Directing effect of Amide Function in Diastereoselective Reactions

of Cyclopropenes and Cyclopropanes

BY

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Submitted to the graduate degree program in Chemistry and the Graduate Faculty

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degree of Doctor of Philosophy

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Directing effect of Amide Function in Diastereoselective Reactions

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Chairperson: Michael Rubin

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“*Из тяжести недоброй*
и я когда-нибудь прекрасное создам”

Осип Мандельштам

“*A time shall come for me*
to likewise make grim bulk a thing of beauty”

Osip Mandelstam

translated by A.Z. Foreman

Abstract

This thesis describes stereoselective directed reactions of cyclopropenes leading to the synthesis of a variety of densely substituted cyclopropanes as well as cyclopropyl containing bicyclic scaffolds. This thesis contains four chapters detailing the background, development, scope and limitations of the featured methodologies.

First chapter presents a literature review on directed reactions of small cycles covering carbometalations and related reactions of cyclopropenes and cyclobutenes as well as directed C-H functionalizations of saturated three and four membered rings.

Chapter two describes strain-release driven, carboxamide-directed addition of aryloxides across the double bond of cyclopropenes providing diastereomerically pure cyclopropyl aryl ethers. Facial selectivity of this transformation is controlled by strong coordination of the amide functionality to potassium cation, which serves as an efficient delivery vehicle for the aryloxide nucleophile.

Chapter three describes a new cyclopropene-based linchpin for an expeditious synthesis of medium-sized heterocyclic compounds. The featured approach utilizes the directing ability of an amide functionality for Cu-catalyzed diastereoselective additions to cyclopropene double bonds, followed by an intramolecular stereoselective ring-closing metathesis facilitated by the rigid cyclopropane core. It was shown that ring sizes 7−10 can be routinely assembled using this approach, but the method fails for larger cycles (11- to 13- membered rings).

Chapter four showcases previously unknown directed stereoselective hydrogenation of cyclopropenes in the presence of heterogeneous catalysts. The facial selectivity of the reaction is governed by the strong chelating effect of the carboxamide function to afford *cis*-

hydrogenation. Additionally, directed site selective hydrogenolysis of cyclopropanes was demonstrated. It was shown that platinum-based catalyst facilitate cleavage of distant C2–C3 bond, while proximal C1–C2 bond is cleaved in the presence of palladium-based catalyst.

Acknowledgments

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Lastly, I would like to express my gratitude to my wonderful wife Daria. Your support, encouragement and care took me where I'm now. This achievement is equally yours as it is mine. Thank you.

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List of Schemes

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List of Abbreviations

°C	degrees Celsius
µL	microliter
2D	two-dimensional
A	acceptor group
Å	angstrom
Ac	acetyl
AcOH	acetic acid
Alk	alkyl
APAO	acetyl-protected aminoethyl quinoline
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
Bu	butyl
C	carbon
cat.	catalyst
Cbz	carboxybenzyl group
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DFT	density functional theory
DG	directing group
DIPEA	*N*,*N*-diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
dt	doublet of triplets
E	electrophile

EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron donating group
equiv.	equivalent
ESI TOF	electrospray ionization time-of-flight
Et	ethyl
et al.	and others
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EtONa	sodium ethoxide
EWG	electron withdrawing group
FID	flame ionization detector
FT IR	Fourier-transform infrared spectroscopy
g	gram
GC	gas chromatography
h or hr	hour
Hal	halogen
HOBT	1-hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
Hz	hertz
i-	Iso-
IR	infrared spectroscopy
J	coupling constant
kcal	calorie (kilocalorie)
L	liter or ligand
L*	chiral ligand
LA	Lewis acid
LDA	lithium diisopropylamide
liq.	liquid
m	multiplet or meter
M	molarity or molecular ion
m-	meta-
M/C	metal on metal carrier support (carbon)
Me	methyl
MeOH	methanol
MeONa	sodium methoxide
mg	milligram
MHz	megahertz

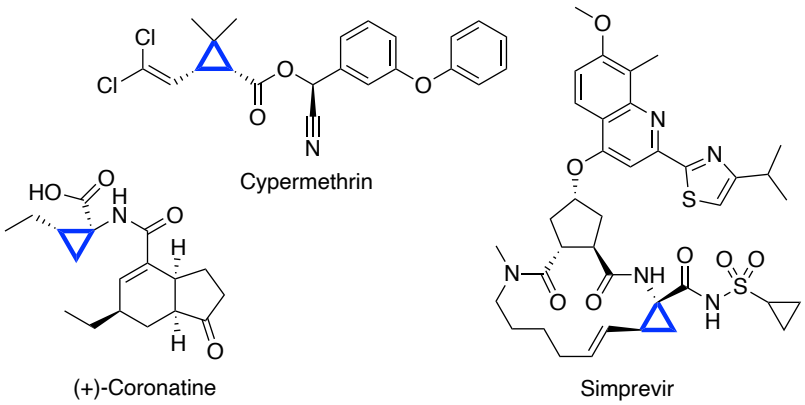
min	minute
mL	milliliter
mmol	millimole
mol	mole
MPAA	monoprotected amino acid
MPAHA	mono-N- protected α-amino-*O*-methylhydroxamic acid
n-	normal-
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o-	ortho-
p-	para-
Ph	phenyl
ppm	parts per million
Pr	propyl
psi	pound per square inch
PTC	phase-transfer catalyst
RCM	ring-closing metathesis
R_f	retention factors
RT or rt	room temperature
s	singlet
sat.	saturated
t	triplet
t-	tert-
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF ES	electrospray ionization time-of-flight
TS	transition state

Chapter 1 Directed reactions of small cycles

1.1 Introduction

The cyclopropane motif is a common structural feature of many biologically active natural products, synthetic industrially produced pesticides as well as commercially available drugs and drug candidates such as (+)-coronatine[1], cypermethrin[2] and Simprevir[3] (**Figure 1.1**). The rigidity of the cyclopropane structural core and its well-defined geometry allows for the unique spatial arrangement of substituents, which is inaccessible in any other scaffold, providing potential for unusual chemical and biological activities. Thus, the development of methods permitting functionalization of cyclopropane core in a stereocontrolled fashion has been a fast-growing area of organic synthesis. The purpose of this chapter is to review recent developments in stereocontrolled functionalizations of small cycles, including cyclopropenes, cyclopropanes, cyclobutenes and cyclobutanes with especial emphasis on diastereoselective reactions controlled by a chelating directing group.

Figure 1.1

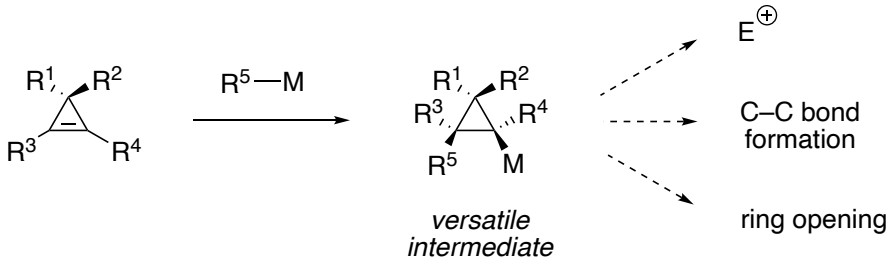


1.1 Directed TM-catalyzed functionalization

1.1.1 Carbometalation

Carbometalations and related processes belong to the one of the most studied classes of reactions of cyclopropenes. Due to their rigid structure, and symmetry properties, cyclopropenes are excellent substrates for development of regio-, diastereo-, and enantioselective reactions *en route* to densely functionalized cyclopropanes. Metalated intermediates of these reactions can also undergo ring-opening transformations and therefore even greater structural diversity of the product can be achieved through the careful selection of reagents and reaction conditions (**Scheme 1.1**). Several comprehensive reviews covering reactions of cyclopropenes, including carbometalations, and their applications in synthesis were published in recent years.[4–11]

Scheme 1. 1

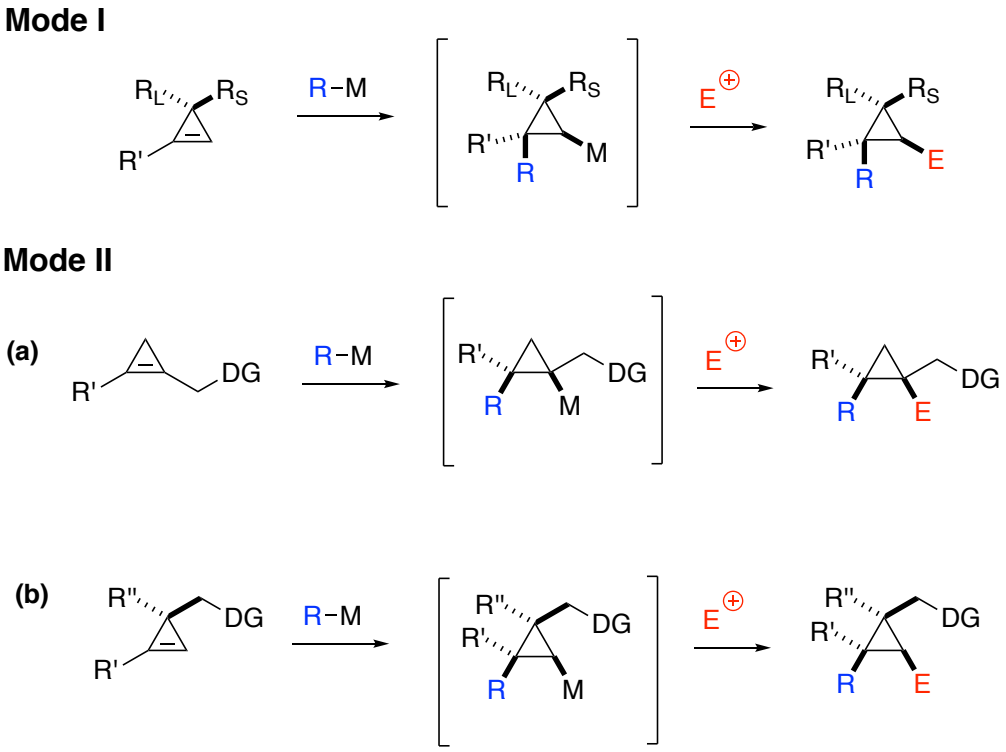


Non-catalyzed additions of organometallic species across cyclopropene double bond were reported as early as 1970s and applied as valuable synthetic methods.[12,13] Such reactions are mostly substrate-dependent and demonstrate high facial selectivity. More recently, transition metal-catalyzed reactions developed after the pioneering work by Nakamura et al. 2000[14] took this chemistry to a new level. Not only are TM-catalyzed transformations more

versatile and efficient, they also offer a wider range of suitable substrates. While these reactions often require a more careful design, they allow high levels of diastereo- and, importantly, enantioselectivity. Both approaches still attract significant attention and remarkable achievements were disclosed in the past decade.[8]

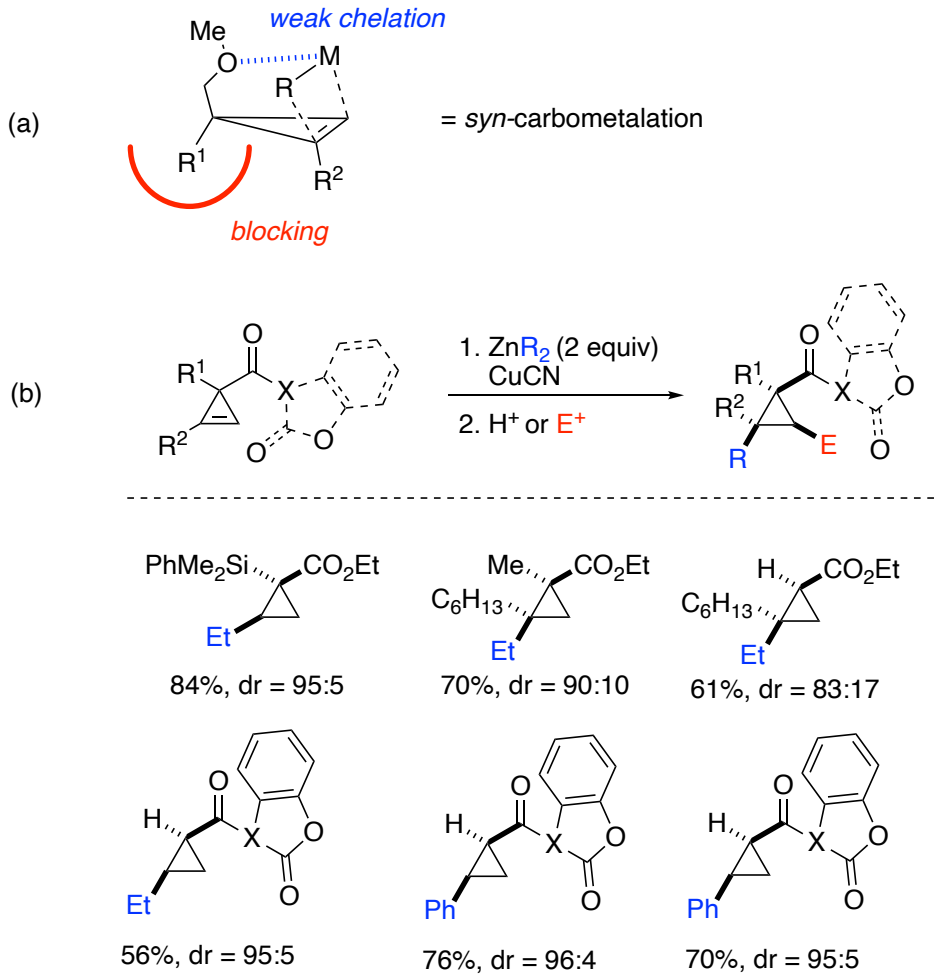
In the aforementioned reactions facial (diastereo-) selectivity is achieved utilizing one of the two general approaches (**Scheme 1.2**). In Mode I, unless the reaction is performed on a symmetrically substituted cyclopropene, the facial selectivity is governed by a steric demand of the substrate where the addition of organometallic species occurs on a less hindered face of the cycle. Enantioselective variants of this approach were also reported.[15,16] Alternative approach (Mode II) involves a diastereoselective carbometallation directed by a suitable chelating functionality tethered to C1, (Mode II, a), or C3 (Mode II, b) of the cyclopropene. In Mode II (a) an alcohol function is typically used as a directing group while in Mode II (b) a variety of directing groups such as alcohols, esters, ethers, and amides were successfully employed.[7–9,17–19] This review is focused on carbometalations governed by directing functionality at C-3 (Mode II, b).

Scheme 1. 2



The directing effect of weakly chelating groups in *syn*-carbometalation of cyclopropenes is commonly utilized in a dual control strategy that combines the directing effect of the group – typically alcohol or ether – with spatial blocking by a sterically demanding substituent, while both are tethered to C3. Fox demonstrated[19] the influence of the substituent at the 3rd position on facial selectivity in iron catalyzed carbomagnesiation of cyclopropenes. The *syn*- addition is explained by the steric effect exerted by the C3 substituent while the weak coordinating effect of the directing group becomes sufficient enough to direct the incoming organometallic species. Similar approach was employed by Marek[17] in diastereoselective carbocupration of cyclopropene (**Scheme 1.3, a**).

Scheme 1. 3

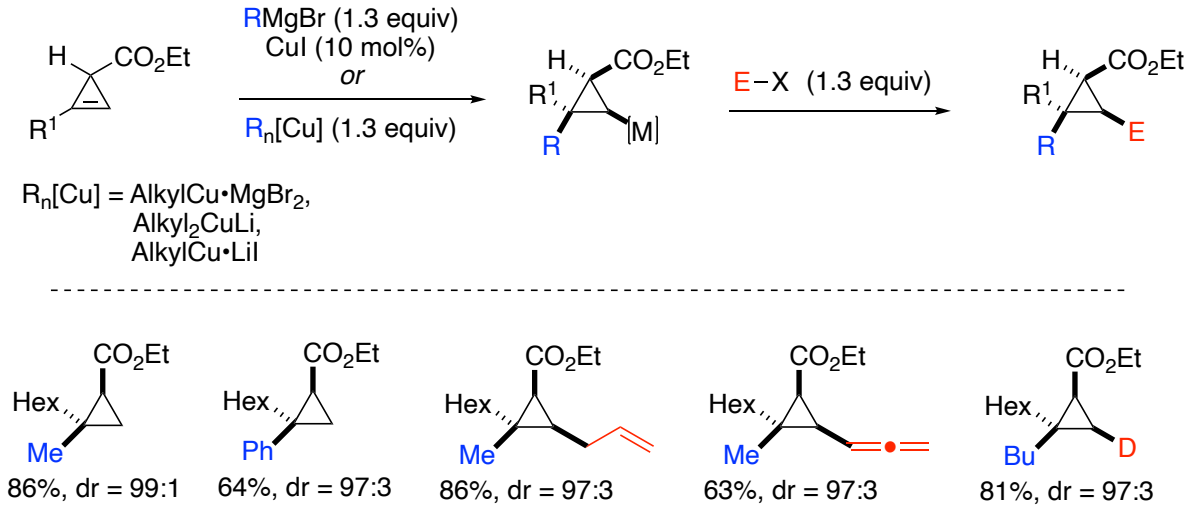


A highly diastereoselective procedure for Cu-catalyzed carbozincation of cyclopropenes was reported by Fox.[18] A transition to stronger directing groups, namely esters and oxazolidinones, allowed for addition of a variety of nucleophiles with excellent facial selectivity without the added steric constraint. Notably, the use of oxazolidinone as a directing group yielded excellent diastereoselectivity even when R^1 = H (**Scheme 1.3, b**).

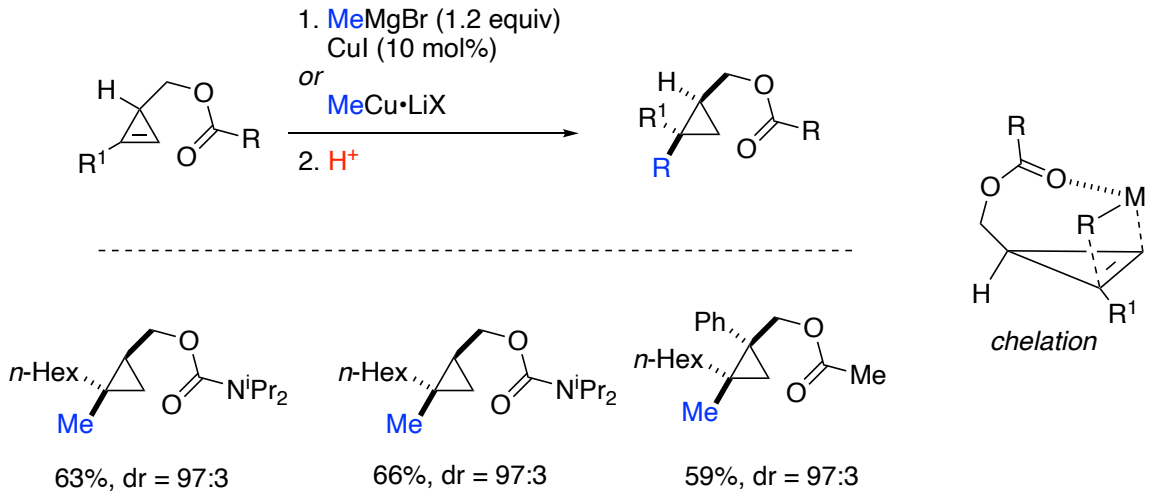
A notable example of copper-catalyzed carbomagnesiation and carbocupration reactions of cyclopropenyl esters was reported by Marek.[20] The reactions proceeds through a *syn*-chelated carbometalation enabling an accurate control of the stereoselectivity (**Scheme 1.4**). The scope of this reaction was further extended to homologous esters and amides. Despite the increased flexibility of such directing groups, the reactions showed excellent diastereoselectivity with both organocopper reagents and copper-catalyzed carbomagnesiation. This transformation is of a great synthetic interest as it allows for installation of two consecutive stereo-defined all-carbon quaternary centers.

Interestingly, when the Lewis acidity of the copper species was decreased (i.e., RCuCNLi) the reactions proceeded with *anti*-selectivity. Such diastereodivergent behavior was explained by low electrophilicity of cyanocuprates insufficient for effective chelation. Thus, depending on the nature of the copper species, the described method enables synthesis of both *syn*- (**Scheme 1.5**) and *anti*- (**Scheme 1.6**) diastereomers from the same precursor.

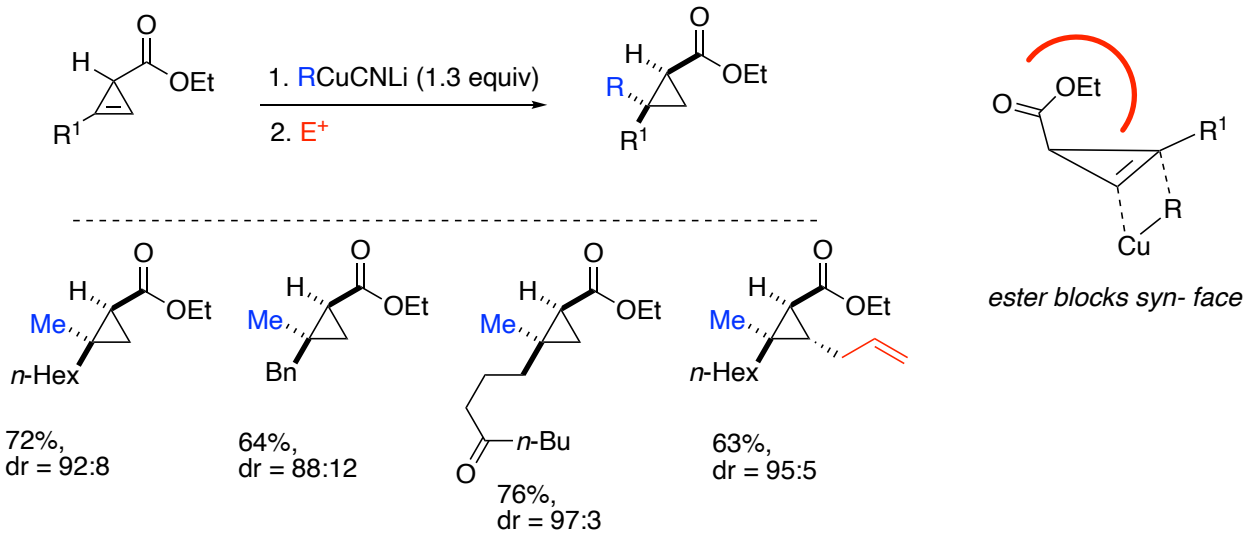
Scheme 1. 4



Scheme 1. 5



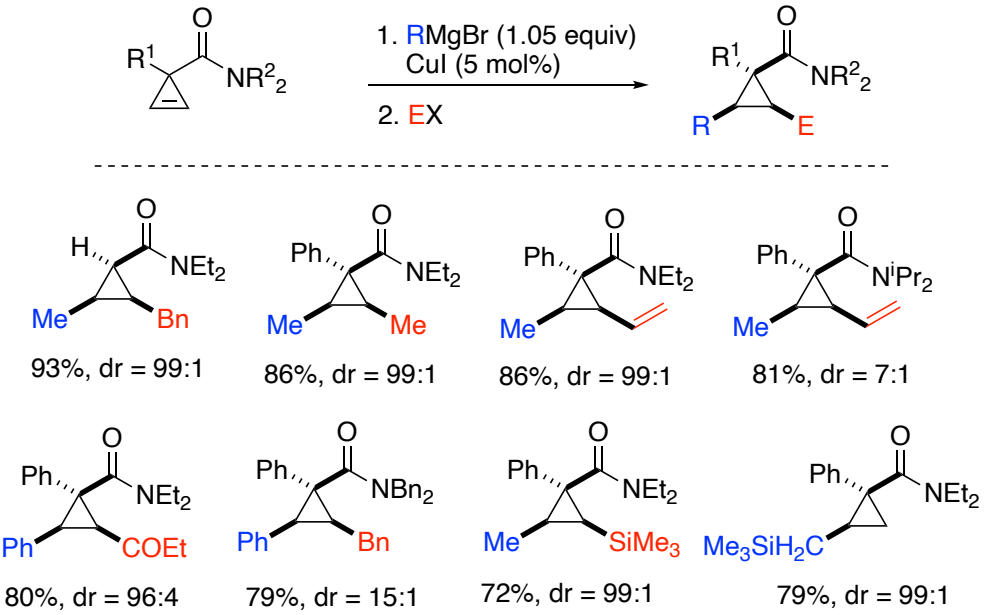
Scheme 1. 6



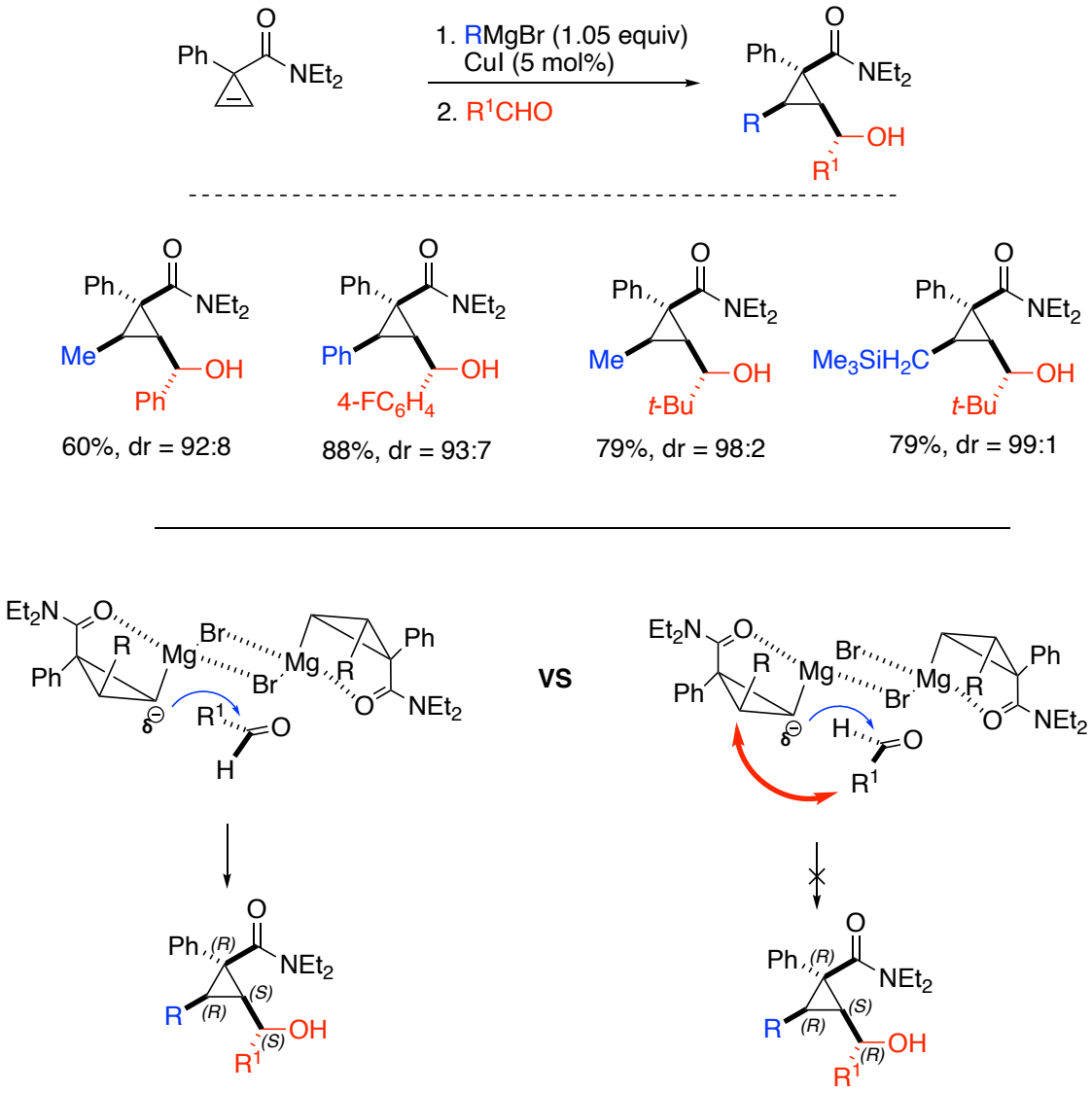
Rubin reported an efficient synthetic protocol for the directed copper-catalyzed carbomagnesiation of cyclopropene-3-carboxamides.[21] It was demonstrated that the carboxamide function is acting as an exceptionally efficient directing group allowing excellent control of the *syn*-facial selectivity. Carboxamides are compatible with a variety of Grignard reagents allowing the synthesis of a wide range of densely substituted cyclopropanes. Such

compatibility favors this reaction over alternative carbozincation and carbocupration processes, as they require less readily available organozinc reagents and over stoichiometric amounts organocuprates, respectively (**Scheme 1.7**). The synthetic potential of this transformation was demonstrated through the use of various electrophiles to trap the cyclopropylmagnesium intermediate. The employment of aldehydes for the electrophilic trapping allowed for the preparation of alcohol products possessing four consecutive stereogenic centers (**Scheme 1.8**).

Scheme 1. 7

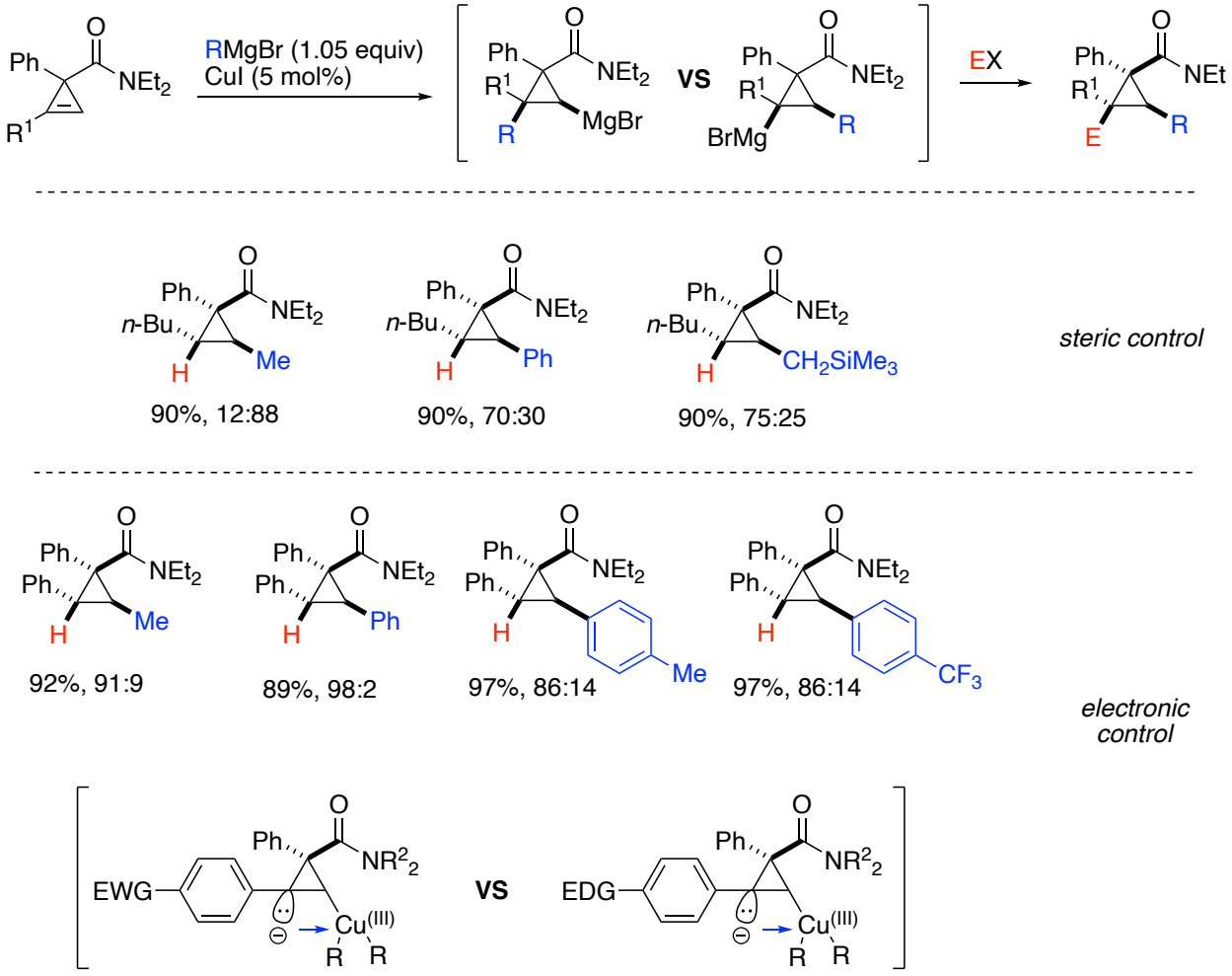


Scheme 1. 8



It is noteworthy that the carbomagnesiation of cyclopropenes reported by Rubin provided regioselectivity opposite to previously reported by Fox and Marek (see above). The reversal of the stereochemical outcome was observed when 1-alkyl substituted cyclopropenes reacted with sterically demanding Grignard reagents such as PhMgBr and Me_3SiCH_2MgBr (**Scheme 1.9**). It was demonstrated that the regioselectivity can be controlled even more accurately by the electronic factors in reactions of 1-aryl cyclopropenes.

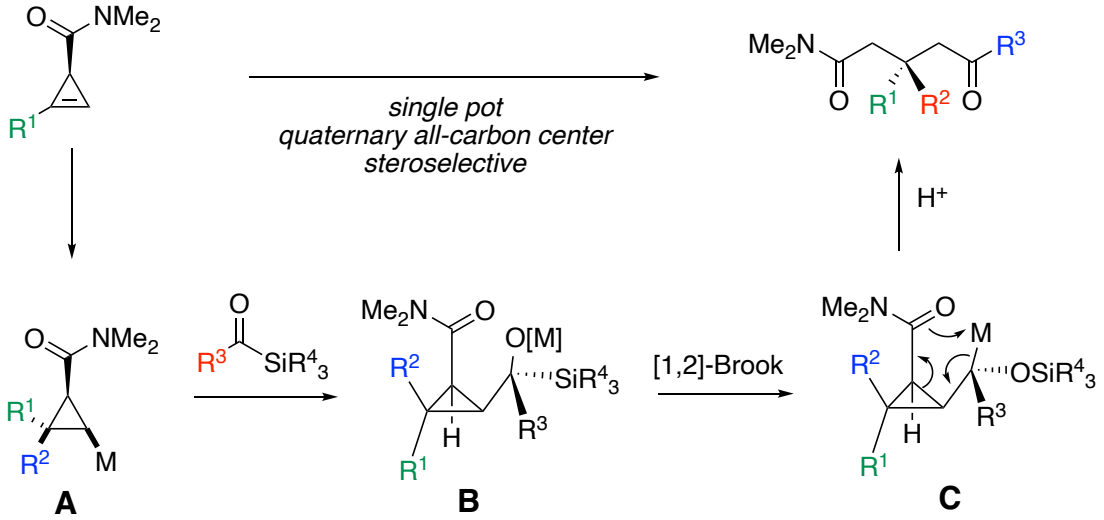
Scheme 1. 9



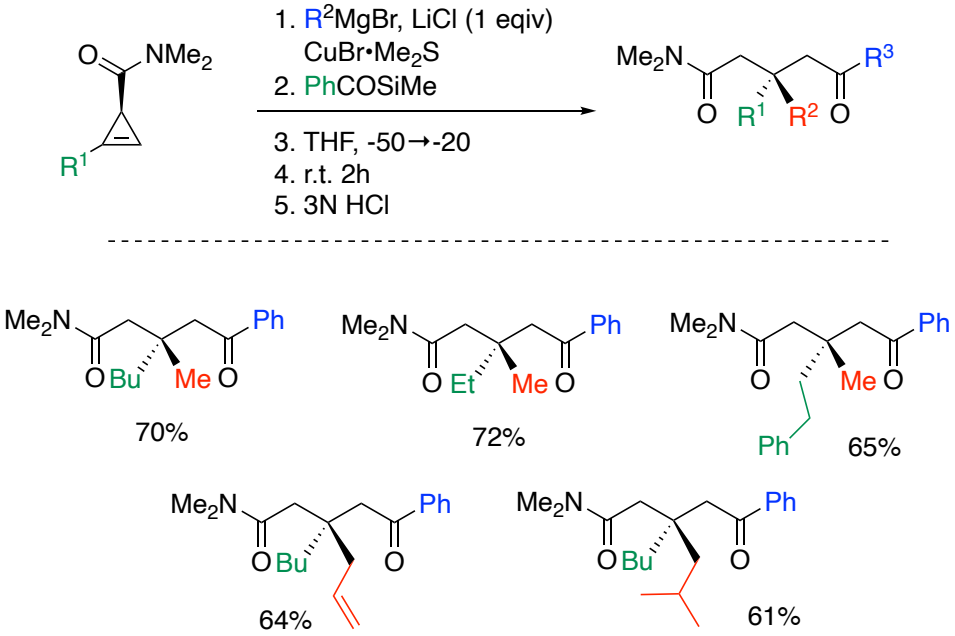
An impressive cascade sequence for the highly stereoselective synthesis of δ-ketoamides containing a quaternary all-carbon center was recently reported by Marek et al.[22] In the first step of the sequence the authors used readily available non-racemic 2-alkyl-*N*,*N*-dimethylcyclopropene carboxamides[23] as the substrates for a copper-catalyzed addition of Grignard reagents (**Scheme 1.10**). A highly diastereoselective formation of cyclopropyl metal intermediate **A** was enabled by the efficient coordination of the organometallic reagent to the carboxamide group. In the second step, the interception of intermediate **A** by acylsilane

electrophiles, followed by [1,2]-Brook rearrangement of α-hydrosilane **B** produces intermediate **C**. The subsequent strain-release driven C–C bond cleavage is followed by acidic hydrolysis of the corresponding silyl enol ether to yield δ-ketoamides as final products with a high enantiomeric ratio. Remarkably, the entire sequence is carried out in a single reaction vessel and demonstrates high selectivities in each step.

