Development of Methods for the Heteroatom Functionalization of Cyclopropenes

By

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

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Development of Methods for the Heteroatom Functionalization of Cyclopropenes

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Chairperson: Dr. Michael Rubin

Date approved:

I dedicate this thesis to my uncle,

Mahmoud Balsha

You will always be missed

Acknowledgements

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B.K.A

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LIST OF ABBREVIATIONS

A-(ACC)	1-aminocyclopropane carboxylic acid
Ar	Aryl Ring
β-HE	Beta Hydride Elimination
BINAP	Binaphthyl
Calcd	Calculated
Bn	Benzyl
^{t}Bu	*tert*-Butyl
cat.	Catalytic Amount
cm^{-1}	Inverse Centimeters
CPDUL	dual carbon proton cryoprobe
Cy	Cyclohexyl
δ	Chemical shifts in ppm downfield from tetramethylsilane
(NMR)	Nuclear Magnetic Resonance
Δ	Heat
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
DOSP	*N*-(dodecylbenzenesulfonyl)prolinate)

LIST OF ABBREVIATIONS (Continued)

ee	Enantiomeric Excess
Et	ethyl
eq,	equiv molar equivalent
EWG	electron withdrawing group
FID	Flame Ionization Detector
FT	Fourier Transform
g	gram
GC	gas chromatography
GCMS	gas chromatography/mass spectrometry
h, hr, hrs	hours
HRMS	high resolution mass spectrometry
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infra-red spectroscopy
J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropyl amide
m	multiplet
mp	melting point
μ	micro

LIST OF ABBREVIATIONS (Continued)

M	molar
MS	mass spectrometry
Me	methyl
Mg	milligram
min	minute
MIRC	Michael initiated ring closure
mL	milliliter
mm	millimeter
mmol	millimole
mol	mole
MHz	megahertz
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
OAc	Acetate
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Triflate
Ph	Phenyl Ring
PHOX	Phosphanyl-oxazoline
ppm	parts per million
Pr	propyl

LIST OF ABBREVIATIONS (Continued

*i*Pr	isopropyl
ps.t.	pseudo triplet or overlapping doublet of doublets (NMR)
q	quartet (NMR)
QNP	Quadruple-band Gradient Probe
rt	room temperature
R_t	retention time
s	singlet (NMR)
SAR	Structure and Activity Relationships
t	triplet (NMR)
TDTAB	tetradecyltrimethylammonium bromide
TDMPP	tris(2,6-dimethoxylphenyl)phosphine
Tf	trifluoromethylsulfonyl (triflate)
TFA	trifluoroacetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol, tol tolyl	Toluene
TPP	triphenylphosphine
Ts	tosyl
UV	ultra-violet

Summary

The main focus of this thesis is the stereoselective funtionalization of cyclopropenes mainly via the addition of H-X (hetroatom-hydrogen) moieties across the strained double bond. It is broken up into three chapters, each one devoted to different methods allowing for direct funtionalization of these uniquely interesting and highly reactive carbocycles.

The first chapter is devoted to the palladium catalyzed hydrophosphorylation and hydrophosphinylation of cyclopropenes. This methodology allows for the direct ring retentive funtionalization of cyclopropenes with a pronucleophilic entity, which up until now has been extremely scarce. Aside from the synthetic value, the methodology also provides access to highly funtionalized stereodefined cyclopropylphosphonates which have a proven track record as medicinaly relevant substrates.

The second chapter focuses on intermolecular formal nucleophilic substitutions of bromocyclopropanes. This method aims for the construction of highly functionalized cyclopropyl ethers via direct nucleophilic attack of *O*-based pronucleophiles to *in situ* generated, highly reactive cyclopropene intermediates. The diastereoselectivity of the reaction is controlled either by sterics or through directing effects providing highly streo-defined donor-acceptor cyclopropanes.

Chapter three describes highly efficient and diastereoselective medium ring closures occurring upon intramolecular attack of a tethered alkoxide nucleophile at bromocyclopropane. The reaction proceeds via initial 1,2-dehydrobromination to produce a cyclopropene

intermediate, followed by nucleophilic addition across the strained C=C bond, to produce cyclopropane-fused medium heterocycles.

Chapter 1. The Diastereoselective Palladium Catalyzed Hydrophosphorylation and Hydrophosphinylation of Cyclopropenes

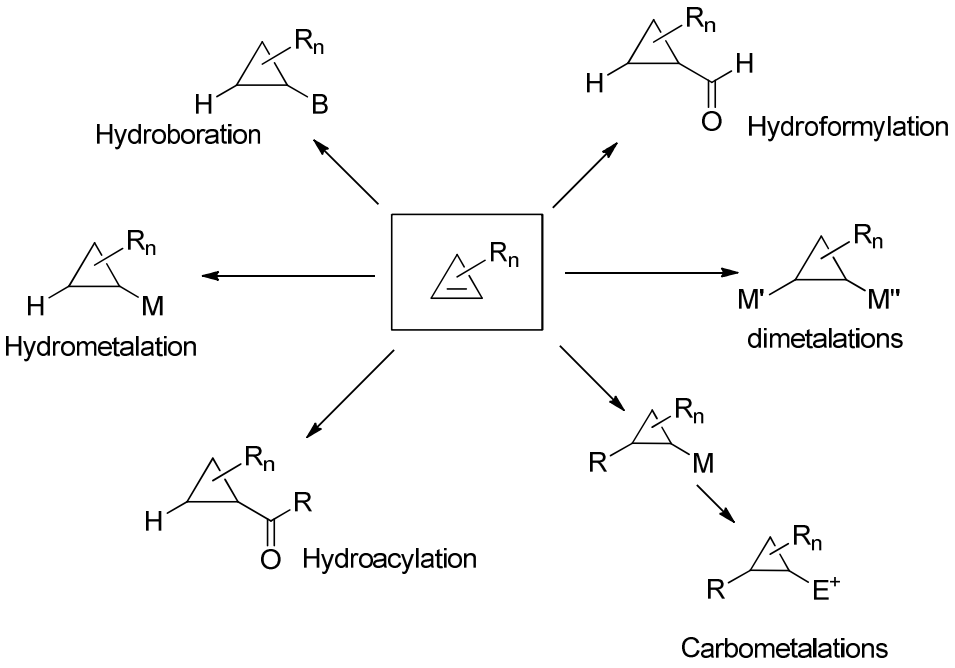
1.1. Introduction

1.1.1. Transition metal assisted additions to cyclopropenes

The rich and versatile chemistry of cyclopropenes has been extensively explored. These three-membered carbocycles are extremely important versatile building blocks for organic chemistry[1]. Their unique structural and electronic properties give rise to a variety of very interesting, characteristic transformations. The increased strain and π-density of its double bond makes cyclopropene a very attractive substrate for π-acceptor transition metals and allows for reactivity unknown for olefins, allenes and alkynes. Employment of catalysts allows for controlling and fine-tuning of the diastereo- and enantioselectivity as well as the efficiency of the reaction. Thus, several recent advances have been made in the transition metal-catalyzed chemistry of cyclopropenes which is a quickly developing area and is the primary focus of many research groups.[2] The inherent strain of cyclopropene presents a challenge in the design of reaction processes in which the integrity of the strained carbocycle is not sacrificed. Several elegant metal assisted additions to cyclopropene have been recently developed, in which stereodefined densely substituted cyclopropanes are efficiently accessed via hydrometalations,

hydroboration, dimetalations, carbometalations, hydroformylation, and hydroacylation (Figure 1).

Figure 1.

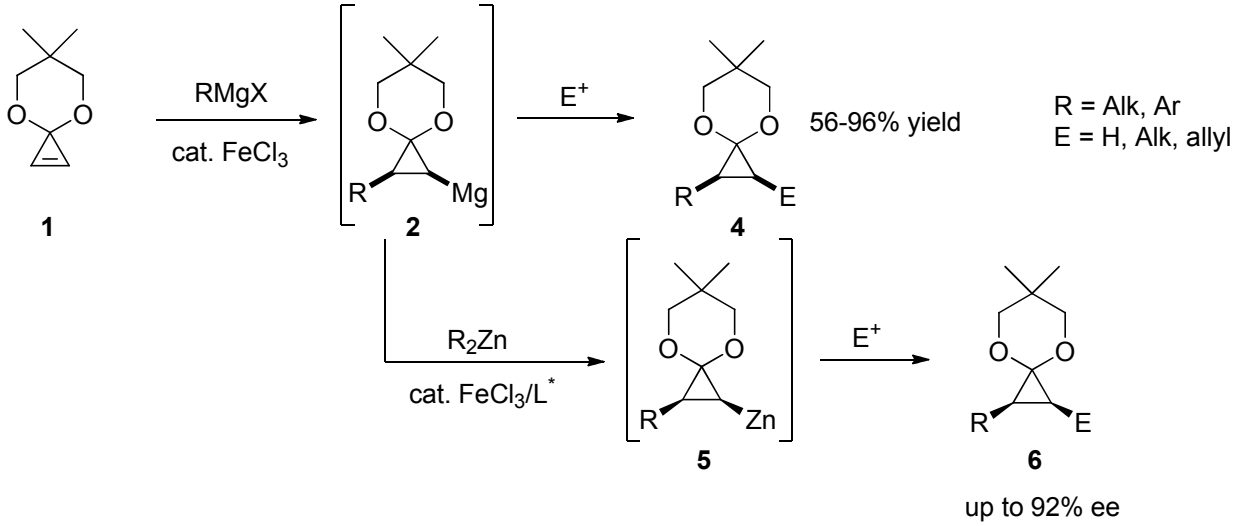


1.1.2. Carbometalations of cyclopropenes

In 2000, Nakamura demonstrated that the use of an iron catalyst facilitated carbomagnesation of cyclopropenone acetals **1** with a wide range of Grignard reagents, including aryl- and alkenylmagnesium halides (Scheme 1.).

Nakamura has also shown catalytic asymmetric carbozincation of cyclopropenone acetals in the presence of an iron catalyst and chiral phosphine ligands. Interestingly, addition of TMEDA was necessary for achieving high enantioselectivities, as racemic products were obtained in the absence of this additive[3]. Both cyclopropyl magnesium **2** and cyclopropyl zinc species **3** were efficiently trapped with a variety of electrophiles to furnish tetra-substituted cyclopropanes.

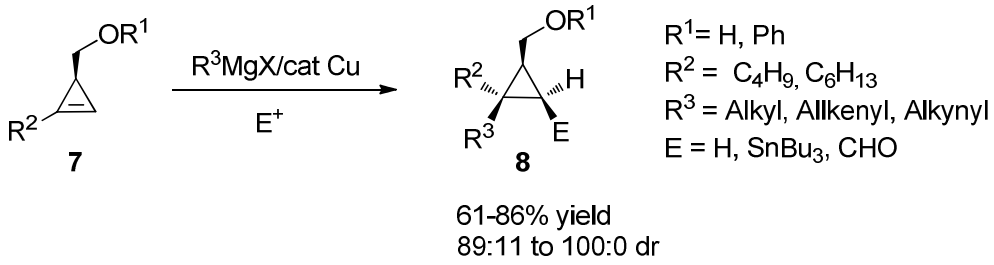
Scheme 1.



In 2002, Fox reported a directed carbomagnesation of hydroxymethylcyclopropenes **7** in the presence of copper catalysts (Scheme 2). Alkyl and vinyl Grignard reagents reacted smoothly in this reaction, generally providing very good *syn*-selectivity. Trapping the

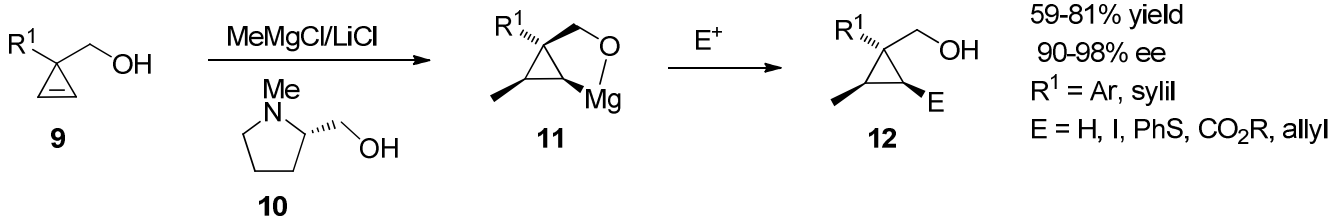
cyclopropylmagnesium intermediate with different electrophiles allowed for easy installation of various functional groups in the three-membered ring.[4]

Scheme 2.



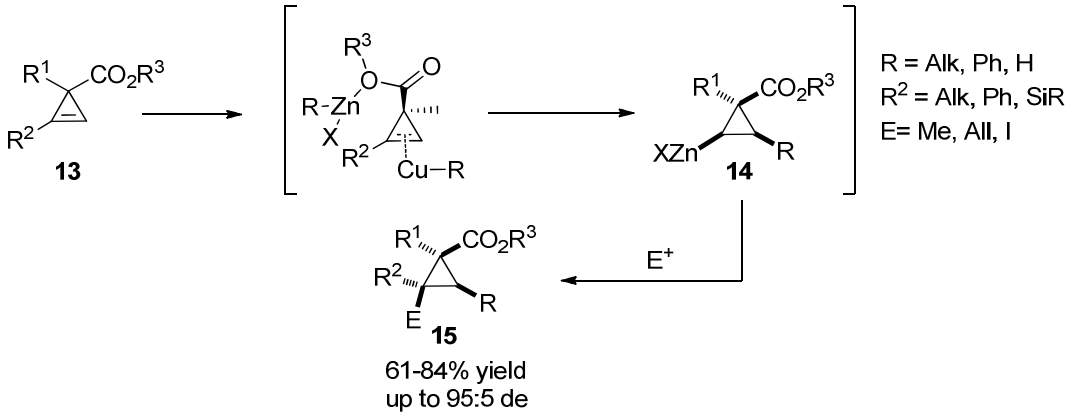
Later in 2006 Fox demonstrated the diastereo- and enantioselective carbomagnesiation reaction of 3-hydroxymethylcyclopropenes **9** in the presence of organic chiral catalyst **10** (Scheme 3). As opposed to previous studies this method allowed for the addition of a wide variety of Grignard reagents. This highly stereoselective transformation permits rapid access to non-racemic tri- and tetrasubstituted hydroxymethylcyclopropanes **12**.[5]

Scheme 3.



The use of Grignard reagents in carbomagnesiation reactions makes them incompatible with cyclopropanes bearing ester functions. In a recent study Fox demonstrated the diastereoselective carbozincation of cyclopropenes in which the diastereoselectivity is efficiently directed through the ester functionality (Scheme 4). Chiral oxazolidinone functions direct the addition of a variety of nucleophiles with excellent facial selectivity. The regioselectivity is also high for carbozincation reactions of 2-alkyl-substituted cycloprop-2-ene carboxylate esters **13**. The resulting cyclopropylzinc species **14** can be intercepted via stereospecific reactions with a variety of electrophiles.[6]

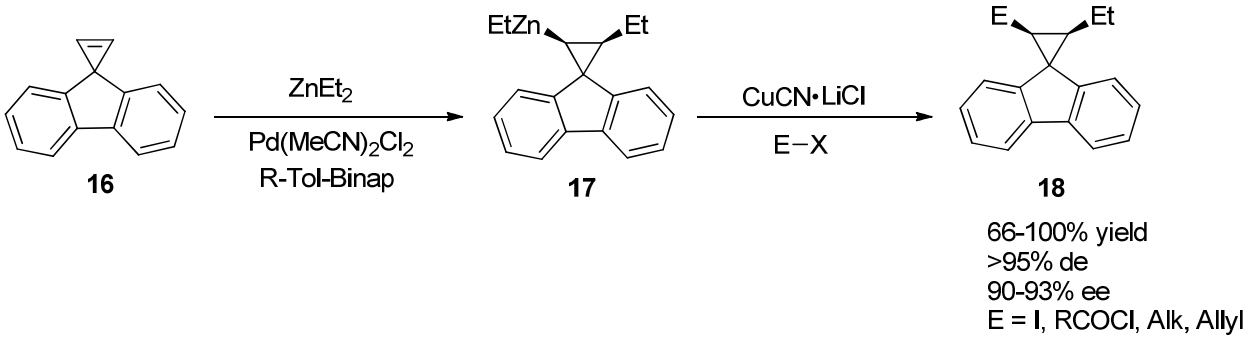
Scheme 4.



Lautens very recently showcased a highly enantioselective palladium-catalyzed carbozincation of cyclopropenes. The cyclopropyl zinc intermediates were successfully trapped with a range of electrophiles (Scheme 5). It was found that trapping of the cyclopropylzinc intermediate **17** with carbon electrophiles required transmetalation with copper.[7] The flourene

derived cyclopropene **16** reacted smoothly to provide tetra-substituted cyclopropanes **18** with ee's up to 93%. However, reactions with other types of cyclopropenes showed only marginal efficiency and selectivity.

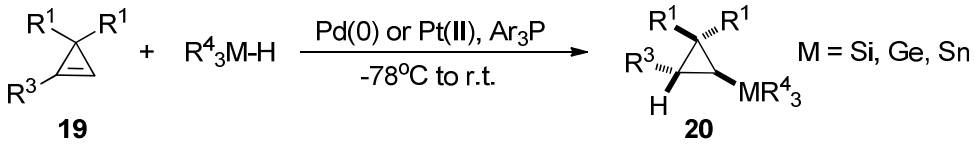
Scheme 5.



1.1.3. Hydrometalations/dimetalations of cyclopropenes

Gevorgyan reported on highly stereo- and regioselective transition metal-catalyzed hydrostannation of cyclopropenes to produce tri-, tetra-, and pentasubstituted cyclopropylstannanes in very good yields (Scheme 6). This reaction proceeded with high *cis*-selectively and with excellent facial selectivity controlled by steric factors. In all cases single diastereomers of cyclopropylstannanes were obtained (Scheme 6).[8b]

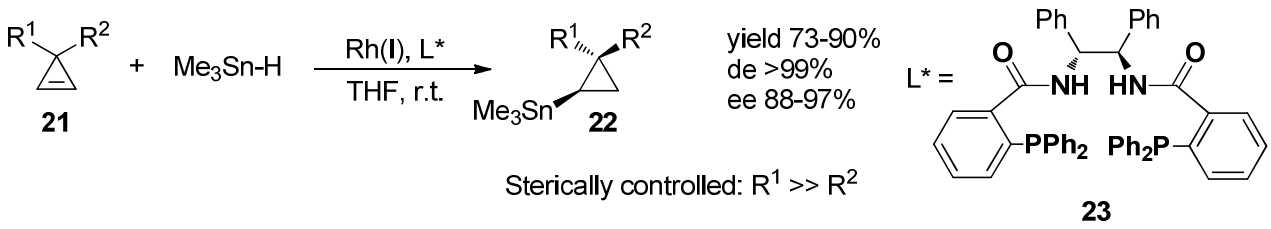
Scheme 6.



It was also found that hydrosilylation[8] of cyclopropene with trichlorosilane proceeds smoothly from the less hindered face in the presence of [(π-allyl)PdCl]$_2$ and a bulky electron rich ligand, tris(2,6-dimethoxyphenyl)phosphine (TDMPP). Exhaustive alkylation of with MeLi afforded the corresponding cyclopropyltrimethylsilane in good overall yield. Efficient hydrosilylation and hydrogermylation with triorganometal hydrides proceed in the presence of catalytic amounts of $PtCl_2$, affording cyclopropylsilanes and cyclopropylgermanes in good to excellent yields. Steric factors efficiently govern the facial selectivity of this reaction.

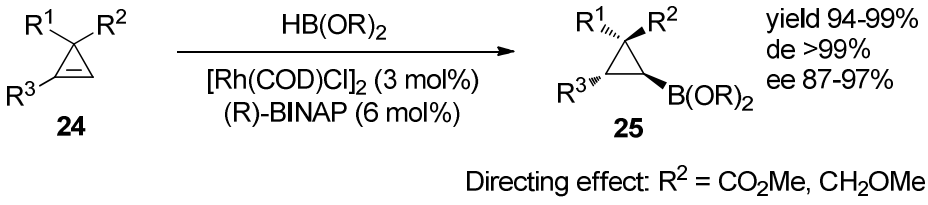
Gevorgyan also disclosed catalytic asymmetric hydrostannation of 3,3-disubstituted cyclopropenes (Scheme 7) in the presence of the Rh(I) complex bearing a chiral diamide[9]-based phosphine ligand **23**. Good yields, high degrees of diastereo- and enantioselectivity, and excellent functional group compatibility are the clear advantages of this approach. This methodology marks the first and only example of catalytic asymmetric hydrostannation known to date.

Scheme 7.



It was further shown by Gevorgyan that the rhodium catalyzed asymmetric hydroboration of 3,3-disubstituted cyclopropenes **24** affords *cis*-cyclopropylboronates **25** with perfect diastereoselectivity and very high enantioselectivity in contrast to the sterically controlled hydrostannation reactions, the enantio- and diastereoselectivities of the hydroboration were controlled by the directing effect of an ester or alkoxymethyl substituents.

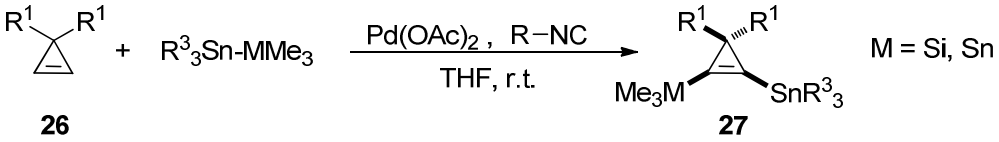
Scheme 8.



Gevorgyan also demonstrated a highly diastereoselective Pd catalyzed silastannation and distannation of cyclopropenes **26** (Scheme 9). Analogous to the Pd catalyzed hydrostannation reaction, the facial selectivity of the dimetalation was entirely controlled by steric factors.

Remarkably, silastannation of cyclopropenes substituted at C-1 proceeded highly regioselectively with the stannyl moiety adding to the most hindered position.[8b]

Scheme 9.

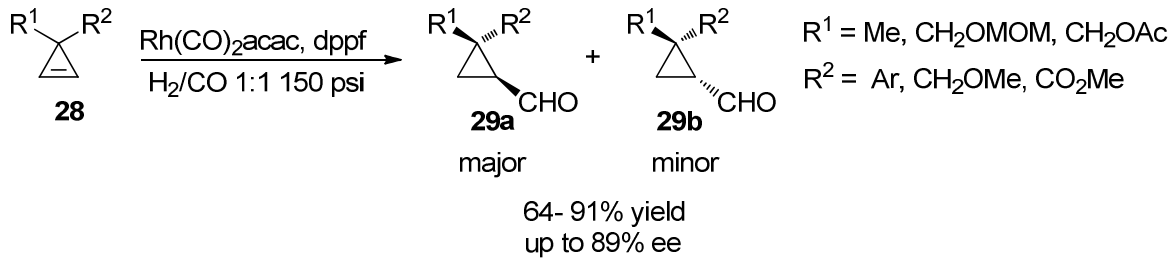


26 **27**

1.1.4. Hydroformylation and hydroacylation of cyclopropenes

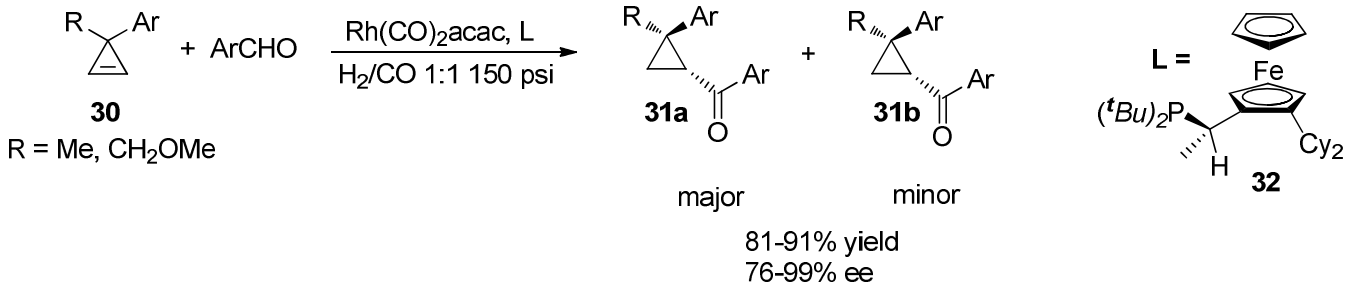
The first catalytic diastereo- and enantioselective hydroformylation of cyclopropenes was demonstrated by Rubin in 2008 (Scheme 10).[10] The reaction proceeds efficiently under very mild conditions and low catalyst loadings providing high yields of cyclopropylcarboxaldehydes **29**. The reaction proceeded with good diastereoselectivity controlled through steric factors. The authors were also able to demonstrate an asymmetric version of this reaction reaching ee's up to 89%. Notably, the well known rhodium-catalyzed dimerization of cyclopropene **28** was avoided via employment of electron rich-phosphine ligands. This novel methodology represents a convenient, atom-economic approach toward optically active cyclopropylcarboxaldehydes **29** from readily available prochiral cyclopropenes.

Scheme 10.



Dong very recently reported an enantioselective desymmetrization of cyclopropenes *via* intermolecular Rh-catalyzed hydroacylation[11] (Scheme 11). Cyclopropylketones **30** bearing quaternary stereocenters, are produced with diastereocontrol (*up to* 20:1) and excellent enantiomeric excess (*up to* 99 %*ee*). To achieve asymmetric induction, various chiral Josiphos ligands **32** were screened and among those tested, the more electron-rich and sterically bulky ligands gave better yields and enantioselectivity. The observed *trans* diastereoselectivity suggests that the reaction is sterically controlled analogous to the previously reported hydroformylation of cyclopropanes.

Scheme 11.

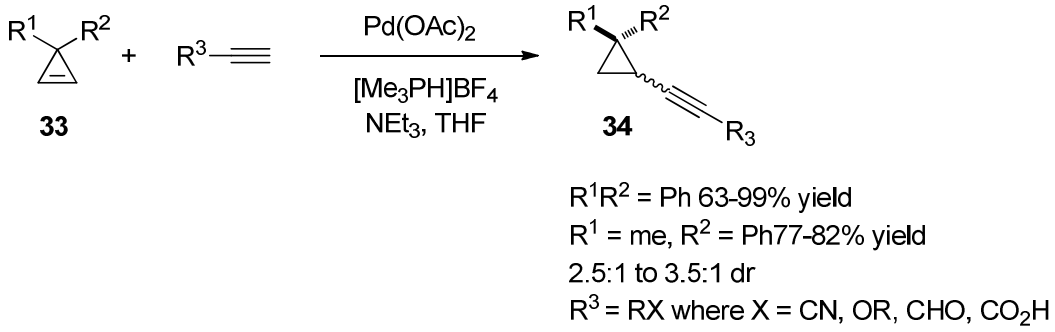


1.1.5. Pronucleophillic additions to cyclopropenes

While a number of elegant transition metal catalyzed transformations of cyclopropanes have been developed, examples involving the addition of a pronucleophilic species have been extremely scarce. Even more so are the transition metal catalyzed processes in which the integrity of the cycloropyl core is kept intact.

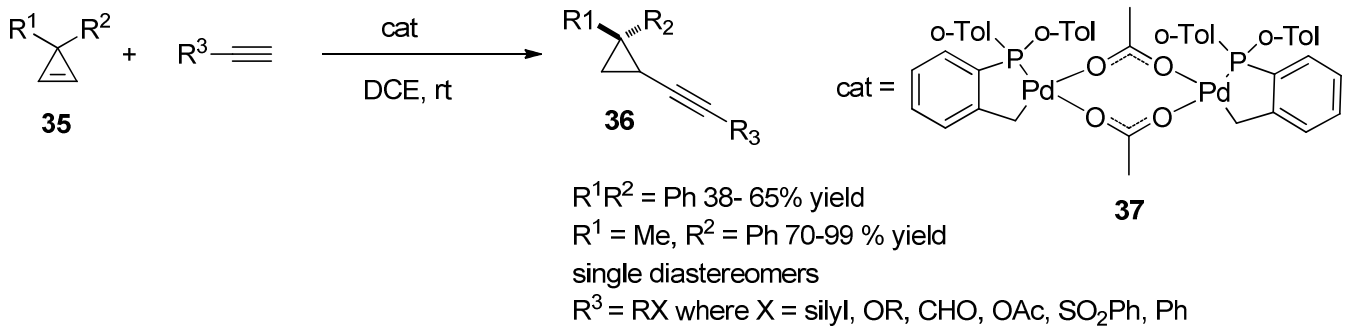
In 2006, Chisholm reported the addition of alkynes to cyclopropenes utilizing palladium acetate and trimethylphosphonium tetrafluoroborate as a catalyst and triethylamine to promote both the release of free electron-rich phosphine and formation of alkynylpalladium species. These mild and neutral conditions permitted installation of functional groups such as aldehydes, carboxylic acids, and alcohols, which are incompatible with basic organometallic reagents. However, the low diastereoselectivity observed with unsymmetrical gem-disubstituted cyclopropenes **33**, affording a 2.5-3.5/1 mixture of *trans*/*cis* adducts **34**, constitutes a major drawback of this coupling[12] (Scheme 12).

Scheme 12.



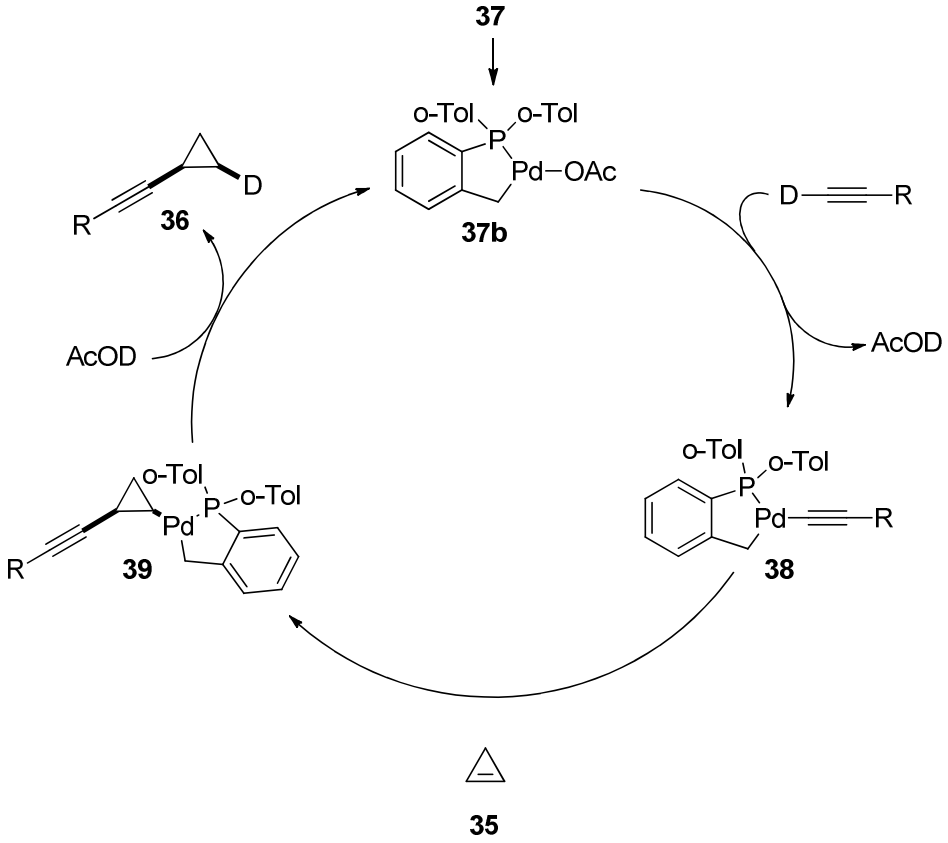
Tenaglia reported a marked improvement to this methodology by the employment of the Herrmann-Beller (H-B) phosphapalladacycle **37** which catalyzed the addition of terminal alkynes to unsymmetrical gem-disubstituted cyclopropanes **35** to give alkynylcyclopropanes **36** as single diastereomers in good to excellent yields (Scheme 13.).[13] The stereofacial discrimination at the approach of the bulky alkynylpalladium species is believed responsible for the diastereoselectivity control of the addition reaction. This was supported by the addition of deuterated alkynes in which the alkyne and the deuterium were found to be exclusively *cis* in relation (Scheme 14).

Scheme 13.



The authors propose plausible mechanism for the coupling of cyclopropanes with terminal alkynes which starts with the mononuclear palladacycle **37b** via the dissociation of the Herrmann-Beller phosphapalladacycle **37**. The alkynylpalladium species **38** could be formed in the presence of alkyne with the loss of acetic acid. Coordination of the cyclopropene double bond followed by the syn carbopalladation afforded cyclopropylpalladium species **39**, which upon protolytic cleavage with acetic acid releases the alkynylcyclopropane **36** and regenerates the catalytic species **37b** (Scheme 14.).

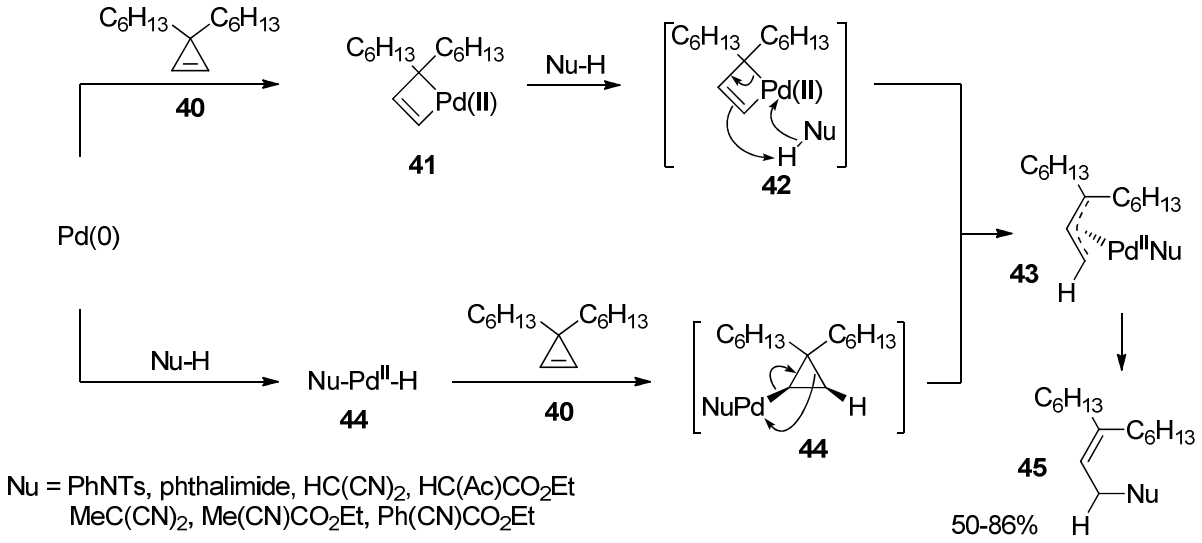
Scheme 14.



The pioneering studies performed by Chisholm and Teneglia[13] were essentially the sole examples of the transition metal-catalyzed pronucleophilic additions to cyclopropenes with retention of the strained cycle (Schemes 12 and 13). In contrast to these studies, in 2006, Yamamoto reported the palladium-catalyzed addition of carbon- and nitrogen-based pronucleophiles to 3,3-dihexylcyclopropene **40.**[14] The reaction occurred at elevated temperatures and was accompanied by ring opening, yielding olefins **45** similar to those obtained through Tsuji-Trost reactions. The proposed mechanistic rationale involved oxidative addition of a Pd(0) species into the C-C bond of cyclopropene **40** to give palladacyclobutene intermediate **42**. The

latter, after reaction with a pronucleophile, afforded π-allylpalladium species **43**. An alternative suggested pathway involved oxidative addition to give Pd(II) species **44** followed by hydropalladation of the strained cyclopropene double bond to give species **44** which undergoes a thermally induced isomerization into the π-allylpalladium complex **43**. Reductive elimination from the latter produced allylic products **45** in moderate to good yields.

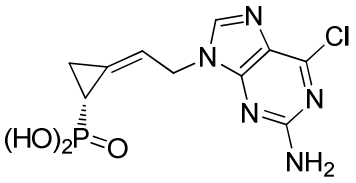
Scheme 15.



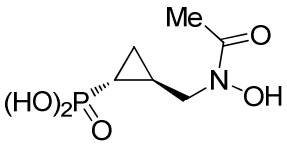
1.1.6. Cyclopropyl-Phosphorus Compounds

For many years clopropylphosphonates and cyclopropylphosphonic acids have been the subject of interest for a variety of reasons. They have been prepared as mimics of 1-aminocyclopropane carboxylic acid (α-ACC) with a high inhibitory activity for the ACC-deaminase and alanine racemase,[15] as analogues of (–)-allonorcoronamic acid[33], as structural moieties of nucleotides, as potential herbicides or plant growth regulators, as potential insecticides[16], as phosphonic analogues of the antidepressant Milnacipran[17] and as constrained analogue of the GABA antagonist phaclophen.[31] Derivatives of cyclopropylphosphonic acid also make attractive targets for drug discovery, as they are many examples of such structures among biologically active compounds (Figure 2) including antiproliferative,[18] antiviral,[19,20] and anti-malarial agents.[21]

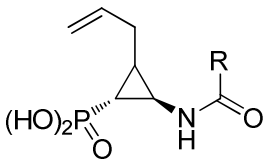
Figure 2.



Antiviral agent against human cytomegalovirus and Epstein-Barr virus.



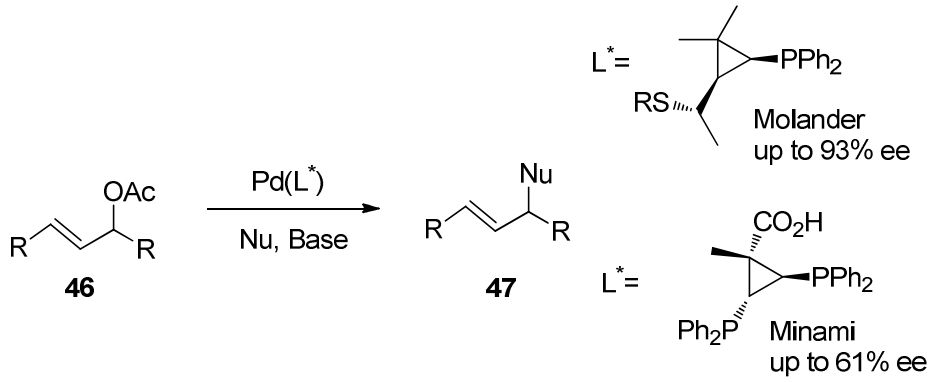
Potent anti-malarial activity.



Hepatitis C virus NS3 protease inhibitors

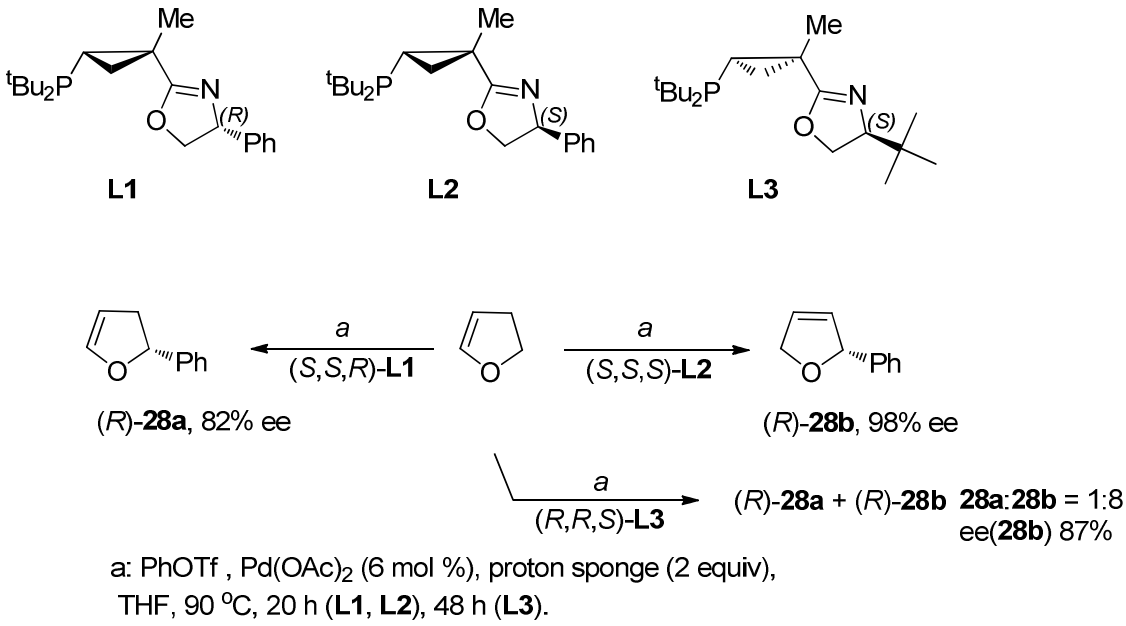
Cyclopropylphosphines have received attention as ligands for asymmetric catalysis since this class of ligands offer an advantageous combination of structural rigidity, low molecular weight on a well-defined and highly variable platform with unusual bond angles. Moreover, recent improvements in the stereoselective synthesis of this ring make exploring the use of cyclopropanes even more attractive. Minami and co-workers evaluated cyclopropyl based diphosphine ligands in an asymmetric allylic alkylation achieving up to 61% ee (Scheme 16).[22] Later, in 2004, Molander and co-workers also evaluated cyclopropyl phosphine ligands in the same reaction, reaching very high yields of the products **47** in 93 % ee (Scheme 16).[23]

Scheme 16.



Rubin recently employed a novel class of chiral phosphanyl-oxazoline (PHOX) ligands with a conformationally rigid cyclopropyl backbone which were tested in the intermolecular asymmetric Heck reaction (Scheme 17). Dramatic stereo- and enantiodivergent effects resulting from subtle modifications to the ligand structure were observed providing ee's up to 98 %.[24]

Scheme 17.

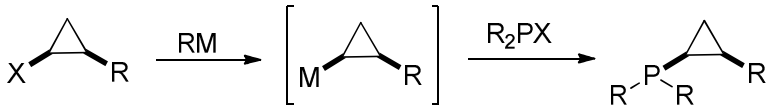


1.1.7 Synthesis of cyclopropylphosphines and phosphonates

Derivatization of an existing cyclopropane scaffold including reactions of *P*-nucleophiles with cyclopropanone equivalents[25] (Scheme 20) or *P*-electrophiles with cyclopropylmetals (

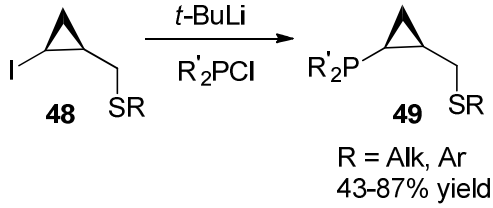
Scheme 18)[26] offer routes to cyclopropyl phosphorus moieties, however, the efficiency of these methods is dramatically decreased with increasing steric demand around the cyclopropyl core.

Scheme 18.



Easily accessible bromo and iodo-cyclopropane[59,60] such as **48** readily undergo halo/lithium exchange without rearrangement upon treatment with *tert*-butyllithium in diethyl ether/pentane at –78 °C, and the resulting 1-lithio-cyclopropane can be trapped with various electrophiles. Molander[23] (Scheme 19) and others[24,27] have utilized electrophillic trapping chlorophosphines in the synthesis of various cyclopropyl- based phosphine ligands.

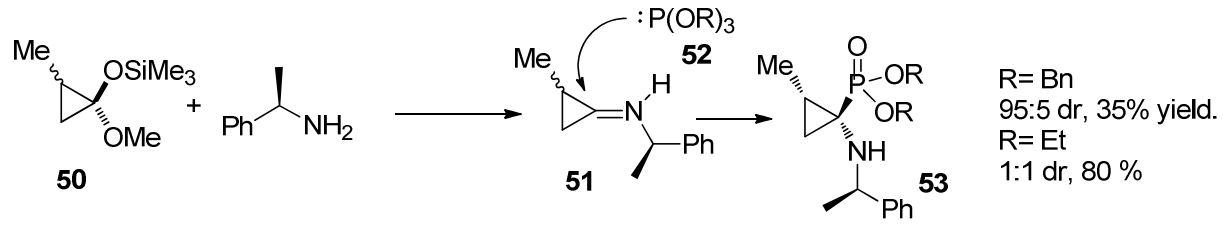
Scheme 19.



Fadel and co-workers reported an interesting approach for the synthesis of a wide variety of chiral aminocyclopropanephosphonic acids from readily available cyclopropyl acetals **50**.[28] The acetals serving as cyclopropanone equivalents are converted into iminium salts **51** in the

presence of a chiral amine and acid which then undergo an Arbuzov reaction with trialkyl phosphite **52** to give the corresponding phosphonates **53** in moderate yields (Scheme 20).

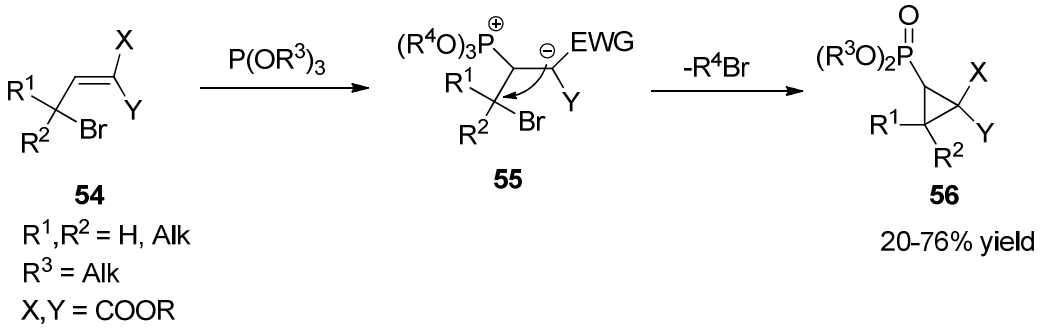
Scheme 20.



The stereoselectivity was controlled through the kinetic differentiation of diastereotopic faces, bulky substituents provided poor yields and good facial selectivity. Decreasing the steric demand increased yield but unfortunately dramatically dereased the facial selectivity (Scheme 20).

Michael-initiated ring closure (MIRC) as well as related 1,3-cyclizations have been utilized in the synthesis of a wide variety of cyclopropyl phosphonates.[29] For example, the reaction initiated by a Michael addition of a phosphite species onto a α-halo Micheal acceptor **54** afforded carbanion **55**, which undergoes an intramolecular 1,3-cyclization to furnish phosphonates **56** in a modified Arbuzov reaction (Scheme 21).

Scheme 21.



54

R^1,R^2 = H, Alk

R^3 = Alk

X,Y = COOR

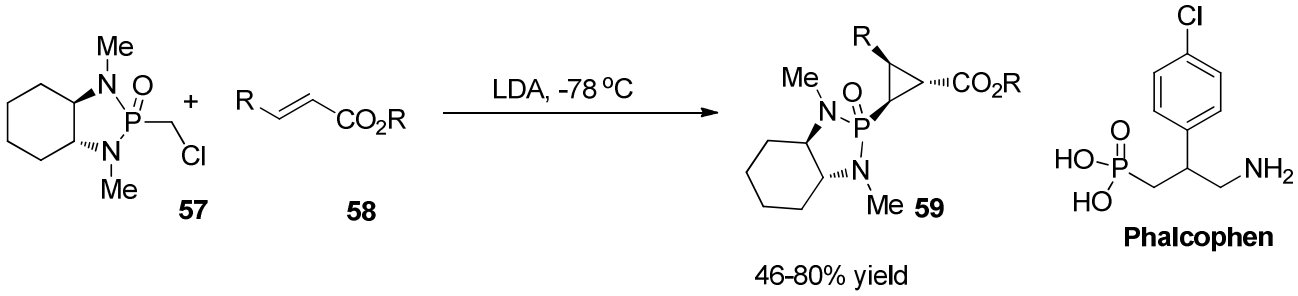
55

56

20-76% yield

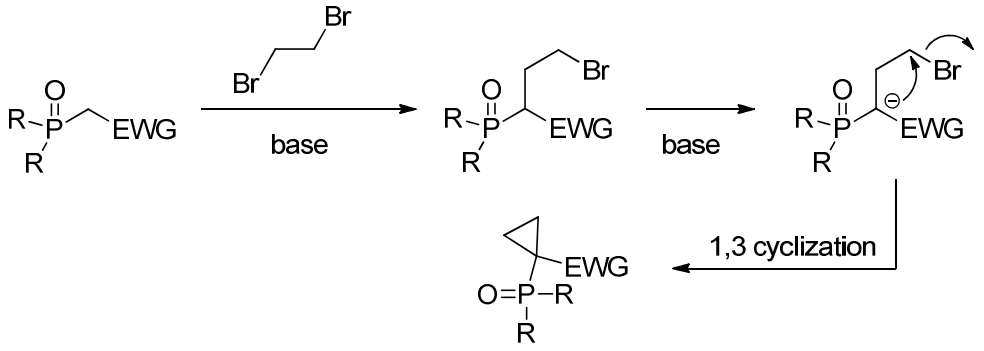
α-Halomethyl phosphonates in the presence of base also undergo Michael addition to α,β-unsaturated carbonyls followed by intamolecular cyclization to furnish cyclopropyl phosphonates This methodology was utilized by Swamy via a stereoselective synthesis of cyclopropylphosphonates from the reaction of readily accesible α-chlorophosphonates with alkyl acrylates and fumarates in the presence of sodium hydride.[30] Similarly, in 1997 a report by Hanessian demonstrated the stereocontrolled conjugate addition of anions derived from chiral α-chlorophosphonamides **57** to α,β-unsaturated esters **58** leading to the corresponding 3-chloro ester adducts which undergo intramolecular expulsion of the chlorine atom to give constrained analogs of the GABA antagonist Phaclophen[59] (Scheme 22).[31]

Scheme 22.



Cyclopropyl phosphine oxides/phosphonates may also be prepared via related 1,3 cyclizations[32] which often involve nucleophillic attack on dibromoethane by a phospha-methylene carbanion followed by intramolecular nucleophilic displacement (Scheme 23).

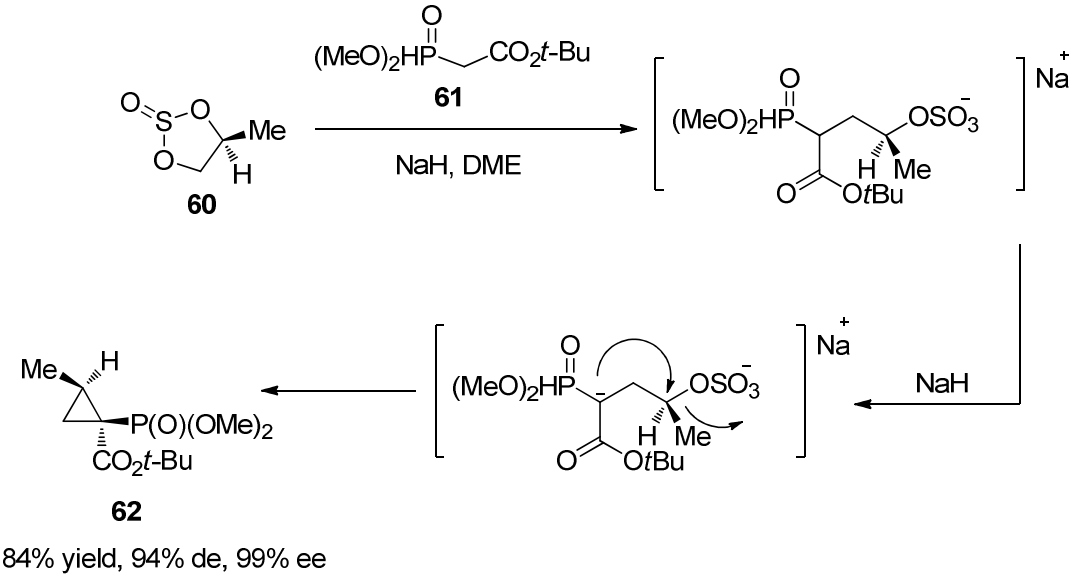
Scheme 23.



An interesting variation of this reaction was developed, for the synthesis of (1*R*,2*R*)-1-amino-2-methylcyclopropanephosphonic acid **62** which was achieved via the intramolecular

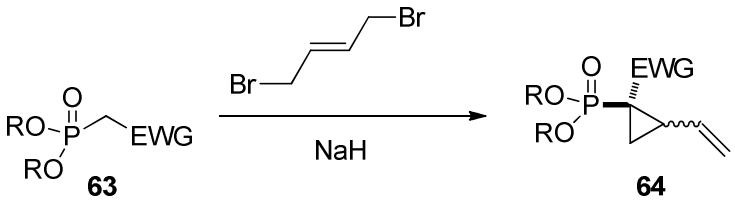
cycilzation of α-methylene phosphonate **61**.[33] The use of a non-racemic sulfonate ester **60** allowed for the efficient construction of the *allo*-norcoronamic acid derivative **62** in 99% ee.

Scheme 24.



Various other *1,3*-cyclizations have been reported.[34] For example, 2-vinyl cyclopropyl phosphonates **64** have been prepared *via* the reaction of *trans*-1,4-dibromo-2-butene with phosphonates **63** via an intramolecular cyclization of *in situ* generated alkylphosphonate anions (Scheme 25).[35]

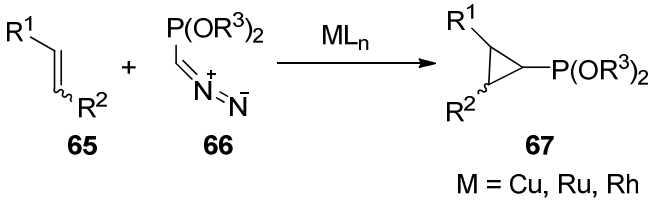
Scheme 25.



63 **64**

The synthesis of cyclopropyl phosphorus moieties **67** spans various modes of 2+1 cycloadditions.[36] One very common method for the synthesis of cyclopropanes, the metal-catalyzed decomposition of diazocompounds in the presence of alkenes, has not been extensively applied to the synthesis of cyclopropylphosphonates. A few copper,[37] rhuthenium,[38] and rhodium[39] catalyzed cycloaddions with diazomethylphosphonate **66** (DAMP) derivitives have been reported (Scheme 26).

Scheme 26.

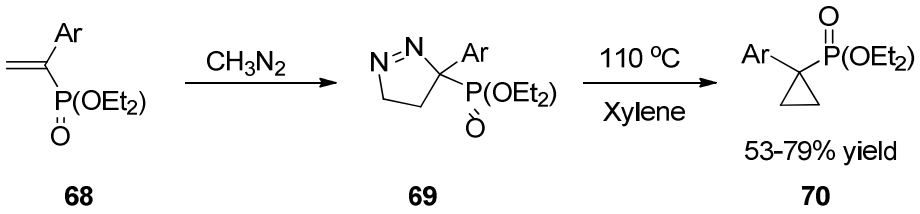


65 **66** **67**

Reactions of diazocompounds with vinyl phosphonates **68** are less prevalent,[40] however, studies have shown [2 + 3] cycloadditions with diazomethane to afford phosphonylated dihydropyrazoles **69**[41] which upon heating provide cyclopropyl phosphonates **70**. Beletskaya and

co-workers demonstrated this as a facile method accessing a rare class of cyclopropyl phosphonates.[42] This reaction is of interest since very few methods enable the synthesis of cyclopropyl phosphonates in the absence of electron withdrawing groups (Scheme 27).

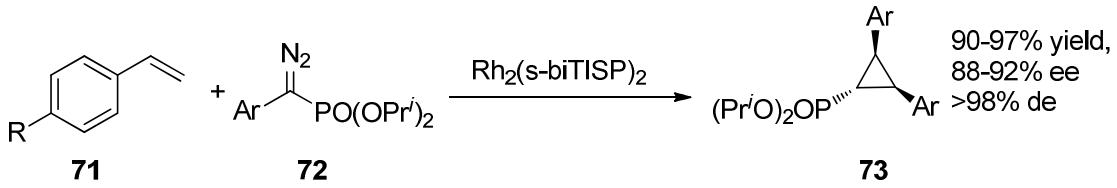
Scheme 27.



68 **69** **70**

In 2004 Davies and coworkers demonstrated the enantioselective synthesis of cyclopropylphosphonates **73** with good yields and high enantioselectivity *via* metal-catalyzed decomposition of diazo compounds **72** in the presence of alkenes **71**[43] (Scheme 28). It is the most general method for enantioselective preparation of cyclopropylphosphonates. Prior to this study only one example of enantioselective intermolecular cyclopropanation was known; the reaction of diisopropyl diazomethylphosphonate with styrene in the presence of a Ruthenium porphyrin complex affording marginal enantioselectivity.[44]

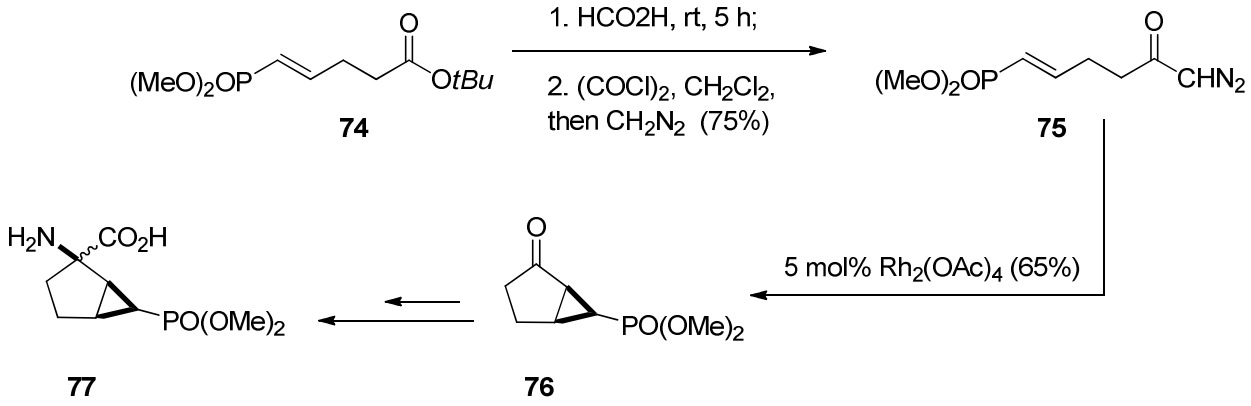
Scheme 28.



71 **72** **73**

Intramolecular versions of this transformation have also been reported, yielding bicyclic fused cyclopropylphosphonates **76**.[45] For example, Mann and co-workers developed a simple and expeditive route toward the synthesis of constrained cycloalkyl analogues of glutamic acid **77** utilizing a rhodium catalyzed intramolecular cyclopropanation of vinyl phosphonate **75**. (Scheme 29).[46]

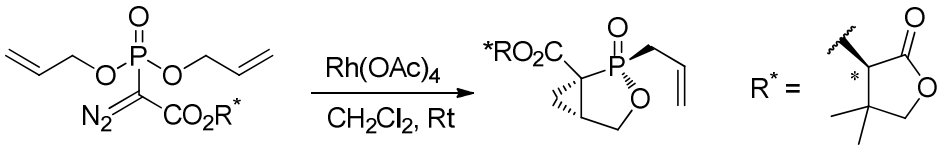
Scheme 29.



74 **75** **76** **77**

Hanson and co-workers have explored diastereoselective intramolecular cyclopropanations[47] with enantiopure allylic diazophosphonates **78**, in which a double diastereotopic differentiation strategy on a phosphonoacetate template was described. The approach utilizes $Rh_2(OAc)_4$ catalyzed intramolecular cyclopropanation (ICP) employing the (*R*)-pantolactone auxiliary **80** in the ester functionality of the phosphonoacetate. The olefinic diastereofacial selectivity of the bicyclic phosphonate **79** is governed by electronic and steric interactions in the reacting carbene intermediate, while the group selectivity is dictated by the chiral auxiliary (Scheme 30).

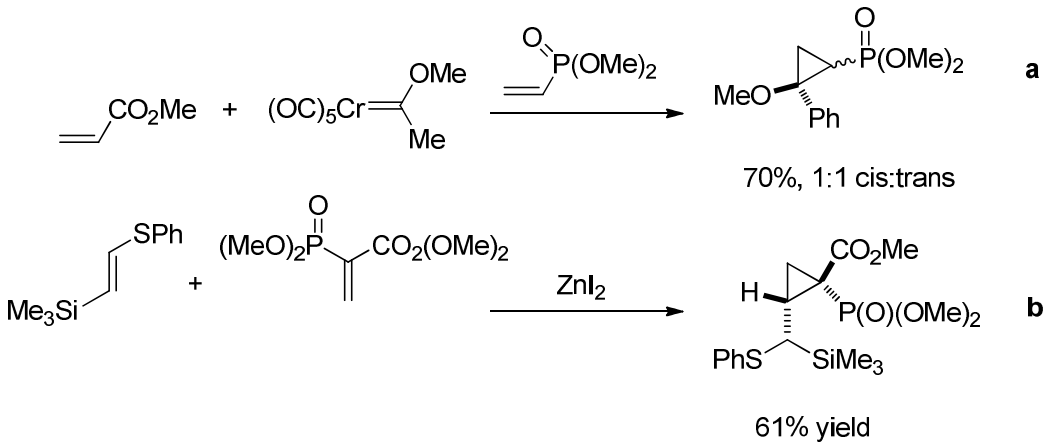
Scheme 30.



78 **79** **80**

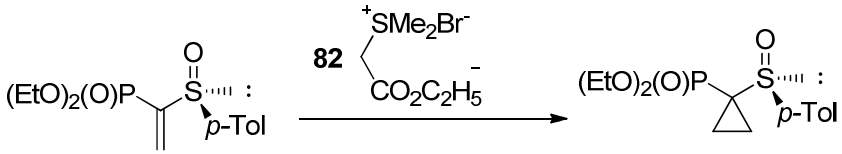
Other modes of [2+1] cycloaddions have been employed in the synthesis of cyclopropylphosphonates, including those involving Lewis acid activation (Scheme 31b)[48] as well as Fischer carbenes (Scheme 31a).[49]

Scheme 31.



Cycloadditions involving sulfur ylides have also been reported. In 2003, Mikolajczyk described asymmetric cyclopropanation of chiral phosphorylvinyl *p*-tolylsulfoxide **81** with ethyl (dimethylsulfuranylidene) acetate **82** (EDSA).[50]

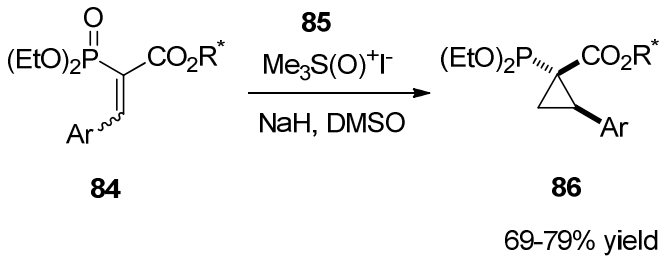
Scheme 32.



Corey-Chaykovsky reactions with sulfoxonium ylides have reported with phosphonoacrylates.[51] The cyclopropanation of aryl-phosphonoacrylates **84** with

dimethyloxosulfonium methylide **85** afforded *trans* cyclopropane derivatives **86** with high diastereoselectivity (Scheme 33).

Scheme 33.

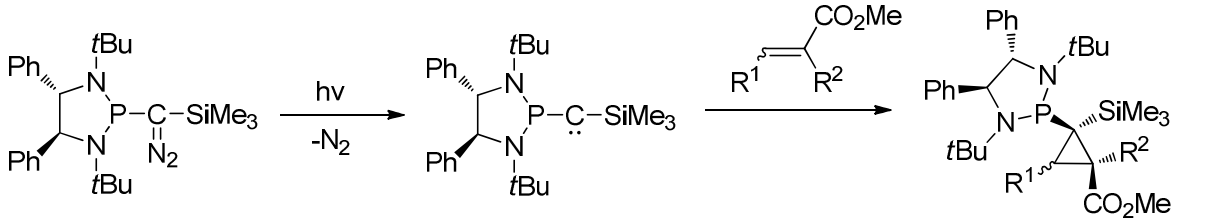


84 **86**

69-79% yield

Stable, enantiopure (phosphanyl)(silyl)carbenes **88**, generated from the decomposition of diazo compound **87** react efficiently with acrylates giving the corresponding cyclopropanes **89** in good yields. All monosubstituted alkenes provided exclusively the *syn* isomer with respect to the phosphanyl group, and the addition to disubstituted alkenes was totally stereospecific (Scheme 34).[52]

Scheme 34.



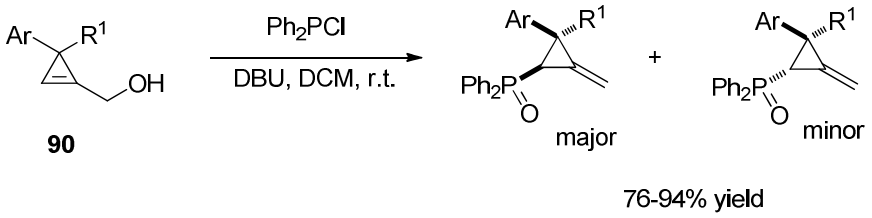
87 **88** **89**

R^1, R^2 = Ph, H, Alk

Up to 98% de

Some exceptional methods have been developed including electrochemical[53] and selective rearrangements.[54] Recently Rubin[55] and Marek[56] independently reported on a novel 2,3-rearrangement of cyclopropenylmethyl phosphinites to methylenecyclopropylphosphine oxides (Scheme 35). Marek reported the reaction was thermally activated however, Rubin found that in striking contrast to the analogous rearrangement known for nonstrained allylic systems, the reaction does not proceed at all upon thermal activation; however, it can be efficiently mediated by Lewis bases. Unique stereoelectronic effects control the diastereoselectivity of this transformation, leading to predominant formation of the more sterically hindered products of densely substituted methylenecyclopropylphosphine derivatives. This methodology represents a valuable alternative to the existing approaches.

Scheme 35.



While a number of methods have been developed for the preparation of cyclopropyl phosphonates, few methods have demonstrated broad scope, stereoselectivity and efficiency simultaneously. The high demand as well as the lack of general synthetic methods prompted the

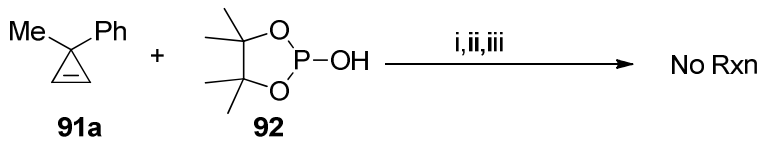
exploration of a new synthetic tool which would allow access to a wide variety of cyclopropylphosphonates and phosphine oxides.

1.2. Results and Discussion

1.2.1. Initial studies

Investigations into possible reaction conditions towards cyclopropylphosphonates began with different modes of possible addition of phosphonate species to cyclopropene. Thus, thermal, radical and base initiated reactions between 3-methyl-3-phenylcyclopropene **91a** and 4,4,5,5-tetramethyl-2-oxo-1,3,2-dioxaphospholane **92** were attempted and did not yield addition to the strained double bond (Scheme 36). Intrigued by the palladium catalyzed pronuclephillic additions to cyclopropanes reported by Yamamoto (Scheme 15), we began our investigations of the ring retentive palladium catalyzed hydrophosphorylation of cyclopropenes.

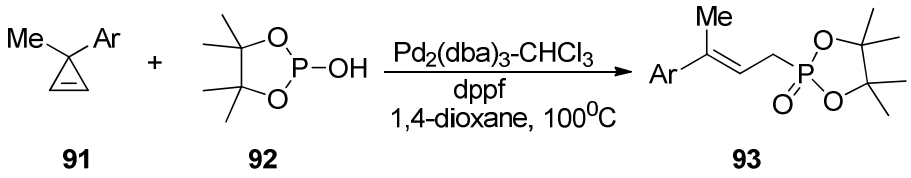
Scheme 36.



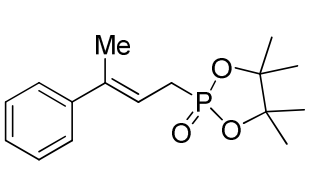
i: 100 °C, THF, ii: AIBN, CH_2Cl_2, iii: K_2CO_3, DMSO, 100 °C

Our optimizations began with cyclopropene **91a** and phosphonate **92** in the presence of various palladium sources and phosphine ligands (Table 1). Our intitial reaction conditions with $Pd(OAc)_2/PPh_3$ in dioxane at 100 ^oC (Table 1, entry 4) provided allylphosphonate **93a** as the sole product. Most catalytic systems tested provided sluggish reactions with mixtures of ring retention to ring opening. Gratifyingly, employment of Pd(0) sources allowed for reactions at lower temperatures and provided ring retentive hydrophosphorylation of cyclopropenes. In the case of relatively electron rich cyclopropenes **91**, we were able to drive the exclusive formation of allylphosphonates **93 a-c** at high reaction temperatures even in the presence of a Pd(0) source (Scheme 37).

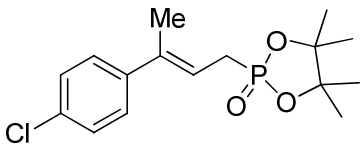
Scheme 37.



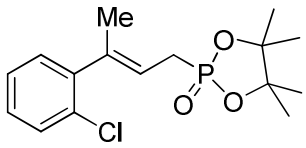
91 **92** **93**



93a, 85%



93b, 67%

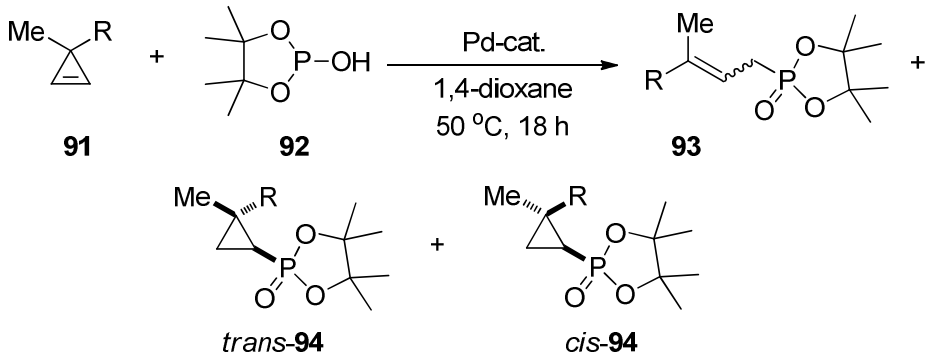


93c, 80%

Varying the structural and electronic properties of the ligand had a marked affect on the outcome of the reaction. For example, TTMPP with $Pd_2dba_3 \cdot CHCl_3$ only yielded a 13% GC conversion to desired phosphonate **94.** Employment of the electron-rich bidentate ligand dppf

provided 98% GC conversion to phosphonate **94** (Table 1 entry 8). However only a moderate facial selectivity of 4:1 (*trans:cis*) was observed. Employment of this catalytic system in the reaction of phosphonate **92** in the presence of cyclopropene **91b** bearing an electron withdrawing carboxylate functionality provided nearly quantative conversion with excellent facial selectivity of 19:1 (Table 1, entry 11), while $Pd(PPh_3)_4$ provided only 3:1 facial selectivity (Table 1, entry 10).

Table 1. Optimizing conditions for ring retentive hydrophosphorylation.



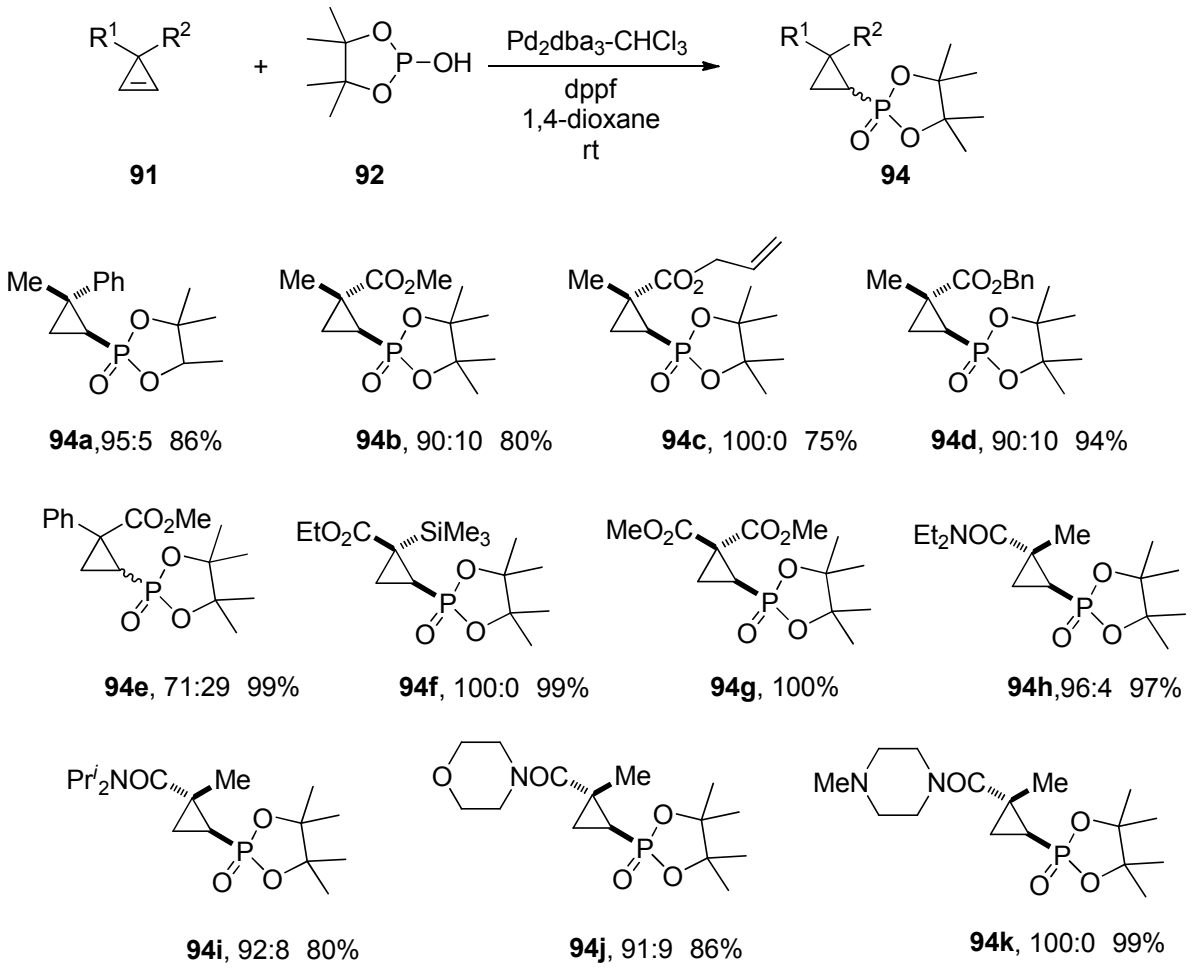
no.	R	catalyst	**94**, % (trans/cis)[b]	**93**, %[b]
1	Ph	(π-allylPdCl)$_2$/TTMPP[c]	60 (2.5:1)	10
2	Ph	(π-allylPdCl)$_2$/ PPh_3	7 (N/D)	-
3	Ph	$Pd(OAc)_2$/TTMPP	45 (15:1)	40
4	Ph	$Pd(OAc)_2/PPh_3$[d]	0	90
5	Ph	$Pd(OAc)_2$/ PPh_3	30 (4.5:1)	34
6	Ph	$Pd_2dba_3 \cdot CHCl_3$/TTMPP	13 (N/D)	-
7	Ph	$Pd_2dba_3 \cdot CHCl_3$/dppe	NR	-
8	Ph	$Pd_2dba_3 \cdot CHCl_3$/dppf	98 (4:1)	-
9	Ph	$Pd(PPh_3)_4$	89 (19:1)	6
10	CO_2Me	$Pd(PPh_3)_4$	100 (3:1)	-
11	CO_2Me	***$Pd_2dba_3 \cdot CHCl_3$/dppf***	97 (9:1)	-

(a) Reactions performed on a 0.1 mmol scale. (b) GC conversion.
(c) TTMPP - tris(2,4,6-trimethoxyphenyl)phosphine.

1.2.2. Hydrophosphorylation of cyclopropenes

We then set out to investigate the scope and limitations of the reaction with the optimized reaction conditions in hand. The installation of electron withdrawing groups at C-3 had a significant effect on the outcome of the reaction. For example, carboxylate and carboxamide substituted cyclopropanes did not provide allylphosphonate products even at elevated temperatures in the presence of Pd(II) sources. In contrast to the phenyl-substituted analog, these more stable carboxylate substituted cyclopropenes reacted smoothly at rt within 1-2 hrs providing densely substituted cyclopropyl phosphonates in excellent yields and good facial selectivities. 3-Carboxamide substituted cyclopropenes required slightly elevated temperatures (Scheme 38).

Scheme 38.



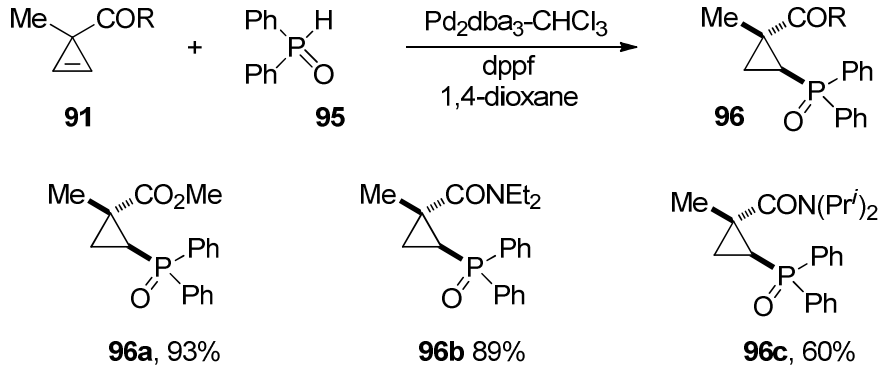
The diastereoselectivity of hydrophosphorylation was controlled by sterics, as evident from the comparison of the results obtained using 1-methyl-substituted cyclopropenylcarboxylates **91b-d** with those of the 1-phenyl- (**91e**) and 1-TMS-substituted analogs (**91f**). Indeed, while the reactions of cyclopropenes **91b-d** predominantly provided

products **94a-d** in a *trans*-configuration, introduction of the bulky phenyl substituent in the structure (**91e**) led to a significant deterioration of the diastereoselectivity (**94e**). Finally, installation of an even larger TMS-group (**91f**) resulted in reversal of diastereoselectivity, affording cyclopropyl phosphonate **94f** with the phosphorus moiety oriented *cis* with respect to the ester function.

1.2.3. Hydrophosphinylation

The recent advances in the development of cyclopropyl based phosphine ligands[23, 24] prompted us to explore the possibility of hydrophosphinylation. To our delight the conditions optimized for hydrophosphorylation also proved efficient for the hydrophosphinylation reaction (Scheme 39). The reactivity pattern was similar to that observed in the hydrophosphorylation reaction. Thus, ester **91b** underwent the transformation quickly at room temperature, while reaction of amides **91i** and **91l** required extended heating at 50-55 ^{o}C for complete conversion. Importantly, in all three cases the corresponding cyclopropylphosphine oxides **96a-c** were obtained in excellent yield as single diastereomers (Scheme 39).

