Synthesis of Densely Functionalized Cyclopropanes via Diastereoselective Nucleophilic Additions to in Situ Generated Cyclopropenes

BY

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Synthesis of Densely Functionalized Cyclopropanes via Diastereoselective Nucleophilic Additions to in Situ Generated Cyclopropenes

Michael Rubin (Chairperson)

Date approved: 12/20/2013

Abstract

This thesis is concerned with the development and application of methods for the diastereoselective synthesis of substituted cyclopropanes. The methodology described in this dissertation is based on the addition of nucleophiles to highly reactive cyclopropene intermediates, to which a variety of oxygen and nitrogen-based nucleophiles can be efficiently employed in this transformation. The presented methodology provides easy access to di-, tri- and tetrasubstituted cyclopropanes which is divided into three chapters and describes not only the methodology developed in our research group but also other synthetic routes to densely substituted cyclopropanes.

Chapter one is a review of synthetic methodologies for the preparation of densely substituted chirally-rich cyclopropanes with three stereocenters. The first part of the chapter will describe the stereoselective addition of zinc carbenoids to substituted alkenes. The following section will cover recent advances in the field of transition-metal-catalyzed carbene chemistry. Other methods including Michael-initiated ring closure and C-H activation reactions will be discussed in the final part of chapter one.

Chapter two focuses on intermolecular formal nucleophilic substitution of bromocyclopropanes with azoles and anilines. The developed methodology aims for the construction of stereodefined di- and trisubstituted cyclopropanes. Formal substitution of bromocyclopropanes proceeds via the dehydrohalogenation of bromocyclopropane generating cyclopropene in situ followed by subsequent addition of a nitrogen-based nucleophile with

Abstract (Continued)

efficient selectivity control achieved by thermodynamically driven epimerization of enolizable carboxamides or directing effect of a substituent on a three-membered cycle.

Chapter three describes a highly efficient and diastereoselective synthesis of tetrasubstituted donor-acceptor cyclopropanes that can be obtained in a homochiral form from corresponding bromocyclopropyl carboxylic acids. A single chiral center on bromocyclopropane dictates the configuration of the other two stereocenters that are successively installed via a sterically controlled addition of a nucleophile to a chiral trisubstituted cyclopropene, followed by a thermodynamically driven epimerization of the resulting enolate intermediate. This new "dual-control" strategy was successfully employed to the synthesis of densely substituted cyclopropanes in inter- and intramolecular fashion.

Keywords: cyclopropene, cyclopropane, bromocyclopropanes, donor-acceptor cyclopropanes, β-aminocyclopropanecarboxylic acid, activated C=C bond, aza-Michael, oxa-Michael, directing groups, cyclopropyl acid.

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My time at KU was made enjoyable in large part due to the many friends and that became a part of my life. I owe many thanks to Kevin Godber, Dr. Igor Zheldakov, Yevhen Holubnyak, Donnie Scott, Moon Young Hur, Alex Melin, Ayrat Sirazhiev, Dr. Muharrem Tunc, Eyyup Shaq, Lawrence and Mayuko Settlers, Nathan Brennan and many others.

Finally, I would like to thank my dear wife Anastasiya Agapova for all her love, support and friendship over the last 8 years. Special thanks to my little daughter Anna for being such a sweet girl and always cheering me up, I love you so much!

I dedicate this thesis to my parents,

Irina and Grigoriy Ryabchuk

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1. “Formal Nucleophilic Substitution of Bromocyclopropanes with Azoles”, Ryabchuk, P.; Rubina, M.; Xu, J.; Rubin, M. *Org. Lett.* **2012**, *14*, 1752.

2. “Formal Substitution of Bromocyclopropanes with Nitrogen Nucleophiles”, Banning, J. E.; Gentillon, J.; Ryabchuk, P. G.; Prosser, A. R.; Rogers, A.; Edwards, A.; Holtzen, A.; Babkov, I.; Rubina, M.; Rubin, M. *J. Org. Chem.,* **2013**, *78*, 7601.

3. “Dual Control of the Selectivity in the Formal Nucleophilic Substitution of Bromocyclopropanes en route to Densely Functionalized, Chirally-Rich Cyclopropyl Derivatives”, Ryabchuk, P.; Edwards, A.; Gerasimchuk, N.; Rubina, M.; Rubin, M. *Org. Lett.* **2013**, *15*, 6010.

Table of Contents

List of Schemes

List of Figures

List of Tables

Chapter 1. Synthesis of Densely Substituted Cyclopropanes with Three Stereocenters

This thesis is concerned with the synthesis of chiral densely functionalized cyclopropanes. For this reason, in the introductory chapter, it is appropriate to provide an overview of synthetic methods, which have been used in their preparation.

1.0. Introduction

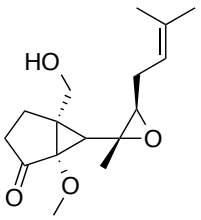
Cyclopropane-based scaffolds are attractive and versatile targets due their innate rigidity, unusual geometry, compact size, and metabolic stability.[1] The cyclopropane unit is an extremely useful tool for controlling the conformation of molecules as the rigid carbon backbone allows the substituents to be organized in three-dimensional space. Despite the importance of this target, the synthesis of enantiomerically and diastereomerically pure cyclopropane derivatives still remains a considerable challenge. Efficient asymmetric assembly of cyclopropanes is often limited to di- and trisubstituted cyclopropanes. Thus, more effort is required in developing new methods to synthesize highly substituted cyclopropanes, especially in intermolecular fashion.[2]

1.1. Occurrence in Nature and Applications

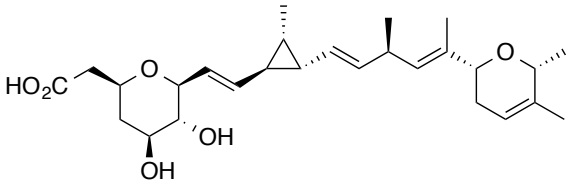
Substituted cyclopropanes are attractive targets because of their biological and pharmaceutical applications.[3] While the cyclopropane ring is highly strained, it is still found in a large number of natural products and biologically active compounds.[4] There is a number of multisubstituted cyclopropanes with impressive biological profiles (Scheme 1). Fumarranol **1** is a member of fumagillin family of natural products and selectively inhibits type 2 methionine aminopeptidase ($MetAP_2$) and endothelial cell proliferation

and is also active in a mouse model of angiogenesis in vivo.[5] The polyketide Ambruticin **2** is an attractive candidate for drug development as an antifungal agent, which was isolated from the fermentation of *Polyangium cellusum var. fulvum*.[6] This trisubstituted *trans*-divinylcyclopropane compound exhibits unprecedented oral activity against histoplasmosis and coccidiomycosis fungal infections. Ambruticin also displays potent inhibitory activity against the yeast strain *Hansenula anomala.*[7] Crispatene **3** is a mild cytotoxic agent, a member of polypropionate natural products which has been isolated from the saccoglossan mollusc *Elysia crispate*[8]. Eglumetad **4** (LY 354740) is a highly potent agonist selective for group II ($mGluR_{2/3}$) receptors (EC_{50} = 5.1 and 24.3 nM at

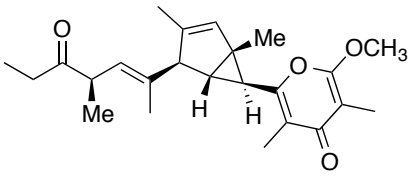
Scheme 1



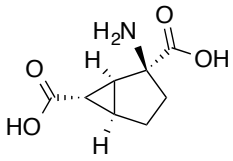
Fumarranol **1**



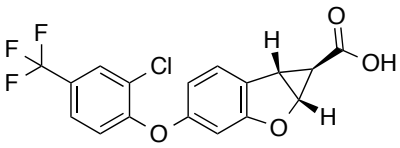
Ambruticin **2**



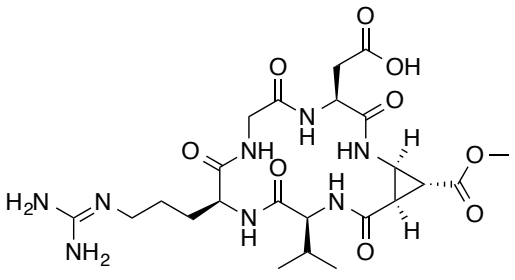
Crispatene **3**



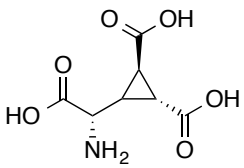
Eglumetad **4**



CHEMBL475027 **5**



CHEMBL272661 **6**



DCG IV **7**

$mGlu_2$ and $mGlu_3$ receptors respectively). Eglumetad is widely used in studies of addiction, epilepsy, schizophrenia, hyperactivity, and sleep. [9] Cyclopropyl benzofuran **5** exhibits good GPR40 agonistic activity with EC_{50} = 0.1nM and is used to treat type 2 diabetes. [10] Cyclopeptide **6** is a novel high-affinity $\alpha_v \beta_3$/ $\alpha_v \beta_5$ integrin binder with EC_{50} = 0.02 μM inhibition of human integrin $\alpha_v \beta_3$ receptor and EC_{50} = 1.5 μM $\alpha_v \beta_5$ receptor inhibition. DCG-IV **7** is a research drug which acts as a group-selective agonist for the group II metabotropic glutamate receptors ($mGluR_{2/3}$). DCG-IV has potent neuroprotective and anticonvulsant effects in animal studies, anti-Parkinsonian effects, but also impairs the formation of memories.[11]

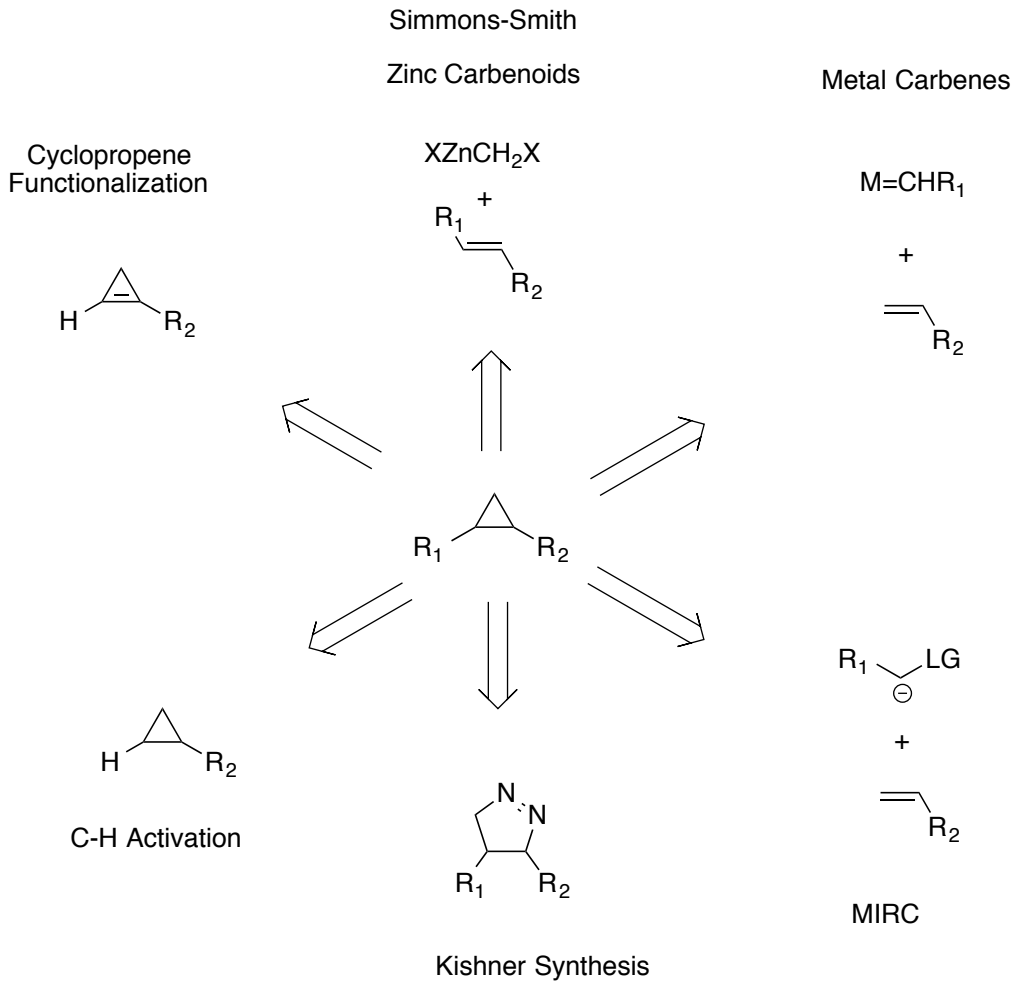
1.2. Synthetic Approach Towards Densely Substituted Cyclopropanes

There have been numerous synthetic studies in the literature, new and more efficient methods for the preparation of trisubstituted cyclopropanes in enantiomerically pure form are still evolving. [12] Several distinct approaches for the construction of densely substituted cyclopropanes include: carbenoid addition to alkenes, also known as the Simmons-Smith cyclopropanation; transition-metal-catalyzed carbene [2+1] cycloaddition, Michael-initiated ring closure (MIRC); Kishner synthesis, pyrolysis and photolysis of pirazolines; functional group manipulation/C-H activation of existing cyclopropanes and cyclopropene functionalization (Scheme 2).

1.3. Simmons-Smith Cyclopropanation

Discovered more than 50 years ago, [13] Simmons-Smith cyclopropanation is the reaction of alkenes with diiodomethane in the presence of activated zinc, affording

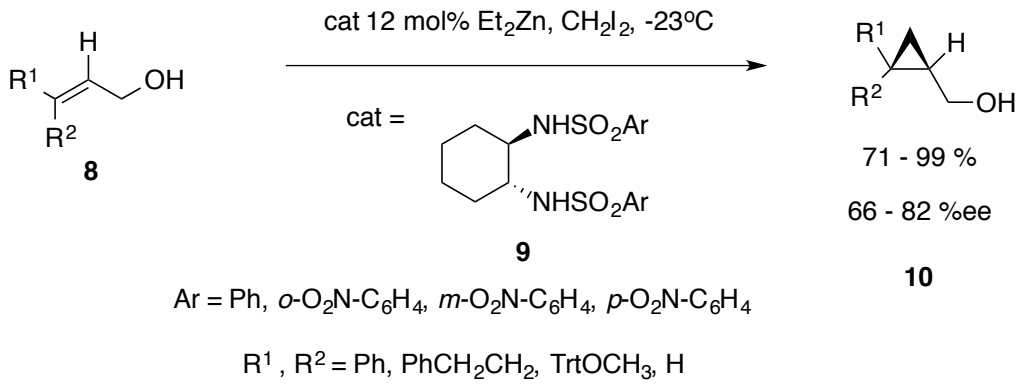
Scheme 2



cyclopropanes. Despite the tremendous progress that was done since its discovery in 1958, the asymmetric Simmons–Smith reaction was only introduced in 1992 by Kobayashi et al.[14] on allylic alcohols **8** in the presence of chiral disulfonamide catalyst **9**. (Scheme 3).

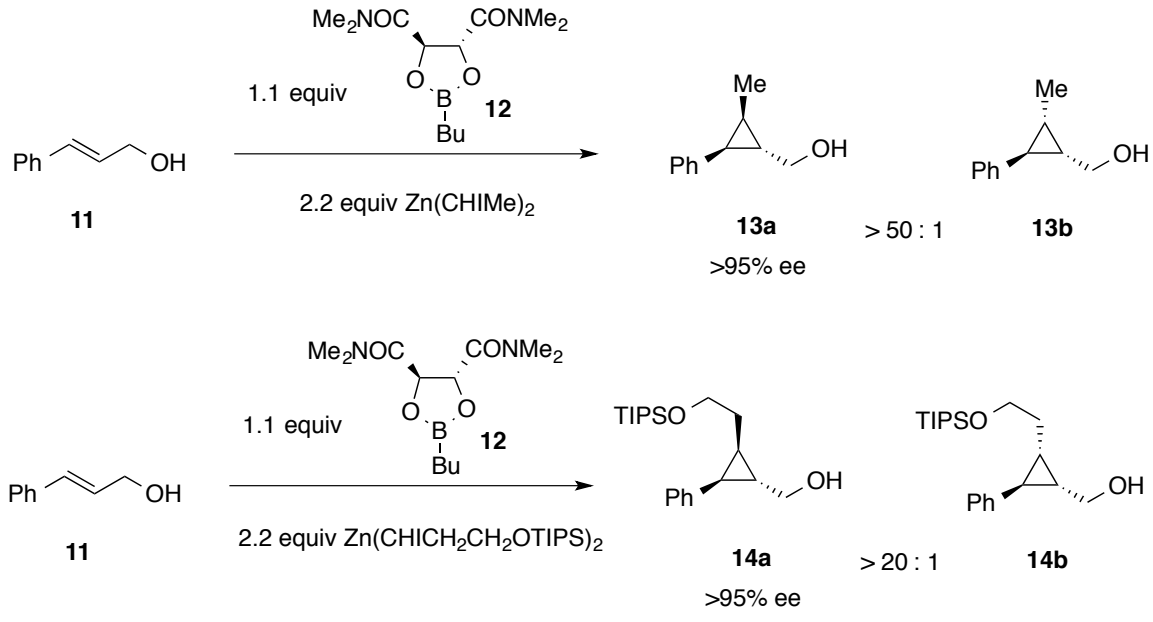
The Simmons-Smith reaction remains one of the most important reactions for the synthesis of cyclopropanes, however the use of Simmon-Smith cyclopropanation to generate 1,2,3-trisubstituted cyclopropanes in enantioselective fashion is very rare.[15] The most common zinc carbenoid reagents derived from diiodomethane are typically used to

Scheme 3



install a methylene group on an alkene substrate. Alternatively, α-substituted (α-halo, α-alkyl and α-arylzinc) zinc carbenoids[16] can be used to prepare substituted cyclopropanes. α-alkylzinc carbenoids may partially decompose via a β-hydride elimination pathway, a careful temperature control and a large excess of reagent is needed to obtain high yields of the cyclopropane.

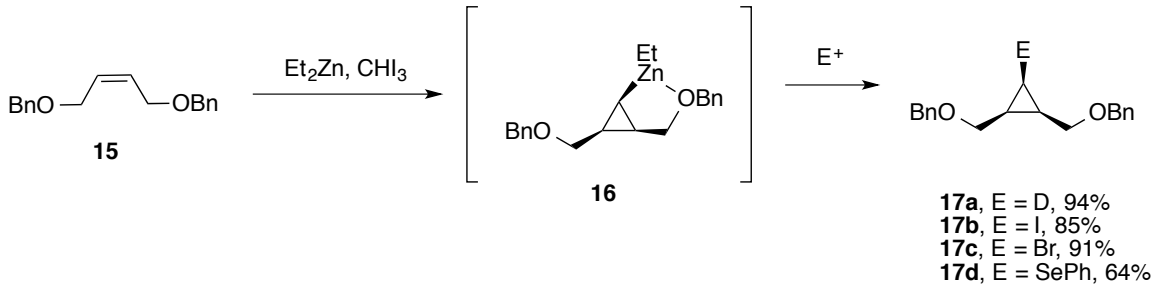
Scheme 4



In 1997 Charette et al.[17] demonstrated a new method to generate 1,2,3-substituted cyclopropanes **13** and **14** with excellent diastereo- and enantiocontrol by using substituted zinc carbenoids in the presence of the chiral dioxaborolane-derived ligand **12** (Scheme 4). High diastereoselectivities and enantioselectivities were obtained with a variety of allylic alcohols, treated with the zinc carbenoid reagents formed by mixing 1,1-diiodoethane and diethylzinc. It was also shown that functionalized 1,1-diiodoalkanes can be used in this reaction, cyclopropane **13a** can be obtained by treating cinnamyl alcohol **11** with zinc-based reagent prepared from l-triisopropylsiIyloxy-3,3-diiodopropanaen and Et_2Zn) in the presence of chiral ligand **12**. These examples clearly show the potential of this methodology as a convergent synthesis of structurally complex cyclopropanes.

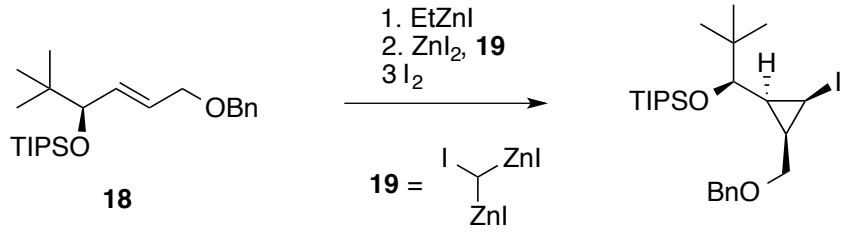
An alternative methodology for the synthesis of 1,2,3-substituted cyclopropanes was developed by Charette et al. in 2002.[18] The new method is based on the preparation of a gem-dizinc carbenoid reagent from iodoform and diethylzinc, which is further transformed into cyclopropylzinc **16** that is easily derivatized into substituted species **17** by quenching the intermediate with a suitable electrophile (Scheme 5). When allylic alcohol is used, the formation of the cyclopropylzinc and the subsequent electrophilic quench are highly diastereoselective.

Scheme 5



Protected alcohols can be used as directing groups in this transformation and the methodology can be applied to the cyclopropanation of enantiopure allylic alcohols (Scheme 6).[19] Zinco-cyclopropanation with *gem*-dizinc carbenoid **19** of enantioenriched *trans*-alkene **18** and quenching with iodine provided with *syn*,*cis*-iodocyclopropane **20**.

Scheme 6



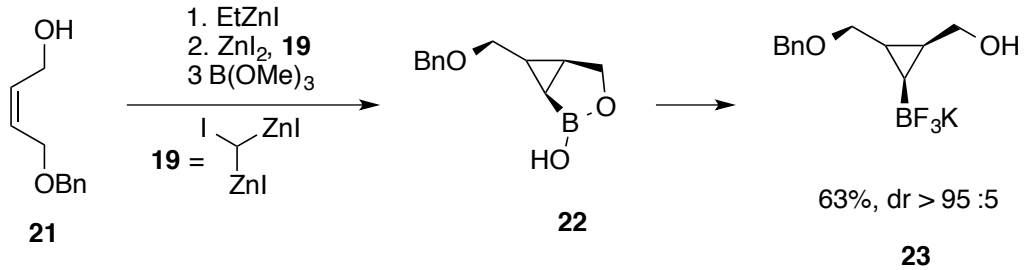
64 %, dr > 95 : 5

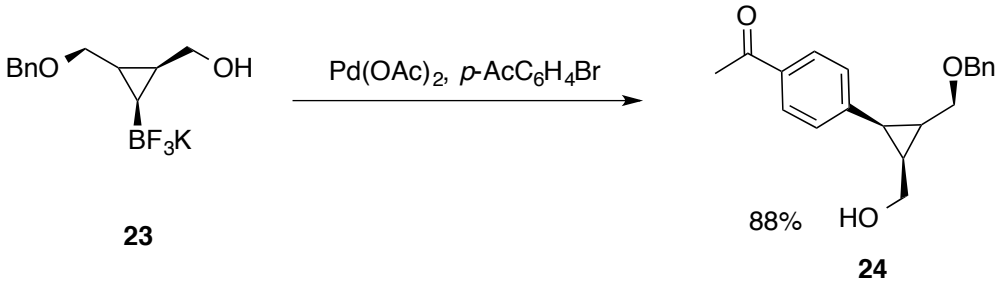
20

Similarly, 1,2,3-*syn*-*cis*-substituted potassium cyclopropyl trifluoroborates **23**[20] can be synthesized from allylic alcohols, readily prepared *gem*-dizinc carbenoids, trimethylborate and KHF_2. This reaction proceeds through a zincboron exchange, by quenching the cyclopropylzinc intermediate with an electrophilic boron source giving **22**, which can be converted into trifluoroborates **23** with KHF_2. Under optimized conditions the reaction is quite general for Z-alkenes, however the yields for E-alkenes are generally lower. Potassium cyclopropyl trifluoroborates can be used in Suzuki–Miyaura cross-coupling reactions,[21] 1,2,3-trisubstituted cyclopropane **24** can be obtained in high yield starting from cyclopropane **23** and 1-(4-bromophenyl)ethan-1-one in the presence of palladium acetate (Scheme 7).

Highly enantio- and diastereoselective tandem generation of iodocyclopropyl alcohols with four contiguous stereocentres was reported by Walsh et al.[22] Instead of

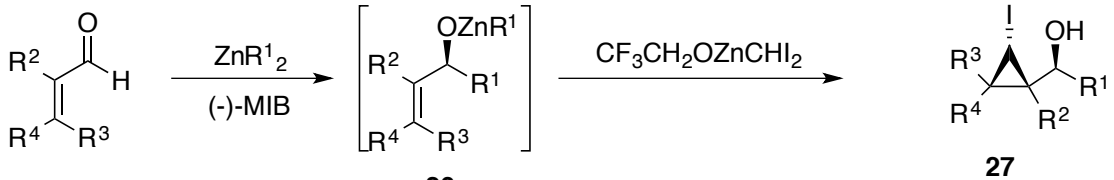
Scheme 7

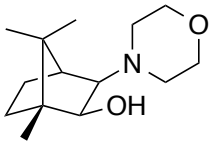




direct enantioselective cyclopropanation, a tandem reaction was designed involving an asymmetric addition to an aldehyde as the first step in the presence of a catalytic amount of Nugent's (-)-MIB.[23] The initial enantioselective C–C bond formation was followed by a diastereoselective cyclopropanation performed with $CF_3CH_2OZnCHI_2$ reagent, derived from iodoform, giving rise to the corresponding iodocyclopropyl alcohol with up to 99% ee (Scheme 8).

Scheme 8





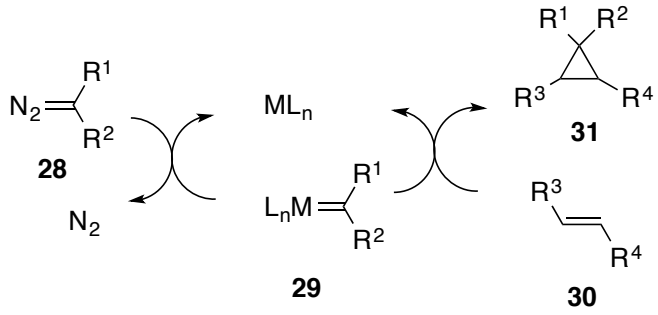
(-)-MIB

27a, R^1 = Et, R^2, R^4 = $(CH_2)_4$, R^3 = H: 68%, ee = 99%
27b, R^1 = R^3 = R^4 = Me, R^2 = H: 78%, ee = 99%
27b, R^1 = Et, R^2 = R^3 = H, R^4 = Ph: 70%, ee = 89%

1.4. Transition-metal-catalysed decomposition of diazoalkanes

Transition-metal-catalysed cyclopropanation of olefins with diazoalkanes is a very powerful tool in an organic chemist's arsenal.[24] Diazocompounds **28** are first reacted with transition metal compounds forming metal carbenoids complexes **29** with concomitant release of nitrogen. These compounds undergo [2+1] cycloaddition with olefins **30**, giving cyclopropanes **31** (Scheme 9). Highly enantioselective syntheses of functionalized cyclopropanes have been achieved, in particular, with catalysts based on copper, rhodium, ruthenium, palladium and other metals. Enantiocontrol in the carbine-transfer step may be achieved by chiral auxiliary tethered to a substrate by chiral ligands surrounding the metal center of the catalyst.

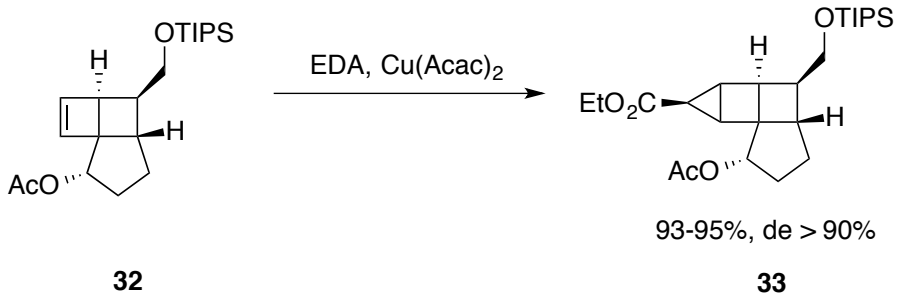
Scheme 9



1.5. Intramolecular cyclopropanation

Copper-based catalysts. 1,2,3-Trisubstituted cyclopropanes can be obtained starting from chiral alkene substrates. High stereochemical control in the ethyl diazoacetate (EDA) cyclopropanation reaction of a chiral cyclobutene **32**, using $Cu(Acac)_2$ as the catalyst is observed (Scheme 10).[25]

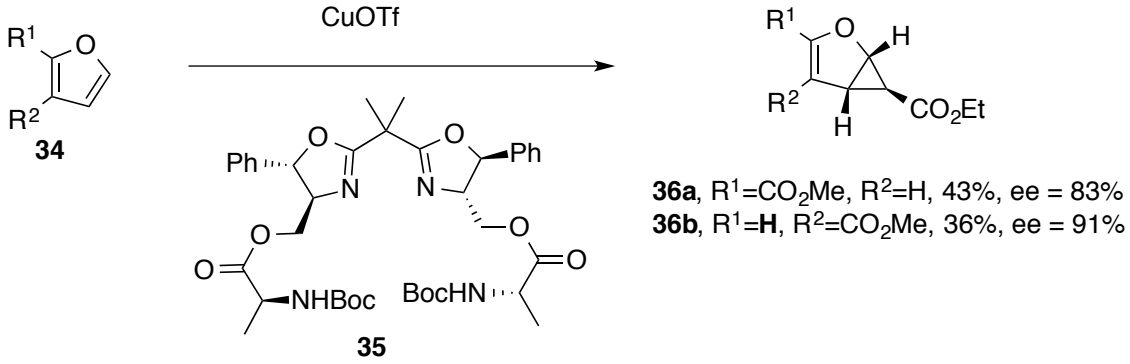
Scheme 10



32 **33**

Chiral ligands such as bidentate C_2-symmetric bisoxazolines are one of the most widely used copper-catalyzed enantioselective cyclopropanation reactions. Electron-rich furans **34** successfully react with EDA as reported by Reiser et al.[26] in the presence of bisoxazoline ligands **35**, provide the corresponding cyclopropanes **36** with high diastereo- and enantioselectivities. This methodology was applied to the total syntheses of paraconic acids[27], and other natural products containing bicyclic and tricyclic γ-butyrolactones (Scheme 11). [28]

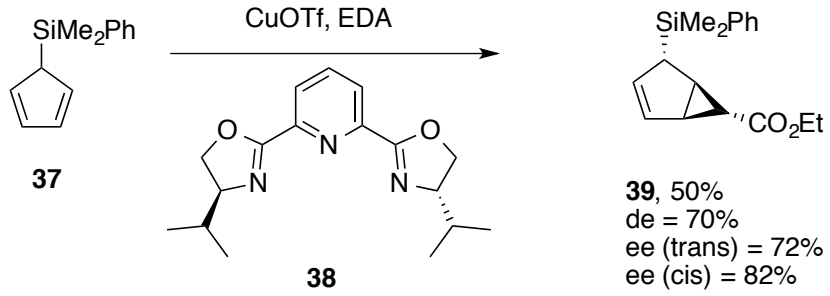
Scheme 11



In 2003, Landais et al.[29] reported a synthesis of densely substituted cyclopropanes bearing a useful allylsilane moiety **39**. The process is based on Cu-catalysed cyclopropanation/ desymmetrization of cyclopentadienylsilane **37** in the presence of a

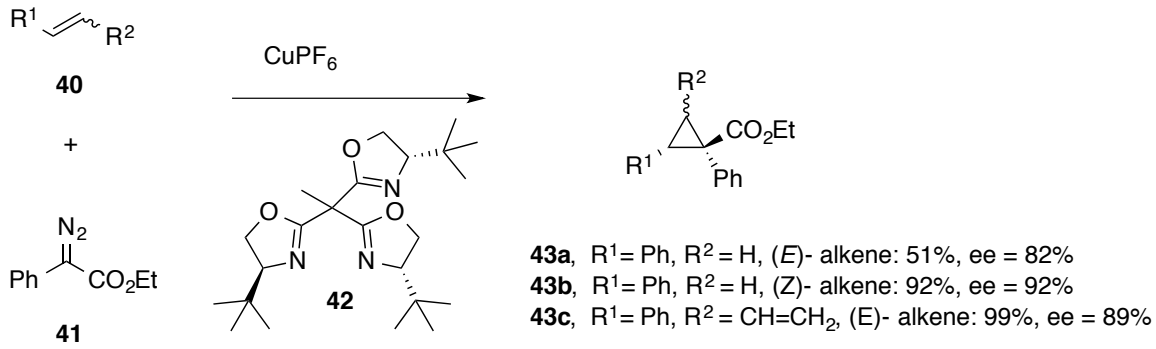
PyBox ligand **38** providing the corresponding cyclopropanes **39** as a mixture of diasteremers in high enantiomeric excess (Scheme 12).

Scheme 12



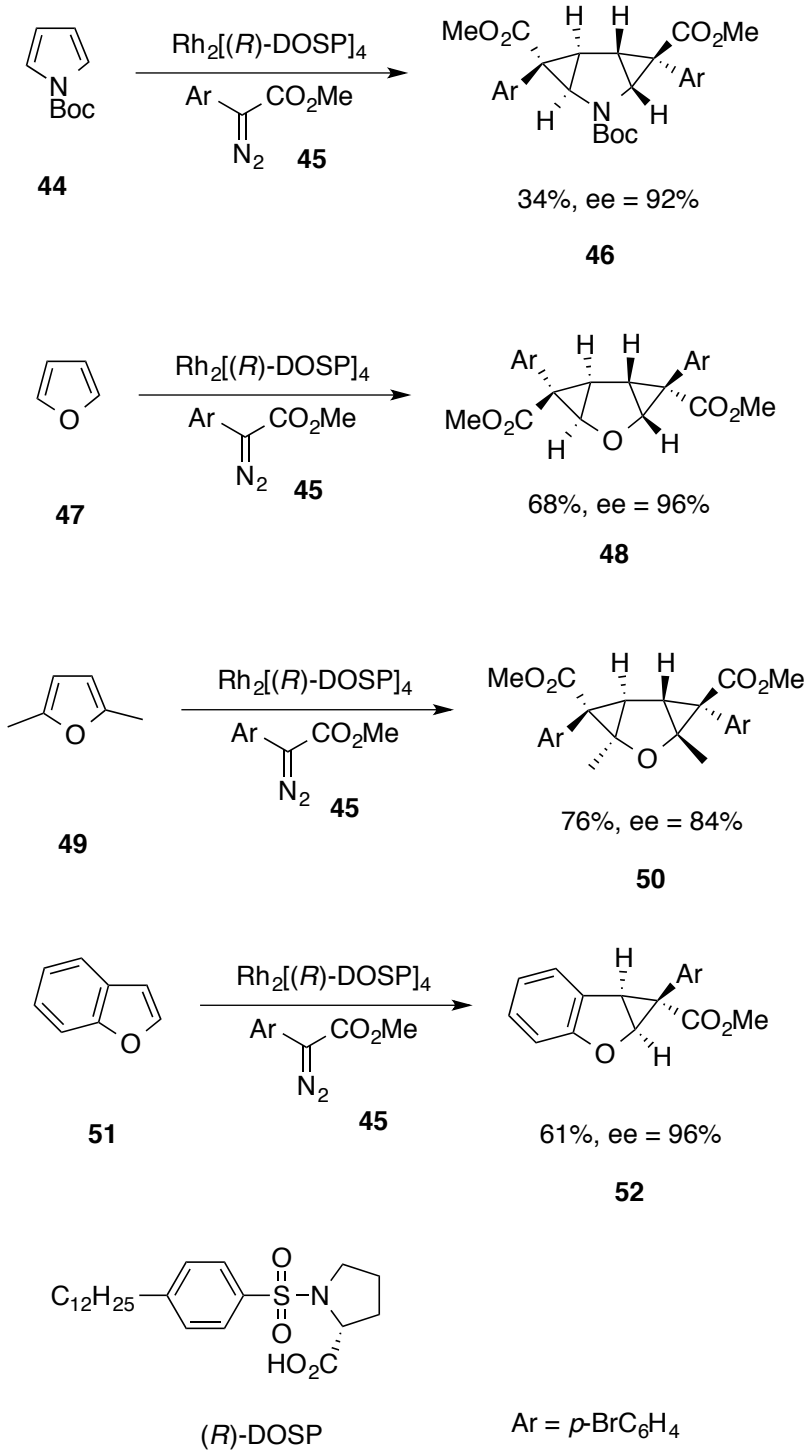
In 2007 Tang et al.[30] introduced a new type of ligand, a bisoxazoline moety with a pendant oxazoline **42**. This structural modification of the ligand greatly improved both the yield and enantioselectivity of the copper-catalyzed cyclopropanation of alkenes **40** with ethylphenyldiazoacetate **41**. This methodology provides an easy access for tri- and tetra-substituted cyclopropane derivatives **43** with high yields and impressive diastereo- and enantioselectivities (Scheme 13).

Scheme 13



Rhodium-based catalysts. Rhodium catalysts have also been extensively used and proveт to be effective catalysts for cyclopropanation using diazo compounds.

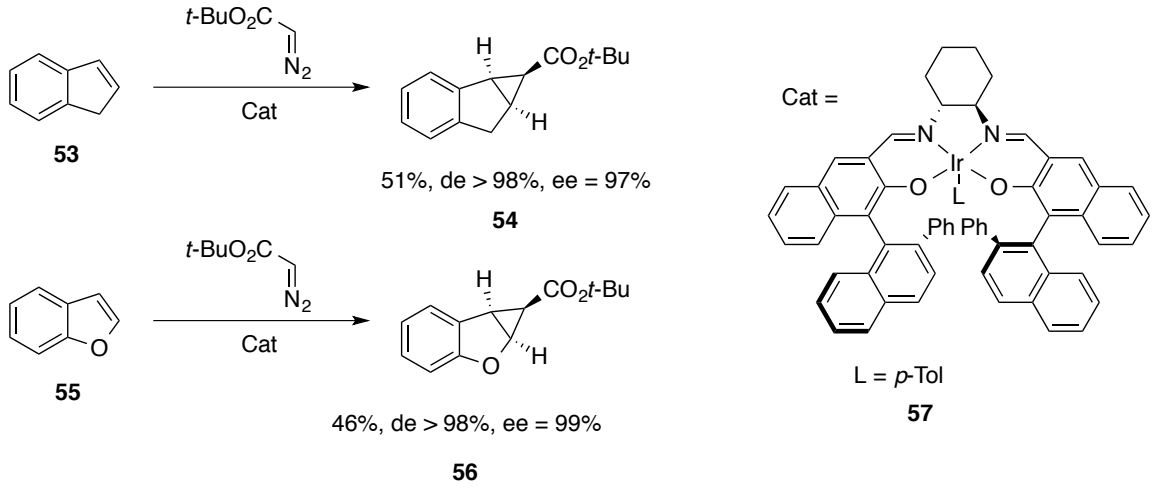
Scheme 14



Dirhodium tetrakis((R)-(N-dodecylbenzenesulfonyl)prolinate) catalyst Rh_2[(R)-DOSP]$_4$ was used by Davies et al.[31] to cyclopropanate aromatic nitrogen and oxygen heterocycles. Rhodium catalyst is used to induce the decomposition of aryldiazoacetates in the presence of heterocycles, resulting in the formation of mono- or biscyclopropanes of the furans and pyrroles. An interesting effect was observed, in these reactions the enantioselectivity was heavily influenced by the structure of the substrate. Upon initial coordination of the carbenoid and the heterocycle, and depending upon which bond of the substrate interacted with the rhodium complex first, either face of the heterocycle can be attacked (Scheme 14).

Iridium-based catalysts. Asymmetric cyclopropanations of alkenes with diazo compounds have also been reported, involving chiral iridium complexes as catalysts. As an example, Katsuki et al.[32] have recently developed highly *cis*-diastereo- and enantioselective cyclopropanations of cyclic olefins such as indene **53** and benzofuran **55** with diazoacetates using chiral aryliridium–salen complex **57** (Scheme 15).

Scheme 15

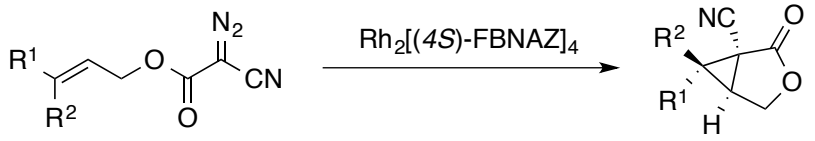


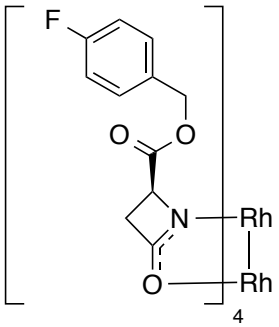
1.6. Intramolecular cyclopropanation

Highly functionalized synthetically versatile [n.1.0]bicycloalkanes can be assembled via the transition-metal-catalysed intramolecular cyclopropanation of alkenes.[33] When both functionalities, the diazo unit and the alkene, are in the same molecule, an intramolecular cyclopropanation is possible in the presence of an appropriate catalyst, thus producing bicyclic structures.

Rhodium-based catalysts. Rh-Catalyzed intramolecular cyclopropanation of 3-substituted-2-propenyl cyanodiazoacetates **58** was reported by Charette et al.[34] Cyclopropanation occurred cleanly to form the corresponding cyclopropane derivatives in high yields. Chiral dirhodium catalyst $Rh_2[(4S)\text{-FBNAZ}]_4$ was used to introduce chirality to cyanolactones. Yield and the level of enantioselection were shown to be heavily dependent on the structure of the starting material.

Scheme 16



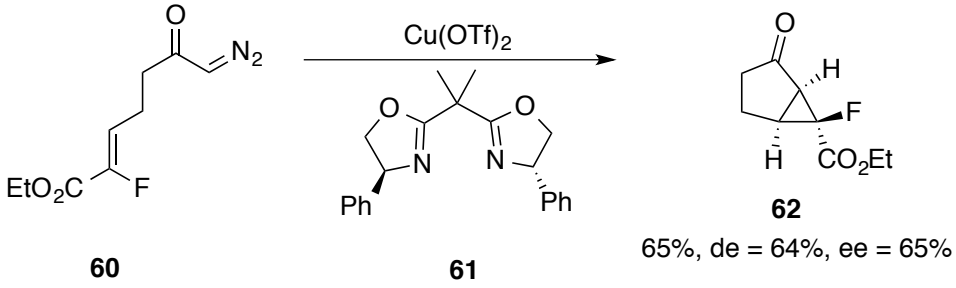


$Rh_2[(4S)\text{-FBNAZ}]_4$

59a, $R^1 = R^2 = H$: 85% ee = 85%
59b, $R^1 = R^2 = Me$: 37% ee = 56%
59c, $R^1 = Ph$, $R^2 = H$: 35% ee = 29%
59d, $R^1 = H$, $R^2 = Br$: 57% ee = 91%
59e, $R^1 = R^2 = Br$: 52% ee = 62%

Copper-based catalysts. When developing the copper-catalyzed asymmetric intramolecular cyclopropanation of substituted fluoroacrylate diazoacetates **60**, Wong et al. [35] synthesized highly functionalized and enantioenriched fluorocyclopropanes **62**[36] (Scheme 17). Copper triflate catalyst promoted the intramolecular cyclopropanation of the fluorodiazoketone **60** in the presence of a bisoxazoline ligand **61**.

Scheme 17

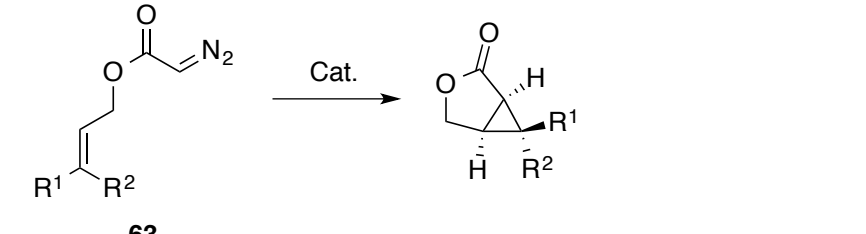


60 **61** **62**

65%, de = 64%, ee = 65%

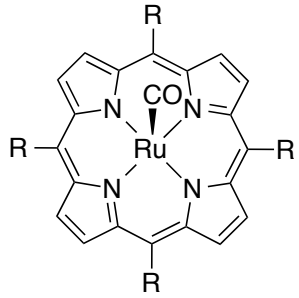
Ruthenium-based catalysts. Ruthenium complexes recently have been introduced in the field of enantioselective cyclopropanation.[37] Ruthenium is a direct neighbor of rhodium

Scheme 18

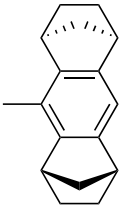


63

65a, R^1 = H, R^2 = Ph: 77% ee = 85%
65b, R^1 = i-Pr-(CH2)2, R^2 = Me: 85% ee = 30%



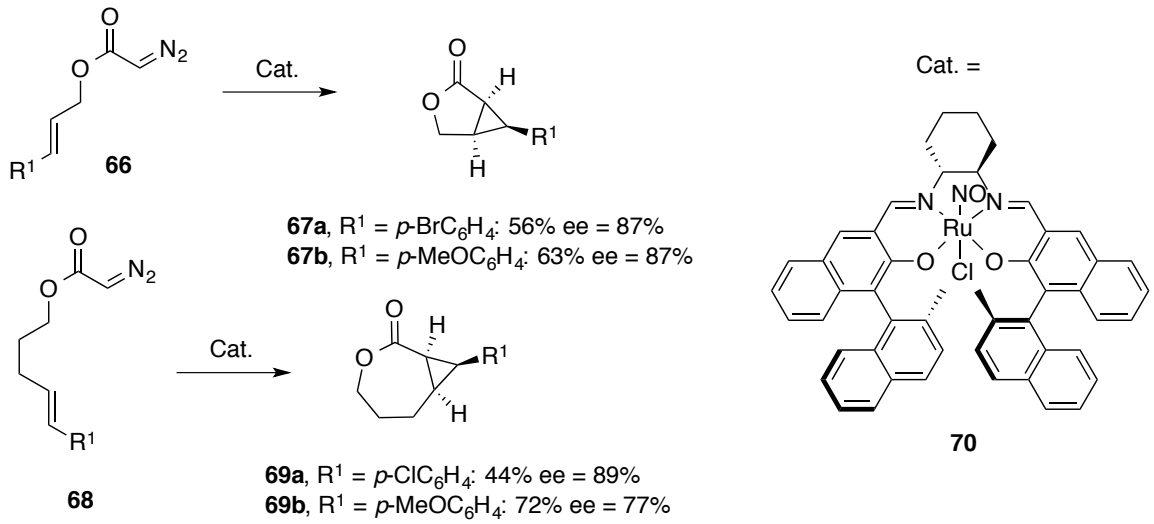
Cat. = **64**

R = 

in the periodic table and offers an advantage because it currently costs roughly one-tenth the price of rhodium. In both inter- and intramolecular cyclopropanation reactions, where ruthenium catalysts work successfully, they often rival established rhodium catalysts in terms of overall effectiveness. Chiral ruthenium D_4-symmetric porphyrin complex **64** has been used to catalyze the intramolecular cyclopropanation of allyl diazoacetates **63**, leading to the corresponding lactones in moderate-to-high enantioselectivitiesis, which is largely dependent on the substitution of the alkene (Scheme 18).[38]

Several types of chiral salen ligands **70**[39] were demonstrated by Katsuki et al.[40] proved to be efficient to induce chirality for the intramolecular cyclopropanation of various alkenyl α–diazoacetates **66**, **68**. It was shown that the cyclization outcome is strongly affected by several factors including the olefin substitution pattern, length and the nature of the linker connecting the olefin and diazomethyl moieties (Scheme 19).

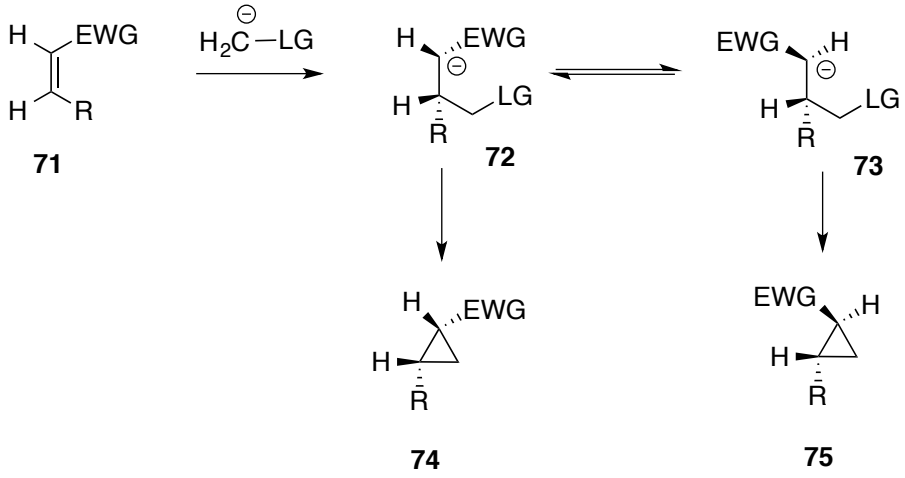
Scheme 19



1.7. Michael-Initiated Ring Closure (MIRC)

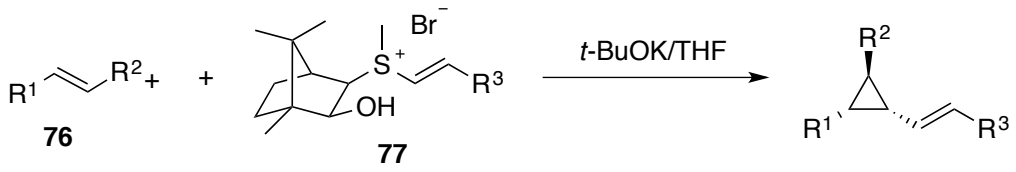
The nucleophilic conjugated addition reaction to an α,β-unsaturated carbonyl compound **71** bearing a γ-leaving group is a common method to prepare densely substituted cyclopropanes. The process is commonly refered as the "Michael-induced ring-closure" reaction (MIRC). Typically, stereospecific cyclopropanations using the MIRC reaction are observed only when the ring-closure process is faster than the rotation around the single C-C bond in the first intermediate formation **72** (Scheme 20).

Scheme 20



Tang et al.[41] reported a method to prepare a series of chiral 1,3-disubstituted-2-vinyl- cyclopropanes based on the addition of chiral sulfur ylides **77**. Camphor-derived sulfur ylides when in the presence of a variety of α,β -unsaturated carbonyl compounds reacted cleanly giving highly substituted cyclopropanes with great enantio- and diastereoselectivities. Interestingly, when the corresponding endo-type sulfonium ylides were used, the diastereoselectivities were not changed, but the absolute configurations of the products became opposite to those of the reactions of exo-type sulfonium ylides (Scheme 21).

Scheme 21

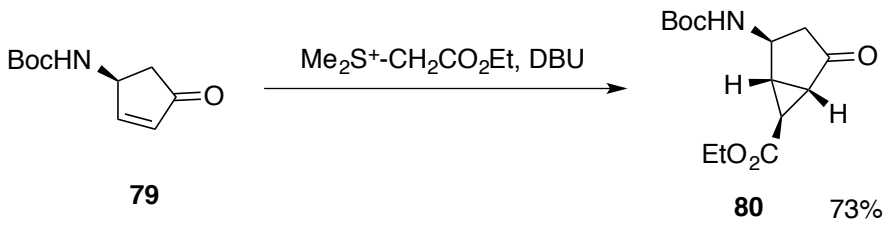


76 **77**

78a, $R^1 = R^3 = Ph$, $R^2 = CO_2Me$: 77% de > 98% ee = 99%
78b, $R^1 = R^3 = Ph$, $R^2 = Bz$: 83% de = 94% ee = 94%
78c, $R^1 = p\text{-}ClC_6H_4$, $R^2 = COt\text{-}Bu$, $R^3 = Ph$: 91% de = 90% ee = 98%
78d, $R^1 = R^3 = Ph$, $R^2 = CON(CH_2)_4$: 98% de > 98% ee = 94%
78e, $R^1 = R^3 = Ph$, $R^2 = CON(CH_2)_2O$: 99% de > 98% ee = 98%
78f, $R^1 = Ph$, $R^2 = CO_2Me$, $R^3 = TMS$: 85% de > 98% ee = 97%
78g, $R^1 = Ph$, $R^2 = CO_2Et$, $R^3 = TMS$: 75% de > 98% ee = 97%

LY354740 analogue **80** can be synthesized via the cyclopropanation of a chiral cyclopentenone **79** with sulfur ylide (Scheme 22)[42]. It is important to point out that bicyclic structure **80** was obtained as a single diastereomer, due to the addition of the ylide being directed by boc-protected amino group.

Scheme 22

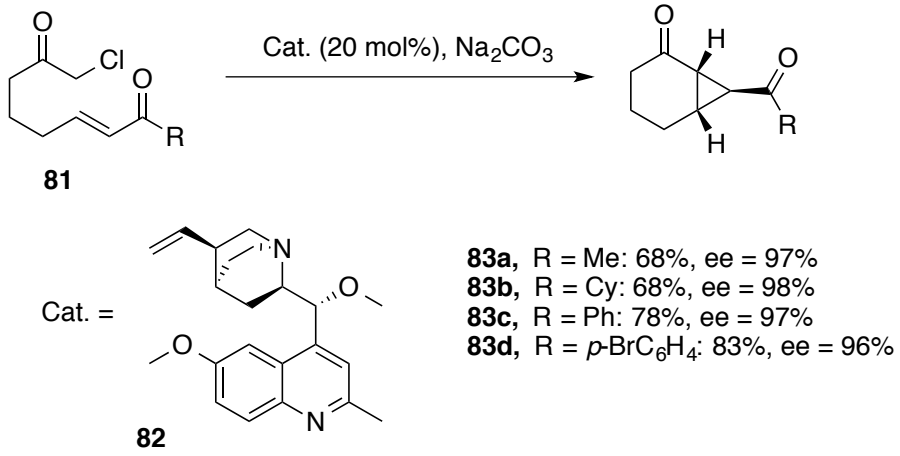


79 **80** 73%

Catalytic methods to generate chiral cyclopropanes via Michael-initiated ring-closure reactions are highy desired, and have obvious advantages compared to the MIRC cyclopropanations discussed above. A new class of catalytic asymmetric cyclopropanations have been developed with the use of chiral organocatalysts. In 2006, Gaunt et al. reported the first example of enantioselective intramolecular cyclopropanation based on the use of a chiral ammonium ylide as an organocatalyst (Scheme 23Scheme 24).[43] This catalytic process proved to be highly efficient, a wide

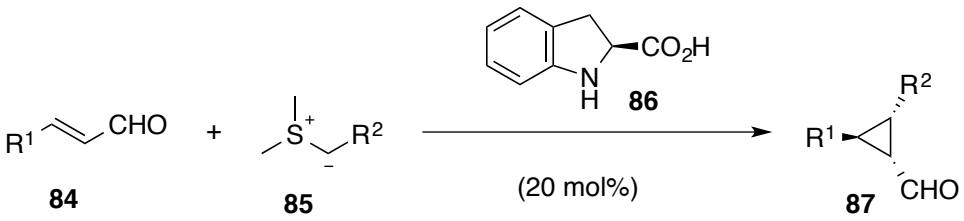
range of chiral functionalized cyclopropanes possessing excellent diastereo- and enantio-selectivities can be produced using this methodology. The method relies heavily on the organocatalyst derived from cinchona alkaloids and offers several advantages, e.g. transition metals are absent, inexpensive starting materials and a large pool of known chiral amines from which potential catalysts can be selected.