Scheme 1. 10



Scheme 1.10, continued

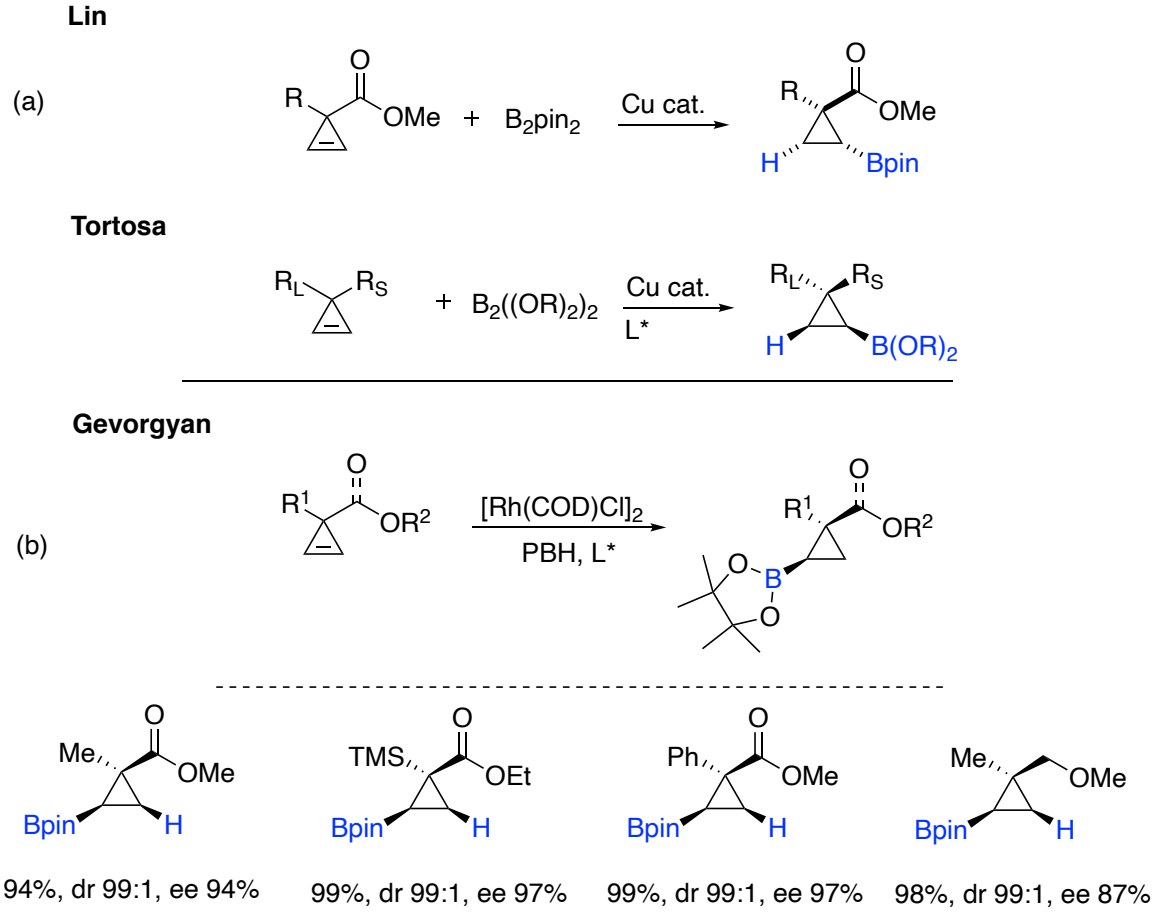


1.1.2 Hydroboration

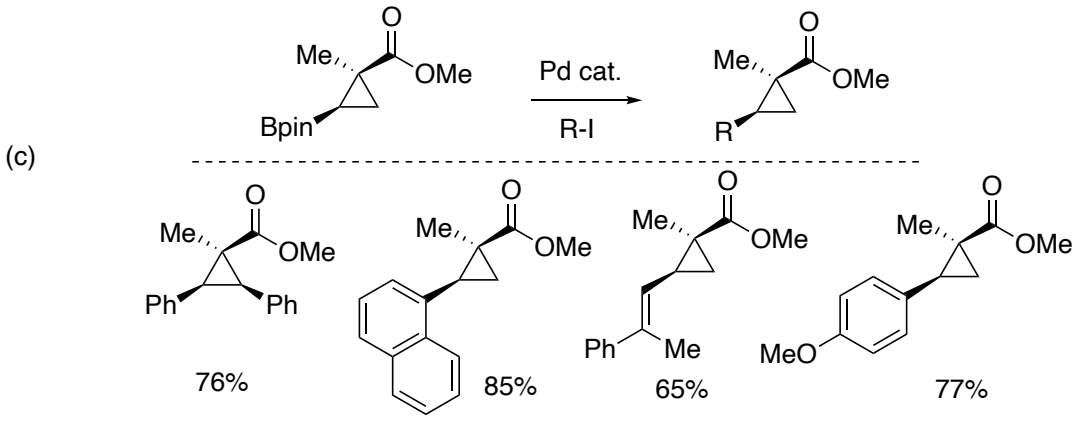
Cyclopropyl boronates are versatile reagents for synthetic organic chemistry as they provide access to structurally and functionally diverse cyclopropanes trough transition metal catalyzed cross-coupling reactions[24–26], ring-retentive oxidation/functionalization[15] or stereochemistry-preserving homologation/derivatization[27]. A few noncatalyzed[28,29] and copper-catalyzed hydroborations[15,30] of cyclopropenes have been reported (**Scheme 1.11, a**). However, the diastereoselectivity of these reactions was controlled by steric effects, where boron species was installed on a less sterically hindered face of the cycle. In contrast, Gevorgyan[31] demonstrated that esters and alkoxymethyl substituents at C3 can serve as effective directing groups in the hydroboration reactions for synthesis of sterically hindered *cis*-substituted cyclopropyl boronates (**Scheme 1.11, b**). These Rh-catalyzed transformations are characterized

by excellent facial selectivity and enantioselectivity when conducted in a presence of a chiral phosphine ligand. The synthetic potential of this reaction was demonstrated through the synthesis of optically active trisubstituted aryl- and vinylcyclopropanes (**Scheme 1.11, c**).

Scheme 1. 11

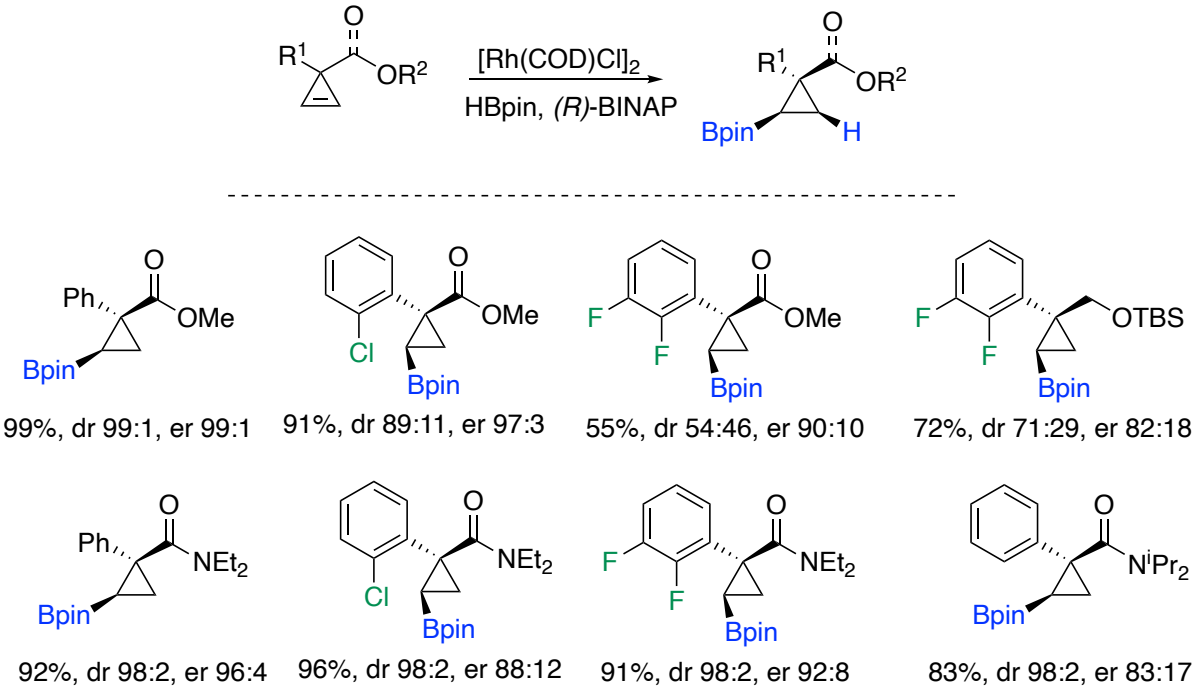


Scheme 1.11, continued

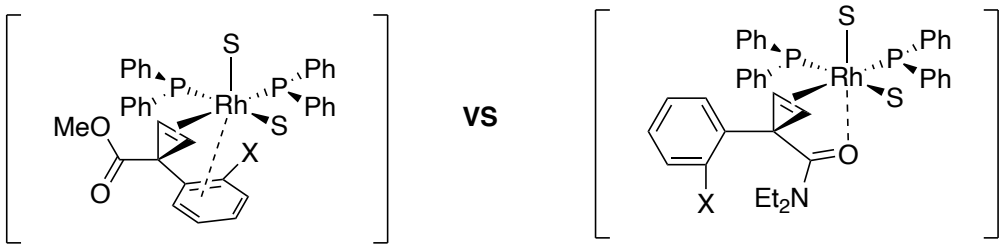


Recently, Rubin published a full account on directed Rh-catalyzed asymmetric hydroboration of prochiral cyclopropenes[32]. The authors evaluated the scope and limitations of ester and carboxamide directing groups and found the latter to be advantageous (**Scheme 1.12**). It was demonstrated that directing ester group is more sensitive to the nature of the substrate, especially the substitution of the aromatic ring at C3. Specifically, a presence of a halogen, especially F, in *ortho*-position of the aromatic ring was proven to be detrimental for both diastereo- and enantioselectivity of the reaction. This effect was explained by a complimentary coordination of such substrates to the Rh catalyst (**Scheme 1.13**). In contrast, a more Lewis basic and therefore stronger chelating carboxamide functionality demonstrated consistently high selectivity for a wider scope of substrates.

Scheme 1. 12



Scheme 1. 13



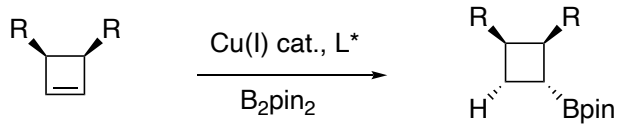
Despite the fact that copper mediated carbometalation and related reactions of strained olefins, such as cyclopropene, were extensively studied, all attempts to extend this methodology to less-strained double bonds have failed. As such, none of the copper-catalyzed carbomagnesiation, carbozincation or carbocupration of cyclobutenes produced the desired

addition of the organometallic reagent across the double bond, most likely due to a smaller energy release of the addition step.[33]

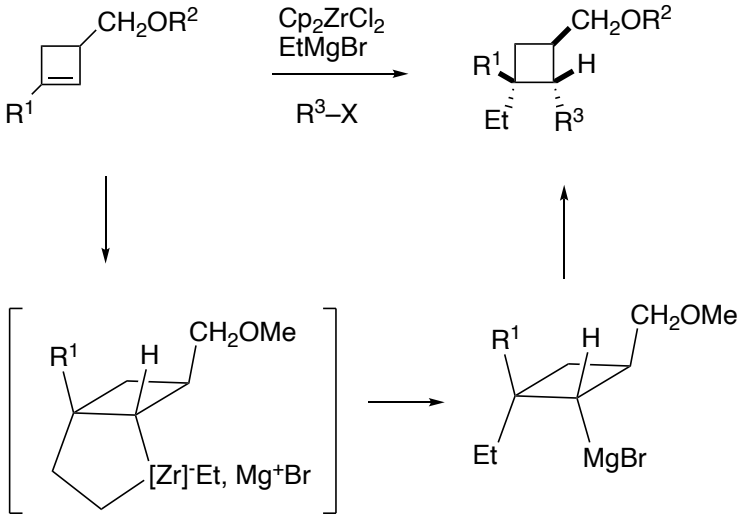
Tortosa[34] recently reported the first desymmetrization of cyclobutenes through the copper-catalyzed borylation of cyclobutenes, while Marek group disclosed zirconocene catalyzed carbometallation of cyclobutenes. In both cases facial selectivity of the reactions was governed by the steric restrictions (**Scheme 1.14**).

Scheme 1. 14

Tortosa



Marek

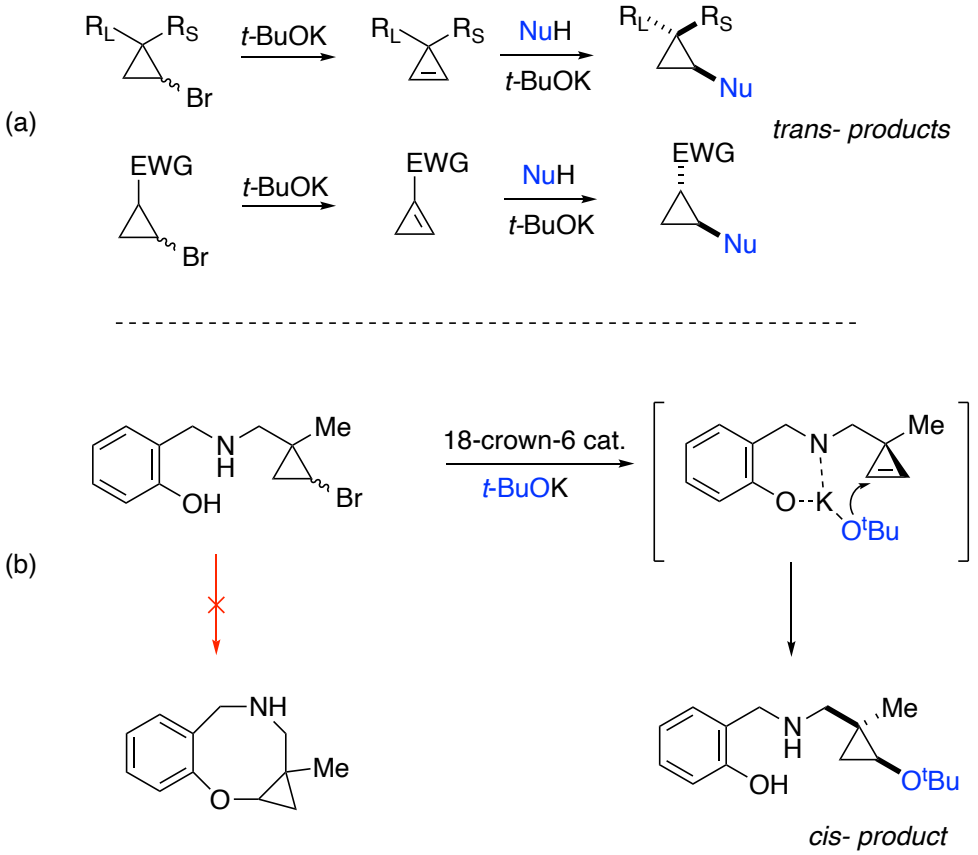


1.2 Nucleophilic additions

Over the past decade Rubin's lab has reported various stereoselective additions of oxygen, nitrogen, phosphorus, and sulfur-based nucleophiles to *in situ* generated cyclopropenes. Cyclopropenes generated from corresponding halocyclopropanes *via* 1,2-elemination were functionalized diastereoselectively in a subsequent reaction with a nucleophile. Several approaches were demonstrated to ensure effective facial selectivity, such as steric control, thermodynamic control *via* epimerization, and directing control (see review[35] for a more detailed discussion). While the steric and thermodynamic methods of control are out of the scope of this review, the discussion on directed nucleophilic additions follows.

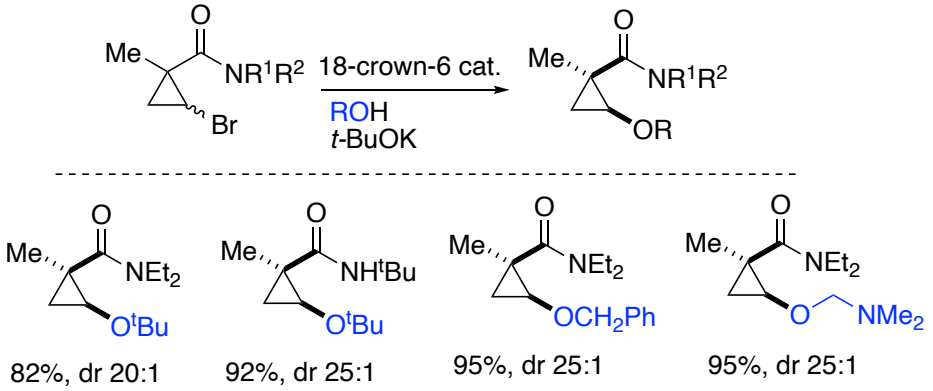
In 2011 Banning with Rubin et al. demonstrated formal nucleophilic substitution of bromocyclopropanes with oxygen and nitrogen-based nucleophiles. While diastereoselectivity of these reactions was controlled sterically or thermodynamically, thus leading to a *trans*-functionalized cyclopropanes (**Scheme 1.15, a**), an attempt to conduct the reaction in intramolecular fashion yielded an unexpected directed addition of *tert*-butoxide nucleophile to a more sterically hindered face. The *cis*-diastereomer was observed exclusively. It was rationalized that the reaction is controlled by a strong chelating effect of the 2-(aminomethyl)phenolate moiety (**Scheme 1.15, b**)[36].

Scheme 1. 15

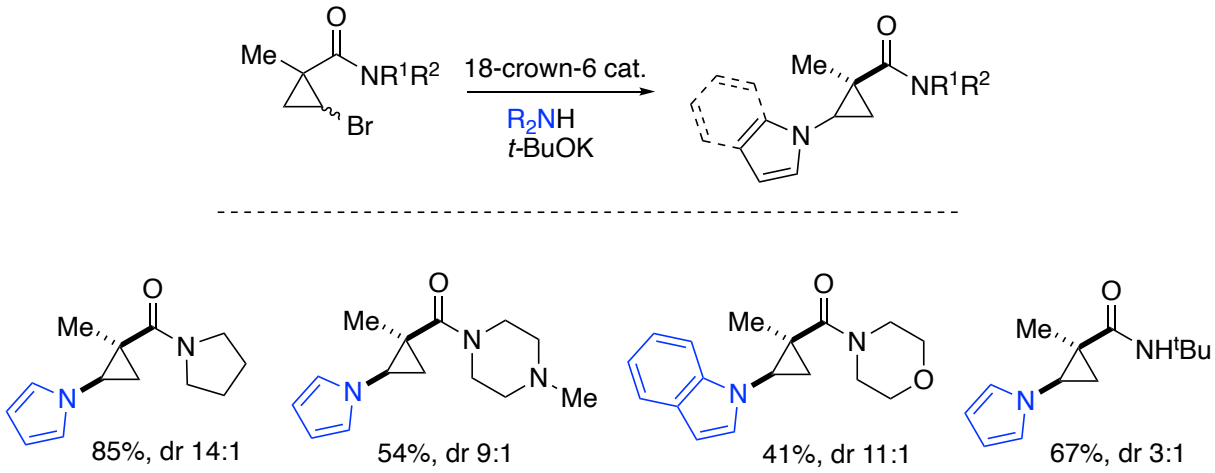


Following this finding, it was demonstrated that carboxamide function also serves as an effective directing group providing *cis*- products with excellent diastereomeric ratios. The scope of the reaction was then expanded to a variety of oxygen-based nucleophiles, although limited to non-conjugated alkoxides (**Scheme 1.16**). Analogously, this methodology was amended for synthesis of conformationally constrained *cis*-cyclopropyl amino acid derivatives using azoles as nitrogen-based nucleophilic agents (**Scheme 1.17**).[37]

Scheme 1. 16



Scheme 1. 17



Nonetheless, thermodynamic, steric, and directed control allows for the facile addition of a variety of nucleophiles, more acidic pronucleophiles such as phenol proved to be ineffective in reactions with in situ generated non-activated 3,3-disubstetuted cyclopropenes. This obstacle was overcome utilizing a stepwise approach involving a directed nucleophilic addition to pre-generated isolable cyclopropene (see Chapter 2).

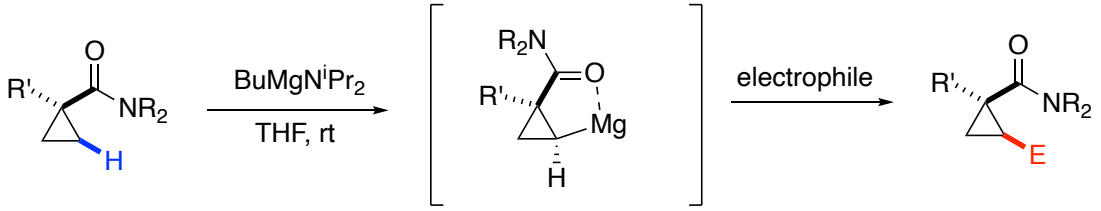
1.3 C-H functionalization

Directing group-assisted C–H functionalization started to gain momentum in the mid-1990s after a landmark contribution from the group of Murai.[38] In these reactions a directing moiety – an "internal ligand" – directs a metal catalyst into a close proximity of a certain C–H bond, leading to a selective cleavage of the bond followed by a functionalization. In cyclopropane chemistry C–H activations occur more readily than usual C(sp^3)–H activation, due to its rigidity and sp^2-like stereo-electronic properties.[39] Substituted as well as non-substituted amides proved to be extremely valuable as directing groups in C–H activation. By now, amides are amongst the most frequently applied DGs in C–H functionalization chemistry.[40]

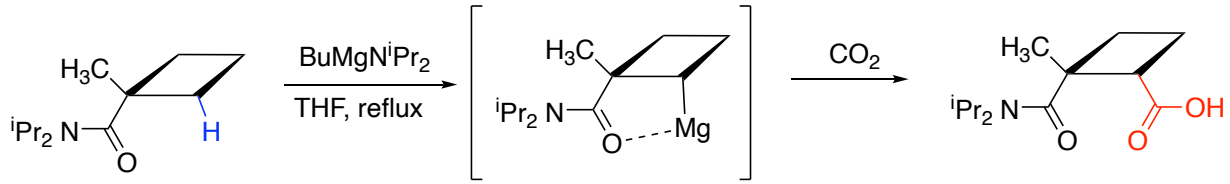
1.3.1 Directed metalation

After the pioneering work by Engel,[41] one of the first examples of direct functionalization of small cycles utilizing directing effect of the amide function was reported by Eaton's group.[42] The authors demonstrated selective *syn* β-metalation of cyclopropyl- and cyclobutylcarboxamides using a magnesium base, specifically BuMgN*i*Pr_2 (**Scheme 1.18**). This metalation is remarkable in a sense that β-metalation is predominant even when highly acidic α-hydrogen is available, activation of which would enable a thermodynamically favored enolate-type intermediate.

Scheme 1. 18

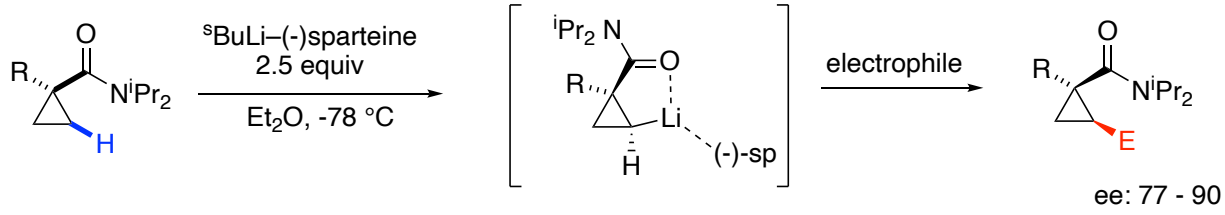


R = Et, ^{i}Pr; R' = H, Me, Ph



Following this discovery, Wilson's group developed an enantioselective synthesis of cyclopropylcarboxamides *via* a chiral base-mediated metalation[43] with synthetically useful yields and high levels of stereoselectivity (**Scheme 1.19**).

Scheme 1. 19

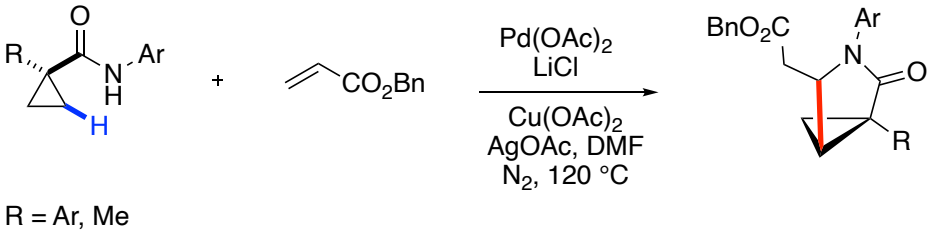


ee: 77 - 90

1.3.2 Directed transition metal catalyzed C(sp^3)–H bond activation

One of the first applications of an amide function as a directing group in Pd(II)-catalyzed C(sp^3)–H activation of cyclopropanes was demonstrated by Yu.[44] The developed reaction involved an amide directed C–H incretion of Pd to generate an alkyl-palladium intermediate, which then reacted with an alkene *via* carbopalladation, followed by *β*-hydride elimination to give the olefin product. The product then underwent a 1,4-conjugated addition to afford bicyclic lactam (**Scheme 1.20**).

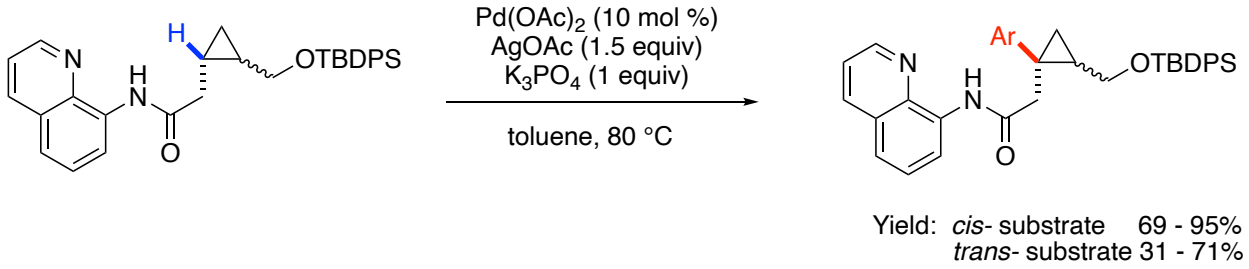
Scheme 1. 20



R = Ar, Me

Shuto's group employed aryl iodides as coupling partners to design a Pd(II)-catalyzed tertiary C(sp^3)–H arylation directed by amide group for construction of a chiral quaternary carbon center on cyclopropanes.[39] In contrast with intermolecular arylation *via* tertiary C(sp^3)–H arylation of cyclopropenes,[45,46] this method required an "*intermolecular*" arylation of the unactivated C–H bond (**Scheme 1.21**). This type of arylation of tertiary sp^3 carbon is extremely rare. A notable example of such transformation is the arylation of a highly active 9-phenyl-9*H*-fluorene reported by Huang.[47]

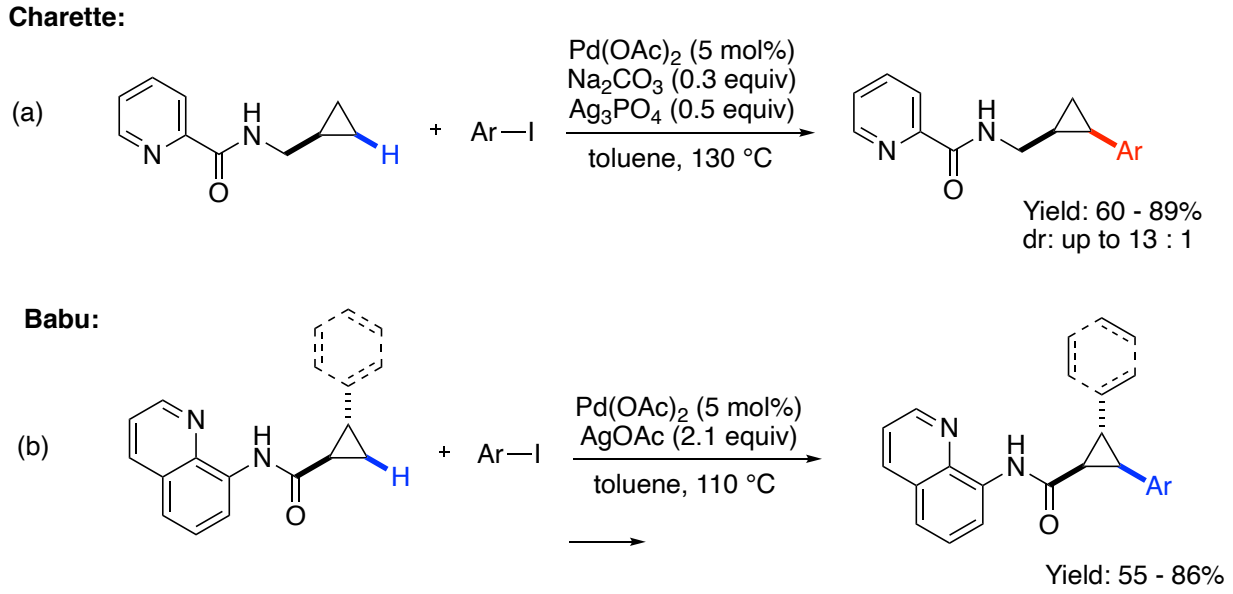
Scheme 1. 21



The chiral cyclopropane substrates, *cis*- and *trans*-, containing an amide function with preinstalled 8-aminoquinoline auxiliary as a directing group were subjected to intramolecular arylations, to prepare chiral arylcyclopropane with both *cis*- and *trans*-1,1,2 substitution patterns. The tertiary C(sp^3)–H bond activation of *cis*-substrate occurred effectively affording the products with good to excellent yields. The reaction of *trans*-substrate was described as more challenging than that of *cis*- and provided only moderate yields because of both the C–H abstraction and the subsequent arylation being impeded by the steric effects of the bulky substituent in the C2 position.

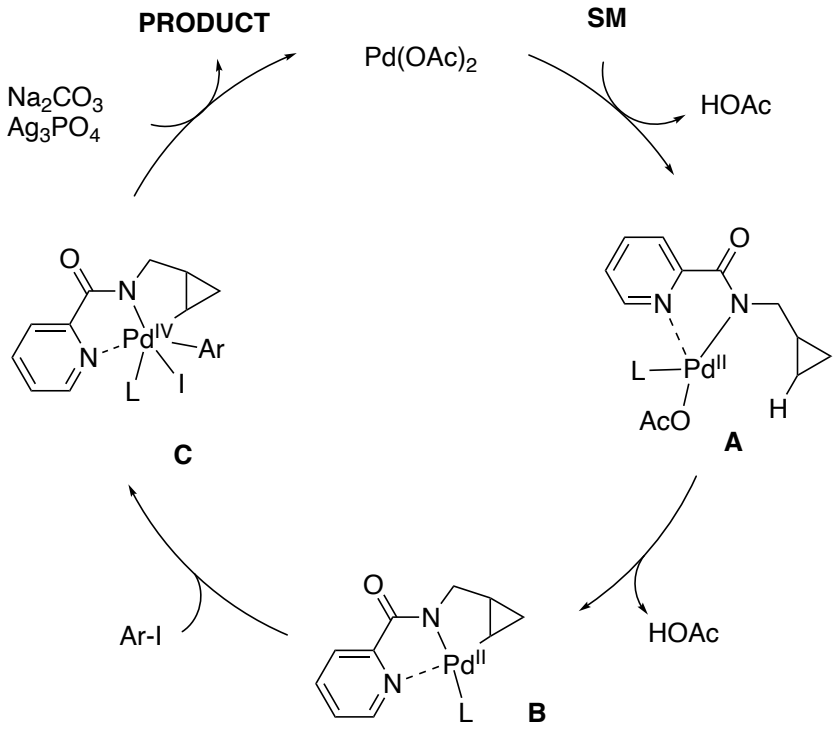
Charette[48] and Babu[49] independently reported Pd-catalyzed direct arylation of methylene C(sp^3)–H bonds of cyclopropenes employing directing effect of picoline (**Scheme 1.22, a**) and quinoline amides respectively (**Scheme 1.22, b**). Both methods were described as highly diastereoselective and allowed access to densely substituted cyclopropane carboxamide scaffolds possessing several contiguous stereogenic centers.

Scheme 1. 22



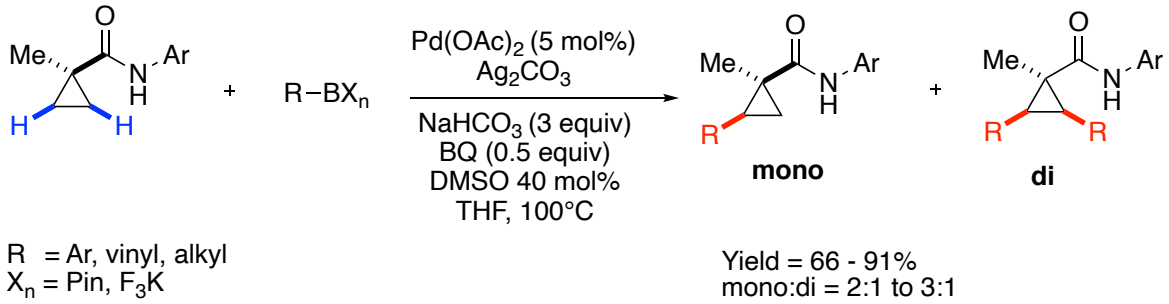
These reactions are believed to operate *via* a mechanism involving Pd(II)/Pd(IV) manifold, as proposed by Daugulis[50]. Initial five-membered metallocycle species **A** is formed, in which Pd complex is stabilized through coordination to the pyridine nitrogen as well as the highly acidic secondary amide moiety (**Scheme 1.23**). C–H palladation mediated by acetate provides intermediate **B**, followed by oxidative addition of the aryl iodide to afford **C**. Reductive elimination provides the final product and the palladium amide **A** is regenerated.

