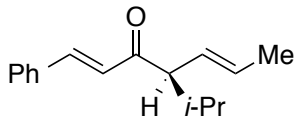
[a] Isolated yields of the major diastereomer of **72**–**82**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Product Functionalization. The synthetic utility of the rhodium-catalyzed sigmatropic rearrangement with the chiral alcohols lies in the ability to generate two adjacent stereogenic centers in a controlled and predictable manner. A distinctive feature of the transformation is the generation of the quaternary hydroxy ester moiety bearing a vicinal stereocenter, which is a structural feature embedded in a number of natural products.[56,57,69–73] In an effort to demonstrate the broader synthetic potential of the reaction, however, we performed a two-step manipulation to convert the rearrangement products to enones, containing an α-chiral center (Table 2.4). Enones containing either tertiary (**83**) or quaternary (**84**) stereocenters α to the carbonyl are readily prepared in short order with excellent yields for the two-step process. Impressively, racemization of the tertiary, allylic α-stereocenter in the synthesis of **83** is not observed. A particularly appealing feature of this approach to chiral enones is the likelihood that a chiral catalyst would not be required because the stereogenic center α to the carbonyl is controlled by the chirality of the starting alcohol.

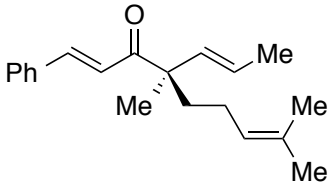
Table 2.4[a,b] Conversion of hydroxy esters to ketones



74 or **82** → **83** or **84**



83
89% yield
>99% ee

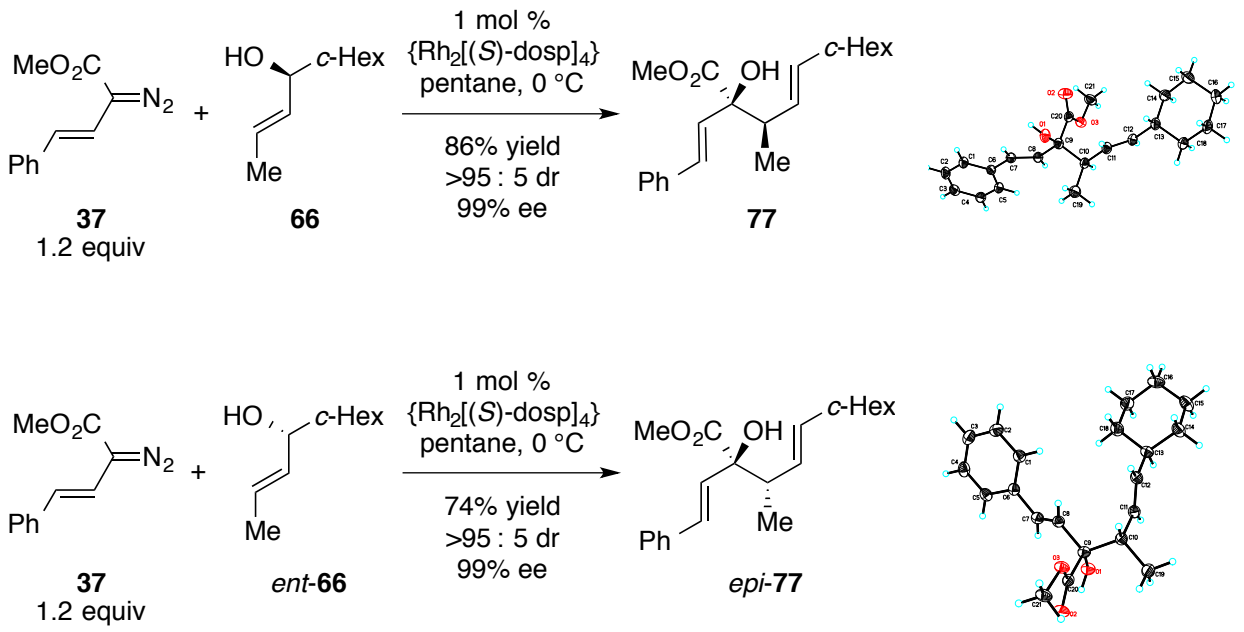


84
90% yield
>99% ee

[a] Isolated yields of **83** and **84**. [b] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Stereochemical Rationale. As an effort to rigorously establish the relative and absolute stereochemistry of the products, we conducted the ylide formation/[2,3]-sigmatropic rearrangement with vinylcarbene precursor **37** and {Rh_2[(*S*)-dosp]$_4$} using each enantiomer of the chiral allyl alcohol (**66** and *ent*-**66**), which produces crystalline products (Scheme 2.10). Thus, reaction between **37** and **66**, previously reported in Table 2.3 entry 6, furnished the (2*R*,3*R*)-stereoisomer of product (**77**) as verified by X-ray crystallographic analysis (**77′**) in excellent yield and levels of stereoselectivity. By analogy, the reaction of **37** and enantiomeric alcohol *ent*-**66** provided the epimeric (2*R*,3*S*)-stereoisomer (*epi*-**77**) as evidenced by X-ray crystallographic determination

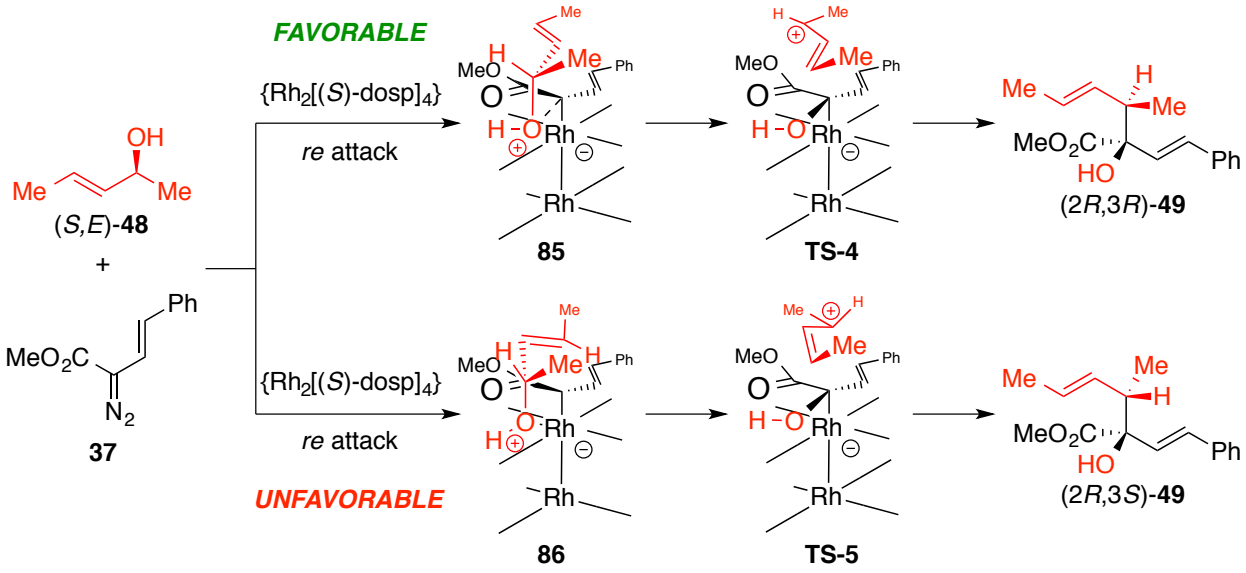
(*epi*-**77′**) in similarly good yield and excellent stereoselection. In addition, the stereochemistry of the other rearrangement products was assigned by analogy.



Scheme 2.10 X-ray crystallography study of chirality transfer from alcohol to product

Due to the uniformly high levels of asymmetric induction for the tandem ylide-formation/[2,3]-sigmatropic rearrangement, we sought a general transition state model which could rationalize the origins of these stereochemical observations.[24,40,74–84] It has been well established that the {Rh_2[(*S*)-dosp]$_4$}-catalyzed reactions of vinyldiazoacetates proceeds *via* selective *re* facial attack of the vinylcarbene intermediate.[85] The [2,3]-sigmatropic rearrangement would be expected to proceed through an envelope-like transition state, in which $A_{1,3}$–strain is minimized.[86–89] A reasonable model, which takes into account the established stereochemical

understanding of these reactions is shown in Scheme 2.11. *Re* attack of the carbene by (*S,E*)-**48** would initially generate the rhodium bound ylide **85**. Rupture of the C–O bond and migration of the alkene, precluding bond rotation provides transition state **TS-4**. Subsequent C–C bond formation from **TS-4** would lead to the formation of the observed (2*R*,3*R*) stereoisomer of **49**. Analogously, the reaction of (*S,E*)-**48** could produce an ylidic intermediate **86**, which is related to **85** by rotation about the carbinol C(1)–alkenyl C(2) bond. The consequent *syn*-position of the carbinol methyl group and the vinylic C–H bond results in substantial $A_{1,3}$–interactions, which make formation of **86** far less favorable. Nonetheless, cleavage of the C–O bond with tandem olefin migration provides the intimate ion pair represented by **TS-5**, and upon C–C bond formation, the diastereomeric product (2*R*,3*S*)-**49** is produced. The $A_{1,3}$–strain present in **TS-5**, and absent from **TS-4**, is likely the operative force responsible for the preferential formation of the (2*R*,3*R*)-diastereomer.



Scheme 2.11 Stereochemical model for the tandem ylide formation/[2,3]-sigmatropic rearrangement

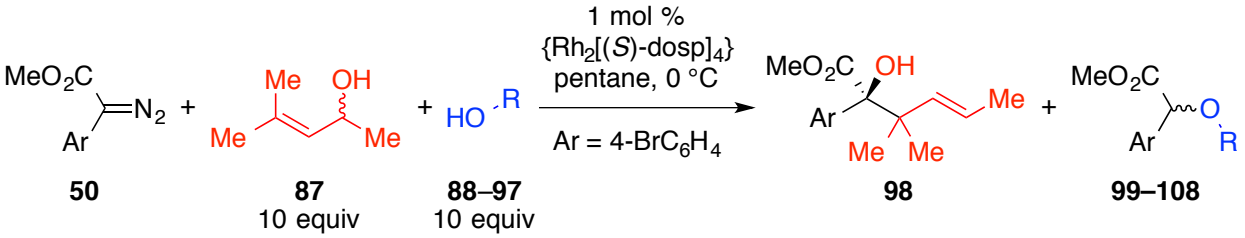
2.2.2 Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement of Primary Allyl Alcohols

From the computational study by Yu and co-workers, briefly summarized by Figure 2.1, we were able to draw additional hypotheses about the behavior of rhodium carbene intermediates and allyl alcohols. Since the [2,3]-sigmatropic rearrangement of secondary allyl alcohols often occurs in the complete absence of the otherwise competitive O–H insertion reaction, the energy barrier for the former reaction must be significantly lower. In addition, the rhodium carbene **9** and rhodium bound ylide **10** intermediates are comparable in energy (0 and 0.6 kcal mol^{-1}, respectively), and the energy for the forward reaction (**TS-2**) is significantly greater than that for dissociation of the ylide (**TS-1**) to regenerate the rhodium carbene (13.6 and 8.7 kcal mol^{-1}, respectively).[32] And so, the oxonium ylide formation process, particularly with alcohols only capable of undergoing formal O–H insertion, might be a reversible process. Therefore, we reasoned that the [2,3]-sigmatropic rearrangement of allyl alcohols could outcompete less-hindered aliphatic and aryl alcohols, thereby providing a new mechanism for selective functionalization of complex polyhydroxylated molecules.[90]

We initiated a study to investigate this hypothesis by adding aryldiazoacetate **50** to an equimolar mixture of *racemic* allyl alcohol **87** and a competing O–H bond source (**88–97**), in the presence of $\{Rh_2[(S)\text{-dosp}]_4\}$ (Table 2.5). Reaction *via* ylide formation/[2,3]-sigmatropic rearrangement with **87** to generate **98** was assigned an arbitrary relative rate (k_{rel}) value of 1.00, such that all of the alcohols (**88–97**) could be compared.[91] The ratio of products formed in the reaction (**98** : **99–108**) as evidenced by ^{1}H NMR analysis of the crude reaction residue, was used as a measure of the relative rate for reaction of alcohols **88–97** compared with **87**. The methynyl α-proton of the O–H insertion product, a singlet at 4.6–5.0 ppm, was integrated relative to the vinyl proton, a doublet at 5.7 ppm. Thus, methanol (**88**) reacted with the rhodium carbene intermedi-

ate to generate an O–H insertion product approximately 10 times faster than **87**. A seemingly innocent increase in carbon chair length by a single methylene unit, as with ethanol (**89**), resulted in more than 50% decrease in rate of reaction (entry 2, **89** k_{rel} = 4.8). By extension, further linear increase in steric bulk of several methylene units (**90**) resulted in a reaction ~50% slower than that observed for ethanol (entry 3, **90**, k_{rel} = 2.3). Despite being more sterically encumbered, benzyl alcohol (**91**) reacted at a comparable rate to *n*-hexanol (k_{rel} = 2.9); however, allyl alcohol (**92**) was markedly slower (k_{rel} = 1.8). The results from reactions with bulkier and/or less nucleophilic "alcohols" were far more gratifying (entries 6–10, **93–97**). Both secondary and tertiary alcohols [*i*-propanol (**93**), *c*-hexanol (**94**), and *t*-butanol (**95**)] were more than an order of magnitude slower to react than **87** (k_{rel} <0.05), as none of the corresponding O–H insertion products was apparent by ^{1}H NMR analysis. Similarly, phenol (**96**) and acetic acid (**97**) both failed to react to any measurable degree, and so, were assigned a k_{rel} value of <0.05.

Table 2.5 Relative rates of reactivity (k_{rel}) for O–H insertion of various alcohols compared with ylide formation/[2,3]-sigmatropic rearrangement with **87**

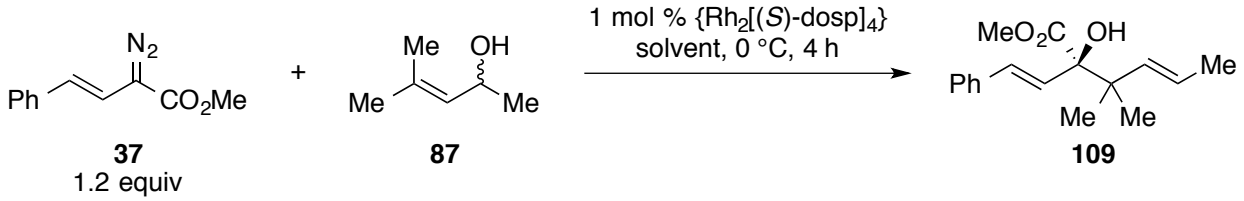


HO, Me	HO, Et	HO, *n*-Hex	HO, Ph	HO
88	**89**	**90**	**91**	**92**
10.3	4.8	2.3	2.9	1.8
HO, *i*-Pr	HO, *c*-Hex	HO, *t*-Bu	HO, Ph	HO, Ac
93	**94**	**95**	**96**	**97**
<0.05	<0.05	<0.05	<0.05	<0.05

We were generally pleased with the potential for regio- and chemoselective functionalization based upon our preliminary findings presented in Table 2.5. With many primary alcohols, however, we encountered issues of incomplete dissolution in the hydrocarbon solvent, which was previously deemed optimal for the rearrangement chemistry. In order to establish the rearrangement chemistry as a synthetic tool for the regio- and chemoselective functionalization of complex molecules, we decided to revisit the reaction optimization[19] for the tandem ylide formation/[2,3]-sigmatropic rearrangement such that accurate rate data might be accrued for more complex substrates which lack sufficient solubility in hydrocarbons. To expedite the study, we relied upon ^{1}H NMR yields based on an internal standard of dibromomethane ($\delta \approx 4.9$ ppm,

measuring the relative integral compared with the vinylic proton of **109** (δ = 5.61 ppm). A racemic sample of **109** for ee determinations was prepared by reaction of **37** and **87** under the catalysis of an equimolar mixture of {Rh_2[(*R*)-dosp]$_4$} and {Rh_2[(*S*)-dosp]$_4$}. And so, we first ran the standard reaction in pentane, for which we recorded an 87% yield and 97% ee for formation of **109** (Table 2.6, entry 1). We hoped that trifluoroethanol might be sufficiently non-nucleophilic solvent while offering a unique solubility profile. Although the product (**109**) was formed in a moderate 42% yield, O–H insertion was a substantial byproduct of the reaction. Moreover, the enantioselectivity was drastically decreased in the highly polar reaction medium (entry 2, 33% ee). These observations promoted us to implement a fairly non-polar, ethereal solvent. Methyl *t*-butyl ether (MTBE) provided **109** in a gratifying 84% yield and 95% ee (entry 3); comparable to the figures recorded for the reaction in pentane. Encouraged by these results and the rate data we had acquired thus far, we thought perhaps a bulky alcohol solvent might be non-nucleophilic and modestly polar to allow for a selective reaction. Indeed, the rhodium-catalyzed reaction in *t*-amyl alcohol provided a respectable 67% yield of **109** in excellent enantiomeric excess (entry 4). We continued our study by exploring more typical laboratory solvents. Reaction in tetrahydrofuran furnished a modest 51% yield of **109**, as C–H insertion into the solvent was a competitive process (entry 6). Nonetheless, the asymmetric induction in the reaction was in the realm of synthetic utility (88% ee). It came without surprise that *i*-propanol was, of the solvents examined, the least effective, as competitive O–H insertion was the dominant reaction pathway (entry 7). We were pleased to find, however, that ethyl acetate furnished a superior combination of both yield and enantioselectivity when compared to pentane (entry 8, 91% yield, 99% ee).

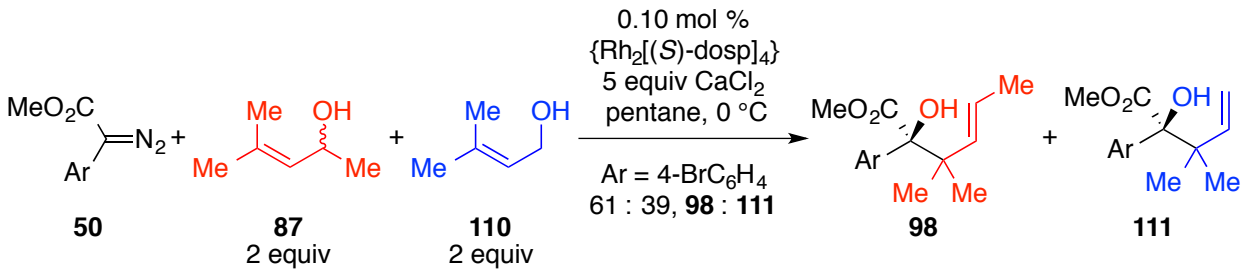
Table 2.6[a,b] Solvent study for the tandem ylide formation/[2,3]-sigmatropic rearrangement



entry	solvent	yield, %	ee, %
1	pentane	87	97
2	CF_3CH_2OH	42	33
3	MTBE	84	95
4	*t*-AmOH	67	97
5	THF	51	88
6	Et_2O	96	92
7	*i*-PrOH	9	91
8	EtOAc	91	99

[a] Yield was determined by ^{1}H NMR analysis of the reaction compared with an internal standard of CH_2Br_2. [b] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

In unpublished work, Li had previously demonstrated that $CaCl_2$ had a beneficial effect on the rearrangement chemistry, enabling reduced catalyst loadings of 0.01 mol % without substantial detriment to yield or enantioselectivity.[92] A rationale and justification for the additive and its effect, however, were not provided. Charette and co-workers have reported beneficial effects of catalytic achiral Lewis and Brønsted acids in enantioselective cyclopropanations of styrenes with acceptor/acceptor rhodium carbenes.[93–96] We were intrigued whether the salt might also play a role in the relative rate of either O–H insertion or [2,3]-sigmatropic rearrangement. For the study, 3-methyl-2-butenol (**110**) was chosen as a substrate as it was expected to have a rate of reaction (k_{rel}) comparable to **87**, but being a primary alcohol, was previously shown to be incapable of participating in rearrangement (Scheme 2.12). Much to our surprise, in addition to the anticipated product (**98**) resulting from reaction with **87**, a [2,3]-sigmatropic rearrangement product **111** arising from reaction with **110** was apparent by ^{1}H NMR analysis of the crude reaction residue. Moreover, only a trace quantity of the product corresponding to O–H insertion with **110** was observed.



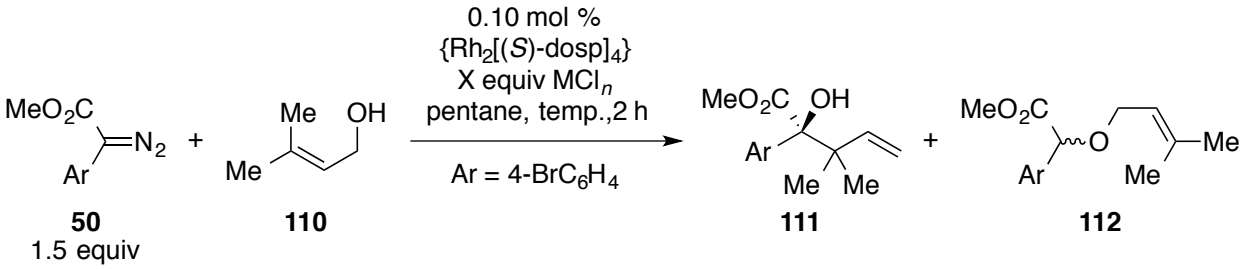
50 **87** 2 equiv **110** 2 equiv **98** **111**

Scheme 2.12 Discovery of a tandem ylide formation/[2,3]-sigmatropic rearrangement of primary allyl alcohols

Since primary allyl alcohols, including **110**, were demonstrated in the seminal study to be incompatible for tandem ylide formation/[2,3]-sigmatropic rearrangement,[19] we were encouraged by the apparent chemodivergent effect afforded by calcium chloride. Thus, our focus shifted from rate and mechanistic analysis of the previously deemed competent substrates, to optimization and understanding the scope of the [2,3]-sigmatropic rearrangement with primary allyl alcohols. We decided to study the efficacy of the rearrangement reaction by pairing of diazo **50** and primary allyl alcohol **110** in the presence of various group I and II chloride salts, which were dried at elevated temperature under vacuum for 12 h prior to use, (Table 2.7) at a low catalyst loading. A control reaction in the absence of any additive was consistent with the previous report, as only O–H insertion product **112** was apparent by ^{1}H NMR analysis of the crude residue (entry 1). Pretreatment of the allyl alcohol and {Rh_2[(*S*)-dosp]$_4$} with superstoichiometric $CaCl_2$, however, resulted in preferential formation of **111**. The rearrangement product was isolated in moderate yield and exceptional level of enantioselectivity (entry 2, 56% yield, >99% ee). Intriguingly, reducing the reaction temperature from 22 to 0 °C resulted in a marked decrease in chemoselectivity (entry 3), whereas increasing the reaction temperature to 35 °C had little measurable effect (entry 4). The lithium, potassium, and strontium chloride salts (entries 5–7, respectively) were all considerably less efficient in promoting the [2,3]-sigmatropic rearrangement than their calcium counterpart. Magnesium chloride, on the other hand, furnished slight improvements in both product ratio and isolated yield of **111** (entry 8, 80 : 20 ratio, 59% yield, >99% ee). The equivalents of additive were then probed. When the loading of $CaCl_2$ was decreased to 1.5 equiv, an unsurprising increase in the formation of O–H insertion product was observed (entry 9). Increasing the loading of additive to 4.0 equiv, however, resulted in a gratifying improve-

ment in product selectivity in favor of [2,3]-sigmatropic rearrangement and improved yields (entry 10, 82 : 18 ratio, 65% yield). Increasing the loading of magnesium chloride did not have an overall beneficial effect on reactivity. Only a slight improvement in product selectivity was observed (compare entries 8 and 11), however, a dramatic decrease in isolated yield of **111** was recorded (49% yield). Notably, when reactions with $MgCl_2$ were stirred for ~0.5 h, the reaction gradually turned from green to pink, which may be attributed to additive-promoted decomposition of the dirhodium catalyst. Thus, increasing the additive loading as in entry 11 accelerates the apparent decomposition of the catalyst, and prevents the reaction from reaching completion.

Table 2.7[a–c] Optimization of the tandem ylide formation/[2,3]-sigmatropic rearrangement of primary alcohols



entry	X equiv MCl_n	temp., °C	ratio, **111** : **112**	yield **111**, %	ee **111**, %
1	–	22	<5 : 95	–	–
2	2.5 equiv $CaCl_2$	22	74 : 26	56	>99
3	2.5 equiv $CaCl_2$	0	55 : 45	–	–
4	2.5 equiv $CaCl_2$	35	73 : 27	52	>99
5	2.5 equiv LiCl	22	65 : 35	–	–
6	2.5 equiv KCl	22	8 : 92	–	–
7	2.5 equiv $SrCl_2$	22	14 : 86	–	–
8	2.5 equiv $MgCl_2$	22	80 : 20	59	>99

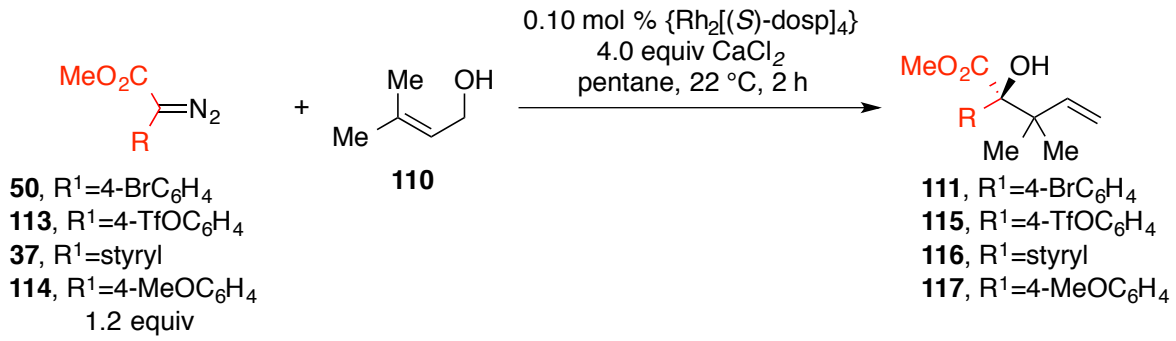
9	1.5 equiv $CaCl_2$	22	69 : 31	–	–
10	4.0 equiv $CaCl_2$	22	82 : 18	65	>99
11	4.0 equiv $MgCl_2$	22	83 : 17	49	>99

[a] Ratio of **111** : **112** was determined by ^{1}H NMR analysis of the crude reaction residue. [b] Isolated yields of **111**. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

The effect of the donor group on the efficacy of promoting [2,3]-sigmatropic rearrangement was then explored with 3-methyl-2-butenol (**110**) and the results are summarized in Table 2.8. The ratios of products formed were determined by integration of the vinylic doublet of **111** and **115–117** (δ = 5.0–5.1 ppm) compared to the methynyl α-proton (δ = 4.8–5.0 ppm). For reference and comparison, the result from Table 2.7 entry 10 is repeated as entry 1. Different electron withdrawing groups at C(4) of the arene were well tolerated as exemplified in formation of **115**. In this case, the [2,3]-sigmatropic rearrangement product was formed with improved chemoselectivity and yield, as compared with the reaction of **50**, and again in excellent enantioselectivity (99% ee). The styryl donor group (**37**) was also effective, however, the product selectivity, and thus the yield, was decreased compared with the diazoacetates in columns 1 and 2 (**116**, 25% yield, 74 : 26 ratio). The lower yield for rearrangement product, despite its preferential formation, may be due to subsequent rearrangement of the hexadiene product (see Chapter 3.2). Further increasing the electron richness of the donor group, as with the 4-methoxyphenyl donor

group (**114**) provided only the corresponding O–H insertion product, as none of the desired product (**117**) was apparent by ^{1}H NMR analysis of the crude reaction mixture.

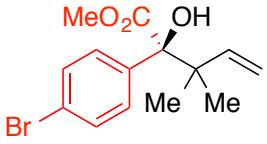
Table 2.8[a–c] Scope of diazoacetate for the tandem ylide formation/[2,3]-sigmaropic rearrangement of primary allyl alcohols



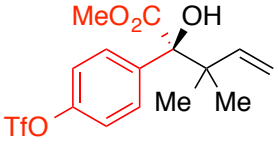
50, R^1=4-BrC_6H_4
113, R^1=4-$TfOC_6H_4$
37, R^1=styryl
114, R^1=4-$MeOC_6H_4$
1.2 equiv

110

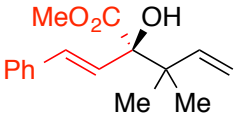
111, R^1=4-BrC_6H_4
115, R^1=4-$TfOC_6H_4$
116, R^1=styryl
117, R^1=4-$MeOC_6H_4$



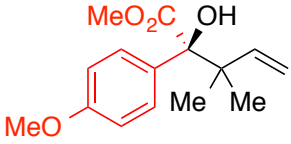
111
65% yield
82 : 18 ratio
99% ee



115
71% yield
89 : 11 ratio
96% ee



116
25% yield
74 : 26 ratio
99% ee



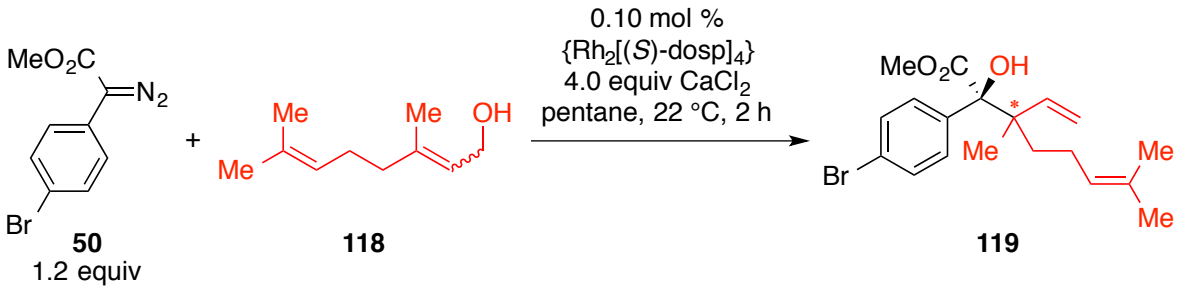
117
<5% yield
<5 : 95 ratio

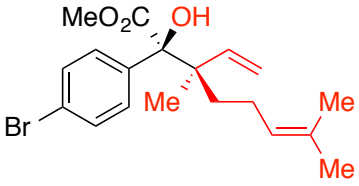
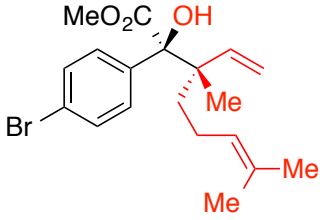
[a] Isolated yields of **111** and **115–117**. [b] Ratio of [2,3]-sigmatropic rearrangement : O–H insertion was determined by ^{1}H NMR analysis of the crude reaction resiude. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Diastereoselective Reaction. In the next set of experiments, we considered the scenario where the C(3,3′)-substituents on the allyl alcohol are no longer equivalent, such that a product contain-

ing two vicinal stereocenters could be forged from two achiral materials. We decided to study the rearrangement of geraniol and nerol, the (*E*)- and (*Z*)-isomers of **118**, which are both inexpensive commercial reagents. The reaction of geraniol provided a 5.5 : 1 mixture of [2,3]-sigmatropic rearrangement product (2*S*,3*R*)-**119** and the O–H insertion product (not shown). The ^{1}H NMR shifts of the vinyl protons for each diastereomer were well resolved, and the relative integrals were used as measure of the diastereomeric ratio. The hydroxy ester was isolated as a mixture of diastereomers in good yield and excellent enantioselectivity (entry 1, 65% yield, 75 : 25 dr, 99% ee). When nerol [(*Z*)-**118**] was implemented, the diastereomeric rearrangement product (2*S*,3*S*)-**119** was formed as the major component, again along with ~20% of the O–H insertion product. The diastereoselectivity of the reaction with (*Z*)-**118** was modestly improved, but the yield and enantioselectivity were consistent (entry 2, 67% yield, 80 : 20 dr, 99% ee). We imagined that the configuration of the hydroxy ester stereocenter, which is governed by the rhodium catalyst, would be the same as in previous studies with secondary allyl and tertiary propargyl alcohols.

Table 2.9[a–c] Tandem ylide formation/[2,3]-sigmatropic rearrangement of primary allyl alcohols to generate products bearing vicinal stereocenters.



entry	(*E* or *Z*)-**118**	**119**	yield, %	dr	ee, %
1	*E*		65	75 : 25	99
2	*Z*		67	80 : 20	99

[a] Combined isolated yields of both diastereomers of **119**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess of the major diastereomer of **119** was determined by HPLC analysis on a chiral stationary phase.

The configuration of the product C(3) stereocenter is *tentatively* assigned by comparison to previous studies; however, X-ray crystallographic confirmation is desirable, but unachievable thus far. Since the alcohol is primary and lacking a carbinol substituent, it cannot exert $A_{1,3}$–

interactions as a source of diastereocontrol to the same degree as the secondary allyl alcohols. The moderate stereocontrol may be due to modest "pseudoaxial *versus* pseudoequatorial" transposition of the C(3)-substituents in an envelope-like transition state or subtle steric repulsions with the catalyst in one geometry *versus* the other. Since both (*E*)- and (*Z*)-isomers of **118** produce the epimers of **119** in comparable diastereomeric ratios, we suspect that interactions with the catalyst are less likely the source of diastereocontrol.

The rationale for the beneficial effect of calcium chloride on reactivity relates to the energy diagram presented in Figure 2.1. Yu and co-workers identified the likely involvement of a secondary equivalent of alcohol in the formal O–H insertion process, which suggests that $CaCl_2$ participates in impeding that process. Coordination of exogenous alcohol to the mildly Lewis acidic calcium chloride would likely prevent the alcohol from playing its typical, requisite role of tandem Brønsted acid/base in the O–H insertion process.

2.3 Conclusions

In summary, we have developed an efficient transformation involving the tandem ylide formation/[2,3]-sigmatropic rearrangement of donor/acceptor rhodium carbenes and allyl alcohols to generate products bearing vicinal stereogenic carbon atoms. The formal O–H insertion reaction, typified for protonated heteroatom nucleophiles, is generally a non-competitive process in these reactions, and in many cases can be suppressed with Lewis acid additive.

When chiral (*E*)-secondary allyl alcohols are implemented, the products are formed in generally high yield and stereocontrol, wherein the configuration of the hydroxy ester stereocenter of the product is controlled by the rhodium tetracarboxylate catalyst and the allylic stereocenter is controlled by the alcohol. Thus, we have demonstrated the ability to prepare all four diastereomers of rearrangement products. In addition, C(3,3′)-substituted alcohols were shown to be effective for forging a product bearing vicinal quaternary stereocenters in exquisite diastereo- and enantiocontrol.

The reaction has been extended to include primary allyl alcohols as competent substrates, which were previously shown to exhibit a dramatic preference for the formal O–H insertion pathway. By adding an excess of calcium chloride, the chemoselectivity of the reaction with this family of nucleophiles was shown to reverse. The role of a mild Lewis acid additive to help preclude competitive O–H insertion is consistent with computational studies on rhodium carbene O–H insertion reactions.

A comprehensive examination of the scope of the nucleophile for the tandem ylide formation/[2,3]-sigmatropic rearrangement of primary allyl alcohols remains to be investigated. In particular, it will be of great interest whether increasing the steric bulk of one of the C(3)-

substituents of the allyl alcohol can effect an increase in the diastereoselectivity of the transformation.

2.4 Experimental Section

2.4.1 General Considerations

All reactions were conducted in oven-dried glassware under an inert atmosphere of dry argon. All chemicals were purchased from either Sigma-Aldrich, TCI America, Acros, AK Scientific, or Alfa-Aesar, and were used as received. Pentane, hexanes, tetrahydrofuran and diethyl ether were obtained from a Grubbs-type solvent purification system. 2,2,2-Trifluoroethanol, methyl *tert*-butyl ether, *tert*-amyl alcohol, *iso*-propanol and ethyl acetate were purchased as the anhydrous reagents from Sigma-Aldrich, and were used as received. Calcium chloride, lithium chloride, potassium chloride, strontium chloride and magnesium chloride were all purchased as the anhydrous salts and used as received. Proton (^{1}H) NMR spectra were recorded at either 400 MHz on an INOVA-400 spectrometer or at 600 MHz on an INOVA-600 spectrometer. Carbon-13 (^{13}C) NMR spectra were recorded at either 100 MHz on an INOVA-400 spectrometer or at 150 MHz on an INOVA-600 spectrometer. NMR spectra were recorded in deuterated chloroform ($CDCl_3$) solutions, with residual chloroform (δ 7.27 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR) or tetramethylsilane (δ 0.00 ppm for ^{1}H NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants were taken from the spectra directly and are uncorrected. Infrared (IR) spectra were collected on a Nicolet iS10 FT-IR spectrometer as neat films. Mass spectrometric determinations were carried out on a Thermo Finnigan LTQ-FTMS spectrometer with electrospray (ESI) or atmospheric pressure chemical (APCI) ionization. Optical rotations were measured on JASCO P-2000 polarimeter. High performance liquid chromatography (HPLC) analysis was performed on a Varian Prostar 350 with hexanes/*iso*propanol as eluent. Gas chromatography (GC) analysis was performed on an Agilent 7890A; column condi-

tions: 30 °C for 1 min, then increasing to 180 °C at a rate of 5 °C/min, then 180 °C for 5 min. Analytical thin layer chromatography (TLC) was performed on silica gel plates using ultraviolet (UV) light or stained with 10% vanillin/1% sulfuric acid/ethanol solution. Flash column chromatography was performed with silica gel 60 A (230-400 mesh) according to the literature procedure.[97] Substrates **37** and **51**,[98] $\{Rh_2[(S)\text{-dosp}]_4\}$ and $\{Rh_2[(R)\text{-dosp}]_4\}$,[85] **18** and **50**,[91] **52** and **53**,[31] and **54**[99] were all synthesized according to published procedures.

2.4.2 General Procedures

2.4.2.1 Enzymatic Kinetic Resolution of Secondary Allylic Alcohols[53]

To a vigorously stirred solution of racemic allylic alcohol (1.0 equiv) and vinyl acetate (2.7 equiv) in hexanes (100 mL) was added Amano AK (30 wt %) and molecular sieves (50 wt %). The mixture was stirred at room temperature with periodic analysis of aliquots by chiral GC or HPLC. After the enantiomeric excess of the alcohol exceeded 98%, the mixture was filtered and concentrated *in vacuo*. Flash chromatography of the crude material on silica gel afforded the enantiomerically pure (*S*)-alcohol.

2.4.2.2 Sharpless Enantioselective Epoxidation/Kinetic Resolution of Secondary Alcohols[100]

To a solution of racemic allylic alcohol (10.0 mmol, 1.0 equiv) and D-(–)-DIPT (2.55 mL, 12.0 mmol, 1.2 equiv) in dichloromethane (100 mL) at -20 °C was slowly added $Ti(O\textit{i}\text{-}Pr)_4$ (3.00 mL, 10.0 mmol, 1.0 equiv). The solution was stirred for 30 min prior to the slow addition of TBHP (5.5 M in decane, 1.1 mL, 6.0 mmol, 0.60 equiv). The reaction mixture was then stirred at -20 °C for 15 h before quenching with cold aqueous citric acid (11 g)/$FeSO_4$ (33 g) solution (100 mL). The mixture was stirred vigorously at ambient temperature until two layers became apparent. The organic layer was set aside and the aqueous layer was extracted with dichloromethane. The combined organic fractions were concentrated *in vacuo*, and the crude residue was dissolved in diethyl ether (100 mL). To the ether solution was added aqueous NaOH (30 g)/NaCl (5 g) solution (90 mL) at 0 °C. The mixture was then stirred at 0 °C for 1 h before addition of H_2O (100 mL). The layers were separated and the organic was dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the crude material on silica gel afforded the enantiomerically pure (*S*)-alcohol.

2.4.2.3 Rhodium(II)-Catalyzed [2,3]-Sigmatropic Rearrangement of Secondary Allyl Alcohols

An oven-dried, 25 mL round-bottomed flask, equipped with a stir bar, was capped with a rubber septum and placed under a dry argon atmosphere. The reaction vessel was charged with $\{Rh_2[(S)\text{-dosp}]_4\}$ (10 mg, 0.0050 mmol, 0.010 equiv) and the allyl alcohol (0.5 mmol, 1.0 equiv) in pentane (1.0 mL). The solution was cooled to 0 °C in an ice bath before adding a pentane solution (9 mL) of the diazo compound (1.0 mmol, 2.0 equiv) dropwise over 1.5 h. Following addition, the reaction was stirred at 0 °C for 0.5 h before warming to room temperature and concentrating *in vacuo*. The product was purified by flash chromatography.

2.4.2.4 Relative Rate of O–H Insertion to [2,3]-Sigmatropic Rearrangement Study

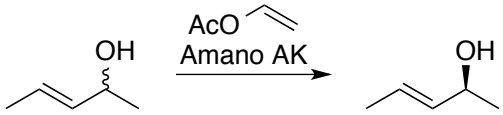
An oven-dried, 25 mL round-bottomed flask, equipped with a stir bar, was capped with a rubber septum and placed under a dry argon atmosphere. The reaction vessel was charged with $\{Rh_2[(S)\text{-dosp}]_4\}$ (5 mg, 0.0050 mmol, 0.01 equiv), **87** (500 mg, 5.0 mmol, 10 equiv), and the aliphatic or aryl alcohol (**88–97**) (5.0 mmol, 10 equiv) in pentane (1.0 mL). The solution was cooled to 0 °C in an ice bath before adding a pentane solution (5.0 mL) of the diazo compound (128 mg, 0.50 mmol, 1.0 equiv) dropwise over 1 h. Following addition, the reaction was stirred at 0 °C for 1 h before warming to ambient temperature and concentrating *in vacuo*. The crude residue was analyzed by ^{1}H NMR to determine the relative ratio of products formed.

2.4.2.5 Rhodium(II)-Catalyzed [2,3]-Sigmatropic Rearrangement of Primary Allyl Alcohols

An oven-dried, 25 mL round-bottomed flask, equipped with a stir bar, was capped with a rubber septum and placed under a dry argon atmosphere. The reaction vessel was charged with $\{Rh_2[(S)\text{-dosp}]_4\}$ (5 mg, 0.0050 mmol, 0.005 equiv), allyl alcohol (0.50 mmol, 1.0 equiv), and $CaCl_2$ (222 mg, 2.0 mmol, 4.0 equiv) in pentane (5.0 mL). The solution was cooled to 0 °C in an

ice bath before adding a pentane solution (5 mL) of the diazo compound (0.60 mmol, 1.2 equiv) dropwise over 1.5 h. Following addition, the reaction was stirred at 0 °C for 1 h before warming to room temperature. The reaction was dilute with additional pentane (15 mL) and transferred to a separatory funnel. The organic layer was washed with water (3 x 5 mL) and brine (10 mL), drived over magnesium sulfate, and the filtrate was the concentrated *in vacuo*. The product was purified by flash chromatography.

2.4.3 Procedures and Characterization Data



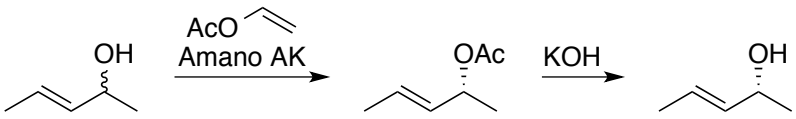
(*S*,*E*)-pent-3-en-2-ol [(*S*,*E*)-48]

Prepared by *General Procedure 2.4.2.1* with racemic (E)-1 (3.0 g, 35 mmol, 1.0 equiv), vinyl acetate (8.7 mL, 94 mmol, 2.7 equiv) and Amano AK enzyme (1.0 g, 30 wt %). The reaction mixture was stirred for 8 h at ambient temperature and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (pentane/diethyl ether, 5:1 → 2:1) to afford the title compound as a colorless oil (0.95 g, 32% yield). Spectral data were consistent with the literature.[53]

$[\alpha]^{20}_{D}$ –14.5° (*c* 3.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (dq, J = 15.2, 6.4 Hz, 1H), 5.53 (dd, J = 15.2, 6.4 Hz, 1H), 4.26 (m, 1H), 1.69 (d, J = 6.4 Hz, 3H), 1.29 (d, J = 6.4 Hz, 3H).

Chiral Capillary GC: 99% ee, (CHIRALDEX BP-M). t_R = 5.10 min (minor), 5.27 min (major).



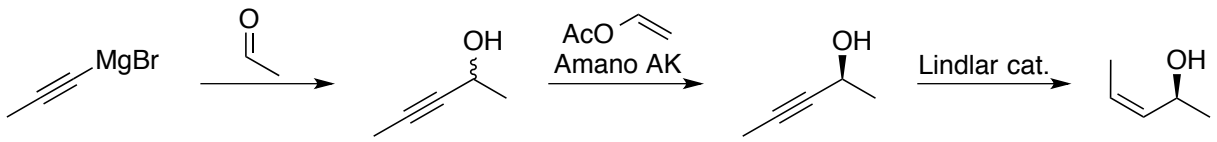
(*R*,*E*)-pent-3-en-2-ol [(*R*,*E*)-1]

Prepared by *General Procedure 2.4.2.1* with racemic (*E*)-1 (3.0 g, 35 mmol, 1.0 equiv), vinyl acetate (8.7 mL, 94 mmol, 2.7 equiv) and Amano AK enzyme (1.0 g, 30 wt %). The reaction mixture was stirred for 2 h at ambient temperature and filtered. After concentration of the fil-

trate, the residue was purified by flash chromatography (pentane/diethyl ether, 5:1 → 2:1) to afford the title compound.

The acetate was dissolved with potassium hydroxide solution (3.9 g KOH in 10 mL EtOH/H_2O, 7:3) and heated to reflux for 3.5 h. Upon cooling to room temperature, the solution was carefully neutralized with aqueous HCl and extracted with diethyl ether. The combined organic fractions were dried over $MgSO_4$, filtered and concentrated in vacuo to afford the title compound as a colorless oil (0.19 g, 13% yield). Spectral data were consistent with that for (*S*,*E*)-**48**.

Chiral Capillary GC: 97% ee, (CHIRALDEX BP-M). t_R = 5.10 min (major), 5.27 min (minor).



(*S*,*Z*)-pent-3-en-2-ol [(*S*,*Z*)-48]

To a solution of 1-propynylmagnesium bromide (0.5 M in THF, 200 mL, 100 mmol, 1.0 equiv) was slowly added acetaldehyde (5.6 mL, 150 mmol, 1.5 equiv) as a diethyl ether solution (20 mL) at 0 °C. After addition, the reaction was allowed to warm to room temperature over 5 h and was subsequently quenched with careful addition of saturated aqueous NH_4Cl. The resultant layers were separated and the organic was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by short path vacuum distillation (20 mm Hg, 55 °C) to afford *racemic* 3-pentyn-2-ol (6.00 g, 71% yield).

The enzymatic kinetic resolution of 3-pentyn-2-ol was performed according to *General Procedure 2.4.2.1* with *racemic* 3-pentyn-2-ol (1.35 g, 11.9 mmol, 1.0 equiv), vinyl acetate (3.0 mL, 32 mmol, 2.7 equiv) and Amano AK enzyme (0.46 g, 30 wt %). The reaction mixture was

stirred for 20 h at 30 °C and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (pentane/diethyl ether, 10:1 → 3:1) to afford (*S*)-3-pentyn-2-ol as a colorless oil (0.43 g, 32% yield).

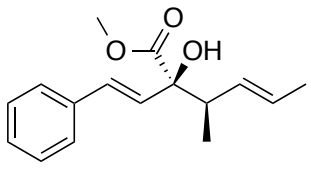
$[\alpha]^{20}_{D}$ –36.9° (*c* 6.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.50-4.48 (m, 1H), 1.84 (d, J = 2.0 Hz, 3H), 1.42 (d, J = 6.4 Hz, 3H).

Chiral Capillary GC: 98% ee, (CHIRALDEX BP-M). t_R = 7.21 min (minor), 7.38 min (major).

To a solution of (*S*)-3-pentyn-2-ol (215 mg, 2.56 mmol, 1.0 equiv) in pentane (2 mL) was added $Pd/CaCO_3$ poisoned with Pb (12 mg) and quinoline (one drop). The reaction vessel was purged with H_2 and stirred at ambient temperature for 20 h. The suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 5:1 → 3:1) to afford the title compound as a colorless oil (120 mg, 54% yield). Spectral data were consistent with the literature.[101]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.55-5.54 (m, 2H), 4.71-4.66 (m, 1H), 1.68 (dd, J = 6.4, 1.2 Hz, 3H), 1.36 (s, 1H), 1.25 (d, J = 6.4 Hz, 3H).



(2*R*,3*R*,*E*)-methyl 2-hydroxy-3-methyl-2-((*E*)-styryl)hex-4-enoate [(2*R*,3*R*)-49]

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (44 mg, 0.50 mmol, 1.0 equiv) and **37** (205 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 10:1) to afford the title compound as a colorless oil (93 mg, 70% yield).

$[\alpha]^{20}_{D}$ +19.7° (*c* 1.0, $CHCl_3$).

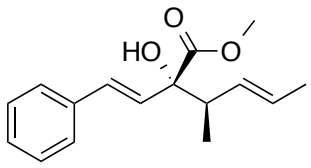
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.41 (m, 2H), 7.35-7.31 (m, 2H), 7.25-7.23 (m, 1H), 6.85 (d, *J* = 15.6 Hz, 1H), 6.26 (d, *J* = 15.6 Hz, 1H), 5.52 (dq, *J* = 15.2, 6.0 Hz, 1H), 5.40 (ddq, *J* = 15.2, 8.4, 1.6 Hz, 1H), 3.78 (s, 3H), 3.33 (s, 1H), 2.70-2.63 (m, 1H), 1.67 (dd, *J* = 6.0, 1.6 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 137.7, 131.4, 130.8, 129.2, 128.7, 127.9, 127.3, 126.8, 80.5, 53.1, 44.9, 18.3, 14.2.

FTIR (neat): ν_{max}/cm^{-1} 3514, 1731, 1448, 1436, 1144.

HRMS (p-APCI): m/z 243.1379 [$(M\text{-}OH)^+$ requires 243.1380].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 17.6 min (major), 21.9 min (minor).



(2*S*,3*R*,E)-methyl 2-hydroxy-3-methyl-2-((*E*)-styryl)hex-4-enoate [(2*S*,3*R*)-49]

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (45 mg, 0.50 mmol, 1.0 equiv), **37** (202 mg, 1.0 mmol, 2.0 equiv) and $\{Rh_2[(R)\text{-dosp}]_4\}$ (9.5 mg, 0.0050 mmol, 001 equiv). The crude

residue was purified by flash chromatography (pentane/diethyl ether, 15:1) to afford the title compound as a colorless oil (73 mg, 54%).

$[\alpha]^{20}_{D}$ +53.1° (*c* 1.0, $CHCl_3$).

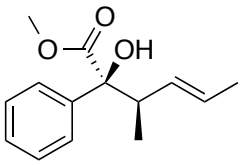
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39(m, 2H), 7.34-7.31 (m, 2H), 7.27-7.23 (m, 1H), 6.78 (d, *J* = 15.6 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 5.52 (dq, *J* = 15.6, 6.4 Hz, 1H), 5.40 (ddq, *J* = 15.2, 7.6, 1.6 Hz, 1H), 3.82 (s, 3H), 3.38 (s, 1H), 2.74-2.67 (m, 1H), 1.65 (dd, *J* = 6.0, 1.6 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 136.8, 130.5, 130.4, 129.9, 128.7, 127.8, 127.4, 126.8, 79.9, 53.3, 44.9, 18.3, 15.3.

FTIR (neat): ν_{max}/cm^{-1} 3515, 1727, 1448, 1436, 1152.

HRMS (p-APCI): m/z 243.1380 [$(M\text{-}OH)^+$ requires 243.1380].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 18.5 min (minor), 19.9 min (major).



(2*S*,3*R*,*E*)-methyl 2-hydroxy-3-methyl-2-phenylhex-4-enoate (55)

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (43 mg, 0.50 mmol, 1.0 equiv) and **18** (175 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 10:1) to afford the title compound as a colorless oil (66 mg, 56%).

$[\alpha]^{20}_{D}$ +70.9° (*c* 1.0, $CHCl_3$).

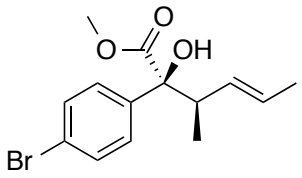
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H), 7.38-7.34 (m, 2H), 7.31-7.27 (m, 1H), 5.59 (dq, *J* = 15.6, 6.4 Hz, 1H), 5.50 (m, 1H), 3.74 (s, 3H), 3.67 (s, 1H), 3.10 (m, 1H), 1.69 (dd, *J* = 6.4, 1.6 Hz, 3H), 0.81 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 140.4, 131.6, 128.3, 127.7, 127.4, 126.3, 81.2, 53.3, 45.2, 18.4, 14.2.

FTIR (neat): ν_{max}/cm^{-1} 3507, 1724, 1447, 1435, 1140, 1005.

HRMS (p-APCI): m/z 252.1596 [$(M+NH_4)^+$ requires 252.1594].

HPLC: >99% ee (S,S-WHELK, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 230 nm). t_R = 9.2 min (major), 10.6 min (minor).



(2*S*,3*R*,*E*)-methyl 2-(4-bromophenyl)-2-hydroxy-3-methylhex-4-enoate (56)

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (45 mg, 0.50 mmol, 1.0 equiv) and **50** (259 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 20:1) to afford the title compound as a colorless oil (109 mg, 66% yield).

$[\alpha]^{20}_{D}$ +80.3° (*c* 1.0, $CHCl_3$).

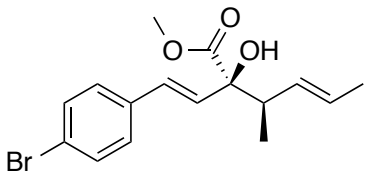
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 5.59 (dq, J = 15.2, 6.4 Hz, 1H), 5.46 (ddq, J = 15.2, 8.4, 1.6 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 1H), 3.02 (m, 1H), 1.68 (dd, J = 6.4, 1.2 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 139.5, 131.4, 131.3, 128.3, 127.7, 121.9, 81.0, 53.5, 45.3, 18.4, 14.1.

FTIR (neat): ν_{max}/cm^{-1} 3503, 1728, 1486, 1436, 1090, 1075, 1010.

HRMS (p-APCI): m/z 295.0331 [(M-OH)$^+$ requires 295.0328].

HPLC: >99% ee (CHIRALPAK AD-H, 1.0% isopropanol/hexanes, 0.7 mL/min, UV: 230 nm). t_R = 13.8 min (minor), 17.5 min (major).



(2*R*,3*R*,*E*)-methyl 2-((*E*)-4-bromostyryl)-2-hydroxy-3-methylhex-4-enoate (57)

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (44 mg, 0.50 mmol, 1.0 equiv) and **51** (281 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 10:1) to afford the title compound as a white solid (119 mg, 69% yield).

MP = 76–78 °C.

$[\alpha]^{20}_D$ +35.2° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 15.6 Hz, 1H), 6.24 (d, J = 15.6 Hz, 1H), 5.51 (dq, J = 15.2, 6.0 Hz, 1H), 5.38 (ddq, J = 15.2, 8.8,

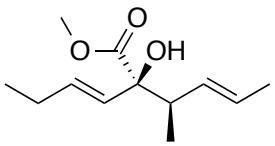
1.6 Hz, 1H), 3.77 (s, 3H), 3.32 (s, 1H), 2.68-2.60 (m, 1H), 1.65 (dd, J = 6.4, 1.6 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 135.6, 131.8, 131.2, 130.0, 129.7, 128.4, 127.5, 121.7, 80.5, 53.2, 44.9, 18.3, 14.2.

FTIR (neat): ν_{max}/cm^{-1} 3512, 1731, 1487, 1435, 1072, 1009.

HRMS (p-APCI): *m/z* 321.0492 [(M-OH)$^+$ requires 321.0485].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 230 nm). t_R = 13.8 min (minor), 14.9 min (major).



(*R*,*E*)-methyl 2-hydroxy-2-((*R*,*E*)-pent-3-en-2-yl)hex-3-enoate (58)

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (43 mg, 0.50 mmol, 1.0 equiv) and **52** (155 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 12:1) to afford the title compound as a colorless oil (64 mg, 60% yield).

$[\alpha]^{20}_D$ –31.0° (*c* 1.0, $CHCl_3$).

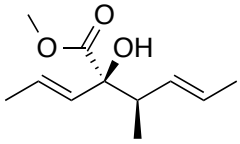
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (dt, J = 15.6, 6.4 Hz, 1H), 5.51-5.54 (m, 2H), 5.35 (ddd, J = 15.6, 8.4, 1.2 Hz, 1H), 3.74 (s, 3H), 3.12 (s, 1H), 2.52 (dq, J = 6.8, 6.8 Hz, 1H), 2.11-2.04 (m, 2H), 1.62 (dd, J = 6.2, 1.2 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 133.8, 131.6, 128.4, 127.0, 80.1, 52.9, 44.5, 25.3, 18.3, 13.9, 13.7.

FTIR (neat): ν_{max}/cm^{-1} 3521, 2965, 2935, 2875, 1732, 1437, 1157.

HRMS (p-APCI): *m/z* 195.1380 [$(M\text{-}OH)^+$ requires 195.1380].

HPLC: >99% ee (CHIRALPAK AD-H, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm). t_R = 21.6 min (minor), 23.4 min (major).



(2*R*,3*R*,*E*)-methyl 2-hydroxy-3-methyl-2-((*E*)-prop-1-en-1-yl)hex-4-enoate (59)

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (43 mg, 0.50 mmol, 1.0 equiv) and **53** (141 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 12:1) to afford the title compound as a colorless oil (55 mg, 55% yield).

$[\alpha]^{20}_D$ –20.6° (*c* 1.0, $CHCl_3$).

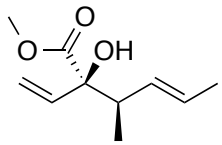
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (dq, J = 15.6, 6.6 Hz, 1H), 5.53-5.49 (m, 1H), 5.48-5.45 (m, 1H), 5.38-5.33 (m, 1H), 3.74 (s, 3H), 3.12 (s, 1H), 2.52 (dq, J = 7.2, 7.2 Hz, 1H), 1.73 (dd, J = 7.2, 1.8 Hz, 3H), 1.63 (dd, J = 6.0, 1.8 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 131.6, 130.6, 127.1, 127.0, 80.1, 52.9, 44.5, 18.3, 17.8, 14.0.

FTIR (neat): ν_{max}/cm^{-1} 3522, 2969, 2919, 2857, 1732, 1438, 1156.

HRMS (p-APCI): *m/z* 181.1225 [$(M\text{-}OH)^+$ requires 181.1223].

HPLC: >99% ee (CHIRALPAK AD-H, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm). t_R = 19.2 min (minor), 20.3 min (major).



(2*R*,3*R*,*E*)-methyl 2-hydroxy-3-methyl-2-vinylhex-4-enoate (60)

Prepared by *General Procedure 2.4.2.3* with (*S*,*E*)-**48** (45 mg, 0.50 mmol, 1.0 equiv) and **54** (160 mg, 1.25 mmol, 2.5 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 20:1) to afford the title compound as a colorless oil (41 mg, 43% yield).

$[\alpha]^{20}_D$ –52.8° (*c* 1.0, $CHCl_3$).

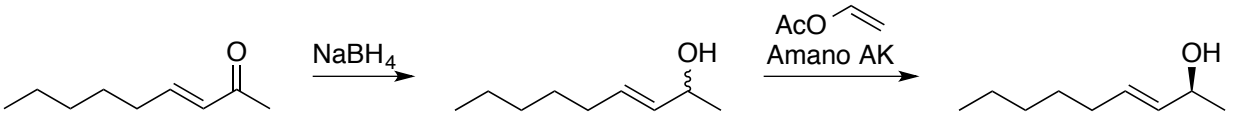
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (dd, J = 17.2, 10.8 Hz, 1H), 5.54-5.44 (m, 2H), 5.39-5.33 (m, 1H), 5.24 (dd, J = 10.4, 1.6 Hz, 1H), 3.75 (s, 3H), 3.15 (s, 1H), 2.56 (m, 1H), 1.64 (dd, J = 6.4, 1.2 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 137.7, 131.4, 127.2, 116.2, 80.6, 53.0, 44.3, 18.3, 14.0.

FTIR (neat): ν_{max}/cm^{-1} 3519, 2975, 2935, 1732, 1437, 1159.

HRMS (p-APCI): *m/z* 185.1173 [$(M+H)^+$ requires 185.1172].

Chiral Capillary GC: >99% ee (CHIRALDEX BP-M). t_R = 14.7 min (major), 15.2 min (minor).

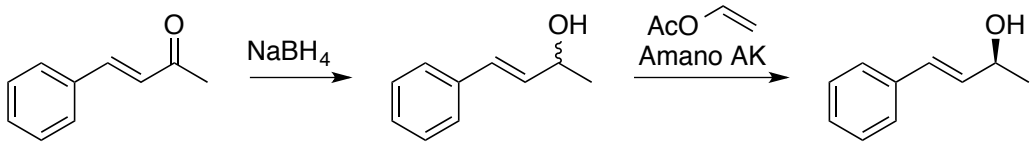


(*S*,*E*)-non-3-en-2-ol (61)

To a solution of (*E*)-3-nonen-2-one (3.0 g, 21 mmol, 1.0 equiv) in methanol (30 mL) at 0 °C was added sodium borohydride (0.9 g, 23 mmol, 1.1 equiv) in methanol (30 mL). The reaction was gradually warmed to room temperature over 3 h and subsequently quenched with saturated aqueous NH_4Cl. The resultant mixture was concentrated *in vacuo* and the residue was extracted with diethyl ether. The combined organic fractions were washed with brine, drived over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 5:1 → 3:1) to afford racemic **61** as a colorless oil (2.7 g, 90% yield). The enzymatic kinetic resolution was performed according to *General Procedure 2.4.2.1* with racemic **61** (2.0 g, 15 mmol, 1.0 equiv), vinyl acetate (3.7 mL, 40 mmol, 2.7 equiv) and Amano AK enzyme (0.60 g, 30 wt %). The reaction mixture was stirred for 3 h at ambient temperature and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (pentane/diethyl ether, 5:1 → 3:1) to afford the title compound as a colorless oil (0.77 g, 39% yield). Spectral data were consistent with the literature.[102]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (dt, J = 15.6, 6.8 Hz, 1H), 5.51 (dd, J = 15.6, 6.8 Hz, 1H), 4.29-4.25 (m, 1H), 2.01 (q, J = 6.8 Hz, 2H), 1.42-1.29 (m, 6H), 1.26 (d, J = 6.0 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H)

Chiral Capillary GC: 99% ee (CHIRALDEX BP-M). t_R = 14.17 min (major), 15.10 min (minor).

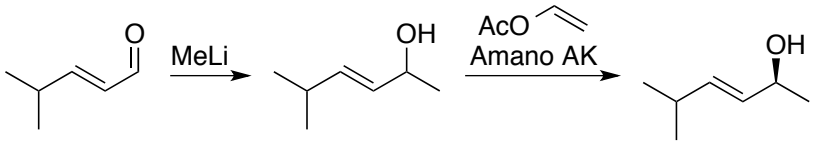


(*S*,*E*)-4-phenylbut-3-en-2-ol (62)

To a solution of (*E*)-4-phenylbut-3-en-2-one (5.0 g, 34 mmol, 1.0 equiv) in methanol (50 mL) was slowly added sodium borohydride (1.4 g, 37 mmol, 1.1 equiv) in methanol (50 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature over 2 h and was subsequently quenched with saturated aqueous NH_4Cl. The resultant mixture was concentrated *in vacuo* and the residue was extracted with diethyl ether. The combined organic fractions were washed with brine, drived over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/ethyl acetate, 3:1) to afford racemic **62** as a white solid (4.9 g, 96% yield). The enzymatic kinetic resolution was performed according to *General Procedure 2.4.2.1* with racemic **62** (1.0 g, 6.7 mmol, 1.0 equiv), vinyl acetate (1.7 mL, 18 mmol, 2.7 equiv) and Amano AK enzyme (0.50 g, 50 wt %). The reaction mixture was stirred for 24 h at ambient temperature and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (pentane/diethyl ether, 3:1) to afford the title compound as a white solid (0.43 g, 42% yield). Spectral data were consistent with the literature.[103]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.27-7.23 (m, 1H), 6.58 (d, J = 16.0 Hz, 1H), 6.28 (dd, J = 16.0, 6.4 Hz, 1H), 4.54-4.47 (m, 1H), 1.63 (d, J = 4.0 Hz, 1H), 1.38 (d, J = 6.4 Hz, 3H).

HPLC: 99% ee (CHIRALCEL OD-H, 5% isopropanol/hexanes, 0.6 mL/min, UV: 254 nm). t_R = 21.9 min (minor), 35.6 min (major).

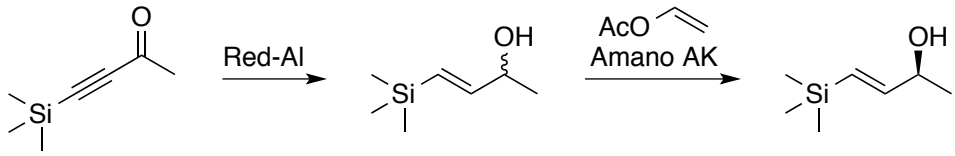


(*S*,*E*)-5-methylhex-3-en-2-ol (63)

To a tetrahydrofuran solution (100 mL) of (*E*)-4-methylpent-2-enal (4.91 g, 50.0 mmol, 1.0 equiv) at 0 °C was slowly added methyllithium (1.6 M in diethyl ether, 48 mL, 76 mmol, 1.5 equiv). After 1 h, the reaction was quenched by careful addition of saturated aqueous NH_4Cl. The resultant layers were separated and the aqueous was extracted with diethyl ether. The combined organic fractions were washed sequentially with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/diethyl ether, 3:1) to afford racemic **63** as a colorless oil (5.40g, 95% yield). The enzymatic kinetic resolution was performed according to *General Procedure 2.4.2.1* with racemic **63** (3.20 g, 28.0 mmol, 1.0 equiv), vinyl acetate (7.80 mL, 84.3 mmol, 3.0 equiv) and Amano AK enzyme (1.60 g, 50 wt %). The reaction mixture was stirred for 2 h at ambient temperature and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (pentane/diethyl ether, 2:1) to afford the title compound as a colorless oil (1.31 g, 41% yield). Spectral data were consistent with the literature.[104,105]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60 (dd, J = 15.5, 6.4 Hz, 1H), 5.45 (dd, J = 15.5, 6.6 Hz, 1H), 4.24 (p, J = 6.4 Hz, 1H), 2.31.2.21 (m, 1H), 1.72 (bs, 1H), 1.25 (t, J = 6.3 Hz, 3H), 0.98 (d, J = 6.7 Hz, 6H).

Chiral Capillary GC: 99% ee, (CHIRALDEX BP-M). t_R = 9.23 min (major), 9.38 min (minor).

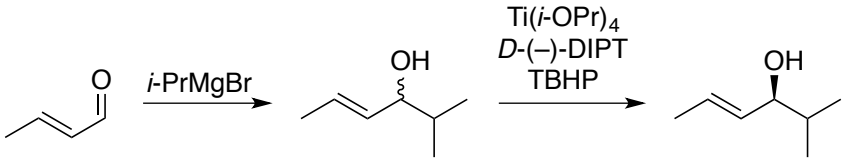


(*S*,*E*)-4-(trimethylsilyl)but-3-en-2-ol (64)

To a solution of 4-(trimethylsilyl)but-3-yn-2-one (2.6 g, 18 mmol, 1.0 equiv) in diethyl ether (40 mL) was added Red-Al (11.0 mL, 36.4 mmol, 2.0 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature over 2 h and was subsequently quenched with H_2O (1 mL) and aqueous H_2SO_4 (2 mL, 3.6 M) at 0 °C. The resultant layers were separated and the aqueous was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 10:1 → 5:1) to afford racemic **64** as a colorless oil (1.62 g, 62% yield). The enzymatic kinetic resolution was performed according to *General Procedure 2.4.2.1* with racemic **64** (1.0 g, 6.9 mmol, 1.0 equiv), vinyl acetate (3.2 mL, 35 mmol, 5.0 equiv) and Amano AK enzyme (0.50 g, 50 wt %). The reaction mixture was stirred for 15 h at 35 °C and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (pentane/diethyl ether, 10:1 → 5:1) to afford the title compound as a colorless oil (0.30 g, 30% yield). Spectral data were consistent with the literature.[106]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (dd, J = 18.8, 5.2 Hz, 1H), 5.84 (d, J = 18.8 Hz, 1H), 4.31-4.27 (m, 1H), 1.53 (d, J = 4.8 Hz, 1H), 1.27 (d, J = 6.4 Hz, 3H), 0.08 (s, 9H).

Chiral Capillary GC: 99% ee, (CHIRALDEX BP-M). t_R = 11.58 min (major), 11.89 min (minor).

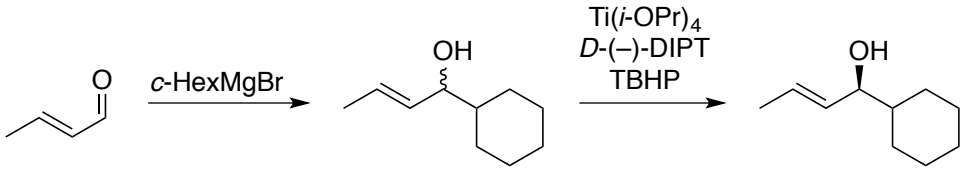


(*S*,*E*)-2-methylhex-4-en-3-ol (65)

To an *iso*propylmagnesium bromide solution (2.0 M in diethyl ether, 43 mL, 86 mmol, 1.2 equiv) at 0 °C was slowly added crotonaldehyde (5.0 g, 71 mmol, 1.0 equiv) in diethyl ether (10 mL). The solution was then allowed to warm to room temperature and stirred for an additional 1 h. The reaction was carefully quenched with saturated aqueous NH_4Cl and the resultant layers were separated. The aqueous was extracted with diethyl ether and the combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by short path vacuum distillation (20 mm Hg, 65 °C) to afford racemic **70** as a colorless oil (5.7 g, 70% yield). The Sharpless kinetic resolution was performed according to *General Procedure 2.4.2.2* with racemic **70** (1.14 g, 10.0 mmol, 1.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 10:1 → 5:1) to afford the title compound as a colorless oil (0.28 g, 25% yield). Spectral data were consistent with the literature.[107]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (dq, J = 15.2, 6.4 Hz, 1H), 5.50 (dd, J = 15.2, 7.2 Hz, 1H), 3.77 (t, J = 6.8 Hz, 1H), 1.71 (dd, J = 6.4, 1.2 Hz, 1H), 1.69-1.67 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 7.2 Hz, 3H).

Chiral Capillary GC: 99% ee, (CHIRALDEX BP-M). t_R = 9.83 min (minor), 9.85 min (major).



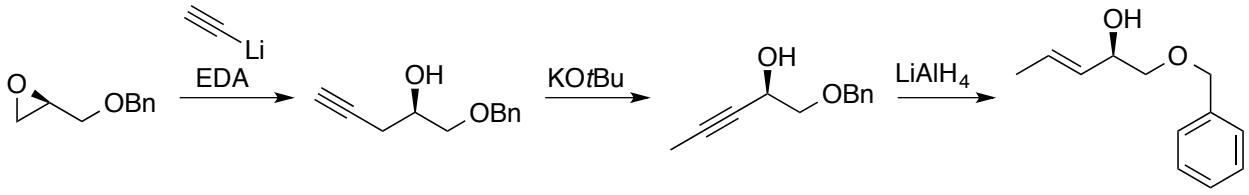
(*S*,*E*)-1-cyclohexylbut-2-en-1-ol (66)

To a cyclohexylmagnesium bromide solution (1.0 M in tetrahydrofuran, 32 mL, 32 mmol, 1.5 equiv) at 0 °C was slowly added crotonaldehyde (1.5 g, 21 mmol, 1.0 equiv) in tetrahydrofuran (10 mL). The solution was then allowed to warm to room temperature and stirred for an additional 1 h. The reaction was carefully quenched with saturated aqueous NH_4Cl and the resultant layers were separated. The aqueous was extracted with diethyl ether and the combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 5:1) to afford racemic **66** as a colorless oil (2.2 g, 67% yield). The Sharpless kinetic resolution was performed according to *General Procedure 2.4.2.2* with racemic **66** (1.54 g, 10.0 mmol, 1.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 5:1) to afford the title compound as a colorless oil (0.55 g, 36% yield). Spectral data were consistent with the literature.[108]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (dq, J = 15.2, 6.4 Hz, 1H), 5.48 (ddq, J = 15.2, 7.6, 1.2 Hz, 1H), 3.79-3.74 (m, 1H), 1.88-1.64 (m, 5H), 1.72 (dd, J = 6.8, 1.6 Hz, 3H), 1.40 (d, J = 3.6 Hz, 3H), 1.39-0.93 (m, 6H).

Mosher ester ^{1}H NMR: 99% ee, A 4 mL scintillation vial equipped with a magnetic stir bar was charged with a pyridine-D^8 (0.75 mL) solution of the title compound (15 mg, 0.10 mmol, 1.0 equiv). DMAP (1 mg, 0.01 mmol, 0.1 equiv) was added with vigorous stirring followed by (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (20 μL, 0.11 mmol, 1.1 equiv). After

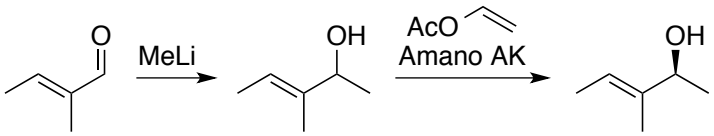
stirring at ambient temperature for 1 h, the reaction mixture was transferred to a NMR tube and a ^{1}H NMR spectrum was recorded at 600 MHz.



(*R*,E)-1-(benzyloxy)pent-3-en-2-ol (67)

To a solution of benzyl (*R*)-(–)-glycidyl ether (3.5 g, 21 mmol, 1.0 equiv) in dimethyl sulfoxide (40 mL) at 0 °C was added lithium acetylide ethylenediamine complex (3.3 g, 33 mmol, 1.6 equiv) in several portions. After 1 h, the reaction was quenched by sequential addition of brine and aqueous HCl (5.0 M). The aqueous was extracted with diethyl ether and the combined organic fractions were washed with aqueous $NaHCO_3$ (5%) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 2:1) to afford (*R*)-1-(benzyloxy)pent-4-yn-2-ol as a pale yellow oil (3.54 g, 89% yield). To a dimethyl sulfoxide (5 mL) solution of (*R*)-1-(benzyloxy)pent-4-yn-2-ol (3.0 g, 16 mmol, 1.0 equiv) was added potassium *tert*-butoxide (3.7 g, 32, 2.0 equiv) as a dimethyl sulfoxide (20 mL) solution. The reaction was stirred at ambient temperature for 1 h before quenching sequentially with brine and HCl (5.0 M). The aqueous was extracted with diethyl ether and the combined organic fractions were washed with aqueous $NaHCO_3$ (5%) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 2:1) to afford (*R*)-1-(benzyloxy)pent-3-yn-2-ol (2.86 g, 95% yield). To a tetrahydrofuran (5 mL) suspension of lithium aluminum hydride (333 mg, 8.77 mmol, 2.0 equiv) was slowly added (*R*)-1-(benzyloxy)pent-3-yn-2-ol (833 mg, 4.38 mmol, 1.0 equiv) as a tetrahydrofuran (5 mL) solu-

tion. Following addition, the reaction was heated to reflux for 4 h. Upon cooling to ambient temperature, the reaction was quenched with aqueous ammonium hydroxide (30%) and the aqueous was extracted with diethyl ether. The organic fractions were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 3:1 → 2:1) to afford the title compound as a colorless oil (730 mg, 87% yield). Spectral data were consistent with the literature.[109]

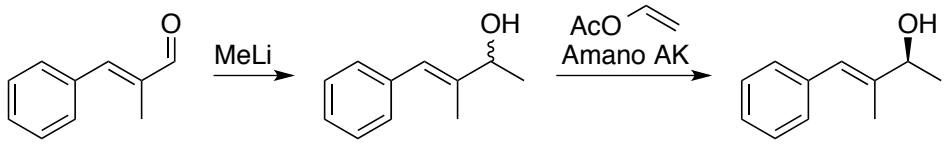


(*S*,*E*)-3-methylpent-3-en-2-ol (68)

To a solution of (*E*)-2-methylbut-2-enal (4.4 g, 52 mmol, 1.0 equiv) in tetrahydrofuran (100 mL) was slowly added methyllithium solution (1.6 M in diethyl ether, 39 mL, 63 mmol, 1.2 equiv) at 0 °C. The reaction was stirred at 0 °C for 4 h and then quenched with saturated aqueous NH_4Cl. The resultant layers were separated and the aqueous was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether, 3:1) to afford racemic **68** as a colorless oil (4.5 g, 86% yield). The enzymatic kinetic resolution was performed according to *General Procedure 2.4.2.1* with racemic **68** (3.5 g, 35 mmol, 1.0 equiv), vinyl acetate (8.7 mL, 94 mmol, 2.7 equiv) and Amano AK enzyme (1.0 g, 29 wt %). The reaction mixture was stirred for 12 h at ambient temperature and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (pentane/diethyl ether, 3:1) to afford the title compound as a colorless oil (1.29 g, 37% yield). Spectral data were consistent with the literature.[110]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (q, J = 6.4 Hz, 1H), 4.25-4.19 (m, 1H), 1.63 (s, 3H), 1.61 (d, J = 7.2 Hz, 3H), 1.39 (bs, 1H), 1.25 (d, J = 6.0 Hz, 3H).

Chiral Capillary GC: 99% ee, (CHIRALDEX BP-M). t_R = 8.76 min (minor), 8.98 min (major).

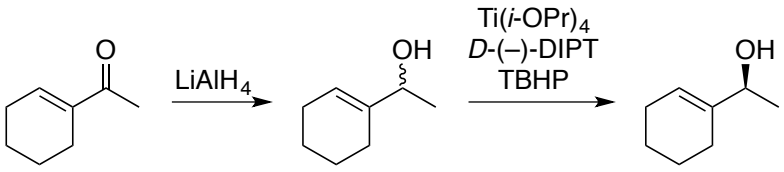


(*S*,*E*)-3-methyl-4-phenylbut-3-en-2-ol (69)

To a tetrahydrofuran solution (250 mL) of (*E*)-α-methylcinnamaldehyde (7.30 mL, 52.0 mmol, 1.0 equiv) at 0 °C was slowly added methyllithium solution (1.6 M in diethyl ether, 60 mL, 96 mmol, 1.8 equiv). After 2 h, the reaction was carefully quenched with saturated aqueous NH_4Cl. The resultant layers were separated and the aqueous was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/ethyl acetate, 4:1) to afford racemic **69** as a colorless oil (7.76 g, 92% yield). The enzymatic kinetic resolution was performed according to *General Procedure 2.4.2.1* with racemic **69** (2.33 g, 14.3 mmol, 1.0 equiv), vinyl acetate (3.60 mL, 38.9 mmol, 2.7 equiv) and Amano AK enzyme (0.70 g, 30 wt %). The reaction mixture was stirred for 12 h at ambient temperature and filtered. After concentration of the filtrate, the residue was purified by flash chromatography (hexanes/ethyl acetate, 3:1) to afford the title compound as a colorless oil (0.93 g, 40% yield). Spectral data were consistent with the literature.[111]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H), 6.52 (s, 1H), 4.39 (q, J = 6.4 Hz, 1H), 1.89 (s, 3H), 1.62 (bs, 1H), 1.37 (6.4 Hz, 3H).

HPLC: 99% ee (S,S-WHELK, 1.5% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 9.7 min (minor), 10.8 min (major).

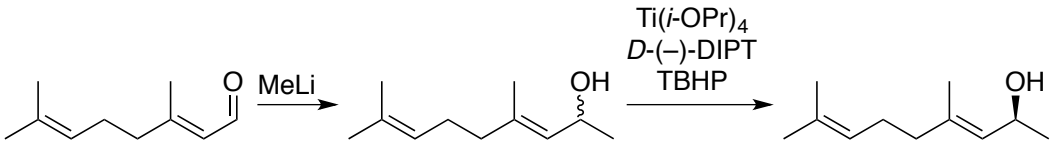


(*S*)-1-(cyclohex-1-en-1-yl)ethanol (70)

To a suspension of lithium aluminum hydride (0.6 g, 17 mmol, 0.5 equiv) in diethyl ether (15 mL) at 0 °C was slowly added 1-acetylcyclohexene (4.0 g, 32 mmol, 1.0 equiv) as a diethyl ether solution (15 mL). Following addition, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. The reaction vessel was again cooled to 0 °C and carefully quenched with cold H_2O followed by aqueous H_2SO_4 (10%, 5 mL). The resultant layers were separated and the organic was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by short path vacuum distillation (20 mm Hg, 100 °C) to afford racemic **70** as a colorless oil (3.8 g, 93% yield). The Sharpless kinetic resolution was performed according to *General Procedure 2.4.2.2* with racemic **70** (1.20 g, 10.0 mmol, 1.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 5:1) to afford the title compound as a colorless oil (0.39 g, 32% yield). Spectral data were consistent with the literature.[108]

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.67 (d, J = 0.6 Hz, 1H), 4.17 (q, J = 6.0 Hz, 1H), 2.06-1.98 (m, 4H), 1.67-1.54 (m, 4H), 1.42 (bs, 1H), 1.26 (d, J = 6.0 Hz, 3H).

Chiral Capillary GC: 99% ee, (CHIRALDEX BP-M). t_R = 16.50 min (minor), 16.60 min (major).

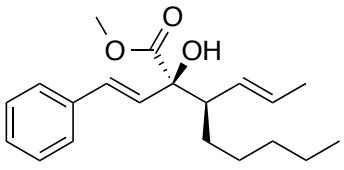


(*S*,*E*)-4,8-dimethylnona-3,7-dien-2-ol (71)

To a diethyl ether solution (150 mL) of (*E*)-geranial (3.9 g, 26 mmol, 1.0 equiv) at -78 °C was slowly added methyl lithium solution (1.6 M in diethyl ether, 21 mL, 33 mmol, 1.3 equiv). After 1.5 h, the reaction was quenched with HCl (*conc*., 1 mL). The organic layer was then washed sequentially with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (pentane/diethyl ether, 6:1 → 3:1) to afford racemic **71** as a colorless oil (3.4 g, 79% yield). The Sharpless kinetic resolution was performed according to *General Procedure 2.4.2.2* with racemic **71** (1.68 g, 10.0 mmol, 1.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 5:1 → 3:1) to afford the title compound as a colorless oil (0.49 g, 29% yield). Spectral data were consistent with the literature.[112]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.21(d, J = 8.4 Hz, 1H), 5.09 (t, J = 6.8 Hz, 1H), 4.61-4.55 (m, 1H), 2.12-2.07 (m, 2H), 2.01-1.97 (m, 2H), 1.68 (s, 6H), 1.60 (s, 3H), 1.33 (bs, 1H), 1.23 (d, J = 6.8 Hz, 3H).

Chiral Capillary GC: 99% ee, (CHIRALDEX BP-M). t_R = 18.92 min (minor), 19.32 min (major).



(2*R*,3*R*)-methyl 2-hydroxy-3-((*E*)-prop-1-en-1-yl)-2-((*E*)-styryl)octanoate (72)

Prepared by *General Procedure 2.4.2.2* with **61** (71 mg, 0.50 mmol, 1.0 equiv) and **37** (206 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 30:1 → 20:1) to afford the title compound as a colorless oil (131 mg, 83% yield).

$[\alpha]^{20}_{D}$ –4.5° (*c* 1.0, $CHCl_3$).

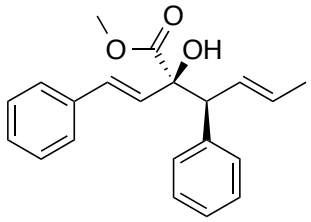
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.34-7.30 (m, 2H), 7.26-7.22 (m, 1H), 6.84 (d, J = 16.0 Hz, 1H), 6.24 (d, J = 16.0 Hz, 1H), 5.48 (dq, J = 15.2, 6.4 Hz, 1H), 5.31 (ddq, J = 15.2, 9.2, 1.6 Hz, 1H), 3.75 (s, 3H), 3.40 (s, 1H), 2.39 (t, J = 11.2 Hz, 1H), 1.67 (dd, J = 6.4, 1.6 Hz, 3H), 1.53-1.50 (m, 1H), 1.31-1.08 (m, 7H), 0.84 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 136.7, 130.8, 130.2, 129.4, 128.7, 127.8, 126.8, 80.9, 53.1, 50.9, 31.9, 27.7, 27.4, 22.8, 18.3, 14.2.

FTIR (neat): ν_{max}/cm^{-1} 3515, 1731, 1447, 1436, 1136.

HRMS (p-APCI): *m/z* 299.2003 [$(M+H)^+$ requires 299.2006].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 13.7 min (major), 16.8 min (minor).



(2*R*,3*S*,*E*)-methyl 2-hydroxy-3-phenyl-2-((E)-styryl)hex-4-enoate (73)

Prepared by *General Procedure 2.4.2.3* with **62** (77 mg, 0.50 mmol, 1.0 equiv) and **37** (203 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 30:1 → 10:1) to afford the title compound as a white solid (119 mg, 71% yield).

MP = 112–114 °C.

$[\alpha]^{20}_{D}$ –148.5° (*c* 1.1, $CHCl_3$).

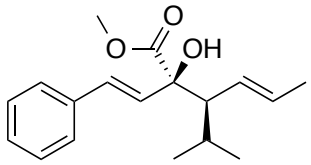
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.32 (m, 2H), 7.27-7.14 (m, 8H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 5.94 (ddq, *J* = 15.2, 9.2, 1.6 Hz), 5.31 (dq, *J* = 15.2, 6.8 Hz, 1H), 3.82 (s, 3H), 3.81 (d, *J* = 9.2 Hz, 1H), 3.59 (s, 1H), 1.69 (dd, *J* = 6.4, 1.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 139.4, 136.7, 130.8, 129.5, 129.1, 129.0, 128.8, 128.6, 128.2, 127.7, 127.0, 126.7, 80.9, 57.2, 53.3, 18.4.

FTIR (neat): ν_{max}/cm^{-1} 3506, 1728, 1448, 1436, 1140, 1118.

HRMS (p-APCI): *m/z* 305.1535 [$(M\text{-}OH)^+$ requires 305.1536].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 25.3 min (major), 32.0 min (minor).



(*2R*,3*R*,*E*)-methyl 2-hydroxy-3-isopropyl-2-((*E*)-styryl)hex-4-enoate (74)

Prepared by *General Procedure 2.4.2.3* with **63** (57 mg, 0.50 mmol, 1.0 equiv) and **37** (202 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 15:1) to afford the title compound as a white solid (100 mg, 70% yield).

MP = 47–48 °C.

$[\alpha]^{20}_{D}$ –26.9° (*c* 1.0, $CHCl_3$).

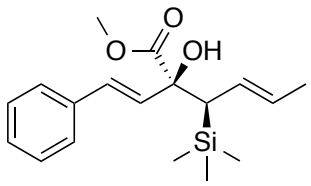
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H), 7.34-7.30 (m, 2H), 7.26-7.22 (m, 1H), 6.88 (d, *J* = 16.0 Hz, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 5.53-5.40 (m, 2H), 3.74 (s, 3H), 3.47 (s, 1H), 2.37 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.05 (dqq, *J* = 6.8, 6.8, 2.8 Hz, 1H), 1.69 (d, *J* = 4.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 136.6, 130.2, 129.7, 129.5, 128.6, 127.6, 126.7, 126.2, 81.5, 55.4, 53.0, 27.1, 23.3, 18.4, 18.2.

FTIR (neat): ν_{max}/cm^{-1} 3508, 3026, 2954, 2873, 1728, 1448, 1436, 1145.

HRMS (p-APCI): *m/z* 271.1697 [$(M\text{-}OH)^+$ requires 271.1693].

HPLC: >99% ee (CHIRALPAK AD-H, 0.3% isopropanol/hexanes, 0.8 mL/min, UV: 230 nm). t_R = 14.6 min (major), 19.2 min (minor).



(2*S*,3*R*,*E*)-methyl 2-hydroxy-2-((*E*)-styryl)-3-(trimethylsilyl)hex-4-enoate (75)

Prepared by *General Procedure 2.4.2.3* with **64** (73 mg, 0.50 mmol, 1.0 equiv) and **37** (208 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 30:1 → 20:1) to afford the title compound as a white solid (68 mg, 42% yield).

MP = 58–60 °C.

$[\alpha]^{20}_{D}$ –67.3° (*c* 1.0, $CHCl_3$).

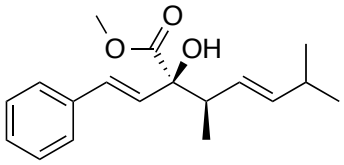
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (m, 2H), 7.35-7.31 (m, 2H), 7.26-7.23 (m, 1H), 6.82 (d, J = 15.6 Hz, 1H), 6.26 (d, J = 15.6 Hz, 1H), 5.50-5.34 (m, 2H), 3.72 (s, 3H), 3.61 (s, 1H), 2.12 (d, J = 7.0 Hz, 1H), 1.67 (d, J = 4.8 Hz, 3H), 0.02 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 136.8, 131.1, 129.8, 128.8, 127.8, 127.5, 126.8, 80.5, 53.1, 43.9, 18.4, -0.3.

FTIR (neat): ν_{max}/cm^{-1} 3512, 2953, 1728, 1448,1436, 1099.

HRMS (p-APCI): *m/z* 301.1620 [$(M\text{-}OH)^+$ requires 301.1618].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 13.1 min (major), 16.5 min (minor).



(2*R*,3*R*,*E*)-methyl 2-hydroxy-3,6-dimethyl-2-((*E*)-styryl)hept-4-enoate (76)

Prepared by *General Procedure 2.4.2.3* with **65** (59 mg, 0.50 mmol, 1.0 equiv) and **37** (201 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 30:1 → 20:1) to afford the title compound as a colorless oil (112 mg, 75% yield).

$[\alpha]^{20}_{D}$ +28.8° (*c* 1.0, $CHCl_3$).

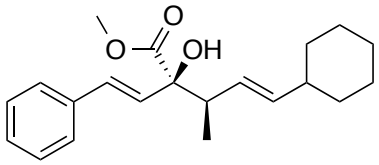
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.41 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.23 (m, 1H), 6.86 (d, J = 16.0 Hz, 1H), 6.26 (d, J = 16.0 Hz, 1H), 5.46 (dd, J = 16.0, 6.8 Hz, 1H), 5.34 (dd, J = 16.0, 8.8 Hz, 1H), 3.77 (s, 3H), 3.36 (s, 1H), 2.66-2.59 (m, 1H), 2.29-2.21 (m, 1H), 1.02 (d, J = 7.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 140.2, 136.7, 130.8, 129.3, 128.7, 127.9, 127.3, 126.9, 80.7, 53.0, 45.0, 31.3, 22.9, 22.8, 14.2.

FTIR (neat): ν_{max}/cm^{-1} 3515, 1731, 1448, 1436, 1142.

HRMS (p-APCI): *m/z* 271.1694 [$(M\text{-}OH)^+$ requires 271.1693].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 15.9 min (minor), 19.6 min (major).



(2*R*,3*R*,*E*)-methyl 5-cyclohexyl-2-hydroxy-3-methyl-2-((*E*)-styryl)pent-4-enoate (77)

Prepared by *General Procedure 2.4.2.3* with **66** (78 mg, 0.50 mmol, 1.0 equiv) and **37** (204 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 20:1 → 10:1) to afford the title compound as a white solid (143 mg, 86% yield).

MP = 130–131 °C.

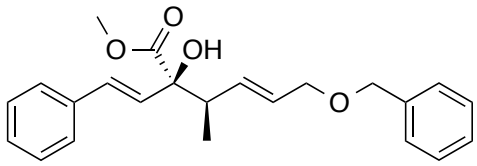
$[\alpha]^{20}_{D}$ +34.1° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.41 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 6.86 (d, *J* = 16.0 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 5.43 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.34 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.77 (s, 3H), 3.35 (s, 1H), 2.66-2.58 (m, 1H), 1.92-1.88 (m, 1H), 1.74-1.64 (m, 1H), 1.31-1.13 (m, 4H), 1.08-1.04 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 139.0 136.7, 130.8, 129.2, 128.8, 127.9, 127.8, 126.8, 80.8, 53.1, 45.1, 40.9, 33.4, 33.3, 26.3, 26.2, 26.1, 14.2.

FTIR (neat): ν_{max}/cm^{-1} 3516, 2922, 2849, 1730, 1447,114. HRMS (p-APCI): *m/z* 311.2005 [(M-OH)$^{+}$ requires 311.2006].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 16.4 min (major), 19.9 min (minor).



(2*R*,3*R*,*E*)-methyl 6-(benzyloxy)-2-hydroxy-3-methyl-2-((*E*)-styryl)hex-4-enoate (78)

Prepared by *General Procedure 2.4.2.3* with **67** (96 mg, 0.50 mmol, 1.0 equiv) and **37** (202 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 10:1) to afford the title compound as a colorless oil (129 mg, 70% yield).

MP = 130–131 °C.

$[\alpha]^{20}_{D}$ +13.1° (*c* 1.0, $CHCl_3$).

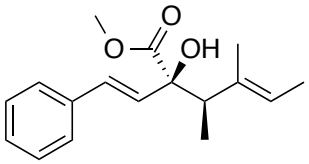
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.36-7.22 (m, 8H), 6.86 (d, J = 15.6 Hz, 1H), 6.25 (d, J = 15.6 Hz, 1H), 5.73-5.62 (m, 2H), 4.51-4.44 (m, 2H), 4.02 -3.92 (m, 2H), 3.77 (s, 3H), 3.39 (s, 1H), 2.79-2.71 (m, 1H), 1.06 (d, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 138.6, 136.6, 134.4, 131.2, 129.0, 128.8, 128.6, 128.0, 127.9, 127.8, 126.9, 80.3, 71.9, 70.7, 83.3, 44.8, 14.0.

FTIR (neat): ν_{max}/cm^{-1} 3512, 3027, 2951, 2852, 1730,1496, 1449, 1144.

HRMS (p-APCI): *m/z* 367.1910 [$(M+H)^+$ requires 367.1917].

HPLC: >99% ee (CHIRALCEL AD-H, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 22.7 min (minor), 23.9 min (major).



(2*R*,3*R*,*E*)-methyl 2-hydroxy-3,4-dimethyl-2-((*E*)-styryl)hex-4-enoate (79)

Prepared by *General Procedure 2.4.2.3* with **68** (45 mg, 0.50 mmol, 1.0 equiv) and **37** (214 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 20:1) to afford the title compound as a colorless oil (86 mg, 61% yield).

$[\alpha]^{20}_{D}$ +29.4° (*c* 1.0, $CHCl_3$).

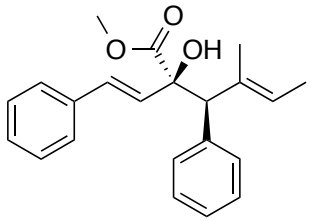
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.41 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.23 (m, 1H), 6.84 (d, J = 16.0 Hz, 1H), 6.28 (d, J = 16.0 Hz, 1H), 5.38 (dq, J = 6.8, 1.2 Hz, 1H), 3.76 (s, 3H), 3.32 (s, 1H), 2.70 (q, J = 7.2 Hz, 1H), 1.65 (t, J = 1.2, 3H), 1.58 (dd, J = 6.8, 0.8 Hz, 3H), 1.08 (d, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 136.8, 136.7, 130.5, 129.8, 128.7, 126.8, 122.3, 81.3, 52.9, 49.7, 14.0, 13.6, 12.8.

FTIR (neat): ν_{max}/cm^{-1} 3513, 1729, 1448, 1436, 1145.

HRMS (p-APCI): *m/z* 257.1536 [$(M\text{-}OH)^+$ requires 257.1536].

HPLC: >99% ee (CHIRALCEL OD-H, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 17.3 min (major), 33.4 min (minor).



(2*R*,3*S*,*E*)-methyl 2-hydroxy-4-methyl-3-phenyl-2-((*E*)-styryl)hex-4-enoate (80)

Prepared by *General Procedure 2.4.2.3* with **69** (81 mg, 0.50 mmol, 1.0 equiv) and **37** (202 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to afford the title compound as a white solid (114 mg, 68% yield).

MP = 106–108 °C.

$[\alpha]^{20}_{D}$ –101.2° (*c* 1.0, $CHCl_3$).

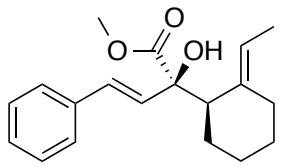
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H), 7.26-7.12 (m, 8H), 6.63 (d, J = 16.0 Hz, 1H), 6.18 (d, J = 16.0 Hz, 1H), 5.75 (q, J = 7.2 Hz, 1H), 3.89 (s, 1H), 3.81 (s, 3H), 3.62 (s, 1H), 1.60 (d, J = 7.2 Hz, 3H), 1.58 (d, J = 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 138.3, 136.5, 135.6, 130.7, 130.3, 130.2, 128.4, 127.7, 127.5, 126.6, 126.5, 122.2, 81.1, 60.1, 53.1, 15.8, 13.7.

FTIR (neat): ν_{max}/cm^{-1} 3510, 1728, 1450, 1436.

HRMS (p-APCI): *m/z* 337.1806 [$(M+H)^+$ requires 337.1798].

HPLC: >99% ee (CHIRALPAK AD-H, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 19.2 min (minor), 21.2 min (major).



(*R*,*E*)-methyl 2-((*R*,*E*)-2-ethylidenecyclohexyl)-2-hydroxy-4-phenylbut-3-enoate (81)

Prepared by *General Procedure 2.4.2.3* with **70** (64 mg, 0.50 mmol, 1.0 equiv) and **37** (202 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 30:1) to afford the title compound as a white solid (117 mg, 77% yield).

MP = 136–137 °C.

$[\alpha]^{20}_{D}$ –58.6° (*c* 1.0, $CHCl_3$).

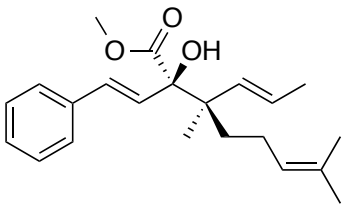
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.33-7.29 (m, 2H), 7.25-7.21 (m, 1H), 6.86 (d, *J* = 16.0 Hz, 1H), 6.24 (d, *J* = 16.0 Hz, 1H), 5.24 (q, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 3.40 (s, 1H), 2.61 (t, *J* = 5.2 Hz, 1H), 2.30-2.25 (m, 2H), 1.89-1.82 (m, 2H), 1.68-1.53 (m, 2H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.44-1.32 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 139.3, 136.7, 130.8, 130.6, 128.7, 127.9, 126.9, 118.5, 82.6, 53.1, 48.9, 27.5, 27.4, 27.3, 24.0, 13.1.

FTIR (neat): ν_{max}/cm^{-1} 3503, 1729, 1447, 1133.

HRMS (p-APCI): *m/z* 283.1690 [$(M\text{-}OH)^+$ requires 283.1693].

HPLC: >99% ee (CHIRALPAK AD-H, 0.3% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 29.7 min (minor), 33.1 min (major).



(2*R*,3*R*)-methyl 2-hydroxy-3,7-dimethyl-3-((*E*)-prop-1-en-1-yl)-2-((*E*)-styryl)oct-6-enoate (82)

Prepared by *General Procedure 2.4.2.3* with **71** (85 mg, 0.50 mmol, 1.0 equiv) and **37** (200 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 30:1 → 10:1) to afford the title compound as a colorless oil (140 mg, 82% yield).

$[\alpha]^{20}_{D}$ –29.4° (*c* 1.0, $CHCl_3$).

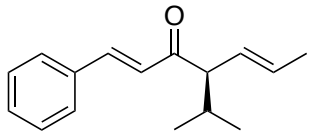
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.2 Hz, 2H), 7.31 (d, J = 7.2 Hz, 2H), 7.24-7.21 (m, 1H), 6.81 (d, J = 15.6 Hz, 1H), 6.46 (d, J = 15.6 Hz, 1H), 5.55 (d, J = 15.6 Hz, 1H), 5.43 (dq, J = 15.6, 6.0 Hz, 1H), 5.07 (t, J = 7.6 Hz, 1H), 3.79 (s, 3H), 3.50 (s, 1H), 1.84-1.77 (m, 2H), 1.74 (d, J = 6.0 Hz, 3H), 1.65 (s, 3H), 1.61-1.56 (m, 1H), 1.42-1.34 (m, 1H), 1.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 137.0, 134.8, 131.3, 130.9, 128.7, 127.8, 127.7, 126.9, 125.9, 125.1, 82.4, 53.0, 47.6, 35.2, 25.9, 23.0, 18.6, 17.8, 17.7.

FTIR (neat): ν_{max}/cm^{-1} 3507, 1721, 1445, 1436, 1144.

HRMS (p-APCI): *m/z* 343.2264 [$(M+H)^+$ requires 343.2268].

HPLC: >99% ee (CHIRALPAK OD-H, 0.3% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 18.1 min (major), 29.7 min (minor).



(*R*,1*E*,5*E*)-4-isopropyl-1-phenylhepta-1,5-dien-3-one (83)

To a tetrahydrofuran (4 mL) solution of **74** (240 mg, 0.83 mmol, 1.0 equiv) at 0 °C was added lithium aluminum hydride solution (1.0 M in tetrahydrofuran, 2.5 mL, 2.5 mmol, 3.0 equiv) dropwise over 30 min. Following addition, the reaction was allowed to warm to room tempera-

ture and stirred for an additional 4 h. The reaction vessel was again cooled to 0 °C and the reaction was carefully quenched by sequential addition of ethyl acetate (5 mL) and saturated aqueous sodium potassium tartrate (25 mL). The mixture was further dilute with ethyl acetate (20 mL) and stirred until two distinct layers formed. The layers were separated and the aqueous was extracted with ethyl acetate. The organic fractions were combined and washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was dissolved in tetrahydrofuran/H_2O (1:1, 10 mL) and sodium periodate (355 mg, 1.66 mmol, 2.0 equiv) was added in one portion with vigorous stirring. The reaction was stirred at room temperature for 4 h and the quenched with addition of aqueous sodium thiosulfate solution (25 mL). The aqueous was extracted with ethyl acetate and the combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/diethyl ether, 15:1) to afford the title compound as a colorless oil (169 mg, 89% yield).

$[\alpha]^{20}_D$ –74.2° (*c* 2.4, $CHCl_3$).

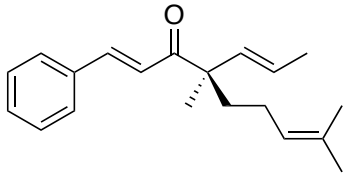
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 16.0 Hz, 1h), 7.57-7.55 (m, 2H), 7.39-7.37 (m, 3H), 6.80 (d, J = 16.0 Hz, 1H), 5.60 (dq, J = 15.2, 6.4 Hz, 1H), 5.43 (m, 1H), 3.02 (t, J = 9.0 Hz, 1H), 2.17-2.05 (m, 1H), 1.71 (dd, J = 6.4, 1.6 Hz, 3H), 0.92 (d, J = 1.6 Hz, 3H), 0.90 (d, J = 1.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0, 142.5, 134.9, 130.5, 129.8, 129.1, 128.5, 128.4, 125.6, 63.1, 30.1, 21.4, 20.1, 18.3.

FTIR (neat): ν_{max}/cm^{-1} 3026, 2959, 2870, 1685, 1652, 1607, 1576, 1465.

HRMS (p-APCI): *m/z* 229.1591 [$(M+H)^+$ requires 229.1587].

HPLC: >99% ee (CHIRALCEL AD-H, 0.4% isopropanol/hexanes, 0.4 mL/min, UV: 254 nm). t_R = 22.6 min (major), 24.9 min (minor).



(*R*,*E*)-4,8-dimethyl-1-phenyl-4-((*E*)-prop-1-en-1-yl)nona-1,7-dien-3-one (84)

To a tetrahydrofuran (4 mL) solution of **82** (270 mg, 0.79 mmol, 1.0 equiv) at 0 °C was added lithium aluminum hydride solution (1.0 M in tetrahydrofuran, 2.4 mL, 2.4 mmol, 3.0 equiv) dropwise over 30 min. Following addition, the reaction was allowed to warm to room temperature and stirred for an additional 4 h. The reaction vessel was again cooled to 0 °C and the reaction was carefully quenched by sequential addition of ethyl acetate (2 mL) and saturated aqueous sodium potassium tartrate (10 mL). The mixture was partitioned between H_2O (15 mL) and ethyl acetate (15 mL) and stirred until two distinct layers formed. The layers were separated and the aqueous was extracted with ethyl acetate. The organic fractions were combined and washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was dissolved in tetrahydrofuran/H_2O (1:1, 10 mL) and sodium periodate (338 mg, 1.58 mmol, 2.0 equiv) was added in one portion with vigorous stirring. The reaction was stirred at room temperature for 6 h and the quenched with addition of aqueous sodium thiosulfate solution (20 mL). The aqueous was extracted with ethyl acetate and the combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (pentane/diethyl ether, 20:1 → 10:1) to afford the title compound as a colorless oil (200 mg, 90% yield).

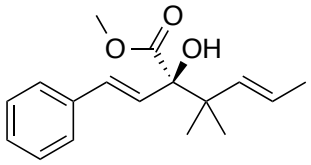
$[\alpha]^{20}_D$ +2.4° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 15.8 Hz, 1H), 7.56-7.53 (m, 2H), 7.39-7.36 (m, 3H), 7.04 (d, *J* = 15.8 Hz, 1H), 5.64-5.53 (m, 2H), 5.11-5.07 (m, 1H), 2.00-1.89 (m, 1H) 1.88-1.76 (m, 2H), 1.74 (d, *J* = 4.8 Hz, 3H), 1.68-1.61 (m, 1H), 1.65 (s, 3H), 1.55 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 142.3, 135.3, 134.7, 132.0, 130.3, 129.0, 128.5, 126.4, 124.5, 122.5, 52.7, 38.0, 25.9, 23.3, 20.9, 18.7, 17.8.

FTIR (neat): ν_{max}/cm^{-1} 3026, 2966, 2915, 2855, 1683, 1608, 1576, 1495, 1448, 1049.