Scheme 23



An asymmetric cyclopropanation of α,β -unsaturated aldehydes was reported by MacMillan et al. using a novel class of iminium organocatalysts based upon directed electrostatic activation.[44] A chiral 2-carboxylic acid dihydroindole **86** was found to be a efficient catalyst for the reaction between a sulfonium ketone ylide **85** and an α,β unsaturated aldehyde **84**, providing the corresponding cyclopropanes **87** with excellent enantioselectivity and yields. It was demonstrated that the organocatalyst and the ylide were engaged in electrostatic association via their pendant carboxylate and thionium substituents (Scheme 24).

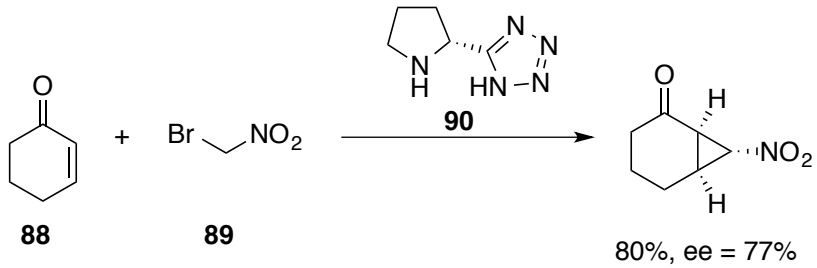
Scheme 24



87a, R^1 = *n*-Pr, R^2 = Bz: 85% de = 94% ee = 95%
87b, R^1 = CH_2Oallyl, R^2 = Bz: 77% de = 90% ee = 91%
87c, R^1 = Me, R^2 = Bz: 67% de = 90% ee = 90%
87d, R^1 = allyl$(CH_2)_3$, R^2 = Bz: 74% de = 92% ee = 96%
87e, R^1 = Ph, R^2 = Bz: 73% de = 94% ee = 89%
87f, R^1 = *i*-Pr, R^2 = Bz: 63% de = 96% ee = 96%
87g, R^1 = *n*-Pr, R^2 = *p*-BrC_6H_4: 67% de = 98% ee = 92%
87h, R^1 = *n*-Pr, R^2 = *p*-$MeOC_6H_4$: 64% de = 84% ee = 93%
87i, R^1 = *n*-Pr, R^2 = C*Ot*-Bu: 82% de = 72% ee = 95%

An excellent example of a one-step enantioselective nitrocyclopropanation was reported by Ley et al.[45] Using chiral 5-(pyrrolidin-2-yl)-1H-tetrazole as an organo-catalyst, the asymmetric nitrocyclopropanation of α,β -unsaturated ketone **88** has been achieved in high yield and with good enantioselective control (Scheme 25).

Scheme 25



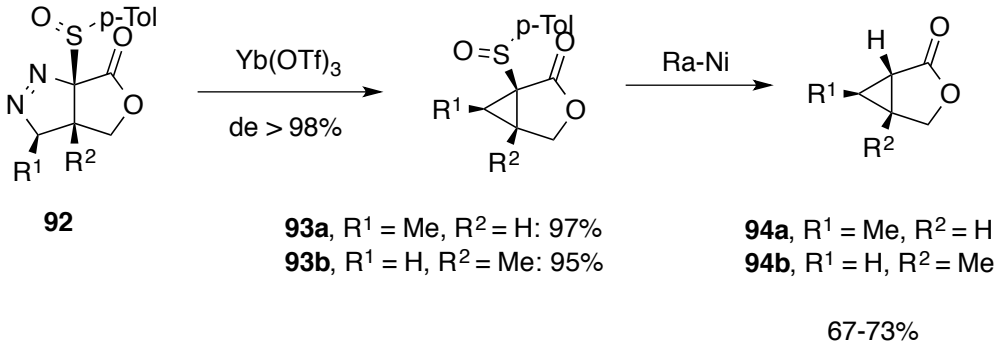
1.8 Kishner Synthesis

The synthesis of cyclopropanes by decomposition of pyrazolines is a well-known reaction.[46] Under thermal conditions along with cyclopropane formation a significant

amount of olefin product may be formed as well. The addition of Bronsted or Lewis acids significantly increases the proportion of cyclopropanes and lowers the temperature required for denitrogenation.

Ruano et al. have described a completely stereoselective denitrogenation of chiral sulfinylpyrazolines **92** into the corresponding cyclopropanes, performed in the presence of $Yb(OTf)_3$ under very mild conditions and in almost quantitative yields with complete retention of the configuration at both carbons flanking the nitrogen atoms (Scheme 26).[47] The metal forms a chelated species with the sulfinyl and carbonyl oxygens, which increases the electronic deficiency at C6 and provokes the concerted migration with extrusion of nitrogen. Raney-Ni desulfinylation of sulfinyl cyclopropanes **93** yielded optically pure bicyclic lactones **94** in good yields.

Scheme 26



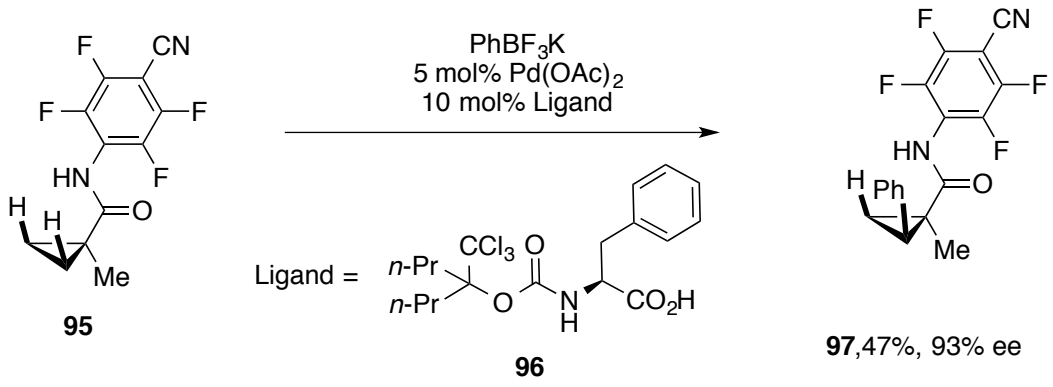
1.9. C–H Activation of Cyclopropanes

The catalytic $C(sp^3)$–H functionalization is a continuously growing field in organic synthesis due to the ubiquity of C–H bonds in nature.[48] However, the direct functionalization of the cyclopropyl unit is via C-H activation chemistry is still in its infancy. The rigidity of the cyclopropyl subunit and orbital hybridization leads to a more

sp^2-like character for its carbon atoms, which should facilitate the C-H activation reactions.

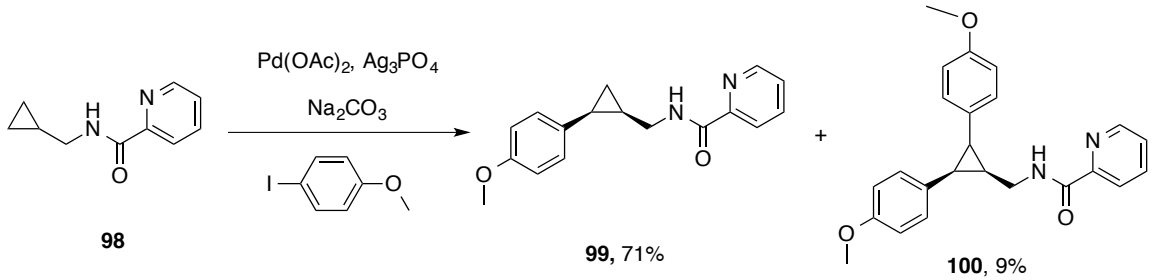
To facilitate cyclopropane $C(sp^3)$−H cleavage Yu and coworkers[49] installed an acidic N-arylamide directing group **95** enabling Pd(II)-catalyzed C−H/R−BX_n cross-coupling under mild conditions. After systematic examination of structurally diverse array of amino acid ligands for stereoinduction, chiral ligand **96** was found to be the most efficient. This method is compatible with aryl-, vinyl-, and alkylboron reagents and tolerates a number of different substituents at the α- position (Scheme 27).

Scheme 27



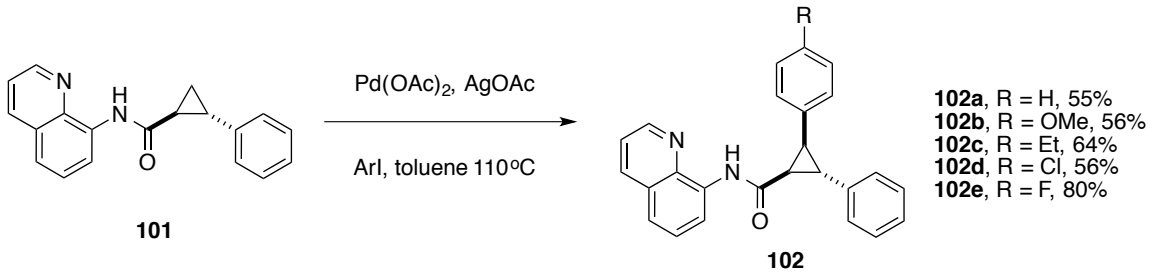
In 2013 Charette and coworkers [50] demonstrated a highly selective C-H functionalization of cyclopropanes employing a picolinamide auxiliary. A Pd-catalyzed, picolinamide-enabled C-H activation of cyclopropanes **98** employing aryl iodides as coupling partners was developed. Various aryl iodides can be employed as coupling partners, providing exclusively *cis*-substituted cyclopropylpicolinamides **99**, however a minor product is obsevered. Along with monoarylated cyclopropane **99**, a product of diarylation **100** is formed as a mixture of *cis* and *trans* (Scheme 28).

Scheme 28



A highly diastereoselective synthesis of di- and trisubstituted cyclopropanecarboxamides was reported by Babu et al.[51] using a N-(quinolin-8-yl)carboxamide as a directing group. The C-H functionalization reaction of cyclopropanecarboxamide **101** occurs in the presence of palladium acetate, installation of aryl groups is performed with various aryl iodides. The arylation of cyclopropanecarboxamide **101** with aryl iodides having electron-donating or -withdrawing groups at the para-position gave the corresponding trisubstituted cyclopropanes as single diastereomers in moderate to good yields (Scheme 29).

Scheme 29

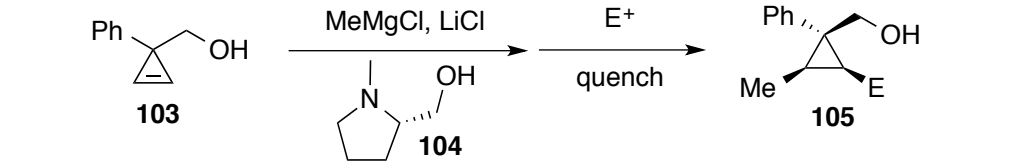


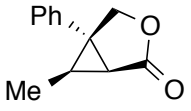
1.10. Cyclopropene Functionalization

Functionalization of cyclopropenes constitutes an attractive alternative to the more mainstream routes to chiral cyclopropanes.[52] Examples of enantioselective synthesis of trisubstituted cyclopropanes from cyclopropene precursors are still rare.

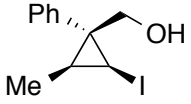
Fox et al.[53] reported the enantioselective carbomagnesation of cyclopropenes **103** performed in the presence of N-methylprolinol **104** as a chiral ligand. Carbometalation is facially selective and the nucleophile is delivered by a hydroxyl functional group, the cyclopropylmetals can be trapped with a variety of electrophiles to generate highly substituted cyclopropanes **105**. The process is highly diastereoselective, only one out of four isomers is formed, and the reaction proceeds with high levels of enantioselectivity and in a good yield (Scheme 30).

Scheme 30

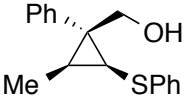




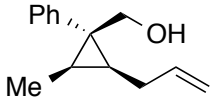
105a, E = CO_2
55%, 96% ee



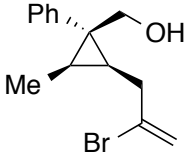
105b, E = I_2
64%, 98% ee



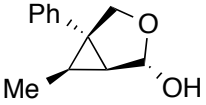
105c, E =$(PhS)_2$
66%, 91% ee



105d, E = *allyl*-Br
65%, 94% ee



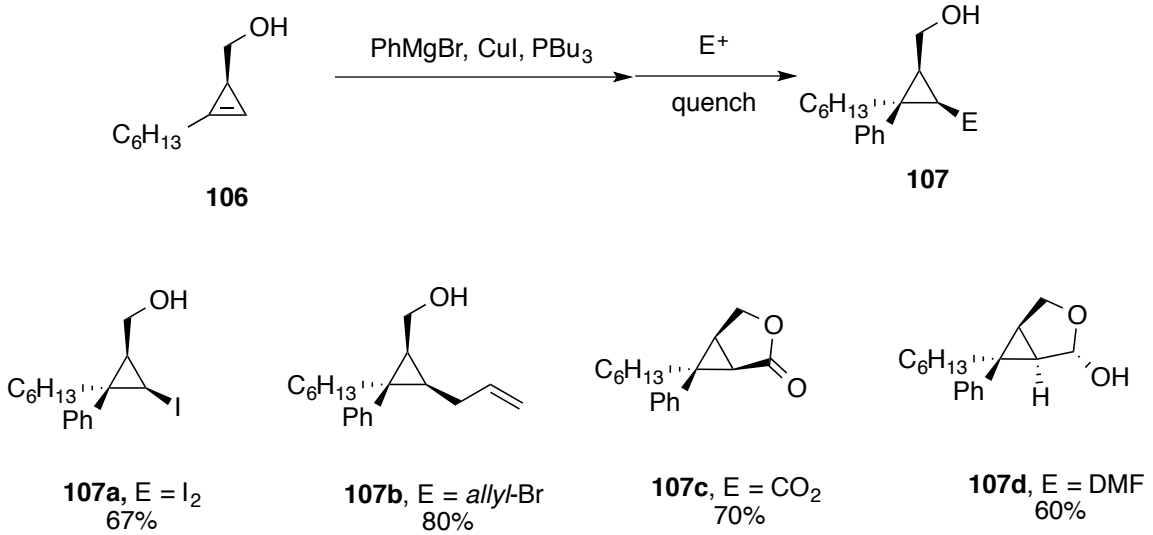
105e, E = 2-bromoallylbromide
69%, 95% ee



105f, E = DMF
66%, 98% ee

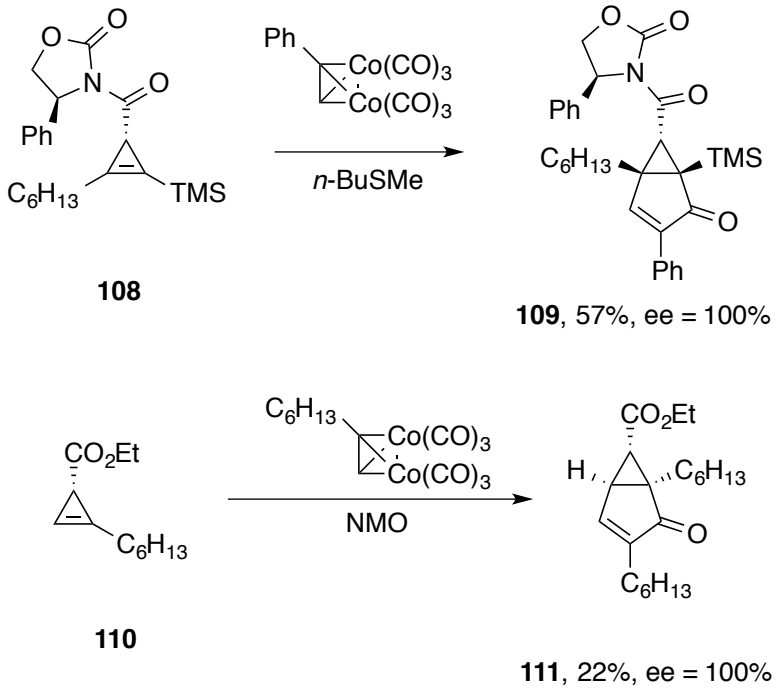
A similar strategy was suggested by the same researchers which was applied to a chiral cyclopropene substrate: Cu-catalyzed addition of aryl Grignard reagents to cyclopropene **106** and subsequent trapping with a suitable electrophile, generating highly substituted cyclopropanes **107**. The reaction proceeds with high regio- and diastereoselectivity (Scheme 31).[54]

Scheme 31



Stereoselective intermolecular Pauson–Khand reaction was demonstrated on chiral cyclopropenes **108** and **110**.[55] (Scheme 32). Enantiomerically pure cyclopentenone derivatives **109** and **111** were isolated in each of the reactions performed in the presence of a dialkylsulfide (*n*-BuSMe) or a N-oxide (N-methylmorpholine N-oxide (NMO)). The cyclopropane ring strongly influences the stereochemistry of the reaction at the enone and the three-membered ring can subsequently be cleaved under mild conditions.

Scheme 32



1.11. Conclusions

1,2,3-Trisubstituted cyclopropanes are basic structural moieties in a wide range of natural and biologically active compounds as well as important building blocks in organic synthesis. Synthetic utility and application in medicinal chemistry resulted in the development of many strategies for their preparation in their optically pure form. However, there are much fewer methods for preparing enantiomerically pure densely substituted cyclopropanes compared to less substituted cyclopropanes.

Helping to address the lack of methods for the synthesis of stereodefined densely substituted cyclopropanes, we have developed a diastereoselective protocol for the additions of nucleophiles to chiral cyclopropropenes in an inter- and intramolecular fashion.

Chapter 2. Formal Nucleophilic Substitution of Bromocyclopropanes with Azoles and Anilines

In this chapter a highly diastereoselective protocol toward N-cyclopropyl azoles and anilines will be described. These amino-substituted cyclopropanes belong to an important class of molecules - β-Aminocyclopropanecarboxylic acid derivatives (β-ACCs). [56]

2.0. Introduction.

β-Aminocyclopropanecarboxylic acid derivative sare important members of a versatile and synthetically challenging family of donor−acceptor cyclopropanes (DAC).[57] β-ACCs have been recognized for their ability to produce surprisingly stable secondary structures in short peptides[58] and serve as useful tools for conformational analysis.[59] They have also been used as key elements in natural products,[60] organocatalysts,[61] prospective drug candidates,[62] including potent antiviral,[63] antitumor,[64] and antihypertensive agents.[65] In contrast to a plethora of natural and synthetic analogues of α-aminocyclopropanecarboxylic acid (α-ACC), which have been extensively exploited in medicinal, chemical, and agricultural research,[66] synthesis of many β-ACC analogues face a number of difficulties and limitations. The problem associated with the stability of the three-membered ring in heteroatom-substituted "push−pull" cyclopropanes,[67] limits access to these structural motifs and limits their further use in the assembly of complex architectures.[68] As a result, substituted aminocyclopropane carboxylic acids possessing an additional stabilizing carboxylic acid group in the three-membered unit have been commonly used as more available β-ACC surrogates.

2.1. General Approach

Stereochemically defined and densely substituted cyclopropanes are readily available from the corresponding cyclopropenes via a number of highly diastereoselective additions of various entities across the strained double bond. This area of research has received major attention during the past decade, particularly due to the recent advances in transition metal-catalyzed transformations of cyclopropenes. At the same time, only a limited number of cyclopropenes can boast a long shelf life most are relatively short-living species and require special handling. This, in part, explains the lack of enthusiasm by the pharmaceutical industry in adopting these novel synthetic tools.

The methodology described in this chapter heavily relies on the addition of pronucleophiles to cyclopropenes, in which the highly reactive cyclopropene intermediates **113** are generated *in situ* from a stable bromocyclopropane precursor **112**, and reacted with nitrogen-based nucleophiles. The described reaction can be also seen as a formal nucleophilic substitution of bromocyclopropanes (Scheme 33).

Scheme 33

112 **113** **114**

Because standard substitution protocols used in larger ring chemistry are prohibitive in cyclopropane analogs due to significant ring strain and high s-character, a sequential dehydrobromination/nucleophile addition has served as a nucleophilic substitution surrogate for these strained substrates. This reaction operates via initial base-

assisted dehydrobromination, followed by the strain-release-driven addition of a pronucleophile to the double bond of a highly reactive cyclopropene intermediate.[69,70]

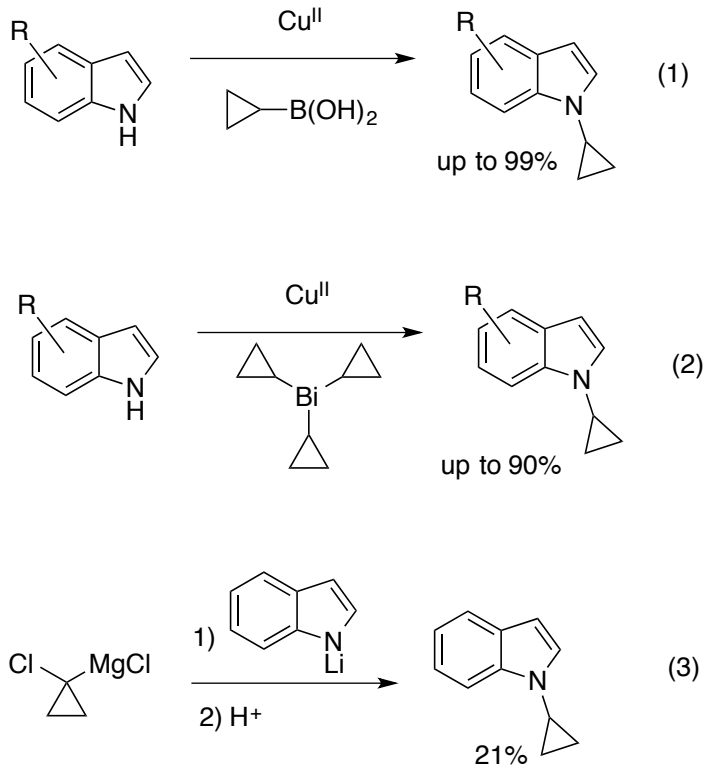
The Rubin group has previously disclosed efficient diastereoselective protocols for the formal nucleophilic substitution of structurally diverse bromocyclopropanes with oxygen- and sulfur-based pronucleophiles.[71] At the same time, attempts to employ amines as nitrogen-based pronucleophiles[72,73] have failed, which was surprising, considering the power and versatility of the analogous aza-Michael reaction.[74] The lack of reactivity was rationalized due to ineffective deprotonation of the N-H bond of 1° or 2° amine using relatively weak bases typically used in this reaction (KOH, t-BuOK). This renders this moiety less nucleophilic as compared to anionic species derived from more acidic alcohols and thiols.

2.2. Formal Nucleophilic Substitution of Bromocyclopropanes with Azoles

Efficient overlap of the cyclopropane's Walsh orbitals with the π-system of the adjacent aromatic substituent allows cyclopropyl(het)arenes with unique conformational features. It has been demonstrated that arylcyclopropanes can efficiently mimic active conformations of the bis-aryl[75] or benzylaryl moieties[76] producing remarkable pharmacological effects. Successful employment of cyclopropyl(het)arenes as bioisosteres is evidenced by a growing number of aryl- and hetarylcyclopropanes with impressive biological profiles, including antimalarial,[77] anti- cancer,[78] anti-HIV,[79] antidepressant,[80] immunemodulatory,[76] antibiotic,[81] and analgesic[82] activity. Assembly of hetarylcyclopropanes possessing a cyclopropyl−N_{HetAr} bond is a challenging task and thus far has been only achieved via Cu-catalyzed coupling of azoles to cyclopropylboronic

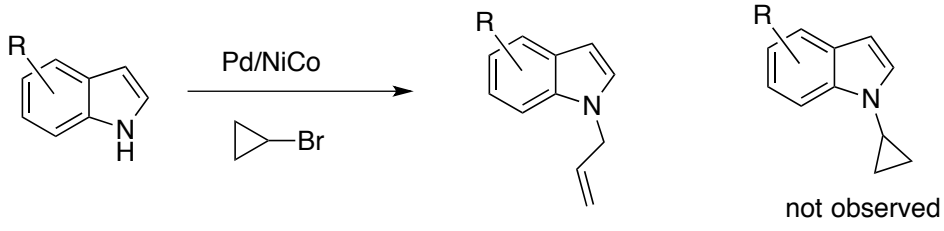
acids (eq. 1)[83] and cyclopropylbismuth reagents (eq. 2),[84] and the reaction of magnesium cyclopropylidene with N-lithioarylamines (eq. 3) (Scheme 34).[85]

Scheme 34



It is also important to note that due to vulnerability of cyclopropyl bromide to ring opening, the coupling reactions of azoles with cyclopropyl bromide using a palladium, nickel, or copper catalyst result in the formation of N-allylated product (Scheme 35).[83]

Scheme 35

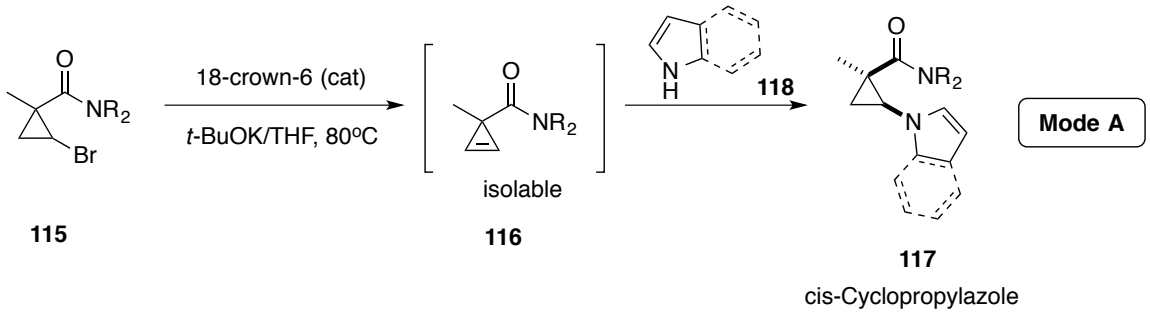


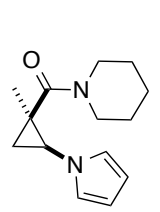
2.2.1. Azoles as Nitrogen-Based Nucleophiles: Mode A

Directed Addition of Nucleophiles, Convergent Approach to Conformationally Constrained cis-Cyclopropyl Amino Acid Derivatives

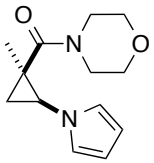
The N−H bond acidity of azoles, whose pKa fall in the same range as values for carboxamides and comparable to many O- based pronucleophiles makes them good candidates for the formal nucleophilic substitution reaction. The lack of success in previous attempts on N-alkylation of azoles via the formal nucleophilic substitution of bromocyclopropane by other groups[86,87] can be attributed to the unstable, electron-rich intermediate - unsubstituted cyclopropene - which undergoes rapid concurrent

Scheme 36

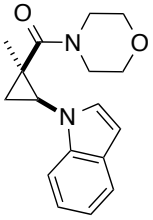




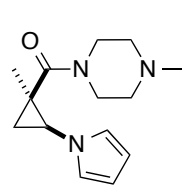
117aa, 85% dr 14:1



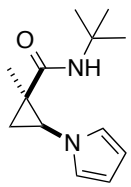
117ba, 61% dr 19:1



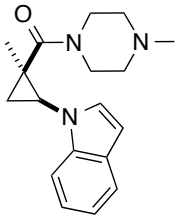
117bb, 41% dr 11:1



117ca, 54% dr 9:1



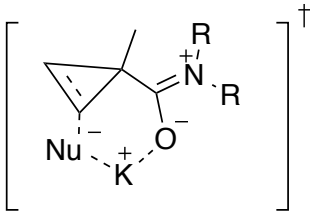
117da, 67% dr 3:1



117cb, 45% dr 10:1

polymerization. Indeed, it was previously shown by the Rubin group that analogous transformation proceeding via a stable, isolable cyclopropene **116a**[88,89] produced N-pyrrolyl cyclopropane **117aa**[71a] in good yield (Scheme 36). Nucleophilic attack of pyrrole **118a** was efficiently directed by the carboxamide function affording predominantly cis diastereomer (Figure 1).

Figure 1



Likewise, trans products were obtained selectively, albeit in slightly lower yields, in the reactions of pyrrole **118a** or indole **118b** with tertiary cyclopropylamides - derivatives of N-methylpiperazine **115c** and morpholine **115b**. In contrast, cyclopropyl bromide **115d** bearing a secondary carboxamide moiety provided adduct **117da** with poor diastereoselectivity. This result was rather surprising as we previously demonstrated that the secondary carboxamide function served as superior directing group in reactions with O- based nucleophiles.[71bc]

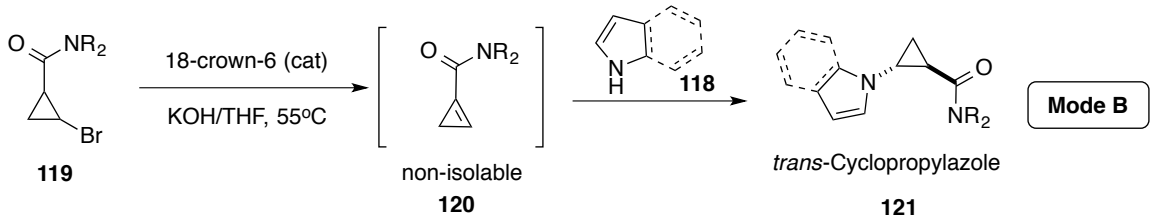
2.2.2. Azoles as Nitrogen-Based Nucleophiles: Mode B.

Nucleophilic Addition Followed by Thermodynamically Driven Base-Assisted Epimerization, Convergent Approach to Conformationally Constrained trans-Cyclopropyl Amino Acid Derivatives

It was shown earlier that conjugation of the strained C=C bond with an electron-withdrawing functionality can enhance the affinity of the cyclopropene intermediate

toward soft nucleophiles, such as phenoxides and thiolates.[71] However, the corresponding rather acidic pronucleophiles reduce the overall basicity of the media leading, to inefficient epimerization at the α-carbon and, consequently, lower diastereoselectivities. Along these lines, 1,2-dehydrobromination of bromocyclopropane **119** in the presence of pyrrole **118a** (mode B) afforded the corresponding cyclopropyl pyrrole **121aa** in high yield but poor diastereomeric ratio (dr), which was addressed by our standard postreaction treatment of a crude mixture with a stronger base (Table 1, entry 1) to give a 98:2 trans selectivity with perfect material balance (Table 1, entry 1). Likewise, reaction of **119a** with 2-cyanopyrrole **118b**, followed by base-assisted epimerization, afforded the corresponding trans adduct **121ab** in high yield and excellent diastereoselectivity (Table 1, entry 2). Indoles reacted cleanly, in spite of their susceptibility to Friedel−Crafts alkylation, dimerization, and polymerization.[90] As expected, skatole **118d**, possessing a substituent at the vulnerable C3 position, provided the best yield in the series (entry 3−7). When imidazole **118g** was used as a nucleophilic component, we stumbled upon isolation issue. Although the corresponding adduct **121ag** was produced in reasonable yield (50% as judged by ^{1}H NMR analysis of crude reaction mixture), chromatographic purification of the product proved inefficient due to its partial decomposition on silica gel (27% isolated yield, entry 8). In contrast, reactions in the presence of its fused analogues benzimidazoles **118h**, **118i**, **118j** proceeded cleanly to afford the corresponding trans products in high yields and excellent diastereoselectivities (entries 9−11). Similarly, pyrazole **118k** was engaged in a very efficient transformation with cyclopropyl bromides **119a** and **119b**, providing good yields of N-cyclopropylpyrazoles **119ak** and **119bk**,

Table 1



119 non-isolable **120** *trans*-Cyclopropylazole **121**

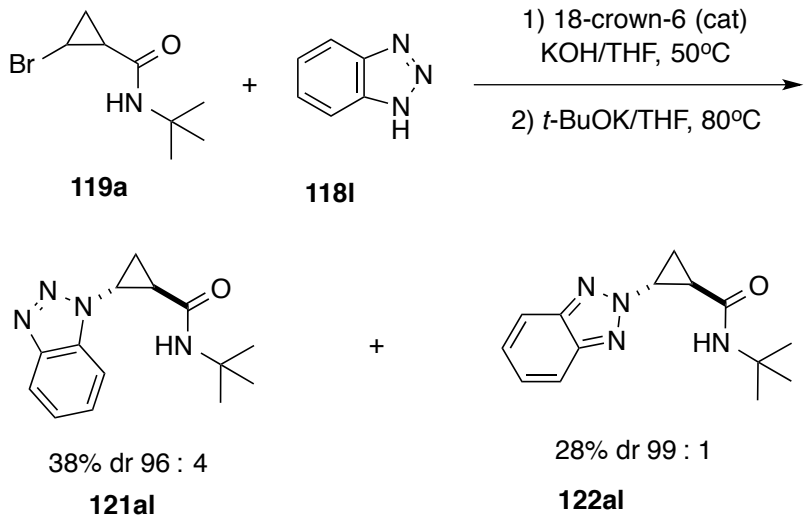
no.	R^1, R^2, **119**	Azole, **118**	**121**	crude dr[b]	Yield,[a] % (dr) upgraded[b]
1	*t*Bu, H, **119a**	pyrrole, **118a**	**121aa**	72:28	66 (98:2)
2	*t*Bu, H, **119a**	2-cyanopyrrole, **118b**	**121ab**	85:15	82 (95:5)
3	*t*Bu, H, **119a**	indole, **118c**	**121ac**	73:27	66 (97:3)
4	Bn, H, **119b**	indole, **118c**	**121bc**	75:25	48 (97:3)
5	*t*Bu, H, **119a**	skatole, **118d**	**121ad**	75:25	73 (99:1)
6	*t*Bu, H, **119a**	5-methoxy-1H-indole, **118e**	**121ae**	75:25	61 (97:3)
7	*t*Bu, H, **119a**	5-bromo-1H-indole, **118f**	**121af**	58:42	48 (97:3)
8	*t*Bu, H, **119a**	imidazole, **118g**	**121ag**	87:13	50 (100:0)[c]
9	*t*Bu, H, **119a**	1H-benzo[d]imidazole, **118h**	**121ah**	87:13	66 (100:1)
10	*t*Bu, H, **119a**	2-methyl-1H-benzo[d] imidazole, **118i**	**121ai**	93:7	84 (95:5)
11	*t*Bu, H, **119a**	5,6-dimethyl-1H-benzo[d]imidazole, **118j**	**121aj**	95:5	72 (97:3)
12	*t*Bu, H, **119a**	pyrazole, **118k**	**121ak**	86:14	85 (99:1)
13	Bn, H, **119b**	pyrazole, **118k**	**121bk**	88:12	73 (97:3)

[a]Isolated yields, unless specified otherwise. [b]Diastereomeric ratio (trans:cis) determined by GC or ^{1}H NMR analyses of crude reaction mixtures. [c]NMR yield.

respectively (entries 12 and 13). The trans configuration of the carboxamide and azole substituents was unambiguously confirmed by X-ray analysis of **119bk**.

It should be mentioned that the scope of this reaction is generally limited to weakly acidic azoles with pKa ~ 16−23. Nonetheless, a more acidic N-heterocycle benzotriazole (**118l**, pKa 11.9) was also reactive, producing two regioisomers, **121al** and **122al** resulting from two tautomeric forms (Scheme 37).[91,92] Attempts on addition of tetrazoles **118m** and **118n** (pKa ~ 8.2) were unsuccessful (Scheme 38), which was expected for such poor aza-Michael donors.[93]

Scheme 37



Scheme 38

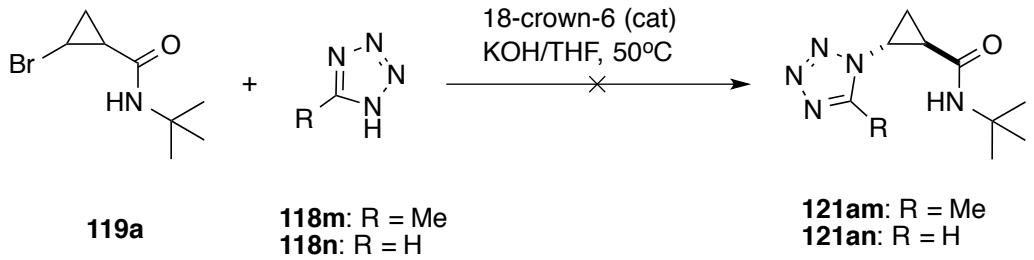
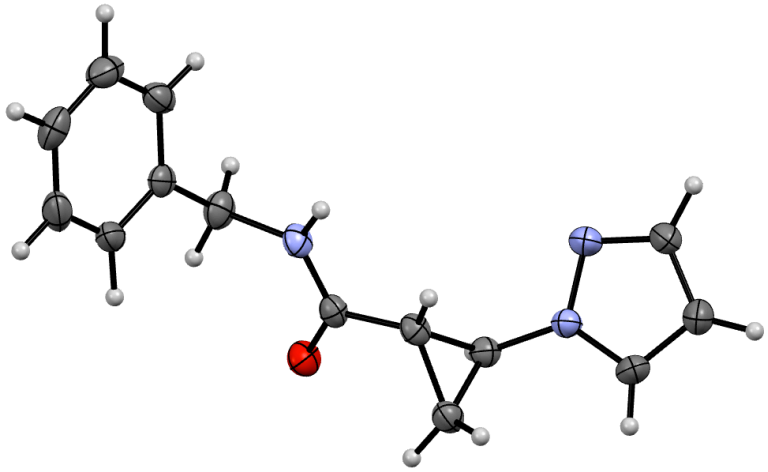


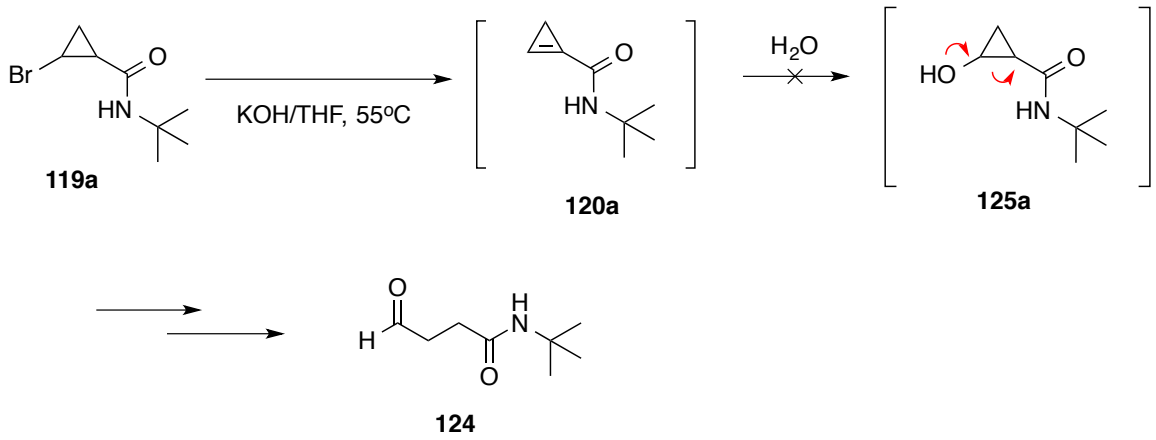
Figure 2 **ORTEP drawing of 121bk showing 50% probability amplitude displacement ellipsoids.**



2.3. Formal Nucleophilic Substitution of Bromocyclopropanes with Anilines

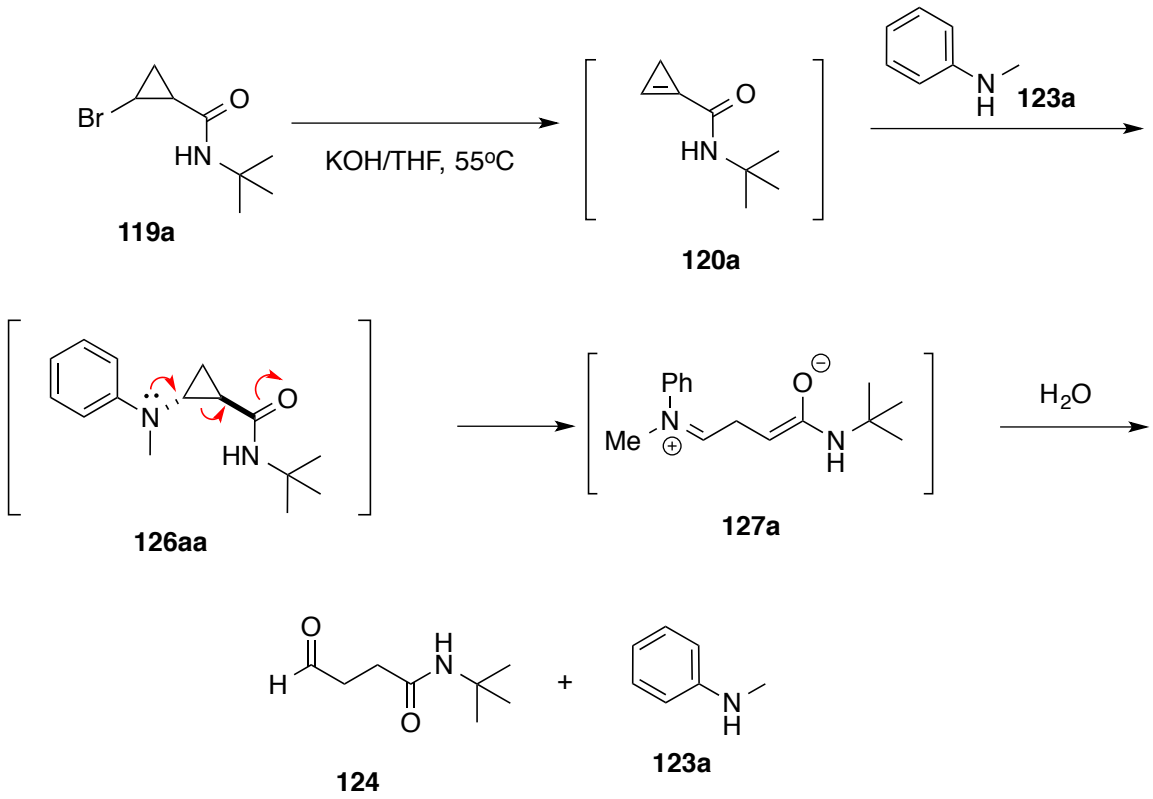
The higher N−H acidity of anilines as compared to alkylamines makes them attractive N-based nucleophiles for the formal substitution reaction. However, our initial test using anilines as nucleophiles proved unsuccessful: reaction of N-methylaniline **123a** with **119a** produced aldehyde **124** as the only isolable compound. Formation of the latter can be envisioned via a formal addition of water to cyclopropene **120a**, followed by a base-assisted cleavage of the intermediate cyclopropanol **125a**; yet product **124** was never observed in our reactions in the absence of the secondary aniline, suggesting an alternative mechanism (Scheme 39).

Scheme 39



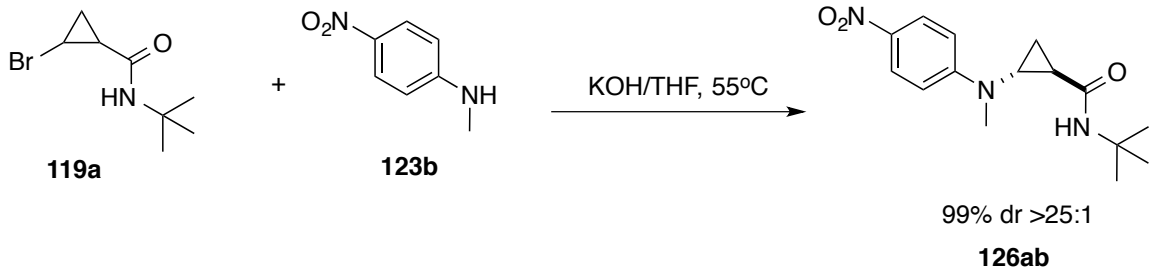
We believe the reaction begins with a base-assisted conjugate addition of aniline species **123a** across the C=C bond of cyclopropene **120a**. The resulting donor−acceptor cyclopropane **126aa** undergoes ring-opening to give the iminium intermediate **127a**, which upon base-assisted hydrolysis produces aldehyde **124** (Scheme 40). It should be emphasized that, mechanistically, this ring-opening process is related to the small cycle cleavage observed in the attempted additions of primary carboxamides.[73] The propensity of the donor−acceptor cyclopropane toward ring-opening depends on the extent of polarization of the C−C bond between the electron-donating (EDG) and electron-with-drawing groups (EWG). Polarization is commonly achieved through installation of strong EWGs, typically two ester functions, additionally activated by a Lewis acid ("pull" strategy).[57] In our case polarization is realized through installation of an EDG with increased electron density, such as anionic N-moiety or a neutral N-group bearing an electron- donating substituents ("push" strategy).[94]

Scheme 40



Accordingly, the aptitude toward small ring cleavage was significantly reduced in cyclopropylanilines possessing electron-deficient nitrogen. Thus, reaction of p-nitroaniline **123b** with **119a** in the presence of tBuOK and 18-crown-6 proceeded smoothly providing a single diastereomer of cyclopropylaniline **126ab** in nearly quantitative yield. (Scheme 41). Several other electron- deficient N-benzyl protected anilines, possessing cyano-, trifluoromethyl- , and nitro- groups in para positions, reacted in a similar manner affording the corresponding aminocyclopropanes in good to excellent yields. Regardless of the yield, the diastereoselectivity of addition was perfect in all these examples.[95]

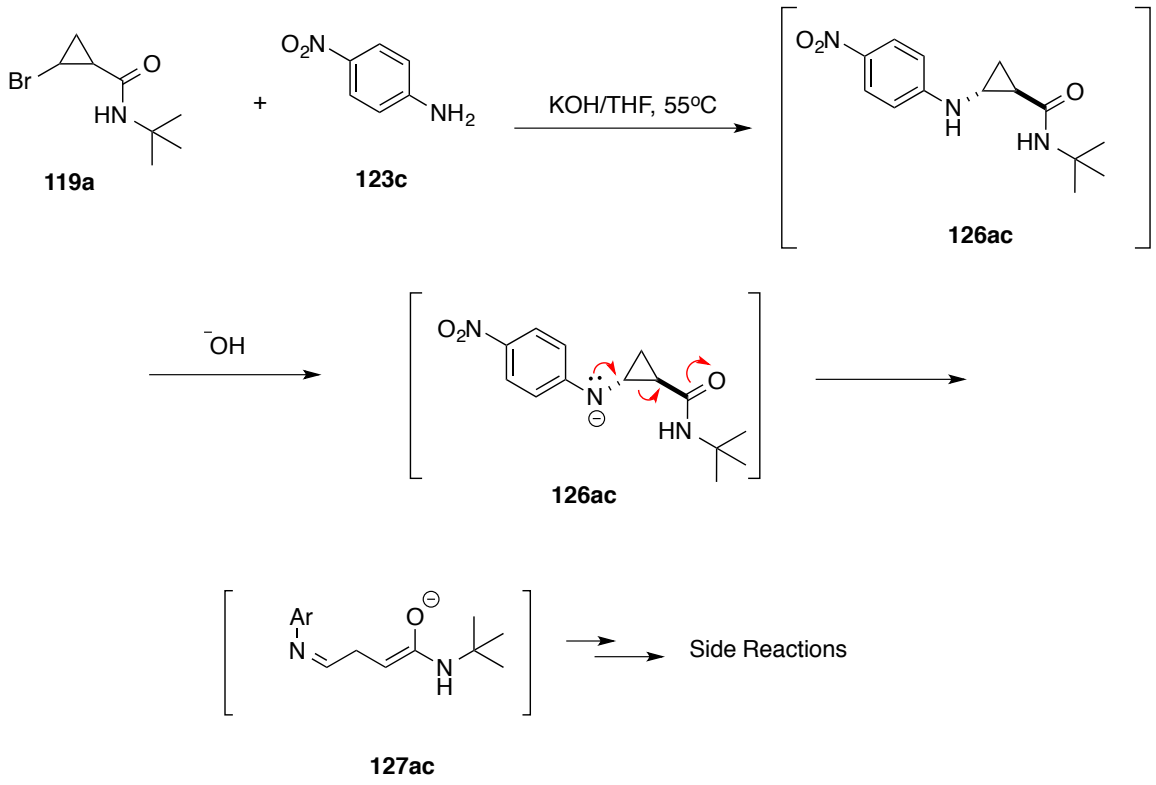
Scheme 41



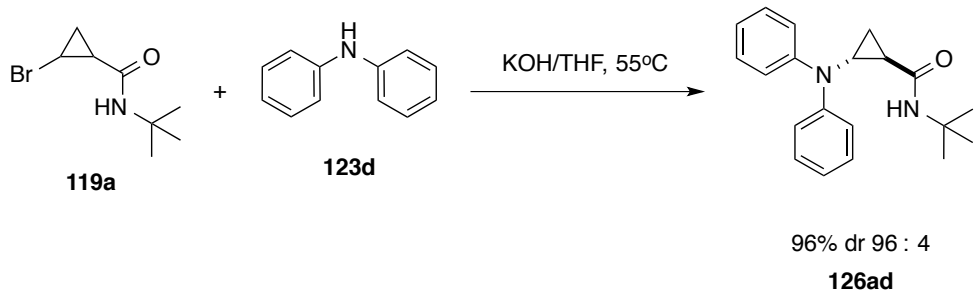
It should be mentioned that no product **126ac** was obtained in the reaction with primary aniline **123c** despite complete consumption of the bromocyclopropane **119a**. We failed to detect any reasonable amounts of cyclopropane-containing products in this reaction. We propose the following rationale to account for the distinct reactivity of primary anilines (Scheme 42). Addition of primary aniline pronucleophile **123c** to cyclopropene **120a** produces aminocyclopropane **126ac**, the high N− H acidity of which is additionally enhanced by the adjacent electron-deficient aromatic ring. As a result, it undergoes facile base-assisted deprotonation under our typical reaction conditions to give an activated DAC species with relatively high electron density on the nitrogen atom. Subsequent facile cleavage of the small ring gives rise to **127ac** and can undergo various side reactions. In contrast, adducts of secondary anilines pronucleophiles do not possess acidic N−H bond and therefore are stable toward ring-opening.

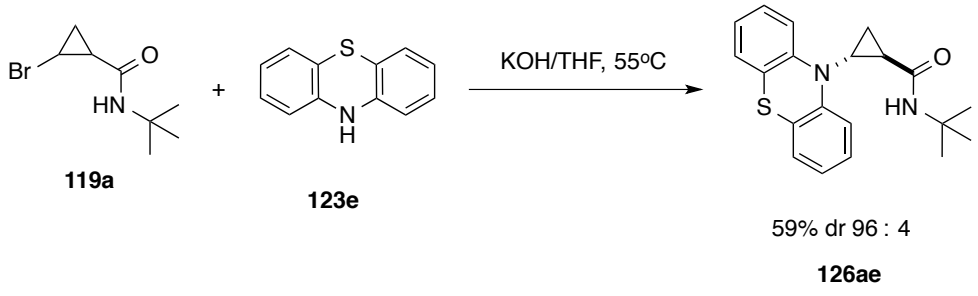
It should be also mentioned that diphenylamine **123d** and 10H-phenothiazine **123e** did not require electron- withdrawing substituents to furnish trans-diastereomers of the corresponding cyclopropylamine derivatives **126ad** and **126ae** in good yields and with high diastereoselectivity (Scheme 43).

Scheme 42



Scheme 43





2.4. Conclusions

An efficient diastereoselective synthesis of β-aminocyclopropylcarboxylic acid derivatives via the formal nucleophilic substitution of bromocyclopropanes with N-based nucleophiles has been developed. This transformation proceeds via dehydrobromination followed by addition of a nucleophilic N-moiety across the strained C=C bond of a cyclopropene intermediate. Strong influence of steric and electronic factors on the efficiency of the formal substitution reaction has been demonstrated. N-Based pronucleophiles, including azoles and secondary anilines, have been successfully employed in the featured transformation. The trans selectivity of the addition is controlled by a thermodynamically driven base assisted epimerization, while cis selectivity is governed by a directed effect of the functional group. This methodology addresses some of the long-standing challenges in the synthesis of DAC and β-ACC derivatives through the synergism of strain release-powered thermodynamics and chelation-enforced selectivity. The diastereoconvergent approach allows for efficient installation of N-substituents in the last step, making the described method very attractive for the diversity oriented synthesis.

2.5. Experimental

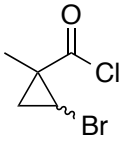
2.5.1. General Information

NMR spectra were recorded on a Bruker Avance DPX-400 instrument, equipped with a quadruple-band gradient probe (H/C/P/F QNP) or a Bruker Avance DRX-500 with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broad-band decoupling. The (+) and (-) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 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 × 0.25 mm × 0.25 mm 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. High resolution mass-spectra were obtained using a LCT Premier (Micromass Technologies) instrument using electrospray ionization and time of flight detection techniques. IR spectra were recorded on a Shimadzu FT-IR 8400S instrument.

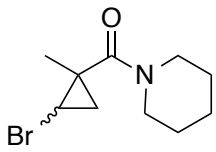
Glassware employed in moisture-free syntheses was flame-dried in vacuum prior to use. Water was purified by dual stage deionization, followed by dual stage reverse osmosis. Anhydrous THF was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent consecutively through two columns filled with activated alumina (Innovative Technology). Anhydrous Et_3N was obtained by

distillation of ACS-grade commercially available materials over calcium hydride in a nitrogen atmosphere. All commercially available reagents were purchased from Sigma-Aldrich, TCI America or Acros Organics and used as received. Synthesis, physical properties and spectral data of all new compounds obtained in a frame of these studies are described below. All manipulations with *t*-BuOK and 18-crown-6 ether were conducted under inert atmosphere (<8 ppm residual oxygen and moisture) using a combination of glovebox and standard Schlenk techniques. After quench the reaction mixtures and compounds were treated on air. All the obtained materials were moisture and oxygen stable at ambient temperatures.

2.5.2. Synthesis of bromocyclopropane derivatives

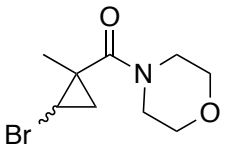


2-Bromo-1-methylcyclopropylcarbonyl chloride (127): 2-Bromo-1-methylcyclopropane- carboxylic acid (**128**,[88] mixture of diastereomers, 1.1:1) (51.8 g, 400 mmol) and freshly distilled thionyl chloride (100 mL) were stirred at room temperature overnight. Excess thionyl chloride was distilled off at ambient pressure. The residue was distilled in vacuum, b.p. 50–53 °C (10 mm Hg). Yield 75.8 g (384 mmol, 96%). This material was used as is in further acylations of primary and secondary amines as described below.



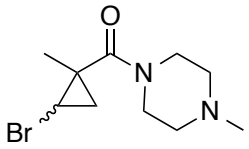
(2-Bromo-1-methylcyclopropyl)(piperidin-1-yl)methanone (115a): Typical procedure: To a stirred solution of freshly distilled piperidine (7.7 mL, 6.6 g, 85 mmol) under an atmosphere of N_2 in anhydrous THF (20 mL) was added the acid chloride **127** (5.10 g, 25.8 mmol) in dry THF (35 mL) dropwise. After ~1 hr of stirring at room temperature, the starting materials were consumed as judged by GCMS analysis; then the precipitate formed in the reaction

mixture was removed by suction filtration and the filter cake was rinsed with THF (2 x 20 mL). Then the precipitate was dissolved in water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried with Mg_2SO_4, combined with the THF filtrate and concentrated in vacuum. Kugelrohr vacuum distillation (oven temperature 150 °C/0.4 Torr) of the resulting residue afforded a mixture of *trans*- and *cis*-isomers of **115a** (1:1) as colorless oil. Yield: 6.26 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): d = [3.70–3.57 (m), 3.49–3.35 (m), S4 H], [3.11 (dd, *J* = 8.1 Hz, 4.8 Hz), 2.94 (dd, *J* = 8.1 Hz, 4.8 Hz), S1 H], 1.65–1.45 (m, 7 H), [1.38 (s), 1.30 (s), S3 H], [1.10 (ps t, *J* = 8.6 Hz, 5.3Hz), 0.82 (pst, *J*=6.8 Hz, 4.8 Hz), S1H]. ^{13}C NMR (100 MHz, $CDCl_3$): d = 170.1, 168.8, 46.9, 43.2, 27.9, 27.5, 26.5, 26.1, 26.0, 25.7, 25.6, 24.6, 24.5, 21.9, 21.7, 21.3, 19.5. IR (film, cm^{-1}): 2934, 2854, 1641, 1431, 1207, 1151, 1014, 854. ESI-HRMS (TOF): *m*/*z* $[M–Br]^+$ calcd for $C_{10}H_{16}NO$: 166.1232; found: 166.1233.