Scheme 39.

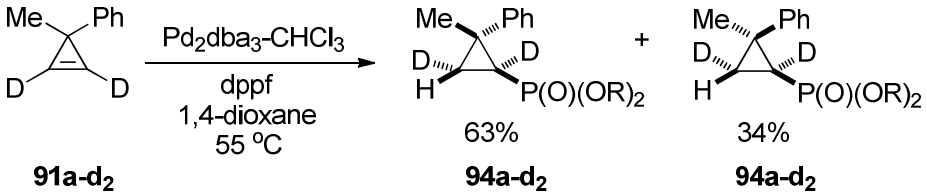


Reaction conditions.**61a**: 1 h at 25 ^{o}C; **61b**: 48 h at 55 ^{o}C; **61c**: 78 h at 50 ^{o}C.

1.2.4. Investigation of the reaction mechanism

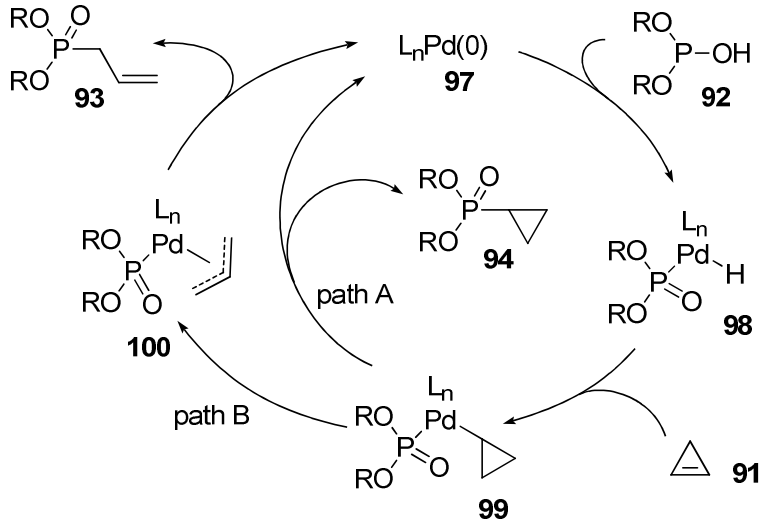
Subjection of deuterated cyclopropene **91a-d$_2$** to the optimized reaction conditions provided a mixture of two diastereomers **94a-d$_2$** and **94a-d$_2$** (Scheme 40). In both cases the deuterium labels were found to have a relative *cis* relationship to each other. This is experimental evidence that the reaction mechanism involves a *syn*-specific concerted hydropalladation step.

Scheme 40. Hydrophosphorylation of dueterated cyclopropene



Based on these observations a plausible mechanistic rationale for this transformation is proposed (Scheme 41). First, oxidative addition of palladium into the P-H bond produces palladium hydride species **98**. Subsequent migratory insertion of cyclopropene **91** affords cyclopropylpalladium complex **99**. The latter, upon reductive elimination (path A), produces cyclopropylphosphonate **94**. Alternatively, at higher temperatures, species **99** would undergo ring cleavage via β-carbon elimination (path B). The resulting π-allylpalladium species **100**, after reductive elimination, would affordallylphosphonate **93**.

Scheme 41. Mechanistic rationale for the Pd-catalyzed hydrophosphorylation of cyclopropenes.

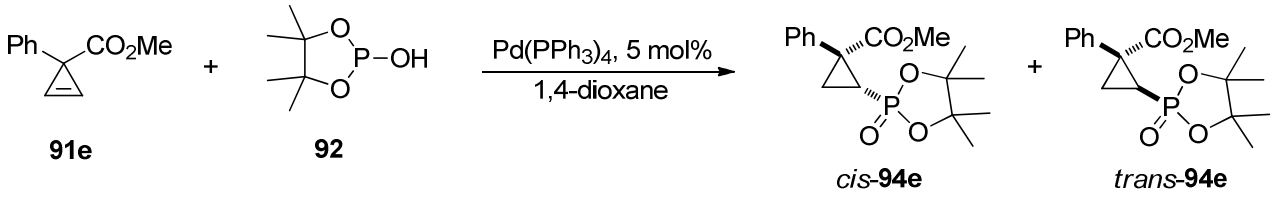


This mechanism is supported by several observations. The steric control of the diastereoselectivity is evidence of the hydropalladation step, since coordination of cyclopropene **91** to species **98** would favor the less hindered face providing the observed *trans*-selectivity. Also, the observation that cyclopropenes bearing electron withdrawing funtionalites did not provide ring opening products **93** could be explained by the destabilization of the π-allylpalladium species **100.** It should also be noted that the installation of bulky ligands around the metal center facilitates reductive elimination thereby avoiding β-carbon elimination which would furnish allyl phosphonate **93**.

According to the mechanistic rationale proposed in Scheme 2, the diastereoselectivity of the reaction is controlled by steric factors at the hydropalladation step **98→99**. Since this step proceeds with release of strain energy, it should be irreversible and, therefore, kinetically-

controlled. Thus, our experiments demonstrated that the diastereoselectivity in the hydrophosphorylation of cyclopropene **91e** deteriorates at higher temperatures (Table 2), which is consistent with the proposed reaction mechanism.

Table 2. Temperature Effect Observed in the Palladium-Catalyzed Hydrophosphorylation of 91e.



no.	temperature, ^{o}C	*trans*/*cis* ratio
1	20	1.63:1
2	40	1.60:1
3	60	1.51:1
4	100	1.10:1

1.3. Conclusion

In conclusion, a novel, efficient transition metal-catalyzed method for diastereoselective addition of cyclic phosphites and phosphine oxides across the strained double bond of cyclopropene was developed. The formation of allylic phosphonates was avoided by employing a Pd(0)/bulky ligand catalyst system which facilitates reductive elimination. The mechanism is supported by experimental evidence which insists on a hydropalladation step, thus providing insight as to the diastereoselectivity. This transformation is applicable to a wide range of 3,3-disubstituted cyclopropenes and is general with respect to the electronic nature of the P-H entity. The discovered method has great potential for providing expeditious access to a series of novel functionalized cyclopropylphosphonic acids and cyclopropylphosphines.

1.4. Experimental Procedures

1.4.1. Materials and Methods.

NMR spectra were recorded on a Bruker Avance DPX-400 instrument, equipped with a quadruple-band gradient probe (H/C/P/F QNP) or Bruker Avance DRX-500 with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broad-band decoupling. Signs (+) and (-) represent positive and negative intensities of signals in the ^{13}C DEPT-135 or in phase-edited HSQC experiments. Column chromatography was carried out

employing silica gel (Selecto Scientific, 63-200 µm). Pre-coated silica gel plates (Merck Kieselgel 60 F-254) were used for thin-layer chromatography. GC/MS analyses were performed on a Shimadzu GC-2010 gas chromatograph interfaced to a Shimadzu GCMS 2010S mass selective detector, and equipped with an AOC-20i auto-injector and an AOC-20S auto-sampler tray (150 vials). 30 m x 0.25 mm x 0.25 µm capillary column, SHR5XLB, polydimethylsiloxane, 5% Ph was employed. Helium (99.96%), additionally purified by passing consecutively through a CRS oxygen/moisture/hydrocarbon trap (#202839) and VICI oxygen/moisture trap (P100-1), was used as a carrier gas.

Anhydrous methanol was obtained from commercially available HPLC-grade solvent by double distillation from sodium metal chunks under inert atmosphere. Anhydrous dioxane was prepared by refluxing commercially available ACS-grade product with sodium-ketyl complex, followed by distillation in slow stream of nitrogen. Anhydrous dimethylsulfoxide was purchased form Sigma-Aldrich and used as received. Palladium complexes and phosphine ligands were obtained from Strem Chemicals.

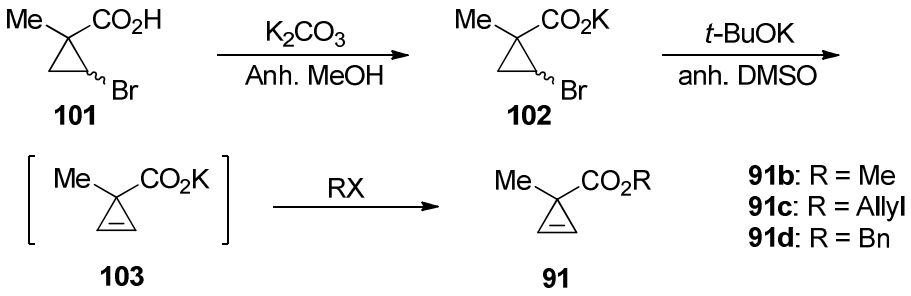
1.4.2. Synthesis of cyclopropene carboxylates

3-methyl-3-phenylcyclopropene **91a**,[57] methyl 1-phenyl-2-cyclopropenecarboxylate[58] **91e**, ethyl 3-(trimethylsilyl)-3-cyclopropenecarboxylate **91f** ,[57] dimethyl cycloprop-2-ene-1,1-dicarboxylate **91g**,[10] and cyclopropenylcarboxamides[113] were prepared according to published procedures. Syntheses of all other cyclopropenes are described in the following section. 4,4,5,5-Tetramethyl-1,3-dioxaphospholane-2-oxide **92** was obtained from pinacol and PCl_3 according to

the published procedure.[58] All other chemicals were purchased from commercial sources and used as received.

Esters of 1-methylcycloprop-2-ene-1-carboxylic acid were prepared according to the modified Baird-Bolesov protocol[59], involving dehydrohalogenation of potassium 2-bromo-1-methylcyclopropyl carboxylate. This approach helps to circumvent problems associated with low stability of the ester function towards nucleophilic attack by *tert*-butoxide under the relatively harsh reaction conditions required for installation of the cyclopropene double bond. To a suspension of K_2CO_3 (50 g, 0.36 mol) in anhydrous MeOH (250 mL) was added 2-bromo-1-methylcyclopropanecarboxylic acid **101**[60] (32.6 g, 0.18 mol) in 100 mL of MeOH. The mixture was stirred overnight, filtered under pressure of dry nitrogen, and evaporated dry to obtain solid potassium 2-bromo-1-methylcyclopropyl carboxylate **102**. To completely remove the remaining methanol, the solid was powdered and dried in vacuum (< 1 torr) at 90-100 ^oC for 15 hrs.

Scheme 42: Synthesis of Cyclopropene Carboxylates



Methyl 1-methylcycloprop-2-ene-1-carboxylate (91b): Typical procedure.

Potassium 2-bromo-1-methylcyclopropyl carboxylate **101** (32.46 g, 149 mmol) was dissolved in 150 mL of anhydrous DMSO and added rapidly via a cannula to a solution of potassium tert-butoxide (20 g, 180 mmol) in 30 mL of DMSO (the solution was prepared by heating the mixture to 60 ^{o}C until the solid was dissolved, then cooling to 30 ^{o}C). The mixture was stirred at 50 ^{o}C for 2 hrs. Over this time, the reaction mixture turned very viscous and further stirring became impossible. Then methyl iodide (37 mL, 0.6 mol) was added with cooling and the liquefied mixture was stirred for 30 min, quenched with water, and extracted with ether. Combined organic solutions were washed with water, brine, dried over $MgSO_4$, filtered, and evaporated. The residue was distilled in vacuum (bp. 68-70 ^{o}C/75 torr) to provide 8.64 g (77.1 mmol, 52%) of titled cyclopropene **91b**. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 6.98 (s, 2H), 3.63 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 177.5, 109.9 (+, 2C), 51.9 (+), 27.7, 21.7 (+).

Allyl 1-methylcycloprop-2-ene-1-carboxylate (73c).

The reaction was carried out according to the typical procedure, starting from 20 g (91.4 mmol) of carboxylate **101** followed by quenching with allyl bromide (17.3 mL, 200 mol) instead of methyl iodide, to afford the titled cyclopropene as a colorless oil, b.p. 60-64 ^{o}C/10 torr. Yield 7.83 g, (56.7 mmol, 62%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.01 (s, 2H), 5.90 (ddt, *J* = 17.2 Hz, 10.6 Hz, 5.6 Hz 1H), 5.28 (dq, *J* = 17.2 Hz, 1.5 Hz, 1H), 5.20 (dq, *J* = 10.6 Hz, 1.5 Hz, 1H), 4.55 (dt, *J* = 5.6 Hz, 1.5 Hz, 2H), 1.41 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 176.6, 132.4 (+), 117.4 (-), 109.8 (+, 2C),

65.2 (-), 27.7, 21.6 (+). GC/MS: m/z 138 (M+) <1%, 123 (M-Me) <1%, 97 (M-All) 15%, 53 (M-CO_2All) 100%.

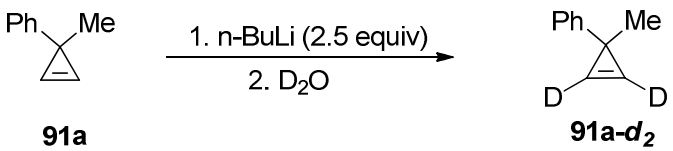
Benzyl 1-methylcycloprop-2-ene-1-carboxylate (91d).

The reaction was carried out according to the typical procedure, starting from 2.0 g (9.14 mmol) of carboxylate **101** followed by quenching with benzyl bromide (1.2 mL, 10 mmol) instead of methyl iodide, to afford the titled cyclopropene. Purification by preparative column chromatography on Silica gel (eluent hexane/EtOAc 20:1, R_f 0.31) afforded a colorless oil, yield 687 mg (3.66 mmol, 40%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.43-7.31 (m, 5H), 7.04 (s, 2H), 5.13 (s, 2H), 1.46 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 176.8, 136.4, 128.4 (+, 2C), 128.9 (+), 127.7 (+, 2C), 109.8 (+, 2C), 66.2 (-), 27.7, 21.7 (+); GC/MS: m/z 188 (M+) <1%, 91 ($PhCH_2^+$) <60%, 53 (M-CO_2Bn) 100%.

1.4.3 Preparation of deuterium-labeled cyclopropene

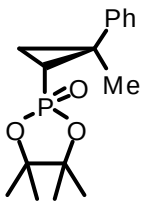
Scheme 43



91a **91a-*d*$_2$**

94a-d_2: To a stirred solution of cyclopropene **91a** (2.00 g, 15.4 mmol) in anhydrous hexanes (20 mL) at -30 ^{o}C was added a solution of *n*-butyllithium (2.5 M in hexane, 15.4 mL, 38.5 mmol, 2.5 equiv). The mixture was stirred for 30 min at 0 ^{o}C and quenched with deuterium oxide (3 mL, 150 mmol, 9.7 equiv). The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was distilled in vacuum (bp 60-62 ^{o}C at 10 torr) to afford **62**-d_2 as a colorless oil. Yield 1.80 g (13.6 mmol, 89%). ^{1}H NMR and EI MS analyses indicated a deuterium incorporation of 80-85% at both the C1 and C2 positions.

1.4.4 Synthesis of Cyclopropylphosphonates



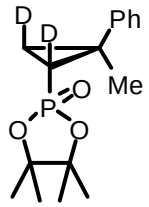
Typical procedure A. **94a:** In a nitrogen filled glove box, a dry 4 ml Wheaton vial was charged with palladium tetrakis (5.8 mg, 0.05 mmol, 10 mol%) and 2.0 ml of dioxane. 4,4,5,5-Tetramethyl-2-oxo-1,3,2-dioxaphospholane (82.0 mg, 0.5 mmol) was added and the resulting mixture was stirred for 1 min. Cyclopropene **91a** (98 mg, 0.75 mmol, 1.5 eq) was added and the reaction mixture was stirred for 1 hr at r.t. The solvent was removed in vacuum and purified by preparative column chromatography on silica gel, eluting with hexane: EtOAc 3:2 to afford 125 mg (0.43 mmol, 86%) of *trans*-**94a**.

Typical procedure B. All loading operations were performed in a nitrogen-filled glovebox. An oven-dried 2 mL Wheaton vial was charged with 1,1'-bis (diphenylphosphino)ferrocene (dppf) (27.7 mg, 0.05 mmol, 10 mol%), tris(dibenzylideneacetone) dipalladium chloroform adduct (12.9 mg, 0.025 mmol, 5 mol%), and dry dioxane (1 mL). The mixture was stirred at r.t. for 5 min, then 4,4,5,5-tetramethyl-2-oxo-1,3,2-dioxaphospholane (**2**) (82.0 mg, 0.5 mmol) and

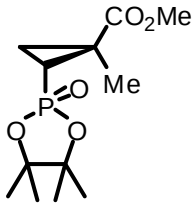
cyclopropene **91a** (98 mg, 0.75 mmol, 1.5 equiv) were added. The reaction mixture was stirred for 18 hrs at 55 ^{o}C. When GC/MS analysis showed the reaction was complete, the mixture was filtered through a short bed of silica gel and concentrated in vacuum. The residue was purified by preparative column chromatography on silica gel, eluting with hexane/EtOAc, 3:2 to afford 131 mg (0.45 mmol, 71%) of major (R_f 0.20) and 19 mg (0.06 mmol, 11%) of minor (R_f 0.15) diastereomer.

Major (*trans*-**94a**): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.33-7.30 (m, 4H), 7.25-7.21 (m, 1H), 1.72 (s, 3H), 1.54 (s, 6H), 1.52-1.44 (m, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.07 (ddd, J = 9.4 Hz, 6.3 Hz, 4.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 146.1 (d, $^{3}J_{PC}$ = 3.7 Hz), 128.5 (+, 2C), 127.3 (+, 2C), 126.5 (+), 87.73, 87.66, 28.4 (d, $^{2}J_{CP}$ = 4.4 Hz), 24.7 (d, $^{3}J_{CP}$ = 3.7 Hz, +), 24.5 (d, $^{3}J_{CP}$ = 3.7 Hz, +, 2C), 23.9 (d, $^{3}J_{CP}$ = 5.9 Hz, +), 22.2 (d, $^{3}J_{CP}$ = 5.1 Hz, +), 20.7 (d, $^{1}J_{CP}$ = 183.7 Hz, +), 19.6 (d, $^{2}J_{CP}$ = 5.1 Hz, -); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 42.1; GC/MS (R_f = 14.25 min) *m/z* 294 (1%, M^{+}), 279 (1% M-Me), 211 (40%), 130 (100%); HRMS (TOF ES) Found 317.1286, Calculated for $C_{16}H_{23}O_3PNa$ (M+Na) 317.1283 (0.9 ppm). **Minor** (*cis*-**94a**): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 1.79 (ddd, $^{3}J_{HP}$ = 19.7 Hz, J_{HH} = 5.8 Hz, 4.6 Hz, 1H), 1.49 (d, $^{4}J_{HP}$ = 2.3 Hz, 3H), 1.46 (s, 3H), 1.42 (s, 6H), 1.37 (s, 3H), 1.26 (ddd, $^{3}J_{HP}$ = 10.1 Hz, J_{HH} = 9.1 Hz, 4.6 Hz, 1H), 1.01 (ddd, $^{2}J_{HP}$ = 5.1 Hz, J_{HH} = 9.1 Hz, 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 141.4 (d, $^{3}J_{PC}$ = 5.1 Hz), 128.9 (+, 2C), 128.1 (+, 2C), 126.9 (+), 87.6, 86.9, 29.5 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 29.3 (d, $^{2}J_{CP}$ = 4.4 Hz), 24.7 (d, $^{3}J_{CP}$ = 2.9 Hz, +), 24.5 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 24.4 (d, $^{3}J_{CP}$ = 5.1 Hz, +), 23.8 (d, $^{3}J_{CP}$ = 6.6 Hz, +), 21.9 (d, $^{1}J_{CP}$ = 185.9 Hz, +), 18.5 (d, $^{2}J_{CP}$ = 5.1 Hz, -);

^{31}P NMR (161.98 MHz, $CDCl_3$) δ 40.6; GC/MS (R_f = 13.91 min) *m/z* 294 (1%, M+), 279 (1% M-Me), 211 (30%), 130 (100%).

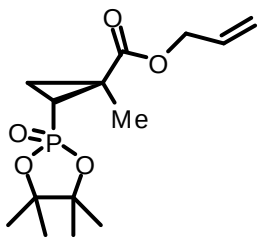


94a-d_2: The reaction was performed according to the typical procedure B starting with 79 mg (0.6 mmol, 1.5 equiv) of cyclopropene **62**-d_2. The residue was purified by preparative column chromatography on silica gel, eluting with hexane:EtOAc, 3:2 to afford 77 mg (0.25 mmol, 63%) of major (R_f 0.20) and 40 mg (0.13 mmol, 34%) of minor (R_f 0.15) diastereomer.



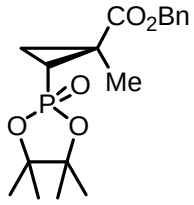
94b: The reaction was performed according to the typical procedure B, employing **91b** (65mg, 0.5mmol). The crude residue was purified by preparative column chromatography eluting with EtOAc/hexanes (3:1) (R_f 0.26). Yield: 110 mg, (0.40 mmol, 80%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ3.72 (s, 3H), 1.62 (s, 3H), 1.60 (m, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.36 (m, 1H) 1.31 (m, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ174.2(d, $^3J_{CP}$ = 4.4 Hz), 88.4, 88.1, 53.0 (+), 24.7 (d, $^2J_{CP}$ = 2.9 Hz), 24.6 (d, $^3J_{CP}$ = 3.7 Hz, +), 24.5 (d, $^3J_{CP}$ = 4.4 Hz, +), 24.1 (d, $^3J_{CP}$ = 5.9 Hz, +), 23.9 (d, $^3J_{CP}$ = 5.9 Hz, +), 21.5 (d, $^1J_{CP}$ = 185.1 Hz, +), 21.1 (d, $^2J_{CP}$ = 5.1 Hz, -), 14.8 (d, $^3J_{CP}$ = 4.4 Hz, +); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 38.8; GC/MS (R_t = 12.48 min) *m/z* 276 (1%, M^+), 261 (3%, M – Me), 245 (10%, M - OMe), 162 (100%); HRMS (TOF ES) Found 277.1205, 299.1017, Calculated for $C_{12}H_{22}O_5P$ (M+H) 277.1205 (0.0 ppm), $C_{12}H_{21}O_5PNa$ (M+Na) 299.1024 (2.3 ppm).



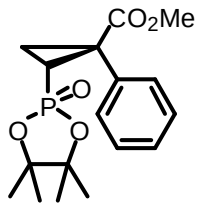
94c: The reaction was performed according to the typical procedure B, employing cyclopropene **91c** (70mg, 0.5mmol). The crude reaction mixture was purified by preparative column chromatography eluting with EtOAc/hexane (1:1) (R_f 0.35) to give 113 mg (0.38 mmol, 75%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.9 (ddt, *J* = 17.2 Hz, 10.9 Hz, 5.6 Hz, 1H), 5.3 (ddt, *J* = 17.2 Hz, 2H), 4.6 (d, *J* = 5.6 Hz, 2H), 1.64 (s, 3H), 1.62 (m, 2H), 1.51 (s, 3H), 1.50 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.60 (s, 3H), 1.35 (m, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 173.3 (d, $^3J_{CP}$ = 5.1 Hz), 131.8 (+), 118.0 (-), 88.3, 88.1, 65.8 (-), 53.4 (+), 24.76, 24.72 (+), 24.6 (d, $^3J_{CP}$ = 3.7 Hz, +), 24.4 (d, $^3J_{CP}$ = 4.4 Hz, +), 24.1 (d, $^3J_{CP}$ = 5.1 Hz, +), 23.9 (d, $^3J_{CP}$ = 5.1 Hz, +), 21.6 (d, $^1J_{CP}$ = 185.9 Hz, +), 21.1 (d, $^2J_{CP}$ = 3.7 Hz, -), 14.8 (+); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 38.7; GC/MS (R_t = 13.22 min) *m/z* 302 (1%, M^+), 287 (3%, M - Me), 245 (10%, M- OC_3H_5), 83 (100%); HRMS (TOF ES) Found 315.1133, Calculated for $C_{18}H_{20}O_3P$ (M+H) 315.1150 (8.3 ppm).



94d: The reaction was performed according to the typical procedure B, employing cyclopropene **91d** (94 mg, 0.5 mmol). The crude residue was purified by preparative column chromatography eluting with EtOAc/Hexanes (2:1) (R_f 0.30). Yield: 169 mg, (0.47 mmol, 94%).

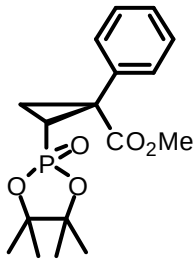
^{1}H NMR (400.13 MHz, $CDCl_3$) δ (m, 5H), 5.16 (d, *J* = 12.6 Hz), 5.14 (d, *J* = 12.6 Hz), 1.71-1.57 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.60 (s, 3H), 1.37-1.32 (m, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ (d, $^{3}J_{CP}$ = 4.4 Hz), 135.7, 128.6 (+, 2C), 128.3 (+), 127.9, (+, 2C), 88.3, 88.2, 67.0 (-), 24.9 (d, $^{2}J_{CP}$ = 2.2 Hz), 24.8 (d, $^{3}J_{CP}$ = 3.7 Hz, +), 24.5 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 24.2 (d, $^{3}J_{CP}$ = 5.1 Hz, +), 23.9 (d, $^{3}J_{CP}$ = 5.9 Hz, +), 21.7 (d, $^{1}J_{CP}$ = 185.2 Hz, +), 21.2 (d, $^{2}J_{CP}$ = 5.1 Hz, -), 15.0 (d, $^{3}J_{CP}$ = 4.4 Hz, +); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 38.6; GC/MS (R_t = 17.01 min) *m/z* 352 (7%, M^+), 91 (100%, $PhCH_2^+$); HRMS (TOF ES) Found 375.1339, Calculated for $C_{18}H_{25}O_5PNa$ (M+Na) 375.1137 (0.5 ppm).



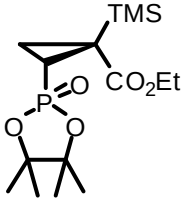
94e: The reaction was performed according to the typical procedure B, employing cyclopropene **91e** (174 mg, 1.0 mmol). The crude residue was separated by preparative column chromatography (eluent: EtOAc/CH_2Cl_2/hexanes 3:1:1) to afford two fractions (R_f 0.32) and (R_f 0.22). Yields 119.4 mg (35 mmol, 71%) and 47.8 mg (14 mmol, 28%), respectively.

Major (*trans*-**94e**): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.57-7.49 (m, 3H), 3.68 (s, 3H), 2.23-2.09 (m, 3H), 1.67 (s, 3H), 1.632 (s, 3H), 1.626 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 173.3, 134.2 (d, $^{3}J_{CP}$ = 5.1 Hz), 130.8 (+, 2C), 127.90 (+), 127.85 (+, 2C), 88.2, 87.6, 53.0 (+), 34.6 (d, $^{2}J_{CP}$ = 2.9 Hz), 24.6 (d, $^{3}J_{CP}$ = 3.7 Hz, +), 24.4 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 24.3 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 23.8 (d, $^{3}J_{CP}$ = 2.9 Hz, +), 22.9 (d, $^{1}J_{CP}$ = 195.4 Hz, +), 19.4 (d, $^{2}J_{CP}$ = 5.1 Hz, -); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 36.5; HRMS (TOF ES): Found 361.1176

(100%), 339.1349 (30%); Calculated for $C_{17}H_{24}O_5PNa$ (M+Na) 361.1181 (0.5 ppm), $C_{17}H_{24}O_5P$ (M+H) 339.1361 (1.2 ppm).

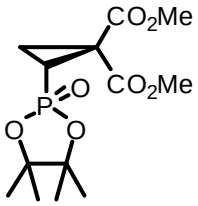


Minor (*cis*-**94e**): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ7.44-7.42 (m, 2H), 7.35-7.29 (m, 3H), 3.71 (s, 3H), 2.19 (ddd, J_{PH} = 20.0 Hz, J = 7.1 Hz, 4.3 Hz, 1H), 1.68-1.55 (m, 2H), 1.533 (s, 3H), 1.528 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.6 (d, $^3J_{CP}$ = 7.3 Hz), 138.1 (d, $^3J_{CP}$ = 3.7 Hz), 129.3 (+, 2C), 128.3 (+, 2C), 127.8 (+), 87.92, 87.87, 52.7 (+), 36.7 (d, $^2J_{CP}$ = 4.4 Hz), 24.6 (d, $^3J_{CP}$ = 3.7 Hz, +), 24.3 (d, $^3J_{CP}$ = 4.4 Hz, +), 24.2 (d, $^3J_{CP}$ = 4.4 Hz, +), 23.8 (d, $^3J_{CP}$ = 5.9 Hz, +), 22.7 (d, $^1J_{CP}$ = 185.2 Hz, +), 18.4 (d, $^2J_{CP}$ = 4.4 Hz, -); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 37.8; HRMS (TOF ES): Found 361.1166 (100%), 339.1354 (80%); Calculated for $C_{17}H_{24}O_5PNa$ (M+Na) 361.1181 (1.5 ppm), $C_{17}H_{24}O_5P$ (M+H) 339.1361 (0.7 ppm).

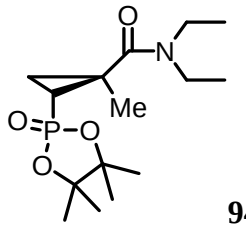


94f: The reaction was performed according to the typical procedure B, employing cyclopropene **91f** (92 mg, 0.5 mmol) using THF as a solvent. The crude residue was purified by preparative column chromatography eluting with EtOAc/hexanes (3:1) to give light-brown oil (R_f 0.31). Yield: 172 mg (0.49 mmol, 99%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 4.20-4.14 (m, 2H), 1.80 (ddd, $^3J_{PH}$ = 17.7 Hz, J = 6.1 Hz, 4.0 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.15 (ddd, $^3J_{PH}$ = 9.9 Hz, J = 8.3 Hz, 4.0 Hz, 1H), 0.93 (ddd, $^2J_{PH}$ = 6.3 Hz, J = 8.3 Hz, 6.1 Hz, 1H), 0.10 (s, 9H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 87.8, 87.4, 61.0 (-), 24.8 (d, $^3J_{CP}$ = 2.9 Hz, +), 24.4 (d, $^3J_{CP}$ = 3.7 Hz, +), 24.3 (d, $^3J_{CP}$ = 4.4 Hz, +), 23.8 (d, $^3J_{CP}$ = 6.6 Hz, +), 21.6 (d, $^2J_{CP}$ = 5.9 Hz),

16.5 (d, $^{1}J_{CP}$ = 184.4 Hz, +), 14.5 (d, $^{2}J_{CP}$ = 3.7 Hz, -), 14.1 (+), -3.1 (-, 3C); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 40.4; GC/MS (R_t = 13.47 min) *m/z* 349 (1%, M + H^+), 333 (45%, M – Me), 303 (20%, M – Et), 73 (100%, Me_3Si^+); HRMS (TOF ES) Found 371.1432, Calculated for $C_{15}H_{29}O_5SiPNa$ (M+Na) 371.1440 (3.2 ppm).

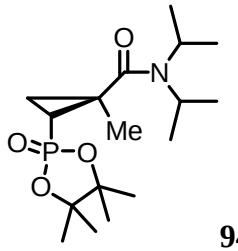


91g: The reaction was performed according to the typical procedure B, employing cyclopropene **91g** (75 mg, 0.5 mmol). The crude reaction mixture was purified by preparative column chromatography eluting with EtOAc/hexane (3:1) (R_f 0.25) to give an orange oil. Yield: 160 mg (0.5 mmol, 100%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.77 (s, 3H), 1.98 (ddd, $^{2}J_{PH}$ = 19.2 Hz, *J* = 7.6 Hz, 4.4 Hz, 1H), 1.78 (ddd, $^{3}J_{PH}$ = 7.8 Hz, *J* = 9.9 Hz, 4.4 Hz, 1H); 1.67 (ddd, $^{3}J_{PH}$ = 4.2 Hz, *J* = 9.9 Hz, 7.6 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.5 (d, $^{3}J_{CP}$ = 4.4 Hz), 166.5 (d, $^{3}J_{CP}$ = 6.6 Hz), 89.0, 88.3, 53.3 (+), 53.2 (+), 34.5 (d, $^{2}J_{CP}$ = 6.6 Hz), 24.6 (d, $^{3}J_{CP}$ = 3.7 Hz, +), 24.4 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 24.1 (d, $^{3}J_{CP}$ = 5.1 Hz, +), 23.9 (d, $^{3}J_{CP}$ = 5.9 Hz, +), 21.3 (d, $^{1}J_{CP}$ = 185.2 Hz, +), 18.6 (d, $^{2}J_{CP}$ = 4.4 Hz, -); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 36.2; GC/MS (R_f = 13.63 min) *m/z* 321 (1%, M + H^+), 262 (30%, M - CO_2CH_2), 204 (100%, M - $(CO_2Me)_2$); HRMS (TOF ES) Found 321.1104, Calculated for $C_{13}H_{22}O_7P$ (M+H) 321.1103 (0.3 ppm).



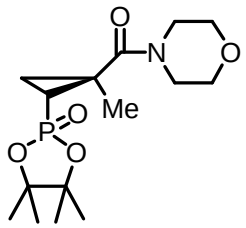
94h: The reaction was performed according to the typical procedure B, employing cyclopropene **91h** (77 mg, 0.5 mmol). The crude residue was filtered through a short bed of silica gel eluting with EtOAc. The obtained residue after removal of solvent was purified by preparative column chromatography eluting with EtOAc/MeOH (1:1) (R_f 0.5) Yield: 154 mg (0.485 mmol, 97%)**.**

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.67-3.51 (br, 4H), 3.37-3.27 (br, 4H), 1.59 (s, 3H), 151-1.47 (m, 1H), H), 1.50 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.29-1.18 (m, 2H), 1.29-1.18 (m, 3H), 1.12-1.04 (br, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 171.8 (d, $^{3}J_{CP}$ = 5.1 Hz), 88.3, 87.9, 41.1 (br, -), 39.0 (br. -), 27.3 (d, $^{2}J_{CP}$ = 5.12 Hz), 24.6 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 24.5 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 24.2 (d, $^{3}J_{CP}$ = 5.1 Hz, +), 24.0 (d, $^{3}J_{CP}$ = 5.1 Hz, +), 18.3 (d, $^{2}J_{CP}$ = 5.9 Hz, -), 18.2 (d, $^{1}J_{CP}$ = 183.0 Hz, +), 17.5 (d, $^{3}J_{CP}$ = 5.1 Hz, +), 13.8 (br, +), 12.4 (br, +); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 40.1; GC/MS (R_t = 12.46 min) *m/z* 317 (1%, M^+), 245 (3%, $M^+ - NEt_2$), 154 (30%, $Et_2NCO(Me)C{=}CH\text{-}CH_2^+$), 72 (100%, Et_2N^+); HRMS (TOF ES) Found 340.1649, Calculated for $C_{15}H_{28}NO_4PNa$ (M+Na) 340.1654 (1.5 ppm).



94i: The reaction was performed according to the typical procedure B, employing cyclopropene **91i** (54 mg, 0.3 mmol) The crude residue was purified by preparative column chromatography on Silica gel eluting with EtOAc (R_f = 0.23). Yield 85 mg (0.24 mmol, 82%).

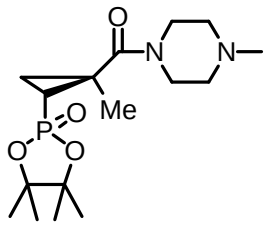
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 4.59 (m, 1H), 3.33 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.51 (m, 1H) 1.50 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.37 (m, 6H), 1.30 (m 2H), 1.22 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.1 (d, $^{3}J_{CP}$ = 5.1 Hz), 88.3, 87.8, 48.4 (+), 45.7 (+), 29.0 (d, $^{2}J_{CP}$ = 5.1 Hz), 24.7 (d, $^{3}J_{CP}$ = 3.7 Hz, +), 24.5 (d, $^{3}J_{CP}$ = 4.4Hz, +), 24.2 (d, $^{3}J_{CP}$ = 4.4Hz , +), 24.1 (m, +, 2C), 20.7 (+),20.5 (+), 20.3 (+), 20.1 (+), 17.9 (d, $^{1}J_{CP}$ = 182.2 Hz, +), 18.1 (d, $^{2}J_{CP}$ = 5.9 Hz, -), 17.5 (d, $^{2}J_{CP}$ = 5.1 Hz); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 40.3; GC/MS (R_f = 14.83 min) *m/z* 345 (1%, M^+), 330 (5%, M - Me), 245 (35%, M - N(i-Pr)$_2$), 135 (100%); HRMS (TOF ES) Found 346.2122, Calculated for $C_{17}H_{33}NO_4P$ (M+H) 346.2147 (7.2 ppm).



94j: The reaction was performed according to the typical procedure B employing cyclopropene **91j** (83 mg, 0.5 mmol). The crude residue was purified by preparative

column chromatography on Silica gel (eluent: EtOAc) (R_f: 0.1). Yield: 142 mg (0.43 mmol, 86%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.61(br. s, 8H), 1.52 (s, 3 H), 1.46-1.42 (m, 1H), 1.44 (s, 3H), 1.43 (m, 1H) 1.34 (s, 6H), 1.20-1.14 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.9 (d, $^3J_{CP}$ = 5.1 Hz), 88.3, 87.9, 66.5 (-, 2C), 46.1 (br. -), 42.3 (br. -), 26.6 (d, $^2J_{CP}$ = 4.4 Hz), 24.4 (d, $^3J_{CP}$ = 3.7 Hz, +, 2C), 24.0 (d, $^2J_{CP}$ = 5.1Hz, +), 23.8 (d, $^2J_{CP}$ = 5.1Hz, +), 18.1 (d, $^1J_{CP}$ = 183.0 Hz, +), 17.6 (d, $^2J_{CP}$ = 5.9 Hz -), 17.2 (d, $^3J_{CP}$ = 5.1 Hz, +); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 39.2; GC/MS (R_f = 16.847 min) *m/z* 331 (1% , M^+), 330 (5%, M - Me), 245 (50% M - $N(CH_2CH_2)_2O$, 163 (98%), 136 (100%); HRMS (TOF ES) Found 354.1434, Calculated for $C_{15}H_{26}NO_5PNa$ (M+Na) 354.1446 (3.4 ppm).

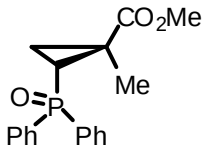


94k: The reaction was performed according to the typical procedure B. employing cyclopropene **91k** (80 mg, 0.5 mmol). The crude residue was purified by preparative column chromatography on Silica gel doped with triethylamine (eluent: EtOAc/MeOH 3:1) (R_f: 0.1). Yield: 172 mg (0.5 mmol, >99%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.89-3.52 (m, 4H), 2.46-2.38 (m, 4 H), 2.32 (s, 3H), 1.61 (s, 3H), 1.52 (m, 1H) 1.52 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.25 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.9 (d, $^3J_{CP}$ = 5.1 Hz), 88.3, 88.0, 46.5 (br. -, 2C), 46.0 (+), 27.1 (d,

$^{2}J_{CP}$ = 4.4 Hz), 24.6 (d, $^{2}J_{CP}$ = 2.9 Hz), 24.2 (d, $^{2}J_{CP}$ = 5.9Hz), 24.0 (d, $^{2}J_{CP}$ = 5.1Hz +), 18.2 (d, $^{1}J_{CP}$ = 185.1 Hz, +), 18.0 (d, $^{2}J_{CP}$ = 5.6 Hz -), 17.5 (d, $^{3}J_{CP}$ = 5.1 Hz, +); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 39.6.

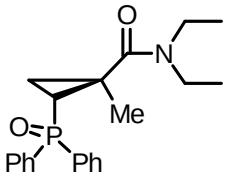
1.4.5. Synthesis of cyclopropylphosphine oxides



96a: ***Typical procedure***. An oven dried 2 mL Wheaton vial was charged with 1,1'-bis (diphenylphosphino)ferrocene (dppf) (27.7 mg, 0.05 mmol, 10 mol%), tris(dibenzylideneacetone) dipalladium chloroform adduct (12.9 mg, 0.025 mmol, 5 mol%), and diphenylphosphine oxide (101.0 mg, 0.5 mmol) under a nitrogen atmosphere. The mixture was then dissolved in dry dioxane (1 ml) and stirred for 5 min. Then, methyl 1-methylcycloprop-2-ene-1-carboxylate (95.8 mg, 0.55 mmol) was added via syringe and the reaction was stirred for 1 hr at 25 ^{o}C. When TLC analysis showed no starting material remained, the reaction mixture was concentrated and the residue was purified by preparative column chromatography (eluent: EtOAc/hexanes 3:1) to afford white a solid (R_f 0.4). Yield: 145.0 mg (47 mmol, 92%).

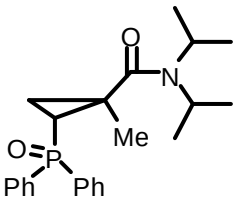
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.82-7.77 (m, 2H), 7.72-7.67 (m, 2H), 7.59-7.55 (m, 1H), 7.53-7.43 (m, 5H), 3.73 (s, 3H), 2.07 (ddd, $^{2}J_{PH}$ = 17.4 Hz, J = 10.1 Hz, 7.3 Hz, 1H), 1.71 (ddd, $^{3}J_{PH}$ = 9.3 Hz, J = 9.4 Hz, 4.0 Hz, 1H), 1.65 (ddd, $^{3}J_{PH}$ = 15.4 Hz, J = 7.3 Hz, 4.0 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 174.5, 134.5 (d, $^{1}J_{CP}$ = 104.7 Hz), 133.2 (d, $^{1}J_{CP}$ = 104.7 Hz), 131.9 (d, $^{4}J_{CP}$ = 2.9 Hz, +), 131.7 (d, $^{4}J_{CP}$ = 2.2 Hz, +), 130.9 (d, $^{2}J_{CP}$ = 10.2 Hz, +,

2C), 130.7 (d, $^{2}J_{CP}$ = 9.5 Hz, +, 2C), 128.7 (d, $^{3}J_{CP}$ = 11.7 Hz, +, 2C), 128.5 (d, $^{3}J_{CP}$ = 11.7 Hz, +, 2C), 52.5 (+), 25.6 (d, $^{2}J_{CP}$ = 2.9 Hz), 22.7 (d, $^{1}J_{CP}$ = 98.8 Hz, +), 18.7 (d, $^{2}J_{CP}$ = 4.4 Hz, -), 14.1 (d, $^{3}J_{CP}$ = 4.4 Hz, +); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 28.4; GC/MS (R_t = 16.48 min) *m/z* 314 (12%, M^+), 202 (100%, Ph_2POH^+); HRMS (TOF ES) Found 315.1133, Calculated for $C_{18}H_{20}O_3P$ (M+H) 315.1150 (5.4 ppm).



96b: The reaction was carried out according to the typical procedure, employing cyclopropene **91h** (46 mg, 0.3 mmol).. The crude residue was purified by preparative column chromatography eluting with EtOAc (R_f 0.15). Yield: 95 mg (0.27 mmol, 89%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.15-8.04 (m, 2H), 7.68-7.59 (m, 2H), 7.53-7.45 (m, 3H), 7.44-7.32 (m, 3H), 3.61-3.28 (m, 4H) 1.86 (ddd, $^{1}J_{PH}$ = 12.1 Hz, ^{2}J = 9.9 Hz, 6.8 Hz, 1H), 1.63 (ddd, $^{3}J_{PH}$ = 14.9 Hz, *J* = 6.8 Hz, 4.3 Hz, 1H), 1.53 (s, 3H) 1.43 (ddd, $^{3}J_{PH}$ = 9.9 Hz, *J* = 8.3 Hz, 4.3 Hz, 1H), 1.14 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 172.0 (d, $^{3}J_{CP}$ = 2.9 Hz), 134.9 (d, $^{1}J_{CP}$ = 103.9 Hz), 133.5 (d, $^{1}J_{CP}$ = 103.9 Hz), 131.6 (d, $^{4}J_{CP}$ = 2.2 Hz, +), 131.2 (d, $^{4}J_{CP}$ = 10.2 Hz, +, 2C), 131.2 (+), 130.4 (d, $^{2}J_{CP}$ = 9.5 Hz, +, 2C), 128.5 (d, $^{2}J_{CP}$ = 12.4 Hz, +, 2C), 128.2 (d, $^{3}J_{CP}$ = 12.4 Hz, +, 2C), 60.16, 40.9 (-), 38.88 (-), 28.9 (d, $^{2}J_{CP}$ = 4.4 Hz), 18.8 (d, $^{1}J_{CP}$ = 100.3 Hz, +), 16.5 (d, $^{3}J_{CP}$ = 4.4 Hz, +), 15.6 (d, $^{2}J_{CP}$ = 4.4 Hz, -), 13.6 (+) 12.3 (+); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 30.0; GC/MS (R_t = 15.68 min) *m/z* 355 (2%, M^+), 340 (7%, M – Me), 382 (15%, M – $HNEt_2$), 255 (42%, M – $CONEt_2$), 201 (23%, Ph_2PO^+), 154 (100%, M – Ph_2PO); HRMS (TOF ES) Found 378.1585, Calculated for $C_{21}H_{26}NO_2PNa$ (M+Na) 378.1599 (3.7 ppm).



96c: The reaction was carried out according to the typical procedure, employing **91i** (77 mg, 0.3 mmol).. The crude residue was purified by preparative column chromatography. Eluent: EtOAc (R_f = 0.2). Yield 106 mg (0.28 mmol, 60%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.11(m, 2H), 7.69 (m, 2H), 7.58-7.39 (m, 6H), 4.39 (m, 1H), 3.30 (m, 1H) 1.84 (ddd, $^2J_{PH}$ = 12.4 Hz, J = 9.9 Hz, 7.1 Hz, 1H), 1.61 (ddd, $^3J_{PH}$ = 15.2 Hz, J = 6.8 Hz, 4.3 Hz, 1H), 1.51 (s, 3H), 1.45 (m, 1H), 1.40 (d, J = 6.6 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H), 1.13 (m, 6H)*;* ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 171.5 (d, $^3J_{CP}$ = 2.9 Hz), 135.3, (d, $^1J_{CP}$ = 103.2 Hz), 133.7 (d, $^1J_{CP}$ = 103.2 Hz), 131.7 (d, $^4J_{CP}$ = 2.2 Hz, +), 131.5 (+), 131.4 (+), 131.3 (+), 130.6 (d, $^2J_{CP}$ = 9.5 Hz, 2C), 128.6 (d, $^3J_{CP}$ = 11.7 Hz, +, 2C), 128.4 (d, $^3J_{CP}$ = 12.4 Hz, +, 2C), 48.6 (+), 45.7 (+), 30.4 ($^2J_{CP}$ = 4.4 Hz), 20.6 (+), 20.4 (+, 2C), 20.1 (+), 19.0 (d, $^1J_{CP}$ = 100.3 Hz, +), 16.6 (d, $^3J_{CP}$ = 5.1 Hz), 15.6 (d, $^2J_{CP}$ = 4.4 Hz); ^{31}P NMR (161.98 MHz, $CDCl_3$) δ 30.2; HRMS (TOF ES) Found 368.1743, Calculated for $C_{20}H_{28}NO_2PNa$ (M-Me+Na) 368.1755 (3.3 ppm).

1.4.6. Assignment of relative configuration

The obtained sample of cyclopropylphosphonate **94a** contained two separable diastereomeric compounds, a less polar major fraction **A** and a more polar minor fraction **B**. Elucidation of the relative configuration was performed based on analysis of NMR spectra, as follows. In the minor product, the carbon next to phosphorus atom (20.7 ppm) was identified

owing to a very characteristic splitting into a doublet with a large coupling constant value ($^1J_{CP}$ = 185.9 Hz). The adjacent proton (1.01 ppm) was assigned based on the ^{1}H-^{13}C HSQC experiment (^{13}13C NMR (CDCl3, 100.67 MHz) δ172.0 see Apendix A.2.). The same experiment allowed for the assignment of protons at 1.79 and 1.26 ppm to the methylene group in the cyclopropane ring. The well resolved signals of all three protons of the cyclopropyl ring in the ^{1}H NMR spectrum of the minor product allowed for the measurement of the corresponding spin-spin coupling constants. Thus, a typical AMX system in 1,1,2-trisubstituted cyclopropane rings usually gives $^3J_{HH}$(*cis*) > $^3J_{HH}$(*trans*) > $^2J_{HH}$, which is consistent with positioning of the protons as depicted in Figure 3. In addition, the same relationship was observed for proton-phosphorus coupling constants (shown in green): $^3J_{PH}$(*cis*) > $^3J_{PH}$(*trans*) > $^2J_{PH}$. Protons in the spectrum of the major diastereomer were assigned in a similar manner (Figure 3), even though complete analysis of the *J*-coupling was impossible due to partial overlapping of the signals in ^{1}H spectrum of the methylene group (1.45 ppm and 1.50 ppm). The configuration of quaternary carbons of the small rings can be assigned based on comparison of chemical shifts of the protons in CH_2 group. Indeed, in cyclopropyl systems the methyl substituent typically demonstrates a minor shielding effect on *cis*-vicinal protons. At the same time, both phenyl and phosphoryl groups have profound deshielding effect. These considerations allowed for the unambiguous assignment of the *cis*-configuration (relative 1*R*,2*R*) for the minor, and the *trans*-configuration (relative 1*S*,2*R*) for the major diastereomer (Figure 3).

Figure 3. Assignment of relative configurations of diastereomeric products **94a**.

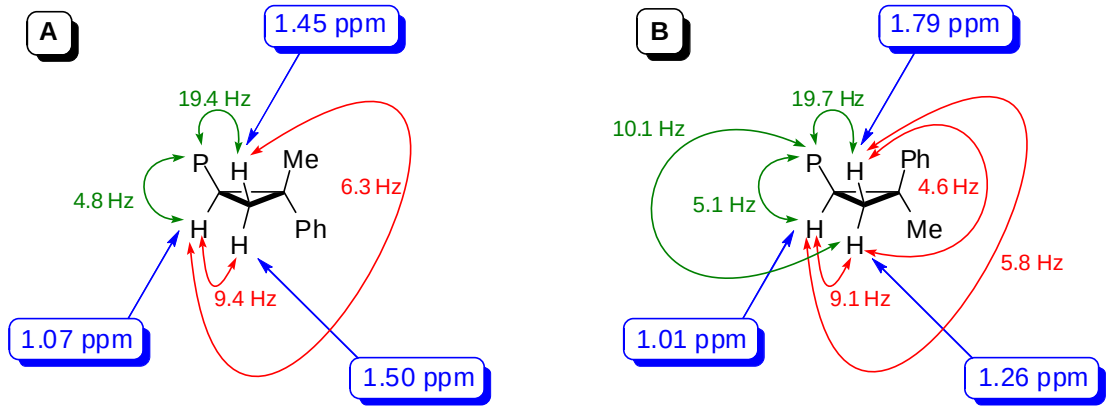


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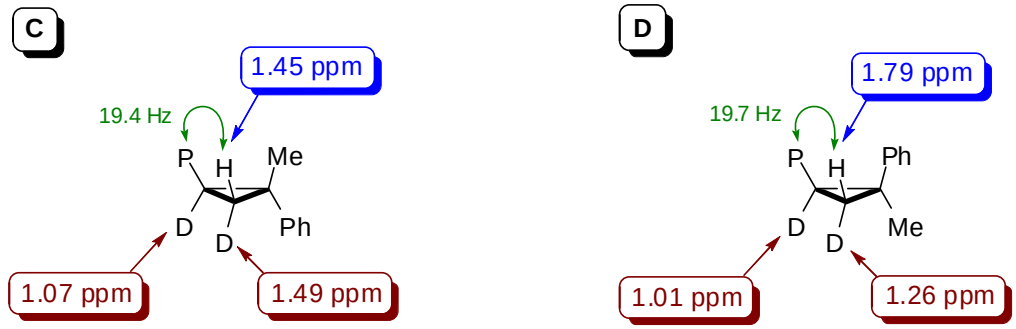
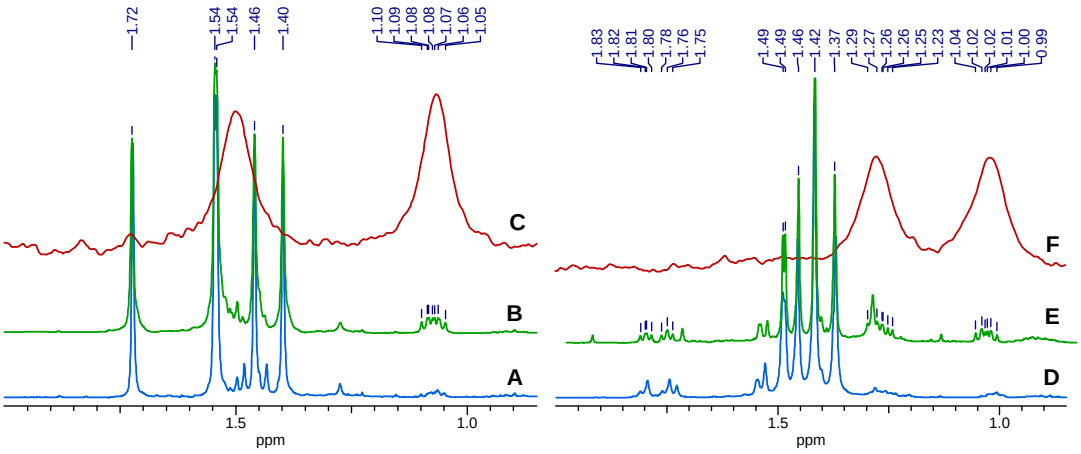
Figure 4. Assignment of relative configuration of deuterium labeled compounds.



Relative configuration of the deuterium-labeled compounds **94a-*d*$_2$**, obtained in the hydrophosphorylation of cyclopropene **191a-*d*$_2$** was assigned based upon the comparison of the ^{1}H, ^{2}H NMR and ^{1}H-^{13}C HSQC NMR data measured for labeled and non-labeled products (see section A.3.). These data showed that for both diastereomeric products all deuterium labels are

located in geminal and *trans*-vicinal positions and no deuterium incorporation was observed into the *cis*-vicinal position. Also, the only spin-spin coupling remained after deuterium incorporation was the *cis*-proton-phosphorus interaction with $^{3}J_{PH}$ ~ 19-20 Hz.The obtained data unambiguously confirmed that the described palladium-catalyzed hydrophosphorylation proceeds exclusively in *syn*-fashion.

Figure 5. . Overlays of ^{1}H and ^{2}H spectra of the products isolated from hydrophosphorylation of **94a** and **94a-*d*$_2$**: A) ^{1}H spectrum of *trans*-**91-*d*$_2$**; B) ^{1}H spectrum of *trans*-**94a**; C) ^{2}H spectrum of *trans*-94a-d_2; D) ^{1}H spectrum of *cis*-**94a-*d*$_2$**; E) ^{1}H spectrum of *cis*-**94a**; F) ^{2}H spectrum of *cis*-**94a-*d*$_2$**.



Relative configuration of diastereomeric compounds **94e** was assigned analogously. Analysis of coupling constants for the major (less polar) diastereomer was impossible due to severe overlapping of proton signals of the cyclopropane ring. However, the corresponding signals were mostly resolved in the spectrum of the minor (more polar) diastereomer. Simulation of the ^{1}H NMR spectrum for the cyclopropane ring AMXP-system (Figure 6)

allowed for the assignments depicted in Figure 7. Assignment of relative configurations of diastereomeric products **94e** (E =CO2Me). Configuration of the quaternary center was assigned based on a NOESY experiment. A NOE effect between the cyclopropyl CH group (1.58 ppm) and the *ortho*-protons of the phenyl ring (7.43 ppm) was observed; accordingly, a *cis*-relationship between these groups was established. Therefore, *cis*-configuration (relative 1*S*,2*R*) was assigned to the minor (more polar) product, while a *trans*-configuration (relative 1*R*,2*R*) was assigned to the major (less polar) diastereomer.

Figure 6. Experimental (blue) and simulated (red) spectra of the minor (more polar) diastereomer 94e.

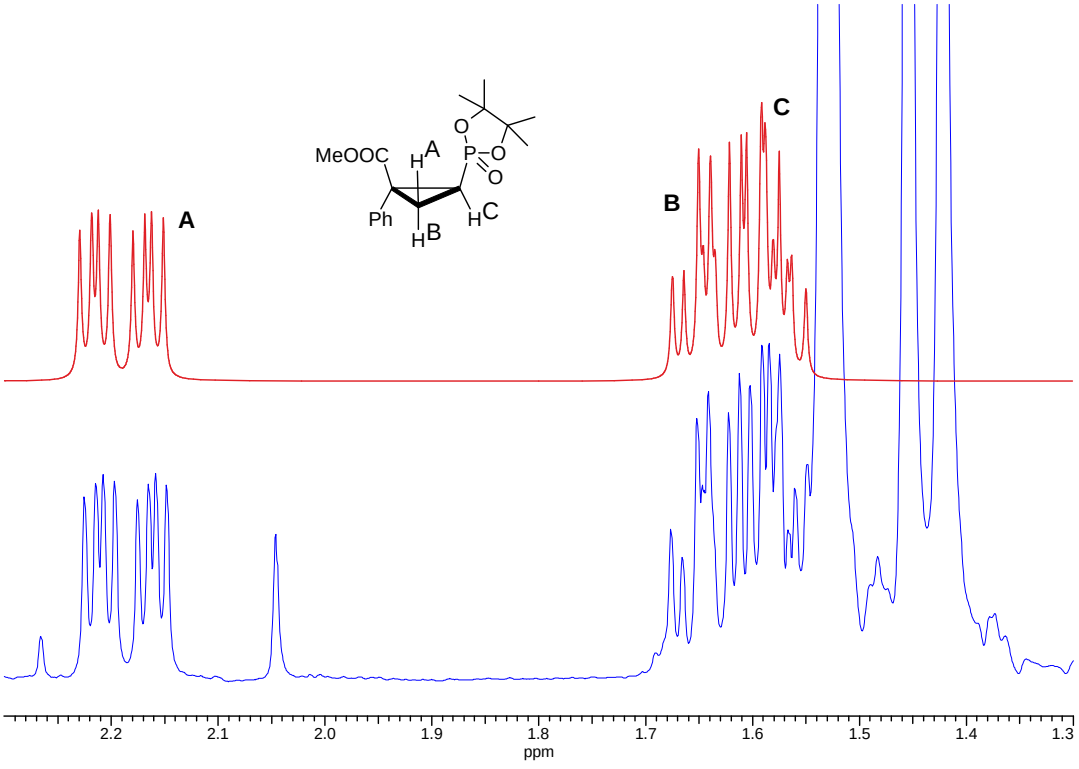
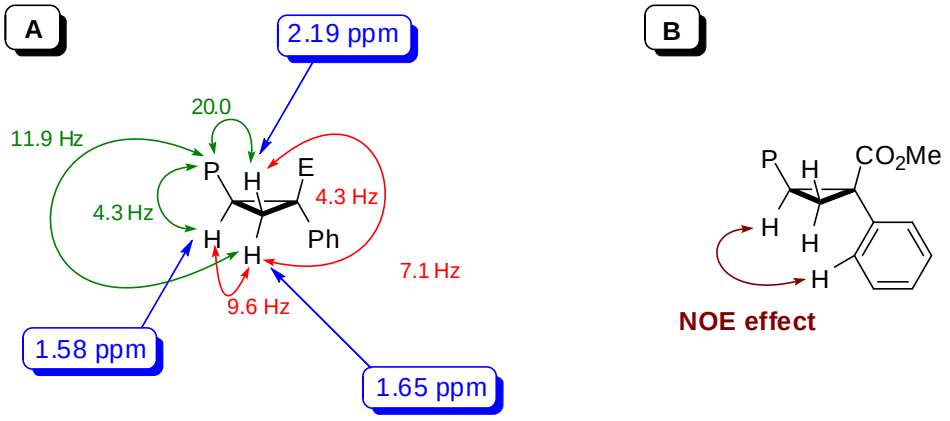


Figure 7. Assignment of relative configurations of diastereomeric products 94e (E =CO^2Me)**.**



In the same way, the *trans*-configuration (relative 1*S*,2*R*) of compound **94f** was assigned. Simulation of the four-spin system of phosphorylcyclopropane ring and the corresponding values of chemical shifts and spin-spin coupling constants are presented in (Figure 8) and (Figure 9A), respectively. Relative configuration of the quaternary center in the three-membered ring was assigned based on a NOESY experiment (Figure 9B). NOE effects were detected between the TMS-group (0.10 ppm) and the two protons in the cyclopropyl ring (0.93 ppm and 1.15 ppm).

Figure 8. Experimental (blue) and simulated (red) spectra of **94f**.

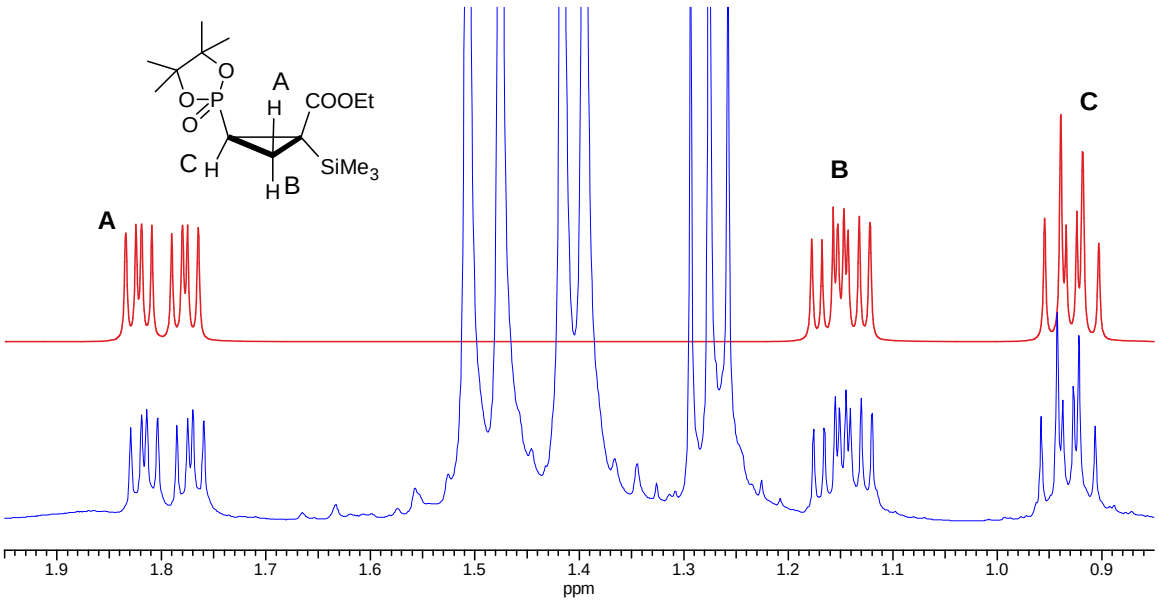
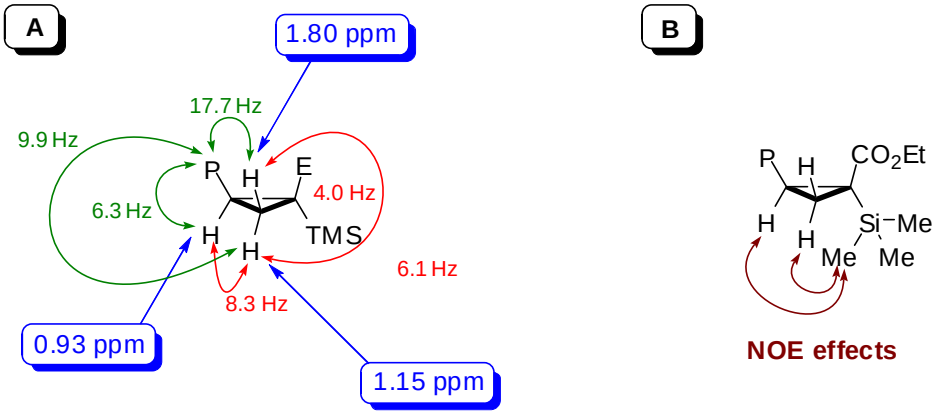


Figure 9. Assignment of relative configurations of diastereomeric products 94f (E = CO_2Et).

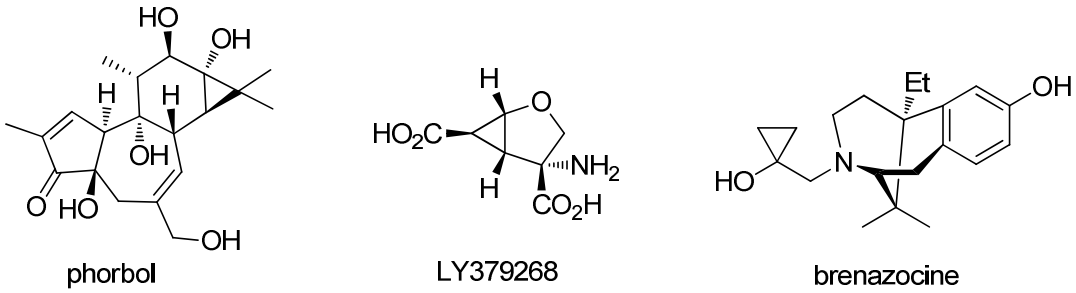


Chapter 2. Formal Nucleophilic Substitution of Bromocyclopropanes

2.1 Introduction

Cyclopropanols and cyclopropyl ethers are an important class of molecules for both organic synthesis[61] and medicinal chemistry. They are a plethora of examples among biologically active natural products[62] and synthetic medicinal agents,[63] such as phorbol,[64] brenazocine,[65] and LY379268[66] (Figure 10).

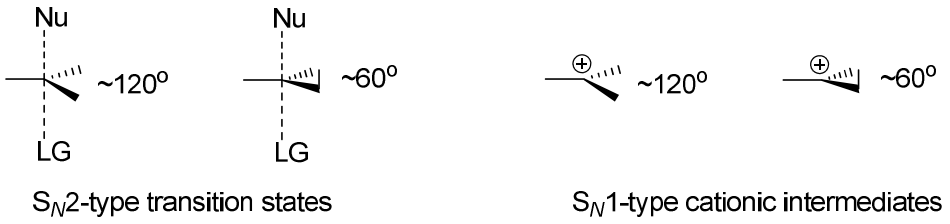
Figure 10.



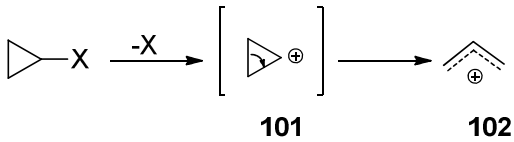
Although a plethora of methods have been developed for construction of cyclopropyl ethers, efficient protocols that allow for direct functionalization of a pre-existing cyclopropane moiety are scarce. Obviously the most efficient method to accomplish such functionalizations would involve a direct nucleophilic substitution onto cyclopropane; however, it is well

recognized that classical nucleophilic substitution in strained carbocycles is highly disfavored.[67] Both the $S_N1$and S_N2 pathways are much higher in energy as compared to non-strained systems due to the distortion of the bond angles from 120° to 60° (Figure 11). Also, the cyclopropyl cation **101** generated in the S_N1 mechanism would likely isomerize into the allyl cation **102** as studies have shown that such isomerization proceeds virtually without a measurable activation barrier (Scheme 44).[68] In fact, only a handful of examples claiming direct nucleophilic substitutions of cyclopropanes have been reported.

Figure 11.



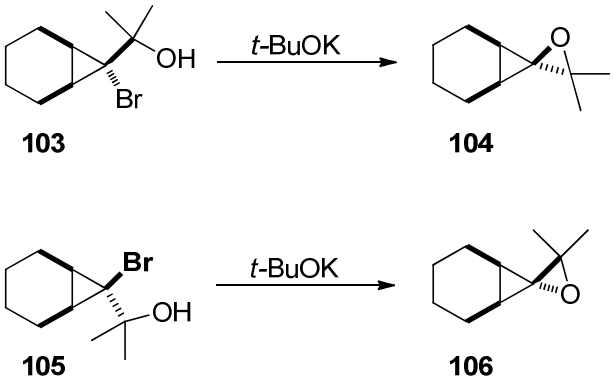
Scheme 44.



2.1.2. Pathways to formal nucleophilic substitution

In 1979, a direct intramolecular S_N2 substitution of bicyclic fused bromocyclopropanes was demonstrated (Scheme 45). Reaction of **103** with *t*-BuOK proceeded to give intramolecular substitution with inversion of configuration with respect to the bromine providing the corresponding spiro-oxirane **104**. Interestingly, the *endo*-diastereomer **105** underwent intramolecular substitution with nucleophilic attack from the more hindered face also proceeding through inversion of configuration to provide spiro-oxirane **106**.[67]

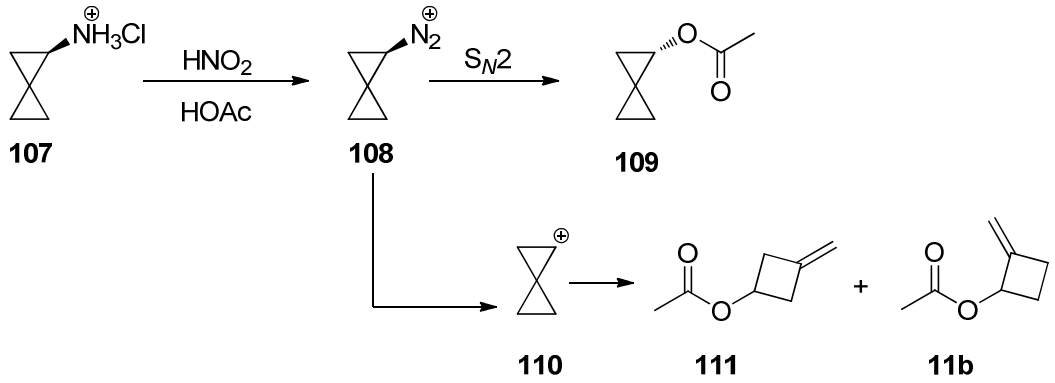
Scheme 45



The stereochemistry of the deamination of (-)-spiropentylamine in acetic acid was studied by Wiberg et al. Reaction of the chiral amine hydrochloride **107** with nitrous acid in acetic acid led to a mixture of 3-methylenecyclobutyl acetate **111**, 2-methylenecyclobutyl acetate **112**, and spiropentyl acetate **109** in a 1:2:3 ratio. It was found that the major product, (-)-spiropentyl acetate, was formed with essentially complete inversion of configuration. This suggests that it is

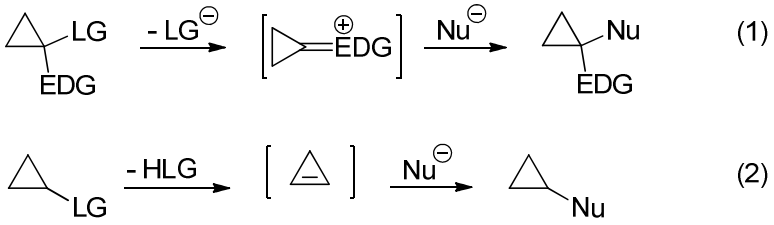
formed via an S_N2 displacement on the spiropentyldiazonium ion. However formation of 2-methylenecyclobutyl acetate and 3-methylenecyclobutyl acetate advocates for concurrent formation of a cyclopropyl cation, which quickly undergoes ring expansion and cleavage (Scheme 46).

Scheme 46



While direct displacements are scarce, S_N1-like nucleophilic substitiutions are possible with halocyclopropanes possessing strongly electron-donating geminal substituents (Scheme 47, eq. 1). Formal nucleophilic substitutions may also proceed via a 1,2-elimination to generate a cyclopropene intermediate, followed by addition of a nucleophile across the strained double bond (Scheme 47, eq. 2).

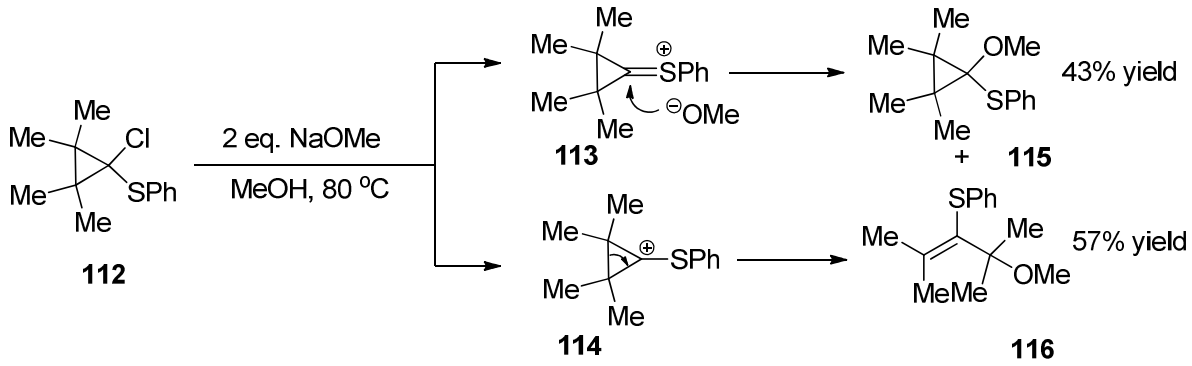
Scheme 47



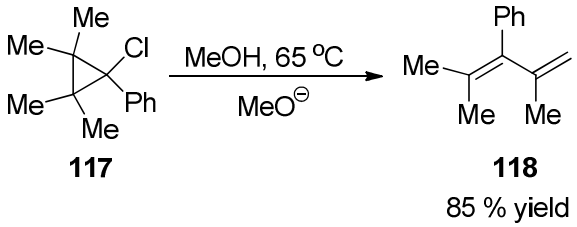
2.1.2. Nucleophilic substitution via stabilization of cyclopropyl cations.

The presence of an electron donating substituent geminal to a leaving group stabilizes the resulting carbocation intermediate, which could be trapped with various nucleophiles. In a study concerning the stabilities of cyclopropyl cations, de Meijere demonstrated that these reactive cationic intermediates may be stabilized with a phenyl thienyl group and hinder the ring opening pathway.[69] For example, methanolysis of chlorocyclopropyl sulfide **112** led to 43% of methoxide substitution **115** along with 57% of the ring opening product **116** (Scheme 48). The necessity of a geminal stabilizing substituent was demonstrated by the methanolysis of **117** which underwent exclusive ring opening to provide the corresponding diene **118** in 85% yield (Scheme 49).

Scheme 48.

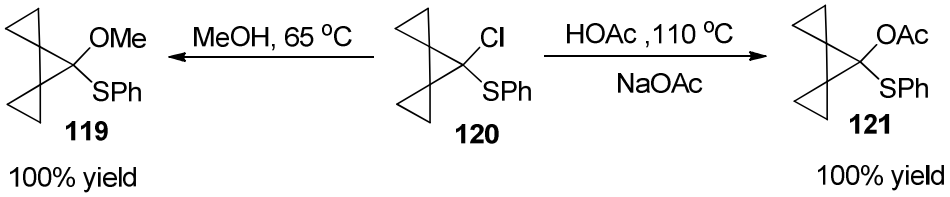


Scheme 49.



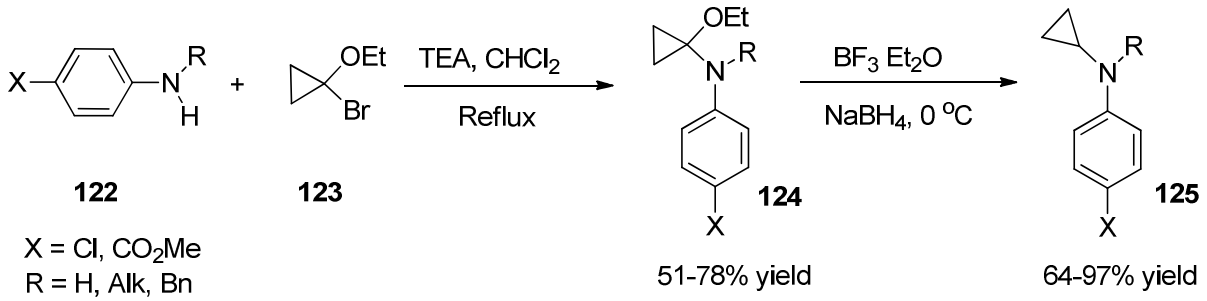
An α-cyclopropyl group is known to have the largest stabilizing effect of any α-alkyl substituent on a carbocation[68] indeed methanolysis of chloro cyclopropyldispiro derivative **120** accordingly proceeded without ring opening to yield only the methyl ether **119**. Exclusive substitution also occurred in the presence of the relatively weak nucleophile NaOAc giving the corresponding cyclopropyl acetate **121** in quantitive yield (Scheme 50).[69]

Scheme 50.



The addition of anilines to *O*-stabilized cationic intermediates was demonstrated by Loeppky in 2000. Reaction of 1-bromo-1-ethoxy cyclopropane **123** with various aniline nucleophiles **123** in the presence of triethylamine provided aminal derivatives **124** in yields up to 78%. The ethoxide moiety was efficiently removed by reaction with $NaBH_4$ to afford the corresponding cyclopropyl anilines **125** (Scheme 51).[70]

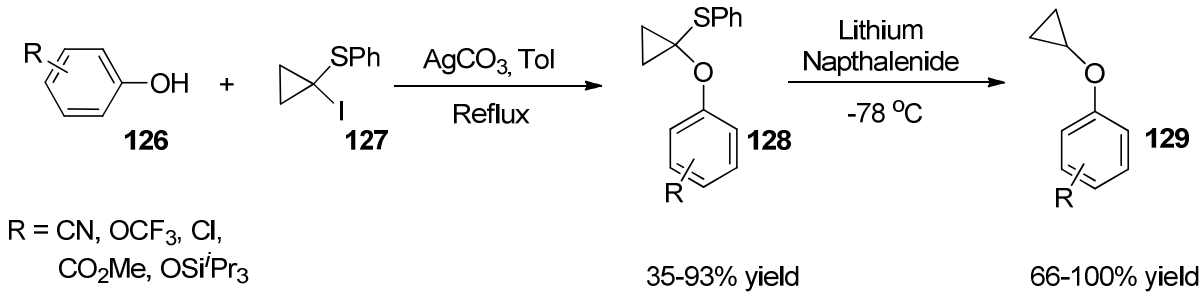
Scheme 51.



It has also been demonstrated that both electron deficient and electron rich phenols **126** serve as nucleophilic partners in additions to stabilized cyclopropyl cations **127**. The reactions were

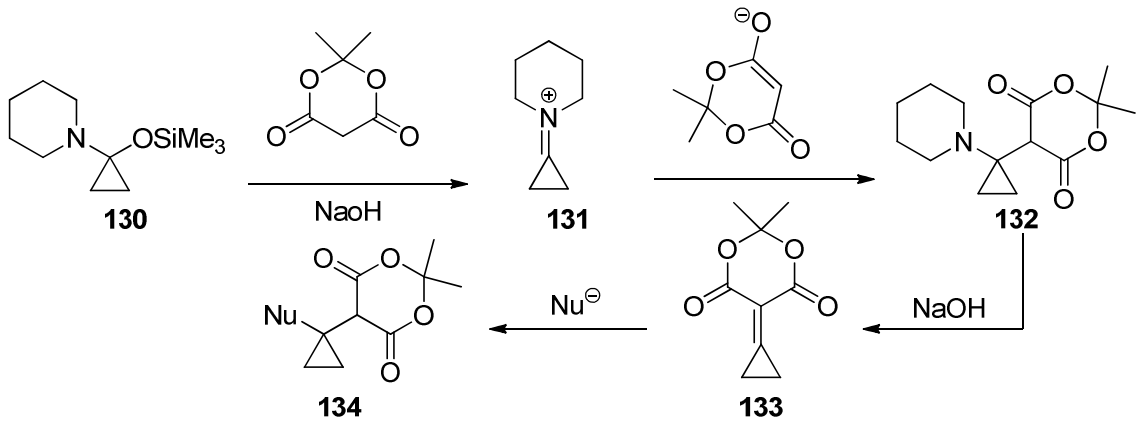
relatively sluggish and required high temperatures, nonetheless various thiocyclopropyl phenols **128** were synthesized in moderate to good yields. Subsequent reduction of **128** with $NaBH_4$ provided the corresponding cyclopropyl phenols **129** in modest overall yields (Scheme 52).[71]

Scheme 52.