HRMS (p-APCI): *m/z* 283.2055 [$(M+H)^+$ requires 283.2056].



methyl (*R*,*E*)-2-hydroxy-3,3-dimethyl-2-((*E*)-styryl)hex-4-enoate (109)

Prepared by *General Procedure 2.4.2.3* with **87** (50 mg, 0.50 mmol, 1.0 equiv) and **37** (200 mg, 1.0 mmol, 2.0 equiv). The crude residue was purified by flash chromatography (pentane/diethyl ether, 10:1) to afford the title compound as a colorless oil (127 mg, 92% yield).

$[\alpha]^{20}_D$ –26.1° (*c* 1.0, $CHCl_3$).

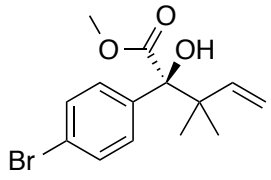
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.25 (m, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.61 (dd, *J* = 16.0, 1.6 Hz, 1H), 5.53-5.46 (m, 1H), 3.80 (s, 3H), 3.44 (s, 1H), 1.72 (dd, *J* = 6.0, 0.8 Hz, 3H), 1.14 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 137.0, 136.4, 130.9, 128.7, 127.8, 127.4, 126.9, 124.4, 81.8, 52.9, 44.4, 23.1, 23.0, 18.5.

FTIR (neat): ν_{max}/cm^{-1} 3507, 1722, 1447, 1435, 1235, 1132.

HRMS (p-APCI): *m/z* 275.1642 [$(M+H)^+$ requires 275.1641].

HPLC: 98% ee (*S,S*-Whelk, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 254 nm). t_R = 12.8 min (major), 15.2 min (minor).



methyl (*S*)-2-(4-bromophenyl)-2-hydroxy-3,3-dimethylpent-4-enoate (111)

Prepared by *General Procedure 2.4.2.5* with **50** (154 mg, 0.60 mmol) **110** (43 mg, 0.50 mmol), calcium chloride (222 mg, 2.0 mmol), and $\{Rh_2[(R)\text{-dosp}]_4\}$ (1 mg, 0.0005 mmol). Purification by flash chromatography (pentane/ether, 10:1) afforded the title compound as acolorless oil (88 mg, 56% yield).

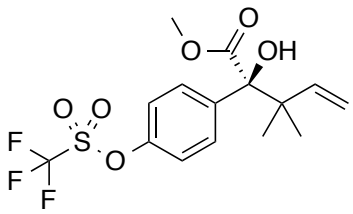
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 6.02 (dd, J = 17.5, 10.8 Hz, 1H), 5.04 (dd, J = 10.8, 1.2 Hz, 1H), 4.94 (dd, J = 17.5, 1.2 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 1H), 1.07 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 143.7, 137.7, 130.5, 129.6, 122.2, 114.1, 82.5, 53.3, 45.1, 22.8, 22.5.

FTIR (neat): ν_{max}/cm^{-1} 3494, 2973, 2953, 2876, 1720, 1587, 1486, 1435.

HRMS (p-APCI): *m/z* 313.0435 [$(M+H)^+$ requires 313.0434].

HPLC: 99% ee (*S,S*-Whelk, 0.3% isopropanol/hexanes, 0.8 mL/min, UV: 230 nm). t_R = 8.6 min (major), 9.5 min (minor).



methyl (*S*)-2-hydroxy-3,3-dimethyl-2-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)pent-4-enoate (115)

Prepared by *General Procedure 2.4.2.5* with **115** (195 mg, 0.60 mmol) **110** (43 mg, 0.50 mmol), calcium chloride (222 mg, 2.0 mmol), and $\{Rh_2[(R)\text{-dosp}]_4\}$ (1 mg, 0.0005 mmol). Purification by flash chromatography (pentane/ether, 10:1) afforded the title compound as acolorless oil (135 mg, 71% yield).

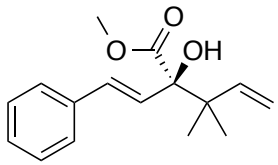
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 6.00 (dd, J = 17.6, 10.8 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 4.91 (d, J = 17.6 Hz, 1H), 3.86 (s, 1H), 3.84 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 149.0, 143.1, 138.8, 129.7, 129.6, 119.8, 114.1, 82.1, 53.2, 45.0, 22.7, 22.1.

FTIR (neat): ν_{max}/cm^{-1} 3500, 3088, 2958, 2880, 1722, 1596, 1498, 14231206, 1137.

HRMS (p-APCI): *m/z* 383.0770 [$(M+H)^+$ requires 383.1771.

HPLC: 96% ee (AD-H, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 230 nm). t_R = 14.9 min (major), 19.0 min (minor).



methyl (*R*,*E*)-2-hydroxy-3,3-dimethyl-2-styrylpent-4-enoate (116)

Prepared by *General Procedure 2.4.2.5* with **37** (122 mg, 0.60 mmol) **110** (43 mg, 0.50 mmol), calcium chloride (222 mg, 2.0 mmol), and $\{Rh_2[(R)\text{-dosp}]_4\}$ (1 mg, 0.0005 mmol). Purification by flash chromatography (pentane/ether, 9:1) afforded the title compound as acolorless oil (28 mg, 22% yield).

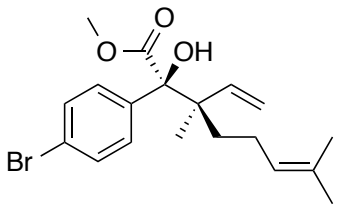
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.37 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.27-7.20 (m, 1H), 6.85 (d, J = 15.8 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H), 6.03 (dd, J = 17.4, 10.8 Hz, 1H), 5.13-5.00 (m, 2H), 3.80 (s, 3H), 3.50 (s, 1H), 1.15 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 143.8, 136.9, 131.2, 128.8, 127.9, 127.1, 126.9, 113.7, 81.5, 53.1, 45.1, 22.7, 22.2.

FTIR (neat): ν_{max}/cm^{-1} 3441, 3029, 2975, 2953, 1731, 1602, 1496.

HRMS (p-APCI): *m/z* 261.1485 [$(M+H)^+$ requires 261.1485].

HPLC: 99% ee (*S,S*-Whelk, 0.3% isopropanol/hexanes, 0.8 mL/min, UV: 254 nm). t_R = 11.3 min (major), 20.6 min (minor).



methyl (2*S*,3*R*)-2-(4-bromophenyl)-2-hydroxy-3,7-dimethyl-3-vinyloct-6-enoate [(2*S*,3*R*)-119]

Prepared by *General Procedure 2.4.2.5* with **50** (154 mg, 0.60 mmol) **118** (77 mg, 0.50 mmol), calcium chloride (222 mg, 2.0 mmol), and $\{Rh_2[(R)\text{-dosp}]_4\}$ (1 mg, 0.0005 mmol). Purification by flash chromatography (pentane/ether, 15:1) afforded a mixture of product diastereomers as a colorless oil (124 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.43-7.41 (m, 2H), 5.79 (dd, J = 17.6, 10.8 Hz, 1H), 5.16 (d, J = 10.8 Hz, 1H), 5.06-4.99 (m, 1H), 4.87 (d, J = 17.6 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 1H), 1.79-1.71 (m, 2H), 1.65 (s, 3H), 1.63-1.56 (m, 1H), 1.53 (s, 3H), 1.42-1.34 (m, 1H), 1.05 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 141.2, 139.0, 131.6, 130.2, 124.8, 123.3, 120.0, 116.5, 83.0, 53.3, 48.8, 34.7, 25.9, 23.2, 17.8, 17.3.

FTIR (neat): ν_{max}/cm^{-1} 3493, 3082, 2953, 2925, 2956, 1719, 1635, 1586, 1486, 1435, 1240, 1076, 1009.

HRMS (p-APCI): *m/z* 381.1061 [$(M+H)^+$ requires 381.1060].

HPLC: 99% ee (CHIRALPAK OD-H, 0.3% isopropanol/hexanes, 0.3 mL/min, UV: 254 nm). t_R = 8.2 min (major), 8.7 min (minor).

2.5 References

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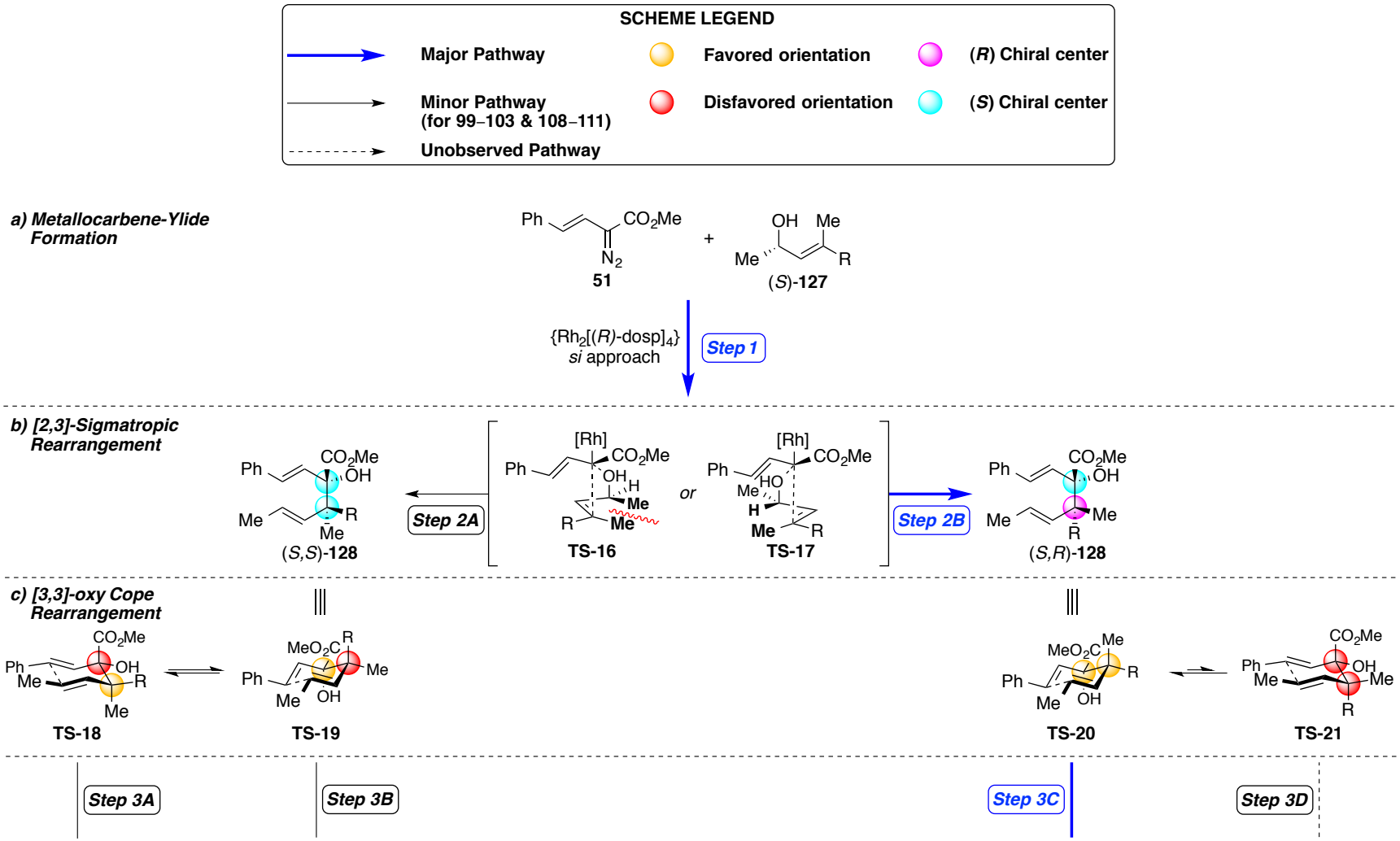
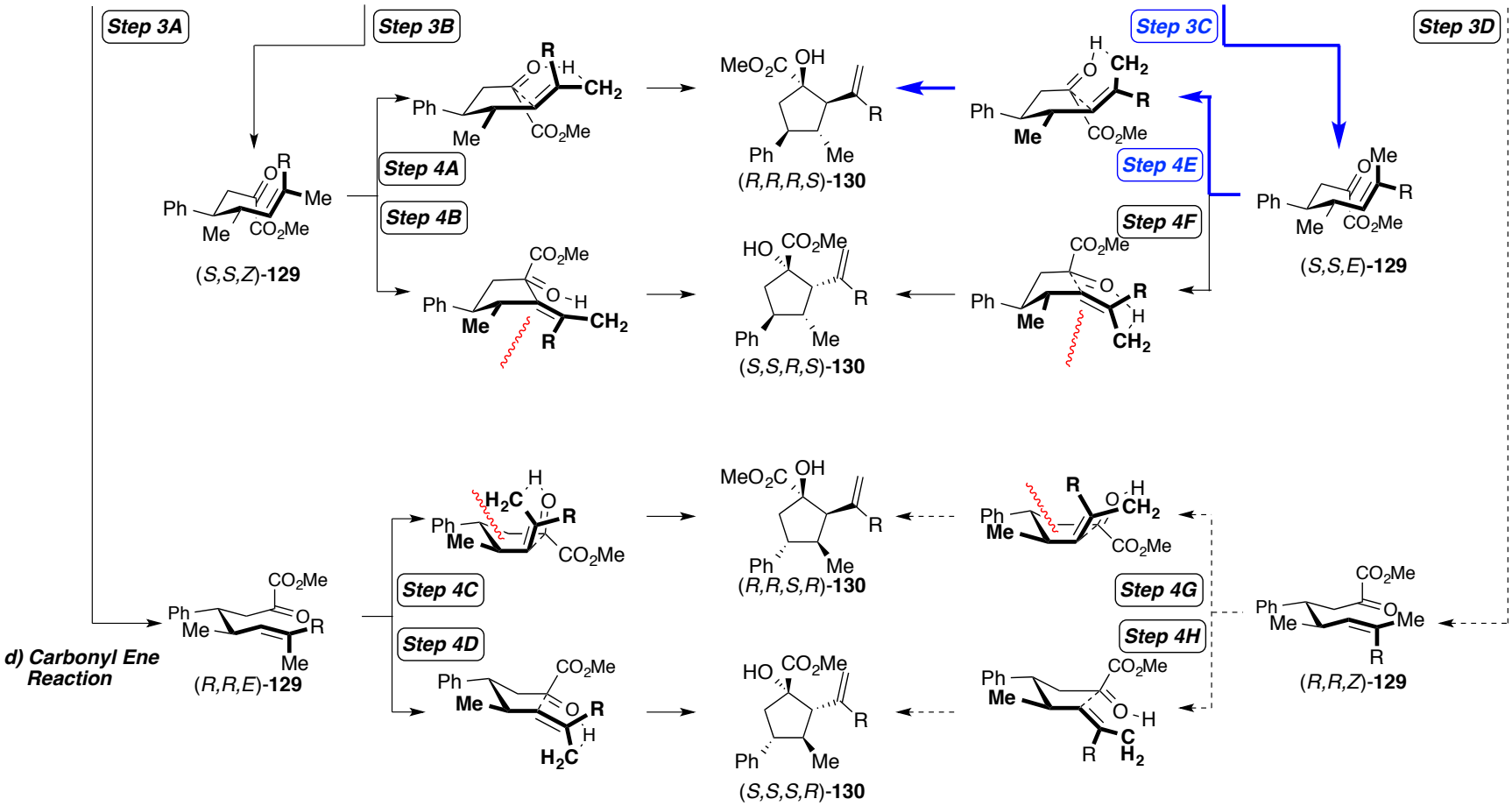

SCHEME LEGEND
Major Pathway
Minor Pathway (for 99–103 & 108–111)
Unobserved Pathway
Favored orientation
Disfavored orientation
(R) Chiral center
(S) Chiral center
a) Metallocarbene-Ylide Formation
51
(S)-127
{Rh2[(R)-dosp]4}
si approach
Step 1
b) [2,3]-Sigmatropic Rearrangement
(S,S)-128
Step 2A
TS-16
or
TS-17
Step 2B
(S,R)-128
c) [3,3]-oxy Cope Rearrangement
TS-18
TS-19
TS-20
TS-21
Step 3A
Step 3B
Step 3C
Step 3D



Scheme 3.22 Overview of chirality transfer processes for the domino sequence

When the allylic alcohol was not 3,3′-disubstituted (*e.g.* **99**–**103** and **108**–**111**), **TS-16** becomes viable in the 2,3-sigmatropic rearrangement leading to the formation of some of the enantiomeric product (*S*,*S*,*S*,*R*)-**130**. Also, **TS-23** becomes viable in the ene reaction leading to the formation of some of the diastereomeric product (*S*,*S*,*R*,*S*)-**130**.

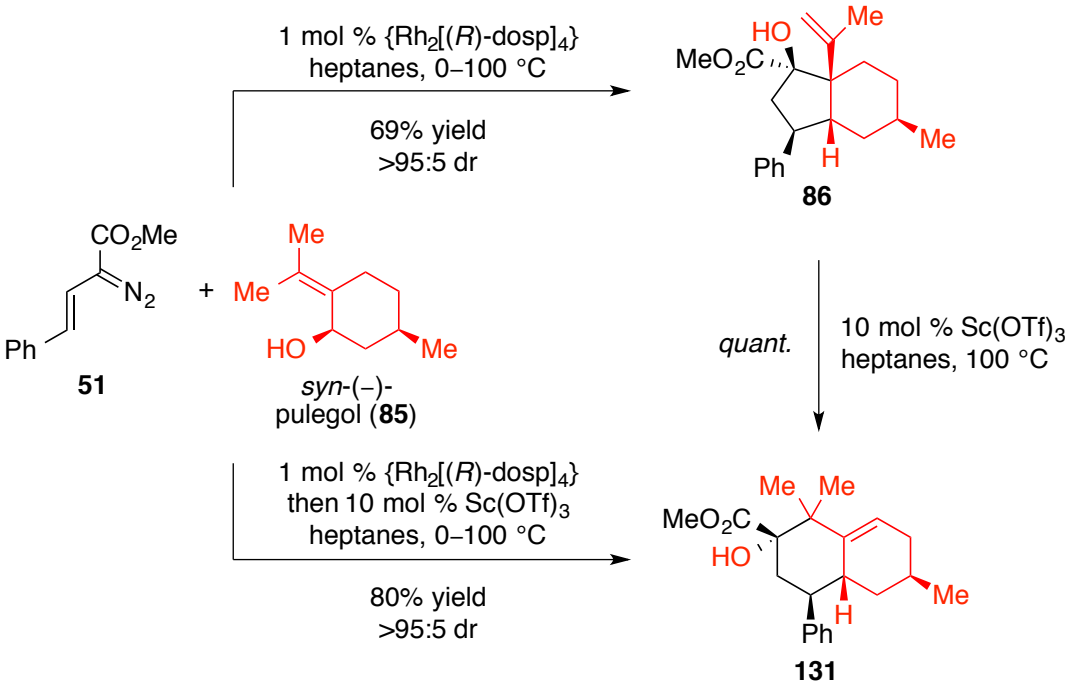
3.2.3 Cyclohexane Synthesis

Convergent synthesis of six membered carbocycles has continued to be a thematic research area for organic chemists over the past century. Although the venerable Diels–Alder [4+2]-cycloaddition reaction has remained state-of-the-art,[3,100–118] many novel annulations, including [3+3]-[119–126] and [5+1]-cycloadditions[124,127–129] have enabled entry into distinct, all carbon frameworks.[130–132] While it is doubtful any convergent annulation strategy can compare with the Diels–Alder reaction in generality, the development of orthogonal approaches to the synthesis of a cyclohexane nucleus, which allow alternative substitution patterns and stereocontrol, is nonetheless desirable.

Donor/acceptor-substituted rhodium carbenes have a rich history of application towards the synthesis of medium-sized carbocycles. For example, cyclopropanation of conjugated dienes by rhodium vinylcarbenes, followed by a Cope rearrangement of the transient *syn* divinylcyclopropane is a powerful approach to the stereoselective construction of cycloheptadienes. In our previous study, we demonstrated the synthesis of functionalized cyclopentanes bearing four stereocenters by through a convergent, cascade strategy involving intercept of a rhodium vinylcarbene intermediate with an allyl alcohol. A rhodium carbene-based, convergent annulation strategy to enable the stereoselective synthesis of a cyclohexane nucleus was not a known reaction at the outset of our investigations.

The discovery of the cyclohexane forming reaction pathway was made during our previous investigations into cyclopentane synthesis with *syn*-(–)-pulegol (**85**). Formation of the octahydroindene **86** could be achieved upon heating of the crude product resulting from {Rh_2[(*R*)-dosp]$_4$}-catalyzed reaction of **85** and styryldiazoacetate **51** (Scheme 3.23).[96] We found, how-

ever, when more vigorous reaction conditions were implemented, specifically incorporating a catalytic quantity of scandium triflate, octahydronaphthalene **131** was formed as the sole product. Moreover, exposure of hydrindane **86** to Lewis acid at elevated temperatures resulted in smooth conversion of **86** to bicycle **131** in quantitative yield. In both instances, **131** was generated as a single diastereoisomer. The relative and absolute stereochemical configuration of the octahydronaphthalene (**131**) was confirmed by X-ray crystallographic analysis. An intriguing observation was that the relative inversion of the hydroxy ester stereocenter in **131** as compared to **86**.

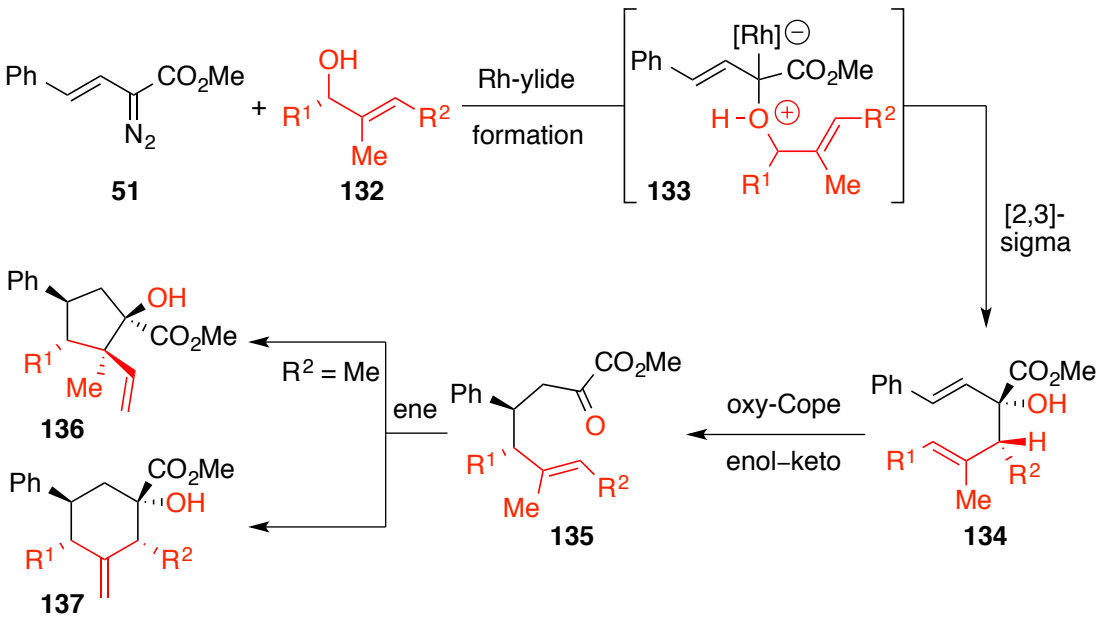


Scheme 3.23 Discovery of a cyclohexane synthesis from a styryldiazoacetate and allyl alcohol

A plausible mechanism for the formation of a generic cyclohexane prouct *via* a cascade sequence is outlined in Scheme 3.24. Rhodium-bound ylide (**133**) formation from diazoacetate **51**-

derived rhodium carbene and allyl alcohol **132** with tandem [2,3]-sigmatropic rearrangement has been discussed in detail in Chapter 2 and Chapter 3.2.1–2.[74,91,97] The 3-hydroxy-1,5-hexadiene **134** participates in a thermally driven oxy-Cope rearrangement *via* a chair-like transition state, as with our previous studies. Upon enol–keto tautomerization, transient formation of α-keto ester **135** would be anticipated. In our previous studies, the R^2 substituent of the allyl alcohol would contain at least one C–H bond available to participate in an intramolecular ene reaction. For example, if the alcohol C(3)-substituent was methyl, a type I ene cyclization event would forge the cyclopentane **136** bearing a vinyl substituent and vicinal quaternary carbon stereocenters.

Alternatively, the presence of a C(2)-methyl group on the alcohol renders a different "ene" component and activates an alternative termination pathway.[95] Thus, cyclization *via* a type II ene reaction would yield the cyclohexane **137** bearing an exocyclic olefin. We hypothesized that the driving force for the formation of **137**, rather than **136**, is alleviation of the strain derived from severe eclipsing interactions of vicinal quaternary carbon centers present in the cyclopentane product. And so under Lewis acid-catalyzed conditions, the cyclopentane (**86**) formed in Scheme 3.23 would conceivably undergo a retro hetero-ene reaction followed by the type II carbonyl ene reaction to generate the octahydronaphthalene product (**131**).



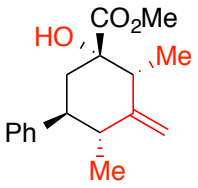
Scheme 3.24 Mechanistic rationale for the formation of cyclohexanes

Alcohol Scope. We pursued the validity of the mechanism proposed for Scheme 3.24 by investigating the reactivity of various allyl alcohols bearing C(2) C–H substituents (**138–143**) combined with the rhodium vinylcarbene derived from {Rh_2[(*R*)-dosp]$_4$}-catalyzed decomposition of **51**, as shown in Table 3.9. It was incidentally found in the preliminary reactions that cyclohexane synthesis could be effected under the same conditions as prescribed for the cyclopentane synthesis; however, the loading of calcium chloride was increased to 3 equiv, as the yields were more consistent and reproducible than at 2 equiv. Similarly, the racemic samples for comparative HPLC analysis to determine the ee were prepared by the reaction of **51** with racemic alcohols (**138–143**) under the catalytic action of an equimolar mixture of {Rh_2[(*R*)-dosp]$_4$} and {Rh_2[(*S*)-dosp]$_4$}. Indeed, the simple pentenol **138**, which differs from substrates used in our cyclopentane synthesis only in presence of a methyl group at the internal position of the alkene,

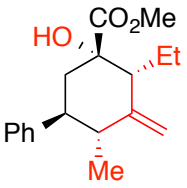
gave rise to the cyclohexane **144** in good yield and excellent stereoselectivity (67% yield, >97 : 3 dr, 99% ee). Variations in the substitution of the alcohol either at the terminal (**139 → 145**), carbinol (**140 → 146**), or both (**141 → 147**) positions were all well tolerated (entries 2–4). The corresponding cyclohexanes were forged in high yields (52–90%) and as single stereoisomers. In addition, cyclic allyl alcohols where the olefin is contained within a cyclopentene or cyclohexene ring (**142** and **143**, respectively) were effective reaction partners. The hydrindene (**148**) and octahydronaphthalene (**149**) products were formed in superb yields (65% and 85%, respectively) and stereoselection (>97 : 3 dr, 99% ee). Notably, in all instances, none of the corresponding cyclopentane products were evident from ^{1}H NMR analysis of the crude reaction residues.

Table 3.9[a–c] Scope of allyl alcohols for the one-pot cyclohexane synthesis

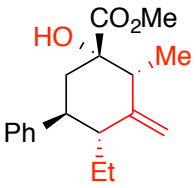
51 **138–143** **144–149**



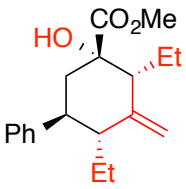
144
67% yield
>97 : 3 dr
99% ee



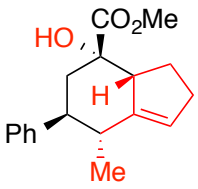
145
90% yield
>97 : 3 dr
99% ee



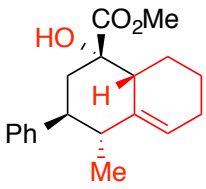
146
52% yield
>97 : 3 dr
99% ee



147
85% yield
>97 : 3 dr
99% ee



148
65% yield
>97 : 3 dr
99% ee



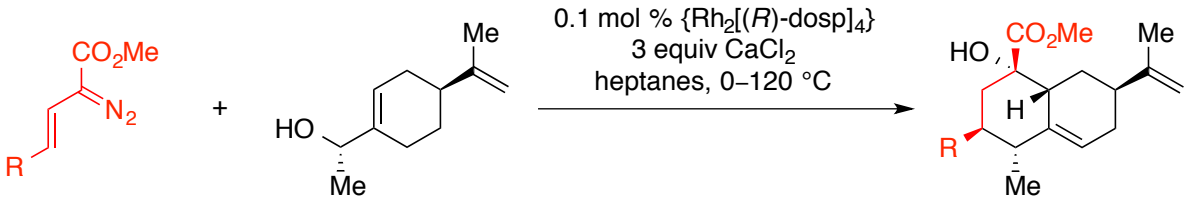
149
85% yield
>97 : 3 dr
99% ee

[a] Isolated yields of **144–149**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Vinylcarbene Scope. Our next series of experiments explored the scope of vinyldiazoacetates (**51** and **150–155**) when partnered with another monoterpenoid substrate, 1-methyl perilic alco-

hol (**155**), as shown in Table 3.10. In contrast to the endocyclic allyl alcohol *syn*-(–)-pulegol (**85**), **155** contains an exocyclic alcohol moiety, which was expected to generate a regioisomeric octahydronaphthalene product. Reaction of phenyl (**51**) and styryl (**150**) substituted vinyldiazoacetates proceeded in good yield to afford a single stereoisomer of the bicyclic products (**156** and **157**, respectively) containing five stereocenters. A *para*-substituent on the arene had minimal implications on reaction efficacy, as the 4-Br (**151**) and 4-CF_3 (**152**) substituted phenyldiazoacetates afforded comparable yields of annulated cyclohexanes, again as a single diastereoisomer. A disubtituted arene was also compatible with the cyclohexane synthesis. The 2-naphthyl (**153**) and 3,4-Cl_2 (**154**) substituted donors provided moderate yields (54 and 56%, respectively) and excellent stereoselectivities (>97 : 3 dr). The relative and absolute stereochemical configuration of octahydronaphthalene **159** was confirmed by X-ray crystallographic analysis and applied to the series of products by analogy.

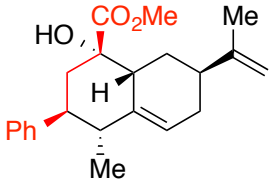
Table 3.10[a,b] Scope of diazoacetates for the one-pot cyclohexane synthesis



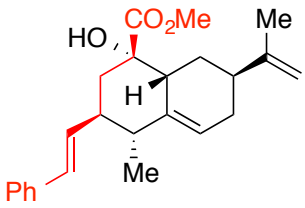
51, R=Ph
150, R=styryl
151, R=4-BrC_6H_4
152, R=4-$CF_3C_6H_4$
153, R=2-Naph
154, R=3,4-$Cl_2C_6H_3$
1.2 equiv

1-methyl perillic alcohol (**155**)

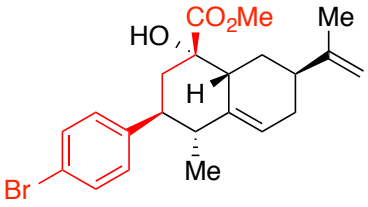
156, R=Ph
157, R=styryl
158, R=4-BrC_6H_4
159, R=4-$CF_3C_6H_4$
160, R=2-Naph
161, R=3,4-$Cl_2C_6H_3$



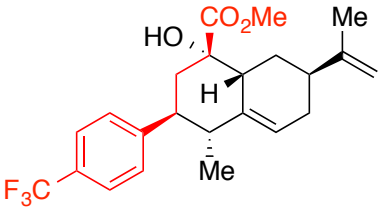
156
66% yield
>97 : 3 dr



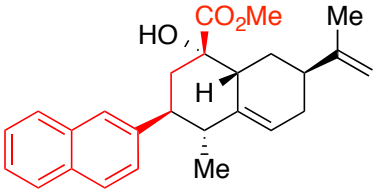
157
58% yield
>97 : 3 dr



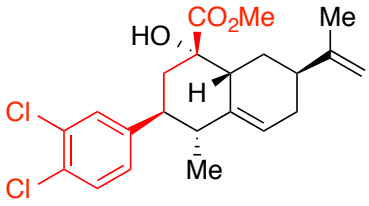
158
56% yield
>97 : 3 dr



159
66% yield
>97 : 3 dr



160
54% yield
>97 : 3 dr



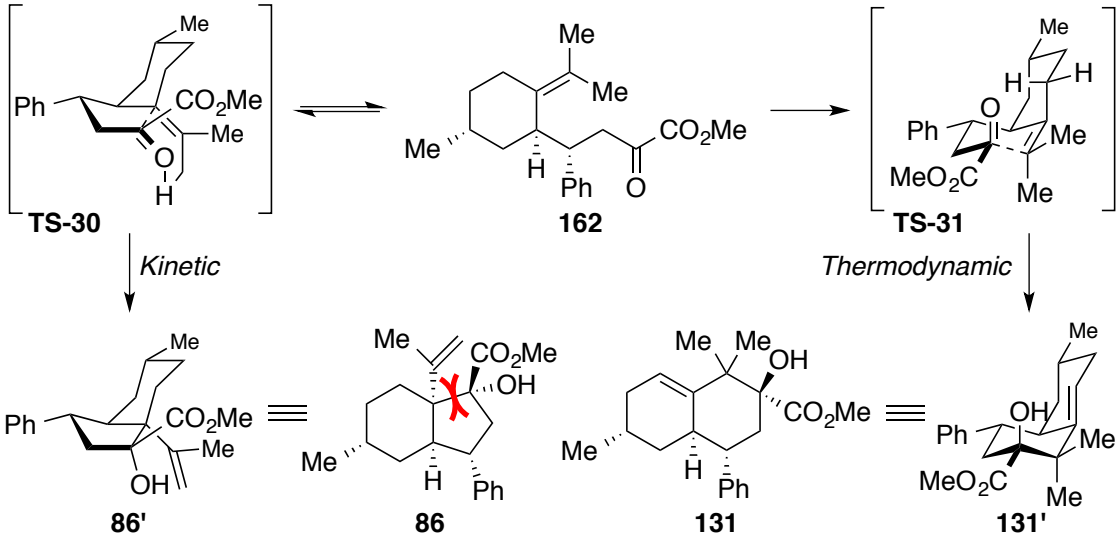
161
56% yield
>97 : 3 dr

---

[a] Isolated yields of **157**–**163**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue.

Stereochemical Rationale. Having established the relative and absolute configuration of several of the cyclohexanes synthesized, we considered a stereochemical rationale for the relative inversion in configuration of the hydroxy ester stereocenter, which is graphically represented in Schemes 3.25 and 3.26. First we considered the reaction of *syn*-(–)-pulegol (**85**) were both the cyclopentane (**86**) and cyclohexane (**131**) products had been isolated and characterized. The keto ester (**162**) could adopt an envelope-like transition state such as **TS-30**, with the phenyl group occupying a pseudoequatorial position, which is consistent with our previous observations. The α-ketone and alkene are oriented syn to achieve requisite orbital overlap, on the convex face of the ensuing bicyclic product. The fact that **86** is the sole hetero-ene product derived from the reaction under mild, non-reversible conditions led us to designate this as the kinetic product. Alternatively, a chair-like intermediate such as **TS-31** could be rendered, where the ring junction, phenyl and carbomethoxy substituents are all oriented in equatorial positions. The axial allylic C–H of the terpenoid ring would be in sufficient proximity to participate in the hetereo-ene reaction. Thus, the ensuing hydroxyl group would be generated anterafacial to the phenyl group in

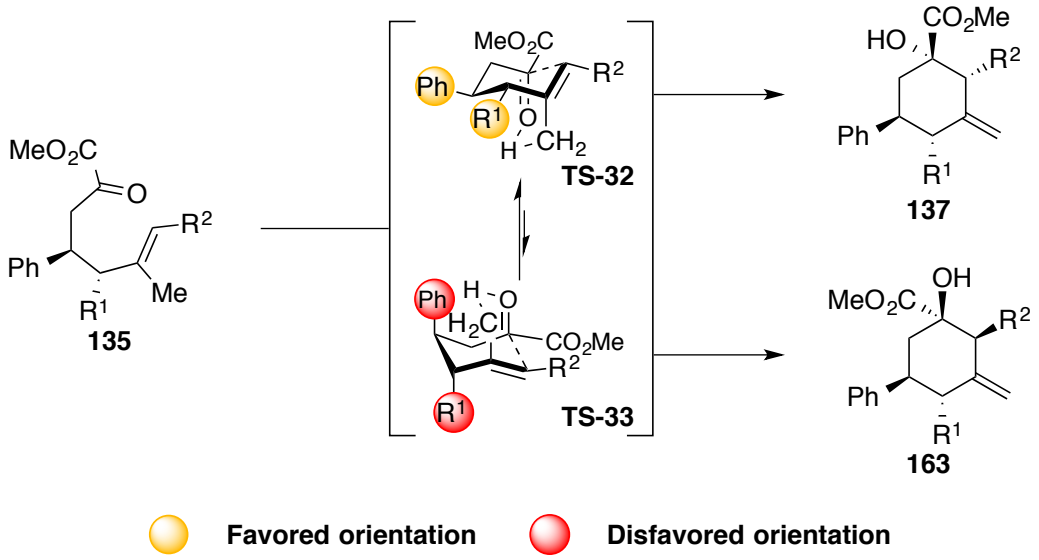
the cyclohexane as observed. Since octahydronaphthalene **131** is formed as the major product under vigorous reaction conditions where the hetero-ene reaction becomes reversible, we deem this the thermodynamic product.



Scheme 3.25 Stereochemical rationale for the formation of cyclopentane **86** and cyclohexane **131**

A stereochemical rationale of the carbonyl ene reaction for substrates wherein the product cyclohexane contains four new stereogenic centers is further analyzed in Scheme 3.26. The α-keto ester (**135**) can be rendered into two possible chair-like transition states (**TS-32** and **TS-33**), which can interconvert by a chair flip. In transition state **TS-32**, all of the more encumbered substitu-ents (carbomethoxy, R^1, and phenyl) occupy the equatorial positions of the chair. The ketone and methyl groups occupy psuedoaxial positions allowing for efficient orbital overlap such that the sigmatropic rearrangement may occur. In the chair flipped transition state, the

bulkier substituents (carbomethoxy, R^1, and phenyl) are all in less favorable axial positions. Again, the ketone and methyl group of the ene are in requisite axial positions to allow the rearrangement to occur, which would also bear the consequence of 1,3-diaxial interactions with the phenyl moiety. Thus, chair-like transition state **TS-32** is solely operative in conversion of the generic ketoester **135** to the cyclohexane **137**, which is consistent with the observed stereochemistry for all substrates.



Scheme 3.26 Stereochemical rationale for the type II carbonyl ene reaction

3.3 Conclusions

In summary we have developed novel convergent strategies for the asymmetric synthesis of saturated cyclopentane and cyclohexane nuclei from vinyldiazoacetates and appropriately substituted chiral allyl alcohols under the catalytic action of $[Rh_2(dosp)_4]$. The reaction cascade features four discrete chirality transfer processes – rhodium-bound ylide formation, [2,3]-sigmatropic rearrangment, oxy-Cope rearrangement, and carbonyl ene reaction – for which we have developed detailed understandings of the mechanism and predictive models to achieve optimal performance. Establishing proper controls for each step of the reaction has enabled a predictive model for the ideal substrates for attaining high stereoselectivity in each reaction cascade. Despite the numerous challenges and myriad of plausible reaction pathways for the cascade sequences outlined, our analysis of each step has enabled development of two novel, robust and selective transformations. Furthermore, calcium chloride has been identified as a powerful stoichiometric additive to enable these reactions to be conducted at reduced loadings of dirhodium tetracarboxylate catalyst.

Future work to employ the one-pot cyclopentane and cyclohexane syntheses *en route* to complex natural products should be considered and pursued. Interception of the cyclopentane cores prepared by Hiersemann and co-workers in jatrophane terpenoid synthesis should present an opportunity to highlight the utility of the former reaction cascade through succinct formal synthesis. In addition, identifying readily engineered allyl alcohols, which could present the opportunity for novel, extended reaction cascades warrants further investigation, as these possibilities have been demonstrated in limited contexts. In addition, investigating the products from the [2,3]-sigmatropic rearrangement of primary allyl alcohols, discussed in Chapter 2, as plausible substrates for cyclopentane and cyclohexane synthesis will be of future interest.

3.4 Experimental Section

3.4.1 General Considerations

All reactions were conducted in oven-dried glassware under an inert atmosphere of dry argon. All chemicals were purchased from either Sigma-Aldrich, TCI America, Acros, AK Scientific, or Alfa-Aesar, and were used as received. Hexanes and toluene were obtained from a Grubbs-type solvent purification system. Heptanes were purchased from Macron Fine Chemicals, and was used as received. Ethyl acetate was purchased from Sigma-Aldrich as the anhydrous reagent, and was used as received. 1,2-Dichloroethane was distilled over CaH_2 under an inert atmosphere of argon prior to use. Cyclohexane was distilled over sodium under an inert atmosphere of argon prior to use. Calcium chloride was dried at 200 °C under vacuum (<1 Torr) for 12 h and stored in a dessicator. Proton (^{1}H) NMR spectra were recorded at either 400 MHz on an INOVA-400 spectrometer or at 600 MHz on an INOVA-600 spectrometer. Carbon-13 (^{13}C) NMR spectra were recorded at either 100 MHz on an INOVA-400 spectrometer or at 150 MHz on an INOVA-600 spectrometer. NMR spectra were recorded in deuterated chloroform ($CDCl_3$) solutions, with residual chloroform (δ 7.27 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR) or tetramethylsilane (δ 0.00 ppm for ^{1}H NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants were taken from the spectra directly and are uncorrected. Infrared (IR) spectra were collected on a Nicolet iS10 FT-IR spectrometer as neat films. Mass spectrometric determinations were carried out on a Thermo Finnigan LTQ-FTMS spectrometer with electrospray (ESI) or atmospheric pressure chemical (APCI) ionization. Optical rotations were measured on JASCO P-2000 polarimeter. High performance liquid chromatography (HPLC) analysis was performed on a Varian Prostar 350 with hexanes/*iso*propanol as eluent.

Gas chromatography (GC) analysis was performed on an Agilent 7890A; column conditions: 30 °C for 1 min, then increasing to 180 °C at a rate of 5 °C/min, then 180 °C for 5 min. Analytical thin layer chromatography (TLC) was performed on silica gel plates using ultraviolet (UV) light or stained with 10% vanillin/1% sulfuric acid/ethanol solution. Flash column chromatography was performed with silica gel 60 A (230–400 mesh) according to the literature procedure.[133] Substrates {Rh_2[(*S*)-dosp]$_4$} and {Rh_2[(*R*)-dosp]$_4$},[134] **51**, **52** and **58–60**,[135] **61**,[136] **62** and **63**,[137] **64** and **82**,[74] **65**,[138] **74–77**, and **118**,[139] **85**,[140] **99**, **101–103**, **108**, **110**, and **120**,[91] **100**, **109**,[141] **111**,[142] and **119**[143] were all synthesized according to published procedures.

3.4.2 General Procedures

3.4.2.1 First Generation Cyclopentane Synthesis

An oven-dried, 25 mL round-bottomed flask, equipped with a stir bar, was capped with a rubber septum and placed under a dry atmosphere of argon. The reaction vessel was charged with {Rh_2[(*S*)-dosp]$_4$} (19 mg, 0.01 mmol, 0.01 equiv) and the allyl alcohol (1.0 mmol, 1.0 equiv) in heptane (1.0 mL). The solution was cooled to 0 °C in an ice bath before adding a heptane solution (10 mL) of the diazo compound (1.1 mmol, 1.1 equiv) drop-wise over 30 min. Following addition, the reaction was stirred at 0 °C for 2 h before warming to ambient temperature for 30 min. The rubber septum was removed and the reaction flask was fixed with a reflux condenser and heated to 80 °C for 24 h or until TLC indicated complete conversion of the [2,3]-rearrangement product to a mixture of oxy-Cope and ene products. Scandium triflate (98 mg, 0.20 mmol, 0.20 equiv) was then added in a single portion and the reaction was maintained at 80 °C for an additional 2 h or until TLC indicated complete conversion of the oxy-Cope product to the cyclopentane. The reaction was then cooled to ambient temperature and concentrated *in vacuo*. The product was purified by flash chromatography eluting with pentane/ether to afford the analytically pure cyclopentane.

3.4.2.2 Second Generation Cyclopentane Synthesis

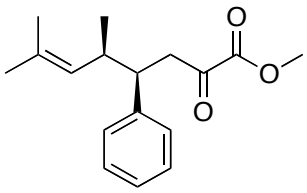
A 35 mL pressure tube, fitted with a rubber septum, was charged with a heptanes (1 mL) suspension of {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv) and enantiopure allyl alcohol (0.50 mmol, 1.0 equiv) was cooled to 0 °C in an ice bath under a dry atmosphere of argon. A heptanes (4 mL) solution of diazoacetate (0.60 mmol, 1.2 equiv) was added to the reaction vessel dropwise over 30 min with vigorous stirring. Following

addition, the reaction was stirred at 0 °C for 2 h and then allowed to warm to ambient temperature for 1 h. The septum was then removed and the reaction vessel was sealed with a screwcap. The reaction mixture was then immersed in an oil bath preheated to 125 °C for 24–48 h. Upon cooling to ambient temperature, the mixture was filtered through a short plug of neutral alumina, eluting with EtOAc (25 mL). The filtrate was concentrated in vacuo. The product was purified by flash chromatography eluting with pentane/ether to afford the analytically pure cyclopentane.

3.4.2.3 Cyclohexane Synthesis

A 35 mL pressure tube, fitted with a rubber septum, was charged with a heptanes (1 mL) suspension of $\{Rh_2[(R)\text{-dosp}]_4\}$ (0.9 mg, 0.0005 mmol, 0.1 mol %), $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv) and enantiopure allyl alcohol (0.50 mmol, 1.0 equiv) was cooled to 0 °C in an ice bath under a dry atmosphere of argon. A heptanes (4 mL) solution of diazoacetate (0.60 mmol, 1.2 equiv) was added to the reaction vessel dropwise over 30 min with vigorous stirring. Following addition, the reaction was stirred at 0 °C for 2 h and then allowed to warm to ambient temperature for 1 h. The septum was then removed and the reaction vessel was sealed with a screwcap. The reaction mixture was then immersed in an oil bath preheated to 125 °C for 24–36 h. Upon cooling to ambient temperature, the mixture was filtered through a short plug of neutral alumina, eluting with EtOAc (25 mL). The filtrate was concentrated in vacuo. The product was purified by flash chromatography eluting with pentane/ether to afford the analytically pure cyclopentane.

3.4.3 Procedures and Characterization Data



(+)-(4*R*,5*R*)-methyl 5,7-dimethyl-2-oxo-4-phenyloct-6-enoate (55)

A 25 mL round-bottomed flask, equipped with a magnetic stirring bar and reflux condenser, was charged with a solution of (*R*,*E*)-methyl 2-hydroxy-3,3-dimethyl-2-((*E*)-styryl)hex-4-enoate (5**4**) (105 mg, 0.38 mmol) in heptane (5 mL). The solution was heated in an oil bath (preheated to 80 °C) for 15 h, until complete consumption of the starting material was apparent by TLC (SiO_2, pentane/ether, 10 : 1). The reaction vessel was cooled to ambient temperature and silica gel (500 mg) was added. The mixture was stirred at room temperature for 2 h before concentrating *in vacuo*. The crude was purified by flash chromatography eluting with pentane : ether (10 : 1) to afford the title compound as a colorless oil (104 mg, quant.).

$[\alpha]^{20}_{D}$ +63.5° (*c* 1.0, $CHCl_3$).

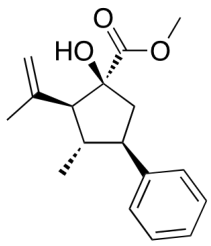
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.30 (m, 2H), 7.17-7.21 (m, 3H), 4.88 (d, J = 10.0 Hz, 1H), 3.77 (s, 3H), 3.20-3.28 (m, 1H), 2.95-3.03 (m, 2H), 2.52-2.62 (m, 1H), 1.68 (d, J =1.2 Hz, 3H), 1.65 (d, J = 1.2 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 161.4, 143.3, 132.8, 130.2, 128.6, 128.3, 126.7, 53.0, 48.3, 44.6, 39.0, 26.0, 19.5, 18.4.

FTIR (neat): ν_{max}/cm^{-1} 1728, 1452, 1268, 1239, 1096, 1061.

HRMS (p-APCI): *m/z* 275.1639 [$(M+H)^+$ requires 275.1642].

HPLC: 82% ee, (*R*,*R*)-Whelk 01, 0.5% isopropanol/hexanes, 0.7 mL/min, UV: 230 nm, t_R: 22.30 min (minor), 34.30 min (major).



(+)-(1*S*,2*S*,3*S*,4*R*)-methyl 1-hydroxy-3-methyl-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (57)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (225 mg, 1.1 mmol, 1.0 equiv) and 4-methyl-3-penten-2-ol (**52**) (101 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9 : 1) to afford the title compound as a white solid (261 mg, 95%).

MP = 40–42 °C.

$[\alpha]^{20}_D$ +9.3° (*c* 1.03, $CHCl_3$).

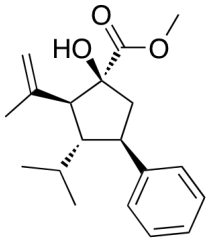
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (m, 5H), 5.08 (s, 1H), 4.80 (s, 1H), 3.81 (s, 3H), 2.98 (s, 1H), 2.83 (dd, *J* = 14.4, 10.2 Hz, 1H), 2.76 (ddd, *J* = 10.2, 8.4, 7.8 Hz, 1H), 2.53 (d, *J* = 12 Hz, 1H), 2.29 (m, 1H), 2.03 (dd, *J* = 14.4, 8.4 Hz, 1H), 1.73 (s, 3H), 0.88 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.9, 144.1, 141.2, 128.4, 127.8, 126.3, 114.8, 81.3, 63.6, 52.7, 51.7, 46.7, 44.8, 23.4, 16.0.

FTIR (neat): ν_{max}/cm^{-1} 3523, 3027, 2950, 1729, 1450, 1431.

HRMS (p-APCI): *m/z* 275.1641 [(M+H)$^+$ requires 275.1642].

HPLC: 82% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 11.54 min (major), 22.08 min (minor).



(–)-(1*S*,2*S*,3*S*,4*R*)-methyl 1-hydroxy-3-isopropyl-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (66)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (226 mg, 1.1 mmol, 1.0 equiv) and 2,5-dimethyl-4-hexen-3-ol (**58**) (127 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a colorless oil (183 mg, 67%).

[α]$^{20}_D$ −10.2° (*c* 1.07, $CHCl_3$).

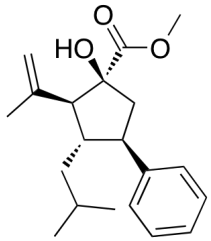
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 5.05 (s, 1H), 4.86 (s, 1H), 3.77 (s, 3H), 3.09 (m, 1H), 3.08 (s, 1H), 2.80 (dd, *J* = 14.4, 10.2 Hz, 1H), 2.77 (d, *J* = 12 Hz, 1H), 2.50 (ddd, *J* = 15.0, 12.6, 2.4 Hz, 1H), 1.92 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.77 (s, 3H), 1.75 (m, 1H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 146.3, 142.2, 128.3, 128.1, 125.9, 114.9, 81.6, 59, 54.2, 52.5, 47.2, 45, 27.7, 23.1, 20.6, 18.5.

FTIR (neat): ν_{max}/cm^{-1} 3512, 3023, 2950, 2923, 1725, 1450, 1431.

HRMS (p-APCI): *m/z* 285.1847 [(M-OH)$^+$ requires 285.1849].

HPLC: 80% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 11.27 min (major), 22.50 min (minor).



(+)-(1*S*,2*S*,3*S*,4*R*)-methyl 1-hydroxy-3-isobutyl-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (67)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (229 mg, 1.1 mmol, 1.0 equiv) and 2,6-dimethyl-2-hepten-4-ol (**59**) (142 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a white solid (232 mg, 73%).

MP = 68–69 °C.

$[\alpha]^{20}_D$ +8.6° (*c* 0.50, $CHCl_3$).

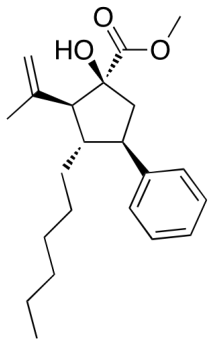
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 5.06 (s, 1H), 4.85 (s, 1H), 3.79 (s, 3H), 3.03 (s, 1H), 2.86 (m, 2H), 2.60 (d, *J* = 12 Hz, 1H), 2.50 (m, 1H), 1.94 (dt, *J* = 7.2, 4.8 Hz, 1H), 1.75 (s, 3H), 1.29 (m, 1H), 1.25 (m, 2H), 0.68 (d, *J* = 6.6 Hz, 3H), 0.51 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.6, 145.8, 141.7, 128.3, 128, 126.1, 114.8, 81.6, 63.1, 52.6, 51.2, 47.8, 47, 43.8, 25.2, 23.9, 23.5, 21.6.

FTIR (neat): ν_{max}/cm^{-1} 3520, 3024, 2950, 1725, 1636, 1450, 1431.

HRMS (p-APCI): *m/z* 317.2107 [$(M+H)^+$ requires 317.2111].

HPLC: 80% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 10.94 min (major), 23.52 min (minor).



(–)-(1*S*,2*S*,3*S*,4*R*)-methyl 3-hexyl-1-hydroxy-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (68)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (228 mg, 1.1 mmol, 1.0 equiv) and 2-methyl-2-decen-4-ol (**60**) (172 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a colorless oil (276 mg, 80%).

$[\alpha]^{20}_D$ –3.6° (*c* 1.28, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 5.07 (s, 1H), 4.83 (s, 1H), 3.79 (s, 3H), 3.01 (s, 1H), 2.93 (dd, J = 18.0, 10.2 Hz, 1H),

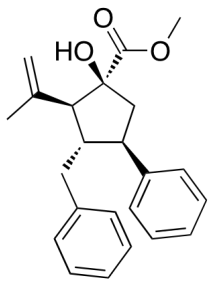
2.82 (dd, J = 14.1, 11.1 Hz, 1H), 2.65 (d, J = 12.6 Hz, 1H), 2.40 (m, 1H), 1.96 (dd, J = 14.1, 7.8 Hz, 1H), 1.74 (s, 3H), 1.28-1.39 (m, 2H), 1.13-1.19 (m, 2H), 1.00-1.13 (m, 6H), 0.81 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 145.3, 141.7, 128.3, 128, 126.1, 114.8, 81.4, 61.5, 52.6, 49.4, 49, 47.1, 31.6, 31.4, 29.5, 26, 23.4, 22.5, 14.0.

FTIR (neat): ν_{max}/cm^{-1} 3520, 2950, 2923, 2849, 1725, 1632, 1454.

HRMS (p-APCI): *m/z* 345.2421 [$(M+H)^+$ requires 345.2424].

HPLC: 78% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 9.63 min (major), 19.58 min (minor).



(–)-(1*S*,2*S*,3*S*,4*R*)-methyl 3-benzyl-1-hydroxy-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (69)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (225 mg, 1.1 mmol, 1.0 equiv) and 4-methyl-1-phenyl-3-penten-2-ol (**61**) (178 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a white solid (147 mg, 42%).

MP = 62–64 °C.

$[\alpha]^{20}_D$ –34.7° (*c* 1.15, $CHCl_3$).

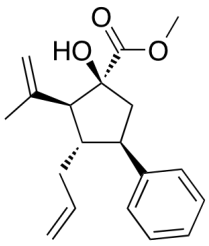
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.16-7.19 (m, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 2H), 5.12 (s, 1H), 4.88 (s, 1H), 3.72 (s, 3H), 2.99 (s, 1H), 2.92 (dt, *J* = 10.8, 7.8 Hz, 1H), 2.67-2.77 (m, 3H), 2.61 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.55 (d, *J* = 12.0 Hz, 1H), 1.90 (dd, *J* = 14.7, 7.2 Hz, 1H), 1.69 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.5, 144.4, 141.0, 138.5, 130.0, 128.4, 128.2, 127.8, 126.2, 125.8, 115.5, 81.0, 60.1, 52.6, 49.7, 47.2, 46.7, 35.4, 23.3.

FTIR (neat): ν_{max}/cm^{-1} 3524, 3062, 3027, 2951, 2922, 2851, 1731, 1602, 1495,1454, 1438, 1231.

HRMS (p-APCI): *m/z* 351.1958 [$(M+H)^+$ requires 351.1955].

HPLC: 92% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 15.80 min (major), 23.47 min (minor).



(–)-(1*S*,2*S*,3*S*,4*R*)-methyl 3-allyl-1-hydroxy-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (70)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (212 mg, 1.0 mmol, 1.0 equiv) and 6-methyl-1,5-heptadien-4-ol (**62**) (172 mg, 0.9 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a colorless oil (232 mg, 86%).

$[\alpha]^{20}_D$ -3.3^o (*c* 1.12, $CHCl_3$).

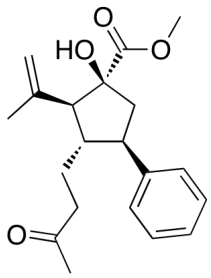
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 5.67 (ddt, *J* = 16.2, 10.2, 7.2 Hz, 1H), 5.10 (s, 1H), 4.97 (s, 1H), 4.94 (dd, *J* = 7.2, 1.2 Hz, 1H), 4.84 (s, 1H), 3.80 (s, 3H), 3.00 (s, 1H), 2.99 (dt, *J* = 10.8, 7.2 Hz, 1H), 2.81 (ddd, *J* = 14.4, 10.8, 1.2 Hz, 1H), 2.67 (d, *J* = 12.0 Hz, 1H), 2.44 (dddd, *J* = 12.0, 11.4, 5.4, 4.8 Hz, 1H), 2.05-2.14 (m, 2H), 2.01 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.73 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 176.7, 144.5, 141.0, 134.9, 128.4, 128.1, 126.3, 117.1, 115.1, 81.1, 60.1, 52.7, 49.1, 47.5, 46.5, 33.6, 23.5.

FTIR (neat): ν_{max}/cm^{-1} 3517, 3074, 2950, 2919, 1725, 1632, 1435.

HRMS (p-APCI): *m/z* 283.1690 $[(M\text{-}OH)^+$ requires 283.1693].

HPLC: 76% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 10.68 min (major), 21.29 min (minor).



(+)-(1*S*,2*S*,3*S*,4*R*)-methyl 1-hydroxy-3-(3-oxobutyl)-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (71)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (223 mg, 1.1 mmol, 1.0 equiv) and 5-methyl-1-(2-methyl-1,3-dioxolan-2-yl)4-hexen-3-ol (**63**) (201 mg, 1.0 mmol,

1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (5:1) to afford the title compound as a colorless oil (149 mg, 45%).

$[\alpha]^{20}_{D}$ +32.7° (*c* 0.50, $CHCl_3$).

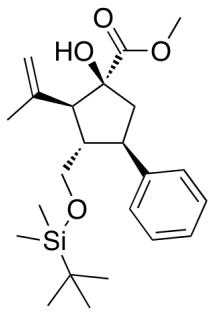
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.21 (dt, *J* = 7.2, 1.2 Hz, 1H), 5.10 (s, 1H), 4.89 (s, 1H), 3.80 (s, 3H), 3.00 (s, 1H), 2.82-2.91(m, 2H), 2.62 (d, *J* = 12.6, 1H), 2.43 (dtd, *J* = 12.0, 7.8, 4.2 Hz, 1H), 2.23 (ddd, *J* = 17.4, 9.0, 7.2 Hz, 1H), 2.12 (ddd, *J* = 17.4, 9.0, 4.8 Hz, 1H), 1.94 (dd, *J* = 13.8, 6.9 Hz), 1.81 (s, 3H), 1.76-1.81 (m, 1H), 1.76 (s, 3H), 1.50 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): 208.6, 176.4, 145.1, 141.2, 128.6, 127.9, 126.4, 115.3, 81.3, 62.1, 52.7, 50.0, 48.0, 47.4, 40.7, 29.6, 26.1, 23.3.

FTIR (neat): ν_{max}/cm^{-1} 3514, 3063, 3027, 2951, 2928, 1728, 1714, 1638, 1602, 1494, 1436.

HRMS (p-APCI): *m/z* 313.1800 [$(M\text{-}OH)^+$ requires 313.1798].

HPLC: 90% ee, CHIRALCEL ODR, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 210 nm, t_R: 11.01 min (major), 35.53 min (minor).



(–)-(1*S*,2*S*,3*S*,4*R*)-methyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-hydroxy-4-phenyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (72)

Prepared by *General Procedure 3.4.2.1*, in the absence of scandium(III) triflate with heating to 98 °C, with methyl styryldiazoacetate (**51**) (225 mg, 1.1 mmol, 1.0 equiv) and 1-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-penten-2-ol (**64**) (230 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a colorless oil (263 mg, 65%).

$[\alpha]^{20}_{D}$ –5.4° (*c* 1.10, $CHCl_3$).

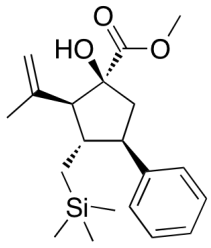
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (m, 5H), 5.09 (s, 1H), 4.81 (s, 1H), 3.82 (s, 3H), 3.51 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.46 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.35 (dt, *J* = 10.2, 7.8 Hz, 1H), 3.04 (d, *J* = 10.2 Hz, 1H), 3.04 (s, 1H), 2.84 (dd, *J* = 14.4, 10.8 Hz, 1H), 2.35 (dt, *J* = 10.8, 2.4 Hz, 1H), 2.07 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.75 (s, 3H), 0.92 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.8, 144.6, 141.2, 128.4, 128.1, 126.2, 114.6, 81.2, 59.3, 56.8, 52.6, 52.3, 45.9, 43.9, 25.8, 23.6, 18.2, -5.6, -5.7.

FTIR (neat): ν_{max}/cm^{-1} 3523.4, 3023.5, 2949.8, 2922.7, 2853, 1729.2, 1457.9.

HRMS (p-APCI): *m/z* 405.2462 [$(M+H)^+$ requires 405.2456].

HPLC: 76% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 8.36 min (major), 10.26 min (minor).



(–)-(1*S*,2*S*,3*S*,4*R*)-methyl 1-hydroxy-4-phenyl-2-(prop-1-en-2-yl)-3-((trimethylsilyl)methyl)cyclopentanecarboxylate (73)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (229 mg, 1.1 mmol, 1.0 equiv) and 4-methyl-1-(trimethylsilyl)-3-penten-2-ol (**65**) (176 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a colorless oil (204 mg, 59%).

$[\alpha]^{20}_{D}$ –0.6° (*c* 1.73, $CHCl_3$).

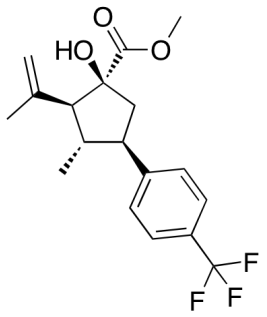
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29-7.35 (m, 4H), 7.21 (tt, *J* = 7.2, 1.2 Hz, 1H), 5.13 (s, 1H), 4.85 (s, 1H), 3.81 (s, 3H), 2.98 (s, 1H), 2.82-2.89 (m, 2H), 2.87 (d, *J* = 12.0 Hz, 1H), 2.57 (dddd, *J* = 15.0, 10.2, 7.2, 3.0 Hz, 1H), 1.93 (m, 1H), 1.75 (s, 3H), 0.74 (dd, *J* = 15.0, 3.0 Hz, 1H), 0.61 (dd, *J* = 15.0, 7.8 Hz, 1H), -0.25 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.8, 144.4, 141.3, 128.4, 128.2, 126.4, 115.3, 80.9, 64.6, 52.6, 52.1, 47.8, 45.7, 23.6, 19.3, –0.4.

FTIR (neat): ν_{max}/cm^{-1} 3523, 3064, 3028, 2951, 2895, 1729, 1638, 1602, 1495, 1455, 1436, 1246, 1201.

HRMS (p-APCI): *m/z* 347.2041 [$(M+H)^+$ requires 347.2037].

HPLC: 83% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 10.24 min (major), 26.93 min (minor).



(+)-(1*S*,2*S*,3*S*,4*R*)-methyl 1-hydroxy-3-methyl-2-(prop-1-en-2-yl)-4-(4-(trifluoromethyl)phenyl)cyclopentanecarboxylate (78)

Prepared by *General Procedure 3.4.2.1* with methyl 4-(trifluoromethyl)styryldiazoacetate (**74**) (315 mg, 1.1 mmol, 1.0 equiv) and 4-methyl-3-penten-2-ol (**52**) (102 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (10:1) to afford the title compound as a white solid (215 mg, 63%).

MP = 71–75 °C.

$[\alpha]^{20}_{D}$ +4.4° (*c* 1.03, $CHCl_3$).

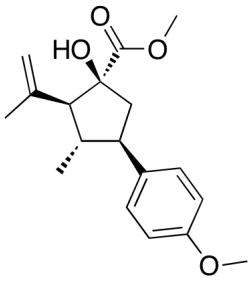
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (d, J = 7.5 Hz, 2H), 7.44 (d, J = 7.5 Hz, 2H), 5.09 (s, 1H), 4.80 (s, 1H), 3.81 (s, 3H), 3.05(s, 1H), 2.81-2.89 (m, 2H), 2.55 (d, J = 12.0 Hz, 1H), 2.30 (m, 1H), 2.02 (ddd, J = 13.8, 10.2, 7.8 Hz, 1H), 1.73 (s, 3H), 0.89 (d, J = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 148.5, 140.8, 128.2, 125.4, 125.3, 125.3, 114.9, 81.4, 63.6, 52.7, 51.4, 46.4, 45.1, 23.3, 15.9.

FTIR (neat): ν_{max}/cm^{-1} 3519, 2955, 1731, 1640, 1618, 1438, 1323, 1120, 1067.

HRMS (p-APCI): *m/z* 343.1516 [$(M+H)^+$ requires 343.1516].

HPLC: 78% ee, CHIRALCEL ODR, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 210 nm, t_R: 5.61 min (major), 7.25 min (minor).



(+)-(1*S*,2*S*,3*S*,4*R*)-methyl 1-hydroxy-4-(4-methoxyphenyl)-3-methyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (79)

Prepared by *General Procedure 3.4.2.1* with methyl 4-methoxystyryldiazoacetate (**75**) (255 mg, 1.1 mmol, 1.0 equiv) and 4-methyl-3-penten-2-ol (**52**) (101 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (4:1) to afford the title compound as a colorless oil (261 mg, 94%).

$[\alpha]^{20}_D$ +4.3° (*c* 1.25, $CHCl_3$).

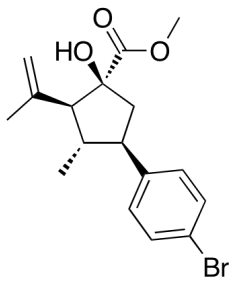
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.07 (s, 1H), 4.79 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.98 (s, 1H), 2.80 (dd, J = 14.1, 10.2 Hz), 2.70 (dd, J = 18.6, 10.2 Hz, 1H), 2.51 (d, J = 12.0 Hz, 1H), 2.23 (ddq, J = 12.6, 10.4, 6.4 Hz, 1H), 1.98 (dd, J = 14.1, 8.2 Hz, 1H), 1.72 (s, 3H), 0.87 (d, J = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 158.1, 141.2, 136.0, 128.7, 114.7, 113.8, 81.1, 63.5, 55.2, 52.6, 50.9, 46.8, 44.8, 23.3, 16.0.

FTIR (neat): ν_{max}/cm^{-1} 3518, 2952, 2835, 1729, 1611, 1512, 1439, 1243,1178, 1036.

HRMS (p-APCI): *m/z* 305.1748 [$(M+H)^+$ requires 305.1747].

HPLC: 87% ee, CHIRALCEL ODR, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 210 nm, t_R: 7.55 min (minor), 11.12 min (major).



(+)-(1*S*,2*S*,3*S*,4*R*)-methyl 4-(4-bromophenyl)-1-hydroxy-3-methyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (80)

Prepared by *General Procedure 3.4.2.1* with methyl 4-bromostyryldiazoacetate (**76**) (319 mg, 1.1 mmol, 1.0 equiv) and 4-methyl-3-penten-2-ol (**52**) (101 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a white solid (171 mg, 48%).

MP = 71–72 °C.

$[\alpha]^{20}_D$ +1.8° (*c* 1.05, $CHCl_3$).

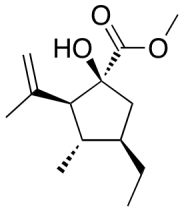
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 5.08 (s, 1H), 4.79 (s, 1H), 3.81 (s, 3H), 3.00 (s, 1H), 2.83 (dd, *J* = 14.1, 10.5 Hz, 1H), 2.72 (td, *J* = 10.5, 8.1 Hz, 1H), 2.56 (d, *J* = 6.0 Hz, 1H), 2.24 (tq, *J* = 6.6, 6.0 Hz, 1H), 1.96 (dd, *J* = 14.1, 8.1 Hz, 1H), 1.72 (s, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.6, 143.2, 141.0, 131.5, 129.6, 120.0, 114.9, 81.2, 63.5, 52.7, 51.1, 46.5, 44.9, 23.3, 15.9.

FTIR (neat): ν_{max}/cm^{-1} 3521, 3072, 2952, 2924, 2868, 1729, 1639, 1487, 1436, 1010.

HRMS (p-APCI): *m/z* 335.0640 [$(M\text{-}OH)^+$ requires 335.0641].

HPLC: 92% ee, CHIRALCEL ADH, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 230 nm, t_R: 13.20 min (major), 14.34 min (minor).



(–)-(1*S*,2*S*,3*S*,4*R*)-methyl 4-ethyl-1-hydroxy-3-methyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (81)

Prepared by *General Procedure 3.4.2.1* with (*E*)-methyl 2-diazo-3-hexenoate (**77**) (174 mg, 1.1 mmol, 1.0 equiv) and 4-methyl-3-penten-2-ol (**52**) (102 mg, 1.0 mmol, 1.0 equiv) at rt. The crude was purified on silica gel eluting with hexanes : ethyl acetate (9:1) to afford the title compound as a colorless oil (142 mg, 63%).

$[\alpha]^{20}_D$ –0.4° (*c* 2.03, $CHCl_3$).

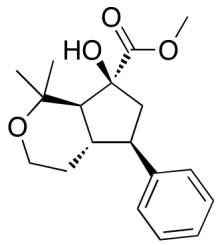
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.04 (s, 1H), 4.75 (s, 1H), 3.77 (s, 3H), 2.80 (s, 1H), 2.54 (dd, *J* = 13.2, 9.0 Hz, 1H), 2.38 (d, *J* = 12.0 Hz, 1H), 1.81-1.87 (m, 1H), 1.68 (s, 3H), 1.64-1.70 (m, 1H), 1.49-1.55 (m, 2H), 1.20-1.27 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 177.3, 141.6, 114.4, 81.1, 63.8, 52.5, 46.6, 44.0, 41.6, 27.1, 23.4, 16.7, 12.5.

FTIR (neat): ν_{max}/cm^{-1} 3526, 3072, 2956, 2926, 2874, 1731, 1639, 1457, 1437, 1233, 1077.

HRMS (p-APCI): *m/z* 227.1640 [$(M+H)^+$ requires 227.1642].

HPLC: 64% ee, CHIRALCEL ADH, 1.0% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 22.09 min (minor), 22.03 min (major).



(+)-(4*aS*,5*R*,7*S*,7*aR*)-methyl 7-hydroxy-1,1-dimethyl-5-phenyloctahydrocyclopenta[*c*]pyran-7-carboxylate (84)

Prepared by *General Procedure 3.4.2.1* with methyl styryldiazoacetate (**51**) (227 mg, 1.1 mmol, 1.0 equiv) and 1-((*tert*-butyldimethylsilyl)oxy)-5-methyl-4-hexen-3-ol (**82**) (244 mg, 1.0 mmol, 1.0 equiv), with an increased loading of $Sc(OTf)_3$ (495 mg, 1.0 mmol, 1.0 equiv) . The crude was purified on silica gel eluting with hexanes : ethyl acetate (4:1) to afford the title compound as a white solid (141 mg, 46%).

MP = 94–96 °C.

$[\alpha]^{20}_D$ +14.0° (*c* 1.07, $CHCl_3$).

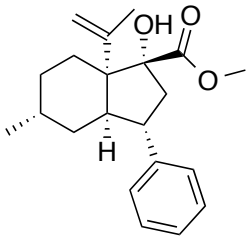
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29-7.33 (m, 4H), 7.21-7.23 (m, 1H), 3.85 (s, 3H), 3.69 (ddd, *J* = 12.0, 5.4, 1.2 Hz, 1H), 3.51 (td, *J* = 12.0, 2.4 Hz, 1H), 3.34 (s, 1H), 2.71 (m, 2H), 2.21 (m, 1H), 1.94 (d, *J* = 13.2 Hz, 1H), (1.91 (dd, *J* = 18.9, 12.9 Hz, 1H), 1.74 (dddd, *J* = 12.6, 1.2, 1.2, 1.2 Hz, 1H), 1.39 (qd, *J* = 12.6, 5.4 Hz), 1.33 (s, 3H), 1.13 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 143.5, 128.5, 127.6, 126.4, 80.3, 74.9, 60.8, 60.2, 53.0, 50.4, 48.8, 44.5, 32.5, 28.8, 21.1.

FTIR (neat): ν_{max}/cm^{-1} 3510, 3026, 2974, 2929, 2861, 1426, 1601, 1436, 1202, 1099.

HRMS (p-APCI): *m/z* 305.1748 [$(M+H)^+$ requires 305.1747].

HPLC: 80% ee, CHIRALCEL ODR, 1.0% isopropanol/hexanes, 01.0 mL/min, UV: 210 nm, t_R: 9.63 min (major), 23.30 min (minor).



(–)-(1*R*,3*S*,3*aR*,5*R*,7*aR*)-methyl 1-hydroxy-5-methyl-3-phenyl-7a-(prop-1-en-2-yl)octahydro-1*H*-indene-1-carboxylate (86)

Prepared by *General Procedure 3.4.2.1*, in the absence of scandium(III) triflate, with methyl styryldiazoacetate (**51**) (229 mg, 1.1 mmol, 1.0 equiv), (–)-(*R*,*R*)-pulegol (**85**) (155 mg, 1.0 mmol, 1.0 equiv) and $\{Rh_2[(R)\text{-dosp}]_4\}$. The crude was purified on silica gel eluting with hexanes : ethyl acetate (7:1) to afford the title compound as a colorless oil (227 mg, 69%).

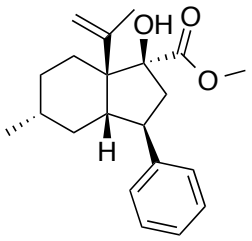
$[\alpha]^{20}_D$ –5.4° (*c* 1.10, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, J = 6.9 Hz, 2H), 7.30 (t, J = 6.9 Hz, 2H), 7.20(t, J = 6.9 Hz, 1H), 5.34 (s, 1H), 4.99 (s, 1H), 3.75 (s, 3H), 3.35 (dt, J = 11.1, 5.4 Hz, 1H), 3.10 (ddd, J = 14.4, 11.7, 2.4 Hz, 1H), 2.96 (d, J = 2.4 Hz, 1H), 2.65 (m, 1H), 2.08 (dd, J = 14.7, 5.1 Hz, 1H), 1.70-1.81 (m, 2H), 1.68 (s, 3H), 1.59-1.64 (m, 2H), 1.41 (m, 1H), 0.99 (ddd, J = 17.7, 12.6, 5.4 Hz, 1H), 0.85 (d, J = 6.6 Hz, 3H), 0.77 (dtd, J = 16.2, 12.0, 3.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 146.2, 143.0, 128.3, 128.2, 126.1, 117.8, 83.9, 59.3, 52.1, 50.0, 44.5, 43.0, 31.6, 30.6, 27.2, 26.4, 22.5, 21.5.

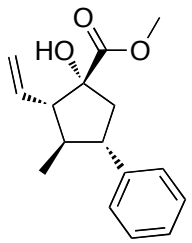
FTIR (neat): ν_{max}/cm^{-1} 3540, 3085, 3026, 2950, 2912, 2868, 2847, 1727, 1629, 1604, 1494, 1447.

HRMS (p-APCI): *m/z* 329.2113 [$(M+H)^+$ requires 329.2111].



(1*S*,3*R*,3a*S*,5*R*,7*aS*)-methyl 1-hydroxy-5-methyl-3-phenyl-7*a*-(prop-1-en-2-yl)octahydro-1*H*-indene-1-carboxylate (87)

Prepared by *General Procedure 3.4.2.1*, in the absence of scandium(III) triflate, with methyl styryldiazoacetate (**51**) (229 mg, 1.1 mmol, 1.0 equiv), (–)-(*R*,*R*)-pulegol (**85**) (155 mg, 1.0 mmol, 1.0 equiv) and $\{Rh_2[(S)\text{-dosp}]_4\}$. The crude was purified on silica gel eluting with hexanes : ethyl acetate (7:1) to afford an inseparable mixture of compounds **86** and **87** (1:2.1) as a colorless oil (combined yield: 187 mg, 59%).



(–)-(1*R*,2*S*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-4-phenyl-2-vinylcyclopentanecarboxylate (97)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **99** (43 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 40 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 10:1) afforded the title compound as a colorless oil (85 mg, 66% yield). A minor component eluted second off the column, which ^{1}H NMR analysis indicated to contain a mixture of **97** and **98**. Preparative HPLC of the mixture (hexanes/*i*-propanol, 99:1) afforded a small quantity of pure **98**.

$[\alpha]^{20}_D$ -7.2^o (*c* 1.65, $CHCl_3$).

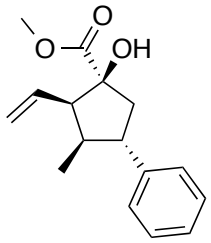
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.33 (m, 4H), 7.19-7.23 (m, 1H), 5.79 (ddd, *J* = 17.2, 10.2, 8.8 Hz, 1H), 5.19 (dd, *J* = 10.2, 2.0 Hz, 1H), 5.07 (m, 1H), 3.81 (s, 1H), 3.17 (s, 1H), 2.72-2.86 (m, 2H), 2.43 (dd, *J* = 11.8, 8.8 Hz, 1H), 2.12-2.23 (m, 1H), 2.01 (dd, *J* = 13.6, 7.2 Hz, 1H), 0.87 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 144.4, 134.8, 128.7, 128.0, 126.5, 119.1, 82.7, 62.0, 53.1, 52.5, 46.8, 46.5, 16.1.

FTIR (neat): ν_{max}/cm^{-1} 3521, 3075, 3027, 2953, 2923, 2868, 1728, 1638, 1602, 1494, 1455, 1437.

HRMS (p-ESI): *m/z* 283.1305 [(M+Na)$^+$ requires 283.1305].

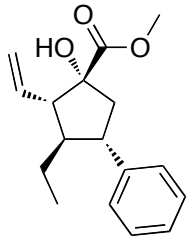
HPLC: 91% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 11.4 min (minor), 19.6 min (major).



(1*S*,2*R*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-4-phenyl-2-vinylcyclopentane-1-carboxylate (98)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34-7.28 (m, 4H), 7.24-7.20 (m, 1H), 5.94 (dt, *J* = 16.8, 10.8 Hz, 1H), 5.16 (dd, *J* = 16.2, 2.1 Hz, 1H), 5.04 (dd, *J* = 17.4, 2.1 Hz, 1H), 3.82 (s, 3H), 3.16-3.07 (m, 3H), 2.42-2.33 (m, 2H), 2.19 (dd, *J* = 13.0, 7.0 Hz, 1H), 0.98 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 144.2, 134.4, 128.7, 127.7, 126.6, 118.6, 84.1, 56.8, 53.1, 52.7, 46.6, 45.0, 16.8.



(–)-(1*R*,2*S*,3*R*,4*S*)-methyl 3-ethyl-1-hydroxy-4-phenyl-2-vinylcyclopentanecarboxylate (104)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **100** (50 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 40 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 12:1) afforded the title compound as a colorless oil (91 mg, 66% yield).

$[\alpha]^{20}_D$ -17.1^o (*c* 2.15, $CHCl_3$).

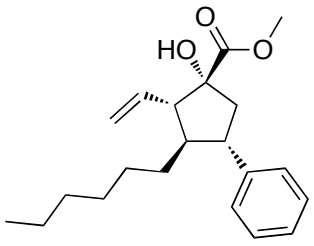
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.36 (m, 4H), 7.17-7.21 (m, 1H), 5.82 (ddd, *J* = 18.4, 10.0, 8.8 Hz, 1H), 5.16 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.06 (dd, *J* = 18.4, 1.6 Hz, 1H), 3.81 (s, 3H), 3.17 (s, 1H), 2.94 (ddd, *J* = 10.0, 7.2, 7.2 Hz, 1H), 2.81 (dd, *J* = 14.4, 10.8 Hz, 1H), 2.59 (dd, *J* = 11.8, 9.0 Hz, 1H), 2.20-2.28 (m, 1H), 1.95 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.33-1.45 (m, 2H), 0.73 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 145.4, 135.7, 128.6, 128.2, 126.4, 118.7, 83.1, 59.5, 53.0, 52.1, 49.4, 47.1, 23.6, 10.9.

FTIR (neat): ν_{max}/cm^{-1} 3520, 3027, 2956, 2918, 2877, 1728, 1638, 1602, 1494, 1456, 1437.

HRMS (p-ESI): *m/z* 297.1462 [$(M+Na)^+$ requires 297.1461].

HPLC: 93% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 11.5 min (minor), 22.2 min (major).



(–)-(1*R*,2*S*,3*R*,4*S*)-methyl 3-hexyl-1-hydroxy-4-phenyl-2-vinylcyclopentanecarboxylate (105)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **101** (78 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 28 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 15:1) afforded the title compound as a colorless oil (118 mg, 71% yield).

$[\alpha]^{20}_D$ -1.4^o (*c* 1.72, $CHCl_3$).

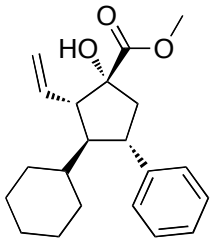
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 5.82 (ddd, J = 17.4, 10.3, 9.0 Hz, 1H), 5.16 (dd, J = 10.3, 1.9 Hz, 1H), 5.06 (dd, J = 17.4, 1.9 Hz, 1H), 3.80 (s, 3H), 3.16 (s, 1H), 2.92 (dt, J = 10.2, 7.2 Hz, 1H), 2.81 (dd, J = 14.4, 10.2 Hz, 1H), 2.56 (dd, J = 12.0, 9.0 Hz, 1H), 2.27 (dtd, J = 11.4, 11.4, 5.4 Hz, 1H), 1.94 (dd, J = 14.4, 7.2 Hz, 1H), 1.28-1.39 (m, 2H), 1.05-1.19 (m, 8H), 0.80 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 145.3, 135.5, 128.4, 128.0, 126.1, 118.5, 83.0, 60.1, 52.8, 50.6, 50.1, 47.0, 31.6, 31.4, 29.5, 26.3, 22.5, 14.0.

FTIR (neat): ν_{max}/cm^{-1} 3525, 3063, 3027, 2953, 2925, 2855, 1730, 1638, 1602, 1494, 1456, 1437.

HRMS (p-APCI): *m/z* 313.2164 [$(M\text{-}OH)^+$ requires 313.2162].

HPLC: 92% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 10.1 min (minor), 19.7 min (major).



(+)-(1*R*,2*S*,3*R*,4*S*)-methyl 3-cyclohexyl-1-hydroxy-4-phenyl-2-vinylcyclopentanecarboxylate (106)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **102** (77 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 40 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 12:1) afforded the title compound as a white solid (115 mg, 70% yield).

MP = 80–82 °C

$[\alpha]^{20}_D$ +4.1° (*c* 1.89, $CHCl_3$).

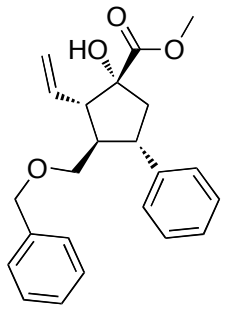
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.36 (m, 2H), 7.27-7.31 (m, 2H), 7.16-7.20 (m, 1H), 5.82 (m, 1H), 5.14 (dd, J = 10.4, 1.6 Hz, 1H), 5.03 (m, 1H), 3.79 (s, 3H), 3.17 (s, 1H), 3.10 (ddd, J = 10.8, 6.8, 6.8 Hz, 1H), 2.72-2.79 (m, 2H), 2.27-2.33 (m, 1H), 1.88 (dd, J = 14.2, 6.8 Hz, 1H), 1.56-1.66 (m, 3H), 1.47 (m, 2H), 1.31-1.39 (m, 1H), 0.95-1.26 (m, 4H), 0.79-0.89 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 146.2, 136.8, 128.6, 128.3, 126.2, 118.3, 83.5, 57.0, 56.0, 53.0, 47.2, 46.3, 38.2, 30.6, 30.5, 27.2, 27.2, 26.9.

FTIR (neat): ν_{max}/cm^{-1} 3513, 3026, 2921, 2851, 1727, 1639, 1601, 1495, 1440.

HRMS (p-ESI): *m/z* 351.1934 [$(M+Na)^+$ requires 351.1931].

HPLC: 90% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 11.1 min (major), 17.4 min (minor).



(+)-(1*R*,2*S*,3*R*,4*S*)-methyl 3-((benzyloxy)methyl)-1-hydroxy-4-phenyl-2-vinylcyclopentanecarboxylate (107)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **103** (96 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 36 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 6:1) afforded the title compound as a pale yellow oil (101 mg, 55% yield).

$[\alpha]^{20}_D$ +1.9° (*c* 1.08, $CHCl_3$).

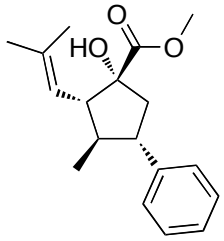
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 9H), 7.22-7.16 (m, 1H), 5.79 (ddd, *J* = 17.3, 10.3, 8.9 Hz, 1H), 5.17 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.09 (dd, *J* = 17.3, 1.7 Hz, 1H), 4.50-4.37 (m, 2H), 3.81 (s, 3H), 3.42-3.31 (m, 3H), 3.24 (d, *J* = 0.8 Hz, 1H), 2.97 (dd, *J* = 12.0, 8.9 Hz, 1H), 2.84 (dd, *J* = 14.3, 11.2 Hz, 1H), 2.36-2.25 (m, 1H), 2.02 (dd, *J* = 14.4, 6.9 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 145.0, 138.8, 134.5, 128.6, 128.5, 128.2, 127.8, 127.7, 126.4, 119.3, 83.0, 73.2, 67.3, 56.0, 53.1, 52.7, 46.0, 45.2.

FTIR (neat): ν_{max}/cm^{-1} 3521, 3063, 2979, 2951, 2854, 2790, 1729, 1638, 1602, 1495, 1455, 1437.

HRMS (p-ESI): *m/z* 389.1726 [(M+Na)$^+$ requires 389.1723].

HPLC: 92% ee, CHIRALPAK ADH, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 210 nm, t_R: 17.9 min (major), 24.7 min (minor).



(–)-(1*R*,2*R*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-2-(2-methylprop-1-en-1-yl)-4-phenylcyclopentanecarboxylate (112)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **108** (57 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 48 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 12:1) afforded the title compound as a colorless oil (102 mg, 71% yield).

[α]$^{20}_D$ –2.1° (*c* 1.82, $CHCl_3$).

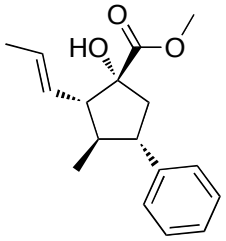
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.36 (m, 4H), 7.19-7.25 (m, 1H), 5.11 (d, J = 10.0 Hz, 1H), 3.80 (s, 3H), 3.06 (s, 1H), 2.68-2.89 (m, 3H), 2.05-2.15 (m, 1H), 2.08 (dd, J = 13.4, 4.8 Hz, 1H), 1.77 (s, 3H), 1.59 (s, 3H), 0.84 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 144.6, 136.9, 128.6, 128.0, 126.4, 120.8, 82.5, 56.5, 53.0, 52.6, 48.0, 46.8, 26.3, 18.5, 16.1.

FTIR (neat): ν_{max}/cm^{-1} 3525, 3061, 3027, 2951, 2922, 2866, 1728, 1602, 14951455, 1436.

HRMS (p-ESI): *m/z* 311.1618 [(M+Na)$^+$ requires 311.1618].

HPLC: 95% ee, CHIRALCEL ODR, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 210 nm, t_R: 4.9 min (minor), 6.8 min (major).



(–)-(1*R*,2*S*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-4-phenyl-2-((*E*)-prop-1-en-1-yl)cyclopentanecarboxylate (113)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **109** (51 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 44 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 11:1) afforded the title compound as a colorless oil (89 mg, 65% yield).

[α]$^{20}_D$ –3.0° (*c* 1.03, $CHCl_3$).

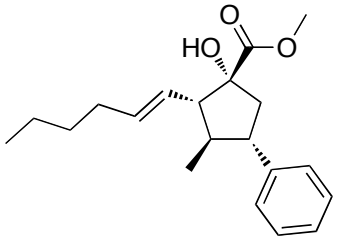
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.28 (m, 4H), 7.24-7.17 (m, 1H), 5.51-5.45 (m, 1H), 5.44-5.35 (m, 1H), 3.80 (s, 3H), 3.08 (s, 1H), 2.85-2.77 (m, 1H), 2.76-2.67 (m, 1H), 2.37 (dd, *J* = 11.7, 8.4 Hz, 1H), 2.16-2.05 (m, 1H), 1.98 (dd, *J* = 13.7, 7.5 Hz, 1H), 1.70 (dd, *J* = 6.1, 1.2 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 144.5, 130.1, 128.6, 128.0, 127.0, 126.4, 82.7, 61.0, 53.0, 52.4, 46.7, 46.6, 18.6, 16.2.

FTIR (neat): ν_{max}/cm^{-1} 3526, 3027, 2952, 2921, 2866, 1731, 1602, 1495, 1455, 1437.

HRMS (p-ESI): *m/z* 297.1461 [(M+Na)$^+$ requires 297.1461].

HPLC: 95% ee, CHIRALCEL ODR, 0.5% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 9.9 min (minor), 14.6 min (major).



(+)-(1*R*,2*S*,3*R*,4*S*)-methyl 2-((*E*)-hex-1-en-1-yl)-1-hydroxy-3-methyl-4-phenylcyclopentanecarboxylate (114)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **110** (71 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 48 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 15:1) afforded the title compound in a mixture of (*E*)- and (*Z*)-isomers as a colorless oil (106 mg, 67% yield). Subsequent purification of the *E*/*Z*-mixture by silver nitrate impregnated silica gel chromatography (1 wt % $AgNO_3/SiO_2$, pentane/Et_2O, 15:1) afforded the pure (*E*)-isomer of the title compound for characterization.

[α]$^{20}_D$ +1.2° (*c* 0.65, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.35 (m, 4H), 7.20 (dq, *J* = 8.6, 5.1, 4.2 Hz, 1H), 5.48 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.36 (dd, *J* = 15.5, 8.5 Hz, 1H), 3.80 (s, 3H), 3.07 (s, 1H), 2.66-2.89 (m,

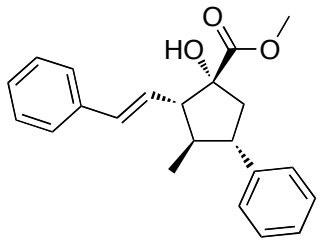
3H), 2.37 (dd, J = 11.8, 8.5 Hz, 1H), 1.94-2.18 (m, 2H), 1.25-1.38 (m, 5H), 0.89 (t, J = 7.1 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 144.6, 135.8, 128.6, 128.0, 126.4, 125.7, 82.8, 61.2, 53.0, 52.5, 46.7, 46.5, 32.7, 31.8, 22.3, 16.2, 14.1.

FTIR (neat): ν_{max}/cm^{-1} 3527, 3027, 2953, 2925, 2870, 1729,1602, 1495, 1455, 1436.

HRMS (p-ESI): *m/z* 339.1931 [$(M+Na)^+$ requires 339.1931].

HPLC: 94% ee, CHIRALPAK ADH, 0.5% isopropanol/hexanes, 1.0 mL/min, UV: 210 nm, t_R: 8.9 min (major), 10.3 min (minor).



(+)-(1*R*,2*S*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-4-phenyl-2-((*E*)-styryl)cyclopentanecarboxylate (115)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **111** (81 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 48 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 9:1) afforded the title compound as a pale yellow solid (134 mg, 80% yield).

MP = 79–82 °C

$[\alpha]^{20}_D$ +9.2° (*c* 1.19, $CHCl_3$).

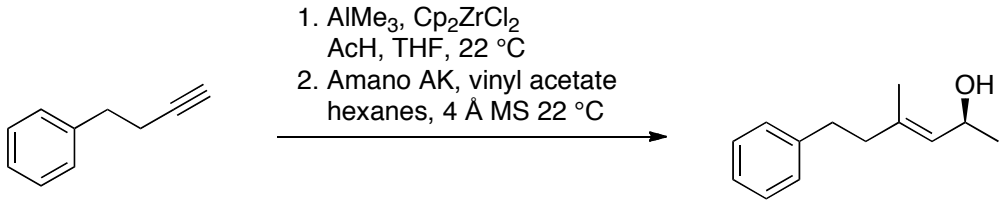
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.39 (m, 8H), 7.19-7.24 (m, 2H), 6.41 (d, J = 16.0 Hz, 1H), 6.23 (dd, J = 16.0, 8.9 Hz, 1H), 3.81 (s, 3H), 3.28 (s, 1H), 2.73-2.94 (m, 2H), 2.60 (dd, J = 11.7, 9.0 Hz, 1H), 2.26 (m, 1H), 2.06 (dd, J = 8.0, 8.0 Hz, 1H), 0.91 (d, J = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 144.4, 137.2, 133.7, 128.7, 128.7, 128.0, 127.6, 126.5, 126.5, 126.2, 82.9, 61.4, 53.2, 52.5, 47.2, 47.0, 16.2.

FTIR (neat): ν_{max}/cm^{-1} 3509, 3026, 2952, 2866, 1728, 1601, 1495, 1450, 1436.

HRMS (p-ESI): *m/z* 359.1617 [$(M+Na)^+$ requires 359.1618].

HPLC: 95% ee, CHIRALPAK ADH, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 230 nm, t_R: 18.5 min (minor), 19.9 min (major).



(*S,E*)-4-methyl-6-phenylhex-3-en-2-ol (121)

The carbometallation procedure for the synthesis of *racemic* **121** was conducted in accordance with the literature procedure[144] using Cp_2ZrCl_2 (8.8 g, 30 mmol, 3.0 equiv), $AlMe_3$ (2.0 M in hexanes, 20 mL, 40 mmol, 4.0 equiv), 4-phenyl-1-butyne (1.75 g, 13 mmol, 1.3 equiv), and acetaldehyde (0.44 g, 10 mmol, 1.0 equiv) and purified by column chromatography (SiO_2, hexanes/ether, 3:1) to afford *racemic* **121** as a colorless oil (1.5 g, 78% yield). Kinetic resolution was conducted in accordance with the literature procedure[145] using **121** (1.0 g, 5.3 mmol, 1.0 equiv), Amano AK Lipase (0.5 g, 50 wt %), vinyl acetate (2.9 mL, 32 mmol, 6.0 equiv), and activated 4 Å molecular sieves (1.0 g, 100 wt %) in hexanes (100 mL) for 24 h. Purification by column

chromatography (SiO_2, hexanes/ether, 3:1) afforded the title compound as a colorless oil (0.48g, 48% yield).

$[\alpha]^{20}_D$ –11.0° (*c* 2.05, $CHCl_3$).

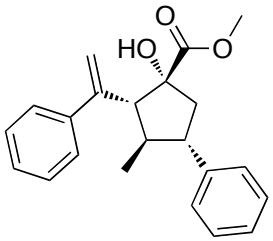
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 2H), 7.23-7.13 (m, 3H), 5.25-5.12 (m, 1H), 5.46 (dq, J = 8.4, 6.2 Hz, 1H), 2.77-2.67 (m, 2H), 2.36-2.23 (m, 2H), 1.73 (d, J = 1.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 137.1, 129.8, 128.6, 128.5, 126.0, 64.9, 41.5, 34.5, 23.7, 16.7.

FTIR (neat): ν_{max}/cm^{-1} 3351, 3026, 2969, 2925, 2858, 1602, 1495, 1453.

HRMS (p-APCI): *m/z* 191.1432 [$(M+H)^+$ requires 191.1430].

HPLC: 99% ee, DIACEL OJ-H, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 230 nm, t_R: 21.6 min (minor), 26.4 min (major).



(+)-(1*R*,2*R*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-4-phenyl-2-(1-phenylvinyl)cyclopentanecarboxylate (122)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **119** (81 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg,

1.0 mmol, 2.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 7:1) afforded the title compound as a white solid (146 mg, 87% yield).

MP = 110–115 °C

$[\alpha]^{20}_D$ +48.2° (*c* 3.40, $CHCl_3$).

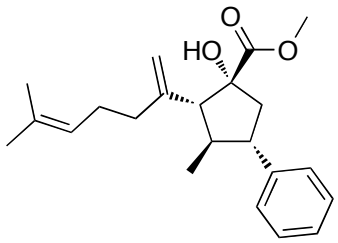
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.50 (m, 10H), 5.52 (s, 1H), 5.19 (s, 1H), 3.19 (s, 3H), 3.17 (d, J = 15.4 Hz, 1H), 2.98 (s, 1H), 2.81-2.93 (m, 1H), 2.36-2.46 (m, 1H), 2.06 (dd, J = 19.2, 12.8 Hz, 1H), 1.02 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 144.7, 144.4, 142.6, 128.7, 128.4,128.1, 127.8, 127.0, 126.6, 117.1, 80.4, 61.8, 52.4, 51.8, 46.2, 45.5, 16.1.

FTIR (neat): ν_{max}/cm^{-1} 3468, 3028, 2952, 1728, 1600, 1494, 1447.

HRMS (p-ESI): *m/z* 359.1621 [$(M+Na)^+$ requires 359.1618].

HPLC: 99% ee, CHIRALCEL ODR, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 230 nm, t_R: 7.1 min (minor), 8.4 min (major).



(+)-(1*R*,2*R*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-2-(6-methylhepta-1,5-dien-2-yl)-4-phenylcyclopentanecarboxylate (123)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **120** (84 mg, 0.50 mmol, 1.0 equiv), $\{Rh_2[(R)\text{-dosp}]_4\}$ (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 15:1) afforded the title compound as a colorless oil (146 mg, 85% yield).

$[\alpha]^{20}_D$ +2.4° (*c* 1.42, $CHCl_3$).

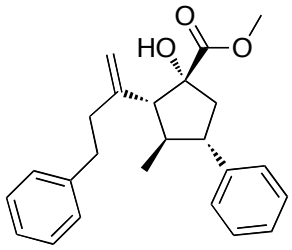
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.33 (m, 4H), 7.19-7.24 (m, 1H), 5.14 (d, J = 1.2 Hz, 1H), 5.06-5.10 (m, 1H), 4.93 (s, 1H), 3.78 (s, 3H), 2.89 (s, 1H), 2.83-2.89 (m, 1H), 2.77 (ddd, J = 10.2, 8.0, 8.0 Hz, 1H), 2.56 (d, J = 12.4 Hz, 1H), 2.23-2.32 (m, 1H), 2.09-2.20 (m, 1H), 1.93-2.08 (m, 3H), 1.82-1.89 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 0.86 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 145.0, 144.3, 132.1, 128.6, 128.1, 126.5, 123.9, 114.0, 80.6, 62.7, 52.8, 51.8, 46.7, 45.5, 37.3, 26.6, 25.9, 17.9, 16.1.

FTIR (neat): ν_{max}/cm^{-1} 3501, 3027, 2952, 2925, 2969, 1730, 1640, 1602, 1495, 1455, 1436.

HRMS (p-ESI): *m/z* 365.2091 [$(M+Na)^+$ requires 365.2093].

HPLC: 99% ee, CHIRALCEL ODR, 0.3% isopropanol/hexanes, 0.5 mL/min, UV: 210 nm, t_R: 9.2 min (minor), 13.5 min (major).



(+)-(1*R*,2*R*,3*R*,4*S*)-methyl 1-hydroxy-3-methyl-4-phenyl-2-(4-phenylbut-1-en-2-yl)cyclopentanecarboxylate (124)

Prepared by *General Procedure 3.4.2.2* with **51** (121 mg, 0.60 mmol, 1.2 equiv), **121** (95 mg, 0.50 mmol, 1.0 equiv), $\{Rh_2[(R)\text{-dosp}]_4\}$ (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 16 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 8:1) afforded the title compound as a white solid (157 mg, 86% yield).

MP = 74–77 °C

$[\alpha]^{20}_D$ +1.2° (*c* 1.09, $CHCl_3$).

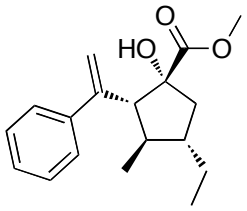
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 6H), 7.24-7.14 (m, 4H), 5.19 (s, 1H), 4.96 (s, 1H), 3.77 (s, 3H), 2.96-2.72 (m, 4H), 2.72-2.58 (m, 2H), 2.37-2.22 (m, 2H), 2.22-2.11 (m, 1H), 2.06 (dd, J = 13.7, 7.6 Hz, 1H), 0.87 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 144.6, 144.2, 141.9, 128.6, 128.5, 128.5, 128.1, 126.6, 126.1, 114.4, 80.7, 62.8, 52.9, 51.7, 46.7, 45.4, 39.0, 34.5, 16.1.

FTIR (neat): ν_{max}/cm^{-1} 3534, 3084, 3061, 3026, 2950, 2925, 2867, 1729, 1602, 1495, 1454, 1435.

HRMS (p-APCI): *m/z* 365.2117 [$(M+H)^+$ requires 365.2111].

HPLC: 99% ee, DACH DNB, 0.5% isopropanol/hexanes, 1.0 mL/min, UV: 230 nm, t_R: 11.2 min (minor), 14.7 min (major).



(+)-(1*R*,2*R*,3*R*,4*S*)-methyl 4-ethyl-1-hydroxy-3-methyl-2-(1-phenylvinyl)cyclopentanecarboxylate (125)

Prepared by *General Procedure 3.4.2.2* with **118** (154 mg, 1.0 mmol, 2.0 equiv), **119** (81 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (111 mg, 1.0 mmol, 2.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 7:1) afforded the title compound as a white solid (130 mg, 90% yield).

MP = 48–52 °C

$[\alpha]^{20}_D$ +20.6° (*c* 0.90, $CHCl_3$).

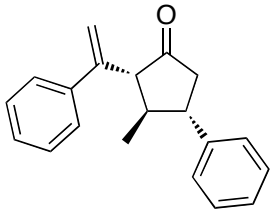
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.18 (m, 5H), 5.49 (s, 1H), 5.16 (s, 1H), 3.17 (s, 3H), 3.01 (d, J = 12.0 Hz, 1H), 2.78 (s, 1H), 2.63-2.50 (dd, J = 13.0, 9.0 Hz, 1H), 2.04-1.91 (m, 1H), 1.79-1.51 (m, 3H), 1.33-1.22 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 145.0, 142.8, 128.3, 127.7, 127.0, 116.8, 80.3, 62.0, 52.2, 46.6, 43.5, 42.2, 27.5, 16.9, 12.7.

FTIR (neat): ν_{max}/cm^{-1} 3527, 3055, 3025, 2957, 2929, 2873, 1730, 1626, 1493, 1437, 1377, 1237.

HRMS (p-APCI): *m/z* 289.1800 [$(M+H)^+$ requires 289.1798].

HPLC: 99% ee, DIACEL OD-H, 0.2% isopropanol/hexanes, 0.5 mL/min, UV: 230 nm, t_R: 8.4 min (minor), 8.9 min (major).



(2*R*,3*R*,4*S*)-3-methyl-4-phenyl-2-(1-phenylvinyl)cyclopentanone (126)

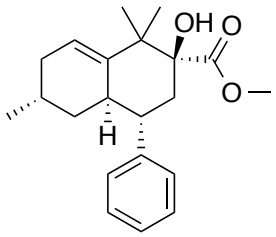
To a THF (0.5 mL) solution of **122** (66 mg, 0.20 mmol, 1.0 equiv), was added lithium borohydride (2.0 M in THF, 0.21 mL, 0.42 mmol, 2.1 equiv) dropwise over 15 min at 0 °C. The reaction was gradually warmed to ambient temperature over 2 h. The reaction was then carefully quenched with pH 7.0 buffer solution (1 drop) and stirred at ambient temperature for an additional 30 min. To the crude mixture was added sodium periodate (430 mg, 2.0 mmol, 10 equiv) in a single portion, and the reaction was then heated in an oil bath to 60 °C for 4h. The reaction was again returned to ambient temperature, dilute with diethyl ether (20 mL), and washed with a saturated, aqueous solution of sodium thiosulfate (3 x 5 mL). The organic was dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, pentane/Et_2O, 15→10:1) afforded the title compound as a pale yellow oil (37 mg, 67% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38-7.27 (m, 7H), 7.27-7.18 (m, 3H), 5.48 (s, 1H), 5.20 (s, 1H), 3.02 (d, 1H), 2.94-2.81 (m, 2H), 2.51 (dd, J = 18.2, 11.5 Hz, 1H), 2.35-2.26 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 145.4, 141.4, 141.4, 128.9, 128.6, 127.8, 127.6, 127.2, 117.8, 66.0, 48.9, 47.4, 44.9, 16.8.

FTIR (neat): ν_{max}/cm^{-1} 3030, 2951, 2873, 1715, 1490, 1451.