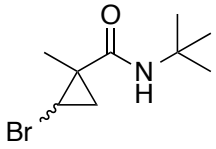
(2-bromo-1-methylcyclopropyl)(morpholino)methanone (115b) : Cyclopropanecarboxamide **115b** was prepared according to the typical procedure from acyl chloride **127** (5.00 g, 25.3 mmol) and freshly distilled morpholine (6.60 mL, 6.62 g, 76 mmol). Kugelrohr vacuum distillation (oven temperature 133 °C/0.6 Torr) of the resulting residue afforded a mixture of *trans*- and *cis*-isomers of **115b** (1.1:1) as a colorless oil. Yield: 5.52 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67–3.64 (m, 8 H), [3.15 (dd, *J* = 8.3 Hz, 5.1 Hz), 2.98 (dd, *J* = 7.6 Hz, 4.8 Hz), Σ1H], [1.70 (ps t, *J* = 8.1), 1.58 (dd, *J* = 6.8 Hz, 4.8 Hz), Σ1H], [1.45 (s), 1.37 (s), Σ3H], [1.20 (ps t, *J* = 7.3 Hz), 0.91 (dd, *J* = 6.6 Hz, 4.8 Hz), Σ1 H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 168.9, 67.1 (–), 66.9 (–), 66.7 (–, 2C), 46.4 (–), 42.6 (–), 27.5 (+),

27.1, 25.6, 25.4 (+), 21.6 (–), 21.4 (+), 21.2 (–), 19.4 (+). IR (film, cm^{-1}): 2962, 2922, 2854, 2897, 1643, 1460, 1429, 1281, 1207, 1153, 1115, 1032, 851, 623, 505. ESI-HRMS (TOF): *m*/*z* [M–Br]+ calcd for $C_9H_{14}NO_2$: 168.1025; found: 168.1026.



(2-Bromo-1-methylcyclopropyl)(4-methylpiperazin-1-yl)methanone (115c):

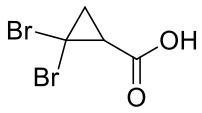
Cyclopropanecarboxamide **115c** was prepared according to the typical procedure from acyl chloride **127** (5.10 g, 25.8 mmol) and freshly distilled piperidine (7.7 mL, 6.6 g, 85 mmol). Kugelrohr vacuum distillation (oven temperature 150 °C/0.4 Torr) of the resulting residue afforded a mixture of *trans*- and *cis*-isomers of **115c** (1:1) as a colorless oil. Yield: 6.26 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ [3.70–3.57 (m), 3.49–3.35 (m), Σ4H], [3.11 (dd, *J* = 8.1 Hz, 4.8 Hz), 2.94 (dd, *J* = 8.1 Hz, 4.8 Hz), Σ1H], 1.65–1.45 (m, 7 H), [1.38 (s), 1.30 (s), Σ3H], [1.10 (ps t, *J* = 8.6 Hz, 5.3Hz), 0.82 (pst, *J*=6.8Hz, 4.8Hz), Σ1H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 168.8, 46.9, 43.2, 27.9, 27.5, 26.5, 26.1, 26.0, 25.7, 25.6, 24.6, 24.5, 21.9, 21.7, 21.3, 19.5. IR (film, cm^{-1}): 2934, 2854, 1641, 1431, 1207, 1151, 1014, 854. ESI-HRMS (TOF): *m*/*z* [M– Br]+ calcd for $C_{10}H_{16}NO$: 166.1232; found: 166.1233.



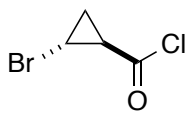
2-Bromo-*N*-*tert*-butyl-1-methylcyclopropanecarboxamide (115d):

Cyclopropanecarboxamide **115d** was prepared according to the typical procedure from acyl chloride **127** (5.10 g, 25.8 mmol) and freshly distilled *tert*-butylamine (1.52 mL, 1.06 g, 14.4 mmol). Vacuum distillation in a Kugelröhr at 150 °C at 0.6 mm Hg gave the product as a pale-yellow oil. Yield 845 mg (3.61 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ [5.66 (br.s) & 5.41 (br.s), Σ1H],

[3.47 (dd, J = 8.1 Hz, 5.1 Hz) & 3.10 (dd, J = 7.6 Hz, 5.8 Hz), Σ1H], [1.91 (dd, J = 6.8 Hz, 5.8 Hz) & 1.84 (dd, J = 8.1 Hz, 5.8 Hz), Σ1H], [1.59 (s) & 1.47 (s), Σ3H], [1.39 (s) & 1.35 (s), Σ9H], [1.16 (dd, J = 7.6 Hz, 6.8 Hz) & 0.86 (ps.-t, J = 5.8 Hz, 5.1 Hz), Σ1H]; ^{13}C NMR ($CDCl_3$, 100.67 MHz) δ 171.2, 169.3, 51.9, 51.5, 29.0 (+), 28.8 (+, 3C), 28.7 (+, 3C), 28.2, 25.9 (+), 24.9 (-), 24.4, 23.9 (-), 21.1 (+), 17.6 (+); HRMS (TOF ES) found 234.0494, calcd for $C_9H_{17}BrNO$ (M+H) 234.0493 (0.4 ppm).

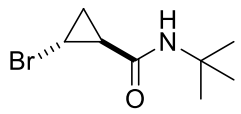


2,2-Dibromocyclopropanecarboxylic acid (**129**): 10.0 g (44.2 mmol) of the 2,2-dibromo-1-vinylcyclopropane **130**[71b] was added to a three necked flask equipped with a reflux condenser and magnetic stir bar. 340 mL of glacial acetic acid and 170 mL of formic acid were then added to the flask which was then placed in an oil bath. While stirring, ozone was bubbled into the solution for ca. two hours. Bubbling was stopped after disappearance of starting material by GC. 120 mL of 30% hydrogen peroxide was then added to the solution which was then refluxed for ca. two hours. The solution was then allowed to cool after disappearance of the intermediate. The solution was then extracted with chloroform (5x300 mL; chloroform was recovered from rotovap and reused for each extraction), the solvent was then removed by rotary evaporation and the product was then placed under a high vacuum overnight, yielding a white crystalline solid, identical to the material previously described in literature. Yield 7.04 g (30.9 mmol; 70%).[71a]

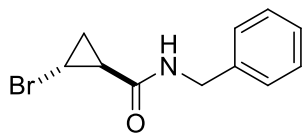


(1*S,2*R**)-2-Bromocyclopropanecarbonyl chloride (131)**: Flame-dried 3000 mL three neck round bottom flask was charged with solution of 2,2-dibromocyclopropanecarboxylic acid (**129**) (27.0 g, 111 mmol) in anhydrous ether

(1300 mL) under nitrogen atmosphere. The mixture was vigorously stirred (500-650 rpm) at -20 ^{o}C, and methyl lithium solution (1.6M in ether, 95 mL, 152 mmol, 1.37 equiv) was added dropwise. For safety reasons it is essential to add methyl lithium directly to a solution rather than draining along the flask wall to minimize the amount of solid precipitate, which might ignite during the following work up. An aliquot of solution (1 mL) was withdrawn from the flask with a syringe, quenched consecutively with brine (2-3 drops) and 5% aqueous HCl (2-3 drops) in 10 mL test tube. The aqueous layer was saturated with NaCl, and extracted with EtOAc (3 x 0.5 mL). The combined organic phases collected with Pasteur pipet were dried with $MgSO_4$ and concentrated. The conversion was measured based on ^{1}H NMR analysis of this probe, and additional amount of MeLi necessary to complete the transformation was assessed (35 mL, 56 mmol). The mixture was quenched at -20 ^{o}C by adding brine (100 mL) and 5% aqueous HCl (100 mL). (It is essential to perform the quenching at low temperature and to maintain inert atmosphere to avoid ignition of the mixture). The mixture was allowed to warm up to rt, then aqueous layer was saturated with NaCl. Ethereal layer was separated, and then aqueous phase was extracted with EtOAc (6 x 100 mL). Combined organic phases were dried with $MgSO_4$, filtered and concentrated, yield 8.79 g (53.3 mmol, 48%). This material was charged into a 25 mL round bottomed flask equipped and thionyl chloride (11.5 g, 110 mmol) was added. The mixture was stirred at room temperature overnight, then an excess of thionyl chloride was distilled off, and the residue was fractionated in vacuum to obtain the title compound as clear oil, bp 56 ^{o}C at 15 torr. Yield 9.19 g (50.1 mmol, 94%).



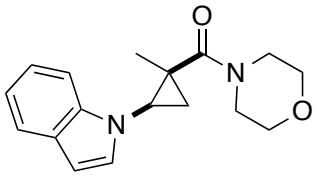
(1*S,2*R**)-2-Bromo-*N*-tert-butylcyclopropanecarboxamide** (**119a**): Typical procedure. To a stirred solution of acyl chloride **131** (1.0 g, 5.5 mmol) in dry THF (40 mL) was added tert-butylamine (3.90 mL, 2.74 g, 45.8 mmol). The mixture was stirred at room temperature overnight, then partitioned between water (100 mL) and EtOAc (50 mL). The organic layer was separated; the aqueous phase was extracted with EtOAc (2 x 50 mL). Combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by vacuum distillation on Kugelröhr (oven temp. 120 ^oC at 0.4 torr) to afford a white crystalline material, mp 87-89 ^oC Yield 1.13 g (5.12 mmol, 93%). ^1H NMR (500.19 MHz, $CDCl_3$) δ 5.87 (br. s., 1H), 3.17 (ddd, *J* = 7.7 Hz, 4.0 Hz, 3.2 Hz, 1H), 1.81–1.72 (m, 1H), 1.58–1.51 (m, 1H), 1.35 (s, 9H), 1.24–1.20 (m., 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.1, 51.6, 28.8 (+, 3C), 26.2 (+), 18.9 (+), 17.2 (-);IR (film, cm^{-1}): 3315, 3080, 2966, 2932, 1641, 1555, 1454, 1391, 1364, 1277, 1225; HRMS (TOF ES): found 220.0340, calculated for $C_8H_{15}BrNO$ (M+H) 220.0337 (1.4 ppm).



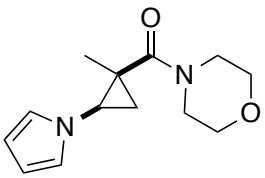
N-Benzyl-2-bromocyclopropanecarboxamide (**119b**): The reaction was performed according to the typical procedure, employing benzylamine (1.10 g, 10.0 mmol, 2.50 equiv.) and 2-bromo-cyclopropanecarbonyl chloride (730 mg, 4.0 mmol). Yield 910 mg (3.57 mmol, 89%). ^1H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.37–7.23 (m, 5H), 6.89 (br. s., 1H), 4.42–4.31 (m, 2H), 3.18 (ddd, *J* = 7.6 Hz, 4.7 Hz, 3.0 Hz, 1H), 1.91 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.0 Hz, 1H), 1.58 (dt, *J* = 7.6 Hz, 5.9 Hz, 1H), 1.27 (dt, *J* = 9.2 Hz, 5.4 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.2, 137.7, 128.6 (+, 2C), 127.6 (+, 2C), 127.5 (+), 43.8 (-),

25.3 (+), 19.0 (+), 17.5 (-); FT IR (NaCl, film, cm^{-1}): 3296, 3088, 3063, 2930, 1634, 1553, 1454, 1213, 1034, 746, 696, 515; HRMS (TOF ES): found 254.0176, calculated for $C_{11}H_{13}BrNO$ (M+H) 254.0181 (2.0 ppm).

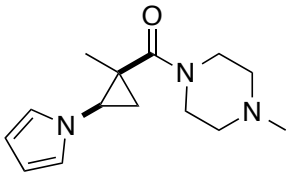
2.5.3. Synthesis of Cyclopropylazoles



((1R*,2S*)-2-(1H-Indol-1-yl)-1-methylcyclopropyl)(morpholino)-methanone (117bb): Typical Procedure. An oven-dried 10 mL Wheaton vial equipped with a magnetic stir bar was loaded under N_2 with potassium tert-butoxide (168 mg, 1.5 mmol), 18-crown-6 (13 mg, 0.05 mmol), (2-bromo-1-methylcyclopropyl) (morpholino)methanone **115**b (124 mg, 0.50 mmol), indole **118c** (117 mg, 1.00 mmol), and THF (5 mL). The mixture was stirred at 80 °C for 12 h, then filtered through a fritted funnel, and concentrated. Preparative column chromatography on silica gel afforded the title compound as an amber oil, R_f 0.46 (CH_2Cl_2:MeOH 20:1). Yield: 58 mg (0.25 mmol, 50%, dr >25:1). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 7.63 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.23 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.14 (dd, *J* = 8.0, 7.0Hz, 1H), 6.95 (d, *J* = 3.4Hz, 1H), 6.45 (d, *J* = 3.3 Hz, 1H), 3.84 (dd, *J* = 8.8, 5.4 Hz, 1H), 3.79−3.69 (br s, 1H), 3.61−3.44 (br s, 2H), 3.19 (br s, 2H), 2.97 (m, 3H), 2.22 (dd, *J* = 6.9, 5.4 Hz, 1H), 1.49 (s, 3H), 1.29 (dd, *J* = 8.7, 6.8 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ ppm 168.8, 137.2, 129.1, 123.8 (+), 121.8 (+), 121.4 (+), 120.0 (+), 108.6 (+), 101.5 (+), 46.1 (−), 42.4(−), 41.0 (+), 28.8, 21.0 (+), 16.1 (−). FT IR (KBr, cm^{-1}): 2962, 2921, 2856, 1635, 1512, 1464, 1223, 847. HRMS (TOF ES): found 284.1530, calculated for $C_{17}H_{20}N_2O_2$ (M+) 284.1525 (1.8 ppm).

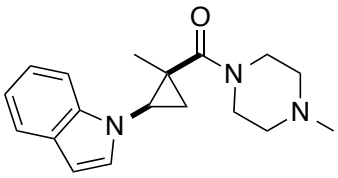


((1R*,2S*)-2-(1H-Pyrrol-1-yl)-1-methylcyclopropyl)(morpholino)-methanone (117ba): This compound was synthesized according to typical procedure, employing (2-bromo-1-methylcyclopropyl)- (morpholino)methanone **115b** (124 mg, 0.50 mmol), pyrrole **118a** (60 mg, 1.00 mmol), potassium tert-butoxide (168 mg, 1.50 mmol), and 18-crown-6 (13 mg, 0.05 mmol) to afford after purification the title compound as yellow oil, R_f 0.34 (hexane/EtOAc 1:1), 72 mg (0.31 mmol, 61%, dr >25:1). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 6.59 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 3.81 (br s, 1H), 3.58 (br s, 1H), 3.49 (dd, J = 8.6, 5.4 Hz, 1H), 3.36 (br s, 1H), 3.46 (br s, 1H), 3.27 (br s, 2H), 3.15 (br s, 1H), 2.59 (br s, 1H), 1.93 (dd, *J* = 6.9, 5.5 Hz, 1H), 1.39 (s, 3H), 1.15 (dd, *J* = 8.6, 7.0 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ ppm 168.9, 119.1 (+), 108.7 (+), 66.1 (−, 2C), 46.0 (−), 44.5 (+), 42.4 (−), 28.7, 21.3 (+), 16.7 (−). FT IR (KBr, cm^{-1}): 2962, 2925, 2901, 2856, 1634, 1494, 1464, 1230, 851. HRMS (TOF ES): found 235.1448, calculated for $C_{13}H_{19}N_2O_2$ (M+) 235.1447 (0.4 ppm).

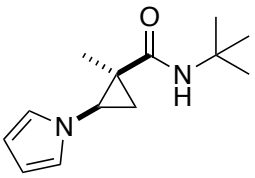


((1R*,2R*)-2-(1H-Pyrrol-1-yl)-1-methylcyclopropyl)(4-methylpiperazin-1-yl)methanone (117cb): This compound was synthesized according to typical procedure, employing (2-bromo-1- methylcyclopropyl)(4-methylpiperazin-1-yl)methanone **115c** (78 mg, 0.30 mmol), pyrrole **118a** (40 mg, 0.60 mmol), potassium tert- butoxide (101 mg, 0.90 mmol), and 18-crown-6 (8 mg, 0.03 mmol) affording after purification the title compound as yellow oil, R_f = 0.23 (CH_2Cl_2/MeOH 20:1). Yield: 39 mg (0.16 mmol, 52%, dr 10:1). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 6.58 (t, *J* = 2.1 Hz, 2H), 6.08 (t, *J* = 2.2 Hz, 2H),

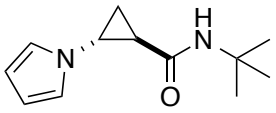
3.73 (br s, 1H), 3.51−3.46 (dd, *J* = 7.8, 5.3 Hz, 1H), 3.40 (br s, 1H), 3.27 (br s, 2H), 2.33 (br s, 1H), 2.23 (br s, 2H), 2.15 (s, 1H), 2.01 (br s, 1H), 1.90 (dd, *J* = 6.9, 5.4 Hz, 1H), 1.39 (s, 3H), 1.14 (dd, *J* = 8.6, 6.9 Hz, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ ppm 168.8, 119.2 (+, 2C), 108.6 (+, 2C), 54.0 (−, 2C), 45.6 (+), 44.5 (+), 41.8 (−, 2C), 28.8, 21.6 (+), 16.9 (−). FT IR (KBr, cm^{-1}): 2935, 2856, 1630, 1492, 1437, 1227, 827. HRMS (TOF ES): found 247.1690, calculated for $C_{14}H_{21}N_3O$ (M+) 247.1685 (2.0 ppm).



((1R*,2S*)-2-(1H-Indol-1-yl)-1-methylcyclopropyl)(4-methylpiper- azin-1-yl)methanone (117cb): This compound was synthesized according to typical procedure, employing (2-bromo-1- methylcyclopropyl)(4-methylpiperazin-1-yl)methanone **115c** (78 mg, 0.30 mmol), indole **118c** (70 mg, 0.60 mmol), potassium tert-butoxide (101 mg, 0.90 mmol), and 18-crown-6 (10 mg, 0.03 mmol) affording after purification the title compound as yellow oil, R_f 0.23 (CH_2Cl_2:MeOH 20:1). Yield: 46 mg (0.15 mmol, 52%, dr >25:1). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ ppm 7.61 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.23 (dd, *J* = 8.0, 7.7 Hz, 1H), 7.13 (dd, *J* =8.1, 7.9 Hz, 1H), 6.96 (d, *J* = 3.4 Hz, 1H), 6.43 (d, *J* =3.3 Hz, 1H), 3.84 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.70 (br, 1H), 3.16 (br, 3H), 2.50−2.26 (m, 1H), 2.25−2.16 (dd, 7.3, 5.4, Hz, 1H), 1.95 (s, 3H), 1.85 (br, 3H), 1.51 (s, 3H), 1.30 (dd, J = 10.5, 5.1 Hz, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 168.7, 137.4, 129.2, 123.9 (+), 121.7 (+), 121.2 (+), 119.9 (+), 108.8 (+), 101.5 (+), 54.0 (−), 45.5 (+), 41.9 (−), 41.0 (+), 28.8, 21.4 (+), 16.4 (−). FT IR (KBr, cm^{-1}): 3325, 2966, 2934, 2874, 1647, 1549, 1508, 1462, 1225, 795. HRMS (TOF ES): found 297.1840, calculated for $C_{18}H_{23}N_3O$ (M+) 297.1841 (0.3 ppm).

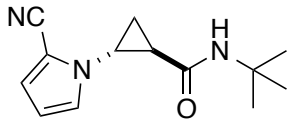


((1R*,2S*)-N-(tert-Butyl)-1-methyl-2-(1H-pyrrol-1-yl)-cyclopropanecarboxamide (117da). This compound was synthesized according to typical procedure employing 2-bromo-N-(tert-butyl)-1-methylcyclopropanecarboxamide (**115d**) (214 mg, 0.91 mmol), pyrrole (**118a**) (112 mg, 1.82 mmol), potassium tert-butoxide (307 mg, 2.74 mmol), and 18-crown-6 (24 mg, 0.09 mmol) to afford after purification the title compound as a light brown solid, mp 80 °C, Rf 0.34 (hexane/EtOAc 1:1), 133 mg (0.61 mmol, 67%, dr 3:1). ^{1}H NMR (400.13 MHz, chloroform-d): δ 6.70 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.1 Hz, 2H), 4.78 (s, 1H), 3.45 (dd, *J* = 7.9, 5.0 Hz, 1H), 1.86 (dd, *J* = 6.0, 5.3 Hz, 1H), 1.41 (s, 3H), 1.23 (dd, *J* = 7.8, 6.4 Hz, 1H), 1.12 (s, 9H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 169.4, 121.4 (+, 2C), 109.0 (+, 2C), 50.9, 42.6 (+), 28.3 (+, 3C), 20.8 (+), 19.3 (−). FT IR (NaCl, cm^{-1}): 3393, 2966, 2929, 1653, 1526, 1495, 1456, 1392, 1364, 1258, 1238, 1221, 725. HRMS (TOF ES): found 220.1577, calculated for $C_{13}H_{20}N_2O$ (M+) 220.1576 (0.5 ppm).



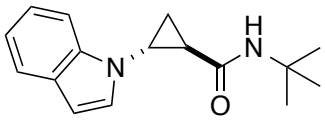
(1R*,2R*)-N-(tert-Butyl)-2-(1H-pyrrol-1-yl)cyclopropane carboxamide (121aa): Typical procedure: An oven-dried 10 mL Weaton vial was charged with 18-crown-6 (6.6 mg, 25 μmol, 10 mol %), powdered KOH (42 mg, 0.75 mmol, 3.0 equiv), pyrrole **118a** (26 μL, 0.38 mmol, 1.5 equiv) and anhydrous THF (5.0 mL). The mixture was stirred at room temperature for 1 minute and bromocyclopropane **119a** (55 mg, 0.25 mmol, 1.0 equiv) was added in a single portion. The reaction mixture was stirred overnight at 55 ^{o}C, then filtered through a short plug of silica gel eluting with CH_2Cl_2. The filtrate was concentrated in vacuum, and the residue

(a mixture of diastereomers, trans:cis 72:28) was dissolved in THF (3.0 mL) and transferred via cannula into another 10 mL Wheaton vial, pre-charged with potassium tert-butoxide (56 mg, 0.5 mmol, 2.0 equiv). The mixture was stirred at 80 ^{o}C overnight when GC analysis showed the epimerization was complete (final trans:cis ratio 98:2). Flash column chromatography on Silica gel afforded the title compound as a yellow solid, R_f 0.20 (hexane-EtOAc 4:1), mp 109.3-110.2 ^{o}C. Yield 34 mg (66%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 6.73 (t, *J* = 2.2 Hz, 2 H), 6.15 (t, *J* = 2.0 Hz, 2 H), 5.54 (br. s., 1 H), 3.80 (ddd, *J* = 7.8, 4.8, 2.8 Hz, 1 H), 1.73 (ddd, *J* = 9.0, 5.8, 2.8 Hz, 1 H), 1.55 (dt, *J* = 7.9, 5.5 Hz, 1 H), 1.45 (dt, *J* = 9.6, 5.0 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 169.4, 120.5 (+, 2C), 108.5 (+, 2C), 51.6, 37.0 (+), 28.9 (+, 3C), 24.6 (+), 13.7 (-); FT IR (KBr, cm^{-1}): 3317, 2966, 2930, 1645, 1549, 1495, 1456, 1394, 1364, 1339, 1286, 1256, 1225, 1198, 1115, 1074, 1053, 1036, 989, 955, 932, 910, 872, 854, 822, 791, 723, 656, 636, 602; HRMS (TOF ES): found 213.1578, calculated for $C_{12}H_{18}N_2OLi$ (M+Li) 213.1579 (0.5 ppm).



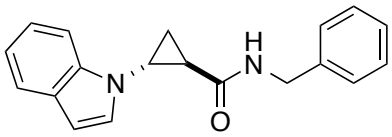
(1R*,2R*)-N-(tert-Butyl)-2-(2-cyano-1H-pyrrol-1-yl)cyclopropanecarboxamide (121ab): This compound was obtained according to a typical procedure employing pyrrole-2-carbonitrile **118b** (42.5 µl, 0.5 mmol, 2.0 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3 equiv) to improve initial 85:15 dr (trans:cis) to the final value of 95:5. The subsequent chromatographic purification afforded title compound as a yellowish solid, R_f 0.28 (hexanes/EtOAc 4:1), mp 93.5−93.8 ^{o}C. Yield 47 mg (0.20 mmol, 82%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 6.87−6.91 (m, 1 H), 6.78 (dd, *J* = 4.0, 1.3 Hz, 1 H), 6.11−6.17 (m, 1 H), 5.90 (br. s., 1 H), 3.65 (ddd,

J = 7.6, 4.6, 3.0 Hz, 1 H), 1.97 (ddd, *J* = 9.2, 6.1, 2.9 Hz, 1 H), 1.76 (dt, *J* = 7.5, 5.7 Hz, 1 H), 1.38−1.43 (m, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125.76 MHz, CDCl3) δ ppm 168.1, 143.1, 127.1 (+), 120.7 (+), 114.3, 109.6 (+), 51.8, 36.0 (+), 28.7 (+, 3C), 24.8 (+), 13.0 (-); FT IR (KBr, cm^{-1}): 2218, 1651, 1541, 1526, 1458, 1437, 1396, 1364, 1312, 1256, 1225, 1151, 1076, 1059, 1026, 974, 912, 891, 860, 785, 737, 692, 679, 648, 602, 579; HRMS (TOF ES): found 232.1449, calculated for $C_{13}H_{18}N_3O$ (M+H) 232.1450 (0.4 ppm).

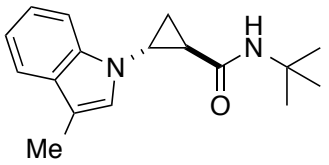


(1R*,2R*)-N-(tert-Butyl)-2-(1H-indol-1-yl)cyclopropanecarboxamide (121ac): This compound was obtained according to a typical procedure from bromocyclopropane **119a** (110 mg, 0.50 mmol, 1.00 equiv), employing indole **118c** (88 mg, 0.75 mmol, 1.50 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (112 mg, 1.00 mmol, 2.00 equiv) to improve initial 73:27 dr (trans:cis) to the final value of 97:3. The subsequent chromatographic purification afforded 85 mg (0.33 mmol, 66%) of the title compound as a light orange solid, R_f 0.37 (hexanes/EtOAc 4:1), mp 106.0−106.5 ^{o}C. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.65 (d, *J* = 7.9 Hz, 1 H), 7.48 (d, *J* = 8.2 Hz, 1 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.09 (d, *J* = 3.2 Hz, 1 H), 6.48 (d, *J* = 3.2 Hz, 1 H), 5.79 (br. s., 1 H), 3.81 (ddd, *J* = 7.6, 4.4, 2.8 Hz, 1 H), 1.66−1.81 (m, 2 H), 1.52 (dt, *J* = 8.7, 4.5 Hz, 1 H), 1.47 (s, 9 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 169.5, 137.1, 128.8, 126.9 (+), 121.8 (+), 121.0 (+), 120.0 (+), 109.8 (+), 101.5 (+), 51.6, 34.2 (+), 28.9 (+, 3C), 24.4 (+), 13.7 (-); FT IR (KBr, cm^{-1}): 3396, 3198, 3086, 3057, 2966, 2930, 2868, 2359, 2341, 1645, 1612, 1549, 1512, 1475, 1464, 1400, 1364, 1340, 1317, 1256, 1225, 1153, 1126, 1094, 1080, 1059, 1032, 1011, 960, 928, 910, 883, 856,

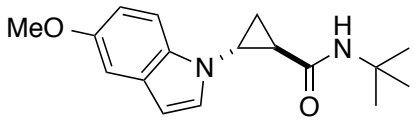
764, 741, 717, 683, 650, 617; HRMS (TOF ES): found 257.1652, calculated for $C_{16}H_{21}N_2O$ (M+H) 257.1654 (0.8 ppm).



(1R*,2R*)-N-benzyl-2-(1H-indol-1-yl)cyclopropanecarboxamide (121bc): This compound was obtained according to a typical procedure from bromocyclopropane **119b** (63.5 mg, 0.25 mmol, 1.00 equiv), employing indole **118c** (44 mg, 0.38 mmol, 1.5 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial 75:25 dr (trans:cis) to the final value of 97:3. NMR yield of 82% was determined by integration of ^{1}H NMR spectrum of the obtained crude mixture, which was recorded in the presence of CH_2Br_2 as internal standard. Subsequent chromatographic purification was accompanied by partial decomposition of the product and afforded the title compound as a colorless solid, R_f 0.17 (hexanes/EtOAc, 3:1), mp: 122.3−124.2 ^{o}C. Yield 35 mg (0.12 mmol, 48%). ^{1}H NMR (500.13 MHz, CDCl3) δ ppm 7.63 (d, *J* = 7.9 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.32−7.44 (m, 5 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.11−7.19 (m, 1 H), 7.05−7.11 (m, 1 H), 6.47 (d, *J* = 3.2 Hz, 1 H), 6.19 (br. s., 1 H), 4.51−4.62 (m, 2 H), 3.84−3.93 (m, 1 H), 1.77−1.88 (m, 2 H), 1.57−1.65 (m, 1 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 170.3, 138.0, 137.2, 128.8, 128.8 (+, 2C), 127.8 (+, 2C), 127.7 (+), 126.9 (+), 121.9 (+), 121.1 (+), 120.1 (+), 109.9 (+), 101.8 (+), 44.0 (-), 34.7 (+), 23.8 (+), 14.2 (-); FT IR (KBr, cm-1): 3298, 3061, 2926, 1717, 1645, 1614, 1556, 1512, 1495, 1475, 1454, 1447, 1404, 1383, 1352, 1339, 1317, 1225, 1198, 1126, 1107, 1082, 1030, 1013, 960, 947, 764, 741, 698, 673, 663, 636, 621, 602, 581, 571, 507, 484, 428, 411; HRMS (TOF ES): found 297.1570, calculated for $C_{19}H_{18}N_2OLi$ (M+Li) 297.1579 (3.0 ppm).

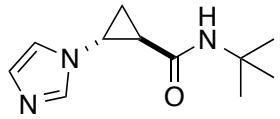


(1R*,2R*)-N-(tert-Butyl)-2-(3-methyl-1H-indol-1-yl)cyclopropanecarboxamide (121ad): This compound was obtained according to a typical procedure employing 3-methylindole **118d** (49 mg, 0.38 mmol, 1.5 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium *tert*-butoxide (56 mg, 0.50 mmol, 2.0 equiv) to improve initial 75:25 dr (trans:cis) to the final value of 99:1. The subsequent chromatographic purification afforded the title compound as a light brown solid, R_f 0.40 (hexanes/EtOAc 4:1), mp: 181.0−181.9 ^{o}C. Yield 49 mg (0.18 mmol, 73%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.57 (d, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 8.1 Hz, 1 H), 7.23−7.30 (m, 1 H), 7.12−7.20 (m, 1 H), 6.87 (s, 1 H), 5.66 (br. s., 1 H), 3.71−3.79 (m, 1 H), 2.31 (s, 3 H), 1.66−1.75 (m, 2 H), 1.48−1.54 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.6, 137.4, 129.1, 124.5 (+), 121.8 (+), 119.3 (+), 119.1 (+), 110.8, 109.7 (+), 51.7, 34.1 (+), 29.0 (+, 3C), 24.5 (+), 13.8 (-), 9.5 (+); FT IR (KBr, cm^{-1}): 3321, 3055, 2966, 2930, 1645, 1614, 1545, 1522, 1466, 1456, 1439, 1402, 1364, 1312, 1256, 1236, 1227, 1207, 1122, 1013, 739, 550, 494, 471, 455, 413, 401; HRMS (TOF ES): found 271.1494, calculated for $C_{17}H_{23}N_2O$ (M+H) 271.1810 (2.2 ppm).



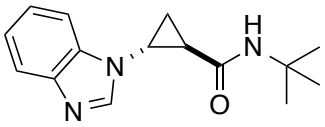
(1R*,2R*)-N-(tert-Butyl)-2-(5-methoxy-1H-indol-1-yl)cyclopropanecarboxamide (121ae): This compound was obtained according to a typical procedure employing 5-methoxylindole **118e** (55 mg, 0.38 mmol, 1.5 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert- butoxide (56 mg, 0.50 mmol, 2.0 equiv) to improve initial 75:25 dr (trans:cis) to the final value of 97:3. The subsequent chromatographic purification afforded the title compound as a light orange solid, R_f 0.25 (hexanes/EtOAc

4:1), mp: 124.2−124.8 °C. Yield 44 mg (0.15 mmol, 61%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.33 (d, *J* = 8.8 Hz, 1 H), 7.08 (d, *J* = 2.5 Hz, 1 H), 7.04 (d, *J* = 2.8 Hz, 1 H), 6.91 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.37 (d, *J* = 3.2 Hz, 1 H), 5.65 (br. s., 1 H), 3.86 (s, 3 H), 3.73−3.80 (m, 1 H), 1.66−1.74 (m, 2 H), 1.46−1.54 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 169.4, 154.5, 132.5, 129.2, 127.4 (+), 112.1 (+), 110.4 (+), 102.9 (+), 101.2 (+), 55.9 (+), 51.7, 34.4 (+), 29.0 (+, 2C), 24.5 (+), 13.8 (-); FT IR (KBr, cm^{-1}): 3323, 2966, 2934, 1647, 1622, 1549, 1516, 1483, 1448, 1400, 1364, 1288, 1246, 1227, 1150, 1030, 800, 754, 717, 455, 428; HRMS (TOF ES): found 293.1848, calculated for $C_{17}H_{22}N_2O_2Li$ (M+Li) 293.1841 (2.4 ppm).



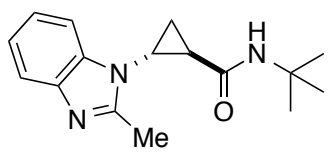
(1R*,2R*)-N-(tert-butyl)-2-(1H-imidazol-1-yl)cyclopropanecarboxamide (121ag): This compound was obtained according to a typical procedure employing imidazole **118g** (34 mg, 0.50 mmol, 2.0 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (56 mg, 0.50 mmol, 2.0 equiv) to improve initial 87:13 dr (trans:cis) to the final value of 100:0. NMR yield of 50% was determined by integration of ^{1}H NMR spectrum of the obtained crude mixture, which was recorded in the presence of CH_2Br_2 as internal standard. Since chromatographic purification was accompanied by partial decomposition of the product, isolation was carried out by crystallization from the mixture cyclohexane-EtOH, which afforded the title compound as a light yellow solid, R_f 0.15 (CH_2Cl_2/MeOH 20:1), mp: 101.5−101.9 °C. Yield 14 mg (0.068 mmol, 27%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.49 (s, 1 H), 6.99 (s, 1 H), 6.94 (s, 1 H), 6.25 (br. s., 1 H), 3.75 (ddd, *J* =

7.9, 4.7, 3.2 Hz, 1 H), 1.81 (ddd, *J* = 9.2, 5.9, 2.8 Hz, 1 H), 1.58 (dt, *J* = 7.9, 5.7 Hz, 1 H), 1.33−1.38 (m, 1 H), 1.39 (s, 9 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.6 (s), 137.0 (s), 129.2 (s), 119.4 (s), 51.7 (s), 34.3 (s), 28.8 (s), 24.0 (s), 13.4 (s); FT IR (KBr, cm^{-1}): 3302, 3065, 2966, 2928, 1651, 1556, 1504, 1456, 1404, 1393, 1364, 1256, 1227, 1200, 1107, 1078, 1061, 1045, 1022, 914, 737, 663, 613, 494, 484, 453; HRMS (TOF ES): found 207.1376, calculated for $C_{11}H_{17}N_3O$ (M+) 207.1372 (1.9 ppm).

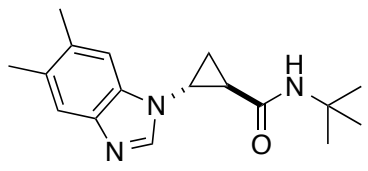


(1R*,2R*)-2-(1H-benzo[d]imidazol-1-yl)-N-(tert-butyl)cyclopropanecarb- oxamide (121ah): This compound was obtained according to a typical procedure employing benzimidazole **118h** (59 mg, 0.50 mmol, 2.0 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial 83:17 dr (trans:cis) to the final value of 100:0. The subsequent chromatographic purification afforded the title compound as a colorless solid, R_f 0.21 (CH_2Cl_2/MeOH 20:1), mp: 182.0-182.6 ^{o}C. Yield 42 mg (0.16 mmol, 66%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.89 (s, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 7.29−7.37 (m, 2 H), 5.78 (br.s.,1H), 3.80−3.87 (m, 1H), 1.75−1.83 (m, 2H), 1.53 (dt, *J* = 8.4, 4.3 Hz, 1H), 1.45 (s, 9H); ^{13}CNMR (125.76 MHz, $CDCl_3$) δ ppm 168.7, 155.8 (+), 143.8, 142.4, 123.3 (+), 122.7 (+), 120.6 (+), 110.0 (+), 51.9, 32.3 (+), 29.0 (+, 3C), 23.7 (+), 13.3 (-); FT IR (KBr, cm^{-1}): 3082, 3067, 2966, 2928, 1651, 1614, 1556, 1497, 1479, 1460, 1441, 1402, 1393, 1364, 1313, 1286, 1259, 1236, 1227, 1150, 1132, 1095, 1084, 1055, 1034, 970, 949, 893, 800, 783, 766, 744, 700, 683, 660, 629, 613, 594, 573, 542, 527, 501, 463, 420,

401; HRMS (TOF ES): found 257.1519, calculated for $C_{15}H_{19}N_3O$ (M+) 257.1528 (3.5 ppm).

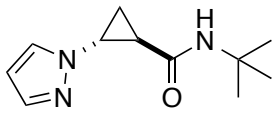


(1R*,2R*)-N-(tert-butyl)-2-(2-methyl-1H-benzo[d]imidazol-1-yl)cyclopropanecarboxamide (121ai): This compound was obtained according to a typical procedure employing 2-methylbenzimidazole **118i** (66 mg, 0.50 mmol, 2.0 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial 93:7 dr (trans:cis) to the final value of 95:5. The subsequent chromatographic purification afforded the title compound as a colorless solid, R_f 0.17 (CH_2Cl_2/MeOH 20:1), mp: 150.0−150.5 ^oC. Yield 57 mg (0.21 mmol, 84%). ^1H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.66−7.71 (m, 1 H), 7.41 (dt, *J* = 5.1, 2.0 Hz, 1 H), 7.23−7.27 (m, 2 H), 5.82 (s, 1 H), 3.66 (ddd, *J* = 7.3, 4.8, 3.0 Hz, 1 H), 2.66 (s, 3 H), 1.80−1.88 (m, 2 H), 1.49−1.54 (m, 1 H), 1.47 (s, 9 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.8, 152.9, 142.2, 135.7, 122.3 (+), 122.1 (+), 119.1 (+), 109.7 (+), 51.9, 31.7 (+), 28.9 (+, 3C), 24.2 (+), 14.7 (+), 14.6 (-); FT IR (KBr, cm^{-1}): 3281, 3055, 2966, 2928, 1651, 1556, 1524, 1460, 1443, 1404, 1364, 1344, 1315, 1285, 1256, 1227, 1200, 741, 467; HRMS (TOF ES): found 278.1847, calculated for $C_{16}H_{21}N_3OLi$ (M+Li) 278.1845 (0.7 ppm).



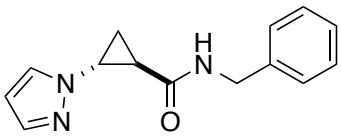
(1R*,2R*)-N-(tert-butyl)-2-(5,6-dimethyl-1H-benzo-[d]imidazol-1- yl)cyclopropanecarboxamide (121aj): This compound was obtained according to a typical procedure employing 5,6-dimethylbenzimid-azole **118j** (73 mg, 0.50 mmol, 2.0 equiv) as

pronucleophile. Epimerization was carried out in the presence of potassium tert- butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial 95:5 dr (trans:cis) to the final value of 97:3. The subsequent chromatographic purification afforded the title compound as a colorless solid, R_f 0.19 (CH_2Cl_2/MeOH 20:1), mp: 200−201 ^oC. Yield 51 mg (0.18 mmol, 72%). ^1H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.75 (s, 1 H), 7.53 (s, 1 H), 7.24 (s, 1 H), 5.93 (br. s., 1 H), 3.77 (ddd, *J* = 7.7, 4.7, 3.2 Hz, 1 H), 2.41 (s, 3 H), 2.38 (s, 3 H), 1.71−1.83 (m, 2 H), 1.49 (dt, *J* = 9.2, 4.7 Hz, 1 H), 1.45 (s, 9 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.9, 142.3, 141.6 (+), 133.4, 132.5, 131.6, 120.5 (+), 110.2 (+), 51.9, 32.4 (+), 29.0 (+, 3C), 23.8 (+), 20.6 (+), 20.2 (+), 13.3 (-); FT IR (KBr, cm^{-1}): 3261, 3211, 3070, 3028, 2966, 2935, 2866, 1651, 1556, 1495, 1472, 1454, 1404, 1393, 1364, 1339, 1308, 1261, 1227, 1175, 1161, 1136, 1086, 1068, 1051, 1022, 999, 970, 947, 930, 910, 866, 843, 800, 766, 737, 702, 646, 615, 586, 569, 548, 528, 467, 417, 403; HRMS (TOF ES): found 308.1749, calculated for $C_{17}H_{23}N_3ONa$ (M+Na) 308.1739 (3.2 ppm).

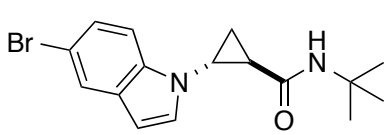


(1R*,2R*)-N-(tert-butyl)-2-(1H-pyrazol-1-yl)cyclopropane-carboxamide (121ak): This compound was obtained according to a typical procedure employing pyrazole **118k** (26 mg, 0.38 mmol, 1.5 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial 86:14 dr (trans:cis) to the final value of 99:1. The subsequent chromatographic purification afforded the title compound as a light orange solid, R_f 0.24 (CH_2Cl_2/MeOH 20:1), mp: 155.5−155.9 ^oC. Yield 44 mg (0.21 mmol, 85%). ^1H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.47 (d, *J* = 2.3 Hz, 1 H), 7.44 (d, *J* = 1.5 Hz, 1 H), 6.21 (t, *J* = 2.1 Hz, 1 H), 6.01 (br. s., 1 H), 3.94 (ddd, *J* = 7.8, 4.9, 2.8 Hz, 1 H), 2.04 (ddd, *J* = 9.1, 6.1, 3.0 Hz, 1 H), 1.51−1.62 (m, 2 H), 1.34 (s, 9 H); ^{13}C NMR

(100.67 MHz, $CDCl_3$) δ ppm 169.1, 139.2 (+), 129.8 (+), 105.7 (+), 51.5, 39.1 (+), 28.8 (+, 3C), 23.8 (+), 13.6 (-); FT IR (KBr, cm^{-1}): 3313, 2966, 2932, 1651, 1553, 1516, 1474, 1456, 1400, 1364, 1273, 1254, 1227, 1205, 1094, 1082, 1053, 987, 955, 937, 910, 752, 644, 611, 500, 434, 403; HRMS (TOF ES): found 214.1531, calculated for $C_{11}H_{17}N_3OLi$ (M+Li) 214.1532 (0.5 ppm).



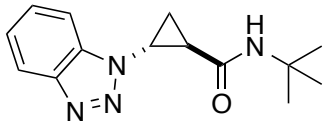
(1R*,2R*)-N-benzyl-2-(1H-pyrazol-1-yl)cyclopropanecarboxamide (121bk): This compound was obtained according to a typical procedure from bromocyclopropane **119b** (63.5 mg, 0.25 mmol, 1.00 equiv), employing pyrazole **118k** (34 mg, 0.50 mmol, 2.0 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial 88:12 dr (trans:cis) to the final value of 97:3. Subsequent chromatographic purification afforded the title compound as a colorless solid, R_f 0.27 (CH_2Cl_2/MeOH, 20:1), mp: 125.0−125.5 ^oC. Yield 44 mg (0.18 mmol, 73%). ^1H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.48 (d, *J* = 2.3 Hz, 1 H), 7.44 (d, *J* = 1.5 Hz, 1 H), 7.24−7.38 (m, 5 H), 6.76 (br. s., 1 H), 6.24 (t, *J* = 2.0 Hz, 1 H), 4.50 (dd, *J* = 14.7, 5.8 Hz, 1 H), 4.42 (dd, *J* = 14.7, 5.6 Hz, 1 H), 4.01 (ddd, *J* = 7.8, 4.9, 2.9 Hz, 1 H), 2.17 (ddd, *J* = 9.2, 6.1, 2.9 Hz, 1 H), 1.59−1.73 (m, 2 H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 170.0, 139.3 (+), 137.9, 129.9 (+), 128.7 (+, 2C), 127.8 (+, 2C), 127.5 (+), 105.8 (+), 43.9 (-), 39.4 (+), 23.3 (+), 13.9 (-); FT IR (KBr, cm^{-1}): 3242, 3113, 3097, 3069, 3030, 2961, 2928, 2872, 1728, 1632, 1605, 1556, 1514, 1495, 1454, 1404, 1339, 1273, 1238, 1223, 1202, 1122, 1082, 1051, 993, 953, 752, 696, 523, 422, 415, 403; HRMS (TOF ES): found 248.1367, calculated for $C_{14}H_{15}N_3OLi$ (M+Li) 248.1375 (3.2 ppm).



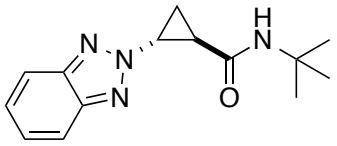
(1R*,2R*)-2-(5-Bromo-1H-indol-1-yl)-N-(tert-butyl)-cyclopropanecarboxamide (121ae): This compound was obtained according to a typical procedure from bromocyclopropane **119a** (55 mg, 0.25 mmol, 1.00 equiv), employing 5-bromo-1H-indole **118e** (147 mg, 0.75 mmol, 3.0 equiv) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial 42:58 dr (trans:cis) to the final value of 97:3. Subsequent chromatographic purification afforded the title compound as an amber oil, R_f 0.27 (hexane/EtOAc 6:1). Yield 40 mg (0.12 mmol, 48%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 7.74 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.34−7.32 (m, 2H), 7.09 (d, *J* = 3.3 Hz, 1H), 6.39 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.68 (s, 1H), 3.84−3.73 (m, 1H), 1.79−1.68 (m, 2H), 1.56−1.48 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ ppm 169.3, 135.8, 130.3, 128.2 (+), 124.8 (+), 123.6 (+), 113.3, 111.3 (+), 101.2 (+), 51.8, 34.3 (+), 29.0 (+, 3C), 24.4 (+), 13.9 (−). FT IR (KBr, cm^{-1}): 3325, 2966, 2934, 2874, 1647, 1549, 1508, 1462, 1225, 795. HRMS (TOF ES): found 357.0570, calculated for $C_{16}H_{19}BrN_2ONa$ (M + Na) 357.0578 (2.2 ppm).

Reaction with benzotriazole 118l: The reaction was carried out according to a standard procedure employing bromocyclopropane **119a** (110 mg, 0.50 mmol, 1.0 equiv) and benzotriazole **118l** (90 mg, 0.76 mmol, 1.5 equiv.) as pronucleophile. Epimerization was carried out in the presence of potassium tert-butoxide (84 mg, 0.75 mmol, 3.0 equiv) to improve initial ratio of 65:35 dr (**121al**, trans:cis) and 70:30 dr (**122al**, trans:cis) to the final values of 96:4 and 99:1, respectively. The subsequent chromatographic purification afforded two fractions: yellowish solid **121al**, mp 132-133 ^{o}C, R_f 0.33 (hexane/EtOAc

6:1) (yield 49 mg, 0.19 mmol, 38%), and colorless solid **122al**, mp 170−172 ^{o}C, R_f 0.29 (hexane/EtOAc 6:1) (yield 36 mg, 0.14 mmol, 28%).



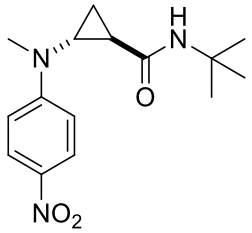
(1R*,2R*)-2-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(tert-butyl)cyclopropanecarboxamide (121al): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.65 (d, *J* = 8.3 Hz, 1 H), 7.48−7.60 (m, 1 H), 7.36−7.41 (m, 1 H), 6.41 (s, 1 H), 4.23 (ddd, *J* = 2.8, 4.7, 7.7 Hz, 1 H), 2.47 (ddd, *J* = 3.0, 6.1, 9.3 Hz, 1 H), 1.87 (ddd, *J* = 5.8, 7.6 Hz, 1 H), 1.71 (ddd, *J* = 4.9, 9.5 Hz, 1 H), 1.44 (s, 9 H); ^{13}C NMR (101MHz , $CDCl_3$) δ 168.8, 145.9, 134.0, 127.7 (+), 124.4 (+), 119.9 (+), 109.7 (+), 77.4, 77.1, 76.8, 51.9, 35.3(+), 28.9 (+, 3C), 23.5 (+), 13.9 (-); FT IR (KBr, cm^{-1}): 3306, 3071, 2968, 2932, 1652, 1456, 1258, 1177, 1095, 909, 745; HRMS (TOF ES): found 257.1405, calculated for $C_{14}H_{17}N_4O$ (M−H) 257.1402 (1.2 ppm).



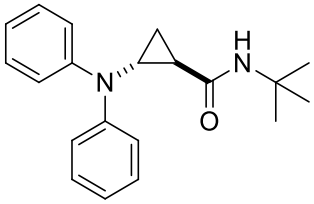
(1R*,2R*)-2-(2H-benzo[d][1,2,3]triazol-2-yl)-N-(tert-butyl)cyclopropanecarboxamide (122al): ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 3.0, 6.6 Hz, 2 H), 7.39 (dd, *J* = 3.2, 6.7 Hz, 2 H), 5.69 (br. s., 1 H), 4.72 (ddd, *J* = 3.0, 4.9, 8.0 Hz, 1H), 2.38 (ddd, *J* = 3.0, 6.4, 9.5 Hz, 1 H), 2.00 (ddd, *J* = 4.3, 5.1, 9.4 Hz, 1 H), 1.85 - 1.93 (m, 1 H), 1.39 (s, 9 H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 168.1, 144.1, 126.5 (+), 117.7 (+), 77.4, 77.0, 76.7, 51.8, 43.5 (+), 28.8 (+), 25.7 (+), 14.8 (-); FT IR (KBr, cm^{-1}): 3324, 2966, 1644, 1455, 1392, 1364, 1326,

1290, 1266, 1256, 1224, 1008, 745; HRMS (TOF ES): found 258.1484, calculated for $C_{14}H_{18}N_4O$ (M+) 258.1481 (1.2 ppm).

2.5.4. Synthesis of Cyclopropylanilines

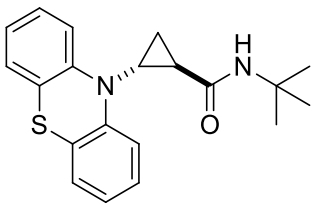


(1R*,2R*)-N-(tert-Butyl)-2-(methyl(4-nitrophenyl)amino)cyclopropanecarboxamide (**126ab**): Typical Procedure: 10 mL Wheaton vial equipped with a magnetic stir bar, under dry nitrogen atmosphere was charged with THF (5 mL), powdered KOH (112 mg, 2.00 mmol), *N*-methyl-4-nitroaniline **123b** (228 mg, 1.50 mmol), 18-crown-6 (13 mg, 0.050 mmol) and 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide **119a** (110 mg, 0.50 mmol). This solution was stirred at 55 ^{o}C for 12h, then filtered through a fritted funnel and concentrated in vacuum. Purification by flash chromatography on silica gel (eluent hexane:EtOAc 3:1) afforded the title compound as yellow solid (R_f 0.18), yield 142 mg (0.49 mmol, 98%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.07 (d, *J* = 9.4 Hz, 2H), 6.76 (d, *J* = 9.4 Hz, 2H), 5.86 (s, 1H), 3.09 (s, 3H), 3.06 (ddd, *J* = 7.6, 4.8, 3.1 Hz, 1H), 1.56 (m, 2H), 1.44 (s, 9H), 1.22 (ddd, *J* = 4.4, 4.9, 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 169.5, 154.6, 138.1, 125.6 (+, 2C), 111.8 (+, 2C), 51.7, 40.6 (+), 38.0 (+), 29.0 (+, 3C), 27.1 (+), 16.3 (-); FT IR (NaCl, cm^{-1}): 3325, 2966, 2930, 2874, 1643, 1547, 1493, 1396, 1315, 1113, 831, 754; HRMS (TOF ES): found 290.1504, calculated for $C_{15}H_{20}N_3O_3$ (M−H) 290.1505 (0.3 ppm).



(1R*,2R*)-N-(tert-Butyl)-2-(diphenylamino)cyclopropanecarboxamide (**126ad**): This compound was synthesized according to the typical procedure employing 2-bromo-N-

(tert-butyl)cyclopropanecarboxamide **119a** (55 mg, 0.25 mmol), powedered KOH (56 mg, 1.0 mmol), 18-crown-6 (6.6 mg, 0.025 mmol), THF (5 mL), and diphenyl amine **123d** (126 mg, 0.75 mmol). Crude mixture (dr 1.1:1) was concentrated in vacuum and treated with potassium *tert*-butoxide (112 mg, 1.0 mmol) in anhydrous THF (5 mL) at 80 ^{o}C for 12h, to improve the dr to 25:1. Flash column chromatography on silica gel afforded the title compound as white solid, mp 111.3 ^{o}C, R_f 0.27 (hexane/EtOAc 6:1). Yield 74 mg (0.24 mmol, 96%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.36–7.29 (m, 4H), 7.08–6.99 (m, 6H), 5.50 (s, 1H), 3.20 (ddd, *J* = 7.5, 4.8, 2.9 Hz, 1H), 1.04 (ddd, *J* = 8.6, 4.8 Hz, 1H), 1.43–1.39 (m, 9H), 1.53 (ddd, *J* = 7.2, 5.4 Hz, 1H), 1.50–1.46 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 170.1, 147.3, 129.2 (+, 4C), 122.3 (+, 2C), 121.4 (+, 4C), 51.5, 40.6 (+), 29.0 (+, 3C), 27.6 (+), 16.5 (-). FT IR (NaCl, cm^{-1}): 3325, 3057, 3044, 2966, 2930, 1647, 1591, 1500, 1456, 1394, 1364, 1313, 1248, 1224, 748; HRMS (TOF ES): found 308.1880, calculated for $C_{20}H_{24}N_2O$ (M+) 308.1889 (2.9 ppm).