Scheme 1. 23



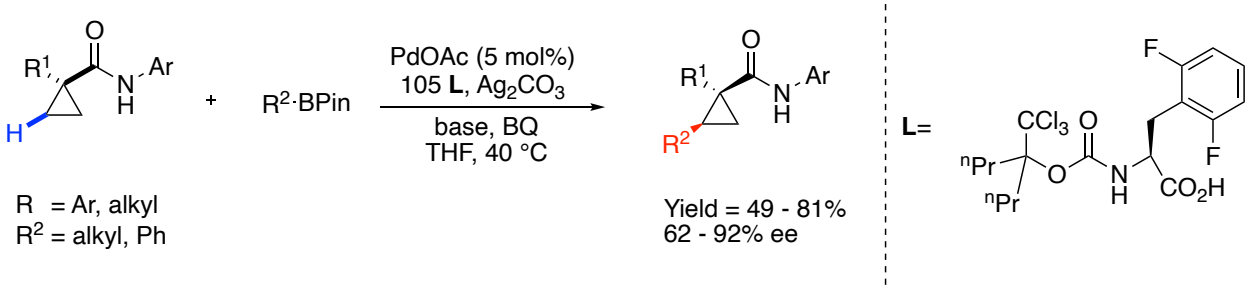
An example of Pd(II)-catalyzed enantioselective C–H activation of cyclopropane derivatives was reported by Yu et al. in 2011.[51] Utilizing acidic *N*-arylamide as a weakly coordinating directing group for C–H functionalization reaction, the authors established a robust cross-coupling reaction of the amide derivative of 1-methylcyclopropanecarboxylic acid with phenyl-, aryl-, alkyl-, and vinylboronic acid pinacol esters (**Scheme 1.24**). The reaction proceeded with good yields and became the first example of Pd(II)-catalyzed cross-coupling of alkyl C–H bonds with vinylboron reagents.

Scheme 1. 24



It was further shown that this methodology could be used for synthesis of chiral substrates. The addition of a carefully chosen mono-*N*-protected aminoacid ligand resulted in a development of a protocol for an enantioselective C–H activation of cyclopropane providing high levels of stereo-induction under mild condition (**Scheme 1.25**). This asymmetric C–H activation/cross-coupling cascade reaction provided a new disconnection for the synthesis of *cis*-substituted chiral cyclopropane amides.

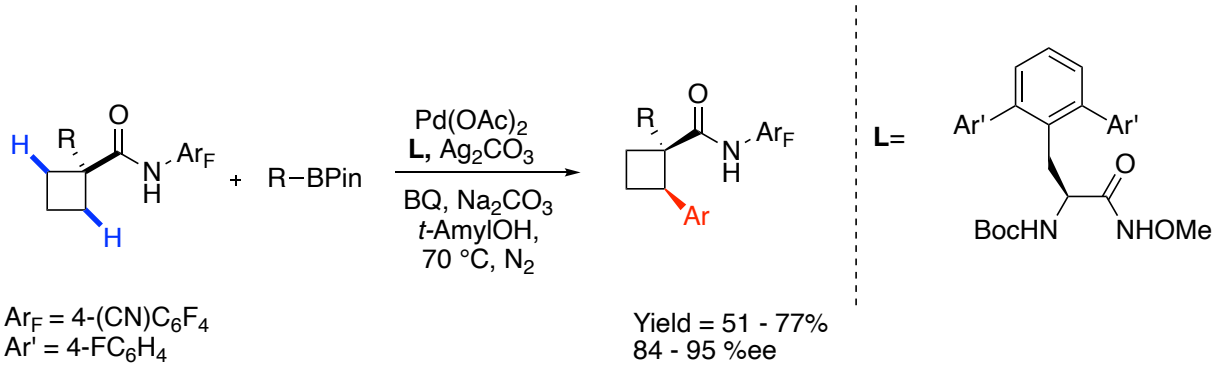
Scheme 1. 25



Similarly to functionalization of the cyclopropane derivatives the directing effect of the amide function was utilized in enantioselective arylation of cyclobutene amides (**Scheme 1.26**).[52] In these Pd(II)-catalyzed cross-coupling reactions the enantioselective functionalization of

prochiral C–H bonds was achieved through the development of a new class of chiral ligands, MPAHA, which derived from mono-*N*-protected amino acids.

Scheme 1. 26

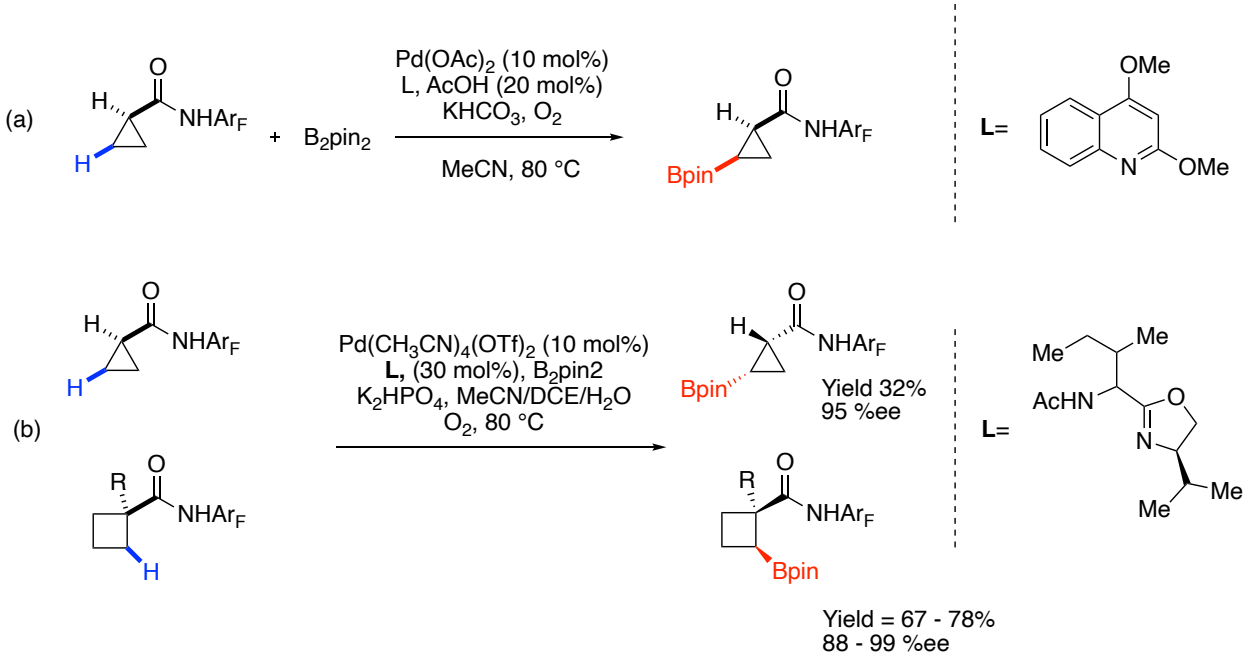


Ar_F = 4-(CN)C_6F_4
Ar' = 4-FC_6H_4

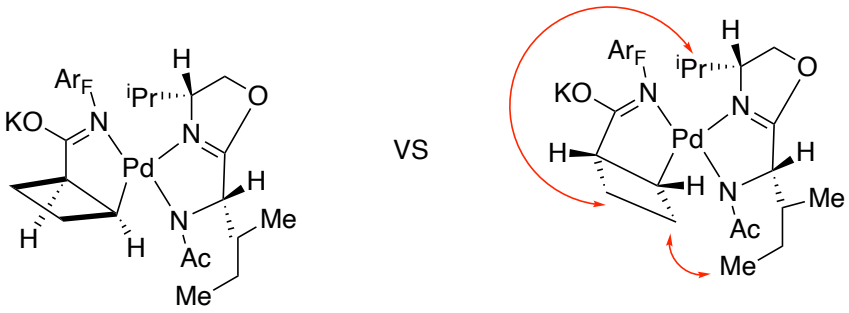
Yield = 51 - 77%
84 - 95 %ee

The developed methods provided high levels of diastereo- and enantioselectivity utilizing a combination of a coordinating monodentate substrate and a chiral ligand (exemplified in **Scheme 1.28**), but are limited to the substrates containing *α*-quaternary carbon centers. A major advancement in functionalization of non-activated C(sp^3)–H bonds in small cycles was achieved through the use of quinoline-based ligands and chiral bidentate acetyl-protected aminoethyl oxazoline (APAO) ligands (**Scheme 1.27**). These methods proved to be compatible with substrates containing *α*-tertiary as well as *α*-quaternary carbon centers. Importantly, these method allowed for development of enantioselective borylation of cyclopropane[53] and cyclobutene[54] (**Scheme 1.27, b**) derivatives en route to the corresponding organoboronates, which can be further converted into various organic products such as chiral *β*-arylated, *β*-hydroxilated, and *β*-fluorinated derivatives.

Scheme 1. 27



Scheme 1. 28



1.4 Conclusion

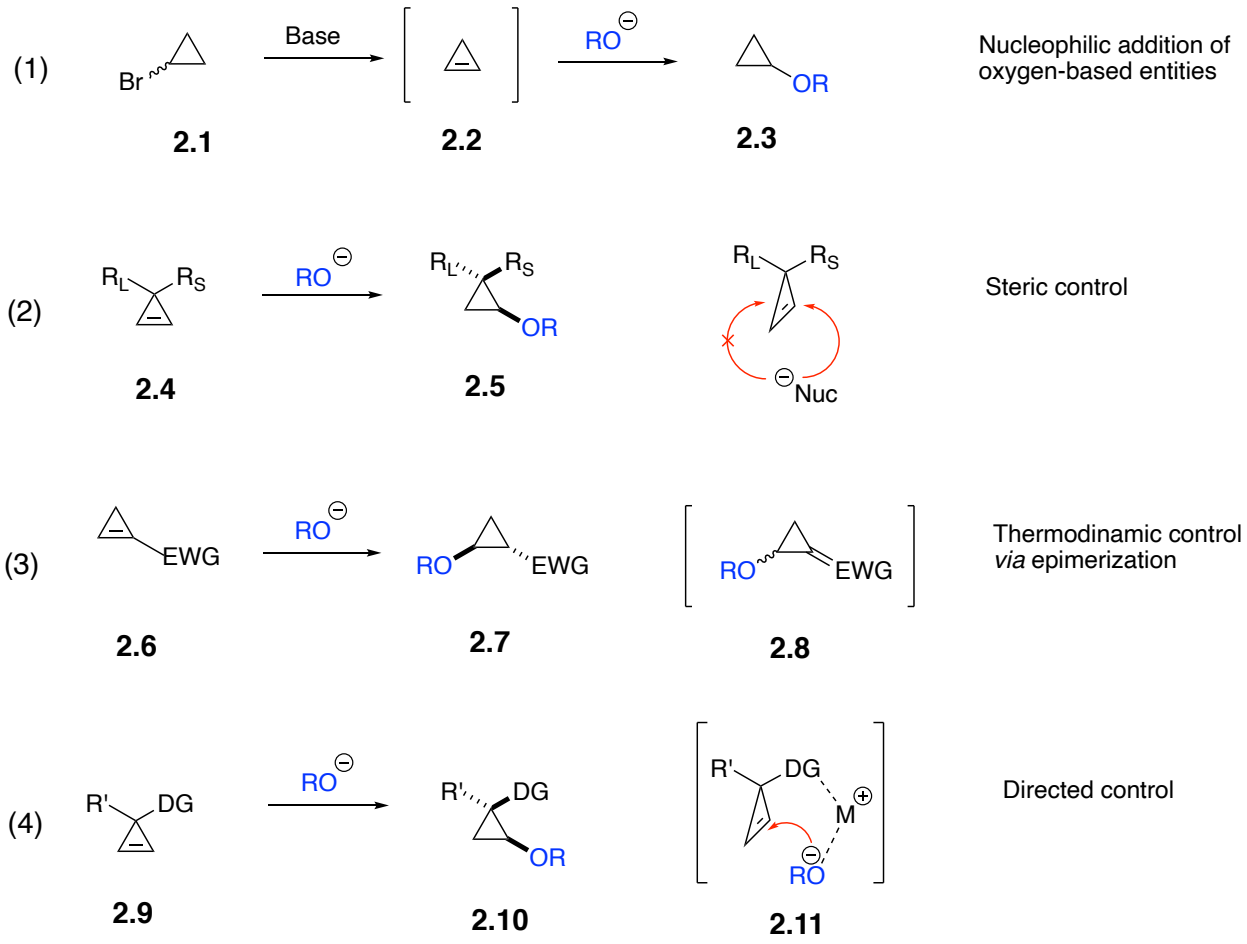
Small cycles such as cyclopropanes and cyclopropenes are appealing synthetic scaffolds. Their unusual bonding and inherent ring strain make possible a variety of synthetic transformations for preparation of larger molecular structures possessing a wide range of biological properties.[11] The expansion of synthetic availability of the smallest carbocycles triggered a rapid growth of the knowledge base of their reactivity and applicability in organic synthesis and biology. A large variety of their diastereo- and enantioselective transformations were reported in recent years utilizing different modes of the stereocontrol. Reactions, in which the stereoselectivity is governed by a directing effect of a pre-installed substituent, such as reviewed in this chapter, are of especial interest as they are often less substrate-dependent. These reactions allow for preparation of densely *cis*-substituted cyclopropanes, while directed C–H activation allows for late-stage functionalization, which is of a great interest for synthetic applications. Moreover, directed diastereo- and enantioselective reactions leading to ring opening products provide access to acyclic molecular structures featuring several consecutive stereogenic centers.

Chapter 2 Directed nucleophilic addition of phenoxides to cyclopropenes

2.1 Introduction

Ring-retentive metal-catalyzed additions to cyclopropenes *en route* to stereochemically defined cyclopropanes have evolved into a rapidly growing area during the past decade[15–18,20,30,31,55–64]. Non- catalytic ring-retentive diastereoselective additions of various nucleophilic entities across the double bond of cyclopropenes are much less common[8,35,65,66]; however, this unorthodox approach towards cyclopropyl-based scaffolds is very attractive from a synthetic standpoint.

Scheme 2. 1



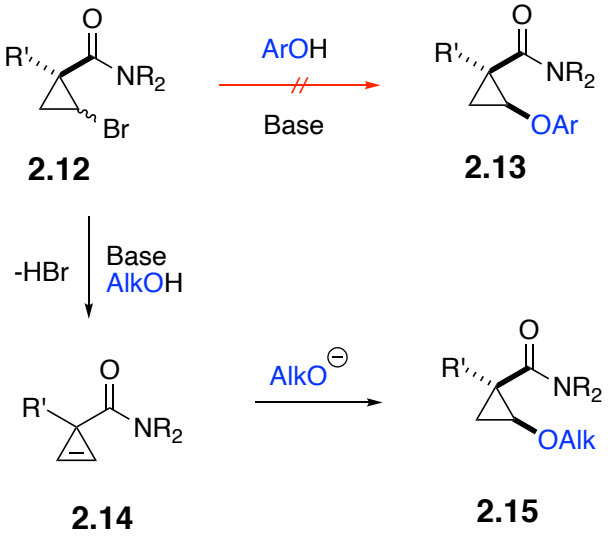
Nucleophilic additions of oxygen-based entities (alkoxides and phenoxides) to unsubstituted cyclopropene **2** (traditionally generated *in situ* from cyclopropylbromide **2.1**) are successfully utilized in medicinal chemistry and drug discovery for the installation of a cyclopropyloxy group into a pharmacophore (**Scheme 2.1**, eqn (1)).[67–74] Related transformations of highly strained symmetric spirocyclic polycyclopropanes are also known.[75] However, the reactions of substituted cyclopropenes are typically not diastereoselective,[76] unless the selectivity is enforced by excessive steric hindrance.[77,78] Rubin et al. have previously reported a formal nucleophilic substitution of bromocyclopropanes operating *via* the dehydrohalogenation/addition of oxygen-based nucleophiles to cyclopropene intermediates, which can be carried out in both inter-[79,80] or intramolecular fashion.[81–83] Diastereoselectivity in these reactions is efficiently controlled by steric effects (**Scheme 2.1**, eqn (2)), *via* a thermodynamically driven epimerization of one of the newly formed centers (eqn (3)), or by a directing effect of a strategically placed functional group, capable of coordination to the alkali metal (eqn (4)). A combination of the above-listed factors was also employed for the diastereoselective installation of several contiguous stereogenic centers.[84]

While all these transformations are fairly general for alkoxides, aryloxides have been previously engaged only in the reactions with the most electrophilic cyclopropenes activated by a conjugate electron-withdrawing group (*i.e*. substrates of type **2.6**, **Scheme 2.1**, eqn (3)).[85–87] In this work we demonstrate diastereocontrolled addition of aryloxides to unactivated 3,3-disubstituted cyclopropenes 2.18.

As mentioned above, superlative electrophilic properties render conjugate cyclopropenes of type **2.6** highly unstable. They, however, can be easily generated *in situ via*

1,2-eliminaiton of HBr from the corresponding α- or β-bromocyclopropanes.[85–87] Much more stable and isolable non-conjugated cyclopropenes **2.14** (R' = Me) can also be obtained *via* a base-assisted 1,2-dehydrobromination of bromocyclopropanes **2.12**.[88]

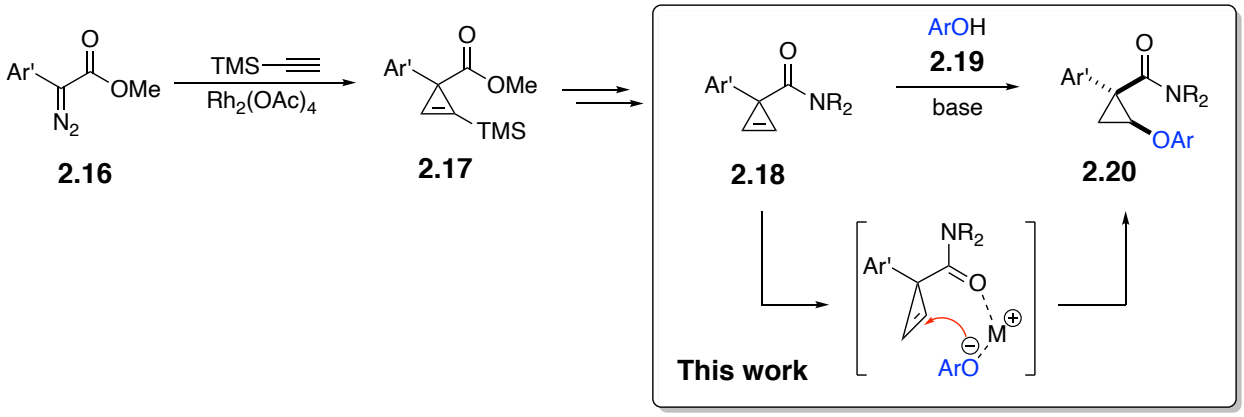
Scheme 2. 2



Both strained olefins **2.6** and **2.14** underwent directed nucleophilic additions of *in situ* generated alkoxides affording alkyl cyclopropyl ethers **2.7** and **2.15** with *trans*- and *cis*-configuration, respectively (**Scheme 2.2**).[79,80] However, an attempt to carry out addition of phenols starting from bromocyclopropane **2.12** failed to produce any cyclopropyl aryl ethers **2.13** and resulted in recovery of the starting material. The lack of reactivity was attributed to lower pK_a's of phenols as compared to alcohols, which lead to reduced effective basicity of the media, rendering it insufficient for the dehydrobromination of **2.12** to take place. We rationalized that a stepwise approach involving a directed nucleophilic addition to pre-generated, isolable cyclopropene **2.14**, could potentially be explored as an alternative route. In addition to the 1,2-

dehydrobromination pathway, cyclopropenes **2.18** with an aryl substituent can also be accessed *via* the Rh(II)-catalyzed cyclopropenation of trimethylsilylacetylene (**Scheme 2.3**).[89,90]

Scheme 2. 3



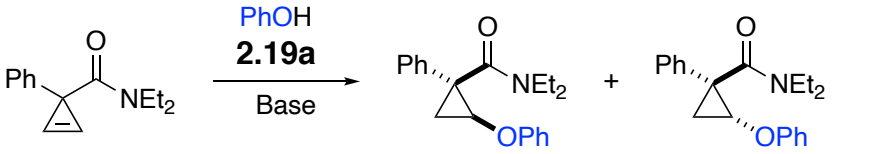
2.2 Initial reaction optimization

To evaluate this idea, we subjected *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide **2.18a** to a reaction with phenol **2.19a** (1.25 equiv.) in the presence of a base. Two conditions were probed, which previously proved best for the base-assisted additions of alkoxides[79–83] and nitrogen-based nucleophiles.[91–94] The first set of conditions employed a suspension of finely powdered KOH (1.50 equiv.) in anhydrous THF (**Table 2.1**, entry 1), and the second exploits a solution of *t*-BuOK (1.50 equiv.) in dry DMSO (entry 2). Test reactions carried out in the presence of these bases at room temperature resulted in recovery of the starting material. To force the reaction, the mixtures were heated to 70 °C (entries 3-4), which gave rise to trace amounts of aryl ether **2.20aa** in the reaction mediated by KOH (entry 3). Further increase of temperature to

90 °C and the use of a suspension of KOH in DMSO allowed for formation of **2.20aa** in low yield as an equimolar mixture of two diastereomers (entry 5).

Table 2. 1

Optimization of reaction conditions for directed nucleophilic addition of phenol to cyclopropene **2.18a**



2.18a *cis*-**2.20aa** *trans*-**2.20aa**

	Base (equiv.)	PhOH (equiv)	Solvent	T, °C	Time, h	Yield[a]	dr (*cis*:*trans*)
1	KOH (1.50)	1.25	THF	RT	10	NR	N/A
2	*t*-BuOK (1.50)	1.25	DMSO	RT	10	NR	N/A
3	KOH (1.50)	1.25	THF	70	10	trace	N/A
4	*t*-BuOK (1.50)	1.25	DMSO	70	10	NR	N/A
5	KOH (1.50)	1.25	DMSO	90	10	12	50:50
6	KOH (1.50)[b]	1.25	DMSO	90	10	NR	N/A
7	KOH (1.50)	1.25	THF	90	24	32	98:2
8	**KOH (3.50)**	**2.00**	**THF**	**90**	**48**	**58**	**97:3**
9	KOH (3.50)[b]	2.00	THF	90	48	12	50:50
10	$LiOH{\cdot}2H_2O$ (1.50)	1.25	THF	90	48	NR	N/A
11	$Ca(OH)_2$ (1.50)	1.25	THF	90	48	NR	N/A
12	NaOH (1.50)	1.25	THF	90	48	NR	N/A
13	DBU (1.50)	1.25	THF	90	48	NR	N/A
14	DBU/LiCl (1.50)	1.25	THF	90	48	NR	N/A
15	$DBU/FeCl_3$ (1.50)	1.25	THF	90	48	NR	N/A
16	$DBU/AgNO_3$ (1.50)	1.25	THF	90	48	NR	N/A
17	DBU/Ag_2O (1.50)	1.25	THF	90	48	NR	N/A
18	DBU/CuCl (1.50)	1.25	THF	90	48	NR	N/A
19	$DBU/CuCl_2$ (1.50)	1.25	THF	90	48	NR	N/A
20	**KOH (6.00)**	**4.00**	**THF**	**90**	**48**	**94**	**95:5**
21	Cs_2CO_3 (6.00)	4.00	THF	90	48	94	90:10

a) Yields are determined by integration of ^1H NMR spectra of samples taken from crude reaction mixtures against dibromomethane as an internal standard. "NR" indicates formation of cyclopropyl aryl ether **2.20aa** was not detected and starting material **2.18a** remained intact.

b) These reactions were performed in the presence of stoichiometric amounts of 18-crown-6 ether.

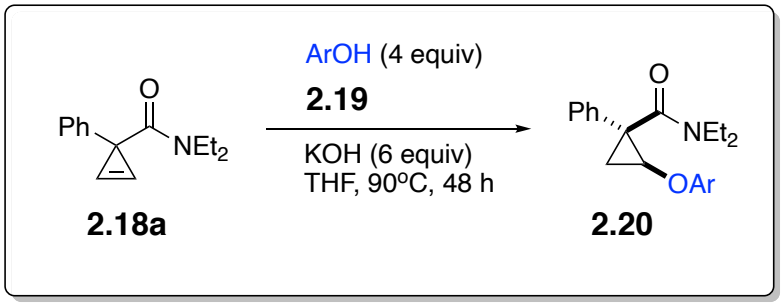
Interestingly, addition of 18-crown-6 ether to the mixture in order to improve the solubility of the base, seemed to have suppressed the reaction (entry 6). Employment of THF as the reaction solvent proved more efficient and selective as compared to DMSO. Thus, heating cyclopropene **2.18a** in the presence of 1.25 equiv. of phenol (**2.19a**) and 1.50 equiv. of base for 24 h at 90 ^{o}C in THF afforded 32% of cyclopropyl aryl ether **2.20aa**. This reaction appeared to be highly diastereoselective, strongly favoring the formation of *cis*-isomer (entry 7). Extending the reaction time to 48 h allowed for 58% conversion while maintaining nearly the same level of *cis*-selectivity (entry 8). Here again, addition of 18-crown-6 had a detrimental effect on both the conversion and the facial selectivity (entry 9). It should be pointed out that the described transformation relies on sufficient Brønsted basicity of the employed base and on the coordinating ability (Lewis acidity) of the metal counter-cation, specifically, potassium hydroxide. Some less basic (but more Lewis acidic) hydroxides of lithium, sodium, and calcium gave no desired reactivity (entries 10-12). We also unsuccessfully attempted to induce this reaction by using a strong organic base, such as DBU (entry 13); including its combinations with various Lewis-acidic metal ions (entries 14-19). Best conversions were achieved only in the presence of a large excess of phenoxide. Thus, a reaction of **2.18a** performed in the presence of 4 equiv. of phenol and 6 equiv. of KOH proceeded to completion affording the desired product **2.20aa** in nearly quantitative NMR yield and high diastereoselectivity (entry 20). Notably, an attempt to employ anhydrous cesium carbonate, which serves as a strong base, but has reduced coordination ability to the amide function, allowed for equally high product yield with lower diastereoselectivity (entry 21).

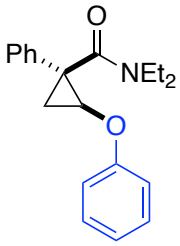
2.3 Nucleophilic addition of phenoxides to cyclopropenes

With optimized conditions in hand, we probed this reaction on a preparative scale. The post-reaction workup required additional optimization, as we discovered that the usual aqueous treatment and acid-base extraction lead to notable decomposition of the product. It was found that neutralization of the reaction mixture with solid ammonium chloride allowed for precipitation of most inorganic salts at pH 8. These salts could be easily filtered off affording clear filtrate which, after concentration in vacuum, was ready for chromatographic purification. This protocol allowed for isolation of cyclopropyl aryl ether **2.20aa** in good yield (**Scheme 2.4**).

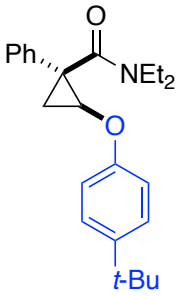
Next, we explored the reactivity of different phenols in this directed addition. As expected, highly nucleophilic, electron-rich, non-bulky phenols bearing electron-donating groups in the *para*- position reacted smoothly providing high yields of the corresponding cyclopropyl aryl ethers **2.20ab** and **2.20ac**, respectively. *meta*-Substituted aryloxides generated from phenols were less reactive due to less efficient localization of the negative charge providing adducts **2.20ad** and **2.20ae** with lower yields. Phenol possessing a weakly deactivating *para*-bromo substituent, as well as sterically hindered 2-naphthol also proved less reactive (products **2.20af** and **2.20ag**). Finally, *N*-(4-hydroxyphenyl)acetamide and *p*-cyanophenol, which allow for efficient stabilization of negative charge in the corresponding anions, did not provide addition products **2.20ai** and **2.20ah** at all.

Scheme 2. 4

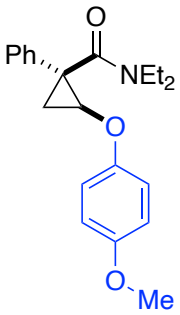




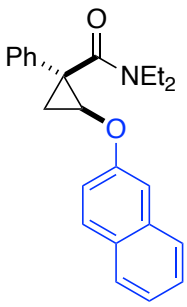
2.20aa, 81%
dr = 95:5



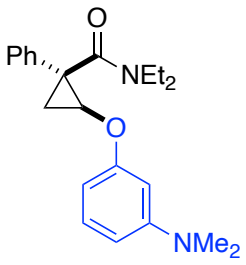
2.20ac, 67%
dr = 97:3



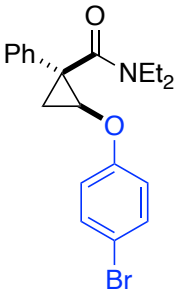
2.20ab, 78%
dr = 96:4



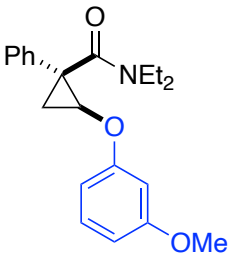
2.20ag, 59%
dr = 95:5



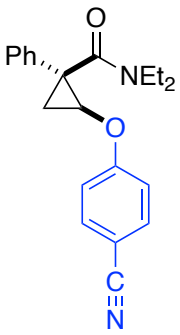
2.20ae, 52%
dr = 95:5



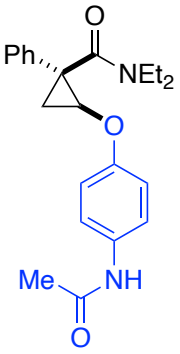
2.20af, 47%
dr = 95:5



2.20ad, 51%
dr = 95:5



2.20ai, 0%

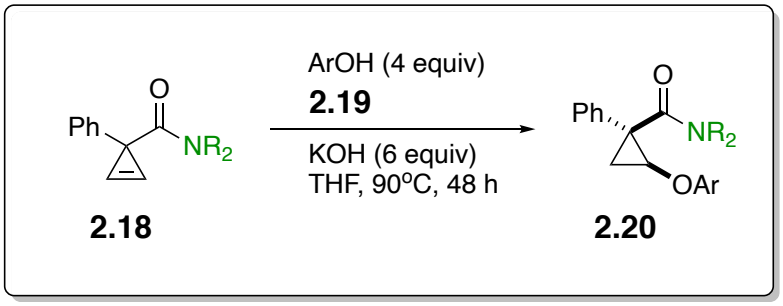


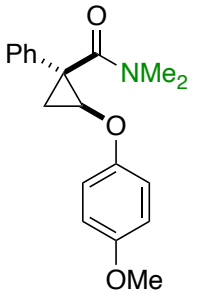
2.20ah, 0%

We next moved on to investigate if steric and electronic environment on the directing carboxamide functionality played any role in the reactivity of cyclopropenes. We reasoned that increased electron density on the carbonyl group would strengthen coordination of the potassium cation, further enhancing the directing effect. On the other hand, steric hindrance as

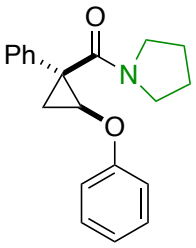
well as acidic hydrogens in secondary amides might impede the reaction. The observed reactivity was in line with the above rationale.

Scheme 2. 5

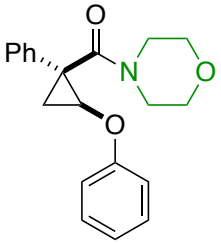




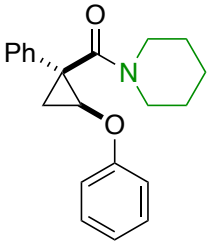
2.20bb, 55%
dr = 98:2



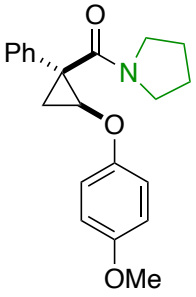
2.20ca, 69%
dr = 97:3



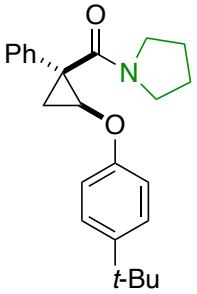
2.20da, 53%
dr = 95:5



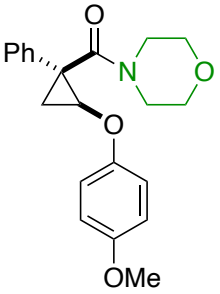
2.20ea, 33%
dr = 88:12



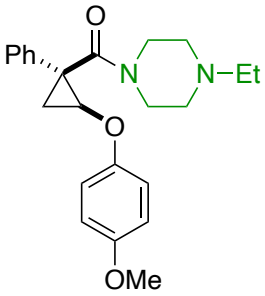
2.20cb, 78%
dr = 83:17



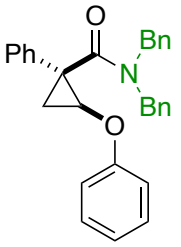
2.20cc, 76%
dr = 86:14



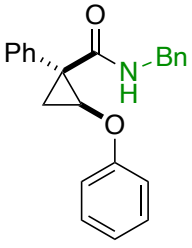
2.20db, 66%
dr = 98:2



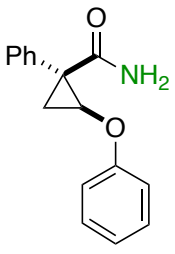
2.20fb, 0%



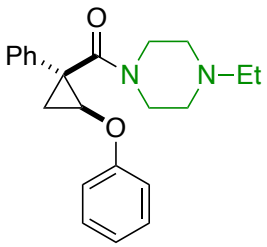
2.20ga, 0%



2.20ha, 0%



2.20ia, 0%

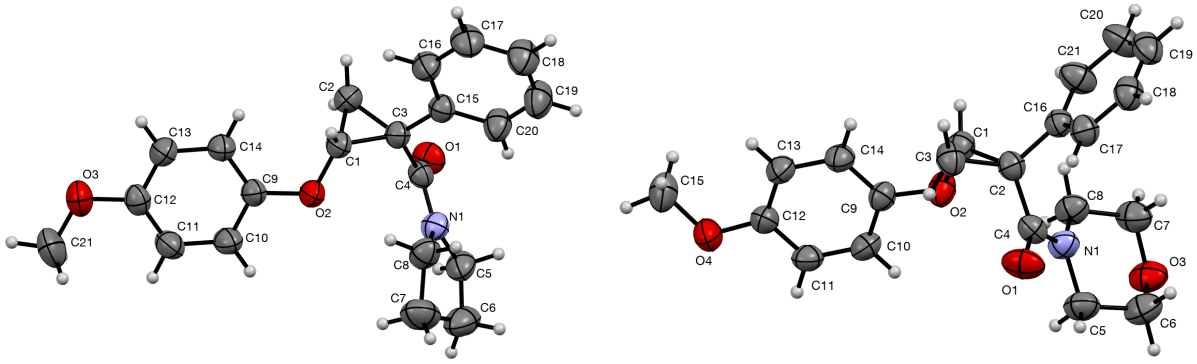


2.20fa, 0%

Thus, cyclopropene **2.18b** (R = Me) derived from dimethylamine afforded notably lower yield of the corresponding *p*-methoxyphenol adduct **2.20bb** (**Scheme 2.5**) as compared to a slightly more electron-rich diethylamine analog **2.20ab**. In contrast, electron-rich and non-bulky pyrrolidine derivative **2.18c** (R = -$(CH_2)_4$-) readily afforded the corresponding products **2.20ca**, **2.20cb**, and **2.20cc** in yields comparable to those obtained for diethylamine analogs. It should be pointed out that anilides are not compatible with this reaction, as the aromatic amide bond is readily cleaved under these reaction conditions.[88] More sterically hindered carboxamides derived from six-membered cyclic secondary amines such as morpholine, (respective adducts **2.20da** and **2.20db**), piperidine (product **2.20ea**), and *N*-ethylpiperazine (products **2.20fa** and **2.20fb**) showed attenuated reactivity. The latter did not react with even the most nucleophilic phenol (**2.18a**) and *p*-methoxyphenol (**2.18b**). Similarly, sterically encumbered *N*,*N*-dibenzylamide **2.18g** proved to be inert under the standard reaction conditions (adduct **2.20ga**). We also failed to obtain adducts **2.20ha** and **2.20ia** from secondary and primary amides, respectively.