HRMS (p-APCI): *m/z* 277.1585 [(M+H)$^+$ requires 277.1587].



methyl (2*S*,4*S*,4a*R*,6*R*)-2-hydroxy-1,1,6-trimethyl-4-phenyl-1,2,3,4,4a,5,6,7-octahydronaphthalene-2-carboxylate (131)

A 35 mL pressure tube, fitted with a rubber septum, was charged with a heptanes (1 mL) solution of {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %) and **85** (77 mg, 0.50 mmol, 1.0 equiv) was cooled to 0 °C in an ice bath under a dry atmosphere of argon. A heptanes (4 mL) solution of **51** (122 mg, 0.60 mmol, 1.2 equiv) was added to the reaction vessel dropwise over 30 min with vigorous stirring. Following addition, the reaction was stirred at 0 °C for 2 h and then allowed to warm to ambient temperature for 1 h. The septum was then removed and the reaction vessel was sealed with a screwcap. The reaction mixture was then immersed in an oil bath preheated to 125 °C for 24 h. The reaction vessel was removed from heat and cooled to ambient temperature before removing the screwcap. $Sc(OTf)_3$ was added in a single portion with vigorous stirring and the reaction vessel was again sealed and immersed in the oil bath for an additional 12 h. Upon cooling to ambient temperature, the mixture was filtered through a short plug of neutral alumina, eluting with EtOAc (25 mL). The filtrate was concentrated *in vacuo*. The product was purified by flash chromatography (SiO_2, pentane/ether, 9:1) to afford the title compound as a crystalline white solid (125 mg, 80% yield).

MP = 40–42 °C

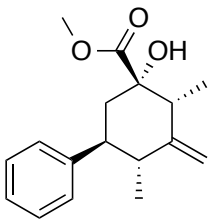
$[\alpha]^{20}_{D}$ –26.6° (*c* 1.6, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.26-7.18 (m, 3H), 5.58 (t, *J* = 3.5 Hz, 1H), 3.77 (s, 3H), 3.18 (s, 1H), 2.84 (td, *J* = 12.4, 4.1 Hz, 1H), 2.71-2.62 (m, 1H), 2.58 (t, *J* = 13.4 Hz, 1H), 2.23 (dt, *J* = 17.2, 4.6 Hz, 1H), 1.80 (dd, *J* = 13.8, 4.2 Hz, 1H), 1.79-1.73 (m, 1H), 1.69-1.60 (m, 1H), 1.34 (s, 3H), 1.34-1.28 (m, 1H), 1.14-1.09 (m, 1H), 1.08 (s, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 175.7, 144.7, 142.7, 128.7, 127.9, 126.6, 120.7, 80.2, 52.7, 45.7, 43.6, 40.0, 36.4, 34.5, 34.1, 26.0, 24.6, 22.2, 20.7.

FTIR (neat): ν_{max}/cm^{-1} 3526, 3023, 2952, 2908, 2876, 1721, 1494, 1453, 1435, 1377.

HRMS (p-APCI): *m/z* 315.1955 [$(M+H)^+$ requires 315.1955].



methyl (1S,2R,4R,5S)-1-hydroxy-2,4-dimethyl-3-methylene-5-phenylcyclohexane-1-carboxylate (144)

Prepared by *General Procedure 3.4.2.3* with **51** (122 mg, 0.60 mmol, 1.2 equiv), **138** (50 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 7:1) afforded the title compound as a colorless oil (91 mg, 67% yield).

$[\alpha]^{20}_D$ +23.2° (*c* 1.0, $CHCl_3$).

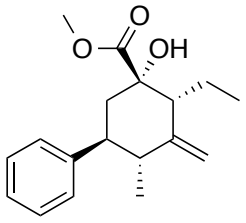
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.27 (m, 2H), 7.23-7.18 (m, 3H), 5.04 (s, 1H), 4.90 (s, 1H), 3.81 (s, 3H), 3.08 (s, 1H), 2.77 (q, *J* = 6.7 Hz, 1H), 2.64 (td, *J* = 12.6, 3.8 Hz, 1H), 2.39 (dq, *J* = 12.8, 6.4 Hz, 1H), 2.24 (t, *J* = 13.1 Hz, 1H), 1.89 (dd, *J* = 13.4, 3.9 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 151.9, 144.6, 128.7, 127.7, 126.6, 107.7, 78.1, 53.2, 48.3, 45.0, 43.6, 43.2, 16.1, 12.4.

FTIR (neat): ν_{max}/cm^{-1} 3509, 3027, 2964, 2916, 2883, 2850, 1726, 1645, 1602, 1495, 1453, 1437, 1227.

HRMS (p-APCI): *m/z* 273.1486 [$(M–H)^+$ requires 273.1486].

HPLC: 99% ee, *S,S*-Whelk, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 230 nm, t_R: 6.7 min (major), 8.4 min (minor).



methyl (1*S*,2*R*,4*R*,5*S*)-2-ethyl-1-hydroxy-4-methyl-3-methylene-5-phenylcyclohexane-1-carboxylate (145)

Prepared by *General Procedure 3.4.2.3* with **51** (122 mg, 0.60 mmol, 1.2 equiv), **139** (57 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg,

1.5 mmol, 3.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 8:1) afforded the title compound as a pale yellow oil (130 mg, 90% yield).

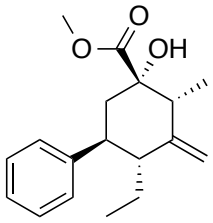
$[\alpha]^{20}_D$ +33.0° (*c* 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.26 (m, 2H), 7.23-7.16 (m, 3H), 5.13 (s, 1H), 4.92 (s, 1H), 3.80 (s, 3H), 3.04 (s, 1H), 2.66-2.53 (m, 2H), 2.35 (dq, *J* = 12.8, 6.4 Hz, 1H), 2.23 (t, *J* = 13.1 Hz, 1H), 1.90-1.72 (m, 2H), 1.17 (dqd, *J* = 14.5, 7.4, 2.8 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 149.2, 144.5, 128.7, 127.6, 126.6, 108.0, 79.0, 53.1, 51.3, 49.2, 45.5, 43.8, 20.1, 16.2, 12.6.

FTIR (neat): ν_{max}/cm^{-1} 3521, 3061, 3027, 2961, 2937, 2878, 2851, 1725, 1644, 1602, 1494, 1453, 1436, 1232, 1148.

HRMS (p-APCI): *m/z* 289.1799 [$(M+H)^+$ requires 289.1798].



methyl (1*S*,2*R*,4*R*,5*S*)-4-ethyl-1-hydroxy-2-methyl-3-methylene-5-phenylcyclohexane-1-carboxylate (146)

Prepared by *General Procedure 3.4.2.3* with **51** (122 mg, 0.60 mmol, 1.2 equiv), **140** (57 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg,

1.5 mmol, 3.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 8:1) afforded the title compound as an amorphous white solid (75 mg, 52% yield).

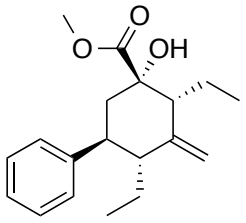
$[\alpha]^{20}_D$ +38.6° (*c* 0.4, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (t, J = 7.5 Hz, 2H), 7.23-7.19 (m, 3H), 5.04 (s, 1H), 4.97 (s, 1H), 3.80 (s, 3H), 3.05 (s, 1H), 2.75 (td, J = 12.0, 4.2 Hz, 2H), 2.25-2.21 (m, 1H), 2.21 (t, J = 12.9 Hz, 1H), 1.88 (dd, J = 13.8, 3.6 Hz, 1H), 1.47-1.39 (m, 1H), 1.33-1.25 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.6, 149.0, 144.7, 128.8, 127.8, 126.6, 108.2, 78.1, 53.2, 50.5, 47.3, 45.6, 44.2, 21.6, 12.4, 12.1.

FTIR (neat): ν_{max}/cm^{-1} 3522, 3061, 3027, 2952, 2878, 1728, 1645, 1601, 1494, 1453, 1437, 1232, 1148.

HRMS (p-APCI): *m/z* 289.1799 [$(M+H)^+$ requires 289.1798].



methyl (1*S*,2*R*,4*R*,5*S*)-2,4-diethyl-1-hydroxy-3-methylene-5-phenylcyclohexane-1-carboxylate (147)

Prepared by *General Procedure 3.4.2.3* with **51** (122 mg, 0.60 mmol, 1.2 equiv), **141** (64 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg,

1.5 mmol, 3.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 9:1) afforded the title compound as a pale yellow oil (128 mg, 85% yield).

$[\alpha]^{20}_D$ +31.1° (*c* 0.5, $CHCl_3$).

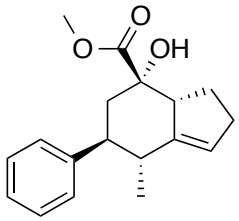
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 2H), 7.22-7.17 (m, 3H), 5.13 (s, 1H), 4.99 (s, 1H), 3.79 (s, 3H), 3.01 (s, 1H), 2.70 (td, *J* = 12.2, 4.0 Hz, 1H), 2.54 (d, *J* = 8.6 Hz, 1H), 2.24-2.13 (m, 2H), 1.88-1.73 (m, 2H), 1.44 (ddq, *J* = 14.4, 10.0, 7.2 Hz, 1H), 1.32-1.22 (m, 1H), 1.22-1.12 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.81 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 146.4, 144.6, 128.7, 127.8, 126.6, 108.4, 78.9, 52.1, 51.4, 48.5, 46.1, 21.7, 20.0, 12.5, 12.1.

FTIR (neat): ν_{max}/cm^{-1} 3522, 3027, 2955, 2878, 2847, 1725, 1645, 1494, 1453, 1436, 1379, 1231.

HRMS (p-APCI): *m/z* 303.1958 [$(M+H)^+$ requires 309.1955].

HPLC: 99% ee, OD-R, 0.3% isopropanol/hexanes, 0.3 mL/min, UV: 210 nm, t_R: 35.4 min (minor), 41.6 min (major).



methyl (4*R*,5*S*,7*S*,7a*R*)-7-hydroxy-4-methyl-5-phenyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-7-carboxylate (148)

Prepared by *General Procedure 3.4.2.3* with **51** (122 mg, 0.60 mmol, 1.2 equiv), **142** (56 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 6:1) afforded the title compound as an amorphous white solid (93 mg, 65% yield).

[α]$^{20}_D$ +16.1° (*c* 0.4, $CHCl_3$).

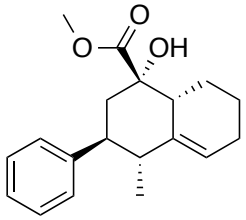
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 2H), 7.23-7.18 (m, 3H), 5.52-5.48 (m, 1H), 3.79 (s, 3H), 3.20-3.12 (m, 1H), 3.15 (s, 1H), 2.64 (td, J = 12.6, 3.5 Hz, 1H), 2.50-2.28 (m, 3H), 2.20 (t, J = 13.1 Hz, 1H), 1.93-1.83 (m, 2H), 1.83-1.70 (m, 1H), 0.95 (d, J = 6.3 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 145.4, 144.3, 128.4, 127.6, 126.4, 123.1, 76.2, 52.9, 52.4, 46.6, 43.6, 38.6, 31.8, 22.6, 16.8.

FTIR (neat): ν_{max}/cm^{-1} 3521, 3058, 3027, 2954, 2899, 2873, 2849, 1723, 1602, 1495, 1452, 1436, 1374, 1232, 1102, 1071.

HRMS (p-APCI): *m/z* 287.1643 [$(M+H)^+$ requires 287.1642].

HPLC: 99% ee, OD-R, 0.5% isopropanol/hexanes, 0.3 mL/min, UV: 210 nm, t_R: 39.0 min (minor), 48.7 min (major).



methyl (1*S*,3*S*,4*R*,8a*R*)-1-hydroxy-4-methyl-3-phenyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-1-carboxylate (149)

Prepared by *General Procedure 3.4.2.3* with **51** (122 mg, 0.60 mmol, 1.2 equiv), **143** (63 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 20 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 6:1) afforded the title compound as an amorphous yellow solid (128 mg, 85% yield).

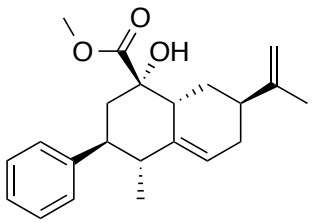
$[\alpha]^{20}_D$ +16.5° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 2H), 7.22-7.15 (m, 3H), 5.80-5.71 (m, 1H), 3.78 (s, 3H), 3.20 (s, 1H), 2.68 (td, *J* = 12.3, 3.6 Hz, 1H), 2.34-2.22 (m, 1H), 2.17 (t, *J* = 13.0 Hz, 1H), 2.08-2.00 (m, 2H), 1.85 (dd, *J* = 13.3, 3.7 Hz, 1H), 1.81-1.73 (m, 1H), 1.61-1.50 (m, 2H), 1.47-1.36 (m, 1H), 0.83 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 145.1, 138.6, 128.7, 127.7, 126.5, 122.7, 77.8, 53.2, 46.9, 44.8, 42.9, 42.0, 25.4, 24.4, 21.2, 15.5

FTIR (neat): ν_{max}/cm^{-1} 3522, 3059, 3027, 2930, 2874, 2859, 2834, 1727, 1602, 1495, 1452, 1426, 1251, 1225.

HRMS (p-APCI): *m/z* 301.1798 [$(M+H)^+$ requires 307.1798].



methyl (1*S*,3*S*,4*R*,7*S*,8a*R*)-1-hydroxy-4-methyl-3-phenyl-7-(prop-1-en-2-yl)-1,2,3,4,6,7,8,8a-octahydronaphthalene-1-carboxylate (156)

Prepared by *General Procedure 3.4.2.3* with **51** (122 mg, 0.60 mmol, 1.2 equiv), **155** (83 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 24 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 7:1) afforded the title compound as a crystalline white solid (112 mg, 66% yield).

MP = 62–65 °C

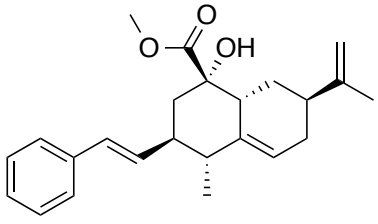
$[\alpha]^{20}_D$ +37.5° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 2H), 7.23-7.17 (m, 3H), 5.77 (dd, *J* = 5.1, 2.2 Hz, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 3.82 (s, 3H), 3.25 (s, 1H), 2.74 (bd, *J* = 6.6 Hz, 1H), 2.70-2.59 (m, 2H), 2.39-2.24 (m, 2H), 2.20 (t, *J* = 13.1 Hz, 1H), 1.97-1.85 (m, 1H), 1.82 (dd, *J* = 13.4, 3.7 Hz, 1H), 1.73 (s, 3H), 1.68-157 (m, 1H), 1.56-1.49 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 149.8, 144.8, 138.2, 128.7, 126.6, 121.4, 108.8, 79.5 53.3, 47.8, 45.6, 42.4, 42.0, 37.6, 30.4, 30.0, 21.3, 15.5.

FTIR (neat): ν_{max}/cm^{-1} 3482, 3062, 3028, 2935, 2874, 1726, 1602, 1495, 1453, 1437, 1377, 1233, 1091, 1069.

HRMS (p-APCI): *m/z* 341.2108 [$(M+H)^+$ requires 341.2111].



methyl (1*S*,3*R*,4*R*,7*S*,8a*R*)-1-hydroxy-4-methyl-7-(prop-1-en-2-yl)-3-((*E*)-styryl)-1,2,3,4,6,7,8,8a-octahydronaphthalene-1-carboxylate (157)

Prepared by *General Procedure 3.4.2.3* with **150** (137 mg, 0.60 mmol, 1.2 equiv), **155** (83 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 24 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 8:1) afforded the title compound as a crystalline white solid (106 mg, 58% yield).

MP = 84–88 °C

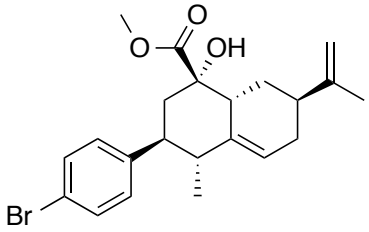
$[\alpha]^{20}_D$ +66.5° (*c* 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 4H), 7.20 (t, *J* = 7.1 Hz, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.03 (dd, *J* = 15.8, 9.2 Hz, 2H), 5.76-5.73 (m, 1H), 4.72 (s, 1H), 4.67 (s, 1H), 3.83 (s, 3H), 3.20 (s, 1H), 2.64-2.55 (m, 2H), 2.35-2.20 (m, 2H), 2.04-1.95 (m, 2H), 1.95-1.82 (m, 1H), 1.78-1.72 (m, 1H), 1.72 (s, 3H), 1.65-1.54 (m, 1H), 1.52-1.46 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 149.8, 137.6, 134.0, 130.7, 128.7, 127.3, 126.2, 121.2, 108.8, 79.4, 53.3, 45.5, 43.9, 41.9, 41.9, 37.6, 30.4, 29.9, 21.3, 15.9.

FTIR (neat): ν_{max}/cm^{-1} 3519, 3081, 3058, 3024, 2961, 2917, 2876, 1725, 1643, 1493, 1448, 1436.

HRMS (p-APCI): *m/z* 367.2273 [$(M+H)^+$ requires 367.2268].



methyl (1*S*,3*S*,4*R*,7*S*,8a*R*)-3-(4-bromophenyl)-1-hydroxy-4-methyl-7-(prop-1-en-2-yl)-1,2,3,4,6,7,8,8a-octahydronaphthalene-1-carboxylate (158)

Prepared by *General Procedure 3.4.2.3* with **151** (168 mg, 0.60 mmol, 1.2 equiv), **155** (83 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 24 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 6:1) afforded the title compound as a crystalline white solid (117 mg, 56% yield).

MP = 135–140 °C

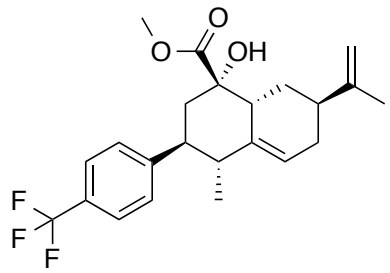
$[\alpha]^{20}_D$ ° +54.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.3 Hz, 2H), 5.79-5.73 (m, 1H), 4.72 (s, 1H), 4.68 (s, 1H), 3.82 (s, 3H), 3.29 (s,1H), 2.72 (bd, J = 6.0 Hz, 1H), 2.67-2.55 (m, 2H), 2.33-2.21 (m, 2H), 2.16 (t, J = 13.0 Hz, 1H), 1.97-1.82 (m, 1H), 1.79 (dd, J = 13.3, 3.7 Hz, 1H), 1.72 (s, 3H), 1.62 (ddd, J = 13.5, 11.4, 7.1 Hz, 1H), 1.55-1.49 (m, 1H), 0.84 (d, J = 6.5 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.9, 149.7, 143.9, 137.8, 131.8, 121.6, 120.2, 108.9, 79.4, 53.4, 47.3, 45.4, 42.4, 42.1, 37.6, 30.4, 29.9, 21.3, 15.5.

FTIR (neat): ν_{max}/cm^{-1} 3515, 2954, 2918, 2874, 2850, 1725, 1643, 1488, 1436, 1225.

HRMS (p-APCI): *m/z* 419.1219 [$(M+H)^+$ requires 409.1222].



methyl (1*S*,3*S*,4*R*,7*S*,8a*R*)-1-hydroxy-4-methyl-7-(prop-1-en-2-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,3,4,6,7,8,8a-octahydronaphthalene-1-carboxylate (159)

Prepared by *General Procedure 3.4.2.3* with **152** (162 mg, 0.60 mmol, 1.2 equiv), **155** (83 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 24 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 7:1) afforded the title compound as a crystalline white solid (135 mg, 66% yield).

MP = 120–123 °C

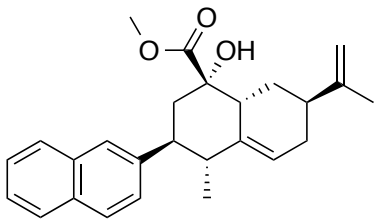
$[\alpha]^{20}_D$ +48.3° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.79 (d, J = 2.7 Hz, 1H), 4.74 (s, 1H), 4.69 (s, 1H), 3.83 (s, 3H), 3.34 (s, 1H), 2.80-2.72 (m, 2H), 2.63 (tt, J = 10.1, 3.9 Hz, 1H), 2.42-2.33 (m, 1H), 2.33-2.25 (m, 1H), 2.21 (t, J = 13.0 Hz, 1H), 2.00-1.87 (m, 1H), 1.81 (dd, J = 13.3, 3.7 Hz, 1H), 1.73 (s, 3H), 1.64 (ddd, J = 13.6, 11.3, 7.1 Hz, 1H), 1.58-1.50 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 149.6, 149.0, 137.5, 128.8 (q, J = 32 Hz), 125.6, 124.3 (q, J = 260 Hz), 121.7, 108.9, 79.2, 53.3, 47.6, 45.3, 42.1, 42.0, 37.5, 30.3, 29.8, 21.3, 15.4.

FTIR (neat): ν_{max}/cm^{-1} 3463, 2956, 2932, 2876, 1724, 1620, 1456, 1437, 1235.

HRMS (p-APCI): *m/z* 409.1985 [$(M+H)^+$ requires 409.1985].



methyl (1*R*,2*S*,4*S*,4a*R*,6*S*)-4-hydroxy-1-methyl-6-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydro-[2,2'-binaphthalene]-4-carboxylate (160)

Prepared by *General Procedure 3.4.2.3* with **153** (151 mg, 0.60 mmol, 1.2 equiv), **155** (83 mg, 0.50 mmol, 1.0 equiv), $\{Rh_2[(R)\text{-dosp}]_4\}$ (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 24 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 6:1) afforded the title compound as a crystalline white solid (105 mg, 54% yield).

MP = 134–137 °C

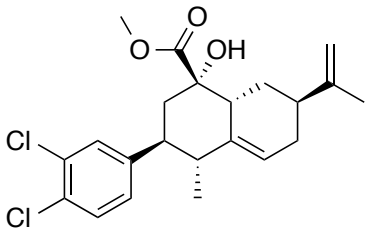
$\mathbf{[\alpha]^{20}_D}$ +54.9° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.71 (m, 3H), 7.62 (s, 1H), 7.48-7.39 (m, 2H), 7.36 (bd, *J* = 8.2 Hz, 1H), 5.81-5.77 (m, 1H), 4.74 (s, 1H), 4.70 (s, 1H), 3.81 (s, 3H), 3.31 (s, 1H), 2.84 (td, *J* = 12.4, 3.2 Hz, 1H), 2.79 (bd, *J* = 6.0 Hz, 1H), 2.66 (tt, *J* = 10.1, 4.1 Hz, 1H), 2.50-2.40 (m, 1H), 2.32 (t, *J* = 13.2 Hz, 1H), 2.32-2.34 (m, 1H), 1.97-1.91 (m, 1H), 1.88 (dd, *J* = 13.2, 4.2 Hz, 1H), 1.74 (s, 3H), 1.65 (ddd, *J* = 13.6, 11.4, 7.1 Hz, 1H), 1.58-1.52 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 149.7, 142.3, 138.1, 133.8, 132.5, 128.3, 127.8, 127.7, 126.1, 125.5, 121.4, 108.8, 79.5, 53.3, 47.9, 45.5, 42.3, 42.1, 37.6, 30.4, 29.9, 21.3, 15.6.

FTIR (neat): ν_{max}/cm^{-1} 3515, 3053, 3016, 2962, 2916, 2876, 2852, 1724, 1643, 1599, 1507, 1436, 1375, 1234, 1224, 1090.

HRMS (p-APCI): *m/z* 391.2269 [(M+H)$^+$ requires 391.2268].



methyl (1*S*,3*S*,4*R*,7*S*,8a*R*)-3-(3,4-dichlorophenyl)-1-hydroxy-4-methyl-7-(prop-1-en-2-yl)-1,2,3,4,6,7,8,8a-octahydronaphthalene-1-carboxylate (161)

Prepared by *General Procedure 3.4.2.3* with **154** (163 mg, 0.60 mmol, 1.2 equiv), **155** (83 mg, 0.50 mmol, 1.0 equiv), {Rh_2[(*R*)-dosp]$_4$} (0.9 mg, 0.0005 mmol, 0.1 mol %), and $CaCl_2$ (165 mg, 1.5 mmol, 3.0 equiv), heating to 125 °C for 24 h. Purification by flash chromatography (SiO_2, pentane/Et_2O, 5:1) afforded the title compound as an amorphous white solid (114 mg, 56% yield).

[α]$^{20}_D$ +27.0° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.79-5.74 (m, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 3.84 (s, 3H), 3.31 (s, 1H), 2.75-2.54 (m, 3H), 2.31-2.22 (m, 2H), 2.14 (t, *J* = 13.0 Hz, 1H), 1.91 (ddt, *J* = 15.9, 8.9, 3.0 Hz, 1H), 1.79 (dd, *J* = 13.3, 3.7 Hz, 1H), 1.72 (s, 3H), 1.67-1.56 (m, 1H), 1.55-1.47 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 149.6, 145.2, 137.4, 132.6, 130.6, 130.3, 129.4, 127.4, 121.8, 108.9, 79.1, 53.4, 47.1, 45.2, 42.3, 42.0, 37.5, 30.3, 29.8, 21.3, 15.5.

FTIR (neat): ν_{max}/cm^{-1} 3473, 3079, 2952, 2880, 1728, 1590, 1561, 1469, 1437, 1403, 1379, 1233, 1132.

HRMS (p-APCI): *m/z* 409.1140 [$(M+H)^+$ requires 409.1132].

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– Chapter 3 –

Asymmetric Cyclopentane/Cyclohexane Synthesis by a Rhodium(II) Carbene-Initiated Cascade

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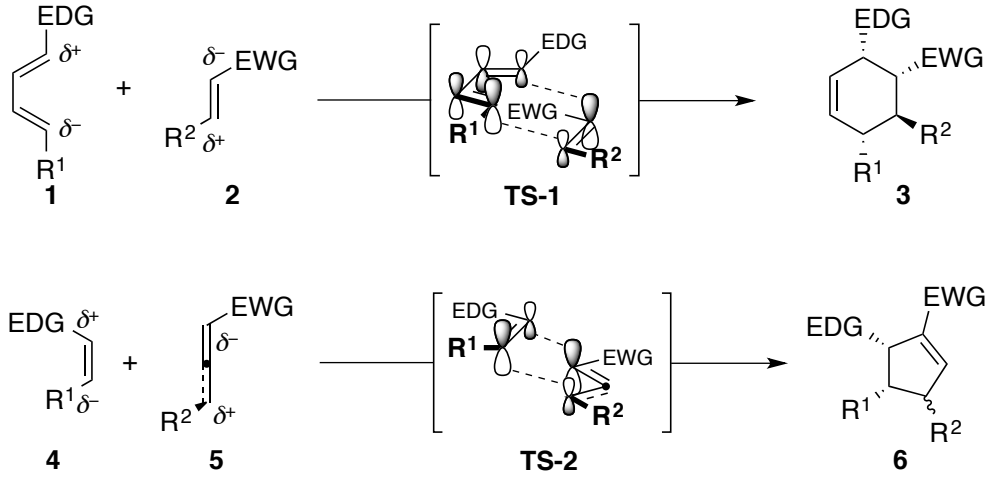
3.1 Introduction

Convergent annulation strategies for the asymmetric synthesis of medium-sized, specifically 5–6 membered, carbocyclic structures are valuable transformations for the synthetic organic community.[1–3] The venerable Diels–Alder reaction has served as the classic and contemporary, asymmetric entry into cyclohexenes, bearing up to four stereocenters. A general, complementary cycloaddition strategy for accessing cyclopentenes, however, has not been identified. From the standpoint of intrinsic reactivity, the challenges associated with direct annulation to form a five membered, compared with a six membered, cycloalkene are multifaceted. While the normal electron demand Diels–Alder reaction disconnects the cyclohexene *via* asymmetric [4 + 2]-cycloaddition to diene (**1**) and dienophile (**2**) (Scheme 3.1). The polarization of **1** and **2** by virtue of the substituents present enable efficient interactions of the molecular orbitals in a concerted fashion, as shown in **TS-1**. By comparison, the molecular orbital picture for the formal [3 + 2]-cycloaddition can be drawn as interaction of a dipolarophile, such as **4**, with a formally or partially charged (1,3)-dipole, such as **5**. Interaction of the HOMO of **4** with the LUMO of **5** renders a transition state analogous to **TS-2**, which upon cycloaddition reaction provides a cy-

clopentene product (**6**). The central challenge associated with achieving asymmetric variants on the formal [3 + 2]-cycloaddition is generation of an all carbon [1,3]-dipole under mild reaction conditions, such that a chiral catalyst can bind efficiently and exert its stereoselective influence.[4] In addition, ionization of an allene-type three carbon component (**5**) is a "stereoablative" process, with respect to axial chirality, and thus, requires an external element of stereocontrol.



Scheme 3.1 Frontier molecular orbital perspective of [4 + 2]- and [3 + 2]-cycloaddition reactions

Synthetic cyclopentanes are a central structural motif common to prostaglandin antagonist antiglaucoma agents, including bimatoprost,[5] latanoprost,[6] unoprostone,[7] tafluprost,[8] and travaprost.[9] Methods for forging cyclopentanes bearing multiple stereocenters in a single synthetic manipulation are particularly attractive, as these are common structural motifs in a number of complex natural products (Figure 3.1).[10–35] Yet, for the most part, each of the three represen-

tative members of landmark synthetic targets (**7**–**9**) in total synthesis spanning several decades, were prepared by methods other than direct cyclopentane or cyclopentene annulations.

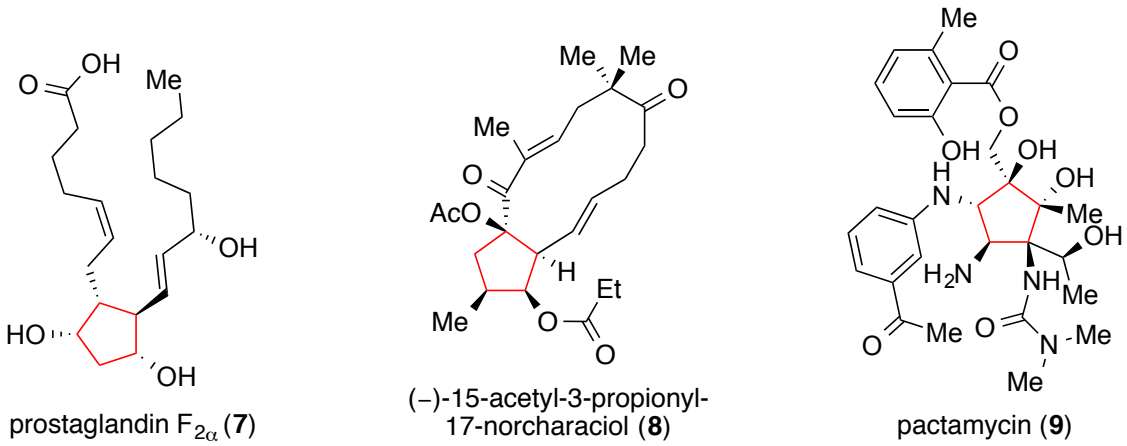
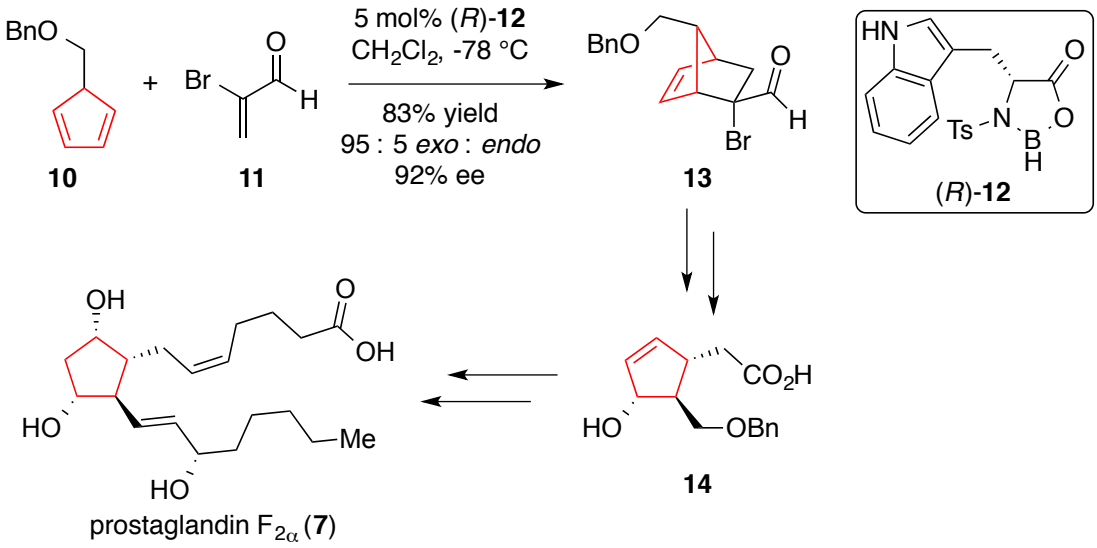


Figure 3.1 Representative cyclopentane containing natural products of synthetic interest

Beginning with the earliest example, the ingenius strategy by Corey and co-workers toward the ubiquitous prostaglandins commences with the cyclopentane nucleus intact, in the form of achiral cyclopentadiene **10** (Scheme 3.2).[11,12,14,18] Although the source of stereoselection in the critical Diels–Alder reaction evolved over several generations of prostaglandin synthesis, the tryptophan-derived chiral oxazaborylidinone [(*R*)-**12**] was ultimately identified as a powerful catalyst for the [4 + 2]-cycloaddition of the benzyloxymethyl-cyclopentadiene (**10**) and α-bromoacrolein (**11**), wherein three of the four stereocenters of the cyclopentane nucleus of **7** are installed with excellent stereoselection. In subsequent steps (**13** → **14**), the six membered ring

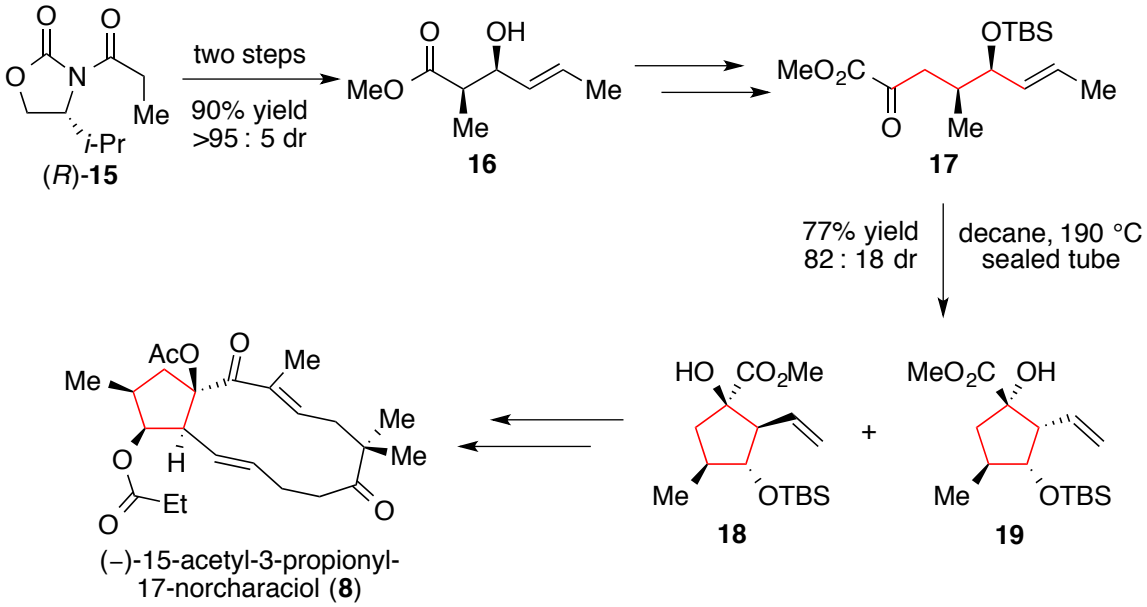
formed during the Diels–Alder reaction is ruptured to unmask the trisubstituted cyclopentene, which was subsequently converted to prostaglandin $F_{2\alpha}$ among other prostanoids.



Scheme 3.2 Strategy for prostaglandin synthesis by Corey and co-workers

The jatrophane terpenoids, such as **8**, are a substantial family of trans-fused [10.3.0] bicyclic molecules, which vary largely in the oxidation state of the macrocycle and the substitution of the *O*-atoms. Hiersemann and co-workers have been particularly active in the field of jatrophane synthesis over the past decade. From the Evan's chiral oxazolidinone [Scheme 3.3, (*R*)-**15**], two chiral centers of the cyclopentane nucleus are installed by stereoselective aldol addition to crotonaldehyde and conversion of the amide to ester, to provide intermediate **16**.[26,28,29,33,36] Functional group manipulations and elongation of the carbon backbone (**16** → **17**) provide a cyclization precursor. An intramolecular carbonyl ene reaction of **17** generated the cyclopentane core while simultaneously installing the two remaining stereocenters in good yield and modest di-

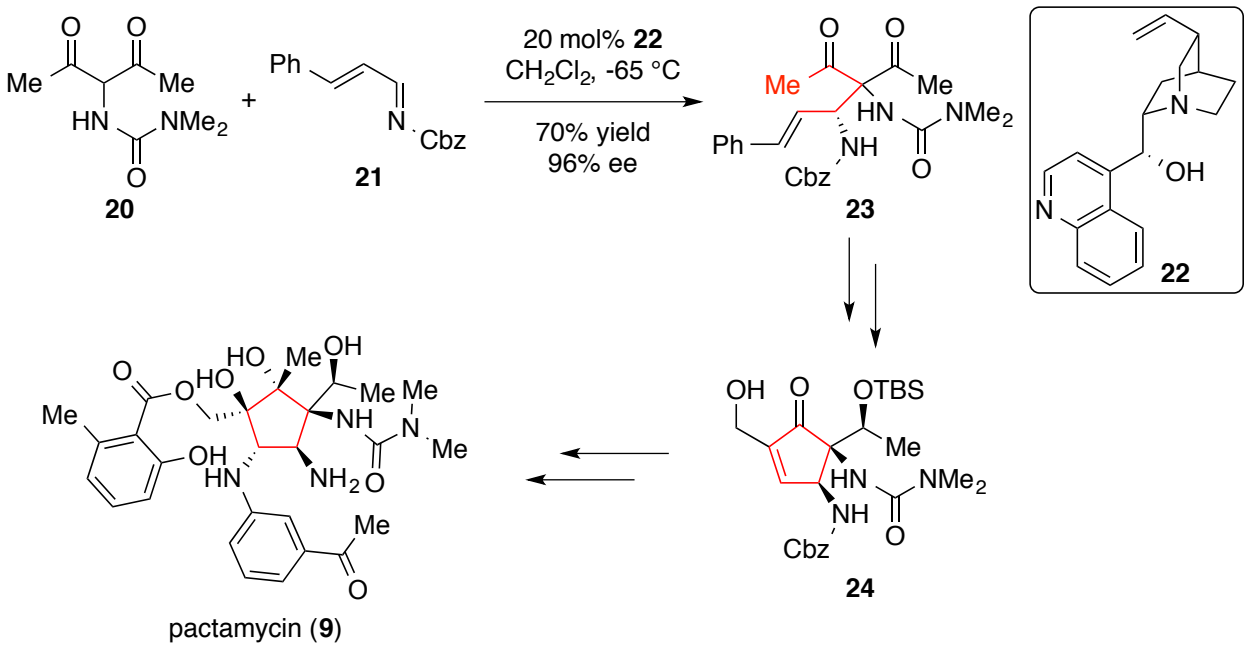
astereoselectivity (**18** + **19**, 77% combined yield, 82 : 18 dr). The major, desired diastereomer (**18**) was converted to (–)-15-acetyl-3-propionyl-17-norcharciol (**8**) through subsequent steps, including inversion of the siloxy stereocenter under Mitsunobu conditions. The diastereoselective hetereo-ene reaction of an α-keto ester to forge a cyclopentane bearing a hydroxy ester quaternary carbon stereocenter has been implemented in subsequent jatrophane syntheses by Hiersemann.



Scheme 3.3 Strategy for jatrophane synthesis by Hiersemann and co-workers

In the recent, concise synthesis of the notorious antitumor antibiotic pactamycin (Scheme 3.4, **9**), reported by Johnson and co-workers, a stepwise construction of the cyclopentane nucleus was also implemented.[35] Thus, enantioselective Mannich reaction of the 1,3-diketone pronucleophile **20** with cinnamaldehyde-derived imine **21**, under the catalytic action of cinchonidine

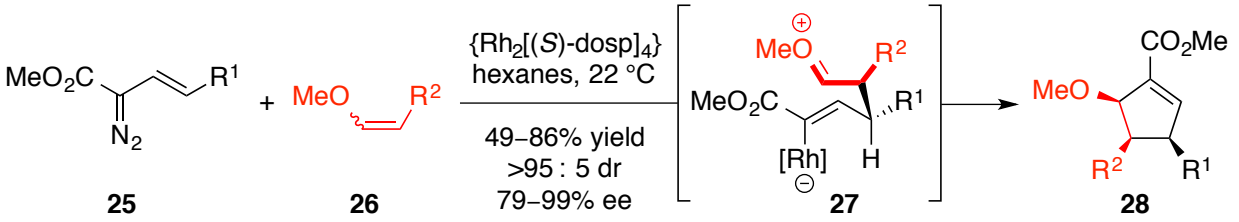
22, led to the desymmetrized product **23** containing the acyclic carbon framework of the cyclopentane core. The cyclopentenone **24** was forged through several manipulations including thermodynamic inversion of the carbamate moiety, and was eventually converted to the natural product (**9**) in short order.



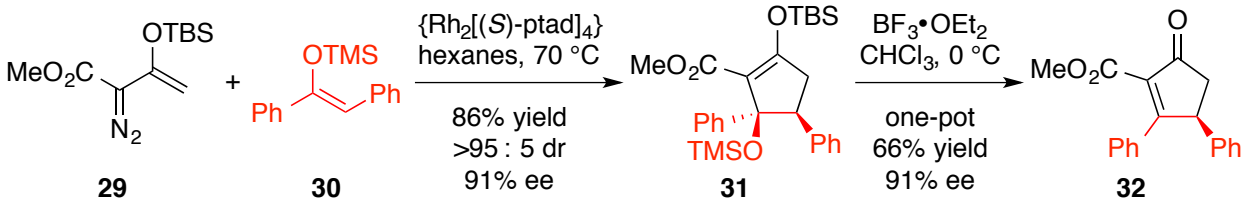
Scheme 3.4 Strategy for pactamycin synthesis by Johnson and co-workers

One might surmise from the three synthetic examples presented, methods for the convergent, stereoselective construction of a cyclopentane or cyclopentene nucleus are either not readily amenable to the complications of natural product synthesis or lack sufficient generality in components involved. As the molecular orbital representation of a formal [3 + 2]-cycloaddition in Scheme 3.1 suggests, the majority of annulation strategies known at the outset of our work in-

volved the synthesis of cyclopentenes, or more specifically, cyclopentene-1-carboxylates. In fact, one of the earliest examples of a convergent, enantioselective cyclopentene synthesis was from the Davies group, involving the reaction of vinyldiazoacetates and enol ethers (Scheme 3.5).[37,38] Addition of either the (*E*)- or (*Z*)-isomer of enol ether **26** to the "vinylogous" position of the rhodium carbene intermediate derived from {Rh_2[(*S*)-dosp]$_4$} and vinyldiazoacetate **25**, was proposed to result in formation of the transient zwitterion **27**. Rapid cyclization of the vinyl rhodium anion onto the oxocarbenium ion provides the cyclopentene-1-carboxylate **28** bearing three contiguous stereocenters (Scheme 3.5a).[37] In a subsequent study from Davies and co-workers, trisubstituted silyl enol ethers such as **30** were also deemed competent for tandem vinylogous addition/cyclization with diazoacetate **29** derived rhodium vinylcarbenes under {Rh_2[(*S*)-ptad]$_4$}-mediated catalysis (Scheme 3.5b).[38] The cyclopentenes **31** were formed in similarly high yield and stereoselection as the previous report. An added feature of the methodology, however, was the ability to effect a Lewis acid mediated elimination of an *O*-silyl substituent in a one-pot process, to yield a cyclopentenone product (**32**) in good yield for the two-step process, and without degradation of enantiopurity.



(a) Seminal vinylogous [3 + 2]-cycloaddition of rhodium vinylcarbene intermediates

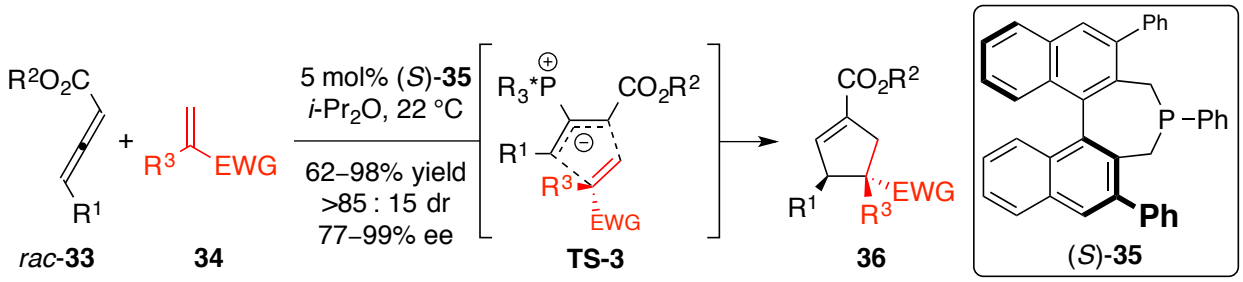


(b) Cyclopentenone synthesis *via* a vinylogous rhodium vinylcarbene [3 + 2]-cycloaddition

Scheme 3.5 Formal [3 + 2]-cycloadditions involving rhodium vinylcarbene intermediates

An alternative formal [3 + 2]-cycloaddition approach to the synthesis of cyclopentene-1-carboxylates employs chiral phosphine- and phosphepine-catalyzed Lu cycloaddition reaction[39–46] Among the more general variants of a stereoselective Lu cycloaddition reaction was that recently disclosed by Fu and co-workers (Scheme 3.6).[47,48] In the presence of chiral phosphepine (*S*)-**35**, racemic 1,3-disubstituted allenyl carboxylate (*rac*-**33**) is resolved *via* a dynamic kinetic asymmetric transformation. Thus, Lewis base activation by (*S*)-**35** generates a (1,3)-dipole in the presence of an α-substituted acryloyl dipolarophile (**34**) to provide **TS-3**. Formal cyclization then leads to the cyclopentene-1-carboxylate (**36**), which is generally formed in high yield and enantioselection, but with variable diastereoselection depending upon the nature of the R^3 substituent. A stereoselective Lu [3 + 2]-cycloaddition with a terminally substituted dipolarophile

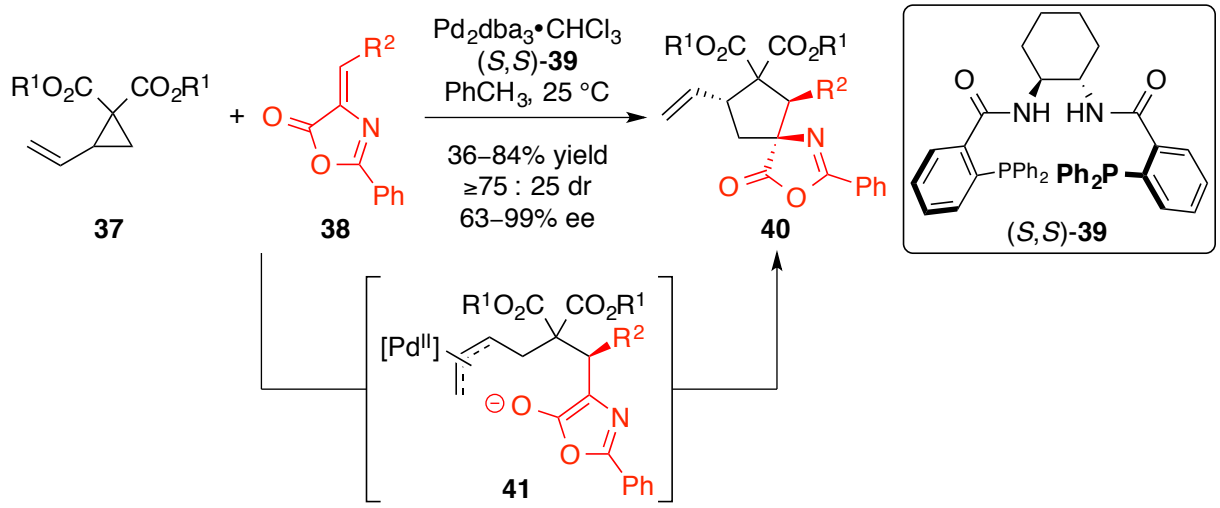
has not been reported; and therefore, only two stereocenters can be generated from this annulation protocol.



Scheme 3.6 Chiral phosphepine-catalyzed stereoselective Lu cycloaddition

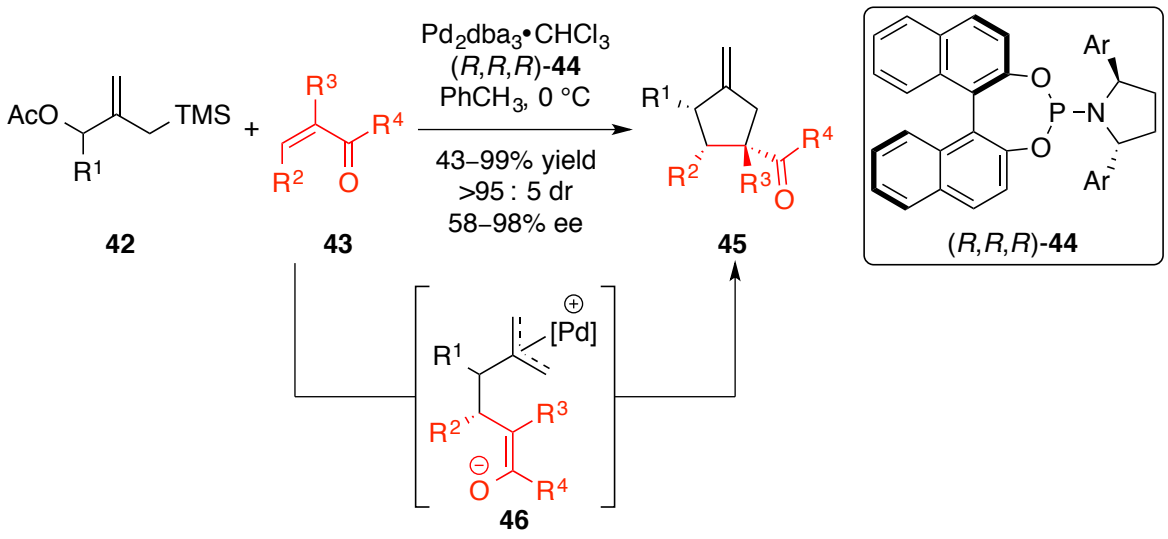
Among the most recent developments in cyclopentane synthesis *via* formal [3 + 2]-cycloaddition has been the stereoselective reactions of cationic palladium π–allyl (1,3)-dipoles and electron-deficient olefins. The palladium-catalyzed tandem allylation/cyclization reactions have, for the most part, been pioneered by Trost and co-workers. Two general strategies for accessing the requisite palladated (1,3)-dipole have been formulated. The first involves transition metal-mediated ring-opening of a vinyl-substituted donor/acceptor cyclopropane (Scheme 3.7, **37**).[4] The pendant malonate then participates in enantioselective conjugate addition to the electrophilic methylidene oxazolone (**38**) providing aromatic intermediate **41**. Diastereoselective intramolecular enolate addition to the palladium-allyl tether, followed by reductive elimination of the transition metal complex generates spirocyclic cyclopentane **40**.[4] In general, the reaction is not tolerant of a great variety of substituents, and the individual reaction components them-

selves (**37** and **38**) limit the product architectures which can be generated through this methodology.



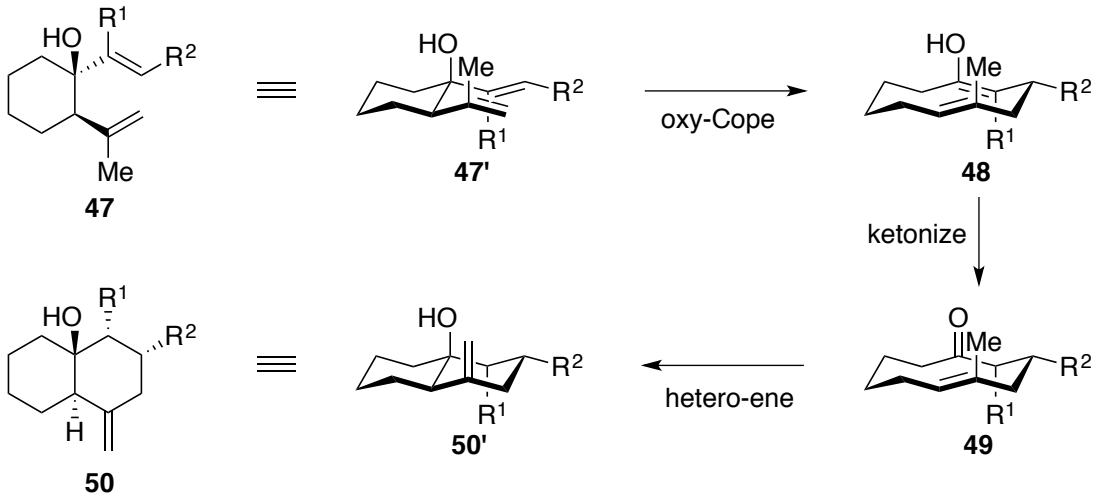
Scheme 3.7 Palladium-catalyzed stereoselective [3 + 2]-cycloaddition of vinylcyclopropanes

The second, parallel strategy for palladium-catalyzed stereoselective cyclopentane synthesis involves generation of a metallated trimethylenemethane-like intermediate, which similarly participates in formal [3 + 2]-cycloaddition with electron-deficient π–bonds.[49–54] The classic protocol for generating a trimethylenemethane diradical intermediate was nitrogen extrusion *via* thermolysis or photolysis of an alkylidene dihydropyrazole.[55–58] The nucleophilic palladium-trimethylenemethane intermediate generated from a palladium phosphoramidate [Pd(*R*,*R*,*R*)-**44**] complex and **42**, also undergoes an enantioselective conjugate addition to the olefin (**43**) providing the zwitterionic intermediate (**46**) as shown in Scheme 3.8. Once again, intramolecular enolate addition to the palladium-allyl species affords a cyclopentane product (**45**).



Scheme 3.8 Palladium-catalyzed stereoselective trimethylenemethane [3 + 2]-cycloaddition

An alternative approach toward the rapid construction of carbocycles is a sigmatropic rearrangement strategy. Examples of sequential sigmatropic rearrangements have been demonstrated *en route* to complex terpenoid scaffolds, such as Nicolaou and co-workers' landmark synthesis of endiandric acids A and B.[59–62] We were particularly inspired, however, by the work in sequential sigmatropic rearrangement methodology as an approach to cyclohexane construction reported by Barriault and co-workers (Scheme 3.9, **47** → **50**).[63,64] A tertiary allyl alcohol with a pendant olefin (**47**) can be rendered into a chair-like geometry (**47′**), obviating its propensity to participate in an oxy-Cope [3,3]-sigmatropic rearrangement. The transient enol intermediate (**48**) undergoes stereoselective ketonization/protonation to furnish macrocyclic ketone **49**. Reaction intermediate **49** is then well configured to undergo an intramolecular carbonyl ene reaction, providing decahydronaphthalenol **50** bearing four contiguous stereocenters.



Scheme 3.9 Tandem oxy-Cope/transannular ene cascade reaction

Engineering a molecule to participate in tandem sigmatropic rearrangements offers a high yielding, atom economical approach to the rapid generation of molecular complexity. The ensuing section will discuss a novel rhodium carbene-initiated domino reaction for the synthesis of saturated cyclopentane nuclei containing four stereocenters. In addition, evolution of the cascade sequence to include a stereoselective cyclohexane synthesis will be discussed.

3.2 Results & Discussion

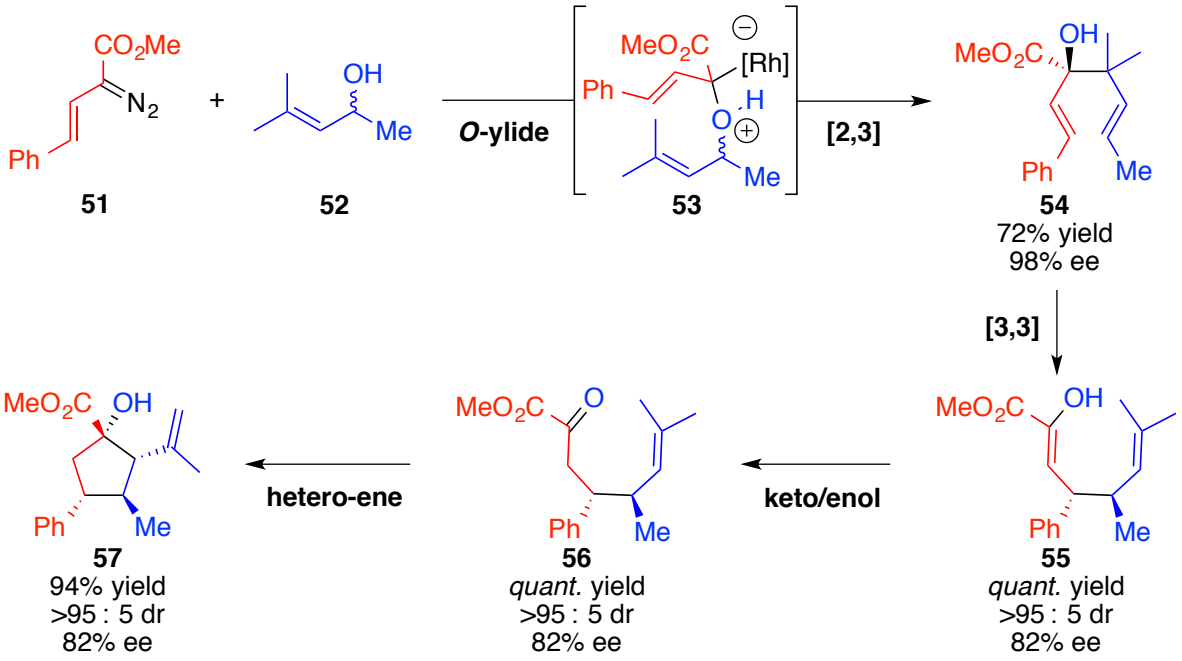
3.2.1 Cyclopentane Synthesis

Discovery and Optimization. The discovery of a novel cyclopentane synthesis originated from our studies in rhodium vinylcarbene chemistry.[65,66] The metal-catalyzed reaction of diazo compounds is a particularly mild, and therefore practical, method for generation of transient metallocarbenes, which have been demonstrated as competent intermediates for initiating subsequent reaction cascades.[67–69] The Davies group has a longstanding interest in the identification of new cascade sequences accessible from vinyldiazoacetate substrates.[70–73] Recall the tandem oxygen ylide formation/[2,3]-sigmatropic rearrangement between styryldiazoacetates (**51**) and allyl alcohols (**52**) which, through intermediacy of a rhodium-bound ylide (**53**), generated dienols (**54**) in 92–98% ee (Scheme 3.10).[74] As the tandem oxygen ylide formation/[2,3]-sigmatropic rearrangement is generally an efficient transformation from the standpoint of asymmetric induction, we became intrigued by the possibility that the products of this reaction ought to be prone to further rearrangement.

To first establish the plausibility of a domino reaction, we examined the reactions of the [2,3]-sigmatropic rearrangement product **54**, which is formed in 98% ee under the catalytic action of $\{Rh_2[(S)\text{-dosp}]_4\}$.[74] Specifically, since **54** contains a 3-hydroxy-1,5-hexadiene moiety with vicinal quaternary carbon atoms, it was anticipated that the molecule would be well-configured to participate in an oxy-Cope [3,3]-sigmatropic rearrangement.[63,64,75–79] Indeed, thermolyzing in hydrocarbon solvents at >80 °C, **54** underwent smooth conversion to the substituted hydroxyacrylate **55**, as a single diastereomer. Studies within the group demonstrated the plausibility of the rearrangement, as conversion of **54** to **55** was observed when stored as a chlo-

roform-D solution over a period of approximately 30 d. These studies did not establish the degree of chirality transfer during the oxy-Cope transformation.[80]

Examination of subsequent reactivity of these intermediates was then considered. Specifically, enol **55** was not expected to be a stable product, and indeed, on attempted purification by silica gel chromatography, smooth tautomerization to α-keto ester **56** was observed, while retaining its diastereo- and enantiomeric integrity through the process. Comparative HPLC analysis with a racemic sample of **56**, prepared by thermolysis of racemic **54**, indicated that the degredation of the enantiomeric excess was occurring during the oxy-Cope rearrangement (98 → 82% ee). The ee of **55** was assigned 82%, as inversion of both chiral centers during the ketonization event (**55** → **56**) would not be expected. As the ketone is vicinal to an ester carbonyl group, **56** was expected to be a reactive, electrophilic moiety itself. Thus, we reasoned that it would be prone to an intramolecular carbonyl ene reaction with the pendant olefin, to form the cyclopentane **57**.[63,64,75] Indeed, the intramolecular hetero-ene reaction was readily catalyzed by scandium(III) triflate[81] at elevated temperatures, which provided for efficient conversion to the cyclopentane **57**. The absolute configuration of 1,5-hexadienol **54** was assigned in the earlier [2,3]-sigmatropic rearrangement studies,[74] and the relative configuration of cyclopentane **57** was determined by X-ray crystallography. The stereochemistry for the conversion of **54** to **57** is consistent with the oxy-Cope rearrangement of **54** to **55** proceeding *via* a chair-like transition state.[63,64,75–79,82–85] Epimerization of the stereocenters in **55** would not be expected in the course of the ketonization event or hetero-ene reaction, and so, consistency in the configuration of **57** was anticipated.

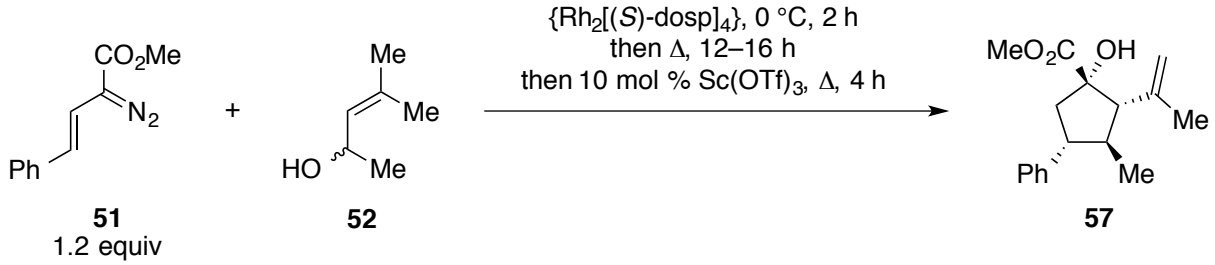


Scheme 3.10 Stepwise view of cyclopentane synthesis from a diazoacetate and an allyl alcohol

Optimization studies were then conducted such that the cascade sequence between the styryldiazoacetate **51** and allyl alcohol **52** to enable an expedient, one-pot synthesis of cyclopentane **57** could be achieved. It was envisioned that after the initial enantioselective rhodium-catalyzed step, the rest of the sequence should be feasible by treatment with the appropriate combination of solvent, temperature, and Lewis acid catalyst. A summary of the optimization for the reaction of **51** and **52** to yield **57** is summarized in Table 3.1. A racemic sample of **57** was prepared by reaction of **51** and **52** under the catalytic action of an equimolar mixture of $\{Rh_2[(R)\text{-dosp}]_4\}$ and $\{Rh_2[(S)\text{-dosp}]_4\}$ under otherwise identical reaction conditions. Previous control studies had demonstrated that the optimum temperature for the tandem oxygen ylide formation/[2,3]-sigmatropic rearrangement was 0 °C.[74] After completion of the [2,3]-rearrangement as evidenced by thin layer chromatographic analysis, the crude product mixture

was heated in the parent solvent for 20 h before treating with a catalytic quantity of scandium(III) triflate (10 mol %) at elevated temperature for 4 h. At temperatures less than ~75 °C, only the [2,3]-product (**54**) was observed in the ^{1}H NMR of the crude reaction mixture after 16 h (entry 1). A modest increase in temperature and an incubation period of 20 h, however, effected formation of the desired product **57**, which was isolated in generally good yields (entries 2 and 4–9). In a more polar solvent system, such as ethyl acetate, attenuated yields and enantioselectivities were observed (entry 3). A surprising depletion in enantioselectivity of the reaction cascade was observed when *c*-hexane was implemented as reaction solvent, which control studies implicated a less efficient [2,3]-sigmatropic rearrangement (entry 5). The optimum conditions were ultimately found to be 1 mol% of the rhodium catalyst in heptane at 80 °C. Under these conditions **57** was formed in 95% yield and 82% ee (entry 7). These conditions were used as the standard for the remainder of the cyclopentane synthesis study; although in some cases, high yield of product could be obtained even in the absence of the scandium(III) triflate catalyst. In these instances, however, extended reaction times were often required as the ene reaction was rather sluggish. It should be noted that decreased rhodium-catalyst loading was tolerated if desired,[86] where upon reducing the catalyst loading to 0.01 mol% (entry 9) only a modest depreciation in yield and enantioselectivity was observed (75% yield, 79% ee). The relative configuration of cyclopentane **57** was determined by X-ray crystallographic analysis, and has been submitted to the Cambridge Crystallographic Data Centre under deposition number CCDC 827543.

Table 3.1[a–c] Optimization of the one-pot cyclopentane synthesis



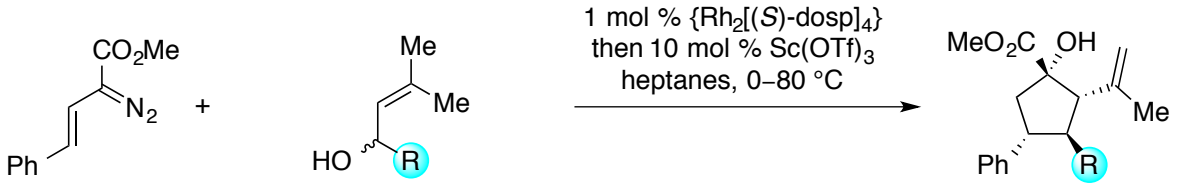
entry	$\{Rh_2[(S)\text{-dosp}]_4\}$	solvent	temp., °C	yield, %	dr	ee, %
1	1 mol %	hexanes	70	0	–	–
2	1 mol%	1,2-DCE	80	43	>95 : 5	54
3	1 mol%	EtOAc	80	20	>95 : 5	51
4	1 mol%	$PhCH_3$	110	71	>95 : 5	70
5	1 mol%	*c*-hexane	80	91	>95 : 5	74
6	1 mol%	heptanes	100	88	>95 : 5	80
7	1 mol%	heptanes	80	95	>95 : 5	82
8	0.1 mol%	heptanes	80	85	>95 : 5	79
9	0.01 mol%	heptanes	80	75	>95 : 5	79

[a] Isolated yields of **57**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Allyl Alcohol Scope. The next series of experiments explored the general scope of the reaction with respect to allyl alcohols (**58**–**65**) bearing a 3,3′-dimethyl moiety (Table 3.2). The steric tolerance of the reaction was probed through substrates with various linear and branched alkyl chains (row 1, columns 1–3). All of the simple aliphatic substituents examined (alcohols **58–60**) proved efficient substrates for the transformation, affording the cyclopentanes (**66–68**, respectively) in good yield and diastereoselectivity, and uniformly moderate enantioselectivity. A benzyl substituent at the carbinol was also tolerated; although the yield suffered slightly for the reaction of alcohol **61**, the corresponding cyclopentane (**69**) was formed in good enantiomeric excess (42% yield, >95 : 5 dr, 87% ee). Alcohols bearing a functionalized R-group substituent, including an olefin, ketal, silyl ether, and silane (row 2, columns 1–4; **62–65**, respectively) were all compatible, indicative of the diverse functionalization one could install at the C(3)-position of the cyclopentane product. For alcohol **62**, cyclopropanation of the monosubstituted alkene was a non-competitive process and the C(3)-allylated cyclopentane (**70**) was isolated in excellent yield and good stereoselection (86% yield, >95 : 5 dr, 76% ee). In the case of a ketal-containg alcohol **63**, the product was obtained as deprotected ketone **71** upon exposure to scandium(III) triflate, due to the acidic reaction medium. The overall yield of 41% for the cascade reaction and an additional deprotection is, nonetheless, impressive in conjunction with the excellent 90% ee with which the product is formed. Similarly, under the prescribed conditions, the silyl ether moiety of alcohol **64** underwent deprotection and subsequent side reactions upon exposure to scandium(III)

triflate. By increasing the reaction temperature to 98 °C after the 20 h period, however, the corresponding cyclopentane **72** was obtained in excellent yield in the absence of Lewis acid catalyst (65% yield, >95 : 5 dr, 78% ee). The silane-substituted alcohol (**65**) enabled synthesis of C(3) (trimethylsilyl)methyl-substituted cyclopentane **73** in moderate yield and good stereoselection (59% yield, >95 : 5 dr, 84% ee).

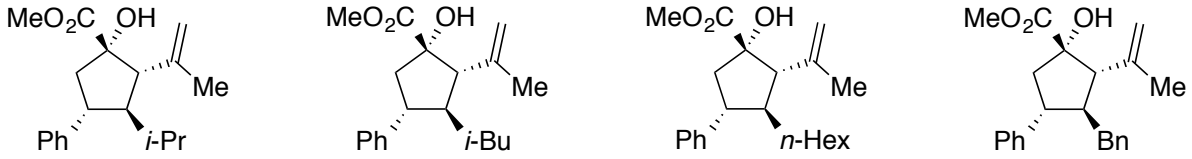
Table 3.2[a–c] Scope of allyl alcohol for the one-pot cyclopentane synthesis



51
1.2 equiv

58, R=*i*-Pr
59, R=*i*-Bu
60, R=*n*-Hex
61, R=Bn
62, R=allyl
63, R=$CH_2CH_2C(OCH_2)_2Me$
64, R=CH_2OTBS
65, R=CH_2TMS

66, R=*i*-Pr
67, R=*i*-Bu
68, R=*n*-Hex
69, R=Bn
70, R=allyl
71, R=CH_2CH_2COMe
72, R=CH_2OTBS
73, R=CH_2TMS

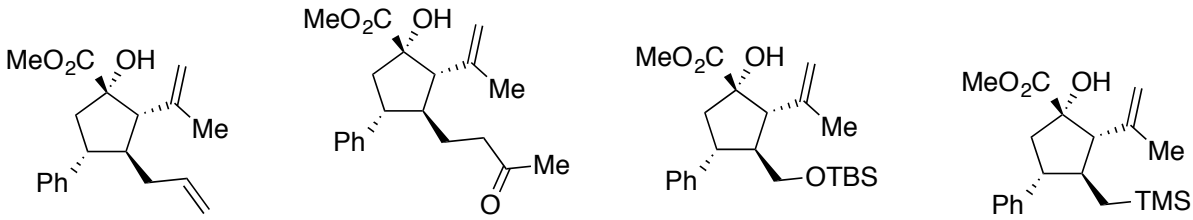


66
67% yield
>95 : 5 dr
80% ee

67
73% yield
>95 : 5 dr
80% ee

68
80% yield
>95 : 5 dr
78% ee

69
42% yield
>95 : 5 dr
87% ee



70
86% yield
>95 : 5 dr
76% ee

71
45% yield
>95 : 5 dr
90% ee

72[d]
65% yield
>95 : 5 dr
78% ee

73
59% yield
>95 : 5 dr
84% ee

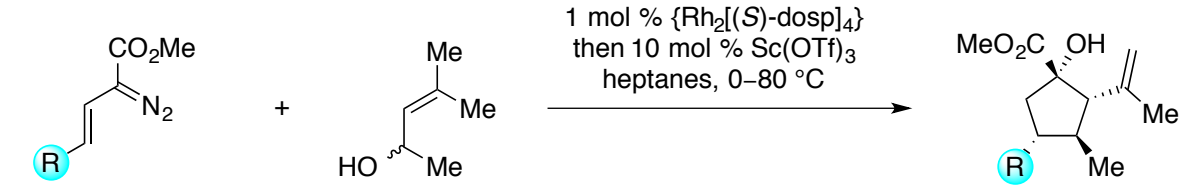
[a] Isolated yields of **66**–**73**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a

chiral stationary phase. [d] Reaction was conducted in the absence of scandium(III) triflate at 100 °C for 24 h.

Vinyldiazoacetate Scope. The reaction of various substituted vinyldiazoacetates (**74**–**77**) was then explored, which introduced different functionality at the C(4)-position of the cyclopentane products (Table 3.3, **78**–**81**). The electronic effect of substituents at the *para*-position of the aryl ring was first probed (row 1, columns 1–3; **74**–**76**). A 4-trifluoromethyl group (**74**) had a measurable detriment on the reaction efficacy as cyclopentane **78** was isolated in moderate yield (63% yield, >95 : 5 dr, 78% ee). The best result was obtained for the electron-rich 4-methoxy group of diazoacetate **75**. The corresponding cyclopentane (**79**) was isolated in excellent yield and good stereoselectivity (94% yield, >95 : 5 dr, 87% ee). As with diazoacetate **74**, the mild inductive withdrawing effect of a 4-bromo substituent (**76**) on the arene had an apparent detriment on the overall yield of the reaction cascade. The relatively low yield for reaction with **76** was attributed to competing O–H insertion versus the [2,3]-sigmatropic rearrangement as evidenced by a diagnostic singlet at 4.92 ppm in the crude ^{1}H NMR; nevertheless, the enantioselectivity was quite high (**80**, 48% yield, >95 : 5 dr, 92% ee).[74] The *E*-methyl hexenoate-derived diazoacetate **77** (entry 4) was also an efficient substrate; however, the enantiomeric excess of the corresponding cyclopentane **81** was modest, which was ostensibly attributed to a less stereoselective [2,3]-sigmatropic rearrangement with further degradation during the oxy-Cope rearrangement (63% yield, >95 : 5 dr, 64% ee). The absolute configuration of cyclopentane **80** was determined by X-ray crystallographic analysis. Since similar transitions states are presumed to be involved in the formation of **57**, **66–73**, **78–79**, and **81**, the absolute configuration of those products was assigned by analogy. The relative and absolute configuration of **80** was determined by X-ray crys-

tallographic analysis, and has been submitted to the Cambridge Crystallographic Data Centre under deposition number CCDC 827544. The absolute configuration of the entire series of cyclopentane products was then assigned by analogy.

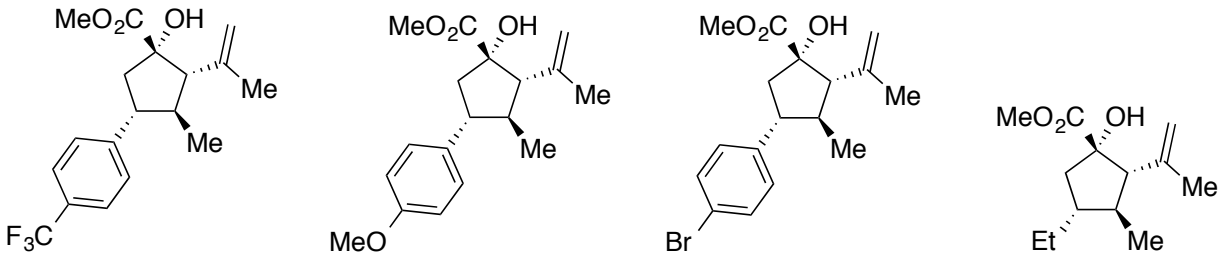
Table 3.3[a–c] Scope of diazoacetate for the one-pot cyclopentane synthesis



74, R=4-$CF_3C_6H_4$
75, R=4-$MeOC_6H_4$
76, R=4-BrC_6H_4
77, R=Et
1.2 equiv

52

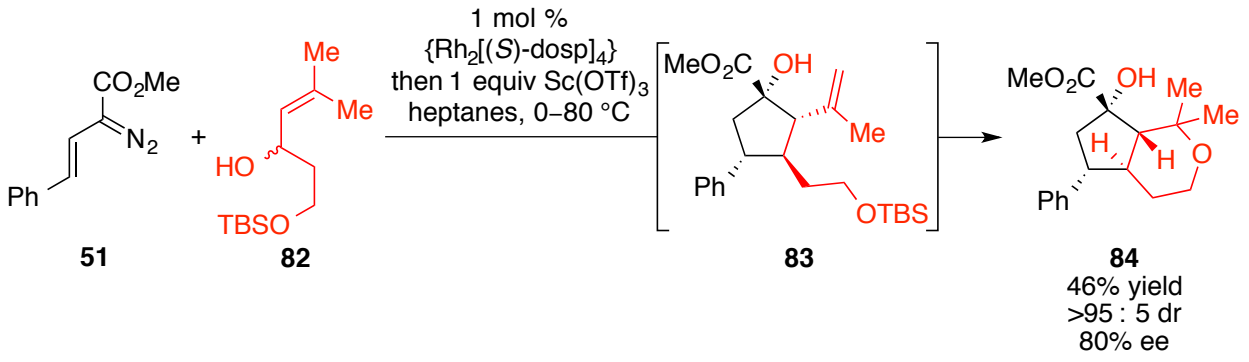
78, R=4-$CF_3C_6H_4$
79, R=4-$MeOC_6H_4$
80, R=4-BrC_6H_4
81, R=Et



78	**79**	**80**	**81**
63% yield	94% yield	48% yield	63% yield
>95 : 5 dr	>95 : 5 dr	>95 : 5 dr	>95 : 5 dr
78% ee	87% ee	92% ee	64% ee

[a] Isolated yields of **78–81**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by chiral HPLC analysis.

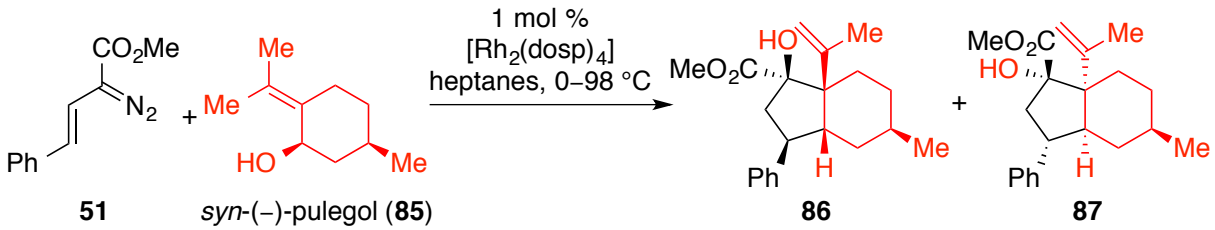
Synthesis of Bicyclic Products. Judicious selection of the reaction partners enabled the domino sequence to be elaborated upon through more inventive manifolds than simple deprotection as in the case of **71**. Two additional steps were achieved when mono-silylated-1,3-diol **82** was selected as substrate (Scheme 3.11). When the standard reaction was conducted, with an increased loading of scandium(III) triflate in refluxing heptanes, the anticipated cyclopentane product **83** was neither isolated nor observed. Rather, the *trans*-fused pyran **84** was isolated in good yield and stereoselection (46% yield, >95 : 5 dr, 80% ee). The formation of **84** was rationalized by silyl deprotection, followed by alkene oxidation *via* a *6-exo-trig* cyclization. The relative configuration of the *trans*-fused cyclopentylpyran ring system (**84**) was determined by X-ray crystallographic analysis and the absolute configuration was assigned by analogy to **80**. The X-ray data for compound **84** has been submitted to the Cambridge Crystallographic Data Centre under deposition number CCDC 827545.



Scheme 3.11 Extended domino sequene for the synthesis of a fused pyran

The synthetic utility of the domino sequence was showcased in the reaction with a readily available diterpenoid alcohol, *syn*-(–)-pulegol (**85**). Formation of two diastereomeric hydrindane products **86** and **87** is conceivable; each containing five stereogenic centers, two of which are quaternary. We have previously demonstrated that the diastereoselectivity of the ylide formation/[2,3]-sigmatropic rearrangement with (–)-pulegol (**85**) is controlled by the chiral catalyst, with $\{Rh_2[(R)\text{-dosp}]_4\}$ as catalyst furnishing a 90 : 10 diastereomeric mixture (**86** : **87**) and $\{Rh_2[(S)\text{-dosp}]_4\}$ providing a 18 : 82 diastereomeric ratio (**86** : **87**), favoring the other diastereomer.[74] Similarly, the enantiomers of the catalyst show distinct levels of diastereocontrol in the domino sequence. For the $\{Rh_2[(R)\text{-dosp}]_4\}$-catalyzed reaction between **51** and **85**, the diastereomer **86** of the hydrindane alone was formed in 69% yield. By contrast, the $\{Rh_2[(S)\text{-dosp}]_4\}$-catalyzed reaction between **51** and **85** yielded a 32 : 68 mixture of the diastereomers **86** and **87**. The stereochemistry of **86** was determined by nOe analysis.

Table 3.4[a,b] Match/mismatch of allyl alcohol and catalyst chirality



51 *syn*-(–)-pulegol (**85**) **86** **87**

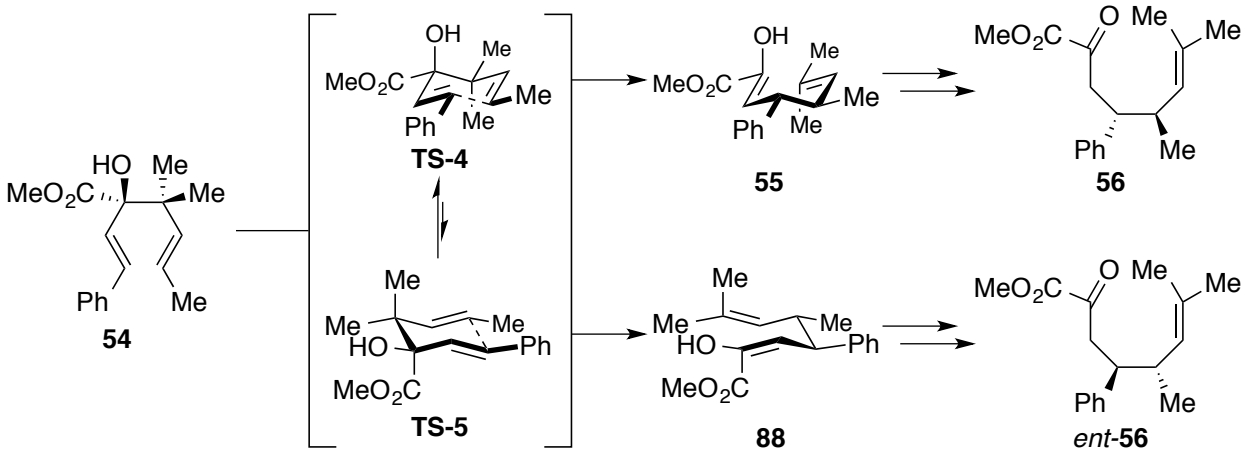
entry	$[Rh_2(dosp)_4]$	yield, %	dr (**86** : **87**)
1	$\{Rh_2[(R)\text{-dosp}]_4\}$	69	>95 : 5
2	$\{Rh_2[(S)\text{-dosp}]_4\}$	57	32 : 68

[a] Combined isolated yields of **86** and **87**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue.

Stereochemical Rationale. One of the most significant features of the domino sequence for the synthesis of congested cyclopentanes is the high level of diastereocontrol consistently achieved in the cascade. Four new stereogenic centers are generated and the monocyclic products are produced as single diastereomers with 64–92% ee. The enantiomeric purity of the cyclopentanes is routinely inferior when compared to that of the initial [2,3]-sigmatropic rearrangement products. The enantioselectivity of the tandem ylide formation/[2,3]-sigmatropic rearrangement for the majority of allyl alcohols used in the cyclopentane study was already established.[74] The stereoselective nature of the oxy-Cope, and especially the anionic oxy-Cope, has been documented in detail by Evans, Paquette, and others.[82–85,87] In the absence of substantial 1,3-diaxial interac-

tions, the reaction characteristically proceeds *via* a chair-like transition state.[87] Two additional stereogenic centers are generated during the hetero-ene reaction, in which the preferred relative stereochemistry is presumably controlled by the preexisting stereocenters.

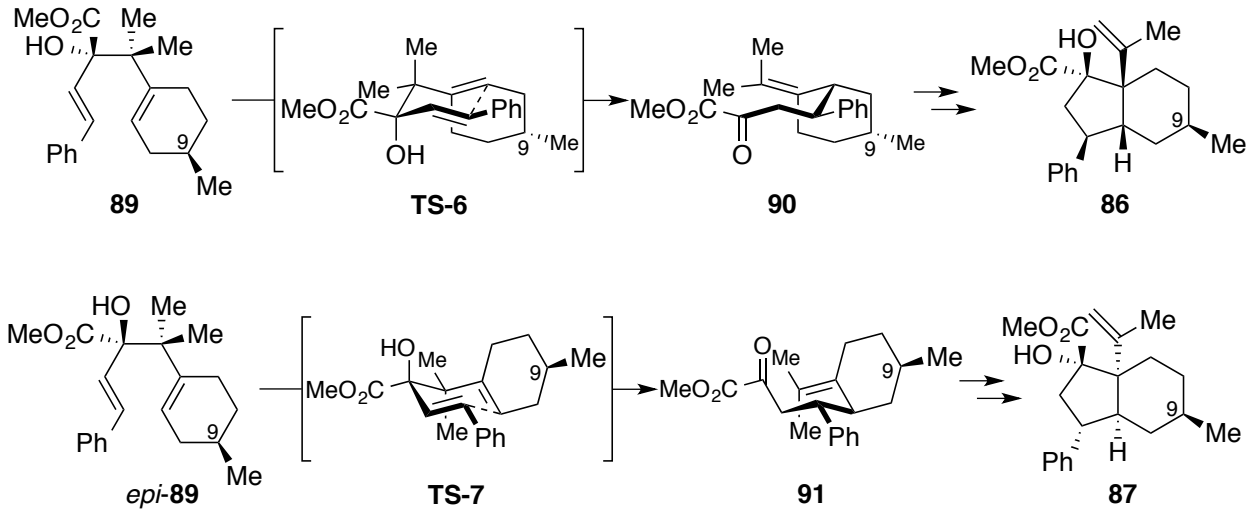
From the preliminary investigations presented in Scheme 3.10, it is clear that the degradation of enantiomeric purity occurs during the oxy-Cope rearrangement. We rationalized the detrimental effect on optical purity by considering the two possible chair-like transition states (**TS-4** and **TS-5**) involved during the [3,3]-rearrangement portrayed in Scheme 3.12. Enantiocontrol will depend on the axial/equatorial preference of the hydroxyl or the carbomethoxy groups. The cyclohexane *A*–values of the hydroxyl and carbomethoxy substituents are 0.60 and 1.25 kcal mol^{-1}, respectively.[88] Determining the actual energy difference between two chair-like transition states with geminal disubstitution is more complex than simply taking the difference in *A* values of each substituent.[89] However, **TS-4**, with the hydroxyl group in an axial position is expected to be favored to some degree, leading ultimately to formation of ketoester **56** as the predominant product. The energy difference between **TS-4** and **TS-5**, however, is likely insufficient to preclude [3,3]-sigmatropic rearrangement *via* **TS-5**. The latter reaction pathway generates the opposite enantiomer of the α-ketoester (*ent*-**56**), but provides the same relative configuration of the product.



Scheme 3.12 Chirality transfer for the oxy-Cope rearrangement

As for the reaction with *syn*-(–)-pulegol (**85**), the major diastereomer produced in the {Rh_2[(*R*)-dosp]$_4$}-catalyzed reaction with **51** has been shown to be the [2,3]-sigmatropic rearrangement product **89**.[74] Compound **89** is optimally configured to undergo a stereoselective oxy-Cope rearrangement as illustrated in Scheme 3.13. In the chair-like transition state (**TS-6**), the less sterically demanding hydroxyl group has adopted an axial position and the remote C(9)-methyl group is oriented away from the site of carbon–carbon bond formation, thereby minimizing any unfavorable steric interactions. Transition state **TS-6** leads to the formation of a ketoester intermediate with a stereochemical configuration that is consistent for the observed hydrindane diastereomer **86**. In the case of the major diastereomer of the [2,3]-sigmatropic rearrangement product from the {Rh_2[(*S*)-dosp]$_4$}-catalyzed reaction, we considered the pathway leading to the modestly preffered diastereoisomer **87**. Again rendering the known [2,3]-sigmatropic rearrangement product (*epi*-**89**) into a chair-like geometry provides transition state **TS-7**. As with **TS-6**, the reaction intermediate is believed to involved equatorial position of the carbomethoxy substituent. In the case of **TS-7**, this results in orienting the C(9)-methyl group

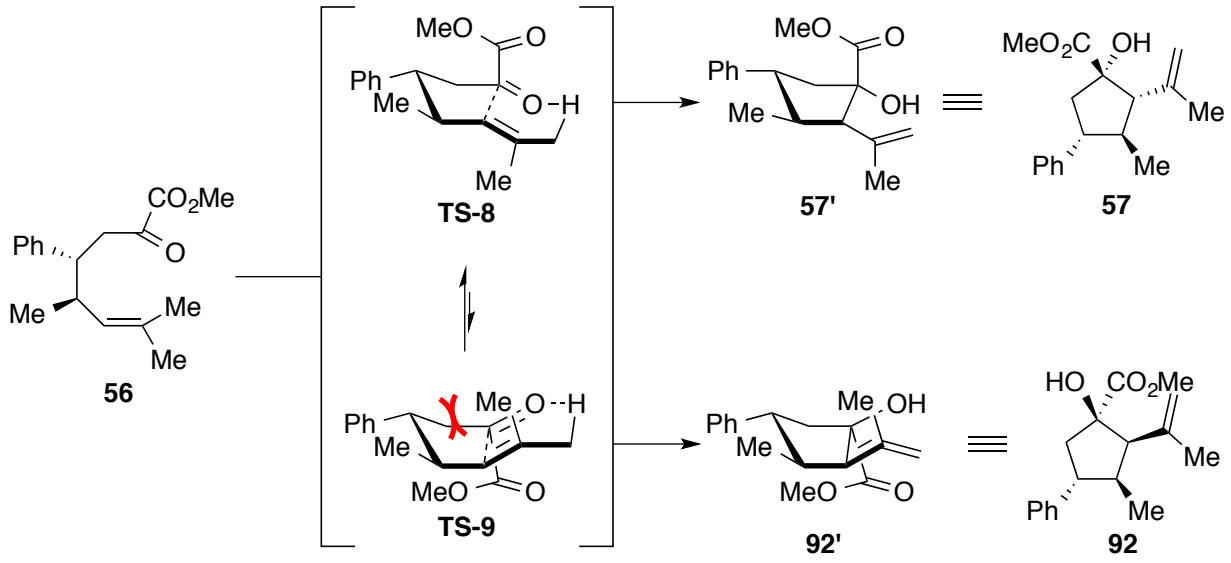
onto the same face of the cyclohexene as the carbon–carbon bond forming event. Thus, a competing chair-like transition state intermediate is presumed to be operative which would provide inversion in the configuration of the two newly formed stereocenters; thereby leading to partial formation of **86** in addition to the major diastereomer **87**.



Scheme 3.13 Matched and mismatched oxy-Cope diastereomers

Next, the exquisite diastereocontrol observed for the carbonyl ene reaction was taken into consideration (Scheme 3.14). The stereoelectronic requirement for transposition of the ene and enophile during an ene reaction limits the viable transition states to the two possible boat-like geometries (**TS-8** and **TS-9**). Previous intramolecular hetero-ene reactions of α-keto esters implicate the Lewis acid in forming a five-membered metal-chelate with the two carbonyl oxygens.[81] Accordingly, in the transition state, they would be expected to be oriented in the *syn*-coplanar geometry shown in Scheme 3.14; however, the $Sc(OTf)_3$ has been omitted for clarity as

the dipole alignment is inconsequential for the stereochemical outcome. The envelope-like portion of the ensuing cyclopentane is drawn with the largest substituent, the phenyl group, occupying a pseudo-equatorial position of the "flap."[90] A dramatic preference for **TS-8** would be expected on the basis of strain minimization. Specifically, positioning of the ene and enophile *syn* facial to the methyl substituent would result in severe $A_{1,3}$–interactions with the vinyl methyl group of the ene. By orienting ene and enophile *antera* facial to the methyl group, analogous $A_{1,3}$–strain is altogether avoided. Thus, cyclization *via* **TS-8** leads to the observed diastereomer of cyclopentane **56**, whereas none of cyclopentane **92** arising from the competing transition state (**TS-9**) is observed.



Scheme 3.14 Plausible transition states for the carbonyl ene reaction

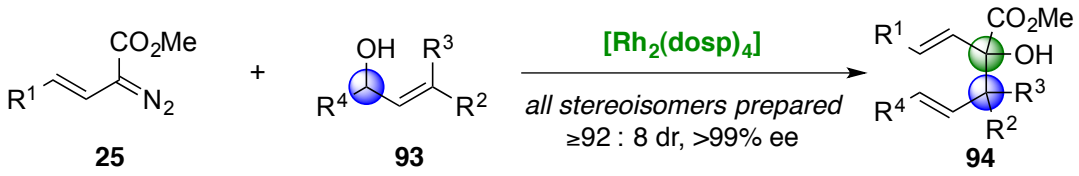
3.2.2 2nd Generation Cyclopentane Synthesis

Though we were pleased with the general efficacy with which a high degree of structural complexity was introduced from readily available building blocks, we sought to overcome the major limitations to the first generation cyclopentane synthesis described in Chapter 3.2.1. Central to our ensuing investigation was development of a general strategy for addressing the moderate enantioselectivity routinely observed in the domino reaction. In addition, by virtue of the 3,3´-dimethyl substituents on the alcohols used in the previous study, the C(2)-position of the cyclopentane products was limited to an *iso*-propenyl moiety.

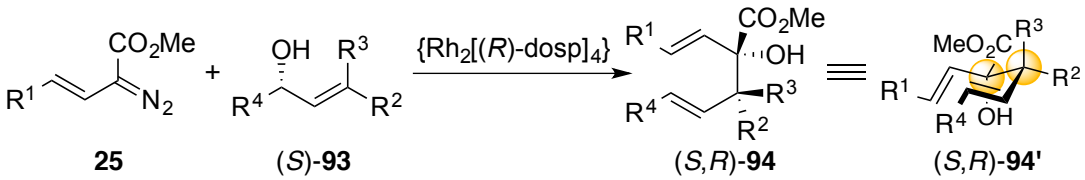
Having analyzed the reaction responsible for partial racemization in the cascade sequence (Scheme 3.10), we honed our efforts toward a general solution to the problematic step: the oxy-Cope rearrangement. On the basis of the hypothesis that competing chair-like transition states during the oxy-Cope rearrangement was the source of poor chirality transfer, we designed new systems that would suppress this equilibration and strongly favor one chair-like transition state over the other.

We envisioned that the tandem ylide formation/[2,3]-sigmatropic rearrangement of readily synthesized chiral allyl alcohols with donor/acceptor substituted rhodium carbenes described in Chapter 2.2.1 ought to provide a solution to both limitations.[91] For alcohols with variable substitution at C(3) (Scheme 3.15, **93**, $R^2 \neq R^3$), rearrangement products bearing vicinal stereocenters (**94**) were forged in exceptional enantiocontrol (>99% ee) and moderately high diastereocontrol (≥92 : 8 dr). Specifically, the rhodium catalyst dictated the configuration of the hydroxyester stereocenter (green sphere) while the allyl alcohol controlled the configuration of the second chiral center (blue sphere). Thus, we demonstrated that the appropriate combination of each

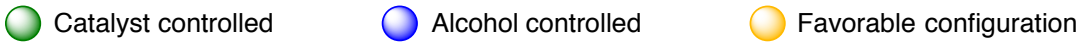
enantiomer of $[Rh_2(dosp)_4]$ and allyl alcohol **93** enabled the synthesis of all four diastereomers of **94**. Synthesis of the requisite configuration of a 3-hydroxy-1,5-hexadiene [(2*S*,3*R*)-**94**, $R^2 > R^3$] should exhibit dramatic preference for a single chair-like configuration, wherein both chiral centers would orient cooperatively [(2*S*,3*R*)-**94´**], with the substituents having larger cyclohexane *A*–values positioned equatorially.



(a) General overview of the tandem ylide formation/[2,3]-sigmatropic rearrangement with chiral allyl alcohols **93**



(b) Envisioned application of hexadienes **94** for stereoretentive oxy-Cope rearrangements



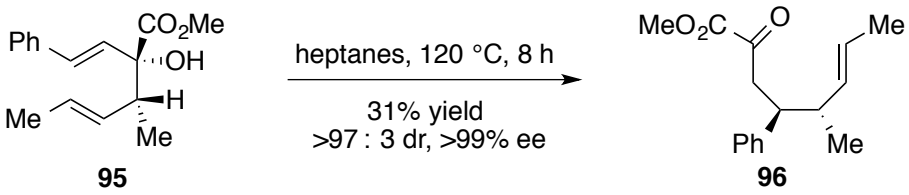
Scheme 3.15 Proposed approach to stabilization of a single chair-like intermediate

Our investigations into the modified cyclopentane synthesis began with a series of control reactions. First, the stereoisomerically pure 3-hydroxy-1,5-hexadiene **95** was heated as a heptanes

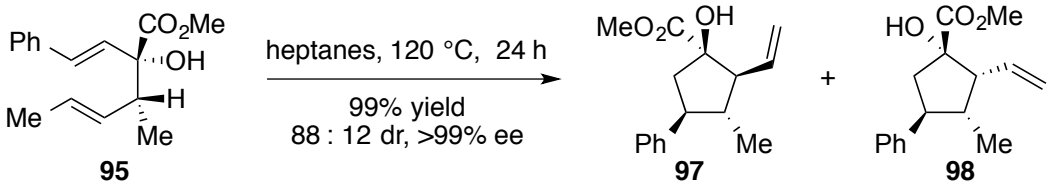
solution in a sealed tube for 12 h. Direct purification by flash chromatography afforded a small amount of α-ketoester **96** as a single stereoisomer (Scheme 3.16a). The modest isolated yield of **96** is attributed to a crude reaction mixture containing both the starting material (**95**), the ketoester (**96**), and the cyclopentane (**97**). Prolonged heating (20–24 h) of **95** furnished the desired cyclopentane **97** in excellent yield and with complete retention in the level of enantioselectivity, as shown in Scheme 3.16b. The product was, however, formed as an 88 : 12 (**97** : **98**) mixture of diastereomers. Having established that the ketoester **96** is formed as a single diastereomer, it appears that the carbonyl ene reaction to form **97** is lacking the exquisite diastereoselectivity that was previously observed for these substrates. Comparison with literature precedent[33,92] and our own analyses of the nuclear Overhauser effects in **97** and **98** are indicative of inversion in the configuration at the C(1)- and C(2)-stereocenters in the minor product (Figure 3.2).

In order for the oxy-Cope rearrangement to proceed with high enantiocontrol, the two chiral centers of the hexadiene must *cooperatively* reinforce a single chair-like transition state, as illustrated in Scheme 3.16a and b. In the negative control reaction with the diastereomeric material *epi*-**95**, the two chiral centers are orientated *competitively*, such that only the carbomethoxy *or* the methyl group can occupy an equatorial position in the two available chair-like forms (Scheme 3.16c). The reaction with *epi*-**95** demonstrated the detrimental effect on enantiocontrol, as the cyclopentane **97** was obtained with considerable racemization (39% ee) due to the competition between chair-like transition states. The identical diastereomeric ratio of product cyclopentanes (**97** : **98**, 88 : 12) observed for the matched and mismatched reactions (Schemes 3.16b and c, respectively) was again consistent with a problematic carbonyl ene reaction. These control studies affirmed the hypothesis that a second stereocenter could be manipulated for enan-

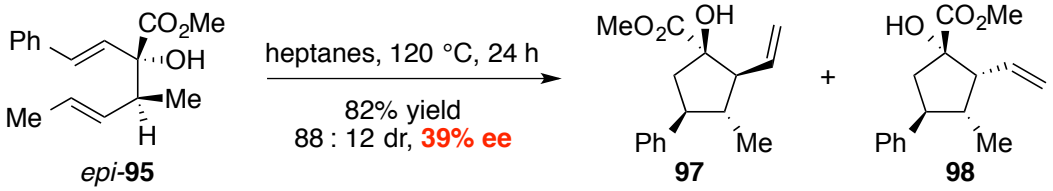
tiocontrol in the oxy-Cope rearrangement, but presented new problems with respect to the diastereoselectivity of the hetero-ene portion of the cascade.



(a) Matched reaction for the synthesis of α-ketoester **96**



(b) Matched reaction for the synthesis of cyclopentane **97**

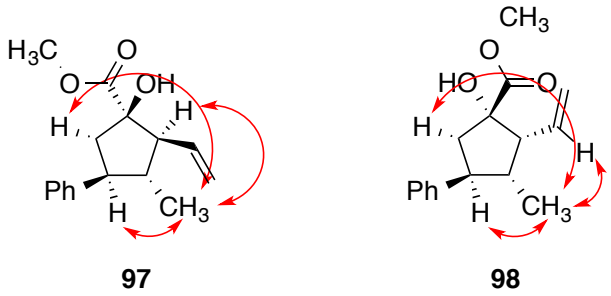


(c) Mismatched reaction for the synthesis of cyclopentane **97**

Scheme 3.16 Control studies for the oxy-Cope and carbonyl ene reactions

Although a nOe correlation between the hydroxy ester stereocenter and a remote proton of the molecule could note be identified, a carbonyl ene reaction, which requires *syn*-position of ene

and enophile, would furnish a cyclopentane with the vinyl and hydroxyl groups in a *syn* configuration. An analogous cyclopentane synthesis *via* intramolecular carbonyl ene reaction of an α-keto ester (Scheme 3.3) by Hiersemann and co-workers, generated mixtures of diastereomers with *syn* configured vinyl and hydroxyl substituents, which was established by nOe analysis.[33,92]

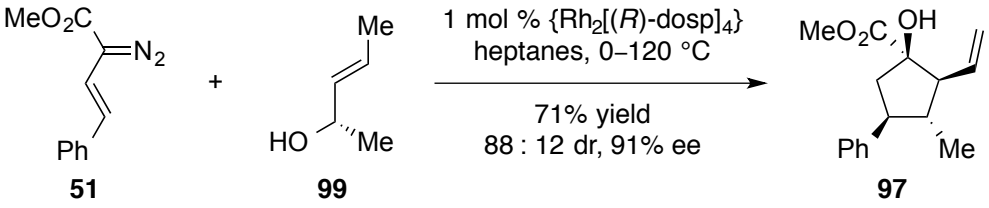


97 **98**

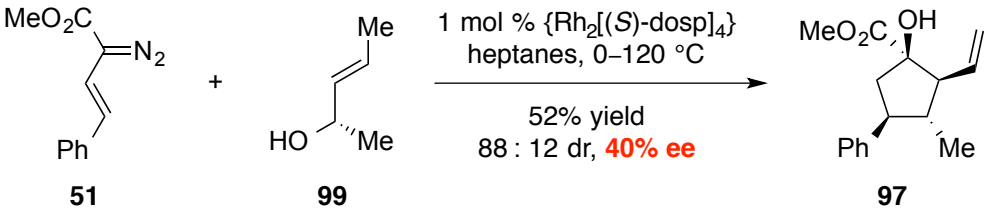
Figure 3.2 nOe correlations for cyclopentanes **97** and **98**

The control studies revealed that the rearrangement of hexadienol **95** to cyclopentane **97** could be achieved under thermal conditions without the use of scandium triflate as a Lewis acid catalyst. Therefore, modified conditions were developed for the one-pot process. {Rh_2[(*R*)-dosp]$_4$}-catalyzed reaction of vinyldiazoacetate **6** with the allyl alcohol **16** followed by heating of the crude mixture for 24 h afforded the desired product in a gratifying 71% yield of the major diastereomer (Scheme 3.17a). While the diastereomeric ratio for the one-pot process was identical to that for the control reaction shown in Scheme 3.16b, an unanticipated decrease in the level of enantioselectivity was observed in the matched reaction to form **97**. The enantiomeric excess was determined to be 91% ee, which was an improvement over the previous studies, but still not ideal. The one-pot mismatched reaction (Scheme 3.17b), conducted by implementing the oppo-

site enantiomer of catalyst {Rh_2[(*S*)-dosp]$_4$}, resulted in an overall less efficacious synthesis of **97**, as expected. The enantioselectivity of the transformation was on par with that observed during the tandem oxy-Cope/hetero-ene study (Scheme 3.16c).



(a) Matched reaction for the one-pot synthesis of cyclopentane **97**

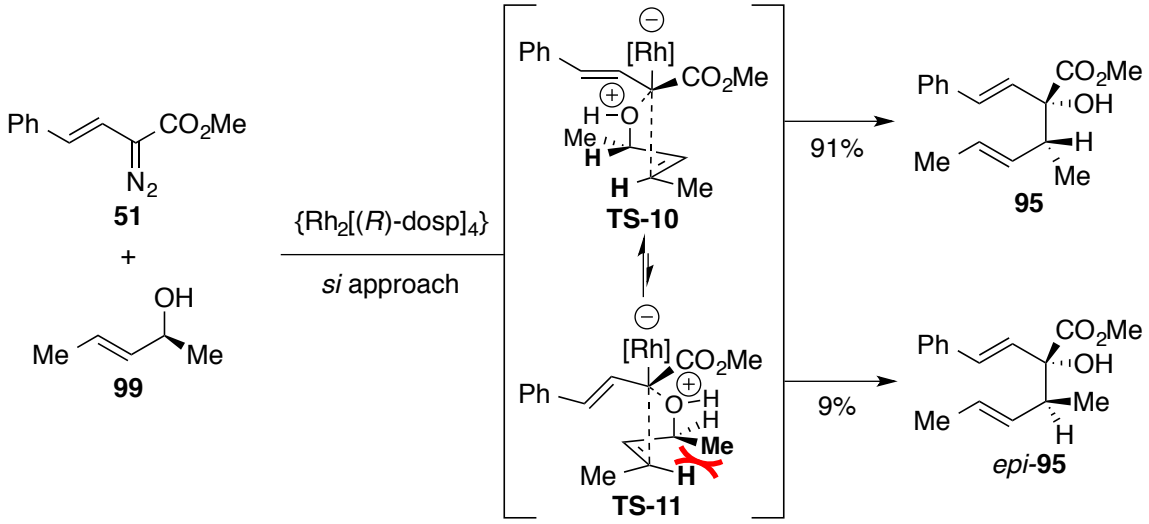


(b) Mismatched reaction for the one-pot synthesis of cyclopentane **97**

Scheme 3.17 One-pot control reactions

The discrepancy in enantioselectivity for the cyclopentane formation in the Cope/ene sequence (Scheme 3.16b) versus the complete one-pot sequence (Scheme 3.17a) is attributed to a minute diastereomeric "imperfection" occurring during the [2,3]-sigmatropic rearrangement (Scheme 3.18). In our previous study, we rationalized the driving force for diastereoselection in the ylide formation/[2,3]-rearrangement to be minimization of $A_{1,3}$–strain in the ylide intermediate. While the strain-minimized transition state (**TS-10**) is preferred, for the pentenol **99**, the

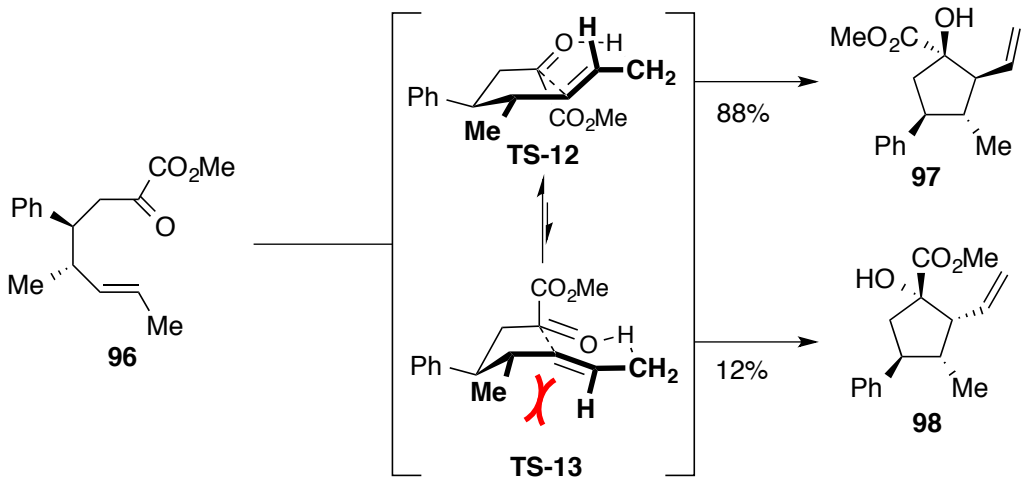
epimeric product (*epi*-**95**) is also formed (**95** : *epi*-**95** ratio, 92 : 8), because the strain formed between a *syn*-pentane methyl and hydrogen group in transition state (**TS-11**) is not prohibitively severe. According to the control study described in Scheme 3.16c, the minor [2,3]-product *epi*-**95** will contribute to formation of the enantiomer of **97**.