(1R*,2R*)-N-(tert-butyl)-2-(10H-phenothiazin-10-yl)cyclopropanecarboxamide (**126ae**): This compound was prepared according to the typical procedure employing 2-bromo-*N*-(tert-butyl)cyclopropanecarboxamide **119a** (55 mg, 0.25 mmol), powdered KOH (56 mg, 1.0 mmol), 18-crown-6 (6.6 mg, 0.025 mmol), THF (5 mL), and 10*H*-phenothiazine **123e** (149 mg, 0.75 mmol). Crude reaction mixture (dr 3.5:1) was concentrated in vacuum and treated with potassium *tert*-butoxide (112 mg, 1.00 mmol) in anhydrous THF (5 mL) at 80 ^{o}C for 12h to improve dr to 49:1. Purification by flash chromatography on silica gel (eluent hexane:EtOAc 8:1) afforded the title compound as white solid, mp 187−188 ^{o}C, R_f 0.52. Yield 50 mg (0.148 mmol, 59%). ^{1}H NMR

(400.13 MHz, $CDCl_3$) δ ppm 7.24–7.12 (m, 4H), 6.98 (t, *J* = 8.0 Hz, 2H), 5.57 (s, 1H), 3.29 (ddd, *J* = 7.2, 4.7, 2.9 Hz, 1H), 1.83 (ddd, *J* = 6.7, 5.8, 4.9 Hz, 1H), 1.57 (ddd, *J* = 5.8, 2.9 Hz, 1H), 1.20 (ddd, *J* = 9.3, 4.8 Hz, 1H). ^{13}C NMR (100.61 MHz, CDCl3) δ ppm 169.8, 127.2, 127.1, 122.93, 51.6, 35.4, 29.0, 28.5, 18.1; FT IR (NaCl, cm^{-1}): 3358, 2992, 2961, 1649, 1542, 1461, 1374, 1367, 1250, 1129, 825, 750; HRMS (TOF ES): found 339.1528, calculated for $C_{20}H_{23}N_2OS$ (M+H) 339.1531 (0.9 ppm).

Chapter 3. Dual Control of the Selectivity in the Formal Nucleophilic Substitution of Bromocyclopropanes

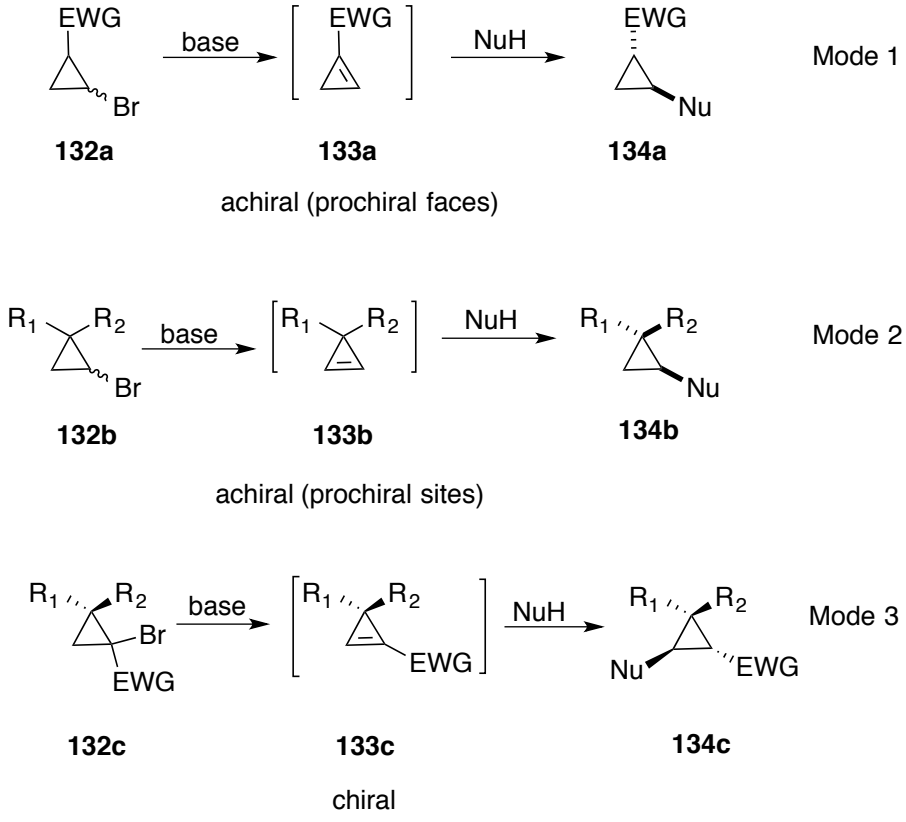
3.0. Introduction

Densely functionalized, chirally rich cyclopropanes have been the focus of rapidly growing interest, as both advanced synthons[9697] and important pharmacophores,[98] as evident from the vast number of emerging publications. Despite impressive achievements in the development of powerful methods for di- and trisubstituted cyclopropanes, and use thereof in the synthesis of complex biologically relevant targets,[99] there is still a significant demand for complementary approaches to analogs with denser substitution patterns and an expanded functional group scope.

In our continuing efforts to develop the diastereoselective formal nucleophilic substitution reaction of halocyclopropanes with heteroatom nucleophiles, we aimed at expanding the scope of this reaction to include multisubstituted substrates. We have shown previously that 1,2-dehydrohalogenation of 1,2-di- and 1,2,2-trisubstitued cyclopropylbromides **132a**, **132b** produces achiral cyclopropenes **133a** and **133b**, which upon in situ addition of a nucleophile furnish heterosubstituted cyclopropanes (modes 1 and 2, Scheme 44). Three alternative means of controlling the diastereoselectivity of addition have been demonstrated: a thermodynamically driven epimerization (mode 1), and a steric or directing effect of the substituents in the cyclopropene (mode 2, Scheme 44). In both of these modes, the generation of cyclopropene intermediates **133a** and **133b** was accompanied by a complete loss of the inherent chiral information and its subsequent reinstallation during the nucleophilic attack at either the prochiral face (mode 1) or

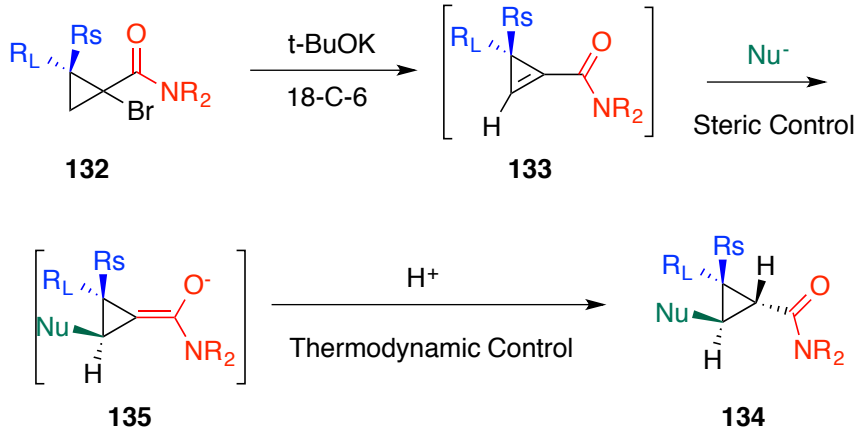
prochiral site (mode 2). Thus, nonracemic products could only be obtained via a diastereoselective addition of an enantiomerically pure nucleophilic reagent.

Scheme 44



Extension of this methodology beyond trisubstituted substrates amplifies the challenge of controlling the stereo- selectivity of addition. Indeed, both modes 1 and 2 required control of a single center only, since the two forming chiral centers were linked to each other. The new mode 3 (Scheme 44) realized in this work utilizes tetrasubstituted substrates **132**, in which installation of two stereogenic centers is synchronized and is controlled by both means (Scheme 45).

Scheme 45

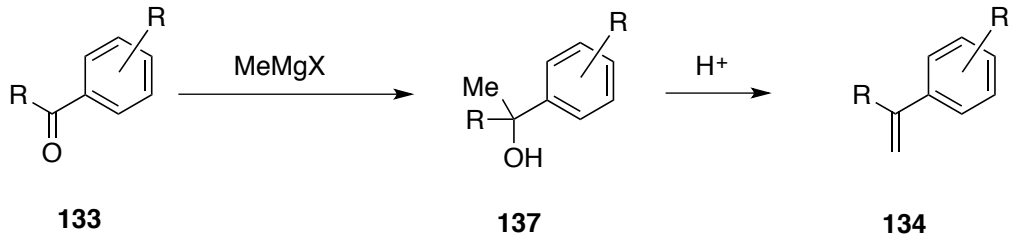


We envisioned that chiral α-bromocyclopropylcarboxamides **132** (easily available from corresponding α-bromocyclopropyl carboxylic acids) would provide convenient probes for this transformation, because the chirality of the β-quaternary center in these substrates would be preserved during the dehydrohalogenation/addition sequence, which would allow for carrying over the asymmetric information from the substrate to the product **134**. The chiral center at C-2 in bromocyclopropane **132** dictates the configuration of the other two stereocenters that are successively installed via a sterically controlled addition of a nucleophile (Steric control), followed by a thermodynamically driven epimerization (Thermodynamic control) of the resulting enolate intermediate **135**.

3.1. Synthesis of Homochiral α-Bromocyclopropyl Carboxylic Acids

Homochiral α-bromocyclopropyl carboxylic acids (α-BCA) **136** can be obtained in multigram quantaties via an efficient chiral resolution protocol and later converted into corresponding α-bromocyclopropylcarboxamides **132** (Scheme 47). The preparation of α-BCA's commences with the synthesis of α-substituted styrenes. Previously, Rubin et al.

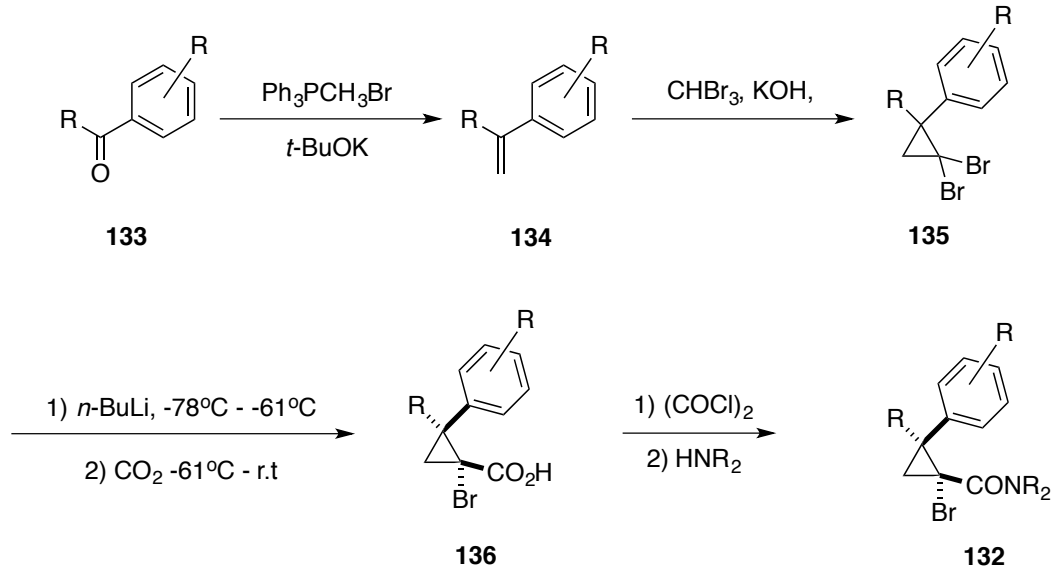
Scheme 46



133 **137** **134**

disclosed an efficient protocol for the synthesis of styrenes **134** from the readily available alkyl benzoates or acetophenones **133** via a two-step sequence including addition of Grignard reagent followed by the acid-catalyzed dehydration of the resulting tertiary alcohols **137** (Scheme 46). It was observed that the rate of the dehydration varies significantly depending on the electronic properties of the substituents at the aromatic ring of styrenes. Thus, electron-poor substrates react very slowly, whereas reaction times for electron-rich alcohols are significantly shorter. It should also be noted that some of the olefins **134** are highly susceptible to acid-catalyzed cationic polymerization, thus in order to avoid the decomposition of the olefin, the preparation of styrenes **134** was carried out via the Wittig olefination (Scheme 47).

Scheme 47

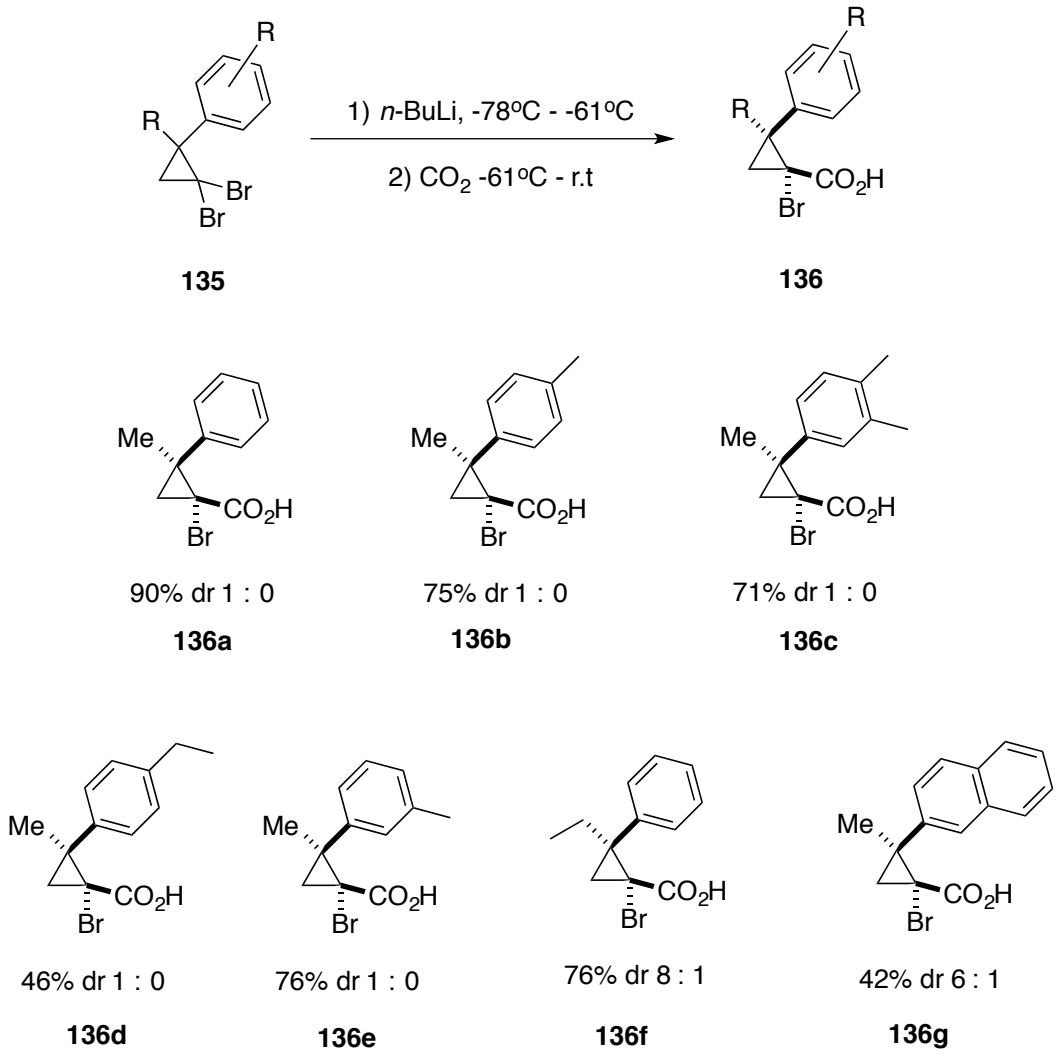


133 **134** **135**

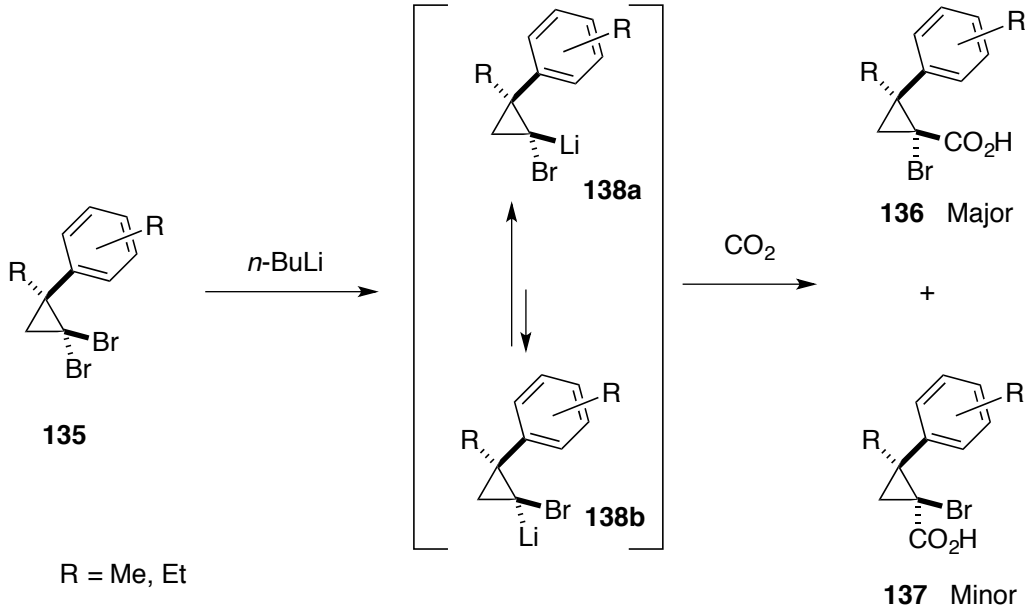
136 **132**

Dibromocyclopropanes **135** were prepared by cyclopropanation of the obtained olefins **134** with dibromocarbene generated under modified Makosza's PTC conditions.[100] Racemic bromoacids **136** were obtained by treatment of gem-dibromides **135** with butyl lithium at -61°C in THF, and exposure of the formed cyclopropyl lithium species to freshly condensed dry carbon dioxide. Carboxylation of gem-dibromocyclopropanes **135** under optimized conditions went smoothly giving trans acid **136** as the major product (Scheme 48).[101,102,103]

Scheme 48



Scheme 49



According to the literature,[104] substituted cyclopropane lithium halocarbenoids **138** favor conformation **138a** rather than **138b**, wherein lithium locates syn to the aromatic system (Scheme 49). It is believed that the lithiated intermediate **138a** is more thermodynamically stable than cyclopropane **138b**, due to the fact that the bulky bromine atom and large phenyl ring are located on the opposite sides of the cyclopropane. Carboxylation of dibromocyclopropanes **135a-e** with a methyl substituent on the ring resulted in selective formation of acids **136a-e** which is consisted with the proposed mechanism. When the size of the smaller substituent was increased from methyl to ethyl, carboxylation of cyclopropane **136f** with gave a mixture of diastereomers **136f** and **137f** (dr 8:1). Surprisingly, reaction of naphthyl substituted dibromocyclorpopane **135g** also resulted in the formation of a mixture of diastereomers (dr 6:1) and the acid **136g** was obtained only in 42% yield. This effect can be attributed to higher activation energies of carboxylation of lithium halocarbenoids **138a** with a bulky substituent, thus carbon dioxide can also react with sterically more accessible intermediate **138b**.

Having substantial amounts of racemic acids **136**, we attempted to resolve them into individual enantiomers via diastereomeric salt formation. The salt forming conditions were found by screening of different resolving agents and solvent combinations for the acid **rac-136a** (). To our delight, both enantiomers of **136a** can be obtained with cinchonine (CN) and with its pseudoenantiomer cinchonidine (CD) (Scheme 50). Treatment of **rac-136a** with stoichiometric amounts with cinchonine in boiling acetone and subsequent cooling resulted in the formation of diastereomeric salt **136aCN**. Isolation of the salt by simple suction filtration, followed by acid-base extraction gave **(+)-136a** in 98% ee. The remaining filtrate was concentrated in vacuum, remaining pseudoracemic acid **136a** was recovered and treated with cinchonidine under the same conditions giving salt **136aCD** which is then converted into **(-)-136a** in highly enantiopure form (91% ee). Enantiomeric excess of acids **136** was determined by chiral GC or HPLC analysis of corresponding esters (See experimental part). The absolute stereochemistry of **(-)-136a** the obtained acids was determined by a single-crystal X-ray analysis of the corresponding chiral salt **136aCD** (Figure 3).

Scheme 50

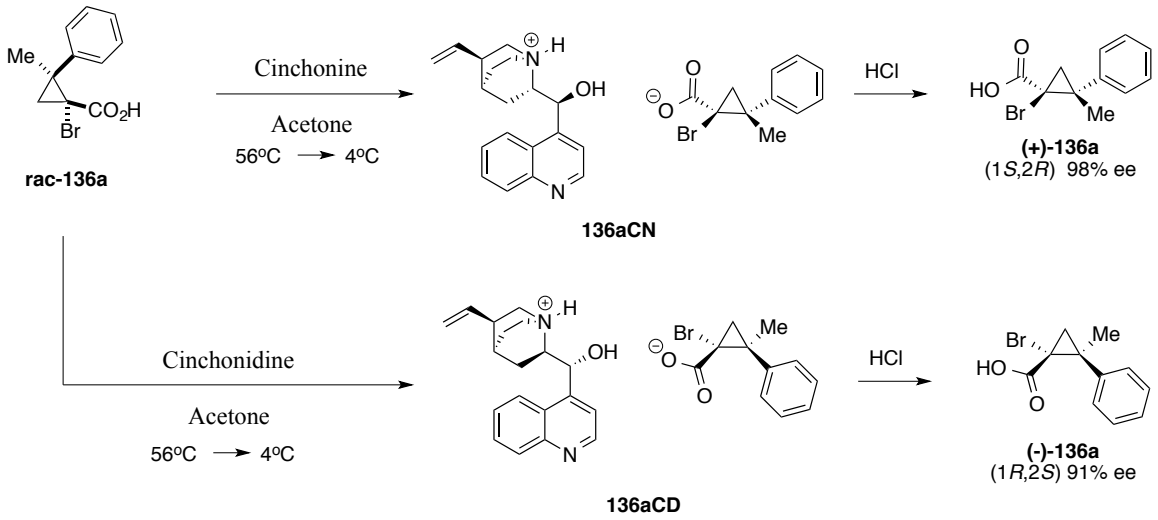
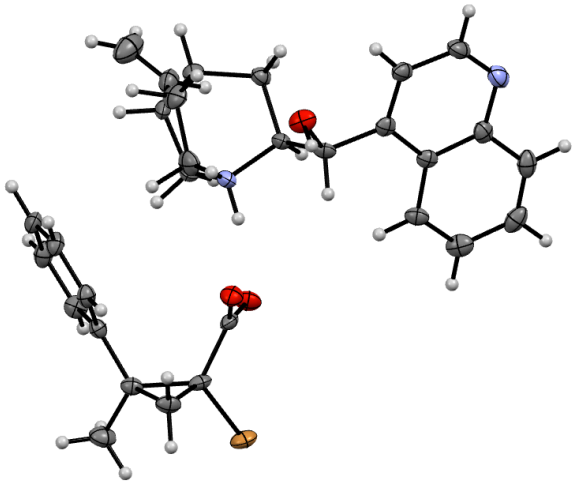


Figure 3 **ORTEP drawing of 136aCD showing 50% probability amplitude displacement ellipsoids.**



We were unable to obtain X-ray quality crystals of the opposite diastereomeric salt **136aCN**. In order to confirm the absolute stereochemistry of the other enantiomer **(+)-136a**, corresponding diethylamide **(+)-132ac** was subjected to X-ray analysis (Figure 4).

Figure 4 **Synthesis and ORTEP drawing of (+)-132a showing 50% probability amplitude displacement ellipsoids.**

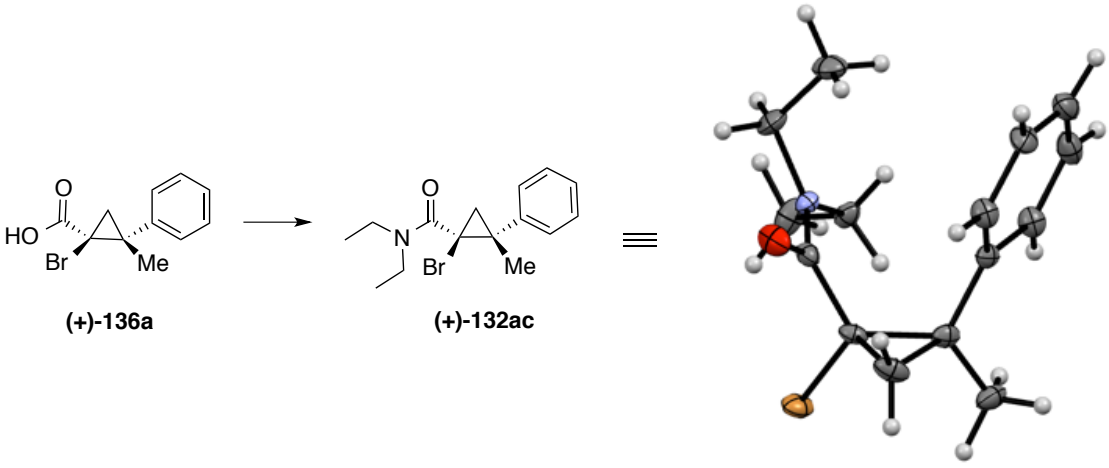


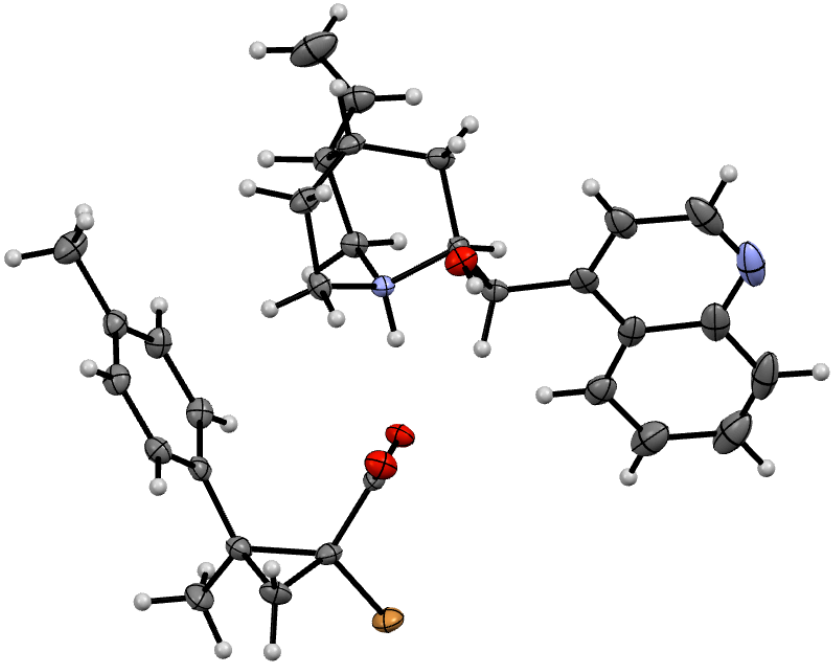
Table 2

Entry	Acid	Resolving agent	%ee	Entry	Acid	Resolving agent	%ee
1	**(+)-136b**	CN	>99	10	**(-)-136b**	CD	>99
2	**(+)-136c**	CN	92	11	**(-)-136c**	CD	52
3	**(+)-136d**	CN	>99	12	**(-)-136d**	CD	>99
4	**(+)-136e**	CN	>99	13	**(-)-136e**	CD	>99
5	**(+)-136f**	CN	>99	14	**(-)-136f**	CD	>99
6	**(+)-136g**	CN	>99	15	**(-)-136g**	CD	54

CN – cinchonine, CD – cinchonidine

Having optimized the resolution conditions, we moved on to other cyclopropyl acids **136b-g** (Table 2). To our delight, resolution with cinchonine and chinchonidine proved to be highly efficient for most of the cyclorpopyl acids. Generally, enantiopure acids (>99% ee) were obtained after a single crystallization with a chiral base. However, acid **(+)-136c** was obtained with 92%ee, as for **(-)-136c** and **(-)-136g** the enantiomeric excess was about 50%. An X-ray analysis of chiral ammonium salt **(-)-136bCD** indicated the same absolute configuration as **(-)-136bCD** (Figure 5). The absolute configuration of acids **136c-g** was assigned by analogy. Enantiopure acids were used to prepare corresponding chiral amides for the formal nucleophilic substitution reaction.

Figure 5 ORTEP drawing of 136bCD showing 50% probability amplitude displacement ellipsoids.

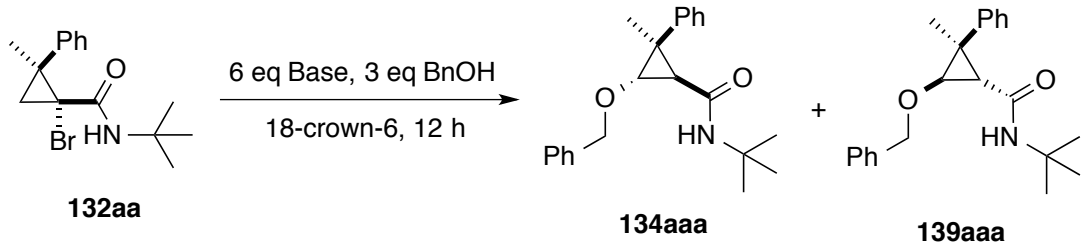


3.2. Optimization of the Reaction Conditions

We began by testing a model reaction of bromocyclopropane **132aa** using benzyl alcohol **140a** as a pronucleophile, using the standard reaction conditions employed previously for the addition of alkoxides.[105] This reaction provided cyclopropyl ether **134aaa** as a major diastereomer (dr = 14:1), albeit in only 49% yield (Table 3, entry 1). The stereoselectivity of the addition followed the predicted pattern: the in situ generated cyclopropene underwent addition of the nucleophile from the least hindered face, while the subsequent thermodynamically driven epimerization at the α-carbon of the amide set the third stereocenter. The minor stereoisomer **139aaa** was isolated, and its relative configuration was established by NMR experiments. It was thus confirmed that the observed diastereoselectivity is a result of the facial differentiation at the nucleophilic

attack step, whereas the last stereocenter is set with perfect diastereoselectivity via a thermodynamically driven epimerization, which occurs very rapidly in the presence of

Table 3



132aa **134aaa** **139aaa**

no.	base	T, °C	solvent	18-c-6, %	yield, %[b]	dr[c]
1	t-BuOK	60	THF	10	49	14:1
2	t-BuOK	80	THF	10	62	11:1
3	t-BuOK	90	THF	10	61	8:1
4	KOH	80	THF	10	37[e]	22:1
5	KOH[d]	80	THF	10	37[e]	19:1
6	t-BuOK	80	Toluene	10	28	2:1
7	t-BuOK	80	DCM	10	-	-
8	t-BuOK	80	DMA	10	59	27:1
9	t-BuOK	80	NMP	10	76	32:1
10	t-BuOK	80	CH_3CN	10	35	19:1
11	t-BuOK	80	DMSO	10	71	36:1
12	**t-BuOK**	**40**	**DMSO**	**10**	**80**	**46:1**
13	t-BuOK	25	DMSO	10	20[e]	50:1

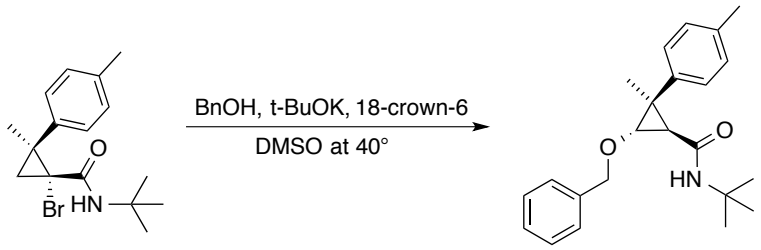
[a]Optimization reactions performed in 0.03 mmol scale. [b]GC yields of major diastereomer **134aaa**. [c]dr (**134aaa**:**139aaa**) was determined by GC of crude reaction mixtures. [d]Reaction time – 1 week. [e]Incomplete conversion.

t-BuOK. Increasing the temperature to 80 °C allowed for an improved yield of **134aaa**, however, at the expense of diastereoselectivity (entry 2). A further temperature increase caused notable deterioration of the diastereomeric ratio with no yield improvement (entry 3). Performing the reaction with a weaker base, KOH, did not proceed to completion, even after prolonged stirring at higher temperatures, despite providing excellent diastereoselectivities. Poor conversions achieved with KOH were attributed to the fact that dehydrohalogenation of **132aa** requires higher effective basicity of the medium as compared to β-bromocyclopropylcarboxamides, in which deprotonation occurs at the more acidic α-carbon. Other alkaline bases such as lithium, sodium, magnesium hydroxides, and tert-butoxides gave no reaction. Solvent screening revealed that polar, aprotic solvents, such as DMSO and NMP, were superior media for this transformation (entries 9 and 11). Accordingly, DMSO was chosen as the medium due to being a safer alternative.[106] A quick temperature optimization in DMSO showed that the best yield and dr's are achieved at 40°C (entry 12).

3.3. Formal Substitution Using Homochiral Substrate

To showcase the efficient transfer of the chiral information from the starting material to the product, homochiral bromocyclopropane **132ba** derived from (1R,2S)-1-bromo-2-methyl-2-(p-tolyl)cyclopropane-1-carboxylic acid **(-)-136b** was cleanly converted into benzyl cyclopropyl ether **134baa** in excellent isolated yield and diastereoselectivity (Scheme 51). The retention of configuration of the quaternary carbon throughout the reaction was confirmed by an X-ray analysis of the product **134bab** (Figure 6 ORTEP drawing of 134bab showing 50% probability amplitude displacement ellipsoids.).

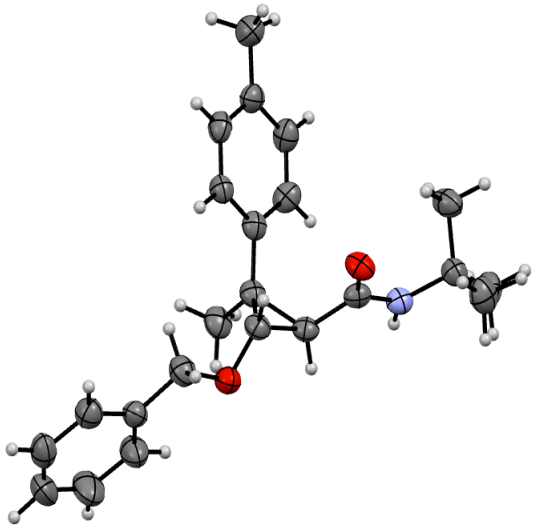
Scheme 51



132ba >99% ee

134baa 92%, 30:1, >99% ee

Figure 6 ORTEP drawing of 134bab showing 50% probability amplitude displacement ellipsoids.



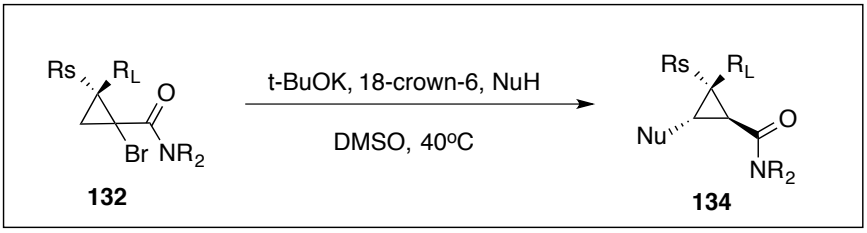
3.4. Oxygen-based Nucleophiles

Having optimized the reaction conditions, we moved on to examine the scope of this reaction. Screening a series of alcohols against a few bromocyclopropylcarboxamides **132** revealed that the sterics of the nucleophiles had a significant effect on their reactivity. Thus, all primary alcohols, including those bearing functional groups, reacted smoothly under optimized conditions (Scheme 52). A brief survey of substituents on the carboxamide group showed that tertiary and bulky secondary amides are compatible with optimized conditions. Reaction in DMSO consistently allowed for high diastereoselectivities, although in a few cases provided lower yields due to partial loss of product upon extraction. The reaction with a secondary alcohol proceeded much more sluggishly in DMSO and led to substantial decomposition; however, a reasonable yield of **134aag** was obtained under alternative conditions in THF at higher temperatures. Attempts to add phenols were not successful. Interestingly, addition of *tert*-butyl alcohol to cyclopropene did not give expected cyclopropyl ether **134aah** even at higher temperatures (80°C in DMSO), instead a carboxamide **141aa** was observed in 66% yield (Scheme 53).

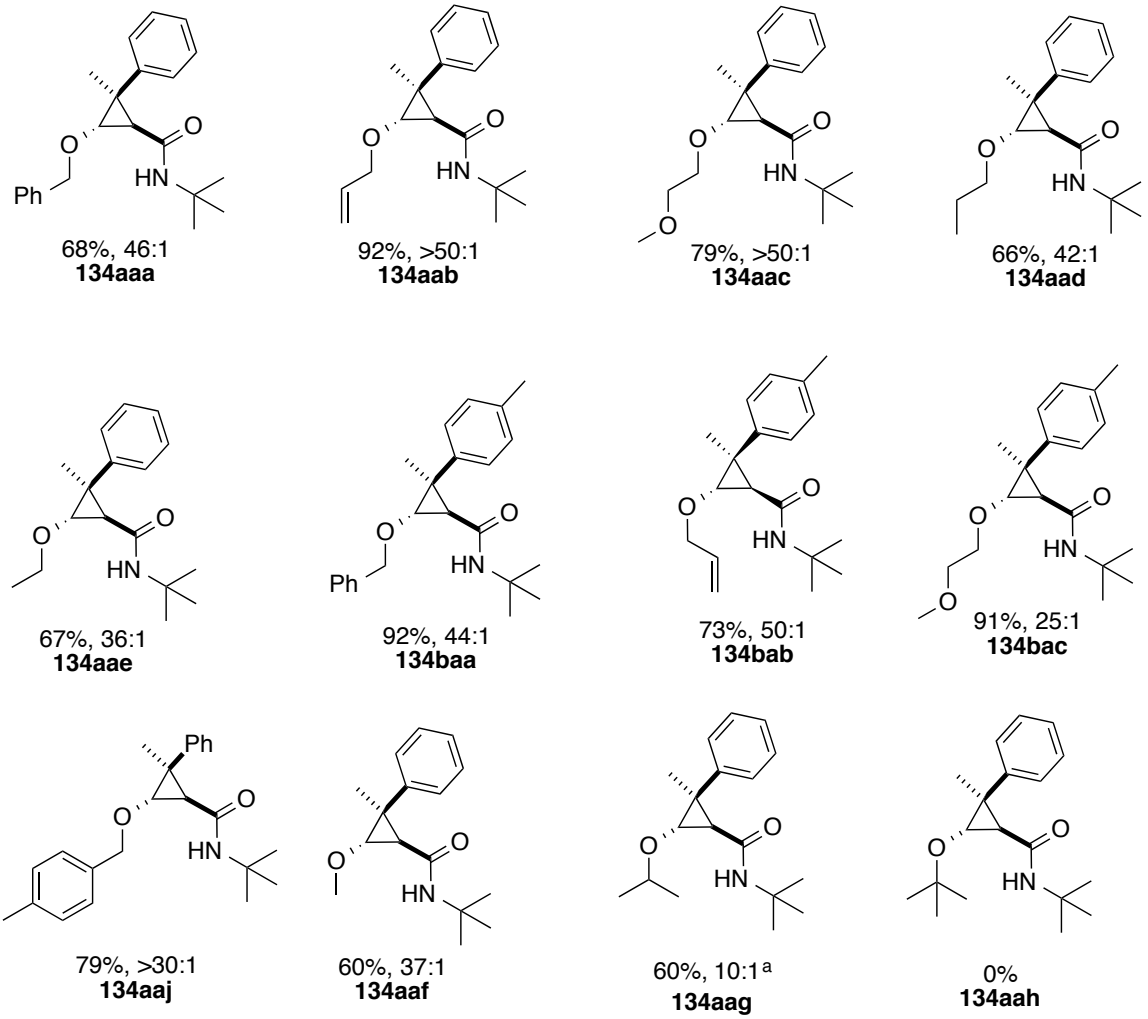
We believe that a bulky tert-butyl alohol adds to cyclopropene **132aa** at higher temperature giving the desired cyclorpopane **134aah** (Scheme 53). However, under basic conditions cyclopropyl ether **134aah** decomposes giving isoprene **142a** and an aldehyde **142b**. The later one is attacked by a *tert*-butoxide forming intermediate **142d** which then gives tert-butyl formate **142f** and enolate **142g**. Upon protonation of **142g** a final product N-(tert-butyl)-3-phenylbutanamide **141aa** is formed. This reaction occurs with a loss of chirality and does not have much value for the synthetic community. Similar compounds

can be obtained in enantiopure form by simple amidation of corresponding carboxylic acids[107] or via stereoselective additions of organometallic species to α,β-enamides[108].

Scheme 52

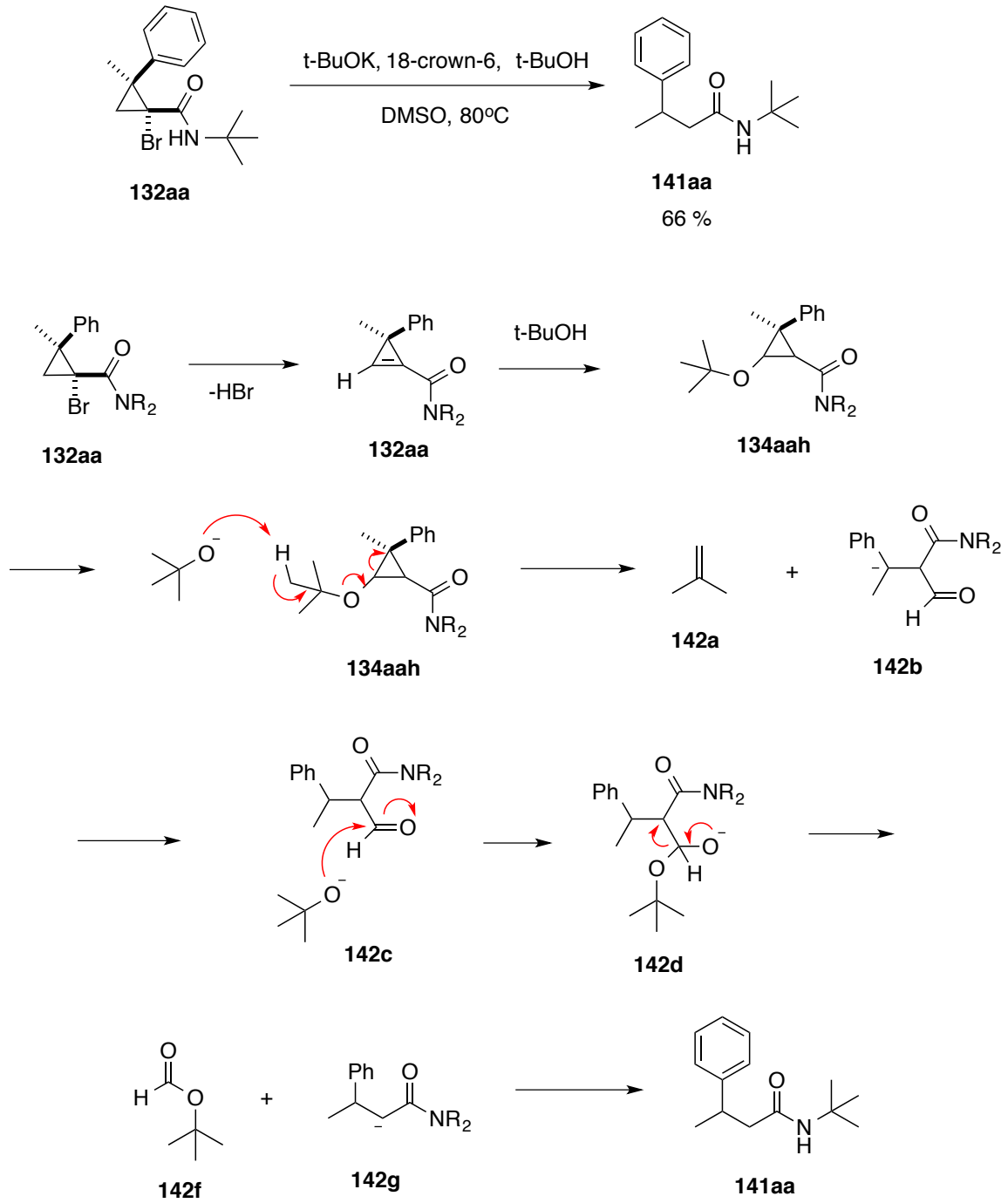


132 **134**



Reactions performed on 0.2 mmol scale; isolated yields are listed. Values of dr are measured by GC or NMR analysis of crude reaction mixtures. [a] Reaction performed in THF, 80°C, 12 h.

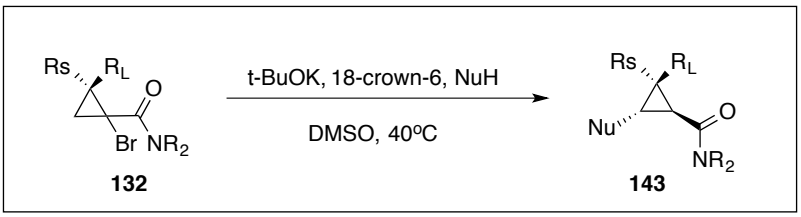
Scheme 53

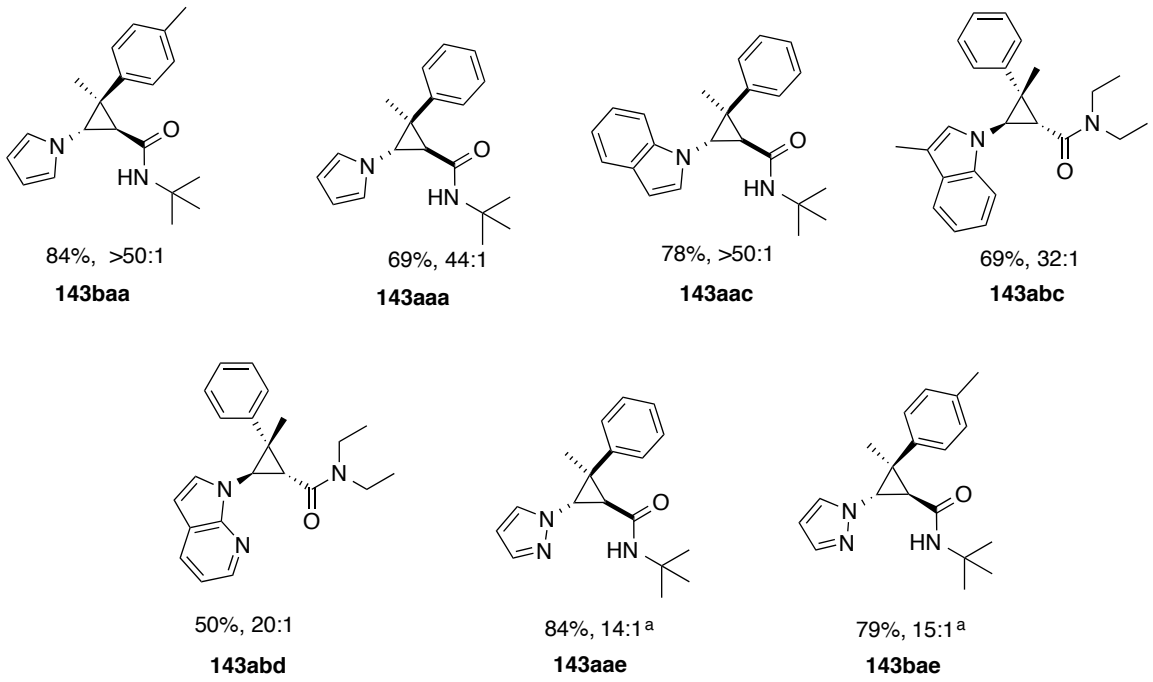

t-BuOK, 18-crown-6, t-BuOH
DMSO, 80ºC
132aa
141aa
66 %
-HBr
t-BuOH
134aah
142a
142b
142c
142d
142f
142g

3.5. Nitrogen-based Nucleophiles

To access β-ACC derivatives through this methodology, we tested a series of different amines as N-pronucleophiles; however, our initial attempts to induce addition primary and secondary amines, as well as carboxamides and sulfonamides, were unsuccessful. We were pleased to find that azoles underwent facile addition to provide substituted hetarylcyclopropanes **143** under previously optimized conditions (Scheme 54). Reaction in the presence of pyrrole afforded the corresponding tetrasubstituted cyclopropanes **143aaa** and **143baa** in high yields and excellent diastereoselectivities. We were happy to find that such problematic nucleophiles such as indoles, known for their susceptibility to Friedel-Crafts alkylation, dimerization, and polymerization,[109] afforded good isolated yields of the corresponding adducts. Substituted indoles and 7-azaindole proceeded cleanly to afford the corresponding cyclopropanes. Similarly, pyrazole was engaged in a very efficient transformation with cyclopropylbromides **132aa** and **132ba**, providing good yields of N-cyclopropylpyrazoles **143aae** and **143bae**, respectively, although longer reaction times were reaquired and the diastereoselectivities were slightly lower. More acidic azoles uncluding imidazoles, benzimidazoles and triazoles did not participate in the title reaction.

Scheme 54

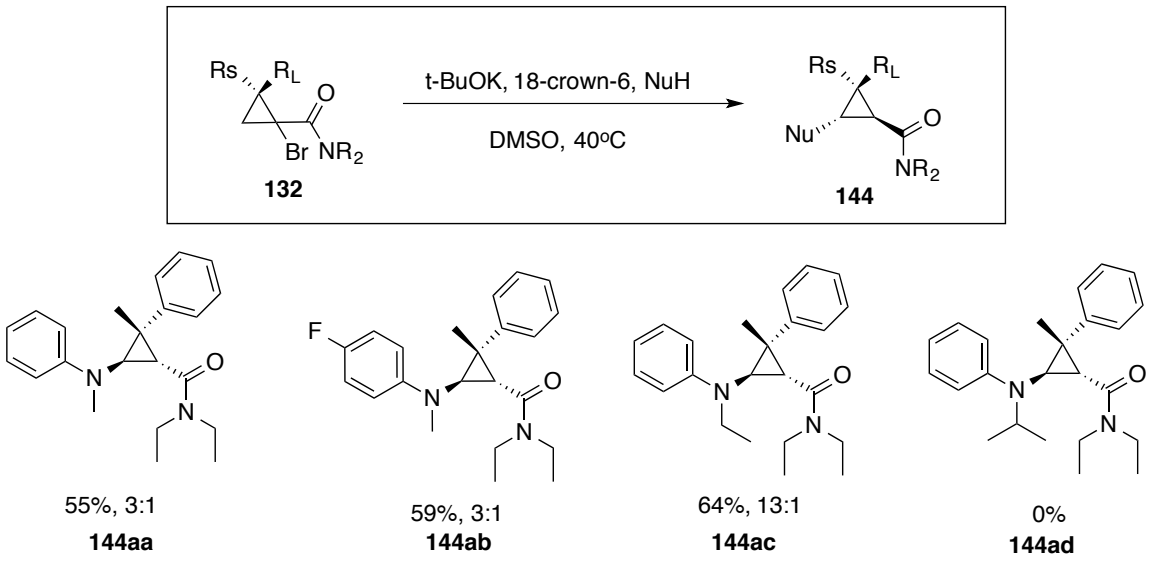




Reactions performed on 0.2 mmol scale; isolated yields are listed. Values of dr are measured by GC or NMR analysis of crude reaction mixtures. [a] Reaction time is 72 h.

Anilines were also tested in this reaction and to our delight N-methylaniline **123a** reacted with **132aa** giving a stable donor-acceptor cyclopropane **144aa** in 55% and dr 3:1. p-Flouro-N-methylaniline **123f** can be utilized in the described reaction providing with a tetrasubstituted cyclopropane **144ab** with similar diastereoselectivity and yield. It was found that increased steric hindrance at the N- termini of the pronucleophile had a significant effect on the reaction course. Thus, aniline bearing an ethyl substituent greatly increased the reaction's efficacy; the diastereoselectivity was much higher for **144ac**.

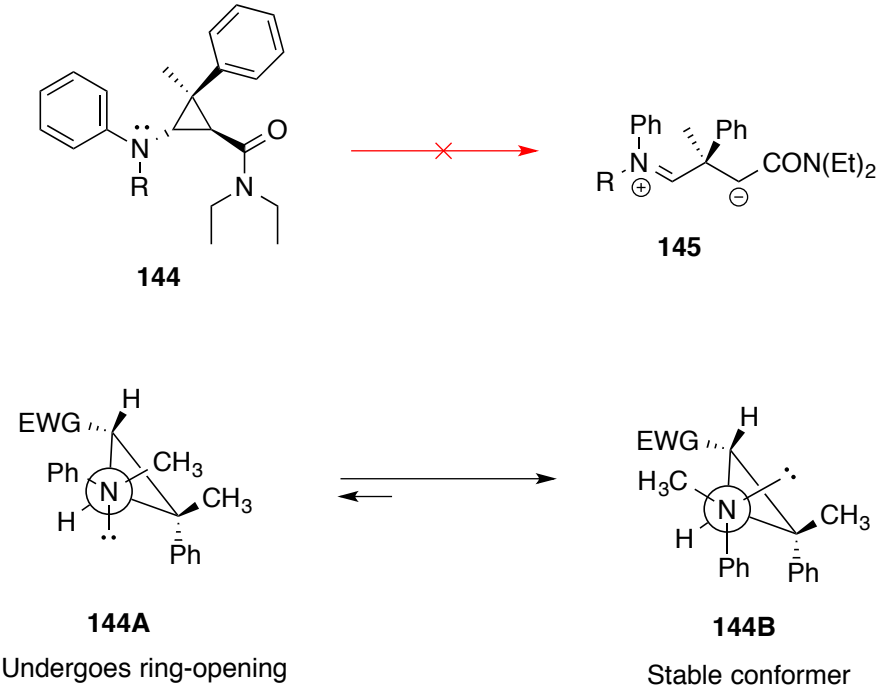
Scheme 55



While substrate with secondary alkyl group at the N-terminus did not undergo the addition at all (**144ad**).