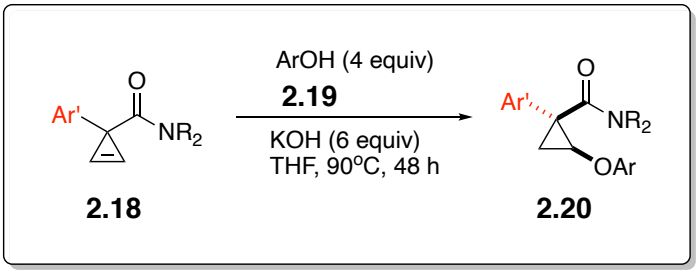
Figure 2. 1

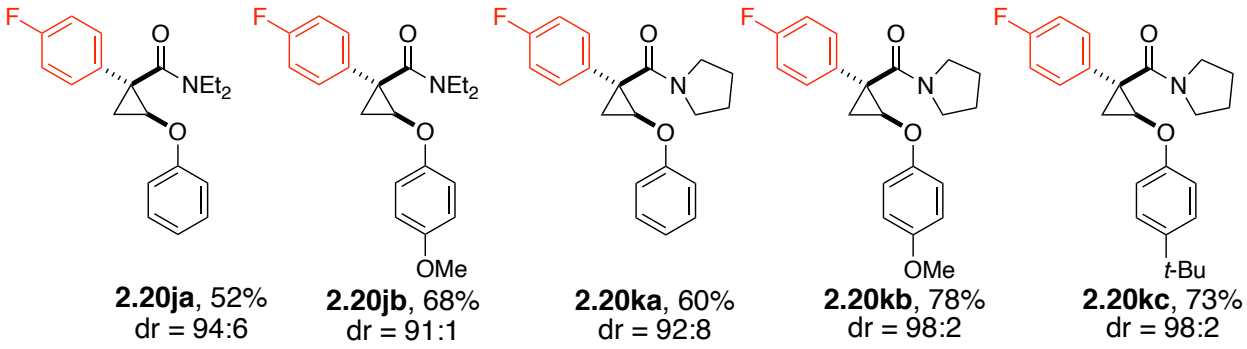
ORTEP drawings of *cis*-2.20cb (CCDC #1571107, left) and *cis*-2.20db (CCDC #1570793, right) showing atom numbering labels and 50% probability amplitude displacement ellipsoids.



Starting materials in these reactions rapidly decomposed upon heating, potentially due to oligomerization involving a base-assisted attack of *N*-nucleophiles generated in the reaction mixture.[91–94] Finally, we found a negligible effect on reactivity of the substituents in the aromatic ring alpha to carboxamide functionality. All such cyclopropenes **2.18j**-**2.18n** provided the corresponding products **2.20j**-**2.20n** in good yields (**Scheme 2.6**). *cis*-Configuration of the obtained adducts was unambiguously confirmed by single crystal X-ray crystallography (**2.20cb** and **2.20db**, **Figure 2.1**) or by 2D-NOESY experiment (**2.20bb**, see Appendix for details).

Scheme 2. 6





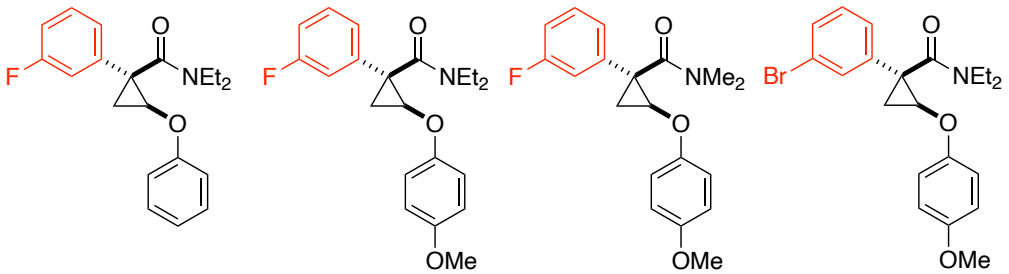
2.20ja, 52%
dr = 94:6

2.20jb, 68%
dr = 91:1

2.20ka, 60%
dr = 92:8

2.20kb, 78%
dr = 98:2

2.20kc, 73%
dr = 98:2



2.20la, 50%
dr = 92:8

2.20lb, 71%
dr = 94:6

2.20mb, 64%
dr = 98:2

2.20nb, 65%
dr = 96:4

2.4 Conclusion

A strain-release driven, carboxamide-directed addition of aryloxides across the double bond of cyclopropenes providing diastereomerically pure cyclopropyl aryl ethers was demonstrated. The facial selectivity of this transformation is controlled by strong coordination of the amide functionality to potassium cation, which served as an efficient delivery vehicle for the aryloxide nucleophile.

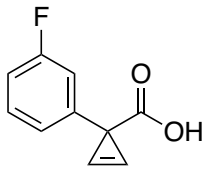
2.5 Experimental

2.5.1 General information

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) with a dual carbon/proton cryoprobe (CPDUL), Bruker III (600 MHz) equipped with BBO probe. ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (–) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a ThermoFisher Nicolet™ iS™ 5 FT-IR Spectrometer. HRMS was carried out on LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried in vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40-63 mm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous dichloromethane was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual stage deionization followed by dual stage reverse osmosis. Cyclopropenes **2.18a**,**c**-**i** were synthesized according to our previously published

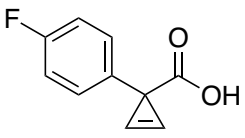
procedure[90] and had physical and spectral properties identical to those earlier reported. Syntheses of cyclopropenes **2.18b**,**j-n** are described below. All other reagents and solvents were purchased from commercial vendors and used as received.

2.5.2 Synthesis of starting materials



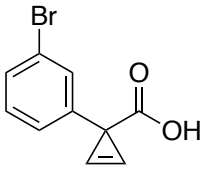
1-(3-Fluorophenyl)cycloprop-2-ene-1-carboxylic acid: Methyl (3-fluorophenyl)acetate (5.86 g, 34.8 mmol, 1.00 equiv) and tosyl azide (7.2 g, 36.5 mmol, 1.05 equiv) were stirred in acetonitrile (100 mL) at 0 ^{o}C, and DBU (6.32 g, 41.5 mmol, 1.2 equiv) was added dropwise. Upon complete addition the reaction was allowed to warm to room temperature and was stirred overnight. Solvent was then evaporated and the residue was partitioned between saturated ammonium chloride and methylene chloride. The aqueous phase was then extracted with methylene chloride (3 x 30 mL). Combined organic phases were then washed with brine, dried with $MgSO_4$, filtered, and concentrated. The recovered material was then immediately filtered through a short pad of Silica gel using a 9:1 mixture of hexane and ethyl acetate. Crude methyl 2-diazo-2-(3-fluorophenyl)acetate was obtained as a red oil. This material was then dissolved in trimethylsilylacetylene (2.5 mL) (insoluble impurities could be ignored and filtered off using a cotton plug), and added via syringe pump over 18 h to a stirring and refluxing suspension of rhodium (II) acetate dimer (2.3 mg, 5.1 μmol, 0.015 mol %) in trimethylsilylacetylene (49 mL, 348 mmol, 10.0 equiv). After complete addition, the reaction was monitored by gas chromatography until complete consumption of the starting material was observed. Once this was achieved, the reflux condenser was replaced with a distillation head and most of the trimethylsilylacetylene was recovered by distillation at

ambient pressure. Residual solvent was then removed under vacuum. The reaction mixture was then purified by short column chromatography eluting with a mixture hexane:CH_2Cl_2 (3:1). Crude ethyl 1-(3-fluorophenyl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate was obtained as a yellowish oil, which was stirred at 0 °C in a mixture of methanol and THF (1:1, 50 mL). An aqueous solution of sodium hydroxide (1.5 M, 15 mL) was added dropwise and the mixture was stirred for 18 hr. Organic solvents were then removed under vacuum and the remaining aqueous solution was washed with dichloromethane (20 mL). The mixture was acidified to pH 2 with 1N aqueous HCl and extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The obtained product was purified by column chromatography on Silica gel eluting with a mixture hexane/EtOAc (2:1). The titled compound was obtained as a colorless crystalline solid, mp 82.0-83.0 °C, Rf 0.33, overall yield 3.212 g (18.0 mmol, 52%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 1H), 7.21 (s, 2H), 7.09 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.05 (ddd, *J* = 10.1, 2.6, 1.6 Hz, 1H), 6.95 (tdd, *J* = 8.4, 2.6, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 180.9, 162.6 (d, *J* = 245.3 Hz), 143.1 (d, *J* = 7.3 Hz), 129.6 (d, *J* = 8.2 Hz), 123.9 (d, *J* = 2.8 Hz), 115.4 (d, *J* = 22.0 Hz), 113.8 (d, *J* = 21.0 Hz), 106.6, 29.9 (d, *J* = 2.3 Hz). FT IR (NaCl, cm^{-1}): 3026, 3007, 1643, 1495, 1435, 1400, 1350, 1215, 1097, 1030, 995, 777, 754, 689. HRMS (TOF ES): found 177.0351, calculated for $C_{10}H_6FO_2$ $(M-H)^-$ 177.0357 (3.4 ppm).



1-(4-Fluorophenyl)cycloprop-2-ene-1-carboxylic acid, **Typical procedure:** A solution of methyl 1-(4-fluorophenyl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate[89] (457 mg, 1.73 mmol, 1.0 equiv.) in a mixture of methanol and THF (1:1, 20 mL) was

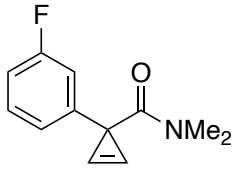
stirred. An aqueous solution of sodium hydroxide (1.5 M, 15 mL) was added dropwise and the mixture was stirred for 18 hr. Organic solvents were then removed under vacuum and the remaining aqueous solution was washed with dichloromethane (20 mL). The mixture was acidified to pH 2 with 1N aqueous HCl and extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The obtained product is typically pure enough to be used in further amide coupling as is, however, if necessary, further purification can be achieved by column chromatography on Silica gel eluting with a mixture hexane/EtOAc (1:1). The titled compound was obtained as colorless solid, mp 102.0-103.4 °C, R_f 0.40. Yield 289 mg (1.66 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 2H), 7.21 (s, 2H), 7.03 – 6.95 (m, 2H); ^{13}C (126 MHz, $CDCl_3$): δ 181.3, 161.8 (d, *J* = 245.6 Hz), 136.5 (d, *J* = 3.2 Hz), 130.1 (+, d, *J* = 8.2 Hz, 2C), 115.1 (+, d, *J* = 21.5 Hz, 2C), 107.2 (+, 2C), 29.7; FT IR (KBr, cm^{-1}): 3155, 3114, 3072, 2972, 2846, 2619, 1693, 1650, 1604, 1512, 1427, 1317, 1222, 1161, 1108, 983, 933, 813, 752; HRMS (TOF ES): HRMS (TOF ES): Found 177.0343, calculated for $C_{10}H_6FO_2$ $(M-H)^-$ 177.0352 (5.1 ppm).



1-(3-Bromophenyl)cycloprop-2-ene-1-carboxylic acid was obtained by hydrolysis of 1-(3-bromophenyl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate[83] (6.90 g, 21.2 mmol) using the typical procedure described for the synthesis of 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (*vide supra*). The titled compound was obtained as colorless crystalline solid, mp 88.4-89.7 °C, R_f 0.33 (Hexanes/EtOAc 2:1). Yield 3.897 g (16.3 mmol, 77%). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.43 (t, *J* = 1.8 Hz, 1H), 7.36 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H), 7.24 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.20 (s, 2H), 7.17 (t, *J* = 7.8

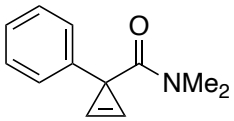
Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 180.6, 142.9, 131.5 (+), 129.9 (+), 129.7 (+), 127.1 (+), 122.2, 106.8, 29.8. FT IR (NaCl, cm^{-1}): 3120, 2981, 1697, 1660, 1594, 1564, 1412, 1267, 1227, 985, 884, 783, 703, 605. HRMS (TOF ES): found 236.9551, calculated for $C_{10}H_6BrO_2$ (M-) 236.9557 (2.5 ppm).

2.5.3 Synthesis of carboxamide intermediates

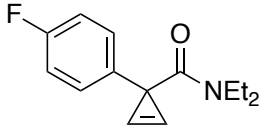


1-(3-Fluorophenyl)-N,N-dimethylcycloprop-2-ene-1-carboxamide (**2.18m**), ***(Typical procedure A)***: A flame-dried round bottom 25 mL flask was charged with 1-(3-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (375 mg, 2.11 mmol, 1.00 equiv.), DMF (1 drop) and freshly distilled anhydrous dichloromethane (15 ml) under nitrogen atmosphere. Oxalyl chloride (271 µL, 401 mg, 3.16 mmol, 1.50 equiv.) was then added dropwise and the mixture was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure to provide a pale yellow solid residue, which was dissolved in anhydrous dichloromethane (5.0 mL) and added dropwise to a solution of dimethylamine (40% water solution) (528 µL, 474 mg, 4.21 mmol, 2.00 equiv.) and triethylamine (608 µL, 426 mg, 4.21 mmol, 2.00 equiv.) in dichloromethane (10.0 mL). The reaction mixture was stirred for 18 hours at RT and then partitioned between water and dichloromethane. The aqueous phase was acidified with 1N HCl to pH 2. The organic phase was then extracted with acidified water (pH 2, 3 x 10 mL). The combined aqueous layers were back-extracted once with dichloromethane, which was combined with other organic phases, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on Silica gel to afford the title compound as a colorless crystalline solid, mp 109.2-109.3 °C, R_f 0.16 (Hexanes/ EtOAc 1:1).

Yield 346 mg (1.67 mmol, 80%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.22 (m, 2H), 7.21 (s, 2H), 6.92 – 6.86 (m, 2H), 6.79 (m, 1H), 2.99 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.2, 163.1 (d, *J* = 246.1 Hz), 146.2 (d, *J* = 6.5 Hz), 130.0 (d, *J* = 8.9 Hz) (+), 121.5 (d, *J* = 2.7 Hz) (+), 113.2 (d, *J* = 21.0 Hz) (+), 112.7 (d, *J* = 21.9 Hz) (+), 108.8 (+), 37.40 (+), 35.1 (+), 31.6 (d, *J* = 2.5 Hz); FT IR (NaCl, cm^{-1}): 3119, 3076, 2931, 1645, 1623, 1584, 1486, 1398, 1265, 1116, 1026, 859, 787, 695, 657, 609; HRMS (TOF ES): found 228.0809, calculated for $C_{12}H_{12}FNONa$ (M+Na) 228.0801 (3.5 ppm).

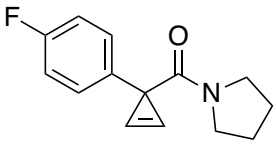


N,N-Dimethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18b**): Was prepared according to Typical Procedure A, employing 1-phenylcycloprop-2-ene-1-carboxylic acid (500 mg, 3.12 mmol, 1.0 equiv) and dimethylamine (40% solution in water, 704 mg, 6.24 mmol, 2.0 equiv.). The reaction was carried out at r.t. for 18 h followed by preparative column chromatography on Silica gel to afford the title compound as a colorless crystalline solid, mp 151.0-151.3 °C, R_f 0.22 (Hexanes/EtOAc 1:1). Yield 325 mg (1.76 mmol, 57%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.27 (m, 2H), 7.23 (s, 2H), 7.22 – 7.17 (m, 1H), 7.13 – 7.11 (m, 1H), 7.11 – 7.09 (m, 1H), 2.98 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ δ 173.9, 143.2, 128.4 (+), 126.2 (+), 125.8 (+), 109.1 (+), 37.4 (+), 35.1 (+), 31.9.; FT IR (NaCl, cm^{-1}): 3118, 3077, 3020, 2925, 1644, 1624, 1494, 1445, 1397, 1266, 1397, 1195, 1029, 741, 655, 606; HRMS (TOF ES): found 210.0898, calculated for $C_{12}H_{13}NONa$ (M+Na) 210.0895 (1.4 ppm).



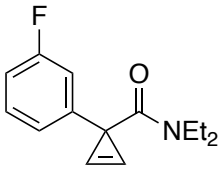
N,N-Diethyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamide (**2.18j**)*:* Was prepared according to Typical Procedure A, employing 1-(4-fluoro-

phenyl)cycloprop-2-ene-1-carboxylic acid (223 mg, 1.28 mmol, 1.0 equiv.) and diethylamine (323 µl, 228 mg, 3.12 mmol, 2.0 equiv.) The reaction was carried out at RT for 18 h followed by preparative column chromatography on Silica gel to afford the title compound as a colorless solid, mp 86.7-88.7 °C, R_f 0.23. Yield 232 mg (0.099 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 2H), 7.12 – 7.05 (m, 2H), 6.99 – 6.93 (m, 2H), 3.38 (q, J = 7.1 Hz, 2H), 3.30 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$): δ 173.0, 161.6 (d, J = 244.9 Hz), 139.4 (d, J = 3.1 Hz), 127.6 (+, d, J = 8.1 Hz, 2C), 115.3 (+, d, J = 21.5 Hz, 2C), 109.9 (+, 2C), 41.9 (–), 39.1 (–), 31.6, 13.8 (+), 12.7 (+); FT IR (KBr, cm^{-1}): 3070, 2975, 2935, 2875, 1620, 1508, 1460, 1429, 1380, 1363, 1313, 1276, 1220, 1159, 1120, 1097, 1012, 825, 810; HRMS (TOF ES): HRMS (TOF ES): Found 256.1121, calculated for $C_{14}H_{16}FNONa$ (M+Na) 256.1114 (2.7 ppm).

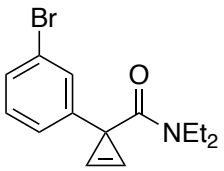


(1-(4-Fluorophenyl)cycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2.18k**): Was prepared according to Typical Procedure A, employing 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid[90] (750 mg, 4.21 mmol, 1.0 equiv.) and pyrrolidine (599 mg, 8.42 mmol, 2.0 equiv.). The reaction was carried out at r.t. for 18 h followed by preparative column chromatography on Silica gel to afford the title compound as a colorless crystalline solid, mp 154.7-155.0 °C, R_f 0.18 (Hexanes/EtOAc 1:1). Yield 845 mg (3.65 mmol, 87%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 (s, 2H), 7.10 (dd, *J* = 8.6, 5.3 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 3.51 (t, *J* = 6.6 Hz, 2H), 3.21 (t, *J* = 6.4 Hz, 2H), 1.91 – 1.69 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 161.5 (d, *J* = 245.1 Hz), 138.7 (d, *J* = 2.8 Hz), 127.6 (+), 115.2 (d, *J* = 21.7 Hz) (+), 109.5 (+), 46.4 (–), 45.8 (–), 32.3, 26.1 (–), 24.1 (–); FT IR (NaCl, cm^{-1}): 3101, 3059, 2973,

2876, 1617, 1507, 1440, 1235, 824, 669, 563; HRMS (TOF ES): found 254.0958, calculated for $C_{14}H_{14}FNONa$ (M+Na) 254.0957 (0.4 ppm).



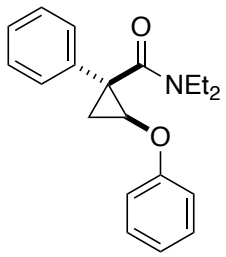
N,N-Diethyl-1-(3-fluorophenyl)cycloprop-2-ene-1-carboxamide (**2.18l**): Was prepared according to Typical Procedure A, employing 1-(3-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (375 mg, 2.11 mmol, 1.00 equiv.) and diethylamine (308 mg, 4.21 mmol, 2.00 equiv.). The reaction was carried out at RT for 18 h followed by preparative column chromatography on Silica gel to afford the title compound as a colorless crystalline solid, mp 78.8-79.0 °C, R_f 0.26 (Hexanes/EtOAc 1:1). Yield 383 mg (1.64 mmol, 78%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.22 – 7.14 (m, 2H), 7.17 (s, 1H), 6.89 – 6.84 (m, 1H), 6.82 (tdd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 6.74 (dt, *J* = 10.2, 1.9 Hz, 1H), 3.34 (q, *J* = 7.1 Hz, 2H), 3.26 (q, *J* = 7.1 Hz, 2H), 1.11 (dd, *J* = 7.5, 6.7 Hz, 3H), 0.88 (dd, *J* = 7.5, 6.7 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.5, 163.1 (d, *J* = 246.1 Hz), 146.6 (d, *J* = 6.4 Hz), 129.9 (d, *J* = 8.2 Hz) (+), 121.6 (d, *J* = 2.7 Hz) (+), 113.2 (d, *J* = 21.0 Hz) (+), 112.8 (d, *J* = 21.9 Hz) (+), 109.5 (+), 41.9 (–), 39.0 (–), 31.8, 13.8 (+), 12.6 (+); FT IR (NaCl, cm^{-1}): 3067, 2979, 2937, 1614, 1583, 1481, 1430, 1265, 1028, 649, 596; HRMS (TOF ES): found 256.1115, calculated for $C_{12}H_{16}FNONa$ (M+Na) 256.1114 (0.4 ppm).



1-(3-Bromophenyl)-N,N-diethylcycloprop-2-ene-1-carboxamide (**2.18n**): Was prepared according to Typical Procedure A, employing 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (375 mg, 1.57 mmol, 1.00 equiv.) and diethylamine (229 mg, 3.14 mmol, 2.0 equiv.). The reaction was carried out at RT for

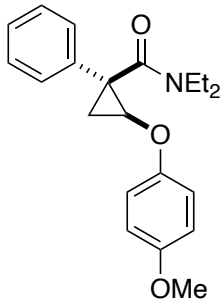
18 h followed by preparative column chromatography on Silica gel to afford the title compound as a colorless crystalline solid, mp 102.2-102.5 °C, R_f 0.23 (Hexanes/EtOAc 1:1). Yield 356 mg (1.21 mmol, 77%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.28 (m, 1H), 7.24 (s, 2H), 7.23 (s, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.11 – 7.06 (m, 1H), 3.40 (q, *J* = 7.1 Hz, 2H), 3.31 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.4, 146.1, 129.9 (+), 129.4 (+), 129.0 (+), 124.8 (+), 122.7, 109.3 (+), 41.88 (–), 39.0(–), 31.8, 13.8 (+), 12.6 (+); FT IR (NaCl, cm^{-1}): 3108, 3063, 2977, 2935, 1617, 1471, 1314, 1284, 1218, 889, 781, 709, 690, 681; HRMS (TOF ES): found 316.0316, calculated for $C_{12}H_{16}BrNONa$ (M+Na) 316.0313 (0.9 ppm).

2.5.4 Nucleophilic additions of aryloxides across cyclopropene double bond

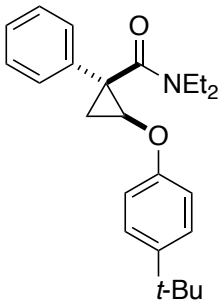


N,N-Diethyl-2-phenoxy-1-phenylcyclopropane-1-carboxamide (**2.20aa**)*,* ***(Typical procedure B)***: A 1 mL vial was charged with *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide[90] (**2.18a**) (50 mg, 0.232 mmol, 1.00 equiv.), phenol (**2.19a**) (87 mg, 0.929 mmol, 4.00 equiv.), KOH (78 mg, 1.393 mmol, 6.00 equiv.) and freshly distilled THF (800 µL). The mixture was stirred at 90 °C for 48 h. Then, the reaction mixture was cooled down to RT and quenched with solid ammonium chloride (150 mg). When pH of the reaction mixtures dropped down to 8 inorganic salts were filtered off using silica plug, filtrate was concentrated under reduced pressure and fractioned using column chromatography on Silica gel to afford title compound as colorless oil, R_f 0.21 (Hexanes/EtOAc 5:1). Yield 58 mg (0.187 mmol, 81%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.20 (m, 7H), 7.05 – 6.94 (m, 3H), 4.55 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.71 – 3.48 (m, 2H), 3.34 – 3.21 (m, 2H), 1.96 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.27 (t, *J* = 6.2 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.1 Hz, 3H); ^{13}C

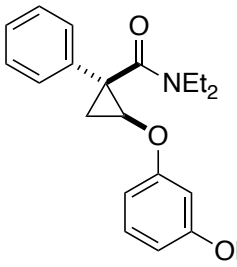
NMR (126 MHz, Chloroform-*d*) δ 167.8, 158.3, 139.5, 129.5 (+), 129.0 (+), 127.0 (+), 126.2 (+), 121.6 (+), 115.3 (+), 58.5 (+), 41.6 (–), 39.4 (–), 36.7, 23.8 (–), 13.0 (+), 12.4 (+); FT IR (NaCl, cm^{-1}): 3061, 2974, 2935, 2874, 1637, 1598, 1494, 1458, 1247, 754, 693; HRMS (TOF ES): found 332.1624, calculated for $C_{20}H_{23}NO_2Na$ (M+Na) 332.1626 (0.6 ppm).



N,N-Diethyl-2-(4-methoxyphenoxy)-1-phenylcyclopropane-1-carboxamide (**2.20ab**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18a**)[90] (50 mg, 0.232 mmol, 1.00 equiv.) and 4-methoxyphenol (**2.19b**) (115 mg, 0.929 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 23:1), colorless oil, R_f 0.19 (Hexanes/EtOAc 5:1). Yield 61.1 mg (0.18 mmol, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.28 (m, 2H), 7.28 – 7.20 (m, 3H), 6.97 – 6.88 (m, 2H), 6.86 – 6.80 (m, 2H), 4.50 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.77 (s, 3H), 3.66 – 3.49 (m, 2H), 3.33 – 3.20 (m, 2H), 1.94 (dd, *J* = 6.2, 3.9 Hz, 1H), 1.23 (t, *J* = 6.2 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.8, 154.4, 152.2, 139.5, 128.9 (+), 126.8 (+), 126.0 (+), 116.1 (+), 114.6 (+), 58.9 (+), 55.7 (+), 41.5 (–), 39.3 (–), 36.6, 23.6 (–), 12.9 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 2973, 2935, 2834, 1637, 1507, 1462, 1430, 1239, 1215, 1034, 826, 752, 700, 520; HRMS (TOF ES): found 340.1914, calculated for $C_{21}H_{26}NO_3$ (M+H) 340.1913 (0.3 ppm).

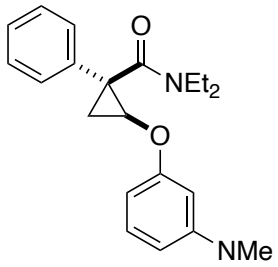


2-(4-(tert-Butyl)phenoxy)-N,N-diethyl-1-phenylcyclopropane-1-carboxamide (**2.20ac**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18a**)[90] (50 mg, 0.232 mmol, 1.00 equiv.) and 4-(*tert*-butyl)phenol (**2.19c**) (140 mg, 0.929 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 33:1), colorless oil, R_f 0.25 (Hexanes/EtOAc 3:1). Yield 57 mg (0.156 mmol, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.28 (m, 4H), 7.27 – 7.21 (m, 3H), 6.97 – 6.91 (m, 2H), 4.52 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.68 – 3.48 (m, 2H), 3.34 – 3.20 (m, 2H), 1.95 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.30 (s, 9H), 1.28 – 1.23 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.7, 155.9, 144.2, 139.5, 128.9 (+), 126.81 (+), 126.2 (+), 126.0 (+), 114.6 (+), 58.5 (+), 41.5 (–), 39.3 (–), 36.5, 34.1 (+), 31.5 (+), 23.7 (–), 12.9 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 2964, 2871, 1640, 1512, 1429, 1461, 1249, 1182, 1146, 829, 759, 699; HRMS (TOF ES): found 388.2253, calculated for $C_{24}H_{31}NO_2Na$ (M+Na) 388.2252 (0.3 ppm).



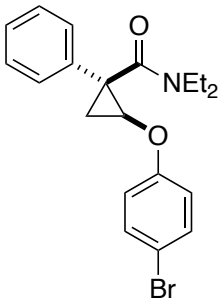
N,N-Diethyl-2-(3-methoxyphenoxy)-1-phenylcyclopropane-1-carboxamide (**2.20ad**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18a**)[90] (50 mg, 0.232 mmol, 1.00 equiv.) and 3-methoxyphenol (**2.19d**) (115 mg, 0.929 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 19:1), colorless oil, R_f 0.21 (Hexanes/EtOAc 5:1). Yield 39.9 mg (0.118 mmol, 51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ

7.39 – 7.28 (m, 2H), 7.28 – 7.15 (m, 4H), 6.67 – 6.59 (m, 1H), 6.58 – 6.52 (m, 2H), 4.53 (dd, *J* = 6.1, 3.9 Hz, 1H), 3.79 (s, 3H), 3.67 – 3.49 (m, 2H), 3.27 (m, 2H), 1.96 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.26 (t, *J* = 6.2 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.7, 160.7, 159.4, 139.4, 129.8 (+), 128.9 (+), 126.9 (+), 126.1 (+), 107.6 (+), 106.8 (+), 101.8 (+), 58.5 (+), 55.3 (+), 41.5 (–), 39.3 (–), 36.5, 23.6 (–), 12.9 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 3086, 2972, 2936, 2836, 1491, 1601, 1637, 1430, 1456, 1160, 762, 700; HRMS (TOF ES): found 362.1734, calculated for $C_{21}H_{25}NO_3Na$ (M+Na) 362.1732 (0.6 ppm).

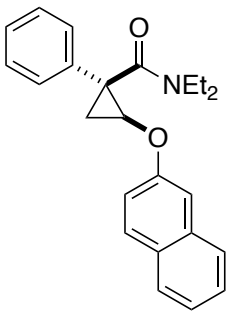


2-(3-(Dimethylamino)phenoxy)-N,N-diethyl-1-phenylcyclopropane-1-carboxamide (**2.20ae**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18a**)[90] (50 mg, 0.232 mmol, 1.00 equiv.) and 3-(dimethylamino)phenol (**2.19e**) (127 mg, 0.929 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 20:1), colorless oil, R_f 0.19 (Hexanes/EtOAc 5:1). Yield 42.5 mg (0.121 mmol, 52%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.29 (m, 2H), 7.29 – 7.19 (m, 3H), 7.14 (t, *J* = 8.2 Hz, 1H), 6.44 (m, 1H), 6.39 (m, 1H), 6.31 (t, *J* = 2.4 Hz, 1H), 4.55 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.69 – 3.50 (m, 2H), 3.27 (m, 2H), 2.92 (s, 6H), 1.97 (dd, *J* = 6.2, 3.9 Hz, 1H), 1.24 (t, *J* = 6.2 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.73 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.8, 159.3, 151.9, 139.6, 129.6 (+), 128.8 (+), 126.8 (+), 126.1 (+), 106.4 (+), 103.0 (+), 100.1 (+), 58.4 (+), 41.5 (–), 40.6 (+), 39.3 (–), 36.4, 23.7 (–), 12.9 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 2973, 2934, 2804, 1638, 1614, 1500, 1429, 1244,

1159, 1139, 758, 699; HRMS (TOF ES): found 375.2035, calculated for $C_{22}H_{28}N_2O_2Na$ (M+Na) 375.2048 (3.5 ppm).

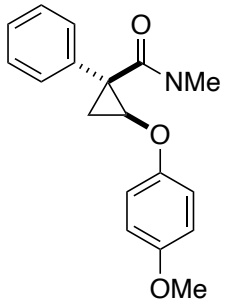


2-(4-Bromophenoxy)-N,N-diethyl-1-phenylcyclopropane-1-carboxamide (**2.20af**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18a**)[90] (50 mg, 0.232 mmol, 1.00 equiv.) and 4-bromophenol (**2.19f**) (161 mg, 0.929 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 20:1), cololess solid, mp 89.3-89.4 °C, R_f 0.29 (Hexanes/EtOAc 3:1). Yield 42.3 mg (0.109 mmol, 47%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 4H), 7.28 – 7.21 (m, 3H), 6.93 – 6.84 (m, 2H), 4.48 (dd, *J* = 6.1, 3.9 Hz, 1H), 3.67 – 3.50 (m, 2H), 3.33 – 3.18 (m, 2H), 1.92 (dd, *J* = 6.4, 3.9 Hz, 1H), 1.29 (t, *J* = 6.3 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.5, 157.3, 139.0, 132.2, 129.0 (+), 127.0 (+), 126.0 (+), 117.0 (+), 113.8 (+), 58.7 (+), 41.5 (–), 39.3 (–), 36.6, 23.2 (–), 12.9 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 3060, 2974, 2934, 2873, 1637, 1486, 1430, 1247, 1227, 699; HRMS (TOF ES): found 410.0731, calculated for $C_{20}H_{22}BrNO_2Na$ (M+Na) 410.0732 (0.2 ppm).



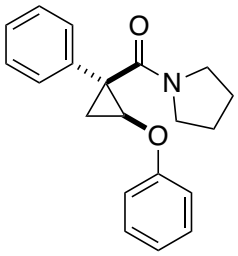
N,N-Diethyl-2-(naphthalen-2-yloxy)-1-phenylcyclopropane-1-carboxamide (**2.20ag**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18a**)[90] (50 mg, 0.232 mmol, 1.00 equiv.) and naphthalen-2-ol (**2.19g**) (134 mg, 0.929 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to

afford the title compound as inseparable mixture of diastereomers (dr = 19:1), colorless oil, R_f 0.31 (Hexanes/EtOAc 5:1). Yield 49.1 mg (0.137 mmol, 59%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.72 (m, 3H), 7.48 – 7.43 (m, 1H), 7.42 – 7.40 (m, 1H), 7.38 – 7.24 (m, 6H), 7.10 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.68 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.71 – 3.51 (m, 2H), 3.43 – 3.21 (m, 2H), 2.02 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.37 (t, *J* = 6.2 Hz, 1H), 1.20 (t, *J* = 7.0 Hz, 3H), 0.77 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.7, 156.1, 139.4, 134.4, 129.4 (+), 129.4, 128.9 (+), 127.7 (+), 126.9 (+), 126.9 (+), 126.4 (+), 126.1 (+), 123.9 (+), 118.6 (+), 108.3 (+), 58.5 (+), 41.5 (–), 39.3 (–), 36.6, 23.7 (–), 12.9 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 3058, 2974, 2934, 2873, 1633, 1600, 1511, 1467, 1430, 1316, 1215, 1177, 842, 748, 699; HRMS (TOF ES): found 382.1775, calculated for $C_{24}H_{25}NO_2Na$ (M+Na) 382.1783 (2.1 ppm).