Scheme 3.18 Transition state analysis for the [2,3]-sigmatropic rearrangement

Another challenge evident with the second-generation reaction partners was the formation of diastereomers during the ene reactions. The modest diastereoselectivity achieved during this step can similarly be rationalized by a transition state analysis. Placing the ene and enophile components of **96** in a *syn* coplanar orientation to allow for requisite orbital overlap,[81,93–95] renders two feasible transition states (Scheme 3.19, **TS-12** and **TS-13**). As with the [2,3]-sigmatropic rearrangement, minimization of $A_{1,3}$–strain is a governing factor in the carbonyl ene reaction. Since the ene consists of a *trans*-1,2-disubstituted alkene, any $A_{1,3}$–strain originates

from interaction between the vinylic proton and the carbinol methyl group. Interestingly, a similar strain interaction occurring during the [2,3]-rearrangement (Scheme 3.18, 91 : 9 dr) and ene reactions produces similar levels of diastereoselectivity. Thus, while diastereomer **97**, arising from *5-exo-trig* cyclization *via* **TS-12** is preferred, some of product **98** originating from a slightly more strained transition state (**TS-13**) is competitively produced.

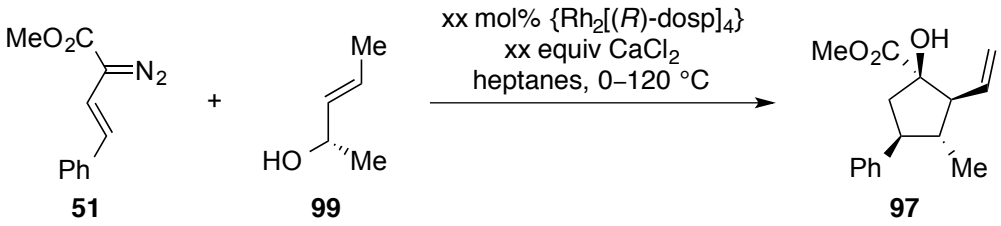


Scheme 3.19 Transition state analysis for the carbonyl ene reaction

As with our previous studies on the tandem ylide formation/[2,3]-sigmatropic rearrangement, we found that incorporating superstoichiometric quantities of calcium chloride had a beneficial effect on the reactivity. The results are summarized below in Table 3.5. A racemic sample of cyclopentane **97** for comparative HPLC analysis was obtained by conducting a reaction with **51** and racemic **99** under the catalytic action of an equimolar mixture of $\{Rh_2[(R)\text{-dosp}]_4\}$ and $\{Rh_2[(S)\text{-dosp}]_4\}$. The baseline one-pot reaction from Scheme 3.17a is recorded as entry 1 for comparison. Decreasing the catalyst loading to 0.1 mol% resulted in marked erosion in yield and

enantioselectivity, but unsurprisingly had no effect on the diastereoselectivity, in the formation of **97** (entry 2, 45% yield, 88 : 12 dr, 91% ee). Incorporating two equivalents of $CaCl_2$, however, enabled a ten-fold reduction in the loading of dirhodium tetracarboxylate catalyst without any obvious detriment to yield or asymmetric induction (entry 4, 67% yield, 89 : 11 dr, 92% ee). Moreover, cyclopentane **97** could be isolated in respectable yield, without significant detriment to stereoselectivity at a $\{Rh_2[(R)\text{-dosp}]_4\}$ loading of 0.01 mol% (entry 5, 51% yield, 87 : 13 dr, 90% ee). A further reduction in dirhodium tetracarboxylate loading to 0.001 mol%, however, was pernicious to reactivity (entry 6, 8% yield, 87 : 13 dr, 90% ee).

Table 3.5[a–c] Additive effect for the one-pot cyclopentane synthesis



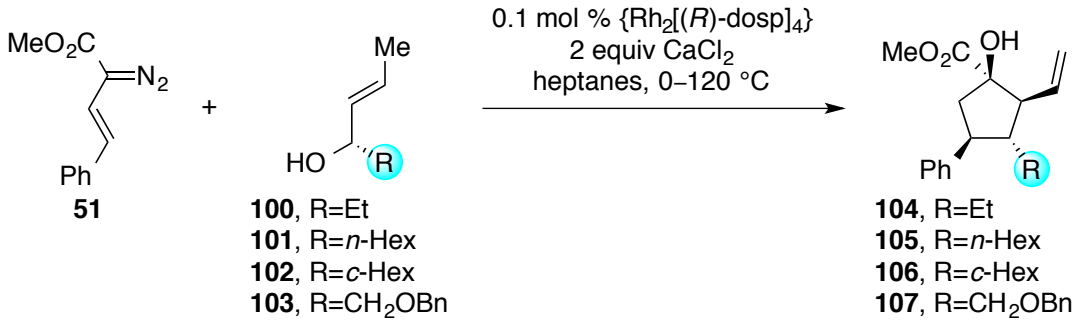
entry	$\{Rh_2[(R)\text{-dosp}]_4\}$	$CaCl_2$	yield, %	dr	ee, %
1	1.0	–	71	88 : 12	91
2	0.1	–	45	88 : 12	86
3	0.5	2.0	68	88 : 12	91
4	0.1	2.0	67	89 : 11	92
5	0.01	2.0	51	87 : 13	90
6	0.001	2.0	8	87 : 13	90

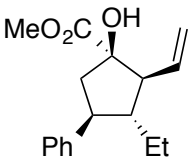
[a] Isolated yields of the major diastereomer **97**. [b] Diastereomeric ratio was determined by ^1H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

These studies affirmed both the feasibility of generating cyclopentanes in high levels of enantioselectivity *via* a one-pot process and the imperative matching of catalyst and alcohol chirality. We decided to investigate whether the reactivity we observed with the allyl alcohol **99** could be extended to other secondary allyl alcohols. The diazoacetate **51** was chosen as the standard carbene precursor as it has been studied extensively in tandem ylide formation/[2,3]-sigmatropic rearrangement chemistry.[74,91,96,97]

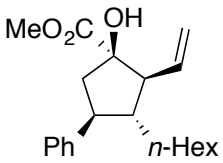
The first series of alcohols (**100–103**) examined, like those in our previous cyclopentane synthesis,[96] varied in carbinol substitution (Table 3.6). We envisioned that an increase in steric bulk at the carbinol (compared with **99**) could enhance the diastereoselectivity of the [2,3]-sigmatropic rearrangement; and therefore, the overall enantioselectivity of the cyclopentane synthesis. Increasing the length of the alkyl chain (entries 1 and 2, **100** and **101**, respectively) had no effect on the stereocontrol of the reaction to form cyclopentanes **104** and **105**, respectively. Introduction of more encumbered secondary carbon or benzylether substituents (entries 3 and 4, **102** and **103**, respectively) adjacent to the carbinol provided comparable yields and levels of enantioselectivity with a slight improvement in the levels of diastereoselectivity for cyclopentanes **106** and **107**, respectively.

Table 3.6[a–c] Effect of the carbinol substituent on the one-pot cyclopentane synthesis

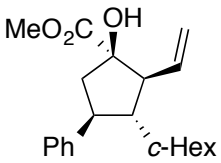




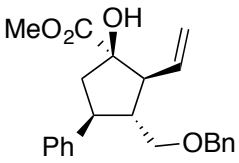
104
65% yield
89 : 11 dr
92% ee



105
71% yield
88 : 12 dr
92% ee



106
70% yield
92 : 8 dr
92% ee



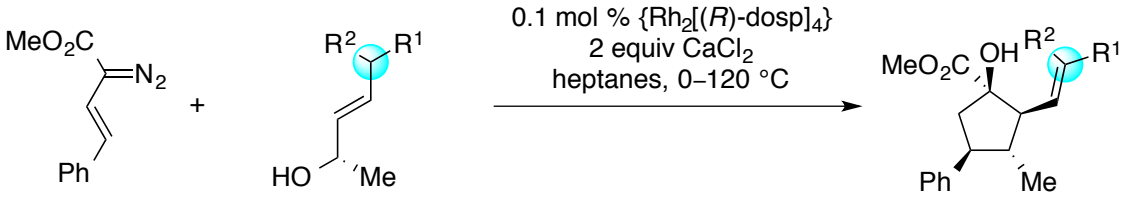
107
55% yield
93 : 7 dr
93% ee

[a] Isolated yields of the major diastereomer of **104**–**107**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

We then explored the effect of increasing the bulk of the alcohol C(3) substitituent, which participates in $A_{1,3}$–interactions during the [2,3]-sigmatropic rearrangement. A modest improvement in enantioselectivity was observed when a C(3)-Me substituent (Scheme 3.17a, **97**) was replaced by an *iso*propyl moiety (Table 3.7, entry 1, **19a**, $R^1 = R^2 = Me$). The diastereoselectivity, however, was similar to that observed for the previous class of allyl alcohols (Table 3.6). For alcohols where R^1 and R^2 were not equivalent, an added element of complexity in the

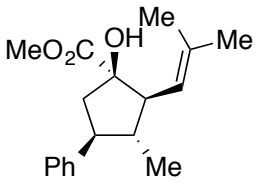
form of olefin geometry was introduced (entries 2–4, **109**–**111**). In these cases, the major diastereomer of the cyclopentane was isolated as a mixture of (*E*)- and (*Z*)-isomers, which, for purposes of characterization, could be separated by a second chromatographic purification on silver nitrate impregnated silica gel. The yields and levels of stereoselectivity were fairly consistent throughout the group; however, (*E*)-selective alkene formation was correlated with the size of R^1. Specifically, linear alkyl chains (**109** and **110**) provided comparable ratios of *E*- and *Z*-diastereomers (entries 2 and 3, *ca*. 3 : 1, *E* : *Z*), but a benzyl substituent afforded cyclopentane (*E*)-**115** in >7 : 1 *E*/*Z* mixture.

Table 3.7[a–d] Effect of the C(3)-substituent on the one-pot cyclopentane synthesis

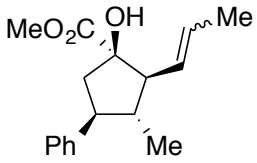


108, R^1=R^2=Me
109, R^1=Me, R^2=H
110, R^1=*n*-Bu, R^2=H
111, R^1=Ph, R^2=H

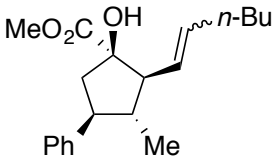
112, R^1=R^2=Me
113, R^1=Me, R^2=H
114, R^1=*n*-Bu, R^2=H
115, R^1=Ph, R^2=H



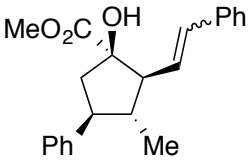
112
71% yield
91 : 9 dr
95% ee



113
65% yield
69 : 31, *E* : *Z*
85 : 15 dr
96% ee



114
67% yield
77 : 23, *E* : *Z*
90 : 10 dr
94% ee

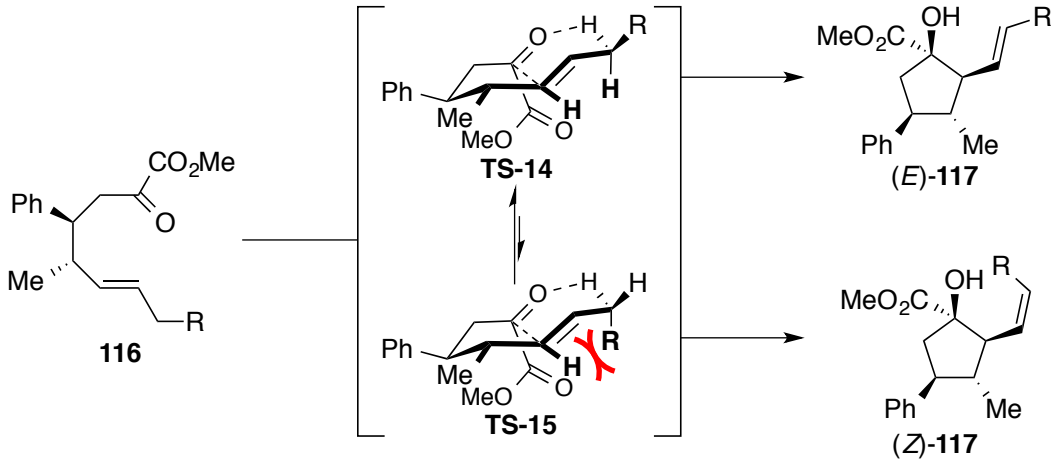


115
80% yield
88 : 12, *E* : *Z*
90 : 10 dr
95% ee

[a] Isolated yields of a mixture of (*E*)- and (*Z*)-isomers of **112**–**115**. [b] Ratio of (*E*)- and (*Z*)-isomers was determined by ^{1}H NMR. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [d] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

The modest preference for the formation of the *E*-isomers of **112**–**115** is consistent with the transition state model presented for the ene reaction of α-ketoester **116** to form generic cyclopentane **117**, illustrated in Scheme 3.20. Minimization of $A_{1,3}$–interactions across the eneophile portion of the molecule dictates the major reaction pathway. By rotating the methylene carbon of the ene fragment (Scheme 3.20, **TS-14** vs. **TS-15**), the allylic R-group would be positioned either

anti or *gauche* to the vinylic proton. The less strained *anti*-intermediate (**TS-14**) would give rise to cyclopentane (*E*)-**117**, and the less preferred *gauche*-intermediate (**TS-115**) would provide (*Z*)-**117**.

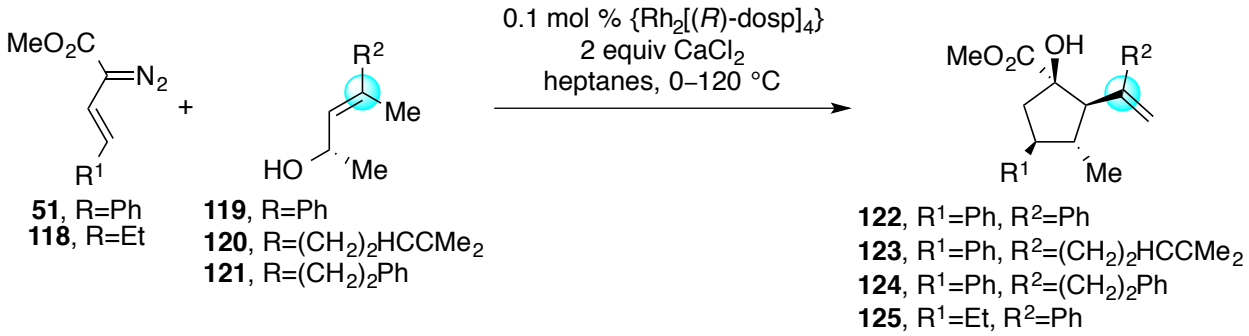


Scheme 3.20 Transition state rationale for the formation of (*E*)- and (*Z*)-substituted cyclopentanes

On the basis of the experimental observations and the transition state analysis, it became apparent that a highly stereoselective entry to cyclopentanes would require effective control of chair transition states in the oxy-Cope rearrangement *and* maximization of the $A_{1,3}$–strain control elements during the [2,3]-sigmatropic rearrangement and the ene reaction. Therefore, we examined a series of alcohols **119**–**121** bearing geminal disubstitution at the C(3) position (Table 3.8). One of the substituents was methyl to help maximize chair selectivity in the oxy-Cope rearrangement and to minimize the formation of olefin regioisomers in the ene reaction by exploiting kinetic control. The desired chiral alcohols were readily prepared from commercially available

enals or by means of carbometallation[91,98,99] of the requisite alkynes and trapping with acetaldehyde. The results of the cyclopentane formation from **119**–**121** are described in Table 3.8. In each case the reaction proceeds in high yield (85–89%) and with excellent levels of stereoselectivity. The cyclopentanes **122**–**125** were formed in >95 : 5 dr and 99% ee. The reaction is likely to be applicable to a range of vinyldiazoacetates as the alkyl-substituted vinyldiazoacetate (**118**, R = Et), was similarly effective in the net transformation. The absolute configuration of cyclopentane **122** was verified by X-ray crystallographic analysis and this assignment was applied to the other products by analogy. Moreover, the absolute configuration was consistent with the absolute and relative stereochemical assignments from our earlier studies. The X-ray data for compound **122** was submitted to the Cambridge Crystallographic Data Centre under deposition number 955223.

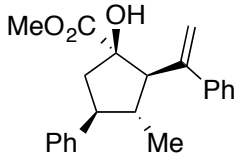
Table 3.8[a–c] Effect of the C(3)-substituent of trisubstituted allyl alcohols in the one-pot cyclopentane synthesis



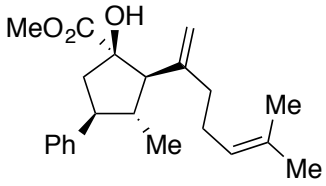
51, R=Ph
118, R=Et

119, R=Ph
120, R=$(CH_2)_2HCCMe_2$
121, R=$(CH_2)_2Ph$

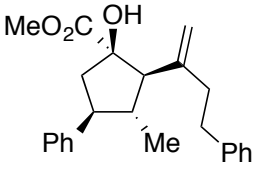
122, R^1=Ph, R^2=Ph
123, R^1=Ph, R^2=$(CH_2)_2HCCMe_2$
124, R^1=Ph, R^2=$(CH_2)_2Ph$
125, R^1=Et, R^2=Ph



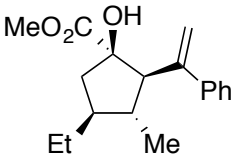
122
87% yield
>95 : 5 dr
99% ee



123
85% yield
>95 : 5 dr
99% ee



124
86% yield
>95 : 5 dr
99% ee

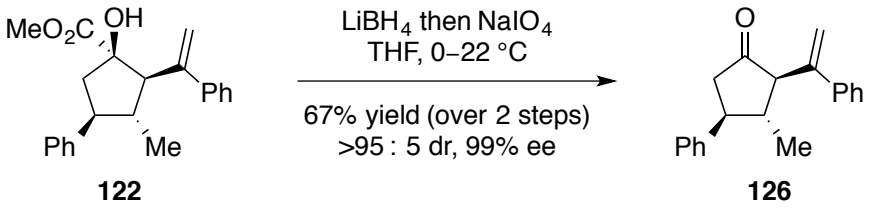


125
89% yield
>95 : 5 dr
99% ee

[a] Isolated yields of a single diastereomer of **122**–**125**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Although the cyclopentane bearing a quaternary hydroxy carbonyl stereocenter is a common structural motif among numerous polyterpenoid natural products (e.g. jatrophane diterpenoids **8** and **19**), we sought to demonstrate the ease with which the products could be converted to the corresponding cyclopentanones. To this end, reduction of cyclopentane carboxylate **122** to a 1,2-diol was affected by lithium borohydride (Scheme 3.21). Quenching with pH 7.0 buffer fol-

lowed by direct treatment of the crude reaction mixture with excess sodium periodate furnished cyclopentanone **126** in good yield with no observable epimerization of the α-stereocenter.



122 **126**

Scheme 3.21 Conversion of a cyclopentane carboxylate to a cyclopentanone

A detailed summary and analysis of the processes involved for stereoselective synthesis of (*R*,*R*,*R*,*S*)-**122** from a trisubstituted allyl alcohol (**119**) is presented in Scheme 3.22. The four discrete steps involved are the following: oxonium ylide formation (Step 1), [2,3]-sigmatropic rearrangement (Step 2), oxy-Cope rearrangement (Step 3), and carbonyl ene reaction (Step 4).

The reaction sequence commences with nucleophilic addition of **119** to the rhodium–bound carbene intermediate derived from diazoacetate **51**. A high degree of enantiocontrol is exerted by the rhodium catalyst, dictating *si* approach to the metallocarbene.[74,91,97] Thererfore, the analysis shown in Scheme 3.22 is limited to compounds which would be generated from *si* face attack. Due to the severe $A_{1,3}$–strain which develops between the allylic methyl substituents in **TS-16**, the reaction proceeds selectively through **TS-17**, affording the hexadiene diastereomer (*S*,*R*)-**128**. Rendering the reaction intermediate into a chair-like transition state produces **TS-20**, where the bulkiest substituents (CO_2Me and Ph) are configured in the equatorial positions. Proceeding through an oxy-Cope rearrangement with tandem enol–keto tautomerization provides the α-

ketoester (*S*,*S*,*E*)-**129**. As with the [2,3]-sigmatropic rearrangement, the driving force for diastereoselectivity in the carbonyl ene reaction is minimization of $A_{1,3}$–interactions. Thus, the transition state where the allylic methyl groups are oriented on opposite faces of the ensuing cyclopentane (**TS-26**) is the dominant pathway. The result is the formation of the observed stereoisomer of the cyclopentane (*R*,*R*,*R*,*S*)-**130**.

– Chapter 4 –

Triazoles as Alkenyl-Substituted Rhodium(II) Carbenes Precursors: Synthesis and Application

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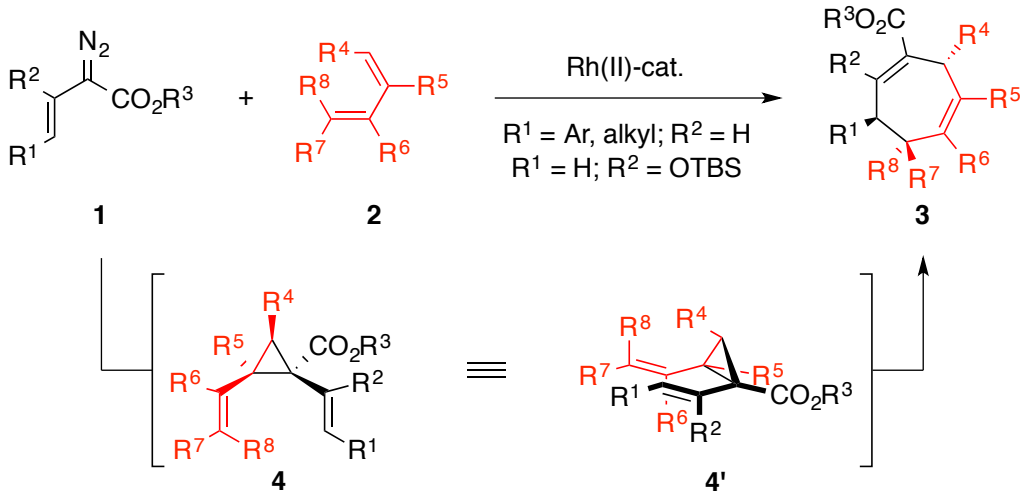
4.1 Introduction

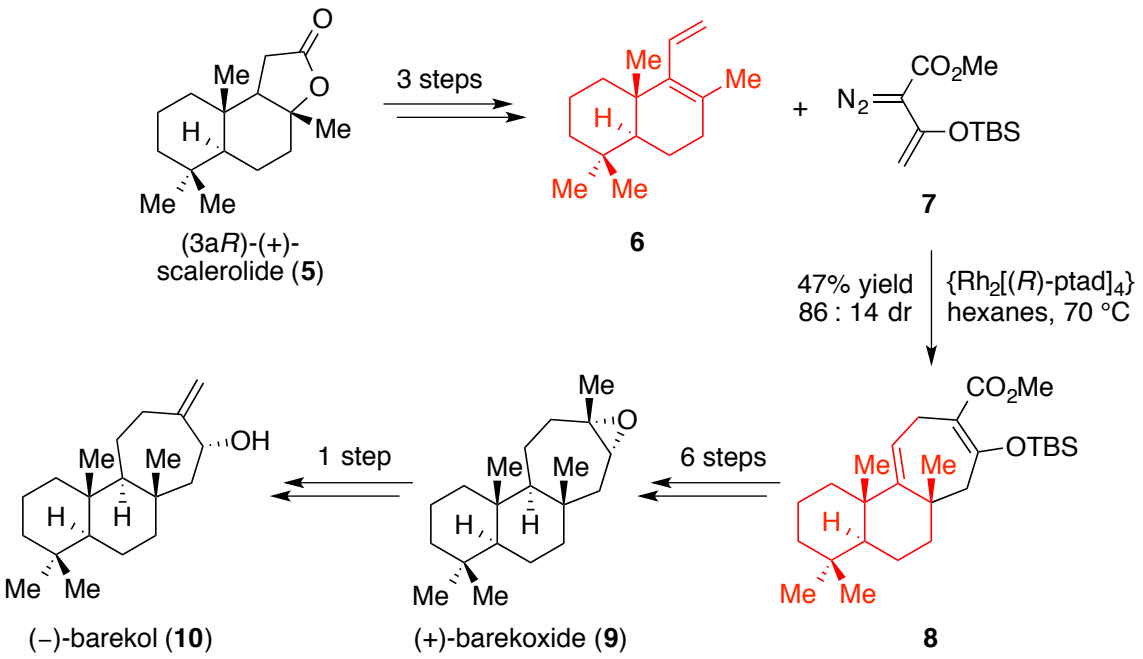
Transition metal-catalyzed decomposition of donor/acceptor substituted diazo compounds has played a central role in the maturation of modern metallocarbene chemistry.[1–5] The stabilization afforded by a π–donating substituent on the carbene enhances their selectivity, leading to a number of synthetically useful intermolecular transformations, such as enantioselective cyclopropanation[6,7] and C–H insertion.[8–10] Alkenyl substituents not only stabilize the carbene, but also participate in a number of novel tranformations.[11–16] One of the most versatile examples is the formal [4 + 3]-cycloaddition reaction shown in Scheme 4.1, which occurs *via* a tandem cyclopropanation/Cope rearrangement.[17–25] Due to the sensitivity of rhodium-bound carbene intermediates to steric factors, cyclopropanation generally occurs with complete and predictable selectivity for the least hindered alkene of a conjugated diene (**2**). Thus, the *cis* divinyl cyclopropane intermediate (**4**) is formed in high regiocontrol, and participates in facile [3,3]-sigmatropic rearrangement exclusively *via* a strain-allowed *endo* boat-like transition state (**4′**) to furnish the substituted cycloheptadiene (**3**). The partnership of chiral dirhodium tetracarboxylate catalysts with appropriate alkenyldiazoacetate (**1**) architectures renders the cyclopropanation, and thus the net

transformation, highly enantioselective. As such, the reaction has found broad application in the stereoslective total syntheses of complex natural products.[18–23]



Scheme 4.1 Overview of the tandem cyclopropanation/Cope rearrangement

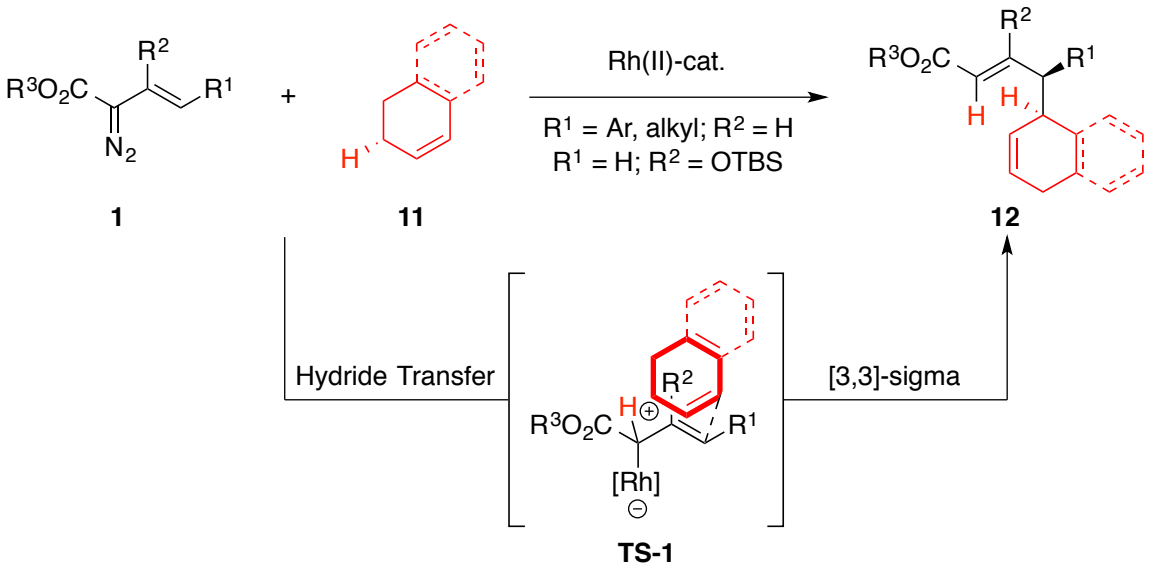
In the recent collaborative effort between Davies and Sarpong toward the enantioselective syntheses of (+)-barekoxide (**9**) and (–)-barekol (**10**), a stereodivergent [4 + 3]-cycloaddition of diene **6**, readily derived from sclareolide (**5**), served as a key transformation in construction of the carbocyclic cores, as shown in Scheme 4.2.[22,26] Thus, {Rh_2[(*R*)-ptad]$_4$} catalyzed decomposition of the siloxyvinyldiazoacetate (**7**) provided the desired diastereomer of cycloheptadiene **8** in high diastereoselectivity through resolution of the diene **6**. Noteably, an epimeric tricyclic relative to product **8** could be forged with equal efficieny by changing the enantiomer of dirhodium catalyst implemented in the carbene transformation.



Scheme 4.2 Application of the formal [4 + 3]-cycloaddition to the syntheses of (+)-barekoxide and (–)-barekol

Another valuable transformation of alkene-substituted rhodium carbene intermediates is the so-called combined C–H functionalization/Cope rearrangement (CHCR), which occurs for certain allylic C–H bonds (Scheme 4.3, **11**).[13,27,28] The scope and mechanism of the CHCR reaction has been studied in immense detail over the past decade. Computational studies implicate a reaction initiated by a hydride transfer event, generating an intimate ion pair (**TS-1**) consisting of an allyl cation and a rhodium-bound allyl anion.[29] A rapid C–C bond formation occurs, precluding any bond rotation, to generate a product (**12**) that is conceptually derived from a C–H insertion, which has been interrupted by a Cope rearrangement. A comparative computational and experimental study has indicated that cyclic allylic C–H bonds undergo the transformation with significant bias for a chair-like transition state, which translates to high diastereocontrol for the CHCR.

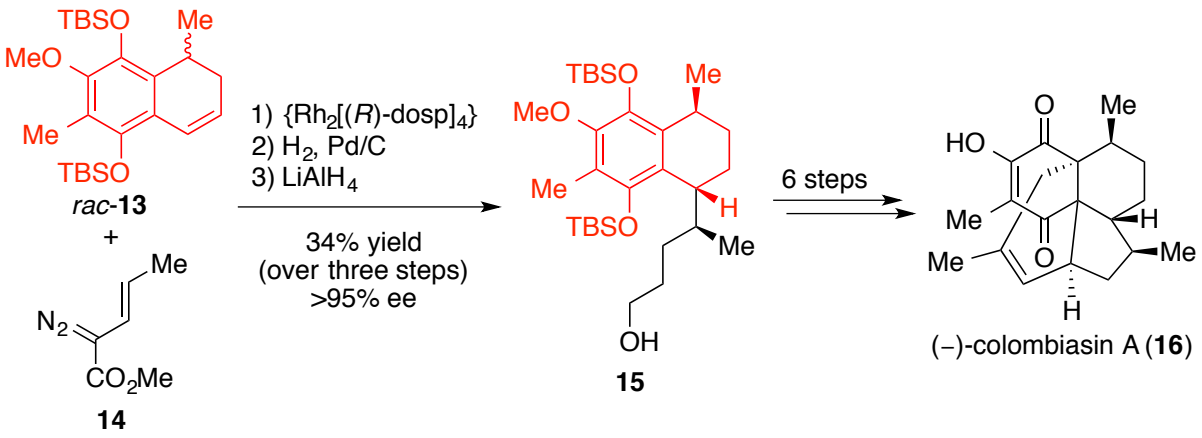
Dihydronapthalenes[30,31] and -indoles,[32] cyclohexenes[33] and cyclohexadienes[34] all proceed with exceptional levels of diastereo- and enantioselectivity (>97 : 3 dr, >97% ee).



Scheme 4.3 Overview of the combined C–H functionalization/Cope rearrangement

As with the formal [4 + 3]-cycloaddition, the CHCR reaction has been applied in the construction of challenging C–C bonds and installation of crucial stereocenters *en route* to a number of natural products.[35–37] The key strategy employed has been an enantiodivergent reaction with racemic dihydronaphthalenes, as demonstrated in the context of the total synthesis of (–)-colombiasin A (**16**) in Scheme 4.4. Reaction of racemic dihydronaphthelene **13** with diazoacetate **14** generates a CHCR product and a cyclopropane (not shown), each derived from different enantiomers of **13**. After hydrogenation and ester reduction, the tetrahydronapthalene derivative (**15**) was isolated in 34% overall yield as a single diastereomer and in >95% ee. In this process,

the three most challenging stereocenters in (–)-colombiasin A (**16**) were controlled in a single step.[36]

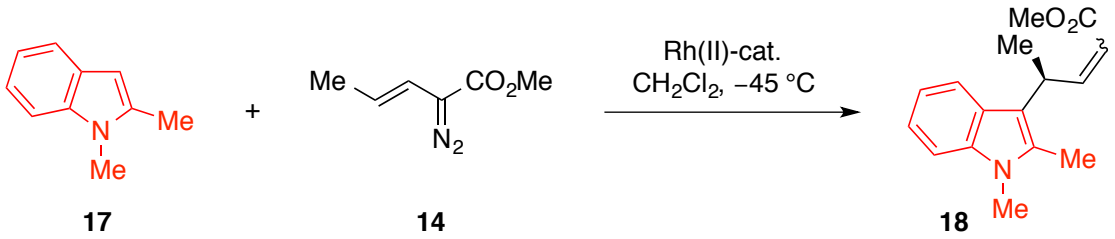


Scheme 4.4 Application of the CHCR reaction to the synthesis of (–)-columbiasin A

In both classes of rhodium vinylcarbene reactivity aforementioned (formal cycloaddition and C–H insertion), correlations between reaction efficacy and alkenyldiazoacetate architecture have been periodically noted. For example, the (*E*)-1,2-disubstituted alkenyldiazo compounds participate in highly enantioselective transformations when partnered with dirhodium tetracarboxylate catalysts bearing prolinate-derived ligands, such as {Rh_2[(*S*)-dosp]$_4$} and {Rh_2[(*S*)-bitisp]$_4$}. A study by Davies and co-workers explored the trap of the rhodium vinylcarbene derived from methyl diazopentenoate (**14**) by nitrogen-containing electron rich heterocycles, such as **17**, results in the enantioselective union of indole or pyrrole C(3) with the vinylogous carbon of the carbene to generate the C(3)-substituted heterocycle **18** (Table 4.1).[16,38] Of central importance, however, is the catalyst dependence in selective formation of the (*Z*)-olefin isomer of product **18**.

Although the steric environment of {Rh_2[(*S*)-ptad]$_4$} preferentially accommodates the diazo compound in a configuration leading to (*Z*)-**18**, the catalyst is not able to impart a significant degree of stereoselectivity (entry 5). On the other hand, {Rh_2[(*S*)-dosp]$_4$} exerts minimal preference on olefin geometry, but provides greater, albeit still modest, levels of enantioselectivity in formation of (*Z*)-**18** (entry 6). When the strapped tetraprolinate catalyst {Rh_2[(*S*)-bitisp]$_4$} is implemented in the reaction, however, a joint improvement in olefin selectivity and enantiomeric excess are observed (entry 7).

Table 4.1[a–c] Catalyst effect in the vinylogous addition of indoles to rhodium vinylcarbene intermediates



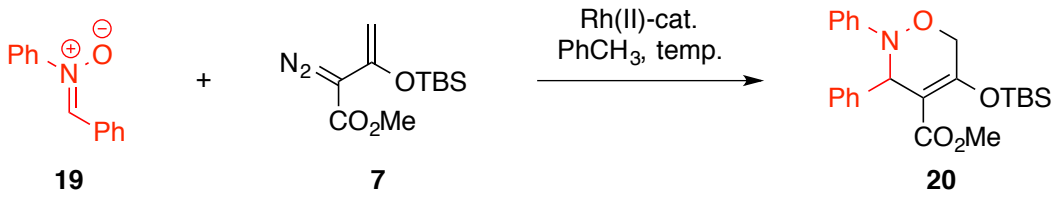
17 **14** **18**

entry	catalyst	ratio, *E* : *Z*	yield, %	ee, %
1	$[Rh_2(OAc)_4]$	65 : 35	57	–
2	$[Rh_2(TFA)_4]$	53 : 47	43	–
3	$[Rh_2(esp)_4]$	74 : 26	52	–
4	$\{Rh_2[(S)\text{-ptad}]_4\}$	83 : 17	55	–8
5	$\{Rh_2[(S)\text{-dosp}]_4\}$	41 : 59	22	17
6	$\{Rh_2[(S)\text{-tisp}]_4\}$	94 : 6	66	39
7	$\{Rh_2[(S)\text{-bitisp}]_4\}$	91 : 9	66	89

[a] *E* : *Z* ratio determined by ^{1}H NMR analysis of crude reaction residue. [b] Isolated yields of **18**. [c] Enantiomeric excess of (*Z*)-**18** was determined by HPLC analysis on a chiral stationary phase.

In a recent study by Doyle and co-workers, the enantioselective formal [3 + 3]-cycloaddition reaction of the siloxyvinyldiazoacetate (**7**) with various (*Z*)-nitrones (**19**) was developed (Table 4.2).[11] The oxazine (**20**) ring is formed with high chemoselectivity irrespective of the catalyst used; indicative of high preference for the (*Z*)-alkene geometry necessary for cyclization. Notably, enantioselectivity for the transformation is lacking entirely when a prolinate catalyst such as $\{Rh_2[(S)\text{-dosp}]_4\}$ is used (entry 2), whereas the various phthalamide protected amino acid catalysts all perform with moderate-to-good stereoselection (entries 3–7).

Table 4.2[a,b] Catalyst effect in the formal [3 + 3]-cycloaddition of nitrones and rhodium vinyl-carbene intermediates

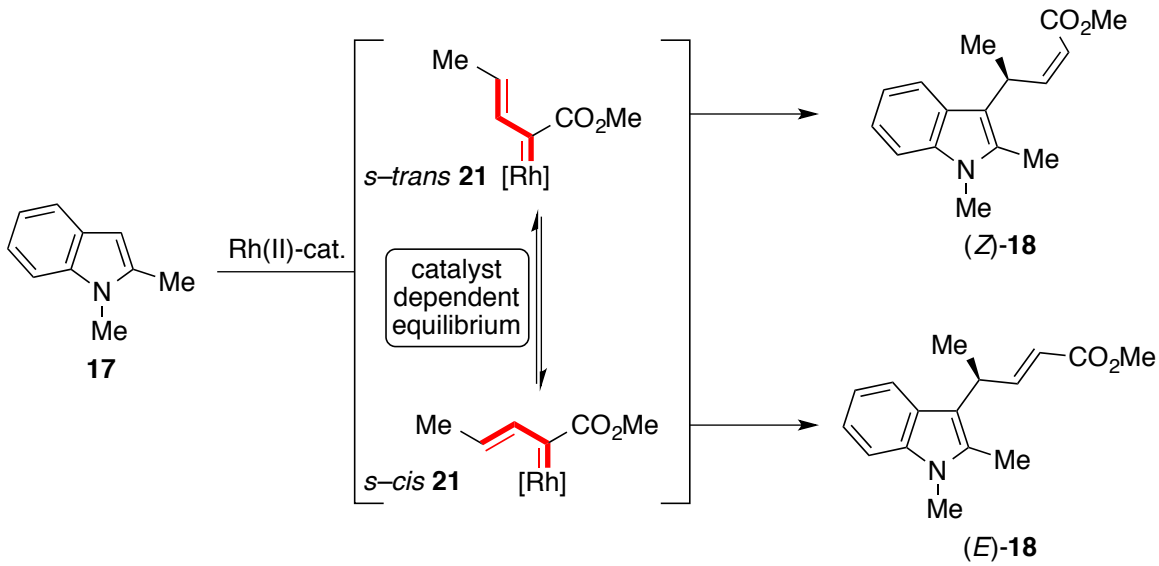


19 **7** **20**

entry	catalyst	temp., °C	yield, %	ee, %
1	$[Rh_2(OAc)_4]$	23	98	–
2	$\{Rh_2[(S)\text{-dosp}]_4\}$	23	80	0
3	$\{Rh_2[(S)\text{-ptpa}]_4\}$	23	98	70
4	$\{Rh_2[(S)\text{-ptpa}]_4\}$	−15	76	80
5	$\{Rh_2[(S)\text{-ptv}]_4\}$	−15	80	62
6	$\{Rh_2[(S)\text{-pttl}]_4\}$	−15	15	60
7	$\{Rh_2[(S)\text{-pta}]_4\}$	−15	85	87

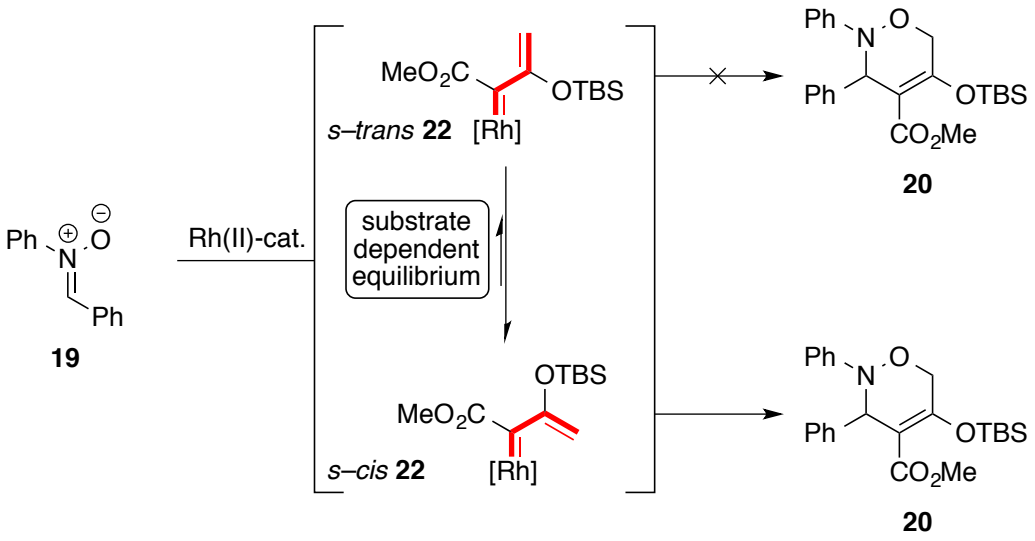
[a] Isolated yields of **20**. [b] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

These two studies provide a foundation for comparing the compatibility of dirhodium tetracarboxylates with different alkenyldiazoacetates. By comparing the geometries of the rhodium bound carbene intermediates in each of the two reactions described above, general hypotheses about the compatibility of diazoacetate architectures with families of rhodium catalysts can be made. The structure of the (*E*)-diazopentenoate **14** is such that, upon denitrogenative decomposition to the rhodium carbene (**21**), it can exist in either a *s–cis* or *s–trans* geometry (Scheme 4.5) without significant inherent bias, as evidenced by the poor (*E* : *Z*)-ratio observed in formation of **18** when achiral catalysts with monodentate acetate ligands are implemented (Table 4.2, entries 1 and 2). In addition, the reaction with chiral catalysts indicates that while the phthalamide-protected amino acid catalysts, such as $\{Rh_2[(S)\text{-ptad}]_4\}$, show an inherent bias toward the *s–trans* geometry of **21** for terminally substituted vinyldiazoacetates, the catalyst is not able to impart significant chiral influence through these reaction intermediates. The *N*-sulfonylprolinate catalysts, such as $\{Rh_2[(S)\text{-tisp}]_4\}$ and $\{Rh_2[(S)\text{-bitisp}]_4\}$, on the other hand, are far more efficacious in providing chiral influence for the reaction through a *s–trans* vinylcarbene intermediate (*s–trans* **21**).



Scheme 4.5 Vinylcarbene geometry in the vinylogous electrophilic aromatic substitution reaction

A different scenario arises for carbene geometry in the enantioselective formal [3 + 3]-cycloaddition between nitrones **19** and siloxyvinyldiazoacetate-derived rhodium carbenes (**22**), as shown in Scheme 4.6. When the rhodium bound carbene intermediate attempts to orient itself in the *s–trans* configuration (*s–trans* **22**), a significant steric repulsion between the sterically encumbered dirhodium tetracarboxylate and *O*-silyl group results. In the *s–cis* rotational isomer (*s–cis* **22**), however, such a steric clash is avoided, and the carbene benefits from the additional stabilization afforded by secondary orbital overlap with the rhodium–carbon bond. As indicated in Table 4.2, the *N*-sulfonyl prolinate catalysts, such as $\{Rh_2[(S)\text{-dosp}]_4\}$, do not provide substantial levels of asymmetric induction in transformations involving siloxyvinyldiazoacetate **7**. For carbene precursor **7**, the phthalamide-protected amino acid-derived catalysts are often far superior in providing a stereoselective transformation.

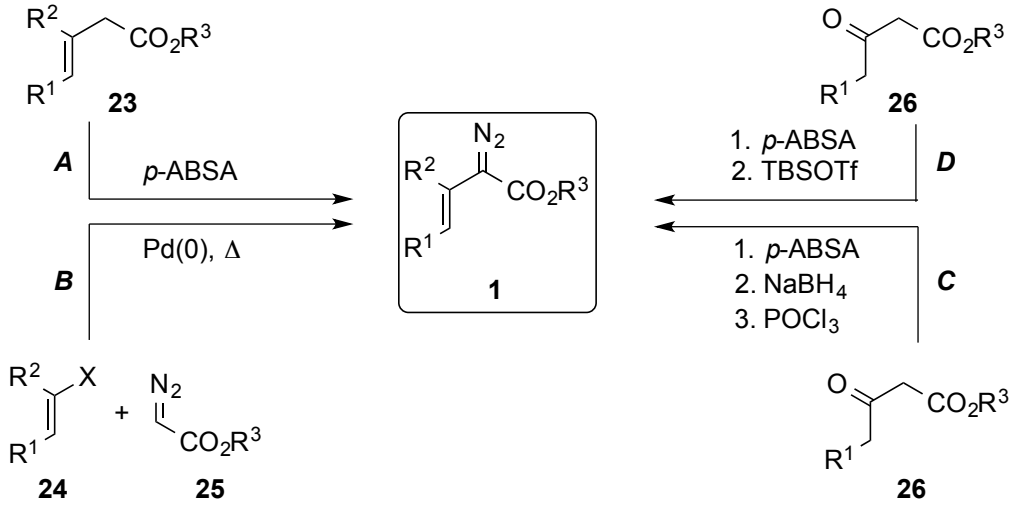


Scheme 4.6 Vinylcarbene geometry in the vinylogous formal [3 + 3]-cycloaddition reaction

Despite the obvious utility of alkenyl substituted diazo compounds (**1**), the pool of donor groups reported in vinylcarbene transformations is relatively shallow when compared to the nucleophilic partners for both the transformations outlined above, as well as a growing number of "vinylogous" cycloadditions with π–nucleophiles. The reason for the apparent disjoint can be accounted for by discussing the two major complications associated with alkenyldiazoacetates.

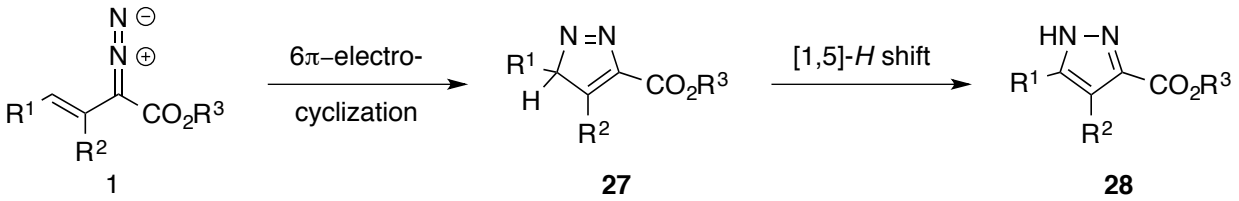
Foremost, there is not a unified, general strategy for the synthesis of these diazo compounds. Consider an approach to generic alkenyl diazo compound **1** shown in Scheme 4.7. For the preparation of simple alkyl and aryl substituted vinyldiazoacetates (**1**; R^1 = alkyl, aryl; R^2 = H; R^3 = Me), the diazo transfer reagent *p*-ABSA in conjunction with the strong amine base DBU is the most straight forward approach (Scheme 4.7 **A**).[39] Said strategy requires, however, that the β,γ-unsaturated ester is either commercially available or readily prepared. Further, in complex syn-

thetic contexts, the *p*-ABSA/DBU approach has not proven robust. More recently, functionalized vinyldiazoacetates have been prepared by the palladium-catalyzed cross coupling of sp^2 C–X (**24**) bonds with diazoacetates (**25**) (Scheme 4.7 **B**).[40–42] Although that approach should be general from a synthetic standpoint, the reactions themselves have proven challenging to reproduce, and under the prescribed reaction conditions present another issue, discussed below. Methods **C** and **D** both involve initial diazotization of a *β*-ketoester (**26**) with *p*-ABSA and a mild amine base, such as triethylamine. By route **C**, the ketone is then selective reduced to the β-hydroxydiazoacetate, which is subsequently dehydrated with phosphorus oxychloride to generate the *E*-1,2-disubstituted alkenyldiazoacetate.[43] A ketoester diazo compound can also be silylated with *t*-butyldimethylsilyl trifluoromethanesulfonate or a similar silyl triflate, with moderate selectivity for *Z*-substituted diazoacetate formation.[7,44] Thus, alkenyldiazoacetates where R^2 is an *O*-silyl group can be prepared.



Scheme 4.7 Overview of alkenyldiazoacetate synthesis

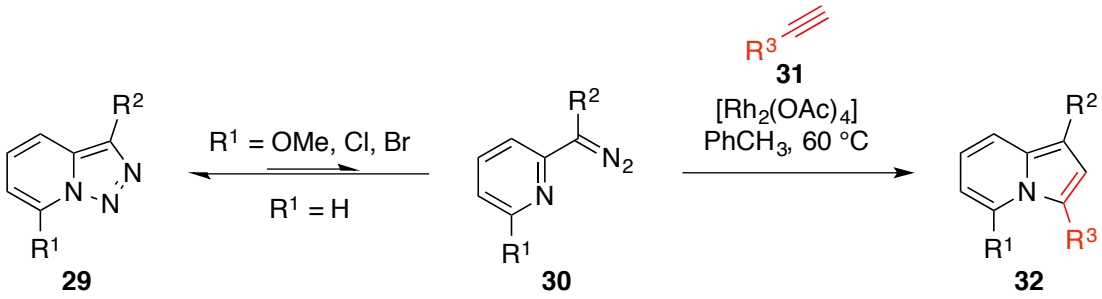
The general challenge associated with synthesis and handling of alkenyldiazoacetates **1**, however, is the propensity for these compounds to undergo a 6π–electrocyclization reaction (Scheme 4.8, **1** → **28**).[42,45] The rate of the electrocyclization event is dependent on a number of factors, including: temperature, solvent and substitution of the alkenyldiazoacetate. Specifically, elevated temperatures and polar solvents, and substituents which increase the electrophilicity of the γ-carbon tend to increase the rate of pyrazolization. Many diazoacetates prepared *via* the palladium-catalyzed cross coupling reaction undergo subsequent cyclization on comparable time scales.[42] In addition, the shelf life of many useful alkenyldiazo compounds is on the order of hours, meaning they must be prepared and used directly in the rhodium-catalyzed reaction. The pyrazole formation is particularly problematic when implementing low catalyst loads in the metal carbene transformation because the basic imine electron lone pair of the heterocycle readily complexes to dirhodium tetracarboxylates, thereby impeding catalysis.



Scheme 4.8 Mechanism for pyrazole formation from vinyldiazoacetates

The potential for pyrazolization would therefore be native to any alkene-substituted diazo architecture. Thus, our attention was drawn to the recent studies by Gevorgyan and Fokin genera-

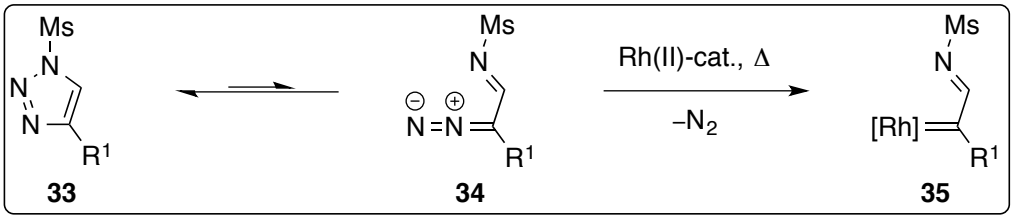
tion and trap of rhodium bound carbene intermediates from 1,2,3-triazole containing heterocycles. The seminal report detailed by Gevorgyan and co-workers entails the generation of rhodium carbenes from pyridotriazoles **29** and monosubstituted alkynes **31** *via* a formal [3 + 2]-cycloaddition to access indolizines **32**, among other classical rhodium carbene transformations.[46,47] The thermodynamic isomer is the pyridotriazole (**29**); however, with a heteroatom substituent at C(7) of **29**, the 1,2,3-triazole is capable of undergoing a ring-to-chain electrocyclization with thermolytic cleavage of a N–N bond to expose a diazo moiety (**30**). In the presence of a dirhodium tetracarboxylate, denitrogenative formation of the transient metal carbene occurs, with subsequent trap by the alkyne nucleophile. Absence of heteroatom substitution at C(7) precludes product formation; and thus, the authors propose that the Coulombic interaction between the R^1 and *peri*–N lone pair are responsible for the facile interconversion of **29** and **30**.

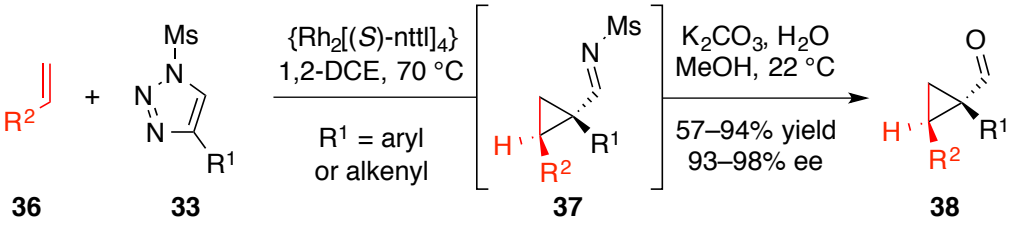


Scheme 4.9 Pyridotriazole-derived rhodium carbenes for formal [3 + 2]-cycloaddition reactions

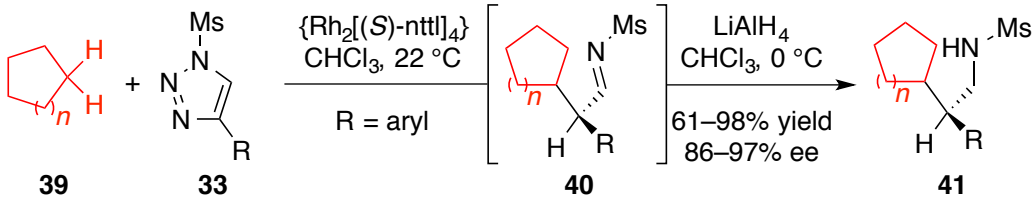
More central to our own studies, however, were the subsequent reports from the Fokin group describing the rhodium-catalyzed decomposition of *N*-sulfonyl-1,2,3-triazoles. With the first

report published in 2008, the retrocyclization of 4-substituted-*N*-sulfonyl-1,2,3-triazoles to generate a donor/acceptor substituted diazo intermediate was observed (Scheme 4.10).[48] In the presence of the chiral dirhodium tetracarboxylate catalyzed $\{Rh_2[(S)\text{-nttl}]_4\}$, the rhodium-bound carbene intermediate **35** underwent stereoselective cyclopropanation reactions with a broad range of olefins. (Scheme 4.10a).[49] Not only were typical π–donor groups such as substituted arenes, heteroaromatics and alkenes tolerated, but also select hyperconjugative alkyl donor groups. Further, non-conjugated alkenes, which perform poorly in stereoselective cyclopropanations of aryldiazoacetates, were competent partners in the [2 + 1]-cycloaddition. A *N*-methanesulfonyl protecting group was initially found superior to achieve high yields and enantioselectivities; however, a subsequent study demonstrated that *N*-trifluoromethanesulfony-1,2,3-triazoles prepared *in situ* were equally efficacious in the cyclopropanation chemistry.[50]





(a) Stereoselective cyclopropanation of alkenes



(b) Stereoselective insertion into cyclic, methylene C–H bonds

Scheme 4.10 Seminal reports of *N*-sulfonyl-1,2,3-triazole-derived rhodium carbene chemistry

Of further interest was the communication of intermolecular C–H insertion reactions of *N*-sulfonyl-1,2,3-triazoles into unactivated, cyclic hydrocarbons. Due to racemization of the α-chiral center, the imine products were reduced in a one-pot protocol to the corresponding homoaryl amines (Scheme 4.10b).[51] An interesting feature of the chemistry, considering the steric demand of the sulfonyl protecting group and rhodium catalyst implemented, is the proclivity of the compounds to undergo insertion at tertiary, rather than secondary, C–H bonds. In general,

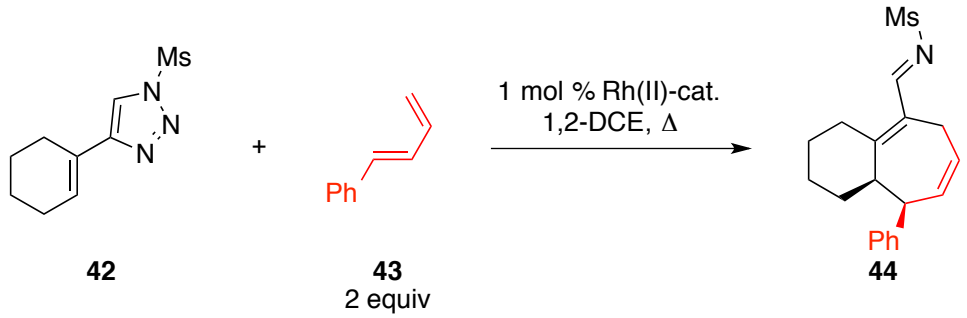
the reactions described proceed with high enantioselectivity in the presence of a broad range of donor groups (**33**, R^1), including heteroaromatics and alkenyl groups.

And so, we envisioned that *N*-sulfonyl-1,2,3-triazoles might serve as stable precursors to the alkenyldiazoacetates for a range of rhodium vinylcarbene transformations. The overwhelming favorability of triazole isomeric structure **33** over the diazoimine **34** under ambient conditions should be prohibitive of pyrazole formation. Moreover, a contemporaneous effort within the Davies group demonstrated that a 4-*N*-phthalimido-substituted *N*-sulfonyl-1,2,3-triazole could serve as a stable precursor to a donor/acceptor carbene with a heteroatom donor.[52] The equivalent diazo compounds cannot be isolated as they rapidly undergo denitrogenative decomposition under diazo transfer conditions. An additional benefit of a 4-alkenyl substituted *N*-sulfonyl-1,2,3-triazole approach to the corresponding alkenyl substituted rhodium carbene intermediates would straightforward and general synthetic entry into these compounds.[53]

4.2 Results & Discussion

Optimization. Our exploratory studies commenced with the C(4)-cyclohexenyl-triazole **42**, which was previously prepared by Fokin and co-workers from the commercially available enyne, and demonstrated to be suitable for the rhodium-catalyzed enantioselective cyclopropanation of styrene.[49] Using 1-phenyl-1,3-butadiene (**43**) as the test substrate and standard conditions for cyclopropanation of alkenes with *N*-sulfonyl-1,2,3-triazoles, an array of chiral dirhodium tetracarboxylate catalysts were examined (Table 1, entries 1–6). A racemic sample of **44** was prepared by reaction of **42** and **43** under the catalytic action of rhodium(II) octanoate, to provide a HPLC trace for determination of the enantiomeric excess of the reaction. To this end, {Rh_2[(*S*)-nttl]$_4$} (entry 6) was the most efficacious for inducing both high yields and high levels of enantioselectivity for formation of 13 (75% yield, >97 : 3 dr, 92% ee). A decrease in temperature from 70 to 60 °C (entries 6 and 7, respectively) brought about an improvement in both yield and enantioselectivity (82% yield, >97 : 3 dr, 97% ee), but further reduction of the reaction temperature was detrimental in terms of overall yield (entry 8). In addition, the basal reaction between *N*-sulfonyl-1,2,3-triazole **42** and phenylbutadiene **43** was not amenable to reduced catalyst loadings. Presumably, the products are not stable for extended periods of time under the prescribed reaction conditions, and decomposition of **44** becomes a competitive process. The relative configuration was assigned through analogy to the established stereospecificity of the cyclopropanation/Cope rearrangement. The absolute configuration of **44** was tentatively assigned by hydrolysis to expose the aldehyde (**92**, *vide infra*), which was then analyzed by X-ray crystallography and has been submitted to the Cambridge Crystallographic Data Centre under deposition number CCDC 938623.

Table 4.3[a–c] Optimization of the *N*-sulfonyl-1,2,3-triazole-derived rhodium carbene formal [4 + 3]-cycloaddition reaction



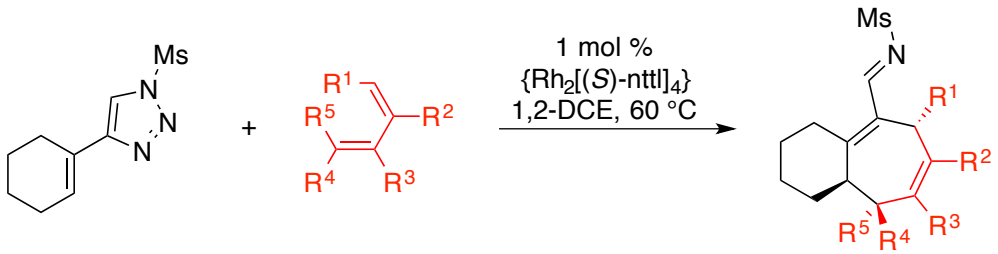
42 **43** 2 equiv **44**

entry	Rh(II)-cat.	temp., °C	yield, %	dr	ee, %
1	$\{Rh_2[(S)\text{-dosp}]_4\}$	70	70	>30:1	-16
2	$\{Rh_2[(S)\text{-btpcp}]_4\}$	70	56	>30:1	15
3	$\{Rh_2[(S)\text{-pta}]_4\}$	70	80	>30:1	40
4	$\{Rh_2[(S)\text{-ptad}]_4\}$	70	67	>30:1	66
5	$\{Rh_2[(S)\text{-pttl}]_4\}$	70	48	>30:1	82
6	$\{Rh_2[(S)\text{-nttl}]_4\}$	70	75	>30:1	92
7	$\{Rh_2[(S)\text{-nttl}]_4\}$	60	82	>30:1	97
8	$\{Rh_2[(S)\text{-nttl}]_4\}$	50	69	>30:1	97

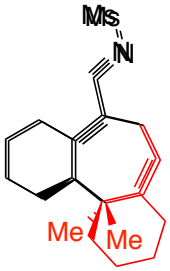
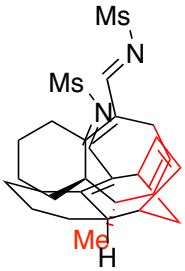
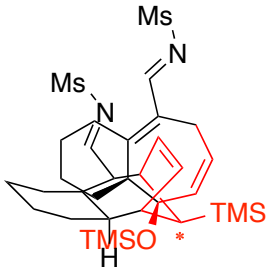
[a] Isolated yields of **44**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Diene Scope. Following the optimization studies of the [4 + 3]-cycloaddition, we were interested in determining whether the reaction would prove general for a variety of diene partners. The results of these studies are reported in Table 4.4. Racemic samples for HPLC analysis were all synthesized through the analogous reactions catalyzed by rhodium octanoate. Reaction of **42** with 4,4′-disubstituted (**45**), (*Z*)-4-substituted (**46**) and (*E*)-4-substituted (**47**) 1,3-dienes provided the corresponding cycloheptadienes (**51–53**, respectively) in uniformly high yield and enantioselectivity (entries 1–3, respectively; 79–84% yield, 90–94% ee). When vinylcyclohexene (entry 4, **48**) was used, the semi-symmetric tricyclic [4.4.3.0] product **54** was isolated in good yield and excellent stereoselectivity (75% yield, 97% ee). In addition, bridged tricyclic products could be prepared from reaction with cyclopentadiene (**49**). Indeed, the cyclic diene provided cycloadduct **55** in very high yield and good enantioselectivity (entry 5, 98% yield, 85% ee). A prochiral diene such as trimethylsilylcyclopentadiene (**50**) was similarly effective. The formal [4 + 3]-cycloaddition afforded the product (**56**) bearing four contiguous chiral centers in good yield and enantioselectivity (entry 6, 92% yield, 86 ee).

Table 4.4[a–c] Scope of the 1,3-diene for the formal [4 + 3]-cycloaddition reaction



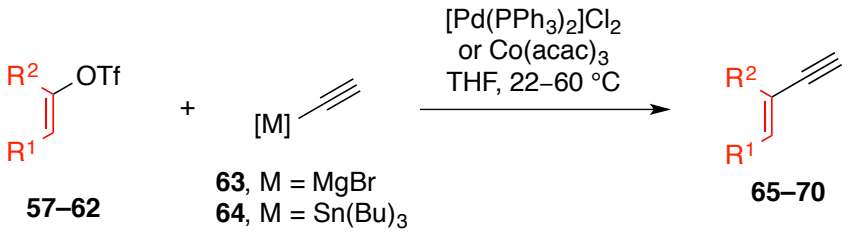
42 **45–50** 2 equiv **51–56**

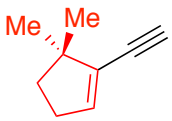
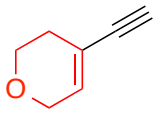
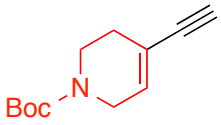
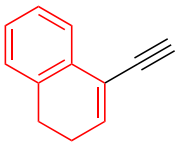
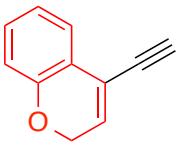
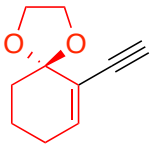
		
51	**52**	**53**
79% yield	81% yield	84% yield
90% ee	>95 : 5 dr	>95 : 5 dr
>95 : 5 dr	94% ee	94% ee
97% ee	85% ee	86% ee
54	**55**	**56**
75% yield	92% yield	92% yield
>95 : 5 dr	>95 : 5 dr	92 : 8 dr
97% ee	94% ee	94% ee

[a] Isolated yields of **51–56**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Synthesis of C(4)-alkenyl-*N*-sulfonyl-1,2,3-triazoles. Having established that a vinyltriazole could be effectively used in the formal [4 + 3]-cycloaddition, practical syntheses to generate a variety of C(4)-vinyltriazoles were developed, as illustrated in Table 4.5. The enynes (**65–70**) were prepared in a single step *via* well-established cross-coupling reactions with organometallic acetylides (**63** and **64**). Specifically, we found that both the Kumada-coupling of Grignard reagent **63**[54] and the Stille-coupling of stannane **64**[55] were both general and high yielding (61–95% yield) procedures for the syntheses of the novel enyne products **65–70**. The Stille protocol provided superior yields for the synthesis of enynes from sterically encumbered vinyl triflates such as **57** and **62**, whereas comparable yields were achieved for either protocol when less bulky vinyl triflates were used (Table 4.5, entries 2–5).

Table 4.5[a] Synthesis of enynes



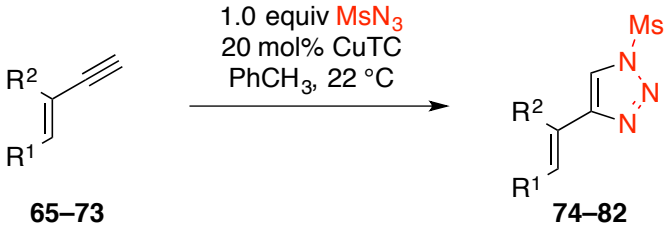
 **65** 61% yield	 **66** 75% yield	 **67** 78% yield
 **68** 95% yield	 **69** 88% yield	 **70** 75% yield

[a] Isolated yields of **65–70**.

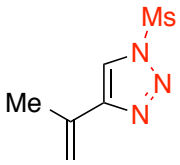
The subsequent copper(I)-catalyzed azide/alkyne cycloaddition (CuAAC) of enynes **65–73** with methanesulfonyl azide provided access to the C(4)-alkenyl-*N*-sulfonyl-1,2,3-triazole **74–82**, as summarized in Table 4.6.[53] The reaction proved tolerant for a range of functional groups and the more sterically demanding substrates. Conversions to the desired triazoles, as determined from ^{1}H NMR analysis of the crude reaction residues, were generally quite high (>90%); however, lower yields were obtained for select triazoles (entries 1–4, **74–77**, respectively) which were not as readily recrystallized as part of the purification protocol. Since the triazole (**33**) is

thermodynamically favored over the diazo imine (**34**) isomer (Scheme 4.10), particularly when stored neat, the undesirable rearrangement of the triazole to a pyrazole was not observed. Gradual hydrolysis of the *N*-sulfonyl protecting group in the presence of atmospheric moisture, which was previously reported by Fokin, was also observed for these substrates.[49] Analogous to the pyrazole formed from alkenyldiazo compounds, the hydrolyzed triazole also binds to the dirhodium tetracarboxylate catalyst, thereby impeding reactivity. We found that the *N*-sulfonyl-1,2,3-triazoles could be stored neat in a freezer at –20 °C for more than two weeks, or frozen in benzene for more than one month, without appreciable hydrolysis.

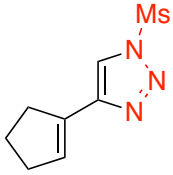
Table 4.6[a] Synthesis of *N*-sulfonyl-1,2,3-triazoles



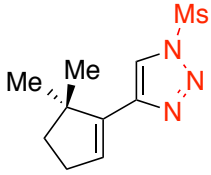
65–73 **74–82**



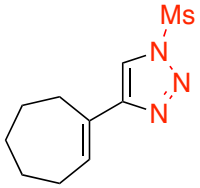
74
52% yield



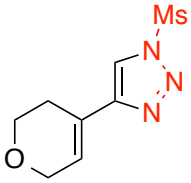
75
75% yield



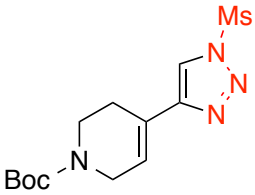
76
71% yield



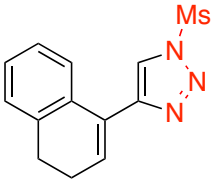
77
72% yield



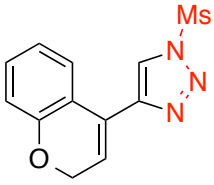
78
91% yield



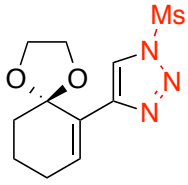
79
86% yield



80
90% yield



81
93% yield



82
82% yield

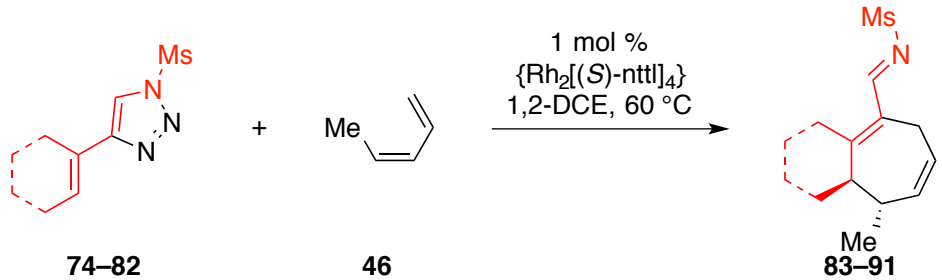
---

[a] Isolated yields of **74–82**.

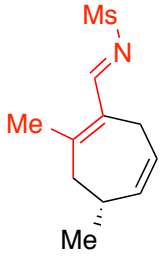
Proceeding with *cis*-1,3-pentadiene (**46**) as nucleophile, we then investigated the scope of the alkenyl carbene precursors prepared in Table 4.7. Another triazole **74**, readily available from a commercial enyne, was first tested in the cycloaddition chemistry. The cycloheptadiene **83** was formed in good yield and enantioselectivity (entry 1, 71% yield, 91% ee). We were more interested, however, in implementing this chemistry as a means to generate a variety of bicyclic [5.*n*.0] products. Thus, we moved forward with the study varying ring sizes and substitution patterns for C(4)-alkenyl-1,2,3-triazoles **75–82**. A decrease in enantioselectivity was observed when the cyclopentenyl-substituted triazole **75** was the carbene precursor, though the yield of the benzazulene product **84** was excellent (entry 2, 93% yield, 68% ee). By increasing the steric demand of the internal carbon of the alkene substituent, as in the 5,5-dimethylcyclopentene-substituted triazole, a dramatic improvement in stereoselectivity of the [4 + 3]-cycloaddition was observed without any detriment to yield (entry 3, **85**, 94% yield, 95% ee). Interestingly, the cycloheptenyl derivative (**77**), performed comparably to the 4-cyclohexenyl-*N*-sulfonyl-1,2,3-triazole (**42**), affording the bicyclo[5.5.0]dodecane (**86**) skeleton in 75% yield and 89% ee (entry 4). Heterocyclic alkenyl donor-groups were also well tolerated, as demonstrated in the syntheses of **87** and **88** (entries 5 and 6). Thus, the fused pyranyl and piperidinyl ring systems were generated in high enantioselectivity (96% and 86% ee, respectively). The triazoles bearing an α-fused arene substituent (entries 7 and 8, **80** and **81**, respectively) were particularly effective substrates, generating the corresponding angular tricyclic products (**89** and **90**) in excellent yield and stereoselectivity. As was observed in entry 3, a more encumbered cyclohexenyl carbene precursor such as **82** (entry 9) bearing an α-quaternary carbon was in fact the most efficient substrate overall. The ketal-bearing product **91** was isolated in 99% yield and 98% ee. The absolute configuration of compounds **85** and **90** were assigned by X-ray crystallographic analysis, and the latter

has been submitted to the Cambridge Crystallographic Data Centre under deposition number 938813. The absolute configuration of the series of products was tentatively assigned by analogy.

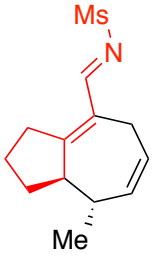
Table 4.7[a–c] Scope of the *N*-sulfonyl-1,2,3-triazole for the formal [4 + 3]-cycloaddition reaction



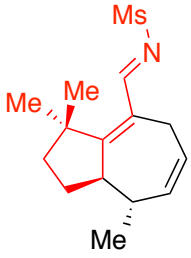
74–82 **46** 2 equiv **83–91**



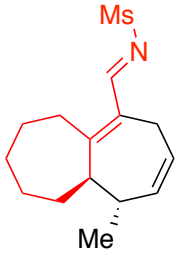
83
71% yield
91% ee



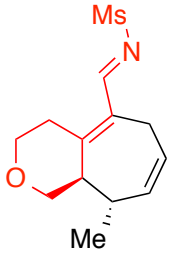
84
93% yield
>95 : 5 dr
68% ee



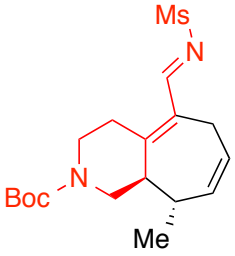
85
94% yield
>95 : 5 dr
95% ee



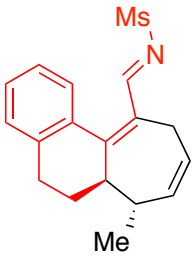
86
75% yield
>95 : 5 dr
89% ee



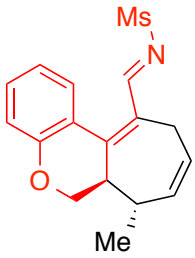
87
90% yield
>95 : 5 dr
96% ee



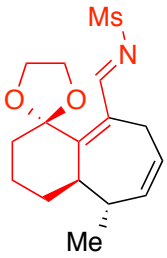
88
73% yield
>95 : 5 dr
86% ee



89
88% yield
>95 : 5 dr
96% ee



90
94% yield
>95 : 5 dr
98% ee

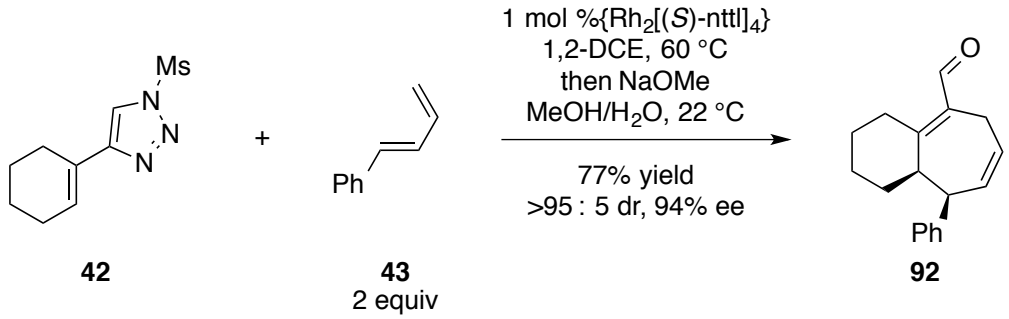


91
99% yield
>95 : 5 dr
98% ee

---

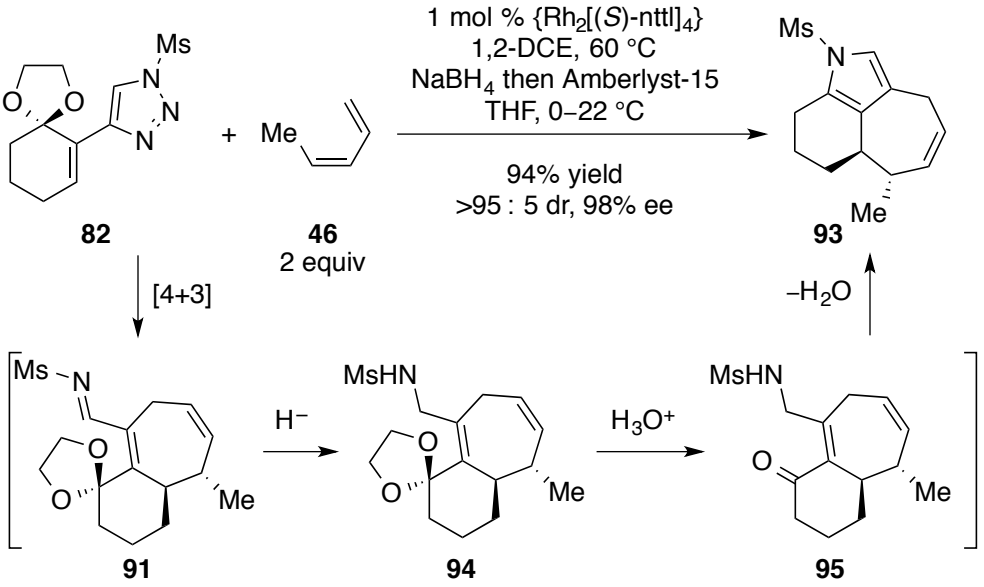
[a] Isolated yields of **83–91**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Synthetic applications. Since the products of the formal [4 + 3]-cycloaddition contain a synthetically useful α,β-unsaturated imine moiety, we sought to demonstrate sequential "one-pot" manipulations could be conducted without epimerization of the γ-chiral center. Indeed, formal [4 + 3]-cycloaddition of **42** and **43** followed by basic hydrolysis afforded the α,β-unsaturated aldehyde (**92**) in high yield with no observable epimerization (Scheme 3.2.1). As previously mentioned, the relative and absolute configuration of aldehyde **92** was further verified by X-ray crystallographic analysis.



Scheme 4.11 One-pot formal [4 + 3]-cycloaddition/*N*-sulfonylimine hydrolysis

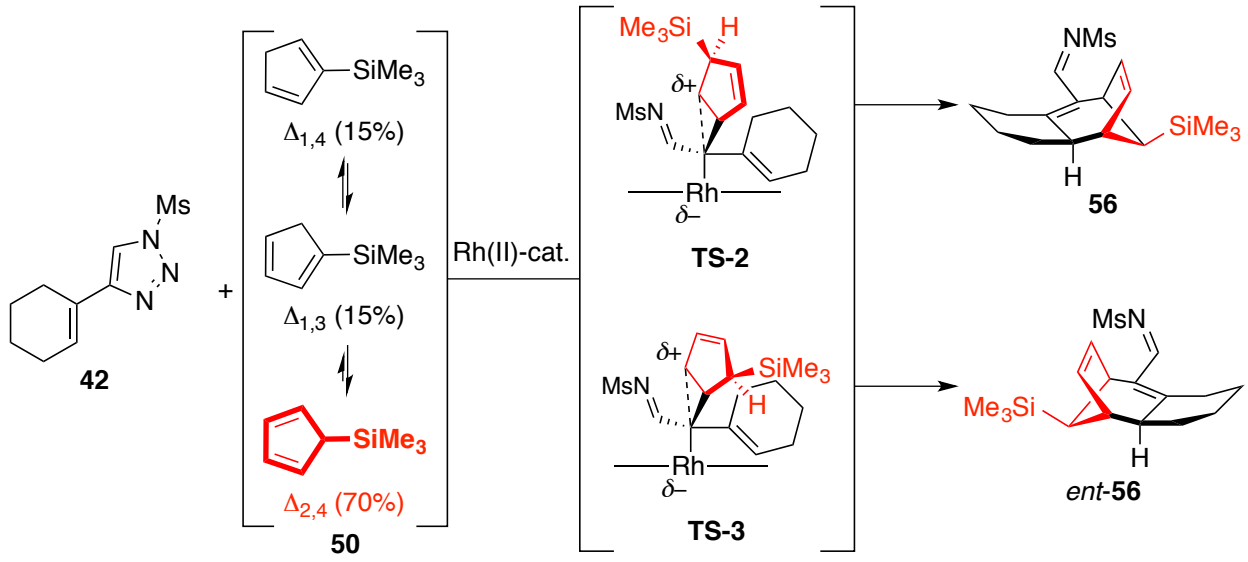
The combined synthetic utility of an appropriately engineered alkenyl donor group and the readily functionalized *N*-sulfonylimine moiety are exemplified in Scheme 4.12. Following the cycloaddition reaction of *N*-sulfonyl-1,2,3-triazole **82** and *cis*-1,3-pentadiene (**46**), mild reduction of imine **91** was accomplished with sodium borohydride providing intermediate **94**. Subsequent acid-catalyzed rupture of the ketal was induced by Amberlyst® 15 resin, with the effect of concomitant cyclodehydration, through intermediacy of **95**, to generate a tetrahydroindole architecture **93** in 94% yield and in excellent stereoselection (>95 : 5 dr, 98% ee) for the one-pot process.



Scheme 4.12 One-pot formal [4 + 3]-cycloaddition/cyclodehydration cascade

Stereochemical considerations. The tandem cyclopropanation/Cope rearrangement of a rhodium vinylcarbene intermediate and trimethylsilyl cyclopentadiene (Table 4.4, entry 6) was not a previously explored reaction. From the extensive literature reports of the complementary Diels-Alder [4 + 2]-cycloaddition of various dieneophiles with **50**, we were able to make some hypotheses about plausible operative mechanisms during our formal [4 + 3]-cycloaddition. Foremost, from NMR studies, diene **50** has been shown to exist at relevant temperatures as an equilibrating mixture of the three regioisomers shown in Scheme 4.13.[56] Based on the structure of the product, we can assert that the $\Delta_{2,4}$ olefin isomer of **50** is the reactive species in the cycloaddition chemistry. Thus, two transition states could be imagined arising from C(3)-addition (**TS-2**) or C(2)-addition (**TS-3**) of the nucleophile to the rhodium carbene intermediate, wherein the trimethylsilyl group is oriented *anterafacial* to C–C bond formation. In the case of **TS-2**, the concerted asynchronous cyclopropanation induces positive charge buildup at C(2) of the nucleo-

phile, which can be stabilized through the *β*–silicon effect, but not through resonance delocalization. On the other hand, addition *via* **TS-3** would results in positive charge accumulation at an allylic position, which could be stabilized directly through resonance delocalization. Further, the "resonance structure" of **TS-3**, would be able to take advantage of *β*–silicon stabilization. The consequence of reaction through **TS-2** *verus* **TS-3** is formation of enantiomeric products (**56** and *ent*-**56**, respectively) belonging to the same diastereomeric series. Unfortunately, attempts to desilylate **56** (or *ent*-**56**) for comparison of optical rotation with **55** to determine the absolute configuration were fruitless.

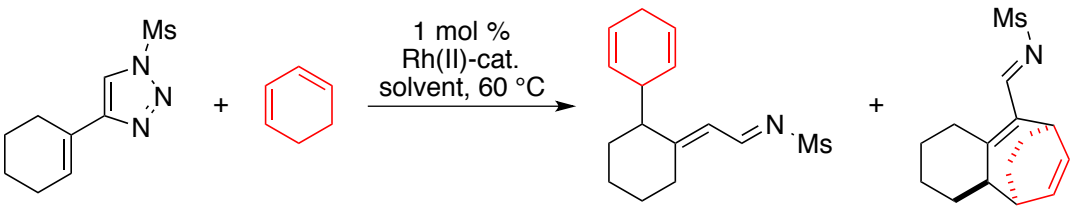


Scheme 4.13 Plausible mechanisms for the formal [4 + 3]-cycloaddition of cyclopentadiene **50**

CHCR Reaction. Pleased with the overall efficiency with which the 4-alkenyl-*N*-sulfonyl-1,2,3-triazoles performed in the tandem cyclopropanation/Cope rearrangement, we were in-

trigued if they might also prove competent substrates for the combined C–H insertion/Cope rearrangement. Moreover, we were interested how a nucleophile such as 1,3-cyclohexadiene, which could foreseeably participate in either a formal [4 + 3]-cycloaddition or CHCR reaction, might perform.[33] Beginning again with the readily available C(4)-1-cyclohexenyl triazole **42**, the reaction was conducted under a select set of conditions., shown in Table 4.8. With rhodium(II) pivaloate as catalyst, which was used as the achiral source for generating racemic samples in the [4 + 3] study, a significant amount of tricycle **98** arising from cyclopropanation/Cope rearrangement was observed in the crude reaction mixture, along with the CHCR product (**97**) as a minor constituent (entry 1). Implementing the chiral catalyst $\{Rh_2[(S)\text{-nttl}]_4\}$, the CHCR product (**97**) was in fact the major product formed in moderate yield and excellent enantioselectivity (entry 2, 60% yield, 99% ee). In the C–H insertion report by Fokin and co-workers, chloroform was the chosen reaction medium,[51] and so we wondered if it might prove more efficacious for the CHCR. Indeed, a gratifying increase in product ratio and isolated yield of **97** accompanied the substitution of 1,2-DCE for $CHCl_3$, without detriment to enantioselectivity (entry 3).

Table 4.8[a–d] Discovery of a combined C–H functionalization/Cope rearrangement



42 **96** 5 equiv **97** **98**

entry	Rh(II)-cat.	solvent	ratio, **97** : **98**	yield, %	ee, %
1	$[Rh_2(piv)_4]$	1,2-DCE	15 : 85	9	–
2	$\{Rh_2[(S)\text{-nttl}]_4\}$	1,2-DCE	76 : 24	60	99
3	$\{Rh_2[(S)\text{-nttl}]_4\}$	$CHCl_3$	82 : 18	71	99

[a] Isolated yields of **97**. [b] Ratio of **97** : **98** was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Isolated yields of **97**. [d] Enantiomeric excess of **97** was determined by HPLC analysis on a chiral stationary phase.

Mechanistic considerations. During our exploratory studies of different alkenylcarbene architectures in the formal [4 + 3]-cycloaddition reaction (Table 4.7), we were intrigued by the dramatic fluctuations in enantioselectivity which accompanied minor changes in the C(4)-substituent. In particular, the variation observed for the unsubstituted cyclopentene (entry 2, **75**) and the 5,5-dimethylcyclopentene (entry 3, **76**) were of particular interest, as these represent one

of the poorest and one of the best substrates from the standpoint of enantioselectivity, respectively. For the former substrate, we envisioned that upon denitrogenative decomposition, it would give rise to either of the rhodium-bound carbene intermediates shown in Scheme 4.14. Since the alkene is restrained in a cyclopentene ring, the vinylic hydrogen does not engage the catalyst wall in significant $A_{1,3}$–interactions while in a *s–cis* geometry (*cis*-**99**). On the other hand, the alkene would not be expected to enjoy as significant a degree of orbital overlap with the rhodium–carbon π–bond as is attained in the cyclohexene analogue. Thus, the preference between *s–cis* and *s–trans* carbene geometries is minimal in this substrate. For the 5,5-dimethylcyclopentene donor group, however, a significant steric bias would be anticipated. Rendering the rhodium-bound carbene in a *s–trans* configuration (*trans*-**100**) would cause the geminal dimethyl substituents to be directly clashing with the rhodium catalyst wall, imparting severe $A_{1,3}$–strain on the system. And so, the transient metal carbene would be expected to exist almost exclusively as its *s–cis* rotational isomer (*cis*-**100**). Therefore, we would hypothesize that C(4)-alkenyl-*N*-sulfonyl-1,2,3-triazoles which exist preferentially in a *s–cis* geometry give rise to highly enantioselective cyclopropanation reactions. Those carbene intermediates which have minimal inherent bias toward the *s–cis* geometry will tend to generate products in poor-to-moderate enantioselectivity.

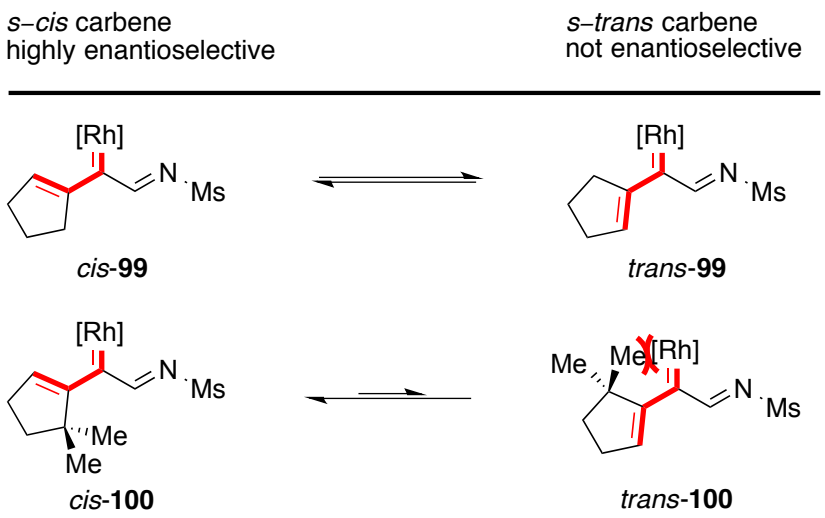


Figure 4.1 Rhodium carbene geometries arising from different 4-cyclopentenyl-*N*-sulfonyl-1,2,3-triazoles

Indeed, many of the *N*-sulfonyl-1,2,3-triazoles in Table 4.7 which exhibit high enantioselectivity in the formal [4 + 3]-cycloaddition reaction would be expected dramatic proclivity for a *s–cis* geometry analogous to *cis*–**100**. Thus, the catalyst $\{Rh_2[(S)\text{-nttl}]_4\}$ would seem to be generally effective in dictating enantioselective approach of a nucleophile toward a carbene with intrinsic propensity for a *s–cis* geometry.

4.3 Conclusions

In summary, we have developed a general strategy for accessing C(4)-alkenyl-*N*-sulfonyl-1,2,3-triazoles, which are capable of participating in classic rhodium vinylcarbene transformations, such as tandem cyclopropanation/Cope rearrangement and combined C–H insertion/Cope rearrangement. A broad range of cyclic alkenyl donor architectures were prepared and effected formal [4 + 3]-cycloaddition in high yields and stereoselectivities. These substrates showcase the value of the *N*-sulfonyl-1,2,3-triazoles as surrogates to alkenyldiazoacetates as they are prepared through a unified synthetic strategy and are relatively more stable. In addition, the donor group could be engineered to participate in subsequent one-pot transformations for the rapid generation of molecular complexity. While the cross coupling and copper-catalyzed azide/alkyne cycloaddition approach is general to the synthesis of these carbene precursors, and the C(4)-alkenyl-*N*-sulfonyl-1,2,3-triazoles are not prone to pyrazole formation, the lability of the *N*-sulfonyl protecting group does preclude long term stability of these compounds unless stored with caution.

Future efforts in C(4)-alkenyl-*N*-sulfonyl-1,2,3-triazole chemistry should involve both the general evaluation of the competence and scope of various donor groups to participate in combined C–H insertion/Cope rearrangement and applications of these carbene precursors to total synthesis. Unlike their diazoacetate counterparts, the presence of a nitrogenous acceptor group offers a unique opportunity for the rapid construction of heterocyclic, or alkaloid, structural motifs native to many natural products.

4.4 Experimental Section

4.4.1 General Considerations

All reactions were conducted in oven-dried glassware under an inert atmosphere of dry argon. All chemicals were purchased from either Sigma-Aldrich, TCI America, Acros Organics, Oakwood Chemical, Matrix Scientific or AK Scientific and were used as received. 1,2-Dichloroethane was distilled over calcium hydride under an inert atmosphere of argon prior to use. Chloroform (stabilized with amylenes) was purchased from Sigma-Aldrich as the anhydrous reagent, and was used as received. ^{1}H NMR spectra were recorded at either 400 MHz on an INOVA-400 spectrometer or at 600 MHz on an INOVA-600 spectrometer. ^{13}C NMR spectra were recorded at 100 MHz on an INOVA-400 spectrometer or 150 MHz on an INOVA-600 spectrometer. NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or deuterated benzene (C_6D_6) solutions, with residual chloroform (δ 7.27 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR), benzene (δ 7.16 ppm for ^{1}H NMR and δ 128.4 for ^{13}C NMR) or tetramethylsilane (δ 0.00 ppm for ^{1}H NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. Coupling constants were taken from the spectra directly and are uncorrected. IR spectra were collected on a Nicolet iS10 FT-IR spectrometer as neat films. Mass spectra determinations were carried out on a Thermo Finnigan LTQ-FTMS spectrometer with electrospray (ESI) or atmospheric pressure chemical (APCI) ionization. Optical rotations were measured on JASCO P-2000 polarimeter. Enantiomeric excess (ee) was determined by high pressure liquid chromatography (HPLC) on a Varian ProStar chromatography system. Analytical thin layer chromatography (TLC) was performed on silica gel plates using UV light or stained with 10% vanillin/1% sulfuric acid/ethanol solution. Flash column chromatography was

performed with silica gel 60 A (230-400 mesh) according to the literature procedure.[57] Substrates **42**,[49] **48**,[58] **57**,[59] **61**,[60] **62**,[61] **66**,[62] **68**,[63] **74**,[64] {Rh_2[(*S*)-dosp]$_4$},[65] {Rh_2[(*S*)-btpcp]$_4$},[66] {Rh_2[(*S*)-pta]$_4$} and {Rh_2[(*S*)-pttl]$_4$},[67] {Rh_2[(*S*)-ptad]$_4$},[68] {Rh_2[(*S*)-nttl]$_4$},[69] copper(I) thiophene-2-carboxylate (CuTC)[70] and methanesulfonyl azide (MsN_3)[71] were prepared according to the literature procedures.

4.4.2 General Procedures

4.4.2.1 Cobalt(III)-catalyzed Kumada coupling

To a tetrahydrofuran (0.5 M) solution of ethynylmagnesium bromide (**15**) (3 equiv) at 40 °C were sequentially added $Co(acac)_3$ (0.05 equiv) and a tetrahydrofuran (1.0 M) solution of vinyl-triflate (1.0 equiv). Reaction progress was monitored by TLC analysis for consumption of vinyl-triflate. Upon cooling to ambient temperature, the reaction was carefully quenched with aqueous HCl (0.50 M). The mixture was extracted (5x) with pentanes and the combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography.

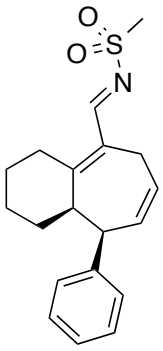
4.4.2.2 Copper(II)-catalyzed azide/alkyne cycloaddition

To a toluene (20 mL) suspension of CuTC (96 mg, 0.50 mmol, 0.20 equiv), was added alkyne (5 mmol, 1.0 equiv) with vigorous stirring. After 10 min, a toluene (5 mL) solution of azide (5.5 mmol, 1.1 equiv) was added dropwise over 15 min. The reaction was stirred at ambient temperature until consumption of the alkyne was apparent by TLC analysis. The crude reaction mixture was concentrate *in vacuo* and the residue was dissolved in a minimal volume of dichloromethane. The crude was filtered through a bed of silica gel eluting with hexanes/EtOAc (50:50) and the fractions containing product were combined and concentrated *in vacuo*. The product was further purified by recrystallization from pentane/diethyl ether at –20 °C to obtain the 4-vinyl-*N*-sulfonyl-1,2,3-triazole as a white solid.

4.4.2.3 Rhodium(II)-catalyzed formal [4 + 3]-cycloaddition

An oven-dried, 20 mL culture tube, equipped with a stir bar, was capped with a rubber septum. The reaction vessel was charged with $\{Rh_2[(S)\text{-nttl}]_4\}$ (7 mg, 0.0050 mmol, 0.010 equiv) and triazole (0.50 mmol, 1.0 equiv). A 1,2-dichloroethane (1.5 mL) solution of diene (1.0 mmol, 2.0 equiv) was then added. The reaction was immersed in an oil bath pre-heated to 60 °C until consumption of the triazole was apparent by TLC analysis. Upon cooling to ambient temperature, the product was purified directly by flash chromatography.

4.4.3 Procedures and Characterization Data



(*E*)-*N*-(((9*R*,9a*R*)-9-phenyl-2,3,4,6,9,9a-hexahydro-1*H*-benzo[7]annulen-5-yl)methylene)methanesulfonamide (44)

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **43** (130 mg, 1.0 mmol). Chromatographic purification with hexanes/EtOAc (80 : 20) afforded the title compound as a white solid (135 mg, 82% yield).

MP = 72–75 °C

$[\alpha]^{20}_{D}$ 250.1° (*c* 1.3, $CHCl_3$).

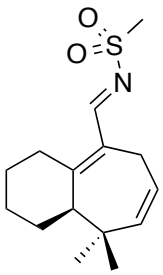
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.09 (s, 1H), 7.29-7.23 (m, 3H), 7.14-7.11 (m, 2H), 3.72 (dd, J = 17.9, 8.8 Hz, 1H), 3.66 (bs, 1H), 3.52 (bs, 1H), 3.24-3.18 (m, 1H), 3.10 (s, 3H), 2.72-2.65 (m, 1H), 1.74-1.69 (m, 1H), 1.65-1.59 (m, 1H), 1.58-1.52 (m, 2H), 1.47-1.35 (m, 2H), 1.29-1.20 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 167.1, 139.9, 132.8, 129.7, 128.5, 128.2, 127.3, 125.8, 48.1, 46.4, 40.7, 27.3, 26.7, 24.4, 23.2, 21.2.

FTIR (neat): ν_{max}/cm^{-1} 3022, 2935, 2866, 1611, 1591, 1556, 1450, 1310, 1141.

HRMS (p-APCI): *m/z* 330.1519 [$(M+H)^+$ requires 330.1522].

HPLC: 97% ee (ADH, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 33.4 min (minor), 39.7 min (major).



(*R*,*E*)-*N*-((9,9-dimethyl-2,3,4,6,9,9a-hexahydro-1*H*-benzo[7]annulen-5-yl)methylene)methanesulfonamide (51)

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **45** (83 mg, 1.0 mmol). Purification with hexanes/EtOAc (85:15) afforded the title compound as a white solid (114 mg, 79% yield).

MP = 35–36 °C.

$[\alpha]^{20}_D$ +12.5° (*c* 0.3, $CHCl_3$).

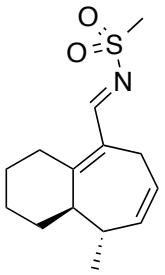
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.08 (s, 1H), 5.49 (ddd, *J* = 11.4, 9.0, 2.5 Hz, 1H), 5.23 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.48 (dd, *J* = 17.6, 8.9 Hz, 1H), 3.20 (dd, *J* = 11.2, 6.3 Hz, 1H), 3.09-3.02 (m, 2H), 3.06 (s, 3H), 2.32-2.21 (m, 1H), 1.99-1.86 (m, 1H), 1.81-1.75 (m, 1H), 1.74-1.68 (m, 1H), 1.67-1.59 (m, 2H), 1.24-1.15 (m, 1H), 1.07 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.5, 167.0, 142.0, 135.2, 122.5, 50.5, 40.7, 38.0, 29.3, 25.6, 23.8, 23.8, 23.3, 23.3, 20.6.

FTIR (neat): ν_{max}/cm^{-1} 3007, 2953, 2867, 1612, 1557, 1443, 1310, 1141.

HRMS (p-APCI): *m/z* 282.1250 [(M+H)$^+$ requires 282.1252].

HPLC: 90% ee (ADH, 3.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 12.4 min (minor), 14.8 min (major).



(*E*)-*N*-(((9*S*,9a*R*)-9-methyl-2,3,4,6,9,9a-hexahydro-1*H*-benzo[7]annulen-5-yl)methylene)methanesulfonamide (52)

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (80:20) afforded the title compound as a colorless oil (108 mg, 81% yield).

[α]$^{20}_{D}$ +18.1° (*c* 0.3, $CHCl_3$).

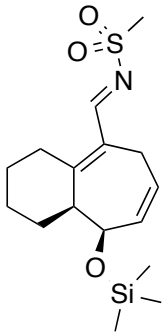
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.10 (s, 1H), 5.70 (dddd, *J* = 10.8, 8.4, 4.2, 2.4 Hz, 1H), 5.38 (dt, *J* = 10.8, 3.0 Hz, 1H), 3.35 (dd, *J* = 17.4, 8.4 Hz, 1H), 3.18-3.13 (m, 1H), 3.06 (s, 3H), 2.87 (ddd, *J* = 11.4, 8.4, 5.4 Hz, 1H), 2.75 (dt, *J* = 14.4, 5.4 Hz, 1H), 2.56 (dt, *J* = 15.0, 7.8 Hz, 1H), 2.33-2.26 (m, 1H), 1.87-1.82 (m, 1H), 1.80-1.74 (m, 1H), 1.74-1.68 (m, 2H), 1.55 (dddd, *J* = 13.8, 11.4, 9.0, 3.0 Hz, 1H), 1.43-1.36 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 172.3, 167.5, 136.8, 134.1, 126.5, 47.3, 40.7, 34.6, 28.5, 26.4, 24.8, 23.6, 21.6, 20.2.

FTIR (neat): ν_{max}/cm^{-1} 3010,2932, 2861, 1608, 1559, 1442, 1309, 1140.

HRMS (p-APCI): *m/z* 268.1364 [$(M+H)^+$ requires 268.1366].

HPLC: 94% ee (ADH, 3.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 16.9 min (minor), 23.1 min (major).



(*E*)-*N*-(((9*R*,9a*S*)-9-((trimethylsilyl)oxy)-2,3,4,6,9,9a-hexahydro-1*H*-benzo[7]annulen-5-yl)methylene)methanesulfonamide (53)

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **47** (0.18 mL, 1.0 mmol). Purification with hexanes/EtOAc (85:15) afforded the title compound as a colorless oil (143 mg, 84% yield).

$[\alpha]^{20}_D$ +50.8° (*c* 0.4, $CHCl_3$).

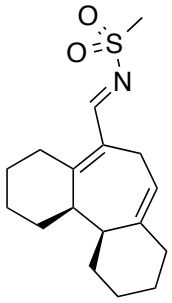
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (s, 1H), 2.85-2.76 (m, 1H), 2.65-2.57 (m, 1H), 4.50 (bs, 1H), 3.58 (dd, *J* = 17.4, 8.8 Hz, 1H), 3.04 (s, 3H), 2.97-2.84 (m, 1H), 2.81-2.58 (m, 1H), 1.94-1.59 (m, 5H), 1.51-1.38 (m, 1H), 0.12 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 167.7, 127.4, 70.7, 48.2, 40.6, 28.0, 25.4, 24.3, 23.0, 0.5.

FTIR (neat): ν_{max}/cm^{-1} 3016, 2932, 2857, 1591, 1556, 1442, 1305, 1250, 1140.

HRMS (p-APCI): *m/z* 342.1552 [$(M+H)^+$ requires 342.1554].

HPLC: 94% ee (ADH, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 17.0 min (minor), 28.8 min (major).