These cyclopropane adducts **144** do not undergo a ring-opening reaction which is observe on disubstituted cyclopropanes **126** (Scheme 40, Chapter 2). Tetrasubstituted cyclopropanes **144** proved to be stable even without the presence of the aromatic system with electron-withdrawing groups. The unusual stability of **144** is caused by stereoelectronic factors (Scheme 56). In order for the ring-opening reaction to occur, the tetrasubstituted cyclopropane **144** has to be in a conformation **144A** with a nitrogen lone pair positioned anti-periplanar to the C1-C3 bond of the cyclopropane. Due to the steric interactions of alkyl substituent on the nitrogen and a methyl group on the cyclopropane ring, conformation **144A** is highly disfavored, thus cyclopropane **144** exists in a more stable conformation **144B.**

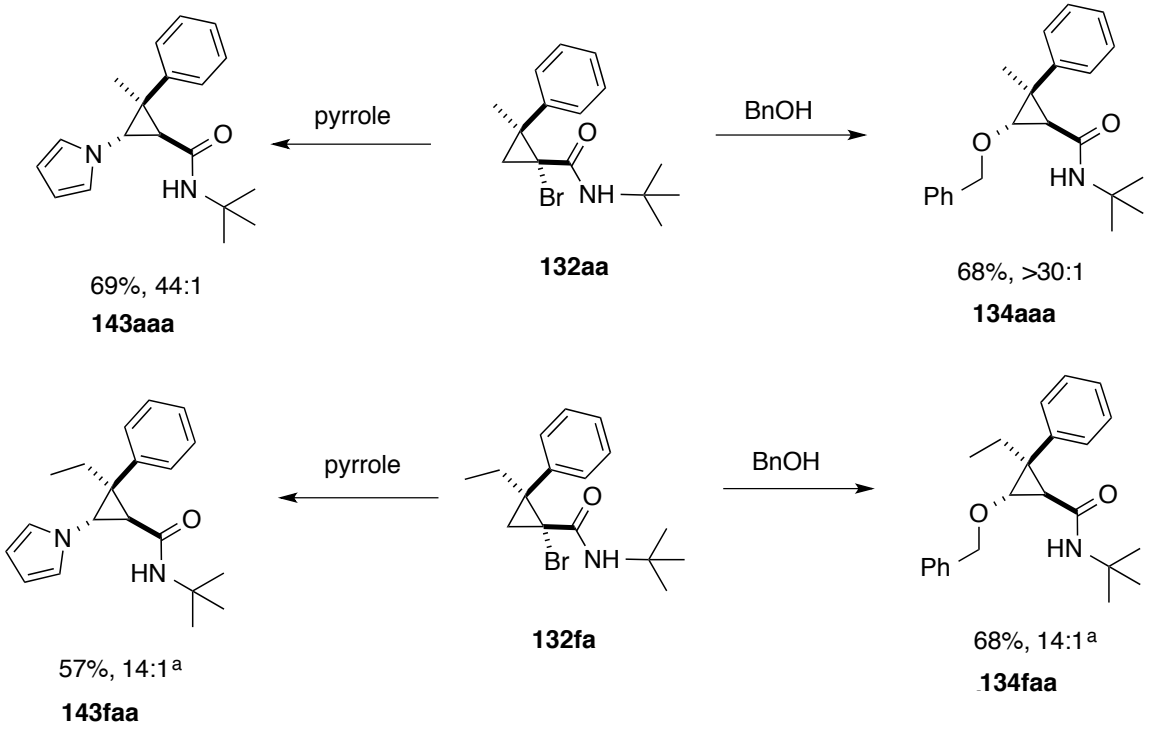
Scheme 56



3.6. Effects of the Substituents on the Cyclopropane

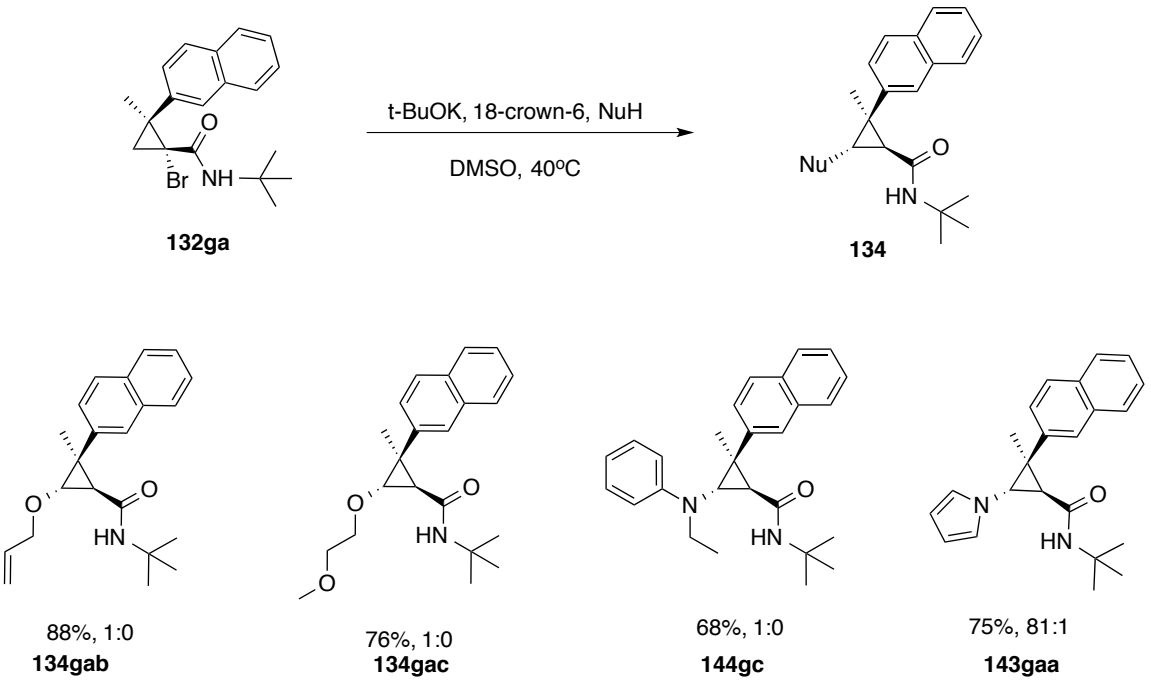
The sensitivity of the reaction to sterics can be further seen by comparing the reactivity of bromocyclopropanes **132aa** and **132fa**, possessing a methyl and an ethyl group, respectively, at the β-quaternary center (Scheme 57). In spite of providing the same isolated yield as **134aaa**, homologue **134faa** reacted very sluggishly at 40°C and required higher temperature to achieve full conversion, which led to a lower, although still respectable, diastereoselectivity. Reaction of **132fa** with pyrrole followed the same trend: the diastereoselectivity and the rate of the reaction were significantly lower. The carboxamides **132ga** possessing a larger naphthyl substituent also participated in a dual-control substitution reaction with known oxygen- and nitrogen-based nucleophiles. As expected such modification of the substrate gave superb diastereselectivities in the title reaction (Scheme 58).

Scheme 57



[a] Reaction stirred at 40°C for 12 h, then at 80°C for 30 minutes.

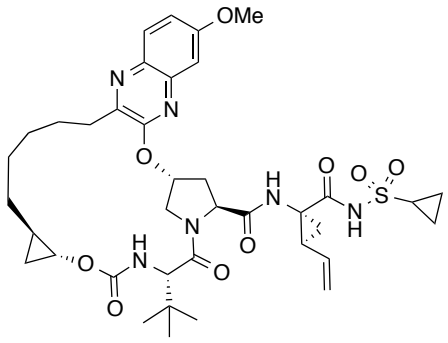
Scheme 58



3.7. Intramolecular formal nucleophilic substitution

We envisioned the intramolecular mode of the dual-control reaction would serve as a convenient probe for stretching the limits of the challenging nucleophilic *endo-trig* medium ring closures and provide a useful tool for the construction of novel types of medium-sized heterocycles. The intramolecular reaction could allow access to several important classes of compounds including medium and large cyclopropyl-fused heterocycles. Besides biologically active bicyclic compounds discussed in Chapter 1 (Scheme 1) it is important to mention cyclopropyl-fused macrocycle MK-5172 discovered at Merck which has the potential to be the cornerstone of an all-oral treatment for hepatitis C virus (Figure 7).[110]

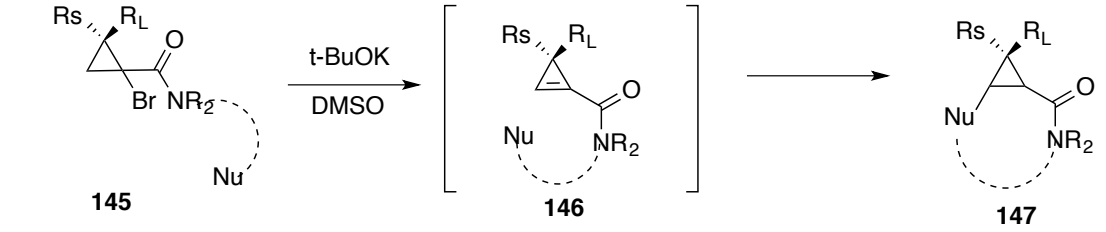
Figure 7

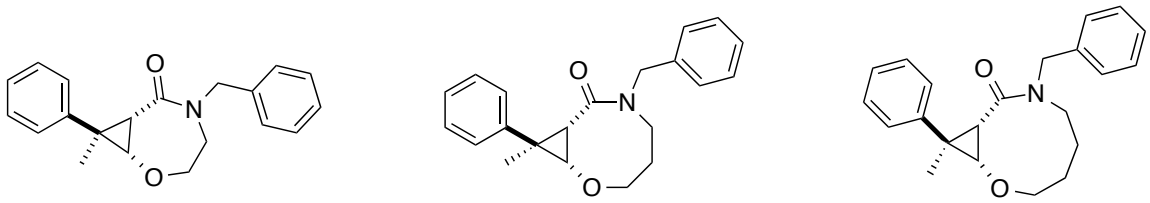


MK-5172

Generation of cyclopropene species **146** from bromocyclopropane **145** bearing a pronucleophilic moiety tethered through the carboxamide would enable an *endo-trig* cyclization, leading to bicyclic scaffolds **147** (Scheme 59). It was indicated that the lengths of the tether plays a crucial role in the cyclization process. Bromocyclopropanes **145b** with a three carbon atom tether underwent highly efficient 8-*endo-trig* cyclization affording the corresponding oxazacanone **147b** in excellent yield. 9-Membered cycle

Scheme 59

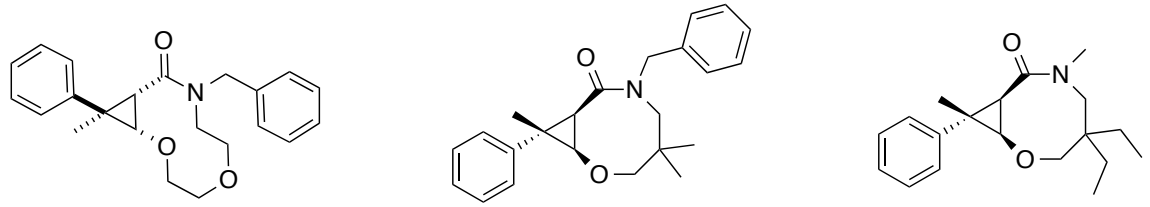




0%
147a

85%
147b

21%
147c



0%
147d

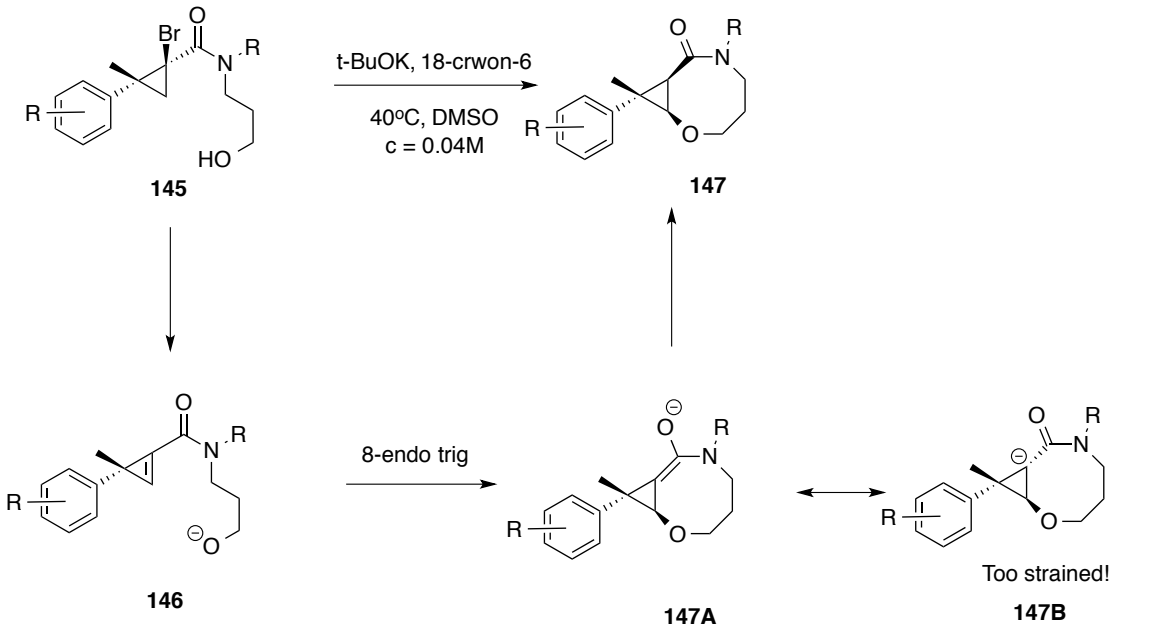
37 %
147e

31 %
147f

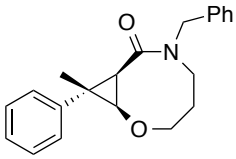
Reactions stirred at 40°C for 12 h, C = 0.04M

147c was obtained in lower yield from a very flexible substrate **147c**, possessing no additional stereoselectivity-inducing elements in the tether. Bromocyclopropanes **145e** and **145f** bearing *gem*-dialkyl substituents on the tether gave corresponding 8-membered heterocycles **147e** and **147f** albeit in 31-37% yield. Due to Thorpe-Ingold effect the geometry of the tether is changed and the nucleophilic oxygen atom is delivered at a different angle, resulting in lower yield compared to **147b**. It should also be mentioned that cyclization did not require high dilutions and afforded consistently high yields in preparatively convenient concentration ranges.

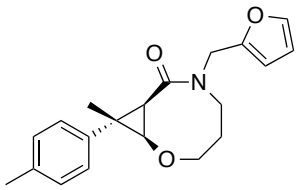
Scheme 60



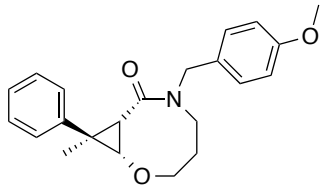
145 **147** **146** **147A** **147B**



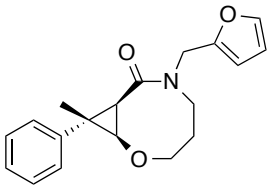
85%
147b



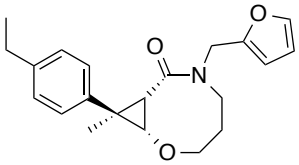
83%
147g



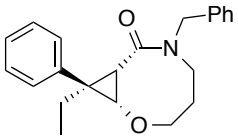
65%
147h



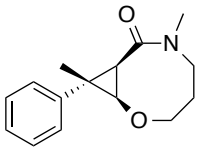
80%
147i



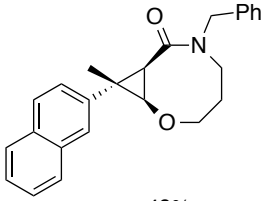
94%
147j



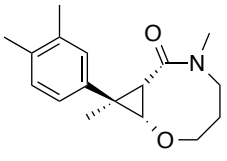
79%
147k



61%
147l



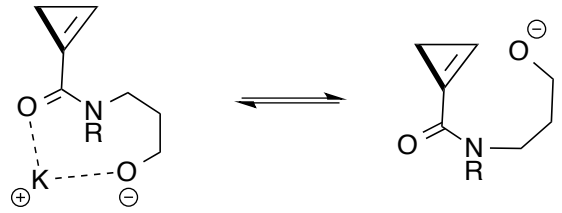
49%
147m



67%
147n

8-*Endo-trig* cyclization of **145** produced *cis*-fused heterocycles **147** exclusively as equilibration to the *trans*-fused diastereomers **147B** is unfavored unlike in the corresponding intermolecular nucleophilic additions to similar substrates (Scheme 60). A series of oxazacanones **147** were obtained in good to excellent yields. It was found that increasing the size of the substituent on the nitrogen has a positive effect on the efficacy of the reaction. Bromocyclopropanes **145l** and **145n** bearing a methyl group on carboxamide function gave bicyclic moieties **147l** and **147n** in lower yield. It is believed that upon the formation of cyclopropene **146**, the nucleophilic alkoxide anion is coordinated to potassium ion, which may also coordinate to the oxygen of the amide (Scheme 61). Such preorganization places the nucleophilic center far from the reactive double bond. By placement of a bulky substituent (e.g. benzyl group) on the amide, reactive conformer **146B** is more favored, due to restricted coordination of potassium and carbonyl oxygen.

Scheme 61



non-reactive

146A

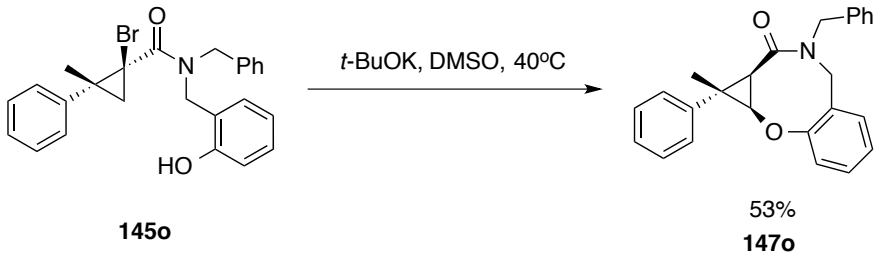
reactive

146B

All oxazacanones were prepared from enantiopure starting material and isolated as single diastereomers, A high level of selectivity was also observed on a bromocyclopropane **145k** with an ethyl substituent on the cyclopropane ring. Heterocycle **147m** was prepared on a smaller scale compared to other oxazacanones **147** and the

isolated yield was only 49%. We were also delighted to obtain benzooxazocinone **147o** from corresponding substrate **145o** under optimized conditions (Scheme 62).

Scheme 62

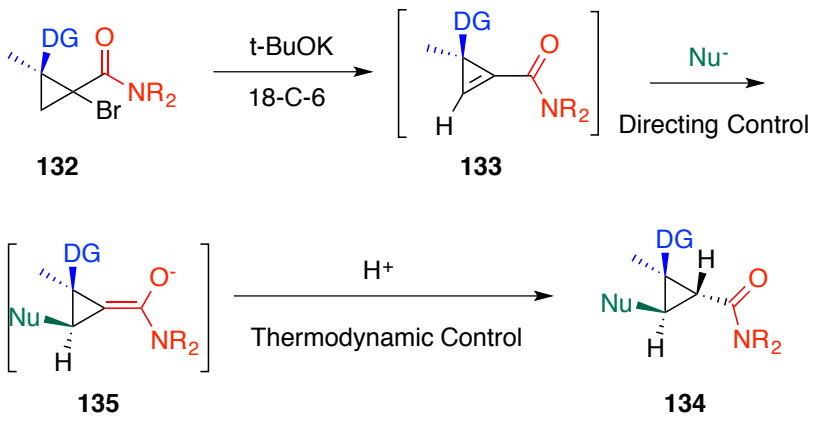


145o **147o**

3.8. Future Directions

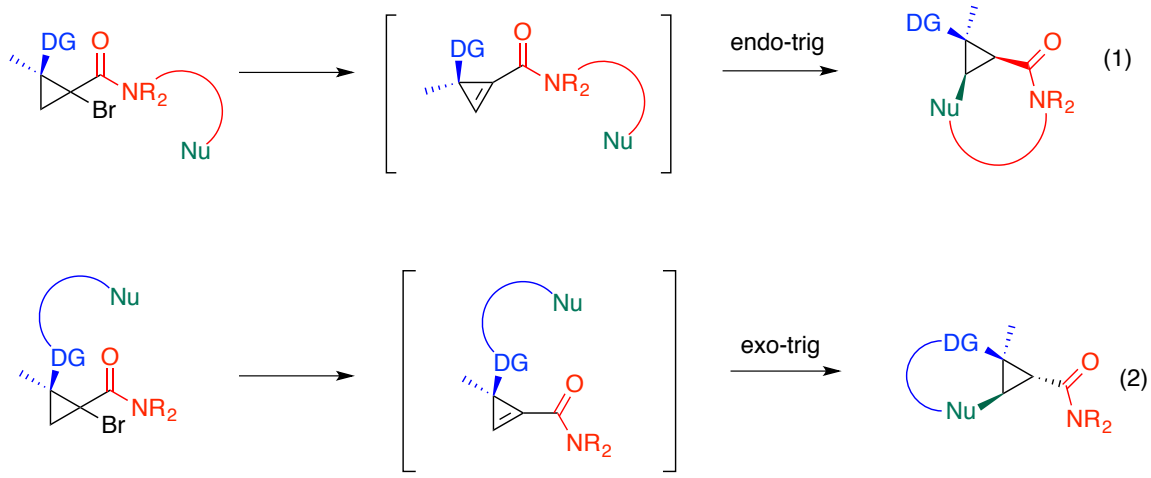
One of the possible future directions of the presented research would be a development of an alternative "dual-control" reaction utilizing a combination of directing and thermodynamic controls. In order to perform a diastereoselective addition in this manner a substrate possessing a suitable directing group should be designed (Scheme 63). This new type of "dual-control" reaction could potentially be performed in an intramolecular fashion. Placement of a nucleophile on the amide function would result in endo-trig cyclization (eq.1). An exo-trig cyclization may be invoked with a nucleophilic moiety tethered to a substrate via the directing group.

Scheme 63



132 **133** **135** **134**

Scheme 64

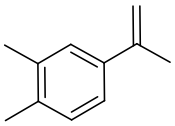


3.9. Conclusions

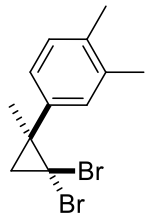
In conclusion, a "dual-control" strategy was successfully employed for a highly diastereoselective inter- and intramolecular addition of nucleophilic species to *in situ* generated cyclopropenes. This reaction afforded tetrasubstituted donor-acceptor cyclopropanes with all three asymmetric carbons in the strained ring. The chiral integrity of the starting material is translated to the product via a sequential installation of two stereogenic centers efficiently controlled by steric and thermodynamic effects.

3.10. Experimental

3.10.1. Synthesis of the Starting Materials

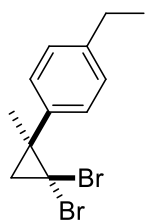


1,2-dimethyl-4-(prop-1-en-2-yl)benzene (134c): A solution of potassium *tert*-butoxide (7.71 g, 68.7 mmol, 0.955 equiv.) in dry THF (75 mL) was added drop wise to a stirred suspension of methyltriphenylphosphonium bromide (41.16 g, 115.2 mmol, 1.6 equiv.) in dry THF (175 mL) at 0 ºC. The resulting yellow mixture was stirred for one hour at 0 ºC and then a solution of 3',4'-dimethylacetophenone (10.7 g, 10.7 mL, 72.0 mmol, 1.0 equiv.) in THF was added drop wise and stirred overnight. The mixture was then quenched with saturated aqueous NH_4Cl and partitioned between water (25 mL) and diethyl ether (3 x 75 mL). Combined ethereal phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by short column chromatography using silica gel and a hexane mobile phase to afford 1,2-dimethyl-4-(prop-1-en-2-yl)benzene as a clear oil in 82% yield (8.6 g, 59 mmol). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.18−7.01 (m, 3H), 5.25 (s, 1H), 4.94 (s, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 2.06 (s, 3H); ^{13}C (126 MHz, $CDCl_3$): δ 143.4, 139.0, 136.4, 136.0, 129.6 (-), 126.9 (-), 123.1 (-), 111.6 (+), 22.0 (-), 20.1 (-), 19.6 (-); FTIR (KBr, cm^{-1}): 3084, 3020, 2970, 2941, 2918, 2887, 2862, 1630, 1566, 1504, 1450, 1371, 1020, 995, 881, 822, 733; HRMS (TOF ES): Found 153.1253, calculated for $C_{11}H_{14}Li$ (M+Li) 153.1256 (2.0 ppm).



(2,2-dibromo-1methylcyclopropyl)-1,2-dimethylbenzene (135c):

(Typical Procedure): 1,2-dimethyl-4-(prop-1-en-2-yl)benzene **134c** (17.48 g, 119.5 mmol, 1.0 equiv.) without further purification was mixed with bromoform (45.24 g, 15.65 mL, 179.0 mmol, 1.5 equiv.), tetradecyltrimethyl-ammonium bromide (TDTAB) (750 mg, 2.23 mmol, 0.019 equiv.), and dichloromethane (200 mL). The mixture was vigorously stirred and 50% aqueous solution of sodium hydroxide (12 g NaOH, 12 mL H_2O) was added drop wise. The mixture was stirred (900-1100 rpm) overnight at 30−35 ºC. When GC analysis indicated full conversion of the olefin, the mixture was quenched with water (300 mL) and extracted with dichloromethane (3 x 50 mL). Combined organic phases were washed with brine, dried with $MgSO_4$**,** filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with hexanes as the mobile phase to afford (2,2-dibromo-1methylcyclopropyl)-1,2-dimethylbenzene as a light yellow oil in 78% yield (29.72 g, 93.25 mmol). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.18–7.01 (m, 3H), 2.29 (s, 3H), 2.27 (s, 3H), 2.15 (d, *J* = 7.5 Hz, 1H), 1.76 (d, *J* = 7.5 Hz, 1H), 1.71 (s, 3H); ^{13}C (126 MHz, $CDCl_3$): δ 139.9, 136.7, 135.7, 129.8 (+), 129.7 (+), 125.9 (+), 37.4 (-), 35.6, 33.8, 28.0 (+), 20.0 (+), 19.7 (+); FTIR (KBr, cm^{-1}): 2980, 2966, 2924, 2864, 2359, 1504, 1447, 1427, 1062, 1022, 822, 692; HRMS (TOF ES): Found 314.9389, calculated for $C_{12}H_{13}Br_2$ (M-H) 314.9384 (1.6 ppm).



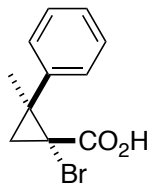
(2,2-dibromo-1-methylcyclopropyl)-4-ethylbenzene (135d):

Compound was obtained via typical procedure using 1-ethyl-4-(prop-1-en-2-yl)benzene **134d** (18.68 g, 127.7 mmol, 1.0 equiv.) mixed with

bromoform (48.52 g, 16.79 mL, 192.0 mmol, 1.5 equiv.), tetradecyltrimethyl-ammonium bromide (TDTAB) (750 mg, 2.23 mmol, 0.017 equiv.), and dichloromethane (200 mL). Sodium hydroxide (13 g, 319 mmol, 2.5 equiv.) in 13 mL of water was added drop wise. (2,2-dibromo-1-methylcyclopropyl)-4-ethylbenzene was obtained as a clear oil in 77% yield (31.1 g, 97.9 mmol). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.25 – 7.18 (m, 4H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.15 (d, *J* = 7.5 Hz, 1H), 1.77 (d, *J* = 7.5 Hz, 1H), 1.71 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$): 143.3, 139.7, 128.5 (+, 2C), 128.0 (+, 2C), 37.3, 35.6, 33.8 (-), 28.6 (-), 27.9 (+), 15.5 (+); FTIR (KBr, cm^{-1}): 3022, 2962, 2928, 2893, 2870, 1512, 1445, 1427, 1377, 1082, 1063, 1051, 1018, 831, 692, 573; HRMS (TOF ES): Found 314.9386, calculated for $C_{12}H_{13}Br_2$ (M-H) 314.9384 (0.6 ppm).

3.10.2. Synthesis of Racemic Bromoarylylcyclopropanecarboxylic Acids

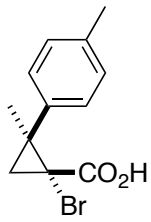
(1R*,2S*)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid (**136a**):



(Typical procedure): Oven-dried 500 mL two-necked flask was charged under nitrogen atmosphere with solution of (2,2-dibromo-1-methylcyclopropyl)benzene **135a** (20.3 g, 70.0 mmol, 1.0 equiv) in 200 mL of anhydrous THF. The solution was cooled to -78 ^{o}C and *n*-BuLi (2.5 M in hexanes, 26.5 mL, 66.5 mmol, 0.95 equiv) was added dropwise through an addition funnel over the course of 15 minutes. After the addition was complete, the reaction mixture was wormed to -61 ^{o}C and stirred for 20 minutes. The cold solution was then cannulated into 1 L flask containing freshly condensed CO_2. The reaction mixture was stirred for 2 hours under constant flow of dry CO_2 gas, while allowed to warm to room temperature. The mixture was partitioned between 140 mL of water and 100 mL of $CHCl_3$ and acidified with 210 mL of 4N HCl. The aqueous layer was extracted with $CHCl_3$ (3 x 40 mL). The

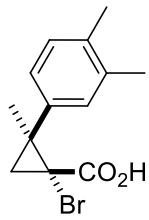
combined organic phases were then back-extracted with saturated $NaHCO_3$ (3 x 40 mL). The combined aqueous extracts were washed with 20 mL $CHCl_3$, acidified to pH < 1, and extracted with $CHCl_3$ (3 x 40 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated in vacuum to yield 15.3 g (60.0 mmol, 90.2%) of 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid as a colorless crystalline solid, mp: 90-92 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.14 (m, 5H), 2.46 (d, J = 6.4 Hz, 1H), 1.74 (s, 3H), 1.41 (d, J = 6.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 140.2, 128.6 (+, 2C), 128.0 (+, 2C), 127.4 (+), 39.4, 37.2, 28.724 (-), 27.8 (+); FT IR (KBr, cm^{-1}): 3384, 2923, 1445, 1238, 1213, 1150, 1109, 1061, 1028, 968, 932, 874, 800, 766, 700, 604, 559, 532; HRMS (TOF ES): found 247.0305, calculated for $C_{11}H_{13}NBrOLi$ (M+Li) 247.0310 (2.0 ppm).

(1R*,2S*)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid (**136b**):



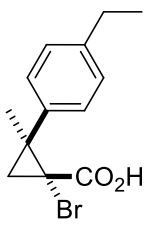
This compound was obtained according to a typical procedure employing 2.5 M *n*-BuLi (26.5 mL, 66.5 mmol) and 1-(2,2-dibromo-1-methylcyclopropyl)-4-methylbenzene **135b (**21.28 g, 70 mmol) as a starting material. Acid-base extraction yielded 13.37 g (49.7 mmol, 75%) of **136b** as a colorless solid, mp: 114.2-114.9 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (td, J = 8.5, 3.3 Hz, 4H), 2.44 (d, J = 6.4 Hz, 1H), 2.31 (s, 3H), 1.71 (s, 3H), 1.37 (d, J = 6.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 137.2, 137.0, 129.3 (+, 2C), 127.9 (+, 2C), 39.5, 36.8, 28.7 (-), 27.8 (+), 21.3 (+); FT IR (KBr, cm^{-1}): 3022, 2984, 2964, 2923, 1699, 1419, 1296, 1278, 1246, 818; HRMS (TOF ES): found 267.0015, calculated for $C_{12}H_{12}NBrO_2$ (M-H) 247.0021 (2.2 ppm).

(1R*,2S*)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid (136c):



A solution of (2,2-dibromo-1methylcyclopropyl)-1,2-dimethylbenzene **135c** (23.7 g, 74.5 mmol, 1.0 equiv.) in dry THF (200 mL) was added to a 500 ml oven dried two neck flask under nitrogen atmosphere. The solution was cooled to -78 ºC and 2.5 M n-BuLi (4.54 g, 28.3 ml, 70.8 mmol, 0.950 equiv.) was added drop wise with an addition funnel over the course of 15 minutes. Immediately following the addition of n-BuLi, the reaction mixture was warmed to -61 ºC and stirred for 20 minutes. The mixture was then cannulated into a 1 L three neck flask containing freshly condensed carbon dioxide and allowed to warm to room temperature with moderate stirring while under a constant flow of dry CO_2 gas. The mixture was quenched with 140 mL of water and then added to 100 mL of chloroform. The mixture was acidified with 210 mL of 4N HCl. The aqueous layer was extracted with chloroform (3 x 40 mL). Combined organic phases were then extracted with saturated sodium bicarbonate (3 x 40 mL). The remaining aqueous solution was washed with 20 mL chloroform. The combined aqueous phases were then acidified to pH<1 and extracted with chloroform (3 x 40 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to afford the product as light yellow crystals in 71% yield (14.2 g, 50.1 mmol). Mp: 127−129 ºC; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.05–6.86 (m, 3H), 2.42 (d, J = 6.3 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 1.70 (s, 3H), 1.36 (d, J = 6.3 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): δ 174.0, 137.5, 136.7, 135.6, 129.8 (+), 129.1 (+), 125.2 (+), 39.6, 36.9, 28.8 (-), 28.0 (+), 19.8 (+), 19.6 (+); FTIR (KBr, cm^{-1}): 3084, 3015, 2982, 2968, 2924, 2885, 2866, 2652, 1699, 1445, 1418, 1302, 1281, 1250, 1221, 1061, 878,

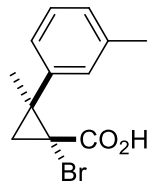
820, 696; HRMS (TOF ES): Found 281.0179, calculated for $C_{13}H_{14}BrO_2$ (M-H) 281.0177 (0.7 ppm).



(1R*,2S*)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropane-carboxylic acid (136d):

Compound was obtained via typical procedure using 1-(2,2-dibromo-1-methylcyclopropyl)-4-ethylbenzene **135d** (22.4 g, 70.4 mmol, 1.0 equiv.) in THF (200 mL) and 2.5 M n-BuLi (4.28 g, 26.8 mL, 66.9 mmol, 0.95 equiv.). (1R*,2S*)-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid was obtained as light brown crystals in 46% yield (8.57 g, 30.3 mmol). MP: 109-111 ºC; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.15–7.03 (m, 4H), 2.61 (q, *J* = 7.6 Hz, 2H), 2.44 (d, *J* = 6.4 Hz, 1H), 1.71 (s, 3H), 1.37 (d, *J* = 6.4 Hz, 1H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$): δ 173.7, 143.3, 137.3, 128.0 (+, 2C), 127.9 (+, 2C), 39.5, 37.0, 28.8 (-), 28.6 (-), 27.8 (+), 15.6 (+); FTIR (KBr, cm^{-1}): 3090, 3049, 3022, 2964, 2928, 2895, 2872, 1701, 1516, 1421, 1377, 1298, 1286, 1250, 1119, 1080, 1063, 1045, 941, 885, 862, 833, 696, 569; HRMS (TOF ES): Found 283.0328, calculated for $C_{13}H_{16}BrO_2$ (M+H) 283.0334 (2.1 ppm).

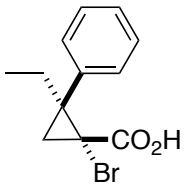
(1R*,2S*)-1-bromo-2-methyl-2-(*m*-tolyl)cyclopropanecarboxylic acid (136e):



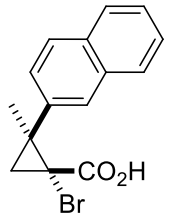
Compound was obtained via typical procedure using 1-(2,2-dibromo-1-methylcyclopropyl)-3-methylbenzene **135e** (23.9 g, 78.5 mmol, 1.0 equiv.) in THF (200 mL) and 2.5 M n-BuLi (4.78 g, 29.9 mL, 74.7 mmol, 0.95 equiv.). (1R*, 2S*)-1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylic acid was obtained as a yellow oil in 76% yield (15.2 g, 56.4 mmol). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.18–6.93 (m, 4H), 2.44 (d, *J* = 6.3 Hz, 1H), 2.30 (s, 3H), 1.71 (s, 3H), 1.38 (d,

J = 6.4 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): δ 172.7, 140.1, 138.2, 128.7 (+), 128.5 (+), 128.2 (+), 125.0 (+), 39.5, 37.1, 28.8 (-), 27.9 (+), 21.5 (+); FTIR (KBr, cm^{-1}): 3400, 3364, 3225, 3180, 3101, 3020, 2984, 2964, 2926, 2864, 1699, 1418, 1379, 1298, 1248, 1200, 1049, 947, 876, 787, 706, 671; HRMS (TOF ES): Found 269.0184, calculated for $C_{12}H_{14}BrO_2$ (M+H) 269.0177 (2.6 ppm).

(***1R*,2S*)-1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid*** (**136f**):



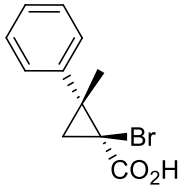
This compound was obtained according to a typical procedure employing 2.5 M *n*-BuLi (21.3 mL, 53.3 mmol) and (2,2-dibromo-1-ethylcyclopropyl)benzene **135f** (17.07 g, 56.15 mmol) as a starting material. Acid-base extraction yielded 10.87 g (42.5 mmol, 76%) of a diastereomeric mixture of acids (8:1). Major diastereomer can be obtained in pure form by recrystallization from ethyl acetate as a colorless solid, mp: 124.3−125.1 ^{o}C. Diastereomeric mixture (2:1) isolated from the mother liquor was used for preparation of carboxamide **3e**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.12 (m, 5H), 2.35 (dd, J = 6.3, 1.5 Hz, 1H), 2.08 (ddd, J = 13.9, 7.4, 1.4 Hz, 1H), 1.89 (dq, J = 14.8, 7.4 Hz, 1H), 1.34 (d, J = 6.3 Hz, 1H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 138.1, 129.0 (+, 2C), 128.4 (+, 2C), 127.4 (+), 42.0, 39.9, 33.6 (-), 27.7 (-), 11.2 (+); FT IR (KBr, cm^{-1}): 3084, 3058, 3026, 2972, 2873, 1699, 1417, 1298, 1286, 1238, 1099, 1066, 879, 754, 700; HRMS (TOF ES): found 275.0254, calculated for $C_{12}H_{13}BrO_2Li$ (M+Li) 275.0259 (1.8 ppm).



(1R*, 2S*)-1-bromo-2-methyl-2(naphthalene-2-yl)cyclopropanecarboxylic acid (136g):

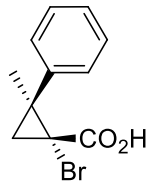
Compound was obtained via typical procedure using 2-(2,2-dibromo-1-methylcyclopropyl)naphthalene **135g** (23.8 g, 70.0 mmol, 1.0 equiv.) in THF (200 mL) and 2.5 M n-BuLi (4.26 g, 26.6 mL, 66.5 mmol, 0.95 equiv.). (1R*, 2S*)-1-bromo-2-methyl-2(naphthalene-2-yl)cyclopropanecarboxylic acid was obtained as dark brown highly viscous oil in 45% yield (9.06 g, 29.7 mmol). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.80–7.13 (m, 7H), 2.46 (d, J = 6.4 Hz, 1H), 1.70 (s, 3H), 1.38 (d, J = 6.4 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): δ 172.6, 137.7, 133.4, 132.6, 128.4 (+), 127.9 (+), 127.8 (+), 126.9 (+), 126.3 (+), 126.1 (+), 126.0 (+), 39.5, 37.3, 29.0 (-), 27.9 (+); FTIR (KBr, cm^{-1}): 3053, 2359, 2341, 1697, 1420, 1292, 1231, 1061, 856, 818, 748, 681, 444, 424, 411; HRMS (TOF ES): Found 303.0027, calculated for $C_{15}H_{12}BrO_2$ (M-H) 303.0021 (2.0 ppm).

3.10.3. Resolution of Bromoarylylcyclopropanecarboxylic Acids



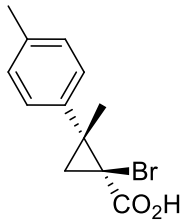
(1S,2R)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid ((+)-136a): Typical Procedure: (1R*, 2S*)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **136a** (13.50 g, 52.92 mmol, 1.0 equiv.) and cinchonine (15.85 g, 53.84 mmol, 1.0 equiv.) were dissolved in a minimum amount of acetone (~300 mL) with stirring and heating. The solution was stirred for 20 minutes and then filtered while hot into an insulated Erlenmeyer flask. The flask was

capped and the mixture was allowed to cool to room temperature over two hours. The capped flask was then placed in the freezer and left overnight. Recovered crystals ($[\alpha]_D$ = +109.1°, c 0.502 CH_2Cl_2) were isolated by suction filtration and dissolved in ethyl acetate (100 mL). The organic phase was added to water and acidified to pH of 2 using 6N hydrochloric acid. The product was extracted using ethyl acetate (3 X 50 mL), dried, filtered, and concentrated. (1S,2R)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid was obtained as a light yellow oil in 62% yield (4.20 g, 16.5 mmol 98% ee). Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +56.5° (c 0.2 CH_2Cl_2).



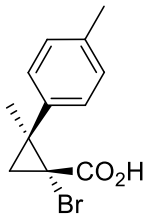
(1R,2S)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid ((-)-136a): Typical Procedure: (1R*, 2S*)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **136a** (13.5 g, 52.9 mmol, 1.0 equiv.) and cinchonidine (11.2 g, 38.0 mmol, 0.72 equiv.) were dissolved in a minimum amount of acetone (~300 mL) with stirring and heating. The solution was stirred for 20 minutes and then filtered while hot into an insulated Erlenmeyer flask. The flask was capped and the mixture was allowed to cool to room temperature over two hours. The capped flask was then placed in the freezer and left overnight. Recovered crystals ($[\alpha]_D$ = -102.2°, c 0.360 CH_2Cl_2) were isolated by suction filtration and dissolved in ethyl acetate (100 mL). The organic phase was added to water and acidified to pH of 2 using 6N hydrochloric acid. The product was extracted using ethyl acetate (3 X 50 mL), dried, filtered, and concentrated. (1S,2R)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid was obtained as a light yellow oil in 53% yield (3.8 g, 14.1 mmol, 91% ee). Spectral

properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): - 49.4°, (c 0.172 CH_2Cl_2).



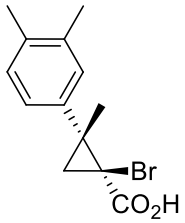
(1S,2R)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid ((+)-136b):

Compound was obtained via typical procedure using racemic (1R*, 2S*)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid **136b** (5.25 g, 19.5 mmol, 1.0 equiv.), cinchonine (5.75 g, 19.5 mmol, 1.0 equiv.), and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = +103.9°, c 0.640 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1S,2R)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid was recovered as a light yellow oil in 50% yield (1.3 g, 4.8 mmol, >99% ee). Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +66.0°, (c 0.106 CH_2Cl_2).

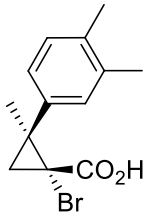


(1R,2S)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid ((-)-136b):

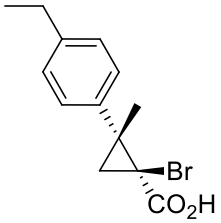
Compound was obtained via typical procedure using racemic 1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid **136b** (5.254 g, 19.52 mmol, 1.0 equiv.), cinchonidine (5.747 g, 19.52 mmol, 1.0 equiv.) and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = -139.3°, c 0.600 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1R,2S)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid was obtained as a cream colored solid in 34% yield (0.879 g, 3.27 mmol, >99% ee). Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -61.0°, (c 0.100 CH_2Cl_2).



(1S,2R)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid ((+)-136c): Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid **136c** (5.00 g, 17.7 mmol, 1.0 equiv.), cinchonine (5.00 g, 16.9 mmol, 0.96 equiv.), and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = +94.1°, c 0.408 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1S,2R)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid was obtained as a light yellow oil in 34% yield (0.85 mg, 3.0 mmol, 92% ee). Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +54.7°, (c 0.172 CH_2Cl_2).

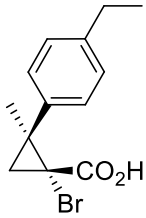


(1R,2S)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropane carboxylic acid ((-)-136c): Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid **136c** (5.00 g, 17.7 mmol, 1.0 equiv.), cinchonidine (3.05 g, 10.2 mmol, 0.58 equiv.), and acetone (200 mL). Recovered crystals ($[\alpha]_D$ = +67.4°, c 0.328 CH_2Cl_2) ([α]= 67.4, c=0.328) were dissolved in ethyl acetate (100 mL). (1R,2S)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid was recovered as a a light yellow oil in 66% yield (1.65 g, 5.83 mmol, 52% ee). Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -31.6°, (c 0.190 CH_2Cl_2).



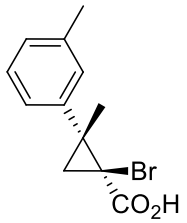
(1S,2R)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropane carboxylic acid ((+)-136d):

Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid **136d** (5.01 g, 17.7 mmol, 1.0 equiv.), cinchonine (2.5 g, 8.5 mmol, 0.48 equiv.), and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = +109.4°, c 0.170 CH_2Cl_2) were dissolved in ethyl acetate (~75 mL). (1R,2S)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid was recovered as a yellowish brown solid in 33% yield (0.82 g, 2.9 mmol, >99% ee). MP: 72.8-74.8 ºC. Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +69.8°, (c 0.116 CH_2Cl_2).



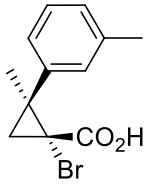
(1R,2S)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropane carboxylic acid ((-)-136d):

Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid **136d** (5.01 g, 17.7 mmol, 1.0 equiv.), cinchonidine (2.5 g, 8.5 mmol, 0.44 equiv.), and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = -70.2°, c 0.124 CH_2Cl_2) were dissolved in ethyl acetate (~75 mL). (1R,2S)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid was recovered as a yellowish-brown solid in 35% yield (0.87 g, 3.1 mmol, >99% ee). MP: 71.0-73.2ºC. Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -55.4°, (c 0.130 CH_2Cl_2).



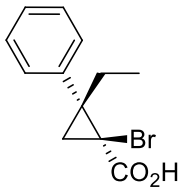
(1S,2R)-1-bromo-2-methyl-2-(m-tolyl)cyclopropane carboxylic acid ((+)-136e):

Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-methyl-2-(*m*-tolyl)cyclopropanecarboxylic acid **136e** (4.78 g, 17.6 mmol, 1.0 equiv.), cinchonine (5.17 g, 17.6 mmol, 1.0 equiv.), and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = +113.9°, c 0.418 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1S,2R)-1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylic acid was obtained as cream colored crystals in 23% yield (0.55 g, 2.0 mmol >99% ee). MP: 92.0-93.4 ºC. Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +77.5°, (c 0.102 CH_2Cl_2).



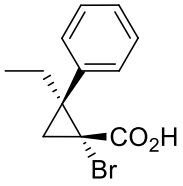
(1R,2S)-1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylic acid ((-)-136e):

Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-methyl-2-(*m*-tolyl)cyclopropanecarboxylic acid **136e** (4.78 g, 17.6 mmol, 1.0 equiv), cinchonidine (2.59 g, 8.79 mmol, 0.5 equiv.), and acetone (~200 mL). Recovered crystals ($[\alpha]_D$ = -93.5°, c 0.184 CH_2Cl_2) were dissolved in ethyl acetate (75 mL). (1R,2S)-1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylic acid was obtained as a grey oil in 11.4% yield (0.27 g, 1.0 mmol, >99% ee). Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -74.6°, (c 0.114 CH_2Cl_2).



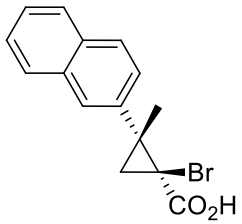
(1S,2R)-1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid ((+)-136f):

Compound was obtained via typical procedure using racemic (1R*, 2S*)-1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid **136f** (5.39 g, 20.0 mmol, 1.0 equiv.), cinchonine (5.89 g, 20.0 mmol, 1.0 equiv.), and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = +93.5°, c 0.306 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1S,2R)-1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid was recovered as a cream colored solid in 57% yield (1.53 g, 5.68 mmol >99% ee). MP: 75-76.5 ºC. Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +69.5°, (c 0.118 CH_2Cl_2).



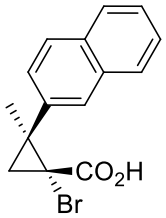
(1R,2S)-1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid ((-)-136f):

Compound was prepared according typical procedure using racemic 1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid **136f** (5.39 g, 20.0 mmol, 1.0 equiv.), cinchonidine (5.89 g, 20.0 mmol, 1.0 equiv.), acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = -74.7°, c 0.418 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1R,2S)-1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid was recovered as a cream colored solid in 40% yield (1.06 g, 3.94 mmol, >99% ee). MP: 72.5-73.4 ºC. Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -43.1°, (c 0.144 CH_2Cl_2).



(1S,2R)-1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylic acid ((+)-136g):

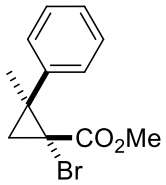
Compound was obtained via typical procedure using racemic (1R*, 2S*)-1-bromo-2-methyl-2(naphthalene-2-yl)cyclopropanecarboxylic acid **136g** (4.68 g, 14.6 mmol, 1.0 equiv.), cinchonine (4.30g, 14.6 mmol, 1.0 equiv.), and acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = +112.0°, c 0.382 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1S,2R)-1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylic acid was recovered as a dark brown solid in 51% yield (1.19 g, 3.72 mmol,* 99% ee). MP: 121.5-123.5 ºC. Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +108.2°, (c 0.122 CH_2Cl_2).



(1R,2S)-1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylic acid ((+)-136g):

Compound was obtained via typical procedure using racemic (1R*, 2S*)-1-bromo-2-methyl-2(naphthalene-2-yl)cyclopropanecarboxylic acid **136g** (4.68 g, 14.6 mmol, 1.0 equiv.), cinchonidine (4.30 g, 14.6 mmol, 1.0 equiv.), acetone (~300 mL). Recovered crystals ($[\alpha]_D$ = -96.1°, c 0.382 CH_2Cl_2) were dissolved in ethyl acetate (100 mL). (1R*, 2S*)-1-bromo-2-methyl-2(naphthalene-2-yl)cyclopropanecarboxylic acid was recovered as a dark brown oil in 73% yield (1.7 g, 5.3 mmol, 54% ee). Spectral properties of this material were identical to those reported above for racemic acid; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -57.4°, (c 0.162 CH_2Cl_2).

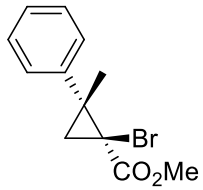
3.10.4. Synthesis of Bromoarylylcyclopropanecarboxylic Acid Methyl Esters



(1R*,2S*)-methyl 1-bromo-2-methyl-2-phenylcyclopropanecarboxylate 136aE

Typical Procedure: (1R,2S)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **136a** (255 mg, 0.947 mmol, 1.0 equiv.), potassium carbonate (276 mg, 2.00 mmol, 2.0 equiv.), and methyl iodide (280 mg, 123 μL, 1.97 mmol, 2.0 equiv.) were combined in dimethyl formamide (10 mL) and stirred vigorously for 12 hours. The mixture was quenched with water (5 mL) and then partitioned between water and dichloromethane. The product was extracted using CH_2Cl_2 (3 X 10 mL), dried ($MgSO_4$), filtered, and concentrated. Recovered material was purified by silica gel chromatography to afford the title compound as a light yellow oil in 71% yield (181 mg, 0.672 mmol). R_f= 0.22 (hexanes/ethyl acetate 50:1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.56–7.01 (m, 5H), 3.34 (s, 3H), 2.55 (d, *J* = 6.4 Hz, 1H), 1.75 (s, 3H), 1.40 (d, *J* = 6.5 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): δ 168.5, 140.7, 128.5 (+, 2C), 128.1 (+, 2C), 127.2 (+), 52.9 (+), 40.4, 35.9, 27.9 (-), 27.5 (+); FTIR (KBr, cm^{-1}): 3026, 2986, 2951, 1732, 1603, 1497, 1434, 1379, 1325, 1298, 1285, 1234, 1115, 1094, 1061, 1026, 982, 876, 775, 758, 721, 700, 559, 542; HRMS (TOF ES): Found 269.0177, calculated for $C_{12}H_{14}BrO_2$ (M+H) 269.0177 (0.0 ppm).

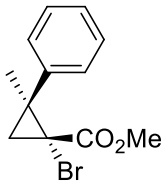
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 120.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): (+) 49.72, (-) 50.57 min.



(1S,2R)-methyl 1-bromo-2-methyl-2-phenylcyclopropanecarboxylate (+)-136aE:

Compound was obtained via typical procedure using (1S,2R)-1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (50 mg, 0.20 mmol, 1.0 equiv.), potassium carbonate (55 mg, 0.40 mmol, 2.0 equiv.), methyl iodide (56.8 mg, 24.9 μL, 0.400 mmol, 2.0 equiv.) and DMF (5 mL). (1S,2R)-methyl 1-bromo-2-methyl-2-phenylcyclopropanecarboxylate was obtained as a light yellow oil in 70% yield (37.7 mg, 0.140 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +34.6°, (c 0.220 CH_2Cl_2).

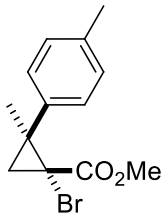
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 120.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 49.72 min.



(1R,2S)-methyl 1-bromo-2-methyl-2-phenylcyclopropanecarboxylate (-)-136aE:

Compound was obtained via typical procedure using (1R,2S)- 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(-)-136a** (50 mg, 0.19 mmol, 1.0 equiv.), potassium carbonate (51.4 mg, 0.372 mmol, 2.0 equiv.), methyl iodide (52.8 mg, 23.2 μL, 0.372 mmol, 2.0 equiv.), and DMF (5 mL). (1R,2S)-methyl 1-bromo-2-methyl-2-phenylcyclopropanecarboxylate was obtained as a light yellow oil in 71% yield (36.3 mg, 0.135 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -32.3°, (c 0.820 CH_2Cl_2).

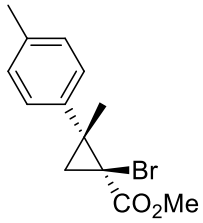
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 120.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 50.57 min.



(1R*,2S*)-methyl 1-bromo-2-methyl-2-(p-tolyl)cyclopropane-carboxylate 136bE::

Compound was obtained via typical procedure using (1R*,2S*)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid **136b** (300 mg, 1.11 mmol, 1.0 equiv.), potassium carbonate (307 mg, 2.22 mmol, 2.0 equiv.), and methyl iodide (315 mg, 138 μL, 2.22 mmol, 2.0 equiv.) and dimethyl formamide (10 mL). (1R*,2S*)-methyl 1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylate was obtained as a light yellow oil in 80% yield (251 mg, 0.888 mmol). R_f: 0.22 (hexanes/ethyl acetate 50:1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.14–7.04 (m, 4H), 3.36 (s, 3H), 2.50 (d, J = 6.4 Hz, 1H), 2.30 (s, 3H), 1.71 (s, 3H), 1.35 (d, J = 6.4 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): δ 168.6, 137.6, 136.8, 129.2 (+, 2C), 127.9 (+, 2C), 53.0 (+), 40.3, 35.6, 27.9 (-), 27.5 (+), 21.2 (+); FTIR (KBr, cm^{-1}): 2984, 2951, 2926, 1732, 1516, 1435, 1377, 1325, 1300, 1281, 1232, 1113, 1094, 1063, 1047, 820, 719, 557; HRMS (TOF ES): Found 283.0335, calculated for $C_{13}H_{16}BrO_2$ (M+H) 283.0334, 0.4 ppm.

GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 131ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): (+) 45.097, (-) 45.636 min.

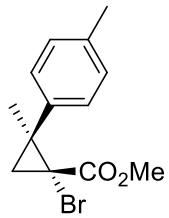


(1S,2R)-methyl 1-bromo-2-methyl-2-(p-tolyl)cyclopropane-carboxylate (+)-136bE:

Compound was obtained via typical procedure using (1S,2R)- 1-

bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid **(+)-136b** (54 mg, 0.20 mmol, 1.0 equiv.), potassium carbonate (55 mg, 0.40 mmol, 2.0 equiv.), methyl iodide (56.5 mg, 24.8 μL, 0.400 mmol, 2.0 equiv.) and DMF (5 mL). (1S,2R)-methyl 1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylate was obtained as light yellow oil in 80% yield (44 mg, 0.16 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +42.6°, (c 0.620 CH_2Cl_2).

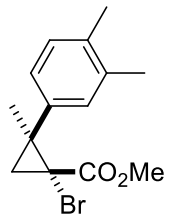
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 131.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): (+) 45.08 min.



(1R,2S)-methyl 1-bromo-2-methyl-2-(p-tolyl)cyclopropane-carboxylate (-)-136bE:

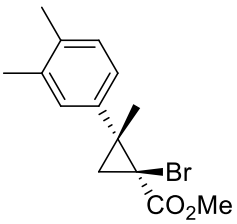
Typical Procedure: (1R,2S)-1-bromo-2-methyl-2-(p-tolyl)cyclopropanecarboxylic acid **(-)-136b** (300 mg, 1.11 mmol, 1.0 equiv.), potassium carbonate (306 mg, 2.22 mmol, 2.0 equiv.), and methyl iodide (315 mg, 138 μL, 2.22 mmol, 2.0 equiv.) were combined in dimethyl formamide (10 mL) and stirred vigorously for 12 hours. The mixture was quenched with water (5 mL) and then partitioned between water and dichloromethane. The product was extracted using DCM (3 X 10 mL), dried ($MgSO_4$), filtered, and concentrated. Recovered material was purified by silica gel chromatography to afford the title compound as a light yellow oil in 80% yield (251 mg, 0.888 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -38.3°, (c 0.300 CH_2Cl_2).

GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 131.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 45.619 min.