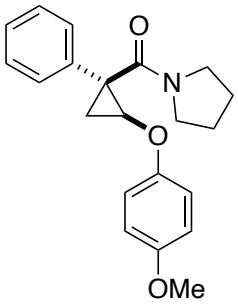


2-(4-Methoxyphenoxy)-N,N-dimethyl-1-phenylcyclopropane-1-carboxamide (**2.20bb**): Was prepared according to Typical Procedure B, employing *N*,*N*-dimethyl-1-phenylcycloprop-2-ene-1-carboxamide (**2.18b**) (50 mg, 0.267 mmol, 1.00 equiv.) and 4-methoxyphenol (**2.19b**) (133 mg, 1.07 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as colorless crystals, mp 125.6-125.9 °C, R_f 0.33 (Hexanes/EtOAc 1:1). Yield 45.5 mg (0.147 mmol, 55%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 2H), 7.27 – 7.19 (m, 3H), 6.98 – 6.92 (m, 2H), 6.88 – 6.80 (m, 2H), 4.44 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.77 (s, 3H), 3.03 (s, 3H), 2.95 (s, 3H), 1.90 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.29 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.7, 154.5, 152.2, 139.1, 128.9 (+), 126.8 (+), 125.8 (+), 116.4 (+), 114.6 (+), 59.8 (+), 55.7 (+), 37.8 (+), 36.3, 35.9 (+), 23.4 (–); FT IR (NaCl, cm^{-1}):3001, 2929, 1644, 1507, 1223,

1034, 827, 755, 700, 609; HRMS (TOF ES): found 334.1419, calculated for $C_{19}H_{21}NO_3Na$ (M+Na) 334.1419 (0.0 ppm).

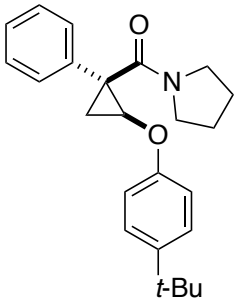


(2-Phenoxy-1-phenylcyclopropyl)(pyrrolidin-1-yl)methanone (**2.20ca**): Was prepared according to Typical Procedure B, employing (1-phenylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2.18c**)[90] (50 mg, 0.234 mmol, 1.00 equiv.) and phenol (**2.19a**) (88 mg, 0.938 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 33:1), colorless oil, R_f 0.20 (Hexanes/ EtOAc 3:1). Yield 49.9 mg (0.162 mmol, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.21 (m, 7H), 7.05 – 6.94 (m, 3H), 4.48 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.71 – 3.45 (m, 3H), 3.07 – 2.91 (m, 1H), 1.99 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.94 – 1.68 (m, 4H), 1.29 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.8, 158.1, 138.7, 129.4 (+), 128.9 (+), 126.9 (+), 126.4 (+), 121.6 (+), 115.4 (+), 58.4 (+), 46.7 (–), 46.4 (–), 37.5, 26.1 (–), 24.2 (–), 22.8 (–); FT IR (NaCl, cm^{-1}): 3059, 2972, 2875, 1637, 1598, 1494, 1429, 1229, 1169, 755, 698; HRMS (TOF ES): found 308.1647, calculated for $C_{20}H_{22}NO_2$ (M+H) 308.1651 (1.3 ppm).



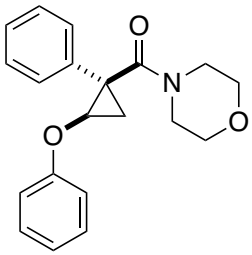
(2-(4-Methoxyphenoxy)-1-phenylcyclopropyl)(pyrrolidin-1-yl)methanone (**2.20cb**): Was prepared according to Typical Procedure B, employing (1-phenylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2.18c**)[90] (50 mg, 0.234 mmol, 1.00 equiv.) and 4-methoxyphenol (**2.19b**) (116 mg, 0.938 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the

title compound as inseparable mixture of diastereomers (dr = 5:1), colorless crystals, mp 103.7-103.8 °C, R_f 0.19 (Hexanes/EtOAc 2:1). Yield 61.6 mg (0.183 mmol, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.29 (m, 2H), 7.29 – 7.20 (m, 3H), 6.98 – 6.90 (m, 2H), 6.87 – 6.78 (m, 2H), 4.43 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.77 (s, 3H), 3.69 – 3.46 (m, 3H), 2.99 (m, 1H), 1.97 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.92 – 1.66 (m, 4H), 1.25 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.9, 154.5, 152.2, 138.8, 128.9 (+), 126.8 (+), 126.4 (+), 116.4 (+), 114.6 (+), 59.2 (+), 55.8 (+), 46.7 (–), 46.4 (–), 37.6, 26.1 (–), 24.2 (–), 22.7 (–); FT IR (NaCl, cm^{-1}): 2970, 2876, 1635, 1507, 1430, 1217, 1036, 826, 756, 725, 700; HRMS (TOF ES): found 360.1559, calculated for $C_{21}H_{23}NO_3Na$ (M+Na) 360.1576 (4.7 ppm).

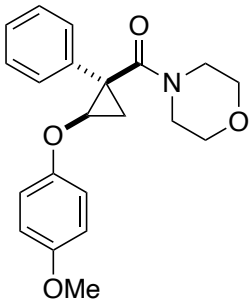


(2-(4-(tert-Butyl)phenoxy)-1-phenylcyclopropyl)(pyrrolidin-1-yl)methanone (**2.20cc**): Was prepared according to Typical Procedure B, employing (1-phenylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2.18c**)[90] (50 mg, 0.234 mmol, 1.00 equiv.) and 4-(*tert*-butyl)phenol (**2.19c**) (141 mg, 0.938 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 6:1), colorless oil, R_f 0.21 (Hexanes/EtOAc 1:1). Yield 60.1 mg (0.165 mmol, 71%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.35 – 7.28 (m, 3H), 7.28 – 7.22 (m, 4H), 6.99 – 6.92 (m, 2H), 4.47 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.66 – 3.54 (m, 2H), 3.54 – 3.47 (m, 1H), 2.97 (dt, *J* = 10.3, 7.3 Hz, 1H), 1.99 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.77 – 1.63 (m, 3H), 1.30 (s, 9H), 1.28 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.9, 155.8, 144.3, 138.8, 128.9 (+), 126.8 (+), 126.4 (+), 126.2 (+), 114.9 (+), 58.6 (+), 46.7 (–), 46.4 (–), 37.5, 34.1 (+), 31.5 (+), 26.1 (–), 24.2 (–), 22.8 (–); FT IR (NaCl, cm^{-1}):

3058, 2963, 2873, 1637, 1511, 1432, 1365, 1251, 1182, 830, 760, 729, 699, 551; HRMS (TOF ES): found 386.2095, calculated for $C_{24}H_{29}NO_2Na$ (M+Na) 386.2096 (0.3 ppm).

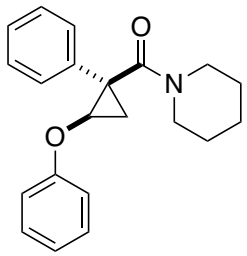


Morpholino(2-phenoxy-1-phenylcyclopropyl)methanone (**2.20da**): Was prepared according to Typical Procedure B, employing morpholino(1-phenylcycloprop-2-en-1-yl)methanone (**2.18d**)[90] (50 mg, 0.218 mmol, 1.00 equiv.) and phenol (**2.19a**) (82 mg, 0.872 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 20:1), colorless oil, R_f 0.32 (Hexanes/EtOAc 4:1). Yield 37.2 mg (0.115 mmol, 53%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.18 (m, 7H), 7.08 – 6.97 (m, 3H), 4.51 (dd, *J* = 6.1, 4.0 Hz, 1H), 4.11 – 3.92 (m, 1H), 3.81 – 3.39 (m, 6H), 3.37 – 3.26 (m, 1H), 1.95 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.36 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.2, 157.9, 138.7, 129.5 (+), 129.1 (+), 127.1 (+), 125.7 (+), 121.8 (+), 115.2 (+), 66.9 (–), 66.8 (–), 58.8 (+), 46.5 (–), 42.9 (–), 35.8, 23.6 (–); FT IR (NaCl, cm^{-1}): 3060, 2963, 2921, 2856, 1644, 1598, 1494, 1432, 1300, 1239, 1114, 755, 695; HRMS (TOF ES): found 346.1417, calculated for $C_{20}H_{21}NO_3Na$ (M+Na) 346.1419 (0.6 ppm).

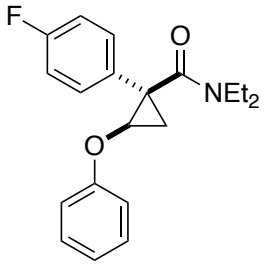


(2-(4-Methoxyphenoxy)-1-phenylcyclopropyl)(morpholino)methanone (**2.20db**): Was prepared according to Typical Procedure B, employing morpholino(1-phenylcycloprop-2-en-1-yl)methanone (**2.18d**)[90] (50 mg, 0.218 mmol, 1.00 equiv.) and 4-methoxyphenol (**2.19b**) (108 mg, 0.872 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the

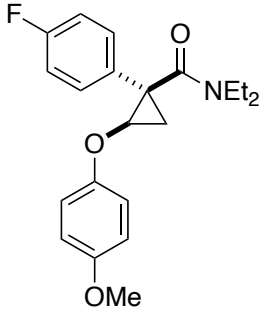
title compound as colorless crystals, mp 135.5-135.9 °C, R_f 0.21 (Hexanes/EtOAc 2:1). Yield 51.1 mg (0.145 mmol, 66%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.29 (m, 2H), 7.29 – 7.17 (m, 3H), 7.01 – 6.91 (m, 2H), 6.88 – 6.82 (m, 2H), 4.46 (dd, *J* = 6.1, 4.0 Hz, 1H), 4.03 – 3.91 (m, 1H), 3.78 (s, 3H), 3.76 – 3.38 (m, 6H), 3.32 (m, 1H), 1.93 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.32 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.2, 154.6, 151.9, 138.8, 129.0 (+), 127.1 (+), 125.7 (+), 116.1 (+), 114.7 (+), 66.9 (–), 66.8 (–), 59.4, 55.8, 46.5 (–), 42.9 (–), 35.8, 23.5 (–); FT IR (NaCl, cm^{-1}): 3056, 2961, 2917, 2855, 1644, 1507, 1433, 1367, 1231, 1205, 1114, 1035, 849, 753, 732, 700, 604; HRMS (TOF ES): found 376.1526, calculated for $C_{21}H_{23}NO_4Na$ (M+Na) 376.1525 (0.3 ppm).



(2-Phenoxy-1-phenylcyclopropyl)(piperidin-1-yl)methanone (**2.20ea**): Was prepared according to Typical Procedure B, employing (1-phenylcycloprop-2-en-1-yl)(piperidin-1-yl)methanone (**2.18e**)[90] (50 mg, 0.22 mmol, 1.00 equiv.) and phenol (**2.19a**) (83 mg, 0.88 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 7:1), colorless oil, R_f 0.18 (Hexanes/ EtOAc 2:1). Yield 23.6 mg (0.073 mmol, 33%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.19 (m, 7H), 7.06 – 6.94 (m, 3H), 4.49 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.81 (dt, *J* = 13.1, 4.9 Hz, 1H), 3.54 (m, 2H), 3.32 (dq, *J* = 12.9, 3.6 Hz, 1H), 1.92 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.67 – 1.43 (m, 5H), 1.33 (t, *J* = 6.2 Hz, 1H), 1.27 – 1.14 (m, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.8, 158.1, 139.3, 129.4 (+), 128.9 (+), 126.8 (+), 125.8 (+), 121.5 (+), 115.3 (+), 59.1 (+), 46.9 (–), 43.4 (–), 36.1, 25.9 (–), 25.7 (–), 24.6 (–), 23.7 (–); FT IR (NaCl, cm^{-1}): 3058, 2938, 2856, 2360, 1637, 1599, 1493, 1440, 1238, 1020, 754, 736, 698; HRMS (TOF ES): found 344.1626, calculated for $C_{21}H_{23}NO_2Na$ (M+Na) 344.1626 (0.0 ppm).

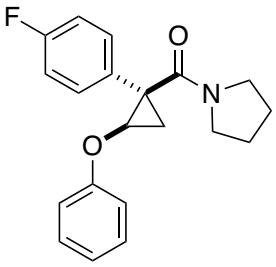


N,N-Diethyl-1-(4-fluorophenyl)-2-phenoxycyclopropane-1-carboxamide (**2.20ja**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamide (**2.18j**) (45 mg, 0.193 mmol, 1.00 equiv.) and phenol (**2.19a**) (73 mg, 0.772 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 17:1), colorless oil, R_f 0.23 (Hexanes/ EtOAc 5:1). Yield 33 mg (0.101 mmol, 52%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.35 – 7.20 (m, 4H), 7.06 – 6.96 (m, 5H), 4.50 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.59 (m, 2H), 3.32 – 3.20 (m, 2H), 1.93 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.23 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.77 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.5, 161.7 (d, *J* = 246.0 Hz), 158.0, 135.2 (d, *J* = 3.3 Hz), 129.4 (+), 127.9 (d, *J* = 8.0 Hz) (+), 121.6 (+), 115.8 (d, *J* = 21.5 Hz) (+), 115.2 (+), 58.4 (+), 41.4 (–), 39.3 (–), 36.0, 23.5 (–), 13.0 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 2973, 2933, 1637, 1599, 1513, 1494, 1430, 1245, 1223, 1166, 1146, 830, 754, 691, 565; HRMS (TOF ES): found 350.1538, calculated for $C_{20}H_{22}FNO_2Na$ (M+Na) 350.1532 (1.7 ppm).



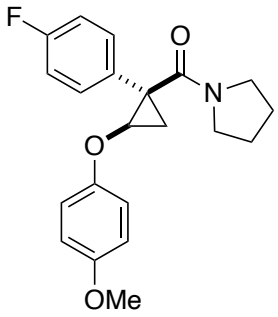
N,N-Diethyl-1-(4-fluorophenyl)-2-(4-methoxyphenoxy)cyclopropane-1-carboxamide (**2.20jb**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamide (**2.18j**) (45 mg, 0.193 mmol, 1.0 equiv.) and 4-methoxyphenol (**2.19b**) (96 mg, 0.772 mmol, 4.0 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of

diastereomers (dr = 10:1), colorless oil, R_f 0.16 (Hexanes/EtOAc 5:1). Yield 47 mg (0.131 mmol, 68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.20 (m, 2H), 7.06 – 6.98 (m, 2H), 6.95 – 6.88 (m, 2H), 6.86 – 6.79 (m, 2H), 4.45 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.77 (s, 3H), 3.65 – 3.49 (m, 2H), 3.25 (m, 2H), 1.92 (dd, *J* = 6.3, 3.9 Hz, 1H), 1.19 (t, *J* = 6.3 Hz, 1H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.6, 161.6 (d, *J* = 246.1 Hz), 154.4, 152.1, 135.26 (d, *J* = 3.5 Hz), 127.8 (d, *J* = 8.1 Hz) (+), 116.1 (+), 115.8 (d, *J* = 21.7 Hz) (+), 114.6 (+), 59.0 (+), 55.7 (+), 41.4 (–), 39.3 (–), 36.1, 23.4 (–), 13.0 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 2974, 2936, 2834, 1637, 1506, 1464, 1431, 1378, 1238, 1222, 1039, 827, 745; HRMS (TOF ES): found 380.1635, calculated for $C_{21}H_{24}FNO_3Na$ (M+Na) 380.1638 (0.8 ppm).

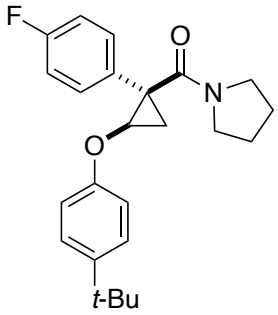


(1-(4-Fluorophenyl)-2-phenoxycyclopropyl)(pyrrolidin-1-yl)methanone (**2.20ka**): Was prepared according to Typical Procedure B, employing (1-(4-fluorophenyl)cycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2.18k**) (50 mg, 0.216 mmol, 1.0 equiv.) and phenol (**2.19a**) (81 mg, 0.865 mmol, 4 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 11:1), colorless oil, R_f 0.17 (Hexanes/ EtOAc 3:1). Yield 42.3 mg (0.13 mmol, 60.1%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 – 7.22 (m, 4H), 7.06 – 6.95 (m, 5H), 4.43 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.62 – 3.54 (m, 1H), 3.53 – 3.46 (m, 1H), 3.03 – 2.96 (m, 1H), 1.96 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.82 – 1.70 (m, 3H), 1.26 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.7, 161.7 (d, *J* = 246.4 Hz), 158.0, 134.4 (d, *J* = 3.3 Hz), 129.4 (+), 128.3 (d, *J* = 8.0 Hz) (+), 121.7 (+), 115.8 (d, *J* = 21.5 Hz) (+), 115.4 (+), 58.4 (+), 46.6 (–), 46.5 (–), 37.0, 26.1 (–), 24.2 (–), 22.6 (–); FT IR (NaCl, cm^{-}

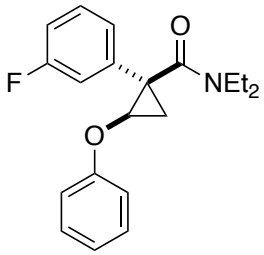
[1]): 3062, 2973, 2876, 1636, 1600, 1434, 1229, 831, 755, 692, 559; HRMS (TOF ES): found 348.1368, calculated for $C_{20}H_{20}FNO_2Na$ (M+Na) 348.1376 (2.3 ppm).



(1-(4-Fluorophenyl)-2-(4-methoxyphenoxy)cyclopropyl)(pyrrolidin-1-yl)methanone (**2.20kb**): Was prepared according to Typical Procedure B, employing (1-(4-fluorophenyl)cycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2.18k**) (50 mg, 0.216 mmol, 1.00 equiv.) and 4-methoxyphenol (**2.19b**) (107 mg, 0.865 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as colorless crystals, mp 116.7-116.9 °C, R_f 0.15 (Hexanes/ EtOAc 3:1). Yield 59.7 mg (0.168 mmol, 78%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.29 – 7.21 (m, 2H), 7.05 – 6.98 (m, 2H), 6.95 – 6.91 (m, 2H), 6.85 – 6.80 (m, 2H), 4.38 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.77 (s, 3H), 3.67 – 3.61 (m, 1H), 3.61 – 3.54 (m, 1H), 3.53 – 3.46 (m, 1H), 3.02 – 2.95 (m, 1H), 1.95 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.81 – 1.70 (m, 3H), 1.21 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.8, 161.7 (d, *J* = 245.5 Hz), 154.5, 152.1, 134.5 (d, *J* = 4.2 Hz), 128.3 (d, *J* = 8.3 Hz) (+), 116.4 (+), 115.8 (d, *J* = 21.0 Hz) (+), 114.6 (+), 59.1 (+), 55.8 (+), 46.6 (–), 46.5 (–), 37.0, 26.1 (–), 24.2 (–), 22.5 (–); FT IR (NaCl, cm^{-1}): 3048, 2972, 2876, 2835, 1635, 1506, 1435, 1220, 1037, 828, 732, 560; HRMS (TOF ES): found 378.1487, calculated for $C_{21}H_{22}FNO_3Na$ (M+Na) 378.1481 (1.6 ppm).

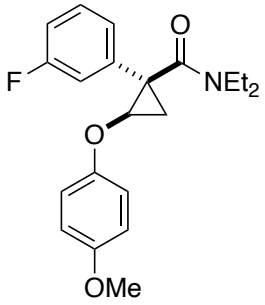


(2-(4-(tert-Butyl)phenoxy)-1-(4-fluorophenyl)cyclopropyl)(pyrrolidin-1-yl)methanone (**2.20kc**): Was prepared according to Typical Procedure B, employing (1-(4-fluorophenyl)cycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2.18k**) (50 mg, 0.216 mmol, 1.00 equiv.) and 4-(*tert*-butyl)phenol (**2.19c**) (130 mg, 0.865 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 75:1), colorless oil, R*f* 0.12 (Hexanes/EtOAc 5:1). Yield 60.1 mg (0.158 mmol, 73%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 2H), 7.06 – 6.98 (m, 2H), 6.96 – 6.90 (m, 2H), 4.42 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.67 – 3.53 (m, 2H), 3.49 (m, 1H), 3.02 – 2.91 (m, 1H), 1.97 (dd, *J* = 6.3, 4.0 Hz, 1H), 1.85 (m, 1H), 1.80 – 1.67 (m, 3H), 1.30 (s, 9H), 1.24 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.7, 161.7 (d, *J* = 246.1 Hz), 155.6, 144.4, 134.6 (d, *J* = 3.5 Hz), 128.3 (d, *J* = 8.1 Hz) (+), 126.2 (+), 115.8 (d, *J* = 21.7 Hz) (+), 114.9 (+), 58.6 (+), 46.6 (–), 46.4 (–), 36.9, 34.1 (+), 31.5 (+), 26.1 (–), 24.2 (–), 22.6 (–); FT IR (NaCl, cm^{-1}): 3043, 2964, 2873, 1637, 1510, 1434, 1250, 1182, 829, 735, 559; HRMS (TOF ES): found 404.2004, calculated for $C_{24}H_{28}FNO_2Na$ (M+Na) 404.2002 (0.5 ppm).



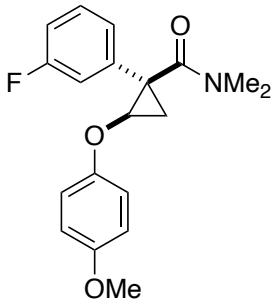
N,N-Diethyl-1-(3-fluorophenyl)-2-phenoxycyclopropane-1-carboxamide (**2.20la**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-(3-fluorophenyl)cycloprop-2-ene-1-carboxamide (**2.18l**) (50 mg, 0.214 mmol, 1.00 equiv.) and phenol (**2.19a**) (81 mg, 0.857 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 12:1), colorless oil, R_f 0.2

(Hexanes/EtOAc 1:1). Yield 35.2 mg (0.108 mmol, 50%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 3H), 7.04 (m, 1H), 7.02 – 6.91 (m, 5H), 4.51 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.68 – 3.48 (m, 2H), 3.35 – 3.23 (m, 2H), 1.98 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.28 (t, *J* = 6.3 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.1, 163.1 (d, *J* = 246.6 Hz), 158.0, 142.0 (d, *J* = 7.6 Hz), 130.4 (d, *J* = 8.4 Hz) (+), 129.4 (+), 121.7 (d, *J* = 2.9 Hz) (+), 121.6 (+), 115.2 (+), 113.9 (d, *J* = 20.9 Hz) (+), 113.1 (d, *J* = 22.2 Hz) (+), 58.6 (+), 41.5 (–), 39.3 (–), 36.3 (d, *J* = 2.2 Hz), 24.0 (–), 13.0 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 3062, 2975, 2935, 2875, 1637, 1588, 1492, 1430, 1365, 1249, 1268, 1138, 842, 754, 692; HRMS (TOF ES): found 350.1534, calculated for $C_{20}H_{22}FNO_2Na$ (M+Na) 350.1532 (0.6 ppm).

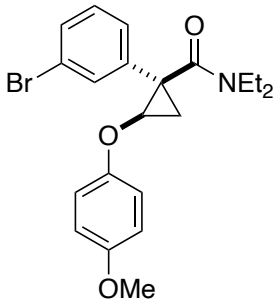


N,N-Diethyl-1-(3-fluorophenyl)-2-(4-methoxyphenoxy)cyclopropane-1-carboxamide (**2.20lb**): Was prepared according to Typical Procedure B, employing *N*,*N*-diethyl-1-(3-fluorophenyl)cycloprop-2-ene-1-carboxamide (**2.18l**) (50 mg, 0.214 mmol, 1.00 equiv.) and 4-methoxyphenol (**2.19b**) (106 mg, 0.875 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 17:1), colorless crystals, mp 104.1-104.4 °C, R_f 0.36 (Hexanes/EtOAc 3:1). Yield 54.3 mg (0.152 mmol, 71%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.32 – 7.27 (m, 1H), 7.03 (m, 1H), 6.97 – 6.90 (m, 4H), 6.85 – 6.81 (m, 2H), 4.46 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.77 (s, 3H), 3.60 (m, 1H), 3.52 (m, 1H), 3.28 (m, 2H), 1.96 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.24 (t, *J* = 6.3 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.2, 163.1 (d, *J* = 246.5 Hz), 154.5, 152.0, 142.1 (d, *J* = 7.6 Hz), 130.4 (d, *J* = 8.4 Hz) (+), 121.7 (d, *J* = 2.9 Hz) (+), 116.1 (+), 114.6 (+), 113.8 (d, *J* = 20.9 Hz) (+),

113.1 (d, *J* = 22.5 Hz) (+), 59.2 (+), 55.7 (+), 41.5 (–), 39.3 (–), 36.4 (d, *J* = 2.1 Hz), 23.9 (–), 13.0 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 2974, 2936, 2835, 1636, 1586, 1506, 1430, 1241, 1216, 1138, 1036, 825, 784, 742, 695; HRMS (TOF ES): found 380.1636, calculated for $C_{21}H_{24}FNO_3Na$ (M+Na) 380.1638 (0.5 ppm).



1-(3-Fluorophenyl)-2-(4-methoxyphenoxy)-N,N-dimethylcyclopropane-1-carboxamide (**2.20mb**): Was prepared according to Typical Procedure B, employing 1-(3-fluorophenyl)-*N*,*N*-dimethylcycloprop-2-ene-1-carboxamide (**2.18m**) (50 mg, 0.244 mmol, 1.00 equiv.) and 4-methoxyphenol (**2.19b**) (121 mg, 0.975 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as colorless crystals, mp 131.5-132.0 °C, R_f 0.17 (Hexanes/EtOAc 5:1). Yield 51.2 mg (0.155 mmol, 64%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.29 (td, *J* = 8.0, 6.1 Hz, 1H), 6.98 (m, 1H), 6.96 – 6.87 (m, 4H), 6.86 – 6.80 (m, 2H), 4.41 (dd, *J* = 6.2, 4.1 Hz, 1H), 3.77 (s, 3H), 3.04 (s, 3H), 2.95 (s, 3H), 1.93 (dd, *J* = 6.5, 4.1 Hz, 1H), 1.30 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.1, 163.2 (d, *J* = 246.2 Hz), 154.6, 152.0, 141.8 (d, *J* = 7.3 Hz), 130.5 (d, *J* = 8.2 Hz) (+), 121.3 (d, *J* = 3.2 Hz) (+), 116.4 (+), 114.6 (+), 113.8 (d, *J* = 20.9 Hz) (+), 112.8 (d, *J* = 22.2 Hz) (+), 60.0 (+), 55.5 (+), 37.4 (+), 36.1, 35.9, 23.7 (–); FT IR (NaCl, cm^{-1}): 3001, 2932, 2835, 2360, 2341, 1645, 1507, 1223, 1137, 1036, 825, 784, 695; HRMS (TOF ES): found 352.132, calculated for $C_{19}H_{20}FNO_3Na$ (M+Na) 352.1325 (1.4 ppm).



1-(3-Bromophenyl)-N,N-diethyl-2-(4-methoxyphenoxy)cyclopropane-1-carboxamide (**2.20nb**): Was prepared according to Typical Procedure B, employing 1-(3-bromophenyl)-*N*,*N*-diethylcycloprop-2-ene-1-carboxamide (**2.18n**) (50 mg, 0.17 mmol, 1.00 equiv.) and 4-methoxy-phenol (**2.19b**) (84 mg, 0.68 mmol, 4.00 equiv.) followed by preparative column chromatography on Silica gel to afford the title compound as inseparable mixture of diastereomers (dr = 25:1), colorless oil, R_f 0.17 (Hexanes/EtOAc 5:1). Yield 46 mg (0.11 mmol, 65%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.34 (m, 2H), 7.20 (dd, *J* = 4.4, 1.4 Hz, 2H), 6.95 – 6.88 (m, 2H), 6.86 – 6.80 (m, 2H), 4.46 (dd, *J* = 6.1, 4.1 Hz, 1H), 3.77 (s, 3H), 3.67 – 3.54 (m, 1H), 3.58 – 3.45 (m, 1H), 3.28 (s, 2H), 1.96 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.24 (t, *J* = 6.3 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.1, 154.5, 152.0, 141.9, 130.4, 130.0 (+), 129.0 (+), 124.9 (+), 123.0 (+), 116.1 (+), 114.6 (+), 59.0 (+), 55.7 (+), 41.5 (–), 39.3 (–), 36.3, 23.8 (–), 13.0 (+), 12.3 (+); FT IR (NaCl, cm^{-1}): 2973, 2934, 2833, 1637, 1507, 1476, 1430, 1364, 1237, 1214, 1037, 853, 825, 784, 695; HRMS (TOF ES): found 418.1003, calculated for $C_{21}H_{25}BrNO_3$ (M+H) 418.1018 (3.6 ppm).

Chapter 3 Cyclopropene-templated assembly of medium cycles *via* Ru-catalyzed ring-closing metathesis

3.1 Introduction

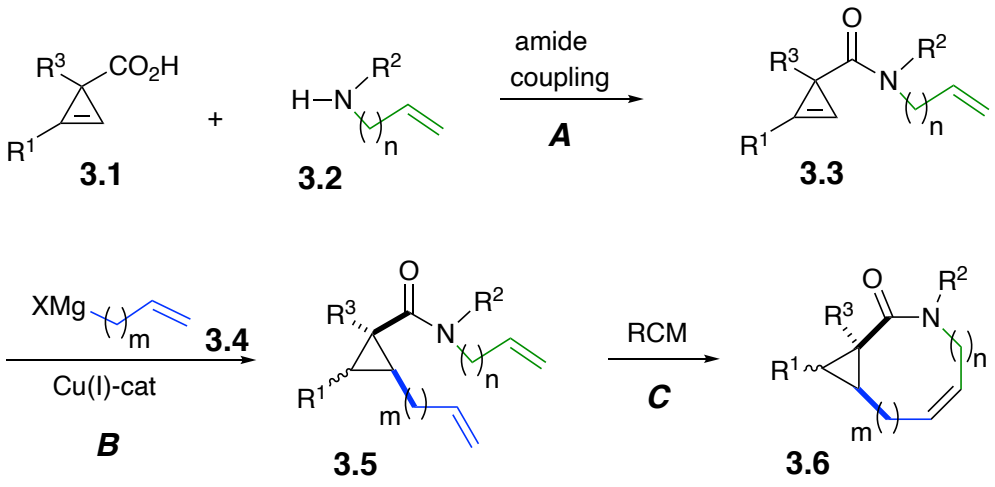
Ring-closing metathesis (RCM) of olefins is one of the most versatile, convenient, and powerful methods to assemble variable-sized cyclic structural entities.[95–99] However, not every ring size can be accessed with the same ease. RCM is very well suited for the highly efficient preparation of five- and six-membered alicyclic and heterocyclic rings and, with certain restrictions, can be successfully employed for the assembly of seven- and eight-membered rings[100–104] and even for macro-cyclization.[105–108] Medium-sized cyclic compounds are still the most difficult to prepare *via* RCM methods due to unfavored enthalpic (increased ring strain in the transition state) and entropic (reduced probability of meeting for the ends of a longer and more flexible chain) factors. The RCM formation of 9- to 12-membered rings represents a major challenge that can be partially addressed *via* conformational fixation or the introduction of excessive steric hinderance.[109,110] Preparative yields of such cyclic products, however, are modest and average 40−60%.

Our research group has extensive experience in controlling the chemo- and stereoselective assembly of medium-sized rings by employing the metal-templated addition of oxygen-[81,111] or nitrogen-based[112] nucleophiles to functionalized cyclopropenes. We showed that this approach allowed for the highly efficient cyclization of 7- to 10-membered rings. We envisioned that a cyclopropene unit could also serve as a practical rigidified linchpin for a "click−click−cyclize" approach[113,114] to prepare medium-sized lactams *via* RCM. In this chapter the design and realization of this diversity-oriented synthetic strategy is demonstrated.

3.2 Proof of concept

As we have recently demonstrated, carboxamides **3.3** can be efficiently assembled by the acylation of unsaturated amines **3.2** with cyclopropenecarboxylic acids **3.1** (step ***A***, **Scheme 3.1**).[90] We assumed that subsequent copper-catalyzed carbomagnesiation[20,60,115–117] (step ***B***) with unsaturated Grignard reagents (or, alternatively, upon postreaction electrophilic quenching with unsaturated alkyl halides) would introduce a second alkene moiety. We expected that this step would strongly benefit from the presence of the amide functionality at C-3, as this moiety can serve as a highly efficient directing group controlling the high regio- and stereoselectivities of the addition.[118] Finally, and most importantly, the Ru-catalyzed RCM used at the cyclization (step ***C***) would afford medium-sized bicyclic lactams **3.6**.

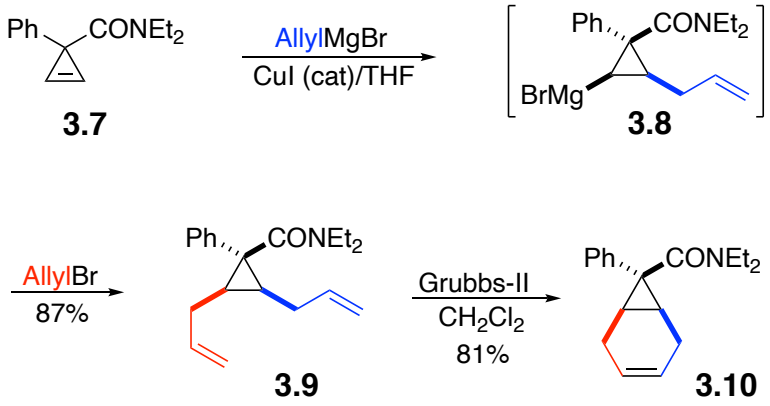
Scheme 3. 1



To provide proof of concept, the easier task of cyclizing a six-membered ring was first examined. The copper(I)-catalyzed allylmagnesiation of *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide **3.7** was performed, providing cyclopropylmagnesium species **3.8** in situ.

Subsequent trapping with allyl bromide led to the formation of vicinal *cis*-diallylcycloclopropane **3.9** in high yield (**Scheme 3.2**). Cyclization in the presence of 5 mol % of Grubbs catalyst (generation II) smoothly proceeded, affording 3-norcarene **3.10** as the sole product, which was isolated in 81% yield. It should be pointed out that the perfect stereoselectivity of the carbomagnesiation was governed by the directing effect of the amide moiety and resulted in the formation of product **3.10** in the diastereomerically pure endo form.

Scheme 3. 2

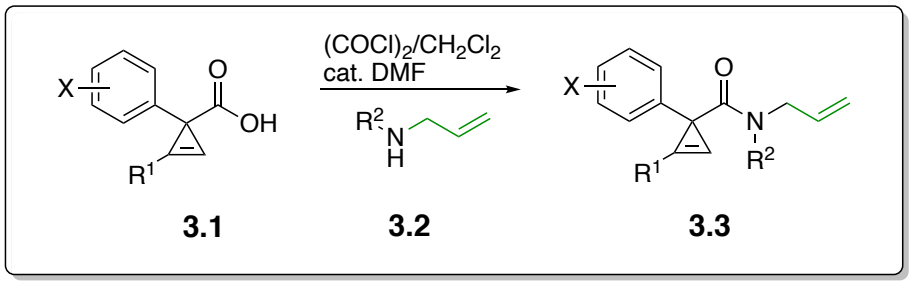


3.3 Synthesis of precursors for RCM

Inspired by this initial result, we then examined the assembly of medium-sized rings *via* the proposed strategy. For the first step, 1-phenylcycloprop-2-ene-1-carboxylic acid (**3.1a**) was treated with oxalyl chloride in anhydrous dichloromethane in the presence of catalytic amounts of DMF. The resulting acyl chloride was used without purification for the acylation of N-methylallylamine **3.2a** to afford *N*-allylcycloprop-2-ene-1- carboxamide **3.3aa** in high yield (**Scheme 3.3**). Other carboxamide derivatives of **3.1a** (**3.3ab** – **3.3ad**) were also obtained uneventfully *via* the same method employing *N*-benzylallylamines **3.2b** – **3.2d**. In addition,

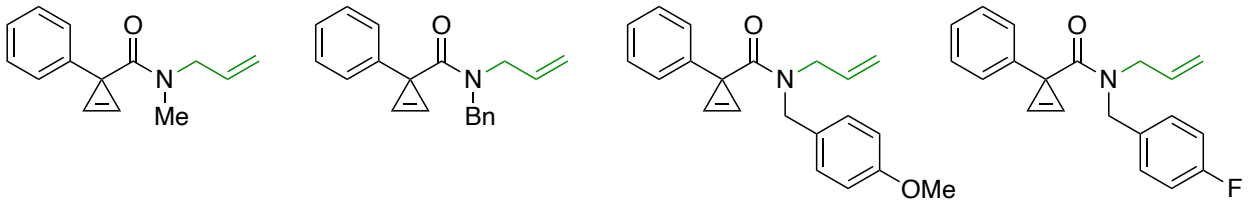
several cycloprop-2-enecarboxamide derivatives with substitution in the aryl ring at C-1 (**3.3bb** – **3.3cb**) or at C-2 of cyclopropene (**3.3db**) were also prepared according to this protocol.