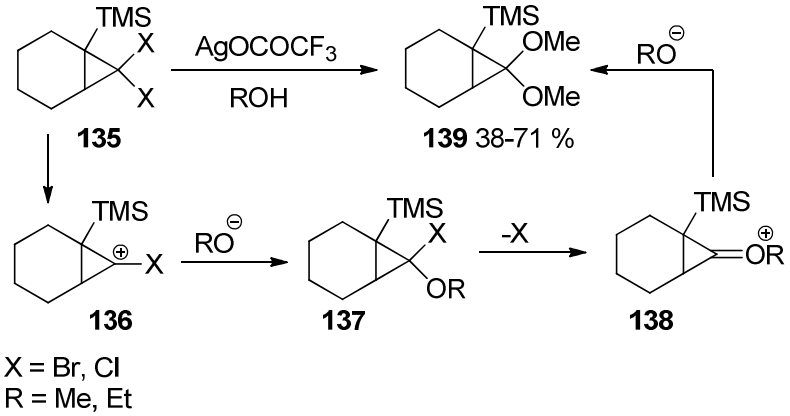
Stabilization of cyclopropyl cations is not limited to oxygen and sulfur. Vilsmaier demonstrated that an amino moiety in silyl-protected hemiaminal **130** promotes the nucleophilic substitution of the geminal $OSiM_3$ group by stabilizing the intermediate cyclopropyl cation **131** (Scheme 53).[72] The addition of Meldrums acid in the presence of NaOH to iminium cyclopropane **131** affords compound **132** via a nucleophilic addition of the enolate to intermediate imine **131**. A twofold substitution occurs in the presence of other carbon[73] and oxygen-based nucleophiles to provide cyclopropyl products **134**.

Scheme 53.

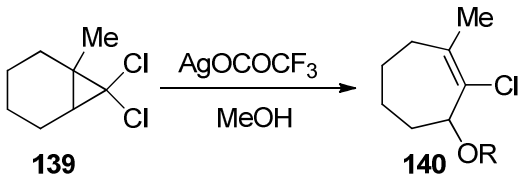


Ishihara demonstrated that stabilized cyclopropyl cations may also be generated in the presence of vicinal silanes and undergo ring retentive nucleophilic attack.[74] Treatment of bicycle **135** with silver trifluorocetate afforded cyclopropyl cation **136** and after nucleophilic attack provided intermediate **137**. Loss of the halide and formation of stabilized carbocation **138** followed by nucleophilic addition gave dialkyl cyclopropyl acetals **139** in medium to high overall yields (Scheme 54). It was also demonstrated that the presence of the β-TMS substituent is essential to ring retentive substitution as subjection of the corresponding methyl substituted derivative **139** underwent exclusive ring expansion to give cycloheptane **140** (Scheme 55).[72]

Scheme 54.



Scheme 55.



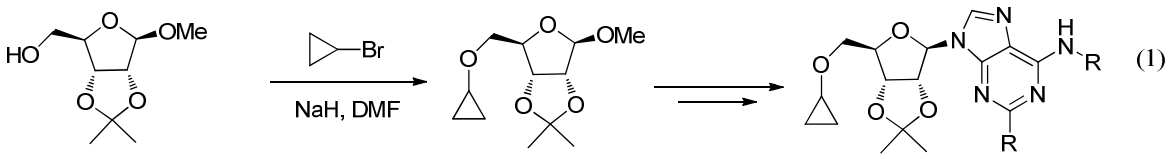
S_N1-type nucleophilic substitution involving stabilized cyclopropyl cation intermediates in certain cases allows for efficient ring retentive derivatization of cyclopropanes. At the same time, cation-stabilizing functionalities introduced as requisite elements in the structure of starting materials makes this methodology very substrate dependent and give little flexibility for process diversification.

An alternative route to nucleophilic substitution involves the base assisted *in situ* generation of cyclopropene intermediates from the corresponding cyclopropyl halides followed by trapping with an appropriate nucleophile.

2.1.3. Formal nucleophilic substitution via trapping of cyclopropene intermediates

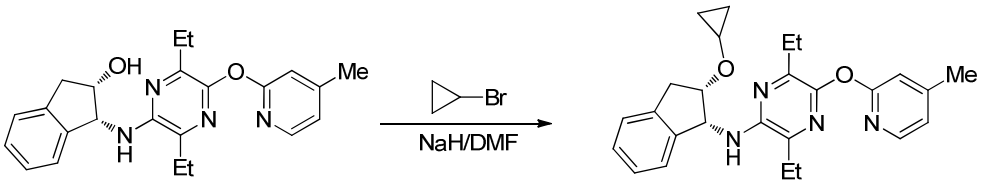
Cyclopropenes are commonly synthesized via dehydrohalogenation of cyclopropyl halides[108] in the presence of base. In the event that a pronucleophile is present the base employed for dehydrohalogenation may also form the corresponding nucleophilic species which undergoes nucleophilic attack across the strained double bond of cyclopropene. Unsubstituted cyclopropyl bromides are the simplest substrates utilized in such a process and have been employed in the synthesis of a number of useful cyclopropane derivatives. For example, alkylation with bromocyclopropane has been performed successfully with alcohols.[75,76] (Scheme 56, eq 1, 2) phenols[77] (Scheme 56, eq. 3) and amides[78] (Scheme 56, eq 4, 5) in the synthesis of various medicinally relevant structures.

Scheme 56.



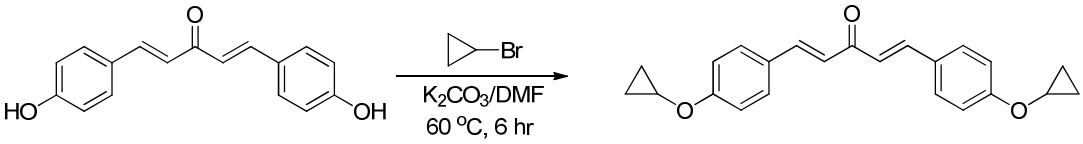
(1)

Agonists for the Adenosine A1 and A3 Receptors



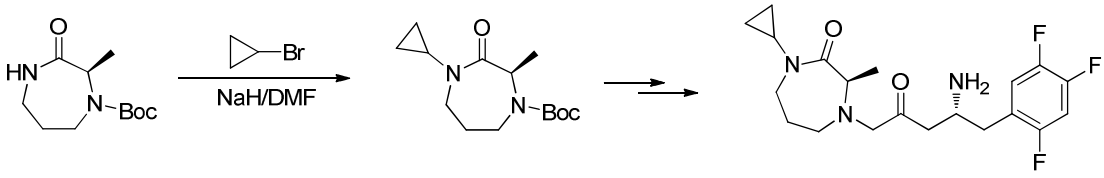
(2)

Corticotropin releasing factor (CRF-1) receptor antagonist



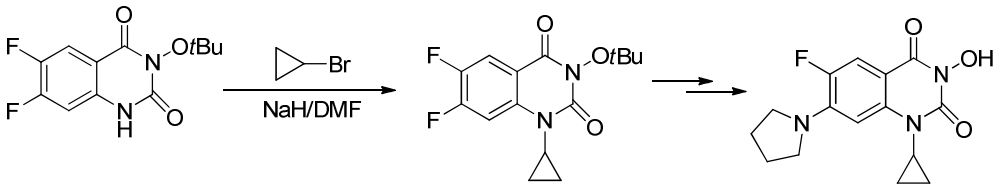
(3)

Antitumor and angiogenic activity



(4)

DPP-4 inhibitor (antidiabetic)

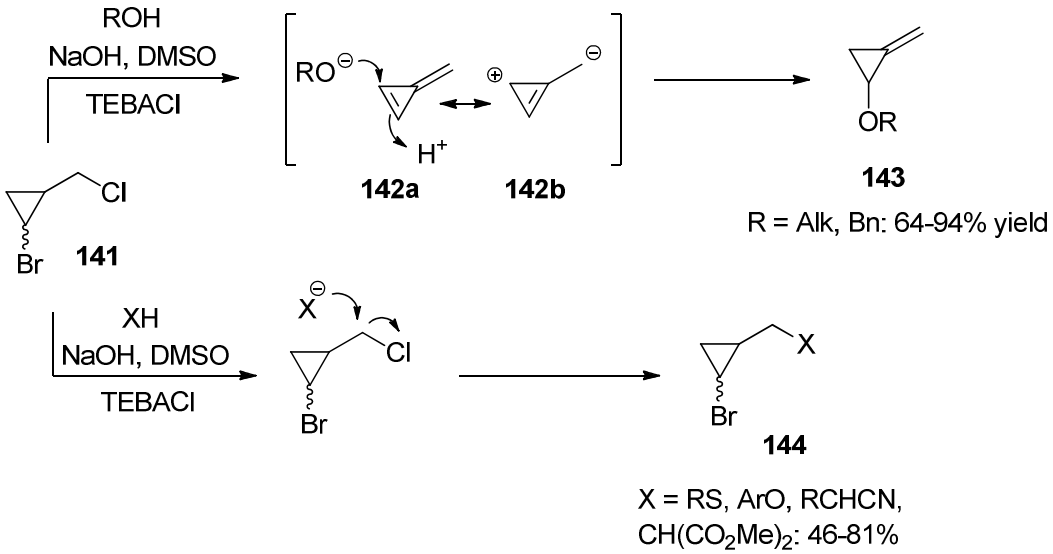


(5)

DNA gyrase inhibitor (antibacterial)

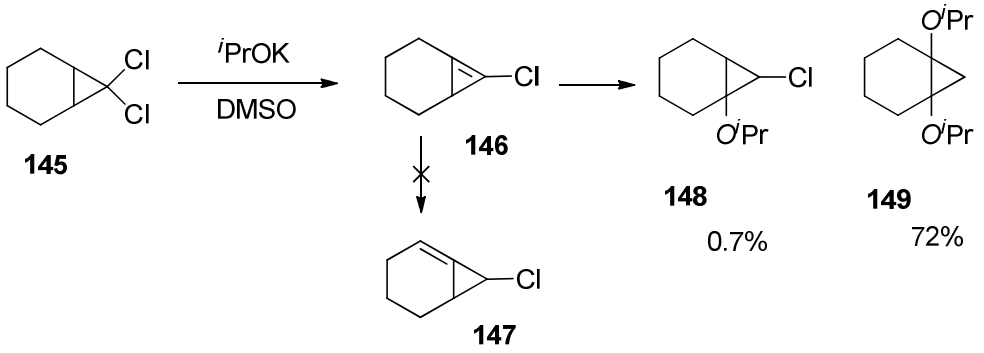
Reactions of this type have been investigated with substituted halocyclopropanes as well as dihalocyclopropanes. However, slight modifications to steric bulk or electronics on the cyclopropane moiety severely complicate the efficiency of nucleophilic substitution as the formation and stability of the generated cyclopropene intermediate are highly dependent on these factors. For example, the reactivity of 1-bromo-2-(chloromethyl)cyclopropane **141** in the presence of NaOH and various nucleophiles was investigated by Jonczyk and co-workers[79]. It was found that simple stirring of **141** with an excess of alcohols, in the presence of powdered sodium hydroxide and triethylbenzylammonium chloride (TEBAC1) as a catalyst, in DMSO, at ambient temperature gives rise to 1-(alkoxymethy1ene)cyclopropanes **143** in high yields (Scheme 57). Alcohols of different structure, including aliphatic, alicyclic, as well as those substituted by an aryl or heterocyclic group reacted efficiently. It was found that the reaction indeed proceeds through cyclopropene **142a** as indicated by crude NMR analysis. The authors do not comment on the possibility of addition to aromatic resonance structure **142b**, as no products of nucleophilic addition corresponding to this species were observed. Interestingly, the addition of more acidic pronucleophiles such as thiols, phenols, and nitriles gave exclusive side chain substitution products **144**. In these cases formation of cyclopropene intermediate **142a** was never observed. This is due to the higher acidities of the pronucleophiles which do not allow for the appropriate pH necessary for formation of **142.**

Scheme 57.



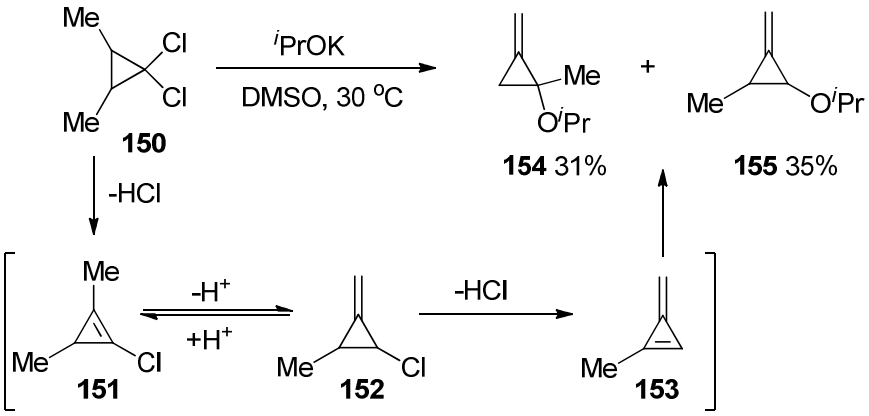
Dihalocyclopropanes also undergo elimination-addition type transformations to provide disubstituted cyclopropanes. It was shown that dichlorocyclopropane **145** in the presence of potassium isopropoxide gave a mixture of mono- and disubstituted products **148** and **149** in 0.7 and 72 % yield respectively (Scheme 58).[80]

Scheme 58.



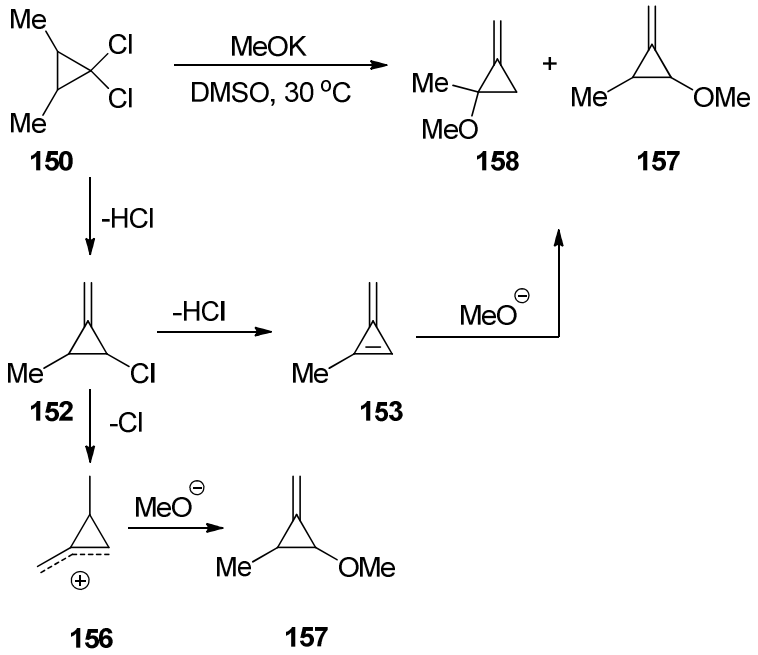
The double bond of cyclopropene **146**, generated from dihalocyclopropane **145** by reaction with potassium isopropoxide, migrates to a position of greater stability to give methylene cyclopropane **147** but when excess potassium isopropoxide is present a facile addition occurs to afford di-substituted cyclopropane **149**. Similarly, it was found that addition of ^{i}PrOK to dichlorocyclopropane **150** afforded substituted methylene cyclopropanes **154** and **155** approximately in a 1:1 ratio. The author proposed that this reaction proceeded via an initial 1,2-dehydrohalogenation to provide cyclopropene intermediate **151**, which further isomerized into methylene cyclopropane **152**. The latter then experienced a second dehydrohalogenation to yield 1-methyl-3-methylenecyclopropene intermediate **153**. Sequential addition afforded **28** and **154** in 31% and **155** in 35% yield. (Scheme 59).

Scheme 59



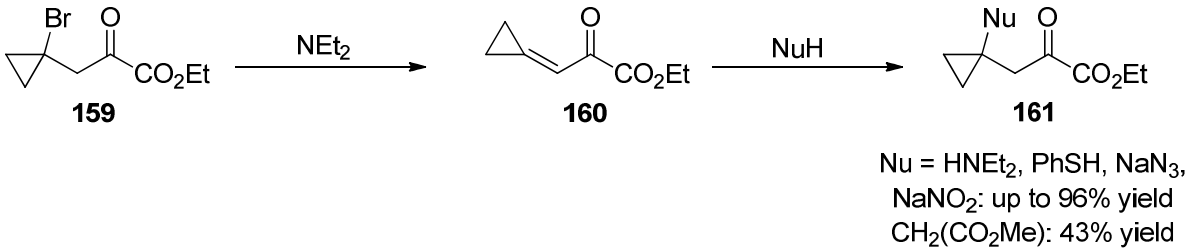
The relative amounts of **154** and **155** formed reflect two opposing factors operating in the transition state. The relative stabilities of developing charge will favor **154**, but steric factors should favor **155**. Thus, the two factors appear to be of nearly equal importance when the nucleophile is isopropoxide ion. Interestingly the use of methoxide ion, a smaller nucleophile, afforded analogous products **158** and **157** in the ratio 2:1 respectively. It is important to note that conversion of intermediate **152** into π-allyl species **156**, since it would provide exclusive formation of **157** (Scheme 60).[80]

Scheme 60.



Substitution may also occur through activated methylene cyclopropane intermediates. For example, deMeijere demonstrated the *in situ* generation of conjugated methylene cyclopropanes **160** generated from bromocyclopropane **159** in the presence of base. These reactive intermediates may be trapped by an various nucleophiles to afford substituted cyclopropanes **161**. Nitrogen and oxygen-based nucleophiles underwent clean nucleophilic addition to give compound **161** in excellent yields. However lower yields were observed in the case of carbon nucleophiles. (Scheme 61).[81]

Scheme 61.

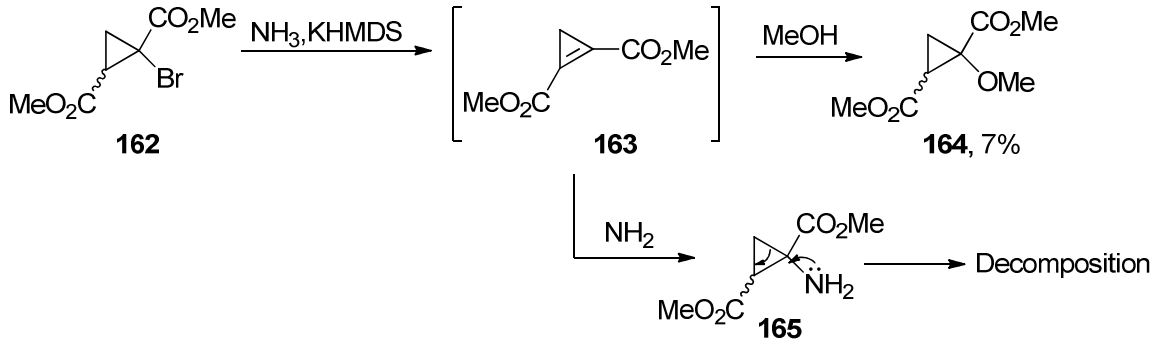


2.1.4. Formal nucleophilic substitution via conjugated cyclopropene intermediates and stereoselective additions.

Conjugated cyclopropenes are inherently extremely reactive and are difficult to isolate.[89] This extraordinary reactivity has proven valuable in the development of formal nucleophilic substitutions with a wider variety of pronucleophiles as compared to the non-conjugated counterparts. To date, only a handful of investigators have utilized these intermediates in formal substitution reactions.

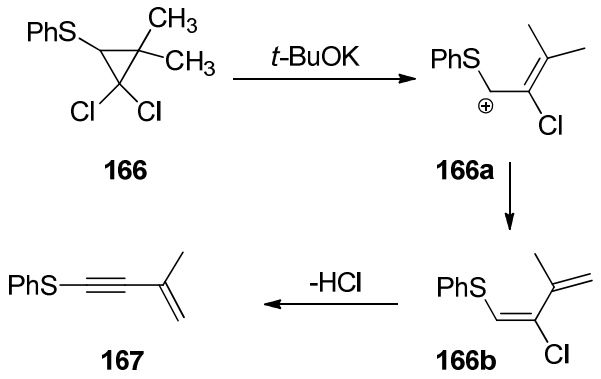
In an attempt to synthesize dimethyl 1-aminocyclopropane-1,2-dicarboxylate **165** via the *in situ* generation of Michael acceptor **163**, it was found that MeOH adduct **164** was the only isolable product. MeOH was unavoidably introduced into the system by partial hydrolysis of **162**. Indeed, intermediate **163** is formed and trapped by NH_2, however, it quickly decomposes to give a mixture of ring opening products.[82] The possibility of formation of a cyclopropyl cation in this case is highly unlikely, as the carboxylate functionality would greatly destabilize the intermediate. Thus, the reaction is assumed to occur via intermediate **163 (**Scheme 62**)**.

Scheme 62.



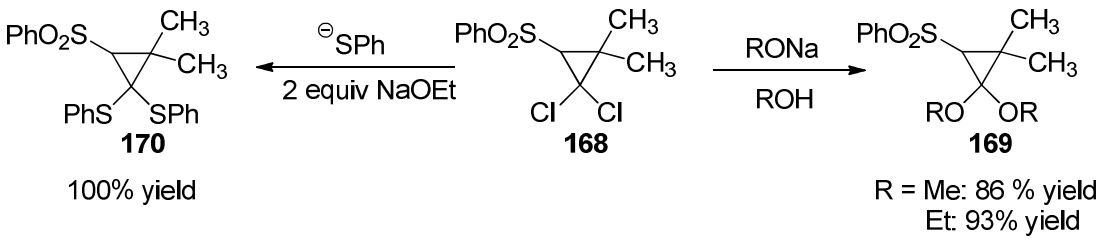
Conjugated intermediates such as **163** have found limited utility in formal nucleophilic substitutions involving dihalides. For example, it was shown that 2,2-dichlorocyclopropyl phenyl sulfides of type **166** are unstable to alcoholysis, and in the presence of the strong base potassium *tert*-butoxide gives enynes **167** as illustrated in (Scheme 63). The accelerating effect of the sulfur atom is considered to be a driving force for this exocyclic ring opening reaction, since sulfur can stabilize the positive charge developed in intermediate **166a**.[83]

Scheme 63.



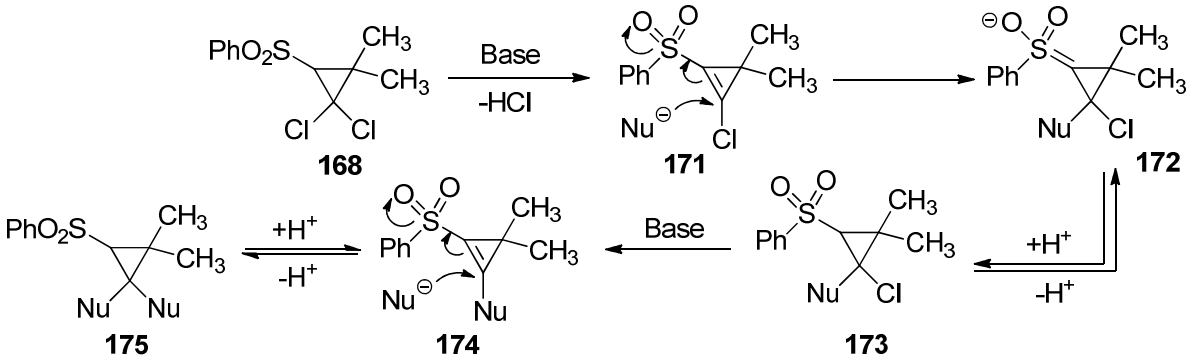
Expectedly, replacement of the phenylmercapto group in **166** by the phenylsulfonyl group (as in **168**) destabilized the intermediate ion corresponding to **166a** and provided ring retention. Thus, subjection of **168** to base in the presence of competing nucleophiles afforded disubstitution products **169** and **170** in excellent yields. Interestingly, **168** in the presence of thiophenol and 2 equivalents of NaOEt gave exclusively the sulfide addition product **170** in quantitative yield and no formation of the cyclopropyl ethyl ether corresponding by attack by ethoxide ion was detected.[84] (Scheme **64**).

Scheme 64.



In the presence of base compounds such as **168** form highly unstable reactive conjugated cyclopropene **171** which are immediately trapped by a nucleophilic species to give, upon protonantion, intermediate **173**. Sequential deprotonation affords conjugated intermediate **174** which undergoes nucleophilic attack to afford disubstituted cyclopropanes **175 (**Scheme 65).

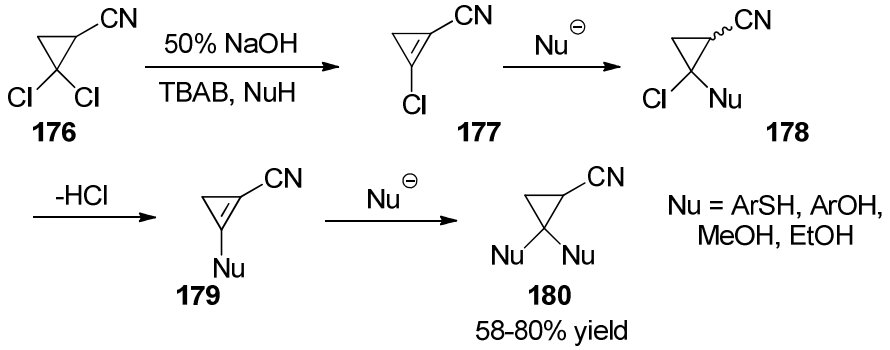
Scheme 65.



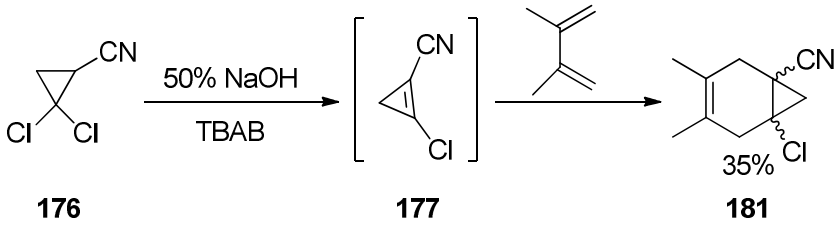
Jonczyk has demonstrated analogous substitutions with 2,2-dichlorocyclopropanecarbonitrile **176** with various nucleophiles in aqueous NaOH and tetrabutylammonium bromide (TBAB) as a phase transfer catalyst.[85] Cyclopropane **176** undergoes dehydrochlorination to give intermediate **177**, which is trapped by the nucleophile. Sequential dehydrochlorination followed by conjugated nucleophilic addition affords disubstituted cyclopropanes **180** in modest to good yields. Phenols, thiophenols, and alcohols reacted well under these conditions. To prove the formation of cyclopropene **177** as a transient product leading to **178**, cyclopropene **177** was

generated *in situ* and trapped with 2,3-dimethylbuta-1,3-diene to afford the Diels-Alder adduct **181** in 35% yield (Scheme 67).

Scheme 66.



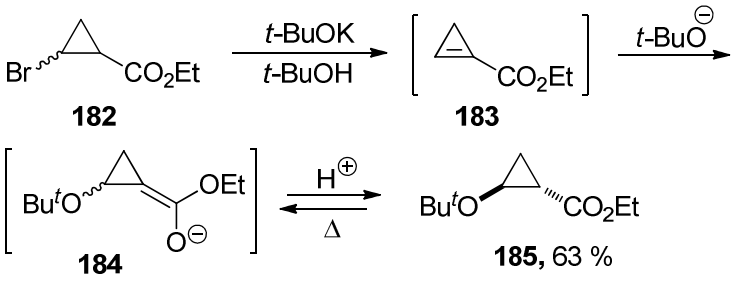
Scheme 67.



Although addition of nucleophiles to *in situ* generated conjugated cyclopropenes is well documented, until recently only a single example demonstrated stereoselective addition. Wiberg showed that bromocyclopropane **182** upon dehydrobromination with *t*-BuOK in *t*-BuOH produced a highly unstable intermediate **183**. The latter once formed, immediately reacted with the *t*-BuO^- nucleophile to afford *trans*-adduct **185**. Since intermediate **183** is planar, addition of

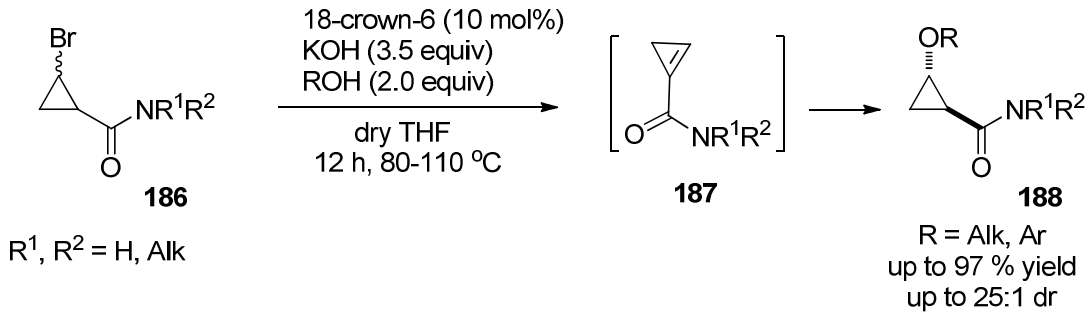
tert-butoxide can occur to either face, however, a thermodynamically-driven epimerization occurs upon heating favoring the more stable *trans* product **185** (Scheme 68**)**.[86]

Scheme 68.



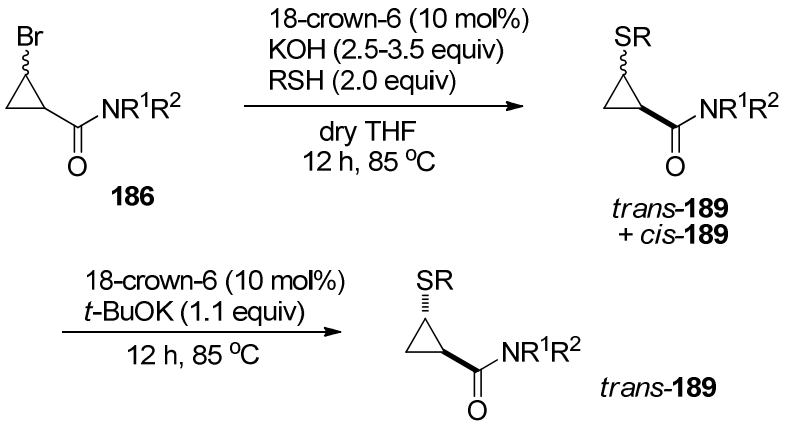
In a remarkable expansion to this methodology Rubin recently showcased diastereoselctive formal nucleophilic substitution of bromocyclopropane carboxamides (Scheme 69). Various primary, secondary and tertiary alcohols reacted smoothly with secondary and tertiary cyclopropyl carboxamides **186.** The use of non-competitive KOH in the presence of 18-crown-6 (10 mol%) allowed for efficient generation of intermediate **187**, which is promptly intercepted by *in situ* generated alkoxide or aryloxide. Remarkably the reaction conditions also enabled base assisted thermodynamically-driven epimerization to afford *trans*-products **188** in very high yields and excellent diastreoselectivities.[87]

Scheme 69.



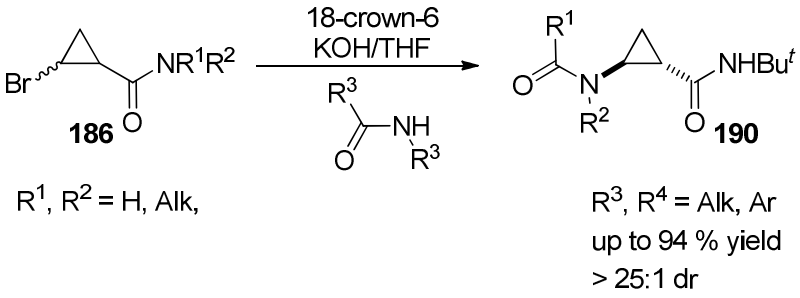
The methodology was also expanded towards the addition of thiols and thiophenols which under similar reaction conditions initially afforded a mixture of *trans*-**189** and *cis*-**189** in a 1:1 ratio. However upon subjection to *t*-BuOK and 10 mole % 18-crown-6 base assisted epimerization allowed to upgrade the selectivity and afforded *trans*-**189** in excellent yields and diastereoselectivities up to 30:1 (Scheme 70).[88]

Scheme 70.



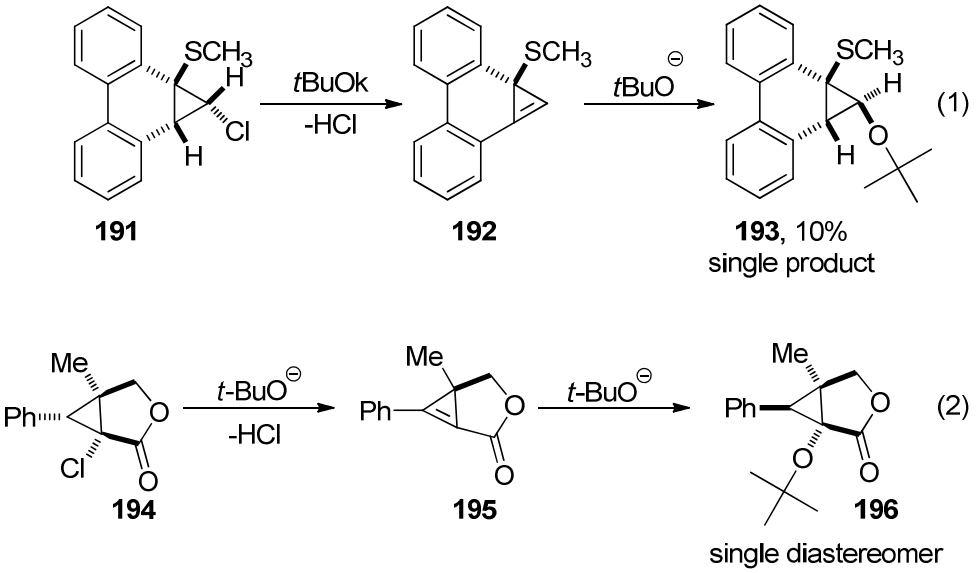
Rubin and co-workers also developed an efficient and highly diastereoselective formal substitution of 2-bromocyclopropane carboxamides **186** with secondary amides. The reaction conditions allowed for the facile construction of a number of conformationally constrained *trans*-cyclopropyl-diamides derivatives **190** as sole products in excellent yields.[89]

Scheme 71.



Few scattered reports exist demonstrating diastereoselective other examples of formal nucleophilic substitution. Diastereoselctivity in all these cases, however, was imparted by excessive rigidity and bulk. For example, addition of *t*-BuOK to chlorocyclopropane **191** afforded cyclopropyl ether **193** in poor yield as a single diastereomer (Scheme 72, eq 1).[90] Analogously treatment of **194** with *t*-BuOK provided addition to the convex face and furnished **196** as a single diastereomer (Scheme 72 eq 2).[91]

Scheme 72.

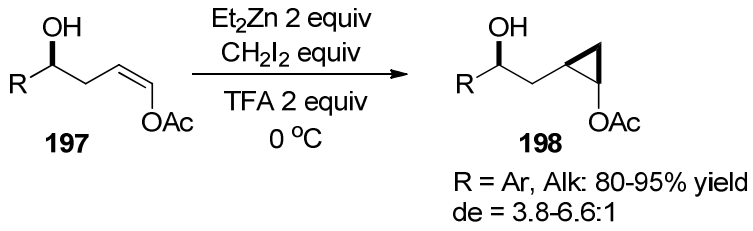


2.1.5. Conventional Methods for the preparation of Cyclopropanol derivatives.

Except for the recent examples of formal nucleophilic substitution demonstrated by Rubin, this methodology has not yet presented itself as a mainsteam method for the preparation of cyclopropanol derivitives. There are, however, a few powerful methods for the preparation of such compounds. Discussed below are selected recent examples showing different approaches to cyclopropanol derivitives. The most important of these methods is the cyclopropanation of enol ethers and esters, which may be performed with several different types of carbene equivalents. For example Connell and coworkers recently demonstrated that the classical Simmons-Smith[132] protocol represents a facile method for the cyclopropanation of enol acetates. Treatment of

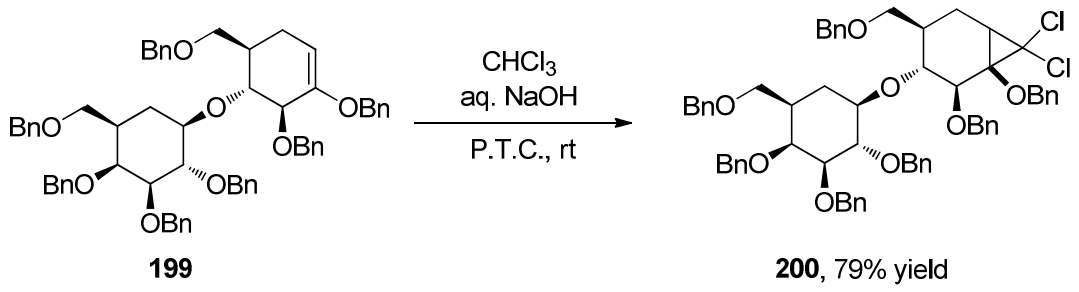
homoallylic alcohol **197** with diethyl zinc and diiodomethane gave cyclopropyl acetates **198** in high yields and decent diastereoselectivity (Scheme 73). [92]

Scheme 73.



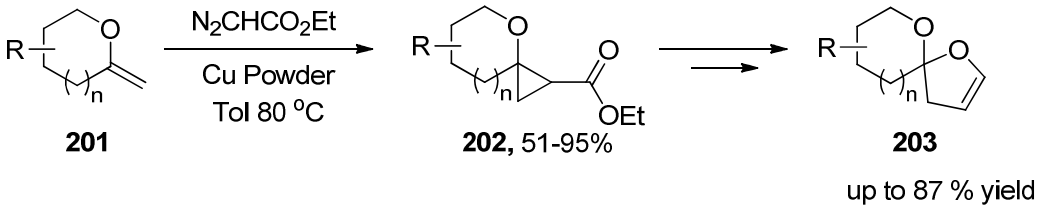
The base-assisted generation of dihalocarbenes in the presence of olefins is one of the widely employed methods for the construction of cyclopropanes. This methodology was recently used in the assembly of polysachride-derived cyclopropyl scaffolds. Treatment of benzyl protected enolate **199** with aq. NaOH in the presence of a chloroform and a phase transfer catalyst afforded the corresponding cyclopropyl ether **200** in 75% yield (Scheme 74).[93]

Scheme 74.



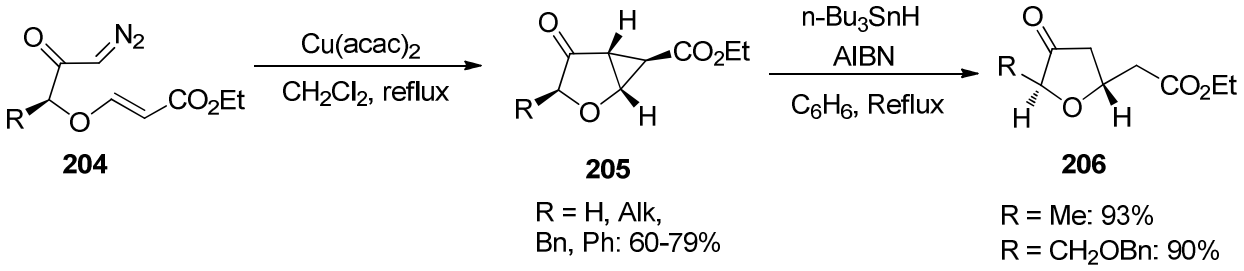
By far the most widely utilized method for the construction of cyclopropyl ethers is the metal assisted cycloaddition of protected enolates and metalo-carbenes generated from the decomposition of diazomethane derivitives. Wertz and coworkers demonstrated the synthesis of spiroacetals which were prepared from the corresponding cyclopropyl ether **67** (Scheme 75).[94] Treatment of enol ether **201** with diazo acetate and copper powder afforded the corresponding donor acceptor cyclopropane **202** in good yields. This type of cycloaddition is also the most commonly employed in the preparation of Donor-acceptor cyclopropanes (DACs).

Scheme 75.



Intramolecular cycloadditions offer routes to useful bicyclic cyclopropyl ethers, which are normally accessed through cycloadditions with cyclic enol ethers.[95] Gharpure developed a highly regio- and diastereoselective synthesis of DACs **205** employing intramolecular cyclopropanation of vinylogous carbonates **204** with carbenes in the presence of $Cu(acac)_2$ as a catalyst (Scheme 76).[96] These substituted DACs display high reactivity allowing for the regioselective cleavage of the cyclopropane leading to THF derivatives **206**.

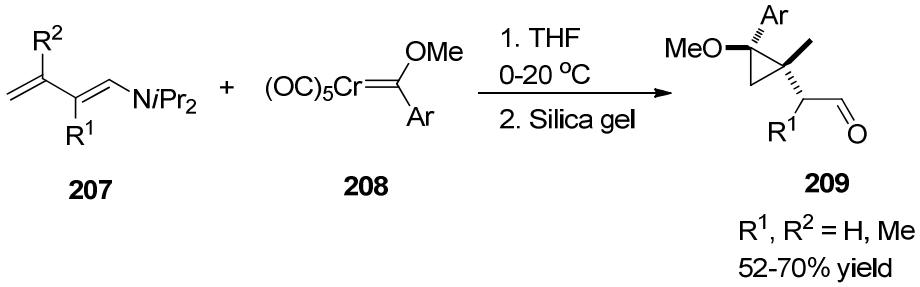
Scheme 76.



204 **205** **206**

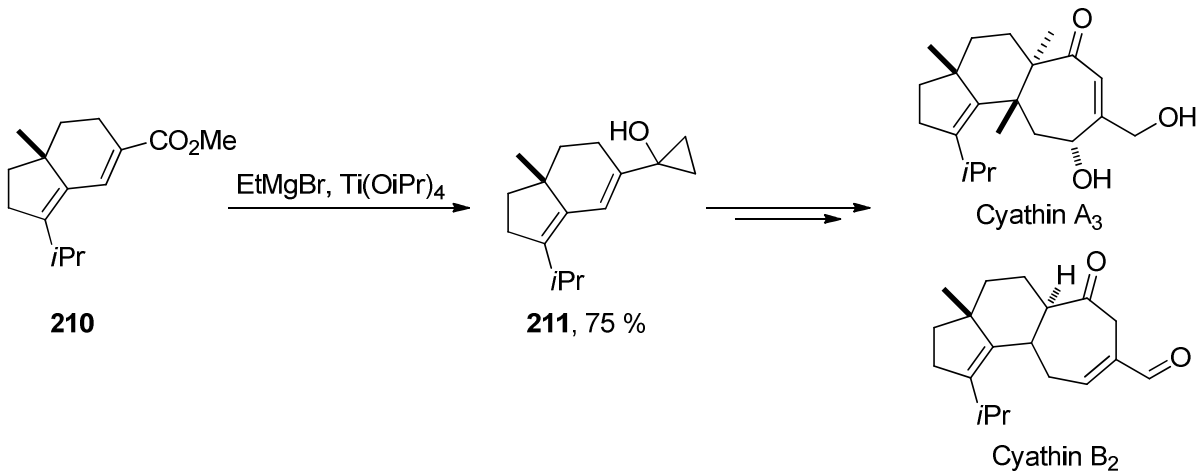
Cyclopropanations of olefins with alkoxycarbene equivalents provides a route to cyclopropyl ethers and DACs, however, most of these protocols are limited by the availability of the corresponding Fisher carbenes. Nonetheless, metalo-carbenes have been extensively employed in the construction of cyclopropanol scaffolds. For example, when arylcarbene chromium complexes **208** were treated in THF at low temperatures, with one equivalent of 1-aminodienes **207**, cyclopropane derivatives **209** were obtained, after hydrolysis with silica gel, in moderate yield and as single diastereoisomers.

Scheme 77.



The Kulinkovich reaction allows for a direct and efficient route to cyclopropanols[97] in one step from readily accessible esters. Its applicability to the synthesis of cyclopropyl ethers is limited, since it requires alkylation of the corresponding alcohol. Nonetheless it is a powerful tool and has been extensively employed in the synthesis of unprotected cyclopropanols. For example, classical Kulinkovich conditions were used in the total synthesis of Cyathins A_3 and B_2 from cyclopropanol **211** dervived from ester **210** (Scheme 78.).[98]

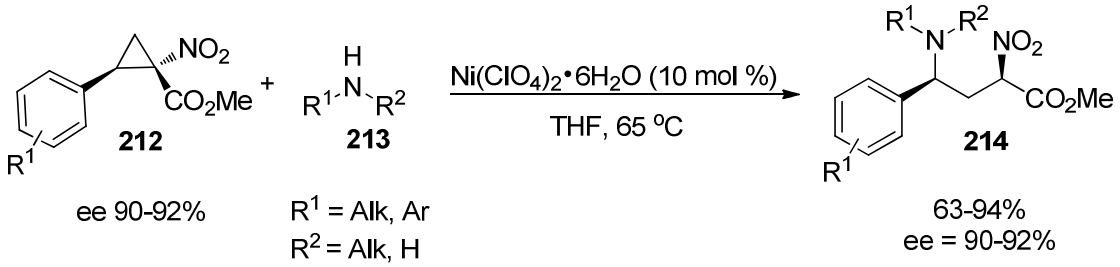
Scheme 78.



2.1.6. Synthetic utility of DACs

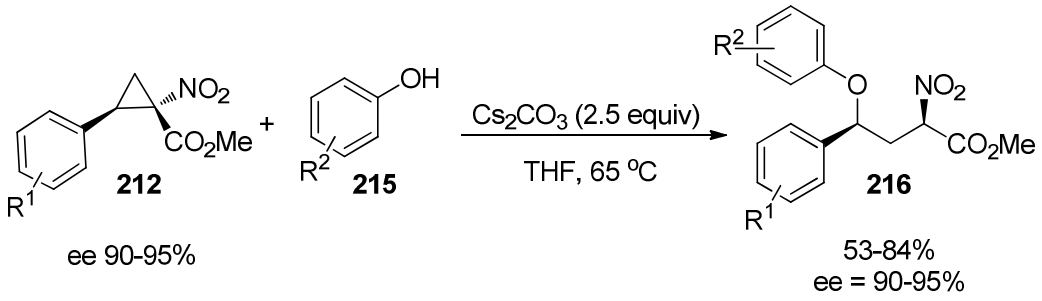
Cyclopropane derivatives vicinally substituted by donor and acceptor groups are particularly suitable for synthetic applications, since electronic effects of these substituents force activation of the cyclopropanes towards ring opening and uncover avenues for a wide variety of interesting transformations. A number of useful protocols employing DACs have been developed. For example DACs serve as efficient electrophiles in nucleophilic addition reactions to provide open chain substitutions.[99] This reactivity has been exploited by Charette in the addition of amine and phenol nucleophiles. The Lewis acid-catalyzed ring-opening of methyl 1-nitrocyclopropanecarboxylates **212** with amine nucleophiles **213** is very efficient and proceeds at room temperature and with complete preservation of the enantiomeric purity from the electrophilic center of the cyclopropane to the acyclic product **214** in good to excellent yields (Scheme 79).[100]

Scheme 79



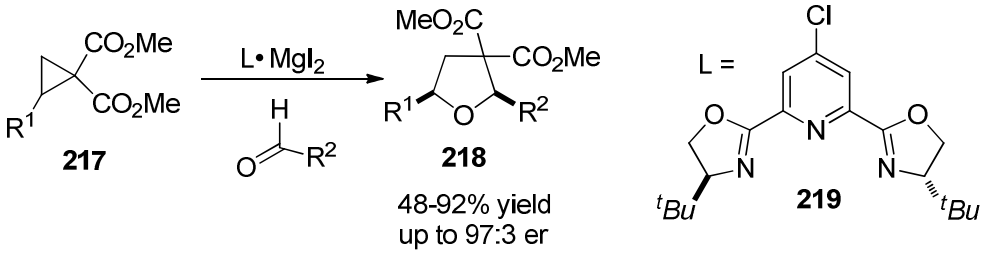
Addition of a wide variety of phenol nucleophiles to **215** in the presence of Cs_2CO_3 also proceeded efficiently to give the corresponding ring opening products **216** in medium to high yields with complete preservation of the enantiomeric purity from the electrophilic center of **212** (Scheme 80)**.**[101]

Scheme 80



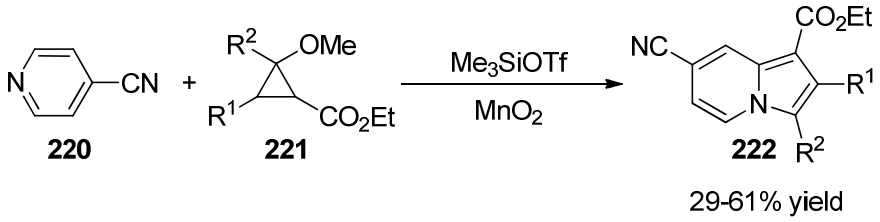
DACs also serve as all carbon 1,3 dipoles in various [3 + 2][102], [3 + 3][103], and [3 + 4.][107]cycloaddition reactions. Johnson and co-workers recently reported an efficient preparation of enantioenriched tetrahydrofuran (THF) derivatives **218** through a dynamic kinetic asymmetric transformation of racemic malonate-derived donor-acceptor cyclopropanes **217** via asymmetric [3 + 2] cycloaddition with aldehydes.[104]

Scheme 81.



Pagenkopf demonstrated annulations between DA-cyclopropanes **221** with pyridines and quinolines for the synthesis of indolizines and benzoindolizines. Despite some limitations in substrate scope, this methodology provides convenient new pathways to access a variety of indolizine scaffolds **222** (Scheme 82).[105]

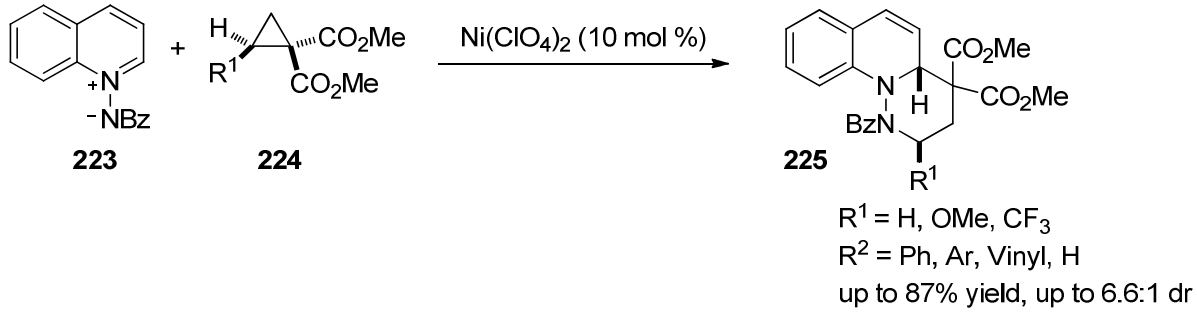
Scheme 82.



A [3+3] cycloaddition of aromatic azomethine imines **223** with 1,1-cyclopropane diesters **224** was achieved by Charette using $Ni(ClO_4)_2$ as a catalyst. The methodology provided access to

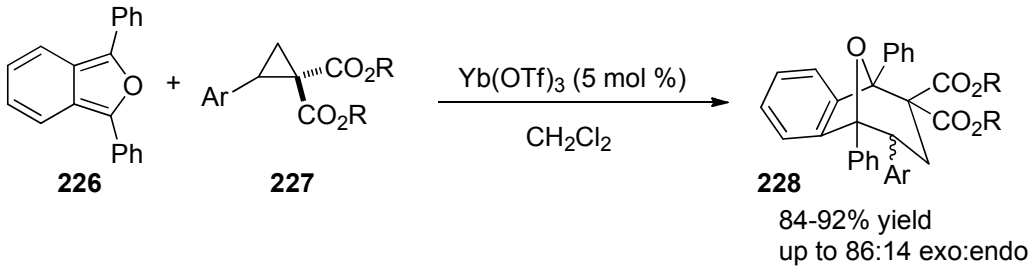
unique tricyclic dihydroquinoline **225** derivatives with dr up to 6.6:1. Notably complete retention of stereogenic information of the cyclopropane was observed (Scheme 83).[106]

Scheme 83.



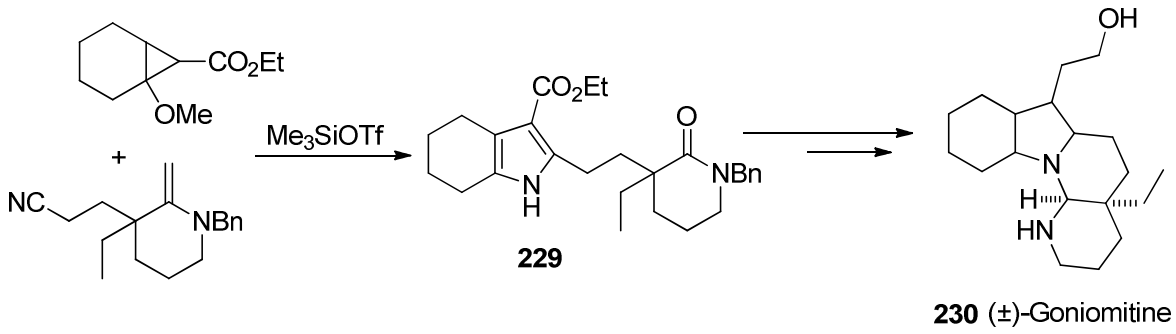
Ivanova and co-workers recently developed an analogue of the Diels–Alder reaction with donor–acceptor cyclopropanes as dienophiles. This formal [4+3] cycloaddition between 2-aryl cyclopropane diesters **227** and 1,3-diphenylisobenzofuran **226** proceeds under mild reaction conditions to yield two isomeric cycloadducts **228** in a combined yield of 84–92□% (Scheme 84).[107]

Scheme 84.



DACs synthetic utility has stretched to its incorporation in the total syntheses of several natural products. For example, the total synthesis of (±)-goniomitine **230** was accomplished in 17 linear steps with 5.2% overall yield. A synthetic highlight included the first application of a formal [3 + 2] cycloaddition between a highly functionalized nitrile and a donor-acceptor cyclopropane to prepare an indole scaffold (Scheme 85)

Scheme 85.

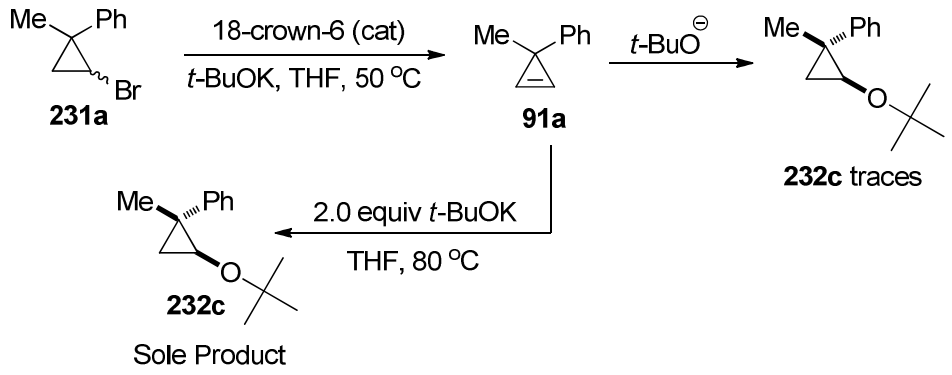


2.2. Results and Discussion

2.2.1. Introduction

While investigating the base-assisted 1,2-dehydrohalogenation of 3,3-disubstituted bromocyclopropanes **231a** into 3,3-disubstituted cyclopropenes **91** possessing a non-conjugate strained double bond,[108] we noticed trace amounts of *t*-BuOH adduct **232c** as a single diastereomer (Scheme 86). This was exciting since additions of oxygen-based nucleophiles to 3,3-disubstituted cyclopropenes are scarce. All reported examples of this transformation were performed on C_2V-symmetric substrates and thus did not have a stereoselectivity issue.[109] We envisioned that the facial selectivity of the nucleophilic addition to these substrates could be efficiently controlled by steric factors. This effect was observed in the previously reported additions of metallic entities to cyclopropenes bearing significantly different by size substituents at C3 (Scheme 7). Also, generation of the strained intermediate **91** in situ would eliminate the olefin isolation step and thus expand the range of applicable substrates to the most sensitive cyclopropenes.

Scheme 86.

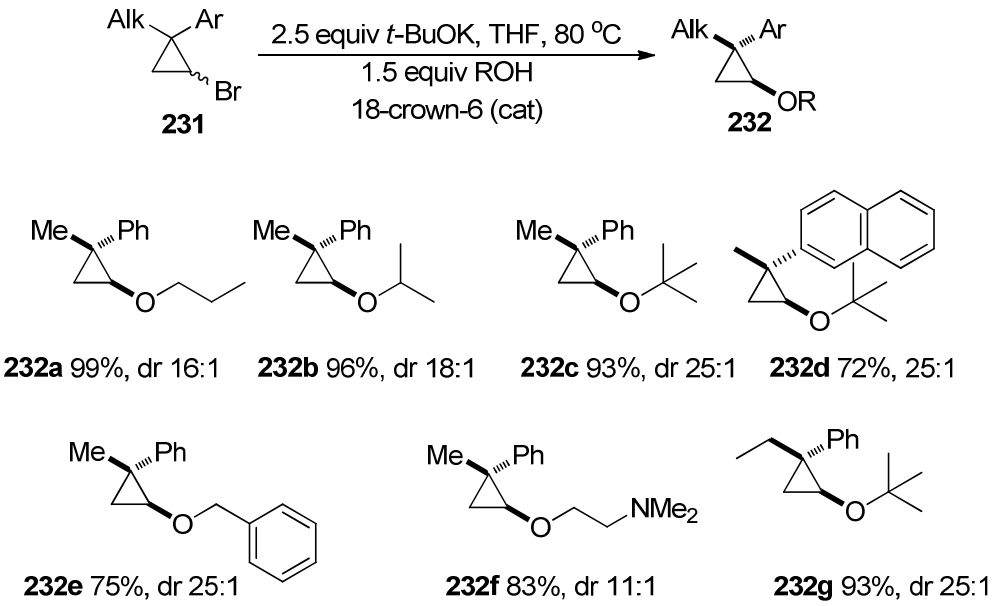


2.2.2. Steric control of diastereoselectivity in the formal nucleophilic substitution of bromocyclopropane

To obtain complete conversion in *t*-BuOK addition, we carried out the reaction of 2-bromo-1-methyl-1-phenylcyclopropane **91a** with excess *t*-BuOK (2.0 equiv) in the presence of catalytic 18-crown-6 ether (10 mol%) at various temperatures. It was found that at 80 °C bromocyclopropane **231a** was transformed into **232c** as the sole product in excellent yield. Remarkably, the addition proceeded with very high facial selectivity, producing a single *trans*-diastereomer. Similarly, the reaction of bromocyclopropane bearing an ethyl substituent at C3, provided *tert*-butyl ether **231g** in high yield and excellent diastereoselectivity, thus confirming the efficient steric control (Scheme 87.). Inspired by this result, we tested a series of more nucleophilic primary and secondary alkoxides in the addition reaction with **91a** in the presence of 1.5 equiv of *t*-BuOK. We were pleased to find that both *n*-propoxide and isopropoxide underwent efficient addition, providing the corresponding cyclopropyl ethers **232a** and **232b** as

sole products in high yields and excellent diastereoselectivities (Scheme 87). Benzyl-protected[110] cyclopropanol **231e** was also obtained in good yield in the reaction carried out in the presence of benzylic alcohol. *O*-Nucleophiles bearing additional functional groups were also successfully employed in this transformation. Thus, 2-(dimethylamino)ethanol reacted uneventfully affording **232f** in high yield.

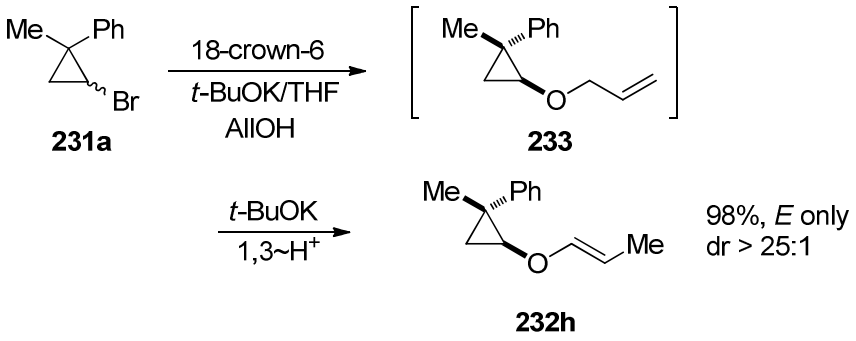
Scheme 87.



The addition of allyl alcohols to **231a** was also investigated and it was found that rather than providing the corresponding allyl ether **97**, cyclopropyl enol undergoes a a base-assisted 1,3-prototropic rearrangement to provide **96h** as the sole product in very high yield and

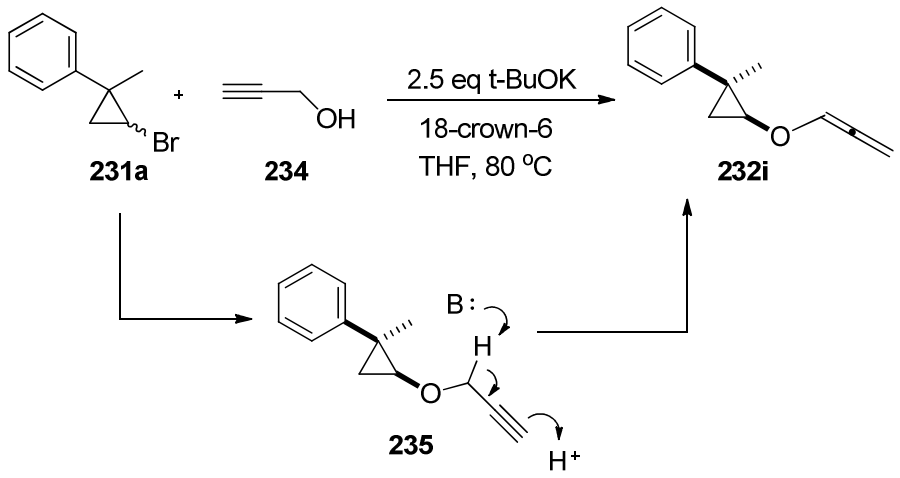
excellent diastereoselectivity. Notably, the thermodynamically driven rearrangement provided only *E*-isomer **(**Scheme 88.)

Scheme 88.



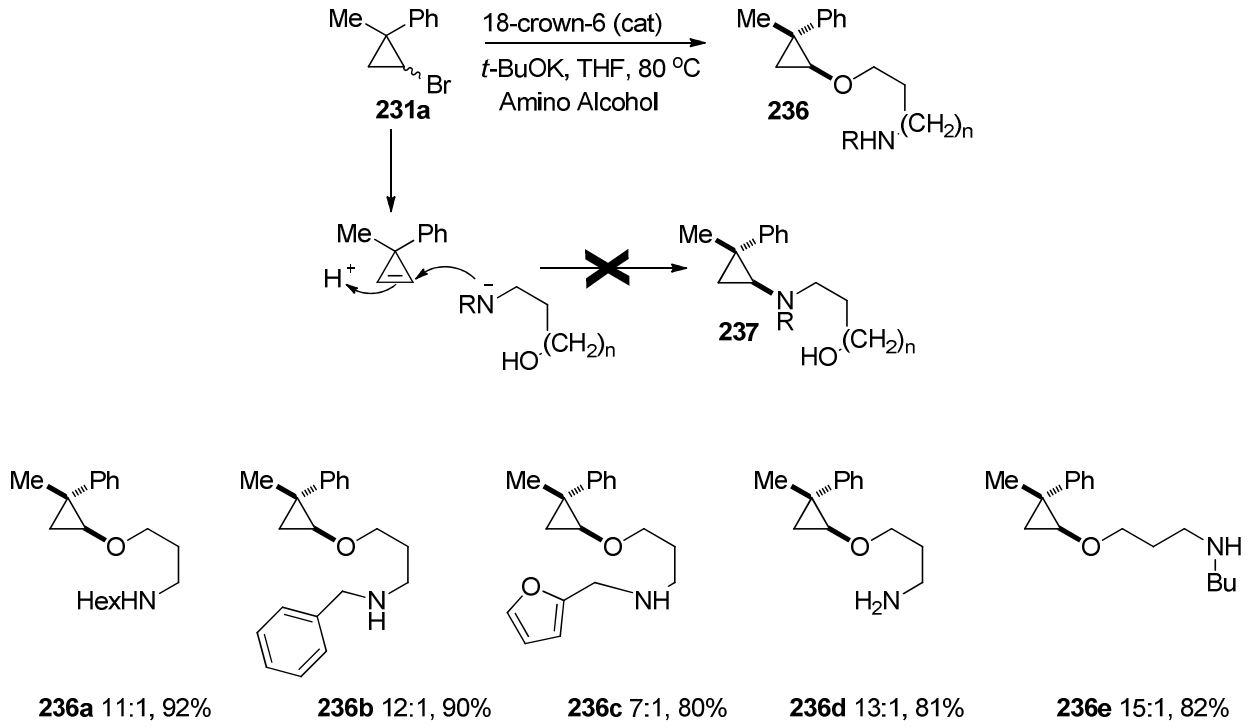
Intrigued by this rearrangement, we investigated the addition of propargylic alcohol to **231a**. This reaction also was accompanied by a formal 1,3-prototropic rearrangement via propargyl ether **235** to provide the corresponding allenyl ether **232i** in 82% yield (Scheme 89)

Scheme 89.



When amino alcohols were employed as competing nucleophiles, only addition by the oxygen terminus was observed. Thus, alkoxides possessing a secondary amine functionality reacted chemoselectively producing cyclopropyl ethers **236a**, **236b**, **236c**, and **236e** with no corresponding cyclopropylamine derivatives **237** detected (Scheme 90). Likewise, the reaction of **95a** with amino alcohol bearing a primary amine function afforded cyclopropyl ether **236d** as a sole product. The free amine is not nucleophilic enough to participate in this process and generation of the more nucleophilic amide is inefficient as *t*-BuOK is not a strong enough base. Therefore the amine is easily outcompeted by the *in situ* generated alkoxide to afford the corresponding ethers exclusively.

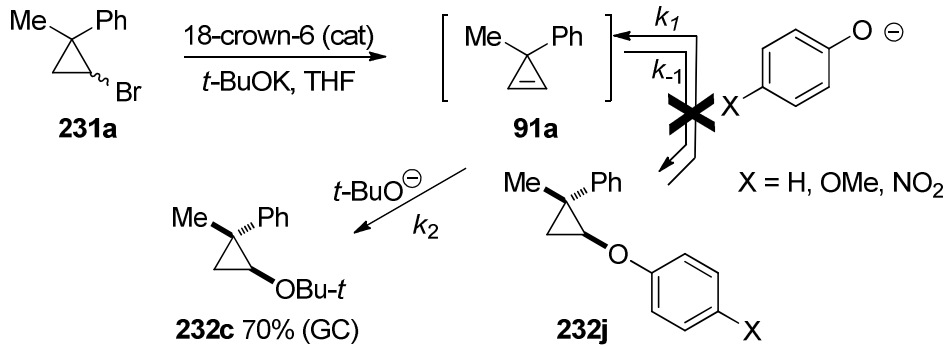
Scheme 90.



Considering the relatively high reactivity of phenoxides in previously reported formal nucleophilic substitutions, and attempting to expand the range of possible nucleophiles for this transformation we explored the possibility of phenoxide addition in the reaction between phenol and **231a**. Surprisingly, only traces of phenylcyclopropyl ether **232j** were detected in the crude reaction mixture; instead *tert*-butyl ether **232c** was obtained as the major product (Scheme 91), while use of KOH instead of *t*-BuOK resulted in no reaction. The addition of *p*-methoxyphenol and *p*-nitrophenol also failed to give the corresponding aryl ethers. To account for this phenomenon, two alternative mechanistic hypotheses can be considered. According to the first rationale, addition of both phenoxide and *tert*-butoxide species to cyclopropene **91a** is irreversible, but the kinetic rate of the phenoxide addition is significantly lower than that of *tert*-

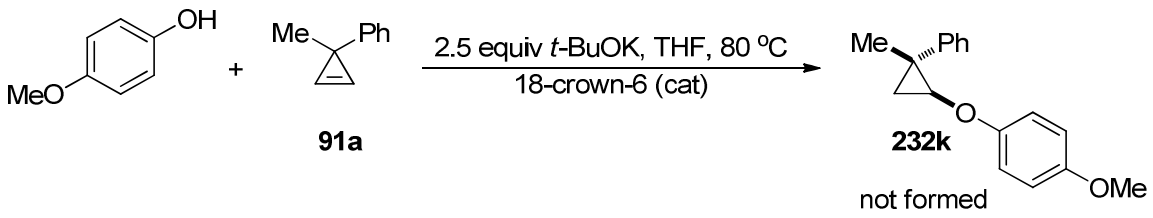
butoxide ($k_2>>k_1$). The second hypothesis presumes that the addition of the more nucleophilic phenoxide is reversible; and the relatively high nucleofugality of phenoxide[111] results in the formation of the thermodynamically favored product (Scheme 91) **232c**.

Scheme 91.



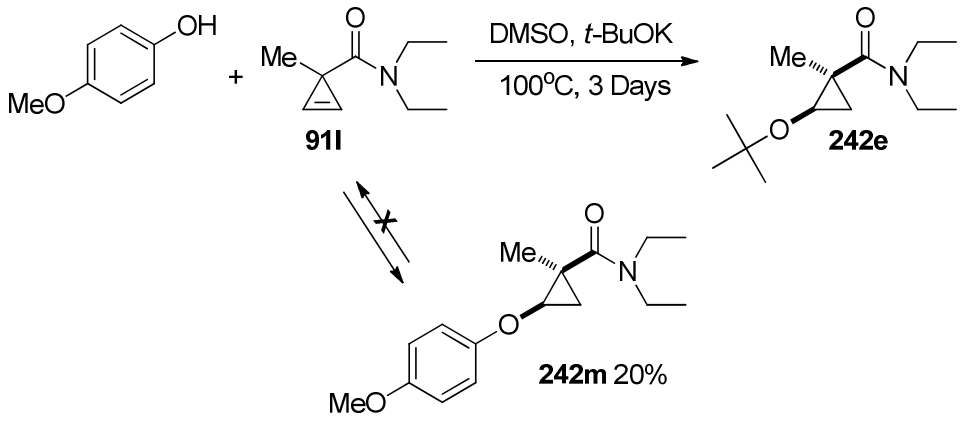
To obtain additional mechanistic evidences that could support or rule out the second pathway, we attempted synthesis of the aryl ether **232k**. However, employment of our standard reaction conditions failed to provide necessary amounts of **232k**. Attempts to prepare **232k** by nucleophilic addition of *p*-methoxyphenol across the C=C bond of the isolated cyclopropene **91** using different base and solvent combinations, were also unsuccessful (Scheme 92).

Scheme 92.



In contrast, a reaction between 4-methoxyphenol and more electron deficient cyclopropene **91l**, generated *in situ* from the corresponding mono bromocyclopropane in the presence of catalytic 18-crown-6 and *t*-BuOK, in DMSO at 100 ^{o}C afforded a 1:1 mixture of phenoxide adduct **242m** and *tert*-butyl ether **242e**. Product **242m** was isolated in 20% yield and re-subjected to the reaction with *t*-BuOK. However no formation of the *tert*-butyl ether **242e** was observed which ruled out the hypothesis about the reversibility of the phenoxide addition, and suggested that addition is controlled by kinetic factors. The inferior reactivity of aryloxides compared to *tert*-butoxide is opposite to that observed in the conjugate addition. Although this phenomenon is not yet completely understood, the non-conjugate strained double bond of cyclopropene **91i** apparently behaves as a relatively hard electrophile as opposed to the soft conjugate double bond in 1-cyclopropene carboxamides described above (Scheme 69).

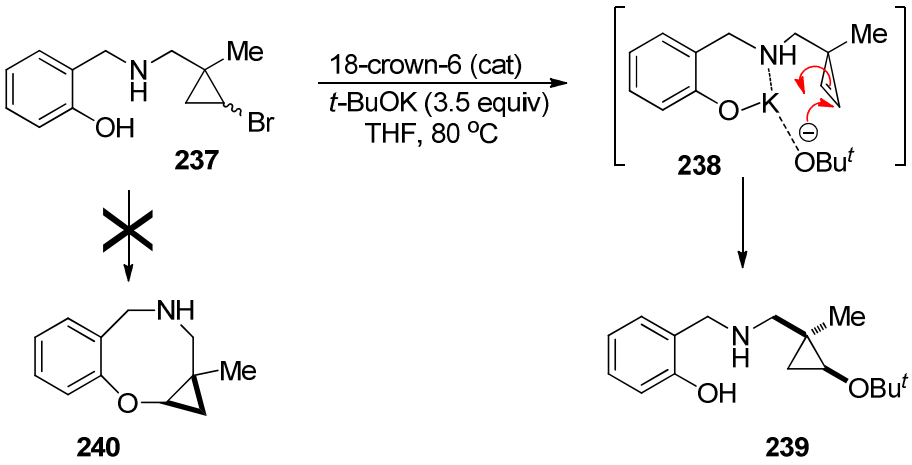
Scheme 93.



2.2.3. Direction control of diastereoselectivity through carboxamides

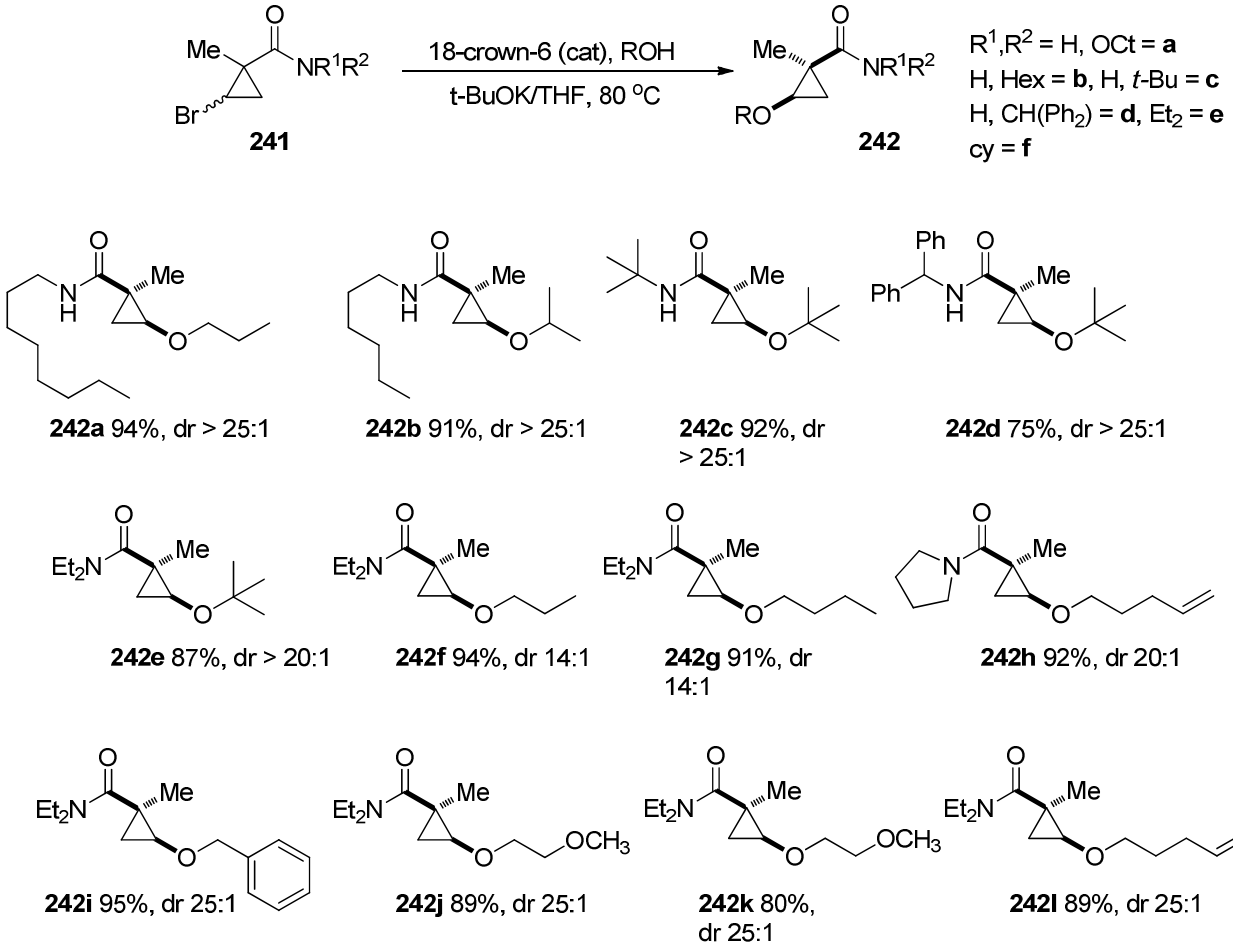
An attempt to facilitate the addition of an aryloxide species was made by carrying out the reaction in an intramolecular fashion. Bromocyclopropane **237** possessing a tethered phenol was treated with a base under the standard reaction conditions (Scheme 94). Nonetheless, no benzoxazacine product **240** was formed; the intermolecular addition of *tert*-butoxide took place instead, providing **239** as a sole product. Remarkably, *cis*-diastereomer of **239** was obtained exclusively, controlled by a strong chelating effect of the 2-(aminomethyl)phenolate moiety in intermediate **238** (Scheme 94).

Scheme 94.



Accordingly, we probed the ability of other functional groups to coordinate to potassium cation which serves as a delivery vehicle in the directed addition of alkoxides from the more sterically hindered face. Gratifyingly, it was found that carboxamide moiety can serve as an excellent directing group, governing the addition of nucleophiles from the more hindered face. Thus, reactions of secondary and tertiary amides **242** with excess *t*-BuOK afforded the corresponding *tert*-butyl ethers **242d** and **242e** in high yield and excellent *cis*-selectivity (Scheme 95). Analogously, high facial selectivity was observed in the reaction of sterically hindered secondary amides. Additions carried out in the presence of competing alkoxides, including primary **242a**, **242f**, **242h,** and secondary **242b,** species revealed both very high diastereo- and chemoselectivity. Finally, *cis*-adducts of 2-methoxyethanol (**242j**), 2-(dimethylamino)ethanol (**242k**), and 4-pentenol (**242h**, **242l**) were obtained in high yields, once again highlighting the excellent functional group compatibility of this transformation.