(1R*, 2S*)-methyl 1-bromo-2-(3,4-dimethylphenyl)-2-methyl-cyclopropanecarboxylate 136cE:

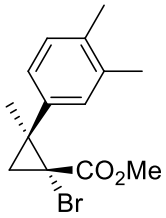
Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid **136c** (50 mg, 0.18 mmol, 1.0 equiv.), potassium carbonate (48.8 mg, 0.353 mmol, 2.0 equiv.), methyl iodide (50.0 mg, 22.0 μL, 0.353 mmol, 2.0 equiv.), and DMF (5 mL). (1R*, 2S*)-methyl 1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylate was obtained as a light yellow oil in 85% yield (45.5 mg, 0.15 mmol). R_f= 0.22 (hexanes/ethyl acetate 50:1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.08–6.90 (m, 3H), 3.38 (s, 3H), 2.48 (d, *J* = 6.4 Hz, 1H), 2.22 (s, 3H), 2.21 (s, 3H), 1.71 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): δ 168.6, 138.1, 136.6, 135.5, 129.7 (+), 129.2 (+), 125.4 (+), 53.0 (+), 40.3, 35.6, 27.9 (-), 27.6 (+), 19.9 (+), 19.6 (+); FTIR (KBr, cm^{-1}): 2982, 2949, 2924, 1732, 1506, 1435, 1377, 1306, 1283, 1236, 1221, 1095, 1063, 874, 822, 717, 600; HRMS (TOF ES): Found 296.0412, Calculated for $C_{14}H_{17}BrO_2$ (M+) 296.0412 (0.0 ppm). HPLC R_t (Column: CHIRALCEL OD-H (250 mm x 4.6 mm), 0.5% iPrOH/hexane, flow = 0.7 mL/min, UV 254 nm): (+) 8.92 min, (-) 9.86 min.



(1S,2R)-methyl 1-bromo-2-(3,4-dimethylphenyl)-2-methyl cyclopropanecarboxylate (+)-136cE:

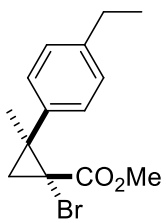
Compound was obtained via typical procedure using (1S,2R)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid **(+)-136c** (50.0 mg, 0.177 mmol, 1.0 equiv.), potassium carbonate (48.9 mg, 0.354 mmol, 2.0 equiv.), methyl iodide (50.2 mg, 21.9 μL, 0.354 mmol, 2.0 equiv.), and DMF (5 mL). (1S,2R)-

methyl 1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylate was obtained as a light yellow oil in 85% yield (45 mg, 0.15 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +35.4°, (c 0.820 CH_2Cl_2). HPLC R_t (Column: CHIRALCEL OD-H (250 mm x 4.6 mm), 0.5% iPrOH/hexane, flow = 0.7 mL/min, UV 254 nm): (+) 8.92 min



(1R,2S)-methyl 1-bromo-2-(3,4-dimethylphenyl)-2-methyl cyclopropanecarboxylate (-)-136cE:

Compound was obtained via typical procedure using (1R,2S)-1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylic acid **(-)-136c** (50.0 mg, 0.186 mmol, 1.0 equiv.), potassium carbonate (51.5 mg, 0.372 mmol, 2.0 equiv.), methyl iodide (52.8 mg, 23.2 µL, 0.372 mmol, 2.0 equiv.) and DMF (5 mL). (1R,2S)-methyl 1-bromo-2-(3,4-dimethylphenyl)-2-methylcyclopropanecarboxylate was obtained as a light yellow oil in 85% yield (47 mg, 0.16 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -20.4°, (c 0.940 CH_2Cl_2). HPLC R_t (Column: CHIRALCEL OD-H (250 mm x 4.6 mm), 0.5% iPrOH/hexane, flow = 0.7 mL/min, UV 254 nm): (-) 9.86 min.

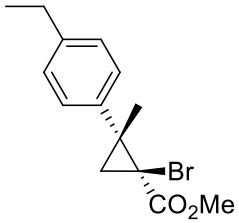


(1R*,2S*)-methyl 1-bromo-2-(4-ethylphenyl)-2-methylcyclo-propanecarboxylate 136cdE:

Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid **136d** (50 mg, 0.18 mmol, 1.0 equiv.), potassium carbonate (48.8 mg, 0.352 mmol, 2.0 equiv.)

methyl iodide (50 mg, 21.9 μL, 0.352 mmol, 2.0 equiv.), and DMF (5ml). (1R*,2S*)-methyl 1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylate was obtained as a light yellow oil in 73% yield (39 mg, 0.13 mmol). R_f= 0.22 (hexanes/ethyl acetate 50:1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.16–7.07 (m, 4H), 3.33 (s, 3H), 2.60 (q, *J* = 7.6 Hz, 2H), 2.50 (d, *J* = 6.5 Hz, 1H), 1.71 (s, 3H), 1.35 (d, *J* = 6.4 Hz, 1H), 1.20 (t, *J* = 7.6 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$): δ 168.6, 143.2, 137.8, 128.0 (+, 2C), 127.9 (+, 2C), 52.9 (+), 40.4, 35.5, 28.6 (-), 27.8 (-), 27.5 (+), 15.6 (+); FTIR (KBr, cm^{-1}): 3022, 2962, 2978, 2872, 1732, 1514, 1435, 1377, 1327, 1300, 1286, 1232, 1113, 1094, 1063, 1045, 982, 833, 716, 571; HRMS (TOF ES): Found 295.0334, calculated for $C_{14}H_{16}BrO_2$ (M-H) 295.0334, 0.0 ppm.

GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 130.5ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): (+) 71.878, (-) 72.685 min.

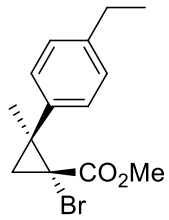


(1S,2R)-methyl 1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylate (+)-136cE:

Compound was obtained via typical procedure using (1S.2R)- 1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid **(+)-136c** (50.0 mg, 0.176 mmol, 1.0 equiv.), potassium carbonate (48.6 mg, 0.352 mmol, 2.0 equiv.), methyl iodide (49.9 mg, 21.9 μL, 0.352 mmol, 2.0 equiv.) and DMF (5 mL). (1S,2R)-methyl 1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylate was obtained as a light yellow oil in 73% yield (38.0 mg, 0.128 mmol). Spectral properties of

this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +42.6°, (c 0.660 CH_2Cl_2).

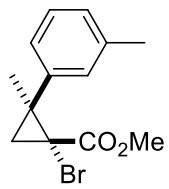
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 130.5ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 71.878 min.



(1R,2S)-methyl 1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylate (-)-136dE:

Compound was obtained via typical procedure using (1R,2S)- 1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid **(-)-136d** (50.0 mg, 0.176 mmol, 1.0 equiv.), potassium carbonate (48.6 mg, 0.352 mmol, 2.0 equiv.), methyl iodide (49.9 mg, 21.9 μL, 0.352 mmol, 2.0 equiv.), DMF (5 mL). (1R,2S)-methyl 1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylate was obtained as a light yellow oil in 40% yield (38.5 mg, 0.128 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -40.3°, (c 0.340 CH_2Cl_2).

GC R_t (Colum: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 130.5ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 72.685 min.

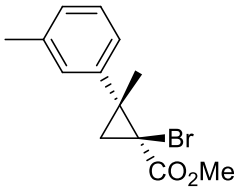


(1R*,2S*)-methyl 1-bromo-2-methyl-2-(m-tolyl)cyclopropane-carboxylate 136eE:

Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-methyl-2-(*m*-tolyl)cyclopropanecarboxylic acid **136e** (50 mg, 0.19 mmol, 1.0 equiv.), potassium carbonate (51.4 mg, 0.372 mmol, 2.0 equiv.), methyl iodide

(52.8 mg, 23.2 μL, 0.372 mmol, 2.0 equiv.), and DMF (5 mL). (1R*,2S*)-methyl 1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylate was obtained as a light yellow oil in 65% Yield (35 mg, 0.12 mmol). R_f=0.22 (hexanes/ethyl acetate 50:1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.19–6.98 (m, 4H), 3.34 (s, 3H), 2.50 (d, *J* = 6.4 Hz, 1H), 2.31 (s, 3H), 1.71 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): δ 168.6, 140.7, 138.1, 128.8 (+), 128.4 (+), 128.0 (+), 125.1 (+), 52.9 (+), 40.4, 35.9, 28.0 (-), 27.6 (+), 21.5 (+); FTIR (KBr, cm^{-1}): 2984, 2951, 2926, 1732, 1607, 1489, 1435, 1377, 1329, 1302, 1279, 1242, 1200, 1117, 1094, 1063, 872, 789, 706; HRMS (TOF ES): Found 282.0248, calculated for $C_{13}H_{15}BrO_2$ (M+) 282.0255 (2.5 ppm).

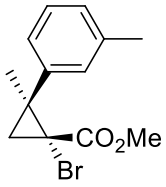
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 125.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): (+) 52.905, (-) 53.985 min.



(1S,2R)-methyl 1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylate (+)-136eE:

Compound was obtained via typical procedure using (1S,2R)-1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylic acid **(+)-136e** (50.0 mg, 0.186 mmol, 1.0 equiv.), potassium carbonate (51.5 mg, 0.372 mmol, 2.0 equiv.), methyl iodide (52.5 mg, 23.2 μL, 0.372 mmol, 2.0 equiv.), and DMF (5 mL). (1S,2R)-methyl 1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylate was obtained as a light yellow oil in 65% yield (34 mg, 0.12 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +23.3°, (c 0.820 CH_2Cl_2).

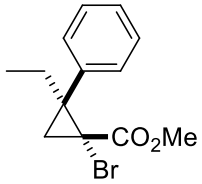
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 125.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 52.905 min.



(1R,2S)-methyl 1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylate (-)-136eE:

Compound was obtained via typical procedure using (1R,2S)- 1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylic acid **(-)-136e** (50.0 mg, 0.186 mmol, 1.0 equiv.), potassium carbonate (51.5 mg, 0.372 mmol, 2.0 equiv.), methyl iodide (52.5 mg, 23.2 μL, 0.372 mmol, 2.0 equiv.), and DMF (5 mL). (1R,2S)-methyl 1-bromo-2-methyl-2-(m-tolyl)cyclopropanecarboxylate was obtained as a light yellow oil in 65% yield (34 mg, 0.12 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -30.2°, (c 0.420 CH_2Cl_2).

GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 125.0ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 53.985 min.

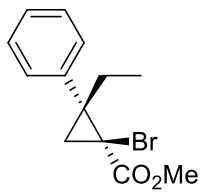


(1R*,2S*)-methyl 1-bromo-2-ethyl-2-phenylcyclopropanecarboxylate 136fE:

Compound was obtained using racemic (1R*,2S*)-1-bromo-2-(4-ethylphenyl)-2-methylcyclopropanecarboxylic acid **136f** (100 mg, 0.372 mmol, 1.0 equiv.), potassium carbonate (103 mg, 0.744 mmol, 2.0 equiv), methyl iodide (106 mg, 46.4 μL, 0.745 mmol, 2.0 equiv.) and DMF (5 mL). (1R*,2S*)-methyl 1-bromo-2-ethyl-

2-phenylcyclopropanecarboxylate was obtained as a light yellow oil in 91% yield (95.7 mg, 0.338 mmol). R_f=0.22 (hexanes/ethyl acetate 50:1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33–7.17 (m, 5H), 3.34 (s, 3H), 2.45 (d, *J* = 6.4, 1H), 2.11 (dtd, *J* = 14.6, 7.3, 1.5 Hz, 1H), 1.92 (dq, *J* = 13.7, 7.4 Hz, 1H), 1.35 (d, *J* = 6.3 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$): δ 168.6, 138.7, 129.1 (+, 2C), 128.3 (+, 2C), 127.3 (+), 52.9 (+), 40.9, 40.9, 33.4 (-), 26.9 (-), 11.2 (+); FTIR (KBr, cm^{-1}): 3026, 2970, 2951, 2934, 1732, 1495, 1435, 1377, 1300, 1286, 1225, 1118, 1090, 1067, 989, 881, 795, 756, 721, 702, 592; HRMS (TOF ES): Found 282.0257, calculated for $C_{13}H_{15}BrO_2$ (M+) 282.0255 (0.7 ppm).

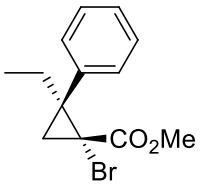
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 134.1ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): (+) 34.635, (-) 34.967 min.



(1S,2R)-methyl 1-bromo-2-ethyl-2-phenylcyclopropane-carboxylate (+)-136fE:

Compound was obtained via typical procedure using (1S,2R)-1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid **(+)-136f** (50 mg, 0.19 mmol, 1.0 equiv.), potassium carbonate (51.4 mg, 0.372 mmol, 2.0 equiv.), methyl iodide (52.8 mg, 23.2 µL, 0.372 mmol, 2.0 equiv.) and DMF (5 mL). (1S,2R)-methyl 1-bromo-2-ethyl-2-phenylcyclopropanecarboxylate was obtained as a light yellow oil in 90% yield (48.4 mg, 0.171 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +19.3°, (c 0.244 CH_2Cl_2).

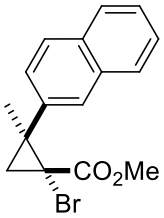
GC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 134.1ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 34.635 min.



(1R,2S)-methyl 1-bromo-2-ethyl-2-phenylcyclopropane-carboxylate (-)-136fE:

Compound was obtained via typical procedure using (1R,2S)- 1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acid **(-)-136f** (50.0 mg, 0.186 mmol, 1.0 equiv.), potassium carbonate (51.4 mg, 0.371 mmol, 2.0 equiv.), methyl iodide (52.6 mg, 23.2 µL, 0.371 mmol, 2.0 equiv.), and DMF (5 mL). (1R,2S)-methyl 1-bromo-2-ethyl-2-phenylcyclopropanecarboxylate was obtained as a light yellow oil in 91% yield (49 mg, 0.17 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -30.9°, (c 0.800 CH_2Cl_2).

HPLC R_t (Column: J&W Scientific Cyclodex-B 30 meter 0.250 mm bore column, 134.1ºC iso, N_2 30.0 mL/min, H_2 40 mL/min, Air 400 mL/min): 34.967 min.

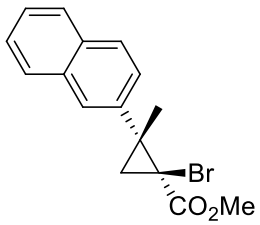


(1R*,2S*)-methyl 1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylate 136gE:

Compound was obtained via typical procedure using racemic (1R*,2S*)-1-bromo-2-methyl-2(naphthalene-2-yl)cyclopropanecarboxylic acid **136g** (50 mg, 0.16 mmol, 1.0 equiv.), potassium carbonate (45.3 mg, 0.328 mmol, 2.0 equiv.), methyl iodide (46.5 mg, 20.4 µL, 0.328 mmol, 2.0 equiv.), and DMF (5 mL). (1R*,2S*)-

methyl 1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylate was obtained as a light brown oil in 71% yield (38 mg, 0.12 mmol). R_f=0.22 (hexanes/ethyl acetate 50:1). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.94–7.33 (m, 7H), 3.26 (s, 3H), 2.66 (d, *J* = 6.5 Hz, 1H), 1.81 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$): 168.5, 138.2, 133.4, 132.6, 128.3 (+), 127.9 (+), 127.8 (+), 126.9 (+), 126.3 (+), 126.1 (+), 126.0 (+), 53.0 (+), 40.4, 36.1, 28.1 (-), 27.5 (+); FTIR (KBr, cm^{-1}): 2984, 2949, 1734, 1435, 1325, 1294, 1271, 1246, 1227, 1196, 1134, 1101, 1063, 982, 955, 895, 858, 820, 746, 717; HRMS (TOF ES): Found 319.0331, calculated for $C_{16}H_{16}BrO_2$ (M+H) 319.0334 (0.9 ppm).

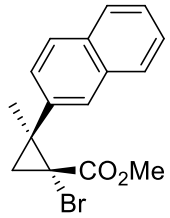
HPLC R_t (Column: CHIRALCEL OD-H (250 mm x 4.6 mm), 0.5% iPrOH/hexane, flow = 0.7 mL/min, UV 254 nm): (+) 16.39 min, (-) 18.42 min.



(1S,2R)-methyl 1-bromo-2-methyl-2-(naphthalen-2yl) cyclopropanecarboxylate (+)-136gE:

Compound was obtained via typical procedure using (1S,2R)-1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylic acid **(+)-136g** (50 mg, 0.16 mmol, 1.0 equiv.), potassium carbonate (45.3 mg, .328 mmol, 2.0 equiv.), methyl iodide (46.6 mg, 0.328 mmol, 2.0 equiv.), and DMF (5 mL). (1S,2R)-methyl 1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylate was obtained as a light brown oil in 75% yield (38 mg, 0.12 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): +90.0°, (c 0.600 CH_2Cl_2).

HPLC R_t (Column: CHIRALCEL OD-H (250 mm x 4.6 mm), 0.5% iPrOH/hexane, flow = 0.7 mL/min, UV 254 nm): (+) 16.39 min

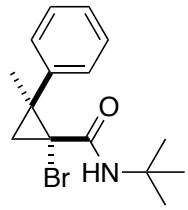


(1R,2S)-methyl 1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylate (-)-136gE:

Compound was obtained via typical procedure using (1R,2S)- 1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylic acid **(-)-136g** (50.0 mg, 0.164 mmol, 1.0 equiv.), potassium carbonate (45.3 mg, 0.328 mmol, 2.0 equiv.), methyl iodide (46.5 mg, 40.8 μL, 0.328 mmol, 2.0 equiv.), and DMF (5 mL). (1R,2S)-methyl 1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropanecarboxylate was obtained as a light yellow oil in 73% yield (38 mg, 0.12 mmol). Spectral properties of this material were identical to those reported above for racemic ester; $[\alpha]_D$ (28.5ºC, 589 nm, 1 dm): -39.8°, (c 0.560 CH_2Cl_2).

HPLC R_t (Column: CHIRALCEL OD-H (250 mm x 4.6 mm), 0.5% iPrOH/hexane, flow = 0.7 mL/min, UV 254 nm): (-) 18.42 min.

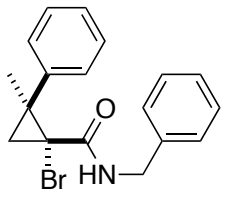
3.10.5. Synthesis of Bromoarylcyclopropanecarboxamides



(1R*,2S*)-1-bromo-N-(tert-butyl)-2-methyl-2- phenylcyclo-propanecarboxamide (**132aa**):

Typical procedure: A flame dried 100 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid (**136a**) (1.28 g, 5.00 mmol, 1.00 equiv), DMF (10 drops) and 40 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (0.65 mL, 7.5 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the

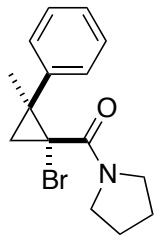
crude acyl chloride was dissolved in 20 mL of dry THF, followed by the addition of a solution of *tert*-butyl amine (1.57 ml, 15.0 mmol, 3.00 equiv) in 20 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 25 mL of EtOAc and 25 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel to afford the titled compound, 1.21 g, 3.90 mmol yield 78% bromocyclopropyl amide (**136a**) as a white solid, mp: 71−73 ^oC, R_f 0.30 (hexanes/EtOAc 6:1). Analytically pure product can be also obtained by recrystallization of a crude product in cyclohexane. ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−6.96 (m, 5H), 6.22 (br. s, 1H), 2.58 (d, J = 6.4 Hz, 1H), 1.71 (s, 3H), 1.24 (d, J = 6.3 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 140.5, 128.3 (+, 2C), 128.1 (+, 2C), 126.9 (+), 51.6, 45.1, 34.8, 28.4 (+, 3C), 27.9 (+), 26.3 (-); FT IR (KBr, cm^{-1}): 3423, 3346, 1678, 1664, 1514, 1223, 771, 750, 692; HRMS (TOF ES): found 310.0807, calculated for $C_{15}H_{21}BrNO$ (M+H) 310.0813 (1.9 ppm).



(1R*,2S*)-N-benzyl-1-bromo-2-methyl-2-phenylcyclopropanecarboxamide (**132ab**):

This compound was obtained according to a typical procedure employing 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid (**136a**) (1.28 g, 5.00 mmol, 1.00 equiv), oxalyl chloride (0.65 mL, 7.5 mmol, 1.5 equiv) and benzyl amine (1.64 mL, 15.0 mmol, 3.0 equiv). Chromatographic purification afforded title compound

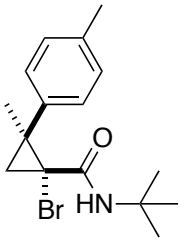
as a white solid, mp: 91−93 °C, R_f 0.36 (hexanes/EtOAc 6:1). Yield 1.29 g (3.75 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.12 (m, 8H), 7.07−6.97 (m, 2H), 6.74 (br. s, 1H), 4.21 (ddd, *J* = 20.1, 14.8, 5.9 Hz, 2H), 2.70 (d, *J* = 6.3 Hz, 1H), 1.71 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 140.4, 138.0, 128.7 (+, 2C), 128.4 (+, 2C), 128.0 (+, 2C), 127.9 (+, 2C), 127.6 (+), 127.1 (+), 44.6 (-), 44.5, 35.5, 28.1 (+), 27.1 (-); FT IR (KBr, cm^{-1}): 3331, 3060, 2930, 1651, 1602, 1518, 1495, 1445,1425,1296, 1284, 1250, 1059, 773, 750, 737, 696; HRMS (TOF ES): found 361.0916, calculated for $C_{18}H_{22}BrN_2O$ (M+NH_4) 361.0915 (0.3 ppm).



((1R*,2S*)-1-bromo-2-methyl-2-phenylcyclopropyl)(pyrrolidin-1-yl)methanone (132ac):

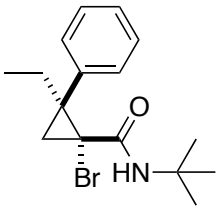
This compound was obtained according to a typical procedure employing 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid (**136a**) (1.28 g, 5.00 mmol, 1.00 equiv), oxalyl chloride (0.65 mL, 7.5 mmol, 1.5 equiv) and pyrrolidine (1.23 mL, 15.0 mmol, 3.00 equiv). Chromatographic purification afforded title compound as a white solid, mp: 78−81 °C, R_f 0.20 (hexanes/EtOAc 6:1). Yield 970 mg (3.15 mmol, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.15 (m, 5H), 3.44−3.32 (m, 1H), 3.24 (ddd, *J* = 12.1, 8.4, 3.7 Hz, 1H), 3.05 (ddd, *J* = 10.7, 7.4, 3.2 Hz, 1H), 2.79 (dt, *J* = 12.1, 8.2 Hz, 1H), 2.62 (d, *J* = 7.4 Hz, 1H), 1.84 (s, 3H), 1.68 (dddd, *J* = 13.3, 10.0, 6.6, 3.5 Hz, 2H), 1.63−1.51 (m, 1H), 1.50−1.40 (m, 1H), 1.35 (d, *J* = 7.4 Hz, 2H), 1.02 (dtt, *J* = 11.9, 9.6, 7.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 138.3, 128.2 (+, 2C), 127.0 (+), 126.3 (+, 2C), 47.6 (-), 46.0 (-), 43.7, 30.5, 27.0 (-), 25.8 (-), 24.4 (+), 23.8 (-); FT IR (KBr, cm^{-1}): 2970, 2951, 2874, 1639, 1499, 1429, 1340, 1194, 1061, 1030, 874, 766, 696, 663, 600,

544; HRMS (TOF ES): found 308.0650, calculated for $C_{15}H_{19}BrNOLi$ (M+H) 308.0646 (1.3 ppm).



(1R*,2S*)-1-bromo-N-(tert-butyl)-2-methyl-2-(p-tolyl) cyclopropanecarboxamide (**132ba**):

This compound was obtained according to a typical procedure employing 1-bromo-2-methyl-2-(*p*-tolyl)cyclopropane carboxylic acid (**136b**) (1.08 g, 4.00 mmol, 1.00 equiv), oxalyl chloride (0.52 mL, 6.0 mmol, 1.5 equiv) and *tert*-butyl amine (1.2 mL, 12 mmol, 3.0 equiv). Chromatographic purification afforded title compound as a white solid, mp: 83.5−84.7 ^{o}C, R_f 0.30 (hexanes/EtOAc 6:1). Yield 1.07 g (3.30 mmol, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18−6.89 (m, 4H), 6.22 (br. s, 1H), 2.54 (d, J = 6.3 Hz, 1H), 2.28 (s, 3H), 1.69 (s, 3H), 1.22 (d, J = 6.3 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 137.5, 136.5, 129.0 (+, 2C), 127.9 (+, 2C), 51.6, 45.2, 34.6, 28.4 (+, 3C), 28.0 (+), 26.4 (-), 21.2 (+); FT IR (KBr, cm-1): 3425, 2964, 1682, 1516, 1454, 1392, 1363, 1296, 1280, 1256, 1223, 1078, 1061, 1042, 818, 719; HRMS (TOF ES): found 322.0806, calculated for $C_{16}H_{21}BrNO$ (M-H) 322.0807 (0.3 ppm).



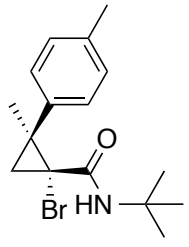
(1R*,2S*)-1-bromo-N-(tert-butyl)-2-ethyl-2-phenylcyclo-propane carboxamide (**132fa**):

This compound was obtained according to a typical procedure employing a mixture of 1-bromo-2-ethyl-2-phenylcyclopropanecarboxylic acids (**136f**) (1.35 g, 5.00 mmol, 1.00 equiv) (dr 2:1), oxalyl chloride (0.65 mL, 7.5 mmol, 1.5 equiv) and *tert*-butyl amine (1.58 mL, 15.0 mmol, 3.00 equiv). Chromatographic purification

afforded title compound as a white solid, mp: 49.1-50.4 ^{o}C, R_f 0.32 (hexanes/EtOAc 6:1). Yield a 2:1 mixture of the title compound 1.57 g (4.84 mmol, 97%) as a white solid. Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.11 (m, 5H), 6.26 (br. s, 1H), 2.49 (dd, *J* = 6.2, 1.7 Hz, 1H), 2.11 (ddd, *J* = 13.8, 7.3, 1.7 Hz, 1H), 1.84 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.19 (d, *J* = 6.2 Hz, 1H), 1.10 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 138.4, 129.0 (+, 2C), 128.0 (+, 2C), 126.9 (+), 51.6, 45.7, 40.1, 33.9 (-), 28.4 (+, 3C), 25.2 (-), 11.4 (+); Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.27 (m, 5H), 6.31 (s, 1H), 2.07 (d, *J* = 6.5 Hz, 1H), 1.93−1.87 (m, 1H), 1.60 (dd, *J* = 13.7, 7.4 Hz, 1H), 1.55 (dd, *J* = 6.4, 1.3 Hz, 1H), 1.41 (s, 9H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 141.4, 129.8 (+, 2C), 128.1 (+, 2C), 127.2 (+), 52.0, 42.9, 41.1, 40.1, 33.9, 28.7 (+, 3C), 27.3 (-), 24.7 (-), 11.6 (+); FT IR (KBr, cm-1): 3423, 3350, 3059, 2966, 2931, 2873, 2359, 2351, 1772, 1734, 1716, 1682, 1653, 1603, 1514, 1452, 1448, 1419, 1392, 1285, 1253, 1221, 1155, 1141, 1121, 1096, 1066, 1045, 1028, 985, 970, 905, 875, 860, 840, 818, 795, 750, 720, 700, 683, 656, 620; HRMS (TOF ES): found 323.0882, calculated for $C_{16}H_{22}BrNO$ (M+) 323.0885 (0.9 ppm).

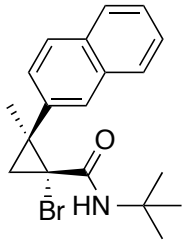
3.10.5. Synthesis of Homochiral Bromoarylcyclopropanecarboxamides

(1R,2S)-1-bromo-N-(tert-butyl)-2-methyl-2-(p-tolyl)cyclopropane-1-carboxamide **(-)-132ba:**



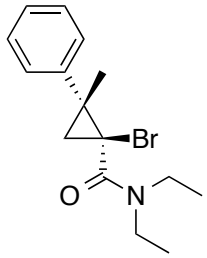
As described above for the analogous reaction of the racemate, a similar experiment that started with (1*R*,2*S*)-1-bromo-2-methyl-2-(*p*-tolyl)cyclopropane-1-carboxylic acid **(-)-136b** gave the title compound as yellow oil. Spectral properties of this material were identical to those reported above for racemic amide; $[\alpha]_D$= –21.3° (c 0.50, CH_2Cl_2).

(1R,2S)-1-bromo-N-(tert-butyl)-2-methyl-2-(naphthalen-2-yl)cyclopropane-1-carboxamide (-)-132ga:



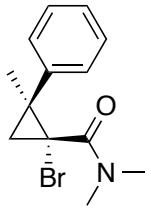
This compound was obtained according to a typical procedure employing a (1R,2S)-1-bromo-2-methyl-2-(naphthalen-2-yl)cyclopropane-1-carboxylic acid **(-)-136g** (0.608 g, 2.00 mmol, 1.00 equiv), oxalyl chloride (0.26 mL, 3.0 mmol, 1.5 equiv) and *tert*-butyl amine (0.63 mL, 6.0 mmol, 3.00 equiv). Chromatographic purification afforded title compound as a white solid, mp: 88.1-89.6 ^{o}C, R_f 0.32 (hexanes/EtOAc 20:1). Yield 0.427 g (1.2 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−7.68 (m, 3H), 7.65 (d, J = 1.2 Hz, 1H), 7.46−7.39 (m, 2H), 7.35 (dd, J = 8.5, 1.8 Hz, 1H), 6.32 (br., s, 1H), 2.69 (d, J = 6.3 Hz, 1H), 1.78 (s, 3H), 1.34 (d, J = 6.3 Hz, 1H), 1.03 (s, 9H). ;^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 138.2, 133.3, 132.5, 128.0 (+), 127.8 (+), 127.7 (+), 126.8 (+), 126.3 (+), 126.1 (+), 125.7 (+), 51.6, 45.2, 35.1, 28.4 (+, 3C), 28.1 (+), 26.6 (-); FT IR (KBr, cm-1): 3421, 3053, 2964, 2925, 1678, 1599, 1512, 1454, 1392, 1363, 1290, 1221, 1134, 1063, 958, 893, 856, 815, 750; HRMS (TOF ES): found 359.0883, calculated for $C_{19}H_{22}BrNO$ (M+) 359.0885 (0.6 ppm). $[\alpha]_D$= −41.87° (c 0.418, CH_2Cl_2).

(1S,2R)-1-bromo-N,N-diethyl-2-methyl-2-phenylcyclopropane-1-carboxamide (+)-132ac:



This compound was obtained according to a typical procedure employing a (1S,2R)-1-bromo-2-methyl-2-phenylcyclopropane-1-carboxylic acid **(+)-136a** (0.510 g, 2.00 mmol, 1.00 equiv), oxalyl chloride (0.26 mL, 3.0 mmol, 1.5 equiv) and diethyl amine (0.823 mL, 6.0 mmol, 3.00 equiv).

Chromatographic purification afforded title compound as a light yellow solid, mp: 74.3–76.2 ^{o}C, R_f 0.34 (hexanes/EtOAc 10:1). Yield 0.537 g (1.7 mmol, 87%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.04 (m, 5H), 3.48 (dt, J = 14.2, 7.1 Hz, 1H), 3.37 (dq, J = 14.2, 7.1 Hz, 1H), 2.71 (dq, J = 14.0, 7.1 Hz, 1H), 2.65 (d, J = 7.3 Hz, 1H), 2.58 (dq, J = 14.0, 7.0 Hz, 1H), 1.85 (s, 3H), 1.33 (d, J = 7.3 Hz, 1H), 1.00 (t, J = 7.1 Hz, 3H), 0.47 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 138.1, 128.1 (+), 127.0 (+), 126.7 (+), 42.4, 42.0 (-), 38.3 (-), 31.0, 26.9 (-), 24.3 (+), 12.6 (+), 11.1 (+); FT IR (KBr, cm-1): 2977, 2933, 1643, 1639, 1498, 1456, 1433, 1380, 1282, 1219, 1064, 719, 696, 582; HRMS (TOF ES): found 309.0724, calculated for $C_{15}H_{20}BrNO$ (M+) 309.0728 (1.3 ppm). $[\alpha]_D$= +17.01° (c 0.194, CH_2Cl_2).



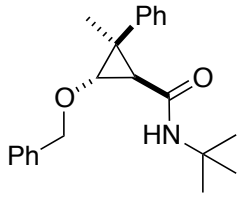
(1R,2S)-1-bromo-N,N,2-trimethyl-2-phenylcyclopropane-1-carboxamide (+)-132ad:

This compound was obtained according to a typical procedure employing a (1R,2S)-1-bromo-2-methyl-2-phenylcyclopropane-1-carboxylic acid (**5b***) (0.510 g, 2.00 mmol, 1.00 equiv), oxalyl chloride (0.26 mL, 3.0 mmol, 1.5 equiv) and 40 wt. % aq. solution oddimethyl amine (0.753 mL, 6.0 mmol, 3.00 equiv). Chromatographic purification afforded title compound as a white solid, mp: 81.7-83.3 ^{o}C, R_f 0.34 (hexanes/EtOAc 10:1). Yield 0.466 g (1.65 mmol, 83%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.10 (m, 5H), 2.65 (s, 3H), 2.57 (d, J = 7.4 Hz, 1H), 2.56 (s, 3H) 1.85 (s, 3H), 1.37 (d, J = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 138.2, 128.1 (+, 2C), 127.1 (+, 2C), 126.3, 42.6, 38.5 (+), 35.3 (+), 30.8, 27.0 (-), 24.1 (+); FT IR (KBr, cm-1): 2927, 1647, 1558, 1496, 1396, 1272, 1176, 1082, 1058, 1029, 954, 763, 696, 680, 669,

650; HRMS (TOF ES): found 281.0415, calculated for $C_{13}H_{16}BrNO$ (M+) 281.0415 (0.0 ppm). $[\alpha]_D$= +13.3° (c 0.098, CH_2Cl_2).

3.10.6. Formal Nucleophilic Substitution of Bromocyclopropanes

3.10.7. Diastereoselective reaction employing racemic substrates



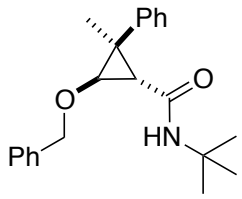
(1R*,2R*,3S*)-3-(benzyloxy)-N-(tert-butyl)-2-methyl-2-phenylcyclopropanecarboxamide (**134aaa**)**:**

Procedure A: An oven-dried 10 mL Weaton vial was charged with 18-crown‐6 (5.3 mg, 20 μmol, 10 mol%), *t*-BuOK (134 mg, 1.20 mmol, 6.00 equiv), benzyl alcohol (62 μL, 0.60 mmol, 3.0 equiv) and anhydrous THF (10.0 mL). The mixture was stirred at room temperature for 1 minute and bromocyclopropane **132aa** (62 mg, 0.20 mmol, 1.0 equiv) was added in a single portion. The reaction mixture was stirred overnight at 80 ^oC, then solvent was removed *in vacuo*, and the residue was partitioned between 15 mL of water and 15 mL of ethyl acetate, aqueous layer was extracted with ethyl acetate (3 x 15 mL). Combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a white solid, mp 133.6–134.9 ^oC, R_f 0.30 (hexane‐EtOAc 6:1), yield 33 mg (0.1 mmol, 49%), dr 11:1.

Procedure B: An oven‐dried 10 mL Weaton vial was charged with 18‐crown‐6 (5.3 mg, 20 μmol, 10 mol%), *t*-BuOK (134 mg, 1.20 mmol, 6.00 equiv), benzyl alcohol (62 μL, 0.6 mmol, 3.0 equiv) and anhydrous DMSO (5.0 mL). The

mixture was stirred at room temperature for 1 minute and bromocyclopropane **132aa** (62 mg, 0.2 mmol, 1.0 equiv) was added in a single portion. The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a white solid, identical to the one described in Procedure **A**. Yield 46 mg (0.136 mmol 68%), dr 46:1.

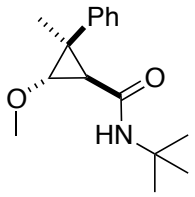
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–6.54 (m, 10H), 4.99 (br. s, 1H), 4.70 (d, *J* = 2.5 Hz, 2H), 4.14 (d, *J* = 3.3 Hz, 1H), 1.68 (d, *J* = 3.4 Hz, 1H), 1.56 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 141.3, 137.7, 128.7 (+, 2C), 128.6 (+, 2C), 128.5 (+, 2C), 128.3 (+, 2C), 128.1 (+), 127.0 (+), 73.5 (-), 66.4 (+), 51.2, 37.3, 37.2 (+), 28.8 (+, 3C), 22.0 (+); FT IR (KBr, cm^{-1}): 3315, 2966, 2927, 1643, 1541, 1497, 1454, 1390, 1375, 1363, 1274, 1226, 1205, 1143, 1103, 1068, 1041, 1026, 983, 752, 739, 698; HRMS (TOF ES): found 360.1941, calculated for $C_{22}H_{27}NO_2Na$ (M+Na) 360.1939 (0.6 ppm).



(1S*,2R*,3R*)-3-(benzyloxy)-N-(tert-butyl)-2-methyl-2-phenylcyclopropanecarboxamide (**139aaa**):

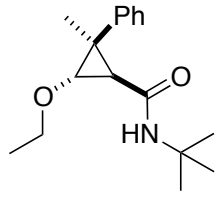
was obtained a minor product by cromatographic separation of diastereomeric mixture obtained in reaction with benzyl alcohol (Procedure **A**). The compound was isolated as a white solid, R_f 0.27 (hexane - EtOAc 6:1). Yeild 1.5 mg (4.4 μmol, 2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.19 (m, 8H), 7.11 (dd, *J* = 7.4, 2.0

Hz, 2H), 5.36 (br. s, 1H), 4.58–4.32 (m, 2H), 3.84 (d, *J* = 3.5 Hz, 1H), 1.95 (d, *J* = 3.5 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 9H).



(1R*,2R*,3S*)-N-(tert-butyl)-3-methoxy-2-methyl-2-phenyl-cyclopropanecarboxamide (**134aaf**):

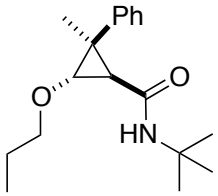
This compound was obtained according to a typical procedure A from bromocyclopropane **132aa** employing methanol (24 μL, 0.6 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 47 mg (0.18 mmol, 90%) of the title compound as a white solid, mp: 163 ^{o}C, R_f 0.31 (hexanes-EtOAc 6:1), dr 15:1. Alternatively, this compound can be obtained according to procedure B with a 31 mg (0.12 mmol, 60%) yield, dr 37:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–6.97 (m, 5H), 5.07 (s, 1H), 4.01 (d, *J* = 3.3 Hz, 1H), 3.51 (s, 3H), 1.65 (d, *J* = 3.3 Hz, 1H), 1.51 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) 167.9, 141.4, 128.7 (+, 2C), 128.5 (+, 2C), 126.9 (+), 67.9 (+), 58.8 (+), 51.2, 37.3, 36.8 (+), 28.8 (+, 3C), 21.6 (+); FT IR (KBr, cm^{-1}): 3323, 3063, 2971, 2958, 2925, 2868,1640, 1547, 1271, 1134, 988; HRMS (TOF ES): found 262.1804, calculated for $C_{16}H_{24}NO_2$ (M+H) 262.1807 (1.1 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-3-ethoxy-2-methyl-2-phenyl-cyclopropanecarboxamide (**134aae**):

This compound was obtained according to procedure A from

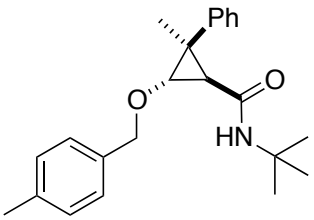
bromocyclopropane **132aa** employing ethanol (35 μL, 0.6 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 49 mg (0.18 mmol, 89%) of the title compound as a white solid, mp: 147.0–147.5 ^{o}C, R_f 0.31 (hexanes/ EtOAc 6:1), dr 7:1. Alternatively, this compound can be obtained according to procedure B with a 37 mg (0.134 mmol, 67%) yield, dr 36:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (tdd, *J* = 8.5, 7.7, 1.6 Hz, 5H), 5.06 (s, 1H), 4.05 (d, *J* = 3.4 Hz, 1H), 3.71 (q, *J* = 7.0 Hz, 2H), 1.65 (d, *J* = 3.4 Hz, 1H), 1.51 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 141.5, 128.7 (+, 2C), 128.5 (+, 2C), 126.9 (+), 66.8 (-), 66.3 (+), 51.2, 37.2, 37.0 (+), 28.8, 21.8, 15.3; FT IR (KBr, cm^{-1}): 3323, 3063, 2971, 2959, 2926, 2869, 1640, 1548, 1442, 1271, 1134, 988; HRMS (TOF ES): found 274.1809, calculated for $C_{17}H_{24}NO_2$ (M-H) 274.1807 (0.7 ppm).



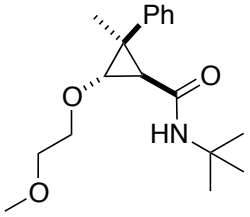
(1R*,2R*,3S*)-N-(tert-butyl)-2-methyl-2-phenyl-3-propoxycyclo propanecarboxamide (**134aad**):

This compound was obtained according to procedure A from bromocyclopropane **132aa** employing *n*-propanol (45 μL, 0.6 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 46 mg (0.16 mmol, 80%) of the title compound as a white solid, mp: 132.5–133.0 ^{o}C, R_f 0.28 (hexanes/EtOAc 6:1), dr 9:1. Alternatively, this compound can be obtained according to procedure B with a 38 mg (0.13 mmol, 66%) yield, dr 42:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.12 (m, 5H), 5.08 (br. s, 1H), 4.04 (d, *J* = 3.3 Hz, 1H), 3.60 (dt, *J* = 8.9, 4.5 Hz, 2H), 1.68 (dd, *J* = 13.1, 5.9 Hz, 2H), 1.66 (d, *J* = 3.2 Hz, 1H), 1.51 (s, 3H), 1.15 (s, 9H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 168.0, 141.5, 128.8 (+, 2C), 128.5 (+, 2C), 126.9 (+), 73.1 (-), 66.4 (+), 51.2, 37.3, 37.1 (+), 28.8 (+, 3C), 23.1 (-),

21.8 (+), 10.9 (+); FT IR (KBr, cm^{-1}): 3307, 2962, 2929, 1643, 1545, 1456, 1389, 1275, 1227, 1158, 763, 699; HRMS (TOF ES): found 312.1938, calculated for $C_{18}H_{27}NO_2Na$ (M+Na) 312.1939 (0.3 ppm).



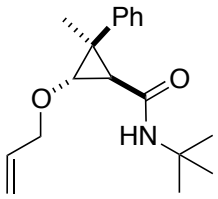
(1R*,2R*,3S*)-N-(tert-butyl)-2-methyl-3-((4-methylbenzyl)oxy)-2-phenylcyclopropanecarboxamide (**134aaj**): This compound was obtained according to a typical procedure B from bromocyclopropane **132aa** employing 4-methylbenzyl alcohol (73 mg, 0.60 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 56 mg (0.16 mmol, 79%) of the title compound as a white solid, mp: 148.2–148.9 ^{o}C, R_f 0.31 (hexanes/EtOAc 6:1), dr 48:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.07 (m, 9H), 4.97 (br. s, 1H), 4.65 (d, J = 1.4 Hz, 2H), 4.11 (d, J = 3.4 Hz, 1H), 2.36 (s, 3H), 1.66 (d, J = 3.4 Hz, 1H), 1.55 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 141.4, 137.8, 134.6, 129.3 (+, 2C), 128.7 (+, 2C), 128.5 (+, 2C), 128.4 (+, 2C), 126.9 (+), 73.4 (-), 66.3 (+), 51.1, 37.3, 37.2 (+), 28.8 (+, 3C), 22.0 (+), 21.4 (+); FT IR (KBr, cm^{-1}): 3325, 3196, 3057, 2970, 2960, 2923, 2738, 1643, 1545, 1363, 1276, 1226, 1144, 1103, 1068, 1024, 808, 761, 700; HRMS (TOF ES): found 351.2201, calculated for $C_{23}H_{29}NO_2$ (M+) 351.2198 (0.9 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-3-(2-methoxyethoxy)-2-methyl-2-phenylcyclopropanecarboxamide (**134aac**):

This compound was obtained according to procedure B from bromocyclopropane **132aa** employing 2-methoxyethanol (47 μL, 0.60 mmol, 3.0

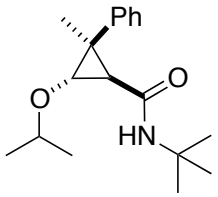
equiv) as pronucleophile. The subsequent chromatographic purification afforded 48 mg (0.16 mmol, 79%) of the title compound as a white solid, mp: 122.2–123.5 ^{o}C, R_f 0.30 (hexanes/EtOAc 2:1), dr >50:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.13 (m, 5H), 5.08 (br. s, 1H), 4.12 (d, *J* = 3.3 Hz, 1H), 3.87 – 3.74 (m, 2H), 3.66 – 3.56 (m, 2H), 3.41 (s, 3H), 1.69 (d, *J* = 3.3 Hz, 1H), 1.52 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 141.4, 128.7 (+, 2C), 128.5 (+, 2C), 126.9 (+), 71.8 (-), 70.5 (-), 66.8 (+), 59.2 (+), 51.1, 37.4, 37.0 (+), 28.8 (+, 3C), 21.8 (+); FT IR (KBr, cm^{-1}): 3317, 2962, 2926, 2872, 2359, 1643, 1547, 1497, 1446, 1391, 1363, 1275, 1226, 1199, 1153, 1126, 1105, 1087, 1070, 1026, 883, 759, 700; HRMS (TOF ES): found 305.1985, calculated for $C_{18}H_{27}NO_3$ (M+) 305.1991 (2.0 ppm).



(1R*,2R*,3S*)-3-(allyloxy)-N-(tert-butyl)-2-methyl-2-phenylcyclo propanecarboxamide (**134aab**):

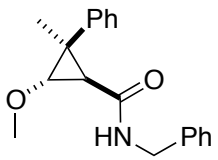
This compound was obtained according to procedure B from bromocyclopropane **132aa** employing allyl alcohol (41 μL, 0.6 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 53 mg (0.18 mmol, 92%) of the title compound as a white solid, mp: 120.9–122.2 ^{o}C, R_f 0.22 (hexanes/EtOAc 5:1), dr >50:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.14 (m, 5H), 6.00 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.04 (br. s, 1H), 4.22–4.14 (m, 2H), 4.10 (d, *J* = 3.3 Hz, 1H), 1.68 (d, *J* = 3.3 Hz, 1H), 1.53 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 141.4, 134.3 (+), 128.7 (+, 2C), 128.6 (+, 2C), 127.0 (+), 117.8 (-), 72.3 (-), 66.2 (+), 51.2, 37.3, 37.1

(+), 28.8 (+, 3C), 21.9 (+); FT IR (KBr, cm^{-1}): 3304, 2964, 2926, 2868, 1731, 1643, 1545, 1454, 1361, 1275, 1226, 1147, 985, 926, 764, 700; HRMS (TOF ES): found 286.1804, calculated for $C_{18}H_{24}NO_2$ (M-H) 286.1807 (1.0 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-3-isopropoxy-2-methyl-2-phenylcyclo propanecarboxamide (**134aag**):

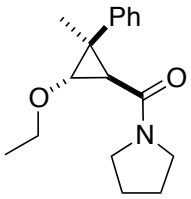
This compound was obtained according to procedure A from bromocyclopropane **132aa** employing isopropanol (45 μL, 0.6 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 35 mg (0.12 mmol, 60%) of the title compound as a white solid, mp: 147.8–148.8 ^{o}C, R_f 0.32 (hexanes/EtOAc 6:1), dr 10:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.13 (m, 5H), 5.07 (br. s, 1H), 4.12 (d, *J* = 3.4 Hz, 1H), 3.85 (dt, *J* = 12.3, 6.2 Hz, 1H), 1.65 (d, *J* = 3.4 Hz, 1H), 1.52 (s, 3H), 1.29 (dd, *J* = 7.5, 6.2 Hz, 6H), 1.16 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 141.6, 128.7 (+, 2C), 128.5 (+, 2C), 126.9 (+), 72.8 (+), 64.5 (+), 51.2, 37.3, 37.2 (+), 28.8 (+, 3C), 22.5 (+), 22.3 (+), 22.0 (+); FT IR (KBr, cm^{-1}): 3254, 3193, 3064, 2970, 2877, 1639, 1550, 1494, 1448, 1434, 1363, 1284, 1275, 1226, 1178, 1139, 698; HRMS (TOF ES): found 288.1964, calculated for $C_{18}H_{26}NO_2$ (M-H) 288.1964 (0.0 ppm).



(1R*,2R*,3S*)-N-benzyl-3-methoxy-2-methyl-2-phenylcyclopropane carboxamide (**134abf**):

This compound was obtained according to a typical procedure A from 69 mg of bromocyclopropane **132ab** employing methanol (24 μL, 0.60 mmol, 3.0 equiv) as

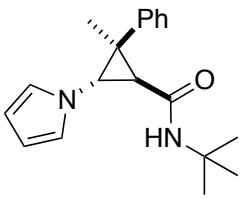
pronucleophile. The subsequent chromatographic purification afforded 48 mg (0.13 mmol, 63%) of the title compound as a yellow solid, 96.2–98.1 ^{o}C, R_f 0.32 (hexanes/EtOAc 5:1), dr 13:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.15 (m, 8H), 7.08 (dd, *J* = 7.7, 1.5 Hz, 2H), 5.58 (br. s, 1H), 4.27 (ddd, *J* = 68.8, 14.6, 5.5 Hz, 2H), 4.13 (d, *J* = 3.3 Hz, 1H), 3.52 (s, 3H), 1.75 (d, *J* = 3.3 Hz, 1H), 1.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 141.1, 138.5, 128.7 (+, 2C), 128.7 (+, 2C), 128.6 (+, 2C), 128.1 (+, 2C), 127.6 (+), 127.1 (+), 68.2 (+), 58.8 (+), 43.8 (-), 37.9, 36.2 (+), 21.7 (+); FT IR (KBr, cm^{-1}): 3300,3061, 3026, 2957, 2871, 1726, 1643, 1602, 1547, 1497, 1417, 1377, 1348, 1267, 1205, 1192, 1134, 1072, 1028, 1013, 760, 752, 698, 651; HRMS (TOF ES): found 295.1579, calculated for $C_{19}H_{21}NO_2$ (M+) 295.1572 (2.4 ppm).



((1R*,2R*,3S*)-3-ethoxy-2-methyl-2-phenylcyclopropyl)(pyrrolidin-1-yl)methanone (**132ace**):

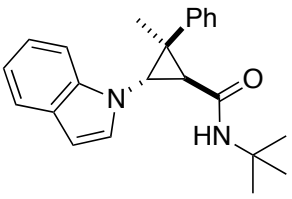
This compound was obtained according to procedure B from 62 mg of bromocyclopropane **132ac** employing ethanol (35 μL, 0.60 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 40 mg (0.15 mmol, 73%) of the title compound as a colorless oil, R_f 0.25 (hexanes/EtOAc 1:1), dr 48:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.06 (m, 5H), 4.29 (d, *J* = 3.4 Hz, 1H), 3.73–3.68 (m, 2H), 3.45 (br., 4H), 1.93 (d, *J* = 3.4 Hz, 1H), 1.89 (br., 4H), 1.58 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 141.6, 128.5 (+, 2C), 128.2 (+, 2C), 126.7 (+), 66.7 (-), 66.2 (+), 46.3 (-, 2C, br.), 37.3, 35.6 (+), 25.4 (-, 2C, br.), 21.3 (+), 15.4 (+); FT IR (KBr, cm^{-1}): 3024, 2974,2927, 2871, 1733, 1679, 1637, 1494, 1445, 1408, 1386, 1360, 1350, 1319, 1267, 1246, 1226, 1180, 1153, 1123, 1105, 1062, 1042,

1022, 881, 763, 700; HRMS (TOF ES): found 273.1727, calculated for $C_{17}H_{23}NO_2$ (M+) 273.1729 (0.7 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-2-methyl-2-phenyl-3-(1H-pyrrol-1-yl)cyclopropanecarboxamide (**143aaa**):

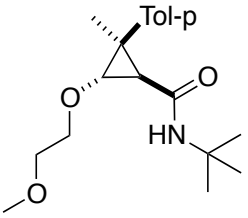
This compound was obtained according to procedure A from bromocyclopropane **132aa** employing pyrrole (42 μL, 0.6 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 16.5 mg (0.056 mmol, 28%) of the title compound as a white solid, mp: 198.4–199.0 ^{o}C, R_f 0.28 (hexanes/EtOAc 5:1), dr 19:1. Alternatively, this compound can be obtained according to procedure B with a 41 mg (0.14 mmol, 69%) yield, dr 44:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.15 (m, 5H), 6.70 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 5.25 (br. s, 1H), 4.26 (d, *J* = 4.2 Hz, 1H), 2.12 (d, *J* = 4.2 Hz, 1H), 1.20 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 140.7, 128.7 (+, 2C), 128.6 (+, 2C), 127.4 (+), 121.6 (+, 2C), 108.7 (+, 2C), 51.6, 44.9 (+), 37.4, 36.7 (+), 28.8 (+, 9C), 22.9 (+); FT IR (KBr, cm^{-1}): 3302, 2966, 2928, 1647, 1548, 1265, 725, 700; HRMS (TOF ES): found 295.1804, calculated for $C_{19}H_{23}N_2O$ (M-H) 295.1810 (2.0 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-3-(1H-indol-1-yl)-2-methyl-2-phenylcyclopropanecarboxamide (**143aac**):

This compound was obtained according to procedure B from bromocyclopropane **132aa** employing indole (70 mg, 0.6 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 54 mg (0.16

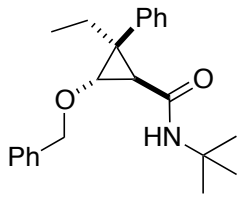
mmol, 78%) of the title compound as a white solid, mp: 179.7–180.6 °C, R_f 0.33 (hexanes/EtOAc 5:1), dr >50:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.60 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.51 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.31 (dt, *J* = 9.1, 4.3 Hz, 1H), 7.28–7.23 (m, 1H), 7.19 – 7.09 (m, 2H), 6.54 (dd, *J* = 3.2, 0.6 Hz, 1H), 5.35 (br. s, 1H), 4.44 (d, *J* = 4.2 Hz, 1H), 2.32 (d, *J* = 4.2 Hz, 1H), 1.33 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 140.5, 137.5, 129.1, 128.9 (+, 2C), 128.6 (+, 2C), 128.2 (+), 127.5 (+), 122.2 (+), 121.2 (+), 120.1 (+), 110.6 (+), 102.0 (+), 51.6, 42.4 (+), 37.3, 37.0 (+), 28.8 (+, 3C), 22.7 (+). FT IR (KBr, cm^{-1}): 3312, 2968, 1647, 1544, 1512, 1479, 1462, 1446, 1363, 1311, 1267, 1224, 1199, 1089, 763, 740, 700; HRMS (TOF ES): found 345.1960, calculated for $C_{23}H_{25}N_2O$ (M-H) 345.1967 (2.0 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-3-(2-methoxyethoxy)-2-methyl-2-(p-tolyl)cyclopropanecarboxamide (**134bac**):

This compound was obtained according to procedure B from 65 mg of bromocyclopropane **132ba** employing 2-methoxyethanol (47 μL, 0.60 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 58 mg (0.18 mmol, 91%) of the title compound as a white solid, mp: 119.3–120.0 °C, R_f 0.25 (hexanes/EtOAc 2:1), dr 25:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 4.08 (d, *J* = 3.1 Hz, 1H), 3.88–3.70 (m, 2H), 3.61 (t, *J* = 4.1 Hz, 2H), 3.41 (s, 3H), 2.29 (s, 3H), 1.67 (d, *J* = 3.1 Hz, 1H), 1.50 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 138.3, 136.4, 129.3 (+, 2C), 128.6 (+, 2C), 71.8 (-), 70.4 (-), 67.0 (+), 59.2 (+), 51.2, 37.2, 36.9 (+), 28.8 (+, 3C), 21.9 (+), 21.2 (+); FT IR

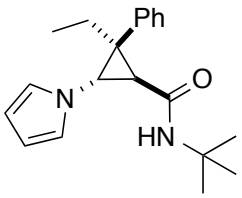
(KBr, cm^{-1}): 3321, 2964, 2924, 2871, 1645, 1541, 1517, 1454, 1390, 1364, 1275, 1226, 1200, 1151, 1126, 1099, 1084, 1043, 817; HRMS (TOF ES): found 342.2047, calculated for $C_{19}H_{29}NO_3Na$ (M+Na) 342.2045 (0.6 ppm).