Scheme 3. 3

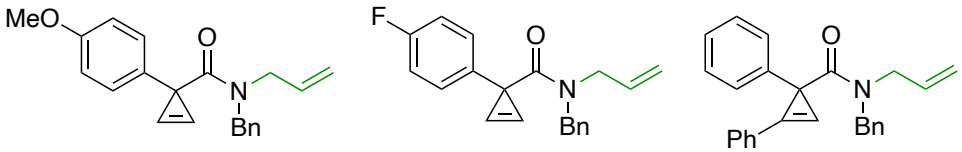


3.1a: X = H, R1 = H;
3.1b: X = 4-OMe, R1 = H;
3.1c: X = 4-F, R1 = H;
3.1d: X = H, R1 = Ph.

3.2a: R2 = Me;
3.2b: R2 = CH_2Ph;
3.2c: R2 = $CH_2C_6H_4OMe$-4;
3.2d: R2 = $CH_2C_6H_4F$-4.



3.3aa, 80% **3.3ab**, 92 **3.3ac**, 64% **3.3ad**, 76%

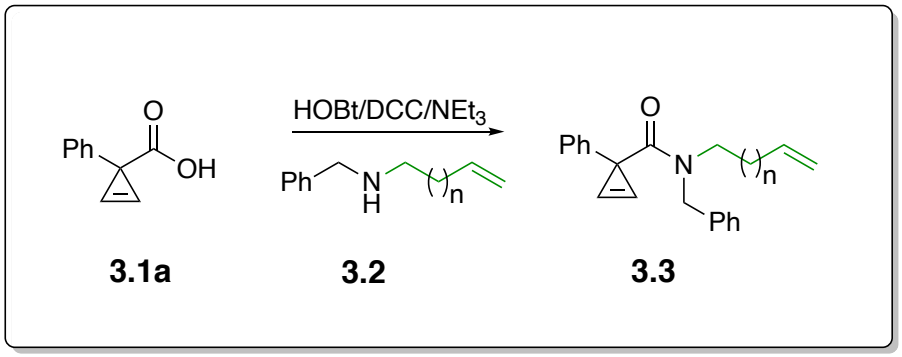


3.3bb, 86% **3.3cb**, 93% **3.3db**, 86%

An alternative method of the amide coupling involving the direct activation of acid **3.1a** in the presence of HOBt and DCC was employed in the synthesis of *N*-homoallylamide **3.3ae** and its higher homologues **3.3af** – **3.3ai** (**Scheme 4**). This reaction provided somewhat lower yields

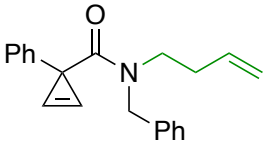
but was still quite attractive because the sequence is a true one-pot procedure (in contrast with the previously described method employing oxalyl chloride activation).

Scheme 3. 4

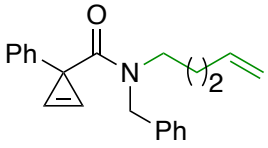


3.1a **3.2** **3.3**

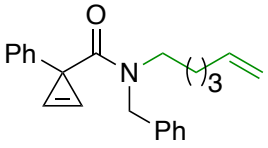
3.2e: n = 1; **3.2h**: n = 4;
3.2f: n = 2; **3.2i**: n = 5.
3.2g: n = 3;



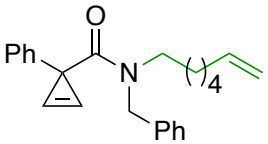
3.3ae, 86%



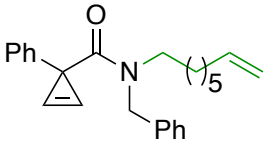
3.3af, 76%



3.3ag, 57%



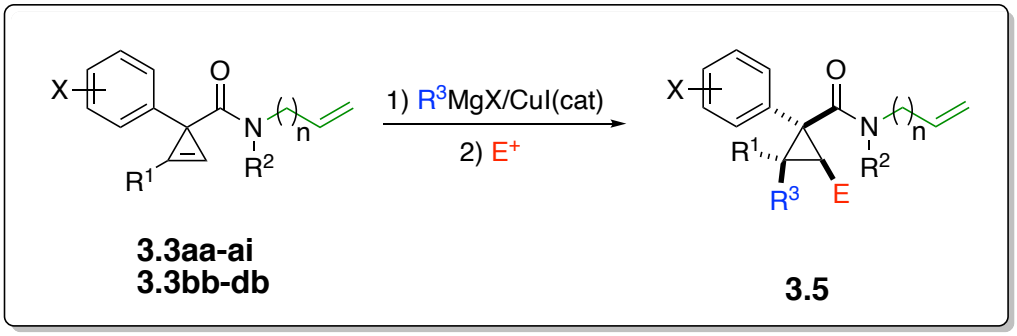
3.3ah, 44%



3.3ai, 67%

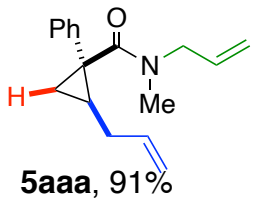
The second step involved an amide-directed copper-catalyzed carbomagnesiation reaction performed according to the procedure recently developed in our laboratory.[118] The treatment of cyclopropenes **3.3** with Grignard reagents in the presence of Cu(I) catalyst led to a diastereoselective nucleophilic addition across the double bond, yielding the corresponding cyclopropylmagnesium intermediates. After electrophilic quenching, this sequence afforded stereochemically defined cyclopropane products **3.5** in good to excellent yield (**Scheme 3.5**). It should be pointed out that the regiochemistry of carbomagnesiation of cyclopropene **3.3db** with methyl- and allylmagnesium bromide was opposite. The reaction with MeMgBr is sterically controlled, which is quite typical for amide-directed carbomagnesiation.[118] Interestingly, the addition of a nucleophilic allyl group is governed by electronic factors, suggesting that this process is much less sterically demanding (probably due to the possibility of allylic transposition).

Scheme 3. 5

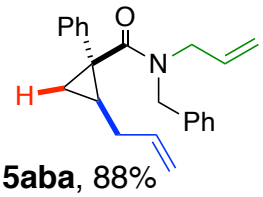


3.3aa-ai
3.3bb-db

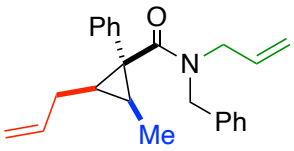
3.5



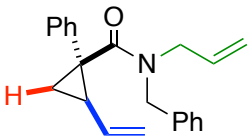
5aaa, 91%



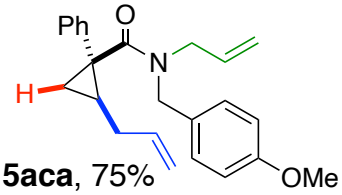
5aba, 88%



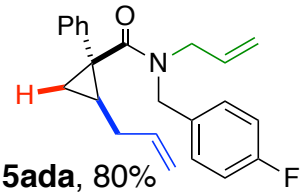
5abb, 93%



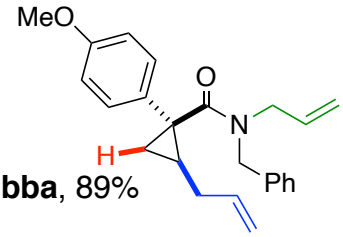
5abc, 82%



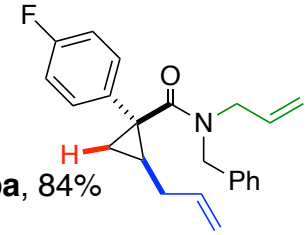
5aca, 75%



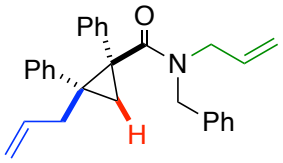
5ada, 80%



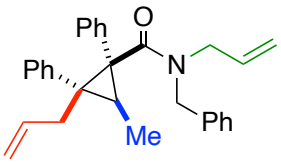
5bba, 89%



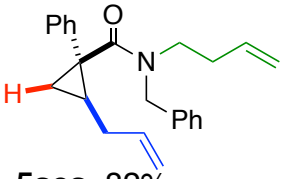
5cba, 84%



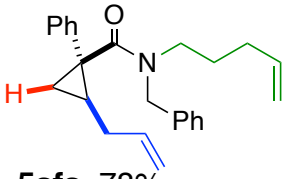
5dba, 89%



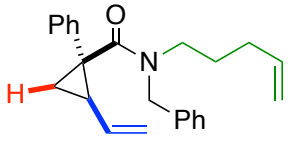
5dbb, 71%



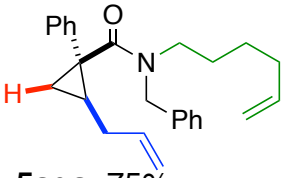
5aea, 82%



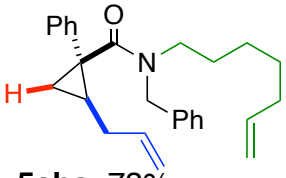
5afa, 78%



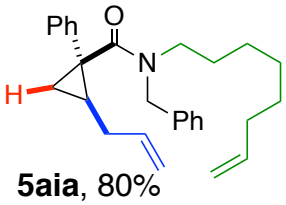
5afc, 68%



5aga, 75%



5aha, 73%



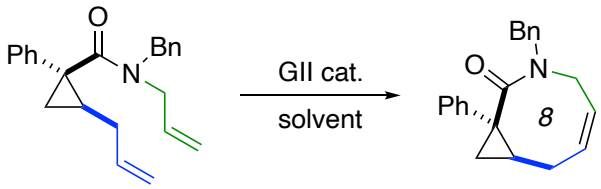
5aia, 80%

3.4 Optimization of the ring-closing metathesis step

Next, we optimized the cyclization step that involved an intramolecular ring-closing olefin metathesis reaction. First, a 5 mM solution of *N*,2-diallyl-*N*-benzyl-1-phenylcyclopropane-1-carboxamide (**3.5aba**) in dichloromethane (DCM) was subjected to a reaction in the presence of 5 mol% of Grubbs II catalyst. After 17 h at room temperature, the RCM product **3.6aba** was obtained in 50% yield (GC) (**Table 3.1**, entry 1). The reaction did not reach complete conversion, and extended reaction times did not change this result. To achieve greater conversion, the same reaction was carried out in refluxing DCM, and after only 1 h, there was no detectable starting material. The product **3.6aba** was obtained in 94% yield by GC (entry 2). Further increases in the reaction temperature resulted in a significant drop of product formation (entry 3). Deviation of the catalyst loading also resulted in reduced yields (entries 4 and 5). The cyclization reaction scales robustly, as the two-fold preparation of **3.6aba** (entry 6) afforded an 84% yield of purified product.

Table 3. 1

Optimization of ring-closing olefin metathesis reaction



3.5aba **3.6aba**

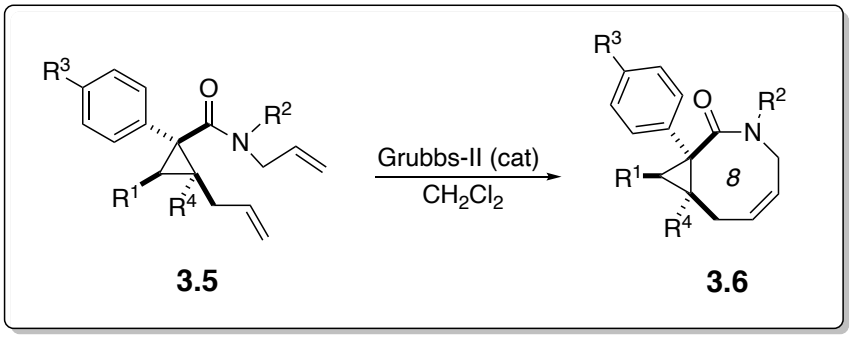
Entry	3.5aba (mmol)	cat. [b] mol%	Solvent	T, °C	Yield % (GC)
1	0.075	5	DCM	r.t.	50
2	**0.075**	**5**	**DCM**	**40**	**94**
3	0.075	5	Toluene	90	63
4	0.075	10	DCM	40	84
5	0.075	3	DCM	40	65
6	**0.151**	**5**	**DCM**	**40**	**86[a]**

a) Isolated yield
b) 2nd generation Grubbs catalyst

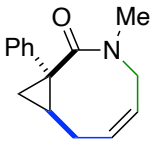
3.5 Assembly of medium cycles *via* Ru-catalyzed RCM

Under conditions optimized for an eight-membered ring closure, the effects of various aryl substituents at position C-1 (geminal to amide group) and the influence of substituents at the nitrogen atom of the amide function were investigated. We first tested the tolerance to electronic effects by introducing electron-donating or electron-withdrawing groups in both the C-1-aryl and *N*-benzyl substituents. In all cases, we observed that the effects were negligible regardless of the substituent's electronic nature (**Scheme 3.6**). With *N*-methyl-substituted amide **3.5aaa** subjected to the RCM reaction, the product **3.6aaa** was isolated in 84% yield. Evidently, the second substituent on the nitrogen atom has little or no effect on the metathesis step, presumably due to being remote from the RCM reaction site. The introduction of additional substituents on the cyclopropane core such as a phenyl geminal to the allyl group (precursor **3.5dba**) and to the vicinal *cis*-methyl group (**3.5abb**) as well as the combination of the two (**3.5dbb**), while creating an additional steric encumbrance around the cyclopropane core, did not significantly affect the reaction and afforded cyclization products **3.6abb**, **3.6dba**, and **3.6dbb** in good yields. In all of these cases, the ring-closing metathesis was diastereoselective, exclusively providing *Z*-olefins. The structures of the compounds **3.6aaa** and **3.6dba** were unambiguously confirmed by X-ray crystallography (**Figure 3.1**). Inspired by the successful closure of the eight-membered rings during the RCM step, we planned the more challenging task of the assembly of larger cycles.

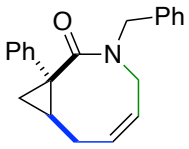
Scheme 3. 6



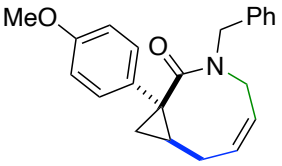
3.5aaa: R1 = H, R2 = Me, R3 = H, R4 = H;
3.5aba: R1 = H, R2 = Bn, R3 = H, R4 = H;
3.5bba: R1 = H, R2 = Bn, R3 = 4-OMe, R4 = H;
3.5cba: R1 = H, R2 = Bn, R3 = 4-F, R4 = H;
3.5aca: R1 = H, R2 = 4-OMeBn, R3 = H, R4 = H;
3.5ada: R1 = H, R2 = 4-FBn, R3 = H, R4 = H;
3.5abb: R1 = Me, R2 = Bn, R3 = H, R4 = H;
3.5dba: R1 = H, R2 = Bn, R3 = H, R4 = Ph;
3.5dbb: R1 = Me, R2 = Bn, R3 = H, R4 = Ph



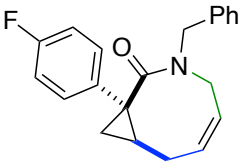
3.6aaa: 87%



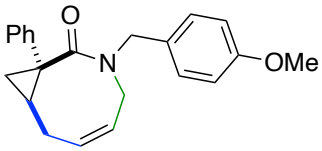
3.6aba: 84%



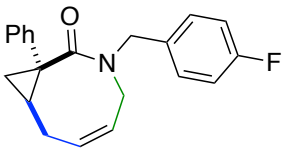
3.6bba: 85%



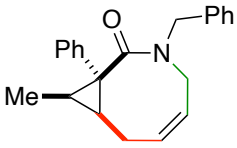
3.6cba: 89%



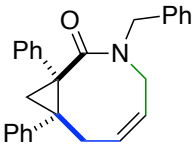
3.6aca: 82%



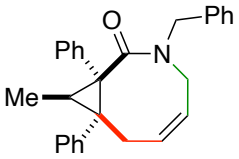
3.6ada: 85%



3.6abb: 93%



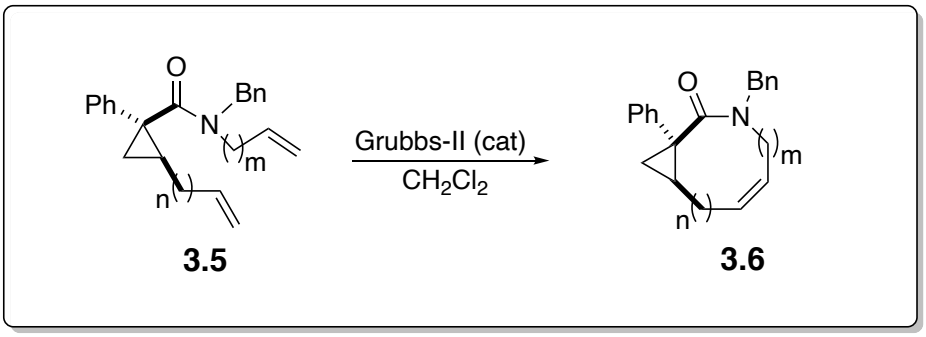
3.6dba: 82%



3.6dbb: 75%

Although an intramolecular construction *via* the RCM of cycles larger than cycloheptene are considered to be quite problematic,[119] we envisioned that this might be feasible in our model. Indeed, because of the rigidity of the cyclopropyl carboxamide core, both reacting olefin units are arranged in a specific 3D spatial orientation that is largely inaccessible in other types

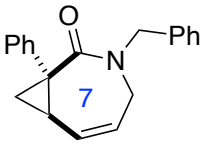
Scheme 3. 7



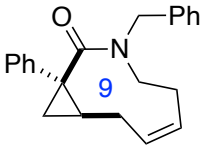
3.5 **3.6**

3.5abc: n = 0, m = 1;
3.5aea: n = 1, m = 2;
3.5afc: n = 0, m = 3;
3.5afa: n = 1, m = 3;

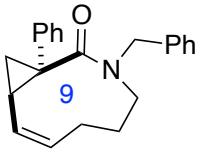
3.5aga: n = 1, m = 4;
3.5aha: n = 1, m = 5;
3.5aia: n = 1, m = 6;



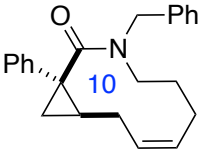
3.6abc: 85%



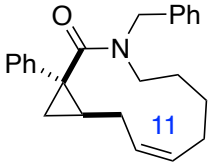
3.6aea: 74%



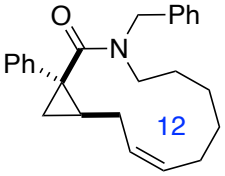
3.6afc: 68%



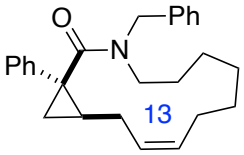
3.6afa: 78%



3.6aga: 0%



3.6aha: 0%

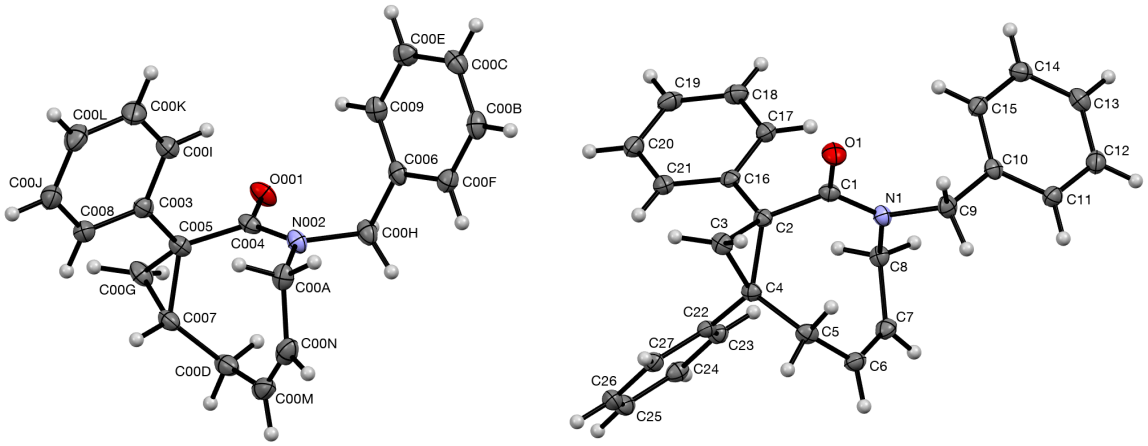


3.6aia: 0%

of scaffolds. We hypothesized that this prearrangement should partially mitigate a negative entropic effect associated with a ring closure. We tested cyclizations of *N*-homoallyl- (*m* = 2) and *N*-pentenyl- (*m* = 3) amides and were pleased to observe the formation of [7.1.0] fused systems **3.6aea** and **3.6afc**, respectively, in good yields (**Scheme 3.7**). These examples all demonstrate that the position of a forming double bond can be easily alternated, thereby

Figure 3. 1

ORTEP drawing of crystal structure of compound **3aaa** (left) and **3dba** (right) showing atom-labeling scheme and 50% probability thermal ellipsoids (see Appendix for details).



imparting additional flexibility for further functionalization of the constructed scaffolds. This is showcased in the synthesis of **3.6afa**, an [8.1.0] system, which was assembled in 78% yield, and features the formation of a 10-membered cycle as a result of the intramolecular RCM. Further extension of the carbon chain bearing an olefin function (n = 4) resulted in the formation of **3.6aga** in only trace amounts, whereas products **3.6aha** and **3.6aia** (n > 4) were never observed in the reaction mixtures. An assembly of a seven-membered ring backbone was also attempted *via* the RCM of the vinylcyclopropane and allylamine moieties in precursor **3.5abc**. This reaction proceeded uneventfully, affording azacycloheptene **3.6abc** in high yield (**Scheme 3.7**).

3.6 Conclusion

A new cyclopropene-based linchpin for an expeditious synthesis of medium-sized heterocyclic compounds was developed. The featured approach utilizes the directing ability of an amide functionality for Cu-catalyzed diastereoselective addition to cyclopropene double bonds, followed by an intramolecular stereoselective ring-closing metathesis facilitated by the rigid cyclopropane core. It was shown that ring sizes 7−10 can be routinely cyclized using this approach, but the method fails for larger cycles (11- to 13- membered rings).

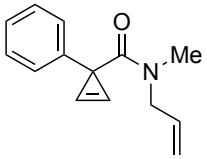
3.7 Experimental

3.7.1 General information

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (–) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a ThermoFisher Nicolet™ iS™ 5 FT-IR Spectrometer. HRMS was carried out on LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried in vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40-63 mm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous solvents, dichloromethane and tetrahydrofuran were obtained by passing degassed commercially available HPLC-grade inhibitor-free solvents consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual stage deionization followed by dual stage reverse osmosis. Anhydrous THF

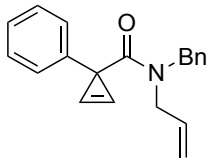
was obtained by refluxing commercially available solvent over calcium hydride followed by distillation in a stream of dry nitrogen.

3.7.2 Synthesis of carboxamides



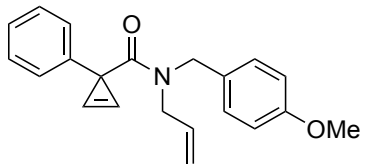
N-Allyl-N-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**3.3aa**). ***(Typical procedure A)***: A flame-dried round bottom flask was charged with 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (500 mg, 1 equiv., 3.12 mmol), 3 drops of freshly distilled DMF were added to anhydrous dichloromethane (15 mL) under argon atmosphere and the solution was cooled on ice bath. Oxalyl dichloride (594 mg, 402 µL, 1.5 equiv., 4.68 mmol) was then added dropwise and the mixture was stirred for 15 min at 0°C and then allowed to room temperature for 2 h. The solution was concentrated under reduced pressure to provide a solid acyl chloride residue, which was dissolved in anhydrous dichloromethane (5.0 mL) and added dropwise to a solution of *N*-methylprop-2-en-1-amine **3.2a** (333 mg, 449 µL, 1.5 equiv., 4.68 mmol) and triethylamine (632 mg, 901 µL, 2 equiv., 6.24 mmol) in anhydrous dichloromethane (10.0 mL). The reaction mixture was stirred for 5 hours at RT and then partitioned between water and dichloromethane. The aqueous phase was acidified with 1M HCl. The organic phase was then washed with water (3 x 10 mL). The combined aqueous layers were back-extracted once with dichloromethane, which was combined with other organic phases, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was fractioned by column chromatography on Silica gel eluting with a hexane/toluene mixture (3:1) to afford the title compound as colorless crystals (m.p. 79.9-81.0, R_f 0.28). Yield 532 mg (3.12 mmol, 80%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1:1. Rotamer A: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H), 7.13 (d, J = 7.6 Hz, 2H), 5.79

(ddt, *J* = 16.5, 10.1, 6.0 Hz, 1H), 5.21 – 5.07 (m, 1H), 5.01 (dd, *J* = 17.0, 1.9 Hz, 1H), 4.03 (d, *J* = 5.9 Hz, 2H), 2.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 174.2 (+), 143.1 (+), 132.8 (+), 128.5 (+), 126.3 (+), 125.9 (+), 117.5 (–), 109.3 (+), 49.8 (–), 34.8 (+), 32.0 (+). Rotamer B: ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.33 – 7.18 (m, 5H), 7.13 (d, *J* = 7.6 Hz, 2H), 5.49 (ddt, *J* = 16.1, 10.5, 5.4 Hz, 1H), 5.21 – 5.07 (m, 2H), 3.90 (d, *J* = 5.4 Hz, 2H), 2.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 173.6 (+), 143.2 (+), 133.2 (+), 128.4 (+), 126.4 (+), 125.9 (+), 117.4 (–), 109.4 (+), 52.5 (–), 32.6 (+), 31.7 (+). FT IR (NaCl, cm^{-1}): 3106, 3068, 2931, 1614, 1491, 1428, 1402, 1292, 1106, 914, 696. HRMS (TOF ES): found 214.1234, calculated for $C_{14}H_{15}NO$ (M + H) 214.1232 (0.9 ppm).

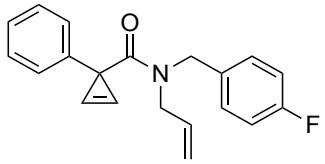


N-Allyl-N-benzyl-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ab**). This compound was synthesized according to typical procedure A from 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (1.00 g, 6.24 mmol) using *N*-benzylprop-2-en-1-amine **3.2b** (1.38 g, 9.37 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (3:1,) to afford the title compound as a pale yellow oil (R_f 0.23). Yield 1.67 g (6.24 mmol, 92%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 5:4. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.04 (m, 12H), 5.38 (ddt, *J* = 16.1, 10.6, 5.5 Hz, 1H), 5.13 – 4.88 (m, 2H), 4.53 (s, 2H), 3.75 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3 (+), 143.1 (+), 137.4 (+), 133.2 (+), 128.5 (+), 128.5 (+), 128.5 (+), 127.3 (+), 126.5 (+), 126.0 (+), 117.8 (–), 109.7 (+), 49.2 (–), 47.0 (–), 31.9 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.04 (m, 8H), 7.02 (s, 2H), 6.89 (d, *J* = 7.3 Hz, 2H), 5.76 (ddt, *J* = 16.6, 10.1, 6.1 Hz, 1H), 5.13 – 4.88 (m, 2H), 4.41 (s, 2H), 3.90 (d, J = 6.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.1 (+), 137.0 (+), 132.7 (+), 128.7 (+), 128.5 (+), 128.5 (+), 127.4 (+),

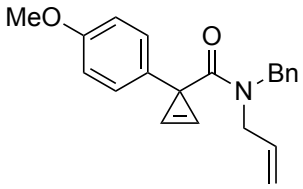
126.5 (+), 125.9 (+), 118.0 (–), 109.5 (+), 50.3 (–), 47.0 (–), 31.9 (+). FT IR (NaCl, cm^{-1}): 3075, 3044, 2926, 1710, 1642, 1495, 1446, 1370, 1274, 1076, 732, 699. HRMS (TOF ES): found 312.1466, calculated for $C_{20}H_{19}NONa$ (M+Na) 312.1364 (0.6 ppm).



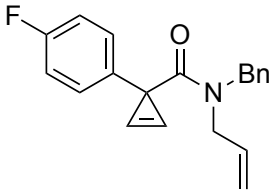
N-Allyl-N-(4-methoxybenzyl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ac**). This compound was synthesized according to typical procedure A from 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (500 mg, 02:52 mmol) using *N*-(4-methoxybenzyl)prop-2-en-1-amine **3.2c** (830 mg, 4.68 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (3:1) to afford the title compound as a light yellow crystals (mp 87.1 - 87.4 °C, R_f 0.23). Yield 638 mg (2.00 mmol, 64%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 5:4. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.10 (m, 10H), 6.91 – 6.79 (m, 1H), 5.54 – 5.38 (m, 1H), 5.12 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.00 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.54 (s, 2H), 3.83 – 3.77 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1 (+), 158.9 (+), 143.2 (+), 133.3 (+), 129.9 (+), 129.6 (+), 128.4 (+), 126.4 (+), 126.0 (+), 117.6 (–), 113.9 (+), 109.6 (+), 55.3 (+), 49.0 (–), 46.4 (–), 31.9 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.10 (m, 7H), 6.91 – 6.79 (m, 4H), 5.82 (ddt, *J* = 16.5, 10.2, 6.1 Hz, 1H), 5.16 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.08 (dd, *J* = 17.3, 1.7 Hz, 1H), 4.43 (s, 2H), 3.94 (d, *J* = 6.2 Hz, 2H), 3.83 – 3.77 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0 (+), 159.0 (+), 143.2 (+), 132.8 (+), 128.8 (+), 128.5 (+), 128.2 (+), 126.5 (+), 126.0 (+), 117.9 (–), 114.1 (+), 109.6 (+), 55.3 (+), 49.7 (–), 46.6 (–), 31.9 (+). FT IR (NaCl, cm^{-1}): 3080, 2928, 2836, 1630, 1512, 1444, 1412, 1247, 1175, 1033, 928, 816, 757, 699. HRMS (TOF ES): found 319.1570, calculated for $C_{21}H_{21}NO_2$ (M+) 319.1572 (0.6 ppm).



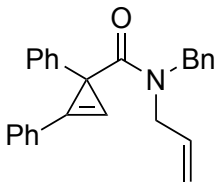
N-Allyl-N-(4-fluorobenzyl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ad**). This compound was synthesized according to typical procedure A from 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (500 mg, 3.12 mmol) using *N*-(4-fluorobenzyl)prop-2-en-1-amine **3.2d** (774 mg, 4.68 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (5:1) to afford the title compound as a colorless oil (R_f 0.22). Yield 726 mg (2.36 mmol, 76%). NMR spectra of this material show two signals of rotamers in a ratio c.a. 5:3. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 10H), 7.04 – 6.94 (m, 1H), 5.50 – 5.39 (m, 1H), 5.12 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.56 (s, 2H), 3.82 (dt, *J* = 5.7, 1.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3 (+), 162.2 (d, *J* = 245.3 Hz) (+), 143.0 (+), 133.3 (d, *J* = 3.3 Hz) (+), 133.2 (+), 130.2 (d, *J* = 8.1 Hz) (+), 128.6 (+), 126.5 (+), 126.0 (+), 117.8 (–), 115.4 (d, *J* = 21.4 Hz) (+), 109.7 (+), 49.3 (–), 46.4 (–), 31.9 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 7H), 7.04 – 6.94 (m, 2H), 6.91 (dd, *J* = 8.5, 5.3 Hz, 2H), 5.81 (ddt, *J* = 16.6, 10.1, 6.2 Hz, 1H), 5.17 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.07 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.46 (s, 2H), 3.95 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1 (+), 162.1 (d, *J* = 246.1 Hz) (+), 142.9 (+), 133.3 (d, *J* = 3.3 Hz) (+), 132.6 (+), 130.2 (d, *J* = 8.1 Hz) (+), 128.5 (+), 128.5 (+), 126.6 (+), 126.0 (+), 118.1 (–), 115.6 (d, *J* = 21.6 Hz) (+), 49.6 (–), 46.8 (–), 31.9 (+). FT IR (NaCl, cm^{-1}): 3081, 2924, 1631, 1509, 1445, 1410, 1222, 1157, 929, 822, 700, 610. HRMS (TOF ES): found 330.1283, calculated for $C_{20}H_{18}FNONa$ (M+Na) 330.1270 (3.9 ppm).



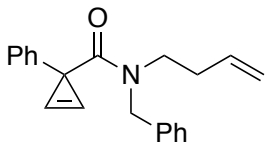
N-Allyl-N-benzyl-1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxamide (**3.3bb**). This compound was synthesized according to typical procedure A from 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid **3.1b** (250 mg, 1.31 mmol) using *N*-benzylprop-2-en-1-amine **3.2b** (290 mg, 1.97 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (3:1) to afford the title compound as a colorless oil (R_f 0.23). Yield 361 mg (1.13 mmol, 86%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 5:4. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 7H), 7.09 – 7.04 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.47 (ddt, *J* = 16.1, 10.6, 5.5 Hz, 1H), 5.21 – 4.96 (m, 2H), 4.60 (s, 2H), 3.83 (d, J = 5.6 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4 (+), 158.3 (+), 137.5 (+), 135.2 (+), 128.5 (+), 128.5 (+), 127.3 (+), 127.1 (+), 127.1 (+), 117.7 (–), 113.9 (+), 110.3 (+), 55.3 (+), 49.2 (–), 47.0 (–), 31.4 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 3H), 7.10 (s, 2H), 7.09 – 7.04 (m, 2H), 7.00 – 6.95 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.82 (ddt, J = 16.5, 10.1, 6.1 Hz, 1H), 5.21 – 4.96 (m, 2H), 4.49 (s, 2H), 3.97 (d, *J* = 6.1 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4 (+), 158.4 (+), 137.1 (+), 135.2 (+), 128.7 (+), 128.5 (+), 127.4 (+), 127.1 (+), 126.8 (+), 117.9 (–), 114.0 (+), 110.1 (+), 55.3 (–), 50.2 (+), 47.0 (–), 31.3 (+). FT IR (NaCl, cm^{-1}): 3083, 3030, 2931, 2835, 1630, 1511, 1452, 1412, 1248, 1029, 826, 702, 617. HRMS (TOF ES): found 320.1661, calculated for $C_{21}H_{22}NO_2$ (M+H) 320.1651 (3.1 ppm).