(*E*)-*N*-(((11a*S*,11b*R*)-2,3,4,6,8,9,10,11,11a,11b-decahydro-1*H*-dibenzo[*a,c*][7]annulen-5-yl)methylene)methanesulfonamide (54)

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **48** (110 mg, 1.0 mmol). Purification with hexanes/EtOAc (90:10) afforded the title compound as a white solid (115 mg, 75% yield).

MP = 74–76 °C.

$[\alpha]^{20}_D$ –15.4° (*c* 0.3, $CHCl_3$).

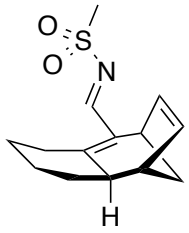
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.08 (s, 1H), 5.37 (d, *J* = 9.1 Hz, 1H), 3.50-3.37 (m, 2H), 3.17-2.98 (m, 2H), 3.07 (s, 3H), 2.24-2.13 (m, 2H), 2.11-2.04 (m, 1H), 2.00-1.86 (m, 2H), 1.84-1.70 (m, 4H), 1.64-1.47 (m, 2H), 1.41-1.30 (m, 2H), 1.29-1.20 (m, 2H), 1.07-.094 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6, 166.9, 144.7, 134.3, 116.5, 46.2, 44.4, 40.7, 39.3, 29.8, 29.2, 27.3, 26.6, 26.2, 23.6, 22.8, 21.4.

FTIR (neat): ν_{max}/cm^{-1} 3023, 2922, 2851, 1614, 1552, 1445, 1309, 1276, 1140.

HRMS (p-APCI): *m/z* 308.1677 [$(M+H)^+$ requires 308.1679].

HPLC: 97% ee (ADH, 3.0% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 17.7 min (minor), 19.6 min (major).



(*E*)-*N*-(((4a*R*,5*S*,8*R*)-2,3,4,4a,5,8-hexahydro-1*H*-5,8-methanobenzo[7]annulen-9-yl)methylene)methanesulfonamide (55)

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **49** (0.085 mL, 1.0 mmol). Purification with hexanes/EtOAc (90:10) afforded the title compound as a white solid (128 mg, 97% yield).

$[\alpha]^{20}_D$ +2.2° (*c* 1.0, $CHCl_3$)

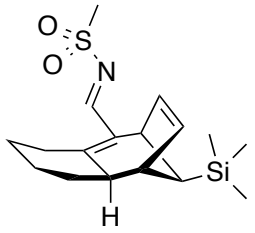
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.06 (s, 1H), 6.30 (dd, *J* = 5.6, 3.0 Hz, 1H), 5.82 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.63-3.59 (m, 1H), 3.19-3.14 (m, 1H), 3.07 (s, 3H), 2.65 (q, *J* = 4.5 Hz, 1H), 2.35 (dt, *J* = 12.7, 4.5 Hz, 1H), 2.15 (dt, *J* = 9.7, 4.8 Hz, 1H), 1.94-1.84 (m, 2H), 1.84-1.77 (m, 2H), 1.66 (d, *J* = 10.2 Hz, 1H), 1.46 (dt, *J* = 13.6, 3.4 Hz, 1H), 1.35 (qd, *J* = 13.2, 4.2 Hz, 1H), 1.28 (dt, *J* = 13.2, 3.6 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 165.7, 140.7, 134.8, 131.8, 44.0, 43.1, 41.1, 40.6, 37.5, 30.6, 30.2, 28.2, 25.9.

FTIR (neat): ν_{max}/cm^{-1} 3033, 2929, 2854, 1591, 1549, 1442, 1299, 1137.

HRMS (p-APCI): *m/z* 266.1207 [$(M+H)^+$ requires 266.1209].

HPLC: 85% ee (ADH, 2.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 17.3 min (major), 19.0 min (minor).



***N*-((*E*)-((4a*R*,5*S*,8*R*,10*S*)-10-(trimethylsilyl)-2,3,4,4a,5,8-hexahydro-1*H*-5,8-methanobenzo[7]annulen-9-yl)methylene)methanesulfonamide (56)**

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **50** (0.17 mL, 1.0 mmol). Purification with hexanes/EtOAc (90:10) afforded the title compound as a white solid (155 mg, 92% yield).

MP = 57–59 °C.

$[\alpha]^{20}_D$ –46.6° (*c* 1.0, $CHCl_3$).

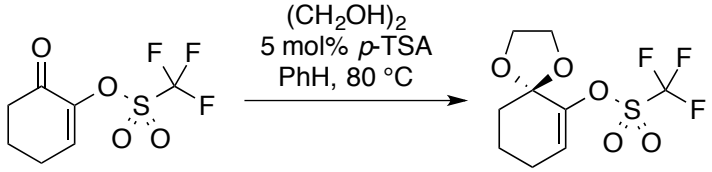
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 6.20 (dd, *J* = 5.6, 3.1 Hz, 1H), 5.69 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.60 (bd, *J* = 3.0 Hz, 1H), 3.19-3.13 (m, 1H), 3.07 (s, 3H), 2.63 (dd, *J* = 4.4, 3.0 Hz, 1H), 2.33 (dt, *J* = 12.5, 4.5 Hz, 1H), 1.93-1.82 (m, 2H), 1.81-1.75 (m, 2H), 1.49-1.37 (m, 1H), 1.36-1.23 (m, 2H), 1.15 (s, 1H), 0.06 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 165.5, 140.6, 137.3, 131.1, 45.8, 45.3, 42.1, 40.7, 39.5, 30.5, 30.3, 28.3, 26.0, 1.4.

FTIR (neat): ν_{max}/cm^{-1} 2930, 2855, 1590, 1557, 1442, 1306, 1246, 1141.

HRMS (p-APCI): *m/z* 338.1607 [$(M+H)^+$ requires 338.1605].

HPLC: 86% ee (ADH, 1.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 12.1 min (major), 13.9 min (minor).



101 **62**

1,4-dioxaspiro[4.5]dec-6-en-6-yl trifluoromethanesulfonate (62)

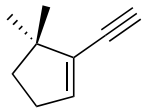
An oven-dried, 250 mL round-bottomed flask equipped with a magnetic stirring bar, Dean-Stark apparatus and reflux condenser, was charged with **101** (5.0 g, 20 mmol) and ethylene glycol (2.2 mL, 40 mmol) in benzene (110 mL). *p*-Toluenesulfonic acid (190 mg, 1.0 mmol) was added in a single portion with vigorous stirring. The reaction was heated to reflux for 12 h, until consumption of **101** was apparent by TLC analysis. Upon cooling to ambient temperature, the reaction was dilute with diethyl ether (200 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatographic purification with hexanes/EtOAc (80:20) afforded the title compound as an amorphous white solid (5.6 g, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95 (t, J = 4.1 Hz, 1H), 4.16-4.08 (m, 2H), 4.03-3.96 (m, 2H), 2.27-2.23 (m, 2H), 1.95-1.92 (m, 2H), 1.84-1.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 124.5, 104.5, 66.0, 35.4, 24.5, 20.3.

FTIR (neat): ν_{max}/cm^{-1} 2956, 2898, 1412, 1365, 1201, 1139.

HRMS (p-APCI): *m/z* 289.0351 [$(M+H)^+$ requires 289.0352].



1-ethynyl-5,5-dimethylcyclopent-1-ene (65)

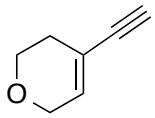
An oven-dried, 250 mL round-bottomed flask equipped with a reflux condenser and stir bar was charged with **57** (4.04 g, 16.5 mmol, 1.0 equiv) under an atmosphere of dry argon. The reaction vessel was charged with ethynylmagnesium bromide **63** (100 mL, 50.0 mmol) and [$Pd(PPh_3)_4$] (969 mg, 0.83 mmol). The reaction mixture was immersed in a preheated oil bath and stirred at vigorous reflux for 6 h. Upon cooling to ambient temperature, the reaction was carefully quenched with aqueous HCl (0.50 M). The mixture was extracted (5x) with pentanes and the combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification with pentane (100%) afforded the title compound as colorless oil (1.20 g, 61% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.02 (t, J = 2.7 H, 1H), 2.98 (s, 1H), 2.38 (td, J = 7.2, 2.7 Hz, 2H), 1.75 (t, J = 7.2 Hz, 2H), 1.12 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 137.3, 133.9, 80.0, 79.4, 47.0, 39.2, 30.8, 27.2.

FTIR (neat): ν_{max}/cm^{-1} 3311, 3055, 2957, 2935, 2897, 2864, 2846, 2095, 1456.

HRMS (p-APCI): *m/z* 121.1012 [$(M+H)^+$ requires 121.1012].



4-ethynyl-3,6-dihydro-2*H*-pyran (66)

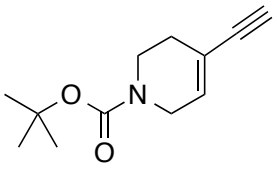
Prepared by *General Procedure 4.4.2.1* with **58** (2.3 g, 10 mmol), ethynylmagnesium bromide (**63**) (60 mL, 30 mmol), and $Co(acac)_3$ (179 mg, 0.50 mmol). Chromatographic purification with pentane/diethyl ether (80:20) afforded the title compound as a pale yellow oil (0.81 g, 75% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.17 (p, J = 3.0 Hz, 1H), 4.19 (qd, J = 2.9, 0.8 Hz, 2H), 3.78 (t, J = 5.5 Hz, 2H), 2.90 (s, 1H), 2.27-2.24 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ

FTIR (neat): ν_{max}/cm^{-1} 3288, 2968, 2930, 2856, 2823, 2096, 1123.

HRMS (p-APCI): *m/z* 109.0648 [$(M+H)^+$ requires 109.0648].



***tert*-butyl 4-ethynyl-5,6-dihydropyridine-1(2*H*)-carboxylate (67)**

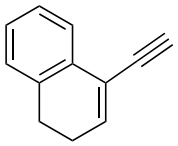
Prepared by *General Procedure 4.4.2.1* with **59** (6.6 g, 20 mmol), ethynylmagnesium bromide (**63**) (120 mL, 60 mmol), and $Co(acac)_3$ (0.36 g, 1.0 mmol). Chromatographic purification with hexanes/EtOAc (98:2) afforded the title compound as an amorphous, colorless solid (3.2 g, 78% yield).

^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): δ 6.10 (bs, 1H), 3.97 (s, 2H), 3.50 (s, 2H), 2.90 (s, 1H), 2.26 (bs, 2H), 1.47 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$, 55 °C): δ 154.9, 132.4, 119.0, 84.0, 80.1, 76.5, 43.8, 29.4, 28.7.

FTIR (neat): ν_{max}/cm^{-1} 3289, 3240, 2974, 2929, 2838, 1658, 1413.

HRMS (p-APCI): *m/z* 206.1173 [$(M-H)^+$ requires 206.1176].



4-ethynyl-1,2-dihydronaphthalene (68)

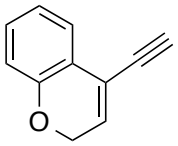
Prepared by *General Procedure 4.4.2.1* with **60** (2.8 g, 10 mmol), ethynylmagnesium bromide (**63**) (60 mL, 30 mmol), and $Co(acac)_3$ (178 mg, 0.50 mmol). Chromatographic purification with hexanes (100%) afforded the title compound as a pale yellow oil (1.45 g, 95% yield).

^{1}H NMR (400 MHz, C_6D_6): δ 7.85 (d, J = 7.0 Hz, 1H), 7.15-7.09 (m, 1H), 7.02 (td, J = 7.4, 1.3 Hz, 1H), 6.89-6.83 (m, 1H), 6.33 (t, J = 4.8 Hz, 1H), 2.79-2.72 (m, 1H), 2.38 (t, J = 8.3 Hz, 2H), 1.84 (td, J = 8.0, 4.9 Hz, 2H).

^{13}C NMR (100 MHz, C_6D_6): δ 136.9, 136.9, 135.1, 132.8, 127.6, 127.0, 125.4, 121.6, 78.6, 78.6, 27.1, 23.5.

FTIR (neat): ν_{max}/cm^{-1} 3286, 3053, 3019, 2936, 2883, 2829, 1487, 1450, 1426.

HRMS (p-APCI): *m/z* 155.0853 [$(M+H)^+$ requires 155.0855].



4-ethynyl-2*H*-chromene (69)

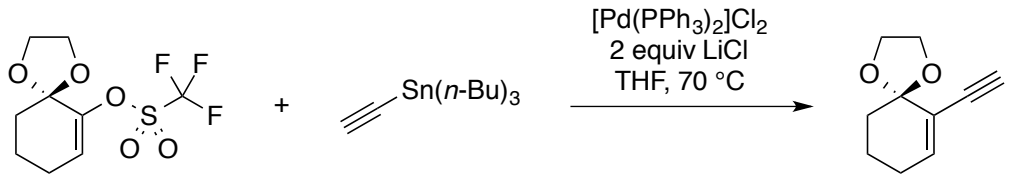
Prepared by *General Procedure 4.4.2.1* with **61** (4.2 g, 15 mmol), ethynylmagnesium bromide (**63**) (90 mL, 30 mmol), and $Co(acac)_3$ (263 mg, 0.75 mmol). Chromatographic purification with hexanes/EtOAc (90:10) afforded the title compound as a pale yellow oil (2.06 g, 88% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (dd, J = 7.6, 1.6 Hz, 1H), 7.16 (td, J = 7.8, 1.6 Hz, 1H), 6.94 (td, J = 7.5, 1.1 Hz, 1H), 6.79 (dd, J = 8.1, 1.1 Hz, 1H), 6.18 (t, J = 4.0 Hz, 1H), 4.83 (dd, J = 4.0, 0.6 Hz, 2H), 3.18-3.10 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 130.2, 128.8, 125.8, 121.8, 121.1, 118.7, 116.1, 80.3, 79.3, 65.4.

FTIR (neat): ν_{max}/cm^{-1} 3287, 3054, 3019, 2933, 2875, 2829, 1486.

HRMS (p-APCI): *m/z* 157.1881 [$(M+H)^+$ requires 157.1880].



6-ethynyl-1,4-dioxaspiro[4.5]dec-6-ene (70)

An oven-dried round-bottomed flask, equipped with a magnetic stirring bar and reflux condenser, was cooled to ambient temperature under vacuum, and subsequently backfilled with an

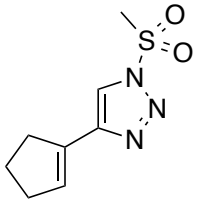
atmosphere of argon three times. The reaction vessel was charged with the **62** (2.9 g, 10 mmol) and tetrahydrofuran (80 mL). To the virogously stirred solution were then added **64** (3.5 g, 11 mmol), LiCl (0.85 g, 20 mmol), and $[Pd(PPh_3)_2]Cl_2$ (212 mg, 0.30 mmol), and the reaction mixture was immersed in a preheated oil bath until consumption of **62** was apparent by TLC analysis. Upon cooling to ambient temperature, the crude reaction mixture was concentrated *in vacuo*. Chromatographic purification with pentane/dichloromethane (75:25) afforded the title compound as an amorphous, colorless solid (3.2 g, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (t, J = 4.1 Hz, 1H), 4.26-4.15 (m, 2H), 4.04-3.94 (m, 2H), 2.84 (s, 1H), 2.16-2.11 (m, 2H), 1.81-1.77 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 123.4, 106.0, 81.7, 77.0, 65.9, 34.4, 25.7, 20.3.

FTIR (neat): ν_{max}/cm^{-1} 3273, 2947, 2887, 2828, 1626, 1437, 1117, 1070.

HRMS (p-APCI): *m/z* 165.0910 [$(M+H)^+$ requires 165.0910].



4-(cyclopent-1-en-1-yl)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (75)

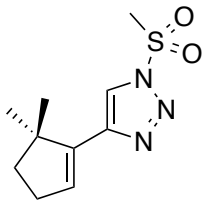
Prepared by *General Procedure 4.4.2.2* with **72** (0.46 g, 5.0 mmol). Recrystallization from pentane/diethyl ether (2:1) afforded the title compound as a crystalline white solid (0.80 g, 75% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (s, 1H), 6.52 (p, J = 2.3 Hz, 1H), 3.52 (s, 3H), 2.69 (dtd, J = 10.1, 4.6, 2.3 Hz, 2H), 2.57 (ddq, J = 10.1, 5.0, 2.5 Hz, 2H), 2.05 (p, J = 7.6 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 181.7, 173.6, 131.1, 118.7, 42.8, 33.5, 33.4, 23.3.

FTIR (neat): ν_{max}/cm^{-1} 2144, 3006, 2954, 2914, 2849, 1419, 1371, 1342, 1330, 1195, 1182.

HRMS (p-APCI): *m/z* 214.0646 [$(M+H)^+$ requires 214.0645].



4-(5,5-dimethylcyclopent-1-en-1-yl)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (76)

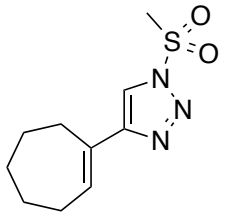
Prepared by *General Procedure 4.4.2.2* with **65** (1.10 g, 9.2 mmol). Recrystallization from pentane/diethyl ether (3:1) afforded the title compound as a crystalline white solid (1.56 g, 71% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (s, 1H), 6.35 (t, J = 2.4 Hz, 1H), 3.54 (s, 3H), 2.47 (td, J = 7.2, 2.4 Hz, 2H), 1.89 (t, J = 7.2 Hz, 3H), 1.28 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.8, 139.7, 131.3, 118.5, 46.2, 42.8, 41.3, 30.3, 27.3.

FTIR (neat): ν_{max}/cm^{-1} 2140, 3005, 2958, 2911, 2851, 1420, 1371, 1346.

HRMS (p-APCI): *m/z* 242.3165 [$(M+H)^+$ requires 242.3165].



4-(cyclohept-1-en-1-yl)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (77)

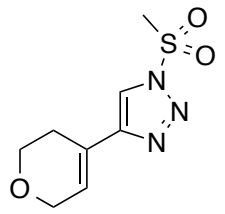
Prepared by *General Procedure 4.4.2.2* with **73** (0.60 g, 5.0 mmol). Recrystallization from pentane/diethyl ether (2:1) afforded the title compound as a crystalline white solid (0.87 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 6.82 (t, J = 6.7 Hz, 1H), 3.51 (s, 3H), 2.66-2.55 (m, 2H), 2.40-2.27 (m, 2H), 1.90-1.77 (m, 2H), 1.74-1.52 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 133.3, 132.4, 117.9, 42.8, 32.2, 31.1, 28.7, 26.6, 26.5.

FTIR (neat): ν_{max}/cm^{-1} 3148, 3015, 2921, 2849, 1536, 1374, 1178.

HRMS (p-APCI): *m/z* 242.0957 [$(M+H)^+$ requires 242.0958].



4-(3,6-dihydro-2*H*-pyran-4-yl)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (78)

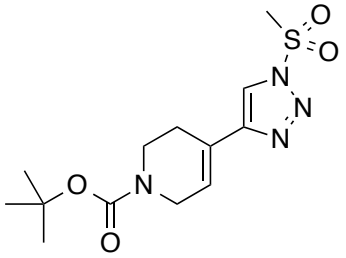
Prepared by *General Procedure 4.4.2.2* with **66** (0.55 g, 5.0 mmol). Recrystallization from pentane/diethyl ether (1:2) afforded the title compound as a crystalline white solid (1.05 g, 91% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (s, 1H), 6.64 (tt, J = 3.0, 1.7 Hz, 1H), 4.34 (q, J = 2.8 Hz, 2H), 3.93 (t, J = 5.5 Hz, 2H), 3.52 (s, 3H), 2.52-2.49 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 147.7, 126.1, 124.0, 118.0, 65.5, 64.0, 42.8, 26.5.

FTIR (neat): ν_{max}/cm^{-1} 3152, 3026, 2998, 2967, 2920, 2843, 1374, 1320, 1174, 1117.

HRMS (p-APCI): *m/z* 230.0593 [$(M+H)^+$ requires 230.0594].



***tert*-butyl 4-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (79)**

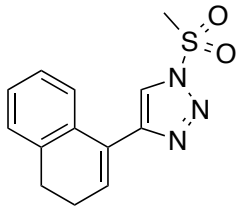
Prepared by *General Procedure 4.4.2.2* with **67** (1.35 g, 5.0 mmol). Recrystallization from pentane/diethyl ether (3:1) afforded the title compound as a crystalline white solid (1.40 g, 86% yield).

^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): δ 7.94 (s, 1H), 6.59 (tt, J = 3.3, 1.5 Hz, 1H), 4.11 (q, J = 2.9 Hz, 2H), 3.65 (t, J = 5.7 Hz, 2H), 3.50 (s, 3H), 2.55-2.47 (m, 2H), 1.49 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$, 55 °C): δ 155.0, 147.8, 125.1, 124.4, 118.1, 80.2, 43.7, 42.8, 28.7, 26.6.

FTIR (neat): ν_{max}/cm^{-1} 3144, 3005, 2976, 2928, 1686, 1540, 1414, 1365, 1179, 1164.

HRMS (p-APCI): *m/z* 329.1277 [$(M+H)^+$ requires 329.1278].



4-(3,4-dihydronaphthalen-1-yl)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (80)

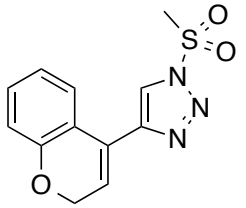
Prepared by *General Procedure 4.4.2.2* with **68** (0.77 g, 5.0 mmol). Recrystallization from pentane/diethyl ether (1:2) afforded the title compound as a crystalline white solid (1.24 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.28-7.25 (m, 1H), 7.23-7.18 (m, 3H), 6.67 (t, J = 4.8 Hz, 1H), 3.57 (s, 3H), 2.84 (t, J = 7.9 Hz, 2H), 2.47-2.42 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 136.7, 132.7, 131.8, 128.1, 127.9, 127.6, 126.8, 124.3, 120.8, 42.8, 27.9, 23.3.

FTIR (neat): ν_{max}/cm^{-1} 3145, 3020, 2931, 2885, 2830, 1486, 1374, 1180.

HRMS (p-APCI): *m/z* 276.0800 [$(M+H)^+$ requires 276.0801].



4-(2*H*-chromen-4-yl)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (81)

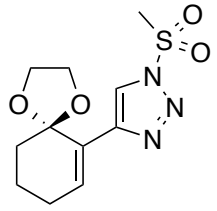
Prepared by *General Procedure 4.4.2.2* with **69** (0.78 g, 5.0 mmol). Recrystallization from pentane/diethyl ether (1:3) afforded the title compound as a crystalline white solid (1.29 g, 93% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.32 (dd, J = 7.7, 1.4 Hz, 1H), 7.22 (td, J = 7.8, 1.5 Hz, 1H), 7.03 - 6.87 (m, 2H), 6.41 (t, J = 4.1 Hz, 1H), 4.86 (d, J = 4.1 Hz, 2H), 3.59 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.5, 143.9, 130.0, 124.9, 124.5, 123.4, 121.6, 121.3, 120.9, 116.6, 64.7, 42.6.

FTIR (neat): ν_{max}/cm^{-1} 3152, 3062, 3020, 2994, 2915, 2844, 1604, 1488, 1376, 1333, 1223, 1176, 1016.

HRMS (p-APCI): *m/z* 278.0594 [$(M+H)^+$ requires 278.0594].



1-(methylsulfonyl)-4-(1,4-dioxaspiro[4.5]dec-6-en-6-yl)-1*H*-1,2,3-triazole (82)

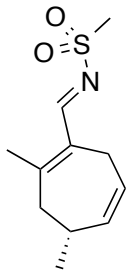
Prepared by *General Procedure 4.4.2.2* with **70** (0.82 g, 5.0 mmol). Recrystallization from pentane/diethyl ether (1:2) afforded the title compound as a crystalline white solid (1.17 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.04 (t, J = 4.0 Hz, 1H), 4.12-4.04 (m, 4H), 3.51 (s, 1H), 2.32-2.28 (m, 2H), 1.92-1.88 (m, 2H), 1.86-1.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 137.2, 127.0, 119.9, 106.7, 64.6, 42.8, 33.0, 25.8, 20.1.

FTIR (neat): ν_{max}/cm^{-1} 3137, 3026, 2934, 2880, 1417, 1372, 1333, 1182.

HRMS (p-APCI): *m/z* 286.0859 [(M+H)$^+$ requires 286.0856].



(*R*,*E*)-*N*-((2,4-dimethylcyclohepta-1,5-dien-1-yl)methylene)methanesulfonamide (83)

Prepared by *General Procedure 4.4.2.3* with **74** (94 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (75:25) afforded the title compound as a white solid (81 mg, 71% yield).

MP = 38–39 °C.

[α]$^{20}_{D}$ –3.2° (*c* 1.0, $CHCl_3$).

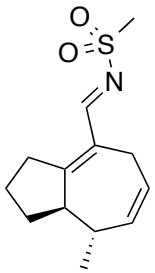
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.06 (s, 1H), 5.60 (dddd, *J* = 11.4, 6.8, 4.8, 2.1 Hz, 1H), 5.45-5.38 (m, 1H), 3.31 (dd, *J* = 17.6, 6.7 Hz, 1H), 3.23-3.13 (m, 1H), 3.06 (s, 3H), 2.73 (dd, *J* = 12.6, 9.9 Hz, 1H), 2.50 (dd, *J* = 12.7, 2.7 Hz, 1H), 2.48-2.42 (m, 1H), 2.23 (s, 3H), 1.09 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 167.9, 165.1, 135.9, 135.2, 124.8, 43.4, 40.7, 31.3, 23.8, 22.6, 21.2.

FTIR (neat): ν_{max}/cm^{-1} 3012, 2958, 2932, 2871, 1621, 1558, 1455, 1308, 1141.

HRMS (p-APCI): *m/z* 228.1051 [$(M+H)^+$ requires 228.1053].

HPLC: 90% ee (ADH, 5.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 12.1 min (minor), 15.6 min (major).



(*E*)-*N*-(((8*S*,8a*R*)-8-methyl-1,2,3,5,8,8a-hexahydroazulen-4-yl)methylene)methanesulfonamide (75)

Prepared by *General Procedure 4.4.2.3* with **75** (107 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (80:20) afforded the title compound as a white solid (118 mg, 93% yield).

MP = 93–95 °C.

$[\alpha]^{20}_D$ –92.2° (*c* 1.0, $CHCl_3$).

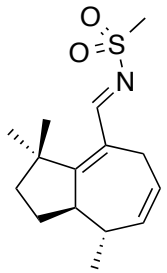
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 5.67-5.54 (m, 1H), 5.42-5.32 (m, 1H), 3.38 (dd, *J* = 17.9, 8.2 Hz, 1H), 3.05 (s, 3H), 3.04-2.89 (m, 3H), 2.69-2.58 (m, 1H), 2.20-2.09 (m, 1H), 2.08-2.00 (m, 1H), 1.97-1.87 (m, 1H), 1.67-1.51 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 169.3, 135.8, 131.6, 124.3, 50.1, 40.7, 36.7, 31.7, 31.6, 24.9, 24.2, 21.4.

FTIR (neat): ν_{max}/cm^{-1} 3012,2960, 2933, 2872, 1632, 1560, 1309, 1142.

HRMS (p-APCI): *m/z* 254.1207 [$(M+H)^+$ requires 254.1209].

HPLC: 68% ee (ADH, 2.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 15.2 min (minor), 16.3 min (major).



_N_-((_E_)-((8_S_)-3,3,8-trimethyl-1,2,3,5,8,8a-hexahydroazulen-4-yl)methylene)methanesulfonamide (85)

Prepared by *General Procedure 4.4.2.3* with **76** (139 mg, 0.57 mmol) and **46** (0.12 mL, 1.2 mmol). Purification with hexanes/EtOAc (80:20) afforded the title compound as a white solid (150 mg, 94% yield).

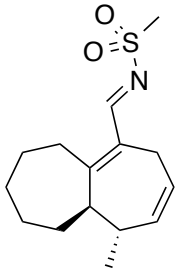
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.27 (s, 1H), 5.61 (ddt, J = 11.4, 5.4, 2.4 Hz, 1H), 5.34 (dt, J = 11.4, 2.4 Hz, 1H), 3.39 (dd, J = 16.8, 9.0 Hz, 1H), 3.24 (ddd, J = 11.4, 7.8, 3.0 Hz, 1H), 3.06 (s, 3H), 2.94 (ddd, J = 16.8, 3.0, 2.4 Hz, 1H), 2.24-2.16 (m, 1H), 1.95-1.88 (m, 1H), 1.81-1.76 (m, 1H), 1.74-1.69 (m, 1H), 1.66-1.61 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.10 (d, J 6.6 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 183.0, 168.5, 135.9, 133.0, 124.6, 52.4, 44.7, 43.1, 40.6, 35.8, 31.0, 30.8, 27.4, 24.5, 21.3.

FTIR (neat): ν_{max}/cm^{-1} 3013, 2960, 2934, 2871, 1612, 1557, 1458, 1309, 1140.

HRMS (p-APCI): *m/z* 282.1521 [$(M+H)^+$ requires 281.1522].

HPLC: 94% ee (ADH, 0.5% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 36.5 min (minor), 44.9 min (major).



(*E*)-*N*-(((5*S*,5a*R*)-5-methyl-2,5,5a,6,7,8,9,10-octahydroheptalen-1-yl)methylene)methanesulfonamide (86)

Prepared by *General Procedure 4.4.2.3* with **77** (121 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (80:20) afforded the title compound as an amorphous solid (105 mg, 75% yield).

$[\alpha]^{20}_D$ +58.8° (*c* 1.0, $CHCl_3$).

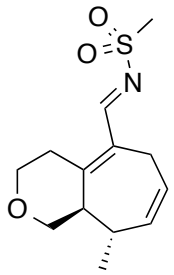
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 5.63-5.51 (m, 1H), 5.17 (dt, *J* = 11.3, 2.3 Hz, 1H), 3.58 (dd, *J* = 17.6, 8.6 Hz, 1H), 2.95-2.87 (m, 1H), 2.75 (td, *J* = 11.3, 4.3 Hz, 1H), 2.52-2.45 (m, 1H), 2.45 (s, 3H), 1.76-1.65 (m, 1H), 1.61-1.34 (m, 5H), 0.97-0.79 (m, 3H), 0.77 (d, *J* = 7.1 Hz, 3H), 0.72-0.59 (m, 1H).

^{13}C NMR (100 MHz, C_6D_6): δ 172.1, 166.9, 136.7, 135.9, 125.2, 49.0, 40.0, 35.6, 30.3, 29.8, 29.5, 27.1, 26.9, 23.8, 19.7.

FTIR (neat): ν_{max}/cm^{-1} 3010, 2919, 2851, 1601, 1552, 1442, 1306, 1137.

HRMS (p-APCI): *m/z* 282.1519 [$(M+H)^+$ requires 282.1522].

HPLC: 89% ee (ADH, 2.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 15.8 min (minor), 17.0 min (major).



(*E*)-*N*-(((9*S*,9a*R*)-9-methyl-1,3,4,6,9,9a-hexahydrocyclohepta[*c*]pyran-5-yl)methylene)methanesulfonamide (87)

Prepared by *General Procedure 4.4.2.3* with **78** (115 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (60:40) afforded the title compound as a colorless oil (121 mg, 90% yield).

$[\alpha]^{20}_D$ –5.4° (*c* 0.3, $CHCl_3$).

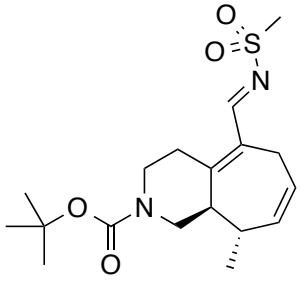
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.08 (s, 1H), 5.73-5.67 (m, 1H), 5.43-5.39 (m, 1H), 3.98-3.93 (m, 1H), 3.86 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.83-3.74 (m, 2H), 3.38 (dd, *J* = 17.3, 8.1 Hz, 1H), 3.21-3.15 (m, 1H), 3.07 (s, 3H), 3.00-2.91 (m, 2H), 2.86-2.79 (m, 1H), 2.51-2.44 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.9, 164.4, 136.8, 135.1, 126.3, 68.3, 67.1, 46.6, 40.7, 32.0, 27.7, 23.6, 19.8.

FTIR (neat): ν_{max}/cm^{-1} 3012, 2966, 2930, 2854, 1611, 1558, 1446, 1308, 1141.

HRMS (p-APCI): *m/z* 270.1156 [$(M+H)^+$ requires 270.1158].

HPLC: 96% ee (ADH, 5.0% isopropanol/hexanes, 1.0 mL/min, UV: xxx nm). t_R = 12.8 min (minor), 13.8 min (major).



(9*S*,9a*R*)-*tert*-butyl 9-methyl-5-((*E*)-((methylsulfonyl)imino)methyl)-3,4,9,9a-tetrahydro-1*H*-cyclohepta[*c*]pyridine-2(6*H*)-carboxylate (88)

Prepared by *General Procedure 4.4.2.3* with **79** (164 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (90:10) afforded the title compound as a white solid (135 mg, 73% yield).

MP = 143–144 °C.

$[\alpha]^{20}_D$ +7.9° (*c* 1.0, $CHCl_3$).

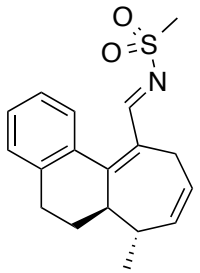
^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ 9.05 (s, 1H), 5.64 (ddt, *J* = 11.1, 8.6, 2.6 Hz, 1H), 5.35 (dt, *J* = 11.3, 2.8 Hz, 1H), 3.57 (bs, 1H), 3.49-3.40 (m, 2H), 3.22 (bs, 1H), 3.10-3.02 (m, 1H), 3.04 (s, 3H), 3.01-2.92 (m, 1H), 2.87 (bs, 1H), 2.23 (bs, 1H), 1.51-1.46 (m, 1H), 1.47 (s, 9H), 1.12 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 55 °C): δ 166.7, 155.3, 136.4, 136.2, 128.6, 125.1, 80.3, 46.4, 42.8, 40.7, 40.7, 33.9, 28.7, 25.6, 23.8, 20.0.

FTIR (neat): ν_{max}/cm^{-1} 3012, 2974, 2931, 2877, 1689, 1621, 1561, 1408, 1312, 1144.

HRMS (p-APCI): *m/z* 369.1842 [$(M+H)^+$ requires 369.1843].

HPLC: 86% ee (ADH, 10.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 12.8 min (minor), 17.0 min (major).



(*E*)-*N*-(((6a*R*,7*S*)-7-methyl-6,6a,7,10-tetrahydro-5*H*-cyclohepta[*a*]naphthalen-11-yl)methylene)methanesulfonamide (89)

Prepared by *General Procedure 4.4.2.3* with **80** (138 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (80:20) afforded the title compound as a white solid (138 mg, 88% yield).

MP = 113–114 °C.

$[\alpha]^{20}_D$ +76.2° (*c* 1.8, $CHCl_3$).

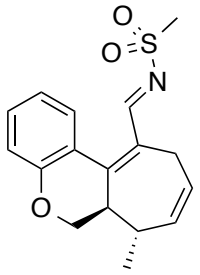
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 5.74 (ddt, *J* = 11.0, 8.9, 2.2 Hz, 1H), 5.41 (dt, *J* = 11.4, 2.8 Hz, 1H), 3.63 (dd, *J* = 17.9, 8.8 Hz, 1H), 3.44 (td, *J* = 10.9, 6.8 Hz, 1H), 3.19 (dq, *J* = 17.9, 3.1 Hz, 1H), 3.04 (s, 3H), 2.73 (dt, *J* = 13.9, 3.0 Hz, 1H), 2.42-2.30 (m, 2H), 2.04-1.96 (m, 1H), 1.13-1.06 (m, 1H), 1.11 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.5, 164.0, 142.9, 137.6, 136.5, 132.9, 131.6, 130.6, 126.9, 126.4, 124.5, 45.3, 40.7, 37.7, 29.8, 29.1, 23.9, 19.8.

FTIR (neat): ν_{max}/cm^{-1} 3013, 2955, 2929, 2874, 2844, 1585, 1549, 1306, 1234, 1140.

HRMS (p-APCI): *m/z* 316.1364 [$(M+H)^+$ requires 316.1366].

HPLC: 96% ee (ADH, 5.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 12.7 min (major), 19.9 min (minor).



(*E*)-*N*-(((6a*R*,7*S*)-7-methyl-6,6a,7,10-tetrahydrocyclohepta[*c*]chromen-11-yl)methylene)methanesulfonamide (90)

Prepared by *General Procedure 4.4.2.3* with **81** (139 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (70:30) afforded the title compound as a white solid (149 mg, 94% yield).

MP = 134 °C (decomp.).

$[\alpha]^{20}_D$ +119.6° (*c* 1.1, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.84 (s, 1H), 7.40-7.36 (m, 1H), 7.12 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.07-7.04 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 5.81-5.76 (m, 1H), 5.45 (dt, *J* = 11.2, 2.6 Hz, 1H),

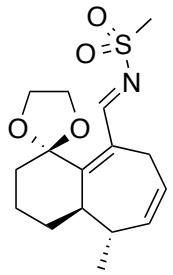
4.48 (dd, J = 11.2, 6.1 Hz, 1H), 3.80-3.76 (m, 1H), 3.62-3.56 (m, 2H), 3.29 (dq, J = 18.3, 3.0 Hz, 1H), 3.07 (s, 3H), 2.41-2.34 (m, 1H), 1.12 (d, J = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.3, 158.2, 157.1, 136.3, 132.7, 131.9, 125.6, 123.0, 122.3, 117.5, 70.5, 46.8, 40.7, 33.8, 24.7, 19.4.

FTIR (neat): ν_{max}/cm^{-1} 3016, 2968, 2931, 2876, 1602, 1551, 1478, 1450, 1309, 1139.

HRMS (p-APCI): *m/z* 318.1155 [$(M+H)^+$ requires 318.1158].

HPLC: 98% ee (ADH, 10.0% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 11.8 min (major), 17.0 min (minor).



(*E*)-*N*-(((4a*R*,5*S*)-5-methyl-2,3,4,4a,5,8-hexahydrospiro[benzo[7]annulene-1,2'-[1,3]dioxolan]-9-yl)methylene)methanesulfonamide (91)

Prepared by *General Procedure 4.4.2.3* with **82** (143 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). Purification with hexanes/EtOAc (70:30) afforded the title compound as a white solid (161 mg, 99% yield).

MP = 151–153 °C

$[\alpha]^{20}_D$ –2.0° (*c* 0.6, $CHCl_3$)

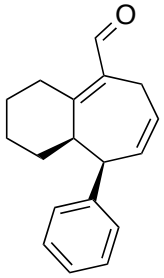
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 5.69 (dddd, J = 10.4, 8.2, 4.0, 2.0 Hz, 1H), 5.39 (ddd, J = 11.0, 3.4, 2.2 Hz, 1H), 4.03-3.88 (m, 2H), 3.81-3.67 (m, 2H), 3.38 (dd, J = 17.2, 8.2 Hz, 1H), 3.13 (ddd, J = 17.2, 6.3, 3.0 Hz, 1H), 3.07 (s, 3H), 2.99 (td, J = 10.6, 5.8 Hz, 1H), 2.45-2.34 (m, 1H), 2.17-2.07 (m, 1H), 1.96 (ddd, J = 14.0, 10.7, 7.7 Hz, 1H), 1.87-1.74 (m, 2H), 1.67-1.56 (m, 1H), 1.49-1.37 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 160.9, 137.5, 137.2, 126.0, 111.2, 64.1, 63.9, 47.5, 40.5 36.3, 36.0, 27.9, 24.8, 20.4, 20.2.

FTIR (neat): ν_{max}/cm^{-1} 3010, 2951, 2874, 1604, 1556, 1452, 1312, 1139.

HRMS (p-APCI): *m/z* 326.1416 [$(M+H)^+$ requires 326.1421].

HPLC: 99% ee (ADH, 10.0% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 9.2 min (major), 10.2 min (minor).



(9*R*,9a*R*)-9-phenyl-2,3,4,6,9,9a-hexahydro-1*H*-benzo[7]annulene-5-carbaldehyde (92)

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **43** (130 mg, 1.0 mmol). The reaction was cooled to 0 °C and dilute with methanol (3.5 mL) and water (10 drops). Sodium methoxide (55 mg, 1.0 mmol) was added in a single portion with vigorous stirring. The reaction was gradually warmed to ambient temperature over 2 h. Sodium sulfate (~500 mg) was added, and the resultant suspension was filtered through a glass frit. The filter

cake was washed with dichloromethane (10 mL) and the filtrate was concentrated *in vacuo*. Purification with hexanes/EtOAc (90:10) afforded the title compound as a white solid (97 mg, 77% yield).

MP = 88–89 °C.

$[\alpha]^{20}_{D}$ +118.9° (*c* 0.3, $CHCl_3$).

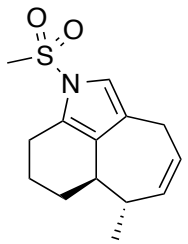
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.30-7.21 (m, 3H), 7.21-7.15 (m, 2H), 5.86 (tdd, *J* = 10.8, 8.4, 2.0 Hz, 1H), 5.71-5.64 (m, 1H), 3.69 (bs, 1H), 3.56 (dd, *J* = 17.9, 8.6 Hz, 1H), 3.41-3.30 (m, 1H), 3.05-2.96 (m, 1H), 2.89-2.78 (m, 1H), 1.75-1.69 (m, 1H), 1.65-1.45 (m, 5H), 1.34-1.24 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 167.0, 140.5, 132.7, 129.8, 128.2, 127.1, 126.5, 47.7, 46.0, 27.2, 25.0, 23.6, 22.7, 21.6.

FTIR (neat): ν_{max}/cm^{-1} 3059, 3007, 2935, 2861, 2753, 1660, 1624, 1595, 1487, 1452.

HRMS (p-APCI): *m/z* 253.1585 [$(M+H)^+$ requires 253.1587].

HPLC: 97% ee (*S,S*-Whelk, 0.5% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 37.2 min (major), 43.0 min (minor).



(6*S*,6a*R*)-6-methyl-1-(methylsulfonyl)-3,6,6a,7,8,9-hexahydro-1*H*-cyclohepta[*cd*]indole (93)

Prepared by *General Procedure 4.4.2.3* with **82** (143 mg, 0.50 mmol) and **46** (0.10 mL, 1.0 mmol). The reaction was cooled to 0 °C and dilute with anhydrous tetrahydrofuran (4.5 mL). Sodium borohydride (29 mg, 0.75 mmol) was added in a single portion. The reaction was then allowed to warm to ambient temperature and stirred for 4 h. The reaction was returned to 0 °C and Amberlyst® 15 (250 mg) was added in a single portion. The reaction was slowly warmed to ambient temperature over 2 h and then filtered through a glass frit. The filtrate was concentrated *in vacuo*. Purification with pentanes/ether/triethylamine (90:10:1) afforded the title compound as a white solid (124 mg, 94% yield).

MP = 70 °C (decomp.).

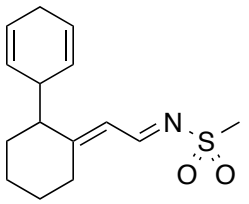
$[\alpha]^{20}_{D}$ –4.0° (*c* 0.6, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.75 (s, 1H), 5.71-5.67 (m, 1H), 5.50-5.47 (m, 1H), 3.25-3.17 (m, 2H), 3.04 (s, 3H), 2.78 (dt, J = 16.8, 4.8 Hz, 1H), 2.71-2.66 (m, 1H), 2.53-2.50 (m, 1H), 2.34-2.27 (m, 1H), 1.97-1.90 (m, 2H), 1.71-1.65 (m, 1H), 1.44-1.38 (m, 1H), 1.10 (d, J = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 138.7, 129.1, 128.1, 125.0, 124.8, 115.7, 42.4, 38.6, 37.9, 27.5, 25.2, 23.7, 21.9, 20.0.

FTIR (neat): ν_{max}/cm^{-1} 3016, 2929, 2870, 1445, 1358, 1166.

HRMS (p-APCI): *m/z* 266.1207 [$(M+H)^+$ requires 266.1209].



***N*-((1*E*,2*E*)-2-([1,1'-bi(cyclohexane)]-2',5'-dien-2-ylidene)ethylidene)methanesulfonamide (97)**

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol) and **96** (0.25 mL, 2.5 mmol). Purification with hexanes/EtOAc (80:20) afforded the title compound as a colorless oil (77 mg, 56% yield).

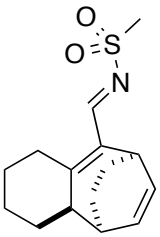
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.05 (d, J = 10.2 Hz, 1H), 6.23 (d, J = 10.2 Hz, 1H), 5.85-5.75 (m, 3H), 5.50-5.46 (m, 1H), 3.21-3.15 (m, 1H), 3.06 (s, 3H), 2.73-2.64 (m, 3H), 2.57 (ddd, J = 12.6, 7.2, 4.8 Hz, 1H), 2.29 (dt, J = 6.6, 4.8 Hz, 1H), 1.82-1.68 (m, 5H), 1.61-1.55 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.6, 167.5, 127.3, 126.2, 125.7, 125.6, 120.8, 52.3, 40.2, 35.0, 29.9, 29.2, 28.5, 26.3, 23.2.

FTIR (neat): ν_{max}/cm^{-1} .

HRMS (p-APCI): *m/z* [(M+H)$^+$].

HPLC: 98% ee (ADH, 5.0% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 14.0 min (major), 16.1 min (minor).



***N*-((*E*)-((4a*R′*,5*S′*,8*R′*)-2,3,4,4a,5,8-hexahydro-1H-5,8-ethanobenzo[7]annulen-9-yl)methylene)methanesulfonamide (98)**

Prepared by *General Procedure 4.4.2.3* with **42** (114 mg, 0.50 mmol), **96** (0.25 mL, 2.5 mmol), and [$Rh_2(piv)_4$] (3 mg, 0.005 mmol). Purification with hexanes/EtOAc (85:15) afforded the title compound as a colorless oil (110 mg, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.19 (s, 1H), 6.35 (t, J = 6.0 Hz, 1H), 6.09 (t, J = 6.0 Hz, 1H), 3.88-3.82 (m, 1H), 3.24-3.17 (m, 1H), 3.07 (s, 3H), 2.37-2.26 (m, 2H), 1.96-1.74 (m, 7H), 1.73-1.48 (m, 3H), 1.37-1.24 (m, 1H).

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– Chapter 5 –

Functionalized Heterocycle Synthesis from Reaction of Triazole Carbene Precursors and Electron Rich π–Bonds

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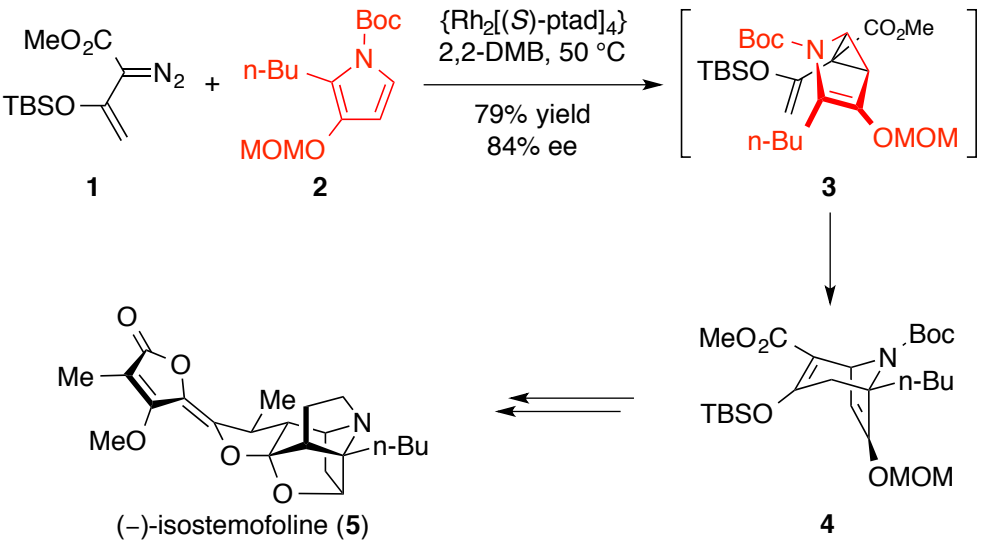
5.1 Introduction

The history of reactivity between donor/acceptor rhodium carbene intermediates and electron rich π–bonds of heteroaromatics and arenes is vast.[1–7] Many of the seminal investigations by Davies and co-workers involved the tandem cyclopropanation/Cope rearrangement between rhodium vinylcarbene intermediates tethered to furans, generating complex, fused oxa- or azabicyclooctane cores in short order.[8–11] As competent, chiral dirhodium tetracarboxylate catalysts suitable for promoting enantioselective, intermolecular formal [4 + 3]-cycloaddition reactions were developed,[12–14] the range of nucleophilic partners which could readily be exploited was increased in dramatic fashion. An important application of the advance in methodology was the development of the {Rh_2[(*S*)-ptad]$_4$}-catalyzed formal [4 + 3]-cycloaddition reaction between pyrroles and siloxyvinyldiazoacetate **1**, enabling a facile and stereoselective entry into tropane-type nuclei.[15] Indeed, the reaction was readily applied to the formal synthesis of the natural product (–)-isostemofoline (**5**)[15] bearing a densely functionazlied alkaloid architecture, which had previously been prepared as a racemate by Kende and co-workers[16] through the rhodium octanoate-catalyzed cycloaddition (Scheme 5.1). Thus, stereoselective cyclopropanation of trisub-

stituted pyrrole **2** with the metallocarbene derived from **1**, under the catalytic action of {Rh_2[(*S*)-ptad]$_4$}, affords intermediate **3**, which participates in a tandem cope rearrangement to intercept intermediate **4**, prepared by Kende and co-workers, in good yield and stereoselectivity (79% yield, 84% ee).

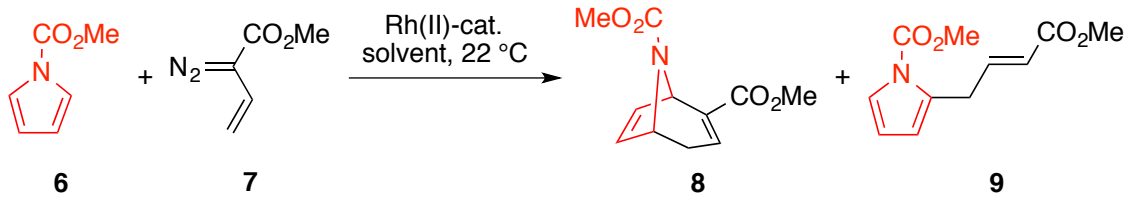


Scheme 5.1 Rhodium-catalyzed tandem cyclopropanation/Cope rearrangement and application to the formal synthesis of (–)-isostemofoline

An interesting aspect of the furan and pyrrole cycloaddition chemistry is the potential for chemodivergence, as solvent, catalyst and carbene electronics have all been demonstrate to play contributing roles in dictating the dominant mode of reactivity. The seminal studies on the substitution of a pyrrole (**6**) nucleus were conducted with the simple vinylcarbene precursor **7** and achiral dirhodium tetracarboxylate catalysts (Table 5.1).[5] Under polarizing reaction conditions, implementing, increasingly electrophilic rhodium catalysts in moderately polar solvent medium,

a marked increased in preferential formation of the vinylogous, electrophilic aromatic substitution product **9** was observed (entries 1–3). For example, the electron rich rhodium hexanoate catalyst provided a moderate preference for formation of **8** (entry 1); however, the increasingly electron deficient catalysts, particularly [$Rh_2(TFA)_4$], afforded increasing quantities of the substitution product **9** (entry 3). In addition, apolar solvents, led to exclusive formation of the tandem cyclopropanation/Cope rearrangement product **8**, as with the reaction of rhodium hexanoate in benzene or *n*-hexane (entries 4 and 5). Even in nonpolar solvents, the electrophilic rhodium trifluoroacetate still exhibited preference for substitution product **9**, rather than the tropane-derivative **8** (entry 6).

Table 5.1[a,b] Solvent and catalyst effects in reactions of pyrroles and rhodium vinylcarbene intermediates



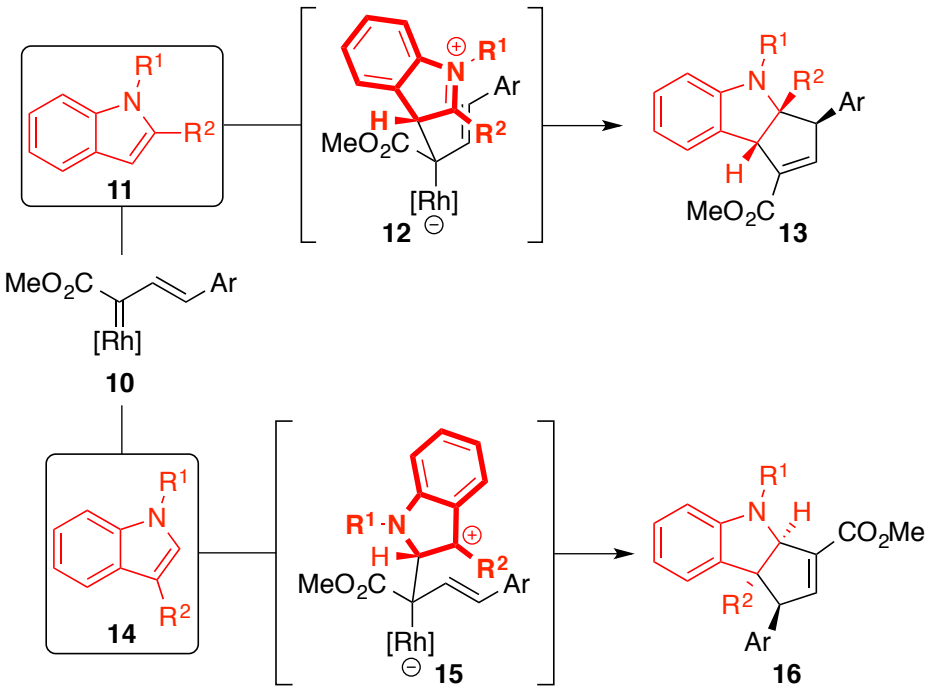
6 **7** **8** **9**

entry	Rh(II)-cat.	solvent	ratio, **8 : 9**	yield, %
1	$[Rh_2(hex)_4]$	1,2-DCE	86 : 14	34
2	$[Rh_2(OAc)_4]$	CH_2Cl_2	55 : 45	35
3	$[Rh_2(TFA)_4]$	CH_2Cl_2	15 : 85	16
4	$[Rh_2(hex)_4]$	PhH	>95 : 5	68
5	$[Rh_2(hex)_4]$	*n*-Hex	>95 : 5	75
6	$[Rh_2(TFA)_4]$	*n*-Hex	26 : 74	29

[a] Ratio **8** : **9** determined by ^{1}H NMR analysis of the crude reaction residue. [b] Isolated yields of **8**.

A number of orthogonal modes of reactivity beyond the tandem cyclopropanation/Cope rearrangement were discovered for rhodium vinylcarbene intermediates as chemical investigations were extended to other electron rich heterocyclic nucleophiles. Indeed, the vinylogous addition of 1,2-disubstituted indoles to the vinylogous carbon atom of the rhodium-bound carbene discussed in the Chapter 4.1 is one such example.[17,18] The foundations for that chemistry were laid by the preliminary investigations of pyrrole functionalization with vinyldiazoacetate. In addition, new modes of annulation chemistry were unveiled. For example, what would seem an innocent change in the dirhodium tetracarboxylate catalyst and alkenylcarbene precursor results in a formal [3 + 2]-cycloaddition reaction to forge a cyclpentene-annulated indoline nucleus.[19] With the styryldiazoacetates **10**, 1,2- and 1,3-disubstituted indoles (**11** and **14**, respectively) participate in stereo- and regiodivergent annulation chemistry, generating the fused tricyclic products in excellent yield and stereoselectivity (Scheme 5.2, **13** and **16**, respectively). The C(2)-substituted indoles are postulated to engage the rhodium-bound carbene intermediate **10** by C(3) electrophilic attack. For the zwitterion **12** to achieve the requisite orbital overlap between the benzylic carbon and the carbonyl of the iminium, the vinylcarbene must orient itself in a *s–trans* configuration. If the carbene were oriented *s–cis*, a significant steric repulsion between the "wall" of the paddlewheel complex and the C(2)-substituent would arise. Thus, cyclization occurs precluding any bond rotation to generate the tricycle **13** with R^2 and the aryl (Ar) substituent oriented *syn*-facially of the molecule. By comparison, a C(3)-substituent on the indole will faciliate a C(2) electrophilic attack of rhodium carbene **10**. The zwitterion **15** is able to achieve efficient orbital overlap between the benzylic carbons of both the nucleophile and carbene with the carbene oriented in a *s–cis* geometry while mitigating steric repulsions between nucleophile and catalyst. And so, during the cyclization event, the C(2)-substituent and the Ar group are ori-

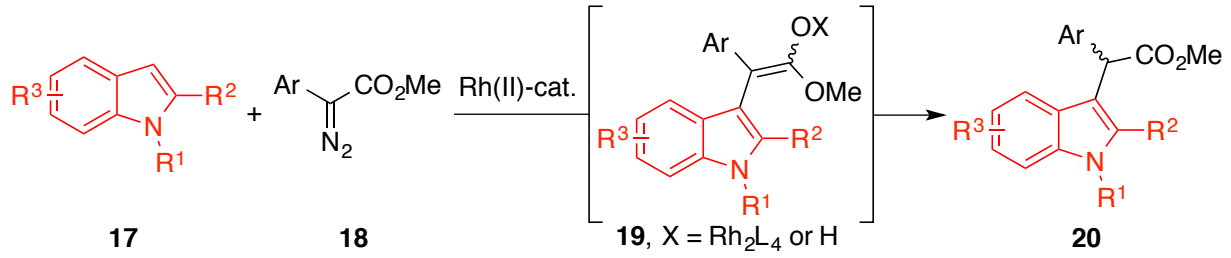
ented *anti* to one another, resulting the *endo* configuration of the aryl moiety observed in the product **16**.



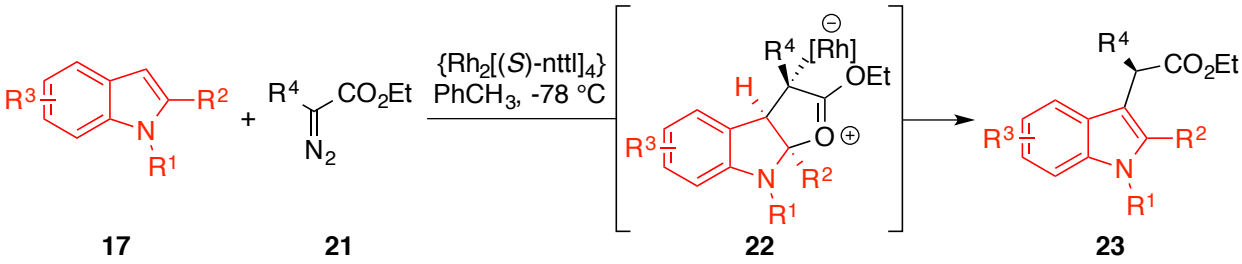
Scheme 5.2 Formal [3 + 2]-annulations of rhodium vinylcarbenes and 1,2- or 1,3-disubstituted indoles

Complementary experimental and computational investigations by Fox and co-workers on alkyldiazoacetate-derived rhodium carbene substitution reactions with indole nucleophiles have bolstered both insights into the mechanism and broadened the utility of these transformations.[20] The reactions of aryl-substituted diazoacetate-derived donor/acceptor carbene precursors **18** with indoles **17** tend to participate in simple electrophilic aromatic substitution reactions (Scheme 5.3a). Due to the proposed intermediacy of a rhodium-bound enolate intermediate (**19**, X =

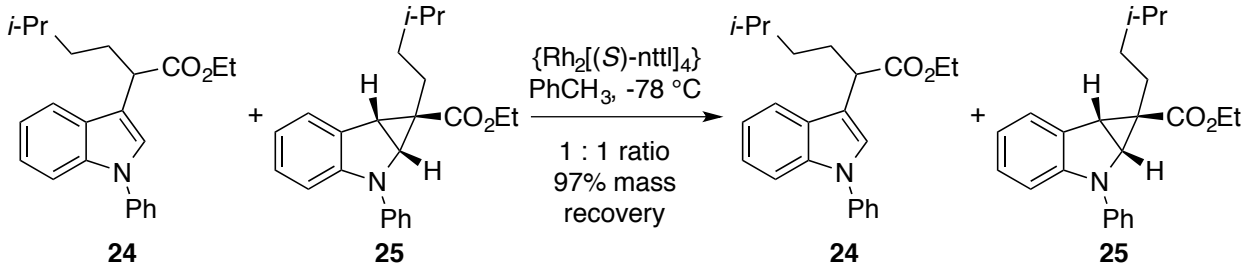
Rh_2L_4), or the free enol ester (**19**, X =H), the chiral influence of the catalyst is lost during the net transformation, with the consequence of racemic product (**20**) formation. When alkyldiazoacetates **21** are implemented in the carbene transformation, however, racemization of the newly formed α-stereocenter is not observed and the 2-substituted heteroauxin-derivative (**23**) is produced in excellent levels of enantioselectivity (Scheme 5.3b).[20] One contributing factor toward the decreased propensity to undergo enol(ate) formation may be the attenuated acidity of the α-proton for the products arising from alkyldiazoacetates (**23**) when compared to their aryl-counterparts (**20**). In addition, computational investigations by Fox identified the pseudo-hemiaminal **22** as a plausible intermediate along the energetic landscape of the substitution reaction. Assuming the latter hypothesis to be accurate, discrete differences in the electronics of the rhodium-bound zwitterionic intermediate are likely operative in formation of the cyclic transient. Noteably, conversion of the indolylcyclopropane **25**, prepared *via* a copper-catalyzed cyclopropanation of the indole with the diazoacetate, was not observed under the reaction conditions prescribed by the Fox group. Subjecting an equimolar mixture of formal C–H insertion product **24** and cyclopropane **25** to the reaction conditions resulted in retention of that ratio, and the two materials were recovered in near quantitative yield. Thus, a mechanism involving cyclopropanation and iminium ion-facilitated ring fragmentation would seem inoperative in the reaction mechanism.



(a) Racemic electrophilic aromatic substitution of indoles with aryldiazoacetates



(b) Enantioselective electrophilic aromatic substitution of indoles with alkyldiazoacetates

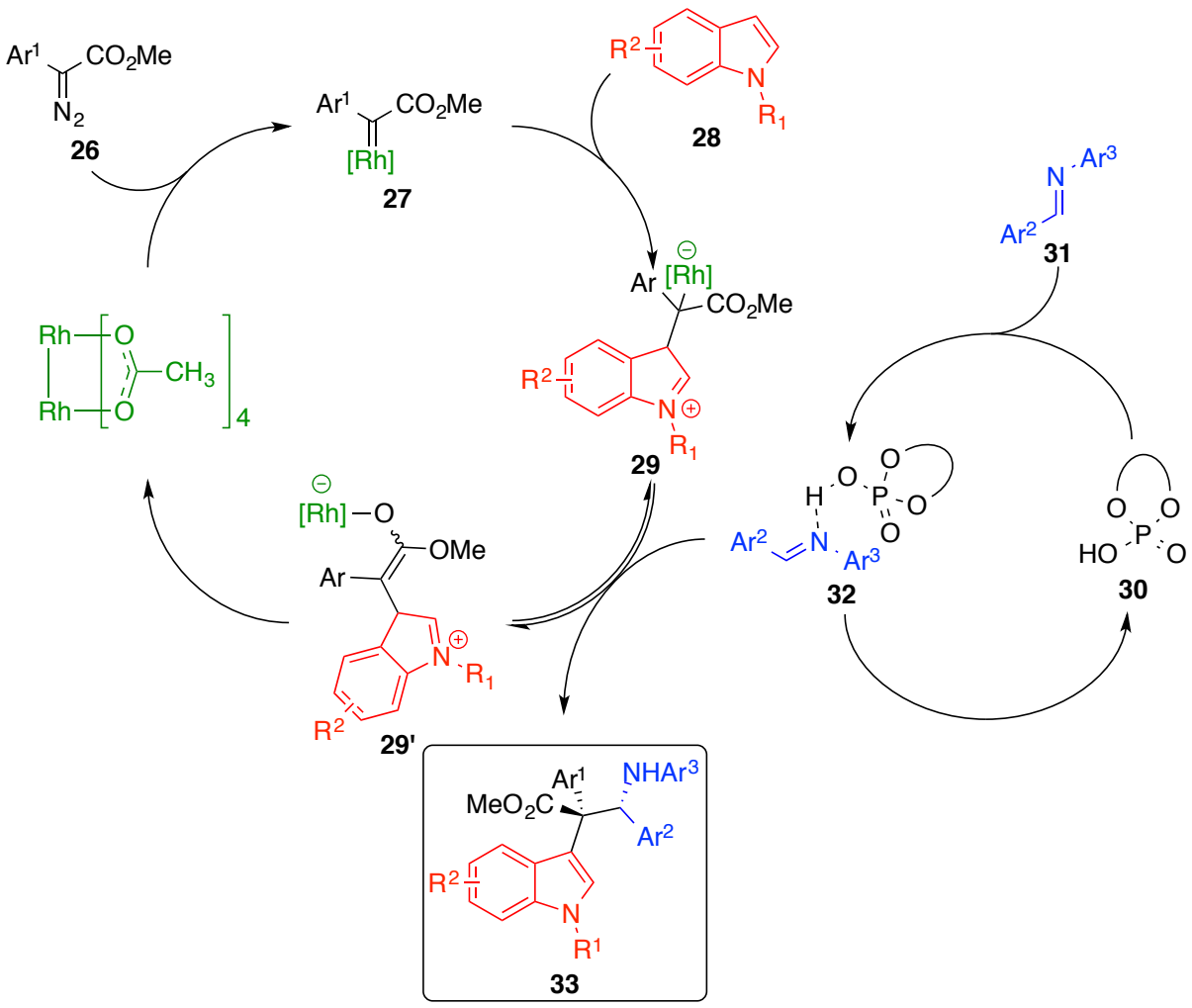


(c) Mechanistic control refuting intermediacy of a cyclopropane intermediate

Scheme 5.3 Electrophilic aromatic substitution of indoles with rhodium carbene intermediates

In a collaborative study, Hu and Doyle reported a creative circumvention to the problematic enolization/racemization of the zwitterionic intermediate generated by pairing of aryl-substituted carbene intermediates with indolyl nucleophiles.[21] Thus, the typical rhodium-bound zwitterion

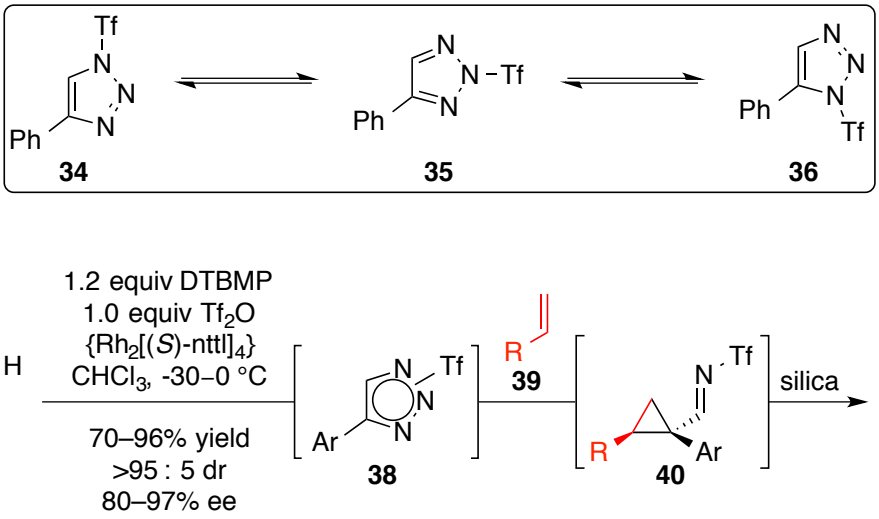
(**29** and **29´**), produced *in situ* from diazoacetate **26**-derived rhodium carbene **27** and indole **28**, participates in a Brønsted acid-catalyzed enantioselective 1,2-addition to chiral phosphonate-activated imine **32** (Scheme 5.4). The complex isotryptophan-derivatives (**33**) were obtained in excellent diastereo- and enantioselection for a variety of reaction partners in the three-component coupling. Analogous studies on the enantioselective N–H insertion of donor/acceptor substituted carbenes with carbamates under contemporaneous catalysis of dirhodium tetracarboxylates and chiral phosphonates identified a rhodium-dependence on enantioselectivity. These results only suggest, however, that either a free ylide or a metal-bound ylide is more efficient in the enantioselective transformation, but do not identify the operative intermediate.



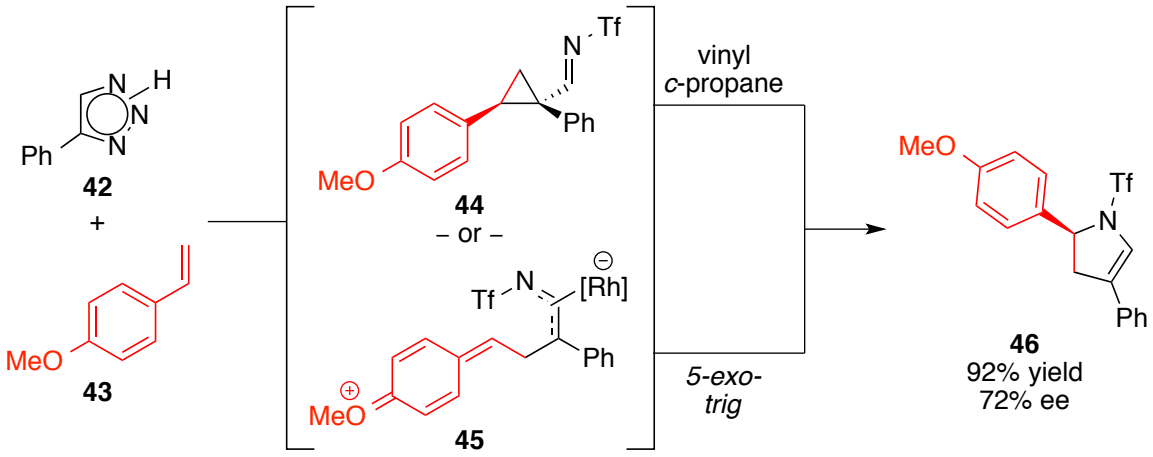
Scheme 5.4 Stereoselective three component coupling of aryldiazoacetates, indoles, and imines

By contrast to aryldiazoacetates, the reactivity of 4-substituted-*N*-sulfonyl-1,2,3-triazoles with a network of electron rich π–bonds, and aromatic heterocycles in particular, has been sparsely studied. *N*-Sulfonyl-1,2,3-triazole-based carbene precursors have proven powerful substrates for the synthesis of various nitrogenated heterocyclic rings.[22–35] Nevertheless, the few examples of the capturing the diazoimine-derived rhodium carbene species with electron rich "π–nucleophiles" attracted our attention. Among the first of such examples was contained tan-

gentially within a study on the *in situ* preparation of *N*-trifluoromethanesulfonyl-1,2,3-triazoles (**34–36**) for subsequent rhodium-catalyzed denitrogenation and cyclopropanation of olefins (Scheme 5.5).[36] The N–S bond of the *N*(1)-triflyl species **34** is quite labile, and thus, the triazole exists as an equilibrating mixture of N(1)-, N(2)- and N(3)-sulfonyl regioisomers (**34–36**, respectively). Accordingly, Fokin and co-workers designed mild conditions for its direct generation, by treating the N–H-1,2,3-triazole (**37**) with trifluoromethanesulfonic acid anhydride and the non-coordinating amine base 2,6-di-*tert*-butyl-4-methylpyridine. Although the cyclopropane carboxaldehyde products (Scheme 5,5a, **41**) were generated in high yield and stereoselectivity under ambient reaction conditions, when 4-vinylanisole was implemented as nucleophile, the *N*-triflyl-2,3-dihydropyrrole (Scheme 5.5b, **46**) was the sole product of the transformation. The formation of **46** could be justified through either of the plausible mechanistic postulates in Scheme 5.5b. Direct formal [2 + 1]-cycloaddition of the olefin (**43**) would generate transient cyclopropane **44**. Due to the increased donor/acceptor character from the *p*-methoxy group, **44** would undergo an *aza*-vinylcyclopropane rearrangement, presumably by a thermal, 4π–electron conrotatory ring expansion. The alternative mechanism would involve formation of the rhodium-bound zwitterionic intermediate **45**, followed by a *5-exo-trig* cyclization of the rhodium-amide to quench the oxocarbenium ion. At least partial coordination of the zwitterion to the rhodium catalyst would be required to impart stereochemical influence, as the product (**46**) is formed with a moderate degree of enantioselectivity (72% ee).



(a) *In situ* generation of *N*-triflyl-1,2,3-triazoles **38** for the enantioselective cyclopropanation



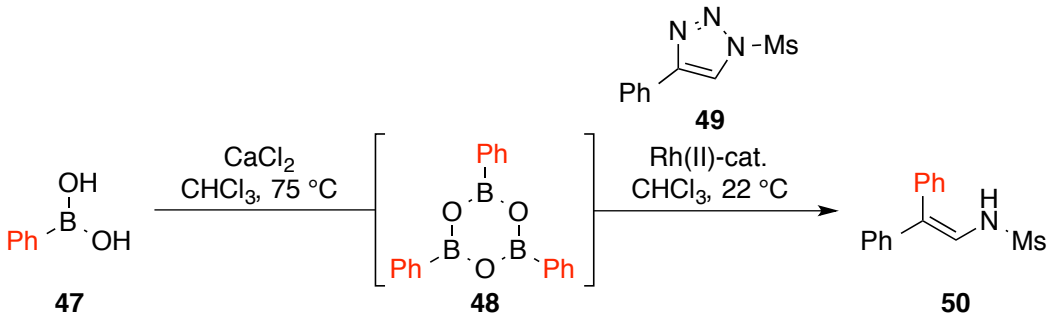
(b) Formal *aza* [3 + 2]-annulation of **43** with **42**-derived *N*-triflyl-1,2,3-triazole

Scheme 5.5 Synthesis and reactivity of *N*-triflyl-1,2,3-triazole-derived rhodium carbenes

The only additional report at the time we initiated our studies into the reactivity of a (hetero)arene nucleus directly with the carbene position of a *N*-sulfonyl-1,2,3-triazole (**49**)-derived rhodium carbene was the reaction of boronic acids (**47**), also from the Fokin group (Table 5.2).[37]

The acid **47** was dehydrated *in situ* by treatment with calcium chloride at elevated temperature to afford the cyclic borate **48**. Exposure to the rhodium carbene intermediate derived from *N*-sulfonyl-1,2,3-triazole **49** led to formation of the secondary enamine product (**50**). As can be seen from the results in Table 5.2, the reaction was catalyst dependent in nature, and ultimately the chiral dirhodium tetracarboxylate $\{Rh_2[(S)\text{-ptad}]_4\}$ was called upon to achieve the achiral union of **47** and **49**. The authors proposed Lewis acid coordination of the transient imine lone pair to the vacant *p*–orbital of the boronate, with the dual effect of increasing the electrophilicty of the carbene and configuring the intermediate for smooth intramolecular addition of the phenyl group to the carbene. Proteodemetallation would then give rise to the observed product (**50**). The report included a single example of a heteroaromatic boronic acid nucleophile, (1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)boronic acid, participating in the reaction, which proved slightly less effective than many of its arenyl counterparts.

Table 5.2[a] Cross coupling reaction of organoborates and rhodium carbene intermediates



entry	Rh(II)-cat.	yield, %
1	$[Rh_2(oct)_4]$	<5
2	$[Rh_2(piv)_4]$	69
3	$[Rh_2(esp)_2]$	52
4	$\{Rh_2[(S)\text{-ptad}]_4\}$	85
5	$\{Rh_2[(S)\text{-nttl}]_4\}$	75

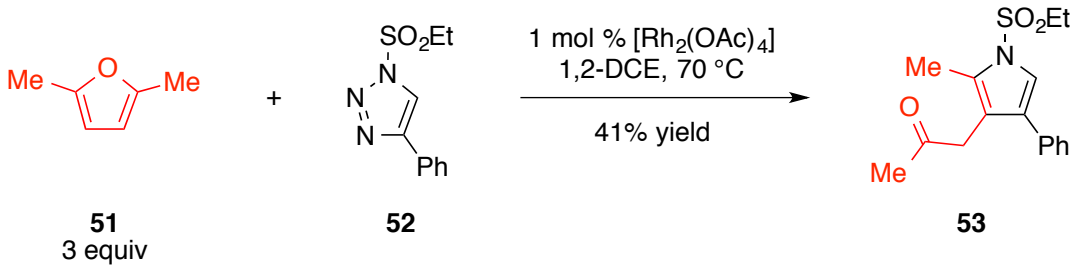
[a] Isolated yields of **50**.

The ensuing studies describe our recent efforts in developing a program surrounding novel reactivity between *N*-sulfonyl-1,2,3-triazole-derived rhodium carbenes and conjugated electron-rich π–bonds of heteroaromatics and arenes.

5.2 Results & Discussion

5.2.1 Pyrrole Synthesis

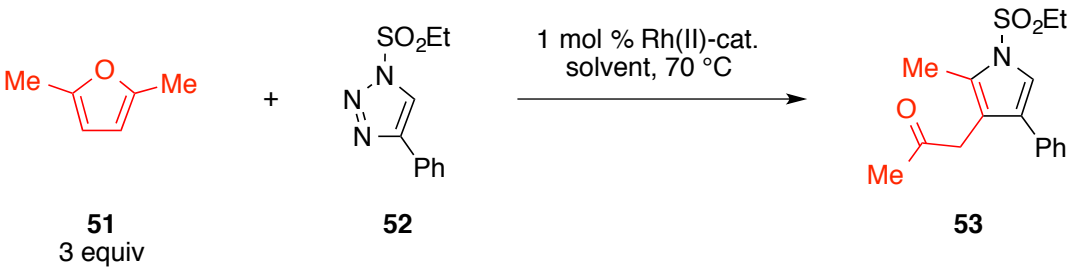
Discovery. Typically donor/acceptor rhodium carbenes undergo facile, stereoselective cyclopropanation with conjugated olefins.[14,38] Therefore, we became intrigued by the anomalous result reported by Fokin on attempted cyclopropanation of *p*-vinylanisole (**43**), which formed a dihydropyrrole (**46**) (Scheme 5.5b).[36] The atypical reaction was only observed with the *N*-triflyl-1,2,3-triazole (**34–36**) when *p*-methoxystyrene (**43**), an electron-rich system, was used as the rhodium carbene trapping agent. Thus, we considered the possibility of unveiling other distinct transformations from rhodium-catalyzed reactions of triazoles with electron rich heterocycles. We began the study by examining the rhodium acetate-catalyzed reaction of 2,5-dimethylfuran **51** with *N*-sulfonyl-1,2,3-triazole **52**. We were pleased to find that the reaction resulted in the unprecedented formation of a pyrrole **53** in 41% yield (Scheme 5.6). Notably, neither mono- or dicyclopropanation of the heteroaromatic nucleus was observed, as would be expected for the reaction of aryldiazoacetates and electron-rich heterocycles.



Scheme 5.6 Rhodium-catalyzed pyrrole synthesis from a furan and a donor/acceptor carbene precursor

Optimization. The conversion of a furan and a triazole into a pyrrole, containing components coming from both of the original heterocycles, is an unprecedented convergent transformation. Thus, we decided to pursue the optimum conditions and scope of this unusual synthetic sequence. The reaction was found to be highly dependent on both the solvent and the dirhodium catalyst, as shown in the optimization studies described by Table 5.3. Initially a number of achiral dirhodium tetracarboxylates were screened (entries 1–6), of which $[Rh_2(oct)_4]$ proved superior (entry 3, 56% yield). Highly electron-deficient catalysts, such as $[Rh_2(TFA)_4]$ and $[Rh_2(pfb)_4]$, did not generate any of the desired pyrrole (**53**) and *N*-sulfonyl-1,2,3-triazole **52** was recovered (entries 5 and 6). A hydrocarbon solvent (entry 7) was substantially less effective than 1,2-dichloroethane. In addition, the use of chloroform, which has been reported as the optimum solvent for rhodium carbene transformations from *N*-sulfonyl-1,2,3-triazoles, provided poor yields of the desired product (entry 8, 29% yield). We also examined a range of the most established chiral catalysts because they often provide improved yields of products over the standard achiral dirhodium tetracarboxylates. When $\{Rh_2[(S)\text{-dosp}]_4\}$ was implemented, an efficient synthesis of pyrrole **53** was achieved in 77% yield (entry 9). In contrast, neither of the imido-protected amino acid-derived catalysts, $\{Rh_2[(S)\text{-nttl}]_4\}$ and $\{Rh_2[(S)\text{-ptad}]_4\}$, proved as efficacious (entries 10 and 11).

Table 5.3[a] Optimization of the pyrrole synthesis



51
3 equiv

52

53

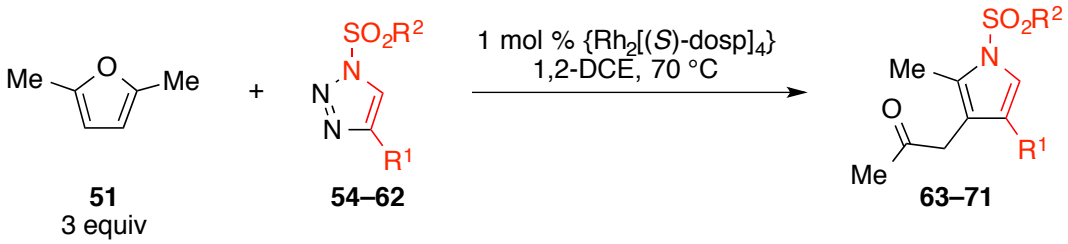
entry	Rh(II)-cat.	solvent	yield, %
1	$[Rh_2(OAc)_4]$	1,2-DCE	41
2	$[Rh_2(esp)_2]$	1,2-DCE	35
3	$[Rh_2(oct)_4]$	1,2-DCE	56
4	$[Rh_2(piv)_4]$	1,2-DCE	31
5	$[Rh_2(TFA)_4]$	1,2-DCE	0
6	$[Rh_2(pfb)_4]$	1,2-DCE	0
7	$[Rh_2(oct)_4]$	$PhCH_3$	42
8	$[Rh_2(oct)_4]$	$CHCl_3$	29
9	$\{Rh_2[(S)\text{-dosp}]_4\}$	1,2-DCE	77

10	$\{Rh_2[(S)\text{-nttl}]_4\}$	1,2-DCE	41
11	$\{Rh_2[(S)\text{-ptad}]_4\}$	1,2-DCE	55

[a] Isolated yields of **53**.

***N*-Sulfonyl-1,2,3-triazole Scope.** With the optimal conditions in hand, the scope of carbene architecture in the pyrrole synthesis was examined (Table 5.4). Steric and electronic variations in the aryl moiety on the *N*-sulfonyl-1,2,3-triazole (**63–65** and **67–70**) had minimal impact on the efficacy of the reaction (compare entries 1–3 and 5–8). The *N*-ethanesulfonyl-1,2,3-triazoles (**54**–**56**) afforded the corresponding pyrroles in comparable yield to **52** (Table 5.3, entry 9). Other *N*-sulfonyl-protecting groups on the triazole were compatible with pyrrole formation (entries 4 and 5); however, the *N*-tosyl group (**58**) furnished the highest yield in formation of **67** (compare entries 3–5). An alkenyl triazole **62**, was also an effective substrate, generating the pyrrole **71** in 70% yield. This reactivity is in marked contrast to that observed with rhodium alkenylcarbenes derived from diazoacetates, as they undergo a tandem cyclopropanation/Cope rearrangement with 2,5-dimethylfuran.[14]

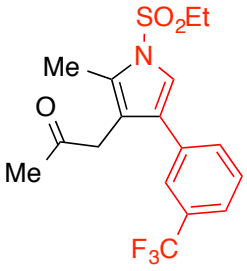
Table 5.4[a] Scope of the *N*-sulfonyl-1,2,3-triazole for the pyrrole synthesis



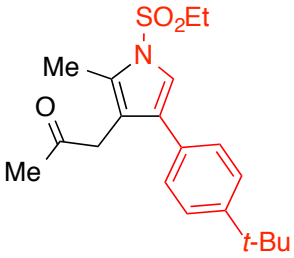
51
3 equiv

54–62

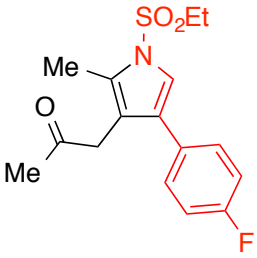
63–71



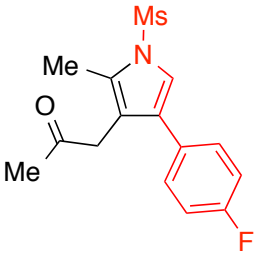
63
76% yield



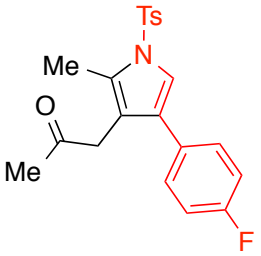
64
74% yield



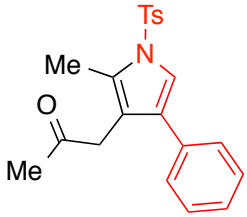
65
79% yield



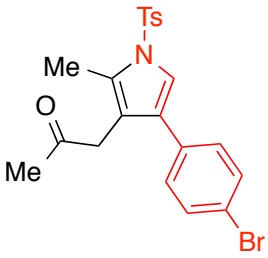
66
81% yield



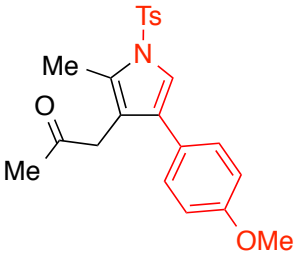
67
98% yield



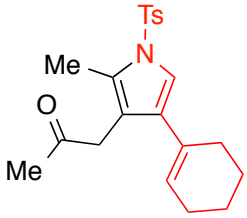
68
84% yield



69
73% yield



70
91% yield



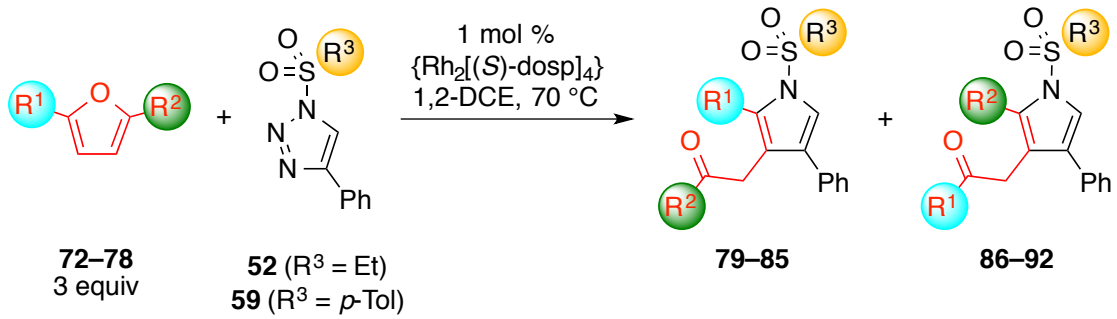
71
70% yield

---

[a] Isolated yields of **63**–**71**.

Furan Scope. The reaction was then extended to a range of furan derivatives (**72**–**78**) and the results are summarized in Table 5.5. Furan itself did not provide a clean transformation, and ring-opened dienal-type products were evident from NMR analysis of the reaction residue.[3] Reaction of 2-methylfuran (**72**) with *N*-ethanesulfonyl-1,2,3-triazole **52** resulted in the formation of a single regioisomer of the 3,4-disubstituted pyrrole (**79**) in moderate yield (41% yield). As with furan, ring-opening of the heterocycle was a competitive reaction pathway. As with **51**, 2,5-diethylfuran (**73**) was an excellent substrate for the pyrrole synthesis, furnishing **80** in 99% yield. The reactions with non-symmetrically 2,5-disubstituted furans generally proceeded in high yields (65–89% yield) but in many instances, mixtures of regiosiomers were formed, as seen with **74**–**76** and **78**. Notably, in the case of 2-(triisopropyl)siloxymethyl-5-methylfuran (**77**), the pyrrole **84** was formed in a highly regioselective manner. Presumably in this case, the combination of steric crowding and electronic deactivation by the C(2)-substituent causes the reaction to operate with exclusive regioselectivity. Insertion of a single methylene unit, as in the case of the tri-isopyopylsilyl-protected homoaryl furol (**78**), however, resulted in dramatic deterioration in the regioselectivity of the pyrolle synthesis, furnishing a ~2 : 1 regioisomeric mixture of **85** and **92**.

Table 5.5[a,b] Scope of the furan for the pyrrole synthesis

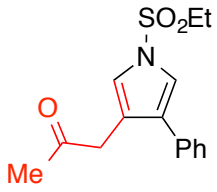


72–78
3 equiv

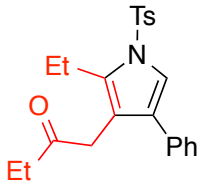
52 (R^3 = Et)
59 (R^3 = *p*-Tol)

79–85

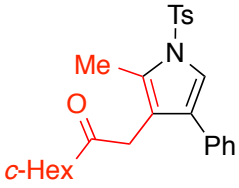
86–92



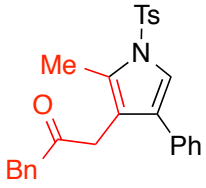
79
41% yield
>90 : 10 ratio



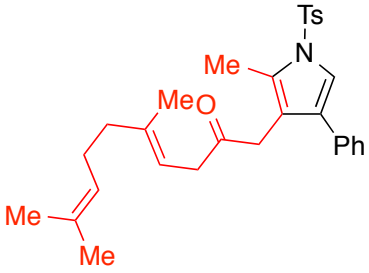
80
99% yield



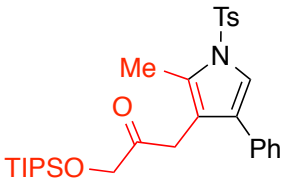
81
67% yield[c]
67 : 33 ratio



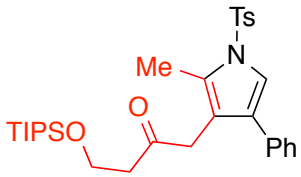
82
71% yield[c]
76 : 24 ratio



83
65% yield[c]
66 : 34 ratio



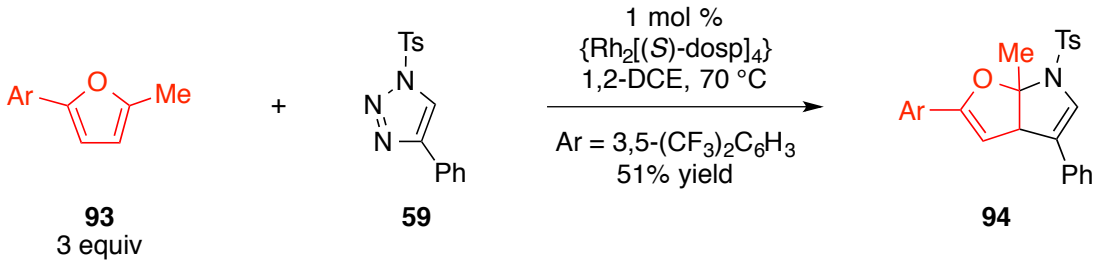
84
83% yield
>90 : 1 ratio



85
89% yield[c]
68 : 32 ratio

[a] Isolated yields of **79**–**85**. [b] Ratio of the two regioisomers was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Combined isolated yields of the two regioisomers.

Mechanistic Rationale. When a moderately electron withdrawing substituent was placed on the furan nucleophile, the reaction trajectory was altered. Thus, generation of the rhodium carbene from triazole **59** in the presence of 2-(3,5-bis(trifluoromethyl)phenyl)-5-methylfuran (**93**) resulted in formation of bicyclic hemiaminal **94** as the major product by ^{1}H NMR analysis of the crude reaction residue (Scheme 5.7).

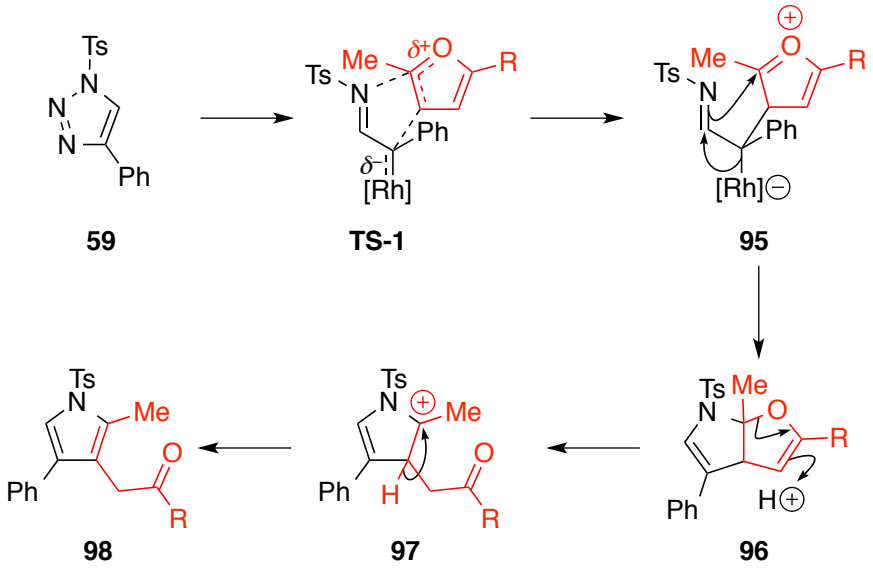


Scheme 5.7 Identification of a hemiaminal intermediate

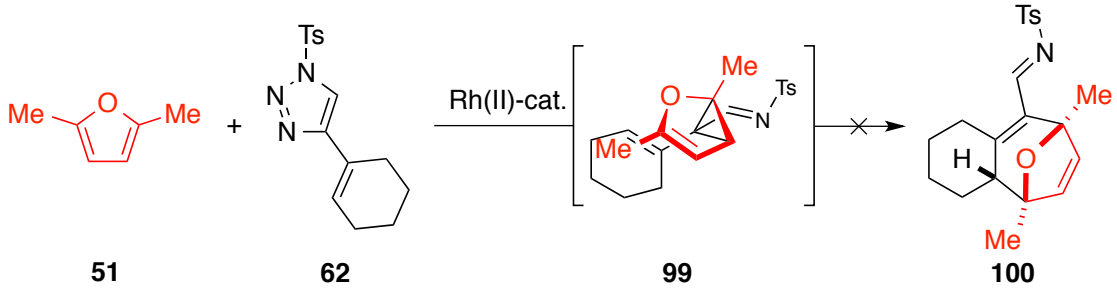
A mechanistic rationale for the formation of pyrrole **98** is provided in Scheme 5.8. Heating the *N*-sulfonyl-1,2,3-triazole **59** in the presence of the dirhodium tetracarboxylate catalyst generates an imino carbene intermediate *via* tandem triazole ring-opening and nitrogen extrusion. The rhodium carbene reacts with a furan at C(3) through **TS-1** to generate a metal-bound zwitterion **95**, which then closes to the hemiaminal **96**. Ring-opening of **96** by initial protonation of the enolic alkene would generate **97**, which is configured to aromatize to the pyrrole **98**. The requirement of attack of the rhodium carbene at the C(3)-position would explain why furan failed to give a clean reaction and the yield with 2-methylfuran was modest. Both of these substrates would tend to react with rhodium carbene intermediates at C(2), and the resulting zwitterionic intermediates have a propensity to ring-open to dienones. The formal [4 + 3]-cycloaddition

product (Scheme 5.8b, **100**), which arises from tandem cyclopropanation/Cope rearrangement, is not apparent in the crude NMR of the reaction between **51** and **62**. Thus, we suspect intermediacy of a cyclopropane (**99**), as opposed to a zwitterion, to be unlikely. Moreover, the increased efficacy of the transformation in more polar solvents, as opposed to hydrocarbon reaction medium, is consistent with intermediacy of a charged species.

The presence of an electron-withdrawing group on the furan, as in the reaction of **93**, results in selective addition across the more electron-rich olefin of the furan (Scheme 5.7). Similarly, the olefin of bicyclic hemiaminal **94** lacks sufficient electron-richness to participate in acid-catalyzed rupture (*e.g.* Scheme 5.8a, **96** → **97**) to produce the pyrrole product under neutral reaction conditions.



(a) Plausible mechanism for the formation of pyrroles

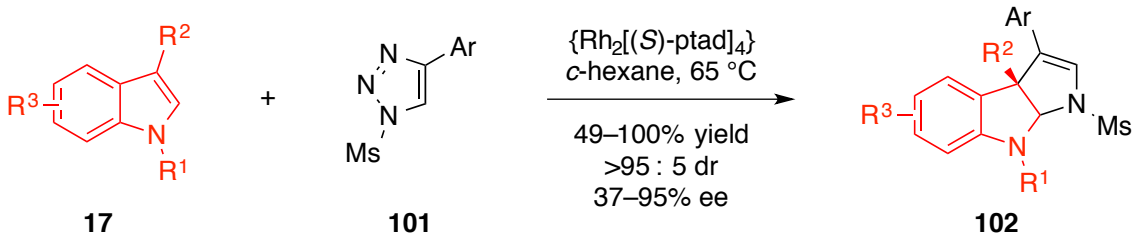


(b) Evidence refuting intermediacy of a cyclopropane

Scheme 5.8 Overview of intermediates in pyrrole synthesis

A subsequent, independent study within the Davies group found that 3-substituted indoles (**17**) behave in a similar capacity (Scheme 5.9). Thus, the *N*-sulfonyl-1,2,3-triazole (**101**)-derived carbene participates in a formal [3 + 2]-cycloaddition with the less-hindered olefin of the heterocyclic nucleus, generating a pyrroloindoline product (**102**) in moderate-to-high yields and enantioselectivities under the catalytic action of {Rh_2[(*S*)-ptad]$_4$}.[39] Notably, the formation of

102 was dependent on a hydrocarbon solvent as reaction medium, which was one piece of evidence which led Davies and co-workers to favor a mechanistic hypothesis involving cyclopropanation and 4π–electrocyclization.

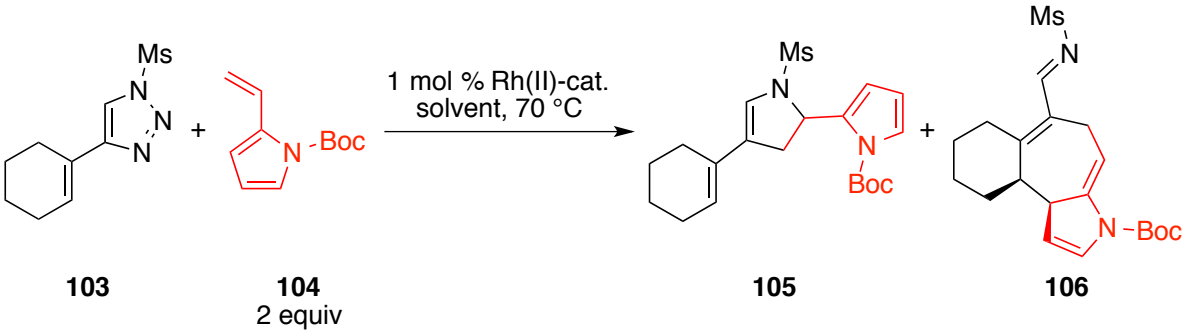


Scheme 5.9 Formal [3 + 2]-cycloaddition of indoles and *N*-sulfonyl-1,2,3-triazoles

5.2.2 Formal [3 + 2]- versus [4 + 3]-Cycloadditions

Chemocontrol. Interesting bifurcations in reactivity, analogous to those previously reported by Fokin and co-workers in the cyclopropanation of styrenes with *N*-trifluoromethanesulfonyl-1,2,3-triazoles, were observed for certain substrates in our study. Specifically, we envisioned preparing a heteroazulene (**106**) nucleus from the tandem cyclopropanation/Cope rearrangement of vinyl-substituted electron rich heterocycles, such as **104**, with C(4)-alkenyl-*N*-sulfonyl-1,2,3-triazoles (**103**) as shown in Table 5.6. Under the standard reaction conditions, however, the major product of the reaction was a dihydropyrrole **(105**), though trace quantities of the cycloheptadiene (**106**) were apparent from ^{1}H NMR analysis of the crude reaction residue (Table 5.6, entry 1). When the solvent polarity was increased, the dihydropyrrole was formed as the exclusive product of the reaction in excellent yield (entry 2, 91% yield). By extension, decreasing the polarity of the reaction medium by implementing hydrocarbon solvent (entry 3), resulted in preferential, albeit modest, formation of tricycle **105** resulting from cyclpropanation (entry 3, 90 : 10 ratio, 81% yield). Utilizing the optimal chiral catalyst for formal [4 + 3]-cycloaddition reactions of *N*-sulfonyl-1,2,3-triazoles, both the dihydropyrrole and cycloheptadiene products could be generated in high yield, again by change in solvent (entries 4 and 5, respectively). When {Rh_2[(*S*)-nttl]$_4$}, the optimal catalyst for a variety of enantioselective *N*-sulfonyl-1,2,3-triazole-based rhodium carbene transformations, was implemented, the asymmetric induction in the synthesis of the dihydropyrrole (**105**) was only modest (28% ee); an observation consistent with the report from Fokin (entry 4). Although the yield of the cycloheptadiene was only moderate by comparison (entry 5, 51% yield), the enantioselectivity in the transformation was on par with that of the dienes explored for formal [4 + 3]-cycloaddition chemistry in Chapter 4 (94% ee).

Table 5.6[a–c] Formal [3 + 2]- and [4 + 3]-cycloadditions of a vinylpyrrole and *N*-sulfonyl-1,2,3-triazole



103 **104** 2 equiv **105** **106**

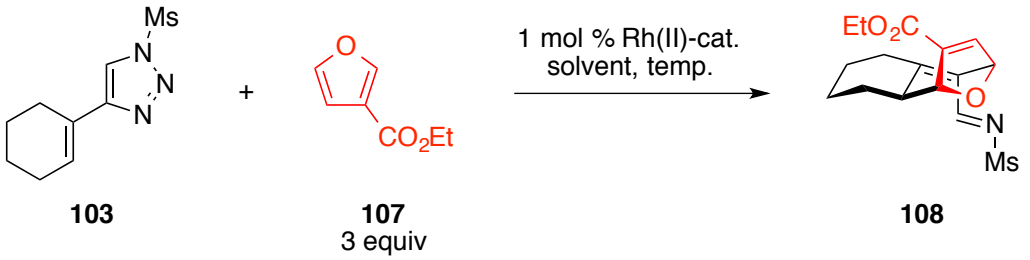
entry	Rh(II)-cat.	solvent	ratio, **105** : **106**	yield, %	ee, %
1	$[Rh_2(oct)_4]$	1,2-DCE	84 : 16	65	–
2	$[Rh_2(oct)_4]$	$CHCl_3$	>97 : 3	91	–
3	$[Rh_2(oct)_4]$	*c*-hexane	90 : 10	81	
4	$\{Rh_2[(S)\text{-nttl}]_4\}$	$CHCl_3$	>97 : 3	85	28
5	$\{Rh_2[(S)\text{-nttl}]_4\}$	*c*-hexane	35 : 65	51	94

[a] Ratio **105** : **106** was determined by ^{1}H NMR analysis of the crude reaction residue. [b] Isolated yields of the major product (**105** or **106**). [c] Enantiomeric excess of the major product was determined by HPLC analysis on a chiral stationary phase.

Formal [4 + 3]-cycloaddition optimization. The next of investigations were conducted in collaboration with Williams and co-workers from the University of Melbourne. We reasoned that the inordinate nucleophilicity of a pyrrole nucleophile is consequent with preferential, or at least competitive reactivity, through zwitterionic intermediates. Thus, the tempered reactivity of a furan bearing an electron-withdrawing group might induce favorable cyclopropanation chemistry, thereby enabling access to new tricyclic scaffolds. Accordingly, we decided to develope the tandem cyclopropanation/Cope rearrangement around commercially available furan-3-carboxylate **107** (Table 5.7), with the Williams and co-workers aspiring to incorporate the methodology in an ongoing total synthesis program within their group. A racemic sample of cycloaddition product **108** for enantiomeric excess determinations was obtained by reaction of **103** and **107** under the catalytic action of rhodium(II) pivaloate. Thus we began with the reaction of *N*-sulfonyl-1,2,3-triazole **103** with **107**, hoping to forge oxa-bicycle **108** in a stereoselective fashion. At 60 °C in *c*-hexane solvent under the catalytic action of $\{Rh_2[(S)\text{-dosp}]_4\}$, none of the desired product was observed (Table 5.7, entry 1). Based on our observations and reports from Fokin and co-workers, the rhodium-catalyzed electrocyclization of *N*-sulfonyl-1,2,3-triazoles to expose the diazo moiety for denitrogenative decomposition is dependent on solvent, catalyst, and temperature. Increasing the reaction temperature to 70 °C, resulted in a gratifying 78% yield of **108**; however, asymmetric induction was absent from the transformation, which is consistent for most reactions of $\{Rh_2[(S)\text{-dosp}]_4\}$ with *N*-sulfonyl-1,2,3-triazoles (entry 2). A measurable increase in both yield and enantiomeric excess was observed when $\{Rh_2[(S)\text{-ptad}]_4\}$was the catalyst; however, the enantioselectivity was only modest (entry 3, 90% yield, 92% ee). Similarly, an increase in asymmetric induction was observed for $\{Rh_2[(S)\text{-pttl}]_4\}$, but was not at the point of ideality (entry 4, 71% ee). A gratifying result was achieved when $\{Rh_2[(S)\text{-nttl}]_4\}$, the opti-

mal catalyst for cyclopropanations, was implemented. The oxabicyclic product (**108**) was isolated in 96% yield and 88% ee (entry 5). We hoped to induce further increases in the enantioselectivity by exploring less polar reaction medium (entry 6) or lower temperatures (entry 7); however, in both instances little if any change in stereoselectivity was recorded, while detriment to the yield was observed.

Table 5.7[a–c] Optimization of a formal [4 + 3]-cycloaddition with a furan



103 **107** 3 equiv **108**

entry	Rh(II)-cat.	solvent	temp., °C	yield, %	dr	ee, %
1	{Rh_2[(*S*)-dosp]$_4$}	*c*-hexane	60	–	–	–
2	{Rh_2[(*S*)-dosp]$_4$}	*c*-hexane	70	78	>95 : 5	<5
3	{Rh_2[(*S*)-ptad]$_4$}	*c*-hexane	70	90	>95 : 5	62
4	{Rh_2[(*S*)-pttl]$_4$}	*c*-hexane	70	95	>95 : 5	71
5	{Rh_2[(*S*)-nttl]$_4$}	*c*-hexane	70	96	>95 : 5	88
6	{Rh_2[(*S*)-nttl]$_4$}	hexanes	70	93	>95 : 5	88
7	{Rh_2[(*S*)-nttl]$_4$}	*c*-hexane	60	81	>95 : 5	89

[a] Isolated yields of **108**. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction residue. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase.