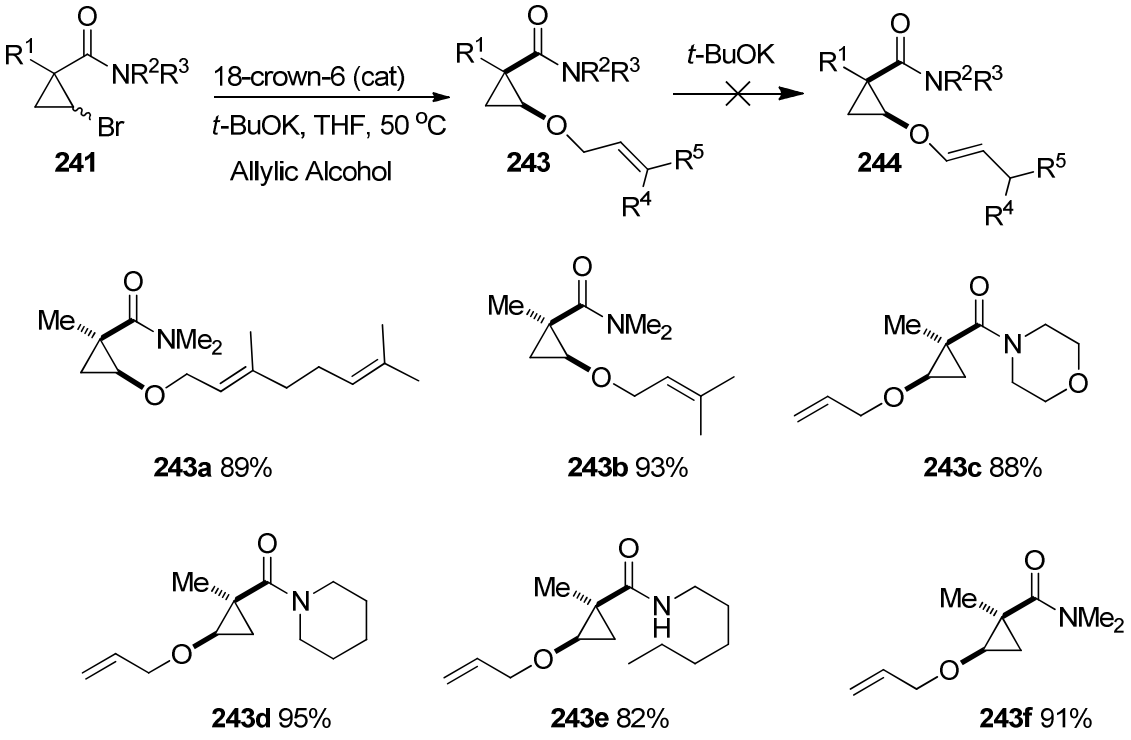
Scheme 95



Cyclopropenylcarboxamides are slightly more reactive as compared to the more electron rich 3-alkyl-3-aryl derivitives. With this in mind the addition of allyl alcohols was investigated and it was hypothesized that at lower temperatures the *1,3*-prototropic rearrangement could be avoided to access cyclopropyl allyl ethers. Initially reaction of **241f** and allylic alcohol carried out at 80 ^{o}C afforded allyl ether **243f** contaminated with the corresponding *E*-prop-1-enyl ether **244f**. However when the reaction temperature was lowered to 50 ^{o}C the rearrangement was

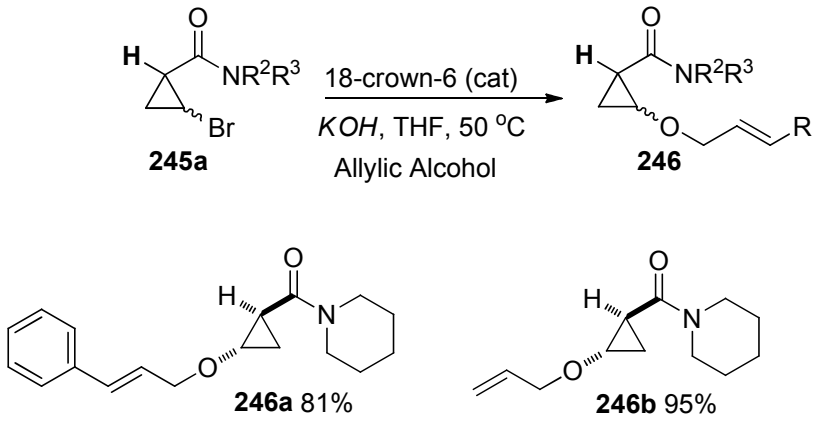
avoided and the corresponding allyl ether **243f** was obtained exclusively in 91% yield. Similarly, other 2-bromocyclopropancarboxamides underwent efficient formal substitution to produce the corresponding allylic ethers **243c-f**. Interestingly reaction of **241** with prenyl and geranyl alcohols proceeded uneventfully to give ethers **243b** and **243a**, respectively (Scheme 96). It should be noted that resubjection of bulkier allyl ethers **243c-d** to the action of *tert*-butoxide at elevated temperatures did not cause rearrangements to enol ethers **244**; this is hypothesized to be due to a steric effect caused by the bulky amide functions.

Scheme 96.

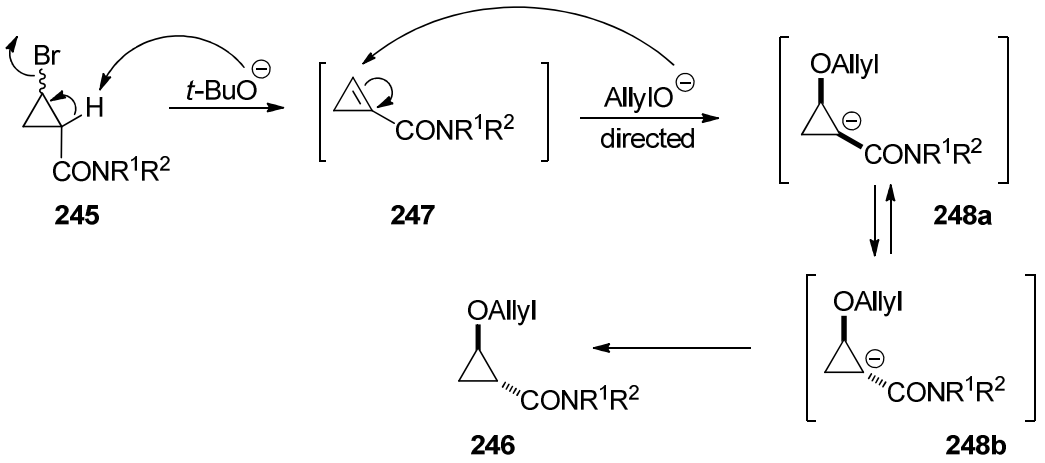


Allyl alcohols also reacted smoothly with enolizable carboxamides **245**. Addition of cinnamyl and allyl alcohols proceeded without rearrangement and the allyl ethers **246a**,**b** were obtained in 81% and 95% yield, respectively. However the facial selectivity was not controlled through directing effects providing *cis*-cyclopropyl allyl ethers, rather the more thermodydnamically favored *trans* adducts were obtained exclusively (Scheme 97). As demonstrated in recent publications by Rubin, the *in situ* generated conjugated cyclopropene **247** undergoes nucleophilic attack and a thermodynamically favored epimerization of **248a** to **248b** affords the corresponding trans adducts **112** (Scheme 98).[88]

Scheme 97.

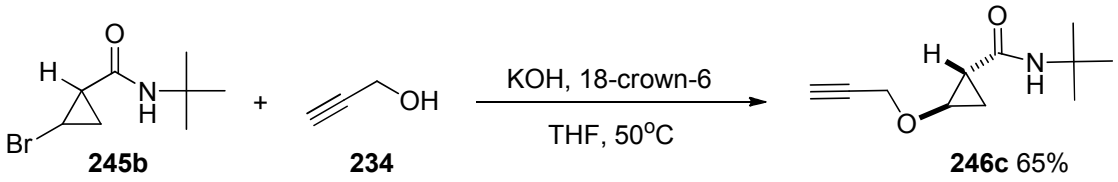


Scheme 98



The addition of propargylic alcohol **234** to enolizable carboxamide **245b** was also investigated. It was hypothesized that in the presence of a weaker base and at lower temperatures the prototropic rearrangement could be avoided. Indeed, the rearrangement into the allenyl ether did not proceed under these conditions, and the reaction afforded propargylic ether **246c** in 65% yield and as a single isomer (Scheme 99).

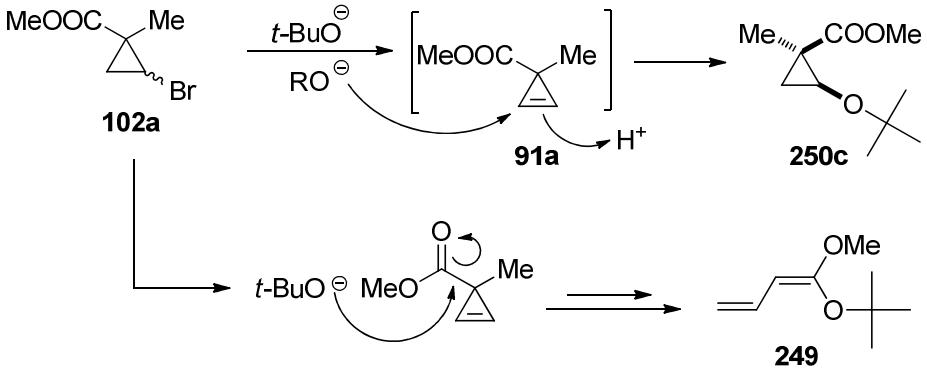
Scheme 99.



2.2.4. Direction control of diastereoselectivity through carboxylates

Having had success in the formal nucleophilic substitution of carboxamides, attention was turned to the possibility of formal substitutions on non-conjugated cyclopropyl carboxylates. Our attempts to add various nucleophiles to carboxylate **102a** provided no substitution and led to quick decomposition of the starting material and formation of dark resins. It is presumed that *tert*-butoxide attacked the more electrophilic carbonyl function of the ester rather than the C=C bond of cyclopropene, which ultimately led to ring opening. A putative structure of the decomposition product **249** is provided below. (Scheme 100).

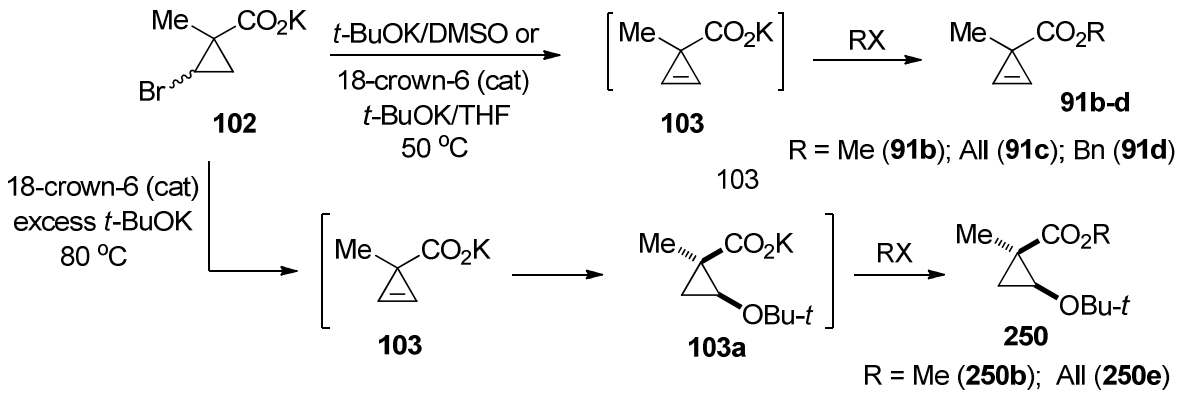
Scheme 100.



It was found, however, that the corresponding diastereomeric mixtures of potassium 1-methyl-2-bromocyclopropylcarboxylates **102** could be efficiently used instead of cyclopropyl esters. Thus, it was previously demonstrated that treatment of **102** with *t*-BuOK in dry DMSO at 50 ^{o}C

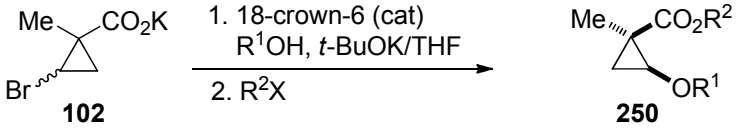
effects 1,2-dehydroboromination to produce cyclopropene-3-carboxylic salt **103**. The latter upon trapping in situ with an S_N2-active alkyl halide affords the corresponding ester.[112] We observed very similar reactivity when carboxylate **102** was treated with the base and catalytic 18-crown-6 in a THF solution at 50 ^oC (Scheme 101). The corresponding cyclopropenylesters **91b** (R = Me), **91c** (R = Allyl), and **91d** (R = Bn) were produced cleanly, as judged by GC/MS and ^1H NMR analysis of the crude reaction mixtures. In contrast, dehydrobromination of **102** carried out at 80 ^oC with excess *t*-BuOK resulted in exclusive formation of salt **103a**, which after subsequent treatment with methyl iodide or allyl bromide afforded the corresponding *cis*-esters **250b** or **250e** as sole products in high yield (Scheme 101). Remarkably, similarly to the carboxamide function, the carboxylate moiety in intermediate **103** served as an effective directing group for the diastereoselective nucleophilic attack.

Scheme 101.

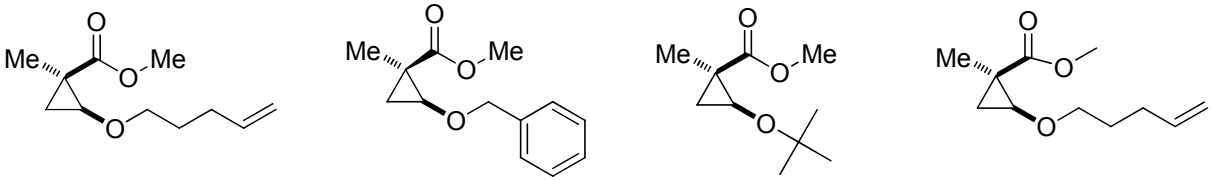


Directed additions of competing *n*-propoxide and isopropoxide nucleophiles gave rise to *cis*-esters **250e** and **250f** in good overall yields and excellent *cis*-selectivities (Scheme 102). Benzyl-protected *cis*-cyclopropanol **250b** was readily produced in the presence of benzyl alcohol. Employment of pent-4-enyl alcohol as a pronucleophile allowed for efficient preparation of cyclopropyl ethers **250c** and **250d** possessing a terminal olefin moiety in the side chain.

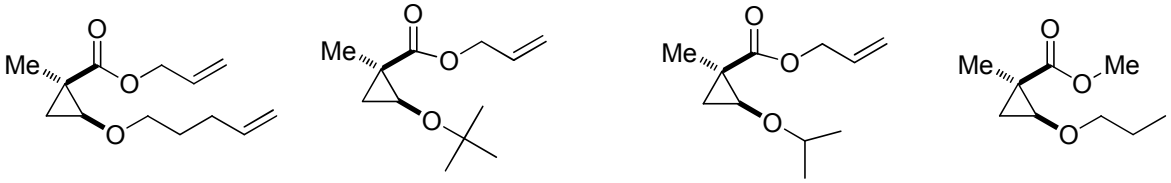
Scheme 102.



102 **250**



250a 72% **250b** 82% **250c** 79% **250d** 68%

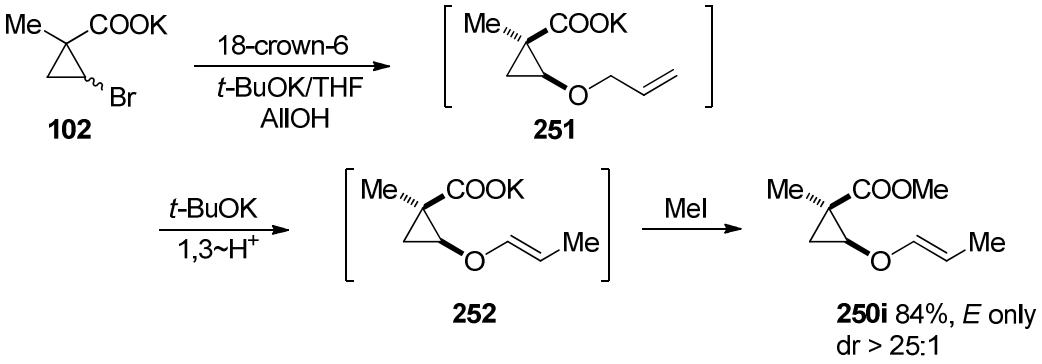


250e 68% **250f** 81% **250g** 76% **250h** 83%

In contrast to the described above nucleophilic attack of allylic alkoxides on carboxamides (Scheme 102.), the analogous addition to carboxylates **102** was accompanied by a

facile base-assisted 1,2-migration of the double bond of **252** to afford, after electrophilic quench, *E*-propenyl ether **250i** (Scheme 103.). Such difference in reactivity can be attributed to a higher kinetic *C-H* acidity of the *cis*-allyloxide moiety, as a result of lower sterical hindrance exerted by the carboxylic moiety compared to a more bulky carboxamide functionality.

Scheme 103.



2.3. Conclusion

An efficient formal nucleophilic substitution of bromocyclopropanes with oxygen-based nucleophiles has been developed. This transformation proceeds via a stereoconvergent dehydrobromination, followed by diastereoselective addition of a nucleophilic species across the strained C=C bond of a cyclopropene intermediate. This methodology is the first to show stereo selective formal nucleophilic substitutions of *3,3*-disubstituted cyclopropanes. The diastereoselective addition can be efficiently controlled by either sterics or a directing effect of

appropriate functional groups, such as carboxamides or carboxylic salts. This methodology also allows access to densly substituted DACs and potentially medicinally valuable cyclopropanol derivitives.

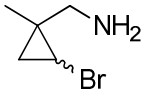
2.4. Experimental Procedures

2.4.1. General Information

See Chapter 1.4.1. for general remarks and list of instrumentation. Anhydrous dimethylsulfoxide was purchased form Acros Organics and used as received. Anhydrous diethyl ether and tetrahydrofuran were obtained by passing degassed HPLC-grade commercially available solvents consecutively through two columns with activated alumina (Innovative Technology). All other chemicals were purchased from Sigma-Aldrich or Acros Organics, and used as received.

2-bromocyclopropane carboxamides **242** were all prepared according to published procedures.[113] For the preparation of 1-methyl-2-bromocyclopropane carboxalates see section 1.4.2. Procedures for all other monobromides are provided below.

2.4.2. Preparation of 2-Bromocyclopropanes

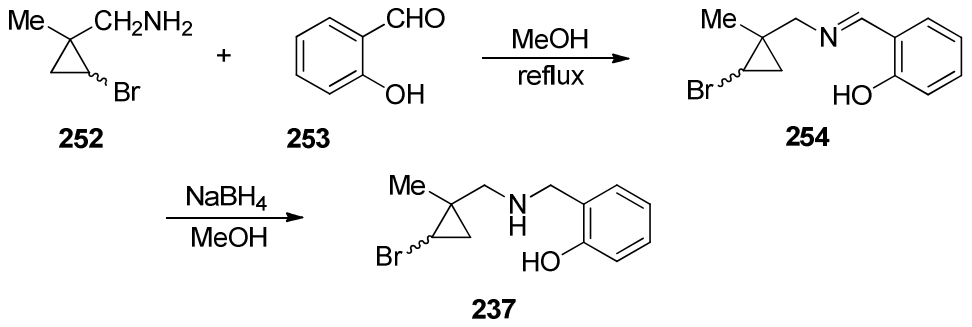


(2-Bromo-1-methylcyclopropyl)methylamine (**252**): 300 mL of 30% aqueous ammonia solution was stirred at 0 ^{o}C in 1000 mL Erlenmeyer flask, closed with a rubber stopper

with one 6 mm hole. Acyl chloride **5** (25.0 g, 127 mmol) was added by small portions using Pasteur pipette. Caution: the addition causes a violent exothermic reaction, which may be accompanied with producing a white fog of ammonium chloride, and even splashing of the ammonia solution. It is essential to carry out the reaction in a well-ventilated fume-hood. The addition of acyl chloride must be slow. The use of an addition funnel is not practical, since it's dropping tube and valve bore can be blocked by ammonium chloride. After the addition was complete the mixture was stirred in the open flask overnight to remove the excess of ammonia. By this time a white solid precipitate was formed, which was filtered on a Büchner funnel. The filter cake was washed with ice-cold distilled water, and then dried: first on air, then in vacuum desiccator over P_2O_5 to obtain 2-bromo-1-methylcyclopropanecarboxamide as white powder. Yield 13.8 g (77.5 mmol, 61%). This material (12.7 g, 71.2 mmol) without further purification was stirred in anhydrous THF (100 mL) and BH_3-SMe_2 complex (11.4 g, 14.2 mL, 150 mmol) was added. The resulting mixture was stirred at reflux for 10 hrs, then the solvent was removed in vacuum, and the glassy residue was digested by 10% aqueous HCl (250 mL). Caution: this process is accompanied with violent gas evolution and stench. All the operations must be performed under well-ventilated fume-hood. The obtained aqueous solution was washed with dichloromethane (75 mL), and basified with solid NaOH at 0 ^oC. Formed oily precipitate was extracted with dichloromethane (3 x 75 mL), washed with brine, dried with anhydrous K_2CO_3, filtered and concentrated. Fractionation in vacuum (bp 72-75 ^oC at 16 mm Hg) gave amine **20** as a colorless oil. Yield 8.14 g (49.6 mmol, 70%). GC R_t 5.09 min (minor), 5.45 min (major) ^1H NMR ($CDCl_3$, 400.13 MHz) δ [2.90 (dd, *J* = 7.8 Hz, 4.3 Hz) & 2.82 (dd, *J* = 7.6 Hz, 4.3 Hz), ∑1H], [2.90 (d, *J* = 13.4 Hz) & 2.55 (d, *J* = 13.4 Hz), ∑1H], [2.74 (d, *J* = 13.4 Hz) & 2.54 (d, *J* =

13.4 Hz), ∑1H], [1.28 (s) & 1.16 (s), ∑3H], 1.18 (br.s, 2H), [1.06 (dd, *J* = 7.8 Hz, 6.4 Hz) & 0.98 (dd, *J* = 7.6 Hz, 6.1 Hz), ∑1H], [0.76 (dd, *J* = 6.1 Hz, 4.3 Hz) & 0.65 (dd, *J* = 6.4 Hz, 4.3 Hz), ∑1H]; ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 49.7 (-), 49.1 (-), 28.4 (+), 27.7 (+), 23.9 (-), 23.3, 21.7, 20.5 (-), 20.2 (+), 18.7 (+); HRMS (TOF ES) found 164.0080, calcd for $C_{15}H_{11}BrN$ (M+H) 164.0075 (3.0 ppm).

Scheme 104 . Preparation of 2-{[(2-Bromo-1methylcyclopropyl) methylamino]methyl}phenol (**237**)

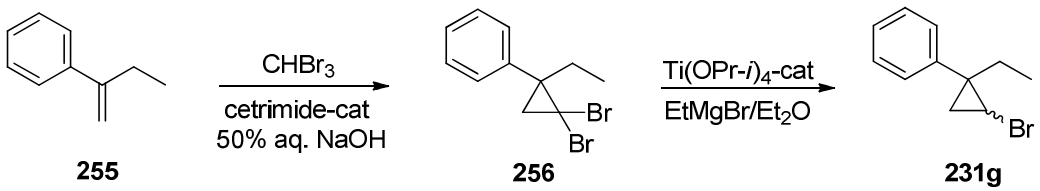


2-{[(2-Bromo-1-methylcyclopropyl)methylamino]methyl}phenol (**237**): amine **252** (500 mg, 3.05 mmol) and salicylic aldehyde (**253**) (372 mg, 3.05 mmol) were stirred in methanol (5 mL) for 24 hrs at room temperature. Then the solvent was removed in vacuum and the residue was purified by preparative column chromatography on Silica gel (eluent hexane-EtOAc 10:1) to obtain 2-(((2-bromo-1-methylcyclopropyl)methylimino)methyl)phenol (**254**) as a yellow oil (R_f 0.4). Yield 595 mg (2.22 mmol, 73%). This material was dissolved in methanol (10 mL) and

$NaBH_4$ (420 mg, 11 mmol) was added in one portion. The mixture was stirred at room temperature for 48 hrs, then methanol was removed in vacuum, the residue was dissolved in 10% aqueous HCl (25 mL) and washed with dichloromethane (20 mL). Then the aqueous phase was basified with solid NaOH and the amine was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried with anhydrous K_2CO_3, filtered and concentrated to obtain the amine **237** as a colorless oil, yield 522 mg (1.93 mmol, 87%). This material was pure enough to carry out the next step without any additional purification.

^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.22-7.18 (m, 1H), [7.03 (d, *J* = 8.1 Hz) & 7.01 (d, *J* = 8.1 Hz), ∑1H], [6.88 (dd, *J* = 8.1 Hz, 1.0 Hz) & 6.86 (dd, *J* = 8.3 Hz, 0.8 Hz), ∑1H], 6.83-6.79 (m, 1H), [4.14 (d, *J* = 13.6 Hz) & 4.04 (d, *J* = 13.6 Hz), ∑1H], [3.97 (d, *J* = 13.9 Hz) & 3.94 (d, *J* = 13.6 Hz), ∑1H], [2.97 (d, *J* = 12.4 Hz) & 2.67 (d, *J* = 12.4 Hz), ∑1H], 2.88 (dd, *J* = 8.1 Hz, 4.6 Hz, 1H), [2.73 (d, *J* = 12.4 Hz) & 2.46 (d, *J* = 12.4 Hz), ∑1H], [1.37 (s) & 1.26 (s), ∑3H], [1.29 (ps.-t, *J* = 6.8 Hz, 6.3 Hz), 1.07 (ps.t, *J* = 7.6 Hz, 6.8 Hz), ∑1H], [0.85 (dd, *J* = 6.3 Hz, 4.3 Hz) & 0.74 (dd, *J* = 6.3 Hz, 4.5 Hz), ∑1H]; ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 158.1, 158.0, 128.8 (+), 128.7 (+), 128.4 (+), 128.3 (+), 122.5, 122.0, 119.1 (+), 119.0 (+), 116.4 (+), 116.3 (+), 55.9 (-), 55.5 (-), 52.9 (-), 52.1 (-), 27.8 (+), 27.7 (+), 22.0 (-), 21.0 (+), 20.8 (-), 19.0 (+); HRMS (TOF ES) found 270.0496, calcd for $C_{12}H_{17}NOBr$ (M + H) 270.0493 (1.1 ppm).

Scheme 105. 2,2-Dibromo-1-ethyl-1-phenylcyclopropane (256g)

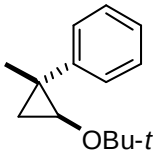


2,2-Dibromo-1-ethyl-1-phenylcyclopropane (**256g**): To a vigorously stirred (1500 rpm) mixture of α-ethylstyrene (**255**)[114] (1.73 g, 13.1 mmol), cetrimide (100 mg), bromoform (9.93 g, 39.3 mmol, 3.0 equiv.), and dichloromethane (5 mL) was added dropwise a 50% aqueous solution of NaOH (10 mL). The mixture was stirred for 20 hrs at room temperature, when GC analysis showed full conversion of the starting styrene. The mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). Combined organic phases were washed consecutively with saturated aqueous NH_4Cl (50 mL), brine (50 mL), then dried with $MgSO_4$, filtered and concentrated in vacuum. The residue was distilled in Kugelröhr (0.4 torr, oven temp. 120-130 ^oC). Yield 3.94 g (13.0 mmol, 99%). ^1H NMR (400.13 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.3 Hz, 2H), 7.34-7.29 (m, 3H), 2.19 (dq, *J* = 14.4 Hz, 7.3 Hz, 1H), 2.08 (d, *J* = 7.6 Hz, 1H), 1.83 (dq, *J* = 14.4 Hz, 7.3 Hz, 1H), 1.76 (d, *J* = 7.6 Hz, 1H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 140.2, 129.5 (+, 2C), 128.1 (+, 2C), 127.2 (+), 41.0, 36.8, 33.7 (-), 32.8 (-), 11.3 (+); GC: R_t = 9.79 min.

2-Bromo-1-ethyl-1-phenylcyclopropane (**231g**): To a stirred solution of dibromocyclopropane **256** (3.94 g, 13.0 mmol) and Ti(OPr-*i*)$_4$ (37 mg, 0.13 mmol, 10 mol%) in anhydrous ether was

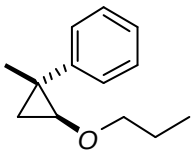
added dropwise 3N solution of EtMgBr (5.2 mL, 15.6 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 1 hr, when GC analysis showed complete conversion. The mixture was quenched with saturated aqueous NH_4Cl (10 mL), then 10% aqueous sulfuric acid (10 mL) and diethyl ether (30 mL) were added. The organic layer was separated; the aqueous phase was extracted with ether (3 x 15 mL). Combined organic phases were washed with brine, dried with $MgSO^4$, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on Silica gel eluting with hexane to afford the title compound as mixture of diastereomers (1.48:1, colorless oil, R_f 0.43, 0.33). Yield 2.226 g (9.89 mmol, 76%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.43-7.26 (m, 5H), [3.32 (dd, *J* = 8.1 Hz, 4.6 Hz) & 3.16 (dd, *J* = 7.6 Hz, 4.3 Hz), ∑1H], [2.08-1.85 (m) & 1.42-1.25 (m), ∑3H], [1.60 (ps.-t, *J* = 7.6 Hz, 6.6 Hz) & 1.07 (dd, *J* = 6.1 Hz, 4.5 Hz), ∑1H], [0.95 (t, *J* = 7.3 Hz) & 0.88 (t, *J* = 7.3 Hz), ∑3H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) major: δ 142.6, 128.8 (+, 2C), 128.3 (+, 2C), 126.6 (+), 31.9, 30.9 (-), 30.1 (+), 21.7 (-), 10.94 (+); minor: 140.3, 130.4 (+, 2C), 127.9 (+, 2C), 126.8 (+), 33.5, 33.4 (-), 27.3 (+), 20.8 (-), 10.87 (+); GC: R_t = 8.47 min (two diastereomers are not resolved); HRMS (TOF ES): found 145.1025, calculated for $C_{11}H_{13}$ (M-Br) 145.1023 (1.4 ppm).

2.4.3. Additions to Alkyl Aryl bromocyclopropanes



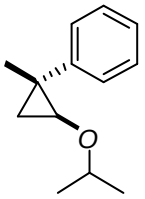
***(1R*,2S*)-tert*-Butyl 2-methyl-2-phenylcyclopropyl ether** (**232c**)**:** An oven-dried 10 mL Weaton vial was charged with *t*-BuOK (2.38 mmol, 266 mg), 18-crown-6 ether (0.12 mmol, 21 mg), 1-methyl-1-phenyl-2-bromocyclopropane (**231a**) (1.19 mmol, 250 mg), and anhydrous THF (5 mL). The mixture was stirred for 18 hr at

80 ^{o}C, then quenched with water, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine, dried with $CaCl_2$, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on Silica gel to obtain (1-methyl-2-tert-butoxycyclopropyl)benzene as a clear oil (R_f 0.20, eluent – hexane). Yield 226 mg (1.11 mmol, 93%). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.35-7.31 (m, 2H), 7.25-7.18 (m, 3H), 3.32 (dd, *J* = 7.3 Hz, 4.0 Hz, 1H), 1.50 (s, 3H), 1.31 (s, 9H), 1.26 (dd, *J* = 7.3 Hz, 6.1 Hz, 1H), 0.79 (dd, *J* = 6.1 Hz, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 146.2, 128.3 (+, 2C), 126.1 (+, 2C), 125.4 (+), 74.3, 58.8 (+), 28.1 (+, 3C), 24.6, 20.8 (-), 18.8 (+); ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) δ 0.79 (4%) upon irradiation at 1.50 ppm; GC: R_t 9.50 min; HRMS (TOF ES) found 227.1412, calcd for $C_{14}H_{20}ONa$ (M + Na) 227.1407 (2.2 ppm).

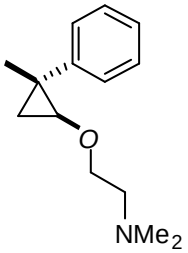


***(1R*,2S*)*-(1-Methyl-2-propoxycyclopropyl)benzene** (**232a**)**:** An oven-dried 10 mL Weaton vial was charged with t-BuOK (2.38 mmol, 266 mg), 18-crown-6 ether (0.12 mmol, 32 mg), 1-methyl-1-phenyl-2-bromocyclopropane (**231a**) (1.19 mmol, 250 mg), and anhydrous THF (5 mL). The mixture was stirred for 2 min, and then *n*-propanol (1.78 mmol, 107 mg) was added. The resulting mixture was stirred for 18 hr at 80 ^{o}C, then quenched with water, and extracted with CH_2Cl_2 (3 x 20 mL). Combined organic phases were washed with brine, dried with $CaCl_2$, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on Silica gel to obtain (1-methyl-2-propoxycyclopropyl)benzene as a clear oil (R_f 0.15, eluent – hexane). Yield 224 mg (1.18 mmol, 99%). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.34-7.30 (m, 2H), 7.26-7.18 (m, 3H), 3.61-3.52 (m, 2H), 3.37 (dd, *J* = 7.1 Hz, 3.8 Hz, 1H), 1.69 (sextet, *J* = 7.1 Hz, 2H), 1.53 (s, 3H), 1.17 (dd, *J* =

7.1 Hz, 6.1 Hz, 1H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.87 (dd, *J* = 6.1 Hz, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 146.0, 128.3 (+, 2C), 126.9 (+, 2C), 125.7 (+), 73.0 (-), 64.5 (+), 26.1, 23.0 (-), 20.4 (-), 18.8 (+), 10.7 (+); ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) δ 0.87 (5%) upon irradiation at 1.53 ppm; GC: R_t 9.54 min; HRMS (TOF ES) found 209.1769, calcd for $C_{13}H_{23}ON$ (M + NH_4) 209.1780 (5.3 ppm).

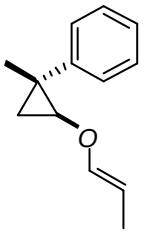


***(1R*,2S*)*-(2-Isopropoxy-1-methylcyclopropyl)benzene** (**232b**): was obtained according to the procedure described for preparation of compound **232a**, employing isopropanol (1.78 mmol, 107 mg) instead of *n*-propanol. Yield 217 mg (1.14 mmol, 96%), colorless oil (R_f 0.35, hexane). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.34-7.31 (m, 2H), 7.26-7.19 (m, 3H), 3.70 (septet, *J* = 6.1 Hz, 1H), 3.43 (dd, *J* = 7.3 Hz, 3.8 Hz, 1H), 1.52 (s, 3H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.19 (dd, *J* = 7.3 Hz, 5.8 Hz, 1H), 0.85 (dd, *J* = 5.8 Hz, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 146.1, 128.3 (+, 2C), 126.7 (+, 2C), 125.6, 72.3 (+), 62.5 (+), 26.1, 22.5 (+), 21.9 (+), 20.4 (-), 19.1 (+); ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) δ 0.85 (3%) upon irradiation at 1.52 ppm; GC: R_t 9.17 min; HRMS (TOF ES) found 197.1527, calcd for $C_{13}H_{18}OLi$ (M + Li) 197.1518 (4.6 ppm).

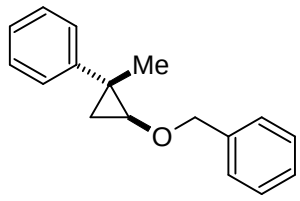


***(1R*,2S*)-N,N*-Dimethyl-2-(2-methyl-2-phenylcyclopropoxy)ethylamine (232f)**: was obtained according to the procedure described for preparation of compound **232a** employing 2-(dimethylamino)ethanol (158 mg, 1.78 mmol) instead of *n*-propanol. Yield 215 mg (0.98 mmol, 83%), colorless oil (R_f 0.1, EtOAc). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.31 (t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 7.1 Hz, 2H),

7.20 (t, *J* = 7.3 Hz, 1H), 3.75-3.65 (m, 2H), 3.39 (dd, *J* = 7.1 Hz, 3.5 Hz, 1H), 2.62-2.57 (m, 2H), 2.32 (s, 6H), 1.53 (s, 3H), 1.16 (ps.-t, *J* = 7.1 Hz, 6.1 Hz, 1H), 0.90 (dd, *J* = 6.1 Hz, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 145.9, 128.3 (+, 2C), 126.8 (+, 2C), 125.7 (+), 69.1 (-), 64.8 (+), 58.8 (-), 45.8 (+), 26.1, 20.3 (-), 18.8 (+); HRMS (TOF ES) found 242.1530, calcd for $C_{14}H_{21}NONa$ (M + Na) 242.1521 (3.7 ppm).

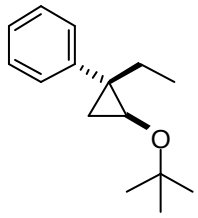


***(1R*,2S*)*-2-Methyl-2-phenylcyclopropyl (1*E*)-prop-1-enyl ether** (**232h**): was obtained according to the procedure described for preparation of compound **232a**, employing allyl alcohol (1.78 mmol, 103 mg) instead of *n*-propanol. Yield 222 mg (1.18 mmol, 98%), colorless oil (R_f 0.25, hexane). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.35-7.20 (m, 5H), 6.18 (dq, *J* = 6.3 Hz, 1.8 Hz, 1H), 4.52 (ps.-quintet, *J* = 6.6 Hz, 1H), 3.69 (dd, *J* = 7.1 Hz, 3.5 Hz, 1H), 1.65 (dd, *J* = 6.8 Hz, 1.8 Hz, 3H), 1.52 (s, 3H), 1.24 (ps.-t, *J* = 7.1 Hz, 6.3 Hz, 1H), 0.99 (dd, *J* = 6.3 Hz, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 145.3, 145.1 (+), 128.4 (+, 2C), 127.0 (+, 2C), 126.0 (+); 102.1 (+), 64.8 (+), 26.1, 20.1 (-), 19.2 (+), 9.2 (+); ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) δ 0.99 (5%) upon irradiation at 1.52 ppm; GC: R_t 9.56 min; HRMS (TOF ES) found 211.1095, calcd for $C_{13}H_{16}ONa$ (M + Na) 211.1099 (1.9 ppm).



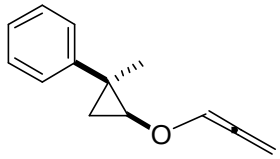
[(1*R,2*S**)-2-(Benzyloxy)-1-methylcyclopropyl]benzene** (**232e**): An oven-dried 10 ml Wheaton vial was charged with potassium *tert*-butoxide (113 mg, 1.05 mmol, 1.5 equiv) and of 18-crown-6 (19 mg, 11 mmol, 10 mol%), and anhydrous THF (8 mL). 2-Bromo-1-methyl-1-phenylcyclopropane

(147 mg, 0.7 mmol, 1.0 equiv) was added, followed by benzyl alcohol (113 mg, 1.05 mmol, 1.5 equiv). The mixture was stirred for 13 hr at 80 ^{o}C, when GC showed the reaction was complete. The mixture was quenched with water (5 ml), and extracted with EtOAc (4 x 10 ml). Combined organic phases were washed with brine (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (R_f = 0.9, Hexane/EtOAc 1:1) to afford the title compound as colorless oil. Yield 125 mg (0.53 mmol, 75%). ^{1}H NMR (400.13 MHz, CDCl3) δ 7.47-7.23 (m, 10H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 3.53 (dd, *J* = 7.1 Hz, 3.8 Hz, 1H), 1.62 (s, 3H), 1.24 (ps.-t, *J* = 7.1 Hz, 5.8 Hz, 1H), 0.98 (dd, *J* = 5.8 Hz, 3.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ145.8, 137.9, 128.4 (+, 2C), 128.3 (+, 2C), 127.9 (+, 2C), 127.7 (+), 126.9 (+, 2C), 125.8 (+), 73.4 (-), 64.4 (+), 26.3, 20.4 (-), 19.0 (+); GC: R_t 11.43 min; HRMS (TOF ES): found 256.1705, calculated for $C_{17}H_{22}NO$ ($M+NH_4$) 256.1701 (1.6 ppm).



[(1*R,2*S**)-2-tert-Butoxy-1-ethylcyclopropyl]benzene** (**232g**): An oven-dried 10 ml Wheaton vial was charged with *tert*-butoxide (235 mg, 2.10 mmol, 3.00 equiv), 18-crown-6 (18 mg, 0.07 mmol, 10 mol%), and anhydrous THF (8 mL). 2-Bromo-1-ethyl-1-phenylcyclopropane (147 mg, 0.70 mmol, 1.0 equiv) was added via syringe. The reaction mixture was stirred at 80 deg for 13 hr, when GC showed the reaction was complete. The mixture was quenched with water (5 mL) and extracted with EtOAc (4 x 10 mL). Combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (R_f = 0.6, Hexane/EtOAc 5:1) to afford a colorless oil. Yield 130 mg (0.56 mmol, 85%). ^{1}H

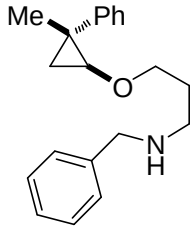
NMR (400.13 MHz, CDCl3) δ 7.33 (ps.-t, *J* = 7.8 Hz, 7.1 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.1 Hz, 1H), 3.28 (dd, *J* = 7.1 Hz, 4.0 Hz, 1H), 1.96 (dqd, *J* = 14.2 Hz, 7.3 Hz, 1.8 Hz, 1H), 1.67 (dq, *J* = 14.2 Hz, 7.3 Hz, 1H), 1.32 (s, 3H), 1.26 (ddd, *J* = 7.1 Hz, 5.8 Hz, 1.8 Hz, 1H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.69 (dd, *J* = 5.8 Hz, 4.0 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 144.4, 128.2 (+, 2C), 127.9 (+, 2C), 125.6 (+), 74.3, 59.0 (+), 31.4, 28.2 (+, 3C), 25.3 (-), 17.8 (-), 11.3 (+); GC: R_t 8.76 min; HRMS (TOF ES): found 219.1748, calculated for $C_{16}H_{23}O$ (M+H) 219.1749 (0.5 ppm).



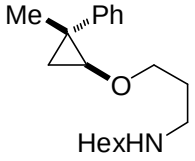
((1R*,2S*)-1-Methyl-2-(propa-1,2-dien-1-yloxy)cyclopropyl)benzene (**232i**): Was prepared according to Typical Procedure, employing (2-bromo-1-methylcyclopropyl)benzene (105 mg, 0.50 mmol, 1.00 equiv) and propargyl alcohol (34 mg, 0.60 mmol, 1.2 equiv). The reaction was carried out at 80^{o}C for 3 hrs. Preparative column chromatography of the residual oil on silica gel afforded the title compound as a colorless oil, R_f 0.20 (hexane). Yield 76 mg (0.41 mmol, 82%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.24-7.16 (m, 4H), 7.11 (tdd, *J* = 6.6 Hz, 2.5 Hz, 1.8 Hz, 1H), 6.69 (t, *J* = 5.9 Hz, 1H), 5.38 (dd, *J* = 8.3 Hz, 6.1 Hz, 1H), 5.34 (dd, *J* = 8.6 Hz, 6.1 Hz, 1H), 3.48 (dd, *J* = 7.1 Hz, 3.8 Hz, 1H), 1.40 (s, 3H), 1.16 (t, *J* = 6.6 Hz, 1H), 0.87 (dd, *J* = 6.2 Hz, 3.7 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 201.6, 145.2, 128.3 (+, 2C), 126.9 (+, 2C), 125.9 (+), 121.5 (+), 90.6 (-), 63.0 (+), 25.8, 20.4 (-), 18.9 (+); FT IR (NaCl, cm^{-1}): 3059, 2932, 2378, 2291, 2253, 1798, 1730, 1686, 1628, 1603, 1578, 1541, 1528, 1508, 1497, 1483, 1464, 1448, 1375, 1364, 1267, 1171, 1121, 1109, 1094, 1070,

1041, 1030, 1011, 918, 808, 764, 700, 588; HRMS (TOF ES): found 187.1119, calculated for $C_{13}H_{15}O$ (M+H) 187.1123 (2.1 ppm).

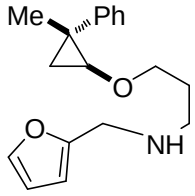
2.4.4. Amino Alcohol Additions



N-Benzyl-3-((1R*,2S*)-2-methyl-2-phenylcyclopropoxy)propan-1-amine (**236b**) (Typical Procedure): To a stirred suspension of *t*-BuOK (141 mg, 1.26 mmol, 2.50 equiv), 18-crown-6 (13 mg, 50 μmol, 10 mol%) in anhydrous THF (1 mL) was added (2-bromo-1-methylcyclopropyl)benzene (**18a**) (106 mg, 0.503 mmol, 1.00 equiv), followed by 3-(benzylamino)propan-1-ol (125 mg, 0.76 mmol, 1.51 equiv). The mixture was stirred at 80 ^{o}C for 18 hrs. Then, the KBr precipitate was filtered off on a fritted funnel and the filtrate was concentrated in vacuum. Preparative column chromatography of a residue on silica gel doped with triethylamine afforded the title compound as a light orange oil, R_f 0.30 (EtOAc). Yield 134 mg (0.45 mmol, 90%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.48-7.21 (m, 10H), 3.88 (s, 2H), 3.78-3.69 (m, 2H), 3.41 (dd, *J* = 7.1 Hz, 3.5 Hz, 1H), 2.85 (t, *J* = 6.9 Hz, 2H), 1.93 (quin, *J* = 6.6 Hz, 2H), 1.57 (s, 3H), 1.21 (t, *J* = 6.4 Hz, 1H), 0.90 (dd, *J* = 5.8 Hz, 3.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 145.7, 140.2, 128.2 (+, 2C), 128.2 (+, 2C), 128.0 (+, 2C), 126.72 (+), 126.68 (+, 2C), 125.6 (+), 69.5 (-), 64.4 (+), 53.9 (-), 46.6 (-), 30.0 (-), 25.9, 20.3 (-), 18.7 (+); FT IR (cm^{-1}, film): 3338, 3061, 3026, 2951, 2828, 2870, 1589, 1495, 1454, 1447, 1360, 1169, 1119, 1092, 1028, 827, 760, 743, 698; HRMS (TOF ES): found 318.1838, calculated for $C_{20}H_{25}NONa$ (M+Na) 318.1834 (1.3 ppm).

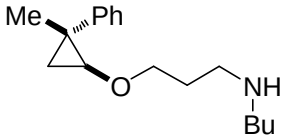


N-(3-((1R*,2S*)-2-Methyl-2-phenylcyclopropoxy)propyl)hexan-1-amine (**236a**): Was prepared according to Typical Procedure, employing (2-bromo-1-methylcyclopropyl) benzene (111 mg, 0.52 mmol, 1.0 equiv) and 3-(hexylamino)propanol (110 mg, 0.69 mmol, 1.3 equiv). Preparative column chromatography on silica gel doped with triethylamine afforded the title compound as a yellowish oil, R_f 0.50 (Hexane/EtOAc 8:1). Yield 139 mg (0.48 mmol, 92%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.26-7.16 (m, 3H), 3.71-3.61 (m, 2H), 3.35 (dd, *J* = 6.9 Hz, 3.7 Hz, 1H), 2.74 (t, *J* = 6.9 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.89-1.80 (m, 2H), 1.50 (s, 3H), 1.53-1.45 (m, 2H), 1.38-1.25 (m, 7H), 1.15 (t, *J* = 6.6 Hz, 1H), 0.93-0.87 (m, 3H), 0.84 (dd, *J* = 5.9 Hz, 3.7 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 145.9, 128.3 (+, 2C), 126.8 (+, 2C), 125.7 (+), 69.8 (-), 64.5 (+), 50.1 (-), 47.4 (-), 31.8 (-), 30.2 (-), 30.1 (-), 27.1, 26.1 (-), 22.6 (-), 20.4 (-), 18.8 (+), 14.0 (+); FT IR (cm^{-1}, film): 3319, 2955, 2928, 2870, 2856, 2816, 1497, 1458, 1447, 1364, 1292, 1240, 1171, 1132, 1090, 1070, 1028, 1013, 997, 933, 891, 827, 762, 744, 727, 698, 534; HRMS (TOF ES): found 312.2305, calculated for $C_{19}H_{31}NONa$ (M+Na) 312.2303 (0.6 ppm).



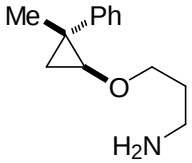
N-(Furan-2-ylmethyl)-3-((1R*,2S*)-2-methyl-2-phenylcyclopropoxy)propan-1-amine (**236c**): Was prepared according to Typical Procedure, employing (2-bromo-1-methylcyclopropyl)benzene (110 mg, 0.52 mmol, 1.0 equiv) followed by 3-((furan-2-ylmethyl)amino)propan-1-ol (124 mg, 0.80 mmol, 1.5 equiv). Preparative column chromatography of the residue on silica gel doped with triethylamine afforded the title compound as a light orange oil, R_f 0.50 (Hex/EtOAc 5:1). Yield 119 mg (0.42 mmol, 80%). ^{1}H

NMR (400.13 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.8 Hz, 0.8 Hz, 1H), 7.35-7.27 (m, 2H), 7.26-7.17 (m, 3H), 6.33 (dd, *J* = 3.2 Hz, 1.9 Hz, 1H), 6.20 (d, *J* = 2.8 Hz, 1H), 3.82 (s, 2H), 3.66 (td, *J* = 6.2 Hz, 2.5 Hz, 2H), 3.35 (dd, *J* = 7.1 Hz, 3.8 Hz, 1H), 2.77 (t, *J* = 6.9 Hz, 2H), 1.86 (quin, *J* = 6.6 Hz, 2H), 1.57 (quin, *J* = 6.4 Hz, 1H), 1.50 (s, 3H), 1.16 (t, *J* = 6.4 Hz, 1H), 0.84 (dd, *J* = 5.8 Hz, 3.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 154.0, 145.9, 141.8 (+), 128.4 (+, 2C), 126.9 (+, 2C), 125.8 (+), 110.1 (+), 106.8 (+), 69.7 (-), 64.6 (+), 46.6 (-), 46.3 (-), 30.1 (-), 26.1, 20.4 (-), 18.8 (+); FT IR (KBr, cm^{-1}): 3105, 3086, 3072, 2951, 2928, 2868, 1161, 1148, 1117, 1092, 1072, 1028, 762, 733, 700; HRMS (TOF ES): found 286.1802, calculated for $C_{18}H_{24}NO_2$ (M+H) 286.1807 (1.7 ppm).



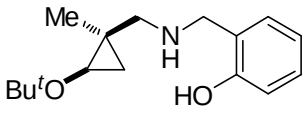
N-(2-(2-((1R*,2S*)-2-Methyl-2-phenylcyclopropoxy)ethoxy)-ethyl)butan-1-amine (**236e**): Was prepared according to Typical Procedure employing (2-bromo-1-methylcyclopropyl)benzene (**231a**) (106 mg, 0.50 mmol, 1.0 equiv) and 2-(2-(butylamino)ethoxy)ethanol (99 mg, 0.62 mmol, 1.3 equiv). Preparative column chromatography of the residue on silica gel doped with triethylamine afforded the title compound as an yiellow oil, R_f 0.50 (EtOAc/MeOH 20:1). Yield 120 mg (0.41 mmol, 82%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.34-7.26 (m, 2H), 7.25-7.16 (m, 3H), 3.79-3.74 (m, 2H), 3.71-3.66 (m, 2H), 3.63 (t, *J* = 5.3 Hz, 2H), 3.43 (dd, *J* = 7.1 Hz, 3.5 Hz, 1H), 3.41-3.33 (m, 1H), 2.84-2.79 (m, 2H), 2.66-2.60 (m, 2H), 1.89 (br. s., 1H), 1.52 (s, 3H), 1.54-1.43 (m, 1H), 1.41-1.30 (m, 2H), 1.16 (t, *J* = 6.6 Hz, 1H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.88 (dd, *J* = 5.8 Hz, 3.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 145.8, 128.3 (+, 2C), 126.8 (+, 2C), 125.7 (+), 70.6 (-), 70.4 (-), 70.1 (-), 64.8 (+), 49.6 (-), 49.3 (-), 32.2 (-), 26.2, 20.43 (-), 20.41 (-), 18.7 (+), 14.0 (+); FT IR (cm^{-1},

film): 3321, 3059, 3024, 2957, 2928, 2872, 1670, 1603, 1578, 1541, 1497, 1458, 1447, 1377, 1348, 1323, 1292, 1246, 1173, 1121, 1095, 1055, 1028, 1013, 995, 951, 920, 872, 827, 762, 748, 698, 669, 650, 596, 534, 473, 409; HRMS (TOF ES): found 292.2271, calculated for $C_{18}H_{30}NO_2$ (M+H) 292.2277 (2.1 ppm).

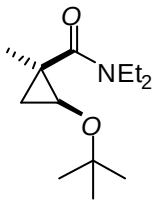


3-((1R*,2S*)-2-Methyl-2-phenylcyclopropoxy)propan-1-amine (**236d**): Was prepared according to Typical Procedure, employing (2-bromo-1-methylcyclopropyl)benzene (**231a**) (102 mg, 0.49 mmol, 1.0 equiv) and 3-aminopropan-1-ol (66 mg, 0.88 mmol, 1.7 equiv). Preparative column chromatography on silica gel doped with triethylamine afforded the title compound as an pale orange oil, R_f 0.50 (EtOAc/MeOH 1:1). Yield 80 mg (0.39 mmol, 81%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.33-7.28 (m, 2H), 7.24-7.18 (m, 3H), 3.71-3.66 (m, 2H), 3.70 (br. s, 2H), 3.36 (dd, *J* = 6.9 Hz, 3.7 Hz, 1H), 2.94 (t, *J* = 6.6 Hz, 1H), 2.03-1.96 (m, 2H), 1.88 (quin, *J* = 6.5 Hz, 1H), 1.50 (s, 3H), 1.16 (app. t, *J* = 6.9 Hz, 6.1 Hz, 1H), 0.84 (dd, *J* = 6.1 Hz, 3.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 145.6, 128.3 (+, 2C), 126.8 (+, 2C), 125.8 (+), 68.7 (-), 64.5 (+), 38.2 (-), 30.2 (-), 26.0, 20.3 (-), 18.8 (+); FT IR (cm^{-1}, film): 3354, 3292, 3057, 3024, 2955, 2928, 2872, 1558, 1539, 1497, 1404, 1362, 1339, 1294, 1250, 1169, 1092, 1028, 1013, 955, 922, 829, 698, 650, 536; HRMS (TOF ES): found 206.1547, calculated for $C_{13}H_{20}NO$ (M+H) 206.1545 (1.0 ppm).

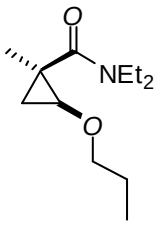
2.4.5. Addition to Amides



***(1R*,2R*)*-2-{[(2-*tert*-Butoxy-1-methylcyclopropyl)methylamino]-methyl}phenol** (**239**): was prepared from bromocyclopropane **237** (135 mg, 0.50 mmol) and *t*-BuOK (170 mg, 1.50 mmol) in the presence of 18-crown-6 (13 mg, 0.05 mmol, 10 mol%). The mixture was stirred in anhydrous THF (5 mL) at 80 ^{o}C for 20 hrs. The mixture was partitioned between water and EtOAc and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative column chromatography on Silica gel, eluent EtOAc to afford yellowish oil. Yield 91 mg (0.35 mmol, 69%). ^{1}H NMR (C_6D_6, 500.13 MHz) δ 7.28 (dd, *J* = 7.3 Hz, 1.5 Hz, 1H), 7.25 (ps.-td, *J* = 8.2 Hz, 6.9 Hz, 1.6 Hz, 1H), 6.97 (dd, *J* = 6.9 Hz, 1.3 Hz, 1H), 6.88 (td, *J* = 7.3 Hz, 1.3 Hz, 1H), 3.77 (d, *J* = 13.9 Hz, 1H), 3.67 (d, *J* = 13.9 Hz, 1H), 2.83 (dd, *J* = 6.0 Hz, 3.5 Hz, 1H), 2.67 (d, *J* = 11.7 Hz, 1H), 2.55 (d, *J* = 11.7 Hz, 1H), 1.14 (s, 9H), 0.96 (s, 3H), 0.39 (dd, *J* = 5.4 Hz, 3.5 Hz, 1H), 0.30 (ps.-t, *J* = 6.0 Hz, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 158.5, 128.5 (+), 128.1 (+), 122.9, 118.7 (+), 116.3 (+), 74.5, 56.4 (+), 53.1 (-), 53.0 (-), 28.1 (+, 3C), 21.2 (+), 19.9 (-), 19.3; ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) δ 1.14 (5%) upon irradiation at 2.83 ppm; HRMS (TOF ES) found 264.1957, calcd for $C_{16}H_{26}NO_2$ (M + H) 264.1963 (2.3 ppm).

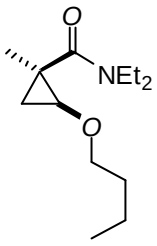


(1*R,2*S**)-2-*tert*-Butoxy-*N*,*N*-diethyl-1-methylcyclopropanecarboxamide** (**242e**): An oven-dried 10 mL Wheaton vial was charged with cyclopropylbromide **241e** (233 mg, 1.00 mmol), *t*-BuOK (343 mg, 3.50 mmol), 18-crown-6 (26.4 mg, 0.100 mmol, 10 mol%), and anhydrous THF (5 mL). The mixture was stirred at 80 ^{o}C overnight when GC showed the reaction was complete. The mixture was quenched with water (5 mL) and extracted with EtOAc (4 x 10 mL). Combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (R_f = 0.15, Hexane/EtOAc 3:1) to afford a colorless oil, yield 197 mg (0.87 mmol, 87%). ^{1}H NMR (500.19 MHz, $CDCl_3$) δ 3.59 (dq, *J* = 14.2 Hz, 6.9 Hz, 1H), 3.53 (dq, *J* = 14.2 Hz, 6.9 Hz, 1H), 3.41 (dq, *J* = 14.2 Hz, 6.9 Hz, 1H), 3.24 (dq, *J* = 14.2 Hz, 6.9 Hz, 1H), 3.13 (dd, *J* = 3.20 (dd, *J* = 5.6 Hz, 3.5 Hz, 1H), 1.22 (s, 3H), 1.23-1.20 (m, 4H), 1.19 (s, 9H), 1.08 (t, *J* = 6.9 Hz, 3H), 0.64 (ps.-t, *J* = 5.8 Hz, 5.6 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 171.2, 74.7, 56.6 (+), 40.7 (-), 38.2 (-), 28.0 (+, 3C), 24.6, 21.0 (-), 20.8 (+), 14.1 (+), 12.2 (+); HRMS (TOF ES) found 228.1968, calcd for $C_{13}H_{26}NO_2$ (M + H) 228.1964 (0.9 ppm).

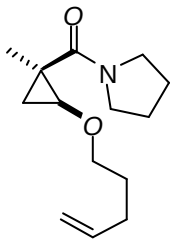


***(1R*,2S*)-N,N*-Diethyl-1-methyl-2-propoxycyclopropanecarboxamide** (**242f**): An oven-dried 10 mL Weaton vial was charged with *t*-BuOK (168 mg, 1.50 mmol), 18-crown-6 ether (26 mg, 0.10 mmol), 2-bromo-*N*,*N*-diethyl-1-methyl-cycloprop-2-enecarboxamide **241e** (248 mg, 1.00 mmol), *n*-propanol (112 µL, 90 mg, 1.50 mmol) and anhydrous THF (5 mL). The mixture was stirred for 18 hrs at 80 ^{o}C, and then partitioned between water and ethylacetate. The organic phase was separated; the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with

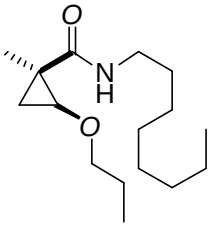
brine, dried with $MgSO_4$, filtered and concentrated. Purification of the residue by preparative column chromatography afforded the title compound as a colorless oil, yield 213 mg (0.94 mmol, 94%). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 3.62 (dq, *J* = 14.2 Hz, 7.1 Hz, 1H), 3.51-3.23 (m, 5H), 3.19 (dd, *J* = 5.6 Hz, 3.5 Hz, 1H), 1.47 (sextet, *J* = 6.8 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.19 (s, 3H), 1.16 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.56 (ps.-t, *J* = 5.8 Hz, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 170.8, 71.8 (-), 62.9 (+), 40.9 (-), 38.5 (-), 27.4, 22.7 (-), 20.5 (+), 18.3 (-), 13.9 (+), 12.2 (+), 10.5 (+); ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) □ 3.19 (5%) and 0.56 (4%) upon irradiation at 1.19 ppm; HRMS (TOF ES) found 214.1813, calcd for $C_{12}H_{24}NO_2$ (M + H) 214.1807 (2.8 ppm).



***(1R*,2S*)*-2-Butoxy-*N*,*N*-diethyl-1-methylcyclopropanecarboxamide** (**242g**): was obtained according to the procedure described for compound **242f**, employing *n*-butanol (137 µL, 11 mg, 1.50 mmol) instead of *n*-propanol. Yield 220 mg (0.91 mmol, 91%), colorless oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 3.63 (dq, *J* = 14.2 Hz, 7.1 Hz, 1H), 3.49-3.34 (m, 4H), 3.24 (dq, *J* = 14.2 Hz, 7.1 Hz, 1H), 3.20 (dd, *J* = 5.6 Hz, 3.5 Hz, 1H), 1.48-1.40 (m, 2H), 1.33-1.25 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.17 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.57 (ps.-t, *J* = 5.8 Hz, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 170.8, 70.0 (-), 62.9 (+), 40.9 (-), 38.5 (-), 31.5 (-), 27.4, 20.5 (+), 19.2 (-), 18.3 (-), 14.0 (+), 13.8 (+), 12.2 (+); HRMS (TOF ES) found 226.1817, calcd for $C_{13}H_{24}NO_2$ (M - H) 226.1807 (4.4 ppm).

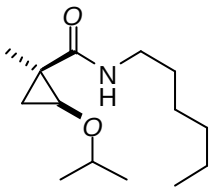


***(1R*,2S*)*-1-{[1-Methyl-2-(pent-4-enyloxy)cyclopropyl]carbonyl}pyrrolidine** (**242h**): was obtained according to the procedure described for compound **242f**, employing bromocyclopropane **241f** (237 mg, 1.00 mmol) and 4-penten-1-ol (155 μL, 129 mg, 1.50 mmol). Yield 218 mg (0.92 mmol, 92%). R_f 0.30 (hexane-EtOAc 2:3). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 5.74 (ddt, *J* = 16.9 Hz, 10.1 Hz, 6.6 Hz, 1H), 4.95 (dq, *J* = 16.9 Hz, 1.5 Hz, 1H), 4.91 (dq, *J* = 10.1 Hz, 1.5 Hz, 1H), 3.84-3.79 (m, 1H), 3.47-3.35 (m, 5H), 3.15 (dd, *J* = 5.6 Hz, 3.5 Hz, 1H), 2.00 (ps.-q, *J* = 7.8 Hz, 6.8 Hz, 1H), 1.94-1.83 (m, 2H), 1.81-1.74 (m, 2H), 1.55 (ps.-quintet, *J* = 7.6 Hz, 6.6 Hz, 2H), 1.21 (s, 3H), 1.18 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 0.55 (ps.-t, *J* = 5.8 Hz, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 169.9, 138.1 (+), 114.6 (-), 69.4 (-), 62.2 (+), 46.3 (-), 45.9 (-), 30.1 (-), 28.5 (-), 28.1, 26.2 (-), 24.1 (-), 19.3 (+), 17.7 (-); HRMS (TOF ES) found 238.1805, calcd for $C_{14}H_{24}NO_2$ (M + H) 238.1807 (0.8 ppm).

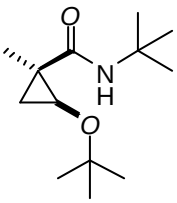


***(1R*,2S*)*-1-Methyl-*N*-octyl-2-propoxycyclopropanecarboxamide** (**242a**): was prepared from bromocyclopropane **241b** (250 mg, 0.861 mmol) according to the procedure described for compound **242f**. Yield 218 mg (0.810 mmol, 94%), colorless oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 6.48 (br.s, 1H), 3.50 (t, *J* = 6.8 Hz, 2H), 3.31 (dd, *J* = 6.6 Hz, 4.3 Hz, 1H), 3.26-3.17 (m, 2H), 1.62 (sextet, *J* = 7.3 Hz, 2H), 1.49-1.42 (m, 2H), 1.30-1.25 (m, 10H), 1.20 (s, 3H), 1.11 (dd, *J* = 6.1 Hz, 4.3 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.91 (ps.-t, *J* = 6.4 Hz, 1H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 173.5, 73.2 (-), 64.8 (+), 39.3 (-), 31.7 (-), 29.5 (-), 29.22 (-), 29.15 (-), 27.0 (-),

25.0, 22.64 (-), 22.58 (-), 22.1 (-), 20.0 (+), 14.0 (+), 10.5 (+); HRMS (TOF ES) found 270.2427, calcd for $C_{16}H_{32}NO_2$ (M + H) 270.3433 (2.2 ppm).

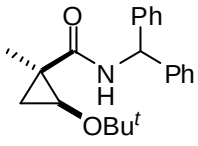


***(1R*,2S*)-N*-Hexyl-2-isopropoxy-1-methylcyclopropanecarboxamide** (**242b**): was prepared from bromocyclopropane **241a** (250 mg, 0.954 mmol) according to the procedure described for compound **242f**, employing isopropanol (110 µL, 86 mg, 1.43 mmol) instead of *n*-propanol. Yield 209 mg (0.868 mmol, 91%), colorless oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 6.54 (br.s, 1H), 3.76 (septet, *J* = 6.1 Hz, 1H), 3.31 (dd, *J* = 6.6 Hz, 4.5 Hz, 1H), 3.27-3.12 (m, 2H), 1.48-1.41 (2H), 1.30-1.24 (m, 6H), 1.21 (d, *J* = 6.1 Hz, 3H), 1.19 (s, 3H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.07 (dd, *J* = 5.8 Hz, 4.5 Hz, 1H), 0.90 (ps.-t, *J* = 6.6 Hz, 5.8 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 173.5, 73.0 (+), 62.5 (+), 39.2 (-), 31.4 (-), 29.4 (-), 26.6 (-), 24.9, 22.5 (-), 22.1 (-), 22.0 (+), 21.6 (+), 20.0 (+), 19.9 (+); HRMS (TOF ES) found 242.2122, calcd for $C_{14}H_{28}NO_2$ (M + H) 242.2120 (0.8 ppm).

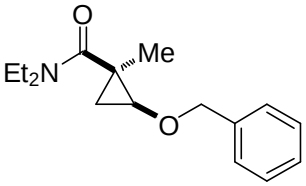


***(1R*,2S*)*-2-*tert*-Butoxy-*N*-(*tert*-butyl)-1-methylcyclopropanecarboxamide** (**242c**): was prepared from bromocyclopropane **241c** (100 mg, 0.43 mmol) and *t*-BuOK (96 mg, 0.85 mmol) according to the procedure described for preparation of compound **242f**. Yield 89 mg (0.39 mmol, 92%), colorless oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 6.57 (br.s, 1H), 3.27 (dd, *J* = 6.8 Hz, 4.6 Hz, 1H), 1.34 (s, 9H), 1.31 (s, 9H), 1.18 (s, 3H), 1.03 (dd, *J* = 6.1 Hz, 4.6 Hz, 1H), 0.94 (ps.-t, *J* = 6.8 Hz, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 173.5, 76.2, 58.3 (+), 50.3, 28.8 (+, 3C), 27.6 (+, 3C), 24.4, 23.0 (-), 19.7 (+); ^{1}H

NOE NMR ($CDCl_3$, 500.13 MHz) δ1.18 (5%) upon irradiation at 3.27 ppm; HRMS (TOF ES) found 228.1973, calcd for $C_{13}H_{26}NO_2$ (M + H) 228.1963 (4.4 ppm).

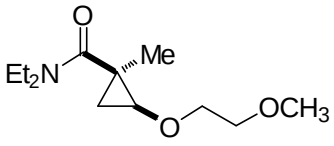


***(1R*,2S*)-N*-Benzhydryl-2-*tert*-butoxy-1-methylcyclopropanecarboxamide** (**242d**): was prepared from bromocyclopropane **241d** (206 mg, 0.50 mmol), *t*-BuOK (201 mg, 1.50 mmol), and 18-crown-6 (16 mg, 0.06 mmol) according to the typical procedure. The crude product was purified by Flash column chromatography on silica gel, eluent hexane-EtOAc 5:1. Yield: 151 mg (0.45 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.42 (d, *J* = 7.3 Hz, 1H), 7.34-7.23 (m, 10H), 6.27 (d, *J* = 7.3 Hz, 1H), 3.35 (dd, *J* = 6.8 Hz, 4.5 Hz, 1H), 1.25 (s, 3H), 1.23 (dd, *J* = 6.4 Hz, 4.5 Hz, 1H), 1.10 (s, 9H), 1.05 (ps.-t, *J* = 6.8 Hz, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 173.5, 142.3, 142.2, 128.6 (+, 2C), 128.4 (+, 2C), 127.8 (+, 2C), 127.3 (+), 126.94 (+), 126.89 (+, 2C), 76.4, 58.5 (+), 56.7 (+), 27.4 (+, 3C), 24.0, 23.4 (-), 19.8 (+); ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) δ 1.25 (7%) upon irradiation at 3.35 ppm; HRMS (TOF ES) found 360.1935, calcd for $C_{22}H_{27}NO_2Na$ (M + Na) 360.1940 (1.4 ppm). 28.1 (+, 3C), 24.1 (+), 14.3 (-); HRMS (TOF ES): found 236.1627, calculated for $C_{12}H_{23}NO_2Na$ (M+Na) 236.1626 (0.4 ppm).



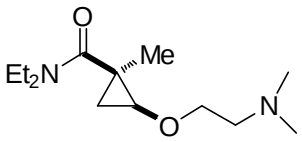
(1S*,2R*)-2-(benzyloxy)-N,N-diethyl-1-methylcyclopropane-carboxamide (**242i**): Typical Procedure: Bromocyclopropane **241e** (70.2 mg, 1.00 eq, 0.30 mmol) was added to a mixture of 66.6 mg of t-BuOK (2.0 eq, 0.60 mmol) and 7.8 mg of 18-crown- 6 ether (10%, 30 μmol). Then 49 mg of Benzyl alcohol (1.5 eq, 0.45 mmol) was added and the reaction mixture was stirred in anhydrous

THF (1 mL) overnight at 80 deg. The reaction mixture was partitioned between water (10ml), brine and EtOAc (3 × 20ml). The combined organic phases were dried with Na_2SO_4, filtered and concentrated. The residue was filtered through a short bed of Silica gel (EtOAc) to afford the title compound as colorless oil. Yield 74 mg (0.28 mmol, 95%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 3.69 (dq, *J* = 14.4 Hz, 7.3 Hz, 1H), 3.54-3.37 (m, 2H), 3.31 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 3.31 (dq, *J* = 14.2 Hz, 7.1 Hz, 1H), 1.32 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 1.24 (s, 3H), 1.22 (t, *J* = 7.3 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.66 (t, *J* = 5.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.7, 138.1, 128.2 (+, 2C), 127.5 (+, 2C), 127.4 (+), 72.3 (-), 62.7 (+), 41.1 (-), 38.6 (-), 27.8, 20.6 (+), 18.5 (-), 14.0 (+), 12.4 (+); FT IR (cm^{-1}, film): 2990, 2980, 1713, 1623, 1433, 1364, 1259, 1223, 1159, 1132, 1090, 1047, 1003, 910, 733, 698, 648, 530; HRMS (TOF ES): found 262.1817, calculated for $C_{16}H_{24}NO_2$ (M+H) 262.1807 (3.8 ppm).

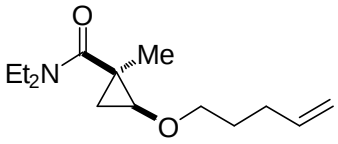


(1R*,2S*)-N,N-Diethyl-2-(2-methoxyethoxy)-1-methylcyclo-propanecarboxamide (**242k**): Was prepared according to Typical Procedure, employing bromo-cyclopropane **241e** (117 mg, 1.00 eq, 0.50 mmol) and ethylene glycol monomethyl ether (57 mg, 1.0 eq, 0.5 mmol). Preparative column chromatography on Silica gel afforded the title compound as a clear oil R_f 0.40 (hexane/EtOAc 3:1). Yield 102 mg (0.44 mmol, 89%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.72-3.56 (m, 2H), 3.53 (ddd, *J* = 10.9 Hz, 4.9 Hz, 3.5 Hz, 1H), 3.47-3.35 (m, 4H), 3.29 (s, 3H), 3.28-3.21 (m, 2H), 1.20-1.18 (m, 1H), 1.18 (s, 3H), 1.18 (t, *J* =

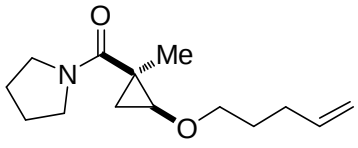
7.2 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.59 (ps.-t, *J* = 5.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.6, 71.6 (-), 69.6 (-), 63.2 (+), 58.9 (+), 41.0 (-), 38.5 (-), 27.6 (+), 20.5, 18.2 (-), 13.9 (+), 12.2 (+); FT IR (cm^{-1}, film): 2968, 2934, 2874, 2824, 2737, 1722, 1634, 1518, 1427, 1379, 1364, 1348, 1323, 1304, 1259, 1219, 1200, 1167, 1128, 1101, 1067, 1030, 957, 920, 903, 860, 800, 760; HRMS (TOF ES): found 229.1677, calculated for $C_{12}H_{23}NO_3$ (M^+) 229.1678 (0.4 ppm).



(1S*,2R*)-2-(2-(Dimethylamino)ethoxy)-N,N-diethyl-1-methylcyclopropanecarboxamide (**242k**): Was prepared according to Typical Procedure VI, employing bromocyclopropane **241e** (117 mg, 1.00 eq, 0.50 mmol) and 2-*N*,*N*-dimethylaminoethanol (67 mg 1.5 eq, 0.75 mmol). Preparative column chromatography on Silica gel to afford the titled compound as a clear oil, R_f 0.20 (EtOAc). Yield 97 mg (0.40 mmol, 80%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.62-3.53 (m, 2H), 3.52-3.39 (m, 2H), 3.37-3.21 (m, 2H), 3.15 (dd, *J* = 5.7 Hz, 3.7 Hz, 1H), 2.31 (t, *J*=5.8 Hz, 2H), 2.11 (s, 6H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.10 (s), 1.11-1.09 (m, 1H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.49 (t, *J* = 5.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.6, 68.7 (-), 63.1 (+), 58.2 (-), 45.7 (+, 2C), 41.0 (-), 38.5 (-), 27.4, 20.4 (+), 18.1 (-), 13.9 (+), 12.3 (+); FT IR (cm^{-1}, film): 2970, 2934, 2874, 1637, 1462, 1427, 1381, 1364, 1348, 1323, 1304, 1219, 1200, 1167, 1128, 1101, 1067, 1030, 957, 903, 473; HRMS (TOF ES): found 243.2080, calculated for $C_{13}H_{27}N_2O_2$ (M+H) 243.2073 (2.9 ppm).

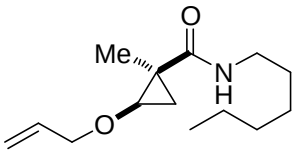


(1S,2R)-N,N-Diethyl-1-methyl-2-(pent-4-enyloxy)cyclopropanecarboxamide (**242i**): Was prepared according to Typical Procedure, employing bromocyclopropane **241i** (117 mg 1.00 eq, 0.50 mmol) and 4-pentene1-ol (87 mg, 1.00 eq, 0.50 mmol). Preparative column chromatography on Silica gel to afford the titled compound as a yellowish oil, R_f 0.50 (hexane/EtOAc 2:1). Yield 117 mg (0.49 mmol, 89%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.2 Hz, 10.1 Hz, 6.6 Hz, 1H), 4.97 (dq, *J* = 17.2 Hz, 1.7 Hz, 1H), 4.92 (ddt, *J* = 10.1 Hz, 2.0 Hz, 1.3 Hz, 1H), 3.63 (dq, *J* = 14.3 Hz, 7.1 Hz, 1H), 3.50-3.33 (m, 4H), 3.24 (dq, *J* = 13.6 Hz, 7.1 Hz, 1H), 3.20 (dd, *J* = 5.6 Hz, 3.5 Hz, 1H), 2.06-1.98 (m, 2H), 1.60-1.50 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.17 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.57 (t, *J* = 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.7, 138.2 (+), 114.6 (-), 69.4 (-), 62.9 (+), 40.9 (-), 38.5 (-), 30.2 (-), 28.6 (-), 27.4, 20.5 (+), 18.3 (-), 14.0 (+), 12.3 (+); FT IR (cm^{-1}, film): 3078, 2970, 2935, 2872, 1641, 1462, 1443, 1425, 1258, 1219, 1165, 1128, 1090, 1005, 960, 912, 636; HRMS (TOF ES): found 262.1774, calculated for $C_{14}H_{25}NO_2Na$ (M+Na) 262.1783 (3.4 ppm).



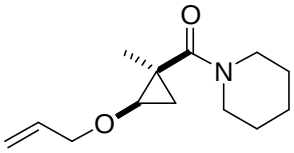
((1S*,2R*)-1-Methyl-2-(pent-4-enyloxy)cyclopropyl)(pyrrolidin-1-yl)methanone (**242h**): Was prepared according to Typical Procedure, employing (2-bromo-1-methylcyclopropyl)(pyrrolidin-1-yl)methanone (**241f**) (250 mg, 1.07 mmol) and pent-4-en-1-ol (138 mg, 1.61 mmol, 1.50 equiv). Preparative column chromatography of a residue on silica gel

afforded the title compound as a yellow oil, R_f 0.30 (hexane/EtOAc 2:3). Yield 219 mg (0.98 mmol, 92%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.0 Hz, 10.3 Hz, 6.7 Hz, 1H), 4.97 (ddt, *J* = 17.2 Hz, 1.8 Hz, 1.5 Hz, 1H), 4.92 (ddt, *J* = 10.4 Hz, 2.2 Hz, 1.2 Hz, 1H), 3.83 (ddd, *J* = 10.1 Hz, 6.2 Hz, 3.7 Hz, 1H), 3.50-3.36 (m, 5H), 3.17 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 2.02 (q, *J* = 7.3 Hz, 2H), 1.96-1.74 (m, 4H), 1.56 (quin *J* = 7.0 Hz, 2H), 1.23 (s, 3H), 1.19 (dd, *J* = 6.1 Hz, 3.5 Hz, 1H), 0.57 (dd, *J* = 6.1 Hz, 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.0, 138.2 (+), 114.6 (-), 69.4 (-), 62.2 (+), 46.3 (-), 45.9 (-), 30.2 (-), 28.6 (-), 28.2, 26.2 (-), 24.1 (-), 19.3 (+), 17.7 (-); FT IR (cm^{-1}, film): 3076, 2937, 2874, 1774, 1726, 1614, 1529, 1344, 1252, 1157, 1090, 1040, 912, 874, 731, 644, 503; HRMS (TOF ES): found 238.1815, calculated for $C_{14}H_{24}NO_2$ (M+H) 238.1807 (3.4 ppm).