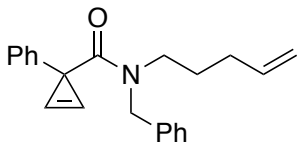
N-Allyl-N-benzyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamide (**3.3cb**). This compound was synthesized according to typical procedure A from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid **3.1c** (250 mg, 1.4 mmol) using *N*-benzylprop-2-en-1-amine **3.2b**) (269 mg, 1.82 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (3:1) to afford the title compound as a colorless oil (R_f 0.20). Yield 403 mg (1.31 mmol, 93%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 5:4. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 7H), 7.16 – 7.06 (m, 2H), 7.03 – 6.92 (m, 2H), 5.51 – 5.41 (m, 1H), 5.13 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.01 (dd, *J* = 17.2, 1.5 Hz, 1H), 4.60 (s, 2H), 3.82 (dt, *J* = 5.6, 1.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0 (+), 161.6 (d, *J* = 245.3 Hz) (+), 138.9 (d, *J* = 3.7 Hz) (+), 137.4 (+), 133.1 (+), 128.6 (+), 128.5 (+), 127.6 (+), 127.5 (+), 127.5 (+), 127.4 (+), 117.9 (–), 115.3 (d, *J* = 21.4 Hz) (+), 110.0 (+), 49.2 (–), 47.0 (–), 31.4 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H), 7.16 – 7.06 (m, 3H), 7.03 – 6.92 (m, 3H), 5.82 (ddt, *J* = 16.5, 10.1, 6.1 Hz, 1H), 5.18 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.08 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.48 (s, 2H), 3.97 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9 (+), 161.7 (d, *J* = 245.3 Hz) (+), 136.9 (+), 132.6 (+), 128.8 (+), 127.6 (+), 127.5 (+), 127.5 (+), 127.4 (+), 126.7 (+), 118.1 (–), 115.4 (d, *J* = 21.2 Hz) (+), 109.8 (+), 50.2 (–), 47.0 (–), 31.4 (+). FT IR (NaCl, cm^{-1}): 3085, 3032, 2922, 1632, 1508, 1416, 1230, 956, 829, 740, 702, 617. HRMS (TOF ES): found 330.1276, calculated for $C_{20}H_{18}FNONa$ (M+Na) 330.1270 (1.8 ppm).



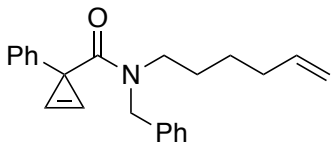
N-Allyl-N-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide (**3.3db**). This compound was synthesized according to typical procedure A from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid **3.1d** (750 mg, 3.17 mmol) using *N*-benzylprop-2-en-1-amine **3.2b** (701 mg, 4.76 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a pale yellow oil (R_f 0.18). Yield 997 mg (2.73 mmol, 86%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 5:4. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.64 (m, 2H), 7.38 – 7.10 (m, 13H), 7.07 (s, 1H), 5.18 – 4.95 (m, 3H), 4.88 (d, *J* = 14.6 Hz, 1H), 4.30 (d, *J* = 14.6 Hz, 1H), 4.01 (dd, *J* = 16.4, 5.4 Hz, 1H), 3.75 (dd, *J* = 16.4, 5.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0 (+), 142.1 (+), 137.6 (+), 133.3 (+), 130.4 (+), 129.8 (+), 128.6 (+), 128.6 (+), 128.5 (+), 127.3 (+), 127.0 (+), 126.4 (+), 126.1 (+), 126.0 (+), 122.6 (+), 117.9 (–), 98.7 (+), 49.5 (–), 46.8 (–), 35.2 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.68 (m, 2H), 7.36 – 7.11 (m, 11H), 7.00 – 6.95 (m, 2H), 6.76 (s, 1H), 5.83 (dddd, *J* = 17.2, 10.2, 7.0, 5.3 Hz, 1H), 5.46 (ddt, *J* = 16.2, 10.7, 5.6 Hz, 1H), 5.17 – 4.96 (m, 1H), 4.80 (d, *J* = 16.3 Hz, 1H), 4.45 (dd, *J* = 15.3, 5.1 Hz, 1H), 4.28 (d, *J* = 16.4 Hz, 1H), 3.42 (dd, *J* = 15.0, 7.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1 (+), 142.1 (+), 137.0 (+), 132.8 (+), 130.5 (+), 129.8 (+), 128.7 (+), 128.5 (+), 128.5 (+), 127.4 (+), 127.0 (+), 126.5 (+), 126.1 (+), 126.0 (+), 122.5 (+), 117.9 (–), 98.2 (+), 50.5 (–), 46.9 (–), 35.1 (+). FT IR (NaCl, cm^{-1}): 3059, 3029, 2924, 1630, 1494, 1445, 1415, 1244, 927, 735, 699. HRMS (TOF ES): found 366.1866, calculated for $C_{26}H_{24}NO$ (M+H) 166.1858 (2.2 ppm).



N-Benzyl-N-(but-3-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ae**), ***(Typical procedure B)***: Oven dried 25 mL round bottom flask was charged with anhydrous THF (15 mL), 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (500 mg, 3.12 mmol, 1.00 equiv.), HOBt (569 mg, 4.21 mmol, 1.35 equiv.), DCC (870 mg, 4.21 mmol, 1.35 equiv.), triethylamine (948 mg, 1.31 mL, 9.37 mmol, 3.00 equiv.), and *N*-benzylbut-3-en-1-amine **3.2e** (554 mg, 1.10 equiv., 3.43 mmol). The reaction mixture was stirred at 50 °C overnight. When the reaction was complete (control by TLC), the formed precipitate was filtered off, the solvent was removed under reduced pressure, and dry residue was separated by Flash column chromatography on Silica gel eluting with a hexane/EtOAc mixture (5:1) to provide the title compound as a pale-yellow oil, R_f = 0.14. Yield 812 mg (2.68 mmol, 86%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.7:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.14 (m, 8H), 7.05 (s, 2H), 6.98 (d, *J* = 7.1 Hz, 2H), 5.81 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.14 – 5.03 (m, 2H), 4.51 (s, 2H), 3.42 (t, *J* = 7.2 Hz, 2H), 2.38 (q, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3 (+), 143.2 (+), 137.3 (+), 135.7 (+), 128.7 (+), 128.4 (+), 127.4 (+), 126.7 (+), 126.4 (+), 126.0 (+), 116.8 (–), 109.2 (+), 51.5 (–), 44.6 (–), 32.0 (+), 31.8 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.14 (m, 12H), 5.43 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 4.92 – 4.81 (m, 2H), 4.65 (s, 2H), 3.31 – 3.25 (m, 2H), 1.99 (q, *J* = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3 (+), 143.2 (+), 137.5 (+), 134.5 (+), 128.5 (+), 128.2 (+), 127.3 (+), 126.5 (+), 126.4 (+), 126.2 (+), 117.0 (–), 110.3 (+), 47.3 (–), 46.3 (–), 32.3 (–), 32.2 (+). FT IR (NaCl, cm^{-1}): 3079, 3027, 2929, 1630, 1446, 1421, 1223, 737, 699, 654. HRMS (TOF ES): found 326.1519, calculated for $C_{21}H_{21}NONa$ $(M+Na)^+$ 326.1521 (0.6 ppm).

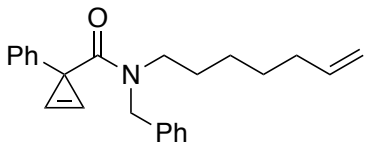


N-Benzyl-N-(pent-4-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3af**). This compound was synthesized according to typical procedure B from 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (161 mg, 1.01 mmol) and *N*-benzylpent-4-en-1-amine **3.2f** (168 mg, 0.958 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (5:1) to afford the title compound as a pale-yellow oil, R_f 0.19. Yield 231 mg (0.728 mmol, 76%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 3:2. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 8H), 7.06 (s, 2H), 7.02 – 6.93 (m, 2H), 5.80 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.06 – 4.80 (m, 2H), 4.49 (s, 2H), 3.37 – 3.31 (m, 2H), 2.11 – 2.03 (m, 2H), 1.77 – 1.67 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.3 (+), 137.9 (+), 137.4 (+), 128.7 (+), 128.5 (+), 128.5 (+), 127.4 (+), 126.7 (+), 125.9 (+), 115.0 (–), 109.3 (+), 51.4 (–), 44.9 (–), 32.0 (+), 31.2 (–), 26.3 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.12 (m, 12H), 5.52 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.06 – 4.80 (m, 2H), 4.64 (s, 2H), 3.24 – 3.17 (m, 2H), 1.77 – 1.67 (m, 2H), 1.36 (quintet, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.2 (+), 137.7 (+), 137.3 (+), 128.5 (+), 128.4 (+), 128.2 (+), 127.3 (+), 126.4 (+), 126.2 (+), 115.3 (–), 110.3 (+), 47.3 (–), 46.4 (–), 32.2 (+), 30.9 (–), 27.1 (–). FT IR (NaCl, cm^{-1}): 3079, 3027, 2932, 1630, 1494, 1422, 737, 699, 653. HRMS (TOF ES): found 340.1681, calculated for $C_{22}H_{23}NONa$ $(M+Na)^+$ 340.1677 (1.2 ppm).



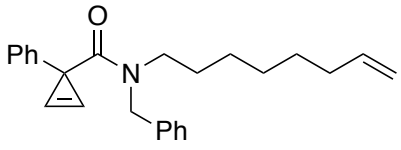
N-Benzyl-N-(hex-5-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ag**). This compound was synthesized according to typical procedure B from 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (500 mg, 3.12 mmol) and *N*-benzylhex-5-en-1-amine **3.2g** (650 mg, 3.43 mmol). The product

was isolated by column chromatography eluting with hexane/EtOAc mixture (5:1) to afford the title compound as a pale-yellow oil, R_f 0.16. Yield 586 mg (1.77 mmol, 57%). NMR spectra of this material show signals of two rotamers in a ratio c.a.3:2. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 6H), 7.17 – 7.12 (m, 2H), 7.06 (s, 2H), 6.98 (d, *J* = 6.9 Hz, 2H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.07 – 4.85 (m, 2H), 4.48 (s, 2H), 3.39 – 3.29 (m, 2H), 2.07 (q, *J* = 7.1 Hz, 2H), 1.66 – 1.58 (m, 2H), 1.40 (quintet, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.3 (+), 138.5 (+), 137.4 (+), 128.7 (+), 128.5 (+), 128.2 (+), 127.4 (+), 126.7 (+), 125.9 (+), 114.7 (–), 109.3 (+), 51.2 (–), 44.8 (–), 33.4 (–), 32.0 (+), 26.4 (–), 26.3 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 10H), 7.17 – 7.12 (m, 2H), 5.63 (ddt, *J* = 17.1, 10.7, 6.7 Hz, 1H), 5.07 – 4.85 (m, 2H), 4.63 (s, 2H), 3.22 – 3.15 (m, 2H), 1.84 (q, *J* = 7.1 Hz, 2H), 1.33 – 1.23 (m, 2H), 1.07 (quintet, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.3 (+), 138.2 (+), 137.7 (+), 128.5 (+), 128.4 (+), 128.2 (+), 127.2 (+), 126.4 (+), 126.2 (+), 114.9 (–), 110.2 (+), 47.2 (–), 46.7 (–), 33.2 (+), 32.2 (+), 27.2 (–), 26.0 (–). FT IR (NaCl, cm^{-1}): 3078, 3027, 2930, 2858, 1630, 1493, 1421, 1228, 912, 736, 699, 653, 604. HRMS (TOF ES): found 354.184, calculated for $C_{23}H_{25}NONa$ $(M+Na)^+$ 354.1834 (1.7 ppm).



N-Benzyl-N-(hept-6-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ah**). This compound was synthesized according to typical procedure B from 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (500 mg, 3.12 mmol) and *N*-benzylhept-6-en-1-amine **3.2h** (698 mg, 3.43 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (5:1) to afford the title compound as a pale-yellow oil, R_f 0.19. Yield 473 mg (1.36 mmol, 44%). NMR

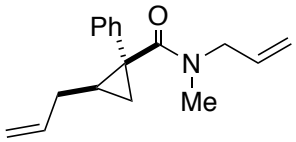
spectra of this material show signals of two rotamers in a ratio c.a. 1.5:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.10 (m, 10H), 7.10 – 7.05 (m, 2H), 5.63 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 4.96 – 4.81 (m, 2H), 4.56 (s, 2H), 3.15 – 3.07 (m, 2H), 1.82 (q, *J* = 7.2 Hz, 2H), 1.28 – 1.15 (m, 2H), 1.09 (quintet, *J* = 7.5 Hz, 2H), 0.90 (quintet, *J* = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.3 (+), 138.9 (+), 137.4 (+), 128.7 (+), 128.5 (+), 127.4 (+), 126.7 (+), 126.4 (+), 125.9 (+), 114.4 (–), 109.3 (+), 51.2 (–), 45.0 (–), 33.7 (–), 32.0 (+), 28.6 (–), 26.9 (–), 26.5 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.10 (m, 6H), 7.10 – 7.05 (m, 2H), 6.98 (s, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 5.72 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 4.96 – 4.81 (m, 2H), 4.41 (s, 2H), 3.25 (t, *J* = 7.6 Hz, 2H), 1.97 (q, *J* = 7.2 Hz, 2H), 1.53 (quintet, *J* = 7.6 Hz, 2H), 1.33 (quintet, *J* = 7.3 Hz, 2H), 1.28 – 1.15 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.3 (+), 138.6 (+), 137.7 (+), 128.5 (+), 128.4 (+), 128.2 (+), 127.2 (+), 126.4 (+), 126.2 (+), 114.5 (–), 110.3 (+), 47.2 (–), 46.9 (–), 33.5 (–), 32.3 (+), 28.4 (–), 27.7 (–), 26.2 (–). FT IR (NaCl, cm^{-1}): 3078, 2929, 2857, 1631, 1446, 1422, 911, 736, 699, 652. HRMS (TOF ES): found 368.2000, calculated for $C_{24}H_{27}NONa$ $(M+Na)^+$ 368.1990 (2.7 ppm).



N-Benzyl-N-(oct-7-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ai**). This compound was synthesized according to typical procedure B from 1-phenylcycloprop-2-ene-1-carboxylic acid **3.1a** (500 mg, 3.12 mmol) using *N*-benzyloct-7-en-1-amine **3.2i** (746 mg, 3.43 mmol). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (5:1) to afford the title compound as a pale-yellow oil, R_f 0.18. Yield 751 mg (2.09 mmol, 67%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 5:2. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 6H), 7.18 – 7.12 (m, 2H), 7.05 (s, 2H), 7.01 – 6.96 (m,

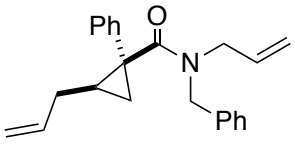
2H), 5.86 – 5.70 (m, 1H), 4.96 – 4.91 (m, 2H), 4.49 (s, 2H), 3.35 – 3.28 (m, 2H), 2.07 – 2.00 (m, 2H), 1.60 (quintet, *J* = 7.3 Hz, 2H), 1.45 – 1.16 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.3 (+), 139.1 (+), 137.4 (+), 128.7 (+), 128.5 (+), 128.2 (+), 127.4 (+), 126.7 (+), 125.9 (+), 114.3 (–), 109.3 (+), 51.2 (–), 45.1 (–), 33.7 (–), 32.0 (+), 28.8 (–), 28.6 (–), 27.0 (–), 26.9 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 10H), 7.18 – 7.12 (m, 2H), 5.86 – 5.70 (m, 1H), 5.02 – 4.96 (m, 2H), 4.63 (s, 2H), 3.24 – 3.13 (m, 2H), 1.95 (q, *J* = 7.1 Hz, 2H), 1.44 – 1.17 (m, 4H), 1.08 (quintet, *J* = 7.0 Hz, 2H), 0.96 (quintet, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (+), 143.3 (+), 138.9 (+), 137.7 (+), 128.5 (+), 128.4 (+), 128.2 (+), 127.2 (+), 126.4 (+), 126.2 (+), 114.4 (–), 110.3 (+), 47.2 (–), 46.9 (–), 33.6 (–), 32.3 (+), 28.8 (–), 28.6 (–), 27.8 (–), 26.6 (–). FT IR (NaCl, cm^{-1}): 3077, 3027, 2928, 2855, 1631, 1494, 1421, 1230, 736, 699, 652, 604. HRMS (TOF ES): found 382.2157, calculated for $C_{25}H_{29}NONa$ $(M+Na)^+$ 382.2147 (2.6 ppm).

3.7.3 Synthesis of precursors for RCM: stereoselective carbomagnesiation of cyclopropenes



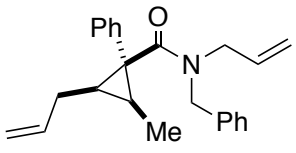
(1S*,2R*)-N,2-Diallyl-N-methyl-1-phenylcyclopropane-1-carboxamide (**3.5aaa**), ***(Typical procedure C)***: A flame dried 10 mL round bottom flask was charged with copper(I) iodide (4.46 mg, 23.4 µmol, 5 mol%) and freshly distilled anhydrous THF (1.0 mL) under an argon atmosphere at 0 °C. Allylmagnesium bromide (0.70 mL, 0.70 mmol, 1.50 equiv, 1M in ether) was added dropwise, and the resulting mixture was stirred for five minutes at 0 °C. *N*-allyl-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide **3.3aa** (100 mg, 0.47 mmol, 1.00 equiv.) was then added dropwise as a solution in dry THF (1.0 mL). After five minutes of stirring at 0 °C, saturated aqueous ammonium chloride (1 mL) was added dropwise and the reaction was stirred for another five minutes. The

resulting mixture was then allowed to room temperature, diluted with water (2 mL) and extracted with diethyl ether (3 x 3 mL). Combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on Silica gel eluting with hexane/EtOAc mixture (5:1). The titled compound was obtained as a viscous colorless oil, R_f = 0.32. Yield 109 mg (0.427 mmol, 91%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.6:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.8 Hz, 2H), 7.22 – 7.15 (m, 3H), 6.00 – 5.89 (m, 1H), 5.76 (ddt, *J* = 16.6, 10.1, 6.1 Hz, 1H), 5.20 – 4.92 (m, 4H), 4.10 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.93 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.75 (s, 3H), 2.51 – 2.38 (m, 1H), 1.93 – 1.76 (m, 2H), 1.47 (s, 1H), 1.03 – 0.98 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (+), 141.2 (+), 137.0 (+), 132.9 (+), 128.7 (+), 126.2 (+), 125.6 (+), 117.6 (–), 115.5 (–), 50.5(–), 35.3 (+), 35.1 (+), 34.0 (–), 24.3 (+), 22.5 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.8 Hz, 2H), 7.22 – 7.15 (m, 3H), 6.00 – 5.89 (m, 1H), 5.20 – 4.92 (m, 5H), 4.20 (dd, *J* = 15.5, 4.6 Hz, 1H), 3.57 (dd, *J* = 15.5, 6.5 Hz, 1H), 2.86 (s, 3H), 2.51 – 2.38 (m, 1H), 1.93 – 1.76 (m, 2H), 1.51 – 1.43 (m, 1H), 1.03 – 0.98 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (+), 141.3 (+), 137.0 (+), 132.9 (+), 128.7 (+), 126.4 (+), 126.2 (+), 118.2 (–), 115.4 (–), 52.8 (–), 35.1 (+), 34.3 (–), 32.6 (+), 24.1 (–), 21.9 (–). FT IR (NaCl, cm^{-1}): 3077, 3003, 2977, 2922, 1640, 1398, 915, 699. HRMS (TOF ES): found 278.1521, calculated for $C_{17}H_{21}NONa$ $(M+Na)^+$ 278.1521 (0.0 ppm).



(1S*,2R*)-N,2-Diallyl-N-benzyl-1-phenylcyclopropane-1-carboxamide (**3.5aba**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-benzyl-1-phenylcycloprop-2-ene-1-

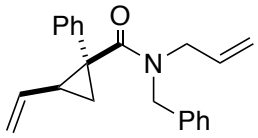
carboxamide **3.3ab** (500 mg, 1.73 mmol) using allylmagnesium bromide (2.33 mL, 2.33 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.30. Yield 501 mg (1.51 mmol, 88%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.9:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.09 (m, 9H), 6.65 (d, *J* = 6.4 Hz, 1H), 6.04 – 5.86 (m, 1H), 5.79 – 5.68 (m, 1H), 5.21 – 4.85 (m, 5H), 4.18 (d, *J* = 14.4 Hz, 1H), 4.12 (dd, *J* = 15.7, 3.8 Hz, 1H), 3.55 (dd, *J* = 15.6, 6.1 Hz, 1H), 2.39 (dd, *J* = 10.3, 7.4 Hz, 1H), 1.93 – 1.79 (m, 2H), 1.53 (t, *J* = 5.3 Hz, 1H), 1.03 (dd, *J* = 8.3, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (+), 141.2 (+), 137.5 (+), 136.9 (+), 132.9 (+), 128.7 (+), 128.7 (+), 128.4 (+), 127.3 (+), 127.0 (+), 126.5 (+), 118.8 (–), 115.4 (–), 49.6 (+), 47.0 (–), 35.2 (+), 34.1 (–), 24.2 (+), 21.7 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.09 (m, 10H), 6.04 – 5.86 (m, 1H), 5.21 – 4.85 (m, 6H), 4.32 – 4.22 (m, 2H), 3.44 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.65 – 2.57 (m, 1H), 1.93 – 1.79 (m, 2H), 1.45 (t, *J* = 5.3 Hz, 1H), 1.08 (dd, *J* = 8.4, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (+), 141.1 (+), 137.1 (+), 136.0 (+), 132.6 (+), 128.8 (+), 128.3 (+), 127.3 (+), 127.2 (+), 126.6 (+), 126.5 (+), 118.1 (–), 115.4 (–), 50.2 (–), 46.9 (–), 35.2 (+), 34.4 (–), 24.3 (+), 20.9 (–). FT IR (NaCl, cm^{-1}): 3063, 3028, 3003, 2923, 2854, 1641, 1495, 1440, 1414, 1197, 994, 916, 727, 699. HRMS (TOF ES): found 332.2018, calculated for $C_{23}H_{26}NO$ $(M+H)^+$ 332.2014 (1.2 ppm).



(1S*,2R*,3S*)-N,2-Diallyl-N-benzyl-3-methyl-1-phenylcyclopropane-1-carboxamide (**3.5abb**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamide **3.3ab** (150 mg, 0.52 mmol) using methylmagnesium

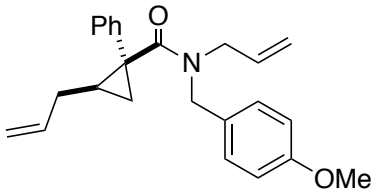
bromide (0.233 mL, 0.70 mmol, 3M in ether). After the Grignard reagent was added the reaction mixture was stirred for 5 min at 0 °C and then allyl bromide (188 mg, 1.56 mmol, 3.00 equiv.) was added and reaction was allowed to room temperature. After 15 min at room temperature saturated aqueous ammonium chloride (1 mL) was added dropwise and the reaction was stirred for another five minutes. The resulting mixture was then diluted with water (2 mL) and extracted with diethyl ether (3 x 3 mL). Combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and then the solvent was removed under reduced pressure. The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a viscous colorless oil, R_f 0.33. Yield 167 mg (0.483 mmol, 93%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 2:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 6.96 (m, 9H), 6.45 (d, *J* = 7.0 Hz, 1H), 5.94 (dddt, *J* = 18.3, 16.6, 10.2, 6.2 Hz, 1H), 5.12 – 4.80 (m, 5H), 4.68 (d, *J* = 14.4 Hz, 1H), 4.30 (d, *J* = 14.4 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.72 – 3.62 (m, 1H), 2.61 (dddd, *J* = 14.6, 7.3, 4.4, 1.6 Hz, 1H), 2.20 – 2.09 (m, 1H), 1.73 (ddq, *J* = 20.0, 9.4, 6.5 Hz, 1H), 1.30 – 1.21 (m, 1H), 1.14 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0 (+), 142.2 (+), 138.1 (+), 137.6 (+), 133.3 (+), 128.7 (+), 128.7 (+), 128.4 (+), 127.2 (+), 126.8 (+), 126.1 (+), 118.9 (–), 114.7 (–), 49.4 (–), 46.1 (–), 36.0 (+), 30.8 (+), 29.7 (–), 22.8 (+), 10.0 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 6.96 (m, 10H), 5.94 (dddt, *J* = 18.3, 16.6, 10.2, 6.2 Hz, 1H), 5.62 (dddd, *J* = 17.1, 10.2, 6.9, 5.8 Hz, 1H), 5.13 – 4.81 (m, 4H), 4.67 (d, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 15.2 Hz, 1H), 3.95 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.51 (dd, *J* = 14.8, 6.9 Hz, 1H), 2.68 (dtt, *J* = 15.8, 5.7, 1.6 Hz, 1H), 2.24 – 2.07 (m, 1H), 1.81 – 1.67 (m, 1H), 1.31 – 1.21 (m, 1H), 1.24 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2 (+), 142.2 (+), 138.2 (+), 136.0 (+), 132.8 (+), 128.8 (+), 128.2 (+), 127.6 (+), 127.2 (+), 126.4 (+), 126.3 (+), 118.0 (–), 114.7 (–), 50.1 (–), 46.0 (–

), 36.4 (+), 30.0 (+), 29.7 (–), 21.9 (+), 10.0 (+). FT IR (NaCl, cm^{-1}): 3063, 2977, 2929, 1642, 1496, 1451, 1413, 1274, 1200, 996, 912, 733, 699. HRMS (TOF ES): found 368.1993, calculated for $C_{24}H_{27}NONa$ $(M+Na)^+$ 368.1990 (0.8 ppm).



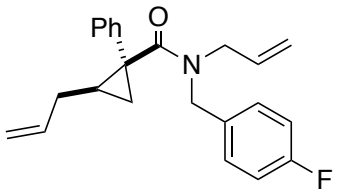
(1S*,2S*)-N-Allyl-N-benzyl-1-phenyl-2-vinylcyclopropane-1-carboxamide (**3.5abc**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamide **3.3ab** (158 mg, 0.55 mmol) using vinylmagnesium bromide (0.74 mL, 0.74 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.23. Yield 142 mg (447 mmol, 82%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 2.0:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.06 (m, 9H), 6.64 – 6.58 (m, 1H), 5.46 (ddd, *J* = 17.0, 10.2, 9.0 Hz, 1H), 5.28 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.04 – 4.85 (m, 5H), 4.21 (dd, *J* = 15.1, 12.1 Hz, 2H), 3.57 – 3.51 (m, 1H), 2.61 – 2.53 (m, 1H), 1.87 (dd, *J* = 6.3, 5.0 Hz, 1H), 1.20 – 1.14 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (+), 140.4 (+), 137.4 (+), 136.5 (+), 133.1 (+), 128.8 (+), 128.6 (+), 128.3 (+), 127.2 (+), 126.9 (+), 126.7 (+), 126.2 (+), 118.8 (–), 116.1 (–), 49.3 (–), 46.9 (–), 37.0 (+), 28.5 (+), 23.0 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.06 (m, 10H), 5.69 (dddd, *J* = 17.4, 10.2, 7.3, 5.1 Hz, 1H), 5.62 – 5.52 (m, 1H), 5.35 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.15 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.10 (dt, *J* = 10.1, 1.4 Hz, 1H), 5.04 – 4.86 (m, 1H), 4.80 (d, *J* = 15.5 Hz, 1H), 4.05 – 3.94 (m, 2H), 3.38 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.61 – 2.53 (m, 1H), 1.83 (dd, *J* = 6.1, 4.9 Hz, 1H), 1.20 – 1.14 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (+), 140.2 (+), 136.5 (+), 135.9 (+), 133.1 (+), 128.9 (+), 128.2 (+), 127.7 (+), 127.2 (+), 126.8 (+), 126.7 (+), 126.2 (+), 117.9 (–), 116.1 (–), 49.9 (–), 46.7 (–), 37.3

(+), 28.0 (+), 22.1 (–). FT IR (NaCl, cm^{-1}): 3082, 3063, 3027, 2922, 1641, 1495, 1450, 1414, 1266, 1196, 992, 910, 758, 699. HRMS (TOF ES): found 340.1671, calculated for $C_{22}H_{23}NONa$ $(M+Na)^+$ 340.1677 (1.8 ppm).



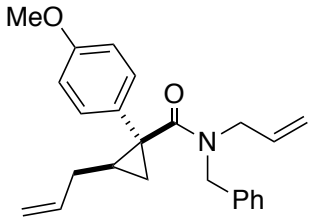
(1S*,2R*)-N,2-Diallyl-N-(4-methoxybenzyl)-1-phenylcyclopropane-1-carboxamide (**3.5aca**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-(4-methoxybenzyl)-1-phenylcycloprop-2-ene-1-carboxamide (**3.3ac**) (150 mg, 0.47 mmol) using allylmagnesium bromide (0.63 mL, 0.63 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless solid, mp 57.4 - 58.2 °C, R_f 0.24. Yield 127 mg (351 mmol, 75%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 2.0:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 5H), 6.86 – 6.78 (m, 2H), 6.67 – 6.63 (m, 1H), 6.56 – 6.47 (m, 1H), 5.90 (dddd, *J* = 16.9, 10.2, 6.8, 5.6 Hz, 1H), 5.20 – 4.87 (m, 6H), 4.14 – 4.03 (m, 2H), 3.79 (s, 3H), 3.57 – 3.48 (m, 1H), 2.41 – 2.32 (m, 1H), 1.93 – 1.77 (m, 2H), 1.51 (dd, *J* = 6.0, 4.7 Hz, 1H), 1.01 (dd, *J* = 8.4, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9 (+), 158.8 (+), 141.2 (+), 137.0 (+), 133.0 (+), 130.1 (+), 129.6 (+), 128.7 (+), 126.6 (+), 126.5 (+), 118.7 (–), 115.4 (–), 113.8 (+), 55.3 (+), 49.4 (–), 46.3 (–), 35.2 (+), 34.1 (–), 24.1 (+), 21.8 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 9H), 5.98 (dddd, *J* = 17.0, 10.3, 6.7, 5.5 Hz, 1H), 5.71 (dddd, *J* = 17.3, 10.1, 7.4, 5.2 Hz, 1H), 5.20 – 4.87 (m, 4H), 4.82 (d, *J* = 15.2 Hz, 1H), 4.24 – 4.16 (m, 2H), 3.74 (s, 3H), 3.42 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.71 – 2.52 (m, 1H), 1.93 – 1.77 (m, 2H), 1.45 (t, *J* = 5.3 Hz, 1H), 1.07 (dd, *J* = 8.0, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (+), 158.8 (+), 141.2 (+), 137.1 (+), 132.7 (+), 128.9

(+), 128.8 (+), 127.8 (+), 127.0 (+), 126.5 (+), 118.0 (–), 115.4 (–), 113.7 (+), 55.2 (+), 49.6 (–), 46.5 (–), 35.3 (+), 34.3 (–), 24.1 (+), 21.0 (–). FT IR (NaCl, cm^{-1}): 3076, 3002, 2915, 2835, 1636, 1512, 1440, 1412, 1247, 1175, 1035, 918, 700. HRMS (TOF ES): found 384.1948, calculated for $C_{24}H_{27}NO2Na$ $(M+Na)^+$ 384.1939 (1.1 ppm).



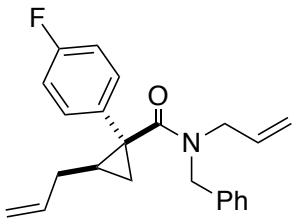
(1S*,2R*)-N,2-Diallyl-N-(4-fluorobenzyl)-1-phenylcyclopropane-1-carboxamide (**3.5ada**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-(4-fluorobenzyl)-1-phenylcyclo-prop-2-ene-1-carboxamide **3.3ad**) (150 mg, 0.488 mmol) using allylmagnesium bromide (0.66 mL, 0.66 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.38. Yield 136 mg (389 mmol, 80%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 2.1:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.06 (m, 7H), 6.94 – 6.85 (m, 2H), 5.82 (ddt, *J* = 16.9, 10.1, 6.2 Hz, 1H), 5.17 – 4.72 (m, 6H), 4.23 – 4.00 (m, 2H), 3.45 (dd, *J* = 15.6, 6.7 Hz, 1H), 2.32 – 2.23 (m, 1H), 1.85 – 1.71 (m, 2H), 1.44 (dd, *J* = 6.1, 4.7 Hz, 1H), 0.95 (dd, J = 8.5, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (+), 162.1 (d, *J* = 245.3 Hz) (+), 141.1 (+), 136.8 (+), 133.3 (d, *J* = 3.4 Hz) (+), 132.8 (+), 130.4 (d, *J* = 8.0 Hz) (+), 128.7 (+), 127.2 (+), 126.5 (+), 118.9 (–), 115.5 (–), 115.2 (d, *J* = 21.0 Hz) (+), 49.7 (–), 46.4 (–), 35.2 (+), 34.0 (–), 24.1 (+), 21.7 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.06 (m, 5H), 6.72 (t, *J* = 8.7 Hz, 2H), 6.46 (dd, *J* = 8.4, 5.3 Hz, 2H), 5.96 – 5.86 (m, 1H), 5.64 (dddd, *J* = 17.4, 10.1, 7.5, 5.1 Hz, 1H), 5.17 – 4.72 (m, 5H), 4.23 – 4.00 (m, 2H), 3.29 (dd, *J* = 14.7, 7.5 Hz, 1H), 2.54 – 2.44 (m, 1H), 1.85 – 1.71 (m, 2H), 1.39 (t, *J* = 5.2 Hz, 1H), 0.98 (dd, *J* = 8.1, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (+), 162.0 (d, *J* = 245.9

Hz) (+), 141.0 (+), 136.9 (+), 132.6 (+), 131.6 (d, *J* = 3.4 Hz) (+), 128.9 (d, *J* = 8.2 Hz) (+), 128.9 (+), 126.7 (+), 126.6 (+), 118.2 (–), 115.5 (–), 115.2 (d, *J* = 21.4 Hz) (+), 49.4 (–), 46.8 (–), 35.4 (+), 34.2 (–), 23.9 (+), 20.8 (–). FT IR (NaCl, cm^{-1}): 3077, 3004, 2920, 1645, 1509, 1441, 1410, 1267, 1223, 995, 919, 825, 700. HRMS (TOF ES): found 372.1755, calculated for $C_{23}H_{24}FNONa$ $(M+Na)^+$ 372.1740 (4.0 ppm).



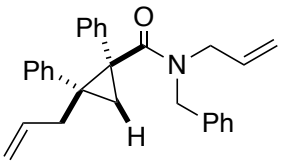
(1S*,2R*)-N,2-Diallyl-N-benzyl-1-(4-methoxyphenyl)cyclopropane-1-carboxamide (**3.5bba**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-benzyl-1-(4-methoxyphenyl)cyclo-prop-2-ene-1-carboxamide **3.3bb** (150 mg, 0.47 mmol) using allyl-magnesium bromide (0.63 mL, 0.63 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.21. Yield 151 mg (418 mmol, 89%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.9:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.11 (m, 7H), 6.85 – 6.78 (m, 2H), 6.02 – 5.85 (m, 1H), 5.20 – 4.87 (m, 6H), 4.20 – 4.09 (m, 2H), 3.78 (s, 3H), 3.59 – 3.52 (m, 1H), 2.43 – 2.33 (m, 1H), 1.89 – 1.71 (m, 2H), 1.47 (dd, *J* = 5.9, 4.6 Hz, 1H), 0.97 (dd, *J* = 8.4, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (+), 158.2 (+), 137.6 (+), 137.0 (+), 133.3 (+), 133.0 (+), 128.7 (+) 128.4 (+), 127.8 (+), 127.2 (+), 118.8 (–), 115.3 (–), 114.1 (+), 55.3 (+), 49.6 (–), 47.0 (–), 34.6 (+), 34.2 (–), 24.0 (+), 21.3 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.11 (m, 5H), 6.78 – 6.72 (m, 2H), 6.67 (dd, *J* = 7.0, 2.6 Hz, 2H), 6.02 – 5.85 (m, 1H), 5.72 (dddd, *J* = 17.4, 10.2, 7.4, 5.2 Hz, 1H), 5.20 – 4.87 (m, 5H), 4.33 – 4.21 (m, 2H), 3.74 (s, 3H), 3.42 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.58 (dt, *J* = 14.6, 5.6 Hz, 1H), 1.89 – 1.71 (m, 2H), 1.40 (dd, *J* = 6.2, 4.8 Hz, 1H),

1.02 (dd, *J* = 8.6, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (+), 158.4 (+), 137.1 (+), 136.1 (+), 133.1 (+), 132.7 (+), 128.4 (+), 128.3 (+), 127.2 (+), 127.1 (+), 118.0 (–), 115.4 (–), 114.2 (+), 55.3 (+), 50.1 (–), 47.0 (–), 34.7 (+), 34.4 (–), 24.1 (+), 20.5 (–). FT IR (NaCl, cm^{-1}): 3075, 3002, 2916, 2836, 1640, 1514, 1450, 1413, 1270, 1247, 917, 831, 738, 702. HRMS (TOF ES): found 384.1944, calculated for $C_{24}H_{27}NO_2Na$ $(M+Na)^+$ 384.1939 (1.3 ppm).