(1R*,2R*,3S*)-3-(benzyloxy)-N-(tert-butyl)-2-ethyl-2-phenylcyclo propanecarboxamide (**134caa**):

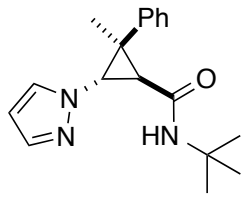
This compound was obtained according to the following protocol: An oven-dried 10 mL Weaton vial was charged with 18-crown-6 (12 mg, 45 μmol, 10 mol %), *t*-BuOK (304 mg, 2.7 mmol, 6.0 equiv), benzyl alcohol (140 μL, 1.35 mmol, 3.0 equiv) and anhydrous DMSO (10.0 mL). The mixture was stirred at room temperature for 1 minute and bromocyclopropane **132fa** (148 mg, 0.45 mmol, 1.0 equiv) was added in a single portion. The reaction mixture was stirred overnight at 40 ^oC, GC analysis showed incomplete conversion (70% based on starting material) and dr 15:1, after heating at 80 ^oC for 30 minutes the reaction was complete. Flash column chromatography on Silica gel afforded the title compound as a white solid, mp: 117.7–118.5 ^oC , R_f 0.31 (hexane-EtOAc 6:1),. Yield 105 mg (0.31 mmol, 68%), dr 14:1. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.03 (m, 10H), 4.95 (br. s, 1H), 4.76–4.61 (m, 2H), 4.10 (d, *J* = 3.3 Hz, 1H), 1.98 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.77 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.66 (d, *J* = 3.3 Hz, 1H), 1.16 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 139.2, 137.8, 129.8 (+, 2C), 128.6 (+, 2C), 128.3 (+, 2C), 128.1 (+, 2C), 127.9 (+), 127.0 (+), 73.4 (-), 67.2 (+), 51.1, 43.1, 36.3 (+), 28.8 (+, 3C), 28.4 (-), 11.6 (+); FT IR (KBr, cm^{-1}): 3411, 3321, 3200, 2966, 2931, 2874, 1726, 1643, 1603, 1541, 1497, 1454,

1388, 1377, 1364, 1329, 1267, 1227, 1196, 1178, 1143, 1109, 1070, 1043, 1027, 1001, 959, 910, 856, 794, 752, 734, 700, 661, 617, 598; HRMS (TOF ES): found 374.2091, calculated for $C_{23}H_{29}NO_2$ (M+Na) 374.2096 (1.3 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-2-ethyl-2-phenyl-3-(1H-pyrrol-1-yl)cyclopropane-1-carboxamide (143faa):

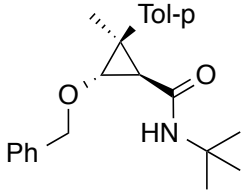
This compound was obtained according to procedure B from 65 mg of bromocyclopropane **132fa** employing pyrrole (42 μL, 0.60 mmol, 3.0 equiv) as pronucleophile. The reaction mixture was stirred overnight at 40 ^{o}C, GC analysis showed incomplete conversion (75% based on starting material) and dr 17:1, after heating at 80 ^{o}C for 30 minutes the reaction was complete. The subsequent chromatographic purification afforded 35 mg (0.114 mmol, 57%) of the title compound as a white solid, mp: 177.5–120.0 ^{o}C, R_f 0.29 (hexanes/EtOAc 6:1), dr 14:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.07 (m, 5H), 6.72 (t, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 2H), 5.28 (br. s, 1H), 4.25 (d, *J* = 4.3 Hz, 1H), 2.12 (d, *J* = 4.3 Hz, 1H), 1.45–1.32 (m, 2H), 1.16 (s, 9H), 0.71 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 138.6, 129.7 (+, 2C), 128.4 (+, 2C), 127.4 (+), 121.7 (+, 2C), 108.6 (+, 2C), 51.6, 46.3 (+), 43.0, 35.1 (+), 28.8 (+, 3C), 28.5 (-), 11.3 (+); FT IR (KBr, cm^{-1}): 3317, 3060, 2968, 2931, 1647, 1545, 1492, 1446, 1263, 1224, 721, 698; HRMS (TOF ES): found 309.1968, calculated for $C_{20}H_{25}N_2ONa$ (M-H) 342.2045 (0.6 ppm).



(1R*,2R*,3S*)-N-(tert-butyl)-2-methyl-2-phenyl-3-(1H-pyrazol-1-yl)cyclopropane-1-carboxamide (**143aae**):

This compound was obtained according to procedure B from 62 mg of bromocyclopropane **132aa**, pyrazole (41 mg, 0.60 mmol, 3.0 equiv) as pronucleophile. The subsequent chromatographic purification afforded 50 mg (0.168 mmol, 84%) of the title compound as a white solid, mp: 191.0–192.5 ^{o}C, R_f 0.4 (CH_2Cl_2/MeOH 20:1), dr 14:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 1.7 Hz, 1H), 7.34–7.22 (m, 4H), 7.21–7.12 (m, 1H), 6.26 (t, *J* = 2.1 Hz, 1H), 5.47 (br. s, 1H), 4.49 (d, *J* = 4.1 Hz, 1H), 2.49 (d, *J* = 4.1 Hz, 1H), 1.16 (s, 9H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.34, 140.58, 139.52 (+), 130.61 (+), 128.67 (+, 2C), 128.59 (+, 2C), 127.35 (+), 106.25 (+), 51.64, 47.02 (+), 37.76, 35.86 (+), 28.82 (+, 3C), 22.55 (+); FT IR (KBr, cm^{-1}): 3305, 2966, 1650, 1544, 1515, 1446, 1392, 1361, 1271, 1226, 1097, 979, 858, 754, 700, 653; HRMS (TOF ES): found 298.1923, calculated for $C_{18}H_{24}N_3O$ (M+H) 298.1919 (1.3 ppm).

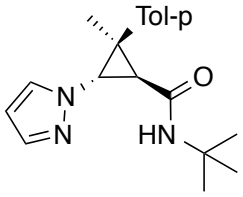
3.10.8. Diastereoselective reaction employing homochiral substrates



(1R,2R,3S)-3-(benzyloxy)-N-(tert-butyl)-2-methyl-2-(p-tolyl)cyclo propanecarboxamide (**134baa**)*:

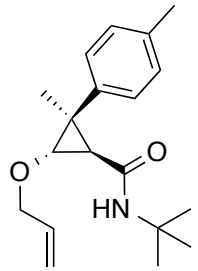
This compound was obtained according to a procedure B from 130 mg of bromocyclopropane **(-)-132ba** employing benzyl alcohol (124 μL, 1.20 mmol, 3.00 equiv) as pronucleophiles. The subsequent chromatographic purification afforded 129 mg (0.367 mmol, 92%) of the title compound as a white solid, mp: 139.8–140.6 ^{o}C, R_f 0.33 (hexanes/EtOAc 6:1), dr 44:1. $[\alpha]_D$= –24.5° (c 1.10, CH_2Cl_2). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.54–7.17 (m, 5H), 7.10 (q, *J* = 8.1 Hz, 4H), 5.03 (br. s, 1H), 4.87–4.53 (m, 2H), 4.12 (d, *J* = 3.3 Hz, 1H), 2.30 (s, 3H), 1.66 (d, *J* = 3.3 Hz, 1H), 1.54 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 138.3, 137.7, 136.4, 129.3 (+, 2C), 128.6 (+, 2C), 128.5 (+, 2C), 128.3 (+, 2C), 128.0 (+), 73.5 (-), 66.6 (+), 51.1, 37.1 (+), 28.8 (+, 3C), 22.1 (+), 21.2 (+); FT IR (KBr, cm^{-1}): 3308, 3063, 3030, 2966, 2926, 2864, 1643, 1543, 1516, 1454, 1431, 1375, 1364, 1346, 1277, 1226, 1204, 1144, 1099, 987, 817, 750, 734, 698; HRMS (TOF ES): found 374.2098, calculated for $C_{23}H_{29}NO_2$ (M+Na) 374.2096 (0.5 ppm).



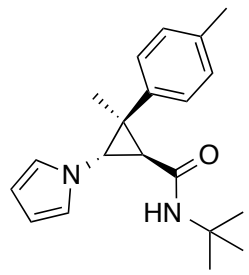
(1R,2R,3S)-N-(tert-butyl)-2-methyl-3-(1H-pyrazol-1-yl)-2-(p-tolyl)cyclopropane-1-carboxamide (**143bae**):

This compound was obtained according to a procedure B from 65 mg of bromocyclopropane **(-)-132ba** employing pyrazole (41 mg, 0.60 mmol, 3.00 equiv) as pronucleophiles. The subsequent chromatographic purification afforded 47 mg (0.158 mmol, 79%) of the title compound as a white solid, mp: 147.9–148.5 °C, R_f 0.35 (CH_2Cl_2/MeOH 20:1), dr 15:1. $[\alpha]_D$= +40.57° (c 0.35, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.1 Hz, 1H), 7.47 (d, *J* = 1.2 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.25 (t, *J* = 1.9 Hz, 1H), 5.69 (br. s, 1H), 4.46 (d, *J* = 4.0 Hz, 1H), 2.61–2.45 (m, 1H), 2.24 (s, 3H), 1.16 (s, 9H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 139.4 (+), 137.6, 136.8, 130.6 (+), 129.4 (+, 2C), 128.4 (+, 2C), 106.2 (+), 51.6, 47.1 (+), 37.4, 35.8 (+), 28.8 (+, 3C), 22.7 (+), 21.3 (+); FT IR (KBr, cm^{-1}): 3306, 2964, 2925, 1649, 1544, 1452, 1392, 1274, 1224, 1089, 1047, 820, 752, 615; HRMS (TOF ES): found 312.2081, calculated for $C_{19}H_{26}N_3O$ (M+H) 312.2076 (1.6 ppm).



(1R,2R,3S)-3-(allyloxy)-N-(tert-butyl)-2-methyl-2-(p-tolyl)cyclopropane-1-carboxamide (134bab):

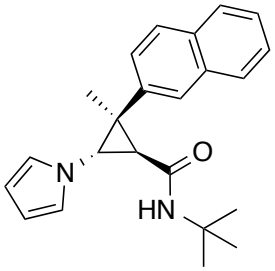
This compound was obtained according to a procedure B from 65 mg of bromocyclopropane **(-)-132ba** employing allyl alcohol (41 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 42 mg (0.146 mmol, 73%) of the title compound as a white solid, mp: 120.6–122.7 °C, R_f 0.38 (hexanes/EtOAc 5:1), dr 50:1. $[\alpha]_D$= -21.8° (c 0.16, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.99 (ddt, *J* = 16.2, 10.5, 5.7 Hz, 1H), 5.36 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.08 (br. s, 1H), 4.27–4.10 (m, 2H), 4.07 (d, *J* = 3.3 Hz, 1H), 2.29 (s, 3H), 1.65 (d, *J* = 3.3 Hz, 1H), 1.50 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 138.3, 136.4, 134.3 (+), 129.3 (+, 2C), 128.5 (+, 2C), 117.7 (-), 72.3 (-), 66.4 (+), 51.1, 37.0 (+), 37.0, 28.8 (+, 3C), 22.0 (+), 21.2 (+); FT IR (KBr, cm^{-1}): 3301, 2966, 2923, 1643, 1546, 1515, 1454, 1226, 1145, 985, 925, 817; HRMS (TOF ES): found 300.1967, calculated for $C_{19}H_{26}NO_2$ (M-H) 300.1964 (1.0 ppm).



(1R,2R,3S)-N-(tert-butyl)-2-methyl-3-(1H-pyrrol-1-yl)-2-(p-tolyl)cyclopropane-1-carboxamide (143baa):

This compound was obtained according to a procedure B from 65 mg of bromocyclopropane **(-)-132ba** employing pyrrole (42 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 52 mg (0.168 mmol, 84%) of the title compound as a white solid, mp: 208.0–210.1 °C, R_f 0.31 (hexanes/EtOAc 6:1), dr 1:0. $[\alpha]_D$= +46.48° (c 0.142,

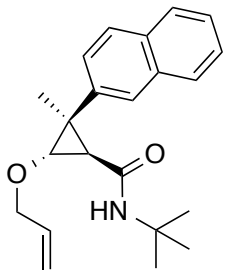
CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.77 (t, *J* = 2.1 Hz, 2H), 6.19 (t, *J* = 2.1 Hz, 2H), 5.35 (br. s, 1H), 4.31 (d, *J* = 4.2 Hz, 1H), 2.32 (s, 3H), 2.17 (d, *J* = 4.2 Hz, 1H), 1.26 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 137.7, 137.0, 129.5 (+, 2C), 128.4 (+, 2C), 121.6 (+, 2C), 108.6 (+, 2C), 51.6, 45.0 (+), 37.1, 36.7 (+), 28.8 (+, 3C), 23.1 (+), 21.3 (+); FT IR (KBr, cm^{-1}): 3319, 2966, 2925, 1645, 1546, 1539, 1492, 1454, 1361, 1265, 1224, 1093, 1066, 981, 817, 721, 700; HRMS (TOF ES): found 309.1974, calculated for $C_{20}H_{25}N_2O$ (M-H) 309.1967 (2.3 ppm).



(1R,2R,3S)-N-(tert-butyl)-2-methyl-2-(naphthalen-2-yl)-3-(1H-pyrrol-1-yl)cyclopropane-1-carboxamide (143gaa):

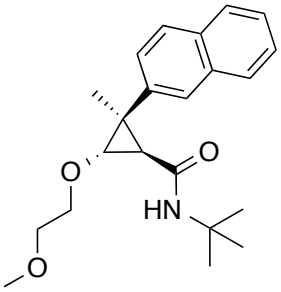
This compound was obtained according to a procedure B from 72 mg of bromocyclopropane **(-)-132ga** employing pyrrole (42 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 52 mg (0.149 mmol, 75%) of the title compound as a white solid, mp: 181.4–183.2 ^{o}C, R_f 0.23 (hexanes/EtOAc 6:1), dr 81:1. $[\alpha]_D$= +15.63° (c 0.096 CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01–7.67 (m, 4H), 7.57–7.35 (m, 3H), 6.85 (t, J = 2.1 Hz, 2H), 6.23 (t, J = 2.1 Hz, 2H), 5.44 (br., s, 1H), 4.46 (d, J = 4.1 Hz, 1H), 2.28 (d, J = 4.2 Hz, 1H), 1.36 (s, H), 1.19 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 138.3, 133.6, 132.7, 128.5 (+), 127.8 (+), 127.8 (+), 127.3 (+), 126.7 (+), 126.3 (+), 126.0 (+), 121.7 (+, 2C), 108.7 (+, 2C), 51.7, 45.2 (+), 37.7, 36.8 (+), 28.8 (+, 3C), 23.0 (+); FT IR (KBr, cm^{-1}): 3305, 2968, 1650, 1548, 1492, 1454, 1392, 1265, 1224, 1132, 1091, 1064,

981, 854, 817, 721, 680, 657; HRMS (TOF ES): found 346.2047, calculated for $C_{23}H_{26}N_2O$ (M+) 346.2045 (0.6 ppm).



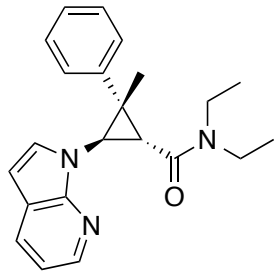
(1R,2R,3S)-3-(allyloxy)-N-(tert-butyl)-2-methyl-2-(naphthalen-2-yl)cyclopropane-1-carboxamide (134gab):

This compound was obtained according to a procedure B from 72 mg of bromocyclopropane **(-)-132ga** employing allyl alcohol (41 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 58 mg (0.172 mmol, 88%) of the title compound as a white solid, mp: 122.2–125.1 ^{o}C, R_f 0.26 (hexanes/EtOAc 4:1), dr 1:0. $[\alpha]_D$= -7.87° (c 0.178, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.72 (m, 3H), 7.69 (s, 1H), 7.50–7.36 (m, 2H), 7.35 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.04 (ddt, *J* = 22.1, 10.5, 5.7 Hz, 1H), 5.41 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.27 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.17 (br. s, 1H), 4.34–4.05 (m, 2H), 4.22 (d, *J* = 3.3 Hz, 1H), 1.75 (d, *J* = 3.3 Hz, 1H), 1.59 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 139.0, 134.3 (+), 133.6, 132.6, 128.2 (+), 127.8 (+), 127.8 (+), 127.3 (+), 127.0 (+), 126.1 (+), 125.7 (+), 117.8 (-), 72.4 (-), 66.5 (+), 51.2, 37.5 , 37.1 (+), 28.8 (+, 3C), 22.0 (+); FT IR (KBr, cm^{-1}): 3319, 2966, 2925, 1643, 1542, 1454, 1361, 1269, 1226, 1147, 1128, 1087, 1062, 1041, 985, 923, 856, 817, 744, 667; HRMS (TOF ES): found 338.2119, calculated for $C_{22}H_{28}NO_2$ (M+H) 338.2120 (0.3 ppm).



(1R,2R,3S)-N-(tert-butyl)-3-(2-methoxyethoxy)-2-methyl-2-(naphthalen-2-yl)cyclopropane-1-carboxamide (134gab):

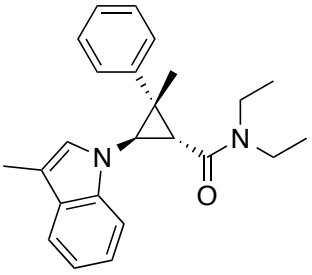
This compound was obtained according to a procedure B from 65 mg of bromocyclopropane **(-)-132ga** employing 2-methoxyethanol (47 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 54 mg (0.151 mmol, 76%) of the title compound as a white solid, mp: 143.2–144.2 ^{o}C, R_f 0.245 (hexanes/EtOAc 2:1), dr 1:0. $[\alpha]_D$= -6.1° (c 0.214, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.65 (m, 4H), 7.54–7.32 (m, 3H), 5.19 (br. s, 1H), 4.23 (d, *J* = 3.3 Hz, 1H), 3.96–3.77 (m, 2H), 3.73–3.60 (m, 2H), 3.44 (s, 3H), 2.17 (s, 3H), 1.76 (d, *J* = 3.3 Hz, 1H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 139.0, 133.6, 132.6, 128.2 (+), 127.8 (+), 127.3 (+), 127.0 (+), 126.0 (+), 125.7 (+), 71.9 (-), 70.5 (-), 67.0 (+), 59.3 (+), 51.2, 37.6, 37.0 (+), 31.1 (+), 28.8 (+, 3C), 21.9 (+); FT IR (KBr, cm^{-1}): 3323, 2966, 2871, 1645, 1541, 1454, 1390, 1363, 1269, 1226, 1151, 1124, 956, 856, 817, 742, 667; HRMS (TOF ES): found 356.2225, calculated for $C_{22}H_{30}NO_3$ (M+H) 356.2226 (0.3 ppm).



(1S,2S,3R)-N,N-diethyl-2-methyl-2-phenyl-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)cyclopropane-1-carboxamide (143abd):

This compound was obtained according to a procedure B from 62 mg of bromocyclopropane **(+)-132ac** employing 7-azaindole (71 mg, 0.60 mmol,

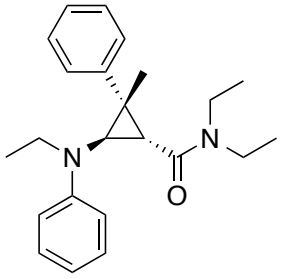
3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 34 mg (0.102 mmol, 50%) of the title compound as a white solid, mp: 113.2–114.0 °C, R_f 0.42 (hexanes/EtOAc 2:1), dr 20:1. $[\alpha]_D$= -5.2° (c 0.669, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.90 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.65–7.51 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 7.08 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.47 (d, *J* = 3.5 Hz, 1H), 4.72 (d, *J* = 4.3 Hz, 1H), 3.85 (dq, *J* = 14.4, 7.1 Hz, 1H), 3.78–3.62 (m, 1H), 3.43 (dq, *J* = 14.3, 7.1 Hz, 1H), 2.97 (dq, *J* = 14.0, 7.0 Hz, 1H), 2.73 (d, *J* = 4.3 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 149.4, 143.6 (+), 141.13, 128.9 (+, 2C), 128.6 (+), 128.6 (+, 2C), 128.3 (+), 127.1 (+), 120.9, 116.3, 100.00, 42.7 (+), 42.1 (-), 40.4 (-), 37.5, 33.3 (+), 22.6 (+), 14.9 (+), 12.8 (+); FT IR (KBr, cm^{-1}): 2972, 2929, 1733, 1637, 1479, 1460, 1448, 1433, 1377, 1265, 1220, 1143, 1097, 1070, 652, 846, 196, 775, 763, 723, 702, 624, 598; HRMS (TOF ES): found 348.2076, calculated for $C_{22}H_{26}N_3O$ (M+H) 348.2076 (0.0 ppm).



(1S,2S,3R)-N,N-diethyl-2-methyl-3-(3-methyl-1H-indol-1-yl)-2-phenylcyclopropane-1-carboxamide (143abc):

This compound was obtained according to a procedure B from 62 mg of bromocyclopropane **(+)-132ac** employing skatole (79 mg, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 50 mg (0.137 mmol, 69%) of the title compound as a white solid, mp: 116.2–117.5 °C, R_f 0.21 (hexanes/EtOAc 5:1), dr 32:1. $[\alpha]_D$= -64.0° (c 0.05, CH_2Cl_2). ^{1}H NMR (500 MHz,

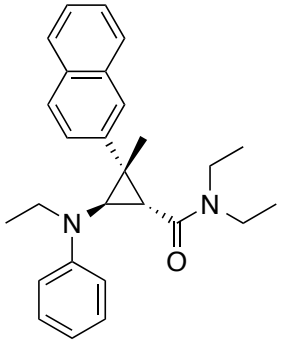
$CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.24–7.20 (m, 1H), 7.14 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.92 (s, 1H), 4.63 (d, *J* = 4.2 Hz, 1H), 3.76 (td, *J* = 14.3, 7.0 Hz, 1H), 3.66 (td, *J* = 13.9, 7.0 Hz, 1H), 3.34 (dq, *J* = 14.3, 7.0 Hz, 1H), 2.93 (dq, *J* = 13.9, 7.0 Hz, 1H), 2.55 (d, *J* = 4.2 Hz, 1H), 2.34 (s, 3H), 1.42 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 140.3, 137.9, 129.4, 128.7 (+, 2C), 128.1 (+, 2C), 127.2 (+), 125.7 (+), 122.0 (+), 119.3 (+), 119.2 (+), 111.1 , 110.5 (+), 42.3 (+), 41.9 (-), 40.2 (-), 37.0, 35.9 (+), 22.1 (+), 15.9 (+), 12.7 (+), 9.8 (+); FT IR (KBr, cm^{-1}): 2972, 2927, 1639, 1465, 1379, 1309, 1263, 1230, 1143, 759, 740, 698; HRMS (TOF ES): found 360.2200, calculated for $C_{24}H_{28}N_2O$ (M+) 360.2202 (0.6 ppm).



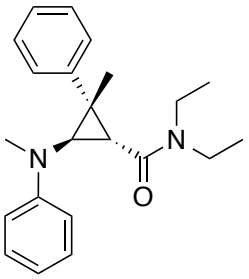
(1S,2S,3R)-N,N-diethyl-3-(ethyl(phenyl)amino)-2-methyl-2-phenylcyclopropane-1-carboxamide (144ac):

This compound was obtained according to a procedure B from 62 mg of bromocyclopropane **(+)-132ac** employing N-ethylaniline (75 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 42 mg (0.128 mmol, 64%) of the title compound as yellow oil, R_f 0.31 (hexanes/EtOAc 5:1), dr 13:1. $[\alpha]_D$= +11.6° (c 0.16, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.14 (m, 7H), 7.01–6.89 (m, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 3.84 (d, *J* = 4.6 Hz, 1H), 3.70–3.42 (m, 4H), 3.14 (dq, *J* = 14.3, 7.1 Hz, 1H), 2.84 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.95 (d, *J* = 4.6 Hz, 1H), 1.60 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 149.2, 141.0,

129.2 (+, 2C), 128.4 (+, 2C), 127.6 (+, 2C), 126.7 (+, 2C), 118.0 (+), 115.7 (+), 46.3 (+), 46.2 (-), 41.5 (-), 39.7 (-) , 36.9 (+), 14.5 (+), 12.5 (+), 11.2 (+); FT IR (KBr, cm^{-1}): 3085, 2972, 2358, 1637, 1598, 1498, 1458, 1444, 1434, 1377, 1259, 1143, 1080, 831, 752, 696, 613; HRMS (TOF ES): found 350.2358, calculated for $C_{23}H_{30}N_2O$ (M-H) 350.2358 (0.0 ppm).

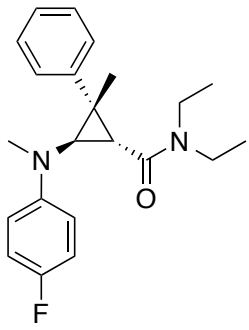


(1S,2S,3R)-N,N-diethyl-3-(ethyl(phenyl)amino)-2-methyl-2-(naphthalen-2-yl)cyclopropane-1-carboxamide (144gc): This compound was obtained according to a procedure B from 72 mg of bromocyclopropane **(-)-132ga** employing N-ethylaniline (75 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 30 mg (0.136 mmol, 68%) of the title compound as a white solid, R_f 0.31 (hexanes/EtOAc 6:1), dr 1:0. $[\alpha]_D$= +10.81° (c 0.074, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97–7.66 (m, 4H), 7.55–7.39 (m, 3H), 7.27–7.19 (m, 2H), 7.06–6.93 (m, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 5.18 (br. s, 1H), 3.71 (d, *J* = 4.4 Hz, 1H), 3.77–3.64 (m, 1H), 3.61–3.48 (m, 1H), 1.73 (d, *J* = 4.4 Hz, 1H), 1.61 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.10 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 149.2, 139.2, 133.6, 132.5, 129.2 (+, 2C), 128.3 (+), 127.9 (+), 127.8 (+), 126.9 (+), 126.8 (+), 126.2 (+), 125.8 (+), 118.3 (+), 116.0 (+), 51.3, 46.8 (+), 46.4 (-), 39.2 (+), 39.0, 28.8 (+, 3C), 21.9 (+), 11.2 (+); FT IR (KBr, cm^{-1}): 2968, 2358, 1645, 1595, 1531, 1498, 1454, 1366, 1255, 1188, 817, 742, 692; HRMS (TOF ES): found 399.2438, calculated for $C_{27}H_{31}N_2O$ (M-H) 399.2436 (1.0 ppm).



(1S,2S,3R)-N,N-diethyl-2-methyl-3-(methyl(phenyl)amino)-2-phenylcyclopropane-1-carboxamide (144aa):

This compound was obtained according to a procedure B from 62 mg of bromocyclopropane **(+)-132ac** employing N-methylaniline (65 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 36 mg (0.11 mmol, 55%) of the title compound as yellow oil, R_f 0.22 (hexanes/EtOAc 5:1), dr 3:1. $[\alpha]_D$= +33.1° (c 0.366, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.12 (m, 7H), 6.95 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 7.3 Hz, 3H), 3.78 (d, *J* = 4.4 Hz, 1H), 3.68–3.55 (m, 2H), 3.19 (dd, *J* = 14.7, 7.2 Hz, 1H), 3.11 (s, 3H), 2.94–2.79 (m, 1H), 1.97 (d, *J* = 4.4 Hz, 1H), 1.62 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 151.0, 141.0, 129.2 (+, 2C), 128.5 (+, 2C), 127.8 (+, 2C), 126.8 (+), 118.1, 114.8 (+, 2C), 48.5 (+), 41.6 (-), 40.4 (+), 39.8 (-), 38.3, 36.9 (+), 21.0 (+), 14.6 (+), 12.6 (+); FT IR (KBr, cm^{-1}): 2972, 2929, 1639, 1598, 1500, 1479, 1444, 1433, 1379, 1305, 1220, 1143, 1116, 1029, 950, 904, 698, 611; HRMS (TOF ES): found 337.2281, calculated for $C_{22}H_{29}N_2O$ (M+H) 3370.2280 (0.3 ppm).

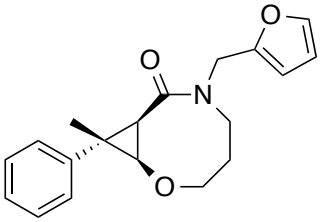


(1S,2S,3R)-N,N-diethyl-3-((4-fluorophenyl)(methyl)amino)-2-methyl-2-phenylcyclopropane-1-carboxamide (144ab):

This compound was obtained according to a procedure B from 62 mg of bromocyclopropane **(+)-132ac** employing 4-fluoro-

N-methylaniline (72 μL, 0.60 mmol, 3.00 equiv) as pronucleophile. The subsequent chromatographic purification afforded 42 mg (0.118 mmol, 59%) of the title compound as a yellow oil, R_f 0.25 (hexanes/EtOAc 4:1), dr 3:1. $[\alpha]_D$= +35.4° (c 0.362, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (m, 4H), 7.21 (ddd, *J* = 5.0, 4.5, 1.9 Hz, 1H), 7.00 – 6.84 (m, 4H), 3.71 (d, *J* = 4.4 Hz, 1H), 3.67–3.55 (m, 2H), 3.18 (dd, *J* = 14.7, 7.2 Hz, 1H), 3.08 (s, 3H), 2.85 (dd, *J* = 13.6, 7.0 Hz, 1H), 1.91 (d, *J* = 4.4 Hz, 1H), 1.62 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 157.2, 155.3, 147.5, 147.5, 140.8, 128.4 (+, 2C), 127.6 (+, 2C), 126.7 (+), 116.0 (+), 116.0 (+), 115.5 (+), 115.3 (+), 48.8 (+), 41.5 (-), 39.7 (-), 36.8(+), 20.8 (+), 14.4 (+), 12.5 (+); FT IR (KBr, cm^{-1}): 2974, 2873, 1635, 1510, 1479, 1458, 1446, 1379, 1263, 1224, 1143, 1022, 825, 763, 698; HRMS (TOF ES): found 353.2028, calculated for $C_{22}H_{26}FN_2O$ (M-H) 353.2029 (0.3 ppm).

3.10.9. Approach to Medium-Sized Rings via endo-trig Cyclization

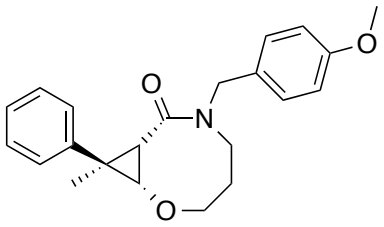


(1R,8R,9S)-6-(furan-2-ylmethyl)-9-methyl-9-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147i):

Typical procedure: A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in

vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-((furan-2-ylmethyl)amino)propan-1-ol (93 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-1-bromo-N-(furan-2-ylmethyl)-N-(3-hydroxypropyl)-2-methyl-2-phenylcyclopropane-1-carboxamide **145i** as a colorless oil. Yield 136 mg (0.345 mmol, 69%), R_f 0.30 (hexanes/EtOAc 1:1). The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (136 mg, 0.345 mmol, 1.0 equiv.), 18-crown‐6 (9.1 mg, 34 μmol, 10 mol%), *t*-BuOK (232 mg, 2.07 mmol, 6.00 equiv), and anhydrous DMSO (8.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil R_f 0.31 (hexanes/EtOAc 2:1). Yield 86 mg (0.276 mmol 80%), dr 1:0. $[\alpha]_D$= -28.5° (c 0.280, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (ddd, *J* = 5.1, 2.6, 1.1 Hz, 3H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.25–7.08 (m, 1H), 6.33 (dt, *J* = 9.4, 2.5 Hz, 2H), 4.95 (d, *J* = 15.2 Hz, 1H), 4.23 (d, J = 15.2 Hz, 1H), 4.20 (dd, J = 12.1, 4.6 Hz, 1H), 4.04 (dd, J = 15.5, 10.4 Hz,

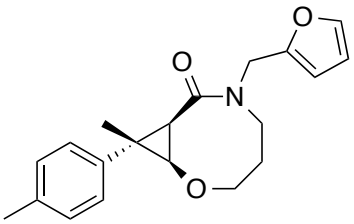
1H), 3.73 (td, *J* = 12.7, 3.1 Hz, 1H), 3.62 (d, *J* = 6.3 Hz, 1H), 3.42 (dd, *J* = 15.5, 7.2 Hz, 1H), 1.97–1.89 (m, 1H), 1.88 (d, *J* = 6.2 Hz, 1H), 1.77–1.57 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 151.4, 146.0, 142.2 (+), 128.6 (+, 2C), 127.9 (+, 2C), 126.5 (+), 110.6 (+), 108.7 (+), 72.8 (-), 68.5 (+), 46.9 (-), 42.0 (-), 31.3 (+), 30.7 (-), 30.1, 17.9 (+); FT IR (KBr, cm^{-1}): 2963, 2927, 1637, 1473, 1436, 1425, 1261, 1149, 1012, 761, 702; HRMS (TOF ES): found 311.1521, calculated for $C_{19}H_{21}NO_3$ (M+) 311.1521 (0.3 ppm).



(1S,8S,9R)-6-(4-methoxybenzyl)-9-methyl-9-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147h):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3 3-((4-methoxybenzyl)amino)propan-1-ol (117mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20

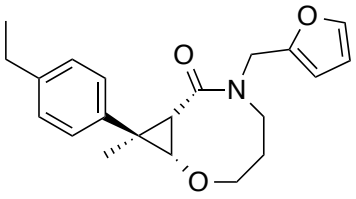
mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1R,2S)-1-bromo-N-(3-hydroxypropyl)-N-(4-methoxybenzyl)-2-methyl-2-phenylcyclopropane-1-carboxamide **145h** as a colorless oil. Yield 113 mg (0.260 mmol, 52%), R_f 0.23 (hexanes/EtOAc 1:1) The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (113 mg, 0.46 mmol, 1.0 equiv.), 18-crown‐6 (6.8 mg, 26 μmol, 10 mol%), *t*-BuOK (174 mg, 2.07 mmol, 6.00 equiv), and anhydrous DMSO (6.0 mL). The reaction mixture was stirred overnight at 40 ^oC, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.33 (hexanes/EtOAc 2:1). Yield 59 mg (0.169 mmol 65%), dr 1:0. $[\alpha]_D$= -28.5° (c 0.280, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.34–7.24 (m, 4H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.14 (d, *J* = 14.5 Hz, 1H), 4.21 (dd, *J* = 12.6, 5.2 Hz, 1H), 3.98 (d, *J* = 14.5 Hz, 1H), 4.00–3.90 (m, 1H), 3.80 (s, 3H), 3.72 (td, *J* = 12.7, 3.0 Hz, 1H), 3.63 (d, *J* = 6.3 Hz, 1H), 3.25 (dd, *J* = 15.4, 7.1 Hz, 1H), 1.98 (dd, *J* = 7.6, 5.1 Hz, 1H), 1.91 (d, *J* = 6.3 Hz, 1H), 1.70–1.57 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 159.1, 146.1, 129.9, 129.8 (+, 2C), 128.6 (+, 2C), 127.9 (+, 2C), 126.5 (+), 114.1 (+, 2C), 72.8 (-), 68.5 (+), 55.4 (+), 48.3 (-), 46.2 (-), 31.5 (+), 30.6 (-), 30.1 (+), 17.9 (+); FT IR (KBr, cm^{-1}): 3406, 1631, 1512, 1477, 1440, 1245, 1222, 927, 883, 815, 802, 761,702, 630, 609; HRMS (TOF ES): found 350.1759, calculated for $C_{19}H_{21}NO_3$ (M+) 350.1756 (0.3 ppm).



(1R,8R,9S)-6-(furan-2-ylmethyl)-9-methyl-9-(p-tolyl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147g):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(-)-132b** (134.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-((furan-2-ylmethyl)amino)propan-1-ol (93 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-1-bromo-N-(furan-2-ylmethyl)-N-(3-hydroxypropyl)-2-methyl-2-(p-tolyl)cyclopropane-1-carboxamide **145g** as a colorless oil. Yield 82 mg (0.20 mmol, 40%), R_f 0.25 (hexanes/EtOAc 2:1) The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (82 mg, 0.20 mmol, 1.0 equiv.), 18-crown‐6 (5.38 mg, 20 μmol, 10 mol%), *t*-BuOK (134 mg, 1.2 mmol, 6.00 equiv), and anhydrous DMSO (5.0 mL). The reaction mixture was stirred

overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.4 (hexanes/EtOAc 2:1). Yield 54 mg (0.166 mmol 83%), dr 1:0. $[\alpha]_D$= -26.8° (c 0.340, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.12 (m, 3H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.33–5.89 (m, 2H), 4.85 (d, *J* = 15.2 Hz, 1H), 4.12 (d, *J* = 15.3 Hz, 1H), 4.10 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.93 (dd, *J* = 15.5, 10.4 Hz, 1H), 3.62 (td, *J* = 12.7, 3.1 Hz, 1H), 3.50 (d, *J* = 6.2 Hz, 1H), 3.32 (dd, *J* = 15.5, 7.1 Hz, 1H), 2.21 (s, 3H), 1.82 (ddd, *J* = 11.7, 4.8, 2.2 Hz, 1H), 1.75 (d, *J* = 6.2 Hz, 1H), 1.63–1.44 (m, H), 1.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 151.4, 143.2, 142.2(+), 136.2, 129.3 (+, 2C), 127.8 (+, 2C), 110.6 (+), 108.8 (+), 72.8 (-), 68.6 (+), 46.9 (-), 42.0 (-), 31.3 (+), 30.7 (-), 21.1 (+), 18.0 (+); FT IR (KBr, cm^{-1}): 3386, 1639, 1477, 1421, 1380, 929, 883, 817, 779, 723, 703, 665, 648, 626, 599; HRMS (TOF ES): found 326.1762, calculated for $C_{20}H_{24}NO_3$ (M+H) 326.1756 (1.8 ppm).

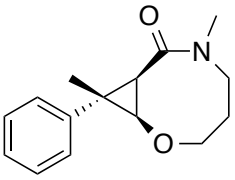


(1S,8S,9R)-9-(4-ethylphenyl)-6-(furan-2-ylmethyl)-9-methyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147j):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(-)-136d** (141.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL,

0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-((furan-2-ylmethyl)amino)propan-1-ol (93 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1R,2S)-1-bromo-2-(4-ethylphenyl)-N-(furan-2-ylmethyl)-N-(3-hydroxypropyl)-2-methylcyclopropane-1-carboxamide **145j** as a colorless oil. Yield 138 mg (0.33 mmol, 65%), R_f 0.36 (hexanes/EtOAc 2:1) The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (138 mg, 0.33 mmol, 1.0 equiv.), 18-crown‐6 (9.7 mg, 33 μmol, 10 mol%), *t*-BuOK (221 mg, 1.98 mmol, 6.00 equiv), and anhydrous DMSO (7.0 mL). The reaction mixture was stirred overnight at 40 ^oC, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.48 (hexanes/EtOAc 2:1). Yield 106 mg (0.310 mmol 94%), dr 1:0. $[\alpha]_D$= +30.0° (c 0.400, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.39–6.26

(m, 2H), 4.95 (d, J = 15.2 Hz, 1H), 4.23 (d, J = 15.3 Hz, 1H), 4.20 (dd, J = 13.6, 4.1 Hz, 1H), 4.03 (dd, J = 15.5, 10.4 Hz, 1H), 3.72 (td, J = 12.7, 3.1 Hz, 1H), 3.60 (d, J = 6.2 Hz, 1H), 3.42 (dd, J = 15.5, 7.1 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.00–1.87 (m, 1H), 1.87 (d, J = 6.2 Hz, 1H), 1.71–1.60 (m, 1H), 1.46 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 151.4, 143.3 (+), 142.5, 142.2, 128.1 (+, 2C), 127.9 (+, 2C), 110.6 (+), 108.7 (+), 72.8 (-), 68.6 (+), 46.9 (-), 42.0 (-), 31.3 (+), 30.7 (-), 29.8, 28.5 (-), 18.0 (+), 15.7 (+); FT IR (KBr, cm^{-1}): 2962, 2931, 2871, 2079, 1992, 1643, 1633, 1514, 1477, 1421, 1380, 1353, 1336, 1301, 1263, 1242, 1211, 1147, 1108, 1089, 1012, 931, 883, 831, 813, 779, 732, 702, 665, 646, 624, 599; HRMS (TOF ES): found 339.1835, calculated for $C_{21}H_{25}NO_3$ (M+) 339.1834 (0.3 ppm). .

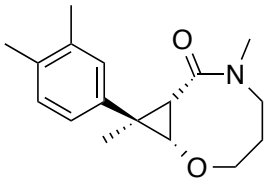


(1R,8R,9S)-6,9-dimethyl-9-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147l):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-methylamino-1-propanol (57 μL, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic

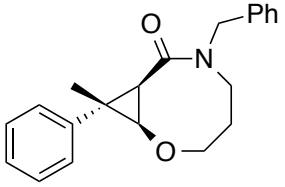
phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-1-bromo-N-(3-hydroxypropyl)-N,2-dimethyl-2-phenylcyclopropane-1-carboxamide **145l** as a colorless oil. Yield 90 mg (0.27 mmol, 52%), R_f 0.22 (hexanes/EtOAc 1:1). The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (90 mg, 0.27 mmol, 1.0 equiv.), 18-crown‐6 (7.1 mg, 27 μmol, 10 mol%), *t*-BuOK (201 mg, 1.8 mmol, 6.00 equiv), and anhydrous DMSO (7.0 mL). The reaction mixture was stirred overnight at 40 ^oC, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.44 (CH_2Cl_2/MeOH 10:1). Yield 41 mg (0.165 mmol 61%), dr 1:0. $[\alpha]_D$= +3.2° (c 0.380, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.34 (m, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.22–7.10 (m, 1H), 4.35–4.07 (m, 2H), 3.74 (td, *J* = 12.7, 3.2 Hz, 1H), 3.61 (d, *J* = 6.3 Hz, 1H), 3.19 (dd, *J* = 15.3, 7.2 Hz, 1H), 2.99 (s, 3H), 2.12–1.98 (m, 1H), 1.87 (d, *J* = 6.2 Hz, 1H), 1.76–1.63 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 146.1, 128.6 (+, 2C), 127.8 (+, 2C), 126.5 (+), 72.7 (-), 68.5 (+), 49.5(-), 33.7 (+), 31.3 (+), 30.4 (-), 30.0, 17.8 (+); FT IR (KBr, cm^{-1}): 2958, 2929, 1633, 1494, 1456, 1444, 1400, 1380, 1352, 1294, 1263, 1218, 1151, 1130, 1091, 1064, 1024, 1010, 931, 763, 702, 684.; HRMS (TOF ES): found 244.1340, calculated for $C_{15}H_{18}NO_2$ (M-H) 244.1338 (0.8 ppm).

(1S,8S,9R)-9-(3,4-dimethylphenyl)-6,9-dimethyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147n):



A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(-)-136c** (141.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-methylamino-1-propanol (57 μL, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1R,2S)-1-bromo-2-(3,4-dimethylphenyl)-N-(3-hydroxypropyl)-N,2-dimethylcyclopropane-1-carboxamide **145n** as a colorless oil. Yield 92 mg (0.26 mmol, 52%), R_f 0.33 (hexanes/EtOAc 1:1) The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (92 mg, 0.26 mmol, 1.0 equiv.), 18-crown‐6 (6.8 mg, 26 μmol, 10 mol%), *t*-BuOK (174 mg, 1.56 mmol, 6.00 equiv), and anhydrous DMSO (7.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned

between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.40 (CH_2Cl_2/MeOH 10:1). Yield 48 mg (0.174 mmol 67%), dr 1:0. $[\alpha]_D$= +7.5° (c 0.320, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 4.41–4.06 (m, 2H), 3.73 (td, *J* = 12.7, 3.2 Hz, 1H), 3.58 (d, *J* = 6.2 Hz, 1H), 3.19 (dd, *J* = 15.3, 7.2 Hz, 1H), 2.99 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 2.10–1.99 (m, 1H), 1.84 (d, *J* = 6.3 Hz, 1H), 1.74–1.63 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 143.7, 136.8, 134.8, 129.9 (+), 129.3 (+), 125.2 (+), 72.7 (-), 68.6 (+), 49.5 (-), 33.7 (+), 31.2 (+), 30.4 (-), 29.7, 19.8 (+), 19.4 (+), 17.9 (+) ;FT IR (KBr, cm^{-1}): 2960, 2933, 2869, 2071, 1633, 1502, 1487, 1454, 1434, 1398, 1382, 1292, 1261, 1222, 1124, 1089, 1022 , 929, 873, 819, 783, 717, 705, 634, 595; HRMS (TOF ES): found 273.1730, calculated for $C_{17}H_{23}NO_2$ (M+) 273. 1730 (0.4 ppm).

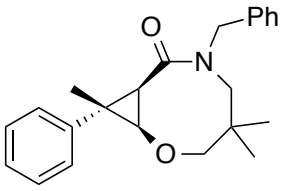


(1R,8R,9S)-6-benzyl-9-methyl-9-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147b):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution

of 3-(benzylamino)propan-1-ol (99 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-N-benzyl-1-bromo-N-(3-hydroxypropyl)-2-methyl-2-phenylcyclopropane-1-carboxamide **145b** as a colorless oil. Yield 110 mg (0.27 mmol, 54%), R_f 0.28 (hexanes/EtOAc 2:1). The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (110 mg, 0.27 mmol, 1.0 equiv.), 18-crown‐6 (7.1 mg, 27 μmol, 10 mol%), *t*-BuOK (183 mg, 1.62 mmol, 6.00 equiv), and anhydrous DMSO (7.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.34 (hexanes/EtOAc 3:1). Yield 74 mg (0.229 mmol 85%), dr 1:0. $[\alpha]_D$= -88.2° (c 0.660, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.07 (m, 10H), 5.16 (d, *J* = 14.7 Hz, 1H), 4.15 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.97 (d, *J* = 14.7 Hz, 1H), 3.98–3.89 (m, 1H), 3.67 (td, *J* = 12.7, 3.1 Hz, 1H), 3.58 (d, *J* = 6.3 Hz, 1H), 3.19 (dd, *J* = 15.5, 7.2 Hz, 1H), 1.99–1.89 (m, 1H), 1.87 (d, *J* = 6.3 Hz, 1H), 1.57 (ddd, *J* = 9.2, 6.6, 2.0 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 146.0, 137.8, 128.7 (+, 2C),

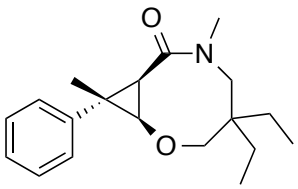
128.6 (+, 2C), 128.4 (+, 2C), 127.9 (+, 2C), 127.5 (+), 126.5 (+), 72.7 (-), 68.5 (+), 48.9 (-), 46.4 (-), 31.4 (+), 30.6 (-), 30.1, 17.9 (+); FT IR (KBr, cm^{-1}): 3031, 1635, 1477, 1419, 1263, 1147, 1110, 1091, 1014, 933, 916, 883, 761, 730, 700, 617; HRMS (TOF ES): found 321.1720, calculated for $C_{21}H_{23}NO_2$ (M+) 321.1729 (2.8 ppm).



(1R,8R,9S)-6-benzyl-9-methyl-9-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147e):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-(benzylamino)-2,2-dimethylpropan-1-ol (116 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-N-benzyl-1-bromo-N-(3-hydroxy-2,2-dimethylpropyl)-2-methyl-2-phenylcyclopropane-1-

carboxamide **145e** as a colorless oil. Yield 90 mg (0.209 mmol, 54%), R_f 0.26 (hexanes/EtOAc 5:1). The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (90 mg, 0.209 mmol, 1.0 equiv.), 18-crown ‑ 6 (5.5 mg, 21 μmol, 10 mol%), *t*-BuOK (140 mg, 1.25 mmol, 6.00 equiv), and anhydrous DMSO (6.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.36 (hexanes/EtOAc 5:1). Yield 27 mg (0.077 mmol 37%), dr 1:0. $[\alpha]_D$= -150.8° (c 0.240, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–6.98 (m, 10H), 5.58 (d, *J* = 14.9 Hz, 1H), 3.88 (d, *J* = 15.6 Hz, 1H), 3.64 (dd, *J* = 19.1, 8.0 Hz, 2H), 3.59–3.48 (m, 1H), 3.41 (d, *J* = 12.3 Hz, 1H), 2.83 (d, *J* = 15.6 Hz, 1H), 1.99–1.69 (m, 1H), 1.44 (s, 3H), 1.14 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 145.8, 137.6, 128.7 (+, 2C), 128.6 (+, 2C), 128.2 (+, 2C), 127.8 (+, 2C), 127.5 (+), 126.5 (+), 84.6 (-), 68.6 (+), 56.1 (-), 51.6 (-), 38.2, 31.6 (+), 29.3, 25.3(+), 23.0(+), 17.9 (+); FT IR (KBr, cm^{-1}): 3388, 2088, 1643, 1633, 1556, 1519, 1473, 1421, 1394, 1355, 1282, 1265, 1249, 1228, 1207, 1143, 1093, 1081, 1062, 1027, 993, 700; HRMS (TOF ES): found 348.1963, calculated for $C_{23}H_{26}NO_2$ (M-H) 348.1964 (0.3 ppm).

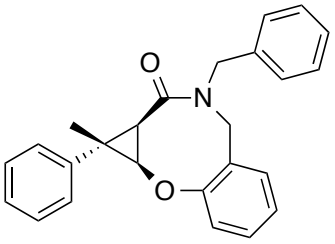


(1R,8R,9S)-6-benzyl-9-methyl-9-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147f):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-

phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution 2-ethyl-2-((methylamino)methyl)butan-1-ol (87 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-1-bromo-N-(2-ethyl-2-(hydroxymethyl)butyl)-N,2-dimethyl-2-phenylcyclopropane-1-carboxamide **145f** as a colorless oil. Yield 168 mg (0.44 mmol, 88%), R_f 0.34 (hexanes/EtOAc 5:1). The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (168 mg, 0.44 mmol, 1.0 equiv.), 18-crown‐6 (11 mg, 44 μmol, 10 mol%), *t*-BuOK (299 mg, 2.64 mmol, 6.00 equiv), and anhydrous DMSO (10.0 mL). The reaction mixture was stirred overnight at 40 ^oC, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.22 (hexanes/EtOAc 5:1). Yield 41 mg (0.136

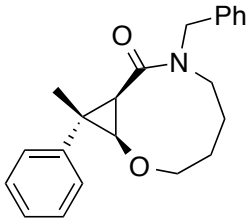
mmol 31%), dr 3:1. $[\alpha]_D$= -8.6° (c 0.30, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.22 (dd, *J* = 10.7, 4.6 Hz, 2H), 7.15–7.09 (m, 1H), 4.03 (d, *J* = 15.4 Hz, 1H), 3.90 (dd, *J* = 12.6, 1.8 Hz, 1H), 3.54 (d, *J* = 6.2 Hz, 1H), 3.22 (dd, *J* = 12.6, 0.9 Hz, 1H), 2.95 (s, 3H), 2.88 (dd, *J* = 15.4, 1.9 Hz, 1H), 1.76 (d, *J* = 6.2 Hz, 1H), 1.61 (ddd, *J* = 20.2, 13.8, 6.3 Hz, 1H), 1.37 (s, 3H), 1.32–1.24 (m, 1H), 1.06 (dt, *J* = 14.8, 7.4 Hz, 1H), 0.97 (ddd, *J* = 21.5, 11.2, 5.0 Hz, 1H), 0.80 (td, *J* = 7.4, 2.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 146.0, 128.6 (+, 2C), 127.9 (+, 2C), 126.5 (+), 78.9 (-), 68.6 (+), 58.2 (-), 42.8, 38.4 (+), 31.4 (+), 25.4 (-), 22.3 (-), 17.8, 7.6 (+), 6.9 (+); FT IR (KBr, cm^{-1}): 2964, 2933, 2088, 1633, 1382, 1271, 1242, 1195, 1143, 869, 796, 761, 700, 648, 615; HRMS (TOF ES): found 301.2041, calculated for $C_{19}H_{27}NO_2$ (M+) 301.2042 (0.3 ppm).



(1S,1aR,9aR)-3-benzyl-1-methyl-1-phenyl-1a,3,4,9a-tetrahydrobenzo[b]cyclopropa[g][1,5]oxazocin-2(1H)-one (147o):

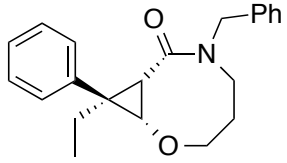
A solution of Me_3SiCl (76.5 µL, 0.6 mmol, 1.20 equiv), NEt_3 (244 µL, 1.75 mmol, 3.5 equiv), and 2-((benzylamino)methyl)phenol (98 mg, 0.55 mmol, 1.10 equiv) was stirred in dry THF (10 mL) overnight under a nitrogen atmosphere. Then 2-bromocyclopropanecarbonyl chloride obtained according to a typical protocol from 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 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 which afforded (1S,2R)-N-benzyl-1-bromo-N-(2-

hydroxybenzyl)-2-methyl-2-phenylcyclopropane-1-carboxamide **145o** as a viscous oil R_f 0.5 (hexanes/EtOAc 5:1). The obtained material was pure enough for the following transformation with no additional purification. Yield 191 mg (0.46 mmol, 92%). An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (191 mg, 0.46 mmol, 1.0 equiv.), 18-crown‐6 (12 mg, 46 μmol, 10 mol%), *t*-BuOK (309 mg, 2.76 mmol, 6.00 equiv), and anhydrous DMSO (10.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.28 (hexanes/EtOAc 5:1). Yield 88 mg (0.244 mmol 31%), dr 1:0. $[\alpha]_D$= -229.7° (c 0.40, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.39–7.20 (m, 9H), 7.12 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.05–6.93 (m, 2H), 5.45 (d, *J* = 16.4 Hz, 1H), 5.17 (d, *J* = 14.7 Hz, 1H), 4.00 (d, *J* = 6.0 Hz, 1H), 3.81 (dd, *J* = 29.3, 15.6 Hz, 2H), 2.44 (d, *J* = 5.9 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 157.1, 145.3, 137.4, 131.3 (+), 129.5 (+), 128.8 (+, 2C), 128.7 (+, 2C), 128.6 (+, 2C), 128.0 (+, 2C), 127.6 (+), 126.9 (+), 125.9, 123.3 (+), 121.7 (+), 63.7 (+), 50.0 (-), 47.9 (-), 32.0 (+), 30.7, 16.9 (+); FT IR (KBr, cm^{-1}): 2972, 1649, 1604, 1488, 1429, 1269, 1224, 1209, 858, 823, 796, 761, 736, 700, 648, 617; HRMS (TOF ES): found 369.1731, calculated for $C_{25}H_{23}NO_2$ (M+) 369.1729 (0.5 ppm).