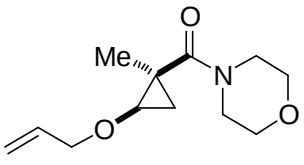


(1S*,2R*)-2-(Allyloxy)-N-hexyl-1-methylcyclopropanecarboxamide (**243e**): Was prepared according to Typical Procedure, employing 2-bromo-*N*-hexyl-1-methylcyclopropanecarboxamide (**241d**) (79 mg, 0.30 mmol) and allylic alcohol (35 mg, 0.60 mmol, 2.0 equiv). The reaction was carried out at 60 ^{o}C for 12 hr. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.25 (hexane-EtOAc 5:1). Yield 59 mg (0.25 mmol, 82%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 6.37 (br. s., 1H), 5.91 (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.8 Hz, 1H), 5.30 (dq, *J* = 17.2 Hz, 1.5 Hz, 1H), 5.23 (dq, *J* = 10.4 Hz, 1.3 Hz, 1H), 4.12-3.99 (m, 2H), 3.36 (dd, *J* = 6.6 Hz, 4.0 Hz, 1H), 3.25-3.16 (m, 2H), 1.50-1.39 (m, 2H), 1.34-1.22 (m, 6H), 1.20 (s, 3H), 1.16 (dd, *J* = 6.3 Hz, 4.3 Hz, 1H), 0.94 (t, *J* = 6.6 Hz, 6.3 Hz, 1H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 173.2, 133.3 (+), 117.9 (-), 72.3 (-), 64.5 (+), 39.3 (-), 31.5 (-),

29.5 (-), 26.7 (-), 25.2, 22.5 (-), 22.1 (-), 20.0 (+), 14.0 (+); FT IR (NaCl, film, cm^{-1}): 3360, 3080, 2957, 2930, 2858, 1645, 1537, 1462, 1445, 1344, 1331, 1211, 1169, 1101, 1043, 991, 922; HRMS (TOF ES): found 240.1969, calculated for $C_{14}H_{26}NO_2$ (M+H) 240.1964 (2.1 ppm).

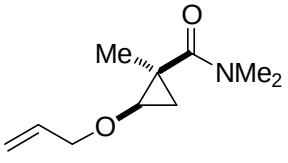


((1S*,2R*)-2-(Allyloxy)-1-methylcyclopropyl)(piperidin-1-yl)-methanone (**243h**): Was prepared according to Typical Procedure, employing (2-bromo-1-methylcyclopropyl)(piperidin-1-yl)methanone (**241h**) (79 mg, 0.30 mmol) and allylic alcohol (35 mg, 0.60 mmol, 2.0 equiv). The reaction was carried out at 60 ^{o}C for 12 hr. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.20 (hexane-EtOAc 3:1). Yield 61 mg (0.27 mmol, 91%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.2 Hz, 10.4 Hz, 5.9 Hz, 5.1 Hz, 1H), 5.23 (dq, *J* = 17.2 Hz, 1.8 Hz, 1H), 5.14 (dq, *J* = 10.4 Hz, 1.5 Hz, 1H), 4.03 (ddt, *J* = 13.1 Hz, 5.1 Hz, 1.8 Hz, 1 H), 3.96 (ddt, *J* = 13.1 Hz, 5.9 Hz, 1.3 Hz, 1H), 3.68-3.54 (m, 3H), 3.54-3.43 (m, 1H), 3.30 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 1.69-1.51 (m, 6H), 1.23 (s, 3H), 1.20 (dd, *J* = 6.1 Hz, 3.5 Hz, 1H), 0.63 (app. t, *J* = 6.1, 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.9, 134.5 (+), 116.4 (-), 71.2 (-), 62.9 (+), 46.7 (-), 43.0 (-), 27.3, 24.7 (-), 20.5 (-), 18.0 (+); FT IR (NaCl, film, cm^{-1}): 3080, 2999, 2934, 2854, 1730, 1643, 1516, 1439, 1350, 1310, 1277, 1256, 1236, 1209, 1163, 1132, 1126, 1090, 1043, 1014, 989, 955, 924, 854, 758, 689, 604, 532, 507, 417; HRMS (TOF ES): found 224.1653, calculated for $C_{13}H_{22}NO_2$ (M+H) 224.1651 (0.8 ppm).



((1S*,2R*)-2-(Allyloxy)-1-methylcyclopropyl)(morpholino)methanone

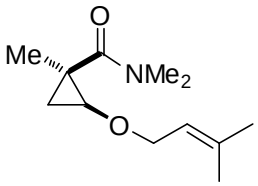
(**243c**): Was prepared according to Typical Procedure, employing(2-bromo-1-methylcyclo-propyl)(morpholino)methanone (**241g**) (74 mg, 0.30 mmol) and allylic alcohol (35 mg, 0.60 mmol, 2.0 equiv). The reaction was carried out at 60 ^{o}C for 12 hr. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.23 (hexane-EtOAc 1:1). Yield 59 mg (0.26 mmol, 88%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.2 Hz, 10.4 Hz, 5.8 Hz, 5.1 Hz, 1H), 5.23 (dq, *J* = 17.2 Hz, 1.7 Hz, 1H), 5.15 (dq, *J* = 10.4 Hz, 1.4 Hz, 1H), 4.03 (ddt, *J* = 12.6 Hz, 5.1 Hz, 1.5 Hz, 1H), 3.95 (ddt, *J* = 12.6 Hz, 5.8 Hz, 1.3 Hz, 1 H), 3.79-3.53 (m, 7H), 3.41-3.31 (m, 1H), 3.29 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 1.23 (s, 3H), 1.21 (dd, *J* = 6.1 Hz, 3.5 Hz, 1H), 0.65 (app. t, *J* = 6.1 Hz, 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.0, 134.2 (+), 116.8 (-), 71.3 (-), 67.3 (-), 66.9 (-), 62.5 (+), 46.3 (-), 42.5 (-), 26.8, 20.2 (+), 17.7 (-); FT IR (KBr, film, cm^{-1}): 3269, 3182, 3080, 2962, 2926, 2899, 2858, 2359, 2125, 1732, 1614, 1514, 1429, 1358, 1310, 1242, 1204, 1198, 1161, 1113, 1068, 1034, 991, 945, 926, 858, 847, 804, 690, 621, 559, 515; HRMS (TOF ES): found 226.1438, calculated for $C_{12}H_{20}NO_3$ (M+H) 226.1443 (2.2 ppm).



(1S*,2R*)-2-(allyloxy)-N,N,1-trimethylcyclopropanecarboxamide

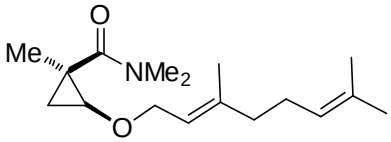
(**243f**): Was prepared according to Typical Procedure, employing 2-bromo-*N*,*N*,1-

trimethylcyclopropanecarboxamide (**241e**) (103 mg, 0.50 mmol) and allylic alcohol (35 mg, 0.60 mmol, 2.0 equiv). The reaction was carried out at 50 ^{o}C for 12 hr. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.35 (hexane-EtOAc 2:1). Yield 93.8 mg (0.46 mmol, 91%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 5.84 (dddd, *J* = 17.3 Hz, 10.4 Hz, 5.8 Hz, 5.1 Hz, 1H), 5.19 (dq, *J* = 17.3 Hz, 1.6 Hz, 1H), 5.11 (dq, *J* = 10.4 Hz, 1.5 Hz, 1H), 4.01 (ddt, *J* = 13.1 Hz, 5.1 Hz, 1.5 Hz, 1H), 3.94 (ddt, *J* = 13.1 Hz, 5.8 Hz, 1.3 Hz, 1H), 3.27 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 3.13 (s, 3H), 2.92 (s, 3H), 1.22 (s, 3H), 1.16 (dd, *J* = 6.1 Hz, 3.5 Hz, 1H), 0.60 (app. t, *J* = 6.1, 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 171.4, 134.4 (+), 116.3 (-), 71.2 (-), 62.5 (+), 37.1 (+), 35.4 (+), 27.2, 20.0 (+), 17.9 (-); FT IR (NaCl, film, cm^{-1}): 3547, 3464, 3080, 3001, 2959, 2934, 2872, 1643, 1634, 1497, 1454, 1396, 1379, 1350, 1265, 1167, 1124, 1101, 1086, 1059, 1043, 991, 964, 926, 858, 704, 606, 575, 569, 517, 492; HRMS (TOF ES): found 206.1156, calculated for $C_{10}H_{17}NO_2Na$ (M+Na) 206.1157 (0.5 ppm).



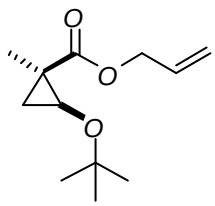
(1S*,2R*)-N,N,1-Trimethyl-2-((3-methylbut-2-en-1-yl)oxy)-cyclopropanecarboxamide (**243b**): Was prepared according to Typical procedure, employing 2-bromo-*N*,*N*,1-trimethylcyclopropanecarboxamide (**241e**) (62 mg, 0.30 mmol) and 3-methylbut-2-en-1-ol (28 mg, 0.33 mmol, 1.1 equiv). The reaction was carried out at 60 ^{o}C for 12 hrs. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane-EtOAc 2:3). Yield 59 mg (0.28 mmol, 93%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 5.25 (t-sept, *J* = 6.9 Hz, 1.3 Hz, 1H), 4.03-3.91 (m, 2H), 3.22 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 3.11 (s, 3H), 2.92 (s, 3H), 1.71 (s,

3H), 1.64 (s, 3H), 1.21 (s, 3H), 1.16 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 0.59 (t, *J* = 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 171.5, 136.5, 120.8 (+), 66.9 (-), 62.2 (+), 37.2 (+), 35.4 (+), 27.2, 25.7 (+), 20.1 (+), 17.97 (-), 17.96 (+); FT IR (NaCl, film, cm^{-1}): 3082, 2962, 2932, 1643, 1448, 1394, 1157, 1126; HRMS (TOF ES): found 212.1653, calculated for $C_{12}H_{22}NO_2$ (M+H) 212.1651 (0.9 ppm).

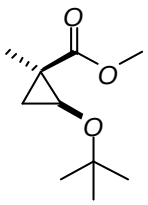


(1S*,2R*)-2-(((E)-3,7-Dimethylocta-2,6-dien-1-yl)oxy)-N,N,1-trimethylcyclopropanecarboxamide (**243a**): Was prepared according to Typical Procedure, 2-bromo-*N*,*N*,1-trimethylcyclopropanecarboxamide (**241e**) (102 mg, 0.60 mmol) and geraniol (93 mg, 0.66 mmol, 1.1 equiv). The reaction was carried out at 60 ^{o}C for 12 hrs. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane-EtOAc 2:3). Yield 149 mg (0.53 mmol, 89%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.31-5.22 (m, 1H), 5.11-5.03 (m, 1H), 4.00 (d, *J* = 6.8 Hz, 2H), 3.23 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 3.12 (s, 3H), 2.92 (s, 3H), 2.13-1.97 (m, 4H), 1.67 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.21 (s, 3H), 1.17 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 0.59 (t, *J* = 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 171.5, 139.8, 131.5, 123.9 (+), 120.6 (+), 66.9 (-), 62.2 (+), 39.5 (-), 37.2 (+), 35.4 (+), 27.2, 26.2 (-), 25.6 (+), 20.1 (+), 18.0 (-), 17.6 (+), 16.3 (+); FT IR (KBr, cm^{-1}): 2964, 2928, 2872, 2858, 1645, 1495, 1450, 1394, 1360, 1126, 1101, 1084, 1041, 986; HRMS (TOF ES): found 302.2084, calculated for $C_{17}H_{29}NO_2Na$ (M+Na) 302.2096 (4.0 ppm).

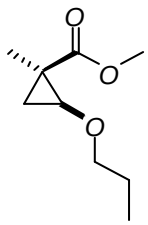
2.4.6. Addition to Carboxylates



***(1R*,2S*)*-Allyl 2-*tert*-butoxy-1-methylcyclopropanecarboxylate** (**250f**): Typical procedure, A mixture of *t*-BuOK (14.5 g, 129 mmol, 2.6 equiv), 18-crown-6 (1.32 g, 5 mmol), and potassium 1-methyl-2-bromocyclopropane carboxylate (10.85 g, 50 mmol) in anhydrous THF (200 mL) was stirred at 80 ^{o}C for 8 hrs, then cooled down to room temperature and freshly distilled allyl bromide (13 mL, 18 g, 150 mmol, 3 equiv.) was added dropwise. The resulting mixture was stirred for 1 hr, then poured in ice-cold water (300 mL) and extracted with diethyl ether (3 x 100 mL). Combined ethereal extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated. The residue was distilled in vacuum to afford allyl 2-*tert*-butoxy-1-methylcyclopropane-carboxylate as colorless oil, bp 61 ^{o}C (1 mm Hg). Yield 8.61 g (40.6 mmol, 81%). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 5.93 (ddt, *J* = 17.2 Hz, 10.6 Hz, 5.8 Hz, 1H), 5.34 (ddt, *J* = 17.2 Hz, 1.5 Hz, 1.5 Hz, 1H), 5.20 (ddt, *J* = 10.6 Hz, 1.5 Hz, 1.5 Hz, 1H), 4.65-4.53 (m, 2H), 3.24 (dd, *J* = 7.1 Hz, 4.8 Hz, 1H), 1.74 (dd, *J* = 6.1 Hz, 4.8 Hz, 1H), 1.25 (s, 3H), 1.18 (s, 9H), 0.87 (dd, *J* = 7.1 Hz, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ172.0, 132.4 (+), 117.7 (-), 74.9, 65.1 (-), 60.5 (+), 27.7 (+, 3C), 26.1, 20.2 (-), 18.7 (+); ^{1}H NOE NMR ($CDCl_3$, 500.13 MHz) δ 1.25 (8%) upon irradiation at 3.24 ppm; TLC: R_f 0.7 (hexane-EtOAc 1:1); GC: R_t 8.80 min; HRMS (TOF ES) found 213.1491, calcd for $C_{12}H_{21}O_3$ (M + H) 213.1491 (0.0 ppm).

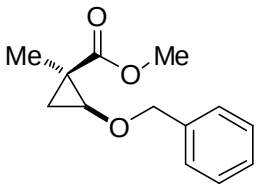


***(1R*,2S*)*-Methyl 2-*tert*-butoxy-1-methylcyclopropanecarboxylate (250c)**: was obtained according to the protocol described for preparation of **250f**, employing methyl iodide (7 mL, 16 g, 112 mmol, 2.24 equiv) instead of allyl bromide. Yield 7.38 g (39.68 mmol, 79%), colorless oil, bp 64 ^{o}C (7 mm Hg). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 3.70 (s, 3H), 3.25 (dd, *J* = 7.3 Hz, 5.1 Hz, 1H), 1.74 (dd, *J* = 6.1 Hz, 5.1 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 9H), 0.89 (dd, *J* = 7.3 Hz, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 172.9, 74.9, 60.6 (+), 51.6 (+), 27.8 (+, 3C), 26.2, 20.1 (-), 18.7 (+); GC: R_t 7.54 min; HRMS (TOF ES) found 209.1147, calcd for $C_{10}H_{18}O_3Na$ (M + Na) 209.1154 (3.3 ppm).

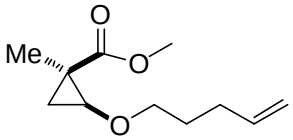


***(1R*,2S*)*-Methyl 1-methyl-2-propoxycyclopropanecarboxylate** (**250h**): A mixture of *t*-BuOK (193 mg, 1.72 mmol, 1.5 equiv), 18-crown-6 (30 mg, 0.11 mmol), and potassium 1-methyl-2-bromocyclopropane carboxylate (250 mg, 1.15 mmol) in anhydrous THF (5 mL) was stirred overnight at 80 ^{o}C, then quenched with methyl iodide (180 µL, 411 mg, 2.88 mmol). The mixture was partitioned between water and diethyl ether, the ethereal phase was washed with brine, dried with $MgSO_4$, filtered and concentrated. Methyl 2-*n*-propoxy-1-methylcyclopropanecarboxylate (R_f 0.9, hexane-EtOAc 1:1) was purified by flash column chromatography on silica gel. Yield 163 mg (0.95 mmol, 83%). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 3.70 (s, 3H), 3.45 (dt, *J* = 9.4 Hz, 6.6 Hz, 1H), 3.32 (dt, *J* = 9.4 Hz, 6.6 Hz, 1H), 3.27 (dd, *J* = 6.6 Hz, 4.5 Hz, 1H), 1.77 (dd, *J* = 5.8 Hz, 4.5 Hz, 1H), 1.55 (sextet, *J* = 6.8 Hz, 2H), 1.25 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.86 (ps.-t, *J* = 6.6 Hz, 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 172.6, 73.1 (-), 66.1 (+), 51.9 (+), 25.8, 22.6 (-),

20.5 (-), 19.0 (+), 10.6 (+); GC: R_t 7.46 min; HRMS (TOF ES) found 173.1179, calcd for $C_9H_{17}O_3$ (M + H) 173.1178 (0.6 ppm).

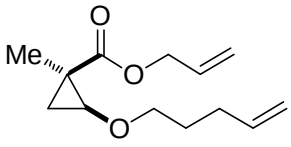


(1S*,2R*)-Methyl2-(benzyloxy)-1-methylcyclopropanecarboxylate (**250b**): Was prepared according to the Typical Procedure employing benzyl alcohol (83 mg, 0.77 mmol, 1.5 equiv) and MeI (93 μL, 213 mg, 1.50 mmol, 3.00 equiv). Preparative column chromatography on silica gel afforded the title compound as a clear oil, R_f 0.40 (hexane/EtOAc 10:1). Yield 100 mg (0.41 mmol, 82%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 3.71 (s, 3H), 3.36 (dd, *J* = 6.6 Hz, 4.5 Hz, 1H), 1.85 (dd, *J* = 5.9 Hz, 4.7 Hz, 1H), 1.27 (s, 3H), 0.90 (t, *J* = 6.6 Hz, 5.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) □ 172.4, 137.1, 128.4 (+, 2C), 128.1 (+, 2C), 127.9 (+), 73.4 (-), 65.6 (+), 52.0 (+), 26.1, 20.7 (-), 19.0 (+); FT IR (film, cm^{-1}): 3088, 3030, 3005, 2907, 2872, 1960, 1880, 1728, 1497, 1454, 1437, 1385, 1356, 1329, 1286, 1269, 1254, 1194, 1155, 1107, 1045, 1028, 993, 943, 903, 866, 833, 795, 737, 698, 606, 554, 490, 451; HRMS (TOF ES): found 221.1188, calculated for $C_{13}H_{17}NO_3$ (M+H) 221.1178 (4.5 ppm).



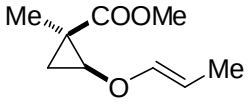
(1S*,2R*)-Methyl1-methyl-2-(pent-4-en-1-yloxy)cyclopropane-carboxylate (**250d**): Was prepared according to the Typical Procedure employing pent-4-en-1-ol (64.5 mg, 0.75 mmol, 1.5 equiv) and MeI (93 μL, 213 mg, 1.50 mmol, 3.00 equiv) was added dropwise. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane/EtOAc 20:1). Yield 71 mg (0.36

mmol, 72%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.1 Hz, 10.3 Hz, 6.7 Hz, 1H), 5.03 (dq, *J* = 17.1 Hz, 1.7 Hz, 1H), 4.97 (ddt, *J* = 10.2 Hz, 2.1 Hz, 1.2 Hz, 1H), 3.72 (s, 3H), 3.51 (dt, *J* = 9.3 Hz, 6.6 Hz, 1H), 3.38 (dt, *J* = 9.3 Hz, 6.4 Hz, 1H), 3.28 (dd, *J* = 6.8 Hz, 4.5 Hz, 1H), 2.16-2.01 (m, 2H), 1.77 (dd, *J* = 5.9 Hz, 4.7 Hz, 1H), 1.64 (quin, *J* = 7.0 Hz, 2H), 1.27 (s, 3H), 0.87 (app. t, *J* = 6.8 Hz, 5.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 172.5, 138.1 (+), 114.8 (-), 70.7 (-), 66.1 (+), 51.9 (+), 30.2 (-), 28.6 (-), 25.9, 20.6 (-), 19.1 (+); FT IR (cm^{-1}, film): 3081, 2949, 2939, 1734, 1437, 1364, 1352, 1329, 1194, 1157, 1107, 1043, 995, 945, 912, 858, 557, 444; HRMS (TOF ES): found 221.1164, calculated for $C_{11}H_{18}O_3Na$ (M+Na) 221.1154 (4.5 ppm).



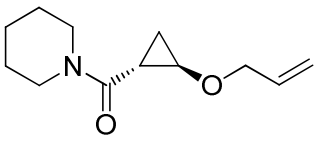
(1S*,2R*)-Allyl1-methyl-2-(pent-4-en-1-yloxy)cyclopropanecarboxylate (**250e**): Was prepared according to the Typical Procedure employing pent-4-en-1-ol (65 mg, 0.75 mmol, 1.5 equiv) and allyl bromide (130 μL, 182 mg, 1.50 mmol, 3.00 equiv). Preparative column chromatography of a residual oil on silica gel afforded the title compound as a clear oil, R_f 0.40 (hexane/EtOAc 20:1). Yield 76 mg (0.34 mmol, 68%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.94 (dddd, *J* = 17.0 Hz, 10.5 Hz, 6.6 Hz, 5.6 Hz, 1H), 5.79 (ddt, *J* = 17.0 Hz, 10.3 Hz, 6.7 Hz, 1H), 5.35 (dq, *J* = 17.3 Hz, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.5 Hz, 1.4 Hz, 1H), 5.02 (ddt, *J* = 17.2 Hz, 2.0 Hz, 1.5 Hz, 1H), 4.96 (ddt, *J* = 10.2 Hz, 2.0 Hz, 1.4 Hz, 1H), 4.62 (dt, *J* = 5.6 Hz, 1.4 Hz, 2H), 3.50 (dt, *J* = 9.1 Hz, 6.6 Hz, 1H), 3.38 (dt, *J* = 9.4 Hz, 6.6 Hz, 1H), 3.29 (dd, *J* = 6.6 Hz, 4.5 Hz, 1H), 2.12-2.03 (m, 2H), 1.78 (dd, *J* = 5.8 Hz, 4.6 Hz, 1H), 1.63 (quin, *J* = 6.9 Hz, 2H), 1.28 (s, 3H), 0.87 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 171.6, 138.0 (+), 132.3 (+),

117.9 (-), 114.7 (-), 70.7 (-), 66.2 (+), 65.3 (-), 30.1 (-), 28.6 (-), 25.9, 20.6 (-), 19.0 (+); FT IR (film, cm^{-1}): 3078, 3005, 2962, 2937, 2874, 1730, 1641, 1462, 1441, 1385, 1364, 1321, 1261, 1155, 1105, 1043, 1032, 989, 914, 858, 795, 768, 635, 557, 505; HRMS (TOF ES): found 247.1304, calculated for $C_{13}H_{20}O_3Na$ (M+Na) 247.1310 (2.4 ppm).



(1R*,2S*)-Methyl1-methyl-2-((E)-prop-1-enyloxy)cyclopropane-carboxylate (**250i**): Was prepared according to the Typical Procedure employing allyl alcohol (51 μL, 44 mg, 0.75 mmol, 1.5 equiv) and MeI (93 μL, 213 mg, 1.50 mmol, 3.00 equiv). Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.38 (hexane/EtOAc 20:1). Yield 71 mg (0.42 mmol, 84%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.96 (dq, *J* = 6.0 Hz, 1.6 Hz, 1H), 4.45 (ps.-quintet, *J* = 6.9 Hz, 6.0 Hz, 1H), 3.67 (s, 3H), 3.54 (dd, *J* = 6.6 Hz, 4.4 Hz, 1H), 1.85 (dd, *J* = 6.0 Hz, 4.4 Hz, 1H), 1.51 (dd, *J* = 6.9 Hz, 1.6 Hz, 3H), 1.27 (s, 3H), 0.91 (ps.-t, *J* = 6.6 Hz, 6.0 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 171.7, 144.0 (+), 103.2 (+), 65.5 (+), 51.9 (+), 25.9, 20.0 (-), 18.8 (+), 9.0 (+); FT IR (NaCl, film, cm^{-1}): 2949, 2873, 1729, 1641, 1462, 1437, 1362, 1329, 1261, 1194, 1157, 1107, 1045, 995, 945, 912, 858, 793, 528; HRMS (TOF ES): found 171.1016, calculated for $C_9H_{15}O_3$ (M+H) 171.1021 (2.9 ppm).

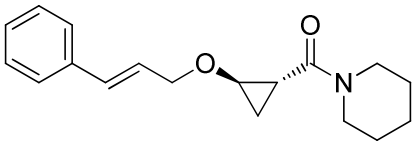
2.4.7. Addition to Enolizable Substrates



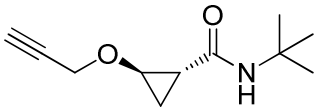
((1R,2R)-2-(Allyloxy)cyclopropyl)(piperidin-1-yl)methanone (**246b**):

An oven-dried 10 mL Weaton vial was charged with (2-bromocyclopropyl)(piperidin-1-yl)methanone (**245a**) (70 mg, 0.3 mmol, 1.0 equiv) and allylic alcohol (19.9 mg, 0.36 mmol, 1.2 equiv). 18-crown-6 (13 mg, 50 μmol, 10 mol%), powdered KOH (62 mg, 1.1 mmol, 2.2 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 85 °C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexane/EtOAc 2:1, R_f 0.40. Yield 59 mg (0.29 mmol, 95%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 17.3 Hz, 10.4 Hz, 5.8 Hz, 1H), 5.28 (dq, *J* = 17.3 Hz, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.4 Hz, 1.3 Hz, 1H), 4.07 (ddt, *J* = 12.6 Hz, 5.6 Hz, 1.3 Hz, 1H), 4.02 (m, *J* = 12.6 Hz, 5.8 Hz, 1.5 Hz, 1H), 3.63 (ddd, *J* = 6.3 Hz, 3.8 Hz, 2.3 Hz, 1H), 3.62-3.52 (m, 4H), 1.97 (ddd, *J* = 9.5 Hz, 5.9 Hz, 2.0 Hz, 1H), 1.71-1.58 (m, 4H), 1.58-1.49 (m, 2H), 1.29 (td, *J* = 6.3 Hz, 5.9 Hz, 5.3 Hz, 1H), 1.14 (ddd, *J* = 9.5 Hz, 5.3 Hz, 3.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.4, 134.0 (+), 117.5 (-), 72.0 (-), 60.2 (+), 46.7 (-), 43.1 (-), 26.6 (-), 25.5 (-), 24.6 (-), 19.3 (+), 14.9 (-); FT IR (KBr, cm^{-1}): 3081, 2935, 2854, 1632, 1454, 1445, 1352, 1250, 1225, 1169, 1136, 1128, 1094, 1053, 1014, 943, 924, 874; HRMS (TOF ES): found 210.1496, calculated for $C_{12}H_{20}NO_2$ (M+H) 210.1494 (1.0 ppm).



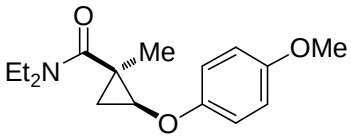
((1R*,2R*)-2-(Cinnamyloxy)cyclopropyl)(piperidin-1-yl)-methanone (**246a**): Was prepared according to procedure for **246a**, employing (2-bromo-cyclopropyl)(piperidin-1-yl)methanone (**245a**) (62 mg, 0.30 mmol, 1.0 equiv) and cinnamyl alcohol (44 mg, 0.36 mmol, 1.2 equiv). The reaction was carried out at 60 ^{o}C for 12 hrs. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane/EtOAc 2:3). Yield 69 mg (0.24 mmol, 81%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.43-7.37 (m, 2H), 7.37-7.30 (m, 2H), 7.30-7.23 (m, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.9 Hz, 6.2 Hz, 1H), 4.27 (ddd, *J* = 12.5 Hz, 5.9 Hz, 1.3 Hz, 1H), 4.20 (ddd, *J* = 12.4 Hz, 6.4 Hz, 1.4 Hz, 1H), 3.71 (ddd, *J* = 6.4 Hz, 4.0 Hz, 2.0 Hz, 1H), 3.66-3.47 (m, 4H), 2.02 (ddd, *J* = 9.6 Hz, 5.9 Hz, 2.1 Hz, 1H), 1.70-1.49 (m, 6H), 1.33 (ddd, *J* = 6.4 Hz, 5.9 Hz, 5.3 Hz, 1H), 1.19 (ddd, *J* = 9.5 Hz, 5.3 Hz, 3.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.5, 136.4, 132.9 (+), 128.5 (+, 2C), 127.8 (+), 126.5 (+, 2C), 125.2 (+), 71.6 (-), 60.3 (+), 46.7 (-), 43.1 (-), 26.6 (-), 25.5 (-), 24.6 (-), 19.5 (+), 14.9 (-); FT IR (KBr, cm^{-1}): 3059, 3024, 2935, 2855, 1634, 1446, 1225; HRMS (TOF ES): found 286.1801, calculated for $C_{18}H_{24}NO_2$ (M+H) 286.1807 (2.1 ppm).



(1R*,2R*)-N-(tert-Butyl)-2-(prop-2-yn-1-yloxy)cyclopropane-carboxamide (**246c**): Was prepared according to procedure for **246b**, employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**245c**) (66 mg, 0.30 mmol, 1.0 equiv) and propargyl alcohol (21 mg, 0.32 mmol, 1.2 equiv). The reaction was carried out at 60 ^{o}C for 3 hrs.

Preparative column chromatography of a residual oil on silica gel afforded the title compound as a colorles oil, R_f 0.30 (hexane/EtOAc, 4:1). Yield 46 mg (0.23 mmol, 78%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.46 (br. s., 1 H), 4.24-4.19 (m, 1H), 4.19-4.14 (m, 1H), 3.71 (ddd, *J* = 6.4 Hz, 4.0 Hz, 2.2 Hz, 1H), 2.46 (t, *J* = 2.5 Hz, 1H), 1.55 (ddd, *J* = 9.6 Hz, 6.0 Hz, 2.0 Hz, 1H), 1.35 (s, 9H), 1.24 (q, *J* = 6.0 Hz, 1H), 1.10 (ddd, *J* = 9.5 Hz, 5.6 Hz, 4.1 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.0, 79.3, 74.7 (+), 59.4 (+), 58.2 (-), 51.3, 28.9 (+, 3C), 23.5 (+), 13.6 (-); FT IR (NaCl, cm^{-1}): 3308, 3078, 2968, 2930, 2870, 1724, 1643, 1549, 1537, 1479, 1454, 1394, 1364, 1331, 1256, 1227, 1202, 1153, 1097, 1061, 1043, 1026, 995, 986, 955, 926, 910, 893, 878, 764, 737, 665, 635; HRMS (TOF ES): found 196.1341, calculated for $C_{11}H_{18}NO_2$ (M+H) 196.1338 (1.5 ppm).

2.4.8. Adition of Phenoxides

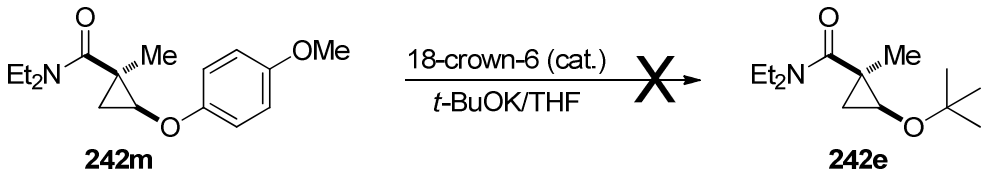


Preparation of (1*R,2*S**)-*N*,*N*-Diethyl-2-(4-methoxyphenoxy)-1-methylcyclopropane-carboxamide** (**242m**): An oven dried 5 mL Wheaton vial was charged with bromocyclopropane **241e** (117 mg, 0.50 mmol), 4-methoxyphenol (62 mg, 0.50 mmol), potassium *tert*-butoxide (29 mg. 0.50 mmol), 18-crown-6 (14 mg, 0.05 mmol, 10 mol%), and anhydrous THF (2 mL). The mixture was stirred at 80 ^{o}C for 20 hrs, after which time GC analysis indicated ca. 40% conversion of the intermediate cyclopropene into a 1:1 mixture of aryl (**242m**) and *tert*-butyl (**242e**) ethers. Attempts to achieve complete conversion by extending reaction time and/or increasing reaction temperature resulted in significant decomposition of the phenol ether **242m**. Accordingly, the reaction was stopped at partial conversion and was quenched with water (10 mL) and extracted with EtOAc (3 x 5 mL). Combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography on Silica gel, eluting with hexane/EtOAc (1:1). The titled compound was obtained as colorless oil, yield 28 mg (0.10 mmol, 20%).

^{1}H NMR (400.13 MHz, CDCl3) δ 6.87 (d, *J* = 9.1 Hz, 2H), 6.81(d, *J* = 9.1 Hz, 2H), 3.77 (s, 3H), 3.69 (dd, *J* = 5.8 Hz, 3.5 Hz, 1H), 3.61-3.48 (m, 2H), 3.39-3.28 (m, 2H), 1.35 (s, 3H), 1.31 (dd, J = 6.1 Hz, 3.5 Hz, 1H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.16 (t, *J* = 7.3 Hz, 3H), 0.93 (ps.-t, *J* = 6.1 Hz, 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ169.9, 154.1, 152.3, 115.8 (+, 2C), 114.4 (+,

2C), 60.6 (+), 55.7 (+), 41.0 (-), 38.6 (-), 27.5, 20.4 (+), 19.5 (-), 14.1 (+), 12.3 (+); ^{1}H NOE NMR (500.13 MHz, CDCl3) δ 1.35 (7%) and 0.95 (5%) upon irradiation at 3.68 ppm; 1.31 (7%), 1.35 (3%), 3.68 (2%) upon irradiation at 0.95 ppm; GC: R_t 12.69 min; HRMS (TOF ES): found 278.1763, calculated for $C_{16}H_{24}NO_3$ (M+H) 278.1756 (2.5 ppm).

Scheme 106. Thermodynamic reversibility of phenoxide addition



242m **242e**

An oven-dried 1.0 mL Wheaton vial was charged with phenoxycyclopropane **242m** (17 mg, 60 µmol), t-BuOK (17 mg, 150 µmol), 18-crown-6 (1.6 mg, 6 µmol, 10 mol%) and anhydrous THF (300 µL). The mixture was stirred at 80 ^{o}C for 48 hrs. No reaction occurred as judged by GC analysis. Then the temperature was raised to 100 ^{o}C, and stirring was continued for another 48 hrs. Notable decomposition of the starting material took place; however, no formation of *tert*-butyl ether **242e** was detected (eq 18).

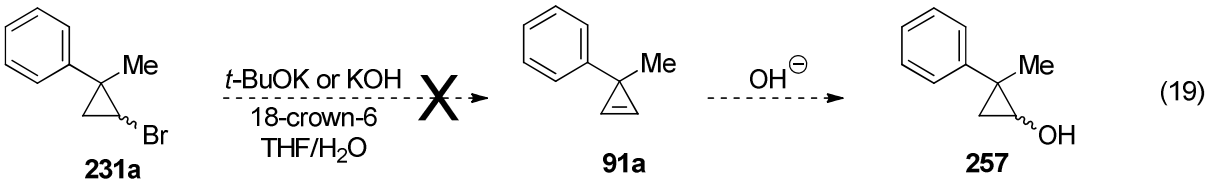
2.4.9. Studies on Formal Substitution with Hydroxide and Silanolate

These experiments were performed in order to asses the possibility of direct addition of water *en route* to cyclopropanol **257** (

Scheme **107**). Also, addition of sylanolate species was tested *en route* to cyclopropyl silyl ether **258**. Two sets of conditions were tested with each pronucleophile, using *t*-BuOK and KOH, respectively. It was found that in the presence of water (**Test 1** and **Test 2**), no reaction between bromocyclopropane **231a** and a base to generate intermediate cyclopropene **91a** was observed, suggesting that moisture adversely affected the first step, 1,2-dehydrobromination reaction. (

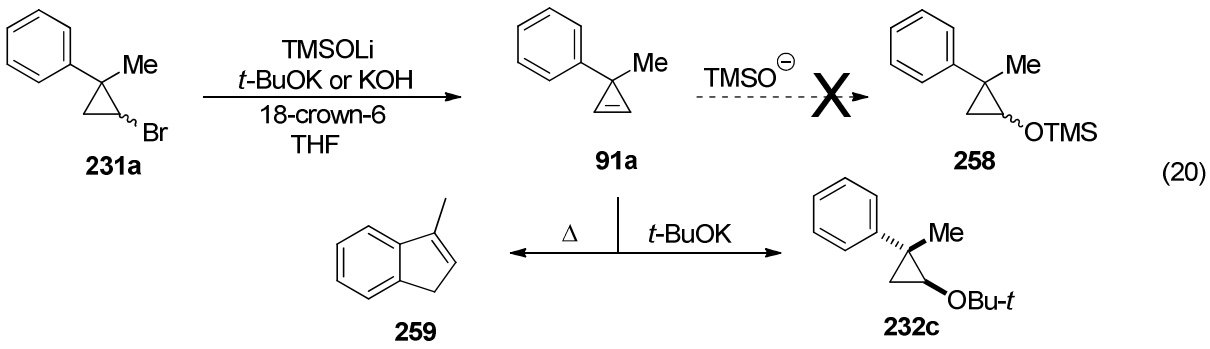
Scheme **107**).

Scheme 107. Addition of hydroxide species



In the presence of anhydrous lithium sylanolate, the 1,2-dehydrobromination of **231a** proceeded smoothly with both bases affording cyclopropene **91a**. However, no addition of sylanolate nucleophile to the cyclopropene was detected. Thus, when *t*-BuOK was employed as a base, nucleophilic attack of *tert*-butoxide resulted in the formation of product **232c** (**Test 3**), whereas in the presence of KOH the cyclopropene either remained intact or slowly decomposed at higher temperatures (**Test 4**).

Scheme 108. Attemted addition silanolates



Test 1. An oven-dried 2 mL Wheaton vial was charged with bromocyclopropane **231a** (63 mg, 0.30 mmol), *t*-BuOK (50 mg, 0.45 mmol, 1.5 equiv), 18-crown-6 (7.9 mg, 30 µmol, 10 mol%), water (11 µL, 0.60 mmol, 2.0 equiv), and anhydrous THF (1 mL). The mixture was stirred at 80 ^{o}C overnight. According to the GC/MS analysis of the crude reaction mixtures, no reaction took place, and bromocyclopropane **231a** remained intact.

Test 2. An oven-dried 2 mL Wheaton vial was charged with bromocyclopropane **231a** (63 mg, 0.30 mmol), KOH (25 mg, 0.60 mmol, 2.0 equiv), 18-crown-6 (7.9 mg, 30 µmol, 10 mol%), water (11 µL, 0.60 mmol, 2.0 equiv), and anhydrous THF (1 mL). The mixture was stirred at 80 ^{o}C overnight. According to the GC/MS analysis of the crude reaction mixtures, no reaction took place, and bromocyclopropane **231a** remained intact.

Test 3. An oven-dried 2 mL Wheaton vial was charged with bromocyclopropane **231a** (63 mg, 0.30 mmol), *t*-BuOK (50 mg, 0.45 mmol, 1.5 equiv), 18-crown-6 (7.9 mg, 30 µmol, 10 mol%), lithium trimethylsylanolate (48 mg, 0.60 mmol, 2.0 equiv), and anhydrous THF (1 mL). The

mixture was stirred at 80 ^{o}C overnight. According to the GC/MS analysis of the crude reaction mixtures, *tert*-butyl ether **232c** was formed as a sole product.

Test 4. An oven-dried 2 mL Wheaton vial was charged with bromocyclopropane **231a** (63 mg, 0.30 mmol), KOH (25 mg, 0.60 mmol, 2.0 equiv), 18-crown-6 (7.9 mg, 30 µmol, 10 mol%), lithium trimethylsylanolate (48 mg, 0.60 mmol, 2.0 equiv), and anhydrous THF (1 mL). The mixture was stirred at 60 ^{o}C overnight. According to the GC/MS analysis of the crude reaction mixtures, cyclopropene **91a** was formed as the sole product. The temperature was gradually increased to 100 ^{o}C, at which point cycloisomerization of cyclopropene into 3-methyl-1*H*-indene (**32**) took place; while no desired addition products were detected.

2.4.10. Assignment of Relative Configuration

Relative configurations of products, **242c**, were assigned based on 1D NOEDIFF experiments. Relative configurations of other products were assigned by analogy. Assignment of the relative configuration of product **242c** is provided in Figure 12 and Figure 13.

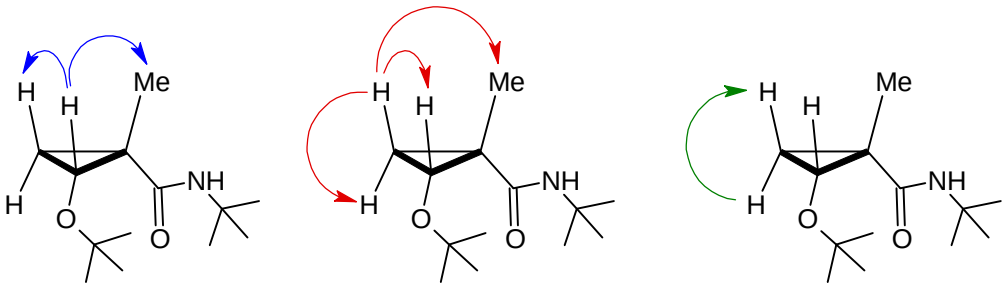


Figure 12. Observed NOEs upon irradiation at 3.27 ppm (blue), 1.03 ppm (red), 0.95 ppm (green) for compound **242c**. For color-coded spectral charts corresponding to these experiments, see Figure 13

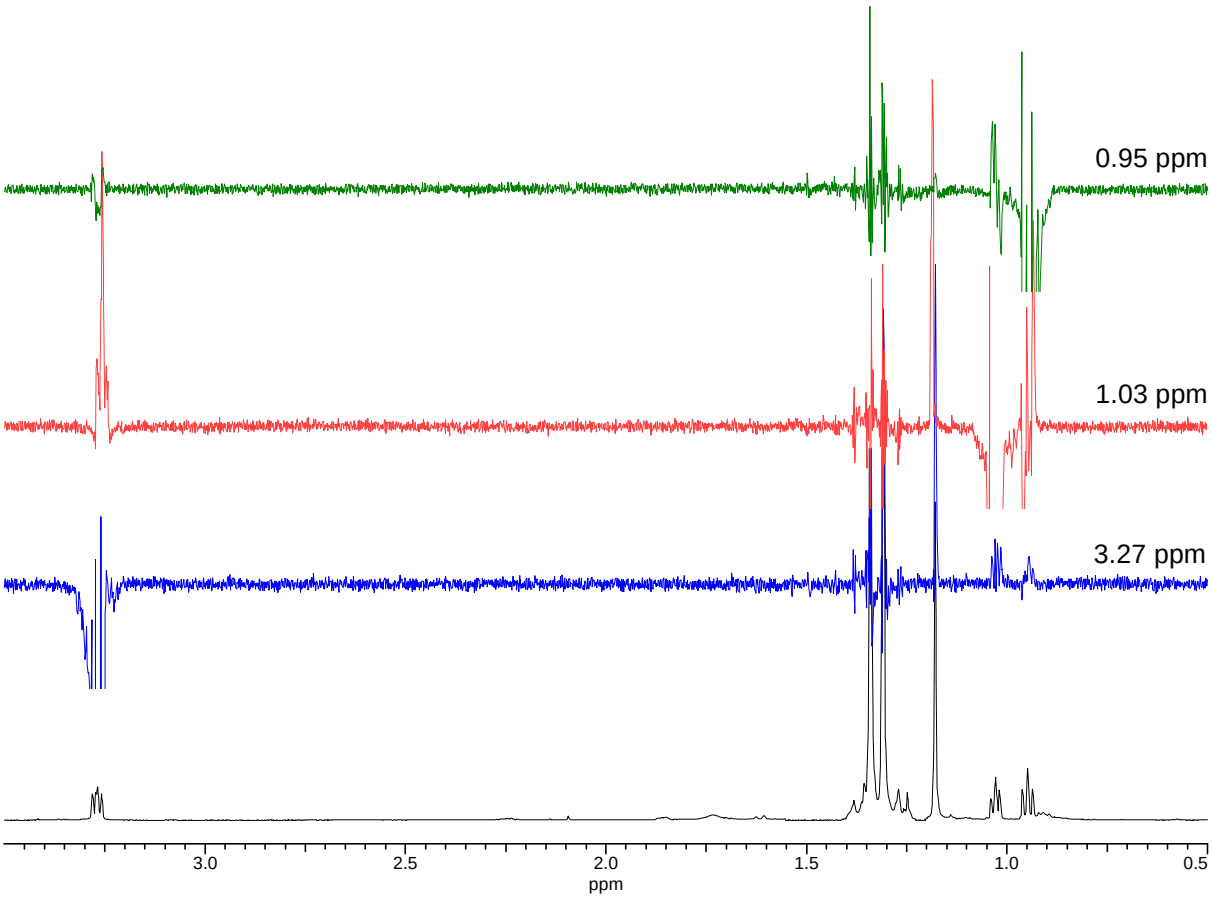


Figure 13. 1D NOEDIFF spectra of **242c**. Chemical shifts of the irradiated multiplets are listed at the right side of each chart.

Chapter 3. Intromolecular fomal nucleophilic substitution of bromocyclopropanes as a method for the synthesis of medium size cyclopropyl fused heterocycles

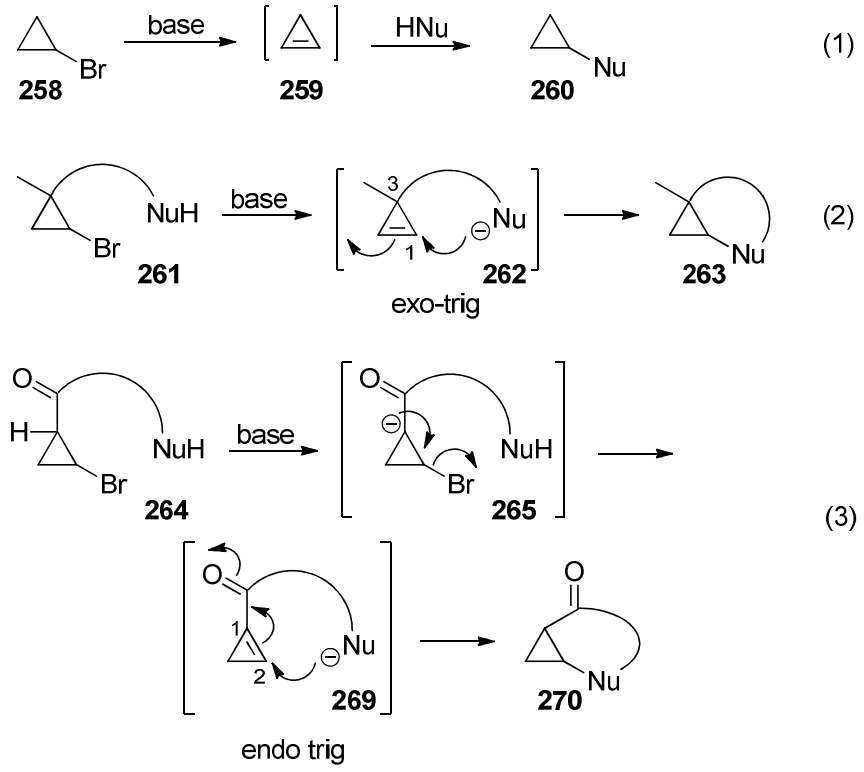
3.1. Introduction

The formal substitution of bromocyclopropanes **258** with O- and N-based nucleophiles allows for the efficient diastereoconvergent assembly of valuable, highly functionalized cyclopropyl scaffolds. In this transformation, bromocyclopropane **258** undergoes dehydrobromination to produce a highly reactive cyclopropene intermediate **259**, which once formed is immediately trapped by an external nucleophile to afford cyclopropanol or cyclopropylamine derivative **260** (Scheme 109, eq 1).

We envisioned the intramolecular mode (Scheme 109, eq 1,2) of this reaction as a useful tool for the construction of novel types of medium heterocycles and a convenient probe investigating challenging nucleophilic *exo*- and *endo*-*trig* medium ring closures. It was expected that stringent enthalpic and entropic requirements would be met in this cyclization as the rigid cyclopropyl moiety in the molecule backbone would endow the system with sufficient constraints, whereas the strain energy release would allow for effective ring closure via the nucleophilic attack of a tethered heteroatom moiety (Scheme 109, eq 2, 3). Thus, generation of cyclopropene species **262** from bromocyclopropane **261** bearing a pronucleophilic moiety tethered through the quaternary carbon would invoke an *exo*-*trig* cyclization, leading to bicyclic scaffold **263** (Scheme 109, eq 2). On the other hand, a more exotic *endo*-*trig* mode can be realized by subjecting to the reaction a substrate of type **264** possessing a tertiary α-carbon. In

contrast to cyclopropene **262** with a nucleophilic entity attached to C3 (Scheme 109, eq 2), the corresponding unstable, non-isolable, conjugate strained olefin **269** suitable for the *endo-trig* cyclization possesses a C1-linked nucleophile (Scheme 109, eq 3).

Scheme 109.



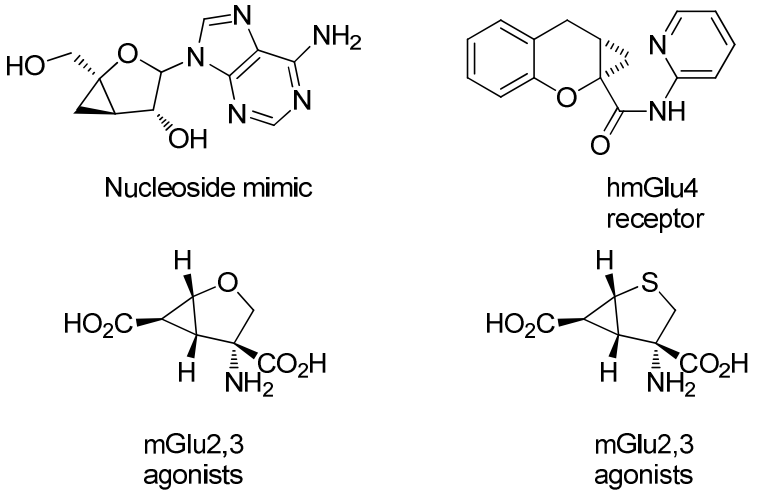
The potential synthetic and medicinal value of this unique transformation was quickly realized as it could allow access to several important classes of compounds including

cyclopropyl fused heterocycles which up to this point have been limited to oxabicyclo[3.1.0]hexane and heptane derivatives (Figure 14).

Incorporation of light weight isosteric cyclopropane fragments with unusual bond angles into the structure of biologically active compounds is used to fine tune the geometry of small molecules without affecting its binding ability and solvent affinity,[115] which becomes very practical in investigation of binding mechanisms.[116]

The steric constraints imparted by a cyclopropane ring could be used to restrict rotational freedom and reinforce binding conformations, which helps achieve more selective interactions between the ligand and the receptor.[117,118] The innate, high metabolic stability of the cyclopropyl-based molecules as compared to the open-chain analogs, can be used to improve the in vivo pharmaceutical profile of a drug candidate.[119]

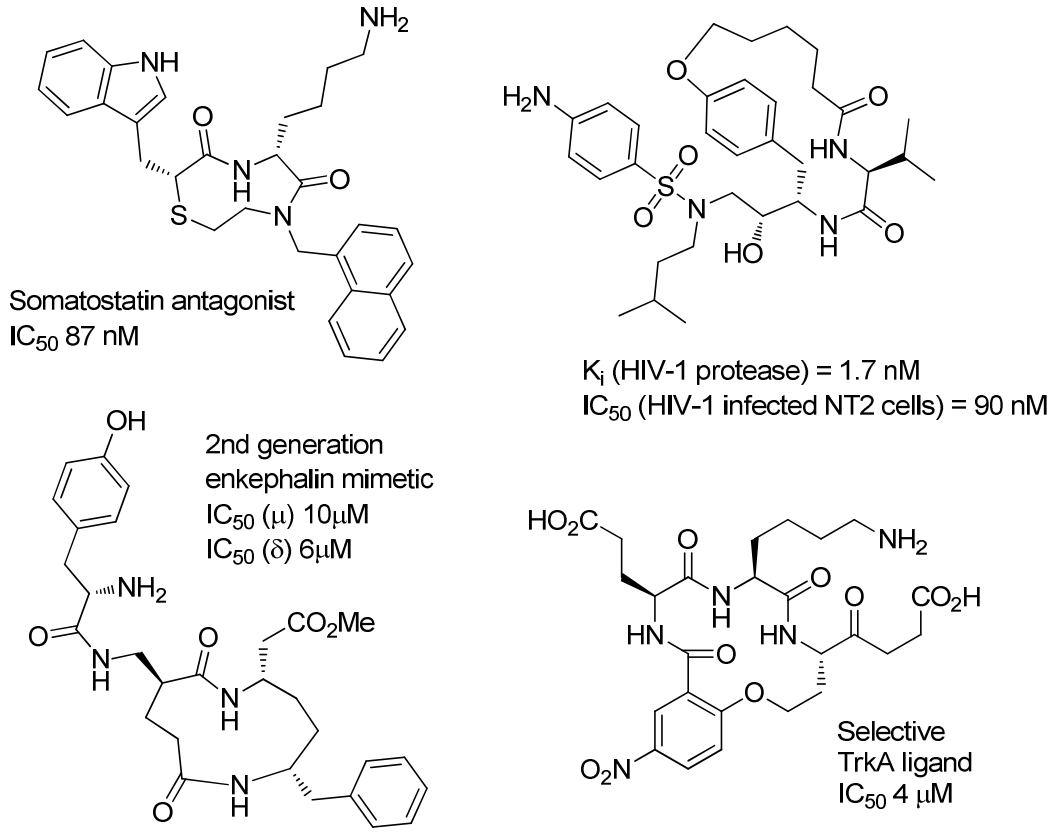
Figure 14.



Over the last decade, cyclopropyl fused ethers have been the subject of intense study as potential nucleoside mimics,[120,121] metabotropic glutamate receptor 4 (mGluR4) positive allosteric modulators,[122] and mGluR2,3 agonists[123] (Figure 14). However, only a handful of methods have emerged allowing for access to medium sized cyclopropyl fused heterocycles. Accordingly, there is a pressing need for the development of alternative routes towards these heterocycles.

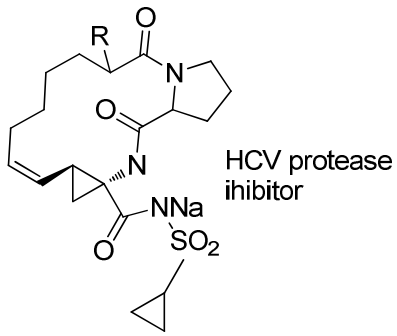
Aside from the potential of this methodology for furnishing functionalized oxabicyclo derivatives, the transformation serves as a possible pathway to medium size conformationaly restricted lactam derivatives. The abundance of medium sized lactams in nature and their position in drug discovery research, particularly as β-turn and β-strand peptidomimetics (Figure 15),[124] generate an increasing demand for efficient synthetic approaches towards there construction.

Figure 15.



While the incorporation of cyclopropyl scaffolds into small heterocycles has been an area of intense research and a plethora of biologically active compounds have been synthesized, examples of medium and large cyclopropane fused heterocycles have remained virtually unexplored. However, recent investigations have revealed potential; for example, cyclopropyl fused heterocycles of type **11** were found to be potent HCV protease inhibitors (Figure 16).[125]

Figure 16.



271

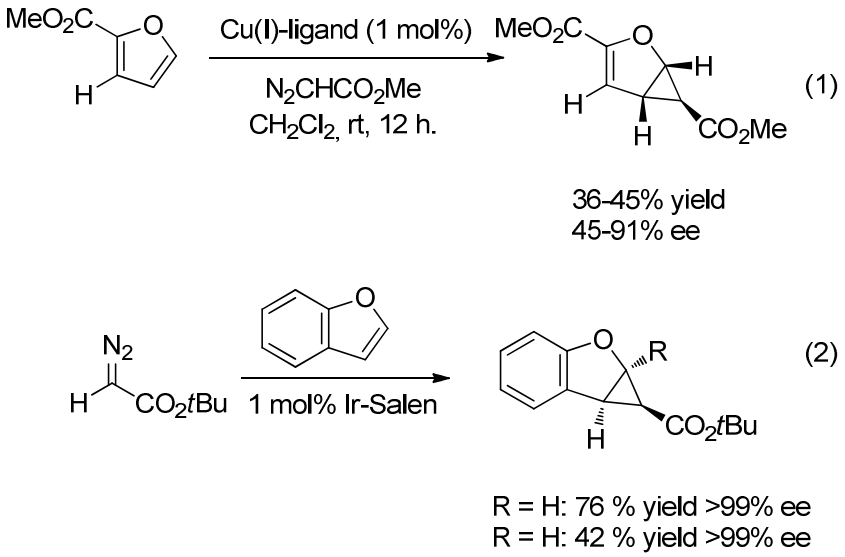
3.1.1. Synthetic approaches for the synthesis of cyclopropyl fused ethers

The synthetic methods employed for the construction of cyclopropyl oxabicyclo[3.1.0]hexane derivatives) span a variety of cyclopropanation reactions with cyclic enol ethers.[95] However, it is generally recognized that efficient stereoselective cyclopropanation of enol ethers represents a challenging task.[126] Cyclopropanation reactions are generally sensitive to sterics and do not allow access to highly funtionalized cyclopropane units. Most of the cyclopropanation reactions involved in formation of cyclopropyl fused ethers are restricted by the availability of the corresponding dihydrofuran or dihydropyran derivatives. Notably cyclopropanation reactions involving dihalocarbenes, which are one of the most useful reactions for the synthesis of functionalized cyclopropane derivatives, often times cannot be utilized as corresponding enol ether undergoes ring opening.[127] The synthesis of cyclopropyl fused cyclic ethers of ring size greater than six utilizing cyclopropanation reactions requires the preparation of medium sized cyclic enol ethers which poses a seperate synthetic challenge. Some recent

examples employing classic cyclopropanation reactions as well as those which providing access to medium size scaffolds are discussed below.

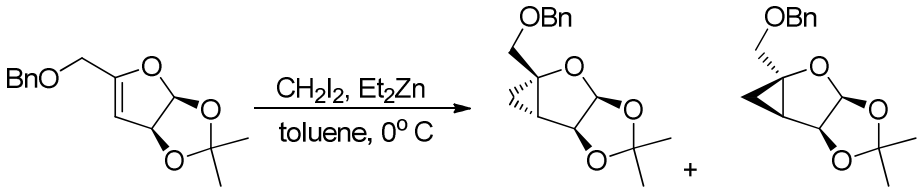
Metal-catalyzed carbene transfer from diazo compounds to olefins is a straightforward method for preparation of cyclopropanes, and much effort has been devoted towards the development of highly effective steroselective cyclopropanations.[128] Several methods have been developed involving [2+1] cycloadditions of diazo acetate derivatives with furans;[129] however, most of the methods are limited in terms of substrate scope, and sensitivity to sterics leads to decreased yields and stereoselectivity (Scheme 110. eq 1).[130] Nonetheless, recent advances have emerged allowing for the preparation of enantiomerically pure oxabicyclo cyclopropane derivatives (Scheme 110., eq. 2).[131]

Scheme 110.



The Simmons-Smith reaction[132] is a powerful tool for the preparation of cyclopropane derivatives from alkenes. Similar to methods based on diazo carbene transfers, this protocol allows for access to cyclopropyl fused ethers upon reaction with cyclic enol ethers; however, it is less sensitive to sterics and often times provides excellent diastereoselectivities. This method is often employed in the synthesis of conformationally restricted nucleoside analogues.[133] For example dihydrofuran **272** underwent diastereoselctive cyclopropanation to afford conformationally restricted sugar **273** in high yields. The most serious drawback of this methodology for the construction fused cyclopropyl scaffolds is its inherent inability to carry out a transfer of functionalized carbenoid equivalents (Scheme 111).

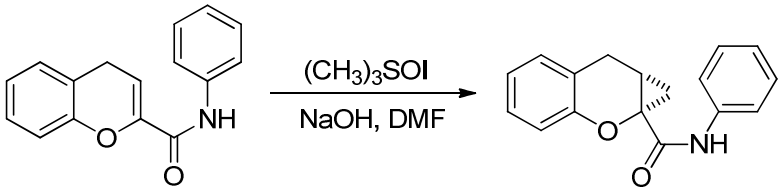
Scheme 111.



272 **273**, 91% **274**,1.5%

Similarly, the Corey-Chaykovsky reaction[134] utilizing trimethylsulfoxonium iodide provides a facile and stereoselective method for preparation of cyclopropyl fused heterocycles through cycloadditions involving cyclic enol ethers. (Scheme 112).[135]

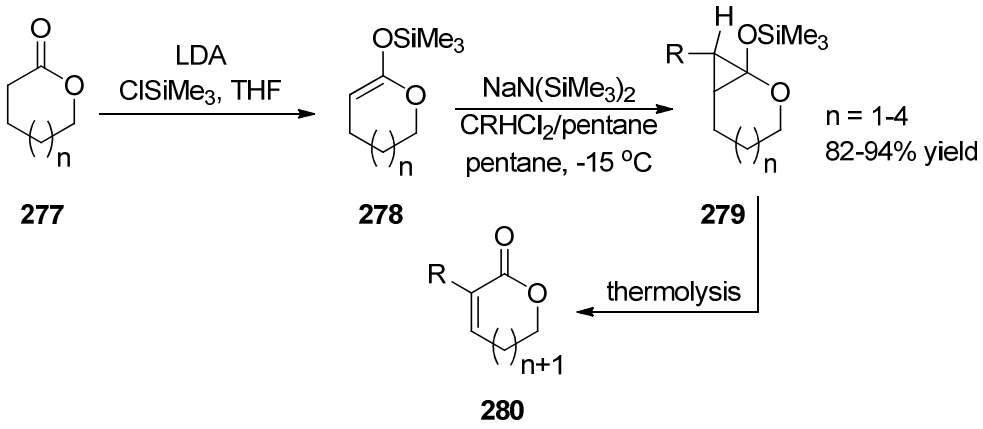
Scheme 112.



275 **276**, 82% yield

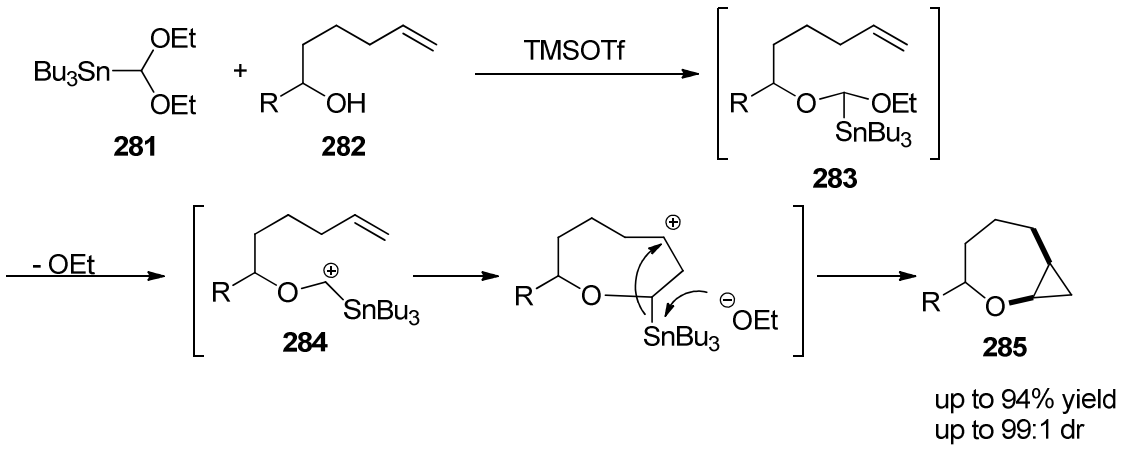
As mentioned above, the exploration of oxabicyclocyclopropane derivitives as medicinal agents has, up to this point, been limited to oxabicyclo[3.1.0]hexane and heptanes derivatives, since [2+1] cycloadditions are primarily executed on dihydrofuran and dihydropyran scaffolds. There are only a handful of efficient methods available that afford bicycles of ring sizes greater than six. Rousseau and co-workers took advantage of easily accessible medium lactones **277** which were converted to enol ethers **278** and subsequently were reacted in the presence of *in situ* generated carbenes to furnish medium size cyclopropyl fused heterocycles **279**. This protocol allowed for the construction of synthetically useful 6, 7, 8, 9, and 10 membered heterocycles in good yields (Scheme 113).

Scheme 113



It was demonstrated that stannyl substituted acetals **281** are effective for intramolecular cyclopropanation via *in situ* transacetalization (Scheme 114).[136] For example, the treatment of **281** with Lewis acids such as TMSOTf and BF_3OEt_2 in the presence of olefinic alcohol **282** gave rise to facile formation of bicyclic cyclopropane **285** in good yields. The reaction seems to proceed by the initial transacetalization of **281** with **282** to give mixed acetal **283** which then undergoes acid promoted elimination of the ethoxy group to generate tin substituted carbocation **284** (Scheme 114). The carbocation adds to the carbon-carbon double bond and the subsequent elimination of tin to achieve the intramolecular cyclopropanation which afforded 5, 6, 7, and 8 membered rings **285** in good to excellent yields.

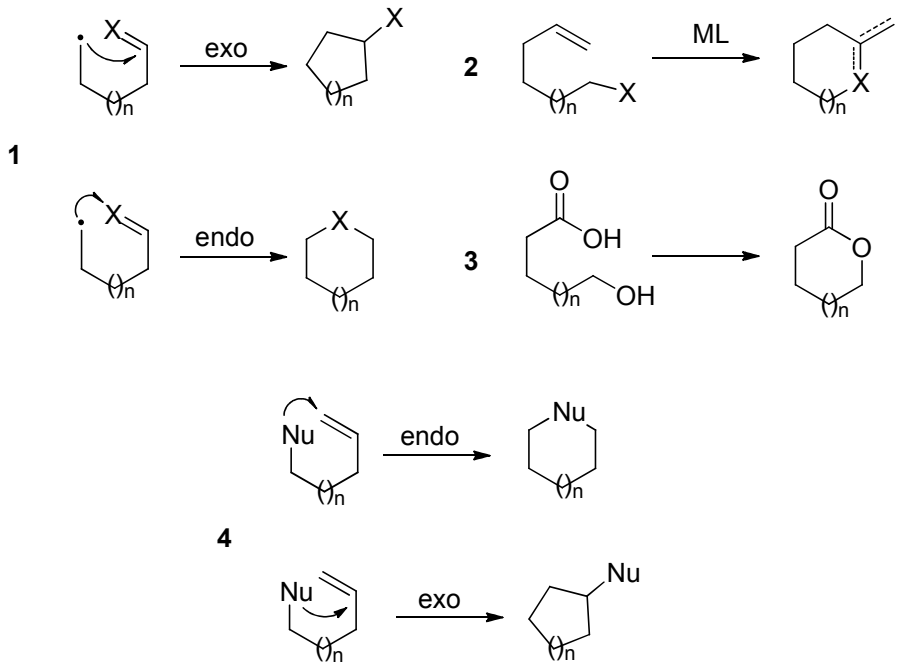
Scheme 114.



3.1.2. Known approaches towards medium size heterocycles

One of the most exciting aspects of the development of a intramolecular nucleophilic substitution (Scheme 109, eq 2, 3) is the potential for construction of medium size heterocycles. Not only are they of medicinal and synthetic value, high yielding diastereoselective non metal-assisted intramolecular substitutions present a rare class of transformations. Medium and large ring closure is typically achieved via radical cyclizations[137] (Scheme 115, eq 1), transition metals[138] (Scheme 115, eq 2), and lactonizations[139] (Scheme 115, eq. 3). While these are valuable tools, there is still much to be explored in the realm of medium ring closure as formation of these are generally unfavored, since the free energy of such cyclizations are typically positive due to a significant increase in the ring strain and loss of conformational freedom.

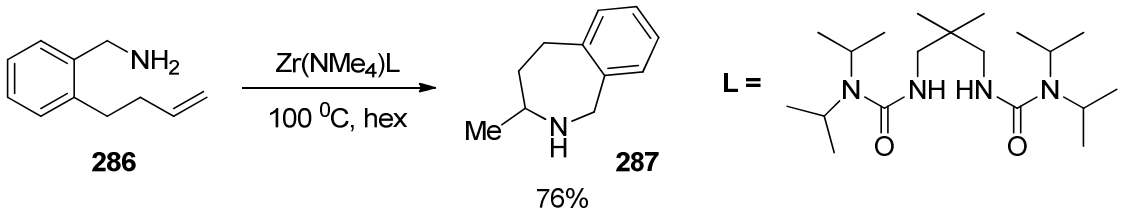
Scheme 115.



Intramolecular nucleophilic attack by tethered pronucleophilic entities is possible in the presence of transition metals or a Lewis acid activator and is a powerful tool in the synthetic arsenal available for construction of medium size heterocycles.[140] While the enthalpic requirements for medium ring closure present serious challenges, kinetic barriers for direct intramolecular nucleophilic addition to unactivated olefins, epoxides, and alkyl halides do not allow for efficient ring closure. However, in the presence of transition metals both *O*- and *N*-pronucleophiles add across olefins and alkynes. An excellent example of this type of methodolology involving hydroamination was recently reported by Schefer, who prepared a zirconium precatalyst with excellent reactivity for intramolecular hydroamination of alkenes.

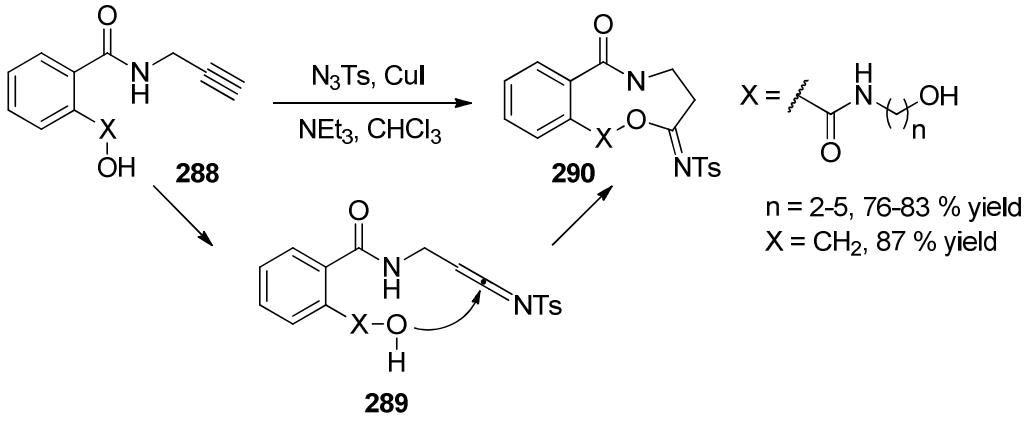
This methodology furnishes *7*-membered cyclic amines **287** via efficient *7-exo-trig* cyclizations of unactivated olefins **286** (Scheme 116).[141]

Scheme 116.



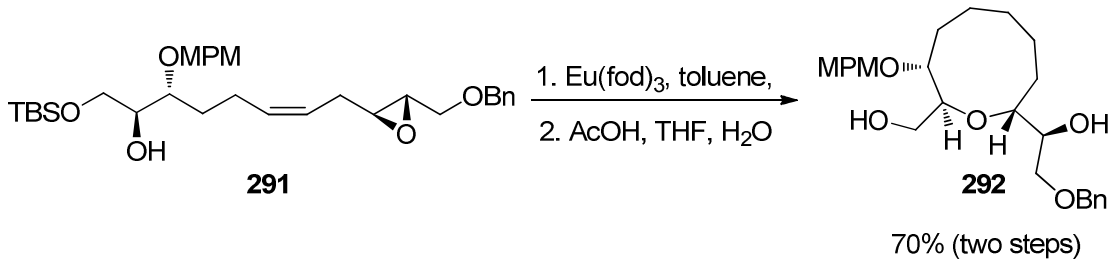
Unless certain conformational restraints are present in acyclic precursors, the generation of medium- and large-sized ring compounds greater than 7 is commonly problematic. Thus, it was shown that decreasing the degrees of rotational freedom via utilization rotationally restricted tethers such as amides allows for intramolecular cyclizations of medium size heterocycles. For example, intramolecular copper catalyzed addition to ynamides **289** generated *in situ via* nucleophilic attack of conformationaly restricted *O*-and *N*- pronculeophiles **288** furnished a variety of highly functionalized medium and large heterocycles **290** (Scheme 117).[142]

Scheme 117.



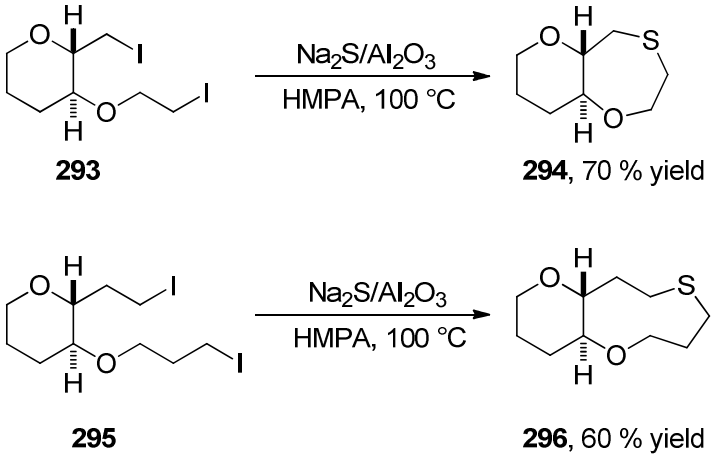
Metal-assisted intramolecular nucleophilic cyclizations involving inherently more activated substrates such as carbonyls and epoxides are more common. Suzuki and co-workers developed an efficient method toward the stereoselective construction of medium-sized cyclic ethers **292** by cyclization of hydroxy epoxides **291** promoted by $Eu(fod)_3$.[143] Stereochemistry was easily controlled since the reaction proceeds via an S_N2 mechanism. The efficiency of the method was proven by employing it in the successful total synthesis of (+)-obtusenyne via an efficient 9-*exo*-*tet* cyclization (Scheme 118).[144]

Scheme 118.



Direct non metal-assisted transformations involving nucleophilic attacks are less common, since oftentimes these methods involve the *in situ* generation of a nucleophilic species followed by S_N2 substitution, which is entropically unfavored. For example, tethered diiodides **293** in the presence of one equivalent of Na_2S/Al_2O_3 first generate the corresponding sulfide which may then undergo an intramolecular S_N2 substitution to afford oxathianes **294** of various sizes (Scheme 119).[145] Unfortunately, these intramolecular cyclizations suffered from poor yields due to intermolecular dimerization which is a common problem among such cyclizations.

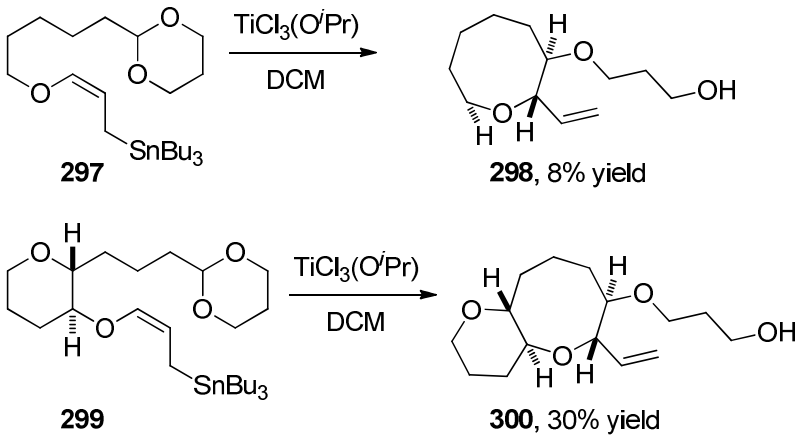
Scheme 119.



The necessity of restricting conformational freedom in such cyclizations is evident in the following example. The reaction of the trialkylstannyl ether acetals **297** in the presence of 2 equivalents of $TiC1_3$ gives intramolecular cyclizations furnishing vinyl cyclic ether of type **298** (Scheme 12). The reaction works very well for the formation of pyran derivatives however

formations of rings larger than six required the incorporation of a cyclohexane ring into the carbon back bone which enhanced the chemical yield of **298** from 8 % to 30 % via decreasing the flexibility of the acyclic precursor.

Scheme 120.



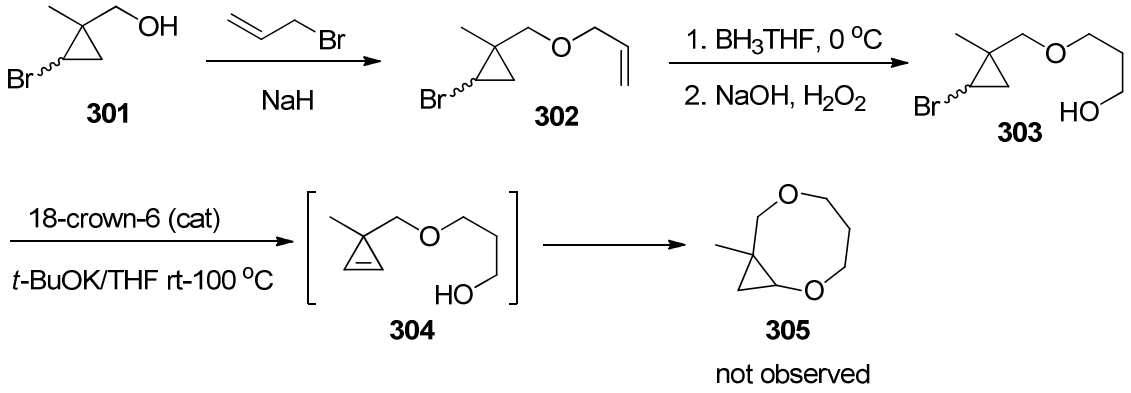
3.2. Results and Discussion

3.2.1. Scope and limitations

We embarked on our investigation of intramolecular formal nucleophilic substitution by first inquiring into the possible structure, length, and rigidity of the tethered moiety as all of these factors greatly influence the outcome of the reaction. It was expected that due to the

conformational restraints imposed by the cyclopropane moiety the employment of conformationaly unrestricted tethers would be possible.