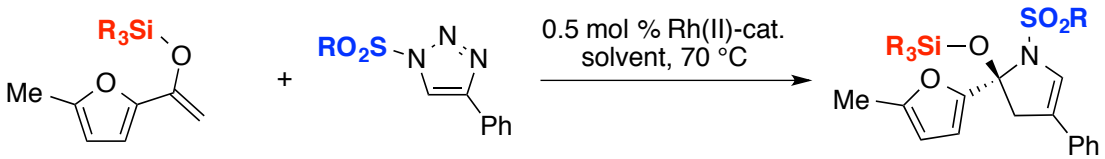
Formal [3 + 2]-cycloaddition optimization. Gratified with the ability to control chemo- and stereoselectivity by appropriate engineering of substrates and reaction conditions, we wondered

whether the same should prove possible for the synthesis of dihydropyrroles from vinylarenes. In addition, we wanted to exhibit the ability to develop another transformation from a furan-derived nucleophile, to exhibit the breadth of transformations achievable from a single substrate family. Since vinylfuran and its derivatives are challenging substrates to prepare and handle, the silyl enol ether of an acetylfuran was envisioned as a suitable alternative. Further, variation in the silyl group would potentially offer another opportunity for tuning the substrate so as to achieve suitable levels of asymmetric induction.

We began our study with the reaction of *t*-butyldimethylsilyl enol ether **109** and 4-phenyl-*N*-methanesulfonyl-1,2,3-triazole **113** to form dihydropyrrole **115** (Table 5.8, entries 1–8). A racemic sample of **115** for enantiomeric excess determinations was obtained by the reaction of **109** and **113** under the catalytic action of rhodium(II) pivaloate. A brief catalyst screen (entries 1–5) readily established $\{Rh_2[(S)\text{-tcptad}]_4\}$ as most efficacious from the standpoint of asymmetric induction (40% ee) as the product was generated in excellent efficiency in all cases (≥83% yield). Varying the solvent, a marked increase in enantioselectivity was observed when a nonpolar hydrocarbon, hexanes, was utilized as reaction medium (entry 6, 94% yield, 54% ee). Increasing the steric bulk of the sulfonyl group to *i*-propyl (**114**) resulted in a modest increase in enantioselectivity for formation of the corresponding dihydropyrrole **116** (entry 8, 94% yield, 59% ee). Desperate for further improvements in stereoselectivity, we probed the isosteric and isoelectronic catalysts $\{Rh_2[(S)\text{-tcpttl}]_4\}$ and $\{Rh_2[(S)\text{-tbpttl}]_4\}$ (entries 9 and 10, respectively). A small, but nonetheless measurable, increase in enantioselectivity for the formation of **116** was observed for the former dirhodium tetracarboxylate complex, generating the product in >95% yield and 61% ee). The identity of the *O*-silyl group on the enol ether was then considered. We rationalized that increasing the steric bulk may exploit some substrate–catalyst interactions, thereby improv-

ing the enantioselectivity. Much to our dismay, however, substituted the *t*-butyldimethylsilyl group on the nucleophile with a tri*iso*propylsilyl group (**110**) resulted in a dramatic decrease in level of enantioselection for formation of the corresponding dihydropyrrole **117** (entry 11, 93% yield, 23% ee). Thus, we considered decreasing the steric bulk of the nucleophile by incorporating a trimethylsilyl enol ether (**111**). Indeed, reaction with carbene precursor **114** afforded dihydropyrrole **118** in a gratifying 80% ee (entry 12). A further decrease in the steric demand of the silyl group, utilizing the less common silacyclobutayl derivative **112**, resulted in an appreciable increase in enantioselectivity for formation of dihydropyrrole **118** (entry 13, >95% yield, 84% ee). Due to the expense of the chlorosilane required to prepare **112**, however, we decided to pursue more economically viable alternatives, which would not be prohibitive to the development of a general methodology. When thought the *N*-tosyl-1,2,3-triazole (**59**), which we had neglected to consider earlier, might afford an unobvious benefit to the enantioselectivity of the transformation. We were pleased to find a significant improvement in the enantioselective formation of the dihydropyrrole product (**119**) without detriment to yield (entry 14, >95% yield, 94% ee).

Table 5.8[a–b] Optimization of a formal [3 + 2]-cycloaddition with a vinylfuran



109 (SiR_3 = TBS)
110 (SiR_3 = TIPS)
111 (SiR_3 = TMS)
112 (SiR_3 = $Si(CH_2)_3Me$)
1.5 equiv

59 (R = *p*-Tol)
113 (R = Me)
114 (R = *i*-Pr)

115–119

entry	SiR_3	SO_2R	Rh(II)-cat.	solvent	yield, %	ee, %
1	TBS	Me	$\{Rh_2[(S)\text{-pttl}]_4\}$	$CHCl_3$	>95	27
2	TBS	Me	$\{Rh_2[(S)\text{-ptad}]_4\}$	$CHCl_3$	>95	27
3	TBS	Me	$\{Rh_2[(S)\text{-nttl}]_4\}$	$CHCl_3$	>95	30
4	TBS	Me	$\{Rh_2[(S)\text{-tcptad}]_4\}$	$CHCl_3$	>95	40
5	TBS	Me	$\{Rh_2[(S)\text{-btpcp}]_4\}$	$CHCl_3$	83	–15
6	TBS	Me	$\{Rh_2[(S)\text{-tcptad}]_4\}$	hexanes	94	54
7	TBS	Me	$\{Rh_2[(S)\text{-tcptad}]_4\}$	$PhCH_3$	90	42
8	TBS	*i*-Pr	$\{Rh_2[(S)\text{-tcptad}]_4\}$	hexanes	94	59

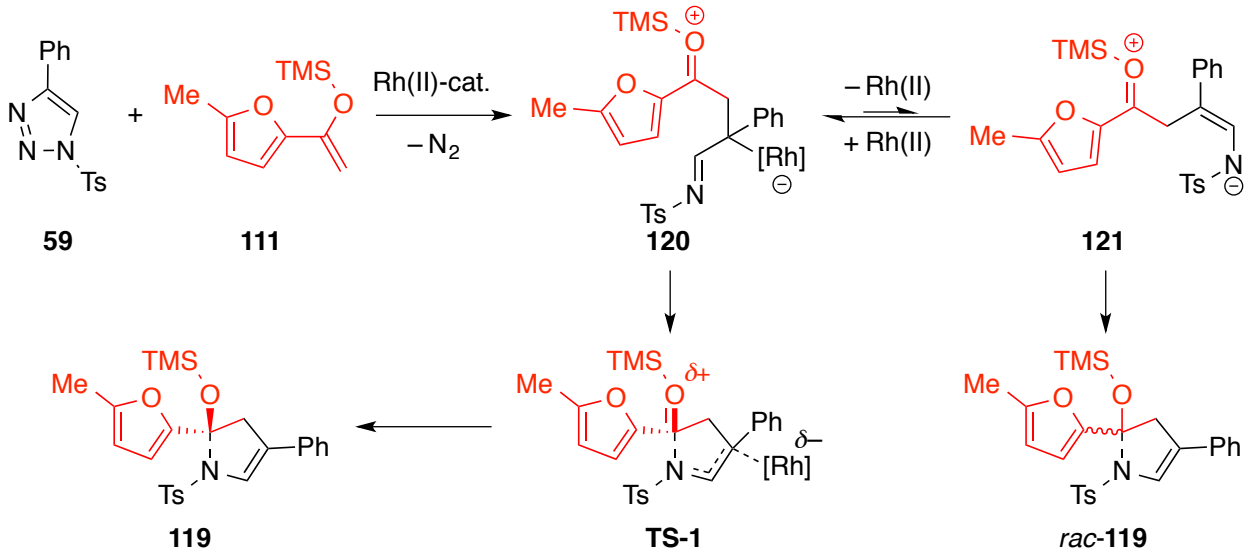
9	TBS	*i*-Pr	{Rh_2[(*S*)-tcpttl]$_4$}	hexanes	>95	61
10	TBS	*i*-Pr	{Rh_2[(*S*)-tbpttl]$_4$}	hexanes	>95	58
11	TIPS	*i*-Pr	{Rh_2[(*S*)-tcpttl]$_4$}	hexanes	93	23
12	TMS	*i*-Pr	{Rh_2[(*S*)-tcpttl]$_4$}	hexanes	>95	80
13	Si(CH_2)$_3$Me	*i*-Pr	{Rh_2[(*S*)-tcpttl]$_4$}	hexanes	>95	84
14	TMS	*p*-Tol	{Rh_2[(*S*)-tcpttl]$_4$}	hexanes	>95	94

[a] Isolated yields of **115**–**119**. [b] Enantiomeric excess was determined by HPLC on a chiral stationary phase.

Mechanistic rationale. Due to the sensitivity of the reaction to a variety of steric and electronic parameters, we considered a reaction mechanism which could rationalize these observations. As was described for the reaction in Scheme 5.5b, the dihydropyrrole synthesis of electron-rich olefins and *N*-sulfonyl-1,2,3-triazole-derived rhodium carbenes could involve either a cyclopropane or zwitterion intermediate. We suspect that the selective formation of dihydropyrrole **105** in polar reaction medium, and the inability for products **105** and **106** to interconvert under reaction conditions, implicates discrete reaction pathways in the formation of each. Since cycloheptadiene **106** is likely to arise *via* a tandem cyclopropanation/Cope rearrangement-type mechanism, it seems implausible that **105** is formed by intermediacy of the same cyclopropane. Thus, we pre-

sume that a rhodium-bound zwitterion is likely to be operative in the formation of dihydropyrroles **115**–**119**.

Addition of silyl enol ether **111** to **59**-derived rhodium carbene generates the rhodium-bound zwitterion **120** (Scheme 5.10). Intramolecular addition of the allylic rhodium amide to the oxacarbenium ion would occur under stereocontrol of the chiral dirhodium tetracarboxylate catalyst *via* **TS-1**, with *5-exo-trig* cyclization affording the enantioenriched product **119**. Liberation of the mildly Lewis acidic rhodium complex from zwitterion would inevitably be a competitive process (**120** → **121**), due to the relative stability of a sulfonyl enamide ion. An analogous *5-exo-trig* cyclization of **121** would by extension generate a racemic product, *rac*-**119**, as the catalyst would be absent during the chirality-generating process.

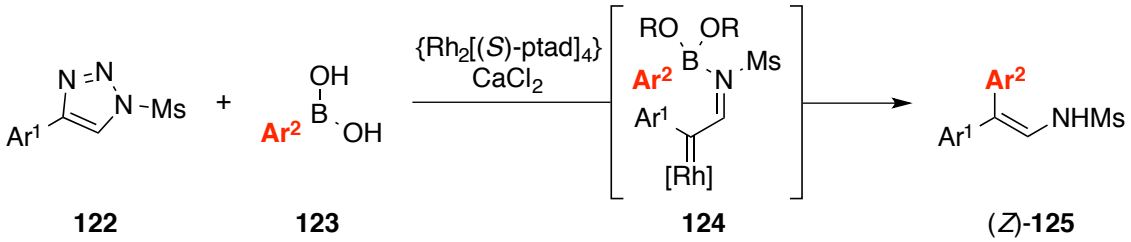


Scheme 5.10 Plausible mechanism for the formation of dihydropyrroles

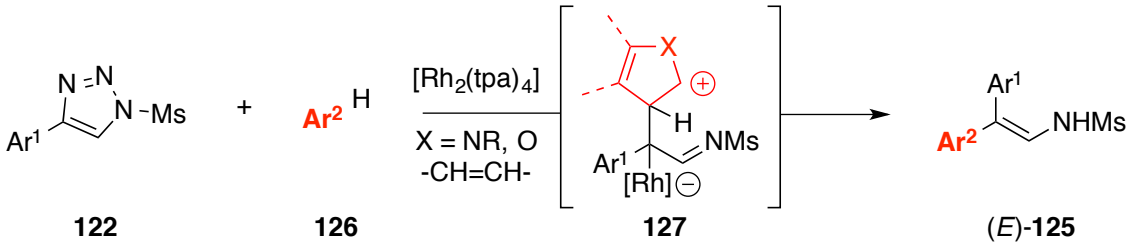
Several factors observed during the course of our optimization study (Table 5.8) can be justified in light of the mechanism in Scheme 5.10. First, the electrophilic {Rh_2[(*S*)-tcpttl]$_4$} catalyst would be expected to exhibit improved stability as the metal anion, and thus metal-bound ylide (**120**), as opposed to the free ylide (**121**). Second, less polar solvents, which would not be effective in stabilizing an ylide through dissipating charge buildup, should induce rapid cyclization (**120** → **119**). Thus, the rate of cyclization *versus* interconversion of metal- and free-ylide intermediates would be increased. Similarly, the increased steric bulk of the *O*-silyl group, the slower the rate of cyclization would be anticipated. The slower the rate of the *5-exo-trig* cyclization, the transient generation of free ylide becomes a competitive process, leading to a greater amount of *rac*-**119** formed during the reaction. Lastly, origins of the compatibility between a *N*-tosyl-1,2,3-triazole and {Rh_2[(*S*)-tcpttl]$_4$} are not entirely clear; however, Charette and co-workers have observed similar phenomena for the enantioselective cyclopropanation of styrenes with acceptor/acceptor diazo compounds. Moreover, a *p*-methoxyketone group was among the most effective acceptor groups due to an efficient π–stacking interaction with a tetrachlorophthalimide ligand of the catalyst.

5.2.3 Enamine Synthesis

Discovery and optimization. Based on our knowledge of the diversity of reactions between donor/acceptor rhodium carbenes and heterocycles, we anticipated that further orthogonal modes of reactivity could be possible with these substrates by appropriate tuning of substrates and conditions. In a recent study, Fokin and co-workers found that arylboronic acids **123**, upon *in situ* dehydration, participate in an efficient and geoisomeric synthesis of trisubstituted enamines (*Z*)-**125** (Scheme 5.11a). They postulated that pre-organization of an intermediate by coordination of the Lewis acidic boronate to the imine moiety (**124**) enables intramolecular *5-exo-trig* delivery of the arene (**123**) with concomitant proteodemetallation. Notable drawbacks to the report were the necessity for using the chiral catalyst $\{Rh_2[(S)\text{-ptad}]_4\}$ to achieve effective yields of enamine (*Z*)-**125** as well as a substantial excess of boronic acid **123** to preform a requisite borate (see Table 5.2). We anticipated, however, that electron-rich arenes and heterocycles (Scheme 5.11b, **126**) would not require the same pre-activation as a boronic acid in order to achieve union with an iminocarbene intermediate. In an effort to broaden the scope of rhodium-catalyzed reactions with electron-rich arenes and heterocycles, we envisioned applying a C–H functionalization approach *via* formal sp^2–sp^2 coupling for generating analogous 2,2′-diaryl enamine architectures. Electrophilic attack of the rhodium-bound carbene intermediate to generate a zwitterion (**127**), with subsequent re-aromatization and proteodemetallation would provide an analogous product architecture [(*E*)-**125**]. We further anticipated that the potential issue of regioselectivity for these reactions might be averted due to the, often predictable, sensitivity of metallocarbene intermediates to substrate sterics and electronics.



(a) Synthesis of enamines from arylboronic acids



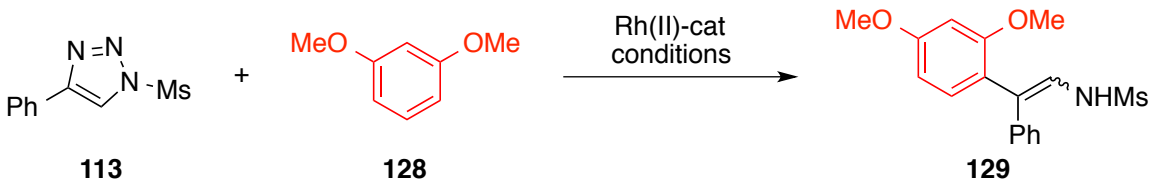
(b) Synthesis of enamines from arenes

Scheme 5.11 Formal C–H functionalization approach to the synthesis of enamines

We commenced our exploratory study with the coupling of 4-phenyl-*N*-methanesulfonyl-1,2,3-triazole (**113**) and 1,3-dimethoxybenzene (**128**) in the formation of enamine **129** (Table 5.9). Combining the substrates under catalyst-free conditions returned the *N*-sulfonyl-1,2,3-triazole without noticeable decomposition (entry 1). Gratifyingly, the use of 1.0 mol% rhodium(II) acetate afforded **129** in good yield as a mixture of *E*- and *Z*-enamine geometric isomers (entry 2, 88 : 12 ratio, 71% yield). Consistent with previous observations, the electrophilic rhodium(II) trifluoroacetate catalyst was entirely ineffective in the enamine synthesis (entry 3).[40] Interestingly, [Rh_2(oct)$_4$], which has proven effective for other triazole-derived carbene reactions, provided a poor yield and ratio of products, with a substantial quantity of non-decomposed **113** still evident in the crude ^{1}H NMR (entry 4). The sterically-bulky and electron-rich catalyst

[$Rh_2(piv)_4$] performed well in the formal C–H functionalization reaction, providing both an improved yield and *E* : *Z* ratio (entry 5, 92 : 8 ratio, 84% yield) for the desired product. By extension, rhodium(II) triphenylacetate furnished near quantitative yields of **129** with a high degree of *E*-selectivity (entry 6, 94 : 6 ratio, 95% yield). A slight improvement in reaction yield was observed when 1,2-dichloroethane was used as the reaction solvent (entry 7, 94 : 6 ratio, 99% yield); however, non-halogenated solvents such as toluene were far less efficacious (entry 8, 90 : 10 ratio, 64% yield). The reaction could be conducted under non-microwave conditions in refluxing 1,2-DCE without depreciation in product yield (entry 9), but extended reaction times were required. In contrast to the enamine synthesis reported by Fokin,[37] analysis of the nuclear Overhauser effects (nOe) present for **129** indicated that the *E*-isomer was the major product of these reactions. We attribute this selectivity to the reaction proceeding *via* an aza–*s*–*cis* metallocarbene (**127**) without the intramolecular-type delivery of the nucleophile exhibited in **124**.

Table 5.9[a,b] Optimization of the enamine synthesis



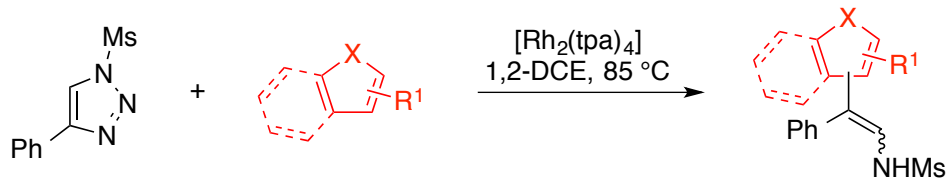
113 **128** **129**

entry	Rh(II)-cat.	conditions	ratio, *E* : *Z*	yield, %
1	none	$CHCl_3$, 120 °C	–	–
2	$[Rh_2(OAc)_4]$	$CHCl_3$, 120 °C	88 : 12	71
3	$[Rh_2(TFA)_4]$	$CHCl_3$, 120 °C	–	–
4	$[Rh_2(oct)_4]$	$CHCl_3$, 120 °C	80 : 20	25
5	$[Rh_2(piv)_4]$	$CHCl_3$, 120 °C	92 : 8	84
6	$[Rh_2(tpa)_4]$	$CHCl_3$, 120 °C	94 : 6	95 (94)
7	$[Rh_2(tpa)_4]$	1,2-DCE, 120 °C	94 : 6	99 (97)
8	$[Rh_2(tpa)_4]$	$PhCH_3$, 120 °C	90 : 10	64
9	$[Rh_2(tpa)_4]$	1,2-DCE, 80 °C	94 : 6	99 (97)

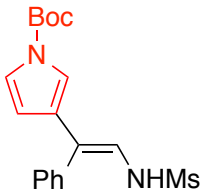
[a] *E* : *Z* ratio of **129** was determined by ^{1}H NMR analysis of the crude reaction residue. [b] Yield of **129** was determined by ^{1}H NMR analysis with an internal standard of CH_2Br_2. [c] Combined isolated yield of *E*- and *Z*-isomers of **129**.

With these optimized reaction conditions in hand we subsequently investigated the efficacy of this reaction for an array of electron-rich arenes and heterocyclic nuclei which had not been investigated in our previous studies to determine the scope of Ar^2 substituents which could be introduced. We first investigated direct substitution of a pyrrole, which is a relatively unexplored class of nucleophile in triazole-based rhodium carbene chemistry. A bulky *N*-Boc group on a pyrrole nucleus (**130**) drives the reaction cleanly corresponding C(3) functionalized product **133** in high yield. Notably, for the pyrrole nucleophile, the [3 + 2]-annulation reaction that would be expected of furans and indoles is not observed under the prescribed reaction conditions. As with **130**, substitution with sterically encumbered groups can be used to manipulate reactivity. Thus, 2-*t*-butyl-5-methylfuran (**131**) undergoes addition exclusively at the less encumbered C(4)-position in respectable yield (**134**, 77% yield, 92 : 8 ratio). From analysis of the crude ^{1}H NMR residue, formation of the corresponding pyrrole product is not a competitive product. Similarly, an1,3-disubstituted indole nucleophile (**132**) was an efficient nucleophile for the enamine synthesis. The corresponding 1,2,3-trisubstituted indole (**135**) was isolated in very high yield and *E* : *Z* ratio (98% yield, >95 : 5 ratio).

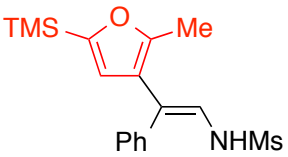
Table 5.10[a,b] Scope of the electron-rich heterocycle for the enamine synthesis



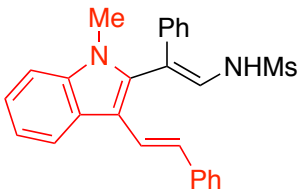
113 **130–132** **133–135**



133
85% yield
83 : 17 ratio



134
77% yield
92 : 8 ratio



135
98% yield
>95 : 5 ratio

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[a] Isolated yields of **136–138**. [b] *E* : *Z* ratio was determined by ^{1}H NMR analysis of the crude reaction residue.

5.3 Conclusions

In summary, we have developed a program involving the reactivity of electron-rich heterocycles and arenes for the syntheses of various new heterocyclic rings and substituted aromatics. Manipulating the substitution of the nucleophile and reaction conditions has enabled the synthesis of formal [4 + 3]- and [3 + 2]-cycloadducts and products of electrophilic aromatic substitution. Specifically, electron-rich furans participate in a rearrangement cascade, which is initiated by a formal [3 + 2]-cycloaddition with the iminocarbene; whereas electron-deficient furans participate in tandem cyclopropanation/Cope rearrangements to form the formal [4 + 3]-cycloaddition products. The novel reaction cascade for the interconversion of heterocyclic aromatic species, converting a furan to a pyrrole, has been discovered and studied in detail. Due to the immature stage of the research, developing a comprehensive understanding of the scope of many of these reactions remains to be examined. Although the synthesis of secondary sulfonylenamides by electrophilic aromatic substitution appears to be a promising reaction, it may not be a competitive strategy compared to the elegant cross coupling methodology reported by Fokin and co-workers with aryl boronic acids. Future work will investigate the utility of modifying reaction conditions, notably solvent and catalyst, to achieve complementary stereoselective [3 + 2]- and [4 + 3]-cycloaddition reactions.

5.4 Experimental Section

5.4.1 General Considerations

All reactions were conducted in oven-dried glassware under an inert atmosphere of dry argon. All chemicals were purchased from either Sigma-Aldrich, TCI America, Acros, AK Scientific, or Alfa-Aesar, and were used as received. Pentane, hexanes, tetrahydrofuran and diethyl ether were obtained from a Grubbs-type solvent purification system. Proton (^{1}H) NMR spectra were recorded at either 400 MHz on an INOVA-400 spectrometer or at 600 MHz on an INOVA-600 spectrometer. Carbon-13 (^{13}C) NMR spectra were recorded at either 100 MHz on an INOVA-400 spectrometer or at 150 MHz on an INOVA-600 spectrometer. NMR spectra were recorded in deuterated chloroform ($CDCl_3$) solutions, with residual chloroform (δ 7.27 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR) or tetramethylsilane (δ 0.00 ppm for ^{1}H NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants were taken from the spectra directly and are uncorrected. Infrared (IR) spectra were collected on a Nicolet iS10 FT-IR spectrometer as neat films. Mass spectrometric determinations were carried out on a Thermo Finnigan LTQ-FTMS spectrometer with electrospray (ESI) or atmospheric pressure chemical (APCI) ionization. Optical rotations were measured on JASCO P-2000 polarimeter. High performance liquid chromatography (HPLC) analysis was performed on a Varian Prostar 350 with hexanes/*iso*propanol as eluent. Gas chromatography (GC) analysis was performed on an Agilent 7890A; column conditions: 30 °C for 1 min, then increasing to 180 °C at a rate of 5 °C/min, then 180 °C for 5 min. Analytical thin layer chromatography (TLC) was performed on silica gel plates using ultraviolet (UV) light or stained with 10% vanillin/1% sulfuric acid/ethanol solution.. Flash column chromatography was performed with silica gel 60 A (230-

400 mesh) according to the literature procedure.[41] The reagents [$Rh_2(TFA)_4$],⁴² [$Rh_2(pfb)_4$],[43] {Rh_2[(*S*)-dosp]$_4$},[38] {Rh_2[(*S*)-nttl]$_4$},[44] {Rh_2[(*S*)-ptad]$_4$},[45] **59**–**62**, **103**, **113**, and **114**,[46] **73**,[47] **74**,[48] **75**,[49] **104**,[50] **109**–**112**,[51] **131**,[52] **132**,[53] CuTC,[54] and the sulfonyl azides[50] were all synthesized according to published procedures.

5.4.2 General Procedures

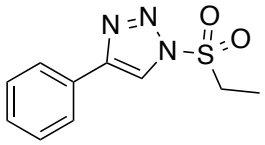
5.4.2.1 Azide-Alkyne Cycloaddition

N-Sulfonyl-1,2,3-triazoles were prepared according to a modified version of the literature procedure. To a toluene (20 mL) suspension of CuTC (0.50 mmol, 0.10 equiv), was added alkyne (5 mmol, 1.0 equiv) with vigorous stirring. After 10 min, a toluene (5 mL) solution of azide (5.5 mmol, 1.1 equiv) was added dropwise over 15 min. The reaction was stirred at ambient temperature until consumption of the alkyne was apparent by TLC analysis. The crude reaction mixture was concentrate *in vacuo* and the residue was dissolved in a minimal volume of dichloromethane. The product was purified by flash chromatography (SiO_2, hexanes/EtOAc) to obtain the triazole as a pure white solid.

5.4.2.2 Pyrrole Synthesis

A 35 mL pressure tube, fitted with a rubber septum, was charged with triazole (0.50 mmol, 1.0 equiv), Rh_2(*S*-DOSP)$_4$ (9 mg, 0.005 mmol, 0.01 equiv) and furan (1.5 mmol, 3.0 equiv). The reaction vessel was evacuated and backfilled with argon three times before adding freshly distilled 1,2-dichloroethane (2.0 mL). The reaction vessel was then sealed with a teflon screwcap and placed in an oil bath preheated to 70 °C. After consumption of the triazole was apparent from TLC analysis, the reaction was cooled to ambient temperature. The crude reaction mixture was concentrated *in vacuo*, and the product was isolated by flash chromatography (SiO_2, hexanes/EtOAc) to obtain analytically pure pyrrole.

5.4.3. Procedures and Characterization Data



1-(ethylsulfonyl)-4-phenyl-1*H*-1,2,3-triazole (52)

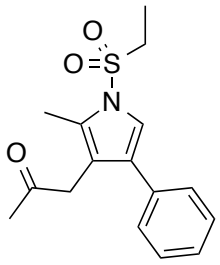
Prepared by *General Procedure 5.4.2.1* with phenylacetylene (0.56 mL, 5.0 mmol, 1.0 equiv), ethanesulfonyl azide (745 mg, 5.5 mmol, 1.1 equiv) and CuTC (95 mg, 0.50 mmol, 0.10 equiv). The reaction mixture was stirred for 8 h at ambient temperature. After concentration of the filtrate, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a white solid (1.00 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.90–7.87 (m, 1H), 7.87–7.85 (m, 1H), 7.51–7.44 (m, 2H), 7.44–7.38 (m, 1H), 3.71 (q, J = 7.4 Hz, 2H), 1.40 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 129.4, 129.3, 128.8, 126.3, 120.0, 50.3, 7.9.

FTIR (neat): ν_{max}/cm^{-1} 2979, 2940, 1484,1450, 1373, 1168.

HRMS (p-APCI): *m/z* 146.0713 [$(M–SO_2Et+H)^+$ requires 146.0713].



1-(1-(ethylsulfonyl)-2-methyl-4-phenyl-1*H*-pyrrol-3-yl)propan-2-one (53)

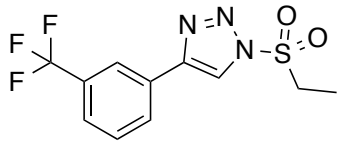
Prepared by *General Procedure 5.4.2.2* with **52** (120 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 4 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a pale yellow oil (117 mg, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.35 (m, 4H), 7.31–7.27 (m, 1H), 7.15 (s, 1H), 4.00 (s, 2H), 3.28 (q, J = 7.4 Hz, 2H), 2.26 (s, 3H), 2.02 (s, 3H), 1.30 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 134.2, 128.7, 128.4, 127.2, 124.7, 122.6, 119.7, 49.8, 40.4, 29.8, 10.7, 8.2.

FTIR (neat): ν_{max}/cm^{-1} 2926, 1717, 1621, 1534, 1449, 1355.

HRMS (p-APCI): *m/z* 306.1162 [$(M+H)^+$ requires 306.1158].



1-(ethylsulfonyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (54)

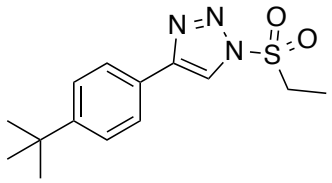
Prepared by *General Procedure 5.4.2.1* with 3-ethynyl-α,α,α-trifluorotoluene (825 mg, 5.0 mmol, 1.0 equiv), ethanesulfonyl azide (745 mg, 5.5 mmol, 1.1 equiv) and CuTC (95 mg, 0.50 mmol, 0.10 equiv). The reaction mixture was stirred for 8 h at ambient temperature. After concentration of the filtrate, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a white solid (941 mg, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.14 (s, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 3.74 (q, J = 7.4 Hz, 2H), 1.43 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 129.9, 129.8, 129.5, 126.1, 123.2, 120.6, 50.4, 8.0.

FTIR (neat): ν_{max}/cm^{-1} 3148, 1456, 1379, 1354.

HRMS (p-APCI): *m/z* 306.0518 [$(M+H)^+$ requires 306.0519].



4-(4-(*tert*-butyl)phenyl)-1-(ethylsulfonyl)-1*H*-1,2,3-triazole (55)

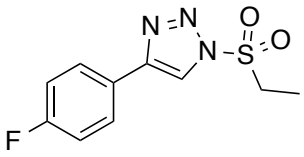
Prepared by *General Procedure 5.4.2.1* with 4-*tert*-butylphenylacetylene (824 mg, 5.0 mmol, 1.0 equiv), ethanesulfonyl azide (745 mg, 5.5 mmol, 1.1 equiv) and CuTC (95 mg, 0.50 mmol, 0.10 equiv). The reaction mixture was stirred for 8 h at ambient temperature. After concentration of the filtrate, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a white solid (996 mg, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 3.71 (q, J = 7.4 Hz, 2H), 1.39 (t, J = 7.4 Hz, 3H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 147.5, 126.2, 126.1, 126.0, 119.2, 50.3, 35.0, 31.4, 8.0.

FTIR (neat): ν_{max}/cm^{-1} 3147, 2962, 2869, 1495, 1456, 1376.

HRMS (p-APCI): *m/z* 294.1270 [$(M+H)^+$ requires 294.1271].



1-(ethylsulfonyl)-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (56)

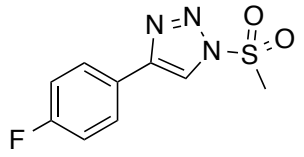
Prepared *General Procedure 5.4.2.1* with 1-ethynyl-4-fluorobenzene (605 mg, 5.0 mmol, 1.0 equiv), ethanesulfonyl azide (745 mg, 5.5 mmol, 1.1 equiv), and CuTC (95 mg, 0.50 mmol, 0.10 equiv). The reaction mixture was stirred for 8 h at ambient temperature. After concentration of the filtrate, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a white solid (1.39 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.91–7.81 (m, 2H), 7.23–7.12 (m, 2H), 3.72 (q, J = 7.4 Hz, 2H), 1.41 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 128.3, 128.2, 119.7, 116.5, 116.3, 50.3, 8.0.

FTIR (neat): ν_{max}/cm^{-1} 3134, 2981, 2948, 1608, 1560, 1495.

HRMS (p-APCI): *m/z* 256.0551 [$(M+H)^+$ requires 256.0551].



4-(4-fluorophenyl)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (57)

Prepared by *General Procedure 5.4.2.1* with 1-ethynyl-4-fluorobenzene (605 mg, 5.0 mmol, 1.0 equiv), methanesulfonyl azide (667 mg, 5.5 mmol, 1.1 equiv), and CuTC (95 mg, 0.50 mmol, 0.10 equiv). The reaction mixture was stirred for 8 h at ambient temperature. After concentra-

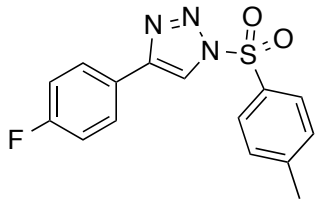
tion of the filtrate, the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to afford the title compound as a white solid (1.04 mg, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.88–7.83 (m, 2H), 7.20–7.14 (m, 2H), 3.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 128.3, 128.2, 118.8, 116.6, 116.3, 42.9.

FTIR (neat): ν_{max}/cm^{-1} 3147, 3034, 3020, 2936, 1904, 1610, 1563, 1496.

HRMS (p-APCI): *m/z* 242.0394 [$(M+H)^+$ requires 242.0394].



4-(4-fluorophenyl)-1-tosyl-1*H*-1,2,3-triazole (58)

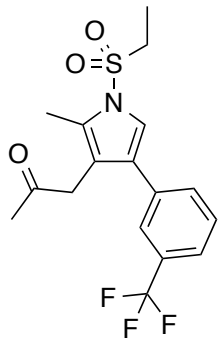
Prepared by *General Procedure 5.4.2.1* with 1-ethynyl-4-fluorobenzene (605 mg, 5.0 mmol, 1.0 equiv), toluenesulfonyl azide (1.08 g, 5.5 mmol, 1.1 equiv), and CuTC (95 mg, 0.50 mmol, 0.10 equiv). The reaction mixture was stirred for 8 h at ambient temperature. After concentration of the filtrate, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a white solid (1.39 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.83–7.78 (m, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.17–7.04 (m, 2H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3 (d, J = 248 Hz), 147.7, 146.6, 133.1, 130.7, 128.9, 128.1 (d, J = 8 Hz), 125.3 (d, J = 3 Hz), 118.9, 116.2 (d, J = 22 Hz), 22.0.

FTIR (neat): ν_{max}/cm^{-1} 3152, 1902, 1611, 1593, 1563, 1495, 1394.

HRMS (p-APCI): *m/z* 318.0706 [(M+H)$^+$ requires 318.0707].



1-(1-(ethylsulfonyl)-2-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-pyrrol-3-yl)propan-2-one (63)

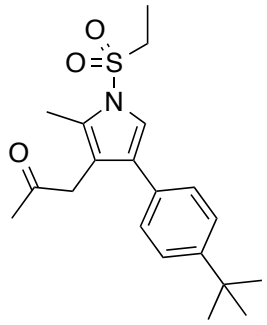
Prepared by *General Procedure 5.4.2.2* with **54** (153 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 3 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a colorless oil (142 mg, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.57–7.47 (m, 3H), 7.21 (d, J = 1.1 Hz, 1H), 4.02 (s, 2H), 3.38–3.25 (m, 3H), 2.28 (d, J = 1.5 Hz, 3H), 2.02 (s, 4H), 1.33 (td, J = 7.4, 1.5 Hz, 4H),

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6, 134.8, 131.4, 130.8 (q, J = 32 Hz), 128.9, 127.0, 125.0, 124.8 (m), 124.0 (q, J = 271 Hz), 123.5 (m), 121.9, 119.9, 49.7, 40.1, 29.5, 10.2, 7.9.

FTIR (neat): ν_{max}/cm^{-1} 2927, 1720, 1616, 1534, 1456.

HRMS (p-APCI): *m/z* 374.1032 [(M+H)$^+$ requires 374.1032].



1-(4-(4-(*tert*-butyl)phenyl)-1-(ethylsulfonyl)-2-methyl-1*H*-pyrrol-3-yl)propan-2-one (64)

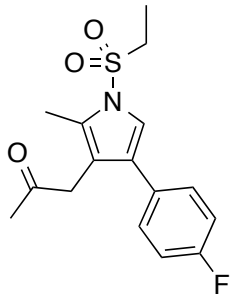
Prepared by *General Procedure 5.4.2.2* with **55** (147 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 8 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a colorless, amorphous solid (133 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.15 (s, 1H), 4.01 (s, 2H), 3.28 (q, J = 7.4 Hz, 2H), 2.27 (s, 3H), 2.04 (s, 3H), 1.34 (s, 9H), 1.33–1.28 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.8, 149.8, 131.0, 128.2, 127.8, 125.4, 124.4, 122.5, 119.3, 49.5, 40.2, 34.4, 31.3, 29.5, 10.4, 7.9.

FTIR (neat): ν_{max}/cm^{-1} 2961, 1721, 1541, 1457, 1354.

HRMS (p-NSI): *m/z* 362.1785 [$(M+H)^+$ requires 362.1784].



1-(1-(ethylsulfonyl)-4-(4-fluorophenyl)-2-methyl-1*H*-pyrrol-3-yl)propan-2-one (65)

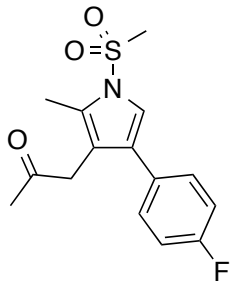
Prepared by *General Procedure 5.4.2.2* with **56** (128 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 4 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a pale yellow oil (129 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.27 (m, 2H), 7.10 (s, 1H), 7.09–7.01 (m, 2H), 3.99 (s, 2H), 3.28 (q, J = 7.4 Hz, 2H), 2.26 (s, 3H), 1.98 (s, 3H), 1.30 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0, 162.2 (d, J = 244 Hz), 130.2, 130.0 (d, J = 8 Hz), 127.6, 124.8, 122.4, 119.6, 115.6 (d, J = 22 Hz), 49.8, 40.4, 29.8, 10.5, 8.2.

FTIR (neat): ν_{max}/cm^{-1} 2926, 1721, 1600, 1538, 1496, 1354.

HRMS (p-NSI): *m/z* 324.1064 [$(M+H)^+$ requires 324.1064.



1-(4-(4-fluorophenyl)-2-methyl-1-(methylsulfonyl)-1*H*-pyrrol-3-yl)propan-2-one (66)

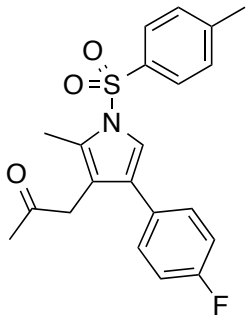
Prepared by *General Procedure 5.4.2.2* with **57** (120 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 2 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a pale yellow oil (123 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2H), 7.14 (s, 1H), 7.10–7.04 (m, 2H), 4.02 (s, 2H), 3.16 (s, 3H), 2.29 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0, 162.1 (d, J = 245 Hz), 130.0 (d, J = 3 Hz), 129.9 (d, J = 8 Hz), 128.4, 125.0, 122.2, 118.6, 115.5 (d, J = 21 Hz), 42.1, 40.3, 29.7, 10.4.

FTIR (neat): ν_{max}/cm^{-1} 2927, 1719, 1601, 1539, 1497, 1354.

HRMS (p-APCI): *m/z* 310.0907 [$(M+H)^+$ requires 310.0908].



1-(4-(4-fluorophenyl)-2-methyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (67)

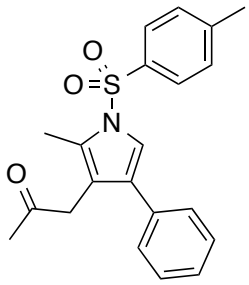
Prepared by *General Procedure 5.4.2.2* with **58** (120 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 6 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as an amorphous, pale yellow solid (187 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.4 Hz, 2H), 7.38–7.26 (m, 5H), 7.17–7.00 (m, 2H), 3.86 (s, 2H), 2.40 (s, 3H), 2.18 (s, 3H), 1.95 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 162.1 (d, J = 245 Hz), 145.3, 136.2, 130.2, 130.2, 129.9 (d, J = 8 Hz), 128.1, 127.0, 124.7, 122.8, 119.2, 115.5 (d, J = 21 Hz), 40.3, 29.4, 21.8, 10.5.

FTIR (neat): ν_{max}/cm^{-1} 2924, 1726, 1597, 1537, 1495, 1357.

HRMS (p-APCI): *m/z* 386.1221 [$(M+H)^+$ requires 386.1221].



1-(2-methyl-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (68)

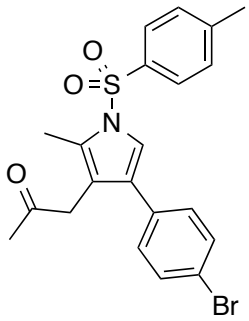
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 2 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a colorless oil (156 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71–7.63 (m, 2H), 7.41–7.36 (m, 4H), 7.34 (s, 1H), 7.32–7.28 (m, 3H), 3.85 (s, 2H), 2.40 (s, 3H), 2.17 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8, 145.2, 136.3, 134.2, 130.2, 129.1, 128.7, 128.4, 127.2, 127.0, 124.7, 123.0, 119.5, 40.4, 29.4, 21.9, 10.7.

FTIR (neat): ν_{max}/cm^{-1} 2924, 1720, 1596, 1534, 1448, 1358.

HRMS (p-APCI): *m/z* 368.1316 [$(M+H)^+$ requires 368.1315].



1-(4-(4-bromophenyl)-2-methyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (69)

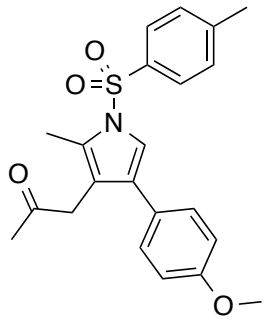
Prepared by *General Procedure 5.4.2.2* with **60** (190 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 2 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a pale yellow, amorphous solid (158 mg, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.0 Hz, 2H), 7.51–7.47 (m, 2H), 7.33 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.25–7.21 (m, 2H), 3.85 (s, 2H), 2.40 (s, 3H), 2.18 (s, 3H), 1.95 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 145.4, 136.1, 133.1, 131.8, 130.3, 129.9, 127.9, 127.0, 124.9, 122.6, 121.1, 119.4, 40.3, 29.4, 21.8, 10.6.

FTIR (neat): ν_{max}/cm^{-1} 2955, 2924, 1720, 1596, 1532.

HRMS (p-APCI): *m/z* 446.0424 [$(M+H)^+$ requires 446.0420].



1-(4-(4-methoxyphenyl)-2-methyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (70)

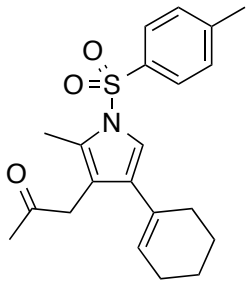
Prepared by *General Procedure 5.4.2.2* with **61** (165 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 10 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a colorless, amorphous solid (181 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 12 Hz, 7.30–7.26 (m, 5H), 6.93 (d, J = 12 Hz, 2H), 3.84 (s, 2H), 3.83 (s, 3H), 2.40 (s, 3H), 2.17 (s, 3H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 158.9, 145.2, 136.4, 130.2, 129.5, 128.8, 127.0, 126.6, 124.6, 123.1, 119.0, 114.1, 55.5, 40.5, 29.4, 21.9, 10.7.

FTIR (neat): ν_{max}/cm^{-1} 2925, 1720, 1614, 1596, 1539, 1497.

HRMS (p-APCI): *m/z* 398.1418 [$(M+H)^+$ requires 398.1421].



1-(4-(cyclohex-1-en-1-yl)-2-methyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (71)

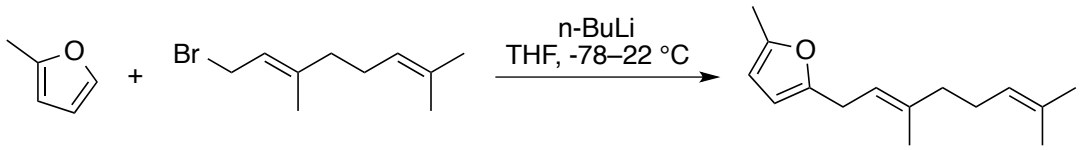
Prepared by *General Procedure 5.4.2.2* with **62** (152 mg, 0.50 mmol, 1.0 equiv), **51** (0.16 mL, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 2 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a colorless oil (130 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.15 (s, 1H), 5.87–5.86 (m, 1H), 3.77 (s, 2H), 2.40 (s, 3H), 2.27–2.22 (m 2H), 2.18–2.13 (m, 2H), 2.11 (s, 3H), 1.95 (s, 3H), 1.75–1.70 (m, 2H), 1.65–1.60 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0, 145.0, 136.5, 130.4, 130.2, 130.1, 126.8, 125.7, 124.3, 122.9, 118.4, 40.2, 29.2, 28.7, 25.8, 23.1, 22.2, 21.8, 11.8.

FTIR (neat): ν_{max}/cm^{-1} 2925, 2857, 2833, 1721, 1596, 1356.

HRMS (p-NSI): *m/z* 372.1629 [(M+H)$^+$ requires 372.1628].



(*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-5-methylfuran (76)

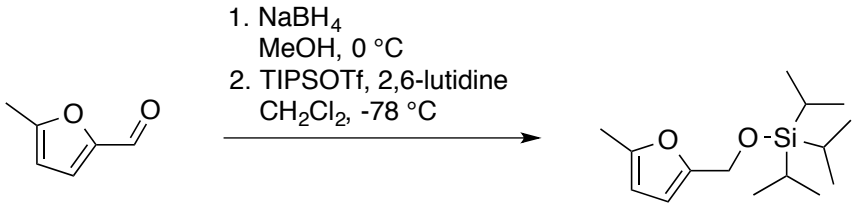
To a THF (150 mL) solution of 2-methylfuran (1.82 mL, 20.0 mmol, 1.0 equiv) under a dry atmosphere of argon was added *n*-butyllithium (2.5 M in hexanes) (12.0 mL, 30.0 mmol, 1.5 equiv) dropwise over 30 minutes *via* syringe pump at -78 °C. The reaction was stirred at -78 °C for an additional 1 h, before warming to ambient temperature for 4 h. The reaction was cooled in an ice bath to 0 °C, and a THF (10 mL) solution of geranyl bromide (6.27 mL, 30.0 mmol, 1.5 equiv) was added dropwise over 30 minutes *via* syringe pump. The reaction was gradually warmed to ambient temperature overnight. The reaction mixture was cooled to 0 °C and carefully quenched with a saturated aqueous solution of ammonium chloride (150 mL). The product was extracted with pentanes (5 x 25 mL) and the combined organic fractions were washed with water (3 x 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, pentane) to afford the title compound as a colorless oil (1.84 g, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88–5.79 (m, 2H), 5.32 (t, J = 7.1 Hz, 1H), 5.11 (t, J = 6.7 Hz, 1H), 3.30 (d, J = 7.1 Hz, 2H), 2.25 (s, 3H), 2.17–2.07 (m, 2H), 2.07–2.01 (m, 2H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 150.6, 137.5, 131.7, 124.4, 119.7, 106.0, 105.4, 39.8, 27.2, 26.8, 25.9, 17.9, 16.3, 13.8.

FTIR (neat): ν_{max}/cm^{-1} 2967, 2921, 2855, 1568, 1448, 1376, 1219, 1019.

HRMS (p-APCI): *m/z* 219.1743 [$(M+H)^+$ requires 219.1743].



triisopropyl((5-methylfuran-2-yl)methoxy)silane (77)

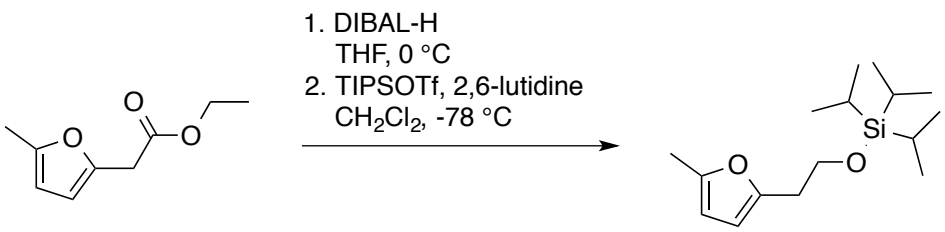
To a methanolic (100 mL) solution of 5-methylfurfural (2.00 mL, 20.0 mmol, 1.0 equiv) was added sodium borohydride (910 mg, 24.0 mmol, 1.2 equiv) in several portions at 0 °C. The reaction was stirred at 0 °C for 1 h, before warming to ambient temperature for an additional 1 h. The crude reaction mixture was concentrated *in vacuo* and partitioned between ether (50 mL) and brine (50 mL). The layers were separated and the aqueous was extracted with additional ether (2 x 50 mL). The combined organic fractions were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was redissolved in CH_2Cl_2 (150 mL) and cooled to -78 °C under an atmosphere of argon. The solution was treated with 2,6-lutidine (4.75 mL, 40 mmol, 2.0 equiv) in a single portion, and then triisopropylsilyl trifluoromethanesulfonate (8.30 mL, 30 mmol, 1.5 equiv) was added dropwise over 30 minutes *via* syringe pump. The reaction was stirred at -78 °C for 8 h, and then warmed to 0 °C for 1h. The reaction was carefully quenched with saturated, aqueous ammonium chloride (100 mL) and the consequent layers were separated. The aqueous was extracted with pentane (3 x 50 mL), and the organic fractions were combined and washed with water (3 x 100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 98:2) to afford the title compound as a colorless oil (3.82 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (d, J = 3.0 Hz, 1H), 5.92–5.85 (m, 1H), 4.65 (s, 2H), 2.27 (s, 3H), 1.20–1.01 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 151.7, 108.0, 106.2, 58.7, 18.2, 13.8, 12.3.

FTIR (neat): ν_{max}/cm^{-1} 2942, 2891, 2865, 1565, 1463.

HRMS (p-NSI): *m/z* 269.1932 [$(M+H)^+$ requires 269.1931].



triisopropyl(2-(5-methylfuran-2-yl)ethoxy)silane (78)

To a THF (100 mL) solution of ethyl 2-(5-methylfuran-2-yl)acetate[55] (2.00 mL, 20.0 mmol, 1.0 equiv) under an inert atmosphere of argon was added DIBAL-H (1.0 M in CH_2Cl_2) (60.0 mL, 60 mmol, 3.0 equiv) dropwise *via* addition funnel at 0 °C. The reaction was stirred at 0 °C for 2 h before quenching by careful addition of saturated, aqueous Rochelle's salt (50 mL). The mixture was stirred until emulsions had disapated (~1 h), and then the product was extracted with ether (4 x 50 mL). The combined organic fractions were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was redissolved in CH_2Cl_2 (150 mL) and cooled to -78 °C under an atmosphere of argon. The solution was treated with 2,6-lutidine (4.75 mL, 40 mmol, 2.0 equiv) in a single portion, and then triisopropylsilyl trifluoromethanesulfonate (8.30 mL, 30 mmol, 1.5 equiv) was added dropwise over 30 minutes *via* syringe pump. The reaction was stirred at -78 °C for 8 h, and then warmed to 0 °C for 1h. The reaction was carefully quenched with saturated, aqueous ammonium chloride (100 mL) and the consequent layers were separated. The aqueous was extracted with pentane (3 x 50 mL), and the organic fractions were combined and washed with water (3 x 100 mL) and brine (100 mL),

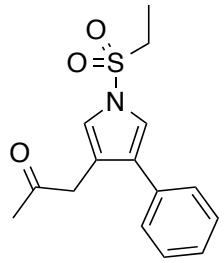
dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc, 98:2) to afford the title compound as a colorless oil (2.65 g, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (d, J = 2.9 Hz, 1H), 5.83 (dd, J = 2.9, 1.0 Hz, 1H), 3.88 (t, J = 7.1 Hz, 2H), 2.81 (t, J = 7.1 Hz, 2H), 2.23 (s, 3H), 1.11–0.96 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 150.6, 106.9, 106.1, 62.4, 32.3, 18.2, 13.7, 12.2.

FTIR (neat): ν_{max}/cm^{-1} 2943, 2924, 2892, 2866, 1570, 1463, 1384, 1108.

HRMS (p-APCI): *m/z* 283.2090 [$(M+H)^+$ requires 283.2088].



1-(1-(ethylsulfonyl)-4-phenyl-1*H*-pyrrol-3-yl)propan-2-one (79)

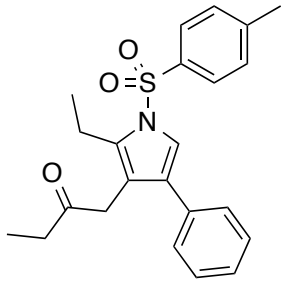
Prepared by *General Procedure 5.4.2.2* with **52** (119 mg, 0.50 mmol, 1.0 equiv), **72** (122 mg, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 2 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford the title compound as a colorless oil (60 mg, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.45 (m, 2H), 7.37 (dd, J = 4.7, 2.7 Hz, 2H), 7.34 (s, 1H), 7.28–7.23 (m, 1H), 6.46 (d, J = 1.9 Hz, 1H), 4.03 (s, 2H), 3.37 (q, J = 7.4 Hz, 2H), 2.27 (s, 3H), 1.36 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.8, 133.4, 129.1, 129.0, 127.2, 127.2, 125.7, 118.8, 114.4, 49.8, 42.7, 29.8, 8.2.

FTIR (neat): ν_{max}/cm^{-1} 3135, 3029, 2983, 2942, 1718, 1608, 1528, 1452, 1358, 1142.

HRMS (p-APCI): *m/z* 291.0921 [$(M+H)^+$ requires 291.0921].



1-(2-ethyl-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)butan-2-one (80)

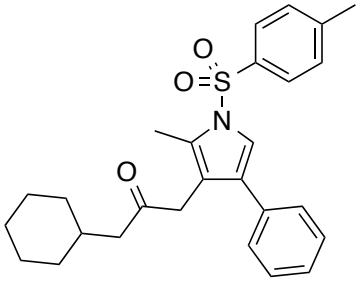
Prepared by *General Procedure 5.4.2.2* with **59** (119 mg, 0.50 mmol, 1.0 equiv), **73** (122 mg, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 2 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford the title compound as a colorless oil (196 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.4 Hz, 2H), 7.39–7.33 (m, 4H), 7.33–7.25 (m, 3H), 7.24 (s, 1H), 3.81 (s, 2H), 2.49 (q, J = 7.3 Hz, 2H), 2.44–2.33 (m, 5H), 1.03 (q, J = 7.3 Hz, 3H), 0.90 (q, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 145.1, 136.4, 134.5, 130.2, 129.3, 128.7, 128.7, 128.4, 127.2, 127.0, 124.4, 119.9, 39.3, 35.2, 21.8, 18.0, 15.2, 7.8.

FTIR (neat): ν_{max}/cm^{-1} 3137, 3059, 2971, 2935, 2875, 1722, 1596, 1362.

HRMS (p-APCI): *m/z* 396.1631 [$(M+H)^+$ requires 396.1628]



1-cyclohexyl-3-(2-methyl-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (81)

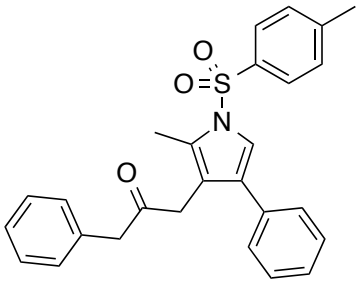
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **74** (267 mg, 1.5 mmol, 3.0 equiv) and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 4 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 8:1) to afford the title compound as a pale yellow oil (101 mg, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.2 Hz, 2H), 7.41–7.35 (m, 4H), 7.35–7.25 (m, 4H), 3.82 (s, 2H), 2.40 (s, 3H), 2.30 (d, J = 6.7 Hz, 2H), 1.97 (s, 3H), 1.83–1.80 (m, 1H), 1.68–1.65 (m, 5H), 1.35–1.20 (m, 2H), 1.20–1.06 (m, 1H), 0.98–0.81 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 145.1, 136.5, 134.3, 130.2, 129.1, 128.7, 128.4, 127.1, 127.0, 124.7, 123.0, 119.5, 49.5, 40.4, 33.6, 33.4, 26.4, 26.3, 21.9, 10.8.

FTIR (neat): ν_{max}/cm^{-1} 2921, 2850, 1718, 1597, 1534, 1448.

HRMS (p-APCI): *m/z* 450.2096 [$(M+H)^+$ requires 450.2097].



1-(2-methyl-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)-3-phenylpropan-2-one (82)

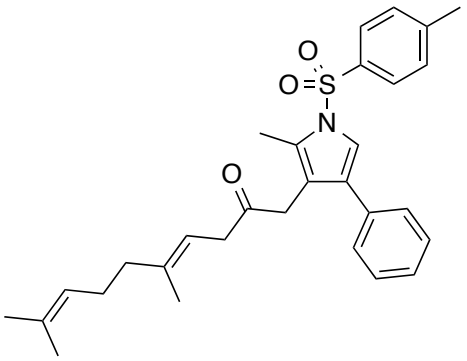
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **75** (258 mg, 1.5 mmol, 3.0 equiv) and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 12 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 6:1) to afford the title compound as a pale yellow, amorphous solid (120 mg, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.60 (m, 2H), 7.40–7.24 (m, 11H), 7.21–7.19 (m, 2H), 3.85 (s, 2H), 3.77 (s, 2H), 2.39 (s, 3H), 1.81 (s, 3H), 1.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 145.2, 136.3, 134.2, 134.2, 130.2, 129.8, 129.2, 128.8, 128.7, 128.4, 127.2, 127.2, 127.0, 124.3, 123.4, 119.5, 49.3, 39.2, 21.9, 10.6.

FTIR (neat): ν_{max}/cm^{-1} 3029, 2923, 1724, 1597, 1495, 1362.

HRMS (p-APCI): *m/z* 444.1625 [$(M+H)^+$ requires 444.1628].



(*E*)-5,9-dimethyl-1-(2-methyl-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)deca-4,8-dien-2-one (83)

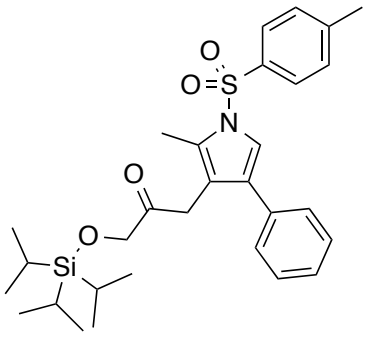
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **76** (327 mg, 1.5 mmol, 3.0 equiv), and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 12 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford the title compound as a colorless oil (107 mg, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.63 (m, 2H), 7.38–7.24 (m, 7H), 5.34–5.26 (m, 1H), 5.12–5.04 (m, 1H), 3.85 (s, 2H), 3.17 (d, J = 6.9 Hz, 2H), 2.38 (s, 3H), 2.10–2.03 (m, 4H), 1.94 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1, 145.1, 139.8, 136.4, 134.3, 131.9, 130.2, 129.1, 128.7, 128.4, 127.1, 127.0, 124.7, 124.2, 123.0, 119.5, 115.7, 41.9, 39.9, 39.2, 26.7, 25.9, 219, 17.9, 16.7, 10.7.

FTIR (neat): ν_{max}/cm^{-1} 3057, 3029, 2964, 2921, 2855, 1722, 1597, 1534, 1447, 1363, 1173, 1098.

HRMS (p-NSI): *m/z* 490.2412 [$(M+H)^+$ requires 490.2410].



1-(2-methyl-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)-3-((triisopropylsilyl)oxy)propan-2-one (84)

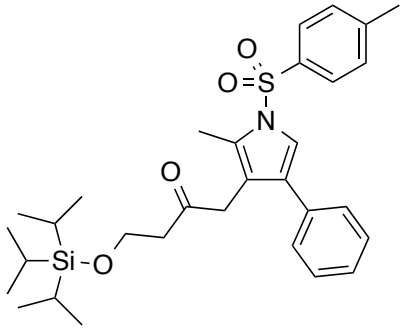
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **77** (403 mg, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 6 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 12:1) to afford the title compound as a pale yellow oil (225 mg, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.64 (m, 2H), 7.38–7.35 (m, 4H), 7.34–7.23 (m, 4H), 4.38 (s, 2H), 4.10 (s, 2H), 2.40 (s, 3H), 1.97 (s, 3H), 1.28–1.03 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 145.0, 136.5, 134.4, 130.1, 129.2, 128.6, 128.4, 127.0, 124.1, 123.2, 119.5, 69.8, 35.9, 21.9, 18.2, 12.1, 10.7.

FTIR (neat): ν_{max}/cm^{-1} 2943, 2865, 1733, 1597, 1535, 1462, 1365.

HRMS (p-APCI): *m/z* 540.2598 [$(M+H)^+$ requires 540.2598].



1-(2-methyl-4-phenyl-1-tosyl-1H-pyrrol-3-yl)-4-((triisopropylsilyl)oxy)butan-2-one (85)

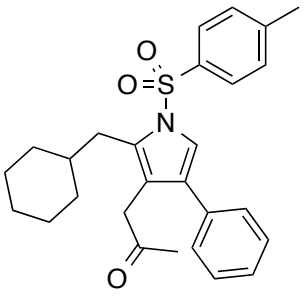
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **78** (424 mg, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 12 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 15:1) to afford the title compound as a pale yellow oil (135 mg, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.38–7.34 (m, 4H), 7.32–7.23 (m, 4H), 3.97 (t, J = 6.3 Hz, 2H), 3.90 (s, 2H), 2.69 (t, J = 6.3 Hz, 2H), 2.38 (s, 3H), 1.96 (s, 3H), 1.15–0.97 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4, 145.1, 136.5, 134.3, 130.2, 129.1, 128.7, 128.4, 127.1, 127.0, 124.6, 123.1, 119.4, 59.3, 45.3, 40.6, 21.9, 18.2, 12.1, 10.7.

FTIR (neat): ν_{max}/cm^{-1} 3030, 2942, 2890, 2865, 1721, 1597, 1534, 1462, 1363, 1174, 1105.

HRMS (p-APCI): *m/z* 554.2761 [$(M+H)^+$ requires 554.2755].



1-(2-(cyclohexylmethyl)-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (88)

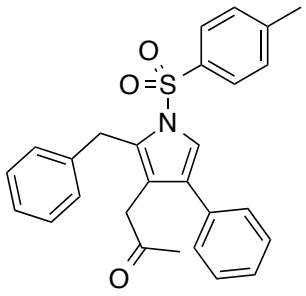
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **74** (267 mg, 1.5 mmol, 3.0 equiv), and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 4 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 8:1) to afford the title compound as a pale yellow oil (50 mg, 22% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.2 Hz, 2H), 7.40–7.24 (m, 8H), 3.83 (s, 2H), 2.40 (s, 3H), 2.29 (d, J = 7.2 Hz, 2H), 2.20 (s, 3H), 1.52–1.50 (m, 3H), 1.43–1.40 (m, 2H), 1.10–1.04 (m, 1H), 1.00–0.90 (m, 3H), 0.68–0.59 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8, 145.2, 136.3, 134.2, 130.2, 129.1, 128.7, 128.4, 127.2, 127.0, 124.7, 123.0, 119.5, 53.7, 40.4, 29.4, 21.9, 10.7.

FTIR (neat): ν_{max}/cm^{-1} 2922, 2850, 1722, 1597, 1532, 1448.

HRMS (p-APCI): *m/z* 450.2098 [$(M+H)^+$ requires 450.2097].



1-(2-benzyl-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (89)

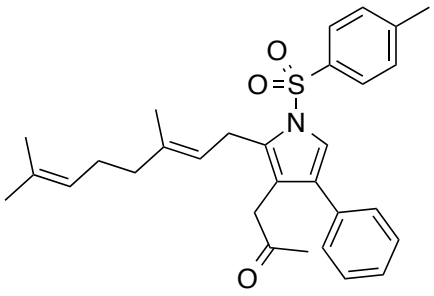
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **75** (258 mg, 1.5 mmol, 3.0 equiv), and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 12 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 6:1) to afford the title compound as a pale yellow, amorphous solid (41 mg, 18% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.65 (m, 2H), 7.37 (s, 1H), 7.35–7.09 (m, 10H), 6.96–6.94 (m, 2H), 3.79 (s, 2H), 3.76 (s, 2H), 2.43 (s, 3H), 2.05 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 145.4, 139.9, 136.3, 133.9, 130.2, 129.7, 128.7, 128.6, 128.6, 128.2, 127.3, 127.1, 126.4, 126.3, 125.3, 120.1, 40.5, 30.2, 29.5, 21.9.

FTIR (neat): ν_{max}/cm^{-1} 3028, 2920, 1722, 1597, 1494, 1452, 1363.

HRMS (p-APCI): *m/z* 444.1625 [$(M+H)^+$ requires 444.1628].



(*E*)-1-(2-(3,7-dimethylocta-2,6-dien-1-yl)-4-phenyl-1-tosyl-1*H*-pyrrol-3-yl)propan-2-one (90)

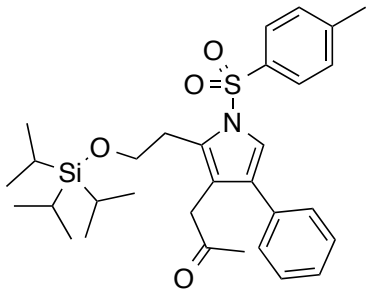
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **76** (327 mg, 1.5 mmol, 3.0 equiv), and $\{Rh_2[(S)\text{-dosp}]_4\}$ (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 12 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford the title compound as a colorless oil (53 mg, 21% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.3 Hz, 2H), 7.38–7.26 (m, 2H), 5.02–4.96 (m, 2H), 3.83 (s, 2H), 3.09 (d, J = 6.4 Hz, 2H), 2.41 (s, 3H), 2.06 (s, 3H), 1.98–1.94 (m, 2H), 1.92–1.86 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 145.2, 136.4, 136.0, 134.2, 131.7, 130.2, 129.1, 128.7, 128.6, 127.1, 126.8, 125.2, 124.3, 122.7, 119.5, 40.4, 39.7, 29.4, 26.7, 25.9, 23.8, 21.9, 17.9, 16.3.

FTIR (neat): ν_{max}/cm^{-1} 3034, 2963, 2855, 1720, 1597, 1447, 1364, 1173, 1098.

HRMS (p-APCI): *m/z* 490.2411 [$(M+H)^+$ requires 490.2410].



1-(4-phenyl-1-tosyl-2-(2-((triisopropylsilyl)oxy)ethyl)-1*H*-pyrrol-3-yl)propan-2-one (92)

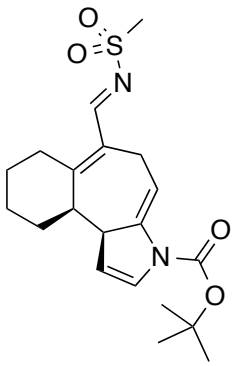
Prepared by *General Procedure 5.4.2.2* with **59** (150 mg, 0.50 mmol, 1.0 equiv), **78** (424 mg, 1.5 mmol, 3.0 equiv), and {Rh_2[(*S*)-dosp]$_4$} (9 mg, 0.005 mmol, 0.01 equiv). The reaction mixture was stirred for 12 h at 70 °C. After concentration of the reaction mixture, the residue was purified by flash chromatography (hexanes/EtOAc, 15:1) to afford the title compound as a pale yellow oil (107 mg, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4 Hz, 2H), 7.38–7.35 (m, 4H), 7.32–7.25 (m, 4H), 3.93 (s, 2H), 3.52 (t, J = 7.1 Hz, 2H), 2.66 (t, J = 7.1 Hz, 2H), 2.41 (s, 3H), 2.21 (s, 3H), 0.92–0.84 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 145.2, 136.4, 134.3, 130.2, 129.0, 128.7, 128.7, 127.3, 127.2, 125.9, 124.2, 119.8, 63.3, 40.6, 29.6, 28.4, 21.9, 18.1, 12.0.

FTIR (neat): ν_{max}/cm^{-1} 3060, 2942, 2891, 2865, 1723, 1597, 1532, 1463, 1366, 1103.

HRMS (p-APCI): *m/z* 554.2760 [$(M+H)^+$ requires 554.2755].



***tert*-butyl (10a*R*,10b*R*)-6-((*E*)-((methylsulfonyl)imino)methyl)-7,8,9,10,10a,10b-hexahydrobenzo[3,4]cyclohepta[1,2-b]pyrrole-3(5H)-carboxylate (106)**

A 22 mL test tube was charged with **103** (113 mg, 0.05 mmol), **104** (193 mg, 1.0 mmol), and $\{Rh_2[(S)\text{-nttl}]_4\}$ (8 mg, 0.005 mmol). The reagents were suspended in freshly distilled cyclohexane (5.0 mL) and immersed in an oil bath preheated to 70 °C. The reaction was stirred at elevated temperature for 16 h and then cooled to ambient temperature. Direct purification by flash chromatography (SiO_2, hexanes/EtOAc, 3:1) afforded the title compound as an amorphous white solid (100 mg, 51% yield).

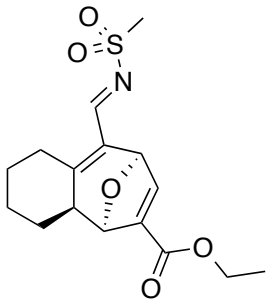
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 6.76 (bs, 1H), 4.96 (bs, 1H), 4.36 (bs, 1H), 3.68 (dd, J = 17.8, 9.1 Hz, 1H), 3.31 (bd, J = 13.0 Hz, 1H), 3.08 (s, 3H), 3.93 (bd, J = 17.8 Hz, 1H), 2.34-2.26 (m, 1H), 2.06-1.78 (m, 5H), 1.53 (s, 9H), 1.55-1.32 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 169.2, 143.1, 132.2, 127.8, 108.4, 105.9, 82.0, 48.3, 46.9, 40.7, 34.5, 31.1, 30.4, 28.6, 26.8, 24.4, 22.5.

FTIR (neat): ν_{max}/cm^{-1} 2978, 2933, 2858, 1713, 1613, 1598, 1556, 1477, 1456, 1393, 1337, 1309, 1136.

HRMS (p-APCI): *m/z* 393.1843 [$(M+H)^+$ requires 393.1843].

HPLC: 94% ee (ADH, 20% isopropanol/hexanes, 1.0 mL/min, UV: 254 nm). t_R = 6.7 min (major) and 7.9 min (minor).



ethyl (4a*S*,5*R*,8*R*)-9-((*Z*)-((methylsulfonyl)imino)methyl)-2,3,4,4a,5,8-hexahydro-1*H*-5,8-epoxybenzo[7]annulene-6-carboxylate (108)

A 22 mL test tube was charged with **103** (102 mg, 0.45 mmol), **107** (0.19 mL, 1.4 mmol), and {Rh_2[(*S*)-nttl]$_4$} (7 mg, 0.005 mmol). The reagents were suspended in freshly distilled cyclohexane (2.0 mL) and immersed in an oil bath preheated to 70 °C. The reaction was stirred at elevated temperature for 0.5 h and then cooled to ambient temperature. Direct purification by flash chromatography (SiO_2, hexanes/EtOAc, 1:1) afforded the title compound as an amorphous white solid (150 mg, 98% yield).

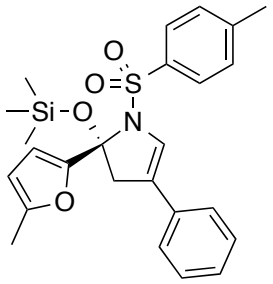
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.45 (d, J = 2.1 Hz, 1H), 5.52 (s, 1H), 5.07 (s, 1H), 4.28-4.16 (m, 2H), 3.21-3.12 (m, 1H), 3.08 (s, 3H), 2.80 (dt, J = 10.7, 5.0 Hz, 1H), 2.09-1.91 (m, 2H), 1.88-1.79 (m, 1H), 1.55-1.41 (m, 1H), 1.40-1.33 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.03-0.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 163.4, 163.1, 148.2, 135.5, 130.5, 79.9, 76.3, 60.7, 41.0, 40.2, 29.5, 28.2, 27.6, 24.9, 14.1.

FTIR (neat): ν_{max}/cm^{-1} 2934, 2858, 1709, 1608, 1559, 1446, 1310, 1142, 1102.

HRMS (p-APCI): *m/z* 340.1215 [$(M+H)^+$ requires 340.1213].

HPLC: 88% ee (ADH, 40% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 7.9 min (major) and 9.8 min (minor).



(*R*)-2-(5-methylfuran-2-yl)-4-phenyl-1-tosyl-2-((trimethylsilyl)oxy)-2,3-dihydro-1*H*-pyrrole (117)

A 22 mL test tube was charged with **59** (78 mg, 0.25 mmol), **111** (74 mg, 0.38 mmol), and $\{Rh_2[(S)\text{-tcpttl}]_4\}$ (1.5 mg, 0.0013 mmol). The reagents were suspended in hexanes (2.0 mL) and immersed in an oil bath preheated to 70 °C. The reaction was stirred at elevated temperature for 3 h and then cooled to ambient temperature. Direct purification by flash chromatography (SiO_2, hexanes/EtOAc, 7:1) afforded the title compound as an amorphous white solid (116 mg, 99% yield).

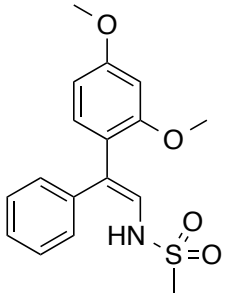
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, J = 8.2 Hz, 2H), 7.35-7.30 (m, 4H), 7.24-7.18 (m, 2H), 7.12 (d, J = 8.2 Hz, 2H), 6.48 (d, J = 3.1 Hz, 1H), 5.87-5.82 (m, 1H), 3.64 (dd, J = 17.0, 2.5 Hz, 1H), 3.06 (d, J = 17.0 Hz, 1H), 2.37 (s, 3H), 1.82 (s, 3H), 0.20 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 151.6, 151.0, 142.5, 137.9, 133.8, 129.0, 128.7, 126.7, 126.6, 124.8, 124.2, 116.6, 106.6, 106.3, 92.2, 47.3, 21.4, 13.2, 1.3.

FTIR (neat): ν_{max}/cm^{-1} 3105, 3031, 2956, 2922, 1632, 1599, 1495, 1447, 1353, 1163.

HRMS (p-APCI): *m/z* 468.1660 [(M+H)$^+$ requires 468.1659].

HPLC: 95% ee (OD, 0.5% isopropanol/hexanes, 1.0 mL/min, UV: 280 nm). t_R = 9.2 min (minor) and 11.4 min (major).



(*E*)-*N*-(2-(2,4-dimethoxyphenyl)-2-phenylvinyl)methanesulfonamide (129)

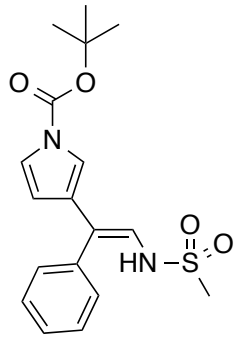
A microwave vial was charged with **113** (22 mg, 0.10 mmol), **128** (0.04 mL, 0.3 mmol), and [$Rh_2(tpa)_4$] (1 mg, 0.001 mmol). The reagents were suspended in freshly distilled 1,2-DCE (1.0 mL) heated in a microwave reactor at 120 °C for 10 min. Direct purification by flash chromatography (SiO_2, hexanes/EtOAc, 1:1) afforded the title compound as an amorphous white solid (32 mg, 95% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.8-7.24 (m, 2H), 7.22-7.17 (m 3H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 11.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.57 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.14 (d, *J* = 11.4 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.03 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 161.4, 158.0, 139.8, 132.6, 128.6, 127.0, 126.3, 121.8, 121.1, 117.1, 106.0, 99.7, 56.0, 55.7, 41.3.

FTIR (neat): ν_{max}/cm^{-1} 3276, 3058, 3006, 2935, 2837, 1639, 1606, 1575, 1505, 1207, 1155.

HRMS (p-APCI): *m/z* 334.1107 [$(M+H)^+$ requires 334.1108].



***tert*-butyl (*E*)-3-(2-(methylsulfonamido)-1-phenylvinyl)-1*H*-pyrrole-1-carboxylate (133)**

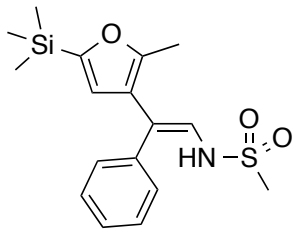
A microwave vial was charged with **113** (44 mg, 0.20 mmol), **130** (100 mg, 0.60 mmol), and $[Rh_2(tpa)_4]$ (2 mg, 0.002 mmol). The reagents were suspended in freshly distilled 1,2-DCE (1.0 mL) heated in a microwave reactor at 100 °C for 20 min. Direct purification by flash chromatography (SiO_2, hexanes/EtOAc, 4:1) afforded the title compound as a colorless oil (62 mg, 85% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44-7.42 (m, 1H), 7.28-7.23 (m, 2H), 7.21-7.16 (m, 1H), 7.11-7.05 (m, 2H), 6.92 (d, J = 11.5 Hz, 1H), 6.69 (d, J = 11.5 Hz, 1H), 6.30 (t, J = 3.3 Hz, 1H), 6.29-6.27 (m, 1H), 3.05 (s, 3H), 1.28 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 148.6, 138.7, 128.6, 127.0, 126.7, 125.0, 123.5, 121.8, 117.9, 116.1, 111.0, 84.5, 41.4, 27.6.

FTIR (neat): ν_{max}/cm^{-1} 3269, 2981, 2933, 1736, 1642, 1478, 1447, 1321, 1148, 1102.

HRMS (p-APCI): *m/z* 363.1369 [$(M+H)^+$ requires 363.1373].



(*E*)-*N*-(2-(2-methyl-5-(trimethylsilyl)furan-3-yl)-2-phenylvinyl)methanesulfonamide (134)

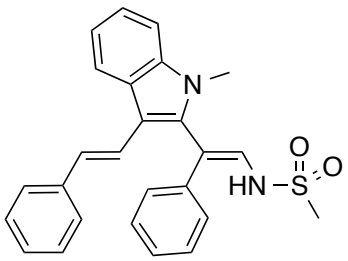
A microwave vial was charged with **113** (22 mg, 0.10 mmol), **131** (51 mg, 0.3 mmol), and $[Rh_2(tpa)_4]$ (1 mg, 0.001 mmol). The reagents were suspended in freshly distilled 1,2-DCE (1.0 mL) heated in a microwave reactor at 120 °C for 10 min. Direct purification by flash chromatography (SiO_2, hexanes/EtOAc, 7:1) afforded the title compound as pale yellow oil (27 mg, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.25-7.21 (m, 3H), 6.80 (d, J = 11.4 Hz, 1H), 6.39 (s, 1H), 6.28 (d, J = 11.4 Hz, 1H), 3.07 (s, 3H), 2.16 (s, 3H), 0.28 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.2, 154.3, 138.7, 128.7, 127.3, 126.2, 121.8, 121.0, 117.0, 114.9, 41.6, 12.9, –1.3.

FTIR (neat): ν_{max}/cm^{-1} 3268, 3029, 2957, 2923, 1644, 1597, 1496, 1449,1329, 1161.

HRMS (p-APCI): *m/z* 350.1244 [$(M+H)^+$ requires 350.1241].



***N*-((*E*)-2-(1-methyl-3-((*E*)-styryl)-1*H*-indol-2-yl)-2-phenylvinyl)methanesulfonamide (135)**

A microwave vial was charged with **113** (112 mg, 0.50 mmol), **132** (235 mg, 1.0 mmol), and $[Rh_2(tpa)_4]$ (7 mg, 0.005 mmol). The reagents were suspended in freshly distilled 1,2-DCE (1.0 mL) heated in a microwave reactor at 120 °C for 10 min. Direct purification by flash chromatography (SiO_2, hexanes/EtOAc, 2:1) afforded the title compound as an amorphous white solid (210 mg, 98% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 7.3 Hz, 2H) 7.36-7.26 (m, 9H), 7.25-7.17 (m, 4H), 7.10 (d, J = 16.5 Hz, 1H), 6.54 (bd, J = 6.8 Hz, 1H), 3.39 (s, 3H), 2.77 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 138.6, 138.3, 137.6, 134.0, 129.3, 129.0, 127.8, 127.4, 127.2, 125.9, 125.9, 125.8, 125.6, 123.3, 121.4, 121.1, 120.7, 113.1, 112.8, 110.1, 42.1, 30.9.

FTIR (neat): ν_{max}/cm^{-1} 3265, 3055, 3025, 2928, 1631, 1596, 1492, 1467, 1450, 1329, 1151.

HRMS (p-APCI): *m/z* 429.1633 [$(M+H)^+$ requires 429.1631].

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APPENDIX: X-ray Crystallographic Data

Chapter 2 Crystallographic Data

2.57

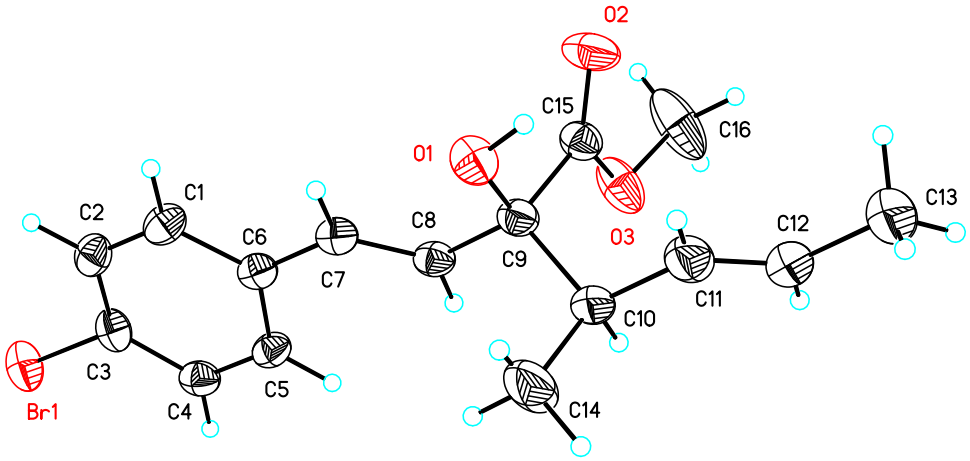


Table 1. Crystal data and structure refinement for **57**.

Identification code	**57**	
Empirical formula	C16 H19 Br O3	
Formula weight	339.22	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2	
Unit cell dimensions	a = 7.9626(3) Å	α= 90°.
	b = 36.6534(11) Å	β= 90°.
	c = 5.6635(2) Å	γ = 90°.
Volume	1652.93(10) $Å^3$	

Z	4
Density (calculated)	1.363 Mg/m^3
Absorption coefficient	3.427 mm^{-1}
F(000)	696
Crystal size	0.48 x 0.12 x 0.03 mm^3
Theta range for data collection	2.41 to 67.55°.
Index ranges	-8<=h<=8, -43<=k<=43, -6<=l<=6
Reflections collected	10887
Independent reflections	2788 [R(int) = 0.0324]
Completeness to theta = 67.55°	94.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9042 and 0.2900
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2788 / 0 / 181
Goodness-of-fit on F^2	1.089
Final R indices [I>2sigma(I)]	R1 = 0.0368, wR2 = 0.0913
R indices (all data)	R1 = 0.0401, wR2 = 0.0926
Absolute structure parameter	0.02(3)
Largest diff. peak and hole	0.452 and -0.340 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **57**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	3150(1)	1730(1)	4087(1)	52(1)
C(1)	1866(6)	2456(1)	9409(6)	40(1)
C(2)	2084(6)	2139(1)	8096(6)	40(1)
C(3)	2888(5)	2159(1)	5959(7)	37(1)
C(4)	3519(5)	2485(1)	5108(7)	38(1)
C(5)	3278(5)	2800(1)	6423(6)	35(1)
C(6)	2434(5)	2791(1)	8582(6)	32(1)
C(7)	2186(5)	3119(1)	10048(6)	34(1)
C(8)	2353(5)	3461(1)	9390(6)	33(1)
C(9)	2057(5)	3783(1)	10984(7)	35(1)
C(10)	3501(5)	4062(1)	10910(10)	48(1)
C(11)	3081(6)	4395(1)	12314(9)	52(1)
C(12)	2888(6)	4727(1)	11509(10)	63(1)
C(13)	2480(8)	5057(1)	12972(12)	80(2)
C(14)	5113(6)	3886(1)	11784(14)	90(2)
C(15)	420(5)	3973(1)	10211(6)	37(1)
C(16)	-950(8)	4287(2)	7148(9)	84(2)
O(1)	1834(4)	3667(1)	13352(4)	43(1)
O(2)	-765(4)	4008(1)	11467(6)	58(1)
O(3)	513(5)	4094(1)	8025(5)	59(1)

Table 3. Bond lengths [Å] and angles [°] for **57**.

Br(1)-C(3)	1.906(3)
C(1)-C(2)	1.389(5)
C(1)-C(6)	1.392(5)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.371(6)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.383(5)
C(4)-C(5)	1.388(5)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.395(5)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.475(5)
C(7)-C(8)	1.315(5)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.504(5)
C(8)-H(8A)	0.9500
C(9)-O(1)	1.419(4)
C(9)-C(10)	1.540(5)
C(9)-C(15)	1.541(5)
C(10)-C(11)	1.494(6)
C(10)-C(14)	1.521(6)
C(10)-H(10A)	1.0000
C(11)-C(12)	1.308(6)
C(11)-H(11A)	0.9500
C(12)-C(13)	1.501(7)
C(12)-H(12A)	0.9500
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800

C(15)-O(2)	1.189(5)
C(15)-O(3)	1.318(4)
C(16)-O(3)	1.450(6)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
O(1)-H(1B)	0.8400

C(2)-C(1)-C(6)	121.2(3)
C(2)-C(1)-H(1A)	119.4
C(6)-C(1)-H(1A)	119.4
C(3)-C(2)-C(1)	119.1(3)
C(3)-C(2)-H(2A)	120.4
C(1)-C(2)-H(2A)	120.4
C(2)-C(3)-C(4)	121.5(3)
C(2)-C(3)-Br(1)	119.9(3)
C(4)-C(3)-Br(1)	118.6(3)
C(3)-C(4)-C(5)	118.8(3)
C(3)-C(4)-H(4A)	120.6
C(5)-C(4)-H(4A)	120.6
C(4)-C(5)-C(6)	121.1(3)
C(4)-C(5)-H(5A)	119.4
C(6)-C(5)-H(5A)	119.4
C(1)-C(6)-C(5)	118.2(3)
C(1)-C(6)-C(7)	119.2(3)
C(5)-C(6)-C(7)	122.6(3)
C(8)-C(7)-C(6)	127.2(3)
C(8)-C(7)-H(7A)	116.4
C(6)-C(7)-H(7A)	116.4
C(7)-C(8)-C(9)	124.2(3)
C(7)-C(8)-H(8A)	117.9
C(9)-C(8)-H(8A)	117.9
O(1)-C(9)-C(8)	110.6(3)

O(1)-C(9)-C(10)	108.6(3)
C(8)-C(9)-C(10)	112.8(3)
O(1)-C(9)-C(15)	107.4(3)
C(8)-C(9)-C(15)	108.5(3)
C(10)-C(9)-C(15)	108.9(3)
C(11)-C(10)-C(14)	111.3(4)
C(11)-C(10)-C(9)	111.2(3)
C(14)-C(10)-C(9)	109.8(3)
C(11)-C(10)-H(10A)	108.1
C(14)-C(10)-H(10A)	108.1
C(9)-C(10)-H(10A)	108.1
C(12)-C(11)-C(10)	126.9(5)
C(12)-C(11)-H(11A)	116.5
C(10)-C(11)-H(11A)	116.5
C(11)-C(12)-C(13)	125.6(5)
C(11)-C(12)-H(12A)	117.2
C(13)-C(12)-H(12A)	117.2
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(10)-C(14)-H(14A)	109.5
C(10)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(10)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
O(2)-C(15)-O(3)	124.8(4)
O(2)-C(15)-C(9)	123.4(3)
O(3)-C(15)-C(9)	111.8(4)
O(3)-C(16)-H(16A)	109.5

O(3)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(3)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(9)-O(1)-H(1B)	109.5
C(15)-O(3)-C(16)	116.2(4)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **57**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	69(1)	41(1)	46(1)	-2(1)	-4(1)	13(1)
C(1)	45(2)	46(2)	28(2)	6(2)	2(2)	-5(2)
C(2)	45(3)	39(2)	34(2)	9(2)	-3(2)	0(2)
C(3)	42(2)	35(2)	33(2)	-2(2)	-11(2)	6(2)
C(4)	32(2)	48(2)	33(2)	4(2)	0(2)	2(2)
C(5)	33(2)	40(2)	31(2)	6(1)	1(2)	-4(2)
C(6)	27(2)	42(2)	28(2)	6(1)	-6(1)	0(1)
C(7)	31(2)	43(2)	28(2)	3(1)	-2(2)	0(2)
C(8)	30(2)	43(2)	27(2)	4(2)	2(1)	3(1)
C(9)	30(2)	40(2)	35(2)	4(2)	2(2)	4(1)
C(10)	30(3)	41(2)	72(3)	-4(2)	7(2)	-2(2)
C(11)	40(3)	49(2)	68(3)	-12(2)	0(3)	-1(2)
C(12)	53(3)	46(2)	90(4)	-4(2)	24(3)	-6(2)
C(13)	65(4)	52(3)	123(5)	-21(3)	20(3)	-2(2)
C(14)	34(3)	55(3)	183(8)	-25(4)	-6(4)	5(2)
C(15)	37(3)	42(2)	33(2)	0(2)	3(2)	5(2)
C(16)	114(5)	85(4)	53(3)	-10(3)	-28(3)	61(4)
O(1)	54(2)	48(1)	28(1)	-1(1)	1(1)	8(1)
O(2)	33(2)	79(2)	60(2)	7(2)	10(2)	12(2)
O(3)	82(3)	60(2)	36(2)	3(1)	0(2)	34(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **57**.

	x	y	z	U(eq)
H(1A)	1320	2443	10898	48
H(2A)	1681	1912	8671	48
H(4A)	4106	2493	3649	45
H(5A)	3695	3026	5843	42
H(7A)	1871	3079	11645	41
H(8A)	2682	3508	7806	40
H(10A)	3674	4138	9230	57
H(11A)	2939	4362	13965	63
H(12A)	3017	4762	9857	76
H(13A)	2410	5272	11949	120
H(13B)	3364	5094	14153	120
H(13C)	1402	5020	13770	120
H(14A)	6031	4064	11718	136
H(14B)	5387	3676	10781	136
H(14C)	4960	3803	13416	136
H(16A)	-749	4364	5516	126
H(16B)	-1162	4501	8135	126
H(16C)	-1928	4125	7199	126
H(1B)	1469	3841	14166	65

Table 6. Torsion angles [°] for **57**.

C(6)-C(1)-C(2)-C(3)	0.6(6)
C(1)-C(2)-C(3)-C(4)	1.5(6)
C(1)-C(2)-C(3)-Br(1)	-178.4(3)
C(2)-C(3)-C(4)-C(5)	-2.2(6)
Br(1)-C(3)-C(4)-C(5)	177.7(3)
C(3)-C(4)-C(5)-C(6)	0.8(6)
C(2)-C(1)-C(6)-C(5)	-1.9(6)
C(2)-C(1)-C(6)-C(7)	-179.5(4)
C(4)-C(5)-C(6)-C(1)	1.2(6)
C(4)-C(5)-C(6)-C(7)	178.7(3)
C(1)-C(6)-C(7)-C(8)	-166.5(4)
C(5)-C(6)-C(7)-C(8)	16.0(6)
C(6)-C(7)-C(8)-C(9)	179.2(3)
C(7)-C(8)-C(9)-O(1)	9.0(5)
C(7)-C(8)-C(9)-C(10)	130.9(4)
C(7)-C(8)-C(9)-C(15)	-108.4(4)
O(1)-C(9)-C(10)-C(11)	-63.0(4)
C(8)-C(9)-C(10)-C(11)	174.0(4)
C(15)-C(9)-C(10)-C(11)	53.5(5)
O(1)-C(9)-C(10)-C(14)	60.6(5)
C(8)-C(9)-C(10)-C(14)	-62.4(5)
C(15)-C(9)-C(10)-C(14)	177.2(4)
C(14)-C(10)-C(11)-C(12)	121.6(6)
C(9)-C(10)-C(11)-C(12)	-115.7(5)
C(10)-C(11)-C(12)-C(13)	-179.4(5)
O(1)-C(9)-C(15)-O(2)	0.2(5)
C(8)-C(9)-C(15)-O(2)	119.7(4)
C(10)-C(9)-C(15)-O(2)	-117.2(4)
O(1)-C(9)-C(15)-O(3)	179.5(3)
C(8)-C(9)-C(15)-O(3)	-61.1(4)
C(10)-C(9)-C(15)-O(3)	62.1(4)
O(2)-C(15)-O(3)-C(16)	0.8(7)

C(9)-C(15)-O(3)-C(16)	-178.4(4)

Table 7. Hydrogen bonds for **57** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1B)...O(3)#1	0.84	2.49	3.250(4)	150.5

Symmetry transformations used to generate equivalent atoms:

#1 x,y,z+1

2.73

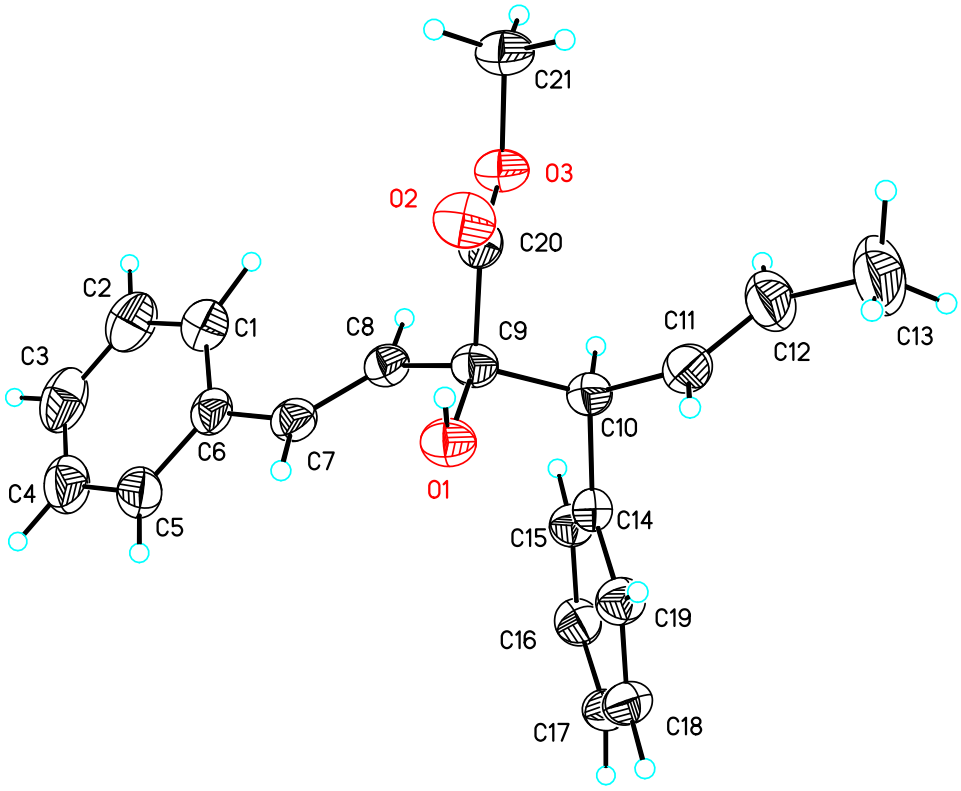


Table 1. Crystal data and structure refinement for **73**.

Identification code	**73**	
Empirical formula	C21 H22 O3	
Formula weight	322.39	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.1117(5) Å	α= 90°.
	b = 5.5288(3) Å	β= 104.084(2)°.
	c = 14.6321(7) Å	γ = 90°.
Volume	871.89(7) $Å^3$	
Z	2	

Density (calculated)	1.228 Mg/m^3
Absorption coefficient	0.646 mm^{-1}
F(000)	344
Crystal size	0.42 x 0.17 x 0.16 mm^3
Theta range for data collection	3.11 to 68.04°.
Index ranges	-12<=h<=13, -6<=k<=5, -16<=l<=17
Reflections collected	6114
Independent reflections	2555 [R(int) = 0.0138]
Completeness to theta = 68.04°	95.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9038 and 0.7732
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2555 / 1 / 305
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0254, wR2 = 0.0692
R indices (all data)	R1 = 0.0258, wR2 = 0.0697
Absolute structure parameter	-0.20(16)
Largest diff. peak and hole	0.143 and -0.133 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **73**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7838(1)	8078(3)	2616(1)	44(1)
C(2)	9030(2)	9020(4)	2923(1)	54(1)
C(3)	9910(2)	7803(4)	3599(1)	56(1)
C(4)	9602(1)	5691(4)	3974(1)	54(1)
C(5)	8419(1)	4749(4)	3671(1)	43(1)
C(6)	7514(1)	5921(3)	2990(1)	33(1)
C(7)	6265(1)	4860(3)	2673(1)	33(1)
C(8)	5242(1)	6061(3)	2264(1)	31(1)
C(9)	3985(1)	4929(3)	1864(1)	31(1)
C(10)	2952(1)	6164(3)	2259(1)	31(1)
C(11)	1674(1)	5447(3)	1697(1)	39(1)
C(12)	817(2)	6987(4)	1279(1)	53(1)
C(13)	-479(2)	6317(7)	57(2)	79(1)
C(14)	3127(1)	5696(3)	3307(1)	30(1)
C(15)	3716(1)	7413(3)	3955(1)	34(1)
C(16)	3844(1)	7080(3)	4914(1)	39(1)
C(17)	3377(1)	5013(3)	5233(1)	39(1)
C(18)	2799(1)	3283(3)	4598(1)	40(1)
C(19)	2679(1)	3610(3)	3639(1)	36(1)
C(20)	3670(1)	5295(3)	790(1)	30(1)
C(21)	3394(2)	8006(3)	-470(1)	40(1)
O(1)	4001(1)	2406(2)	2035(1)	36(1)
O(2)	3484(1)	3623(2)	245(1)	41(1)
O(3)	3649(1)	7599(2)	539(1)	35(1)

Table 3. Bond lengths [Å] and angles [°] for **73**.

C(1)-C(2)	1.392(2)
C(1)-C(6)	1.395(2)
C(1)-H(1)	1.031(19)
C(2)-C(3)	1.384(3)
C(2)-H(2)	0.97(3)
C(3)-C(4)	1.368(3)
C(3)-H(3)	0.93(2)
C(4)-C(5)	1.383(2)
C(4)-H(4)	0.99(2)
C(5)-C(6)	1.392(2)
C(5)-H(5)	0.94(2)
C(6)-C(7)	1.4737(19)
C(7)-C(8)	1.327(2)
C(7)-H(7)	0.96(2)
C(8)-C(9)	1.5122(18)
C(8)-H(8)	0.989(19)
C(9)-O(1)	1.4166(18)
C(9)-C(20)	1.5388(17)
C(9)-C(10)	1.5624(19)
C(10)-C(11)	1.5100(18)
C(10)-C(14)	1.5198(17)
C(10)-H(10)	0.979(18)
C(11)-C(12)	1.313(2)
C(11)-H(11)	0.95(2)
C(12)-C(13)	1.503(3)
C(12)-H(12)	1.04(3)
C(13)-H(13A)	0.98(3)
C(13)-H(13B)	1.00(3)
C(13)-H(13C)	1.00(4)
C(14)-C(15)	1.388(2)
C(14)-C(19)	1.390(2)
C(15)-C(16)	1.387(2)

C(15)-H(15)	0.942(17)
C(16)-C(17)	1.383(2)
C(16)-H(16)	0.948(19)
C(17)-C(18)	1.379(2)
C(17)-H(17)	0.949(18)
C(18)-C(19)	1.388(2)
C(18)-H(18)	0.95(2)
C(19)-H(19)	0.964(18)
C(20)-O(2)	1.2049(17)
C(20)-O(3)	1.3240(18)
C(21)-O(3)	1.4510(16)
C(21)-H(21A)	0.96(2)
C(21)-H(21B)	0.966(17)
C(21)-H(21C)	0.94(2)
O(1)-H(1O)	0.882(19)

C(2)-C(1)-C(6)	57(16)
C(2)-C(1)-H(1)	118.5(11)
C(6)-C(1)-H(1)	120.8(11)
C(3)-C(2)-C(1)	120.01(19)
C(3)-C(2)-H(2)	122.3(12)
C(1)-C(2)-H(2)	117.6(12)
C(4)-C(3)-C(2)	119.94(16)
C(4)-C(3)-H(3)	117.6(13)
C(2)-C(3)-H(3)	122.3(13)
C(3)-C(4)-C(5)	120.25(17)
C(3)-C(4)-H(4)	120.3(13)
C(5)-C(4)-H(4)	119.5(13)
C(4)-C(5)-C(6)	121.27(18)
C(4)-C(5)-H(5)	119.9(11)
C(6)-C(5)-H(5)	118.7(11)
C(5)-C(6)-C(1)	117.94(14)
C(5)-C(6)-C(7)	120.07(14)

C(1)-C(6)-C(7)	121.97(13)
C(8)-C(7)-C(6)	125.48(14)
C(8)-C(7)-H(7)	116.8(10)
C(6)-C(7)-H(7)	117.7(10)
C(7)-C(8)-C(9)	125.22(14)
C(7)-C(8)-H(8)	121.4(9)
C(9)-C(8)-H(8)	113.3(9)
O(1)-C(9)-C(8)	111.60(11)
O(1)-C(9)-C(20)	107.45(11)
C(8)-C(9)-C(20)	107.41(10)
O(1)-C(9)-C(10)	110.14(11)
C(8)-C(9)-C(10)	111.64(11)
C(20)-C(9)-C(10)	108.42(10)
C(11)-C(10)-C(14)	112.18(11)
C(11)-C(10)-C(9)	111.19(12)
C(14)-C(10)-C(9)	111.91(10)
C(11)-C(10)-H(10)	107.3(8)
C(14)-C(10)-H(10)	107.9(8)
C(9)-C(10)-H(10)	106.0(9)
C(12)-C(11)-C(10)	124.24(18)
C(12)-C(11)-H(11)	119.5(11)
C(10)-C(11)-H(11)	116.2(11)
C(11)-C(12)-C(13)	125.0(2)
C(11)-C(12)-H(12)	117.8(13)
C(13)-C(12)-H(12)	117.2(13)
C(12)-C(13)-H(13A)	107.7(17)
C(12)-C(13)-H(13B)	109.3(14)
H(13A)-C(13)-H(13B)	109(2)
C(12)-C(13)-H(13C)	107.6(18)
H(13A)-C(13)-H(13C)	108(3)
H(13B)-C(13)-H(13C)	115(3)
C(15)-C(14)-C(19)	118.54(12)
C(15)-C(14)-C(10)	119.76(12)

C(19)-C(14)-C(10)	121.67(12)
C(16)-C(15)-C(14)	121.04(14)
C(16)-C(15)-H(15)	119.7(9)
C(14)-C(15)-H(15)	119.2(9)
C(17)-C(16)-C(15)	119.82(14)
C(17)-C(16)-H(16)	119.5(10)
C(15)-C(16)-H(16)	120.7(10)
C(18)-C(17)-C(16)	119.78(13)
C(18)-C(17)-H(17)	120.9(12)
C(16)-C(17)-H(17)	119.2(12)
C(17)-C(18)-C(19)	120.37(15)
C(17)-C(18)-H(18)	120.2(11)
C(19)-C(18)-H(18)	119.4(11)
C(18)-C(19)-C(14)	120.44(14)
C(18)-C(19)-H(19)	121.0(10)
C(14)-C(19)-H(19)	118.6(10)
O(2)-C(20)-O(3)	124.49(12)
O(2)-C(20)-C(9)	122.31(13)
O(3)-C(20)-C(9)	113.19(11)
O(3)-C(21)-H(21A)	104.5(11)
O(3)-C(21)-H(21B)	109.5(10)
H(21A)-C(21)-H(21B)	112.5(16)
O(3)-C(21)-H(21C)	110.5(11)
H(21A)-C(21)-H(21C)	109.6(18)
H(21B)-C(21)-H(21C)	110.1(15)
C(9)-O(1)-H(1O)	103.7(12)
C(20)-O(3)-C(21)	114.63(12)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **73**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	41(1)	47(1)	47(1)	-1(1)	15(1)	0(1)
C(2)	48(1)	54(1)	65(1)	-10(1)	24(1)	-12(1)
C(3)	36(1)	79(1)	56(1)	-23(1)	14(1)	-11(1)
C(4)	35(1)	78(1)	46(1)	-4(1)	7(1)	7(1)
C(5)	38(1)	53(1)	40(1)	0(1)	11(1)	7(1)
C(6)	33(1)	40(1)	30(1)	-6(1)	11(1)	3(1)
C(7)	37(1)	34(1)	30(1)	0(1)	12(1)	1(1)
C(8)	34(1)	31(1)	29(1)	-1(1)	10(1)	0(1)
C(9)	33(1)	28(1)	31(1)	2(1)	8(1)	0(1)
C(10)	32(1)	31(1)	31(1)	3(1)	8(1)	0(1)
C(11)	35(1)	49(1)	35(1)	2(1)	10(1)	-4(1)
C(12)	38(1)	75(1)	41(1)	-3(1)	2(1)	11(1)
C(13)	37(1)	134(3)	58(1)	-13(2)	-1(1)	13(1)
C(14)	27(1)	33(1)	32(1)	3(1)	9(1)	3(1)
C(15)	35(1)	32(1)	35(1)	3(1)	10(1)	0(1)
C(16)	40(1)	42(1)	34(1)	-3(1)	8(1)	4(1)
C(17)	42(1)	46(1)	31(1)	8(1)	14(1)	10(1)
C(18)	43(1)	39(1)	43(1)	11(1)	19(1)	4(1)
C(19)	38(1)	34(1)	38(1)	2(1)	11(1)	-2(1)
C(20)	28(1)	31(1)	31(1)	-2(1)	8(1)	-1(1)
C(21)	52(1)	41(1)	28(1)	0(1)	10(1)	0(1)
O(1)	44(1)	28(1)	36(1)	1(1)	10(1)	-1(1)
O(2)	50(1)	36(1)	37(1)	-6(1)	7(1)	-3(1)
O(3)	45(1)	32(1)	27(1)	1(1)	9(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **73**.

	x	y	z	U(eq)
H(1)	7223(17)	8940(40)	2071(13)	54(5)
H(2)	9218(19)	10500(50)	2631(14)	64(6)
H(3)	10726(19)	8320(40)	3791(13)	62(5)
H(4)	10229(19)	4810(40)	4457(14)	65(6)
H(5)	8227(17)	3240(40)	3901(13)	53(5)
H(7)	6178(15)	3150(40)	2770(11)	40(4)
H(8)	5251(13)	7830(30)	2167(10)	35(4)
H(10)	3039(13)	7910(30)	2171(10)	28(4)
H(11)	1492(16)	3760(40)	1672(12)	46(5)
H(12)	1050(20)	8810(50)	1302(16)	77(7)
H(13A)	-620(30)	6980(60)	120(20)	111(10)
H(13B)	-1080(20)	7070(50)	1078(18)	99(9)
H(13C)	-520(30)	4510(70)	700(20)	103(10)
H(15)	3987(14)	8870(30)	3736(11)	31(4)
H(16)	4249(15)	8260(40)	5353(12)	43(4)
H(17)	3508(16)	4760(30)	5892(13)	48(5)
H(18)	2514(16)	1830(40)	4815(12)	45(5)
H(19)	2267(15)	2420(40)	3189(11)	39(4)
H(21A)	3422(17)	9740(40)	-534(13)	54(5)
H(21B)	2591(16)	7340(40)	-770(11)	43(4)
H(21C)	4009(16)	7290(40)	-719(12)	48(5)
H(1O)	3795(16)	1770(30)	1466(13)	48(5)

Table 6. Torsion angles [°] for **73**.