(1R,9R,10S)-7-benzyl-10-methyl-10-phenyl-2-oxa-7-azabicyclo[7.1.0]decan-8-one (147c): A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136a** (127.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution 4-(benzylamino)butan-1-ol (107 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-N-benzyl-1-bromo-N-(4-hydroxybutyl)-2-methyl-2-phenylcyclopropane-1-carboxamide **145c** as a colorless oil. Yield 155 mg (0.37 mmol, 74%), R_f 0.37 (hexanes/EtOAc 1:1). The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (155 mg, 0.37 mmol, 1.0 equiv.), 18-crown‐6 (10 mg, 37 μmol, 10 mol%), *t*-BuOK (250 mg, 2.22 mmol, 6.00 equiv), and anhydrous DMSO (10.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and

was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.36 (hexanes/EtOAc 3:1). Yield 26 mg (0.077 mmol 21%), dr 1:0. $[\alpha]_D$= -27.7° (c 0.36, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 6.94 (m, 10H), 5.35 (d, *J* = 14.7 Hz, 1H), 4.29 (dd, *J* = 12.8, 7.5 Hz, 1H), 4.23–4.11 (m, 1H), 3.86 (d, *J* = 14.7 Hz, 1H), 3.52 (d, *J* = 6.4 Hz, 1H), 3.42 (ddd, *J* = 12.8, 7.8, 1.0 Hz, 1H), 3.17 (ddd, *J* = 14.8, 4.9, 1.7 Hz, 1H), 1.96 (d, *J* = 6.4 Hz, 1H), 2.00–1.87 (m, 1H), 1.81 (ddd, *J* = 15.0, 7.3, 3.6 Hz, 1H), 1.61 (s, 3H), 1.59–1.49 (m, 1H), 1.46–1.33 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 146.6, 137.7, 128.7 (+, 2C), 128.6 (+, 2C), 128.5 (+, 2C), 127.9 (+, 2C), 127.4 (+), 126.5 (+), 72.2 (-), 66.7 (+), 45.8 (-), 43.5 (-), 31.4 (+), 29.9, 27.6 (-), 25.0 (-), 17.3 (+); FT IR (KBr, cm^{-1}): 2927, 1643, 1633, 1444, 1429, 1151, 1091, 810, 763, 734, 700, 648, 599, 559; HRMS (TOF ES): found 334.1807, calculated for $C_{22}H_{24}NO_2$ (M-H) 334.1807 (1.5 ppm).

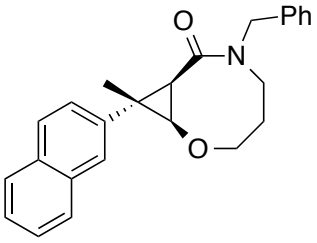


(1S,8S,9R)-6-benzyl-9-ethyl-9-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147k):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(-)-136f** (134.5 mg, 0.50 mmol, 1.00 equiv), DMF (3 drops) and 10 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (65 μL, 0.75 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-

(benzylamino)propan-1-ol (99 mg, 0.6 mmol, 1.20 equiv) and triethyl amine (209 μL, 1.50 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1R,2S)-N-benzyl-1-bromo-2-ethyl-N-(3-hydroxypropyl)-2-phenylcyclopropane-1-carboxamide **145k** as a colorless oil. Yield 200 mg (0.48 mmol, 96%), R_f 0.30 (hexanes/EtOAc 2:1). The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (200 mg, 0.48 mmol, 1.0 equiv.), 18-crown - 6 (12.7 mg, 48 μmol, 10 mol%), *t*-BuOK (324 mg, 2.88 mmol, 6.00 equiv), and anhydrous DMSO (10.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.38 (hexanes/EtOAc 3:1). Yield 127 mg (0.379 mmol 79%), dr 1:0. $[\alpha]_D$= +9.1° (c 0.780, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.04 (m, 10H), 5.28 (d, *J* = 14.7 Hz, 1H), 4.23 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.99 (d, *J* = 14.8 Hz, 1H), 3.99–3.92 (m, 1H), 3.77–3.62 (m, 2H), 3.23 (dd, *J* = 15.5, 7.2 Hz, 1H), 2.12–1.93 (m, 2H), 1.88 (d, *J* = 6.2 Hz, 1H), 1.77 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.64 (ddd, *J* = 15.0, 6.6, 1.9 Hz, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 143.9, 137.8, 129.4 (+,

2C), 128.7 (+, 2C), 128.4 (+, 2C), 128.4 (+, 2C), 127.5 (+), 126.6 (+), 72.9 (-), 68.3 (+), 48.8 (-), 46.3 (-), 35.2, 32.4 (+), 30.6 (-), 24.9 (-), 11.4 (+); FT IR (KBr, cm^{-1}): 3056, 2966, 2935, 1633, 1477, 1421, 1357, 1265, 1247, 1357, 1265, 1247, 1220, 114, 1105, 1014, 935, 887, 763, 736, 702, 682, 659, 617, 595; HRMS (TOF ES): found 335.1891, calculated for $C_{22}H_{25}NO_2$ (M+) 335.1885 (1.8 ppm).



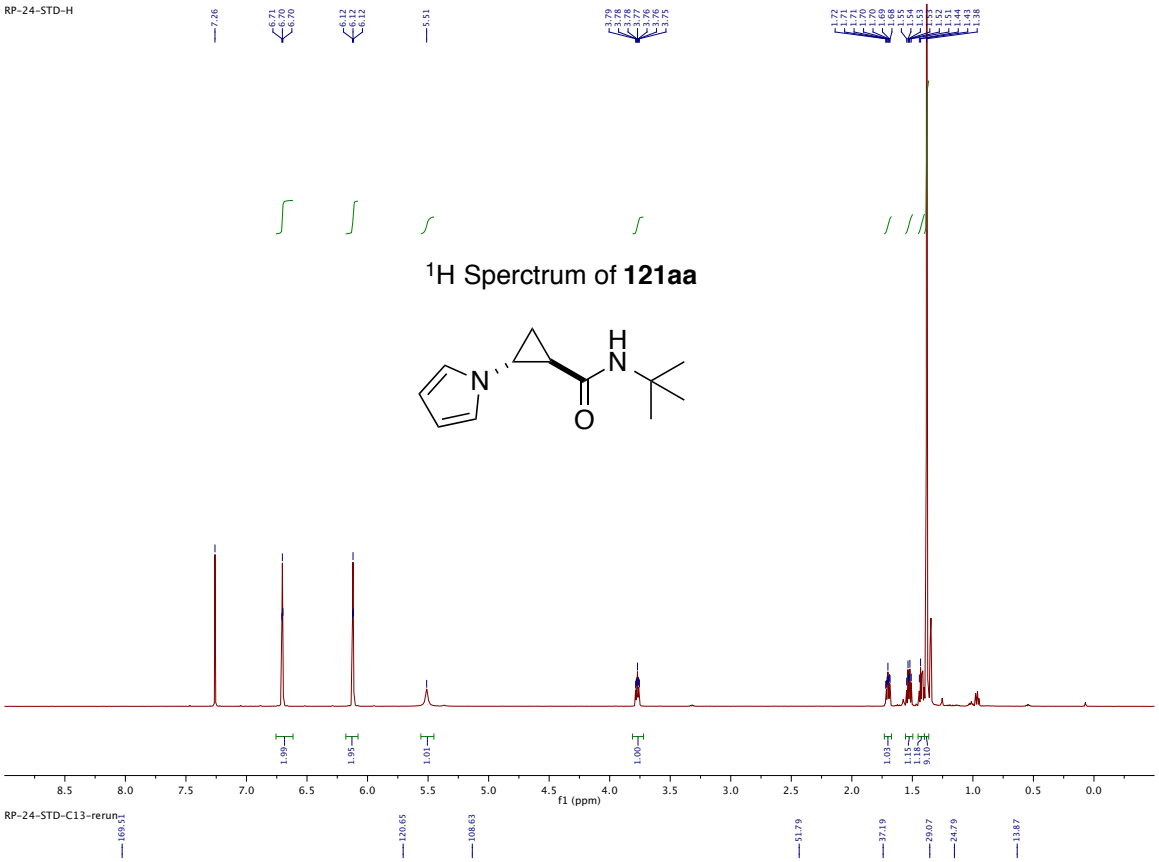
(1R,8R,9S)-6-benzyl-9-methyl-9-(naphthalen-2-yl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (147m):

A flame dried 25 mL round-bottom flask equipped with a drying tube and magnetic stir bar was charged with 1-bromo-2-methyl-2-phenylcyclopropanecarboxylic acid **(+)-136g** (88 mg, 0.20 mmol, 1.00 equiv), DMF (3 drops) and 3 mL of CH_2Cl_2. The mixture was then treated with oxalyl chloride (26 μL, 0.30 mmol, 1.5 equiv) at 0℃, stirred for 15 min, then warmed to room temperature and additionally stirred for 2 hours. The solvent was then removed in vacuum and the crude acyl chloride was dissolved in 10 mL of dry THF and added dropwise to a solution of 3-(benzylamino)propan-1-ol (40 mg, 0.24 mmol, 1.20 equiv) and triethyl amine (84 μL, 0.60 mmol, 3.00 equiv.) in 10 mL of THF. The reaction mixture was stirred overnight. After the reaction was complete, the solvent was removed in vacuum and the resulting residue was partitioned between 10 mL of EtOAc and 10 mL of water. The organic phase was separated; the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was filtered through a short plug of Silica gel, eluting with EtOAc to afford (1S,2R)-N-benzyl-1-bromo-N-(3-hydroxypropyl)-2-methyl-2-(naphthalen-2-yl)cyclopropane-1-carboxamide **145m** as a colorless oil. Yield 70 mg (0.155 mmol, 78%), R_f 0.28 (hexanes/EtOAc 3:1).

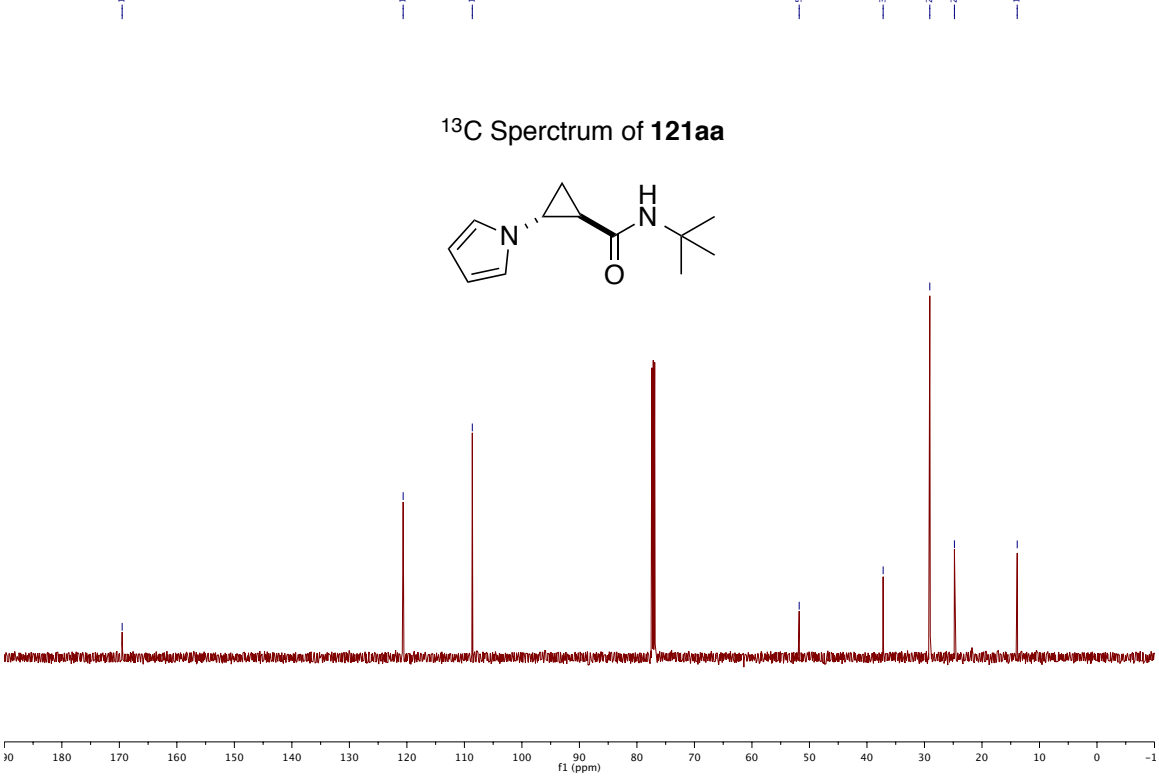
The crude material was used without further purification. An oven-dried 10 mL Weaton vial was charged with obtained bromocyclopropane (70 mg, 0.155 mmol, 1.0 equiv.), 18-crown‐6 (4.1 mg, 48 μmol, 10 mol%), *t*-BuOK (113 mg, 2.88 mmol, 6.00 equiv), and anhydrous DMSO (4.0 mL). The reaction mixture was stirred overnight at 40 ^{o}C, and then the reaction mixture was poured into a separatory funnel and was partitioned between 10 mL of water and 100 mL of ethyl acetate. Organic layers were washed with water (3 x 10 mL) and brine (10 mL). Organic extract was dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on Silica gel afforded the title compound as a colorless oil. R_f 0.27 (hexanes/EtOAc 3:1). Yield 28 mg (0.076 mmol 49%), dr 1:0. $[\alpha]_D$= +25.8° (c 0.60, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 7.8, 7.1, 2.0 Hz, 4H), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.51–7.41 (m, 2H), 7.35 (d, *J* = 4.4 Hz, 4H), 7.32–7.27 (m, 1H), 5.27 (dd, *J* = 14.7, 0.7 Hz, 1H), 4.25 (dd, *J* = 12.6, 5.2 Hz, 1H), 4.05 (d, *J* = 14.8 Hz, 1H), 4.06–3.98 (m, 1H), 3.78 (dd, *J* = 12.7, 3.1 Hz, 1H), 3.74 (d, *J* = 6.3 Hz, 1H), 3.27 (dd, *J* = 15.5, 7.2 Hz, 1H), 2.05 (d, *J* = 6.2 Hz, 1H), 2.04 (dd, *J* = 10.4, 7.6 Hz, 1H), 1.66 (ddd, *J* = 13.2, 5.6, 1.8 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 143.4, 137.8, 133.6, 132.3, 128.7 (+, 2C), 128.5 (+, 2C), 127.8 (+), 127.7 (+), 127.5 (+), 126.6 (+), 126.2 (+), 125.8 (+), 72.8 (-), 68.5 (+), 49.0 (-), 46.5 (-), 31.5 , 30.6 (+), 30.4 (-), 17.9 (+); FT IR (KBr, cm^{-1}): 3058, 1633, 1475, 1421, 1261, 858, 819, 748, 734, 702, 676, 659, 648, 609; HRMS (TOF ES): found 372.1966, calculated for $C_{25}H_{26}NO_2$ (M+H) 372.1964 (0.5 ppm).

Appendix

A1. ^{1}H and ^{13}C Specta for 121aa

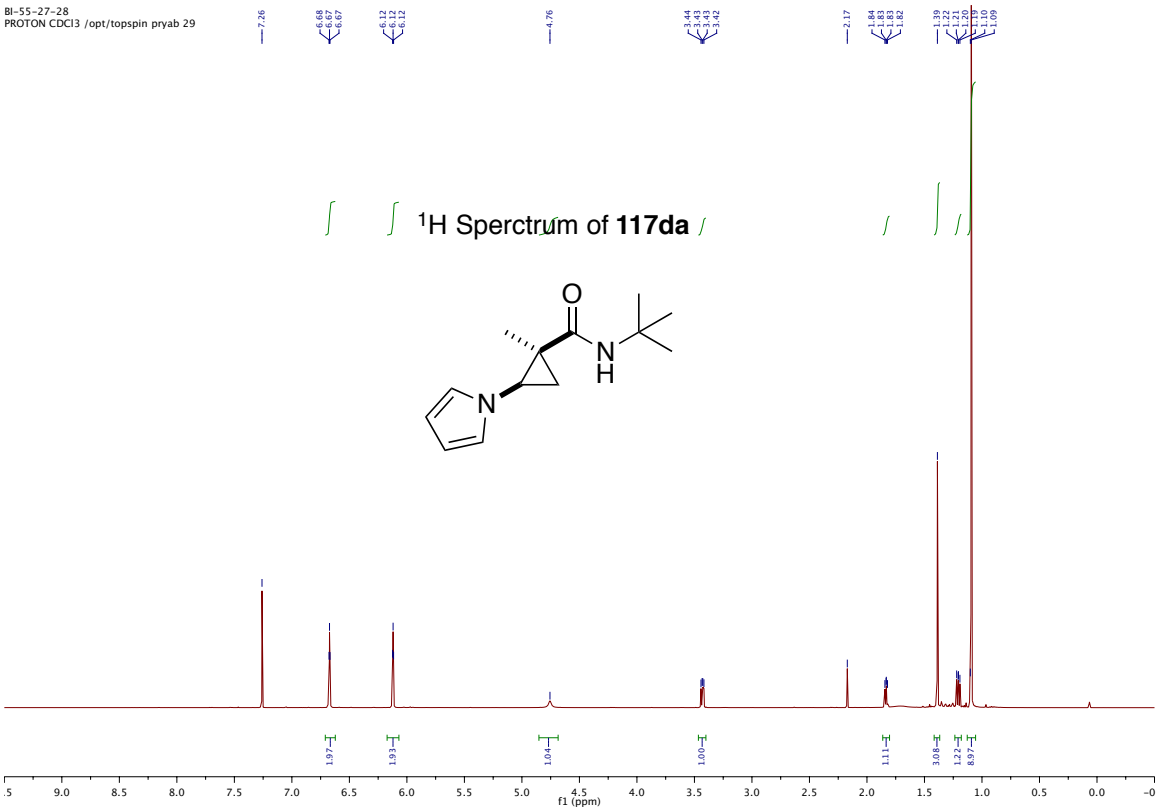


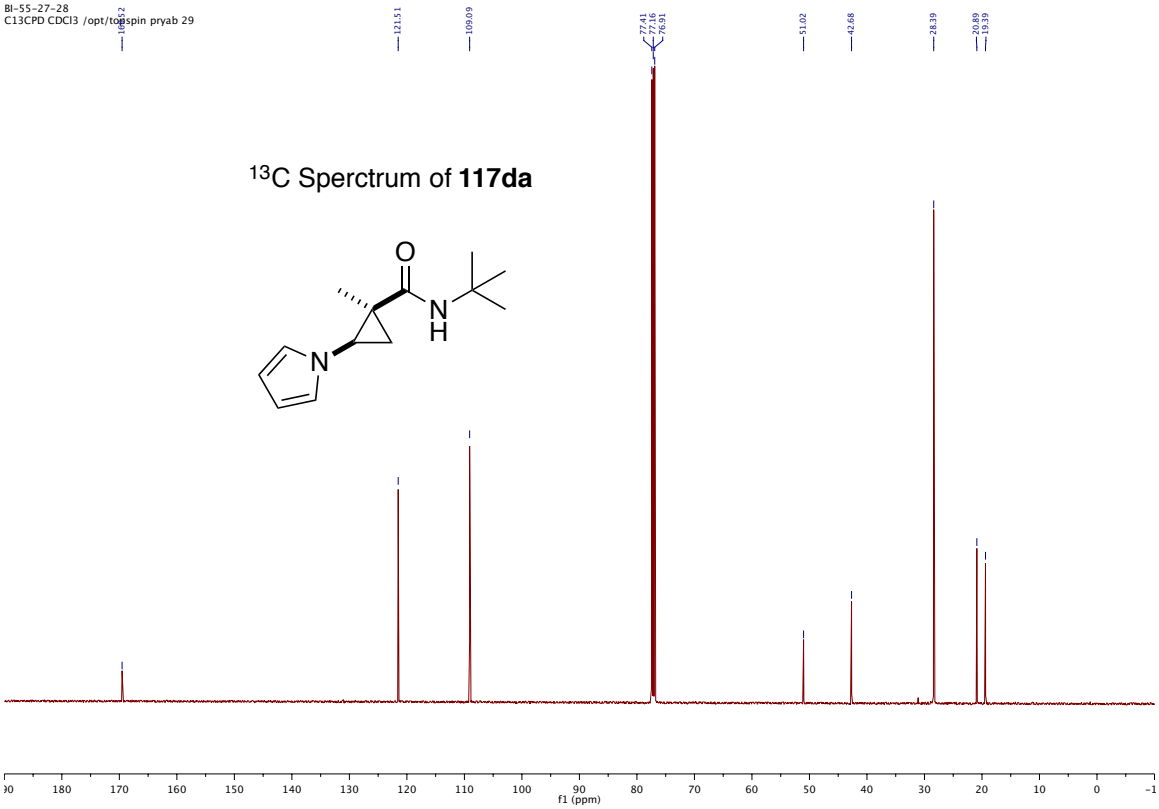
^{1}H Sperctrum of **121aa**



^{13}C Sperctrum of **121aa**

A2. ^{1}H and ^{13}C Specta for 117da





A3. NOE Data for 117da

Figure 8. 1D NOEDIFF spectra of xx. Chemical shifts of the irradiated multiplets are listed at the right side of each chart.

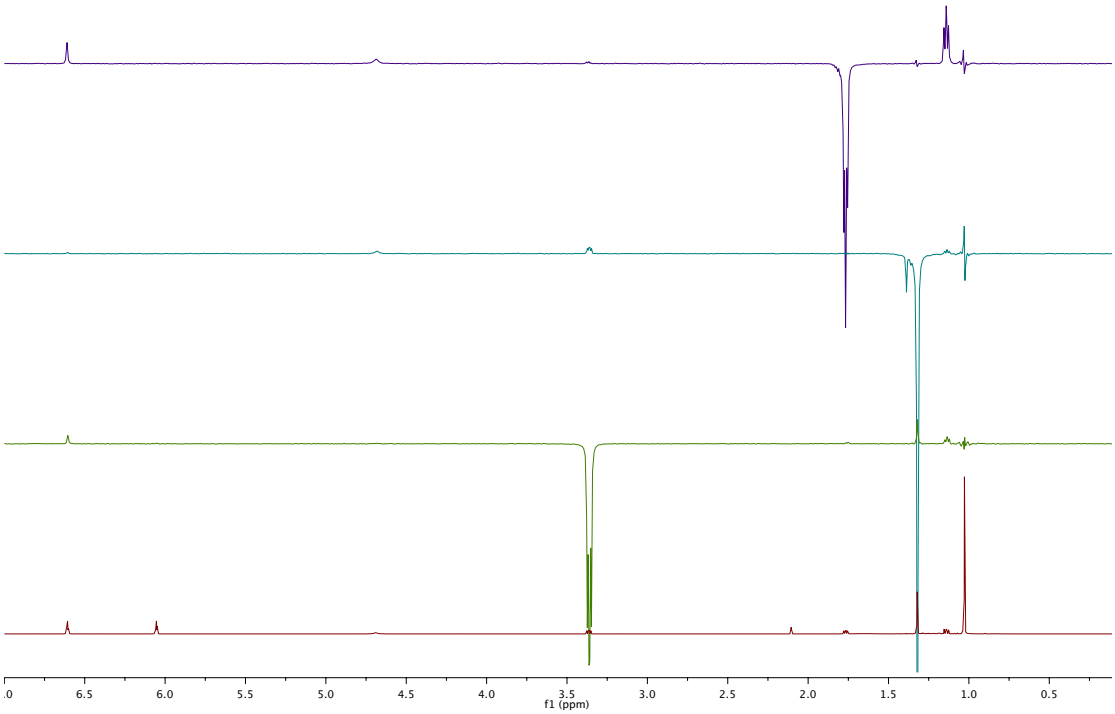
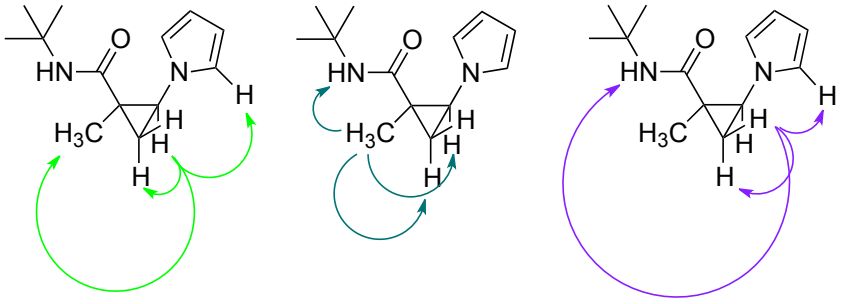


Figure 9 Observed NOEs upon irradiation at 3.36 ppm (green), 1.32 ppm (teal), 1.77 ppm (purple) for compound xx. For color-coded spectral charts corresponding to these experiments, see Figure 8.



A4. NOE Data for 147o

Figure 10 1D NOEDIFF spectra of **147o**. Chemical shifts of the irradiated multiplets are listed at the right side of each chart.

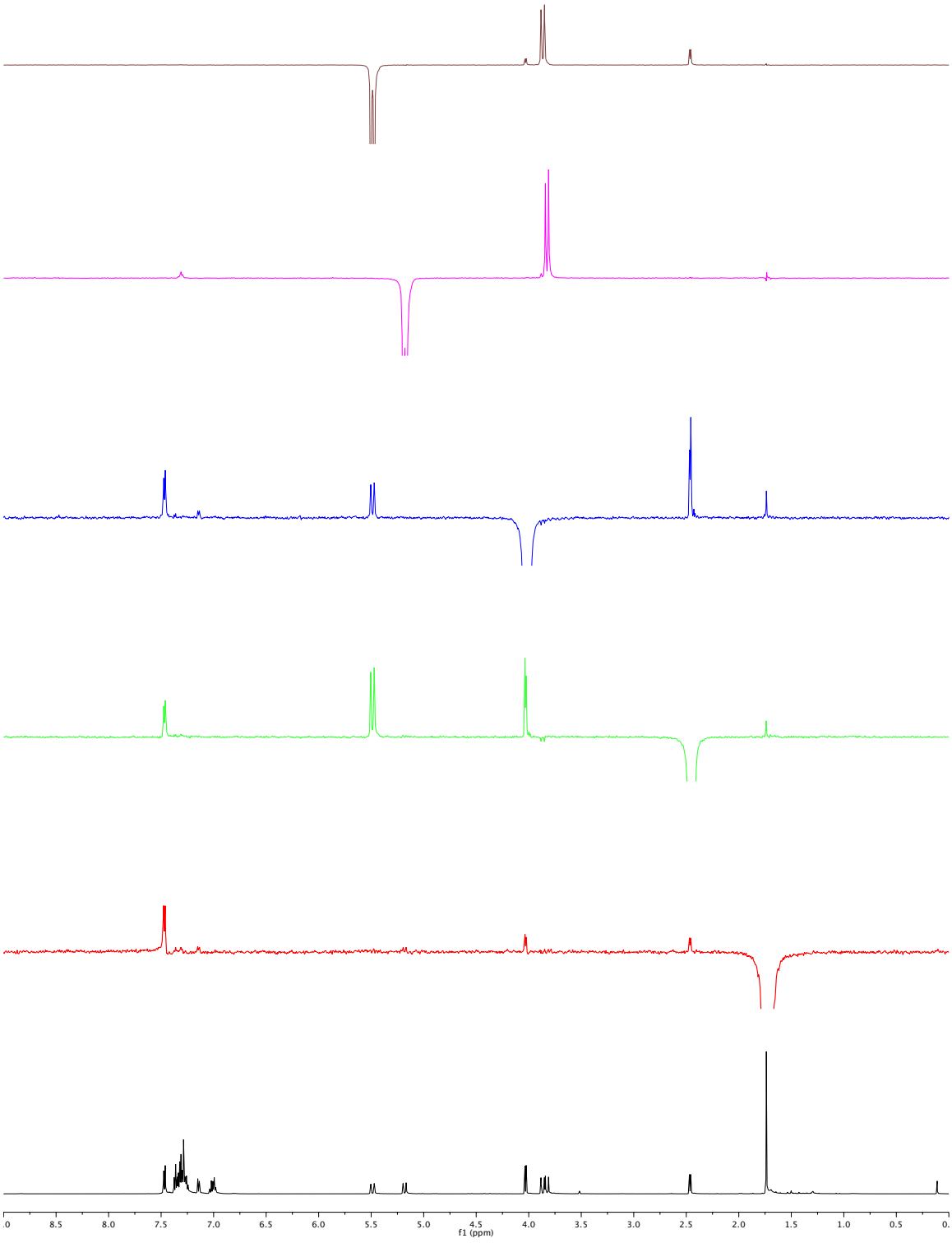
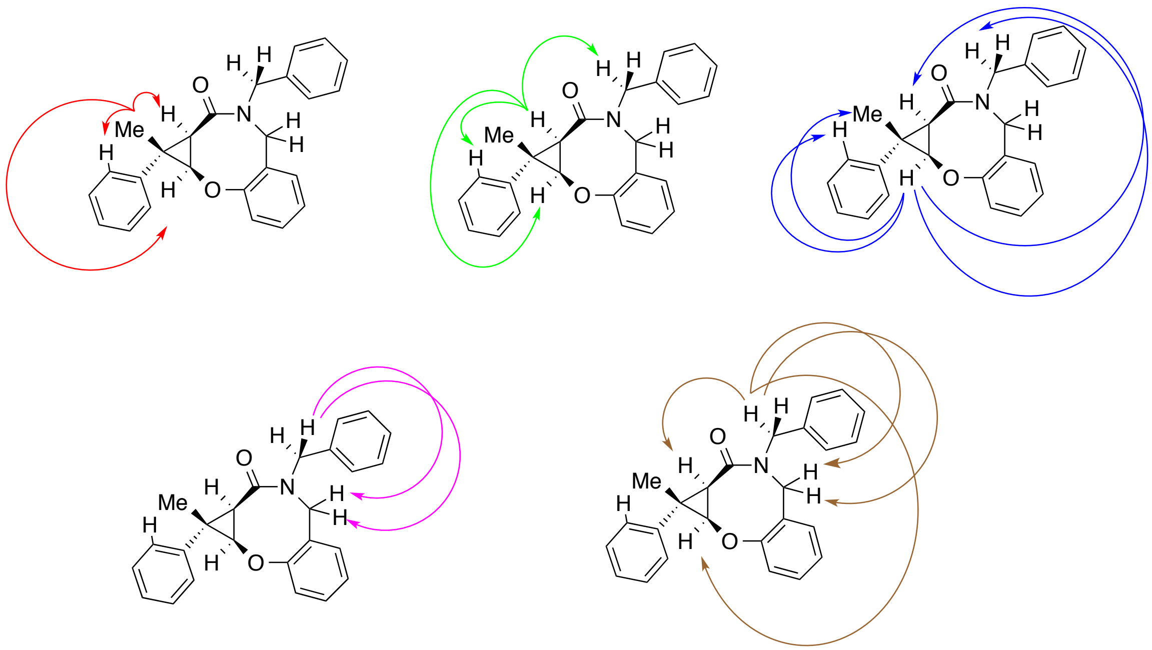
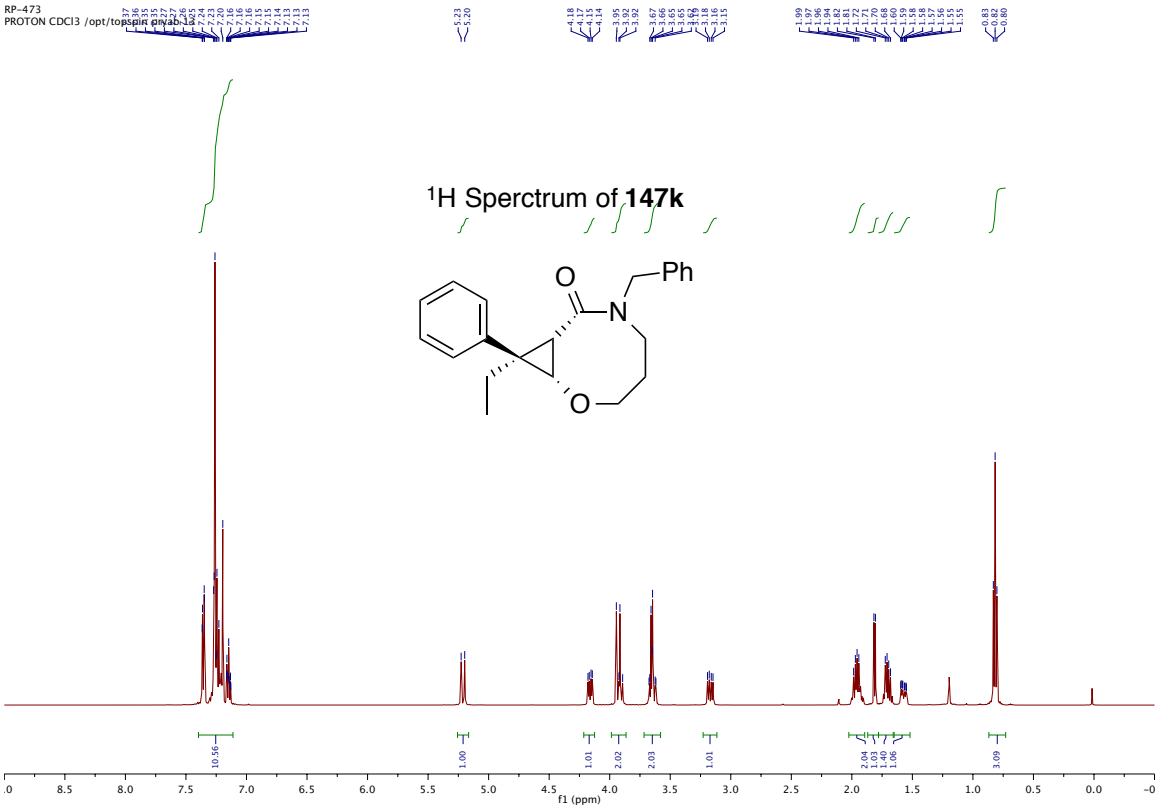
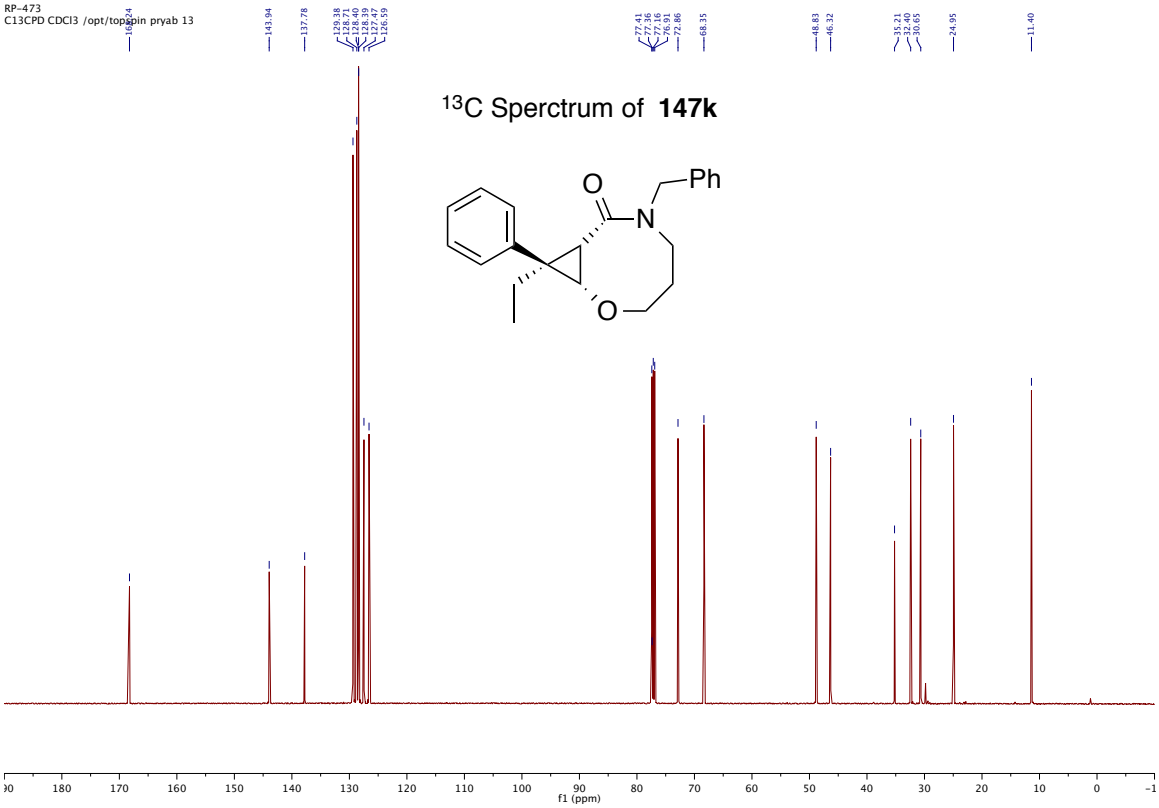


Figure 11 Observed NOEs upon irradiation at 1.71 ppm (red), 2.44 ppm (green), , 4.00 ppm (blue), 5.17 ppm (purple), 5.45 ppm (brown) for compound **147o**. For color-coded spectral charts corresponding to these experiments, see Figure 10.



A5. ^{1}H and ^{13}C Specta for 147k





A6. Crystallographic Data for 121bk

Figure 12 ORTEP drawing of cyclopropylazole **121bk** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown.

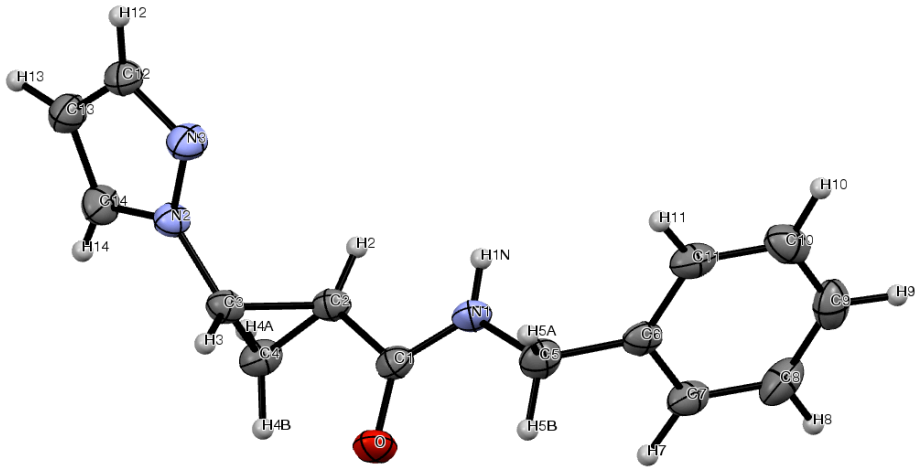
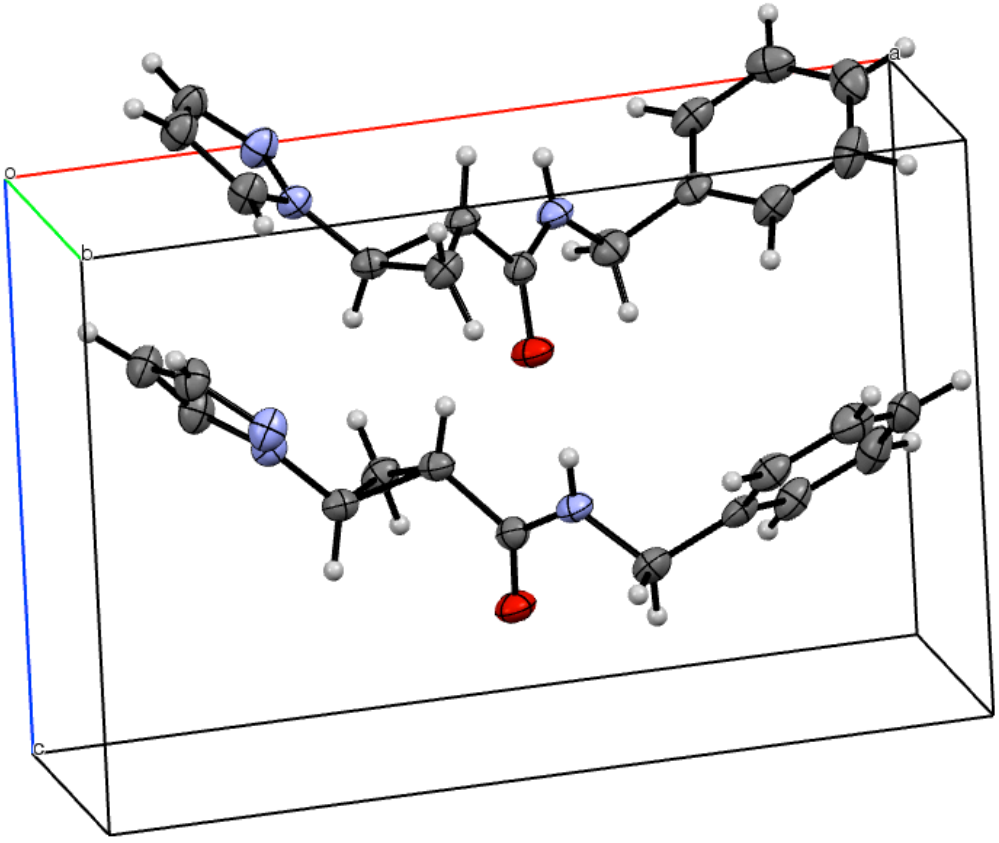


Figure 13 Packing of **121bk** molecules in the crystalline lattice cell.



A7. Crystallographic Data for 134aaf

Figure 14 ORTEP drawing of cyclopropylazole **134aaf** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown.

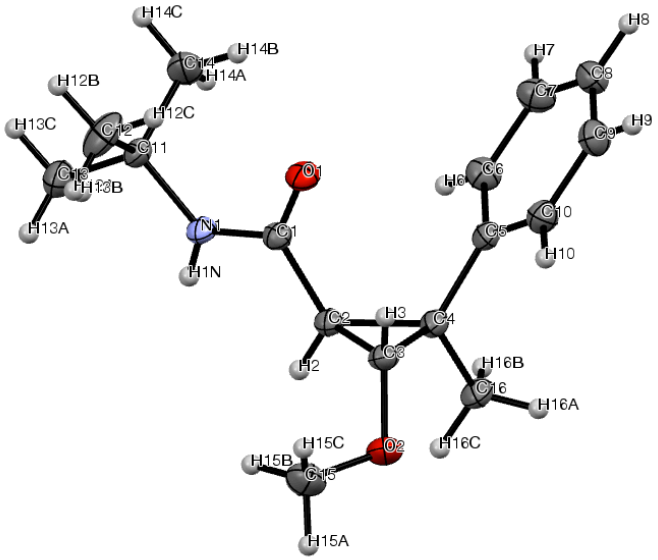
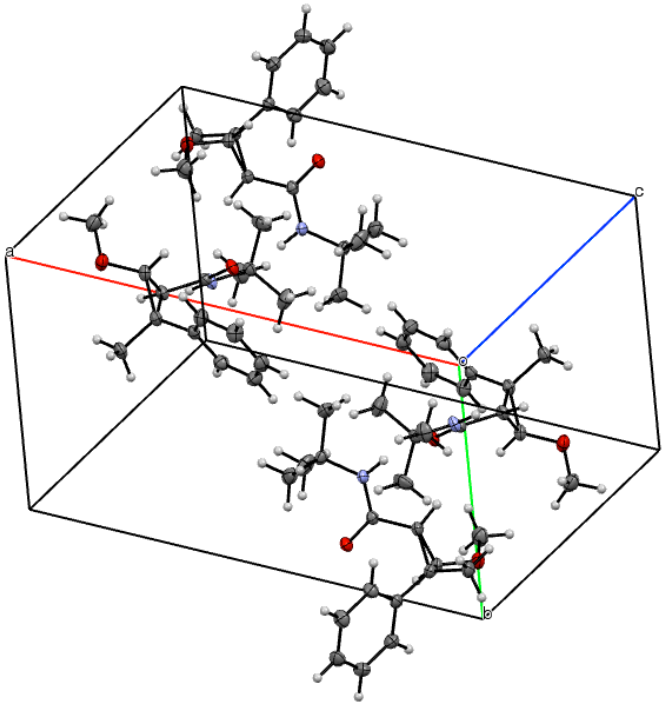


Figure 15 Packing of **134aaf** molecules in the crystalline lattice cell



A8. Crystallographic Data for (-)-136aCD

Figure 16 ORTEP drawing of cyclopropylazole **(-)-136aCD** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown.

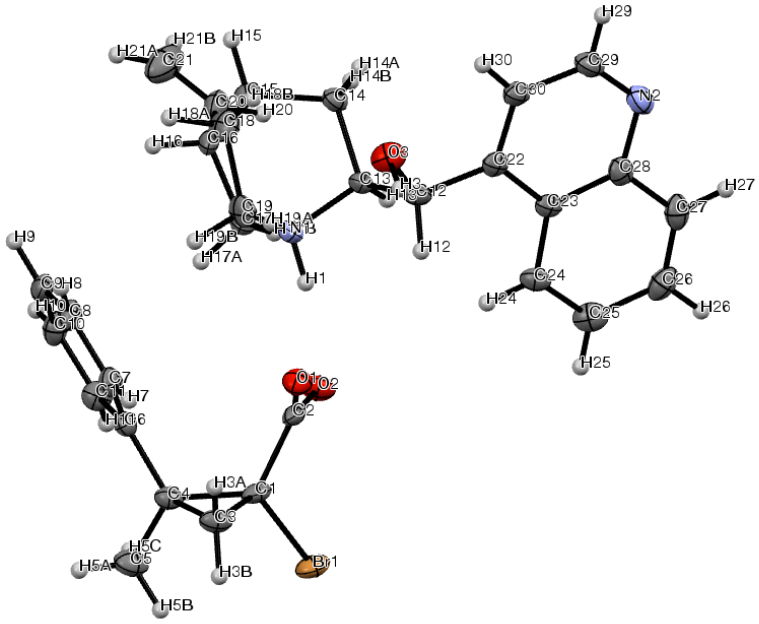
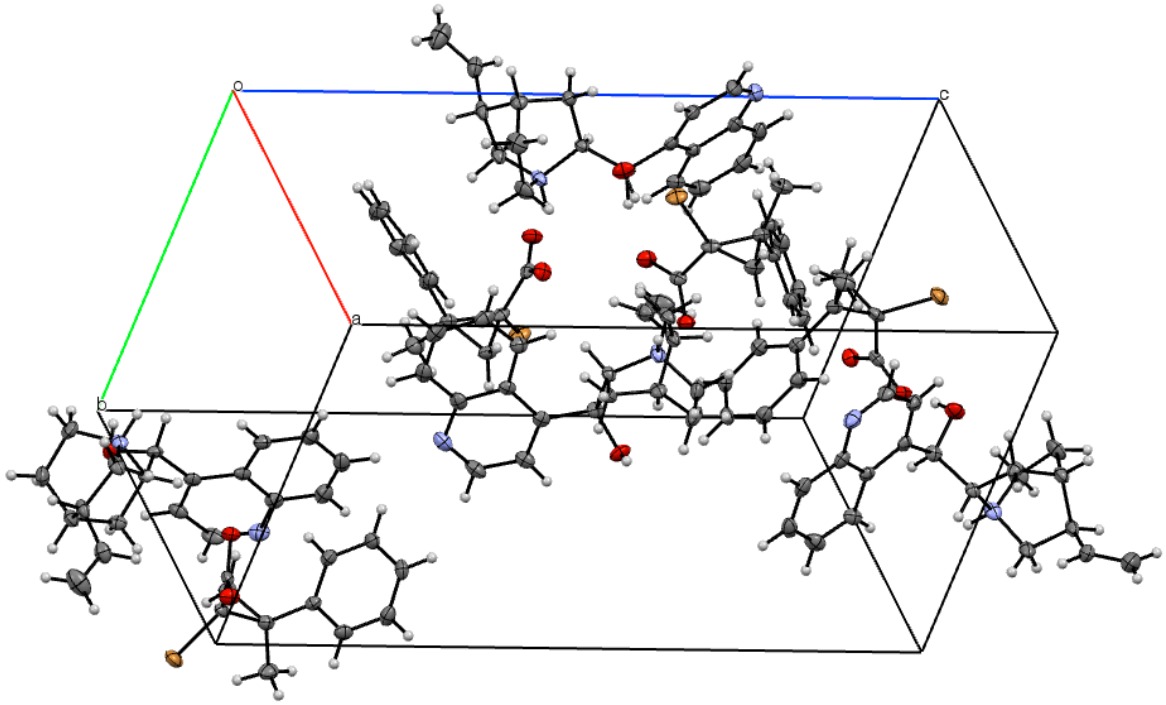


Figure 17 Packing of **(-)-136aCD** molecules in the crystalline lattice cell



A9. Crystallographic Data for (-)-136bCD

Figure 18 ORTEP drawing of cyclopropylazole **(-)-136bCD** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown

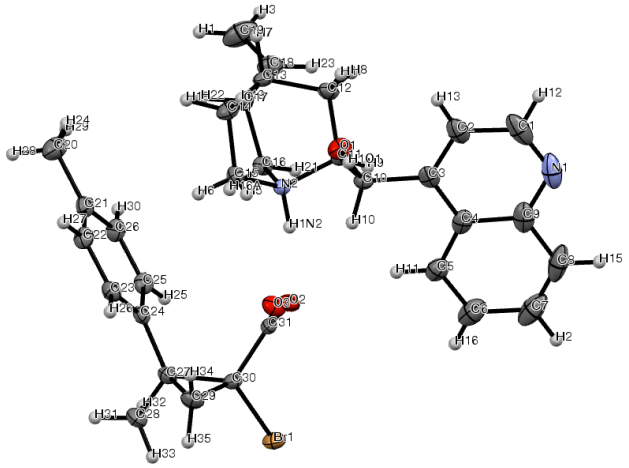
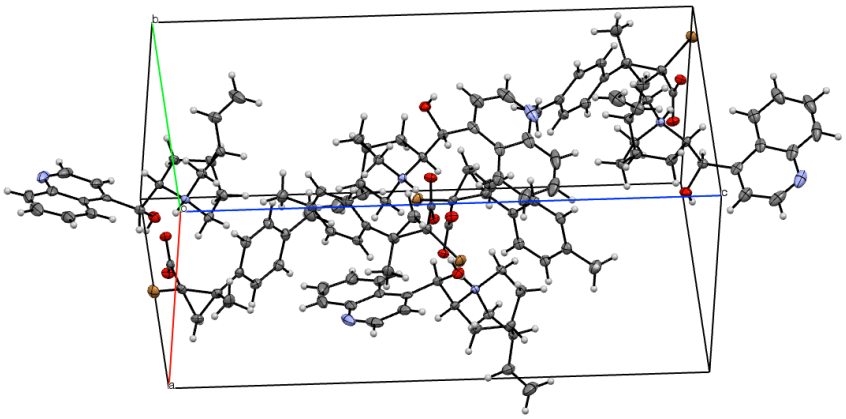


Figure 19 Packing of **(-)-136bCD** molecules in the crystalline lattice cell



A10. Crystallographic Data for (+)-132ac

Figure 20 ORTEP drawing of cyclopropylazole **(+)-132ac** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown

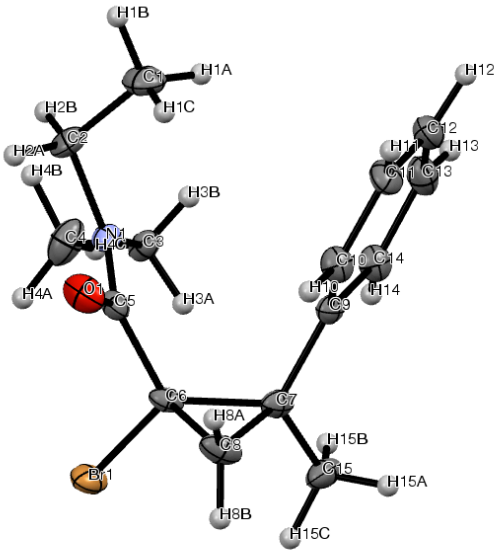
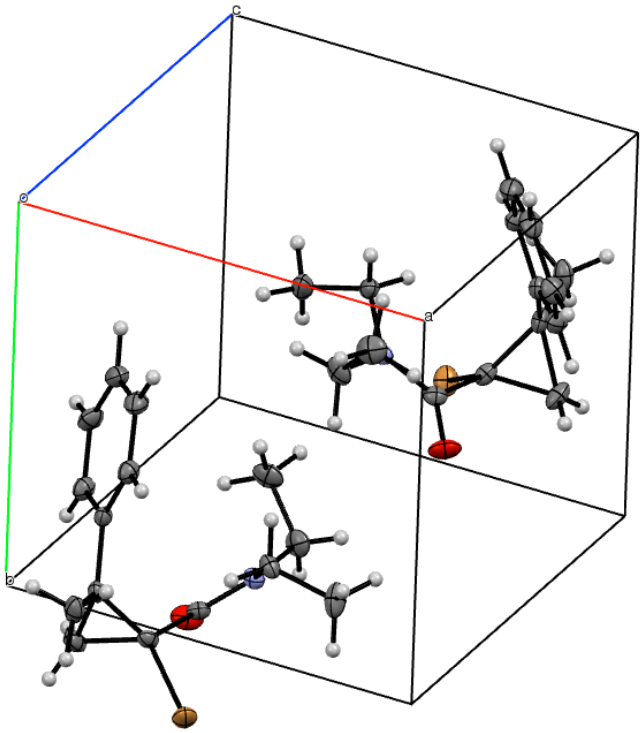


Figure 21 Packing of **(+)-132ac** molecules in the crystalline lattice cell



A11. Crystallographic Data for 134baa

Figure 22 ORTEP drawing of cyclopropylazole **134baa** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown

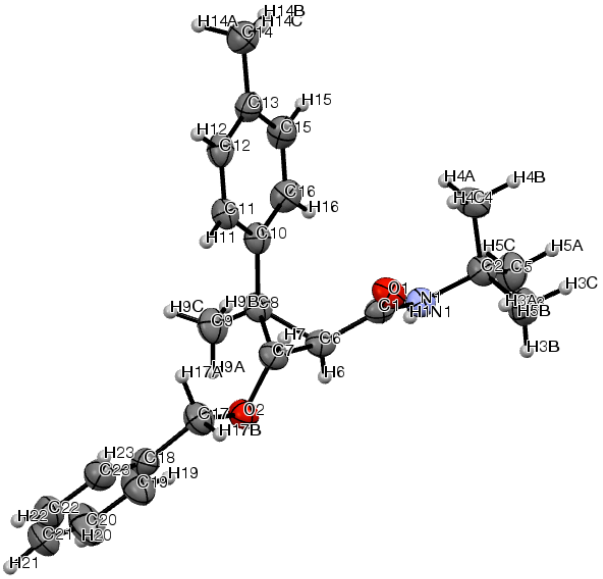
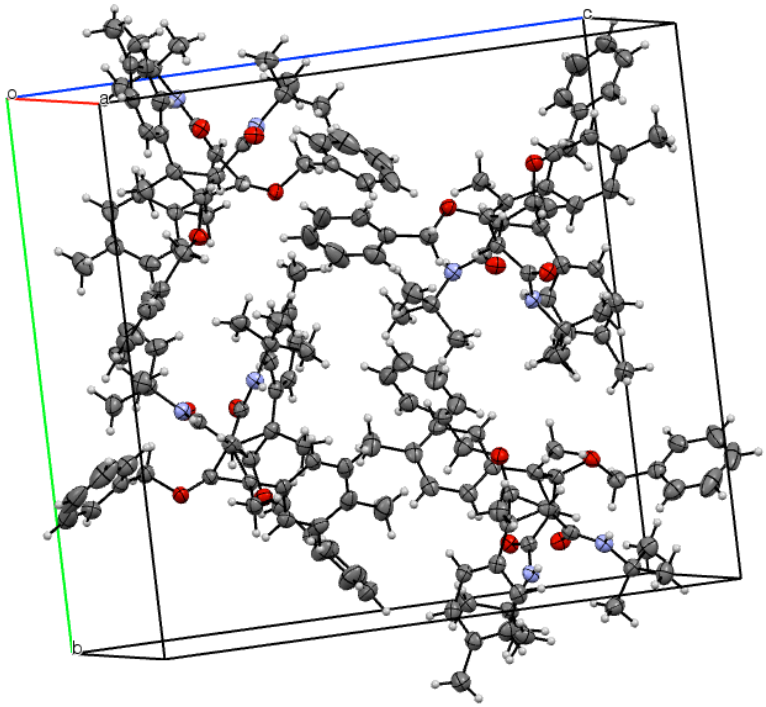


Figure 23 Packing of **134baa** molecules in the crystalline lattice cell



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