Scheme 121

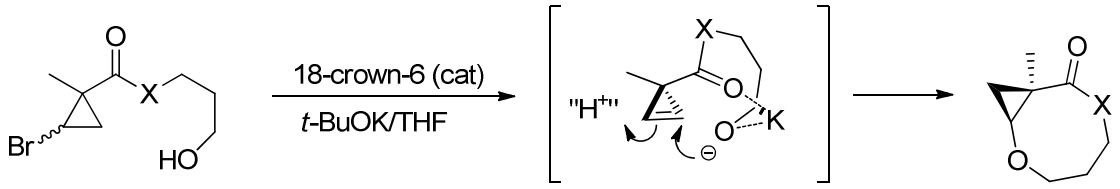


Thus, bromocyclopropane **303** was synthesized from **301** via a simple protocol shown in (Scheme 121). Disappointingly subjection of **303** to our optimized conditions developed for the intermolecular mode of this reaction did not yield cyclization and **305** was not detected (Scheme 121). Surprisingly attempts to induce intermolecular nucleophilic attack of *t*-BuOK to *in situ* generated intermediate **304** failed to give conclusive results. Increasing the reaction temperature only yielded a complex mixture as observed by GC/MS analysis. Addition of 1.1 equivalents *t*-BuOK at room temperature generated trace amounts of **304**, nonetheless attempts at isolation failed.

It was hypothesized that the installation of an amide or carboxylate functionality into the tether would provide additional conformational restraint in acyclic precursors **306** thereby circumventing possible entropic factors hindering intramolecular attack and providing heterocycles of type **308** (

Scheme 122). The directing effects of carboxylate and amide functionalities observed in the intermolecular addition of nucleophiles (Scheme 94) were also expected to greatly effect the outcome of cyclization by not only providing rotational constaints, but also to serve as part of a preorganized template **307** for cyclization. This template would be based on coordination of potassium to both the carboxylate functionality and the *in situ* generated tethered nucleophile (Scheme 122).

Scheme 122.

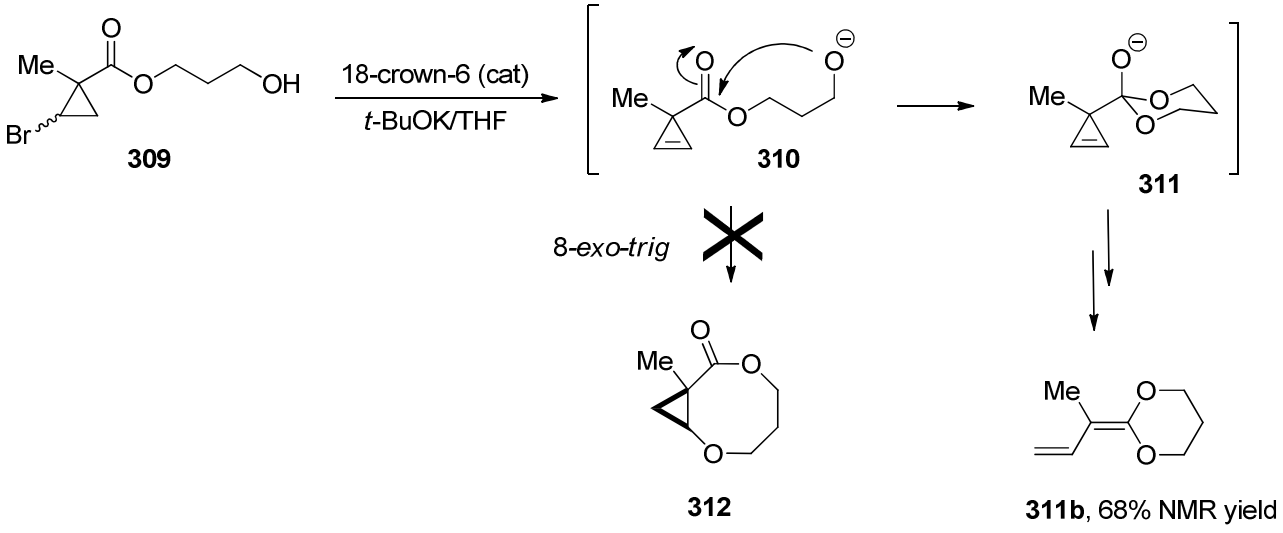


306 **307** **308**

To test this hypothesis, monobromocyclopropane **309** was synthesized from the corresponding acid chloride **313**. While it was observed that ester containing

bromocyclopropanes undergo decomposition upon subjection to *t*-BuOK, intramolecular nucleophilic addition was expected to outcompete the addition of *t*-BuOK to the carboxylate. Surprisingly, intramolecular addition did take place, however attack occurred at the carbonyl rather than to the cyclopropene providing ylidene **311b** in 68 % NMR yield via proposed intermediate **311** (Scheme 123). Unfortunately attempts to avoid this rearrangement at various temperatures and obtain dioxacanone **312** via an 8-*exo-trig* cyclization were unsuccessful. To address this issue we substituted the ester function with a more electron-rich carboxamide functionality. It has previously shown that 2-bromocyclopropylcarboxamides can be readily converted into the corresponding cyclopropenes in the presence of nucleophilic reagents with complete preservation of the amide function.

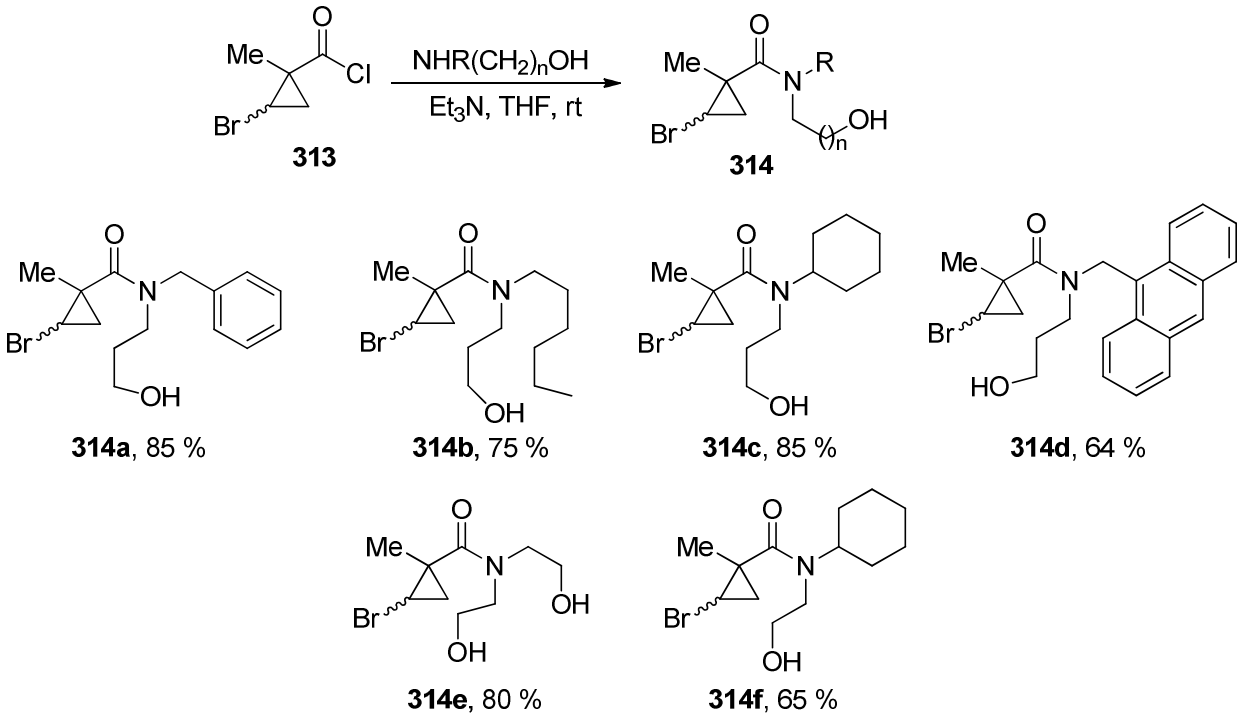
Scheme 123.



3.2.2. Medium Ring Closures

Accordingly, we set out to synthesis a library of ethanolamine and propanol amine derived acyclic precursors which upon cyclization would provide oxazepanones (n = 1) and oxazacanones (n = 2) via *7*- and *8-exo trig* cyclizations respectively. All amino alcohols reacted chemoselectively with acid chloride **313** in the presence of triethyl amine to furnish acyclic precursors **314a-e** in reasonable yields (Scheme 124).

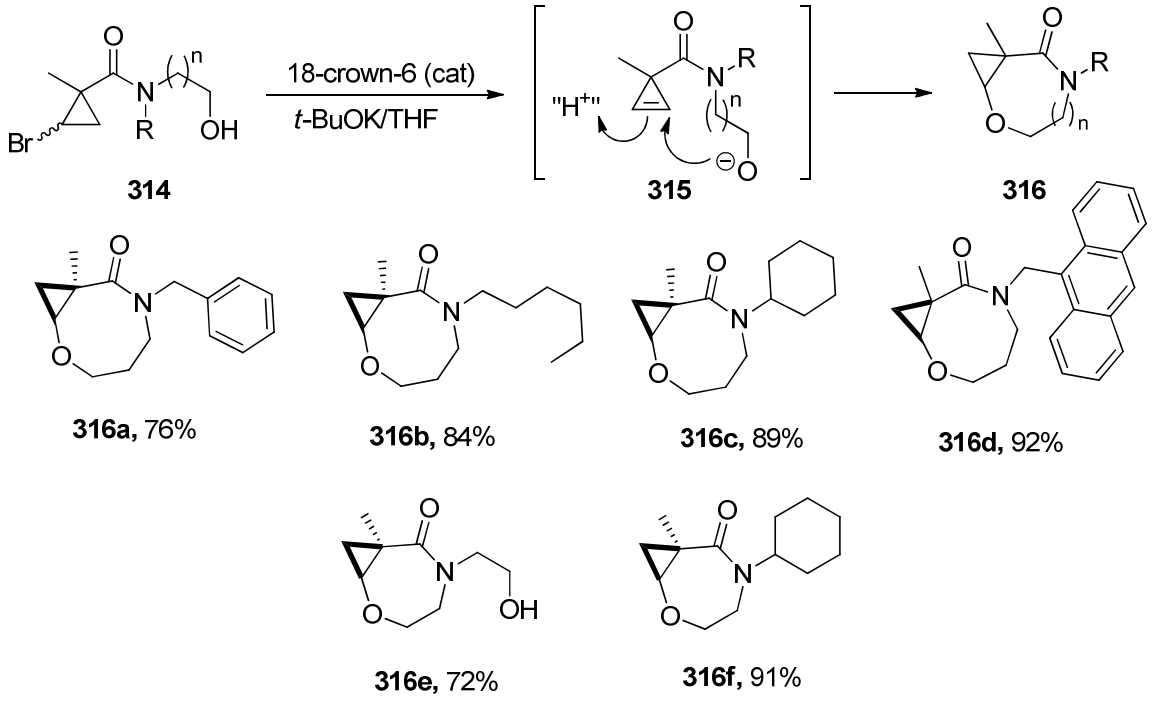
Scheme 124.



We performed test reactions employing 2-ethanolamine-derived substrates 314e-f. To our delight, the corresponding oxazepanones 316e-f were formed as sole products in high yield (Scheme 125). In both cases the cis-fused isomer was formed exclusively from a mixture of diastereomers. Notably no traces of the intermolecular addition of *t*-BuOK were detected by GC/MS analysis or by crude NMR analysis. Expectedly, the reaction times were shorter as compared to the intermolecular reaction. However, substrate **316f** required heating to 80 ^{o}C in order to efficiently form cyclopropene intermediate **315**.

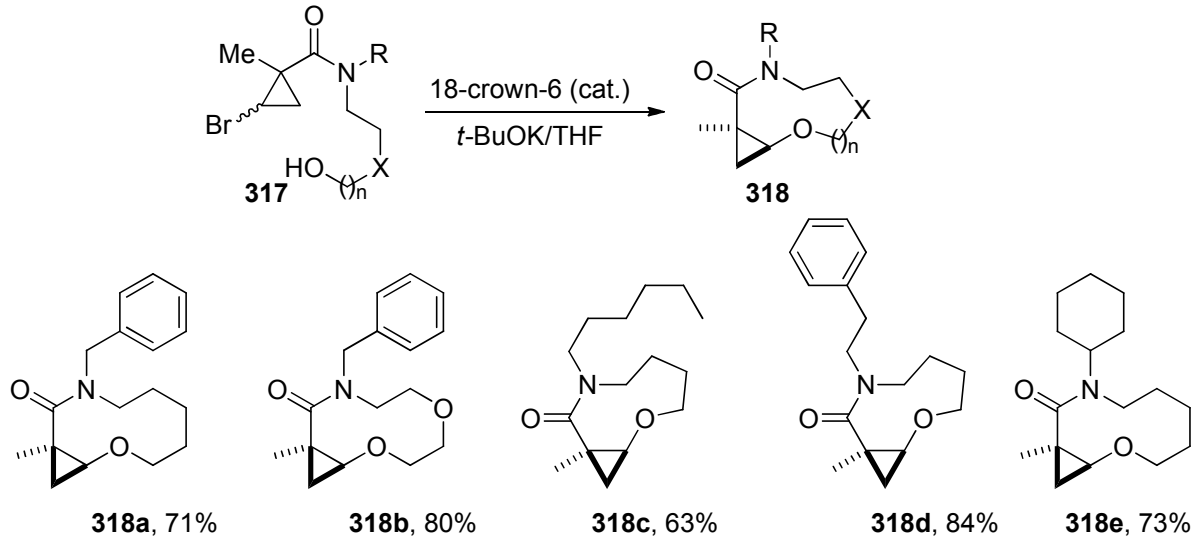
Inspired by these results we set out to investigate the possibility of *8-exo trig* cyclizations employing acyclic precursors **314a-c**. Upon reaction of acyclic precursors **314a-c** with 2-2.5 equiv. of *t*-BuOK in the presence of 18-crown-6 in THF, oxazacanone derivatives were all obtained in good yields as single diastereomers. Interestingly, anthracenyl acycyclic precursor **314d** also reacted uneventfuly to provide oxazacanone **316d** in 92% yield as a single diastreomer (Scheme 125).

Scheme 125.



The *8-exo-trig* cyclizations were especially intriguing since classical Baldwin's rules do not encompass ring closures larger than 7,[146] and we wondered if this preorganized template proposed could induce cyclizations of longer tethers. Indeed oxazananones **318d** and **318e** were obtained as single diastereomers from acyclic precursors **317d** and **317e** via *9-exo-trig* cyclizations. Remarkably acyclic precursors **317a-c** underwent *10-exo*-trig cyclizations affording oxazecanones **318a-c** (Scheme 125), and dioxazecanone **318b** in excellent yields. All described transformations proceeded in a highly diastereoselective fashion affording *cis*-fused bicyclic products starting from a diastereomeric mixture of bromocyclopropanes.

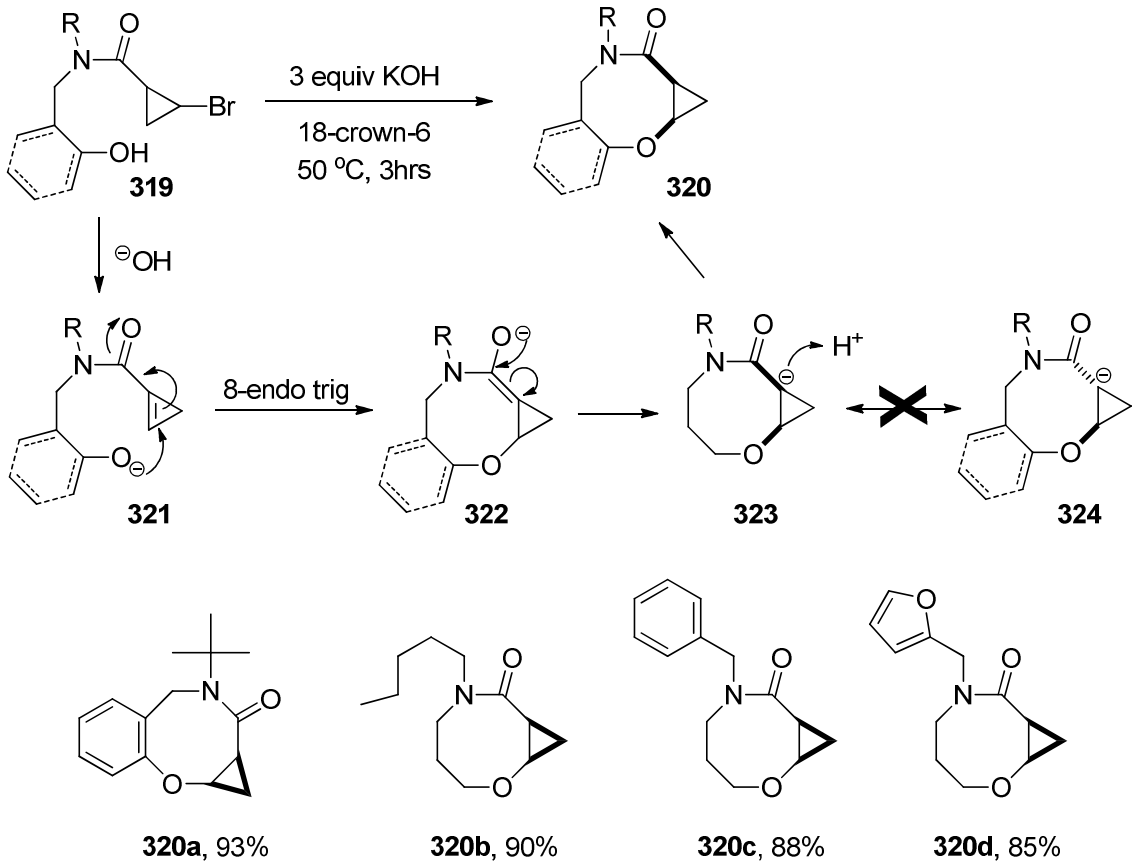
Scheme 126.



The high degree of diastereoselectivity was observed even in 9- and 10-membered ring closures of very flexible substrates, possessing no additional stereoselectivity-inducing elements in the tether. Remarkably, the reactions did not require high dilutions and afforded consistently high yields in preparatively convenient 0.05-0.2 M concentration range. The unique feature of this sequential transformation, in which the reactive intermediate is generated in very low quantities, permitted carrying out the reaction at such unusually high for medium ring closure concentrations. It should be mentioned that, despite the efficient assembly of 7-10 membered heterocycles we failed to obtain 11 and 12-membered rings via this approach.

Having met success with the *exo-trig* ring closure, we tested a corresponding *endo-trig* cyclization.[147] Our attempts to enable a 7-*endo-trig* ring closure were unsuccessful; however, 2-bromocyclopropylcarboxamides **319** cyclized smoothly via an 8-*endo-trig* pathway upon exposure to powdered KOH in the presence of 18-crown-6 ether, to give the corresponding oxazacanones **320b-c** high yields (Scheme 127). Furthermore, under similar conditions bromo-cyclopropane **319a** bearing a tethered phenoxide pronucleophile, provided oxazacinone **320a** in excellent yield. 8-*endo-trig* cyclization via **319** produced *cis*-fused heterocycles exclusively as equilibration to the *trans*-fused diastereomers **324** is unfavored unlike in the corresponding intermolecular nucleophilic additions to substrates of type **319** (Scheme 127).

Scheme 127

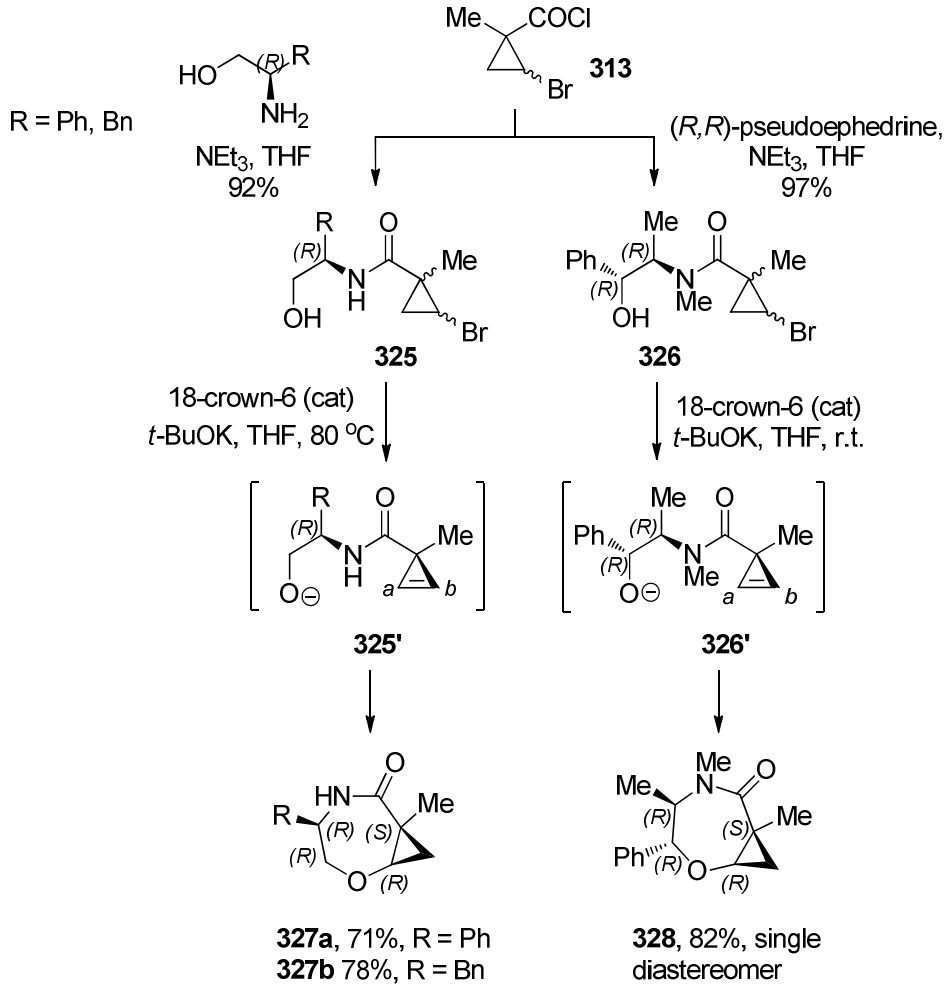


3.2.3. Construction of chiral bicycles

To further showcase the synthetic potential of this methodology, we explored intramolecular addition of tethered chiral alcohols en route to nonracemic bicyclic products (Scheme 128). Acylation of chiral amino alcohols with a racemic acyl chloride **313** provided amides **325** and **326** as mixtures of four diastereomers, which were subjected to the dehydrobromination conditions. Gratifyingly, both reactions exhibited perfect site selectivity: the

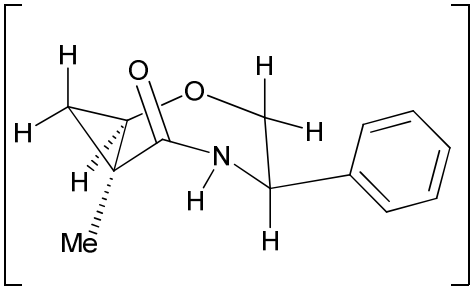
intramolecular nucleophilic attack of the alkoxides in the cyclopropene intermediates **325'** and **326'** proceeded at only one of the diastereotopic sp^2-carbon atoms (*a*), efficiently producing the corresponding bicyclic oxazepinones **327a, b** and **328** as sole products.

Scheme 128.



It was rationalized that the observed excellent diastereoselectivity results from a significant preference of the thermodynamically more favorable transition state **TS327a** with pseudo-equatorial orientation of the bulky substituents (Figure 17). The geometry of this transition state is very close to the most stable conformation of the obtained cyclic product, established by both NMR analysis and X-ray crystallography (Figure 17).[148] To further examine how the structure of the acyclic precursor affects the stereohemical outcome of the reaction, (+)-Ephedrine was employed as a tether to ptovide acyclic precursor **326b,** which upon cyclization gave **329** as a single diastereomer in 90% yield. (Figure 18).

Figure 17. Thermodynamically most favored geometry of transition state **TS327a** (AM1) and X-ray structure of **327a** see Appendix Figure 28



TS 327a

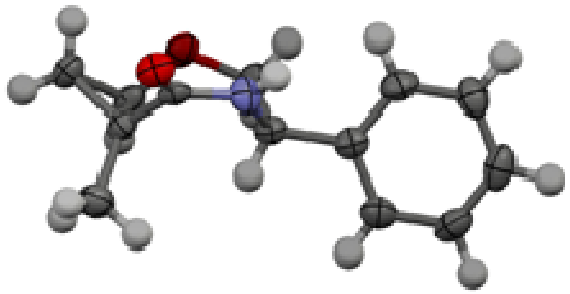
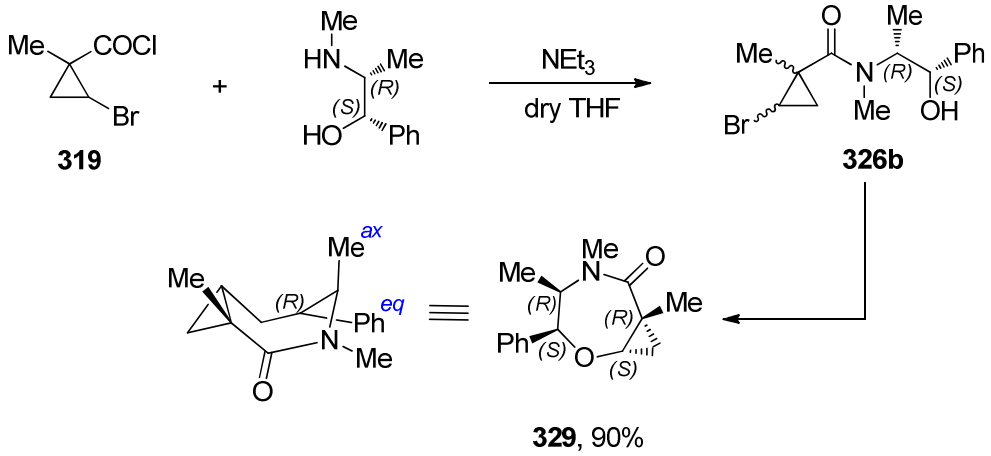


Figure 18.



3.3. Conclusion

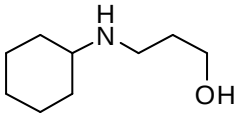
In conclusion, we have developed a very facile and general *exo-trig* cyclization of seven- through ten-membered rings, achieved as a result of highly efficient pre-organization of conformationally constrained precursors and the strain energy release. The described transformation can be carried out in a highly diastereoselective fashion, affording a single *cis*-fused bicyclic product starting from a diastereomeric mixture of bromocyclopropanes. This being the case even for relatively flexible tethered substrates, leading to [9.1.0] and [10.1.0] bicyclic systems. The developed transformation also involves a novel 8-*endo-trig* nucleophilic cyclizations and it was demonstrated that this reaction proceeds highly efficiently with both alkoxides and phenoxide nucleophiles.

3.4. Experimental Procedures

3.4.1. General Information

See Chapter 1.4.1. for general remarks and list of instrumentation. Anhydrous triethylamine was obtained by distillation of ACS-grade commercially available materials over calcium hydride in a nitrogen atmosphere. 3-Benzylamino-1-propanol, 4-benzylamino-1-butanol, 5-benzylamino-1-pentanol, and 2-cyclohexylamino-1-ethanol were purchased from TCI America and used as received. All other commercially available reagents were purchased from Sigma-Aldrich or Acros Organics. 2-Bromo-cyclopropanecarbonyl chloride[87] and 2-bromo-1-methylcyclopropanecarbonyl chloride,[113], Bromocyclopropanes **301** and **302** were prepared according to published procedures. Preparation of other non-commercially available starting materials is described below.

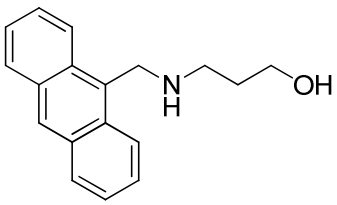
3.4.2. Preparation of Amino Alcohols



3-Cyclohexylamino-1-propanol:[149] Three neck round bottom flask (250 mL) equipped with a reflux condenser, a thermometer, and addition funnel (100 mL) was charged with $LiAlH_4$ (1.30 g, 38.4 mmol, 1.50 eq) and anhydrous THF (30 mL). The resulting suspension was stirred at 0 ^{o}C and a solution of methyl 3-(cyclohexyl-amino)propanoate[150] (4.40 g, 23.2 mmol, 1.00 equiv) in dry THF (50 mL) was added drop wise over 30 min. Once addition was complete the mixture was stirred at reflux overnight, then

quenched at 0 ^{o}C consecutively with water (20 mL) and a concentrated aqueous solution of NaOH (5.0 g in 5 mL of water). The resulting suspension was diluted with water (30 mL) and THF (50 mL) and filtered through a fritted funnel. The filter cake was washed with THF (3 x 20 ml), and the washing liquids were combined with the filtrate. The resulting solution was saturated with NaCl and extracted with THF (3 x 20 ml). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by vacuum distillation (bp 60 ^{o}C at 15 torr) to afford the titled compound as colorless oil, solidifying upon standing. Yield 2.4 g (15.1 mmol, 65%).

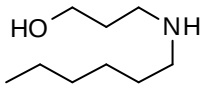
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.80 (t, *J* = 5.2 Hz, 2H), 2.89 (t, *J* = 5.7 Hz, 2H), 2.41 (tt, *J* = 10.3 Hz, 3.6 Hz, 1H), 2.05 (br. s, 2H), 1.97-1.79 (m, 2 H), 1.77-1.52 (m, 5H), 1.31-1.13 (m, 3H), 1.11-0.99 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 64.5 (-), 56.6 (+), 46.9 (-), 33.4 (-, 2C), 31.2 (-), 26.0 (-), 24.9 (-, 2C); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.77 (t, *J* = 5.6 Hz, 2H), 2.84 (t, *J* = 5.8 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 2H), 1.67 (quin, *J* = 5.6 Hz, 2H), 1.44 (quin, *J* = 7.1 Hz, 2H), 1.35-1.19 (m, 6H), 0.86 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 64.1 (-), 49.9 (-), 49.8 (-), 31.6 (-), 30.7 (-), 29.8 (-), 26.9 (-), 22.5 (-), 13.9 (+);



3-((Anthracen-9-ylmethyl)amino)propan-1-ol:[151] To a stirred solution of anthracene-9-carbaldehyde (2.0 g, 9.6 mmol) in methanol (200 mL) was added 3-aminopropanol (800 mg, 10.7 mmol, 1.1 equiv.). The mixture was stirred for 30 min at room temperature, then cooled to 0 ^{o}C, and $NaBH_4$ (547 mg, 14.4 mmol, 1.50 equiv) was added by small portions over 5 min. The formed suspension was stirred for 3 hrs, then most of the solvent was removed in vacuum, and the

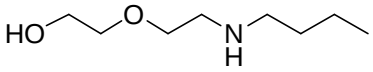
residue was quenched with 2% aqueous KOH and extracted with dichloromethane (4 x 20 mL). Combined organic phases were dried with MgSO4, filtered and concentrated. The obtained yellow solid was recrystallized from hexane-EtOAc 10:1 mixture to afford the title compound as yellow needles, mp 82-83 ^{o}C, yield 1.8 g (6.78 mmol, 71%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.31 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.59-7.54 (m, 2H), 7.50-7.47 (m, 2H), 4.76 (s, 2H), 3.84 (app. t, *J* = 5.2 Hz, 2H), 3.15 (app. t, *J* = 5.7 Hz, 2H), 2.05 (br. s, 2H), 1.79 (quin, *J* = 5.6 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 131.4 (2C), 130.7, 130.2 (2C), 129.2 (+, 2C), 127.4 (+), 126.2

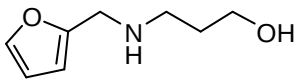


3-(Hexylamino)propan-1-ol:[152] Three neck round bottom flask (250 mL) equipped with a reflux condenser, a thermometer, and addition funnel (100 ml) was charged with $LiAlH_4$ (1.50 g, 38.4 mmol, 1.5 equiv) and anhydrous THF (30 mL). The resulting suspension was stirred at 0 ^{o}C, a solution of methyl 3-(hexylamino)propanoate[153] (4.80 g, 25.6 mmol, 1.00 equiv) in dry THF (50 mL) and was added dropwise over 30 min. Once addition was complete the mixture was stirred at reflux overnight, and then quenched consecutively with water (20 mL) and a concentrated solution of NaOH (5.00 g in 5 ml of water) at 0 ^{o}C. The mixture was diluted with THF (50 mL) and of water (30 mL) and the resulting suspension was filtered through a fritted funnel. The filter cake was washed with THF (3 x 20 mL), and the washing liquid was combined with the filtrate. The resulting filtrate was saturated with NaCl and extracted with THF (3 x 20 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated. The resulting yellowish oil was purified by vacuum distillation to afford the titled compound as colorless oil. Yield 2.80 g (15.9 mmol, 62%). ^{1}H

NMR (400.13 MHz, $CDCl_3$) δ 3.77 (t, *J* = 5.6 Hz, 2H), 2.84 (t, *J* = 5.8 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 2H), 1.67 (quin, *J* = 5.6 Hz, 2H), 1.44 (quin, *J* = 7.1 Hz, 2H), 1.35-1.19 (m, 6H), 0.86 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 64.1 (-), 49.9 (-), 49.8 (-), 31.6 (-), 30.7 (-), 29.8 (-), 26.9 (-), 22.5 (-), 13.9 (+);



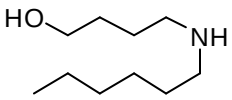
2-(2-(Butylamino)ethoxy)ethanol:[154] A two neck round bottom flask equipped with a reflux condenser and addition fummel (30 mL) was charged with neat *n*-butylamine (7.00 g, 9.46 mL, 96.7 mmol, 3.00 equiv), and a 2-(2-chloroethoxy)ethanol (4.00 g, 32.1 mmol, 1.00 equiv) in MeOH (20 ml) was added dropwise over 10 min. Once addition was complete, the mixture was heated at reflux for 18 hrs. The solvent was removed in vacuum; the resulting salt was washed with hexane (3 × 10 mL) and dissolved in a solution of KOH (1.89 g, 33.7 mmol) in water 10 (mL). The resulting slurry was partitioned between THF (10 mL) and brine (10 mL) and extracted with THF (3 × 20 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated to obtain the title compound as colorless oil, pure enough to be used in further transformation without additional purification. Yield 3.60 g (22.8 mmol, 71%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.68 (t, *J* = 4.6 Hz, 2H), 3.58 (t, *J* = 5.2 Hz, 2H), 3.55 (t, *J* = 4.6 Hz, 2H), 2.77 (t, *J* = 5.2 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 1.54 (quin, *J* = 7.3 Hz, 2H), 1.31 (sxt, *J* = 7.3 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 72.6 (-), 70.1 (-), 61.5 (-), 49.5 (-), 49.3 (-), 32.0 (-), 20.4 (-), 14.0 (+);



3-((Furan-2-ylmethyl)amino)propan-1-ol:[155] To a stirred solution of

furfural (5.00 g, 52.0 mmol, 1.00 equiv) in MeOH (30 mL) was added 3-aminopropan-1-ol (4.00 g, 53.3 mmol, 1.00 equiv), and the mixture was stirred for 30 min at room temperature, then cooled to 0 ^{o}C and $NaBH_4$ (2.90 g, 76.6 mmol, 1.50 equiv) was added by small portions over 10 min. The suspension was stirred for 4 hrs at room temperature and the solvent was removed in vacuum. An aqueous solution of KOH (5.00 g, 47.8 mmol, 1.7 equiv in 20 mL of water) was added and the solution was partitioned between EtOAC and brine. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The resulting crude oil was distilled (130 ^{o}C) to afford the title compound as a colorless viscous oil. Yield 7.50 g (48.4 mmol, 93%).

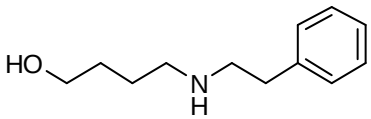
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 1.8 Hz, 0.8 Hz, 1H), 6.27 (dd, *J* = 3.2 Hz, 1.9 Hz, 1H), 6.14 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 2.78 (t, *J* = 6.1 Hz, 2H), 1.66 (quin, *J* = 5.9 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 153.2, 141.7 (+), 110.0 (+), 106.9 (+), 63.0 (-), 48.0 (-), 45.7 (-), 30.9 (-);



4-Hexylamino-1-butanol:[156] Two neck round bottom flask equipped with a reflux condenser was charged with neat *n*-hexylamine (5.60 g, 55.2 mmol, 3.00 equiv), and a solution of 4-chlorobutan-1-ol (2.00 g, 18.4 mmol 1.00 equiv) and MeOH (20 mL) was added dropwise over 30 min. Once addition was complete the mixture was heated at reflux for 12 hr. The solvent was removed in vacuum and the resulting salt was washed with hexane (3 x 10 ml) and dissolved in a solution of KOH (3.10 g, 55.2 mmol, 3.00 equiv) in water (20 mL). Then the mixture was partitioned between THF (20 ml) and brine (20 ml) and the aqueous phase was extracted with THF (3 x 20 ml). The combined organic phases were dried

with Na_2SO_4, filtered, and concentrated. The resulting crude material was purified by vacuum distillation (100 ^oC at 1 torr) to afford the titled compound as colorless oil. Yield 1.6 g (9.2 mmol, 50 %).

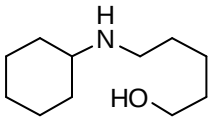
^1H NMR (400.13 MHz, $CDCl_3$) δ 3.75 (br.s, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 2.64 (t, *J* = 5.8 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 1.88-1.80 (m, 2H), 1.67-1.59 (m, 4H), 1.48 (quin, *J* = 7.3 Hz, 2H), 1.31-1.24 (m, 4H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 62.5 (-), 49.6 (-), 49.5 (-), 32.6 (-), 31.7 (-), 29.6 (-), 28.8 (-), 26.9 (-), 22.5 (-), 14.0 (+);



4-(Phenethylamino)butan-1-ol:[157] Two neck round bottom flask equipped with a reflux condenser was charged with neat 2-phenylethanamine (13.4 g, 110 mmol, 3.00 equiv), and a solution of 4-chlorobutan-1-ol (4.00 g, 36.8 mmol, 1.00 equiv) in MeOH (30 mL) was added dropwise over 30 min. Once addition was complete the mixture was heated at reflux for 12 hr. The solvent was removed in vacuum, the resulting salt was washed with hexane (3 x 10 mL) and dissolved in a solution of KOH (6.2 g, 110.4 mmol, 3 equiv) in water (30 mL). The resulting mixture was partitioned between THF (20 ml) and brine (20 ml) and extracted with THF (3 x 20 ml). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The resulting greenish oil was purified by vacuum distillation (110 ^oC at 1 torr) to afford the titled compound as colorless oil. Yield 6.00 g (31.1 mmol, 85 %).

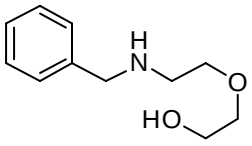
^1H NMR (400.13 MHz, $CDCl_3$) δ 7.33-7.25 (m, 2H), 7.24-7.07 (m, 3H), 3.57 (t, *J* = 5.3 Hz, 2H), 2.90-2.84 (m, 2H), 2.84-2.77 (m, 2H), 2.64 (t, *J* = 5.8 Hz, 2H), 1.72-1.52 (m, 4H); ^{13}C

NMR (100.67 MHz, $CDCl_3$) δ 139.4, 128.5 (+, 2C), 128.3 (+, 2C), 126.1 (+), 62.2 (-), 50.3 (-), 49.3 (-), 35.7 (-), 32.1 (-), 28.2 (-);



5-(Cyclohexylamino)pentan-1-ol:[158] A two neck round bottom flak equipped with a reflux condenser was charged with neat cyclohexylamine (3.00 g, 33.7 mmol, 3.00 equiv), and a solution 5-chloropentan-1-ol (1.53 g, 12.5 mmol, 1.00 equiv) in MeOH (10 ml) was added dropwise over 10 min. Once addition was complete the mixture was heated at reflux for 18 hrs. The solvent was removed in vacuum; the resulting salt was washed with hexane (3 x 10 ml) and dissolved in a solution of KOH (1.89 g, 33.7 mmol) in water 10 (mL). The resulting mixture was partitioned between THF (10 mL) and brine (10 mL) and extracted with THF (3 x 20 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The resulting oil was distilled (bp 115 ^oC at 1 torr) to afford the title compound as colorless oil. Yield 1.39 g (20.2 mmol, 60%).

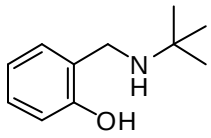
^1H NMR (400.13 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 2.42 (tt, *J* = 10.6 Hz, 3.7 Hz, 1H), 2.05 (br. s., 2H), 1.97-1.83 (m, 2H), 1.80-1.68 (m, 2H), 1.68-1.48 (m, 4H), 1.48-1.38 (m, 4H), 1.32-1.02 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 62.4 (-), 56.9 (+), 46.6 (-), 33.4 (-, 2C), 32.4 (-), 29.7 (-), 26.1 (-), 25.1 (-, 2C), 23.5 (-);



2-(2-(Benzylamino)ethoxy)ethanol[159]: A solution of 2-(2-chloroethoxy)ethanol (5.0 g, 40.1 mmol) in methanol (30 mL) was added to stirred neat benzylamine (12.9 g, 120.4 mmol, 3.0 equiv). The mixture was heated at reflux

(bath temperature 100 ^{o}C) for 24 hr, then solvent was removed in vacuum. The obtained crystalline residue was washed with hexane (3 x 50 mL) and dissolved in water (50 mL), basified with solid KOH (6.5 g), and extracted with EtOAc (3 x 80 mL). Combined organic phases were dried with Na_2SO_4, filtered, and concentrated in vacuum. The residue was distilled in vacuum, bp 110 oC (0.5 torr). Yield 4.23 g (21.7 mmol, 54%).

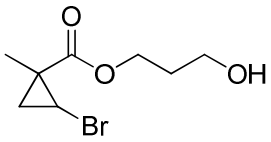
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.37-7.21 (m, 5H), 3.79 (s, 2H), 3.68 (app. t, *J* = 4.6 Hz, 2H), 3.59 (app. t, *J* = 5.2 Hz, 2H), 3.54 (app. t, *J* = 4.6 Hz, 2H), 2.80 (app. t, *J* = 5.2 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 139.6, 128.3 (+, 2C), 128.1 (+, 2C), 126.9 (+), 72.4 (-), 70.0 (-), 61.3 (-), 53.6 (-), 48.4 (-).



2-((*tert*-Butylamino)methyl)phenol[160]: A solution of salicyl aldehyde (1.22 g, 10.0 mmol, 1.00 equiv.) and *tert*-butyl amine (1.46 g, 20.0 mmol, 2.00 equiv.) was stirred in dry MeOH (40 mL) for 1 hr. $NaBH_4$ (600 mg, 16.0 mmol, 1.60 equiv.) was added causing a color change from yellow to clear over the course of 10 min, after which the reaction was quenched with 5% aqueous HCl (15 mL). The resulting mixture was then partitioned between Et_2O (25 mL) and brine (25 mL). The aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The obtained crystalline material was pure enough to be used for the following transformations without additional purification. Yield 1.45 g (8.01 mmol, 81%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.17 (td, *J* = 8.0 Hz, 1.8 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.84 (dd, *J* = 8.1 Hz, 1.0 Hz, 1H), 6.79 (td, *J* = 7.4 Hz, 1.1 Hz, 1H), 3.92 (s, 2H), 1.23 (s, 9H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 158.3, 128.2 (+), 127.7 (+), 123.4, 118.6 (+), 116.2 (+), 50.8, 45.8 (-), 28.3 (+); HRMS (TOF ES): found 180.1383, calculated for $C_{11}H_{18}NO$ (M+H) 180.1388 (2.8 ppm).

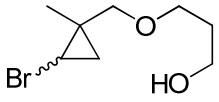
3.4.3. Syntheses of Bromocyclopropanes



3-Hydroxypropyl 2-bromo-1-methylcyclopropanecarboxylate (**309**): To a stirred solution of 1,3-propanediol (520 μL, 551 mg, 7.24 mmol, 5.00 equiv) in anhydrous pyridine (2 mL) was added dropwise 2-bromo-1-methylcyclopropanecarbonyl chloride (200 μL, 286 mg, 1.45 mmol). The mixture was stirred for 2 hr at 0 ^{o}C, then quenched with water (20 mL) and extracted with EtOAc (3 × 10 mL). Combined organic phases were washed consequitively with 10% aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered and concentrated in vacuum. Preparative column chromatography of a residue (eluent hexane/EtOAc, gradient from 4:1 to 1:1) afforded two fractions. Less polar fraction (R_f 0.50, eluent hexane/EtOAc 4:1) contained a mixture of diastereomeric propane-1,3-diyl bis(2-bromo-(methyl)cyclopropanecarboxylates) as a yellowish oil, yield 115 mg (0.29 mmol, 40%). More polar fraction (R_f 0.50, eluent hexane/EtOAc 1:1)

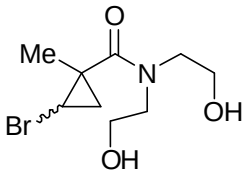
represented a colorless oil which was identified as a title compound. Yield 200 mg (0.84 mmol, 58%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ [4.34-4.22 (m) & 4.19 (t, *J* = 6.3 Hz), ∑2H], [3.69 (t, *J* = 6.1 Hz) & 3.65 (t, *J* = 6.1 Hz), ∑2H], [3.48 (dd, *J* = 8.1 Hz, 5.3 Hz) & 2.94 (dd, *J* = 7.6 Hz, 5.6 Hz), ∑1H], 2.43 (br. s, 1H), 1.91-1.74 (m, 3H), [1.44 (s) & 1.36 (s), ∑3H], [1.23 (dd, *J* = 7.6 Hz, 6.6 Hz) & 0.99 (app. t, *J* = 6.1 Hz, 5.6 Hz), ∑1H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 173.5, 62.1 (-), 58.77 (-), 31.5 (-), 28.7 (+), 25.1 (-), 23.7, 16.7 (+); minor: 171.3, 62.1 (-), 58.84 (-), 31.6 (-), 26.6, 25.9 (+), 22.5 (-), 19.6 (+); FT IR (NaCl, film, cm^{-1}): 3427, 2961, 2887, 1726, 1429, 1398, 1369, 1350, 1250, 1205, 1178, 1155, 1099, 1051, 922, 905, 590; HRMS (TOF ES): found 258.9952, calculated for $C_8H_{13}BrNaO_3$ (M+Na) 258.9946 (2.3 ppm).

3-((2-bromo-1-methylcyclopropyl)methoxy)propan-1-ol (303):



In a 2-neck 50 mL flask containing a stirred solution of **302** (1.8g, 8.7 mmol) in 20 mL of THF under N_2 at 0 ^{o}C was added 660 µL (8.8 mmol) of BH_3SMe_2. The solution was stirred for 2 hr at room temp when a solution of 1g of NaOH (3 equiv) in 2 mL of THF was added dropwise over 5 min. Finally 3 mL of H_2O_2 was added via syring over 5 min at 0 ^{o}C. The reaction was allowed to stir for one hour and 5 ml of water was added. The solution was extracted with 20 mL of EtOAC (20 mL) 3 times, washed with Na_2CO_3, dried with $MgSO_4$ and filtered. The residue was purified by preparative column chromatography eluting with 3:1 EtOAC/hexanes. Yield: 1.64 g, 85% yield.

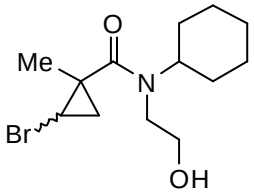
^{1}H NMR (400.13 MHz, $CDCl_3$) δ [3.75-3.62 (m) , ∑3H], [3.61-3.65 (m), ∑2H], [3.56-3.50 (m), ∑2H], 4.44 (br. s, 1H), 3.3 (dd, 1.72 Hz) [3.2-3.17 (m), 1H], [2.97-2.92 m, 1H); 2.83-2.82 (m) 1H; 1.85-1.74 m, 3H; 1.26 s, 3H; 1.15, s 3H; 1.13-1.08 m, 1H; 0.99 (t, *J* = 7.1 Hz 1H); 0.77 (t , *J* = 7.5 Hz); 0.64 (t, *J* = 6.8 Hz. ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 76.16 (+), 76.1 (+), 70.0 (+), 69.52, (+) 67.77 (+), 32.05 (+) 27.57 (-), 28.48 (-), 27.20 (-), 20.92, 20.54 (-), 19.38 (+); HRMS (TOF ES): found 245.01.0153, calculated for $C_8H_{13}BrNaO_3$ (M+Na) 245.01460 (2.3 ppm).



2-Bromo-N,N-bis(2-hydroxyethyl)-1-methylcyclopropanecarboxamide (**31d**): To a stirred solution of 2,2-diethanolamine (1.17 g, 11.2 mmol, 2.2 equiv) in dry THF (4 mL) was added dropwise a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (1.00 g, 5.1 mmol, 1.0 equiv) in dry THF (4 mL). The mixture was stirred for 1 hr, then quenched with brine and extracted with EtOAc (3 x 25 mL). Combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuum. Crude residue was purified by preparative column chromatography on silica gel (eluting with EtOAc) to afford the title compound. Yield 1.09 g (4.08 mmol, 80%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 4.32 (br.s, 2H), 4.06-3.28 (m, 8H), [3.37 (dd, *J* = 8.2 Hz, 5.1 Hz) & 2.99 (dd, *J* = 6.9 HZ, 4.7 Hz), Σ1H], [1.66 (ps.-t, *J* = 8.2 Hz, 6.9 Hz) & 1.54 (dd, *J* = 6.0 Hz, 4.7 Hz), Σ1H], [1.47 (s) & 1.43 (s), Σ3H], [1.19 (ps.-t, *J* = 6.9 Hz, 6.0 Hz) & 0.89 (app. t, *J* =

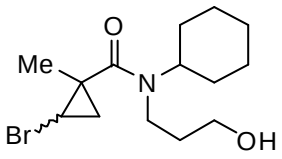
6.9 Hz, 5.1 Hz), Σ1H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 174.0, 60.0 (-), 59.2 (-), 51.1 (-), 48.6 (-), 27.9, 25.9 (+), 21.5 (-), 19.6 (+); minor: 172.5, 60.1 (-), 59.7 (-), 51.5 (-), 48.9 (-), 27.9 (+), 25.7, 22.2 (-), 21.8 (+); FT IR (cm^{-1}, film): 3421, 2988, 2941, 2908, 2876, 2837, 2658, 2621, 2442, 2363, 2332, 2230, 1757, 1610, 1290, 1232, 1213, 1132, 1088, 1020, 928, 862, 831, 712, 685, 650, 604, 523, 473; HRMS (TOF ES): found 266.0388, calculated for $C_9H_{17}NO_3Br$ (M+H) 266.0392 (1.5 ppm).



2-Bromo-N-cyclohexyl-N-(2-hydroxyethyl)-1-methylcyclopropane-carboxamide (**314e**): To a stirred solution of 2-(cyclohexylamino)ethanol (158 mg, 1.10 mmol, 1.10 equiv) and triethylamine (422 μL, 308 mg, 3.00 mmol, 3.00 equiv) in dry THF (10 mL) was added (dropwise over 10 min) a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (200 mg, 1.01 mmol, 1.0 equiv) in dry THF (10 mL). The resulting suspension was stirred for 30 min at room temperature and then filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 mL). The combined organic solution was concentrated in vacuum. Preparative column chromatography of a crude residual oil on silica gel afforded the title compound as a clear oil, R_f 0.30 (hexane-EtOAc, 1:2). Yield 196 mg (0.65 mmol, 65 %).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ [3.99 (br. s.) & 3.83-3.68 (m) & 3.67-3.43 (m) & 3.39-3.25 (m), Σ5H], [3.11 (dd, *J* = 8.2 Hz, 4.9 Hz) & 2.99 (dd, *J* = 7.5 Hz, 4.7 Hz), Σ1H], [2.05 (d, *J* = 11.4 Hz) & 1.81 (br. s.) & 1.73-1.58 (m) & 1.58-1.50 (m) & 1.49-1.27 (m), Σ11H], [1.38 (s) & 1.31 (s), Σ3H], [1.22-1.00 (m) & 0.86 (dd, *J* = 6.8 Hz, 5.1 Hz, 1H), Σ2H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 173.4, 171.6, 62.6 (-), 62.5 (-), 57.4 (+), 57.2 (+), 45.5 (-), 44.8 (-), 32.6 (-), 31.9

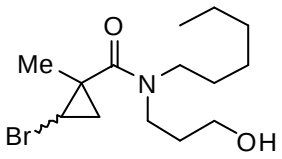
(-), 31.6 (-), 31.4 (-), 28.1, 27.0 (+), 25.8, 25.7 (-), 25.6 (-), 25.52 (-), 25.47 (-), 25.3 (+), 25.04 (-), 25.02 (-), 23.0 (-), 21.6 (+), 21.2 (-), 19.5 (+); FT IR (cm^{-1}, film): 3402, 2932, 2856, 1618, 1470, 1454, 1423, 1375, 1319, 1298, 1197, 1163, 1144, 1074, 1053, 894, 731, 623, 509; HRMS (TOF ES): found 304.0913, calculated for $C_{13}H_{23}NOBr$ (M+H) 304.0912 (0.3 ppm).



2-Bromo-N-cyclohexyl-N-(3-hydroxypropyl)-1-methylcycloprop-anecarboxamide (**314c**): To a stirred solution of 3-(cyclohexyl-amino)propan-1-ol (**4c**) (580 mg, 3.80 mmol, 1.10 equiv) and triethylamine (1.45 mL, 1.06 g, 10.5 mmol, 3.00 equiv) in dry THF (25 mL) a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (620 mg, 3.14 mmol, 0.90 equiv) in THF (20 mL) was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room temperature and then filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 ml). The combined filtrates were concentrated in vacuum. Preparative column chromatography of the residual crude oil on silica gel afforded the title compound as a yellowish crystalline solid, R_f 0.45 (hexane-EtOAc 1:1). Yield 946 mg (2.90 mmol, 85 %).

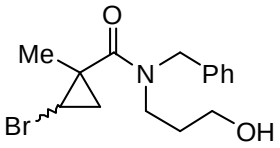
^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.96-3.76 (m, 2H), 3.61-3.38 (m, 3H), 3.34-3.22 (m, 1H), [3.13 (dd, *J* = 8.2 Hz, 4.7 Hz) & 3.02 (dd, *J* = 7.6 Hz, 4.7 Hz), Σ1H], 1.94-1.79 (m, 2H), 1.79-1.64 (m, 4H), 1.64-1.48 (m, 4H), [1.43 (s) & 1.35 (s), Σ3H], 1.48-1.42 (m, 1H), 1.41-1.33 (m, 1H), 1.13 (tt, *J* = 13.0 Hz, 3.7 Hz, 1H), 0.90 (dd, *J* = 6.6 Hz, 5.4 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ major 172.8, 59.0 (-), 57.6 (+), 37.9 (-), 33.2 (-), 32.1 (-), 31.8 (-), 27.2 (+), 26.1, 26.0 (-), 25.8 (-), 25.3 (-), 21.4 (-), 19.8 (+); minor: 170.9, 59.0 (-), 58.0 (+), 38.4 (-), 33.4 (-), 33.2 (-), 32.4 (s, 1 C), 28.5 (+), 26.0, 25.3 (-), 24.4 (-), 23.6 (-), 22.0 (-), 19.8 (+); FT IR (cm^{-1},

film): 3400, 2932, 2856, 1616, 1472, 1454, 1425, 1369, 1350, 1325, 1298, 1269, 1240, 1197, 1157, 1144, 1059, 986, 933, 897, 870, 756, 733, 623, 509; HRMS (TOF ES): found 340.0886, calculated for $C_{14}H_{24}NO_2BrNa$ (M+Na) 340.0888 (0.6 ppm);



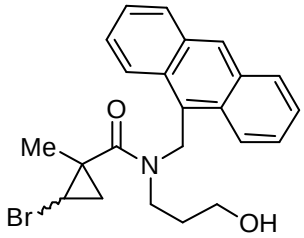
2-Bromo-N-hexyl-N-(3-hydroxypropyl)-1-methylcyclopropane-carboxamide (**314b**): To a stirred solution of 3-(hexylamino)propan-1-ol (500 mg, 3.15 mmol, 1.00 equiv) and triethylamine (1.30 mL, 950 mg, 9.50 mmol, 3.00 equiv) in dry THF (25 ml) a solution of 2-bromo-1-methylcyclopropane-carbonyl chloride (620 mg, 3.14 mmol, 0.90 equiv) in dry THF (20 mL was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room temperature and then filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 ml), and the combined filtrates were concentrated in vacuum. Preparative column chromatography of the residual crude oil on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane-EtOAc, 1:1). Yield 736 mg (2.30 mmol, 73%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.66 (br. s., 1H), 3.63-3.52 (m, 1H), 3.52-3.31 (m, 4H), 3.19 (dd, *J* = 8.2 Hz, 4.9 Hz, 1H), 1.75-1.67 (m, 3H), 1.66-1.57 (m, 2H), 1.49 (s, 3H), 1.36 (m, 7H), 0.99-0.84 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 173.2, 58.2 (-), 47.5 (-), 40.3 (-), 31.5 (-), 30.2 (-), 28.4 (-), 27.4, 26.6 (+), 26.0 (-), 22.5 (-), 21.6 (-), 19.8 (+), 13.9 (+); FT IR (cm^{-1}, film): 3410, 2934, 2874, 1614, 1497, 1472, 1454, 1427, 1379, 1358, 1325, 1298, 1271, 1236, 1184, 1078, 1057, 1030, 1001, 933, 870, 825, 739, 698, 625, 573, 544, 490, 463; HRMS (TOF ES): found 342.1043, calculated for $C_{14}H_{26}NO_2BrNa$ (M+Na) 342.1045 (0.6 ppm);



N-Benzyl-2-bromo-N-(3-hydroxypropyl)-1-methylcyclopropane-carboxamide (**314a**): To a stirred solution of 3-(benzylamino)propan-1-ol (850 mg, 5.10 mmol, 1.02 equiv) and triethylamine (2.06 mL, 1.50 g, 15.0 mmol, 3.00 equiv) in dry THF (25 mL) a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (1.0 g, 5.0 mmol, 1.0 equiv) in dry THF (20 mL) was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room temperature and filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 mL). The combined organic filtrates were concentrated in vacuum. Preparative column chromatography of a resulting crude oil on silica gel afforded the title compound as a colorless oil, R_f 0.30 (hexane-EtOAc, 1:3). Yield 1.30 g (4.00 mmol, 80%)

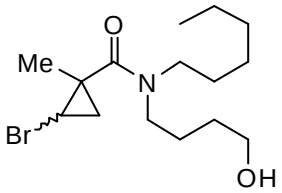
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.39-7.15 (m, 5H), [5.12 (d, *J* = 16.9 Hz) & 4.71 (d, *J* = 16.4 Hz), Σ1H], [4.66 (d, *J* = 16.4 Hz) & 4.45 (d, *J* = 16.9 Hz), Σ1H], 4.00-2.90 (m, 5H), 1.75-1.57 (m, 3H), [1.49 (s) & 1.33 (s), Σ3H], [1.21 (ps.-t, *J* = 7.3 Hz, 6.8 Hz) & 0.92 (dd, *J* = 6.8 Hz, 5.1 Hz), Σ1H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 173.5, 172.1, 135.7, 135.6, 128.9 (+, 2C), 128.8 (+, 2C), 127.7 (+), 127.5 (+), 126.6 (+, 2C), 126.5 (+, 2C), 58.3 (-), 58.2 (-), 50.4 (-, 2C), 40.9 (-), 40.7 (-), 29.3 (-), 29.2 (-), 28.0, 27.0 (+), 25.9 (+), 25.8 (+), 22.4, 21.7 (+), 21.6 (-), 19.8 (-); FT IR (cm^{-1}, film): 3400 (br), 3075, 2985, 1624, 1421, 1265, 1186, 894, 739, 704; HRMS (TOF ES): found 246.1501, calculated for $C_{15}H_{20}NO_2$ (M-Br) 246.1494 (2.8 ppm).



N-(Anthracen-9-ylmethyl)-2-bromo-N-(3-hydroxypropyl)-1-methylcyclopropanecarboxamide (**314d**): To a stirred solution of 3-

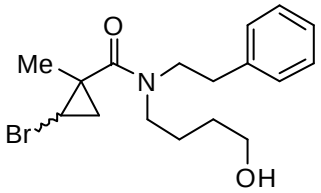
((anthracen-9-ylmethyl)amino)propan-1-ol (295 mg, 1.11 mmol, 1.11 equiv) and triethylamine (420 μL, 307 mg, 3.03 mmol, 3 equiv.) in dry THF (20 mL) was added dropwise a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (200 mg, 1.01 mmol, 1 equiv) in dry THF (10 mL). The mixture was stirred overnight, then concentrated in vacuum. The residue was quenched with brine and extracted with EtOAc (3 x 15 mL). Combined organic phases were dried with $MgSO_4$, filtered and concentrated. Preparative column chromatography of the residual crude oil on silica gel afforded the title compound as yellowish solid, R_f 0.15 and 0.35 (hexane-EtOAc 1:1). Yield 276 mg (0.65 mmol, 64%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ [8.51 (s) & 8.41 (s), Σ1H], 8.26 (d, *J* = 8.8 Hz, 2H), [8.06 (d, *J* = 8.8 Hz) & 7.98 (d, *J* = 8.1 Hz), Σ2H], 7.60-7.43 (m, 4H), [5.93 (d, *J* = 14.4 Hz) & 5.88 (d, *J* = 15.4 Hz), Σ1H], [5.72 (d, *J* = 14.4 Hz) & 5.65 (d, *J* = 15.4 Hz), Σ1H], 3.43-2.96 (m, 5H), [1.86-1.82 (m) & 1.71-1.57 (m), Σ3H], [1.82 (s) & 1.37 (s), Σ3H], [1.44 (app. t, *J* = 7.1 Hz) & 1.28 (app. t, *J* = 7.1 Hz), Σ1H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 170.5, 131.2 (2C), 130.9 (2C), 129.1 (+, 2C), 128.2 (+), 127.3, 126.3 (+, 2C), 125.0 (+, 2C), 124.3 (+, 2C), 59.9 (-), 43.1 (-), 40.3 (-), 32.1 (-), 28.3, 25.9 (+), 23.3 (s, 1 C), 21.9 (+); minor: 172.2, 131.6 (2C), 131.2 (2C), 129.5 (+, 2C), 129.2 (+), 127.0 (+, 2C), 125.1 (+, 2C), 124.4, 123.4 (+, 2C), 58.1 (-), 44.5 (-), 40.3 (-), 31.6 (-), 28.5, 25.9 (+), 23.9 (-), 21.7 (+); FT IR (cm^{-1}, film): 3397, 3053, 2957, 2932, 2876, 1718, 1672, 1626, 1614, 1429, 1377, 1285, 1229, 1173, 1159, 1095, 1055, 932, 854, 735, 700; HRMS (TOF ES): found 448.0894, calculated for $C_{23}H_{24}NO_2BrNa$ (M+Na) 448.0888 (1.3 ppm);



2-Bromo-N-hexyl-N-(4-hydroxybutyl)-1-methylcyclopropane-carboxamide (**317e**): A 25 ml round-bottomed flask was charged with 4-(hexylamino)butan-1-ol (88 mg, 0.56 mmol, 1.1 equiv), triethylamine (212 μL, 154 mg, 1.53 mmol, 3.00 equiv), and dry THF (5 mL). The mixture was stirred, and a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (100 mg, 0.51 mmol, 1.00 equiv) in THF (5 mL) was added dropwise over 5 min. The resulting suspension was stirred for 30 min at room temperature, then filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 ml). The combined filtrates were concentrated in vacuum. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.2 (Hexane-EtOAc 1:1). Yield 128 mg (0.38 mmol, 75%).

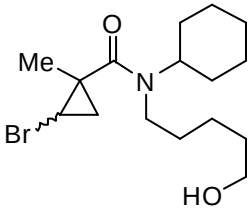
^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 3.77-3.61 (m, 2H), 3.48-3.29 (m, 3H), 3.28-3.11 (m, 2H), 2.42 (br. s, 1H), 1.71-1.43 (m, 8H), 1.45 (s, 3H), 1.41-1.31 (m, 3H), 1.28 (br. s., 2H), 0.98-0.81 (m, 4H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 171.7, 62.1 (-), 47.5 (-), 44.2 (-), 31.5 (-), 29.5 (-), 28.5 (-), 27.5 (+), 26.6 (-), 26.0, 23.6 (-), 22.5 (-, 2C), 21.4 (-), 14.0 (+); minor: 171.4, 62.1 (-), 47.0 (-), 44.4 (-), 31.5 (-), 29.9 (-), 28.5 (-), 27.7 (+), 27.0 (-), 26.0, 24.9 (-), 22.5 (-, 2C), 21.4 (-), 19.7 (+); FT IR (cm^{-1}, film): 3418, 3404, 2932, 2860, 1622, 1462, 1429, 1377, 1325, 1178, 1130, 1082, 1068, 1034, 615; HRMS (TOF ES): found 334.1388, calculated for $C_{15}H_{29}NO_2Br$ (M+H) 334.1382 (1.8 ppm);



2-Bromo-N-(4-hydroxybutyl)-1-methyl-N-phenethylcyclo-propanecarboxamide (**317d**): To a stirred solution of 4-(phenethyl-

amino)butan-1-ol (250 mg, 1.29 mmol, 1.00 equiv) and triethylamine (550 µL, 400 mg, 3.96 mmol, 3.0 equiv) in dry THF (10 ml) a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (260 mg, 1.29 mmol, 1.00 equiv) in dry THF (10 mL) was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room temperature and filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 mL). The combined filtrates were concentrated in vacuum. Preparative column chromatography o f the crude residual oil on silica gel afforded the title compound as a colorles oil, R_f 0.20 (hexane-EtOAc, 1:1). Yield 300 mg (0.85 mmol, 66%), mixture of diastereomers 1:1).

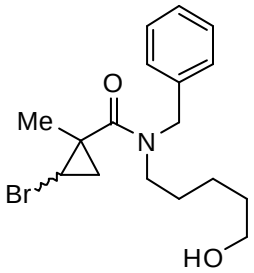
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.37-7.21 (m, 5H), 3.72-3.58 (m, 4H), 3.45-3.11 (m, 2H), 2.90-2.85 (m, 2H), 1.84 (br. s, 1H), 1.73-1.55 (m, 6H), [1.44 (s) & 1.42 (s), Σ3H], 0.90-0.84 (m, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 171.9, 171.6, 138.8, 137.6, 128.7 (+, 4C), 128.6 (+, 2C), 128.3 (+, 2C), 126.8 (+),126.3 (+), 61.9 (-), 61.8 (-), 48.8 (-), 47.5 (-), 46.1 (-), 44.1 (-), 34.5 (-), 33.2 (-), 29.7 (+), 29.4 (+), 27.4, 27.2, 25.9 (-), 25.8 (-), 24.7 (-), 23.4 (-), 21.3 (-), 21.2 (-), 19.6 (+, 2C); FT IR (cm^{-1}, film): 3416, 2935, 2870, 2361, 2341, 1622, 1454, 1427, 1171, 1068, 1032, 750, 700; HRMS (TOF ES): found 354.1060, calculated for $C_{17}H_{25}NO_2Br$ (M+H) 354.1069 (2.5 ppm);



2-Bromo-N-cyclohexyl-N-(5-hydroxypentyl)-1-methylcyclopropane-carboxamide (**317c**), mixture of diastereomers, 1.1:1. 25 ml round-bottomed flask was charged with 5-(cyclohexylamino)pentan-1-ol (122 mg, 0.66 mmol, 1.10 equiv) and triethylamine (246 µL, 179 mg, 1.77 mmol, 3.00 equiv), and dry THF (5 mL). A solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (116.5 mg, 0.59

mmol, 1.00 equiv) in THF (5 mL) was added dropwise over 5 min. The resulting suspension was stirred for 30 min at room temperature, and then filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 mL). The combined filtrates were concentrated in vacuum. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.30 (Hexane-EtOAc 1:2). Yield 143 mg (0.41 mmol, 70%).

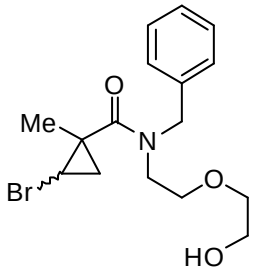
^{1}H NMR (400.13 MHz, $CDCl_3$) δ [3.85-3.70 (m) & 3.62 (t, *J* = 6.4 Hz), 3.28-3.09 (m) & 3.09-2.97 (m), Σ7H], [2.11 (d, *J* = 13.1 Hz) & 1.93-1.78 (m) & 1.78-1.66 (m) & 1.62-1.53 (m), Σ10H], [1.42 (s) & 1.34 (s), Σ3H], [1.52-1.41 (m) & 1.39-1.33 (m) & 1.27-1.23 (m) & 1.21-1.09 (m) & 0.91-0.81 (m), Σ8H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 171.2, 169.4, 62.0 (-), 61.9 (-), 57.3 (+), 57.0 (+), 42.7 (-), 42.2 (-), 32.6 (-), 32.1 (-), 31.98 (-), 31.96 (-), 31.7 (-), 31.5 (-), 28.5 (-), 28.4, 28.3 (-), 28.2 (+), 27.2 (+), 25.9 (-), 25.8 (-), 25.7 (-), 25.6 (-), 25.4, 25.2 (-), 25.1 (-), 23.3 (-), 23.3 (-), 23.0 (-), 21.8 (+), 21.1 (-), 19.5 (+); FT IR (cm^{-1}, film): 3434, 2978, 2934, 2860, 2797, 2642, 2621, 2492, 1732, 1614, 1568, 1553, 1539, 1454, 1423, 1385, 1306, 1188, 1161, 1084, 764, 613, 579, 519, 471; HRMS (TOF ES): found 368.1209, calculated for $C_{16}H_{28}BrNO_2Na$ (M+Na) 368.1201 (2.2 ppm).



N-Benzyl-2-bromo-N-(5-hydroxypentyl)-1-methylcyclopropane-carboxamide (**417a**): To a stirred solution of 5-(benzylamino)pentan-1-ol (700 mg, 3.60 mmol, 1.10 equiv) and triethylamine (1.47 mL, 1.07 g, 10.6 mmol, 3.00 equiv) in dry THF (25 mL) a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (640 mg, 3.20 mmol, 1.00 equiv) in dry THF (20 mL) was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room

temperature and filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 ml). The combined filtrates were concentrated in vacuum. Preparative column chromatography of the residual crude oil on silica gel afforded the title compound as a colorless oil, R_f 0.20 (hexane-EtOAc, 1:3). Yield 882 mg (2.50 mmol, 78%).

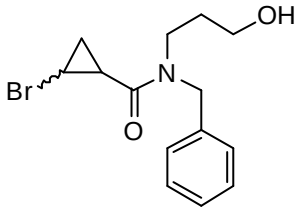
^{1}H NMR (400.13 MHz, $CDCl_3$) δ [7.47-7.34 (m) & 7.34-7.19 (m), Σ5H], [5.09 (d, *J* = 17.2 Hz) & 4.86 (d, *J* = 15.2 Hz), Σ1H], [4.50 (d, *J* = 16.9 Hz) & 4.48 (d, *J* = 15.2 Hz), Σ1H], [3.80 (dddd, *J* = 13.9 Hz, 9.6 Hz, 5.8 Hz, 1.2 Hz) & 3.57-3.51 (m), Σ1H], 3.61 (t, *J* = 6.6 Hz) & 3.57 (t, *J* = 6.6 Hz), Σ2H], [3.25 (ddd, *J* = 14.1 Hz, 11.4 Hz, 4.8 Hz) & 2.77 (ddd, *J* = 13.5 Hz, 9.8 Hz, 5.3 Hz), Σ1H], 2.95 - 3.10 (m, 1H), 2.18 (br. s., 2H), 1.87-1.72 (m, 1H), 1.72-1.46 (m, 4H), [1.41 (s) & 1.31 (s), Σ3H], 1.37-1.26 (m, 1H), 1.26-1.11 (m, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 170.7, 136.5, 128.7 (+, 2C), 127.4 (+), 126.6 (+, 2C), 62.4 (-), 50.6 (-), 45.3 (-), 32.2 (-), 27.9, 26.0 (-), 25.9 (+), 23.1 (-), 22.4 (-), 21.7 (+); minor: 170.6, 137.1, 128.3 (+, 2C), 128.0 (+, 2C), 127.1 (+), 62.3 (-), 47.5 (-), 46.7 (-), 32.2 (-), 28.0 (-), 27.9, 25.9 (+), 23.3 (-), 22.5 (-), 21.8 (+); FT IR (cm^{-1}, film): 3412, 2934, 2849, 1628, 1495, 1452, 1427, 1373, 1358, 1323, 1300, 1236, 1205, 1184, 1076, 1041, 1030, 1003, 957, 939, 735, 698, 609, 461; HRMS (TOF ES): found 376.0888, calculated for $C_{17}H_{24}NO_2BrNa$ (M+Na) 376.0888 (0.0 ppm);



N-Benzyl-2-bromo-N-(2-(2-hydroxyethoxy)ethyl)-1-methylcyclo-propanecarboxamide (**317b**): mixture of diastereomers 1.1:1. 25 mL round bottomed flask was charged with 2-(2-(benzylamino)ethoxy)ethanol (110 mg, 0.56 mmol, 1.1 equiv), triethylamine (152 mg, 1.50 mmol, 3.0

equiv) and anhydrous THF (5 mL). A solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (100 mg, 0.51 mmol, 1.0 equiv) in dry THF (5 mL) was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room temperature, and then filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 mL). The combined filtrates were concentrated in vacuum. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.25 (Hexane-EtOAc 1:1). Yield 89 mg (0.25 mmol, 50%).

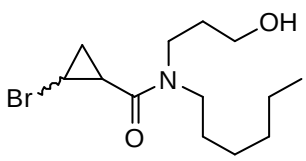
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.40-7.27 (m, 3H), 7.20-7.16 (m, 2H), [4.86-4.76 (m) & 4.52-4.45 (m), Σ2H], 3.72-3.67 (m, 2H), 3.63-3.57 (m, 2H), 3.54-3.45 (m, 4H), 3.26-3.20 (m, 1H), 2.27-2.18 (m, 1H), 1.80-1.73 (m, 1H), 1.51 (m, 3H), 0.96-0.91 (m, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 172.8 (2C), 137.2, 136.3, 128.9 (+, 2C), 128.6 (+, 2C), 127.6 (+, 4C), 126.6 (+, 2C), 72.4 (-), 72.2 (-), 68.3 (-), 67.9 (-), 61.7 (-, 2C), 51.6 (-), 47.6 (-), 46.5 (-), 44.3 (-), 28.5 (+), 27.2 (+), 26.0, 25.8, 21.6 (-, 2C), 19.7 (+, 2C); FT IR (cm^{-1}, film): 3435, 2926, 1634, 1452, 1423, 1188, 1124, 1070, 1030, 737, 698, 625, 604, 571; HRMS (TOF ES): found 356.0862, calculated for $C_{16}H_{23}BrNO_3$ (M+H) 356.0861 (0.3 ppm).



N-Benzyl-2-bromo-N-(3-hydroxypropyl)cyclopropanecarboxamide (**319c**): To a stirred solution of (3-benzylamino)propane-1-ol (550 mg, 3.3 mmol, 1.1 equiv) and triethylamine (610 mg, 6 mmol, 2 equiv) in dry THF (30 mL) was added 2-bromocyclopropanecarbonyl chloride (550 mg, 3.0 mmol). The

mixture was stirred for 1 hr at room temperature, then the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). The organic layer was separated and washed consecutively with 10% aqueous HCl (3 x 10 mL) and 4N aqueous NaOH (5 mL), dried with $MgSO_4$, filtered, and concentrated. The title compound was obtained as colorless oil, mixture of diastereomers, 2:1. This material was pure enough to be used for the following transformations without additional purification. Yield 690 mg (2.22 mmol, 74%).