C(6)-C(1)-C(2)-C(3)	0.7(2)
C(1)-C(2)-C(3)-C(4)	-0.9(3)
C(2)-C(3)-C(4)-C(5)	0.9(3)
C(3)-C(4)-C(5)-C(6)	-0.6(3)
C(4)-C(5)-C(6)-C(1)	0.4(2)
C(4)-C(5)-C(6)-C(7)	179.27(14)
C(2)-C(1)-C(6)-C(5)	-0.5(2)
C(2)-C(1)-C(6)-C(7)	-179.30(14)
C(5)-C(6)-C(7)-C(8)	158.53(14)
C(1)-C(6)-C(7)-C(8)	-22.7(2)
C(6)-C(7)-C(8)-C(9)	174.43(12)
C(7)-C(8)-C(9)-O(1)	4.06(19)
C(7)-C(8)-C(9)-C(20)	-113.46(14)
C(7)-C(8)-C(9)-C(10)	127.81(14)
O(1)-C(9)-C(10)-C(11)	-68.77(14)
C(8)-C(9)-C(10)-C(11)	166.66(12)
C(20)-C(9)-C(10)-C(11)	48.54(15)
O(1)-C(9)-C(10)-C(14)	57.56(14)
C(8)-C(9)-C(10)-C(14)	-67.01(14)
C(20)-C(9)-C(10)-C(14)	174.87(11)
C(14)-C(10)-C(11)-C(12)	110.54(17)
C(9)-C(10)-C(11)-C(12)	-123.28(16)
C(10)-C(11)-C(12)-C(13)	-176.81(16)
C(11)-C(10)-C(14)-C(15)	-137.08(14)
C(9)-C(10)-C(14)-C(15)	97.13(14)
C(11)-C(10)-C(14)-C(19)	40.96(18)
C(9)-C(10)-C(14)-C(19)	-84.83(15)
C(19)-C(14)-C(15)-C(16)	-0.78(19)
C(10)-C(14)-C(15)-C(16)	177.33(12)
C(14)-C(15)-C(16)-C(17)	-0.2(2)
C(15)-C(16)-C(17)-C(18)	0.7(2)
C(16)-C(17)-C(18)-C(19)	-0.3(2)

C(17)-C(18)-C(19)-C(14)	-0.7(2)
C(15)-C(14)-C(19)-C(18)	1.22(19)
C(10)-C(14)-C(19)-C(18)	-176.84(12)
O(1)-C(9)-C(20)-O(2)	0.15(16)
C(8)-C(9)-C(20)-O(2)	120.35(14)
C(10)-C(9)-C(20)-O(2)	-118.87(14)
O(1)-C(9)-C(20)-O(3)	-178.85(11)
C(8)-C(9)-C(20)-O(3)	-58.65(14)
C(10)-C(9)-C(20)-O(3)	62.13(13)
O(2)-C(20)-O(3)-C(21)	-0.83(18)
C(9)-C(20)-O(3)-C(21)	178.15(11)

Table 7. Hydrogen bonds for **73** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...O(2)	0.882(19)	2.014(19)	2.6288(14)	125.7(16)

2.77

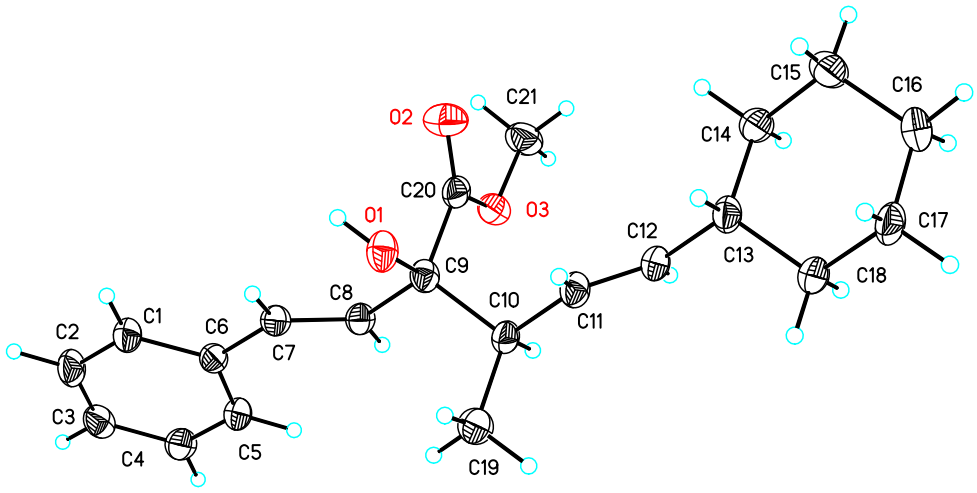


Table 1. Crystal data and structure refinement for **77**.

Identification code	**77**	
Empirical formula	C21 H28 O3	
Formula weight	328.43	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 5.5849(4) Å	α= 116.623(5)°.
	b = 9.4558(6) Å	β= 94.611(6)°.
	c = 9.9361(7) Å	γ = 90.704(4)°.
Volume	466.88(6) $Å^3$	
Z	1	
Density (calculated)	1.168 Mg/m^3	
Absorption coefficient	0.604 mm^{-1}	
F(000)	178	
Crystal size	0.25 x 0.18 x 0.09 mm^3	
Theta range for data collection	5.00 to 67.44°.	
Index ranges	-6<=h<=6, -11<=k<=11, -11<=l<=11	

Reflections collected	3568
Independent reflections	1969 [R(int) = 0.0221]
Completeness to theta = 67.44°	82.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9477 and 0.8637
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1969 / 3 / 217
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0448, wR2 = 0.1175
R indices (all data)	R1 = 0.0484, wR2 = 0.1214
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.200 and -0.203 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **77**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-2307(5)	-9699(3)	-4730(4)	36(1)
C(2)	-640(6)	-10279(4)	-3999(4)	41(1)
C(3)	1493(5)	-9456(4)	-3307(4)	39(1)
C(4)	2021(5)	-8038(4)	-3343(4)	37(1)
C(5)	392(5)	-7454(3)	-4079(4)	33(1)
C(6)	-1791(5)	-8280(3)	-4788(3)	30(1)
C(7)	-3563(5)	-7712(3)	-5591(3)	30(1)
C(8)	-3141(4)	-6641(3)	-6066(3)	29(1)
C(9)	-5058(4)	-6134(3)	-6907(3)	29(1)
C(10)	-5068(4)	-4302(3)	-6244(3)	30(1)
C(11)	-6930(5)	-3852(3)	-7143(3)	32(1)
C(12)	-6537(5)	-3162(3)	-8004(3)	32(1)
C(13)	-8505(5)	-2727(3)	-8861(3)	33(1)
C(14)	-8172(6)	-3432(3)	-10550(3)	40(1)
C(15)	-10283(6)	-3052(4)	-11404(4)	47(1)
C(16)	-10576(6)	-1272(4)	-10739(4)	46(1)
C(17)	-10812(5)	-540(4)	-9054(4)	41(1)
C(18)	-8694(5)	-939(3)	-8215(4)	37(1)
C(19)	-5555(6)	-3570(4)	-4580(4)	41(1)
C(20)	-4571(5)	-6847(3)	-8577(4)	31(1)
C(21)	-1845(6)	-6927(4)	-10283(4)	44(1)
O(1)	-7369(3)	-6737(2)	-6853(3)	36(1)
O(2)	-5972(4)	-7755(3)	-9582(3)	49(1)
O(3)	-2447(3)	-6335(2)	-8750(2)	35(1)

Table 3. Bond lengths [Å] and angles [°] for **77**.

C(1)-C(6)	1.396(4)
C(1)-C(2)	1.399(4)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.365(5)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.387(4)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.390(4)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.393(4)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.475(4)
C(7)-C(8)	1.321(4)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.517(3)
C(8)-H(8A)	0.9500
C(9)-O(1)	1.419(3)
C(9)-C(20)	1.535(4)
C(9)-C(10)	1.553(3)
C(10)-C(11)	1.504(3)
C(10)-C(19)	1.529(4)
C(10)-H(10A)	1.0000
C(11)-C(12)	1.317(4)
C(11)-H(11A)	0.9500
C(12)-C(13)	1.508(4)
C(12)-H(12A)	0.9500
C(13)-C(18)	1.524(4)
C(13)-C(14)	1.531(4)
C(13)-H(13A)	1.0000
C(14)-C(15)	1.537(4)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900

C(15)-C(16)	1.524(4)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.516(5)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.540(4)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-O(2)	1.198(4)
C(20)-O(3)	1.329(3)
C(21)-O(3)	1.439(4)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
O(1)-H(1B)	0.8400

C(6)-C(1)-C(2)	120.4(3)
C(6)-C(1)-H(1A)	119.8
C(2)-C(1)-H(1A)	119.8
C(3)-C(2)-C(1)	120.7(3)
C(3)-C(2)-H(2A)	119.6
C(1)-C(2)-H(2A)	119.6
C(2)-C(3)-C(4)	119.6(3)
C(2)-C(3)-H(3A)	120.2
C(4)-C(3)-H(3A)	120.2
C(3)-C(4)-C(5)	120.3(3)
C(3)-C(4)-H(4A)	119.8

C(5)-C(4)-H(4A)	119.8
C(4)-C(5)-C(6)	120.7(2)
C(4)-C(5)-H(5A)	119.7
C(6)-C(5)-H(5A)	119.7
C(5)-C(6)-C(1)	118.3(2)
C(5)-C(6)-C(7)	122.5(2)
C(1)-C(6)-C(7)	119.2(2)
C(8)-C(7)-C(6)	126.2(2)
C(8)-C(7)-H(7A)	116.9
C(6)-C(7)-H(7A)	116.9
C(7)-C(8)-C(9)	123.1(2)
C(7)-C(8)-H(8A)	118.4
C(9)-C(8)-H(8A)	118.4
O(1)-C(9)-C(8)	110.6(2)
O(1)-C(9)-C(20)	107.2(2)
C(8)-C(9)-C(20)	108.6(2)
O(1)-C(9)-C(10)	109.1(2)
C(8)-C(9)-C(10)	111.7(2)
C(20)-C(9)-C(10)	109.49(18)
C(11)-C(10)-C(19)	110.6(2)
C(11)-C(10)-C(9)	110.0(2)
C(19)-C(10)-C(9)	110.3(2)
C(11)-C(10)-H(10A)	108.6
C(19)-C(10)-H(10A)	108.6
C(9)-C(10)-H(10A)	108.6
C(12)-C(11)-C(10)	126.9(2)
C(12)-C(11)-H(11A)	116.5
C(10)-C(11)-H(11A)	116.5
C(11)-C(12)-C(13)	124.0(2)
C(11)-C(12)-H(12A)	118.0
C(13)-C(12)-H(12A)	118.0
C(12)-C(13)-C(18)	112.1(2)
C(12)-C(13)-C(14)	111.8(2)

C(18)-C(13)-C(14)	109.8(2)
C(12)-C(13)-H(13A)	107.7
C(18)-C(13)-H(13A)	107.7
C(14)-C(13)-H(13A)	107.7
C(13)-C(14)-C(15)	110.5(2)
C(13)-C(14)-H(14A)	109.5
C(15)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
C(15)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	108.1
C(16)-C(15)-C(14)	111.2(3)
C(16)-C(15)-H(15A)	109.4
C(14)-C(15)-H(15A)	109.4
C(16)-C(15)-H(15B)	109.4
C(14)-C(15)-H(15B)	109.4
H(15A)-C(15)-H(15B)	108.0
C(17)-C(16)-C(15)	111.9(2)
C(17)-C(16)-H(16A)	109.2
C(15)-C(16)-H(16A)	109.2
C(17)-C(16)-H(16B)	109.2
C(15)-C(16)-H(16B)	109.2
H(16A)-C(16)-H(16B)	107.9
C(16)-C(17)-C(18)	111.1(3)
C(16)-C(17)-H(17A)	109.4
C(18)-C(17)-H(17A)	109.4
C(16)-C(17)-H(17B)	109.4
C(18)-C(17)-H(17B)	109.4
H(17A)-C(17)-H(17B)	108.0
C(13)-C(18)-C(17)	110.7(2)
C(13)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18A)	109.5
C(13)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18B)	109.5

H(18A)-C(18)-H(18B)	108.1
C(10)-C(19)-H(19A)	109.5
C(10)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(10)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(2)-C(20)-O(3)	125.3(3)
O(2)-C(20)-C(9)	122.8(2)
O(3)-C(20)-C(9)	111.9(2)
O(3)-C(21)-H(21A)	109.5
O(3)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(3)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(9)-O(1)-H(1B)	109.5
C(20)-O(3)-C(21)	115.9(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **77**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	44(1)	30(1)	38(2)	19(1)	5(1)	4(1)
C(2)	58(2)	32(2)	44(2)	24(1)	11(2)	14(1)
C(3)	48(2)	38(2)	35(2)	20(1)	7(1)	19(1)
C(4)	41(1)	33(1)	37(2)	15(1)	3(1)	8(1)
C(5)	38(1)	29(1)	37(2)	17(1)	3(1)	5(1)
C(6)	40(1)	25(1)	27(2)	12(1)	7(1)	9(1)
C(7)	31(1)	28(1)	30(2)	13(1)	2(1)	5(1)
C(8)	29(1)	27(1)	32(2)	14(1)	3(1)	6(1)
C(9)	25(1)	30(1)	34(2)	18(1)	-1(1)	3(1)
C(10)	34(1)	24(1)	34(2)	15(1)	1(1)	4(1)
C(11)	33(1)	28(1)	37(2)	17(1)	3(1)	8(1)
C(12)	37(1)	26(1)	36(2)	15(1)	3(1)	7(1)
C(13)	37(1)	28(1)	38(2)	19(1)	3(1)	6(1)
C(14)	52(2)	30(2)	33(2)	11(1)	2(1)	14(1)
C(15)	59(2)	45(2)	34(2)	16(2)	-4(2)	12(2)
C(16)	58(2)	41(2)	49(2)	30(2)	-2(2)	9(1)
C(17)	45(1)	27(1)	52(2)	21(1)	-1(1)	10(1)
C(18)	45(1)	27(1)	38(2)	15(1)	2(1)	9(1)
C(19)	51(2)	36(2)	37(2)	16(1)	5(1)	13(1)
C(20)	33(1)	25(1)	36(2)	15(1)	-3(1)	5(1)
C(21)	52(2)	49(2)	30(2)	16(1)	8(1)	7(1)
O(1)	29(1)	37(1)	49(1)	27(1)	2(1)	3(1)
O(2)	48(1)	51(1)	38(1)	12(1)	-5(1)	-6(1)
O(3)	36(1)	38(1)	31(1)	16(1)	2(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **77**.

	x	y	z	U(eq)
H(1A)	-3799	-10273	-5188	43
H(2A)	-996	-11257	-3984	50
H(3A)	2609	-9853	-2804	46
H(4A)	3504	-7461	-2863	44
H(5A)	773	-6481	-4097	40
H(7A)	-5161	-8159	-5785	35
H(8A)	-1561	-6166	-5872	35
H(10A)	-3450	-3890	-6316	36
H(11A)	-8563	-4093	-7084	38
H(12A)	-4917	-2922	-8091	39
H(13A)	-10065	-3183	-8758	39
H(14A)	-8075	-4595	-10968	48
H(14B)	-6647	-2992	-10688	48
H(15A)	-9997	-3470	-12483	56
H(15B)	-11784	-3582	-11348	56
H(16A)	-9165	-762	-10922	56
H(16B)	-12025	-1071	-11256	56
H(17A)	-12341	-940	-8876	49
H(17B)	-10859	625	-8649	49
H(18A)	-7178	-455	-8314	44
H(18B)	-8928	-490	-7127	44
H(19A)	-5565	-2416	-4177	62
H(19B)	-4293	-3841	-4005	62
H(19C)	-7121	-3984	-4492	62
H(21A)	-257	-6478	-10288	66
H(21B)	-3050	-6621	-10863	66
H(21C)	-1818	-8084	-10743	66
H(1B)	-7372	-7727	-7209	54

Table 6. Torsion angles [°] for **77**.

C(6)-C(1)-C(2)-C(3)	1.3(4)
C(1)-C(2)-C(3)-C(4)	-0.7(5)
C(2)-C(3)-C(4)-C(5)	0.0(5)
C(3)-C(4)-C(5)-C(6)	0.0(4)
C(4)-C(5)-C(6)-C(1)	0.6(4)
C(4)-C(5)-C(6)-C(7)	-179.5(3)
C(2)-C(1)-C(6)-C(5)	-1.2(4)
C(2)-C(1)-C(6)-C(7)	178.9(3)
C(5)-C(6)-C(7)-C(8)	17.8(4)
C(1)-C(6)-C(7)-C(8)	-162.3(3)
C(6)-C(7)-C(8)-C(9)	179.1(2)
C(7)-C(8)-C(9)-O(1)	10.7(4)
C(7)-C(8)-C(9)-C(20)	-106.7(3)
C(7)-C(8)-C(9)-C(10)	132.4(3)
O(1)-C(9)-C(10)-C(11)	-59.4(3)
C(8)-C(9)-C(10)-C(11)	178.0(2)
C(20)-C(9)-C(10)-C(11)	57.7(2)
O(1)-C(9)-C(10)-C(19)	62.8(3)
C(8)-C(9)-C(10)-C(19)	-59.8(3)
C(20)-C(9)-C(10)-C(19)	179.9(2)
C(19)-C(10)-C(11)-C(12)	124.9(3)
C(9)-C(10)-C(11)-C(12)	-113.0(3)
C(10)-C(11)-C(12)-C(13)	-179.2(3)
C(11)-C(12)-C(13)-C(18)	110.9(3)
C(11)-C(12)-C(13)-C(14)	-125.4(3)
C(12)-C(13)-C(14)-C(15)	176.6(2)
C(18)-C(13)-C(14)-C(15)	-58.3(3)
C(13)-C(14)-C(15)-C(16)	56.2(3)
C(14)-C(15)-C(16)-C(17)	-54.3(4)
C(15)-C(16)-C(17)-C(18)	54.3(4)
C(12)-C(13)-C(18)-C(17)	-176.6(2)
C(14)-C(13)-C(18)-C(17)	58.5(3)

C(16)-C(17)-C(18)-C(13)	-56.6(3)
O(1)-C(9)-C(20)-O(2)	-0.9(3)
C(8)-C(9)-C(20)-O(2)	118.7(3)
C(10)-C(9)-C(20)-O(2)	-119.1(3)
O(1)-C(9)-C(20)-O(3)	179.2(2)
C(8)-C(9)-C(20)-O(3)	-61.3(2)
C(10)-C(9)-C(20)-O(3)	60.9(2)
O(2)-C(20)-O(3)-C(21)	0.7(4)
C(9)-C(20)-O(3)-C(21)	-179.3(2)

2.*epi*-77

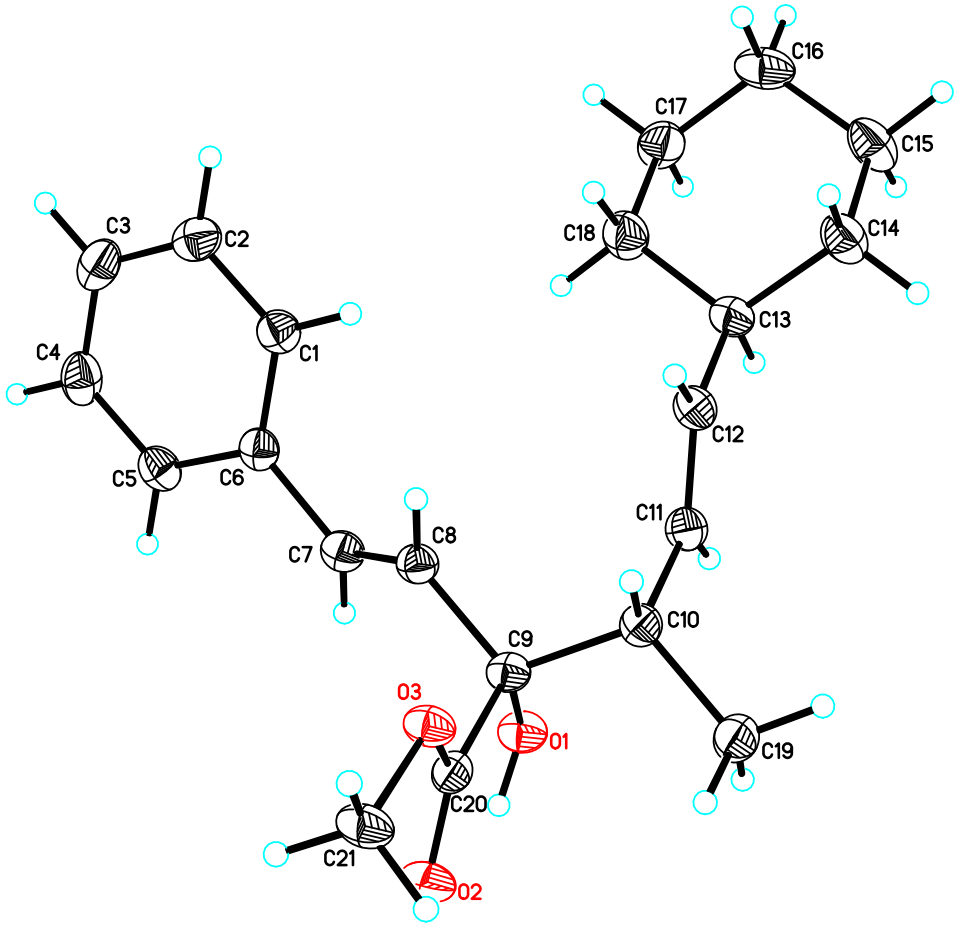


Table 1. Crystal data and structure refinement for *epi*-**77**.

Identification code	*epi*-**77**	
Empirical formula	C21 H28 O3	
Formula weight	328.43	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.4496(4) Å	α= 90°.
	b = 13.7116(8) Å	β= 90°.

	c = 25.4795(15) Å γ = 90°.
Volume	1903.9(2) $Å^3$
Z	4
Density (calculated)	1.146 Mg/m^3
Absorption coefficient	0.592 mm^{-1}
F(000)	712
Crystal size	0.41 x 0.09 x 0.07 mm^3
Theta range for data collection	3.47 to 65.51°.
Index ranges	-6<=h<=4, -16<=k<=16, -29<=l<=30
Reflections collected	16001
Independent reflections	3218 [R(int) = 0.0341]
Completeness to theta = 65.51°	99.6 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3218 / 0 / 218
Goodness-of-fit on F^2	1.176
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0832
R indices (all data)	R1 = 0.0527, wR2 = 0.0970
Absolute structure parameter	0.1(3)
Extinction coefficient	0.0037(4)
Largest diff. peak and hole	0.176 and -0.195 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for *epi*-**77**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8707(4)	4366(2)	9942(1)	39(1)
C(2)	9687(5)	4390(2)	10444(1)	45(1)
C(3)	8532(5)	3911(2)	10849(1)	50(1)
C(4)	6391(5)	3402(2)	10756(1)	48(1)
C(5)	5397(4)	3381(2)	10258(1)	40(1)
C(6)	6552(4)	3852(1)	9840(1)	34(1)
C(7)	5471(4)	3795(1)	9311(1)	37(1)
C(8)	6693(4)	3878(1)	8867(1)	34(1)
C(9)	5552(4)	3836(1)	8328(1)	32(1)
C(10)	6691(4)	4619(1)	7963(1)	35(1)
C(11)	6344(4)	5612(1)	8204(1)	37(1)
C(12)	8112(4)	6139(1)	8411(1)	37(1)
C(13)	7841(4)	7110(1)	8676(1)	38(1)
C(14)	9447(5)	7891(2)	8415(1)	50(1)
C(15)	9342(5)	8861(2)	8704(1)	56(1)
C(16)	10009(5)	8744(2)	9277(1)	55(1)
C(17)	8346(5)	8008(2)	9538(1)	52(1)
C(18)	8466(5)	7028(2)	9258(1)	49(1)
C(19)	5614(4)	4556(2)	7408(1)	45(1)
C(20)	5968(4)	2821(1)	8100(1)	33(1)
C(21)	8802(4)	1616(1)	7852(1)	42(1)
O(1)	2969(3)	3980(1)	8360(1)	40(1)
O(2)	4317(3)	2279(1)	7980(1)	45(1)
O(3)	8343(3)	2590(1)	8052(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for *epi*-**77**.

C(1)-C(2)	1.387(3)
C(1)-C(6)	1.393(3)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.376(3)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.380(3)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.379(3)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.395(3)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.473(2)
C(7)-C(8)	1.318(3)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.510(2)
C(8)-H(8A)	0.9500
C(9)-O(1)	1.424(2)
C(9)-C(20)	1.525(3)
C(9)-C(10)	1.549(3)
C(10)-C(11)	1.506(3)
C(10)-C(19)	1.533(3)
C(10)-H(10A)	1.0000
C(11)-C(12)	1.315(3)
C(11)-H(11A)	0.9500
C(12)-C(13)	1.500(3)
C(12)-H(12A)	0.9500
C(13)-C(18)	1.527(3)
C(13)-C(14)	1.534(3)
C(13)-H(13A)	1.0000
C(14)-C(15)	1.522(3)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900

C(15)-C(16)	1.512(3)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.511(3)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.523(3)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-O(2)	1.207(2)
C(20)-O(3)	1.338(2)
C(21)-O(3)	1.451(2)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
O(1)-H(1B)	0.8400

C(2)-C(1)-C(6)	120.52(19)
C(2)-C(1)-H(1A)	119.7
C(6)-C(1)-H(1A)	119.7
C(3)-C(2)-C(1)	120.3(2)
C(3)-C(2)-H(2A)	119.9
C(1)-C(2)-H(2A)	119.9
C(2)-C(3)-C(4)	119.93(19)
C(2)-C(3)-H(3A)	120.0
C(4)-C(3)-H(3A)	120.0
C(5)-C(4)-C(3)	120.1(2)
C(5)-C(4)-H(4A)	120.0

C(3)-C(4)-H(4A)	120.0
C(4)-C(5)-C(6)	121.0(2)
C(4)-C(5)-H(5A)	119.5
C(6)-C(5)-H(5A)	119.5
C(1)-C(6)-C(5)	118.22(17)
C(1)-C(6)-C(7)	122.28(17)
C(5)-C(6)-C(7)	119.50(19)
C(8)-C(7)-C(6)	125.4(2)
C(8)-C(7)-H(7A)	117.3
C(6)-C(7)-H(7A)	117.3
C(7)-C(8)-C(9)	124.8(2)
C(7)-C(8)-H(8A)	117.6
C(9)-C(8)-H(8A)	117.6
O(1)-C(9)-C(8)	110.42(16)
O(1)-C(9)-C(20)	107.19(16)
C(8)-C(9)-C(20)	108.66(15)
O(1)-C(9)-C(10)	109.60(16)
C(8)-C(9)-C(10)	110.78(16)
C(20)-C(9)-C(10)	110.11(15)
C(11)-C(10)-C(19)	112.23(16)
C(11)-C(10)-C(9)	109.36(15)
C(19)-C(10)-C(9)	111.16(17)
C(11)-C(10)-H(10A)	108.0
C(19)-C(10)-H(10A)	108.0
C(9)-C(10)-H(10A)	108.0
C(12)-C(11)-C(10)	124.7(2)
C(12)-C(11)-H(11A)	117.7
C(10)-C(11)-H(11A)	117.7
C(11)-C(12)-C(13)	126.6(2)
C(11)-C(12)-H(12A)	116.7
C(13)-C(12)-H(12A)	116.7
C(12)-C(13)-C(18)	110.45(16)
C(12)-C(13)-C(14)	111.61(17)

C(18)-C(13)-C(14)	110.21(19)
C(12)-C(13)-H(13A)	108.2
C(18)-C(13)-H(13A)	108.2
C(14)-C(13)-H(13A)	108.2
C(15)-C(14)-C(13)	112.27(18)
C(15)-C(14)-H(14A)	109.2
C(13)-C(14)-H(14A)	109.2
C(15)-C(14)-H(14B)	109.2
C(13)-C(14)-H(14B)	109.2
H(14A)-C(14)-H(14B)	107.9
C(16)-C(15)-C(14)	111.4(2)
C(16)-C(15)-H(15A)	109.3
C(14)-C(15)-H(15A)	109.3
C(16)-C(15)-H(15B)	109.3
C(14)-C(15)-H(15B)	109.3
H(15A)-C(15)-H(15B)	108.0
C(17)-C(16)-C(15)	110.6(2)
C(17)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16A)	109.5
C(17)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	108.1
C(16)-C(17)-C(18)	110.97(19)
C(16)-C(17)-H(17A)	109.4
C(18)-C(17)-H(17A)	109.4
C(16)-C(17)-H(17B)	109.4
C(18)-C(17)-H(17B)	109.4
H(17A)-C(17)-H(17B)	108.0
C(17)-C(18)-C(13)	112.35(17)
C(17)-C(18)-H(18A)	109.1
C(13)-C(18)-H(18A)	109.1
C(17)-C(18)-H(18B)	109.1
C(13)-C(18)-H(18B)	109.1

H(18A)-C(18)-H(18B)	107.9
C(10)-C(19)-H(19A)	109.5
C(10)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(10)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(2)-C(20)-O(3)	123.51(18)
O(2)-C(20)-C(9)	123.23(19)
O(3)-C(20)-C(9)	113.26(17)
O(3)-C(21)-H(21A)	109.5
O(3)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(3)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(9)-O(1)-H(1B)	109.5
C(20)-O(3)-C(21)	114.62(16)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for *epi*-**77**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	42(2)	37(1)	38(1)	-2(1)	2(1)	0(1)
C(2)	42(2)	44(1)	49(1)	-8(1)	-7(1)	6(1)
C(3)	64(2)	48(1)	37(1)	-3(1)	-8(1)	16(1)
C(4)	68(2)	42(1)	35(1)	3(1)	10(1)	8(1)
C(5)	45(2)	34(1)	41(1)	-2(1)	8(1)	-1(1)
C(6)	39(1)	29(1)	34(1)	-3(1)	3(1)	6(1)
C(7)	35(1)	34(1)	40(1)	-3(1)	1(1)	1(1)
C(8)	33(1)	31(1)	37(1)	-2(1)	-3(1)	1(1)
C(9)	24(1)	34(1)	38(1)	-3(1)	-2(1)	2(1)
C(10)	37(1)	32(1)	35(1)	-1(1)	-1(1)	3(1)
C(11)	38(1)	33(1)	39(1)	0(1)	-1(1)	3(1)
C(12)	38(1)	32(1)	41(1)	-1(1)	3(1)	2(1)
C(13)	38(1)	33(1)	44(1)	-3(1)	-1(1)	-2(1)
C(14)	61(2)	36(1)	52(1)	-1(1)	8(1)	-6(1)
C(15)	69(2)	35(1)	63(1)	-4(1)	16(1)	-7(1)
C(16)	48(2)	44(1)	73(2)	-21(1)	-5(1)	-1(1)
C(17)	67(2)	44(1)	44(1)	-7(1)	-5(1)	4(1)
C(18)	63(2)	39(1)	46(1)	-3(1)	2(1)	0(1)
C(19)	57(2)	40(1)	38(1)	0(1)	-4(1)	2(1)
C(20)	35(1)	36(1)	29(1)	2(1)	-2(1)	0(1)
C(21)	43(2)	31(1)	52(1)	-13(1)	-1(1)	1(1)
O(1)	30(1)	41(1)	49(1)	-6(1)	-2(1)	3(1)
O(2)	38(1)	40(1)	58(1)	-10(1)	-4(1)	-8(1)
O(3)	30(1)	31(1)	46(1)	-9(1)	-1(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for *epi*-**77**.

	x	y	z	U(eq)
H(1A)	9510	4702	9665	47
H(2A)	11162	4739	10508	54
H(3A)	9208	3931	11192	60
H(4A)	5601	3066	11034	58
H(5A)	3903	3041	10199	48
H(7A)	3752	3688	9288	44
H(8A)	8417	3972	8888	40
H(10A)	8494	4490	7938	41
H(11A)	4734	5877	8206	44
H(12A)	9725	5878	8391	44
H(13A)	6088	7318	8645	46
H(14A)	11168	7660	8405	59
H(14B)	8894	7987	8049	59
H(15A)	10492	9326	8537	67
H(15B)	7666	9135	8676	67
H(16A)	11735	8526	9307	66
H(16B)	9856	9381	9457	66
H(17A)	6637	8252	9534	62
H(17B)	8846	7924	9909	62
H(18A)	7304	6570	9428	59
H(18B)	10138	6754	9296	59
H(19A)	6367	5056	7186	68
H(19B)	3837	4662	7423	68
H(19C)	5949	3910	7260	68
H(21A)	10575	1507	7827	63
H(21B)	8058	1548	7504	63
H(21C)	8081	1135	8092	63
H(1B)	2243	3481	8249	60

Table 6. Torsion angles [°] for *epi*-**77**.

C(6)-C(1)-C(2)-C(3)	-0.4(3)
C(1)-C(2)-C(3)-C(4)	0.1(3)
C(2)-C(3)-C(4)-C(5)	-0.6(3)
C(3)-C(4)-C(5)-C(6)	1.4(3)
C(2)-C(1)-C(6)-C(5)	1.1(3)
C(2)-C(1)-C(6)-C(7)	-179.01(18)
C(4)-C(5)-C(6)-C(1)	-1.6(3)
C(4)-C(5)-C(6)-C(7)	178.51(19)
C(1)-C(6)-C(7)-C(8)	26.0(3)
C(5)-C(6)-C(7)-C(8)	-154.1(2)
C(6)-C(7)-C(8)-C(9)	-178.80(18)
C(7)-C(8)-C(9)-O(1)	16.9(3)
C(7)-C(8)-C(9)-C(20)	-100.4(2)
C(7)-C(8)-C(9)-C(10)	138.6(2)
O(1)-C(9)-C(10)-C(11)	64.4(2)
C(8)-C(9)-C(10)-C(11)	-57.7(2)
C(20)-C(9)-C(10)-C(11)	-177.93(17)
O(1)-C(9)-C(10)-C(19)	-60.1(2)
C(8)-C(9)-C(10)-C(19)	177.83(16)
C(20)-C(9)-C(10)-C(19)	57.6(2)
C(19)-C(10)-C(11)-C(12)	-127.8(2)
C(9)-C(10)-C(11)-C(12)	108.4(2)
C(10)-C(11)-C(12)-C(13)	-177.13(17)
C(11)-C(12)-C(13)-C(18)	113.9(2)
C(11)-C(12)-C(13)-C(14)	-123.1(2)
C(12)-C(13)-C(14)-C(15)	-175.66(19)
C(18)-C(13)-C(14)-C(15)	-52.5(3)
C(13)-C(14)-C(15)-C(16)	55.1(3)
C(14)-C(15)-C(16)-C(17)	-56.8(3)
C(15)-C(16)-C(17)-C(18)	57.2(3)
C(16)-C(17)-C(18)-C(13)	-56.2(3)
C(12)-C(13)-C(18)-C(17)	177.0(2)

C(14)-C(13)-C(18)-C(17)	53.2(3)
O(1)-C(9)-C(20)-O(2)	-0.2(2)
C(8)-C(9)-C(20)-O(2)	119.2(2)
C(10)-C(9)-C(20)-O(2)	-119.3(2)
O(1)-C(9)-C(20)-O(3)	-179.55(15)
C(8)-C(9)-C(20)-O(3)	-60.2(2)
C(10)-C(9)-C(20)-O(3)	61.3(2)
O(2)-C(20)-O(3)-C(21)	-1.4(2)
C(9)-C(20)-O(3)-C(21)	178.03(14)

Table 7. Hydrogen bonds for *epi*-**77** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1B)...O(2)	0.84	2.11	2.6306(19)	119.5
O(1)-H(1B)...O(3)#1	0.84	2.50	3.2562(19)	150.0

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z

2.81

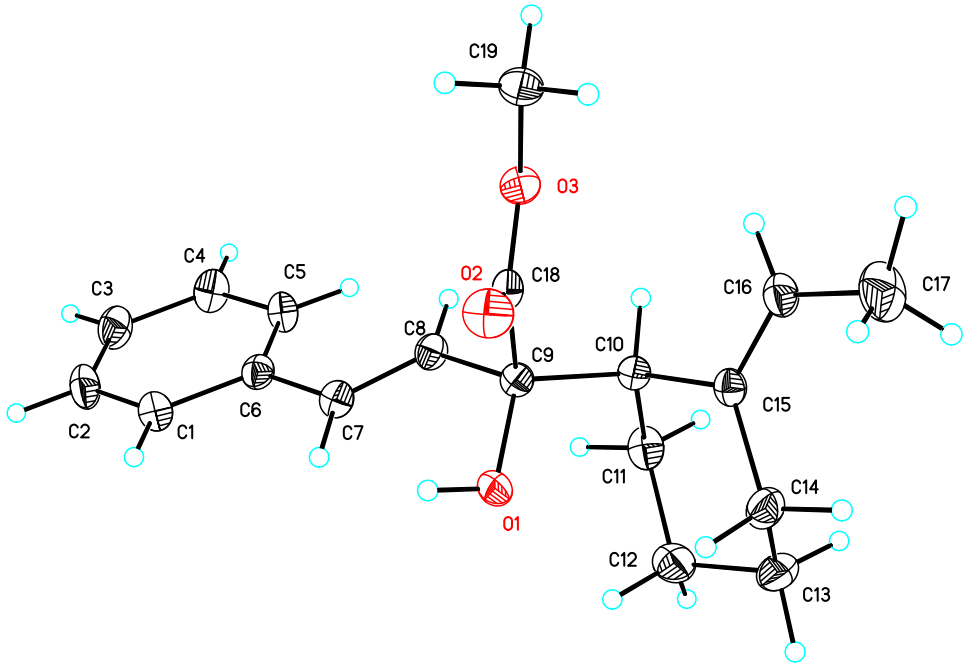


Table 1. Crystal data and structure refinement for **81**.

Identification code	**81**	
Empirical formula	C19 H24 O3	
Formula weight	300.38	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 5.7546(12) Å	α= 104.48(2)°.
	b = 12.147(2) Å	β= 90.08(3)°.
	c = 12.151(2) Å	γ = 90.16(3)°.
Volume	822.4(3) $Å^3$	
Z	2	
Density (calculated)	1.213 Mg/m^3	
Absorption coefficient	0.641 mm^{-1}	

F(000)	324
Crystal size	0.34 x 0.10 x 0.09 mm^3
Theta range for data collection	3.76 to 65.09°.
Index ranges	-6<=h<=5, -14<=k<=14, -14<=l<=13
Reflections collected	8095
Independent reflections	3637 [R(int) = 0.0146]
Completeness to theta = 65.09°	87.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9446 and 0.8115
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3637 / 3 / 398
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0860
R indices (all data)	R1 = 0.0300, wR2 = 0.0861
Absolute structure parameter	-0.02(16)
Extinction coefficient	0.0100(9)
Largest diff. peak and hole	0.194 and -0.138 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **81**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-4649(4)	-10986(2)	-2261(2)	34(1)
C(2)	-6004(4)	-11964(2)	-2567(2)	38(1)
C(3)	-8104(4)	-11946(2)	-3097(2)	38(1)
C(4)	-8882(4)	-10946(2)	-3323(2)	37(1)
C(5)	-7531(4)	-9966(2)	-3029(2)	33(1)
C(6)	-5408(4)	-9967(2)	-2482(2)	27(1)
C(7)	-3926(4)	-8946(2)	-2136(2)	28(1)
C(8)	-4577(4)	-7892(2)	-2085(2)	26(1)
C(9)	-3022(3)	-6859(2)	-1670(2)	24(1)
C(10)	-3470(4)	-5963(2)	-2371(2)	25(1)
C(11)	-3018(4)	-6423(2)	-3647(2)	32(1)
C(12)	-493(4)	-6412(2)	-4000(2)	39(1)
C(13)	534(4)	-5221(2)	-3549(2)	41(1)
C(14)	317(4)	-4825(2)	-2261(2)	34(1)
C(15)	-2139(4)	-4862(2)	-1875(2)	25(1)
C(16)	-3171(4)	-4012(2)	-1138(2)	32(1)
C(17)	-2059(5)	-2903(2)	-520(3)	50(1)
C(18)	-3627(4)	-6326(2)	-421(2)	26(1)
C(19)	-6572(4)	-5466(2)	853(2)	35(1)
O(1)	-660(2)	-7197(1)	-1711(1)	29(1)
O(2)	-2234(3)	-6195(1)	336(2)	37(1)
O(3)	-5870(3)	-6047(1)	-287(1)	29(1)
C(1B)	-4419(4)	-4075(2)	-5532(2)	34(1)
C(2B)	-3119(5)	-3082(2)	-5360(2)	40(1)
C(3B)	-1047(5)	-3076(2)	-5918(2)	42(1)
C(4B)	-262(5)	-4052(2)	-6648(2)	40(1)
C(5B)	-1546(4)	-5054(2)	-6829(2)	35(1)
C(6B)	-3637(4)	-5079(2)	-6271(2)	28(1)
C(7B)	-5067(4)	-6121(2)	-6431(2)	27(1)

C(8B)	-4320(4)	-7171(2)	-6886(2)	26(1)
C(9B)	-5828(4)	-8222(2)	-7011(2)	26(1)
C(10B)	-5282(4)	-9103(2)	-8161(2)	25(1)
C(11B)	-5836(4)	-8652(2)	-9207(2)	33(1)
C(12B)	-8385(5)	-8737(2)	-9569(2)	41(1)
C(13B)	-9288(4)	-9943(2)	-9707(2)	42(1)
C(14B)	-8965(4)	-10334(2)	-8609(2)	36(1)
C(15B)	-6450(4)	-10245(2)	-8239(2)	27(1)
C(16B)	-5264(4)	-11087(2)	-7996(2)	32(1)
C(17B)	-6157(5)	-12257(2)	-8002(3)	52(1)
C(18B)	-5225(4)	-8773(2)	-6040(2)	27(1)
C(19B)	-2321(4)	-9659(2)	-5204(2)	37(1)
O(1B)	-8199(2)	-7920(1)	-6907(1)	29(1)
O(2B)	-6649(3)	-8945(1)	-5377(2)	38(1)
O(3B)	-2979(3)	-9029(1)	-6022(1)	30(1)

Table 3. Bond lengths [Å] and angles [°] for **81**.

C(1)-C(2)	1.390(3)
C(1)-C(6)	1.401(3)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.372(4)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.386(3)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.390(3)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.390(3)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.474(3)
C(7)-C(8)	1.321(3)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.518(3)
C(8)-H(8A)	0.9500
C(9)-O(1)	1.419(2)
C(9)-C(18)	1.535(3)
C(9)-C(10)	1.562(3)
C(10)-C(15)	1.526(3)
C(10)-C(11)	1.534(3)
C(10)-H(10A)	1.0000
C(11)-C(12)	1.516(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.530(3)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.524(4)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(15)	1.494(3)

C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.327(3)
C(16)-C(17)	1.509(3)
C(16)-H(16A)	0.9500
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-O(2)	1.199(3)
C(18)-O(3)	1.335(3)
C(19)-O(3)	1.447(3)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
O(1)-H(1B)	0.8400
C(1B)-C(2B)	1.388(3)
C(1B)-C(6B)	1.398(3)
C(1B)-H(1BA)	0.9500
C(2B)-C(3B)	1.373(4)
C(2B)-H(2BA)	0.9500
C(3B)-C(4B)	1.370(4)
C(3B)-H(3BA)	0.9500
C(4B)-C(5B)	1.391(3)
C(4B)-H(4BA)	0.9500
C(5B)-C(6B)	1.386(3)
C(5B)-H(5BA)	0.9500
C(6B)-C(7B)	1.479(3)
C(7B)-C(8B)	1.329(3)
C(7B)-H(7BA)	0.9500
C(8B)-C(9B)	1.518(3)
C(8B)-H(8BA)	0.9500
C(9B)-O(1B)	1.411(3)
C(9B)-C(18B)	1.535(3)

C(9B)-C(10B)	1.566(3)
C(10B)-C(15B)	1.521(3)
C(10B)-C(11B)	1.539(3)
C(10B)-H(10B)	1.0000
C(11B)-C(12B)	1.527(3)
C(11B)-H(11C)	0.9900
C(11B)-H(11D)	0.9900
C(12B)-C(13B)	1.522(4)
C(12B)-H(12C)	0.9900
C(12B)-H(12D)	0.9900
C(13B)-C(14B)	1.535(4)
C(13B)-H(13C)	0.9900
C(13B)-H(13D)	0.9900
C(14B)-C(15B)	1.511(3)
C(14B)-H(14C)	0.9900
C(14B)-H(14D)	0.9900
C(15B)-C(16B)	1.324(3)
C(16B)-C(17B)	1.509(3)
C(16B)-H(16B)	0.9500
C(17B)-H(17D)	0.9800
C(17B)-H(17E)	0.9800
C(17B)-H(17F)	0.9800
C(18B)-O(2B)	1.204(3)
C(18B)-O(3B)	1.332(3)
C(19B)-O(3B)	1.449(3)
C(19B)-H(19D)	0.9800
C(19B)-H(19E)	0.9800
C(19B)-H(19F)	0.9800
O(1B)-H(1BB)	0.8400

C(2)-C(1)-C(6)	120.7(2)
C(2)-C(1)-H(1A)	119.6
C(6)-C(1)-H(1A)	119.6

C(3)-C(2)-C(1)	120.2(2)
C(3)-C(2)-H(2A)	119.9
C(1)-C(2)-H(2A)	119.9
C(2)-C(3)-C(4)	119.8(2)
C(2)-C(3)-H(3A)	120.1
C(4)-C(3)-H(3A)	120.1
C(3)-C(4)-C(5)	120.4(2)
C(3)-C(4)-H(4A)	119.8
C(5)-C(4)-H(4A)	119.8
C(6)-C(5)-C(4)	120.53(19)
C(6)-C(5)-H(5A)	119.7
C(4)-C(5)-H(5A)	119.7
C(5)-C(6)-C(1)	118.31(18)
C(5)-C(6)-C(7)	122.69(18)
C(1)-C(6)-C(7)	119.0(2)
C(8)-C(7)-C(6)	125.8(2)
C(8)-C(7)-H(7A)	117.1
C(6)-C(7)-H(7A)	117.1
C(7)-C(8)-C(9)	124.0(2)
C(7)-C(8)-H(8A)	118.0
C(9)-C(8)-H(8A)	118.0
O(1)-C(9)-C(8)	110.04(16)
O(1)-C(9)-C(18)	107.53(16)
C(8)-C(9)-C(18)	107.64(16)
O(1)-C(9)-C(10)	112.04(16)
C(8)-C(9)-C(10)	110.64(16)
C(18)-C(9)-C(10)	108.79(16)
C(15)-C(10)-C(11)	112.04(17)
C(15)-C(10)-C(9)	111.29(16)
C(11)-C(10)-C(9)	113.30(17)
C(15)-C(10)-H(10A)	106.6
C(11)-C(10)-H(10A)	106.6
C(9)-C(10)-H(10A)	106.6

C(12)-C(11)-C(10)	115.09(19)
C(12)-C(11)-H(11A)	108.5
C(10)-C(11)-H(11A)	108.5
C(12)-C(11)-H(11B)	108.5
C(10)-C(11)-H(11B)	108.5
H(11A)-C(11)-H(11B)	107.5
C(11)-C(12)-C(13)	109.88(19)
C(11)-C(12)-H(12A)	109.7
C(13)-C(12)-H(12A)	109.7
C(11)-C(12)-H(12B)	109.7
C(13)-C(12)-H(12B)	109.7
H(12A)-C(12)-H(12B)	108.2
C(14)-C(13)-C(12)	111.32(18)
C(14)-C(13)-H(13A)	109.4
C(12)-C(13)-H(13A)	109.4
C(14)-C(13)-H(13B)	109.4
C(12)-C(13)-H(13B)	109.4
H(13A)-C(13)-H(13B)	108.0
C(15)-C(14)-C(13)	112.08(19)
C(15)-C(14)-H(14A)	109.2
C(13)-C(14)-H(14A)	109.2
C(15)-C(14)-H(14B)	109.2
C(13)-C(14)-H(14B)	109.2
H(14A)-C(14)-H(14B)	107.9
C(16)-C(15)-C(14)	123.95(19)
C(16)-C(15)-C(10)	119.94(19)
C(14)-C(15)-C(10)	116.10(18)
C(15)-C(16)-C(17)	126.4(2)
C(15)-C(16)-H(16A)	116.8
C(17)-C(16)-H(16A)	116.8
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5

C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
O(2)-C(18)-O(3)	124.8(2)
O(2)-C(18)-C(9)	123.2(2)
O(3)-C(18)-C(9)	111.93(17)
O(3)-C(19)-H(19A)	109.5
O(3)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
O(3)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(9)-O(1)-H(1B)	109.5
C(18)-O(3)-C(19)	115.93(18)
C(2B)-C(1B)-C(6B)	120.5(2)
C(2B)-C(1B)-H(1BA)	119.7
C(6B)-C(1B)-H(1BA)	119.7
C(3B)-C(2B)-C(1B)	120.3(2)
C(3B)-C(2B)-H(2BA)	119.9
C(1B)-C(2B)-H(2BA)	119.9
C(4B)-C(3B)-C(2B)	119.9(2)
C(4B)-C(3B)-H(3BA)	120.1
C(2B)-C(3B)-H(3BA)	120.1
C(3B)-C(4B)-C(5B)	120.5(2)
C(3B)-C(4B)-H(4BA)	119.7
C(5B)-C(4B)-H(4BA)	119.7
C(6B)-C(5B)-C(4B)	120.5(2)
C(6B)-C(5B)-H(5BA)	119.8
C(4B)-C(5B)-H(5BA)	119.8
C(5B)-C(6B)-C(1B)	118.33(19)
C(5B)-C(6B)-C(7B)	122.67(19)
C(1B)-C(6B)-C(7B)	119.0(2)
C(8B)-C(7B)-C(6B)	125.0(2)

C(8B)-C(7B)-H(7BA)	117.5
C(6B)-C(7B)-H(7BA)	117.5
C(7B)-C(8B)-C(9B)	123.4(2)
C(7B)-C(8B)-H(8BA)	118.3
C(9B)-C(8B)-H(8BA)	118.3
O(1B)-C(9B)-C(8B)	110.44(16)
O(1B)-C(9B)-C(18B)	107.68(16)
C(8B)-C(9B)-C(18B)	108.20(16)
O(1B)-C(9B)-C(10B)	112.41(17)
C(8B)-C(9B)-C(10B)	110.07(17)
C(18B)-C(9B)-C(10B)	107.89(15)
C(15B)-C(10B)-C(11B)	111.44(17)
C(15B)-C(10B)-C(9B)	112.03(16)
C(11B)-C(10B)-C(9B)	112.95(16)
C(15B)-C(10B)-H(10B)	106.6
C(11B)-C(10B)-H(10B)	106.6
C(9B)-C(10B)-H(10B)	106.6
C(12B)-C(11B)-C(10B)	115.12(19)
C(12B)-C(11B)-H(11C)	108.5
C(10B)-C(11B)-H(11C)	108.5
C(12B)-C(11B)-H(11D)	108.5
C(10B)-C(11B)-H(11D)	108.5
H(11C)-C(11B)-H(11D)	107.5
C(13B)-C(12B)-C(11B)	110.50(18)
C(13B)-C(12B)-H(12C)	109.6
C(11B)-C(12B)-H(12C)	109.6
C(13B)-C(12B)-H(12D)	109.6
C(11B)-C(12B)-H(12D)	109.6
H(12C)-C(12B)-H(12D)	108.1
C(12B)-C(13B)-C(14B)	111.24(19)
C(12B)-C(13B)-H(13C)	109.4
C(14B)-C(13B)-H(13C)	109.4
C(12B)-C(13B)-H(13D)	109.4

C(14B)-C(13B)-H(13D)	109.4
H(13C)-C(13B)-H(13D)	108.0
C(15B)-C(14B)-C(13B)	111.1(2)
C(15B)-C(14B)-H(14C)	109.4
C(13B)-C(14B)-H(14C)	109.4
C(15B)-C(14B)-H(14D)	109.4
C(13B)-C(14B)-H(14D)	109.4
H(14C)-C(14B)-H(14D)	108.0
C(16B)-C(15B)-C(14B)	124.08(19)
C(16B)-C(15B)-C(10B)	120.13(19)
C(14B)-C(15B)-C(10B)	115.79(18)
C(15B)-C(16B)-C(17B)	127.1(2)
C(15B)-C(16B)-H(16B)	116.4
C(17B)-C(16B)-H(16B)	116.4
C(16B)-C(17B)-H(17D)	109.5
C(16B)-C(17B)-H(17E)	109.5
H(17D)-C(17B)-H(17E)	109.5
C(16B)-C(17B)-H(17F)	109.5
H(17D)-C(17B)-H(17F)	109.5
H(17E)-C(17B)-H(17F)	109.5
O(2B)-C(18B)-O(3B)	124.8(2)
O(2B)-C(18B)-C(9B)	122.9(2)
O(3B)-C(18B)-C(9B)	112.39(17)
O(3B)-C(19B)-H(19D)	109.5
O(3B)-C(19B)-H(19E)	109.5
H(19D)-C(19B)-H(19E)	109.5
O(3B)-C(19B)-H(19F)	109.5
H(19D)-C(19B)-H(19F)	109.5
H(19E)-C(19B)-H(19F)	109.5
C(9B)-O(1B)-H(1BB)	109.5
C(18B)-O(3B)-C(19B)	115.55(18)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **81**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	36(1)	29(1)	35(1)	8(1)	0(1)	2(1)
C(2)	48(2)	25(1)	44(2)	13(1)	1(1)	0(1)
C(3)	47(1)	28(1)	38(1)	7(1)	-1(1)	-10(1)
C(4)	39(1)	36(1)	36(1)	11(1)	-7(1)	-10(1)
C(5)	38(1)	26(1)	35(1)	10(1)	-3(1)	-2(1)
C(6)	34(1)	25(1)	23(1)	5(1)	6(1)	-1(1)
C(7)	31(1)	29(1)	25(1)	8(1)	-2(1)	-1(1)
C(8)	28(1)	27(1)	24(1)	6(1)	0(1)	-2(1)
C(9)	22(1)	26(1)	24(1)	6(1)	0(1)	1(1)
C(10)	24(1)	25(1)	26(1)	5(1)	-2(1)	-1(1)
C(11)	42(1)	31(1)	23(1)	7(1)	-3(1)	-1(1)
C(12)	46(2)	43(1)	28(1)	10(1)	9(1)	11(1)
C(13)	34(1)	46(1)	46(2)	21(1)	13(1)	3(1)
C(14)	28(1)	33(1)	45(2)	16(1)	-2(1)	-4(1)
C(15)	26(1)	24(1)	27(1)	10(1)	-3(1)	-1(1)
C(16)	39(1)	24(1)	32(1)	7(1)	-1(1)	-1(1)
C(17)	67(2)	29(1)	48(2)	-2(1)	-2(2)	-6(1)
C(18)	29(1)	21(1)	29(1)	10(1)	-3(1)	-3(1)
C(19)	41(1)	32(1)	29(1)	3(1)	8(1)	3(1)
O(1)	23(1)	28(1)	36(1)	9(1)	-2(1)	2(1)
O(2)	37(1)	45(1)	29(1)	8(1)	-9(1)	0(1)
O(3)	31(1)	29(1)	25(1)	4(1)	2(1)	1(1)
C(1B)	39(1)	30(1)	34(1)	7(1)	4(1)	2(1)
C(2B)	52(2)	26(1)	37(1)	-1(1)	3(1)	-1(1)
C(3B)	53(2)	30(1)	41(2)	7(1)	-4(1)	-15(1)
C(4B)	41(1)	38(1)	39(1)	8(1)	2(1)	-11(1)
C(5B)	39(1)	29(1)	33(1)	3(1)	3(1)	-3(1)
C(6B)	33(1)	28(1)	24(1)	10(1)	-5(1)	-2(1)
C(7B)	32(1)	27(1)	23(1)	7(1)	-1(1)	-1(1)

C(8B)	26(1)	28(1)	24(1)	8(1)	-1(1)	0(1)
C(9B)	25(1)	25(1)	26(1)	5(1)	2(1)	1(1)
C(10B)	23(1)	24(1)	26(1)	6(1)	4(1)	0(1)
C(11B)	41(1)	32(1)	27(1)	9(1)	4(1)	3(1)
C(12B)	46(2)	47(1)	30(1)	11(1)	-3(1)	14(1)
C(13B)	33(1)	50(1)	36(1)	-2(1)	-9(1)	5(1)
C(14B)	28(1)	33(1)	41(1)	1(1)	-1(1)	-3(1)
C(15B)	26(1)	27(1)	25(1)	2(1)	4(1)	-3(1)
C(16B)	33(1)	26(1)	35(1)	6(1)	3(1)	1(1)
C(17B)	61(2)	33(1)	63(2)	17(1)	5(2)	-6(1)
C(18B)	30(1)	24(1)	25(1)	3(1)	1(1)	-4(1)
C(19B)	42(1)	38(1)	36(1)	18(1)	-4(1)	2(1)
O(1B)	25(1)	28(1)	31(1)	5(1)	3(1)	0(1)
O(2B)	37(1)	49(1)	32(1)	17(1)	7(1)	-2(1)
O(3B)	30(1)	31(1)	30(1)	12(1)	-1(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **81**.

	x	y	z	U(eq)
H(1A)	-3192	-11007	-1899	40
H(2A)	-5473	-12648	-2408	46
H(3A)	-9023	-12617	-3310	45
H(4A)	-10348	-10931	-3679	44
H(5A)	-8062	-9289	-3204	39
H(7A)	-2366	-9056	-1931	33
H(8A)	-6109	-7774	-2322	32
H(10A)	-5159	-5770	-2289	30
H(11A)	-3603	-7214	-3884	38
H(11B)	-3927	-5966	-4064	38
H(12A)	-380	-6638	-4840	46
H(12B)	397	-6966	-3694	46
H(13A)	2194	-5227	-3763	49
H(13B)	-286	-4681	-3902	49
H(14A)	1285	-5315	-1907	41
H(14B)	914	-4037	-2002	41
H(16A)	-4765	-4112	-986	38
H(17A)	-3211	-2429	-27	75
H(17B)	-1484	-2504	-1075	75
H(17C)	-759	-3055	-58	75
H(19A)	-8236	-5297	858	52
H(19B)	-5691	-4756	1103	52
H(19C)	-6263	-5954	1369	52
H(1B)	112	-6712	-1235	43
H(1BA)	-5853	-4072	-5144	41
H(2BA)	-3665	-2405	-4855	48
H(3BA)	-159	-2395	-5797	50
H(4BA)	1170	-4045	-7034	48
H(5BA)	-985	-5726	-7338	42

H(7BA)	-6640	-6034	-6189	33
H(8BA)	-2761	-7268	-7147	31
H(10B)	-3568	-9240	-8171	29
H(11C)	-5351	-7845	-9045	39
H(11D)	-4891	-9079	-9854	39
H(12C)	-9320	-8203	-8990	49
H(12D)	-8549	-8519	-10298	49
H(13C)	-8445	-10465	-10334	50
H(13D)	-10958	-9974	-9910	50
H(14C)	-9931	-9858	-7999	43
H(14D)	-9495	-11132	-8735	43
H(16B)	-3676	-10937	-7796	38
H(17D)	-4889	-12711	-7805	77
H(17E)	-6752	-12629	-8760	77
H(17F)	-7409	-12193	-7444	77
H(19D)	-647	-9810	-5258	55
H(19E)	-3174	-10382	-5364	55
H(19F)	-2696	-9213	-4435	55
H(1BB)	-8936	-8396	-6646	43

Table 6. Torsion angles [°] for **81**.

C(6)-C(1)-C(2)-C(3)	0.4(4)
C(1)-C(2)-C(3)-C(4)	-0.4(4)
C(2)-C(3)-C(4)-C(5)	1.0(4)
C(3)-C(4)-C(5)-C(6)	-1.5(4)
C(4)-C(5)-C(6)-C(1)	1.5(3)
C(4)-C(5)-C(6)-C(7)	-179.0(2)
C(2)-C(1)-C(6)-C(5)	-1.0(3)
C(2)-C(1)-C(6)-C(7)	179.5(2)
C(5)-C(6)-C(7)-C(8)	14.3(4)
C(1)-C(6)-C(7)-C(8)	-166.2(2)
C(6)-C(7)-C(8)-C(9)	177.0(2)
C(7)-C(8)-C(9)-O(1)	19.1(3)
C(7)-C(8)-C(9)-C(18)	-97.8(2)
C(7)-C(8)-C(9)-C(10)	143.5(2)
O(1)-C(9)-C(10)-C(15)	-63.7(2)
C(8)-C(9)-C(10)-C(15)	173.14(18)
C(18)-C(9)-C(10)-C(15)	55.1(2)
O(1)-C(9)-C(10)-C(11)	63.7(2)
C(8)-C(9)-C(10)-C(11)	-59.5(2)
C(18)-C(9)-C(10)-C(11)	-177.58(17)
C(15)-C(10)-C(11)-C(12)	45.0(2)
C(9)-C(10)-C(11)-C(12)	-82.0(2)
C(10)-C(11)-C(12)-C(13)	-52.9(3)
C(11)-C(12)-C(13)-C(14)	57.4(3)
C(12)-C(13)-C(14)-C(15)	-55.7(3)
C(13)-C(14)-C(15)-C(16)	-131.9(2)
C(13)-C(14)-C(15)-C(10)	48.6(2)
C(11)-C(10)-C(15)-C(16)	138.0(2)
C(9)-C(10)-C(15)-C(16)	-94.0(2)
C(11)-C(10)-C(15)-C(14)	-42.5(3)
C(9)-C(10)-C(15)-C(14)	85.5(2)
C(14)-C(15)-C(16)-C(17)	-3.4(4)

C(10)-C(15)-C(16)-C(17)	176.0(2)
O(1)-C(9)-C(18)-O(2)	3.3(2)
C(8)-C(9)-C(18)-O(2)	121.8(2)
C(10)-C(9)-C(18)-O(2)	-118.3(2)
O(1)-C(9)-C(18)-O(3)	-175.92(13)
C(8)-C(9)-C(18)-O(3)	-57.4(2)
C(10)-C(9)-C(18)-O(3)	62.53(19)
O(2)-C(18)-O(3)-C(19)	4.9(3)
C(9)-C(18)-O(3)-C(19)	-175.89(15)
C(6B)-C(1B)-C(2B)-C(3B)	0.1(4)
C(1B)-C(2B)-C(3B)-C(4B)	0.2(4)
C(2B)-C(3B)-C(4B)-C(5B)	-0.2(4)
C(3B)-C(4B)-C(5B)-C(6B)	-0.1(4)
C(4B)-C(5B)-C(6B)-C(1B)	0.4(3)
C(4B)-C(5B)-C(6B)-C(7B)	-179.9(2)
C(2B)-C(1B)-C(6B)-C(5B)	-0.4(3)
C(2B)-C(1B)-C(6B)-C(7B)	179.9(2)
C(5B)-C(6B)-C(7B)-C(8B)	16.5(3)
C(1B)-C(6B)-C(7B)-C(8B)	-163.8(2)
C(6B)-C(7B)-C(8B)-C(9B)	178.52(19)
C(7B)-C(8B)-C(9B)-O(1B)	17.5(3)
C(7B)-C(8B)-C(9B)-C(18B)	-100.1(2)
C(7B)-C(8B)-C(9B)-C(10B)	142.2(2)
O(1B)-C(9B)-C(10B)-C(15B)	-65.9(2)
C(8B)-C(9B)-C(10B)-C(15B)	170.57(17)
C(18B)-C(9B)-C(10B)-C(15B)	52.7(2)
O(1B)-C(9B)-C(10B)-C(11B)	61.0(2)
C(8B)-C(9B)-C(10B)-C(11B)	-62.6(2)
C(18B)-C(9B)-C(10B)-C(11B)	179.53(17)
C(15B)-C(10B)-C(11B)-C(12B)	45.6(3)
C(9B)-C(10B)-C(11B)-C(12B)	-81.5(2)
C(10B)-C(11B)-C(12B)-C(13B)	-52.2(3)
C(11B)-C(12B)-C(13B)-C(14B)	56.7(3)

C(12B)-C(13B)-C(14B)-C(15B)	-56.4(3)
C(13B)-C(14B)-C(15B)-C(16B)	-128.3(2)
C(13B)-C(14B)-C(15B)-C(10B)	51.3(2)
C(11B)-C(10B)-C(15B)-C(16B)	134.3(2)
C(9B)-C(10B)-C(15B)-C(16B)	-98.1(2)
C(11B)-C(10B)-C(15B)-C(14B)	-45.3(3)
C(9B)-C(10B)-C(15B)-C(14B)	82.4(2)
C(14B)-C(15B)-C(16B)-C(17B)	-2.0(4)
C(10B)-C(15B)-C(16B)-C(17B)	178.5(2)
O(1B)-C(9B)-C(18B)-O(2B)	3.6(2)
C(8B)-C(9B)-C(18B)-O(2B)	123.0(2)
C(10B)-C(9B)-C(18B)-O(2B)	-118.0(2)
O(1B)-C(9B)-C(18B)-O(3B)	-176.29(16)
C(8B)-C(9B)-C(18B)-O(3B)	-56.9(2)
C(10B)-C(9B)-C(18B)-O(3B)	62.15(19)
O(2B)-C(18B)-O(3B)-C(19B)	6.3(3)
C(9B)-C(18B)-O(3B)-C(19B)	-173.82(17)

Table 7. Hydrogen bonds for **81** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1B)...O(3)#1	0.84	2.62	3.361(2)	148.5
O(1B)-H(1BB)...O(3B)#2	0.84	2.62	3.354(2)	146.7

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z #2 x-1,y,z

Chapter 3 Crystallographic Data

3.57

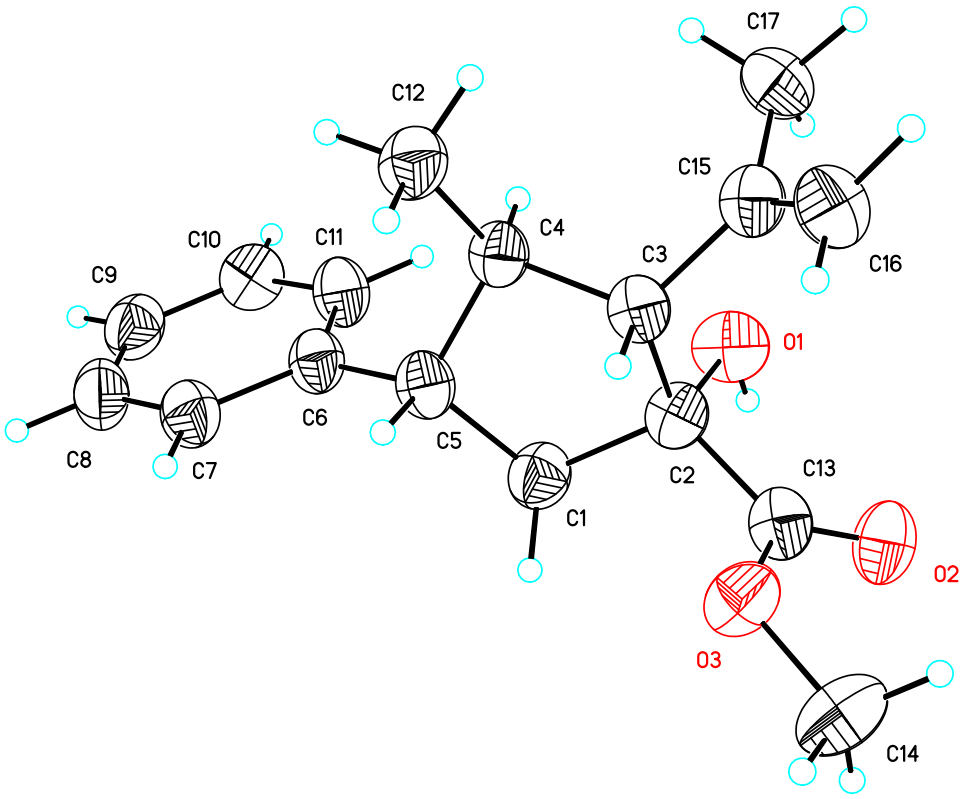


Table 1. Crystal data and structure refinement for **57**.

Identification code	**57**	
Empirical formula	C17 H22 O3	
Formula weight	274.35	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 12.7496(10) Å	α= 90°.
	b = 10.6190(12) Å	β= 90°.
	c = 22.4445(18) Å	γ = 90°.
Volume	3038.7(5) $Å^3$	

Z	8
Density (calculated)	1.199 Mg/m^3
Absorption coefficient	0.646 mm^{-1}
F(000)	1184
Crystal size	0.14 x 0.13 x 0.04 mm^3
Theta range for data collection	3.94 to 69.41°.
Index ranges	-15<=h<=15, -12<=k<=12, -27<=l<=24
Reflections collected	15922
Independent reflections	2779 [R(int) = 0.0829]
Completeness to theta = 69.41°	97.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9721 and 0.9150
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2779 / 0 / 190
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0761, wR2 = 0.1951
R indices (all data)	R1 = 0.1217, wR2 = 0.2347
Extinction coefficient	0.0009(3)
Largest diff. peak and hole	0.285 and -0.395 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **57**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2628(3)	2173(3)	2767(2)	56(1)
C(2)	2095(3)	2524(3)	3365(1)	49(1)
C(3)	1169(3)	1559(3)	3416(1)	47(1)
C(4)	817(3)	1418(3)	2767(1)	47(1)
C(5)	1856(3)	1294(3)	2427(2)	49(1)
C(6)	1793(3)	1553(3)	1765(2)	49(1)
C(7)	2183(3)	697(3)	1352(2)	57(1)
C(8)	2146(3)	947(4)	746(2)	65(1)
C(9)	1725(3)	2047(4)	537(2)	65(1)
C(10)	1326(3)	2910(3)	941(2)	62(1)
C(11)	1361(3)	2662(3)	1546(2)	56(1)
C(12)	71(3)	308(3)	2666(2)	58(1)
C(13)	2834(3)	2453(3)	3891(2)	52(1)
C(14)	3921(4)	1142(4)	4473(2)	78(1)
C(15)	343(3)	1831(3)	3874(1)	51(1)
C(16)	295(4)	1167(4)	4375(2)	62(1)
C(17)	-467(3)	2845(3)	3748(2)	62(1)
O(1)	1691(2)	3769(2)	3330(1)	64(1)
O(2)	3057(2)	3350(2)	4192(1)	67(1)
O(3)	3207(2)	1298(2)	3980(1)	62(1)

Table 3. Bond lengths [Å] and angles [°] for **57**.

C(1)-C(2)	1.550(5)
C(1)-C(5)	1.556(5)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-O(1)	1.421(4)
C(2)-C(13)	1.513(5)
C(2)-C(3)	1.568(4)
C(3)-C(15)	1.499(5)
C(3)-C(4)	1.533(4)
C(3)-H(3A)	1.0000
C(4)-C(12)	1.531(4)
C(4)-C(5)	1.534(5)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.513(5)
C(5)-H(5A)	1.0000
C(6)-C(11)	1.390(5)
C(6)-C(7)	1.392(5)
C(7)-C(8)	1.386(5)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.368(6)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.386(5)
C(9)-H(9A)	0.9500
C(10)-C(11)	1.384(5)
C(10)-H(10A)	0.9500
C(11)-H(11A)	0.9500
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-O(2)	1.201(4)
C(13)-O(3)	1.330(4)

C(14)-O(3)	1.442(5)
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-C(16)	1.328(5)
C(15)-C(17)	1.519(5)
C(16)-H(16A)	0.99(4)
C(16)-H(16B)	0.93(4)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
O(1)-H(1C)	0.8400

C(2)-C(1)-C(5)	106.9(3)
C(2)-C(1)-H(1A)	110.3
C(5)-C(1)-H(1A)	110.3
C(2)-C(1)-H(1B)	110.3
C(5)-C(1)-H(1B)	110.3
H(1A)-C(1)-H(1B)	108.6
O(1)-C(2)-C(13)	108.4(3)
O(1)-C(2)-C(1)	109.5(3)
C(13)-C(2)-C(1)	113.0(3)
O(1)-C(2)-C(3)	109.9(3)
C(13)-C(2)-C(3)	112.3(3)
C(1)-C(2)-C(3)	103.6(2)
C(15)-C(3)-C(4)	117.7(3)
C(15)-C(3)-C(2)	116.9(3)
C(4)-C(3)-C(2)	102.4(2)
C(15)-C(3)-H(3A)	106.3
C(4)-C(3)-H(3A)	106.3
C(2)-C(3)-H(3A)	106.3
C(12)-C(4)-C(3)	113.4(3)

C(12)-C(4)-C(5)	113.4(3)
C(3)-C(4)-C(5)	103.2(3)
C(12)-C(4)-H(4A)	108.9
C(3)-C(4)-H(4A)	108.9
C(5)-C(4)-H(4A)	108.9
C(6)-C(5)-C(4)	115.2(3)
C(6)-C(5)-C(1)	114.0(3)
C(4)-C(5)-C(1)	104.6(3)
C(6)-C(5)-H(5A)	107.6
C(4)-C(5)-H(5A)	107.6
C(1)-C(5)-H(5A)	107.6
C(11)-C(6)-C(7)	117.3(3)
C(11)-C(6)-C(5)	121.5(3)
C(7)-C(6)-C(5)	121.2(3)
C(8)-C(7)-C(6)	121.1(3)
C(8)-C(7)-H(7A)	119.4
C(6)-C(7)-H(7A)	119.4
C(9)-C(8)-C(7)	120.9(3)
C(9)-C(8)-H(8A)	119.6
C(7)-C(8)-H(8A)	119.6
C(8)-C(9)-C(10)	119.0(4)
C(8)-C(9)-H(9A)	120.5
C(10)-C(9)-H(9A)	120.5
C(11)-C(10)-C(9)	120.2(4)
C(11)-C(10)-H(10A)	119.9
C(9)-C(10)-H(10A)	119.9
C(10)-C(11)-C(6)	121.5(3)
C(10)-C(11)-H(11A)	119.3
C(6)-C(11)-H(11A)	119.3
C(4)-C(12)-H(12A)	109.5
C(4)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5

C(4)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
O(2)-C(13)-O(3)	124.2(3)
O(2)-C(13)-C(2)	123.1(3)
O(3)-C(13)-C(2)	112.7(3)
O(3)-C(14)-H(14A)	109.5
O(3)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(3)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(16)-C(15)-C(3)	120.7(3)
C(16)-C(15)-C(17)	120.2(4)
C(3)-C(15)-C(17)	119.1(3)
C(15)-C(16)-H(16A)	123(2)
C(15)-C(16)-H(16B)	123(2)
H(16A)-C(16)-H(16B)	114(3)
C(15)-C(17)-H(17A)	109.5
C(15)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(2)-O(1)-H(1C)	109.5
C(13)-O(3)-C(14)	116.5(3)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **57**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	58(2)	60(2)	50(2)	0(2)	0(2)	-7(2)
C(2)	56(2)	37(2)	54(2)	2(1)	-1(2)	-7(1)
C(3)	54(2)	37(1)	49(2)	1(1)	2(2)	-2(1)
C(4)	55(2)	37(2)	48(2)	0(1)	-1(2)	0(1)
C(5)	60(2)	36(2)	52(2)	-2(1)	2(2)	1(1)
C(6)	57(2)	37(2)	52(2)	-5(1)	2(2)	-4(1)
C(7)	64(3)	48(2)	60(2)	-7(2)	0(2)	1(2)
C(8)	72(3)	67(2)	56(2)	-17(2)	4(2)	-5(2)
C(9)	64(3)	80(3)	51(2)	-6(2)	2(2)	-14(2)
C(10)	69(3)	56(2)	61(2)	7(2)	-3(2)	-3(2)
C(11)	73(3)	42(2)	54(2)	-3(1)	4(2)	0(2)
C(12)	62(3)	44(2)	67(2)	-6(2)	-3(2)	-5(2)
C(13)	63(2)	41(2)	53(2)	0(1)	6(2)	-9(2)
C(14)	76(3)	80(3)	78(3)	18(2)	-27(2)	-11(2)
C(15)	60(2)	39(2)	54(2)	-1(1)	1(2)	-4(1)
C(16)	72(3)	56(2)	57(2)	6(2)	10(2)	1(2)
C(17)	62(3)	55(2)	68(2)	2(2)	10(2)	5(2)
O(1)	70(2)	35(1)	88(2)	8(1)	-1(1)	-4(1)
O(2)	87(2)	54(1)	59(2)	-9(1)	-5(1)	-13(1)
O(3)	69(2)	49(1)	68(2)	2(1)	-17(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **57**.

	x	y	z	U(eq)
H(1A)	3300	1735	2842	67
H(1B)	2771	2941	2531	67
H(3A)	1492	735	3531	56
H(4A)	460	2212	2639	56
H(5A)	2110	410	2479	59
H(7A)	2480	-73	1487	69
H(8A)	2418	348	472	78
H(9A)	1705	2215	122	78
H(10A)	1029	3676	802	74
H(11A)	1083	3262	1817	68
H(12A)	-130	275	2244	87
H(12B)	-558	418	2911	87
H(12C)	423	-478	2776	87
H(14A)	4144	260	4495	117
H(14B)	3569	1379	4844	117
H(14C)	4536	1682	4413	117
H(17A)	-954	2905	4084	92
H(17B)	-858	2628	3386	92
H(17C)	-113	3655	3691	92
H(16A)	-260(30)	1290(30)	4678(16)	60(11)
H(16B)	740(30)	500(40)	4454(16)	67(11)
H(1C)	2190	4282	3302	96

Table 6. Torsion angles [°] for **57**.

C(5)-C(1)-C(2)-O(1)	-103.1(3)
C(5)-C(1)-C(2)-C(13)	135.9(3)
C(5)-C(1)-C(2)-C(3)	14.1(3)
O(1)-C(2)-C(3)-C(15)	-49.1(4)
C(13)-C(2)-C(3)-C(15)	71.7(4)
C(1)-C(2)-C(3)-C(15)	-166.1(3)
O(1)-C(2)-C(3)-C(4)	81.1(3)
C(13)-C(2)-C(3)-C(4)	-158.1(3)
C(1)-C(2)-C(3)-C(4)	-35.8(3)
C(15)-C(3)-C(4)-C(12)	-62.8(4)
C(2)-C(3)-C(4)-C(12)	167.5(3)
C(15)-C(3)-C(4)-C(5)	174.1(2)
C(2)-C(3)-C(4)-C(5)	44.4(3)
C(12)-C(4)-C(5)-C(6)	75.5(3)
C(3)-C(4)-C(5)-C(6)	-161.4(2)
C(12)-C(4)-C(5)-C(1)	-158.6(3)
C(3)-C(4)-C(5)-C(1)	-35.5(3)
C(2)-C(1)-C(5)-C(6)	139.5(3)
C(2)-C(1)-C(5)-C(4)	12.9(3)
C(4)-C(5)-C(6)-C(11)	53.2(4)
C(1)-C(5)-C(6)-C(11)	-67.6(5)
C(4)-C(5)-C(6)-C(7)	-127.9(3)
C(1)-C(5)-C(6)-C(7)	111.2(4)
C(11)-C(6)-C(7)-C(8)	0.4(6)
C(5)-C(6)-C(7)-C(8)	-178.5(4)
C(6)-C(7)-C(8)-C(9)	0.0(6)
C(7)-C(8)-C(9)-C(10)	-0.3(6)
C(8)-C(9)-C(10)-C(11)	0.2(6)
C(9)-C(10)-C(11)-C(6)	0.2(6)
C(7)-C(6)-C(11)-C(10)	-0.5(6)
C(5)-C(6)-C(11)-C(10)	178.4(3)

O(1)-C(2)-C(13)-O(2)	-3.9(5)
C(1)-C(2)-C(13)-O(2)	117.7(4)
C(3)-C(2)-C(13)-O(2)	-125.5(4)
O(1)-C(2)-C(13)-O(3)	176.5(3)
C(1)-C(2)-C(13)-O(3)	-61.9(4)
C(3)-C(2)-C(13)-O(3)	54.9(4)
C(4)-C(3)-C(15)-C(16)	131.3(4)
C(2)-C(3)-C(15)-C(16)	-106.0(4)
C(4)-C(3)-C(15)-C(17)	-46.4(4)
C(2)-C(3)-C(15)-C(17)	76.2(4)
O(2)-C(13)-O(3)-C(14)	0.2(6)
C(2)-C(13)-O(3)-C(14)	179.9(3)

3.80

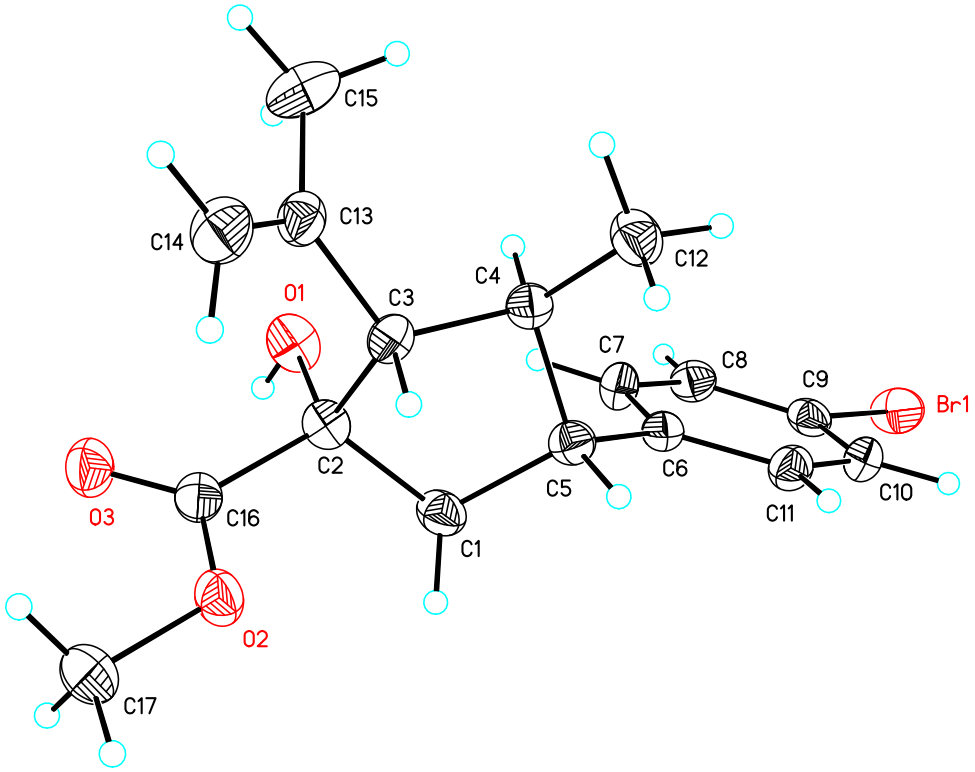


Table 1. Crystal data and structure refinement for **80**.

Identification code	**80**	
Empirical formula	C17 H21 Br O3	
Formula weight	353.25	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.8343(3) Å	α= 90°.
	b = 7.4644(4) Å	β= 90°.
	c = 37.7001(18) Å	γ = 90°.
Volume	1641.82(14) $Å^3$	
Z	4	

Density (calculated)	1.429 Mg/m^3
Absorption coefficient	3.473 mm^{-1}
F(000)	728
Crystal size	0.36 x 0.20 x 0.16 mm^3
Theta range for data collection	2.34 to 69.24°.
Index ranges	-7<=h<=6, -9<=k<=6, -41<=l<=45
Reflections collected	13100
Independent reflections	2837 [R(int) = 0.0216]
Completeness to theta = 69.24°	97.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6065 and 0.3678
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2837 / 0 / 190
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0243, wR2 = 0.0653
R indices (all data)	R1 = 0.0245, wR2 = 0.0654
Absolute structure parameter	0.024(16)
Largest diff. peak and hole	0.289 and -0.308 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **80**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	3377(1)	306(1)	8152(1)	45(1)
C(1)	1529(5)	-1691(3)	6375(1)	33(1)
C(2)	2954(4)	-1357(3)	6039(1)	29(1)
C(3)	2374(4)	629(3)	5952(1)	27(1)
C(4)	2487(4)	1498(3)	6320(1)	27(1)
C(5)	1105(4)	171(3)	6548(1)	28(1)
C(6)	1677(4)	245(3)	6941(1)	27(1)
C(7)	3774(4)	-379(3)	7065(1)	31(1)
C(8)	4286(4)	-362(3)	7425(1)	32(1)
C(9)	2681(4)	308(3)	7658(1)	30(1)
C(10)	618(4)	981(3)	7544(1)	33(1)
C(11)	121(4)	942(3)	7184(1)	30(1)
C(12)	1588(5)	3405(3)	6332(1)	37(1)
C(13)	3721(4)	1465(3)	5653(1)	33(1)
C(14)	2814(5)	1564(4)	5333(1)	46(1)
C(15)	6048(5)	2194(5)	5735(1)	54(1)
C(16)	2416(4)	-2559(3)	5726(1)	30(1)
C(17)	-405(5)	-3703(4)	5343(1)	47(1)
O(1)	5321(3)	-1541(2)	6121(1)	39(1)
O(2)	185(3)	-2629(2)	5651(1)	36(1)
O(3)	3871(3)	-3302(2)	5556(1)	42(1)

Table 3. Bond lengths [Å] and angles [°] for **80**.

Br(1)-C(9)	1.907(2)
C(1)-C(2)	1.538(3)
C(1)-C(5)	1.554(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-O(1)	1.422(3)
C(2)-C(16)	1.515(3)
C(2)-C(3)	1.556(3)
C(3)-C(13)	1.507(3)
C(3)-C(4)	1.533(3)
C(3)-H(3A)	1.0000
C(4)-C(12)	1.517(3)
C(4)-C(5)	1.541(3)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.517(3)
C(5)-H(5A)	1.0000
C(6)-C(7)	1.390(3)
C(6)-C(11)	1.392(3)
C(7)-C(8)	1.391(3)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.377(3)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.374(3)
C(10)-C(11)	1.388(3)
C(10)-H(10A)	0.9500
C(11)-H(11A)	0.9500
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(14)	1.322(4)
C(13)-C(15)	1.495(4)

C(14)-H(14A)	0.9962
C(14)-H(14B)	0.9202
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-O(3)	1.199(3)
C(16)-O(2)	1.333(3)
C(17)-O(2)	1.451(3)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
O(1)-H(1C)	0.8400

C(2)-C(1)-C(5)	106.72(17)
C(2)-C(1)-H(1A)	110.4
C(5)-C(1)-H(1A)	110.4
C(2)-C(1)-H(1B)	110.4
C(5)-C(1)-H(1B)	110.4
H(1A)-C(1)-H(1B)	108.6
O(1)-C(2)-C(16)	108.28(19)
O(1)-C(2)-C(1)	109.24(19)
C(16)-C(2)-C(1)	115.8(2)
O(1)-C(2)-C(3)	110.42(18)
C(16)-C(2)-C(3)	110.84(18)
C(1)-C(2)-C(3)	102.15(18)
C(13)-C(3)-C(4)	118.54(19)
C(13)-C(3)-C(2)	116.00(19)
C(4)-C(3)-C(2)	101.74(17)
C(13)-C(3)-H(3A)	106.6
C(4)-C(3)-H(3A)	106.6
C(2)-C(3)-H(3A)	106.6
C(12)-C(4)-C(3)	114.16(19)

C(12)-C(4)-C(5)	113.9(2)
C(3)-C(4)-C(5)	102.22(17)
C(12)-C(4)-H(4A)	108.8
C(3)-C(4)-H(4A)	108.8
C(5)-C(4)-H(4A)	108.8
C(6)-C(5)-C(4)	113.97(18)
C(6)-C(5)-C(1)	113.99(18)
C(4)-C(5)-C(1)	104.89(17)
C(6)-C(5)-H(5A)	107.9
C(4)-C(5)-H(5A)	107.9
C(1)-C(5)-H(5A)	107.9
C(7)-C(6)-C(11)	118.4(2)
C(7)-C(6)-C(5)	120.70(19)
C(11)-C(6)-C(5)	120.9(2)
C(6)-C(7)-C(8)	121.0(2)
C(6)-C(7)-H(7A)	119.5
C(8)-C(7)-H(7A)	119.5
C(9)-C(8)-C(7)	118.6(2)
C(9)-C(8)-H(8A)	120.7
C(7)-C(8)-H(8A)	120.7
C(10)-C(9)-C(8)	122.0(2)
C(10)-C(9)-Br(1)	119.50(18)
C(8)-C(9)-Br(1)	118.52(18)
C(9)-C(10)-C(11)	118.8(2)
C(9)-C(10)-H(10A)	120.6
C(11)-C(10)-H(10A)	120.6
C(10)-C(11)-C(6)	121.1(2)
C(10)-C(11)-H(11A)	119.5
C(6)-C(11)-H(11A)	119.5
C(4)-C(12)-H(12A)	109.5
C(4)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5

C(4)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(14)-C(13)-C(15)	122.1(2)
C(14)-C(13)-C(3)	119.8(2)
C(15)-C(13)-C(3)	118.1(2)
C(13)-C(14)-H(14A)	120.8
C(13)-C(14)-H(14B)	124.6
H(14A)-C(14)-H(14B)	114.3
C(13)-C(15)-H(15A)	109.5
C(13)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(13)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(3)-C(16)-O(2)	124.0(2)
O(3)-C(16)-C(2)	122.9(2)
O(2)-C(16)-C(2)	113.0(2)
O(2)-C(17)-H(17A)	109.5
O(2)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(2)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(2)-O(1)-H(1C)	109.5
C(16)-O(2)-C(17)	115.0(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **80**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	50(1)	58(1)	26(1)	0(1)	-3(1)	-16(1)
C(1)	43(1)	28(1)	28(1)	1(1)	-1(1)	-7(1)
C(2)	30(1)	29(1)	28(1)	1(1)	-5(1)	3(1)
C(3)	24(1)	30(1)	26(1)	3(1)	0(1)	4(1)
C(4)	26(1)	28(1)	28(1)	0(1)	-1(1)	0(1)
C(5)	28(1)	30(1)	27(1)	1(1)	-1(1)	-2(1)
C(6)	29(1)	25(1)	27(1)	-1(1)	3(1)	-3(1)
C(7)	30(1)	35(1)	30(1)	-3(1)	4(1)	4(1)
C(8)	29(1)	35(1)	32(1)	2(1)	-2(1)	-2(1)
C(9)	40(1)	27(1)	22(1)	-1(1)	-1(1)	-9(1)
C(10)	33(1)	34(1)	32(1)	-4(1)	10(1)	-1(1)
C(11)	27(1)	30(1)	34(1)	1(1)	3(1)	2(1)
C(12)	46(1)	29(1)	37(1)	-1(1)	1(1)	3(1)
C(13)	39(1)	28(1)	32(1)	3(1)	7(1)	5(1)
C(14)	61(2)	47(2)	30(1)	8(1)	3(1)	-1(1)
C(15)	36(2)	65(2)	60(2)	15(2)	8(1)	-8(1)
C(16)	35(1)	26(1)	29(1)	3(1)	2(1)	2(1)
C(17)	45(2)	56(2)	38(1)	-12(1)	-6(1)	-10(1)
O(1)	37(1)	36(1)	42(1)	-1(1)	-11(1)	10(1)
O(2)	34(1)	42(1)	32(1)	-10(1)	-4(1)	0(1)
O(3)	36(1)	47(1)	44(1)	-13(1)	4(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **80**.

	x	y	z	U(eq)
H(1A)	2371	-2482	6541	39
H(1B)	53	-2268	6314	39
H(3A)	728	655	5878	32
H(4A)	4116	1495	6402	33
H(5A)	-557	466	6520	34
H(7A)	4873	-824	6901	38
H(8A)	5714	-803	7509	38
H(10A)	-450	1464	7708	39
H(11A)	-1304	1398	7102	37
H(12A)	2542	4171	6181	56
H(12B)	1638	3846	6577	56
H(12C)	3	3429	6246	56
H(14A)	1357	930	5276	69
H(14B)	3517	2084	5140	69
H(15A)	6726	2692	5518	81
H(15B)	7026	1230	5825	81
H(15C)	5918	3139	5914	81
H(17A)	-2068	-3672	5307	70
H(17B)	88	-4943	5382	70
H(17C)	367	-3219	5133	70
H(1C)	5610	-2618	6167	58

Table 6. Torsion angles [°] for **80**.

C(5)-C(1)-C(2)-O(1)	93.5(2)
C(5)-C(1)-C(2)-C(16)	-144.02(19)
C(5)-C(1)-C(2)-C(3)	-23.5(2)
O(1)-C(2)-C(3)-C(13)	57.2(3)
C(16)-C(2)-C(3)-C(13)	-62.8(2)
C(1)-C(2)-C(3)-C(13)	173.3(2)
O(1)-C(2)-C(3)-C(4)	-73.0(2)
C(16)-C(2)-C(3)-C(4)	167.05(19)
C(1)-C(2)-C(3)-C(4)	43.1(2)
C(13)-C(3)-C(4)-C(12)	61.6(3)
C(2)-C(3)-C(4)-C(12)	-169.9(2)
C(13)-C(3)-C(4)-C(5)	-174.91(19)
C(2)-C(3)-C(4)-C(5)	-46.4(2)
C(12)-C(4)-C(5)-C(6)	-79.5(2)
C(3)-C(4)-C(5)-C(6)	156.86(18)
C(12)-C(4)-C(5)-C(1)	155.2(2)
C(3)-C(4)-C(5)-C(1)	31.5(2)
C(2)-C(1)-C(5)-C(6)	-130.0(2)
C(2)-C(1)-C(5)-C(4)	-4.7(2)
C(4)-C(5)-C(6)-C(7)	-70.4(3)
C(1)-C(5)-C(6)-C(7)	50.0(3)
C(4)-C(5)-C(6)-C(11)	109.5(2)
C(1)-C(5)-C(6)-C(11)	-130.2(2)
C(11)-C(6)-C(7)-C(8)	2.0(3)
C(5)-C(6)-C(7)-C(8)	-178.2(2)
C(6)-C(7)-C(8)-C(9)	-0.8(4)
C(7)-C(8)-C(9)-C(10)	-1.0(4)
C(7)-C(8)-C(9)-Br(1)	179.35(18)
C(8)-C(9)-C(10)-C(11)	1.6(4)
Br(1)-C(9)-C(10)-C(11)	-178.81(19)
C(9)-C(10)-C(11)-C(6)	-0.3(3)

C(7)-C(6)-C(11)-C(10)	-1.4(3)
C(5)-C(6)-C(11)-C(10)	178.7(2)
C(4)-C(3)-C(13)-C(14)	-140.0(2)
C(2)-C(3)-C(13)-C(14)	98.4(3)
C(4)-C(3)-C(13)-C(15)	38.8(3)
C(2)-C(3)-C(13)-C(15)	-82.7(3)
O(1)-C(2)-C(16)-O(3)	-9.6(3)
C(1)-C(2)-C(16)-O(3)	-132.7(3)
C(3)-C(2)-C(16)-O(3)	111.6(3)
O(1)-C(2)-C(16)-O(2)	173.4(2)
C(1)-C(2)-C(16)-O(2)	50.4(3)
C(3)-C(2)-C(16)-O(2)	-65.4(3)
O(3)-C(16)-O(2)-C(17)	0.5(4)
C(2)-C(16)-O(2)-C(17)	177.4(2)

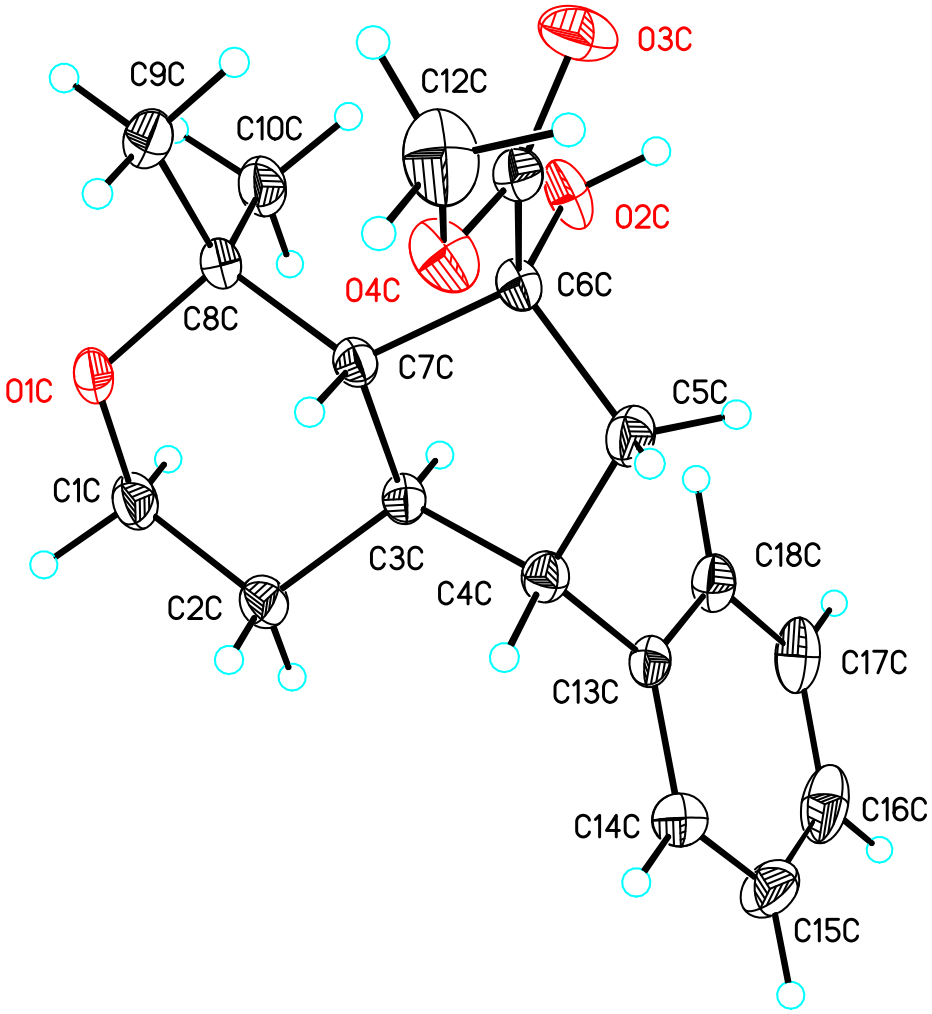
Table 7. Hydrogen bonds for **80** [Å and °].

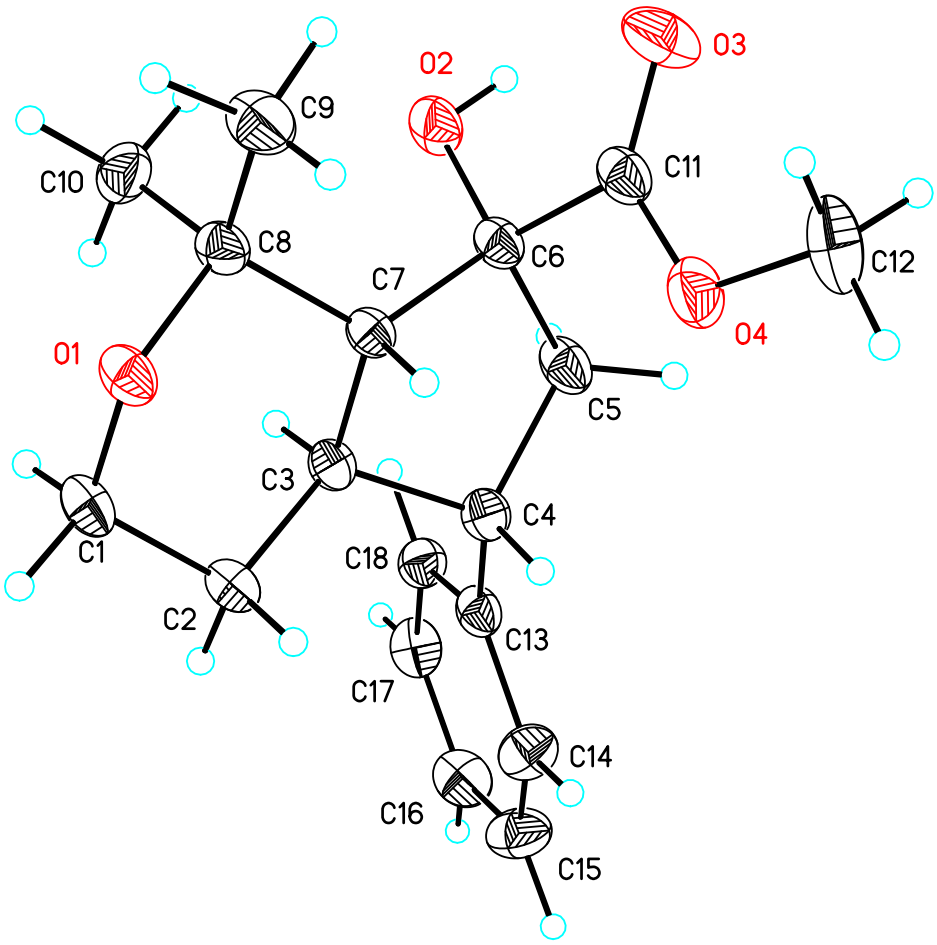
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1C)...Br(1)#1	0.84	3.05	3.6918(17)	134.5

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+3/2

3.84


O3C
C12C
C9C
C10C
O2C
O4C
C6C
C8C
C7C
O1C
C5C
C1C
C3C
C18C
C4C
C2C
C17C
C13C
C16C
C14C
C15C


O3
O2
C9
C11
C10
C8
C6
C12
C7
O4
O1
C5
C3
C4
C1
C18
C2
C13
C17
C14
C16
C15

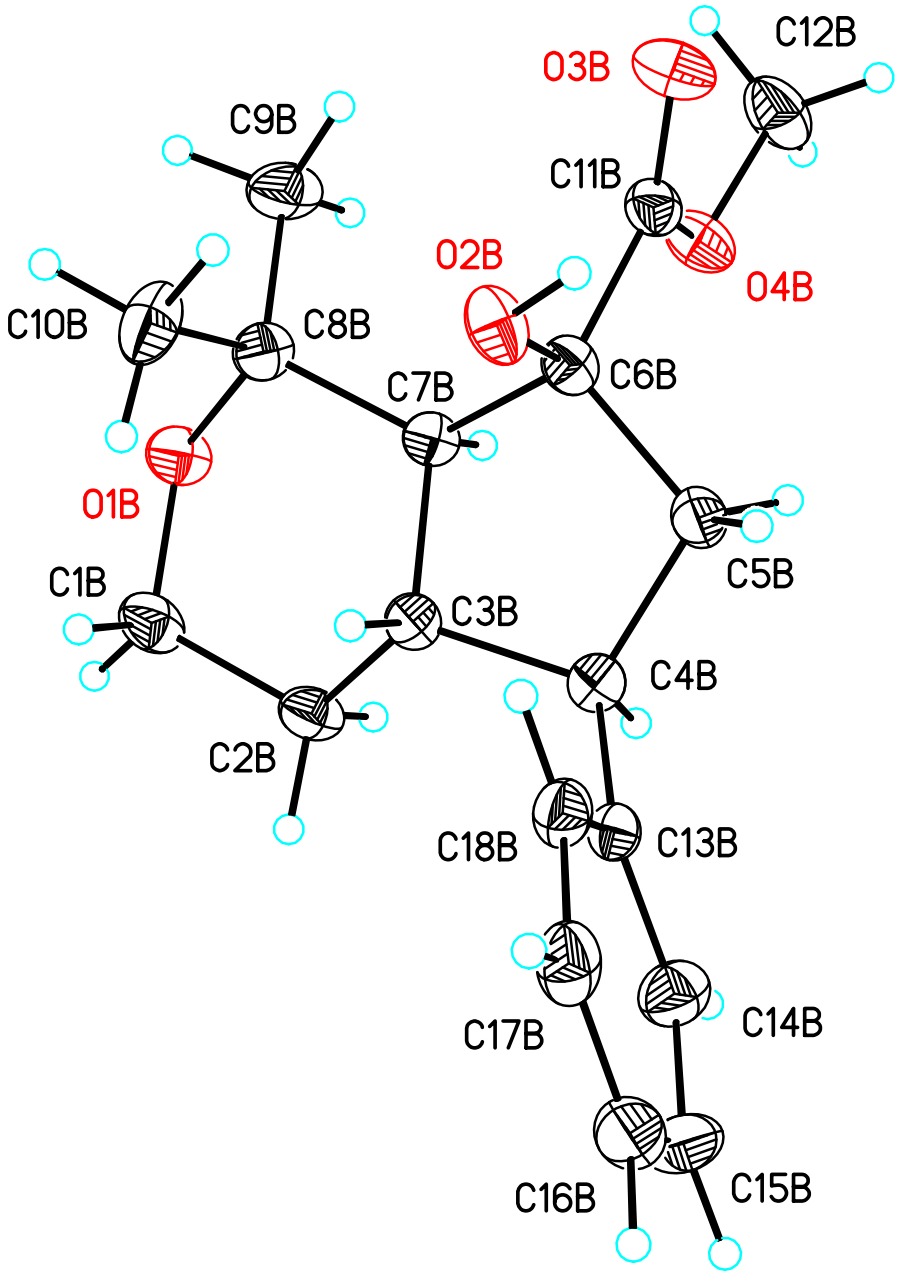


Table 1. Crystal data and structure refinement for **84**.

Identification code	**84**
Empirical formula	C18 H24 O4
Formula weight	304.37
Temperature	173(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic

Space group	P2(1)/n	
Unit cell dimensions	a = 12.1533(3) Å	α= 90°.
	b = 35.1495(7) Å	β= 110.6840(10)°.
	c = 12.2922(3) Å	γ = 90°.
Volume	4912.5(2) $Å^3$	
Z	12	
Density (calculated)	1.235 Mg/m^3	
Absorption coefficient	0.696 mm^{-1}	
F(000)	1968	
Crystal size	0.40 x 0.25 x 0.13 mm^3	
Theta range for data collection	2.51 to 67.32°.	
Index ranges	-14<=h<=14, -37<=k<=41, -14<=l<=13	
Reflections collected	41157	
Independent reflections	8401 [R(int) = 0.1191]	
Completeness to theta = 67.32°	95.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9149 and 0.7681	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8401 / 0 / 596	
Goodness-of-fit on F^2	1.132	
Final R indices [I>2sigma(I)]	R1 = 0.0801, wR2 = 0.2275	
R indices (all data)	R1 = 0.0976, wR2 = 0.2637	
Extinction coefficient	0.00078(18)	
Largest diff. peak and hole	0.395 and -0.592 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **84**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5739(3)	239(1)	1776(3)	38(1)
C(2)	5803(2)	35(1)	2887(2)	35(1)
C(3)	6875(2)	170(1)	3888(2)	31(1)
C(4)	6977(2)	53(1)	5116(2)	34(1)
C(5)	7880(3)	339(1)	5880(3)	41(1)
C(6)	7800(2)	706(1)	5141(3)	33(1)
C(7)	6860(2)	605(1)	3950(2)	30(1)
C(8)	6826(2)	797(1)	2816(3)	36(1)
C(9)	6588(3)	1219(1)	2822(3)	49(1)
C(10)	7898(3)	723(1)	2464(3)	44(1)
C(11)	7414(2)	1047(1)	5692(2)	36(1)
C(12)	5967(3)	1267(1)	6417(3)	63(1)
C(13)	7275(2)	-362(1)	5398(2)	35(1)
C(14)	6475(3)	-601(1)	5627(3)	43(1)
C(15)	6714(3)	-984(1)	5862(3)	48(1)
C(16)	7757(3)	-1137(1)	5859(3)	46(1)
C(17)	8570(3)	-905(1)	5633(3)	43(1)
C(18)	8323(2)	-519(1)	5402(3)	39(1)
O(1)	5771(2)	646(1)	1916(2)	37(1)
O(2)	8893(2)	786(1)	5022(2)	42(1)
O(3)	7947(2)	1339(1)	5977(2)	59(1)
O(4)	6405(2)	973(1)	5850(2)	50(1)
C(1B)	845(3)	1412(1)	-3083(3)	43(1)
C(2B)	1044(3)	1661(1)	-2016(3)	39(1)
C(3B)	2015(2)	1487(1)	-979(2)	32(1)
C(4B)	2237(2)	1667(1)	217(2)	35(1)
C(5B)	2651(3)	1330(1)	1091(3)	38(1)
C(6B)	2612(2)	965(1)	364(2)	33(1)
C(7B)	1706(2)	1073(1)	-833(2)	31(1)

C(8B)	1534(2)	833(1)	-1920(3)	38(1)
C(9B)	1002(3)	446(1)	-1850(3)	50(1)
C(10B)	2626(3)	782(1)	-2250(3)	51(1)
C(11B)	2250(2)	618(1)	910(3)	35(1)
C(12B)	713(3)	360(1)	1449(3)	52(1)
C(13B)	3086(3)	1997(1)	459(3)	35(1)
C(14B)	2748(3)	2363(1)	632(3)	46(1)
C(15B)	3532(3)	2668(1)	798(3)	55(1)
C(16B)	4641(3)	2605(1)	777(3)	50(1)
C(17B)	4995(3)	2242(1)	621(3)	45(1)
C(18B)	4226(2)	1943(1)	467(3)	38(1)
O(1B)	608(2)	1025(1)	-2872(2)	41(1)
O(2B)	3704(2)	899(1)	235(2)	41(1)
O(3B)	2847(2)	346(1)	1282(2)	51(1)
O(4B)	1166(2)	665(1)	939(2)	43(1)
C(1C)	9901(3)	1933(1)	3197(3)	40(1)
C(2C)	9725(3)	1678(1)	2144(3)	41(1)
C(3C)	8787(2)	1853(1)	1079(2)	32(1)
C(4C)	8628(2)	1674(1)	-102(2)	36(1)
C(5C)	8194(3)	2006(1)	-992(3)	40(1)
C(6C)	8257(2)	2375(1)	-268(2)	32(1)
C(7C)	9116(2)	2266(1)	946(2)	32(1)
C(8C)	9255(3)	2509(1)	2026(3)	37(1)
C(9C)	9791(3)	2894(1)	1951(3)	48(1)
C(10C)	8156(3)	2562(1)	2336(3)	48(1)
C(11C)	8656(3)	2710(1)	-832(3)	35(1)
C(12C)	10229(3)	2951(1)	-1345(3)	61(1)
C(13C)	7837(2)	1328(1)	-387(2)	33(1)
C(14C)	8243(3)	977(1)	-606(3)	43(1)
C(15C)	7505(3)	659(1)	-861(3)	54(1)
C(16C)	6373(3)	690(1)	-879(3)	56(1)
C(17C)	5949(3)	1039(1)	-669(3)	48(1)

C(18C)	6676(3)	1353(1)	-430(3)	40(1)
O(1C)	10162(2)	2318(1)	2984(2)	38(1)
O(2C)	7151(2)	2459(1)	-188(2)	44(1)
O(3C)	8063(2)	2976(1)	-1279(2)	55(1)
O(4C)	9763(2)	2661(1)	-790(2)	46(1)

Table 3. Bond lengths [Å] and angles [°] for **84**.

C(1)-O(1)	1.439(3)
C(1)-C(2)	1.521(4)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.518(4)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.526(4)
C(3)-C(7)	1.534(3)
C(3)-H(3A)	1.0000
C(4)-C(13)	1.514(3)
C(4)-C(5)	1.538(4)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.561(3)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-O(2)	1.415(3)
C(6)-C(11)	1.529(3)
C(6)-C(7)	1.547(4)
C(7)-C(8)	1.535(4)
C(7)-H(7A)	1.0000
C(8)-O(1)	1.465(3)
C(8)-C(9)	1.513(3)
C(8)-C(10)	1.532(3)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-O(3)	1.200(3)

C(11)-O(4)	1.333(3)
C(12)-O(4)	1.449(3)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(18)	1.386(4)
C(13)-C(14)	1.387(3)
C(14)-C(15)	1.386(4)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.378(4)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.384(4)
C(16)-H(16A)	0.9500
C(17)-C(18)	1.398(3)
C(17)-H(17A)	0.9500
C(18)-H(18A)	0.9500
O(2)-H(2C)	0.8400
C(1B)-O(1B)	1.435(3)
C(1B)-C(2B)	1.523(4)
C(1B)-H(1BA)	0.9900
C(1B)-H(1BB)	0.9900
C(2B)-C(3B)	1.526(4)
C(2B)-H(2BA)	0.9900
C(2B)-H(2BB)	0.9900
C(3B)-C(7B)	1.530(3)
C(3B)-C(4B)	1.534(4)
C(3B)-H(3BA)	1.0000
C(4B)-C(13B)	1.510(3)
C(4B)-C(5B)	1.557(4)
C(4B)-H(4BA)	1.0000
C(5B)-C(6B)	1.556(3)
C(5B)-H(5BA)	0.9900

C(5B)-H(5BB)	0.9900
C(6B)-O(2B)	1.409(3)
C(6B)-C(11B)	1.529(3)
C(6B)-C(7B)	1.542(4)
C(7B)-C(8B)	1.532(4)
C(7B)-H(7BA)	1.0000
C(8B)-O(1B)	1.471(3)
C(8B)-C(9B)	1.520(3)
C(8B)-C(10B)	1.528(4)
C(9B)-H(9BA)	0.9800
C(9B)-H(9BB)	0.9800
C(9B)-H(9BC)	0.9800
C(10B)-H(10D)	0.9800
C(10B)-H(10E)	0.9800
C(10B)-H(10F)	0.9800
C(11B)-O(3B)	1.192(3)
C(11B)-O(4B)	1.341(3)
C(12B)-O(4B)	1.446(3)
C(12B)-H(12D)	0.9800
C(12B)-H(12E)	0.9800
C(12B)-H(12F)	0.9800
C(13B)-C(14B)	1.390(3)
C(13B)-C(18B)	1.395(4)
C(14B)-C(15B)	1.402(4)
C(14B)-H(14B)	0.9500
C(15B)-C(16B)	1.375(5)
C(15B)-H(15B)	0.9500
C(16B)-C(17B)	1.379(4)
C(16B)-H(16B)	0.9500
C(17B)-C(18B)	1.375(4)
C(17B)-H(17B)	0.9500
C(18B)-H(18B)	0.9500

O(2B)-H(2BC)	0.8400
C(1C)-O(1C)	1.432(3)
C(1C)-C(2C)	1.527(4)
C(1C)-H(1CA)	0.9900
C(1C)-H(1CB)	0.9900
C(2C)-C(3C)	1.529(4)
C(2C)-H(2CA)	0.9900
C(2C)-H(2CB)	0.9900
C(3C)-C(7C)	1.530(3)
C(3C)-C(4C)	1.531(4)
C(3C)-H(3CA)	1.0000
C(4C)-C(13C)	1.513(3)
C(4C)-C(5C)	1.558(4)
C(4C)-H(4CA)	1.0000
C(5C)-C(6C)	1.560(3)
C(5C)-H(5CA)	0.9900
C(5C)-H(5CB)	0.9900
C(6C)-O(2C)	1.413(3)
C(6C)-C(11C)	1.530(3)
C(6C)-C(7C)	1.537(4)
C(7C)-C(8C)	1.538(4)
C(7C)-H(7CA)	1.0000
C(8C)-O(1C)	1.462(4)
C(8C)-C(9C)	1.518(3)
C(8C)-C(10C)	1.525(4)
C(9C)-H(9CA)	0.9800
C(9C)-H(9CB)	0.9800
C(9C)-H(9CC)	0.9800
C(10C)-H(10G)	0.9800
C(10C)-H(10H)	0.9800
C(10C)-H(10I)	0.9800
C(11C)-O(3C)	1.190(3)

C(11C)-O(4C)	1.340(3)
C(12C)-O(4C)	1.450(3)
C(12C)-H(12G)	0.9800
C(12C)-H(12H)	0.9800
C(12C)-H(12I)	0.9800
C(13C)-C(14C)	1.391(3)
C(13C)-C(18C)	1.396(4)
C(14C)-C(15C)	1.397(4)
C(14C)-H(14C)	0.9500
C(15C)-C(16C)	1.373(5)
C(15C)-H(15C)	0.9500
C(16C)-C(17C)	1.388(5)
C(16C)-H(16C)	0.9500
C(17C)-C(18C)	1.379(4)
C(17C)-H(17C)	0.9500
C(18C)-H(18C)	0.9500
O(2C)-H(2CC)	0.8400

O(1)-C(1)-C(2)	111.8(2)
O(1)-C(1)-H(1A)	109.3
C(2)-C(1)-H(1A)	109.3
O(1)-C(1)-H(1B)	109.3
C(2)-C(1)-H(1B)	109.3
H(1A)-C(1)-H(1B)	107.9
C(3)-C(2)-C(1)	109.7(2)
C(3)-C(2)-H(2A)	109.7
C(1)-C(2)-H(2A)	109.7
C(3)-C(2)-H(2B)	109.7
C(1)-C(2)-H(2B)	109.7
H(2A)-C(2)-H(2B)	108.2
C(2)-C(3)-C(4)	117.7(2)
C(2)-C(3)-C(7)	109.3(2)

C(4)-C(3)-C(7)	102.51(19)
C(2)-C(3)-H(3A)	109.0
C(4)-C(3)-H(3A)	109.0
C(7)-C(3)-H(3A)	109.0
C(13)-C(4)-C(3)	114.4(2)
C(13)-C(4)-C(5)	115.3(2)
C(3)-C(4)-C(5)	102.7(2)
C(13)-C(4)-H(4A)	108.0
C(3)-C(4)-H(4A)	108.0
C(5)-C(4)-H(4A)	108.0
C(4)-C(5)-C(6)	107.4(2)
C(4)-C(5)-H(5A)	110.2
C(6)-C(5)-H(5A)	110.2
C(4)-C(5)-H(5B)	110.2
C(6)-C(5)-H(5B)	110.2
H(5A)-C(5)-H(5B)	108.5
O(2)-C(6)-C(11)	109.6(2)
O(2)-C(6)-C(7)	110.8(2)
C(11)-C(6)-C(7)	111.0(2)
O(2)-C(6)-C(5)	110.9(2)
C(11)-C(6)-C(5)	110.8(2)
C(7)-C(6)-C(5)	103.6(2)
C(3)-C(7)-C(8)	112.9(2)
C(3)-C(7)-C(6)	104.9(2)
C(8)-C(7)-C(6)	122.2(2)
C(3)-C(7)-H(7A)	105.1
C(8)-C(7)-H(7A)	105.1
C(6)-C(7)-H(7A)	105.1
O(1)-C(8)-C(9)	103.9(2)
O(1)-C(8)-C(10)	109.3(2)
C(9)-C(8)-C(10)	110.5(2)
O(1)-C(8)-C(7)	105.21(19)

C(9)-C(8)-C(7)	111.7(2)
C(10)-C(8)-C(7)	115.4(2)
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(8)-C(10)-H(10A)	109.5
C(8)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(8)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
O(3)-C(11)-O(4)	123.6(2)
O(3)-C(11)-C(6)	125.6(2)
O(4)-C(11)-C(6)	110.8(2)
O(4)-C(12)-H(12A)	109.5
O(4)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(4)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(18)-C(13)-C(14)	117.9(2)
C(18)-C(13)-C(4)	122.0(2)
C(14)-C(13)-C(4)	120.1(2)
C(15)-C(14)-C(13)	121.3(3)
C(15)-C(14)-H(14A)	119.3
C(13)-C(14)-H(14A)	119.3
C(16)-C(15)-C(14)	120.3(3)
C(16)-C(15)-H(15A)	119.8
C(14)-C(15)-H(15A)	119.8

C(15)-C(16)-C(17)	119.5(3)
C(15)-C(16)-H(16A)	120.3
C(17)-C(16)-H(16A)	120.3
C(16)-C(17)-C(18)	119.8(3)
C(16)-C(17)-H(17A)	120.1
C(18)-C(17)-H(17A)	120.1
C(13)-C(18)-C(17)	121.2(2)
C(13)-C(18)-H(18A)	119.4
C(17)-C(18)-H(18A)	119.4
C(1)-O(1)-C(8)	115.4(2)
C(6)-O(2)-H(2C)	109.5
C(11)-O(4)-C(12)	116.4(2)
O(1B)-C(1B)-C(2B)	111.7(2)
O(1B)-C(1B)-H(1BA)	109.3
C(2B)-C(1B)-H(1BA)	109.3
O(1B)-C(1B)-H(1BB)	109.3
C(2B)-C(1B)-H(1BB)	109.3
H(1BA)-C(1B)-H(1BB)	107.9
C(1B)-C(2B)-C(3B)	109.2(2)
C(1B)-C(2B)-H(2BA)	109.8
C(3B)-C(2B)-H(2BA)	109.8
C(1B)-C(2B)-H(2BB)	109.8
C(3B)-C(2B)-H(2BB)	109.8
H(2BA)-C(2B)-H(2BB)	108.3
C(2B)-C(3B)-C(7B)	109.3(2)
C(2B)-C(3B)-C(4B)	117.2(2)
C(7B)-C(3B)-C(4B)	104.3(2)
C(2B)-C(3B)-H(3BA)	108.6
C(7B)-C(3B)-H(3BA)	108.6
C(4B)-C(3B)-H(3BA)	108.6
C(13B)-C(4B)-C(3B)	112.5(2)
C(13B)-C(4B)-C(5B)	114.6(2)

C(3B)-C(4B)-C(5B)	104.64(19)
C(13B)-C(4B)-H(4BA)	108.3
C(3B)-C(4B)-H(4BA)	108.3
C(5B)-C(4B)-H(4BA)	108.3
C(6B)-C(5B)-C(4B)	107.1(2)
C(6B)-C(5B)-H(5BA)	110.3
C(4B)-C(5B)-H(5BA)	110.3
C(6B)-C(5B)-H(5BB)	110.3
C(4B)-C(5B)-H(5BB)	110.3
H(5BA)-C(5B)-H(5BB)	108.5
O(2B)-C(6B)-C(11B)	110.3(2)
O(2B)-C(6B)-C(7B)	108.5(2)
C(11B)-C(6B)-C(7B)	113.3(2)
O(2B)-C(6B)-C(5B)	111.1(2)
C(11B)-C(6B)-C(5B)	111.1(2)
C(7B)-C(6B)-C(5B)	102.2(2)
C(3B)-C(7B)-C(8B)	112.7(2)
C(3B)-C(7B)-C(6B)	102.9(2)
C(8B)-C(7B)-C(6B)	121.9(2)
C(3B)-C(7B)-H(7BA)	106.1
C(8B)-C(7B)-H(7BA)	106.1
C(6B)-C(7B)-H(7BA)	106.1
O(1B)-C(8B)-C(9B)	103.5(2)
O(1B)-C(8B)-C(10B)	109.6(2)
C(9B)-C(8B)-C(10B)	109.8(2)
O(1B)-C(8B)-C(7B)	105.70(19)
C(9B)-C(8B)-C(7B)	111.9(2)
C(10B)-C(8B)-C(7B)	115.6(2)
C(8B)-C(9B)-H(9BA)	109.5
C(8B)-C(9B)-H(9BB)	109.5
H(9BA)-C(9B)-H(9BB)	109.5
C(8B)-C(9B)-H(9BC)	109.5

H(9BA)-C(9B)-H(9BC)	109.5
H(9BB)-C(9B)-H(9BC)	109.5
C(8B)-C(10B)-H(10D)	109.5
C(8B)-C(10B)-H(10E)	109.5
H(10D)-C(10B)-H(10E)	109.5
C(8B)-C(10B)-H(10F)	109.5
H(10D)-C(10B)-H(10F)	109.5
H(10E)-C(10B)-H(10F)	109.5
O(3B)-C(11B)-O(4B)	124.0(2)
O(3B)-C(11B)-C(6B)	125.4(2)
O(4B)-C(11B)-C(6B)	110.6(2)
O(4B)-C(12B)-H(12D)	109.5
O(4B)-C(12B)-H(12E)	109.5
H(12D)-C(12B)-H(12E)	109.5
O(4B)-C(12B)-H(12F)	109.5
H(12D)-C(12B)-H(12F)	109.5
H(12E)-C(12B)-H(12F)	109.5
C(14B)-C(13B)-C(18B)	118.1(2)
C(14B)-C(13B)-C(4B)	121.6(2)
C(18B)-C(13B)-C(4B)	120.3(2)
C(13B)-C(14B)-C(15B)	120.6(3)
C(13B)-C(14B)-H(14B)	119.7
C(15B)-C(14B)-H(14B)	119.7
C(16B)-C(15B)-C(14B)	119.5(3)
C(16B)-C(15B)-H(15B)	120.3
C(14B)-C(15B)-H(15B)	120.3
C(15B)-C(16B)-C(17B)	120.6(3)
C(15B)-C(16B)-H(16B)	119.7
C(17B)-C(16B)-H(16B)	119.7
C(18B)-C(17B)-C(16B)	119.7(3)
C(18B)-C(17B)-H(17B)	120.2
C(16B)-C(17B)-H(17B)	120.2

C(17B)-C(18B)-C(13B)	121.5(2)
C(17B)-C(18B)-H(18B)	119.3
C(13B)-C(18B)-H(18B)	119.3
C(1B)-O(1B)-C(8B)	115.7(2)
C(6B)-O(2B)-H(2BC)	109.5
C(11B)-O(4B)-C(12B)	116.7(2)
O(1C)-C(1C)-C(2C)	111.9(2)
O(1C)-C(1C)-H(1CA)	109.2
C(2C)-C(1C)-H(1CA)	109.2
O(1C)-C(1C)-H(1CB)	109.2
C(2C)-C(1C)-H(1CB)	109.2
H(1CA)-C(1C)-H(1CB)	107.9
C(1C)-C(2C)-C(3C)	109.2(2)
C(1C)-C(2C)-H(2CA)	109.8
C(3C)-C(2C)-H(2CA)	109.8
C(1C)-C(2C)-H(2CB)	109.8
C(3C)-C(2C)-H(2CB)	109.8
H(2CA)-C(2C)-H(2CB)	108.3
C(2C)-C(3C)-C(7C)	109.2(2)
C(2C)-C(3C)-C(4C)	116.9(2)
C(7C)-C(3C)-C(4C)	103.8(2)
C(2C)-C(3C)-H(3CA)	108.9
C(7C)-C(3C)-H(3CA)	108.9
C(4C)-C(3C)-H(3CA)	108.9
C(13C)-C(4C)-C(3C)	114.0(2)
C(13C)-C(4C)-C(5C)	114.1(2)
C(3C)-C(4C)-C(5C)	104.82(19)
C(13C)-C(4C)-H(4CA)	107.8
C(3C)-C(4C)-H(4CA)	107.8
C(5C)-C(4C)-H(4CA)	107.8
C(4C)-C(5C)-C(6C)	106.7(2)
C(4C)-C(5C)-H(5CA)	110.4

C(6C)-C(5C)-H(5CA)	110.4
C(4C)-C(5C)-H(5CB)	110.4
C(6C)-C(5C)-H(5CB)	110.4
H(5CA)-C(5C)-H(5CB)	108.6
O(2C)-C(6C)-C(11C)	109.4(2)
O(2C)-C(6C)-C(7C)	108.7(2)
C(11C)-C(6C)-C(7C)	114.6(2)
O(2C)-C(6C)-C(5C)	110.9(2)
C(11C)-C(6C)-C(5C)	110.1(2)
C(7C)-C(6C)-C(5C)	103.0(2)
C(3C)-C(7C)-C(6C)	103.1(2)
C(3C)-C(7C)-C(8C)	112.8(2)
C(6C)-C(7C)-C(8C)	122.0(2)
C(3C)-C(7C)-H(7CA)	105.9
C(6C)-C(7C)-H(7CA)	105.9
C(8C)-C(7C)-H(7CA)	105.9
O(1C)-C(8C)-C(9C)	104.0(2)
O(1C)-C(8C)-C(10C)	109.4(2)
C(9C)-C(8C)-C(10C)	109.8(2)
O(1C)-C(8C)-C(7C)	105.15(19)
C(9C)-C(8C)-C(7C)	111.2(2)
C(10C)-C(8C)-C(7C)	116.4(2)
C(8C)-C(9C)-H(9CA)	109.5
C(8C)-C(9C)-H(9CB)	109.5
H(9CA)-C(9C)-H(9CB)	109.5
C(8C)-C(9C)-H(9CC)	109.5
H(9CA)-C(9C)-H(9CC)	109.5
H(9CB)-C(9C)-H(9CC)	109.5
C(8C)-C(10C)-H(10G)	109.5
C(8C)-C(10C)-H(10H)	109.5
H(10G)-C(10C)-H(10H)	109.5
C(8C)-C(10C)-H(10I)	109.5

H(10G)-C(10C)-H(10I)	109.5
H(10H)-C(10C)-H(10I)	109.5
O(3C)-C(11C)-O(4C)	123.8(2)
O(3C)-C(11C)-C(6C)	125.3(2)
O(4C)-C(11C)-C(6C)	110.9(2)
O(4C)-C(12C)-H(12G)	109.5
O(4C)-C(12C)-H(12H)	109.5
H(12G)-C(12C)-H(12H)	109.5
O(4C)-C(12C)-H(12I)	109.5
H(12G)-C(12C)-H(12I)	109.5
H(12H)-C(12C)-H(12I)	109.5
C(14C)-C(13C)-C(18C)	118.2(2)
C(14C)-C(13C)-C(4C)	121.2(2)
C(18C)-C(13C)-C(4C)	120.6(2)
C(13C)-C(14C)-C(15C)	120.6(3)
C(13C)-C(14C)-H(14C)	119.7
C(15C)-C(14C)-H(14C)	119.7
C(16C)-C(15C)-C(14C)	120.0(3)
C(16C)-C(15C)-H(15C)	120.0
C(14C)-C(15C)-H(15C)	120.0
C(15C)-C(16C)-C(17C)	120.2(3)
C(15C)-C(16C)-H(16C)	119.9
C(17C)-C(16C)-H(16C)	119.9
C(18C)-C(17C)-C(16C)	119.6(3)
C(18C)-C(17C)-H(17C)	120.2
C(16C)-C(17C)-H(17C)	120.2
C(17C)-C(18C)-C(13C)	121.4(3)
C(17C)-C(18C)-H(18C)	119.3
C(13C)-C(18C)-H(18C)	119.3
C(1C)-O(1C)-C(8C)	115.4(2)
C(6C)-O(2C)-H(2CC)	109.5
C(11C)-O(4C)-C(12C)	116.4(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **84**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	46(2)	26(1)	46(2)	-5(1)	22(1)	2(1)
C(2)	38(2)	25(1)	47(2)	-5(1)	21(1)	-2(1)
C(3)	37(1)	22(1)	43(2)	-2(1)	25(1)	1(1)
C(4)	39(2)	27(1)	45(2)	0(1)	26(1)	3(1)
C(5)	59(2)	25(1)	45(2)	0(1)	26(2)	1(1)
C(6)	38(2)	25(1)	41(2)	-2(1)	21(1)	-2(1)
C(7)	37(1)	22(1)	39(2)	-3(1)	22(1)	0(1)
C(8)	41(2)	25(1)	47(2)	1(1)	23(1)	-2(1)
C(9)	70(2)	24(1)	55(2)	3(1)	24(2)	-1(1)
C(10)	45(2)	48(2)	47(2)	5(1)	27(2)	-4(1)
C(11)	43(2)	28(1)	40(2)	-2(1)	19(1)	-1(1)
C(12)	78(3)	63(2)	62(2)	-14(2)	40(2)	20(2)
C(13)	49(2)	23(1)	40(2)	-1(1)	26(1)	0(1)
C(14)	45(2)	37(1)	57(2)	6(1)	33(2)	4(1)
C(15)	53(2)	37(2)	61(2)	10(1)	28(2)	-7(1)
C(16)	61(2)	26(1)	51(2)	6(1)	22(2)	3(1)
C(17)	50(2)	32(1)	54(2)	4(1)	28(2)	11(1)
C(18)	47(2)	31(1)	48(2)	4(1)	30(2)	1(1)
O(1)	44(1)	26(1)	43(1)	-1(1)	18(1)	1(1)
O(2)	40(1)	45(1)	48(1)	-6(1)	24(1)	-5(1)
O(3)	74(2)	29(1)	86(2)	-16(1)	40(2)	-10(1)
O(4)	57(1)	46(1)	61(2)	-17(1)	39(1)	-2(1)
C(1B)	50(2)	30(1)	50(2)	4(1)	21(2)	-8(1)
C(2B)	47(2)	25(1)	49(2)	6(1)	22(2)	-1(1)
C(3B)	38(2)	22(1)	45(2)	0(1)	24(1)	-4(1)
C(4B)	40(2)	25(1)	51(2)	-2(1)	30(1)	-2(1)
C(5B)	53(2)	28(1)	43(2)	-1(1)	27(2)	-8(1)
C(6B)	37(2)	26(1)	44(2)	3(1)	26(1)	-1(1)
C(7B)	35(1)	21(1)	45(2)	1(1)	23(1)	-3(1)

C(8B)	43(2)	25(1)	48(2)	-1(1)	19(1)	2(1)
C(9B)	61(2)	26(1)	57(2)	-2(1)	13(2)	-5(1)
C(10B)	53(2)	53(2)	53(2)	-14(2)	28(2)	7(1)
C(11B)	44(2)	25(1)	43(2)	3(1)	26(1)	-1(1)
C(12B)	61(2)	43(2)	66(2)	13(2)	39(2)	-12(1)
C(13B)	50(2)	21(1)	43(2)	-1(1)	29(2)	-2(1)
C(14B)	56(2)	30(1)	58(2)	-4(1)	30(2)	5(1)
C(15B)	81(3)	24(1)	66(2)	-5(1)	34(2)	-3(1)
C(16B)	65(2)	39(2)	50(2)	-4(1)	26(2)	-21(1)
C(17B)	49(2)	46(2)	48(2)	-5(1)	28(2)	-11(1)
C(18B)	46(2)	32(1)	46(2)	-5(1)	29(2)	-6(1)
O(1B)	50(1)	27(1)	49(1)	2(1)	19(1)	-3(1)
O(2B)	37(1)	47(1)	49(1)	6(1)	26(1)	3(1)
O(3B)	58(1)	32(1)	71(2)	14(1)	33(1)	8(1)
O(4B)	46(1)	34(1)	60(1)	13(1)	34(1)	-1(1)
C(1C)	47(2)	31(1)	43(2)	4(1)	19(2)	-3(1)
C(2C)	54(2)	26(1)	47(2)	5(1)	25(2)	0(1)
C(3C)	40(2)	23(1)	41(2)	0(1)	24(1)	-3(1)
C(4C)	43(2)	24(1)	51(2)	-3(1)	31(2)	-3(1)
C(5C)	56(2)	30(1)	40(2)	0(1)	25(2)	-7(1)
C(6C)	36(2)	25(1)	45(2)	3(1)	25(1)	0(1)
C(7C)	38(2)	22(1)	43(2)	0(1)	24(1)	-2(1)
C(8C)	45(2)	25(1)	46(2)	-2(1)	22(2)	2(1)
C(9C)	60(2)	28(1)	54(2)	-3(1)	17(2)	-5(1)
C(10C)	50(2)	49(2)	53(2)	-8(1)	27(2)	10(1)
C(11C)	46(2)	25(1)	43(2)	0(1)	25(1)	0(1)
C(12C)	69(2)	61(2)	65(2)	14(2)	41(2)	-19(2)
C(13C)	45(2)	23(1)	41(2)	-1(1)	27(1)	-3(1)
C(14C)	49(2)	32(1)	55(2)	-3(1)	28(2)	3(1)
C(15C)	78(2)	27(1)	61(2)	-7(1)	30(2)	-4(1)
C(16C)	72(2)	47(2)	51(2)	-3(2)	26(2)	-29(2)
C(17C)	46(2)	61(2)	44(2)	-4(2)	23(2)	-16(1)

C(18C)	48(2)	36(1)	49(2)	-6(1)	32(2)	-5(1)
O(1C)	42(1)	29(1)	45(1)	2(1)	18(1)	-1(1)
O(2C)	35(1)	59(1)	46(1)	7(1)	23(1)	6(1)
O(3C)	71(2)	31(1)	72(2)	17(1)	39(1)	15(1)
O(4C)	45(1)	46(1)	58(1)	16(1)	32(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **84**.

	x	y	z	U(eq)
H(1A)	6408	158	1549	45
H(1B)	5003	166	1142	45
H(2A)	5082	87	3061	42
H(2B)	5854	-243	2784	42
H(3A)	7601	87	3746	37
H(4A)	6204	105	5205	41
H(5A)	8682	230	6122	49
H(5B)	7701	399	6587	49
H(7A)	6090	670	4027	37
H(9A)	5897	1261	3040	73
H(9B)	6443	1324	2045	73
H(9C)	7272	1346	3385	73
H(10A)	7798	857	1736	66
H(10B)	7972	450	2353	66
H(10C)	8609	816	3077	66
H(12A)	5227	1183	6489	95
H(12B)	5832	1501	5953	95
H(12C)	6547	1316	7193	95
H(14A)	5748	-500	5622	51
H(15A)	6157	-1141	6026	57
H(16A)	7916	-1400	6011	55
H(17A)	9294	-1008	5634	51
H(18A)	8884	-361	5245	46
H(2C)	9378	856	5667	63
H(1BA)	174	1514	-3741	51
H(1BB)	1552	1421	-3306	51
H(2BA)	308	1680	-1845	47
H(2BB)	1273	1921	-2165	47
H(3BA)	2766	1492	-1140	39

H(4BA)	1471	1762	239	42
H(5BA)	3461	1376	1639	46
H(5BB)	2125	1302	1543	46
H(7BA)	924	1079	-733	37
H(9BA)	298	480	-1645	75
H(9BB)	1577	291	-1255	75
H(9BC)	786	318	-2605	75
H(10D)	2430	623	-2947	76
H(10E)	3249	659	-1607	76
H(10F)	2898	1031	-2406	76
H(12D)	-81	424	1422	78
H(12E)	1229	323	2260	78
H(12F)	685	124	1013	78
H(14B)	1979	2407	638	55
H(15B)	3300	2918	925	66
H(16B)	5167	2812	871	60
H(17B)	5767	2200	621	54
H(18B)	4476	1694	363	45
H(2BC)	4193	823	869	62
H(1CA)	9178	1930	3394	48
H(1CB)	10553	1832	3873	48
H(2CA)	9475	1421	2292	49
H(2CB)	10475	1653	2003	49
H(3CA)	8015	1849	1199	39
H(4CA)	9421	1593	-92	43
H(5CA)	7376	1959	-1520	48
H(5CB)	8702	2029	-1465	48
H(7CA)	9913	2257	880	38
H(9CA)	9861	3044	2644	72
H(9CB)	9286	3029	1256	72
H(9CC)	10573	2858	1904	72
H(10G)	8342	2724	3026	72

H(10H)	7881	2314	2497	72
H(10I)	7539	2683	1683	72
H(12G)	11040	2887	-1262	91
H(12H)	10218	3198	-977	91
H(12I)	9745	2966	-2173	91
H(14C)	9030	952	-583	52
H(15C)	7786	421	-1022	65
H(16C)	5878	472	-1035	67
H(17C)	5163	1061	-690	58
H(18C)	6381	1591	-292	48
H(2CC)	6676	2520	-846	66

Table 6. Torsion angles [°] for **84**.

O(1)-C(1)-C(2)-C(3)	-54.1(3)
C(1)-C(2)-C(3)-C(4)	169.13(19)
C(1)-C(2)-C(3)-C(7)	52.9(2)
C(2)-C(3)-C(4)-C(13)	72.6(3)
C(7)-C(3)-C(4)-C(13)	-167.5(2)
C(2)-C(3)-C(4)-C(5)	-161.6(2)
C(7)-C(3)-C(4)-C(5)	-41.7(2)
C(13)-C(4)-C(5)-C(6)	152.1(2)
C(3)-C(4)-C(5)-C(6)	26.9(2)
C(4)-C(5)-C(6)-O(2)	-120.6(2)
C(4)-C(5)-C(6)-C(11)	117.5(2)
C(4)-C(5)-C(6)-C(7)	-1.7(2)
C(2)-C(3)-C(7)-C(8)	-57.5(3)
C(4)-C(3)-C(7)-C(8)	177.0(2)
C(2)-C(3)-C(7)-C(6)	167.14(18)
C(4)-C(3)-C(7)-C(6)	41.6(2)
O(2)-C(6)-C(7)-C(3)	94.7(2)
C(11)-C(6)-C(7)-C(3)	-143.27(19)
C(5)-C(6)-C(7)-C(3)	-24.3(2)
O(2)-C(6)-C(7)-C(8)	-35.4(3)
C(11)-C(6)-C(7)-C(8)	86.6(3)
C(5)-C(6)-C(7)-C(8)	-154.4(2)
C(3)-C(7)-C(8)-O(1)	57.5(3)
C(6)-C(7)-C(8)-O(1)	-175.89(19)
C(3)-C(7)-C(8)-C(9)	169.6(2)
C(6)-C(7)-C(8)-C(9)	-63.8(3)
C(3)-C(7)-C(8)-C(10)	-63.1(3)
C(6)-C(7)-C(8)-C(10)	63.5(3)
O(2)-C(6)-C(11)-O(3)	0.4(4)
C(7)-C(6)-C(11)-O(3)	-122.3(3)
C(5)-C(6)-C(11)-O(3)	123.1(3)

O(2)-C(6)-C(11)-O(4)	-177.8(2)
C(7)-C(6)-C(11)-O(4)	59.5(3)
C(5)-C(6)-C(11)-O(4)	-55.1(3)
C(3)-C(4)-C(13)-C(18)	62.6(4)
C(5)-C(4)-C(13)-C(18)	-56.3(4)
C(3)-C(4)-C(13)-C(14)	-115.4(3)
C(5)-C(4)-C(13)-C(14)	125.7(3)
C(18)-C(13)-C(14)-C(15)	0.5(5)
C(4)-C(13)-C(14)-C(15)	178.6(3)
C(13)-C(14)-C(15)-C(16)	-0.8(5)
C(14)-C(15)-C(16)-C(17)	0.8(5)
C(15)-C(16)-C(17)-C(18)	-0.5(5)
C(14)-C(13)-C(18)-C(17)	-0.2(5)
C(4)-C(13)-C(18)-C(17)	-178.2(3)
C(16)-C(17)-C(18)-C(13)	0.2(5)
C(2)-C(1)-O(1)-C(8)	59.9(3)
C(9)-C(8)-O(1)-C(1)	-176.5(2)
C(10)-C(8)-O(1)-C(1)	65.5(3)
C(7)-C(8)-O(1)-C(1)	-59.0(2)
O(3)-C(11)-O(4)-C(12)	-1.0(5)
C(6)-C(11)-O(4)-C(12)	177.3(3)
O(1B)-C(1B)-C(2B)-C(3B)	54.6(3)
C(1B)-C(2B)-C(3B)-C(7B)	-53.9(3)
C(1B)-C(2B)-C(3B)-C(4B)	-172.2(2)
C(2B)-C(3B)-C(4B)-C(13B)	-86.8(3)
C(7B)-C(3B)-C(4B)-C(13B)	152.2(2)
C(2B)-C(3B)-C(4B)-C(5B)	148.2(2)
C(7B)-C(3B)-C(4B)-C(5B)	27.3(2)
C(13B)-C(4B)-C(5B)-C(6B)	-125.5(2)
C(3B)-C(4B)-C(5B)-C(6B)	-1.9(3)
C(4B)-C(5B)-C(6B)-O(2B)	91.8(3)
C(4B)-C(5B)-C(6B)-C(11B)	-144.9(2)

C(4B)-C(5B)-C(6B)-C(7B)	-23.7(2)
C(2B)-C(3B)-C(7B)-C(8B)	58.0(3)
C(4B)-C(3B)-C(7B)-C(8B)	-175.9(2)
C(2B)-C(3B)-C(7B)-C(6B)	-168.90(19)
C(4B)-C(3B)-C(7B)-C(6B)	-42.8(2)
O(2B)-C(6B)-C(7B)-C(3B)	-77.0(2)
C(11B)-C(6B)-C(7B)-C(3B)	160.15(19)
C(5B)-C(6B)-C(7B)-C(3B)	40.5(2)
O(2B)-C(6B)-C(7B)-C(8B)	50.5(3)
C(11B)-C(6B)-C(7B)-C(8B)	-72.3(3)
C(5B)-C(6B)-C(7B)-C(8B)	168.0(2)
C(3B)-C(7B)-C(8B)-O(1B)	-57.0(3)
C(6B)-C(7B)-C(8B)-O(1B)	179.97(19)
C(3B)-C(7B)-C(8B)-C(9B)	-169.0(2)
C(6B)-C(7B)-C(8B)-C(9B)	68.0(3)
C(3B)-C(7B)-C(8B)-C(10B)	64.4(3)
C(6B)-C(7B)-C(8B)-C(10B)	-58.7(3)
O(2B)-C(6B)-C(11B)-O(3B)	6.8(4)
C(7B)-C(6B)-C(11B)-O(3B)	128.6(3)
C(5B)-C(6B)-C(11B)-O(3B)	-116.9(3)
O(2B)-C(6B)-C(11B)-O(4B)	-174.4(2)
C(7B)-C(6B)-C(11B)-O(4B)	-52.5(3)
C(5B)-C(6B)-C(11B)-O(4B)	61.9(3)
C(3B)-C(4B)-C(13B)-C(14B)	117.7(3)
C(5B)-C(4B)-C(13B)-C(14B)	-123.0(3)
C(3B)-C(4B)-C(13B)-C(18B)	-59.6(4)
C(5B)-C(4B)-C(13B)-C(18B)	59.8(3)
C(18B)-C(13B)-C(14B)-C(15B)	0.5(5)
C(4B)-C(13B)-C(14B)-C(15B)	-176.8(3)
C(13B)-C(14B)-C(15B)-C(16B)	0.7(5)
C(14B)-C(15B)-C(16B)-C(17B)	-1.5(5)
C(15B)-C(16B)-C(17B)-C(18B)	1.1(5)

C(16B)-C(17B)-C(18B)-C(13B)	0.2(5)
C(14B)-C(13B)-C(18B)-C(17B)	-1.0(5)
C(4B)-C(13B)-C(18B)-C(17B)	176.4(3)
C(2B)-C(1B)-O(1B)-C(8B)	-59.4(3)
C(9B)-C(8B)-O(1B)-C(1B)	175.9(2)
C(10B)-C(8B)-O(1B)-C(1B)	-67.0(3)
C(7B)-C(8B)-O(1B)-C(1B)	58.2(3)
O(3B)-C(11B)-O(4B)-C(12B)	-0.4(4)
C(6B)-C(11B)-O(4B)-C(12B)	-179.2(2)
O(1C)-C(1C)-C(2C)-C(3C)	-54.3(3)
C(1C)-C(2C)-C(3C)-C(7C)	52.9(3)
C(1C)-C(2C)-C(3C)-C(4C)	170.3(2)
C(2C)-C(3C)-C(4C)-C(13C)	83.8(3)
C(7C)-C(3C)-C(4C)-C(13C)	-155.9(2)
C(2C)-C(3C)-C(4C)-C(5C)	-150.7(2)
C(7C)-C(3C)-C(4C)-C(5C)	-30.4(3)
C(13C)-C(4C)-C(5C)-C(6C)	131.9(2)
C(3C)-C(4C)-C(5C)-C(6C)	6.4(3)
C(4C)-C(5C)-C(6C)-O(2C)	-96.4(3)
C(4C)-C(5C)-C(6C)-C(11C)	142.4(2)
C(4C)-C(5C)-C(6C)-C(7C)	19.7(3)
C(2C)-C(3C)-C(7C)-C(6C)	168.81(19)
C(4C)-C(3C)-C(7C)-C(6C)	43.4(2)
C(2C)-C(3C)-C(7C)-C(8C)	-57.7(3)
C(4C)-C(3C)-C(7C)-C(8C)	176.9(2)
O(2C)-C(6C)-C(7C)-C(3C)	79.1(2)
C(11C)-C(6C)-C(7C)-C(3C)	-158.11(19)
C(5C)-C(6C)-C(7C)-C(3C)	-38.6(2)
O(2C)-C(6C)-C(7C)-C(8C)	-48.8(3)
C(11C)-C(6C)-C(7C)-C(8C)	74.0(3)
C(5C)-C(6C)-C(7C)-C(8C)	-166.5(2)
C(3C)-C(7C)-C(8C)-O(1C)	57.8(3)

C(6C)-C(7C)-C(8C)-O(1C)	-178.60(19)
C(3C)-C(7C)-C(8C)-C(9C)	169.8(2)
C(6C)-C(7C)-C(8C)-C(9C)	-66.7(3)
C(3C)-C(7C)-C(8C)-C(10C)	-63.5(3)
C(6C)-C(7C)-C(8C)-C(10C)	60.1(3)
O(2C)-C(6C)-C(11C)-O(3C)	-9.7(4)
C(7C)-C(6C)-C(11C)-O(3C)	-132.0(3)
C(5C)-C(6C)-C(11C)-O(3C)	112.4(3)
O(2C)-C(6C)-C(11C)-O(4C)	172.3(2)
C(7C)-C(6C)-C(11C)-O(4C)	49.9(3)
C(5C)-C(6C)-C(11C)-O(4C)	-65.6(3)
C(3C)-C(4C)-C(13C)-C(14C)	-121.1(3)
C(5C)-C(4C)-C(13C)-C(14C)	118.5(3)
C(3C)-C(4C)-C(13C)-C(18C)	58.5(4)
C(5C)-C(4C)-C(13C)-C(18C)	-61.9(3)
C(18C)-C(13C)-C(14C)-C(15C)	-0.1(5)
C(4C)-C(13C)-C(14C)-C(15C)	179.6(3)
C(13C)-C(14C)-C(15C)-C(16C)	-1.0(5)
C(14C)-C(15C)-C(16C)-C(17C)	1.4(5)
C(15C)-C(16C)-C(17C)-C(18C)	-0.7(5)
C(16C)-C(17C)-C(18C)-C(13C)	-0.4(5)
C(14C)-C(13C)-C(18C)-C(17C)	0.8(5)
C(4C)-C(13C)-C(18C)-C(17C)	-178.9(3)
C(2C)-C(1C)-O(1C)-C(8C)	60.6(3)
C(9C)-C(8C)-O(1C)-C(1C)	-176.5(2)
C(10C)-C(8C)-O(1C)-C(1C)	66.2(3)
C(7C)-C(8C)-O(1C)-C(1C)	-59.6(3)
O(3C)-C(11C)-O(4C)-C(12C)	-0.9(4)
C(6C)-C(11C)-O(4C)-C(12C)	177.2(3)

Table 7. Hydrogen bonds for **84** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2C)...O(1B)#1	0.84	1.98	2.817(3)	175.7
O(2B)-H(2BC)...O(1)	0.84	1.99	2.776(3)	154.5
O(2C)-H(2CC)...O(1C)#2	0.84	1.98	2.771(3)	157.2

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z+1 #2 x-1/2,-y+1/2,z-1/2

3.122

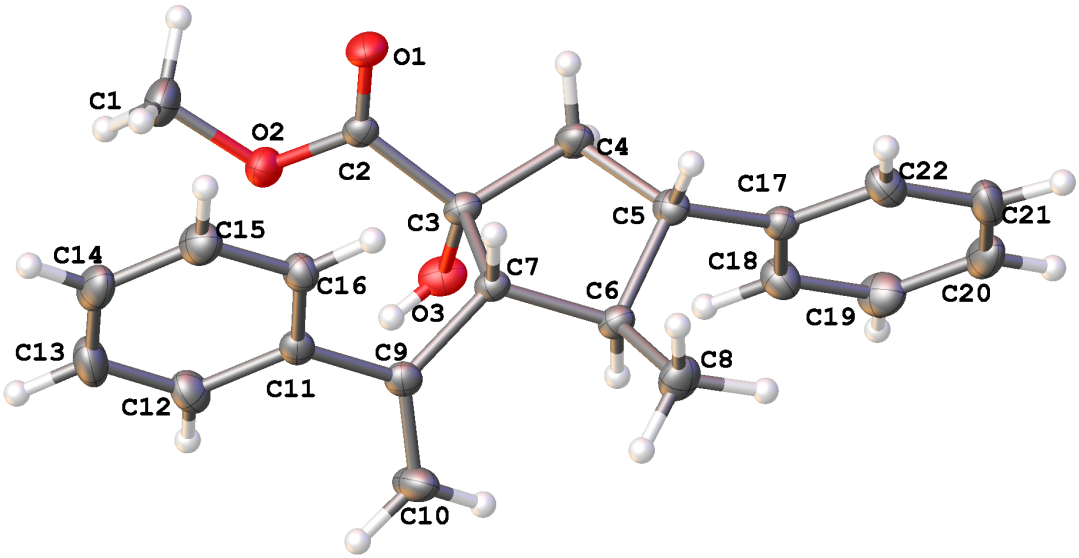


Table 1. Crystal data and structure refinement for **122**.

Identification code	**122**	
Empirical formula	C22 H24 O3	
Formula weight	336.41	
Temperature	173.19 K	
Wavelength	0.71073 ≈	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.7838(17) ≈	a= 90∞.
	b = 10.543(2) ≈	b= 90∞.
	c = 21.905(5) ≈	g = 90∞.
Volume	1797.6(7) $\approx^3$	
Z	4	
Density (calculated)	1.243 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	720	
Crystal size	0.55 x 0.329 x 0.226 mm^3	
Theta range for data collection	1.86 to 28.24∞.	

Index ranges	-10<=h<=10, -13<=k<=14, -25<=l<=29
Reflections collected	13258
Independent reflections	4424 [R(int) = 0.0309]
Completeness to theta = 28.24∞	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.6657
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4424 / 0 / 322
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.0930
R indices (all data)	R1 = 0.0422, wR2 = 0.0955
Absolute structure parameter	-0.2(8)
Largest diff. peak and hole	0.280 and -0.209 e.≈$^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (≈^{2}x 10^3) for **122**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-1953(1)	-2987(1)	-79(1)	26(1)
O(2)	-940(1)	-4544(1)	-680(1)	24(1)
O(3)	-2443(1)	-6350(1)	-75(1)	25(1)
C(16)	-5075(2)	-3051(1)	-1229(1)	22(1)
C(6)	-5963(2)	-5666(1)	312(1)	18(1)
C(2)	-1918(2)	-4088(1)	-232(1)	18(1)
C(11)	-4710(2)	-4337(1)	-1310(1)	19(1)
C(8)	-7896(2)	-5444(2)	297(1)	28(1)
C(5)	-5119(2)	-5207(1)	909(1)	19(1)
C(9)	-5163(2)	-5304(1)	-837(1)	19(1)
C(15)	-4634(2)	-2164(2)	-1674(1)	28(1)
C(17)	-5450(2)	-6084(1)	1443(1)	19(1)
C(4)	-3194(2)	-4997(1)	748(1)	23(1)
C(18)	-4830(2)	-7330(1)	1444(1)	25(1)
C(10)	-5646(2)	-6474(2)	-995(1)	30(1)
C(7)	-4947(2)	-4930(1)	-173(1)	16(1)
C(14)	-3810(2)	-2547(2)	-2202(1)	31(1)
C(22)	-6416(2)	-5684(1)	1940(1)	26(1)
C(3)	-3050(2)	-5111(1)	51(1)	18(1)
C(13)	-3425(2)	-3823(2)	-2287(1)	34(1)
C(12)	-3882(2)	-4706(2)	-1849(1)	26(1)
C(21)	-6769(2)	-6492(2)	2425(1)	32(1)
C(19)	-5158(2)	-8133(1)	1931(1)	31(1)
C(1)	106(2)	-3623(2)	-994(1)	36(1)
C(20)	-6127(2)	-7714(2)	2422(1)	32(1)

Table 3. Bond lengths [≈] and angles [∞] for **122**.

O(1)-C(2)	1.2078(16)
O(2)-C(1)	1.442(2)
O(2)-C(2)	1.3316(16)
O(3)-C(3)	1.4166(16)
O(3)-H(3)	0.78(2)
C(2)-C(3)	1.5249(18)
C(3)-C(7)	1.5679(18)
C(3)-C(4)	1.5360(19)
C(4)-C(5)	1.555(2)
C(5)-C(6)	1.5417(19)
C(5)-C(17)	1.5135(19)
C(6)-C(7)	1.5353(18)
C(6)-C(8)	1.5226(19)
C(7)-C(9)	1.5155(19)
C(9)-C(11)	1.4965(19)
C(9)-C(10)	1.335(2)
C(11)-C(12)	1.400(2)
C(11)-C(16)	1.397(2)
C(12)-C(13)	1.383(2)
C(13)-C(14)	1.391(3)
C(14)-C(15)	1.382(2)
C(15)-C(16)	1.394(2)
C(17)-C(22)	1.388(2)
C(17)-C(18)	1.3994(19)
C(18)-C(19)	1.386(2)
C(19)-C(20)	1.385(2)
C(20)-C(21)	1.382(2)
C(21)-C(22)	1.390(2)
C(1)-H(1A)	0.95(3)
C(1)-H(1B)	1.01(2)
C(1)-H(1C)	1.00(2)
C(4)-H(4A)	0.956(18)

C(4)-H(4B)	0.960(17)
C(5)-H(5)	1.014(18)
C(6)-H(6)	0.976(15)
C(7)-H(7)	0.961(15)
C(8)-H(8A)	1.000(19)
C(8)-H(8B)	0.98(2)
C(8)-H(8C)	1.06(2)
C(10)-H(10A)	0.971(18)
C(10)-H(10B)	0.961(17)
C(12)-H(12)	0.979(19)
C(13)-H(13)	0.97(2)
C(14)-H(14)	0.952(19)
C(15)-H(15)	1.00(2)
C(16)-H(16)	0.952(16)
C(18)-H(18)	1.019(17)
C(19)-H(19)	0.97(2)
C(20)-H(20)	0.96(2)
C(21)-H(21)	0.98(2)
C(22)-H(22)	0.989(18)

C(1)-O(2)-C(2)	115.52(11)
C(3)-O(3)-H(3)	106.7(16)
O(1)-C(2)-C(3)	123.62(12)
O(2)-C(2)-C(3)	111.97(10)
O(1)-C(2)-O(2)	124.37(12)
O(3)-C(3)-C(2)	112.33(10)
O(3)-C(3)-C(7)	111.43(10)
C(2)-C(3)-C(4)	113.03(11)
O(3)-C(3)-C(4)	106.91(11)
C(4)-C(3)-C(7)	103.50(10)
C(2)-C(3)-C(7)	109.30(10)
C(3)-C(4)-C(5)	106.48(11)
C(4)-C(5)-C(17)	115.17(11)

C(6)-C(5)-C(17)	113.07(11)
C(4)-C(5)-C(6)	105.30(10)
C(5)-C(6)-C(8)	113.00(11)
C(7)-C(6)-C(8)	114.62(11)
C(5)-C(6)-C(7)	102.02(10)
C(3)-C(7)-C(9)	111.95(10)
C(6)-C(7)-C(9)	118.31(10)
C(3)-C(7)-C(6)	101.93(10)
C(7)-C(9)-C(10)	121.40(12)
C(10)-C(9)-C(11)	121.04(12)
C(7)-C(9)-C(11)	117.45(11)
C(9)-C(11)-C(12)	120.26(12)
C(12)-C(11)-C(16)	118.06(13)
C(9)-C(11)-C(16)	121.68(12)
C(11)-C(12)-C(13)	121.08(15)
C(12)-C(13)-C(14)	120.19(14)
C(13)-C(14)-C(15)	119.61(15)
C(14)-C(15)-C(16)	120.27(14)
C(11)-C(16)-C(15)	120.79(13)
C(5)-C(17)-C(18)	121.08(12)
C(18)-C(17)-C(22)	118.04(13)
C(5)-C(17)-C(22)	120.86(12)
C(17)-C(18)-C(19)	120.75(14)
C(18)-C(19)-C(20)	120.19(14)
C(19)-C(20)-C(21)	119.90(14)
C(20)-C(21)-C(22)	119.68(14)
C(17)-C(22)-C(21)	121.43(14)
O(2)-C(1)-H(1A)	107.7(17)
O(2)-C(1)-H(1B)	102.7(12)
O(2)-C(1)-H(1C)	109.4(12)
H(1A)-C(1)-H(1B)	114(2)
H(1A)-C(1)-H(1C)	111.9(19)
H(1B)-C(1)-H(1C)	111.0(18)

C(3)-C(4)-H(4A)	111.2(10)
C(3)-C(4)-H(4B)	108.1(10)
C(5)-C(4)-H(4A)	111.0(10)
C(5)-C(4)-H(4B)	112.0(10)
H(4A)-C(4)-H(4B)	108.2(14)
C(4)-C(5)-H(5)	108.3(9)
C(6)-C(5)-H(5)	106.6(9)
C(17)-C(5)-H(5)	108.0(9)
C(5)-C(6)-H(6)	109.0(9)
C(7)-C(6)-H(6)	109.5(9)
C(8)-C(6)-H(6)	108.4(9)
C(3)-C(7)-H(7)	106.0(9)
C(6)-C(7)-H(7)	108.0(9)
C(9)-C(7)-H(7)	109.8(9)
C(6)-C(8)-H(8A)	109.7(9)
C(6)-C(8)-H(8B)	110.5(13)
C(6)-C(8)-H(8C)	107.0(13)
H(8A)-C(8)-H(8B)	107.6(15)
H(8A)-C(8)-H(8C)	109.4(15)
H(8B)-C(8)-H(8C)	112.7(17)
C(9)-C(10)-H(10A)	121.6(11)
C(9)-C(10)-H(10B)	120.0(10)
H(10A)-C(10)-H(10B)	118.4(15)
C(11)-C(12)-H(12)	117.6(10)
C(13)-C(12)-H(12)	121.1(10)
C(12)-C(13)-H(13)	120.4(13)
C(14)-C(13)-H(13)	119.4(13)
C(13)-C(14)-H(14)	122.0(12)
C(15)-C(14)-H(14)	118.3(12)
C(14)-C(15)-H(15)	120.4(12)
C(16)-C(15)-H(15)	119.3(12)
C(11)-C(16)-H(16)	119.5(10)
C(15)-C(16)-H(16)	119.7(10)

C(17)-C(18)-H(18)	119.8(10)
C(19)-C(18)-H(18)	119.5(10)
C(18)-C(19)-H(19)	118.5(12)
C(20)-C(19)-H(19)	121.3(12)
C(19)-C(20)-H(20)	117.7(12)
C(21)-C(20)-H(20)	122.4(12)
C(20)-C(21)-H(21)	118.2(12)
C(22)-C(21)-H(21)	122.0(12)
C(17)-C(22)-H(22)	117.7(10)
C(21)-C(22)-H(22)	120.8(10)

Table 4. Anisotropic displacement parameters ($\approx^2$x 10^3) for **122**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	30(1)	19(1)	28(1)	-3(1)	2(1)	-7(1)
O(2)	21(1)	26(1)	25(1)	-2(1)	3(1)	-2(1)
O(3)	25(1)	17(1)	33(1)	2(1)	-6(1)	3(1)
C(16)	23(1)	25(1)	18(1)	1(1)	0(1)	0(1)
C(6)	17(1)	18(1)	20(1)	3(1)	-3(1)	-3(1)
C(2)	15(1)	20(1)	17(1)	1(1)	-4(1)	-2(1)
C(11)	15(1)	24(1)	17(1)	1(1)	-3(1)	-1(1)
C(8)	19(1)	35(1)	30(1)	4(1)	-1(1)	-2(1)
C(5)	22(1)	17(1)	19(1)	2(1)	-1(1)	0(1)
C(9)	16(1)	22(1)	19(1)	0(1)	-3(1)	0(1)
C(15)	32(1)	27(1)	26(1)	5(1)	-2(1)	-3(1)
C(17)	19(1)	21(1)	18(1)	0(1)	-2(1)	-2(1)
C(4)	21(1)	28(1)	20(1)	2(1)	-5(1)	-6(1)
C(18)	29(1)	24(1)	21(1)	0(1)	0(1)	2(1)
C(10)	41(1)	27(1)	23(1)	0(1)	-7(1)	-10(1)
C(7)	16(1)	16(1)	18(1)	1(1)	-3(1)	-1(1)
C(14)	32(1)	40(1)	22(1)	9(1)	-2(1)	-10(1)
C(22)	25(1)	30(1)	22(1)	-4(1)	0(1)	3(1)
C(3)	17(1)	16(1)	21(1)	2(1)	-3(1)	-2(1)
C(13)	32(1)	48(1)	20(1)	-1(1)	7(1)	-3(1)
C(12)	25(1)	31(1)	23(1)	-4(1)	2(1)	3(1)
C(21)	28(1)	48(1)	19(1)	-2(1)	3(1)	-6(1)
C(19)	38(1)	24(1)	30(1)	7(1)	-6(1)	-3(1)
C(1)	34(1)	41(1)	32(1)	0(1)	12(1)	-11(1)
C(20)	35(1)	40(1)	22(1)	10(1)	-4(1)	-14(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\approx^2$x 10^3) for **122**.

	x	y	z	U(eq)
H(7)	-5200(20)	-4043(14)	-124(7)	16(4)
H(16)	-5620(20)	-2777(15)	-863(7)	16(4)
H(4A)	-2810(20)	-4185(17)	886(8)	23(4)
H(8A)	-8140(20)	-4516(18)	331(8)	35(5)
H(6)	-5750(20)	-6573(14)	264(7)	17(4)
H(8B)	-8380(30)	-5739(18)	-91(9)	40(5)
H(8C)	-8420(30)	-5920(20)	677(9)	45(5)
H(12)	-3560(20)	-5599(18)	-1891(8)	29(4)
H(20)	-6310(30)	-8292(18)	2753(9)	38(5)
H(22)	-6870(20)	-4808(17)	1933(8)	31(4)
H(14)	-3510(30)	-1918(18)	-2495(8)	32(5)
H(15)	-4870(30)	-1246(19)	-1599(9)	40(5)
H(19)	-4660(30)	-8972(19)	1926(9)	40(5)
H(21)	-7520(30)	-6240(20)	2762(10)	46(6)
H(5)	-5650(20)	-4353(17)	1007(7)	24(4)
H(1A)	-630(40)	-3130(20)	-1245(12)	72(8)
H(10A)	-5890(30)	-7119(18)	-691(8)	36(5)
H(1B)	930(30)	-4170(20)	-1231(10)	52(6)
H(1C)	730(30)	-3090(20)	-688(10)	51(6)
H(10B)	-5750(20)	-6696(15)	-1419(8)	30(5)
H(13)	-2860(30)	-4090(20)	-2662(10)	54(7)
H(18)	-4110(20)	-7647(17)	1087(8)	32(5)
H(4B)	-2470(20)	-5633(17)	928(8)	23(4)
H(3)	-2500(30)	-6440(20)	-428(11)	46(7)

Table 6. Torsion angles [∞] for **122**.

C(1)-O(2)-C(2)-O(1)	-0.80(19)
C(1)-O(2)-C(2)-C(3)	176.85(11)
O(1)-C(2)-C(3)-O(3)	-163.17(13)
O(1)-C(2)-C(3)-C(4)	-42.09(17)
O(1)-C(2)-C(3)-C(7)	72.60(16)
O(2)-C(2)-C(3)-O(3)	19.16(15)
O(2)-C(2)-C(3)-C(4)	140.24(11)
O(2)-C(2)-C(3)-C(7)	-105.07(12)
O(3)-C(3)-C(4)-C(5)	-99.53(12)
C(2)-C(3)-C(4)-C(5)	136.36(11)
C(7)-C(3)-C(4)-C(5)	18.23(13)
O(3)-C(3)-C(7)-C(6)	75.06(12)
O(3)-C(3)-C(7)-C(9)	-52.37(14)
C(2)-C(3)-C(7)-C(6)	-160.20(10)
C(2)-C(3)-C(7)-C(9)	72.38(12)
C(4)-C(3)-C(7)-C(6)	-39.50(12)
C(4)-C(3)-C(7)-C(9)	-166.92(10)
C(3)-C(4)-C(5)-C(6)	9.66(13)
C(3)-C(4)-C(5)-C(17)	134.92(11)
C(4)-C(5)-C(6)-C(7)	-34.25(12)
C(4)-C(5)-C(6)-C(8)	-157.84(11)
C(17)-C(5)-C(6)-C(7)	-160.81(10)
C(17)-C(5)-C(6)-C(8)	75.60(14)
C(4)-C(5)-C(17)-C(18)	-57.40(17)
C(4)-C(5)-C(17)-C(22)	124.31(14)
C(6)-C(5)-C(17)-C(18)	63.73(16)
C(6)-C(5)-C(17)-C(22)	-114.55(14)
C(5)-C(6)-C(7)-C(3)	45.38(11)
C(5)-C(6)-C(7)-C(9)	168.59(10)
C(8)-C(6)-C(7)-C(3)	167.87(11)
C(8)-C(6)-C(7)-C(9)	-68.92(15)
C(3)-C(7)-C(9)-C(10)	92.84(15)

C(3)-C(7)-C(9)-C(11)	-83.44(13)
C(6)-C(7)-C(9)-C(10)	-25.20(18)
C(6)-C(7)-C(9)-C(11)	158.51(11)
C(7)-C(9)-C(11)-C(12)	141.25(13)
C(7)-C(9)-C(11)-C(16)	-38.09(17)
C(10)-C(9)-C(11)-C(12)	-35.04(19)
C(10)-C(9)-C(11)-C(16)	145.61(14)
C(9)-C(11)-C(12)-C(13)	-178.80(13)
C(16)-C(11)-C(12)-C(13)	0.6(2)
C(9)-C(11)-C(16)-C(15)	179.67(13)
C(12)-C(11)-C(16)-C(15)	0.3(2)
C(11)-C(12)-C(13)-C(14)	-1.1(2)
C(12)-C(13)-C(14)-C(15)	0.8(2)
C(13)-C(14)-C(15)-C(16)	0.1(2)
C(14)-C(15)-C(16)-C(11)	-0.7(2)
C(5)-C(17)-C(18)-C(19)	-179.10(13)
C(22)-C(17)-C(18)-C(19)	-0.8(2)
C(5)-C(17)-C(22)-C(21)	178.20(13)
C(18)-C(17)-C(22)-C(21)	-0.1(2)
C(17)-C(18)-C(19)-C(20)	0.8(2)
C(18)-C(19)-C(20)-C(21)	0.0(2)
C(19)-C(20)-C(21)-C(22)	-0.9(2)
C(20)-C(21)-C(22)-C(17)	1.0(2)

Table 7. Hydrogen bonds for **122** [≈ and ∞].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(4A)...O(1)	0.956(18)	2.551(18)	2.9512(19)	105.3(12)
C(6)-H(6)...O(3)#1	0.976(15)	2.589(15)	3.3898(18)	139.4(12)
C(7)-H(7)...O(1)#2	0.961(15)	2.577(15)	3.4929(17)	159.3(12)
C(16)-H(16)...O(1)#2	0.952(16)	2.447(15)	3.3984(19)	178.1(10)

Symmetry transformations used to generate equivalent atoms:

#1+1 #2+1

4.85

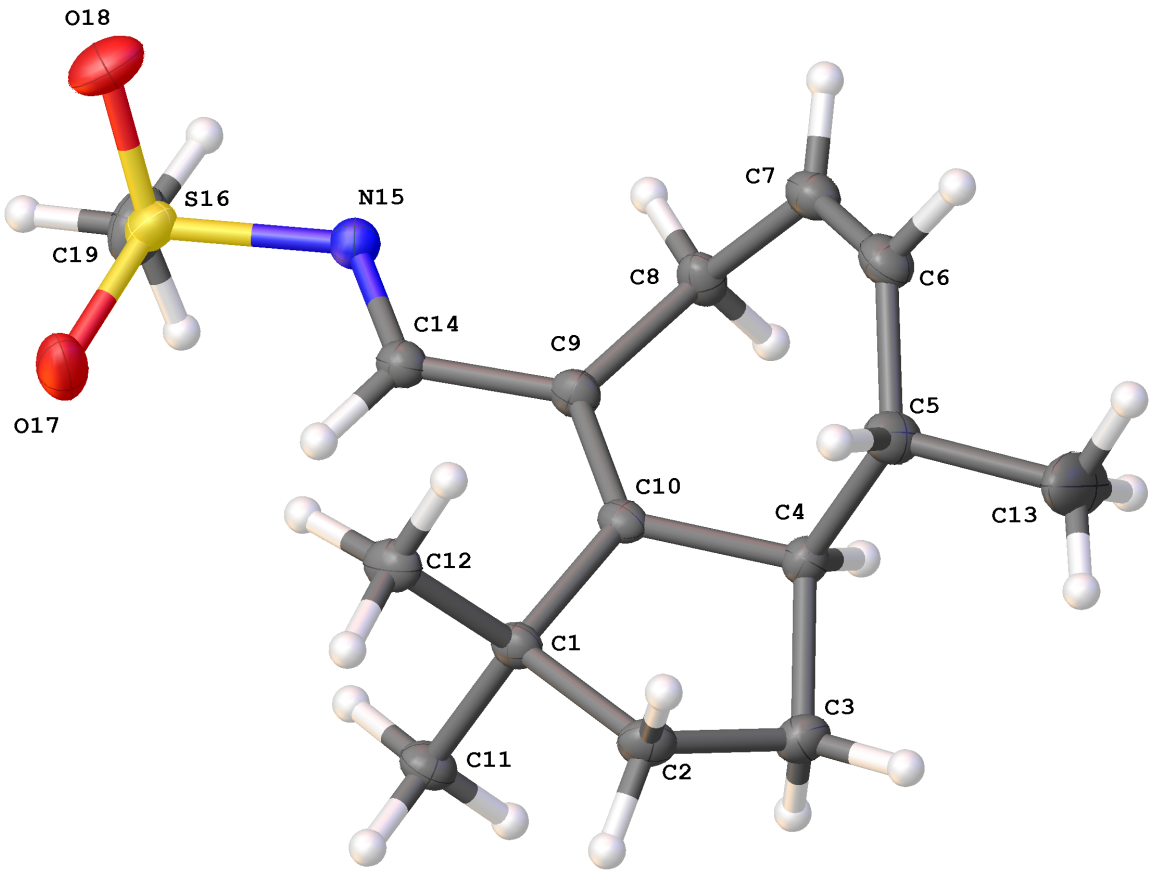


Table 1. Crystal data and structure refinement for **85**.

Identification code	**85**	
Empirical formula	C15 H23 N O2 S	
Formula weight	281.40	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.1456(5) Å	α= 90°.
	b = 13.3051(10) Å	β= 90°.
	c = 18.6922(14) Å	γ = 90°.
Volume	1528.4(2) Å3	
Z	4	
Density (calculated)	1.223 Mg/m3	

Absorption coefficient	0.210 mm-1
F(000)	608
Crystal size	0.494 x 0.189 x 0.156 mm3
Theta range for data collection	1.879 to 31.502°.
Index ranges	-7<=h<=9, -19<=k<=19, -27<=l<=27
Reflections collected	13829
Independent reflections	4851 [R(int) = 0.0350]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7462 and 0.5885
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	4851 / 8 / 216
Goodness-of-fit on F2	1.061
Final R indices [I>2sigma(I)]	R1 = 0.0508, wR2 = 0.1208
R indices (all data)	R1 = 0.0590, wR2 = 0.1268
Absolute structure parameter	0.04(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.757 and -0.275 e.Å-3

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103) for **85**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(16)	747(1)	4314(1)	4563(1)	20(1)
O(17)	383(4)	5364(1)	4424(1)	34(1)
N(15)	2230(3)	4129(1)	5302(1)	19(1)
O(18)	1747(4)	3720(2)	4014(1)	34(1)
C(9)	4413(4)	4871(2)	6226(1)	16(1)
C(6)	8767(4)	4130(2)	6874(1)	22(1)
C(10)	5294(3)	5711(2)	6517(1)	15(1)
C(1)	5251(4)	6798(2)	6242(1)	16(1)
C(14)	3072(4)	4919(2)	5585(1)	18(1)
C(4)	6485(4)	5660(2)	7231(1)	17(1)
C(3)	6530(4)	6767(2)	7474(1)	22(1)
C(2)	6774(4)	7348(2)	6772(1)	20(1)
C(8)	4764(4)	3854(2)	6571(1)	19(1)
C(7)	7132(4)	3565(2)	6652(1)	21(1)
C(5)	8783(4)	5193(2)	7156(1)	22(1)
C(12)	6138(4)	6922(2)	5477(1)	21(1)
C(11)	2958(4)	7255(2)	6302(1)	21(1)
C(19)	-1735(5)	3753(2)	4805(2)	32(1)
C(13)	9975(6)	5186(3)	7881(2)	47(1)

Table 3. Bond lengths [Å] and angles [°] for **85**.

S(16)-O(17)	1.4382(19)
S(16)-N(15)	1.673(2)
S(16)-O(18)	1.434(2)
S(16)-C(19)	1.758(3)
N(15)-C(14)	1.285(3)
C(9)-C(10)	1.356(3)
C(9)-C(14)	1.456(3)
C(9)-C(8)	1.514(3)
C(6)-C(7)	1.322(4)
C(6)-C(5)	1.510(3)
C(10)-C(1)	1.536(3)
C(10)-C(4)	1.523(3)
C(1)-C(2)	1.547(3)
C(1)-C(12)	1.539(3)
C(1)-C(11)	1.538(3)
C(4)-C(3)	1.541(3)
C(4)-C(5)	1.549(3)
C(3)-C(2)	1.531(3)
C(8)-C(7)	1.513(3)
C(5)-C(13)	1.541(4)

O(17)-S(16)-N(15)	112.15(10)
O(17)-S(16)-C(19)	108.93(15)
N(15)-S(16)-C(19)	101.38(12)
O(18)-S(16)-O(17)	118.19(13)
O(18)-S(16)-N(15)	106.05(12)
O(18)-S(16)-C(19)	108.78(14)
C(14)-N(15)-S(16)	116.03(16)
C(10)-C(9)-C(14)	121.36(19)
C(10)-C(9)-C(8)	120.6(2)
C(14)-C(9)-C(8)	118.06(18)
C(7)-C(6)-C(5)	130.4(2)

C(9)-C(10)-C(1)	129.41(19)
C(9)-C(10)-C(4)	120.43(19)
C(4)-C(10)-C(1)	110.15(18)
C(10)-C(1)-C(2)	102.68(17)
C(10)-C(1)-C(12)	113.97(17)
C(10)-C(1)-C(11)	111.27(18)
C(12)-C(1)-C(2)	109.30(19)
C(11)-C(1)-C(2)	108.69(18)
C(11)-C(1)-C(12)	110.54(19)
N(15)-C(14)-C(9)	122.1(2)
C(10)-C(4)-C(3)	102.97(18)
C(10)-C(4)-C(5)	112.14(18)
C(3)-C(4)-C(5)	113.18(19)
C(2)-C(3)-C(4)	103.35(17)
C(3)-C(2)-C(1)	104.58(18)
C(7)-C(8)-C(9)	114.04(19)
C(6)-C(7)-C(8)	128.1(2)
C(6)-C(5)-C(4)	113.7(2)
C(6)-C(5)-C(13)	107.8(2)
C(13)-C(5)-C(4)	110.9(2)

Table 4. Anisotropic displacement parameters (Å2x 103) for **85**. The anisotropic displacement factor exponent takes the form: -2π2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(16)	26(1)	18(1)	17(1)	-2(1)	-1(1)	-2(1)
O(17)	49(1)	21(1)	32(1)	3(1)	-19(1)	-1(1)
N(15)	20(1)	18(1)	19(1)	0(1)	-1(1)	-1(1)
O(18)	39(1)	36(1)	26(1)	-11(1)	7(1)	-3(1)
C(9)	17(1)	14(1)	18(1)	2(1)	1(1)	-2(1)
C(6)	18(1)	22(1)	25(1)	2(1)	2(1)	5(1)
C(10)	15(1)	15(1)	16(1)	1(1)	4(1)	2(1)
C(1)	18(1)	14(1)	18(1)	1(1)	2(1)	-1(1)
C(14)	18(1)	16(1)	18(1)	0(1)	2(1)	1(1)
C(4)	18(1)	18(1)	16(1)	0(1)	-1(1)	0(1)
C(3)	24(1)	20(1)	21(1)	-4(1)	-1(1)	0(1)
C(2)	22(1)	15(1)	24(1)	-3(1)	0(1)	-2(1)
C(8)	20(1)	15(1)	22(1)	3(1)	-2(1)	-2(1)
C(7)	22(1)	18(1)	22(1)	2(1)	3(1)	3(1)
C(5)	16(1)	23(1)	28(1)	-4(1)	-2(1)	1(1)
C(12)	23(1)	18(1)	22(1)	3(1)	5(1)	-2(1)
C(11)	18(1)	19(1)	26(1)	-1(1)	1(1)	4(1)
C(19)	23(1)	46(2)	26(1)	-1(1)	-3(1)	-10(1)
C(13)	41(2)	49(2)	50(2)	-22(2)	-28(2)	19(2)

Table 5. Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 10 3) for **85**.

	x	y	z	U(eq)
H(4)	5609	5255	7578	20
H(12A)	7524	6563	5433	31
H(12B)	6366	7637	5376	31
H(12C)	5089	6645	5134	31
H(11A)	1954	6882	5993	31
H(11B)	3000	7960	6153	31
H(11C)	2461	7213	6800	31
H(19A)	-2348	4105	5219	48
H(19B)	-1487	3046	4929	48
H(19C)	-2754	3794	4403	48
H(13A)	9074	4844	8238	70
H(13B)	10246	5879	8035	70
H(13C)	11365	4832	7831	70
H(2A)	8220(40)	7340(20)	6599(15)	19(7)
H(2B)	6360(50)	8031(15)	6803(14)	16(7)
H(3A)	7650(50)	6890(20)	7835(15)	29(8)
H(3B)	5150(40)	6915(19)	7704(13)	10(6)
H(5)	9650(50)	5610(20)	6813(16)	20(7)
H(7)	7480(60)	2909(17)	6493(18)	36(9)
H(6)	10180(40)	3800(20)	6908(15)	20(7)
H(8A)	4050(50)	3339(18)	6302(15)	24(8)
H(8B)	4090(50)	3860(20)	7045(12)	21(7)
H(14)	2720(50)	5569(16)	5377(13)	20(7)

Table 6. Torsion angles [°] for **85**.

S(16)-N(15)-C(14)-C(9)	-179.57(17)
O(17)-S(16)-N(15)-C(14)	-8.9(2)
O(18)-S(16)-N(15)-C(14)	121.48(19)
C(9)-C(10)-C(1)-C(2) -	173.4(2)
C(9)-C(10)-C(1)-C(12)	-55.4(3)
C(9)-C(10)-C(1)-C(11)	70.4(3)
C(9)-C(10)-C(4)-C(3)	-162.1(2)
C(9)-C(10)-C(4)-C(5)	75.9(3)
C(9)-C(8)-C(7)-C(6)	43.9(3)
C(10)-C(9)-C(14)-N(15)	179.9(2)
C(10)-C(9)-C(8)-C(7)	-57.6(3)
C(10)-C(1)-C(2)-C(3)	-30.1(2)
C(10)-C(4)-C(3)-C(2)	-34.8(2)
C(10)-C(4)-C(5)-C(6)	-60.5(3)
C(10)-C(4)-C(5)-C(13)	178.0(2)
C(1)-C(10)-C(4)-C(3)	16.4(2)
C(1)-C(10)-C(4)-C(5)	-105.6(2)
C(14)-C(9)-C(10)-C(1)	-4.8(4)
C(14)-C(9)-C(10)-C(4)	173.41(19)
C(14)-C(9)-C(8)-C(7)	123.6(2)
C(4)-C(10)-C(1)-C(2)	8.2(2)
C(4)-C(10)-C(1)-C(12)	126.3(2)
C(4)-C(10)-C(1)-C(11)	-107.9(2)
C(4)-C(3)-C(2)-C(1)	41.1(2)
C(3)-C(4)-C(5)-C(6)	-176.41(19)
C(3)-C(4)-C(5)-C(13)	62.0(3)
C(8)-C(9)-C(10)-C(1)	176.5(2)
C(8)-C(9)-C(10)-C(4)	-5.3(3)
C(8)-C(9)-C(14)-N(15)	-1.3(3)
C(7)-C(6)-C(5)-C(4)	3.7(4)
C(7)-C(6)-C(5)-C(13)	127.0(3)
C(5)-C(6)-C(7)-C(8)	4.4(4)

C(5)-C(4)-C(3)-C(2)	86.5(2)
C(12)-C(1)-C(2)-C(3)	-151.41(19)
C(11)-C(1)-C(2)-C(3)	87.9(2)
C(19)-S(16)-N(15)-C(14)	-124.96(19)

4.90

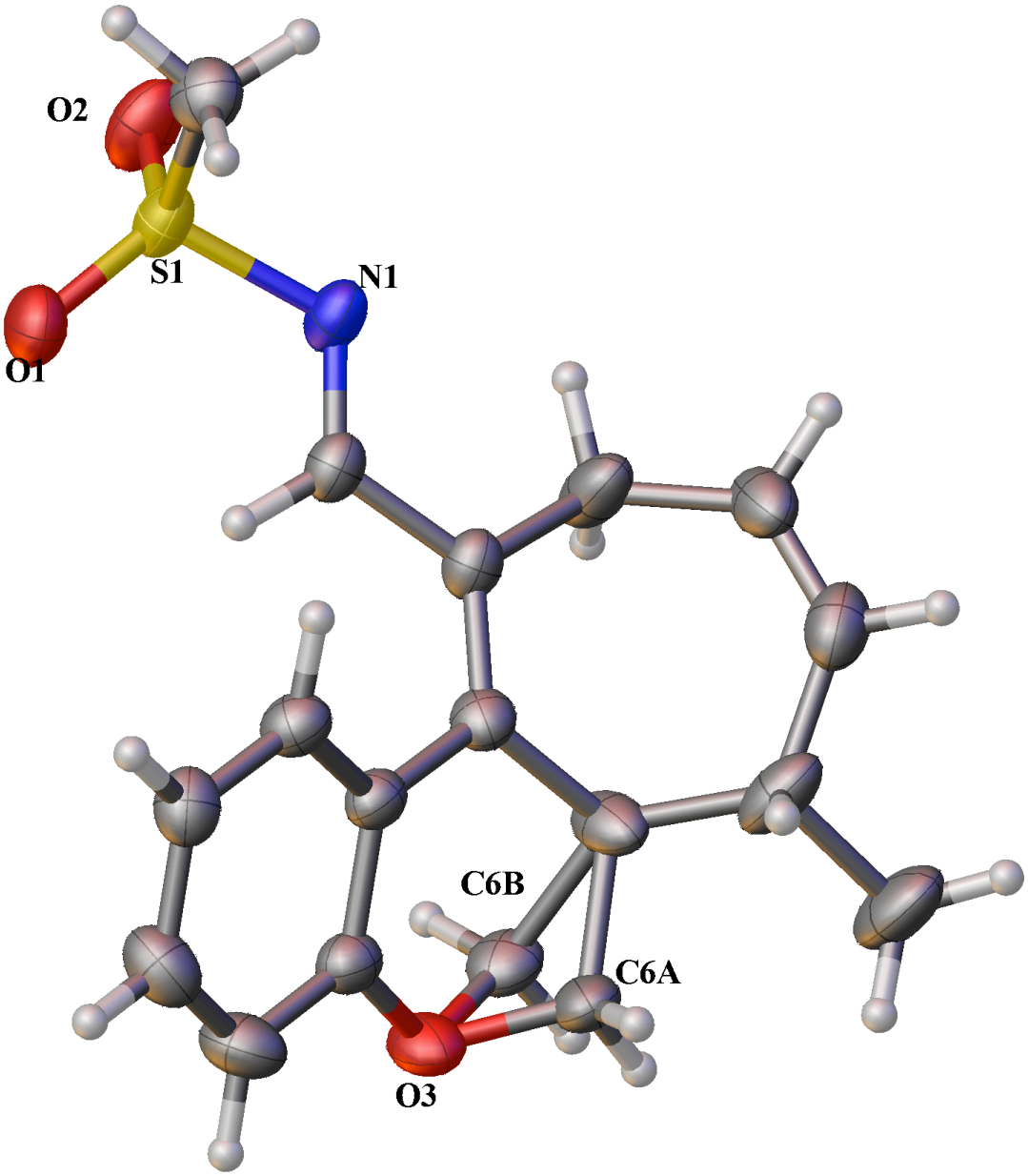


Table 1 Crystal data and structure refinement for **90**

Identification code	**90**
Empirical formula	C17H19NO3S
Formula weight	317.40
Temperature/K	173(2)
Crystal system	orthorhombic
Space group	P212121

a/Å	5.5688(17)
b/Å	14.034(5)
c/Å	20.131(6)
α/°	90
β/°	90
γ/°	90
Volume/Å3	1573.3(9)
Z	4
ρcalcmg/mm3	1.340
m/mm‑1	0.218
F(000)	672.0
Crystal size/mm3	0.856 × 0.680 × 0.198
2Θ range for data collection	4.046 to 63.278°
Index ranges	$-7 \leq h \leq 8$, $-20 \leq k \leq 18$, $-29 \leq l \leq 21$
Reflections collected	11850
Independent reflections	5146[R(int) = 0.0390]
Data/restraints/parameters	5146/17/215
Goodness-of-fit on F2	1.044
Final R indexes [I>=2σ (I)]	R1 = 0.0562, wR2 = 0.1348
Final R indexes [all data]	R1 = 0.0724, wR2 = 0.1453
Largest diff. peak/hole / e Å-3	0.47/-0.26
Flack parameter	-0.07(4)

Table 2 Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for **90**. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S1	3511.2(14)	3985.5(5)	871.7(3)	35.17(18)
O1	4423(5)	4926.8(15)	767.3(11)	45.7(6)
O3	7187(5)	6103.4(14)	3997.3(11)	45.9(6)
O2	1048(4)	3807.5(19)	703.1(12)	51.9(6)
N1	3819(5)	3623.9(17)	1653.7(12)	37.0(6)
C3	6194(6)	4545.2(17)	3192.7(14)	32.7(6)
C5	8425(6)	6020.2(18)	3414.2(13)	33.7(5)
C1	4822(5)	4203.6(19)	2060.1(14)	32.2(6)
C4	8025(5)	5237.4(18)	2995.4(13)	30.9(6)
C16	9417(6)	5186.5(19)	2416.2(14)	35.5(6)
C2	4864(5)	4016.8(19)	2768.2(14)	33.1(5)
C10	4150(7)	2539(2)	3469.7(15)	47.0(9)
C11	3109(7)	3278(3)	3026.5(16)	50.0(9)
C9	5641(8)	2655(2)	3964.8(16)	48.9(9)
C7	5690(7)	4465(2)	3935.4(15)	45.6(8)
C8	6636(7)	3546(3)	4257.8(15)	49.7(8)
C17	5311(7)	3164(2)	452.7(16)	42.2(7)
C15	10982(6)	5908(2)	2242.4(16)	37.5(6)
C14	11280(7)	6674(2)	2659.6(18)	46.5(8)
C12	6072(10)	3548(3)	5011.5(16)	68.2(13)
C13	10020(7)	6733(2)	3247.5(18)	47.1(8)
C6A	7087(9)	5244(3)	4337.6(19)	39.9(13)
C6B	5170(15)	5540(5)	4121(6)	43(3)

Table 3 Anisotropic Displacement Parameters (Å2×103) for **90**. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+...+2hka×b×U12]

Atom	U11	U22	U33	U23	U13	U12
S1	32.7(4)	46.2(3)	26.6(3)	7.9(3)	-0.8(3)	-2.6(3)
O1	56.6(14)	43.6(10)	36.8(12)	10.7(9)	2.8(11)	-1.9(10)
O3	64.9(16)	39.3(9)	33.6(11)	-10.7(9)	9.9(10)	-3.4(10)
O2	35.0(14)	79.3(16)	41.6(13)	13.0(12)	-6(1)	-2.8(11)
N1	36.7(15)	47.2(12)	27.0(12)	7.7(9)	-1.5(11)	-5.4(10)
C3	36.9(16)	32.4(11)	28.7(13)	-3.2(10)	6.4(11)	2.7(10)
C5	37.1(14)	34.1(11)	29.9(13)	-3.2(10)	-2.1(12)	4.4(12)
C1	29.4(14)	39.1(13)	28.2(13)	4.8(10)	0.9(11)	2.5(10)
C4	34.3(15)	32.6(11)	25.8(12)	-1.2(9)	-0.9(11)	3.8(10)
C16	36.0(15)	40.8(13)	29.7(14)	-3.5(11)	2.0(12)	-0.2(11)
C2	30.7(14)	38.6(12)	30.2(13)	5.1(11)	0.9(11)	1.3(11)
C10	73(3)	36.0(13)	32.1(15)	-0.3(11)	13.6(16)	-6.2(14)
C11	53(2)	67(2)	30.1(15)	8.8(13)	-7.6(15)	-24.5(17)
C9	61(2)	48.5(16)	37.3(17)	9.1(13)	5.7(16)	15.0(15)
C7	65(2)	39.1(13)	32.5(15)	-8.6(11)	19.1(15)	-10.7(14)
C8	40.9(18)	83(2)	25.2(14)	3.1(14)	-3.1(14)	-4.7(17)
C17	42.2(19)	47.5(16)	36.9(16)	2.6(12)	7.1(14)	-3.7(13)
C15	33.3(16)	41.1(14)	38.3(15)	5.0(11)	6.8(12)	7.0(11)
C14	45.0(19)	34.7(13)	60(2)	0.1(13)	10.1(17)	-0.7(13)
C12	80(3)	97(3)	27.3(17)	3.4(17)	-6.7(19)	-19(2)
C13	50(2)	38.9(14)	52.0(19)	-13.0(13)	5.5(17)	-6.0(13)
C6A	58(3)	38.0(19)	23.6(19)	-4.2(14)	-2.6(18)	-2.9(18)
C6B	53(6)	45(5)	31(5)	-9(4)	5(5)	7(4)

Table 4 Bond Lengths for **90**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.431(2)	C1	C2	1.450(4)
S1	O2	1.435(3)	C4	C16	1.402(4)
S1	N1	1.663(2)	C16	C15	1.381(4)
S1	C17	1.745(3)	C2	C11	1.516(4)
O3	C5	1.366(4)	C10	C11	1.486(5)
O3	C6A	1.388(4)	C10	C9	1.307(5)
O3	C6B	1.396(7)	C9	C8	1.489(5)
N1	C1	1.282(4)	C7	C8	1.537(5)
C3	C4	1.463(4)	C7	C6A	1.567(5)
C3	C2	1.352(4)	C7	C6B	1.581(6)
C3	C7	1.525(4)	C8	C12	1.549(5)
C5	C4	1.403(4)	C15	C14	1.374(4)
C5	C13	1.379(4)	C14	C13	1.378(5)

Table 5 Bond Angles for **90**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	O2	117.72(16)	C3	C2	C1	122.1(3)
O1	S1	N1	112.60(13)	C3	C2	C11	120.7(3)
O1	S1	C17	109.59(15)	C1	C2	C11	116.8(3)
O2	S1	N1	105.62(14)	C9	C10	C11	128.2(3)
O2	S1	C17	108.64(17)	C10	C11	C2	115.6(3)
N1	S1	C17	101.35(15)	C10	C9	C8	130.0(3)
C5	O3	C6A	111.7(3)	C3	C7	C8	114.4(3)
C5	O3	C6B	120.7(5)	C3	C7	C6A	111.3(3)
C1	N1	S1	117.1(2)	C3	C7	C6B	101.2(5)
C4	C3	C7	116.3(2)	C8	C7	C6A	101.4(3)
C2	C3	C4	125.0(3)	C8	C7	C6B	139.8(5)
C2	C3	C7	118.6(3)	C9	C8	C7	114.2(3)
O3	C5	C4	120.2(3)	C9	C8	C12	108.3(3)
O3	C5	C13	118.2(3)	C7	C8	C12	110.0(3)
C13	C5	C4	121.6(3)	C14	C15	C16	119.7(3)
N1	C1	C2	121.3(3)	C15	C14	C13	120.7(3)
C5	C4	C3	117.9(2)	C14	C13	C5	119.6(3)
C16	C4	C3	125.3(2)	O3	C6A	C7	111.8(3)
C16	C4	C5	116.9(3)	O3	C6B	C7	110.5(5)
C15	C16	C4	121.5(3)				

Table 6 Torsion Angles for **90**.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	N1	C1	C2	171.0(2)	C2	C3	C7	C6A	-170.5(3)
O1	S1	N1	C1	-0.6(3)	C2	C3	C7	C6B	-123.8(4)
O3	C5	C4	C3	2.3(4)	C10	C9	C8	C7	2.0(6)
O3	C5	C4	C16	-178.1(3)	C10	C9	C8	C12	124.9(5)
O3	C5	C13	C14	-179.4(3)	C11	C10	C9	C8	3.7(7)
O2	S1	N1	C1	-130.4(3)	C9	C10	C11	C2	45.2(5)
N1	C1	C2	C3	170.5(3)	C7	C3	C4	C5	-26.5(4)
N1	C1	C2	C11	-16.8(4)	C7	C3	C4	C16	153.9(3)
C3	C4	C16	C15	175.1(3)	C7	C3	C2	C1	165.5(3)
C3	C2	C11	C10	-56.2(4)	C7	C3	C2	C11	-6.9(4)
C3	C7	C8	C9	-59.1(4)	C8	C7	C6A	O3	159.1(3)
C3	C7	C8	C12	178.9(3)	C8	C7	C6B	O3	90.7(9)
C3	C7	C6A	O3	37.1(5)	C17	S1	N1	C1	116.4(3)
C3	C7	C6B	O3	-61.9(8)	C15	C14	C13	C5	-0.7(5)
C5	O3	C6A	C7	-63.1(4)	C13	C5	C4	C3	-176.3(3)
C5	O3	C6B	C7	46.3(9)	C13	C5	C4	C16	3.3(4)
C5	C4	C16	C15	-4.6(4)	C6A	O3	C5	C4	44.1(4)
C1	C2	C11	C10	131.0(3)	C6A	O3	C5	C13	-137.2(3)
C4	C3	C2	C1	-11.1(4)	C6A	O3	C6B	C7	-48.5(5)
C4	C3	C2	C11	176.5(3)	C6A	C7	C8	C9	-179.0(3)
C4	C3	C7	C8	-107.8(3)	C6A	C7	C8	C12	59.0(4)
C4	C3	C7	C6A	6.4(4)	C6A	C7	C6B	O3	47.0(5)
C4	C3	C7	C6B	53.1(5)	C6B	O3	C5	C4	-13.9(6)
C4	C5	C13	C14	-0.8(5)	C6B	O3	C5	C13	164.8(5)
C4	C16	C15	C14	3.3(5)	C6B	O3	C6A	C7	49.7(5)
C16	C15	C14	C13	-0.5(5)	C6B	C7	C8	C9	150.7(5)
C2	C3	C4	C5	150.2(3)	C6B	C7	C8	C12	28.7(7)
C2	C3	C4	C16	-29.5(4)	C6B	C7	C6A	O3	-47.9(5)
C2	C3	C7	C8	75.3(4)					

Table 7 Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for **90**.

Atom	x	y	z	U(eq)
H16	9284	4655	2143	43
H10	3682	1915	3384	56
H11A	1842	3605	3266	60
H11B	2375	2962	2649	60
H9	6160	2095	4165	59
H7	3963	4526	4017	55
H8	8385	3533	4204	60
H17A	5116	3245	-18	63
H17B	4844	2529	575	63
H17C	6962	3265	570	63
H15	11829	5876	1845	45
H14	12343	7158	2544	56
H12A	4395	3674	5078	102
H12B	7005	4034	5227	102
H12C	6467	2938	5197	102
H13	10244	7249	3530	57
H6AA	6300	5342	4762	48
H6AB	8707	5022	4424	48
H6BA	3826	5772	3861	51
H6BB	4742	5584	4587	51
H1	5470(70)	4810(20)	1910(16)	39(9)

4.92

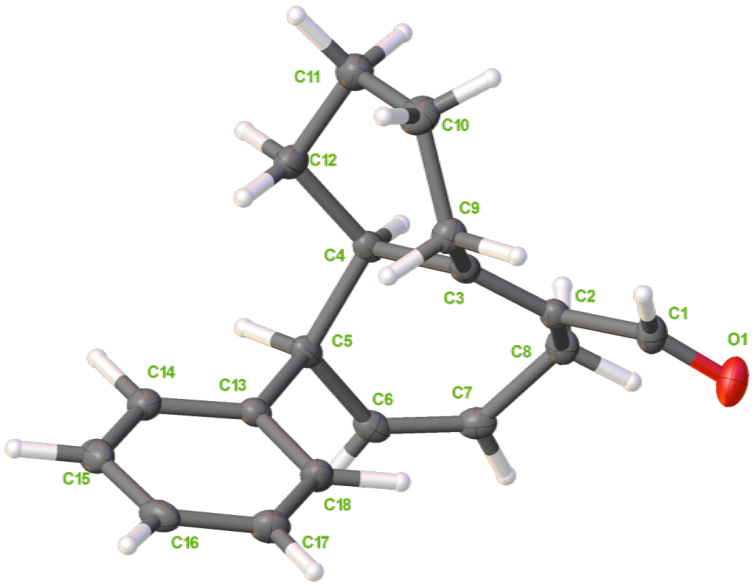


Table 1 Crystal data and structure refinement for **92**

Identification code	**92**
Empirical formula	C18 H20 O
Formula weight	252.34
Temperature/K	173.2
Crystal system	orthorhombic
Space group	P212121
a/Å	6.3966(11)
b/Å	7.7514(14)
c/Å	28.062(5)
α/°	90
β/°	90
γ/°	90
Volume/Å3	1391.4(4)
Z	4
ρcalcmg/mm3	1.205
m/mm‐1	0.556
F(000)	544.0
Crystal size/mm3	0.55 × 0.401 × 0.226

2Θ range for data collection	6.3 to 137.028°
Index ranges	$-7 \leq h \leq 7$, $-6 \leq k \leq 9$, $-32 \leq l \leq 33$
Reflections collected	5798
Independent reflections	2363[R(int) = 0.0182]
Data/restraints/parameters	2363/2/246
Goodness-of-fit on F2	1.089
Final R indexes [I>=2σ (I)]	R1 = 0.0442, wR2 = 0.1145
Final R indexes [all data]	R1 = 0.0445, wR2 = 0.1149
Largest diff. peak/hole / e Å-3	0.56/-0.34
Flack parameter	0.21(10)

Table 2 Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for **92**. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
C1	3105(4)	6338(4)	2219.9(8)	34.4(6)
C2	1262(4)	5644(3)	1973.1(8)	27.5(5)
C3	1426(4)	4306(3)	1666.7(8)	26.5(5)
C4	-534(4)	3597(3)	1432.9(8)	27.6(5)
C5	-1459(4)	4815(3)	1042.6(8)	28.2(5)
C6	-2280(4)	6493(3)	1240.1(9)	31.2(5)
C7	-2044(4)	7165(3)	1671.4(9)	31.6(5)
C8	-813(4)	6477(3)	2088.2(8)	31.4(5)
C9	3412(4)	3411(3)	1522.7(9)	31.7(5)
C10	3331(5)	1470(4)	1622.0(11)	41.5(6)
C11	1139(5)	710(4)	1575.8(10)	42.6(7)
C12	-183(5)	1759(3)	1235.4(10)	38.4(6)
C13	-8(4)	5101(3)	617.9(8)	27.4(5)
C14	-369(4)	4248(3)	189.7(9)	32.8(5)
C15	973(5)	4449(3)	-197.0(9)	37.6(6)
C16	2707(4)	5501(3)	-157.1(9)	35.5(6)
C17	3065(4)	6391(3)	262.9(9)	36.5(6)
C18	1709(4)	6199(3)	647.9(8)	33.1(5)
O1	3077(3)	7609(3)	2474.8(7)	49.2(5)

Table 3 Anisotropic Displacement Parameters (Å2×103) for **92**. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+...+2hka×b×U12]

Atom	U11	U22	U33	U23	U13	U12
C1	31.7(13)	41.4(13)	29.9(11)	-4.0(11)	-1.5(9)	-5.6(11)
C2	27.6(12)	31.0(11)	23.9(10)	3.2(9)	1.2(8)	-4.6(10)
C3	26.6(11)	28.1(11)	24.9(10)	3.6(9)	-0.2(8)	-4.9(10)
C4	23.9(11)	32.1(12)	26.9(10)	4.6(10)	-1.6(9)	-6.4(10)
C5	23.0(11)	33.9(11)	27.9(11)	4.9(9)	-3.0(9)	-5.7(10)
C6	24.1(12)	36.9(12)	32.8(11)	9.1(11)	0.3(9)	-0.3(10)
C7	26.6(12)	29.8(12)	38.4(12)	4.7(10)	7.7(10)	1.7(10)
C8	28.9(12)	36.6(12)	28.7(11)	-1.9(11)	4.5(10)	-1.2(11)
C9	25.0(12)	35.3(12)	35.0(12)	-0.5(10)	2.9(9)	-2.9(10)
C10	37.7(15)	36.3(14)	50.7(16)	-3.8(12)	0.7(12)	4.9(12)
C11	50.6(16)	39.5(14)	37.8(13)	1.6(12)	-0.7(12)	-4.2(13)
C12	42.3(15)	31.4(11)	41.6(13)	1.7(10)	-9.2(11)	-8.6(11)
C13	28.2(12)	27.1(10)	26.9(10)	5.3(8)	-1.0(9)	-0.6(10)
C14	37.2(13)	28.1(11)	33.1(11)	1.3(10)	-1.1(10)	-0.6(11)
C15	50.9(16)	31.1(11)	30.7(11)	-1.7(10)	3.1(11)	6.5(12)
C16	39.7(14)	35.6(12)	31.2(11)	8.1(10)1	2.0(11)	6.9(11)
C17	34.0(13)	35.6(12)	39.9(13)	7.4(11)	6.4(10)	-5.4(12)
C18	37.3(13)	32.9(11)	29.0(11)	2.9(10)	1.2(9)	-7.9(11)
O1	47.1(12)	54.3(12)	46.3(11)	-19.6(10)	-8.5(9)	-5.4(10)

Table 4 Bond Lengths for **92**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.469(3)	C7	C8	1.507(4)
C1	O1	1.218(3)	C9	C10	1.531(4)
C2	C3	1.352(3)	C10	C11	1.527(4)
C2	C8	1.511(3)	C11	C12	1.513(4)
C3	C4	1.518(3)	C13	C14	1.391(3)
C3	C9	1.503(3)	C13	C18	1.392(3)
C4	C5	1.562(3)	C14	C15	1.393(4)
C4	C12	1.545(4)	C15	C16	1.381(4)
C5	C6	1.508(3)	C16	C17	1.385(4)
C5	C13	1.527(3)	C17	C18	1.393(4)
C6	C7	1.326(4)			

Table 5 Bond Angles for **92**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	C1	C2	124.1(2)	C6	C7	C8	128.9(2)
C1	C2	C8	116.6(2)	C7	C8	C2	116.4(2)
C3	C2	C1	121.3(2)	C3	C9	C10	112.1(2)
C3	C2	C8	122.1(2)	C11	C10	C9	113.3(2)
C2	C3	C4	119.3(2)	C12	C11	C10	111.1(2)
C2	C3	C9	126.2(2)	C11	C12	C4	110.5(2)
C9	C3	C4	114.52(19)	C14	C13	C5	120.3(2)
C3	C4	C5	113.39(19)	C14	C13	C18	118.3(2)
C3	C4	C12	111.6(2)	C18	C13	C5	121.4(2)
C12	C4	C5	111.16(18)	C13	C14	C15	121.2(2)
C6	C5	C4	113.29(19)	C16	C15	C14	119.9(2)
C6	C5	C13	111.92(19)	C15	C16	C17	119.7(2)
C13	C5	C4	113.89(19)	C16	C17	C18	120.3(2)
C7	C6	C5	129.4(2)	C13	C18	C17	120.6(2)

Table 6 Torsion Angles **92**.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C3	C4	178.0(2)	C6	C5	C13	C18	53.7(3)
C1	C2	C3	C9	-2.5(4)	C6	C7	C8	C2	39.0(4)
C1	C2	C8	C7	124.7(2)	C8	C2	C3	C4	-0.6(3)
C2	C3	C4	C5	72.4(3)	C8	C2	C3	C9	178.9(2)
C2	C3	C4	C12	-161.1(2)	C9	C3	C4	C5	-107.1(2)
C2	C3	C9	C10	123.6(3)	C9	C3	C4	C12	19.4(3)
C3	C2	C8	C7	-56.6(3)	C9	C10	C11	C12	26.7(3)
C3	C4	C5	C6	-66.2(3)	C10	C11	C12	C4	-64.3(3)
C3	C4	C5	C13	63.2(3)	C12	C4	C5	C6	167.1(2)
C3	C4	C12	C11	39.8(3)	C12	C4	C5	C13	-63.5(3)
C3	C9	C10	C11	31.7(3)	C13	C5	C6	C7	-119.1(3)
C4	C3	C9	C10	-56.9(3)	C13	C14	C15	C16	0.5(4)
C4	C5	C6	C7	11.3(3)	C14	C13	C18	C17	-2.1(4)
C4	C5	C13	C14	103.0(2)	C14	C15	C16	C17	-1.9(4)
C4	C5	C13	C18	-76.5(3)	C15	C16	C17	C18	1.4(4)
C5	C4	C12	C11	167.5(2)	C16	C17	C18	C13	0.6(4)
C5	C6	C7	C8	2.4(4)	C18	C13	C14	C15	1.5(4)
C5	C13	C14	C15	-177.9(2)	O1	C1	C2	C3	175.0(2)
C5	C13	C18	C17	177.4(2)	O1	C1	C2	C8	-6.4(4)
C6	C5	C13	C14	-126.9(2)					

Table 7 Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for **92**.

Atom	x	y	z	U(eq)
H4	-1550(40)	3660(30)	1675(9)	23(6)
H5	-2720(50)	4210(40)	910(10)	37(8)
H6	-3030(50)	7020(40)	1018(11)	30(7)
H7	-2740(50)	8240(40)	1748(10)	34(7)
H8A	-1680(50)	5740(40)	2256(10)	34(7)
H8B	-660(50)	7470(40)	2306(10)	32(7)
H9A	3580(70)	3530(50)	1182(14)	65(11)
H10A	4490(70)	1050(50)	1390(13)	63(11)
H10B	3790(70)	1370(60)	1961(15)	73(12)
H11A	380(60)	610(40)	1899(11)	43(8)
H11B	1410(80)	-560(70)	1414(16)	94(15)
H12A	-1549	1183	1189	24(6)
H12B	524	1828	922	67(11)
H14	-1490(50)	3410(50)	150(11)	46(8)
H15	680(50)	3800(40)	-508(11)	44(8)
H16	3540(50)	5570(40)	-402(11)	31(7)
H17	4300(50)	7170(40)	282(10)	32(7)
H18	2000(50)	6850(40)	969(11)	34(7)
H1	4380(30)	5510(30)	2168(11)	45(8)
H9B	4710(30)	4000(40)	1684(10)	41(8)