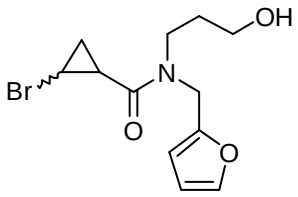
^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm [7.48-7.36 (m) & 7.36-7.27 (m) & 7.26-7.19 (m), Σ5H], [4.74 (d, *J* = 17.2 Hz) & 4.65 (d, *J* = 14.9 Hz), Σ1H], [4.66 (d, *J* = 17.4 Hz) & 4.54 (d, *J* = 14.9 Hz), Σ1H], 3.88 (br. s., 1 H), 3.71-3.42 (m, 4H), [3.30 (ddd, *J* = 7.6 Hz, 4.6 Hz, 3.0 Hz) & 3.27 (ddd, *J* = 7.8 Hz, 4.8 Hz, 3.0 Hz), Σ1H], [2.37 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.0 Hz) & 2.17 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.2 Hz), Σ1H], [1.83 (tt, *J* = 7.1 Hz, 6.1 Hz) & (1.78-1.64 (m), Σ3H], [1.37 (ddd, *J* = 9.4 Hz, 5.6 Hz, 4.8 Hz) & 1.33 (ddd, *J* = 9.1 Hz, 5.6 Hz, 4.8 Hz), Σ1H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 171.9, 136.0, 128.9 (+, 2C), 127.8 (+), 126.2 (+, 2C), 58.2 (-), 51.0 (-), 42.8 (-), 29.8 (-), 22.6 (+), 19.9 (+), 18.3 (-), minor: 170.4, 137.3, 128.4 (+, 2C), 127.9 (+, 2C), 127.3 (+), 58.9 (-), 49.0 (-), 43.9 (-), 31.5 (-), 22.3 (+), 20.2 (+), 18.1 (-); FTIR (NaCl, film, cm^1) 3387, 2930, 2874, 1620, 1450, 1215, 1055, 731, 698, 581; HRMS (TOF ES): found 334.0217, calculated for $C_{14}H_{18}NO_2BrNa$ (M+Na) 334.0419 (0.6 ppm);



2-Bromo-N-hexyl-N-(3-hydroxypropyl)cyclopropanecarboxamide (**319b**): mixture of diastereomers, 5:1. To a solution of (3-

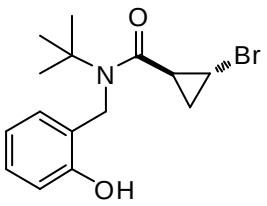
hexylamino)propan-1-ol (350 mg, 2.2 mmol, 1.1 equiv) and triethylamine (410 g, 4.0 mmol, 2.0 equiv) in dry THF (15 mL) stirred at 0 ^{o}C was added a solution of 2-bromocyclopropane-carbonyl chloride (370 mg, 2.0 mmol, 1.0 equiv.) in dry THF (15 mL). The mixture was stirred for 5 hr at RT, then the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). The organic layer was separated and washed consecutively with 10% aqueous HCl (3 x 10 mL) and 4N aqueous NaOH (5 mL), dried with $MgSO_4$, filtered, and concentrated. The title compound was obtained as colorless oil, mixture of diastereomers, 5:1. This material was pure enough to be used for the following transformations without additional purification. Yield 527 mg (1.72 mmol, 86%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.90 (br. s., 2H), [3.68 (t, *J* = 5.7 Hz) & 3.56 (sxt, *J* = 6.8 Hz) & 3.49 (td, *J* = 6.1 Hz, 2.3 Hz) & 3.44 (t, *J* = 5.3 Hz) & 3.41-3.34 (m) & 3.34-3.23 (m) & 3.20 (ddd, *J* = 7.8 Hz, 4.7 Hz, 3.2 Hz), Σ7H], [2.26 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.0 Hz) & 2.12 (ddd, *J* = 9.2 Hz, 6.0 Hz, 3.0 Hz), Σ1H], [1.85 (quin, *J* = 6.3 Hz) & 1.77-1.56 (m) & 1.56-1.43 (m), Σ5H], 1.43-1.19 (m, 7H), [0.89 (t, *J* = 7.1 Hz) & 0.86 (t, *J* = 6.8 Hz), Σ3H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 171.2, 58.0 (-), 48.2 (-), 42.6 (-), 31.3 (-), 30.2 (-), 29.4 (-), 26.4 (-), 22.5 (+), 22.4 (-), 19.9 (+), 18.1 (-), 13.9 (+); minor: 169.7, 59.0 (-), 46.7 (-), 44.7 (-), 32.0 (-), 31.5 (-), 27.6 (-), 26.5 (-), 22.4 (+), 22.3 (-), 20.2 (+), 17.8 (-), 13.9 (+); FT IR (NaCl, film, cm^{1}) 3408, 2955, 2930, 2858, 1620 1462, 1377, 1229, 1190, 1057, 725, 588; HRMS (TOF ES): found 328.0887, calculated for $C_{13}H_{24}BrNO_2Na$ (M+Na) 328.0888 (0.3 ppm);



2-Bromo-N-(furan-2-ylmethyl)-N-(3-hydroxypropyl)cyclopropanecarboxamide (**319d**): To a stirred solution of 3-((furan-2-ylmethyl)amino)propan-1-ol (282 mg, 1.81 mmol, 1.10 equiv) and triethylamine (686 µL, 500 mg, 4.95 mmol, 3.00 equiv) in dry THF (5 mL) a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (300 mg, 1.65 mmol, 1.00 equiv) in dry THF (5 mL) was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room temperature, and then filtered through a fritted funnel. The filter cake was washed with EtOAc (3 x 10 ml). Combined organic solution was concentrated in vacuum. Preparative column chromatography of a crude residue on silica gel afforded the title compound as a colorless oil, R_f 0.50 (DCM-EtOAc, 3:1). Yield 310 mg (1.02 mmol, 62%), mixture of two diastereomers, 2:1. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ [7.36 (s) & 7.29 (s), Σ1H], [6.35-6.28 (m) & 6.25 (d, *J* = 3.0 Hz) & 6.19 (d, *J* = 3.0 Hz), Σ2H], [4.59 (d, *J* = 16.9 Hz) & 4.53 (d, *J* = 15.4 Hz) & 4.53 (d, *J* = 16.9 Hz) & 4.48 (d, *J* = 15.4 Hz), Σ2H], [3.63-3.53 (m) & 3.54-3.44 (m) & 3.40 (t, *J* = 5.6 Hz) & 3.20 (ddd, *J* = 7.5 Hz, 4.7 Hz, 2.9 Hz), Σ4H], [2.35 (ddd, *J* = 9.1 Hz, 5.9 Hz, 3.2 Hz) & 2.28 (ddd, *J* = 9.1 Hz, 5.9 Hz, 3.2 Hz), Σ1H), [1.76 (quin, *J* = 6.5 Hz) & 1.69-1.55 (m), Σ3H], [1.34 (dt, *J* = 9.1 Hz, 5.6 Hz, 1H) & 1.29 (dt, *J* = 9.1 Hz, 5.3 Hz), Σ1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 171.5, 149.5, 142.6 (+), 110.3 (+), 108.2 (+), 58.0 (-), 44.7 (-), 42.8 (-), 29.8 (-), 22.6 (+), 19.7 (+), 18.1 (-); minor: 170.1, 150.6, 141.9 (+), 110.2 (+), 108.4 (+), 58.6 (-), 44.3 (-), 42.1 (-), 31.4 (-), 22.1 (+), 20.1 (+), 18.0 (-); FT IR (NaCl, film, cm^1): 3414, 3117, 2932, 2876, 2341, 1626, 1504, 1477, 1454, 1373, 1356, 1229, 1188, 1072, 1055, 1013, 922, 741, 598,

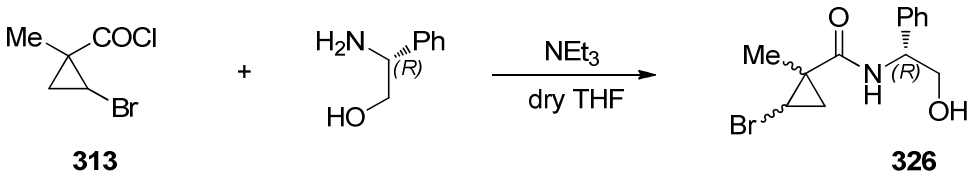
586; HRMS (TOF ES): found 302.0391, calculated for $C_{12}H_{17}NO_3Br$ (M+H) 302.0392 (0.3 ppm);

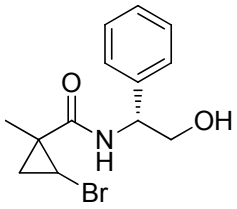


2-Bromo-N-(tert-butyl)-N-(2-hydroxybenzyl)cyclopropanecarboxamide (**319a**) A solution of Me_3SiCl (261 mg, 2.40 mmol, 1.20 equiv), NEt_3 (708 mg, 975 μL, 7.00 mmol, 3.50 equiv), and 2-((*tert*-butylamino)-methyl)phenol (394 mg, 2.20 mmol, 1.10 equiv) was stirred in dry THF (30 mL) overnight under a nitrogen atmosphere. Then cyclopropylmonobromo acid chloride (367 mg, 2 mmol, 1 equiv) was added and allowed to stir for 3 hours. The solvent was removed by rotary evaporation and then partitioned between 10 mL 5% HCl & 10 mL EtOAc. The organic layer was washed with 5% HCl (3 x 15 mL) then dried with $MgSO_4$, filtered, and concentrated. The obtained crystalline material (mp 165-168 ^oC) was pure enough for the following transformation with no additional purification. Yield 583 mg (1.78 mmol, 89%).

^1H NMR (500.13 MHz, CD_3OD) δ ppm 7.04 (d, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.67 (d, *J* = 19.2 Hz, 1H), 4.62 (d, *J* = 19.2 Hz, 1H), 3.04 (ddd, *J* = 7.6 Hz, 4.4 Hz, 3.2 Hz, 1H), 1.88 (ddd, *J* = 9.0 Hz, 6.0 Hz, 3.0 Hz, 1H), 1.41 (ddd, *J* = 7.6 Hz, 6.0 Hz, 5.0 Hz, 1H), 1.29 (s, 9H), 1.09 (dt, *J* = 9.5 Hz, 5.0 Hz, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 174.0, 155.4, 129.2 (+), 127.7 (+), 126.6, 120.8 (+), 116.0 (+), 59.3, 45.4 (-), 28.8 (+, 3C), 26.6 (+), 20.4 (+), 18.6 (-); FT IR (NaCl, film, cm^1): 3300, 2964,2930,1622,1595,1456,1427,1364, 1227, 1192, 754; HRMS (TOF ES): found 325.0670, calculated for $C_{15}H_{20}BrNO_2$ (M^+) 325.0677 (2.2 ppm).

Scheme 129. Synthesis of 326





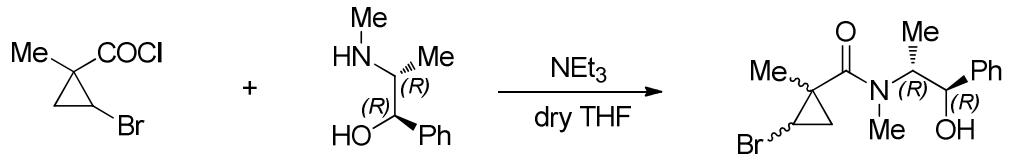
2-Bromo-*N*-((*R*)-2-hydroxy-1-phenylethyl)-1-methylcyclopropane-carboxamide: (*R*)-phenylglycinol (871 mg, 6.35 mmol) and triethylamine (2.55 mL, 1.84 g, 18.2 mmol) were stirred in anhydrous THF (20 mL) at room temperature, and a solution of racemic acylchloride **5** (1.26 g, 6.35 mmol) in dry THF (35 mL) was added dropwise. The reaction mixture was stirred for 2 hrs, followed by filtration through a Buchner funnel. The precipitate was rinsed with THF, dissolved in water and extracted with EtOAc. The organic phases were combined with THF filtrate and concentrated in vacuum. Preparative column chromatography on Silica gel eluting with hexane-EtOAc 1:1 afforded three fractions (R_f 0.38, 0.19, and 0.13; eluent hexane-EtOAc 1:3). NMR spectra were recorded for these individual fractions. For further transformation the fractions were combined to afford a mixture of four diastereomeric amides as white crystalline material, 1.74 g (5.84 mmol, 92%). HRMS (TOF ES) found 298.0439, calcd for $C_{13}H_{17}BrNO_2$ (M+H) 298.0443 (1.3 ppm).

Fraction 1: R_f 0.38 (eluent: hexane-EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.41-7.38 (m, 2H), 7.35-7.31 (m, 1H), 7.31-7.32 (m, 2H), 6.63 (br.d, *J* = 6.1 Hz, 1H), 5.05 (dt, *J* = 6.1 Hz, 5.1 Hz, 1H), 3.90 (d, *J* = 5.1 Hz, 2H), 3.55 (dd, *J* = 8.1 Hz, 5.3 Hz, 1H), 2.33 (br.s, 1H), 1.88 (dd, *J* = 8.1 Hz, 5.6 Hz, 1H), 1.58 (s, 3H), 0.95 (ps.-t, *J* = 5.6 Hz, 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 172.7, 138.8, 129.0 (+, 2C), 128.0 (+), 126.5 (+, 2C), 66.4 (-), 56.1 (+), 29.1 (+), 24.5 (-), 24.0, 17.2 (+);

Fraction 2: R_f 0.19 (eluent: hexane-EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.43-7.39 (m, 2H), 7.36-7.32 (m, 1H), 7.32-7.30 (m, 2H), 6.60 (br.d, *J* = 6.8 Hz, 1H), 5.05 (dt, *J* = 6.8 Hz, 5.1 Hz, 1H), 3.90 (d, *J* = 5.1 Hz, 2H), 3.52 (dd, *J* = 8.1 Hz, 5.3 Hz, 1H), 2.36 (br.s, 1H), 1.91 (dd, *J* = 8.1 Hz, 5.8 Hz, 1H), 1.58 (s, 3H), 0.98 (ps.t, *J* = 5.8 Hz, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 172.7, 138.7, 129.0 (+, 2C), 128.0 (+), 126.5 (+, 2C), 66.5 (-), 56.2 (+), 29.0 (+), 24.7 (-), 24.0, 17.1 (+);

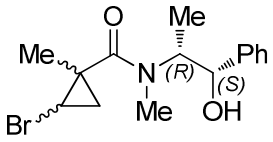
Fraction 3: R_f 0.13 (eluent: hexane-EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.40-7.29 (m, 5H), 6.58-6.56 (br.m, 1H), 5.16-5.08 (m, 1H), 3.93-3.89 (m, 2H), [2.94 (dd, *J* = 7.6 Hz, 5.1 Hz) & 2.93 (dd, *J* = 7.6 Hz, 5.1 Hz), Σ1H], 2.60 (br.s, 1H), [1.74 (dd, *J* = 6.6 Hz, 5.1 Hz) & 1.70 (dd, *J* = 6.6 Hz, 5.1 Hz), Σ1H], 1.44 (s, 3H), 1.24-1.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ [170.5 & 170.3], [138.9 & 138.8], [128.78 (+) & 128.73 (+), Σ2C], 127.8 (+), [126.8 (+) & 126.7 (+), Σ2C], 66.2 (-), [56.2 (+) & 56.0 (+)], 27.8, [25.32 (+) & 25.27 (+)], [21.6 (-) & 21.5 (-)], [20.9 (+) & 20.8 (+)].

Scheme 130. Synthesis of Pseudoephedrine analog 326



2-Bromo-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,1-dimethylcyclopropanecarboxamide (**326**): (*R,R*)-(-)-pseudoephedrine (1.00 g, 6.05 mmol) and triethylamine (2.55 mL, 1.84 g, 18.2 mmol) were stirred in anhydrous THF (20 mL) at room temperature, and solution of racemic acylchloride **5** (1.26 g, 6.35 mmol) in dry THF (35 mL) was added dropwise. The reaction mixture was stirred for 2 hrs, and then filtered through a Buchner funnel. The precipitate was rinsed with THF, dissolved in water and extracted with EtOAc. The organic phases were combined with THF filtrate and concentrated in vacuum. Preparative column chromatography on Silica gel eluting with hexane-EtOAc 1:1 (two spots are resolved: R_f 0.42, 0.29, eluent hexane-EtOAc 1:3) afforded 1.91 g (5.85 mmol, 97%) of mixture of four diastereomeric amides as colorless glass. GC: R_t 13.18 min, 13.32 min, 13.36 min (three peaks are resolved). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.55-7.28 (m, 5H), 4.78-4.14 (m, 2H), 3.75-2.98 (m, 1H), [3.07 (s) & 2.97 (s), & 2.92 (s), & 2.86 (s), Σ3H], 1.87-0.89 (m, 3H), [1.47 (s) & 1.39 (s), & 1.37 (s), & 1.35 (s), Σ3H], [1.19 (s) & 1.18 (s), & 1.17 (s), & 1.15 (s), Σ3H]; ^{13}C NMR

($CDCl_3$, 100.67 MHz) δ [173.2 & 173.0, & 172.7, & 172.2], [141.97 & 141.95, & 141.9, & 141.6], 128.4, 128.3, 128.03, 127.98, 127.9, 127.3, 127.2, 127.0, 126.3, 126.0, 125.9, 125.8, 75.4, 75.3, 74.8, 74.7, 58.3 (br), 57.64, 57.59, 56.9 (br), 32.0, 29.4, 28.1, 28.0, 27.5, 27.3, 26.9, 26.6, 26.1, 25.8, 25.70, 25.67, 25.5 21.7, 21.5, 21.2, 20.3, 20.0, 19.7, 18.3, 15.4, 15.0, 13.8, 13.7, 13.5; HRMS (TOF ES) found 326.0757, calcd for $C_{15}H_{21}BrNO_2$ (M+H) 326.0756 (0.3 ppm).

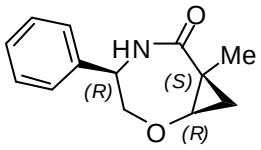


2-bromo-N-((1S,2R)-1-hydroxy-1-phenylpropan-2-yl)-N,1-dimethylcyclopropanecarboxamide (326b): D-ephedrine (500 mg, 6.05 mmol) and triethylamine (766 mg, 7.6 mmol) were stirred in anhydrous THF (20 mL) at room temperature, and solution of racemic acylchloride **5** (418mg, 2.53 mmol) in dry THF (20 mL) was added dropwise. The reaction mixture was stirred for 2 hrs, and then filtered through a Buchner funnel. The precipitate was rinsed with EtOAc, and concentrated in vacuum. Preparative column chromatography on Silica gel eluting with hexane-EtOAc 2:1 (three spots are resolved: R_f 0.43, 0.30, 0.2 eluent hexane-EtOAc 2:1) afforded 536 mg (5.85 mmol, 65%) of mixture of four diastereomeric amides as a white powder. ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.42-7.23 (m, 5H), 4.65 (d, *J* = 7.0 Hz, 1H), 4.13 (br, 1H), 3.05 (m, 1H), 2.95 (s, 3H), 1.59 (dd, *J* = 4.8 Hz, 6.95 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 100.67 MHz) δ 172.4, 142.3, 128.2 (+, 2C), 127.22 (+), 126.14 (+), 75.86 (+), 58.3 (-), 28.46, 25.95 (+), 21.86 (-), 20.34 (+), 13.96 (+); HRMS (TOF ES) found 348.0567, calcd for $C_{15}H_{20}NO_2Na$ (M + Na) 348.0575 (2.3 ppm) FT IR (cm^{-1}, film): 3382, 3226, 3045, 1633, 1384, 891, 784, 709.

^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.43-7.21 (m, 5H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.21 (br, 1H), 3.10 (s, 3H), 3.10 (dd, *J* = 4.3 Hz, 7.2 Hz, 1H), 1.59 (dd, *J* = 4.8 Hz, 6.9 Hz, 1H), 1.32 (s, 3H) 1.12 (d, *J* = 6.8 Hz, 3H), 0.99 (m, 1H) 0.86 (d, *J* = 4.8 Hz, 6.7 Hz, 1H); ^{13}C NMR (C_6D_6, 100.67 MHz) δ 171.75, 142.0, 128.4 (+, 2C), 127.72 (+), 126.59 (+), 75.83 (+), 58.02 (-) 28.36, 25.90 (+), 21.87 (-), 20.66 (+), 13.0 (+).

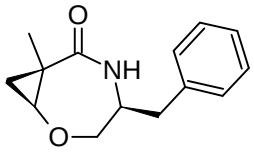
^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.45-7.22 (m, 5H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.52 (br, 1H), 3.06 (s, 3H), 2.98 (dd, *J* = 4.7 Hz, 7.4 Hz, 1H), 1.57 (dd, *J* = 4.6 Hz, 6.8 Hz, 1H), 1.35 (s, 3H) 1.13 (d, *J* = 6.9 Hz, 3H), 1.01 (m, 1H) 0.88 (d, *J* = 5.3 Hz, 6.8 Hz, 1H); ^{13}C NMR (C_6D_6, 100.67 MHz) δ 171.77, 141.9, 128.41 (+, 2C), 127.45 (+), 126.58 (+), 75.91 (+), 58.1 (-) 27.45, 25.87 (+), 21.89 (-), 20.69 (+), 14.07 (+).

3.4.4. Medium Size Ring Cyclizations



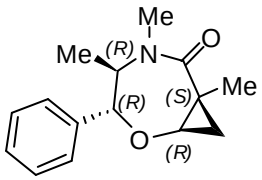
(1*R*,4*R*,7*S*)-7-methyl-4-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**327b**): A mixture of bromocyclopropane **325a** (mixture of four diastereomers, 100 mg, 0.34 mmol), 18-crown-6 (8.9 mg, 0.03 mol, 10 mol%), and potassium *tert*-butoxide (120 mg, 1.07 mmol, 3.2 equiv.) was stirred in dry THF (2.5 mL) at 80 ^{o}C overnight. The mixture was quenched with brine (10 mL) and extracted with EtOAc (3 x 10 mL). Combined organic phases were dried with $MgSO_4$, filtered and condensed in vacuum. Column chromatography on Silica gel (eluent hexane-EtOAc 1:1, R_f 0.23) afforded the title

compound as a colorless solid material, yield 51 mg (0.23 mmol, 71%). ^{1}H NMR ($CDCl_3$, 500.13 MHz) δ 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 2H), 5.91 (br.s, 1H), 5.00 (dt, *J* = 11.7 Hz, 5.4 Hz, 1H), 3.85 (dd, *J* = 11.0 Hz, 5.1 Hz, 1H), 3.66 (ps.-t, *J* = 11.4 Hz, 1H), 3.19 (dd, *J* = 6.0 Hz, 2.8 Hz, 1H), 1.34 (s, 3H), 1.22 (dd, *J* = 6.6 Hz, 2.8 Hz, 1H), 0.89 (ps.-t, *J* = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 174.1, 135.7, 129.3 (+, 2C), 128.9 (+), 127.1 (+, 2C), 71.4 (-), 56.8 (+), 55.0 (+), 26.1, 17.88 (+), 17.85 (+); HRMS (TOF ES) found 218.1181, calcd for $C_{13}H_{16}NO_2$ (M + H) 218.1181 (0.0 ppm); $[\alpha]^{25}_{D}$ = +43.2^{o} (c 0.5, CH_2Cl_2);

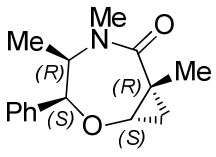


(1R,4R,7S)-4-benzyl-1-methyl-3-azabicyclo[5.1.0]octan-2-one (**327b**): A mixture of amide **325b** (100 mg, 0.32 mmol), *t*-BuOK (72 mg, 0.64 mmol, 2.0 equiv), 18-crown-6 ether (9 mg, 0.03 mmol, 10 mol%) was stirred in anhydrous THF (4 mL) at 60 ^{o}C overnight. Then the mixture was partitioned between water (10 mL) and EtOAc (10 mL), and extracted with EtOAc (3 x 5 mL). Combined organic phases were dried with Na_2SO_4, filtered and concentrated. Preparative column chromatography on Silica gel afforded the title compound as yellowish oil, R_f 0.1 (hexane-EtOAc 2:3). Yield 58 mg (0.25 mmol, 78%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 6.64 (d, *J* = 5.3 Hz, 1H), 4.22-4.12 (m, 1H), 3.69 (dd, *J* = 10.9 Hz, 4.5 Hz, 1H), 3.39 (t, *J* = 11.1 Hz, 1H), 3.02 (dd, *J* = 6.1 Hz, 2.8 Hz, 1H), 2.79 (d, *J* = 7.1 Hz, 2H), 1.28-1.23 (m, 1H), 1.20 (s, 3H), 1.12 (dd, *J* = 6.6 Hz, 2.7 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 174.9, 136.6, 128.6 (+, 4C), 126.9 (+), 70.5 (-), 56.7 (+), 51.5

(+), 36.3 (-), 26.2, 17.8 (-), 17.6 (+); HRMS (TOF ES): found 232.1335, calculated for $C_{14}H_{18}NO_2$ (M+H) 232.1338 (1.3 ppm).

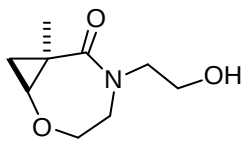


(1*R*,3*R*,4*R*,7S)-4,5,7-trimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]-octan-6-one (**328**): the mixture of bromocyclopropane **328b** (200 mg, 0.61 mmol), 18-crown-6 (16.1 mg, 0.06 mmol, 10 mol%), and potassium *tert*-butoxide (144 mg, 1.28 mmol, 2.0 equiv.) was stirred in anhydrous THF (8 mL) at room temperature for 12 hrs. The mixture was filtered and concentrated in vacuum to afford the title compound as a yellowish viscous oil. Yield 123 mg (0.50 mmol, 82%). ^{1}H NMR (C_6D_6, 400.13 MHz) δ 7.29-7.21 (m, 5H), 4.59 (dq, *J* = 10.6 Hz, 7.1 Hz, 1H), 4.22 (d, *J* = 10.6 Hz, 1H), 3.08 (dd, *J* = 6.3 Hz, 2.8 Hz, 1H), 2.87 (s, 3H), 1.47 (dd, *J* = 6.3 Hz, 2.8 Hz, 1H), 1.18 (s, 3H), 0.76 (d, *J* = 7.1 Hz, 3H), 0.63 (ps.-t, *J* = 6.3 Hz, 6.3 Hz, 1H); ^{13}C NMR (C_6D_6, 100.67 MHz) δ 172.9, 138.4, 129.0 (+, 2C), 128.58 (+), 128.55 (+, 2C), 80.2 (+), 54.0 (+), 51.4 (+), 26.9 (+), 26.5, 19.4 (-), 18.0 (+), 14.7 (+); HRMS (TOF ES) found 268.1310, calcd for $C_{15}H_{20}NO_2$ (M + H) 268.1313 (0.8 ppm). $[\alpha]^{25}_D$ = +18.6^o (c 1.32, MeOH);



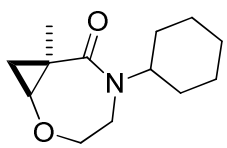
(1R,3S,4R,7S)-4,5,7-trimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**329**): the mixture of bromocyclopropane **328b** (100 mg, 0.31 mmol), 18-crown-6 (8 mg, 0.03 mmol, 10 mol%), and potassium *tert*-butoxide (72 mg, .65 mmol, 2.0 equiv.) was stirred in anhydrous THF (4 mL) at room temperature for 12 hrs. The mixture was filtered and

concentrated in vacuum. Preparative column chromatography on Silica gel afforded the title compound as white powder, R_f 0.2 (hexane-EtOAc 1:1). Yield 66 mg (0.27 mmol, 90%). ^{1}H NMR (C_6D_6, 400.13 MHz) δ 7.46-7.35 (m, 5H), 4.82 (dq, *J* = 10.8 Hz, 7.0 Hz, 1H), 4.22 (d, *J* = 10.8 Hz, 1H), 3.08 (dd, *J* = 6.2 Hz, 2.8 Hz, 1H), 2.96 (s, 3H), 1.37 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.11 (dd, *J* = 6.5 Hz, 2.8 Hz, 1H), 0.83 (ps t, *J* = 6.4 Hz); ^{13}C NMR (C_6D_6, 100.67 MHz) δ 173.7, 137.2, 129.0 (+, 2C), 128.85 (+), 128.16 (+, 2C), 80.2 (+), 53.6 (+), 51.4 (+), 27.3 (+), 26.4, 19.1 (-), 18.1 (+), 15.0 (+); HRMS (TOF ES) found 268.1310, calcd for $C_{15}H_{20}NO_2$ (M + Na) 268.1313 (1.1 ppm) FT IR (cm^{-1}, film): 3389, 2955, 1643, 1274, 763, 750.



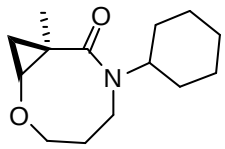
(1S*,7R*)-5-(2-Hydroxyethyl)-7-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**316d**): To a mixture of *t*-BuOK (155 mg, 1.38 mmol, 2.00 equiv), 18-crown-6 ether (18.2 mg, 0.70 mmol, 10 mol%) in THF (5 mL) was added bromocyclopropane **314d** (186 mg, 0.70 mmol, 1.00 equiv). The mixture was stirred for 1 hr at 40 ^{o}C. Then the mixture was partitioned between water (10ml) and EtOAc (10ml), and extracted with EtOAc (3 x 10 ml). The combined organic phases were dried with Na_2SO_4, filtered and concentrated. No further purification was necessary. Yield 93 mg (0.50 mmol, 72%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 4.16 (ddd, *J* = 15.4 Hz, 12.6 Hz, 5.1 Hz, 1H), 3.75-3.73 (m, 2H), 3.67 (dd, *J* = 11.1 Hz, 5.1 Hz, 1H), 3.56 (dt, *J* = 14.2 Hz, 5.8 Hz, 1H), 3.48 (dt, *J* = 14.4 Hz, 4.8 Hz, 1H), 3.22 (dd, *J* = 15.2 Hz, 4.6 Hz, 1H), 2.97 (dd, *J* = 5.8 Hz, 2.8 Hz, 1H), 1.24 (s, 3H), 1.06 (dd, *J* = 6.8 Hz, 2.8 Hz, 1H), 0.82 (ps.-t, *J* = 6.8 Hz, 5.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 174.3, 64.2 (+), 61.7 (+), 56.5 (-), 50.3 (+), 47.1 (+), 26.3, 18.1 (+), 17.8 (-); FT IR

(cm^{-1}, film): 3389, 2955, 2920, 2866, 1626, 1481, 1439, 1371, 1209, 1153, 1097, 1056, 1040, 789, 700, 660; HRMS (TOF ES): found 229.1677, calculated for $C_{12}H_{23}NO_3$ (M^+) 229.1678 (0.4 ppm);



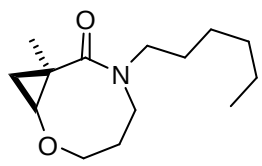
(1S*,7R*)-5-Cyclohexyl-7-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**316e**): To a mixture of *t*-BuOK (82 mg, 0.73 mmol, 2.4 equiv), 18-crown-6 ether (13.2 mg, 0.03 mmol, 10 mol%) in THF (3 mL) was added bromocyclopropane **314e** (92 mg, 0.3 mmol, 1.0 equiv). The mixture was stirred for 4 hrs at 80 ^oC. The KBr precipitate was filtered off on a fritted funnel and the solvent was removed in vacuum. Flash column chromatography of the residue through a silica plug in EtOAc afforded the title compound as a yellowish oil, Yield 60 mg (0.27 mmol, 91%).

^1H NMR (400.13 MHz, $CDCl_3$) δ ppm 4.38 (tt, *J* = 12.0 Hz, 3.6 Hz, 1H), 3.80 (ddd, *J* = 15.4 Hz, 12.6 Hz, 4.8 Hz, 1H), 3.71 (dd, *J* = 11.0 Hz, 4.9 Hz, 1H), 3.56 (ddd, *J* = 12.4 Hz, 11.1 Hz, 4.5 Hz, 1H), 3.21 (dd, *J* = 15.3 Hz, 4.7 Hz, 1H), 2.92 (dd, *J* = 6.1 Hz, 2.8 Hz, 1H), 1.83-1.60 (m, 4H), 1.44-1.22 (m, 6H), 1.20 (s, 3H), 1.09-1.02 (m, 1H), 0.80 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 172.1, 66.4 (-), 56.5 (+), 51.6 (+), 39.7 (-), 30.5 (-), 26.6, 25.5 (-), 25.32 (-), 25.29 (+), 17.8 (-); FT IR (cm^{-1}, film): 2930, 2856, 1645, 1472, 1423, 1379, 1366, 1329, 1263, 1236, 1211, 1196, 1157, 1140, 1092, 1040, 789, 665; HRMS (TOF ES): found 246.1441, calculated for $C_{13}H_{21}NO_2Na$ (M+Na) 246.1470 (2.4 ppm).



(1S*,8R*)-6-Cyclohexyl-8-methyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**316c**): To a mixture of *t*-BuOK (139 mg, 1.25 mmol, 2.5 equiv), 18-crown-6 ether (13 mg, 0.05 mmol, 10 mol%) in dry THF (5 mL) was added bromocyclopropane **314c** (160 mg, 0.5 mmol, 1.0 equiv). The mixture was stirred for 12 hrs at 80 ^{o}C. The KBr precipitate was filtered and the solvent was removed in vacuum. Preparative column chromatography on silica gel afforded the title compound as a colorless oil, R_f 0.30 (hexane-EtOAc 2:1). Yield 105 mg (0.45 mmol, 89%).

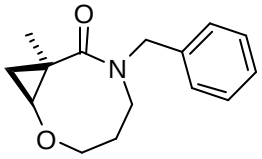
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 4.38 (ddt, *J* = 15.1 Hz, 7.7 Hz, 3.6 Hz, 1H), 4.09 (dd, *J* = 12.5 Hz, 5.2 Hz, 1H), 3.80 (dd, *J* = 15.7 Hz, 9.9 Hz, 1H), 3.61 (td, *J* = 12.7 Hz, 3.2 Hz, 1H), 3.42 (dd, *J* = 15.7 Hz, 7.3 Hz, 1H), 3.18 (dd, *J* = 7.2 Hz, 3.9 Hz, 1H), 2.02-1.84 (m, 3H), 1.84-1.54 (m, 5H), 1.51-1.28 (m, 4H), 1.18 (s, 3H), 1.12 (dd, *J* = 6.4 Hz, 3.9 Hz, 1H), 0.75 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 172.1, 72.8 (-), 67.7 (+), 53.8 (+), 41.8 (-), 33.4 (-), 31.5 (-), 30.3 (-), 27.9, 26.0 (-), 25.7 (-), 25.6 (-), 20.1 (+), 16.8 (-); FT IR (cm^{-1}, film): 2932, 2856, 2360, 2351, 1612, 1458, 1421, 1325, 1198, 1057, 986; HRMS (TOF ES): found 238.1804, calculated for $C_{14}H_{24}NO_2$ (M+H) 238.1807 (1.3 ppm);



(1S*,8R*)-6-Hexyl-8-methyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**316b**): To a mixture of *t*-BuOK (72.9 mg, 0.65 mmol, 2.0 equiv), 18-crown-6 ether (8.6 mg, 0.033 mmol, 10 mol%) in THF (3 mL) was added bromocyclopropane **314b** (103 mg, 0.33 mmol, 1.0 equiv). The mixture was stirred for 12 hrs at 80 ^{o}C. The KBr precipitate was filtered off on a fritted funnel and the solvent was removed in

vacuum. Preparative column chromatography on silica gel afforded the title compound as a clear oil, R_f 0.35 (hexane-EtOAc 1:1). Yield 65.3 mg (0.27 mmol, 84%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 4.08 (dd, *J* = 12.6 Hz, 5.3 Hz, 1H), 3.97 (dd, *J* = 15.3 Hz, 10.5 Hz, 1H), 3.93-3.78 (m, 1H), 3.61 (td, *J* = 12.7 Hz, 3.2 Hz, 1H), 3.27 (dd, *J* = 15.2 Hz, 7.1 Hz, 1H), 3.15 (dd, *J* = 7.3 Hz, 3.8 Hz, 1H), 2.73 (ddd, *J* = 13.6 Hz, 8.2 Hz, 5.9 Hz, 1H), 1.92 (dddd, *J* = 15.1 Hz, 12.7 Hz, 10.1 Hz, 5.3 Hz, 1H), 1.62 (ddd, *J* = 15.2 Hz, 7.1 Hz, 3.0 Hz, 1H), 1.58-1.46 (m, 2H), 1.26 (br. s., 6H), 1.19 (s, 3H), 1.09 (dd, *J* = 6.6 Hz, 3.8 Hz, 1H), 0.90-0.79 (m, 3H), 0.68 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 171.9, 72.6 (-), 67.5 (+), 46.1 (-), 45.7 (-), 31.5 (-), 30.5 (-), 27.4 (-), 27.3, 26.4 (-), 22.4 (-), 19.7 (+), 16.7 (-), 13.9 (+); FT IR (cm^{-1}, film): 2955, 2930, 2858, 1637, 1481, 1464, 1441, 1423, 1364, 1325, 1250, 1203, 1150, 1132, 1103, 1070, 1045, 1009, 733, 559, 500, 424; HRMS (TOF ES): found 262.1785, calculated for $C_{14}H_{25}NO_2Na$ (M+Na) 262.1783 (0.8 ppm);

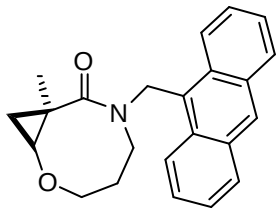


(1S*,8R*)-6-benzyl-8-methyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one

7crown-6 ether (13.2 mg, 0.05 mmol, 10 mol%) in THF (5 mL) was added bromocyclopropane **4e** (163 mg, 0.50 mmol, 1.00 equiv). The mixture was stirred for 2 hrs at 80 ^{o}C. The KBr precipitate was filtered off on a fritted funnel and the solvent was removed in vacuum. Filtration of the residue through a silica plug in EtOAc afforded the title compound as a crystalline solid, Yield 93 mg (0.38 mmol, 76%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 5.32 (d, *J* = 14.9 Hz, 1H), 4.13 (dd, *J* = 12.8 Hz, 5.4 Hz, 1H), 3.96 (dd, *J* = 15.7 Hz, 10.9 Hz, 1H), 3.90 (d, *J* = 14.9 Hz, 1H), 3.64 (td, *J* = 12.7 Hz, 3.2 Hz, 1H), 3.28-3.18 (m, 2H), 2.07-1.86 (m, 1H), 1.59 (ddd, *J* = 15.2 Hz, 7.1 Hz,

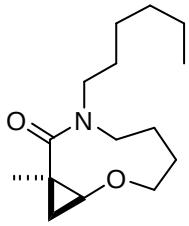
3.0 Hz, 1H), 1.29 (s, 3H), 1.21 (dd, *J* = 6.8 Hz, 3.8 Hz, 1H), 0.79 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 172.6, 137.5, 128.5 (+, 2C), 127.7 (+, 2C), 127.2 (+), 72.6 (-), 67.5 (+), 48.3 (-), 45.3 (-), 29.9 (-), 27.1, 19.7 (+), 16.8 (-); FT IR (cm^{-1}, film): 2982, 2962, 2943, 2908, 2874, 1738, 1697, 1636, 1479, 1423, 1393, 1373, 1300, 1244, 1103, 1047, 1001, 916, 849, 733, 700, 648, 635, 608, 461; HRMS (TOF ES): found 246.1490, calculated for $C_{15}H_{20}NO_2$ (M+H) 246.1494 (1.6 ppm).



(1S*,8R*)-6-(Anthracen-9-ylmethyl)-8-methyl-2-oxa-6-azabi-cyclo[6.1.0]nonan-7-one (**316d**): To a stirred suspension of *t*-BuOK (62 mg, 0.55 mmol, 2.5 equiv), 18-crown-6 (6.0 mg, 22 μmol, 10 mol%) in anhydrous THF (3 mL) was added bromocyclopropane **314d** (94 mg, 0.22 mmol, 1.0 equiv). The resulting dark-brown mixture was stirred for 6 hrs at 60 ^{o}C. The KBr precipitate was filtered off and the filtrate was concentrated in vacuum. Preparative column chromatography of a residue on silica gel afforded the title compound as an orange solid, R_f 0.20 (hexane-EtOAc 1:1). Yield 70.0 mg (0.20 mmol, 92%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.48 (s, 1H), 8.33 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.55 (ddd, *J* = 8.4 Hz, 6.6 Hz, 1.5 Hz, 2H), 7.49 (dd, *J* = 7.3 Hz, 6.8 Hz, 2H), 6.33 (d, *J* = 15.2 Hz, 1H), 5.10 (d, *J* = 15.2 Hz, 1H), 4.12 (dd, *J* = 12.6 Hz, 5.1 Hz, 1H), 3.64 (dd, *J* = 15.5 Hz, 10.0 Hz, 1H), 3.56 (td, *J* = 12.9 Hz, 3.0 Hz, 1H), 3.20 (dd, *J* = 7.2 Hz, 3.7 Hz, 1H), 2.91 (dd, *J* = 15.7 Hz, 7.3 Hz, 1H), 2.23-2.09 (m, 1H), 1.48 (dd, *J* = 16.5 Hz, 6.9 Hz, 1H), 1.37 (dd, *J* = 6.6 Hz, 3.8 Hz, 1H), 1.14 (s, 3H), 0.83 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 172.6, 131.5 (2C), 131.4 (2C), 129.2 (+, 2C), 128.24 (+), 128.17, 126.5 (+, 2C), 125.1 (+, 2C), 124.0 (+,

2C), 72.7 (-), 67.7 (+), 43.3 (-), 39.1 (-), 30.5 (-), 27.9, 19.5 (+), 16.8 (-); FT IR (cm^{-1}, film): 2957, 2928, 2868, 1634, 1445, 1423, 1362, 1312, 1244, 1202, 1188, 1146, 1109, 1070, 966, 928, 891, 854, 762, 737; HRMS (TOF ES): found 346.1806, calculated for $C_{23}H_{24}NO_2$ (M+H) 346.1807 (0.3 ppm).

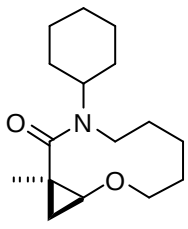


(1S*,9R*)-7-Hexyl-9-methyl-2-oxa-7-azabicyclo[7.1.0]decan-8-one (**318e**): To a mixture of *t*-BuOK (65.1 mg, 0.56 mmol, 2.00 equiv), 18-crown-6 ether (8 mg, 0.03 mmol, 10 mol%) in THF (3 mL) was added bromocyclopropane **317e** (92.2 mg, 0.29 mmol, 1.00 equiv). The mixture was stirred for 3 hrs at 80 ^oC. The KBr precipitate was filtered off on a fritted funnel and the solvent was removed in vacuum. Preparative column chromatography on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane-EtOAc 1:1). Yield 97.0 mg (0.24 mmol, 84%).

^1H NMR (400.13 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 12.8 Hz, 7.2 Hz, 1H), 4.11 (td, *J* = 13.9 Hz, 2.8 Hz, 1H), 3.86 (m, *J* = 14.0 Hz, 8.2 Hz, 7.8 Hz, 0.8 Hz, 1H), 3.35 (dd, *J* = 14.1 Hz, 4.3 Hz, 1H), 3.28 (dd, *J* = 12.8 Hz, 6.7 Hz, 1H), 3.11 (dd, *J* = 7.1 Hz, 3.5 Hz, 1H), 2.77 (ddd, *J* = 13.7 Hz, 8.8 Hz, 5.3 Hz, 1H), 2.01-1.90 (m, 1H), 1.84-1.70 (m, 2H), 1.66-1.38 (m, 4H), 1.35-1.26 (m, 6H), 1.21 (s, 3H), 1.23 (dd, *J* = 6.4 Hz, 3.7 Hz, 1H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.72 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 171.6, 71.6 (-), 65.7 (+), 43.5 (-), 42.5 (-), 31.5 (-), 27.7, 27.3 (-), 26.8 (-), 26.5 (-), 25.4 (-), 22.6 (-), 20.3 (+), 17.0 (-), 14.0 (+); FT IR (cm^{-1}, film): 2953, 2930, 2870, 1636, 1468, 1427, 1194, 1159, 1099; HRMS (TOF ES): found 276.1937, calculated for $C_{15}H_{27}NO_2Na$ (M+Na) 276.1939 (0.7 ppm).

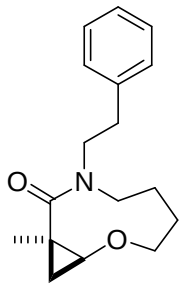
(1S,9R)-9-methyl-7-phenethyl-2-oxa-7-azabicyclo[7.1.0]decan-8-one (**318d**): To a mixture of *t*-BuOK (62.7 mg, 0.56 mmol, 2.00 equiv), 18-crown-6 ether (7.4 mg, 0.028 mmol, 10 mol%) in THF (3 mL) was added bromocyclopropane **317d** (100 mg, 0.28 mmol, 1.00 equiv). The mixture was stirred for 6 hrs at 60 ^{o}C. The KBr precipitate was filtered off on a fritted funnel and the filtrate was concentrated in vacuum. Preparative column chromatography on silica gel afforded the title compound as a colorless oil, R_f 0.36 (hexane-EtOAc 1:1). Yield 65.0 mg (0.24 mmol, 86%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 4.17 (dd, *J* = 12.8 Hz, 6.9 Hz, 1H), 4.13-4.05 (m, 1H), 4.00 (td, *J* = 14.0 Hz, 2.9 Hz, 1H), 3.24 (dd, *J* = 12.8 Hz, 6.9 Hz, 1H), 3.09 (dd, *J* = 6.8 Hz, 3.3 Hz, 1H), 3.12-3.04 (m, 1H), 3.04-2.94 (m, 2H), 2.90-2.81 (m, 1H), 2.01-1.86 (m, 1H), 1.81-1.71 (m, 1H), 1.49-1.31 (m, 2H), 1.24 (dd, *J* = 6.6 Hz, 3.5 Hz, 1H), 1.13 (s, 3H), 0.71 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 171.7, 139.3, 128.8 (+, 2C), 128.3 (+, 2C), 126.2 (+), 71.5 (-), 65.6 (+), 44.3 (-), 44.2 (-), 33.2 (-), 27.6, 27.3 (-), 25.3 (-), 20.1 (+), 16.8 (-); FT IR (cm^{-1}, film): 3084, 3024, 2932, 2870, 2359, 1637, 1468, 1441, 1425, 1362, 1280, 1192, 1167, 1099, 1047, 983, 748, 702, 505; HRMS (TOF ES): found 296.1618, calculated for $C_{17}H_{23}NO_2Na$ (M+Na) 296.1626 (2.7 ppm);

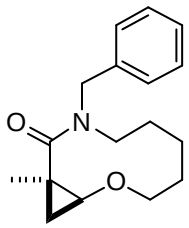


(1S*,10R*)-8-cyclohexyl-10-methyl-2-oxa-8-azabicyclo[8.1.0]undecan-9-one (**318c**): To a mixture of *t*-BuOK (67.3 mg, 0.60 mmol, 2.00 equiv), 18-crown-6

ether (8 mg, 0.03 mmol, 10 mol%) in THF (3 mL) was added bromocyclopropane **317c** (104 mg, 0.30 mmol, 1.00 equiv). The mixture was stirred overnight at 80 ^{o}C. The KBr precipitate was filtered off on a fritted funnel and the filtrate was concentrated in vacuum. Preparative column chromatography on silica gel afforded the title compound as a colorless oil, R_f 0.25 (hexane-EtOAc 1:1). Yield 69.3 mg (0.42 mmol, 87%).



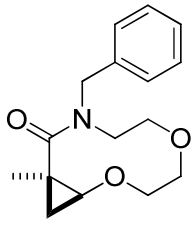
^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 3.94 (ddd, *J* = 14.4 Hz, 11.4 Hz, 4.9 Hz, 1H), 3.85 (ddd, *J* = 11.2 Hz, 7.6 Hz, 3.7 Hz, 1H), 3.70-3.60 (m, 2H), 3.26 (ddd, *J* = 14.2 Hz, 4.9 Hz, 3.4 Hz, 1H), 3.06 (dd, *J* = 7.6 Hz, 4.3 Hz, 1H), 1.97-1.79 (m, 4H), 1.78-1.54 (m, 6H), 1.40 (dd, *J* = 6.6 Hz, 4.6 Hz, 1H), 1.47-1.23 (m, 5H), 1.20 (s, 3H), 1.22-1.07 (m, 1H), 0.68 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 172.1, 70.4 (-), 65.6 (+), 57.4 (+), 43.7 (-), 30.9 (-), 30.0 (-), 28.6, 27.9 (-), 26.9 (-), 26.4 (-), 26.3 (-), 25.8 (-), 21.4 (+), 17.7 (-), 17.2 (-); FT IR (cm^{-1}, film): 2930, 2854, 1630, 1448, 1420, 1367, 1360, 1327, 1306, 1259, 1192, 1173, 1148, 1136, 1105, 1051, 1020, 785, 710, 503; HRMS (TOF ES): found 288.1944, calculated for $C_{16}H_{27}NO_2Na$ (M+Na) 288.1939 (1.7 ppm);



(1S*,10R*)-8-Benzyl-10-methyl-2-oxa-8-azabicyclo[8.1.0]undecan-9-one (**318a**): To a mixture of *t*-BuOK (140 mg, 1.25 mmol, 2.50 equiv), 18-crown-6 ether (13.2 mg, 0.05 mmol, 10 mol%) in THF (3 mL) was added bromocyclopropane **317a** (177 mg, 0.50 mmol, 1.00 equiv). The mixture was stirred for 4 hrs at 80 ^{o}C. The KBr precipitate was filtered off on a fritted funnel and the solvent

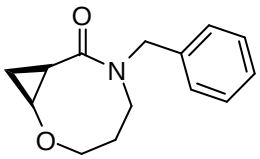
was removed in vacuum. Preparative column chromatography on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane-EtOAc 1:3). Yield 97 mg (0.35 mmol, 70%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.37-7.30 (m, 2H), 7.30-7.22 (m, 3H), 5.53 (d, *J* = 14.9 Hz, 1H), 3.98 (td, *J* = 13.1 Hz, 4.6 Hz, 1H), 3.92 (td, *J* = 6.3 Hz, 4.3 Hz, 1H), 3.72 (d, *J* = 14.9 Hz, 1H), 3.66 (ddd, *J* = 11.3 Hz, 8.8 Hz, 2.8 Hz, 1H), 3.12 (dd, *J* = 7.6 Hz, 4.3 Hz, 1H), 3.10 (ddd, *J* = 13.9 Hz, 5.2 Hz, 2.1 Hz, 1H), 2.07-1.93 (m, 1H), 1.82-1.70 (m, 1H), 1.49 (dd, *J* = 6.6 Hz, 4.3 Hz, 1H), 1.58-1.38 (m, 3H), 1.27 (s, 3H), 1.34 - 1.22 (m, 1H), 0.78 (dd, *J* = 7.3 Hz, 6.6 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 172.5, 137.3, 128.5 (+, 2C), 127.9 (+, 2C), 127.1 (+), 70.2 (-), 65.3 (+), 45.4 (-), 43.5 (-), 27.8, 27.4 (-), 24.7 (-), 20.7 (+), 17.3 (-), 16.3 (-); FT IR (cm^{-1}, film): 3026, 2930, 2874, 1630, 1441, 1425, 1356, 1236, 1192, 1150, 1105, 1051, 1032, 739, 700; HRMS (TOF ES): found 296.1621, calculated for $C_{17}H_{23}NO_2Na$ (M+Na) 296.1626 (1.7 ppm).



(1S*,10R*)-8-Benzyl-10-methyl-2,5-dioxa-8-azabicyclo[8.1.0]undecan-9-one (**318b**): To a mixture of *t*-BuOK (37 mg, 0.33 mmol, 2.5 equiv), 18-crown-6 (3.5 mg, 13 μmol, 10 mol%) in THF (2 mL) was added bromocyclopropane **317b** (49 mg, 0.13 mmol, 1.0 equiv). The resulting mixture was stirred at 50 ^{o}C for 12 hrs. The KBr precipitate was filtered off and the filtrate was concentrated in vacuum. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.20 (hexane-EtOAc 1:1). Yield 29 mg (0.10 mmol, 80%).

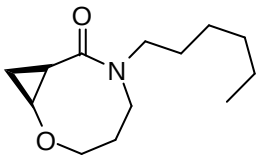
^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.35-7.30 (m, 2H), 7.29-7.23 (m, 3H), 5.44 (d, *J* = 15.4 Hz, 1H), 4.35-4.21 (m, 1H), 4.04-3.90 (m, 3H), 3.76-3.62 (m, 3H), 3.29 (d, *J* = 12.3 Hz, 1H), 3.15 (dd, *J* = 7.3 Hz, 4.1 Hz, 1H), 2.98 (br. s., 1H), 1.73 (dd, *J* = 6.6 Hz, 4.1 Hz, 1H), 1.34 (s, 3H), 0.76 (dd, *J* = 7.3 Hz, 6.6 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 172.0, 137.5, 128.6 (+, 2C), 127.8 (+), 127.2 (+, 2C), 70.0 (-), 66.8 (-), 65.3 (+), 64.7 (-), 47.1 (-), 44.4 (-), 27.5, 21.2 (+), 18.4 (-); FT IR (cm^{-1}, film): 2957, 2922, 2860, 2359, 2339, 2330, 1634, 1448, 1425, 1263, 1146, 1115, 741, 698; HRMS (TOF ES): found 298.1422, calculated for $C_{16}H_{21}NO_3Na$ (M+Na) 298.1422 (1.0 ppm).



(1S*,8R*)-6-Benzyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**320c**): An oven-dried 50 mL round bottom flask was charged with bromocyclopropane **319c** (140 mg, 0.45 mmol, 1.0 equiv), 18-crown-6 (11.8 mg, 0.045 mmol, 10 mol%), KOH (88 mg, 1.57 mmol, 3.5 equiv) and anhydrous THF (10 mL). The mixture was stirred at RT for 2.25 hrs. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography on silica gel (R_f 0.28, eluent EtOAc) to obtain a title compound as a colorless crystalline solid, mp 51-55 ^{o}C. Yield 91 mg (0.40 mmol, 88%)

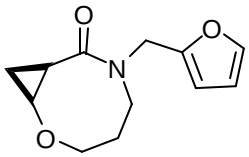
^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.29-7.23 (m, 2H), 7.23-7.17 (m, 3H), 5.24 (d, *J* = 14.8 Hz, 1H), 3.85 (d, *J* = 15.1 Hz, 1H), 3.60 (td, *J* = 12.8 Hz, 3.2 Hz, 1H), 3.45 (ddd, *J* = 6.9 Hz, 6.1 Hz, 4.1 Hz, 1H), 3.17 (dd, *J* = 15.4 Hz, 6.9 Hz, 1H), 1.96 - 1.80 (m, 1H), 1.63 (dt, *J* = 10.2 Hz, 6.5 Hz, 1H), 1.53 (ddd, *J* = 15.2 Hz, 7.2 Hz, 3.2 Hz, 1H), 1.17 (td, *J* = 6.9 Hz, 3.9 Hz, 1H), 1.03

(dt, *J* = 10.2 Hz, 7.1 Hz, 1H); ^{13}C NMR (125.76 MHz, CD_3Cl) δ 169.7, 137.5, 128.5 (+, 2C), 128.1 (+, 2C), 127.3 (+), 72.8 (-), 61.0 (+), 48.6 (-), 46.0 (-), 30.1 (-), 22.7 (+), 10.5 (-); FTIR (NaCl, film, cm^1) 2928, 2870, 1634, 1481, 1439, 1229, 1080, 735, 698; HRMS (TOF ES): found 232.1332, calculated for $C_{14}H_{18}NO_2$ (M+H) 232.1338 (2.6 ppm).



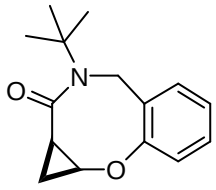
(1S*,8R*)-6-Hexyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**320b**): An oven-dried 50 mL round bottom flask was charged with bromocyclopropane **319b** (165 mg, 0.53 mmol, 1.0 equiv), 18-crown-6 (14 mg, 0.053 mmol, 10 mol%), KOH (74 mg, 1.33 mmol, 2.5 equiv.) and anhydrous THF (10 mL). The mixture was stirred at RT for 2.25 hrs. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography on silica gel, eluting first with mixture EtOAc/hexane 3:1, and then with mixture EtOAc/MeOH 3:1, to obtain a title compound as a colorless amorphous solid, R_f 0.83 EtOAc/MeOH 3:1. Yield 107 mg (90%, 0.48 mmol).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 4.22-4.06 (m, 2H), 3.88 (dddd, *J* = 13.4 Hz, 8.1 Hz, 6.6 Hz, 1.0 Hz, 1H), 3.66 (td, *J* = 12.7 Hz, 3.2 Hz, 1H), 3.48 (td, *J* = 6.7 Hz, 4.0 Hz, 1H), 3.28 (dd, *J* = 15.3 Hz, 6.9 Hz, 1H), 2.76 (ddd, *J* = 13.9 Hz, 8.8 Hz, 5.6 Hz, 1H), 2.02-1.86 (m, 1H), 1.71-1.43 (m, 4H), 1.13-1.21 (m, 6H), 1.15 (td, *J* = 6.8 Hz, 3.8 Hz, 1H), 1.03 (dt, *J* = 10.2 Hz, 7.0 Hz, 1H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.1, 72.8 (-), 61.0 (+), 46.8 (-), 45.9 (-), 31.6 (-), 30.7 (-), 27.6 (-), 26.6 (-), 22.9 (+), 22.6 (-), 14.0 (+), 10.3 (-); FTIR (NaCl, film, cm^1) 2955, 2930, 2858, 1626, 1485, 1462, 1373, 1225, 1095, 725; HRMS (TOF ES): found 226.1807, calculated for $C_{13}H_{24}NO_2$ (M+H) 226.1807 (0.0 ppm).



(1S*,8R*)-6-(Furan-2-ylmethyl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**320d**): To a stirred suspension of powdered KOH (46 mg, 0.83 mmol, 2.5 equiv) and 18-crown-6 ether (8.7 mg, 0.033 mmol, 10 mol%) in dry THF (3 mL) was added bromocyclopropane **320d** (100 mg, 0.33 mmol, 1.0 equiv). The mixture was vigorously stirred at 25 ^{o}C for 3 hrs. The KBr precipitate was filtered off on a fritted funnel and the filtrate wa concentrated in vacuum. Preparative column chromatography of a residual oil on silica gel afforded the title compound as a crystalline solid, R_f 0.30 (CH_2Cl_2-EtOAc, 3:1). Yield 69 mg (0.31 mmol, 95%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.37 (d, *J* = 1.0 Hz, 1H), 6.37-6.31 (m, 1H), 6.29 (d, *J* = 3.3 Hz, 1H), 5.06 (d, *J* = 15.4 Hz, 1H), 4.22-4.08 (m, 2H), 3.68 (td, *J* = 12.6 Hz, 3.3 Hz, 1H), 3.55-3.48 (m, 1H), 3.41 (dd, *J* = 15.4 Hz, 6.8 Hz, 1H), 1.95-1.80 (m, 1H), 1.74-1.59 (m, 3H), 1.22 (td, *J* = 6.9 Hz, 3.9 Hz, 1H), 1.08 (dt, *J* = 10.2 Hz, 6.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.5, 151.0, 142.1 (+), 110.5 (+), 108.6 (+), 72.8 (-), 60.9 (+), 46.4 (-), 41.7 (-), 30.2 (-), 22.7 (+), 10.4 (-); FT IR (NaCl, film, cm^1): 3115, 2959, 2932, 2872, 1728, 1634, 1504, 1479, 1464, 1423, 1393, 1362, 1337, 1281, 1248, 1225, 1200, 1165, 1148, 1121, 1107, 1080, 1041, 1011, 982, 964, 932, 885, 833, 762, 743, 600, 540, 417; HRMS (TOF ES): found 222.1129, calculated for $C_{12}H_{16}NO_3$ (M+H) 222.1130 (0.5 ppm).



(1aR*,9aS*)-3-(tert-Butyl)-1,3,4,9a-tetrahydrobenzo[b]cyclopropa[g]-[1,5]oxazocin-2(1aH)-one (**320a**): An oven-dried 50 mL round bottom flask was charged with bromocyclopropane **319b** (184mg, 0.56 mmol, 1 equiv), 18-crown-6 (14.9 mg, 0.056 mmol, 10 mol%), KOH (78.6 mg, 1.4 mmol, 2.5 equiv.) and anhydrous

THF (15 mL). The mixture was stirred at 50 ^{o}C for 12 hrs. The solvent was removed by rotary evaporation. The residue was absorbed onto silica gel and then purified by flash column chromatography on silica gel being flushed (eluent EtOAc/hexane 1:2 R_f :.3 product). Yield 129 mg (93%, 0.52 mmol) clear crystalline solid, mp 115-116 ^{o}C.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.24 (td, *J* = 7.6 Hz, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.6 Hz, 1.5 Hz, 1H), 7.09-7.03 (m, 2H), 5.59 (d, *J* = 17.2 Hz, 1H), 4.35 (d, *J* = 16.9 Hz, 1H), 3.79 (td, *J* = 6.2 Hz, 3.0 Hz, 1H), 2.22 (dt, *J* = 10.1 Hz, 6.3 Hz, 1H), 1.41 (td, *J* = 6.9 Hz, 3.2 Hz, 1H), 1.35 (s, 9H), 1.15 (dt, *J* = 10.1 Hz, 6.7 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.9, 157.5, 130.8 (+), 128.9 (+), 128.7, 123.6 (+), 121.8 (+), 57.7, 56.9 (+), 48.9 (-), 28.5 (+, 3C), 26.6 (+), 10.4 (-); FT IR (NaCl, film, cm^{1}): 3456, 2993, 2966, 2924, 1651, 1489, 1408, 1358, 1225, 1194, 1111, 754; HRMS (TOF ES): found 268.1311, calculated for $C_{15}H_{19}NO_2Na$ (M+Na) 268.1313 (0.7 ppm).

3.5. Assignment of Relative Configurations

3.5.1 Assignment of relative configurations for compounds 316d, 318d, and 318c

^{1}H NOE DIFF experiments unambiguously confirmed *cis*-configurations of cyclopropane moiety in representative products, obtained in 8-*exo*-*trig* (**316d**), 9-*exo*-*trig* (**318d**), and 10-*exo*-*trig* (**318c**) cyclizations. The corresponding spectral charts and 3D molecular structures showcasing the significant NOE responses are shown below. In each case NOE responses have

been detected between the corresponding methyl group and a set of two hydrogen atoms in cyclopropane, one of them being a deshielded proton next to ethereal oxygen. Relative configurations of the products obtained in *exo-trig* cyclizations were assigned by analogy.

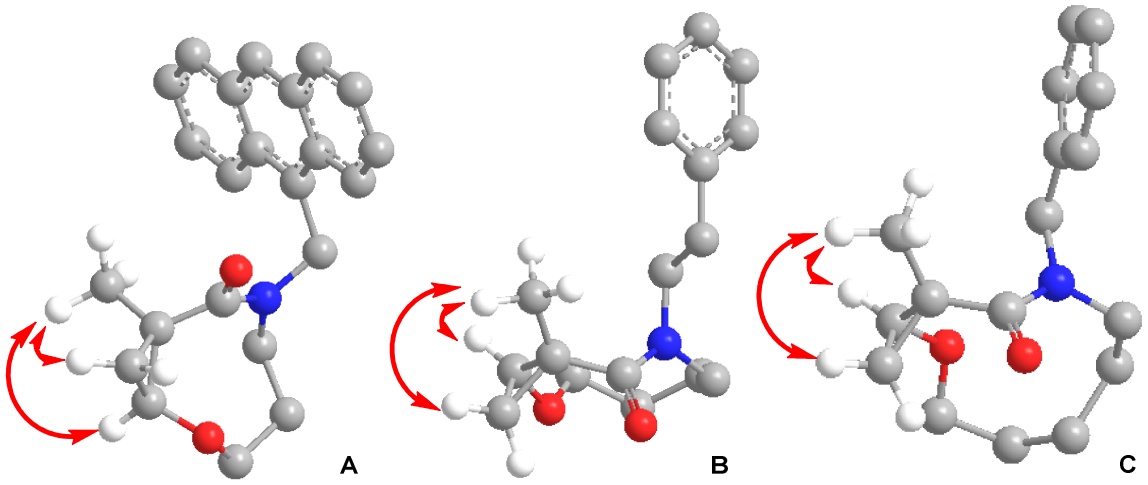


Figure 19. MM2-Optimized 3D molecular structures of three cyclization products: **316d** (A), **318d** (B), and **318c** (C). NOE responses, imperative for the assignment of the relative configuration are shown as red arrows connecting the corresponding hydrogen atoms.

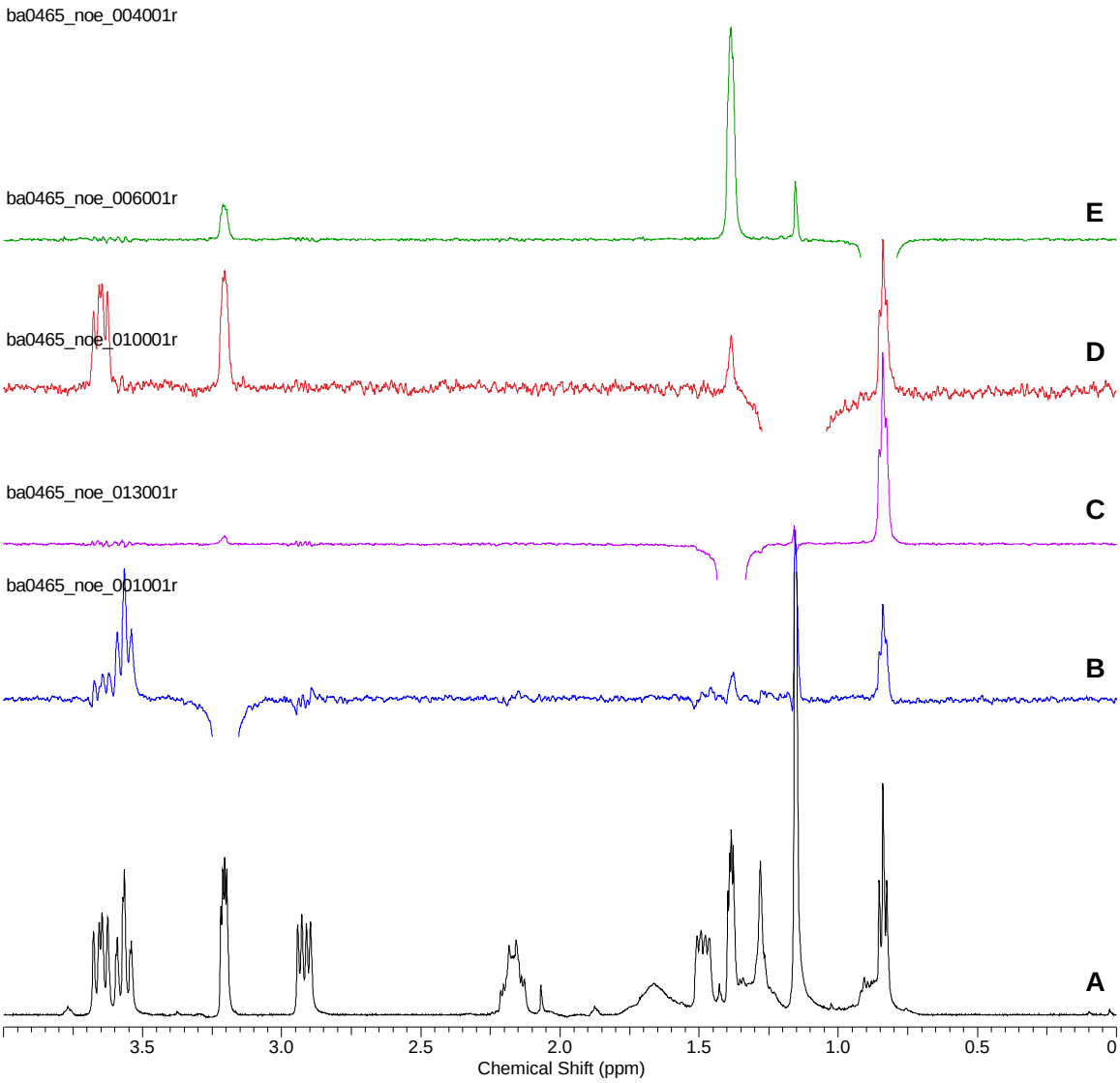


Figure 20. NOE experiments performed for compound **316d** All spectra were registered at 500.13 MHz. The charts represent: (A) – reference ^{1}H NMR spectrum; (B) NOE DIFF experiment with excitation at 3.21 ppm and mixing time 100 ms; (C) - NOE DIFF experiment with excitation at 1.39 ppm and mixing time 1.0 s; (D) - NOE DIFF experiment with excitation at 1.16 ppm and mixing time 500 ms; (E) - NOE DIFF experiment with excitation at 0.84 ppm and mixing time 1 s.

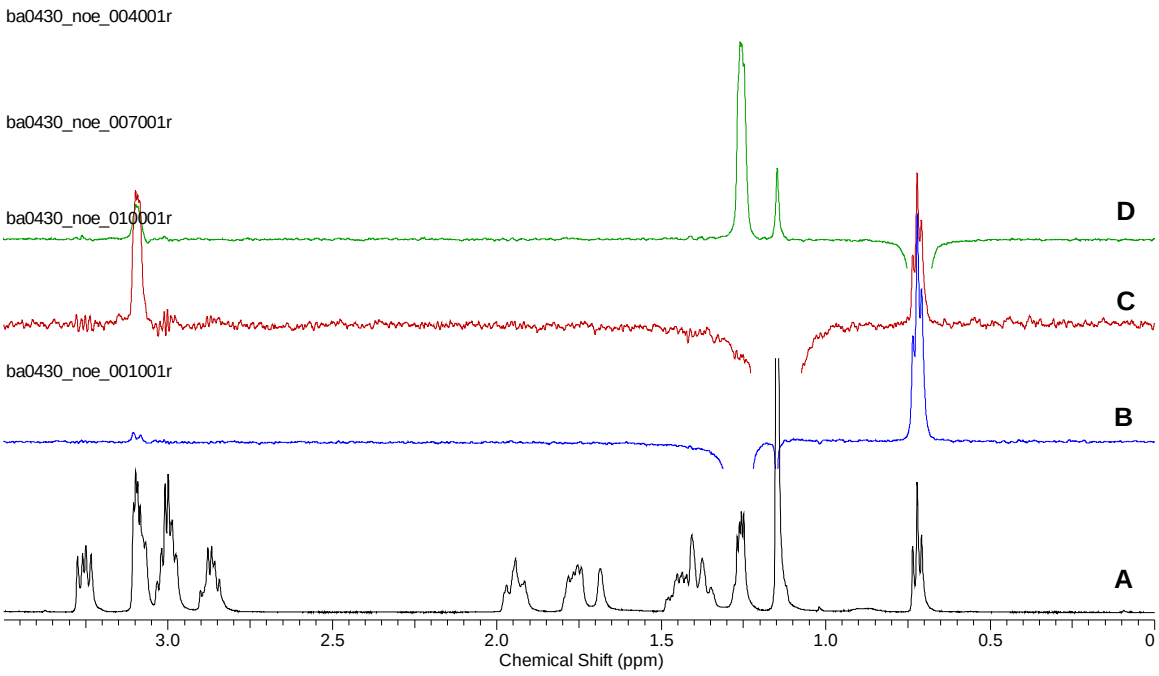


Figure 21. NOE experiments performed for compound **318d**. All spectra were registered at 500.13 MHz. The charts represent: (A) – reference 1H NMR spectrum; (B) – NOE DIFF experiment with excitation at 1.26 ppm and mixing time 1 s; (C) - NOE DIFF experiment with excitation at 1.15 ppm and mixing time 1.0 s; (D) - NOE DIFF experiment with excitation at 0.72 ppm and mixing time 1 s.

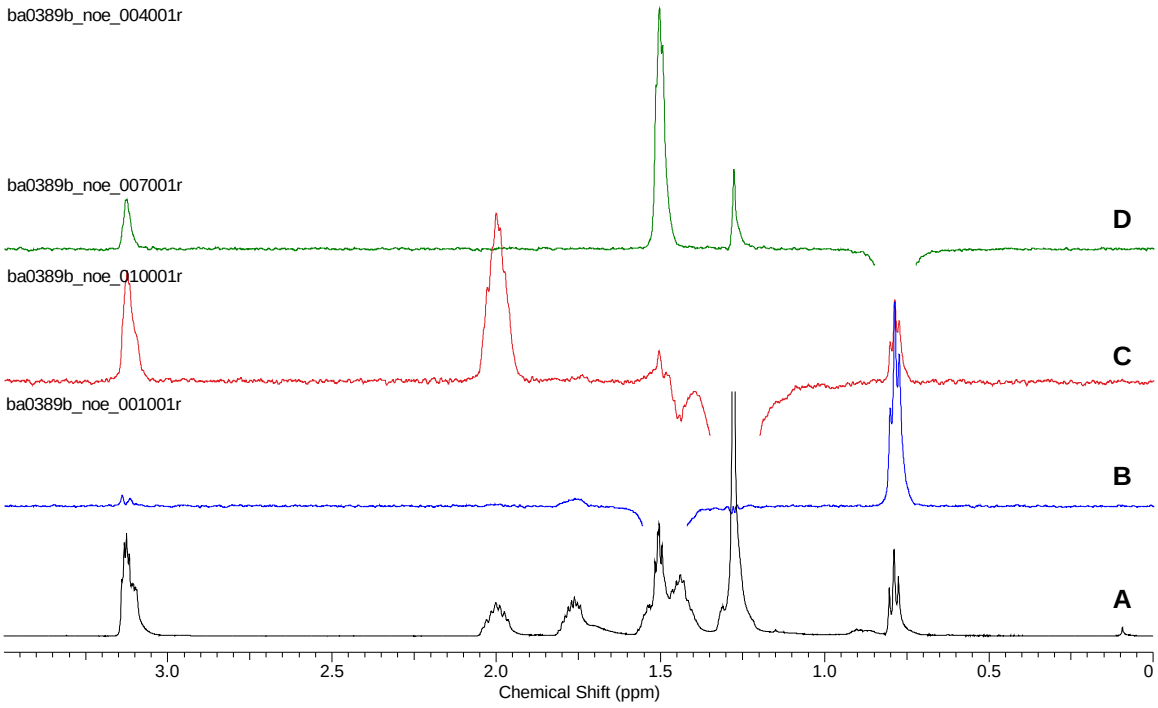
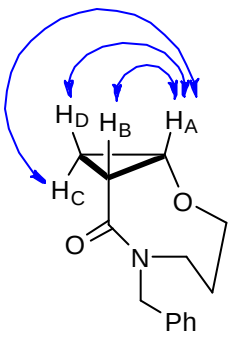


Figure 22. NOE experiments performed for compound **318c**. All spectra were registered at 500.13 MHz. The charts represent: (A) – reference ^{1}H NMR spectrum; (B) – NOE DIFF experiment with excitation at 1.51 ppm and mixing time 1 s; (C) - NOE DIFF experiment with excitation at 1.28 ppm and mixing time 1.0 s; (D) - NOE DIFF experiment with excitation at 0.79 ppm and mixing time 1 s.



$^{3}J_{cis}$ (AB) = 6.94 Hz
$^{3}J_{trans}$ (AD) = 6.10 Hz
$^{3}J_{trans}$ (AC) = 4.10 Hz

Relative configurations of all the products obtained in 8-endo-trig cyclizations were assigned based on analysis of the coupling constants in the multiplets corresponding to the cyclopropyl methine nex to ethereal oxygen. Signal at 3.45 ppm in the 1H NMR

spectrum of compound **316c** is the representative example that is discussed below. Coupling constant values were determined by multiplete simulation using ACD/SpecManager 11.01 (Figure 23). The observation of two *cis*-^{3}J coupling constants (6.94 Hz, 6.10 Hz) and only one *trans*-^{3}J coupling constant (4.10 Hz) allowed for unambiguous assignment of the *cis*-configuration to product **316c**.

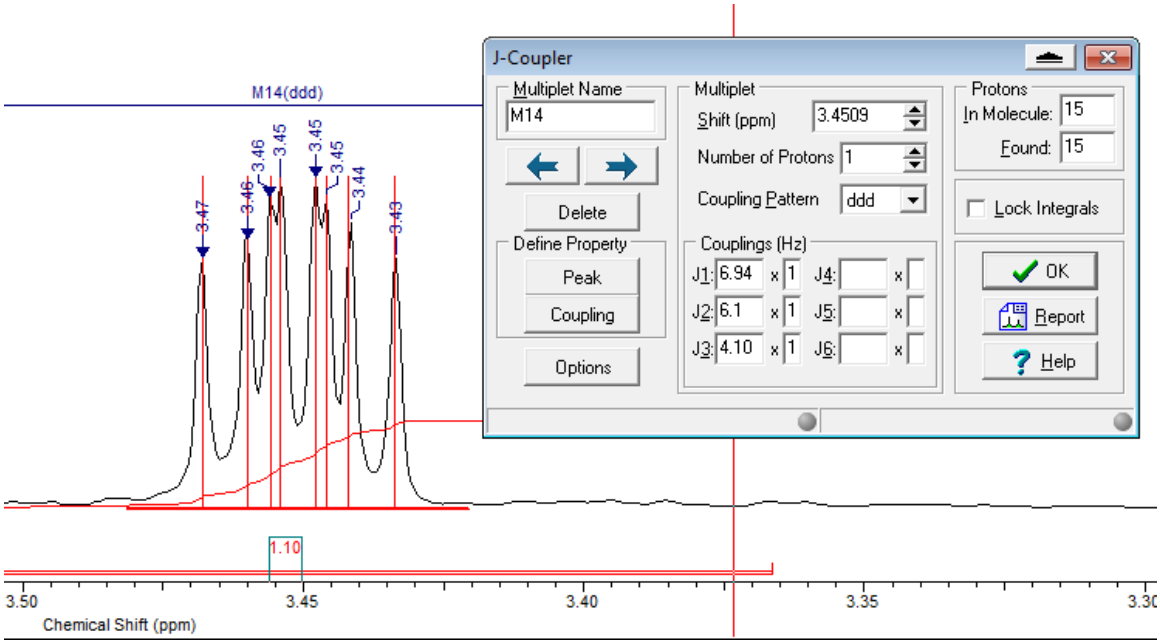


Figure 23. Analysis of coupling constants in ^{1}H NMR signal of proton A in compound **316a**.

3.5.2. Assignment of relative configurations for compounds 327a and 328

Structure elucidations were performed for compounds **327a**, and **328** are provided below. The minimum energy conformation for the fused 2-oxa-5-azabicyclo[5.1.0]octan-6-one system is depicted in Figure 24 and Figure 25. Relative stability of these conformations is governed by the *pseudo*-equatorial phenyl group at position 4 for compound **327a**, and both the equatorial phenyl at position 3 and the equatorial methyl group at position 4 for compound **328**. The observed ^{1}H-^{1}H NOE effects are listed in Figure 24 and Figure 25, the corresponding color-coded spectral charts are shown in Figure 26 and Figure 27.

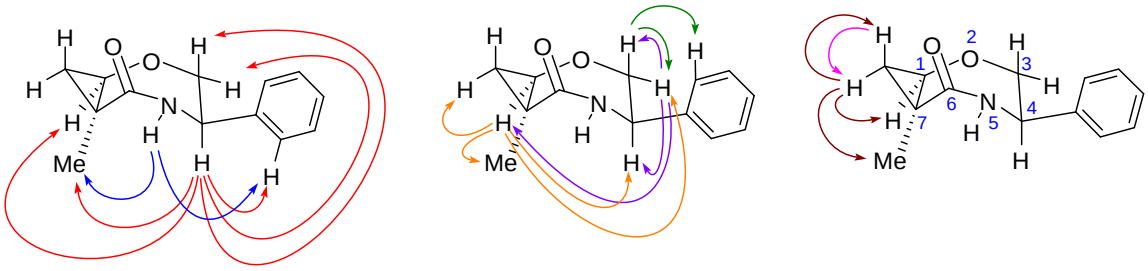


Figure 24. Observed NOEs upon irradiation at 5.91 ppm (blue), 5.00 ppm (red), 3.86 ppm (lilac), 3.66 ppm (green), 3.19 ppm (orange), 1.21 ppm (pink), 0.89 ppm (brown) for compound **327a**. For color-coded spectral charts corresponding to these experiments, see Figure 26. Atom numbering in the seven-membered ring is provided according to IUPAC nomenclature.

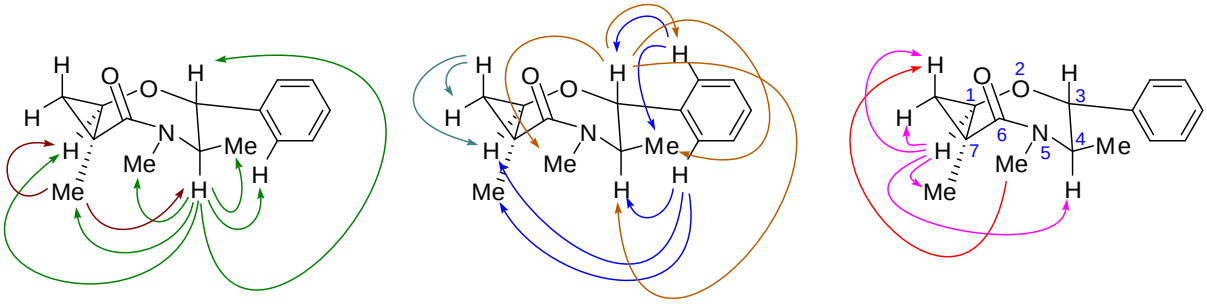


Figure 25. Observed NOEs upon irradiation at 7.24 ppm (blue), 4.58 ppm (green), 4.21 ppm (terracotta), 3.08 ppm (pink), 2.87 ppm (red), 1.46 ppm (spruce), 1.18 ppm (brown) for compound **328**. For color-coded spectral charts corresponding to these experiments, see Figure 27. Atom numbering in the seven-membered ring is provided according to IUPAC nomenclature.

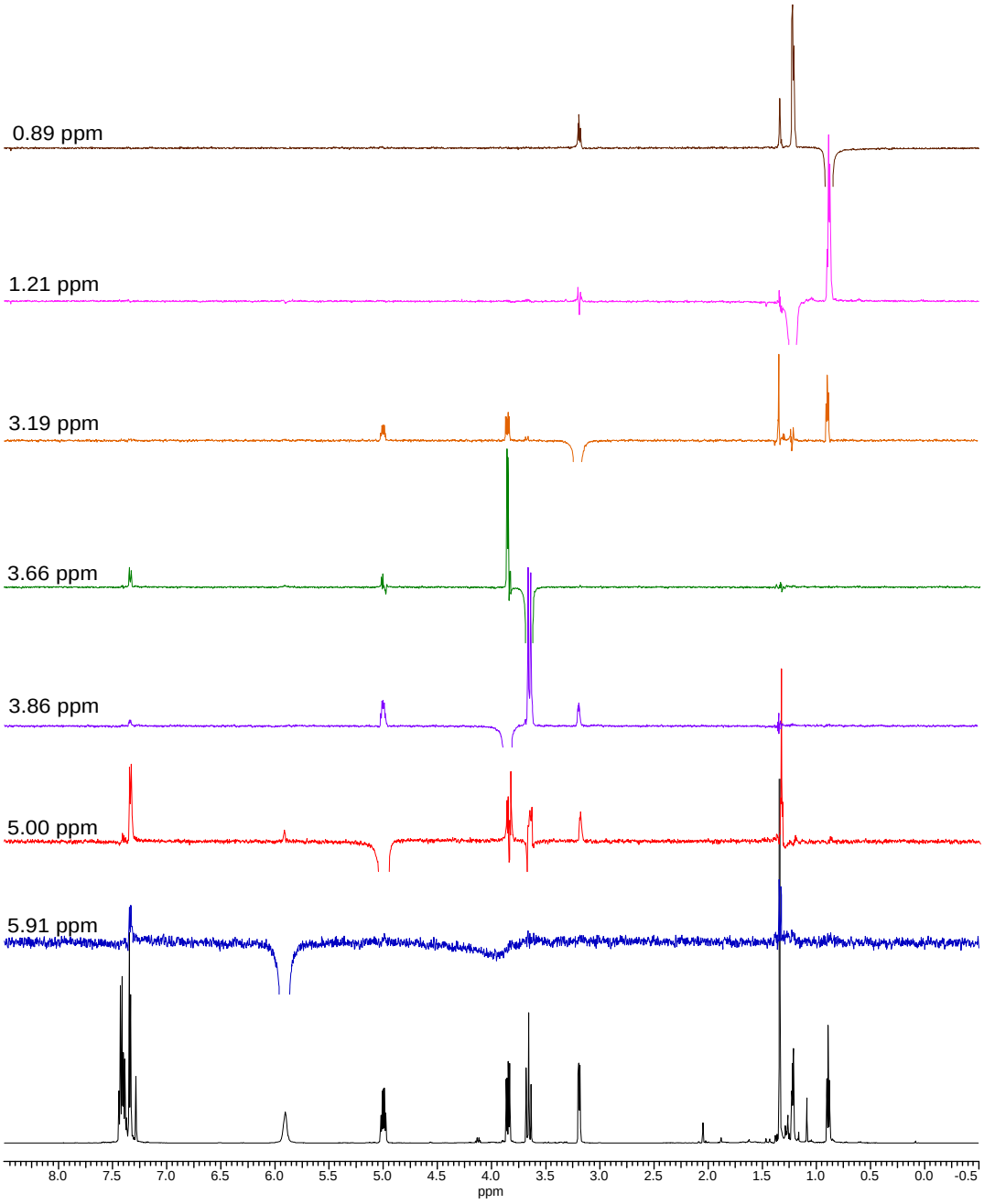


Figure 26. 1D NOEDIFF spectra of **327a**. Chemical shifts of the irradiated multiplets are listed at the left side of each chart

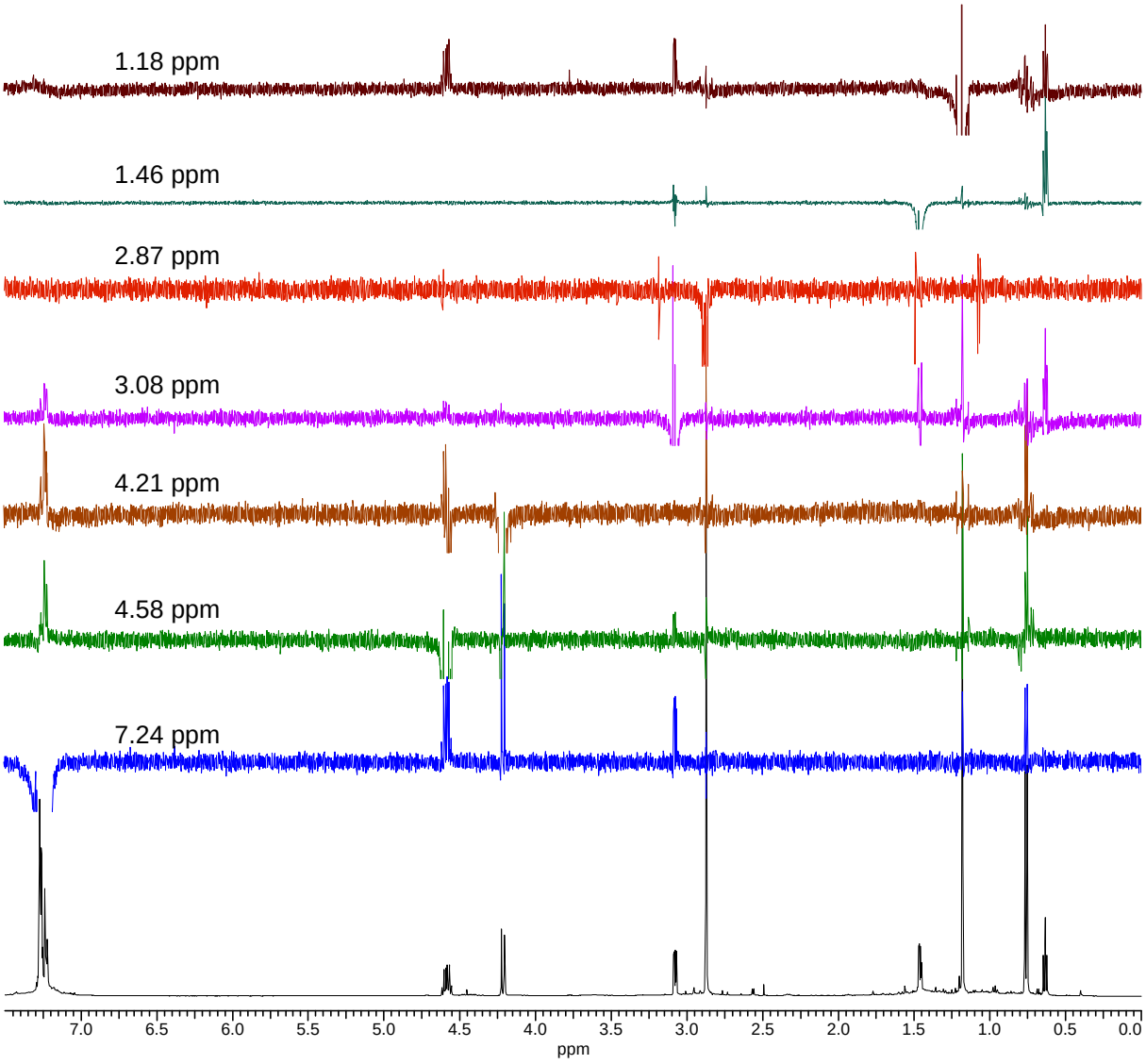
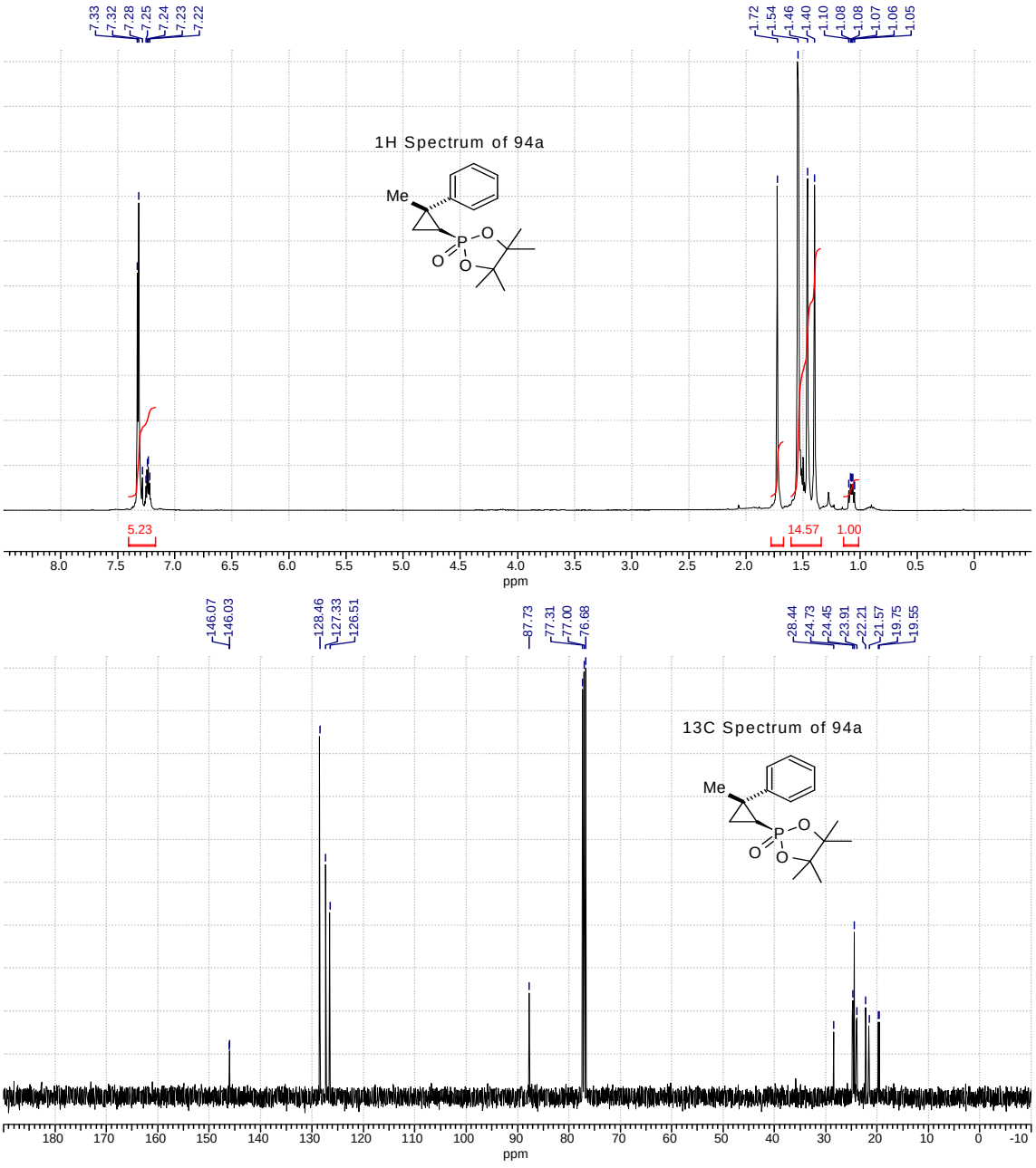


Figure 27. 1D NOEDIFF spectra of 328. Chemical shifts of the irradiated multiplets are listed at the left side of each chart.

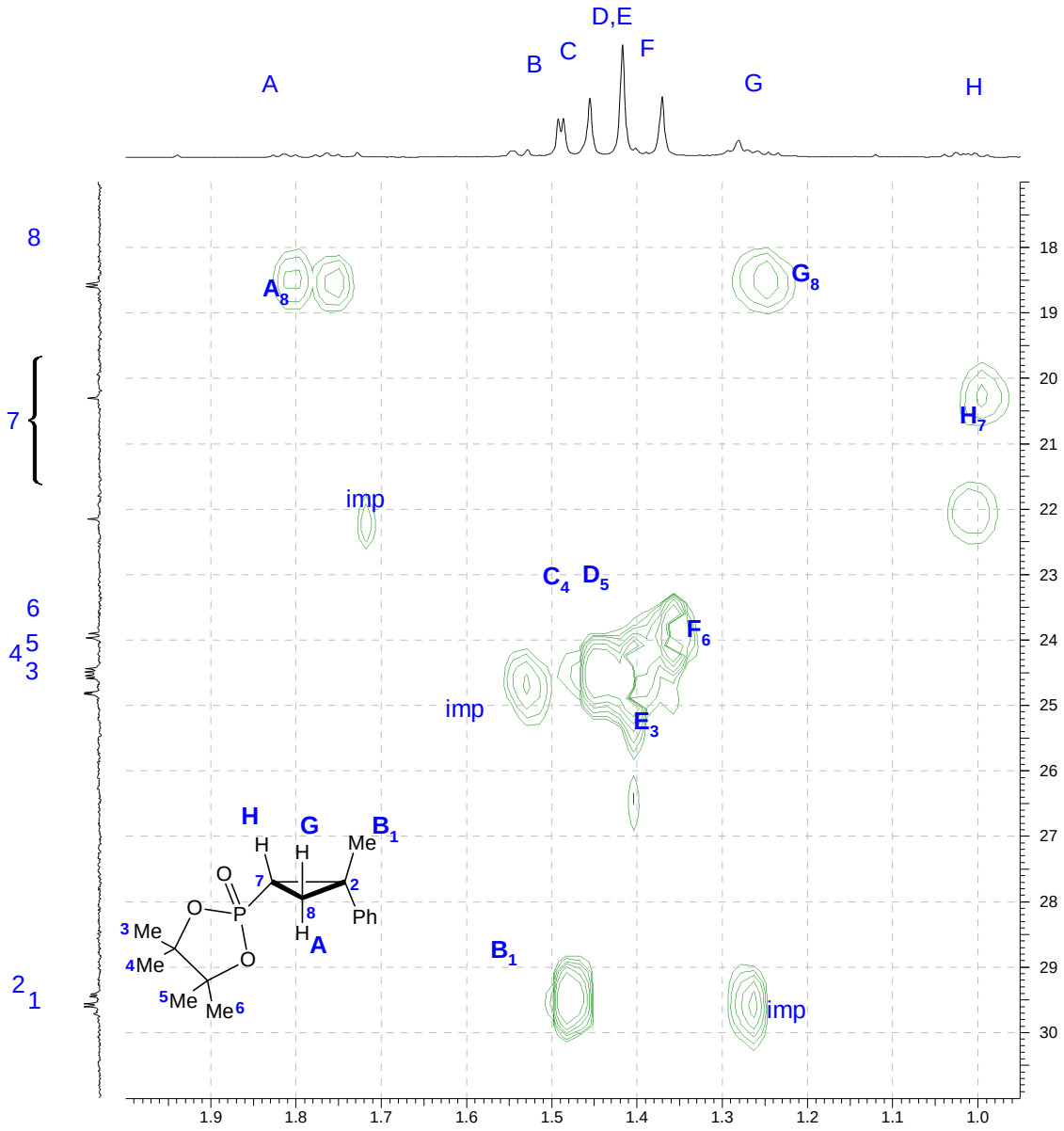
Appendix

A.1. ^{1}H and ^{13}C Specta for 94 A



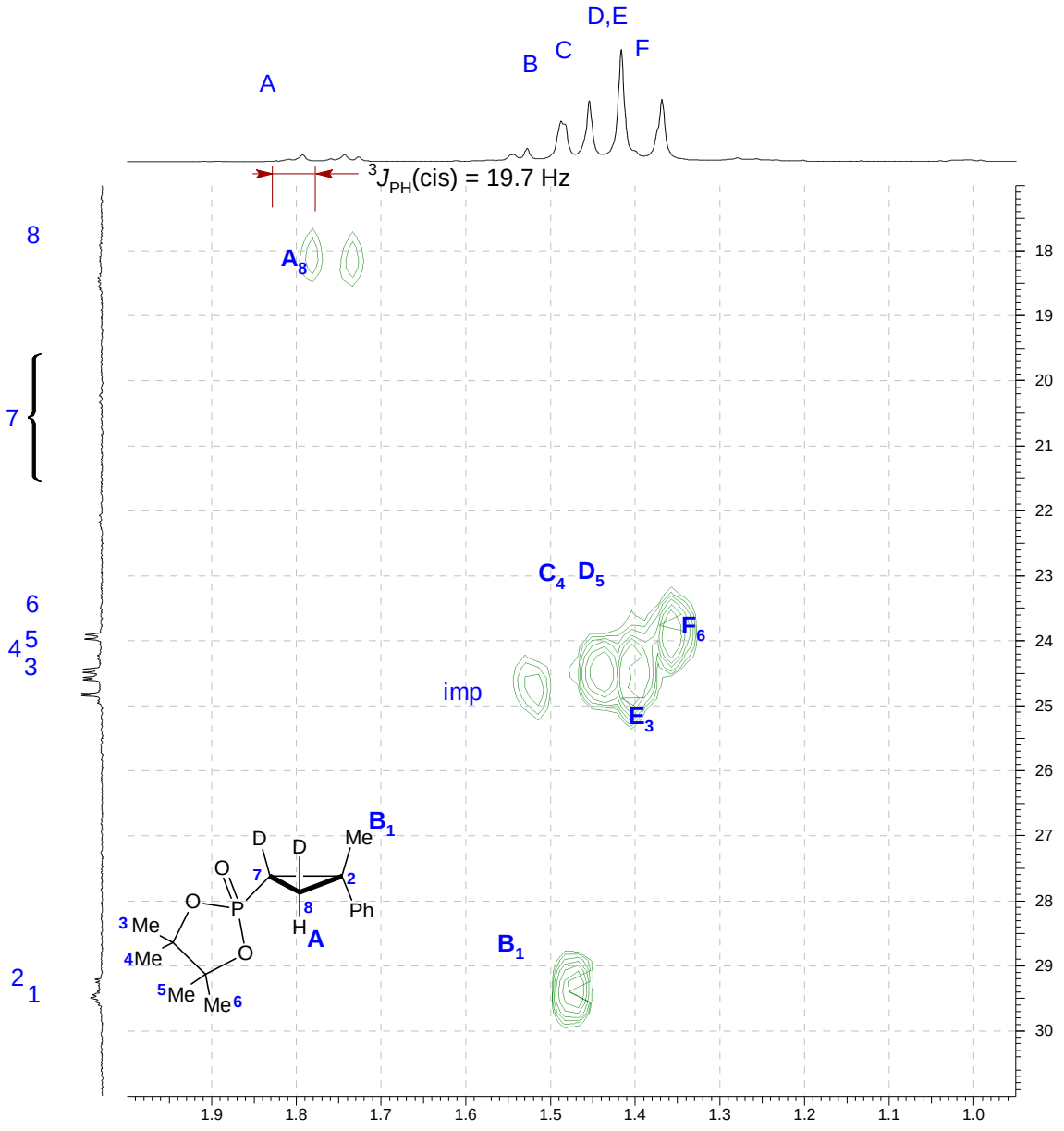
A.2. ^{1}H-^{13}C HSQC spectrum of trans-94a

Acquisition Time (sec)	(0.0614, 0.1597)	***Comment***	Imported from UXNMR/XWINNMR
Date	30 Apr 2008 15:29:40		
File Name	\ba0139A-2D-Minor\5\pdata\1\2rr		
Frequency (MHz)	(100.61, 400.13)	***Nucleus***	(13C, 1H)
Number of Transients	2	***Original Points Count***	(1024, 1024)
Points Count	(1024, 1024)	***Pulse Sequence***	hsqcetgpsisp2
Solvent	CDCl3	***Sweep Width (Hz)***	(16666.67, 6410.26)
Temperature (degree C)	23.160		

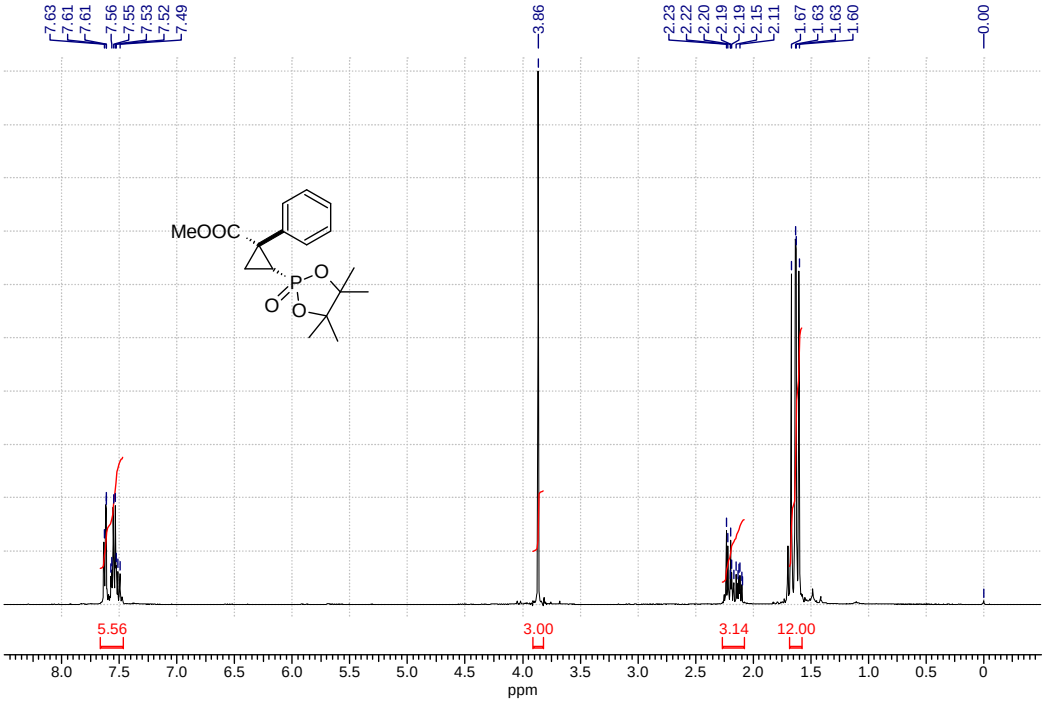


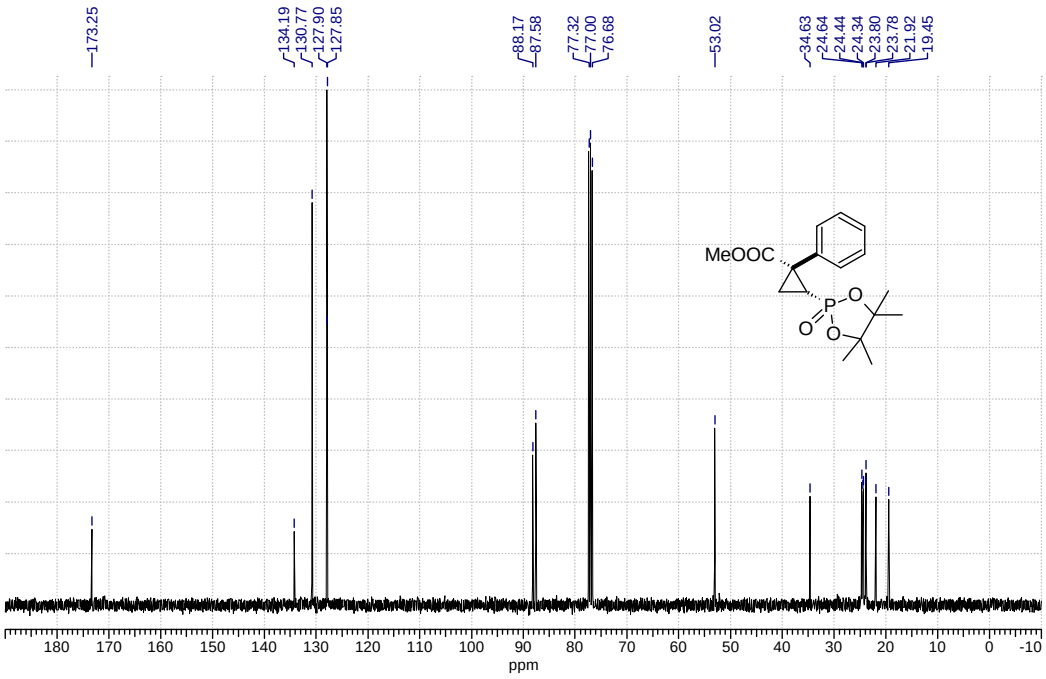
A.3. ^{1}H-^{13}C HSQC spectrum of cis-94a-d_2

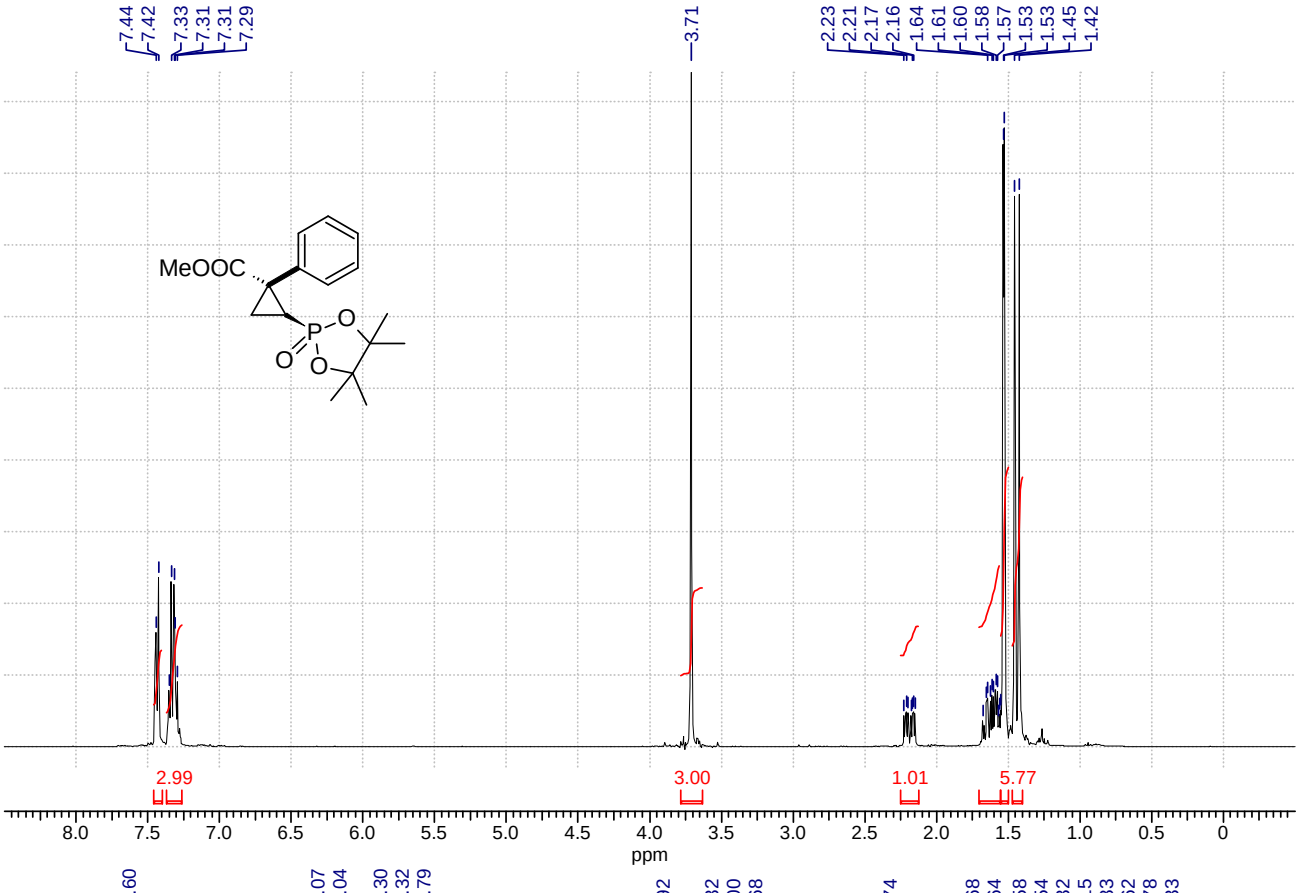
Acquisition Time (sec)	(0.0614, 0.1597)	***Comment***	Imported from UXNMR/XWINNMR		
Date	30 Apr 2008 15:34:40				
File Name	\\SERVER1\GROUP\CHEM\MAR_GRP\Sam\NMR DATA\ba0141f2\5\pdata\1\2rr				
Frequency (MHz)	(100.61, 400.13)	***Nucleus***	(13C, 1H)	***Number of Transients***	2
Original Points Count	(1024, 1024)	***Points Count***	(1024, 1024)	***Pulse Sequence***	hsqcetgpsisp2
Solvent	CDCl3	***Sweep Width (Hz)***	(16666.67, 6410.26)	***Temperature (degree C)***	23.160

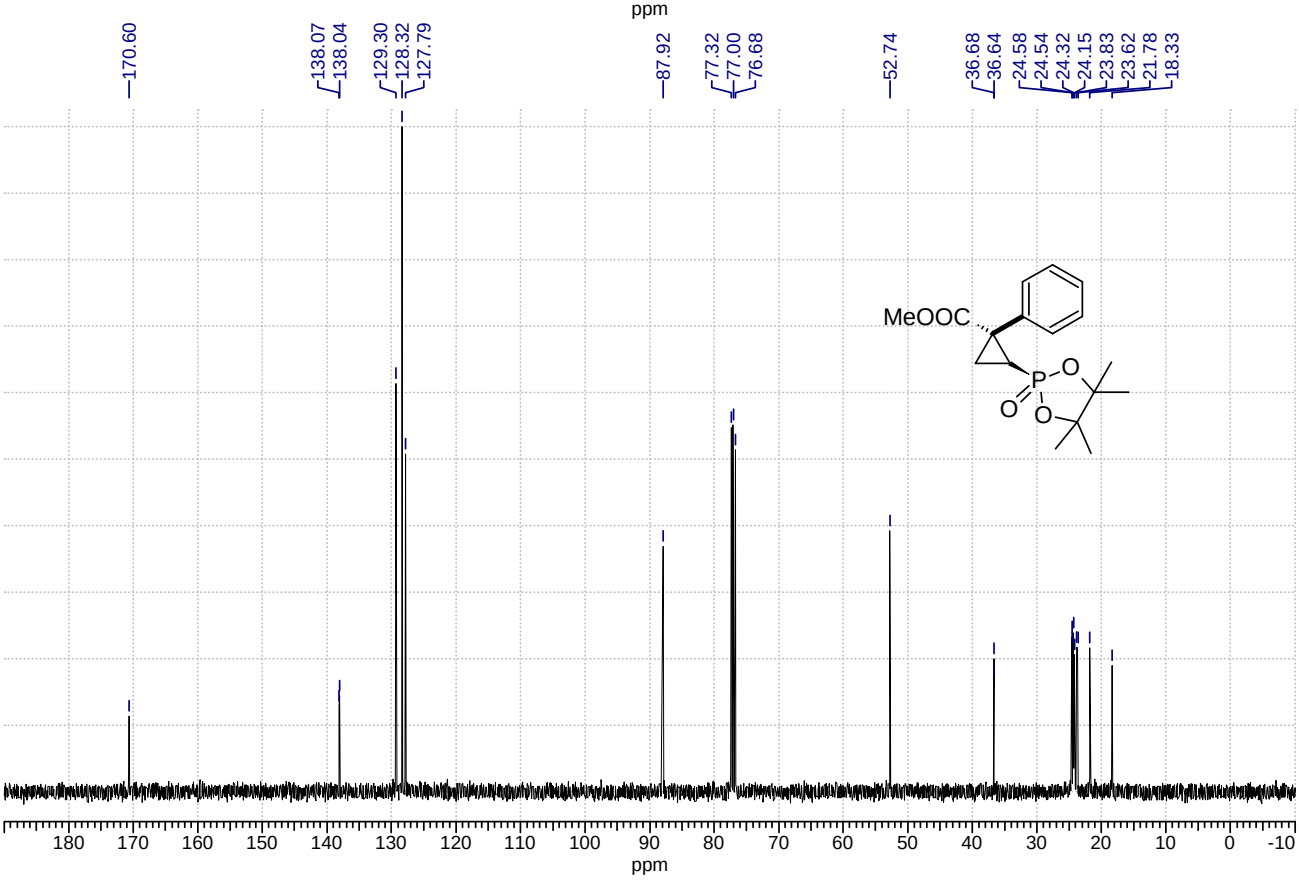


A.4. ^{1}H and ^{13}C spectra of *trans* and *cis* 94e






7.44
7.42
7.33
7.31
7.31
7.29
3.71
2.23
2.21
2.17
2.16
1.64
1.61
1.60
1.58
1.57
1.53
1.53
1.45
1.42
MeOOC
P
O
O
O
2.99
3.00
1.01
5.77
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
ppm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138.07
138.04
129.30
128.32
127.79
87.92
77.32
77.00
76.68
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36.68
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24.58
24.54
24.32
24.15
23.83
23.62
21.78
18.33
MeOOC
P
O
O
O
180
170
160
150
140
130
120
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30
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10
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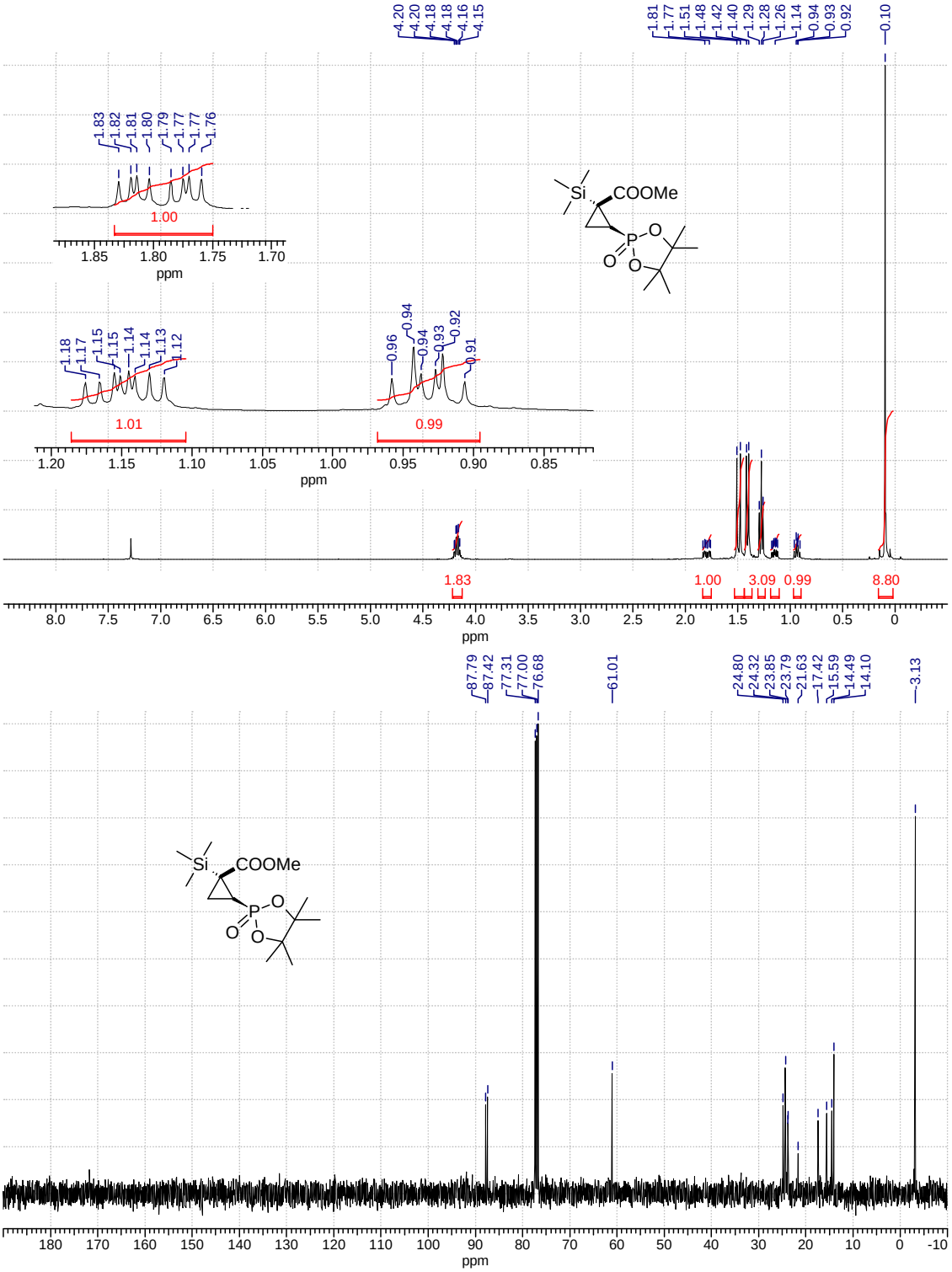
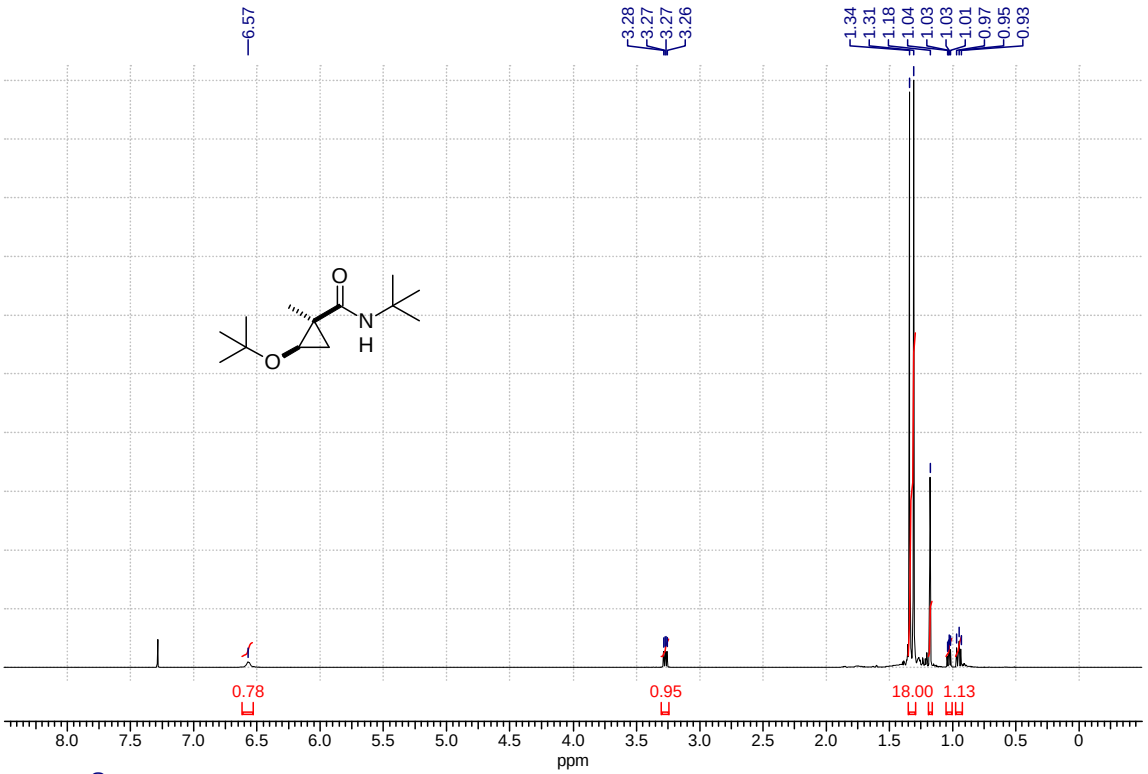
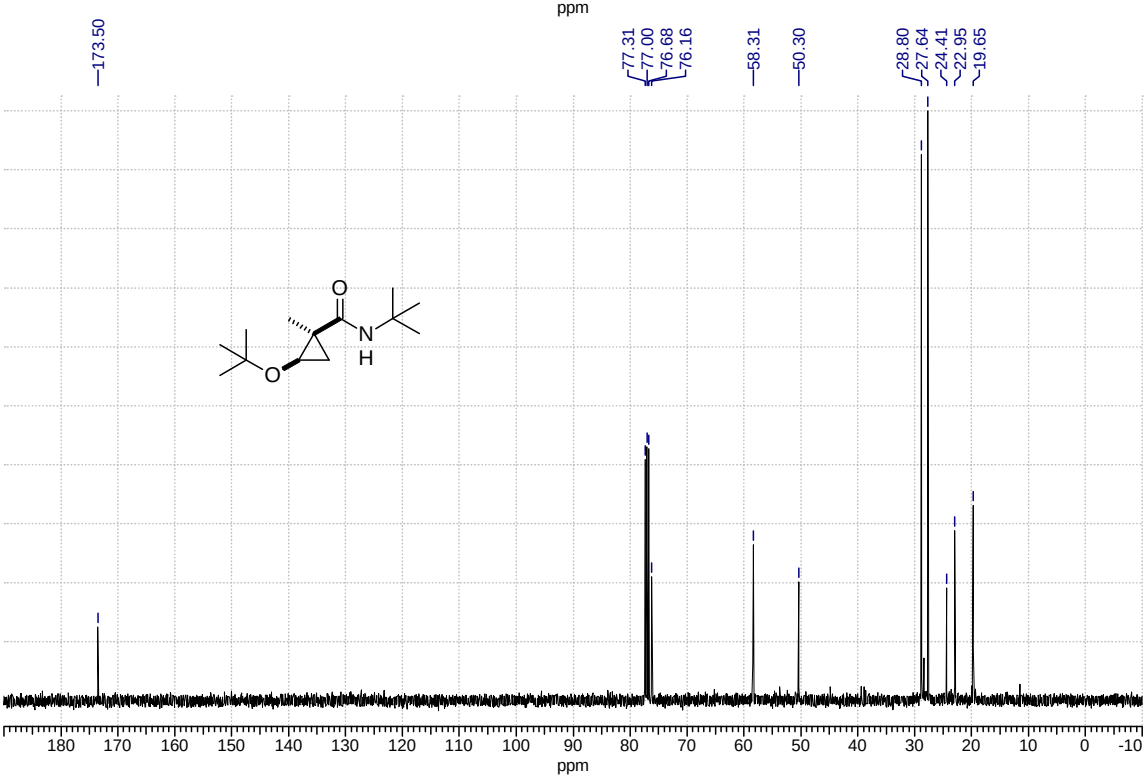
-10
ppm

A.5. ^{1}H and ^{13}C spectra of 94f

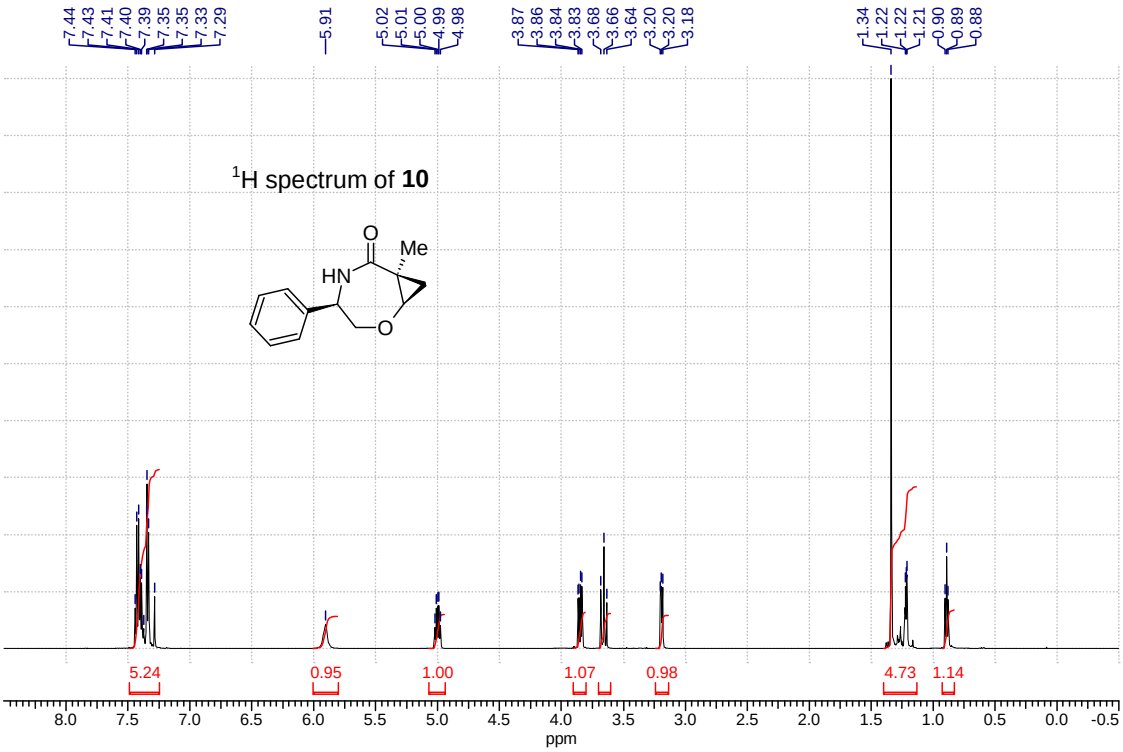


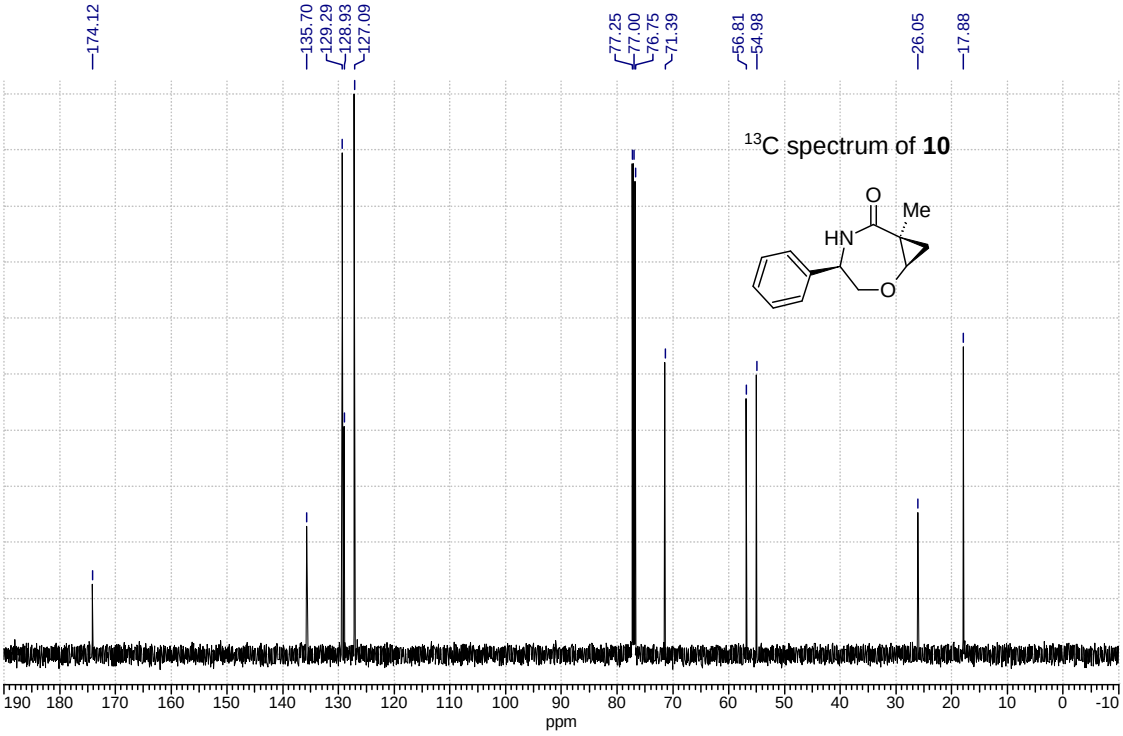
A.6. ^{1}H and ^{13}C spectra of 242c



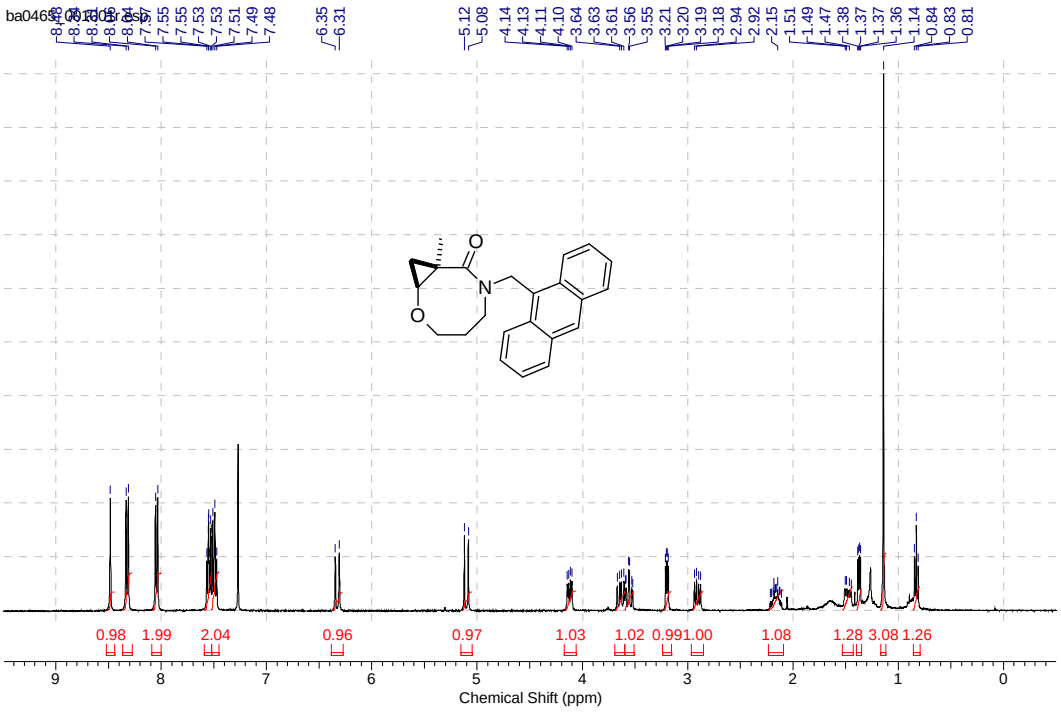


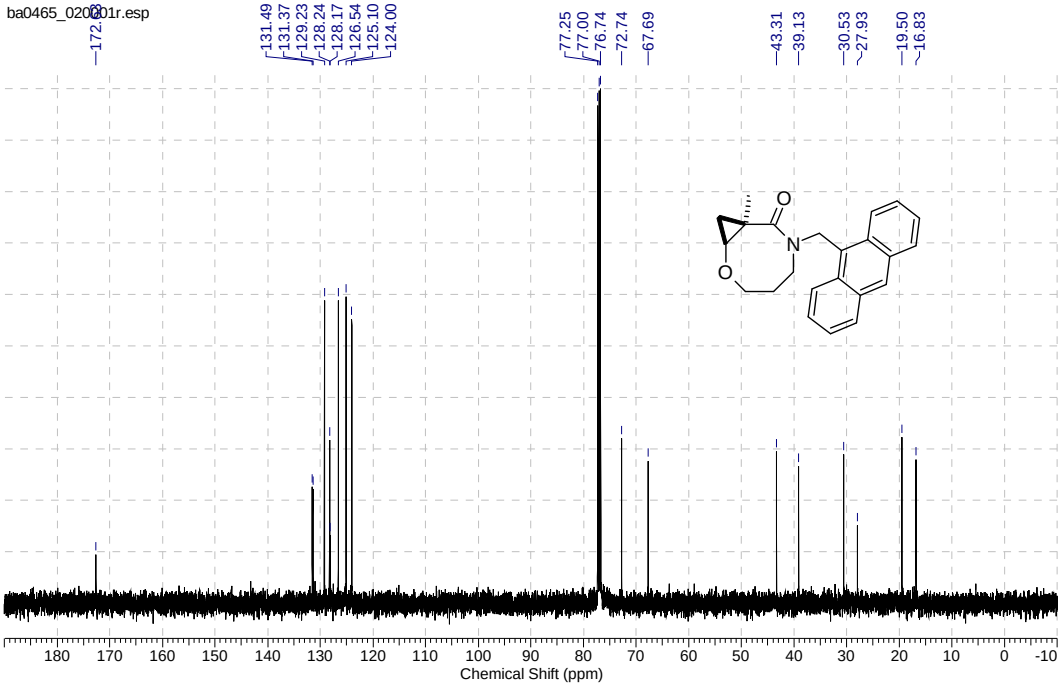
A.7. ^{1}H and ^{13}C spectra for 327a



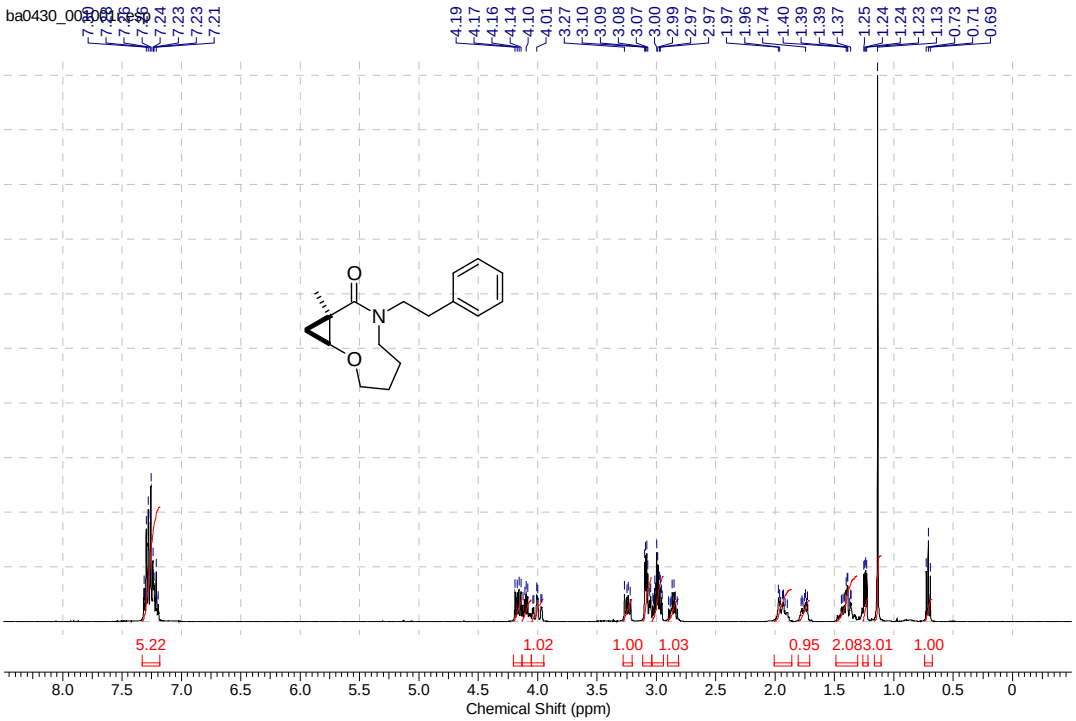


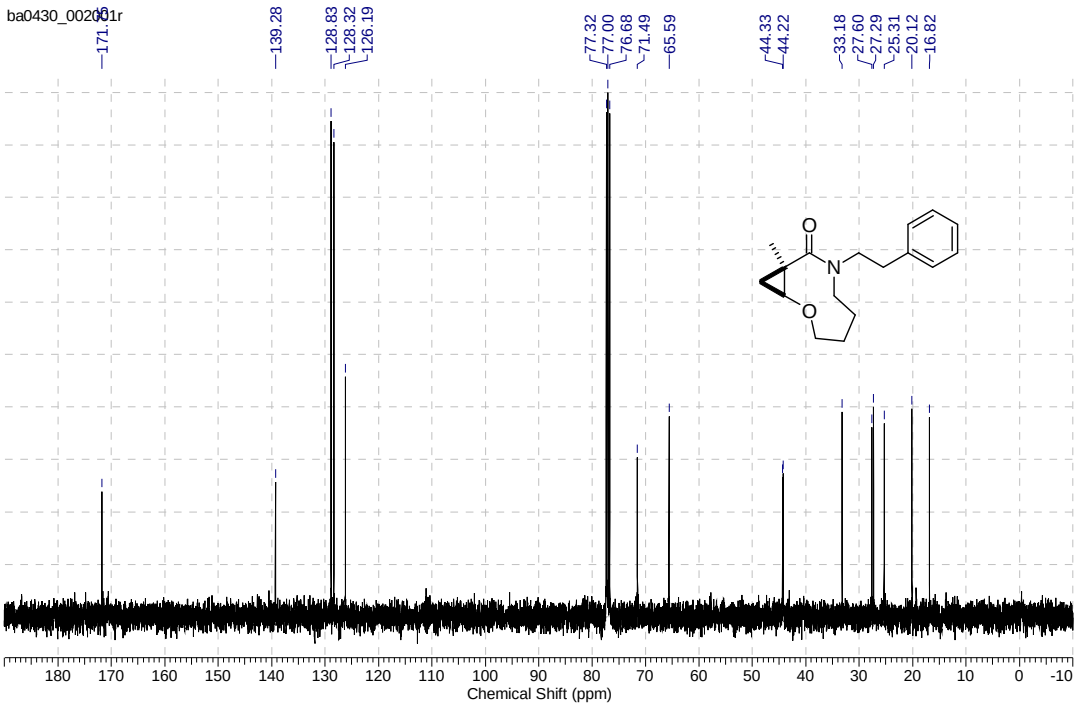
A.8. ^{1}H and ^{13}C spectra for 316d



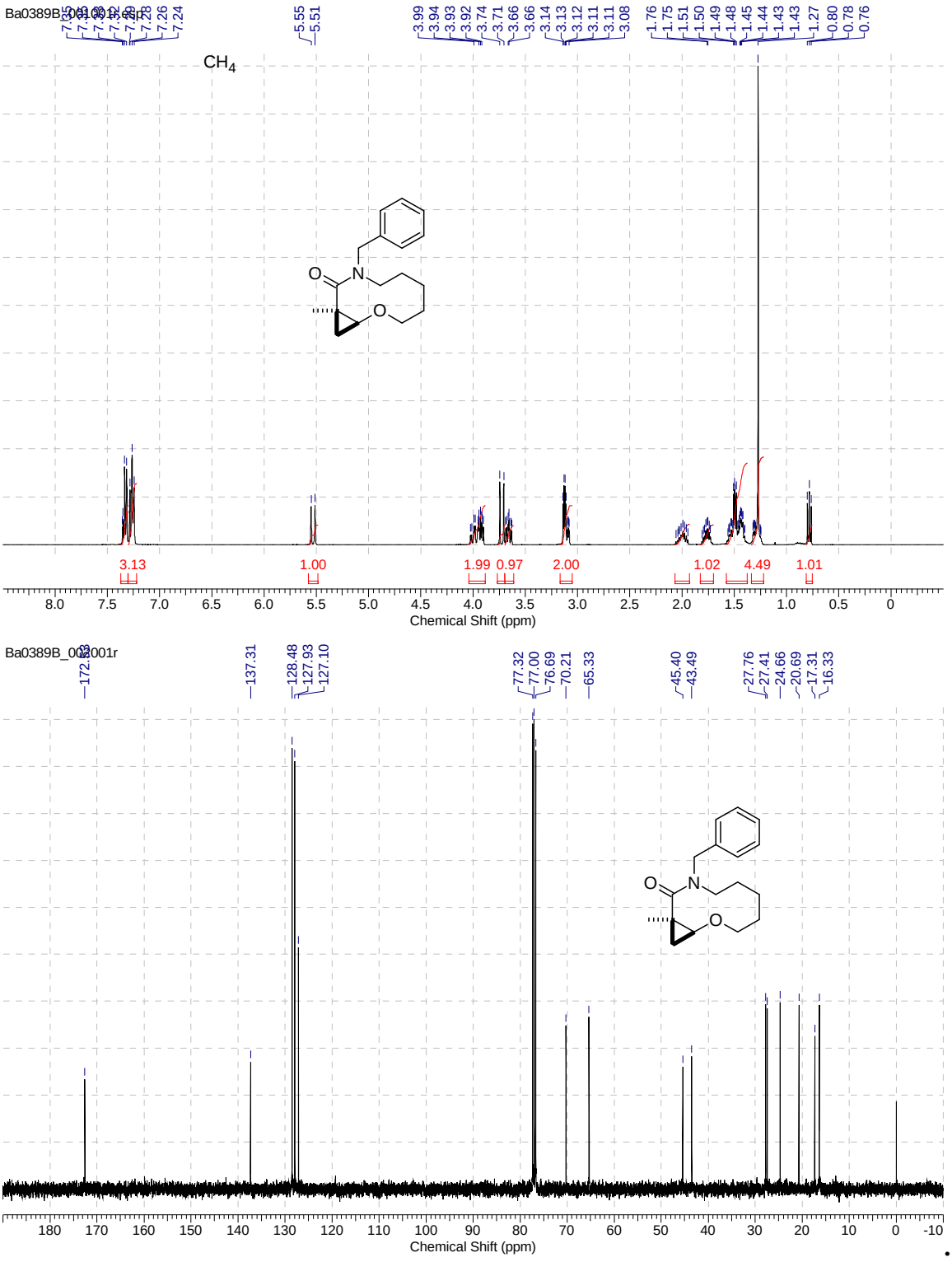


A.9. ^{1}H and ^{13}C for 318d.





A.10. ^{1}H and ^{13}C for 318c



A.11. Crystallographic Data for 327a

To a solution of compound **327a** (25 mg) in dichloromethane (10 mL) was added hexane (10 mL) and the mixture was left overnight in the flask, closed with a cotton ball to ensure slow evaporation of the solvents. Well-formed colorless needles were obtained, which were collected, washed with hexane, and analyzed by single crystal X-ray crystallography.

Colorless crystals of $C_{13}H_{15}NO_2$ are, at 100(2) K, orthorhombic, space group $P2_12_12_1$–D_2^4 (No. 19) with **a** = 8.6537(6) Å, **b** = 9.4166(6) Å, **c** = 13.4394(9) Å, V = 1095.2(1) Å and Z = 4 molecules {d_{calcd} = 1.318 g/cm^3; μ_a(MoKα) = 0.089 mm^{-1}}. A full hemisphere of diffracted intensities (1850 20-second frames with a ω scan width of 0.30°) was measured for a single-domain specimen using graphite-monochromated MoKα radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 3007 reflections. A total of 13228 integrated reflection intensities having 2θ((MoKα)< 60.99° were produced using the Bruker program SAINT; 3298 of these were unique and gave R_{int} = 0.050 with a coverage which was 99.4% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.951 to 1.000. The Bruker software package SHELXTL was used to solve the structure using “direct methods” techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. A total of 205 parameters were refined using no restraints, 3298 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0465\ P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.050 for 3043 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 60.99°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.056 and wR_2(weighted, based on F^2) = 0.100 for all 3298 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 60.99°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.36 and -0.26 $e^-/Å^3$, respectively. With oxygen being the heaviest atom present, the absolute structure could not be reliably determined experimentally. The absolute configuration for the molecule was therefore assigned using the known configuration at carbon atom C(6).

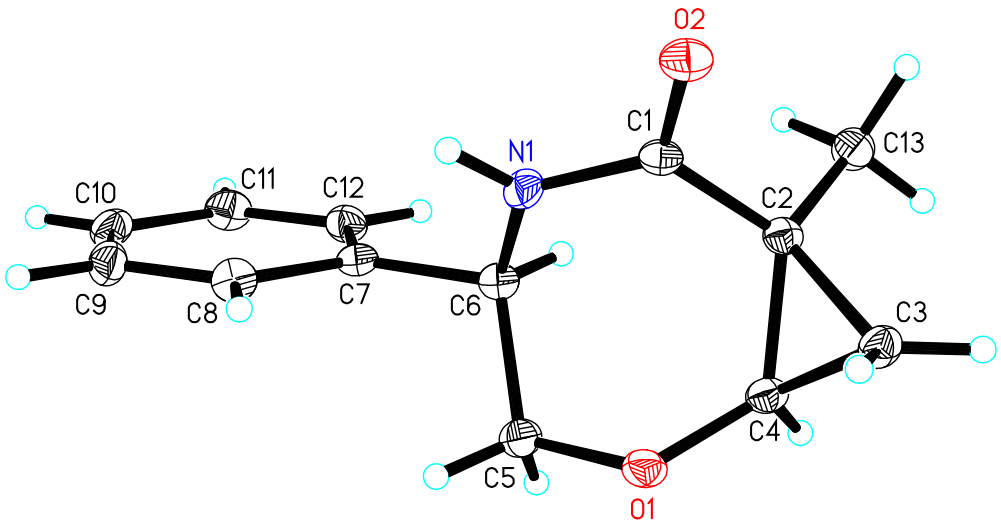


Figure 28. ORTEP drawing of **327a**, showing the atom-numbering scheme; 50% probability amplitude displacement ellipsoids are shown. The asymmetric unit contains one $C_{13}H_{15}NO_2$ molecule.

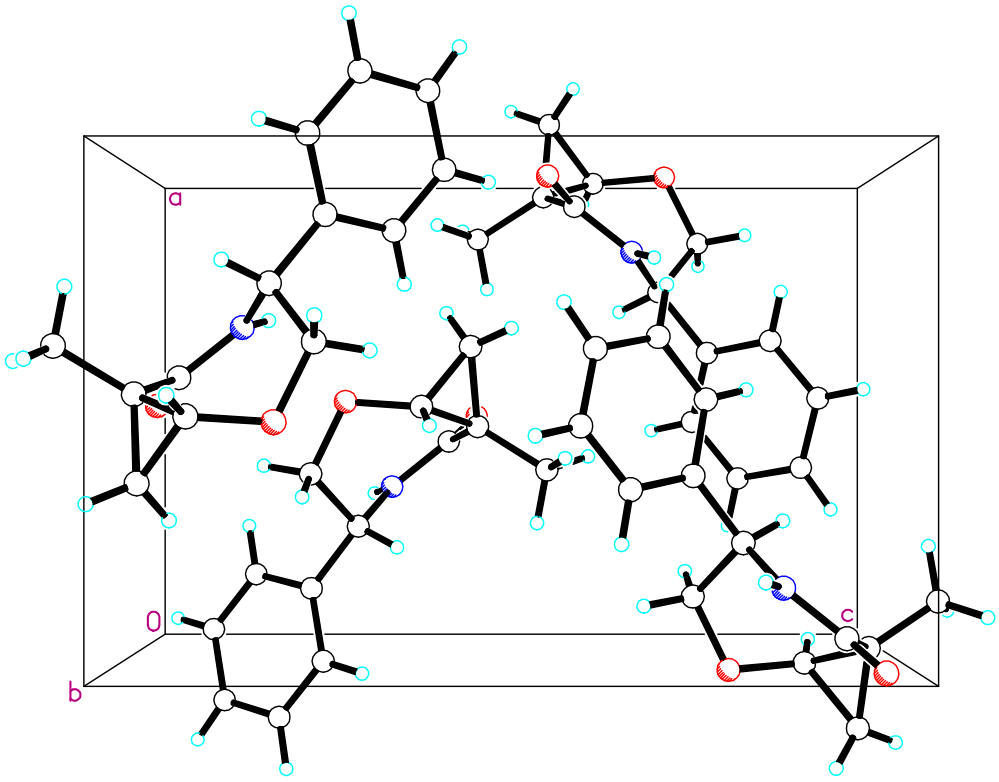


Figure 29. Packing of 327a molecules in the crystalline lattice cell.

Table 3. Crystal data and structure refinement for $C_{13}H_{15}NO_2$.

Empirical formula	$C_{13}H_{15}NO_2$	
Formula weight	217.26	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$– D_2^4 (No. 19)	
Unit cell dimensions	**a** = 8.6537(6) Å	α = 90.000°
	b = 9.4166(6) Å	β = 90.000°
	c = 13.4394(9) Å	γ = 90.000°
Volume	1095.2(1) $Å^3$	
Z	4	
Density (calculated)	1.318 g/cm^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	464	
Crystal size	0.24 x 0.22 x 0.04 mm^3	
Theta range for data collection	2.64°to 30.50°	
Index ranges	$-12 \leq h \leq 12$, $-13 \leq k \leq 13$, $-19 \leq l \leq 19$	
Reflections collected	13228	
Independent reflections	3298 [R_{int} = 0.050]	
Completeness to theta = 30.50°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.951	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3298 / 0 / 205	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R_1 = 0.050, wR_2 = 0.098	
R indices (all data)	R_1 = 0.056, wR_2 = 0.100	
Absolute structure parameter	0.5(12)	
Largest diff. peak and hole	0.36 and -0.26 $e^-/Å^3$	

$R_1 = \Sigma \, ||F_O| - |F_C|| \, / \, \Sigma \, |F_O|$

$wR_2 = \{ \Sigma \, [w(F_O^2 - F_C^2)^2] \, / \, \Sigma \, [w(F_O^2)^2] \}^{1/2}$

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for $C_{13}H_{15}NO_2$. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	5199(1)	4518(1)	2813(1)	17(1)
O(2)	4895(1)	1184(1)	4513(1)	18(1)
N(1)	3379(2)	2207(1)	3352(1)	15(1)
C(1)	4351(2)	2261(2)	4137(1)	13(1)
C(2)	4682(2)	3722(2)	4549(1)	13(1)
C(3)	6334(2)	4248(2)	4461(1)	16(1)
C(4)	5094(2)	4880(2)	3823(1)	14(1)
C(5)	3714(2)	4391(2)	2343(1)	17(1)
C(6)	2589(2)	3455(2)	2936(1)	14(1)
C(7)	1256(2)	3013(2)	2280(1)	14(1)
C(8)	1495(2)	2119(2)	1465(1)	17(1)
C(9)	275(2)	1737(2)	846(1)	19(1)
C(10)	-1199(2)	2254(2)	1038(1)	20(1)
C(11)	-1454(2)	3140(2)	1847(1)	20(1)
C(12)	-232(2)	3508(2)	2466(1)	17(1)
C(13)	3788(2)	4106(2)	5474(1)	18(1)

Table 5. Bond lengths [Å] for $C_{13}H_{15}NO_2$.

O(1)-C(4)	1.403(2)	C(6)-C(7)	1.511(2)
O(1)-C(5)	1.436(2)	C(6)-H(6)	0.94(2)
O(2)-C(1)	1.227(2)	C(7)-C(12)	1.392(2)
N(1)-C(1)	1.350(2)	C(7)-C(8)	1.396(2)
N(1)-C(6)	1.470(2)	C(8)-C(9)	1.392(2)
N(1)-H(1N)	0.85(2)	C(8)-H(8)	0.95(2)
C(1)-C(2)	1.511(2)	C(9)-C(10)	1.390(2)
C(2)-C(4)	1.506(2)	C(9)-H(9)	0.96(2)
C(2)-C(13)	1.508(2)	C(10)-C(11)	1.389(2)
C(2)-C(3)	1.518(2)	C(10)-H(10)	0.95(2)
C(3)-C(4)	1.496(2)	C(11)-C(12)	1.389(2)
C(3)-H(3A)	0.94(2)	C(11)-H(11)	0.97(2)
C(3)-H(3B)	0.95(2)	C(12)-H(12)	0.94(2)
C(4)-H(4)	1.03(2)	C(13)-H(13A)	0.97(2)
C(5)-C(6)	1.536(2)	C(13)-H(13B)	0.95(2)
C(5)-H(5A)	0.97(2)	C(13)-H(13C)	0.97(2)
C(5)-H(5B)	0.98(2)		

Table 6. Bond angles [°] for $C_{13}H_{15}NO_2$.

C(4)-O(1)-C(5)	112.8(1)	N(1)-C(6)-C(7)	110.9(1)
C(1)-N(1)-C(6)	123.8(1)	N(1)-C(6)-C(5)	111.2(1)
C(1)-N(1)-H(1N)	118(1)	C(7)-C(6)-C(5)	109.8(1)
C(6)-N(1)-H(1N)	118(1)	N(1)-C(6)-H(6)	107(1)
O(2)-C(1)-N(1)	122.0(1)	C(7)-C(6)-H(6)	108(1)
O(2)-C(1)-C(2)	121.9(1)	C(5)-C(6)-H(6)	110(1)
N(1)-C(1)-C(2)	116.0(1)	C(12)-C(7)-C(8)	118.7(1)
C(4)-C(2)-C(13)	118.8(1)	C(12)-C(7)-C(6)	120.6(1)
C(4)-C(2)-C(1)	117.8(1)	C(8)-C(7)-C(6)	120.7(1)
C(13)-C(2)-C(1)	115.1(1)	C(9)-C(8)-C(7)	120.8(2)
C(4)-C(2)-C(3)	59.3(1)	C(9)-C(8)-H(8)	121(1)
C(13)-C(2)-C(3)	118.0(1)	C(7)-C(8)-H(8)	118(1)
C(1)-C(2)-C(3)	116.5(1)	C(10)-C(9)-C(8)	119.7(2)
C(4)-C(3)-C(2)	59.9(1)	C(10)-C(9)-H(9)	121(1)
C(4)-C(3)-H(3A)	116(1)	C(8)-C(9)-H(9)	120(1)
C(2)-C(3)-H(3A)	118(1)	C(11)-C(10)-C(9)	120.1(2)
C(4)-C(3)-H(3B)	117(1)	C(11)-C(10)-H(10)	116(1)
C(2)-C(3)-H(3B)	115(1)	C(9)-C(10)-H(10)	124(1)
H(3A)-C(3)-H(3B)	118(2)	C(10)-C(11)-C(12)	119.8(2)
O(1)-C(4)-C(3)	114.3(1)	C(10)-C(11)-H(11)	119(1)
O(1)-C(4)-C(2)	117.8(1)	C(12)-C(11)-H(11)	122(1)
C(3)-C(4)-C(2)	60.7(1)	C(11)-C(12)-C(7)	120.9(2)
O(1)-C(4)-H(4)	114(1)	C(11)-C(12)-H(12)	119(1)
C(3)-C(4)-H(4)	120(1)	C(7)-C(12)-H(12)	120(1)
C(2)-C(4)-H(4)	120(1)	C(2)-C(13)-H(13A)	112(1)
O(1)-C(5)-C(6)	112.8(1)	C(2)-C(13)-H(13B)	112(1)
O(1)-C(5)-H(5A)	108(1)	H(13A)-C(13)-H(13B)	103(2)
C(6)-C(5)-H(5A)	109(1)	C(2)-C(13)-H(13C)	110(1)
O(1)-C(5)-H(5B)	108(1)	H(13A)-C(13)-H(13C)	110(2)
C(6)-C(5)-H(5B)	109(1)	H(13B)-C(13)-H(13C)	110(2)
H(5A)-C(5)-H(5B)	111(1)		

Table 7. Anisotropic displacement parameters ($Å^2$ x 10^3) for $C_{13}H_{15}NO_2$. 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}
O(1)	13(1)	21(1)	16(1)	4(1)	1(1)	-2(1)
O(2)	17(1)	15(1)	20(1)	3(1)	2(1)	1(1)
N(1)	19(1)	10(1)	17(1)	0(1)	-2(1)	-1(1)
C(1)	10(1)	15(1)	13(1)	1(1)	4(1)	0(1)
C(2)	12(1)	13(1)	14(1)	3(1)	-1(1)	1(1)
C(3)	12(1)	17(1)	18(1)	1(1)	0(1)	-1(1)
C(4)	12(1)	15(1)	17(1)	3(1)	1(1)	-1(1)
C(5)	16(1)	18(1)	17(1)	3(1)	-2(1)	-3(1)
C(6)	13(1)	13(1)	15(1)	1(1)	2(1)	1(1)
C(7)	14(1)	12(1)	16(1)	3(1)	2(1)	0(1)
C(8)	15(1)	16(1)	20(1)	0(1)	1(1)	3(1)
C(9)	23(1)	15(1)	18(1)	-2(1)	-2(1)	-1(1)
C(10)	18(1)	20(1)	22(1)	5(1)	-6(1)	-6(1)
C(11)	12(1)	24(1)	23(1)	3(1)	2(1)	1(1)
C(12)	17(1)	18(1)	17(1)	0(1)	3(1)	0(1)
C(13)	18(1)	19(1)	16(1)	-2(1)	3(1)	-2(1)

Table 8. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for $C_{13}H_{15}NO_2$.

	x	y	z	U(eq)
H(1N)	3210(20)	1400(20)	3078(14)	20(5)
H(3A)	7050(20)	3670(20)	4130(14)	20(5)
H(3B)	6700(20)	4800(20)	5003(13)	20(5)
H(4)	4710(20)	5902(19)	3950(13)	18(4)
H(5A)	3870(20)	3970(18)	1696(13)	14(4)
H(5B)	3272(18)	5343(18)	2286(12)	7(4)
H(6)	2178(19)	3969(18)	3474(13)	9(4)
H(8)	2520(20)	1790(20)	1345(14)	20(5)
H(9)	460(20)	1110(20)	291(15)	28(5)
H(10)	-2080(20)	2043(19)	648(13)	15(5)
H(11)	-2490(20)	3490(20)	1966(16)	29(6)
H(12)	-430(20)	4110(20)	3012(13)	18(5)
H(13A)	4060(20)	3500(20)	6036(15)	26(5)
H(13B)	4040(20)	5030(20)	5703(14)	23(5)
H(13C)	2680(20)	4050(20)	5344(15)	24(5)

Table 9. Hydrogen bonds for $C_{13}H_{15}NO_2$ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.85(2)	2.55(2)	3.221(2)	137(2)

Symmetry transformations used to generate equivalent atoms: #1: -x+1, y-1/2, -z+1/2.

Table 10. Torsion angles [°] for $C_{13}H_{15}NO_2$.

C(6)-N(1)-C(1)-O(2)	174.14(14)
C(6)-N(1)-C(1)-C(2)	-3.6(2)
O(2)-C(1)-C(2)-C(4)	134.64(15)
N(1)-C(1)-C(2)-C(4)	-47.60(19)
O(2)-C(1)-C(2)-C(13)	-77.30(19)
N(1)-C(1)-C(2)-C(13)	100.46(16)
O(2)-C(1)-C(2)-C(3)	67.06(19)
N(1)-C(1)-C(2)-C(3)	-115.18(15)
C(13)-C(2)-C(3)-C(4)	-108.64(16)
C(1)-C(2)-C(3)-C(4)	108.07(15)
C(5)-O(1)-C(4)-C(3)	146.49(13)
C(5)-O(1)-C(4)-C(2)	78.09(16)
C(2)-C(3)-C(4)-O(1)	-109.49(14)
C(13)-C(2)-C(4)-O(1)	-149.00(14)
C(1)-C(2)-C(4)-O(1)	-2.2(2)
C(3)-C(2)-C(4)-O(1)	103.76(16)
C(13)-C(2)-C(4)-C(3)	107.24(16)
C(1)-C(2)-C(4)-C(3)	-105.93(15)
C(4)-O(1)-C(5)-C(6)	-49.44(17)
C(1)-N(1)-C(6)-C(7)	-163.39(14)
C(1)-N(1)-C(6)-C(5)	74.07(19)
O(1)-C(5)-C(6)-N(1)	-40.19(18)
O(1)-C(5)-C(6)-C(7)	-163.35(13)
N(1)-C(6)-C(7)-C(12)	123.87(15)
C(5)-C(6)-C(7)-C(12)	-112.82(17)
N(1)-C(6)-C(7)-C(8)	-57.22(19)
C(5)-C(6)-C(7)-C(8)	66.09(18)
C(12)-C(7)-C(8)-C(9)	0.4(2)
C(6)-C(7)-C(8)-C(9)	-178.51(14)
C(7)-C(8)-C(9)-C(10)	0.2(2)
C(8)-C(9)-C(10)-C(11)	-0.4(2)
C(9)-C(10)-C(11)-C(12)	-0.1(2)
C(10)-C(11)-C(12)-C(7)	0.8(2)
C(8)-C(7)-C(12)-C(11)	-0.9(2)
C(6)-C(7)-C(12)-C(11)	178.01(15)

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