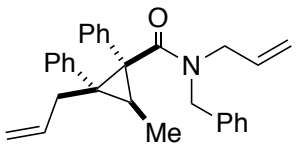
(1S*,2R*)-N,2-Diallyl-N-benzyl-1-(4-fluorophenyl)cyclopropane-1-carboxamide (**3.5cba**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-benzyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamide **3.3cb** (150 mg, 0.49 mmol) using allylmagnesium bromide (0.66 mL, 0.66 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f = 0.22. Yield 144 mg (412 mmol, 84%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 2.0:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.03 (m, 7H), 6.94 – 6.86 (m, 2H), 5.87 – 5.77 (m, 1H), 5.14 – 4.76 (m, 6H), 4.10 (d, *J* = 14.4 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.54 – 3.45 (m, 1H), 2.30 (dt, *J* = 14.5, 4.6 Hz, 1H), 1.83 – 1.65 (m, 2H), 1.43 (dd, *J* = 6.0, 4.7 Hz, 1H), 0.92 (dd, *J* = 8.4, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8 (+), 161.5 (d, *J* = 245.3 Hz) (+), 137.4 (+), 136.9 (+), 136.8 (+), 132.7 (+), 128.7 (+), 128.4 (+), 128.3 (d, *J* = 7.6 Hz) (+), 127.4 (+), 118.9 (–), 115.5 (d, *J* = 21.6 Hz) (–), 115.5 (+), 49.5 (–), 47.1 (–), 34.6 (+), 34.1 (–), 24.4 (+), 21.5 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.03 (m, 5H), 6.82 (t, *J* = 8.6 Hz, 2H), 6.63 – 6.56 (m, 2H), 5.95 – 5.87 (m, 1H), 5.65 (dddd, *J* = 17.4, 10.2, 7.4, 5.2 Hz, 1H), 5.14 – 4.76 (m, 5H), 4.28 – 4.14 (m, 2H), 3.35 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.51 (dt, *J* = 14.8, 5.6 Hz, 1H), 1.83 – 1.65 (m, 2H),

1.36 (dd, *J* = 6.2, 4.9 Hz, 1H), 0.97 (dd, *J* = 8.7, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (+), 161.6 (d, *J* = 245.6 Hz) (+), 137.0 (+), 137.0 (+), 135.8 (+), 132.5 (+), 128.9 (d, *J* = 8.1 Hz) (+), 128.4 (+), 127.3 (+), 127.0 (+), 118.2 (–), 115.6 (–), 115.5 (d, *J* = 21.6 Hz) (+), 50.1 (–), 47.1 (–), 34.7 (+), 34.3 (–), 24.5 (+), 20.7 (–). FT IR (NaCl, cm^{-1}): 3076, 3004, 2921, 1640, 1511, 1450, 1415, 1231, 995, 918, 837, 725, 702, 560. HRMS (TOF ES): found 372.1732, calculated for $C_{23}H_{24}FNONa$ $(M+Na)^+$ 372.1740 (2.1 ppm).



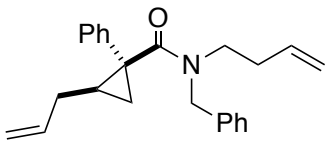
(1R*,2R*)-N,2-diallyl-N-benzyl-1,2-diphenylcyclopropane-1-carboxamide (**3.5dba**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide **3.3db** (200 mg, 0.55 mmol) using allylmagnesium bromide (0.79 mL, 0.79 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.28. Yield 199 mg (488 mmol, 89%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.3:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 6.86 (m, 15H), 5.69 – 5.53 (m, 1H), 5.30 (ddt, *J* = 16.3, 10.8, 5.7 Hz, 1H), 5.08 – 4.78 (m, 3H), 4.64 (d, *J* = 14.8 Hz, 1H), 4.40 (d, *J* = 14.7 Hz, 1H), 4.04 (dd, *J* = 16.2, 5.8 Hz, 1H), 4.01 – 3.95 (m, 1H), 3.81 (dd, *J* = 16.2, 5.7 Hz, 1H), 3.23 – 3.12 (m, 1H), 2.13 – 2.03 (m, 2H), 1.47 (d, *J* = 5.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (+), 139.4 (+), 137.5 (+), 136.7 (+), 136.1 (+), 133.2 (+), 129.7 (+), 128.5 (+), 128.2 (+), 128.1 (+), 127.8 (+), 127.6 (+), 127.0 (+), 126.4 (+), 126.0 (+), 118.1 (–), 116.2 (–), 49.3 (–), 46.8 (–), 44.3 (–), 40.6 (+), 39.2 (+), 21.3 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 6.86 (m, 15H), 6.79 – 6.74 (m, 2H), 5.69 – 5.53 (m, 1H), 5.08 – 4.78 (m, 4H), 4.74 (d, *J* = 15.9 Hz, 1H), 4.48 (d, *J* = 15.9 Hz, 1H),

3.64 (dd, *J* = 15.2, 6.2 Hz, 1H), 3.23 – 3.12 (m, 1H), 2.13 – 2.03 (m, 2H), 1.42 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (+), 139.4 (+), 137.5 (+), 136.8 (+), 136.1 (+), 132.5 (+), 129.7 (+), 128.6 (+), 128.4 (+), 128.2 (+), 128.0 (+), 127.6 (+), 127.2 (+), 126.4 (+), 126.0 (+), 117.4 (–), 116.3 (–), 50.2 (–), 46.6 (–), 44.3 (–), 40.6 (+), 39.0 (+), 21.2 (–). FT IR (NaCl, cm^{-1}): 3062, 3027, 2977, 2923, 1634, 1496, 1451, 1413, 1251, 914, 699. HRMS (TOF ES): found 430.2142, calculated for $C_{29}H_{29}NONa$ $(M+Na)^+$ 430.2147 (1.2 ppm).



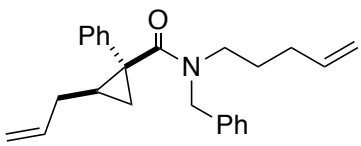
(1R*,2R*,3S)-N,2-Diallyl-N-benzyl-3-methyl-1,2-diphenylcyclopropane-1-carboxamide (**3.5dbb**). This compound was synthesized according to typical procedure **C** from *N*-allyl-*N*-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide **3.3db** (100 mg, 0.247 mmol) using methylmagnesium bromide (0.37 mmol, 0.12 mL, 3M in ether). After the Grignard reagent was added the reaction mixture was stirred for 5 min at 0 °C and then allyl bromide (99.3 mg, 0.821 mmol, 3 equiv.) was added and reaction was allowed to room temperature. After 15 min at room temperature saturated aqueous ammonium chloride (1 mL) was added dropwise and the reaction was stirred for another five minutes. The resulting mixture was then diluted with water (2 mL) and extracted with diethyl ether (3 x 3 mL). Combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and then the solvent was removed under reduced pressure. The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as colorless crystals, mp 92.5 - 93.7 °C, R_f 0.37. Yield 82.2 mg (0.195 mmol, 71%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 2.6:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 6.80 (m, 14H), 6.37 – 6.30 (m, 1H), 5.54 (dtd, *J* = 17.2,

7.0, 3.1 Hz, 1H), 5.06 – 5.00 (m, 1H), 4.96 – 4.73 (m, 4H), 4.61 (dddd, *J* = 17.4, 10.0, 7.8, 4.8 Hz, 1H), 4.04 (ddd, *J* = 15.2, 4.8, 1.5 Hz, 1H), 3.99 (d, *J* = 14.5 Hz, 1H), 3.49 (dd, *J* = 15.2, 7.9 Hz, 1H), 3.18 – 3.07 (m, 1H), 2.70 – 2.57 (m, 1H), 2.42 (q, *J* = 6.5 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1 (+), 141.6 (+), 137.9 (+), 137.6 (+), 136.9 (+), 133.0 (+), 130.2 (+), 128.6 (+), 128.4 (+), 127.9 (+), 127.9 (+), 127.3 (+), 127.2 (+), 126.1 (+), 125.6 (+), 118.9 (–), 116.0 (–), 49.5 (–), 46.2 (+), 42.6 (–), 41.1 (+), 38.8 (–), 23.7 (+), 10.7 (+). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 6.80 (m, 15H), 5.65 (dddd, *J* = 17.5, 10.2, 7.7, 5.1 Hz, 1H), 5.54 (dtd, *J* = 17.2, 7.0, 3.1 Hz, 1H), 5.06 – 5.00 (m, 1H), 4.96 – 4.73 (m, 4H), 4.30 (dd, *J* = 14.7, 5.0 Hz, 1H), 4.17 (d, *J* = 15.0 Hz, 1H), 3.21 (dd, *J* = 14.8, 7.7 Hz, 1H), 3.18 – 3.07 (m, 1H), 2.70 – 2.57 (m, 1H), 2.48 (q, *J* = 6.6 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2 (+), 141.6 (+), 138.1 (+), 136.9 (+), 135.9 (+), 132.8 (+), 130.1 (+), 128.2 (+), 128.1 (+), 127.9 (+), 127.8 (+), 127.3 (+), 127.2 (+), 126.2 (+), 125.6 (+), 118.0 (-F), 116.0 (–), 50.3 (–), 46.0 (–), 42.9 (+), 40.4 (+), 38.7 (–), 23.5 (+), 10.9 (+). FT IR (NaCl, cm^{-1}): 3061, 3026, 2977, 2934, 1633, 1449, 1411, 1242, 1195, 912, 701. HRMS (TOF ES): found 444.2310, calculated for $C_{30}H_{31}NONa$ $(M+Na)^+$ 444.2303 (1.6 ppm).



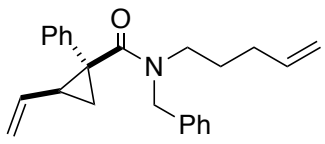
(1S*,2R*)-2-Allyl-N-benzyl-N-(but-3-en-1-yl)-1-phenylcyclopropane-1-carboxamide (**3.5aea**). This compound was synthesized according to typical procedure **C** from *N*-benzyl-*N*-(but-3-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide **3.3ae** (150 mg, 0.494 mmol) using allylmagnesium bromide (0.667 mmol, 0.667 mL, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless solid, mp 66.8 - 67.5 °C, R_f 0.30. Yield 140 mg (0.41 mmol, 82%). NMR spectra of

this material show signals of two rotamers in a ratio c.a. 1.1:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.09 (m, 10H), 5.94 (dddt, *J* = 40.1, 16.8, 10.2, 6.1 Hz, 1H), 5.29 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.09 – 4.80 (m, 4H), 4.71 (dt, *J* = 17.1, 1.6 Hz, 1H), 4.28 (d, *J* = 14.7 Hz, 1H), 3.62 – 3.48 (m, 1H), 2.96 (ddd, *J* = 14.2, 11.1, 5.0 Hz, 1H), 2.36 (dt, 1H), 2.23 (q, *J* = 7.3 Hz, 1H), 1.99 – 1.74 (m, 2H), 1.52 (dd, *J* = 6.2, 4.7 Hz, 1H), 1.20 (tt, *J* = 11.9, 5.9 Hz, 1H), 0.99 (dd, *J* = 8.6, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (+), 141.4 (+), 137.7 (+), 137.0 (+), 134.5 (+), 128.8 (+), 128.5 (+), 128.3 (+), 127.3 (+), 126.8 (+), 126.6 (+), 116.7 (–), 115.4 (–), 48.0 (–), 46.4 (–), 35.4 (+), 33.9 (–), 31.3 (–), 23.6 (+), 21.6 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.09 (m, 8H), 6.68 (dd, *J* = 7.4, 2.2 Hz, 2H), 5.94 (dddt, *J* = 40.1, 16.8, 10.2, 6.1 Hz, 1H), 5.69 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.16 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.09 – 4.80 (m, 4H), 4.34 (d, *J* = 15.7 Hz, 1H), 3.62 – 3.48 (m, 1H), 3.06 (dt, *J* = 13.4, 7.4 Hz, 1H), 2.60 (dt, *J* = 13.5, 4.8 Hz, 1H), 2.23 (q, *J* = 7.3 Hz, 1H), 1.99 – 1.74 (m, 3H), 1.41 (dd, *J* = 6.1, 4.8 Hz, 1H), 1.08 (dd, *J* = 8.4, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (+), 141.1 (+), 137.1 (+), 136.2 (+), 135.6 (+), 128.8 (+), 128.5 (+), 128.4 (+), 127.3 (+), 126.9 (+), 126.6 (+), 116.6 (–), 115.3 (–), 51.2 (–), 44.2 (–), 35.3 (+), 34.6 (–), 31.5 (–), 24.4 (+), 21.0 (–). FT IR (NaCl, cm^{-1}): 3063, 2924, 5853, 1638, 1444, 1419, 914, 700. HRMS (TOF ES): found 368.1988, calculated for $C_{24}H_{27}NONa$ $(M+Na)^+$ 368.1990 (0.5 ppm).



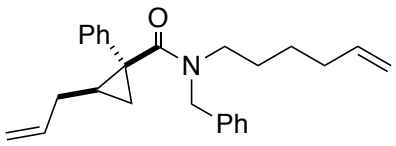
(1S*,2R*)-2-Allyl-N-benzyl-N-(pent-4-en-1-yl)-1-phenylcyclopropane-1-carboxamide (**3.5afa**). This compound was synthesized according to typical procedure **C** from *N*-benzyl-*N*-(pent-4-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide **3.3af** (150 mg, 0.47 mmol) using allylmagnesium bromide (0.69 mL, 0.69 mmol, 1M in ether). The product was isolated by column chromatography

eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.28. Yield 133 mg (0.37 mmol, 78%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.2:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.10 (m, 10H), 6.06 – 5.83 (m, 1H), 5.44 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.11 – 4.76 (m, 5H), 4.28 (dd, *J* = 17.4, 15.2 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.01 – 2.87 (m, 1H), 2.41 – 2.31 (m, 1H), 2.02 – 1.76 (m, 2H), 1.63 – 1.54 (m, 2H), 1.51 (t, *J* = 6.1 Hz, 1H), 1.31 (ddt, *J* = 17.2, 7.7, 4.8 Hz, 1H), 1.00 (dd, *J* = 8.5, 4.7 Hz, 1H), 0.64 – 0.53 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (+), 141.4 (+), 137.9 (+), 137.1 (+), 137.0 (+), 128.8 (+), 128.7 (+), 128.4 (+), 128.3 (+), 127.2 (+), 126.7 (+), 126.5 (+), 115.3 (–), 115.0 (–), 47.9 (–), 44.5 (–), 34.0 (–), 30.9 (–), 26.2 (–), 23.7 (+), 21.7 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.10 (m, 8H), 6.72 – 6.63 (m, 2H), 6.06 – 5.83 (m, 1H), 5.72 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.11 – 4.76 (m, 5H), 4.28 (dd, *J* = 17.4, 15.2 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.01 – 2.87 (m, 1H), 2.66 – 2.53 (m, 1H), 2.02 – 1.76 (m, 4H), 1.63 – 1.54 (m, 2H), 1.42 (t, *J* = 5.3 Hz, 1H), 1.06 (dd, *J* = 8.3, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (+), 141.2 (+), 137.8 (+), 137.4 (+), 136.3 (+), 128.8 (+), 128.7 (+), 128.4 (+), 128.3 (+), 127.2 (+), 126.9 (+), 126.5 (+), 115.4 (–), 114.9 (–), 51.1 (–), 46.6 (–), 34.4 (–), 31.2 (–), 25.7 (–), 24.3 (+), 20.9 (–). FT IR (NaCl, cm^{-1}): 3064, 3002, 2928, 1637, 1420, 1305, 1194, 912, 738, 700. HRMS (TOF ES): found 382.2152, calculated for $C_{25}H_{29}NONa$ $(M+Na)^+$ 382.2147 (1.3 ppm).



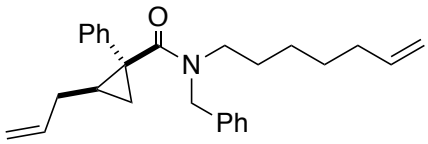
(1S*,2S*)-N-Benzyl-N-(pent-4-en-1-yl)-1-phenyl-2-vinylcyclopropane-1-carboxamide (**3.5afc**). This compound was synthesized according to typical procedure **C** from *N*-benzyl-*N*-(pent-4-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide **3.3af** (100 mg, 0.32 mmol) using vinylmagnesium

bromide (0.43 mL, 0.43 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.21. Yield 74 mg (0.21 mmol, 68%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.02:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.07 (m, 10H), 5.44 (dddd, *J* = 16.9, 13.4, 9.7, 6.3 Hz, 2H), 5.28 (dd, *J* = 17.0, 1.6 Hz, 1H), 5.00 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.98 – 4.74 (m, 3H), 4.30 (d, *J* = 14.8 Hz, 1H), 3.34 (ddd, *J* = 14.1, 11.7, 4.9 Hz, 1H), 2.95 – 2.85 (m, 1H), 2.62 – 2.52 (m, 1H), 2.00 – 1.88 (m, 1H), 1.85 (dd, *J* = 6.2, 4.9 Hz, 1H), 1.63 – 1.56 (m, 2H), 1.38 – 1.27 (m, 1H), 1.20 – 1.10 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (+), 140.6 (+), 137.6 (+), 137.5 (+), 136.6 (+), 128.7 (+), 128.3 (+), 128.2 (+), 127.2 (+), 126.8 (+), 126.4 (+), 116.0 (–), 114.9 (–), 47.8 (–), 44.3 (–), 37.2 (+), 30.9 (–), 28.1 (+), 26.2 (–), 22.9 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.06 (m, 8H), 6.66 – 6.61 (m, 2H), 5.71 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.55 (ddd, *J* = 17.0, 10.2, 9.1 Hz, 1H), 5.34 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.14 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.98 – 4.74 (m, 3H), 4.21 (d, *J* = 15.6 Hz, 1H), 3.43 (dt, *J* = 13.5, 7.8 Hz, 1H), 2.95 – 2.85 (m, 1H), 2.62 – 2.52 (m, 1H), 2.00 – 1.88 (m, 1H), 1.80 (dd, *J* = 6.1, 4.9 Hz, 1H), 1.52 (p, *J* = 7.6 Hz, 2H), 1.20 – 1.10 (m, 1H), 0.73 – 0.58 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (+), 140.3 (+), 137.9 (+), 136.7 (+), 136.2 (+), 128.8 (+), 128.2 (+), 127.6 (+), 127.2 (+), 126.8 (+), 126.7 (+), 116.0 (–), 114.8 (–), 50.8 (–), 46.1 (–), 37.5 (+), 31.2 (–), 28.1 (+), 25.7 (–), 22.3 (–). FT IR (NaCl, cm^{-1}): 3063, 3027, 2934, 1637, 1495, 1422, 1307, 1191, 992, 909, 699. HRMS (TOF ES): found 368.1987, calculated for $C_{24}H_{27}NONa$ $(M+Na)^+$ 368.1990 (0.8 ppm).



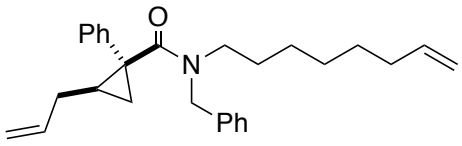
(1S*,2R*)-2-Allyl-N-benzyl-N-(hex-5-en-1-yl)-1-phenylcyclo-propane-1-carboxamide (**3.5aga**). This compound was synthesized according to typical procedure **C** from *N*-benzyl-*N*-(hex-5-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide **3.3ag** (150 mg, 0.45 mmol) using allylmagnesium bromide (0.61 mL, 0.61 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a pale-yellow oil, R_f = 0.27. Yield 127 mg (0.34 mmol, 75%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.2:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.10 (m, 10H), 6.04 – 5.86 (m, 1H), 5.58 (ddt, *J* = 17.2, 10.8, 6.7 Hz, 1H), 5.10 – 4.80 (m, 5H), 4.23 (d, *J* = 14.7 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.01 – 2.85 (m, 1H), 2.40 – 2.33 (m, 1H), 1.94 – 1.77 (m, 2H), 1.78 – 1.67 (m, 1H), 1.54 – 1.44 (m, 1H), 1.34 – 1.19 (m, 2H), 0.99 (dd, *J* = 8.5, 4.8 Hz, 1H), 0.97 – 0.85 (m, 2H), 0.48 (dtd, *J* = 16.7, 10.7, 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (+), 141.5 (+), 138.3 (+), 137.8 (+), 137.0 (+), 128.7 (+), 128.4 (+), 128.3 (+), 127.2 (+), 126.6 (+), 126.5 (+), 115.3 (–), 114.6 (–), 47.8 (–), 46.8 (–), 35.4 (+), 34.0 (–), 33.2 (–), 26.5 (–), 26.0 (–), 23.7 (+), 21.7 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.09 (m, 8H), 6.72 – 6.66 (m, 2H), 6.04 – 5.86 (m, 1H), 5.73 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.20 – 5.12 (m, 1H), 5.10 – 4.80 (m, 4H), 4.31 (d, *J* = 15.7 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.01 – 2.85 (m, 1H), 2.64 – 2.56 (m, 1H), 1.99 (q, *J* = 7.3 Hz, 2H), 1.94 – 1.77 (m, 2H), 1.54 – 1.44 (m, 2H), 1.41 (t, *J* = 5.3 Hz, 1H), 1.34 – 1.19 (m, 1H), 1.07 (dd, *J* = 8.4, 4.9 Hz, 1H), 0.97 – 0.84 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (+), 141.2 (+), 138.5 (+), 137.2 (+), 136.3 (+), 128.8 (+), 128.3 (+), 127.2 (+), 127.2 (+), 126.9 (+), 126.5 (+), 115.3 (–), 114.6 (–), 51.0 (–), 44.6 (–), 35.3 (+), 34.5 (–), 33.3 (–), 26.3 (–), 25.9 (–), 24.4 (+), 21.0 (–). FT

IR (NaCl, cm^{-1}): 3063, 2930, 2859, 1637, 1495, 1420, 912, 735, 700. HRMS (TOF ES): found 396.2304, calculated for $C_{26}H_{31}NONa$ $(M+Na)^+$ 396.2303 (0.3 ppm).



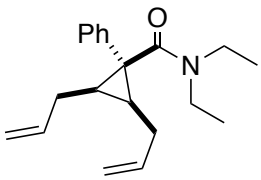
(1S*,2R*)-2-Allyl-N-benzyl-N-(hept-6-en-1-yl)-1-phenylcyclopropane-1-carboxamide (**3.5aha**). This compound was synthesized according to typical procedure **C** from *N*-benzyl-*N*-(oct-7-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide **3.3ah** (150 mg, 0.43 mmol) using allylmagnesium bromide (0.59 mL, 0.59 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a pale-yellow oil, R_f 0.22. Yield 122 mg (0.304 mmol, 73%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.3:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.10 (m, 10H), 6.05 – 5.85 (m, 1H), 5.81 – 5.64 (m, 1H), 5.10 – 4.89 (m, 5H), 4.25 (d, *J* = 14.7 Hz, 1H), 3.50 – 3.39 (m, 1H), 3.01 – 2.83 (m, 1H), 2.42 – 2.32 (m, 1H), 1.93 – 1.75 (m, 3H), 1.51 (dd, *J* = 6.1, 4.7 Hz, 1H), 1.28 – 1.13 (m, 2H), 1.13 – 1.02 (m, 2H), 0.99 (dd, *J* = 8.6, 4.8 Hz, 1H), 0.92 – 0.75 (m, 2H), 0.54 – 0.42 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 141.5, 138.7, 137.9, 137.0, 128.6, 128.4, 128.3, 127.2, 126.6, 126.5, 115.3, 114.4, 47.8, 46.9, 35.4, 34.0, 33.5, 28.4, 26.8, 26.2, 23.7, 21.7. Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.10 (m, 8H), 6.68 (dd, *J* = 7.3, 2.2 Hz, 2H), 6.05 – 5.85 (m, 1H), 5.81 – 5.64 (m, 1H), 5.19 – 5.12 (m, 1H), 5.10 – 4.89 (m, 3H), 4.86 (d, *J* = 15.7 Hz, 1H), 4.30 (d, *J* = 15.7 Hz, 1H), 3.50 – 3.39 (m, 1H), 3.01 – 2.83 (m, 1H), 2.64 – 2.56 (m, 1H), 2.01 – 1.95 (m, 2H), 1.93 – 1.76 (m, 3H), 1.46 (quintet, *J* = 7.8 Hz, 2H), 1.41 (dd, *J* = 6.0, 4.7 Hz, 1H), 1.33 (quintet, *J* = 7.5 Hz, 2H), 1.28 – 1.13 (m, 1H), 1.13 – 1.02 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 141.2, 138.8, 137.2, 136.3, 128.8, 128.4, 128.3, 127.2, 126.9,

126.5, 115.3, 114.4, 51.0, 44.7, 35.3, 34.5, 33.6, 28.5, 26.5, 26.3, 24.4, 21.0. FT IR (NaCl, cm^{-1}): 3063, 2929, 2857, 1638, 1495, 1421, 911, 733, 700. HRMS (TOF ES): found 410.2456, calculated for $C_{27}H_{33}NONa$ $(M+Na)^+$ 410.2460 (1.0 ppm).



(1S*,2R*)-2-Allyl-N-benzyl-N-(oct-7-en-1-yl)-1-phenylcyclopropane-1-carboxamide (**3.5aia**). This compound was synthesized according to typical procedure **C** from *N*-benzyl-*N*-(oct-7-en-1-yl)-1-phenylcycloprop-2-ene-1-carboxamide **3.3ai** (150 mg, 0.42 mmol) using allylmagnesium bromide (0.65 mL, 0.65 mmol, 1M in ether). The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a pale-yellow oil, R_f 0.23. Yield 134 mg (0.33 mmol, 80%). NMR spectra of this material show signals of two rotamers in a ratio c.a. 1.3:1. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.10 (m, 10H), 6.03 – 5.86 (m, 1H), 5.83 – 5.69 (m, 1H), 5.10 – 4.89 (m, 5H), 4.25 (d, *J* = 14.6 Hz, 1H), 3.50 – 3.39 (m, 1H), 2.99 – 2.85 (m, 1H), 2.37 (dt, *J* = 14.6, 5.0 Hz, 1H), 1.96 – 1.76 (m, 4H), 1.51 (dd, *J* = 6.1, 4.7 Hz, 1H), 1.28 – 1.11 (m, 6H), 0.90 – 0.73 (m, 2H), 0.48 (dtd, *J* = 16.8, 10.8, 5.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (+), 141.5 (+), 138.9 (+), 137.9 (+), 137.1 (+), 128.6 (+), 128.4 (+), 128.3 (+), 127.2 (+), 126.9 (+), 126.6 (+), 115.3 (–), 114.3 (–), 47.8 (–), 47.0 (–), 35.4 (+), 34.0 (–), 33.6 (–), 28.8 (–), 28.6 (–), 26.9 (–), 26.6 (–), 23.7 (+), 21.7 (–). Minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.10 (m, 8H), 6.72 – 6.65 (m, 2H), 6.03 – 5.86 (m, 1H), 5.83 – 5.69 (m, 1H), 5.16 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.10 – 4.89 (m, 3H), 4.86 (d, *J* = 15.7 Hz, 1H), 4.30 (d, *J* = 15.7 Hz, 1H), 3.50 – 3.39 (m, 1H), 2.99 – 2.85 (m, 1H), 2.64 – 2.57 (m, 1H), 2.02 – 1.96 (m, 2H), 1.96 – 1.76 (m, 2H), 1.49 – 1.38 (m, 3H), 1.36 – 1.28 (m, 2H), 1.06 (dd, *J* = 8.4, 5.0 Hz, 1H), 1.04 –

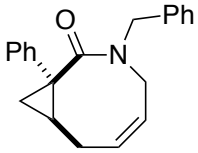
0.91 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (+), 141.2 (+), 139.1 (+), 137.2 (+), 136.3 (+), 128.8 (+), 128.4 (+), 128.3 (+), 127.2 (+), 127.2 (+), 126.5 (+), 115.3 (–), 114.2 (–), 51.0 (–), 44.8 (–), 35.3 (+), 34.5 (–), 33.7 (–), 28.8 (–), 28.6 (–), 26.9 (–), 26.4 (–), 24.4 (+), 21.0 (–). FT IR (NaCl, cm^{-1}): 3063, 2928, 2855, 1638, 1495, 1420, 994, 910, 734, 699. HRMS (TOF ES): found 424.2621, calculated for $C_{28}H_{35}NONa$ $(M+Na)^+$ 424.2616 (1.2 ppm).



(1*S*,2*R,3*S**)-*2,3-Diallyl-N,N-diethyl-1-phenylcyclopropane-1-carboxamide* (**3.9**). This compound was synthesized according to typical procedure **C** from *N,N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide **3.7** (70 mg, 0.33 mmol) using allylmagnesium bromide (0.44 mL, 0.44 mmol, 1M in ether). After the Grignard reagent was added the reaction mixture was stirred for 5 min at 0 °C and then allyl bromide (120 mg, 0.98 mmol, 3.00 equiv.) was added and reaction was allowed to room temperature. After 15 min at room temperature saturated aqueous ammonium chloride (1 mL) was added dropwise and the reaction was stirred for another five minutes. The resulting mixture was then diluted with water (2 mL) and extracted with diethyl ether (3 x 3 mL). Combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and then the solvent was removed under reduced pressure. The product was isolated by column chromatography eluting with hexane/EtOAc mixture (10:1) to afford the title compound as a colorless oil, R_f 0.25. Yield 84 mg (0.28 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.14 (m, 4H), 7.13 – 7.07 (m, 1H), 5.96 (ddt, *J* = 16.6, 10.2, 6.3 Hz, 2H), 5.03 (dq, *J* = 17.2, 1.8 Hz, 2H), 4.95 (dq, *J* = 10.3, 1.6 Hz, 2H), 3.28 (q, *J* = 7.1 Hz, 2H), 3.23 (q, *J* = 7.0 Hz, 2H), 2.54 – 2.45 (m, 2H), 2.16 – 2.06 (m, 2H), 1.50 – 1.43 (m, 2H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1 (+), 142.4

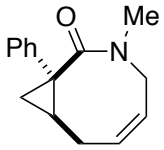
(+), 138.2 (+), 128.7 (+), 126.1 (+), 125.9 (+), 115.0 (–), 41.8 (–), 38.6 (–), 35.7 (+), 29.6 (–), 29.3 (+), 12.6 (+), 12.5 (+). FT IR (NaCl, cm^{-1}): 3074, 2976, 2934, 1635, 1445, 1424, 994, 908, 699. HRMS (TOF ES): found 320.1994, calculated for $C_{20}H_{27}NONa$ $(M+Na)^+$ 320.1990 (1.2 ppm).

3.7.4 Synthesis of medium sized rings via RCM reaction

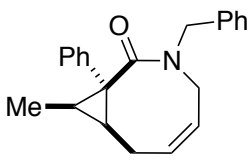


(1R*,8S*,Z)-3-Benzyl-1-phenyl-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6aba**), ***(Typical procedure D)***: Oven dried 50 mL round bottom flask was charged with *N*,2-diallyl-*N*-benzyl-1-phenylcyclopropane-1-carboxamide **3.5aba** (50 mg, 0.15 mmol, 1.00 equiv.), freshly distilled dry CH_2Cl_2 (30.2 mL) and the solution was degassed under Ar atmosphere for 30 minutes. Then the solution was heated up to boiling point and the 2nd generation of Grubbs catalyst (6.4 mg, 7.5 mmol, 5 mol%) was added to the reaction mixture and the mixture was stirred at boiling point for 1h. When the reaction was complete (control by TLC) the solvent was removed under reduced pressure and the dry residue was fractioned on silica gel eluting with hexane/EtOAc mixture (5:1) to afford the title compound as colorless crystals, m.p. 136.9-137.5 °C, R_f 0.36. Yield 40 mg (0.13 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 7H), 7.23 – 7.15 (m, 3H), 5.87 (ddt, *J* = 11.5, 8.6, 3.1 Hz, 1H), 5.51 (ddt, *J* = 10.8, 7.0, 3.2 Hz, 1H), 5.22 (dd, *J* = 14.6, 1.4 Hz, 1H), 4.43 – 4.30 (m, 1H), 3.97 (d, *J* = 14.6 Hz, 1H), 3.18 (dd, *J* = 17.2, 7.3 Hz, 1H), 2.76 (ddd, *J* = 16.7, 8.7, 3.0 Hz, 1H), 1.95 – 1.82 (m, 1H), 1.81 – 1.69 (m, 1H), 1.33 (t, *J* = 5.4 Hz, 1H), 0.96 (dd, *J* = 8.3, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (+), 140.8 (+), 137.7 (+), 132.9 (+), 128.8 (+), 128.5 (+), 128.4 (+), 127.4 (+), 126.7 (+), 126.4 (+), 124.6 (+), 49.3 (–), 44.6 (–), 35.5 (+), 29.7 (–), 23.9 (+), 22.8 (–). FT IR (NaCl, cm^{-1}): 3022, 2916, 2750, 1634, 1469,

1428, 1265, 1200, 1162, 756, 707, 609. HRMS (TOF ES): found 304.1707, calculated for $C_{21}H_{22}NO$ $(M + H)^+$ 304.1701 (2.0 ppm).

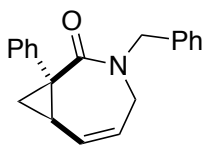


(1R*,8S*,Z)-3-Methyl-1-phenyl-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6aaa**). This compound was synthesized according to typical procedure **D** from *N*,2-diallyl-*N*-methyl-1-phenylcyclopropane-1-carboxamide **3.5aaa** (20 mg, 0.078 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (3:1) to give the title compound as colorless crystals, mp 80.0 - 80.4 °C, R_f 0.19. Yield 15 mg (0.066 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 5.91 (ddt, *J* = 11.5, 8.6, 3.0 Hz, 1H), 5.62 (ddt, *J* = 10.8, 7.0, 3.3 Hz, 1H), 4.55 (dq, *J* = 17.0, 3.3 Hz, 1H), 3.17 (dd, *J* = 17.0, 7.3 Hz, 1H), 2.74 (ddd, *J* = 16.9, 8.7, 3.1 Hz, 1H), 1.83 (dddd, *J* = 11.4, 8.6, 5.8, 3.1 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.28 (dd, *J* = 5.8, 5.1 Hz, 1H), 0.94 (dd, *J* = 8.4, 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7 (+), 141.0 (+), 133.0 (+), 128.9 (+), 126.6 (+), 126.5 (+), 124.6 (+), 47.9 (–), 35.7 (+), 34.3 (+), 29.9 (–), 24.4 (+), 23.0 (–). FT IR (NaCl, cm^{-1}): 3022, 2921, 1643, 1498, 1432, 1396, 1263, 1202, 1083, 771, 698. HRMS (TOF ES): found 228.1393, calculated for $C_{15}H_{18}NO$ $(M+H)^+$ 228.1388 (2.2 ppm).



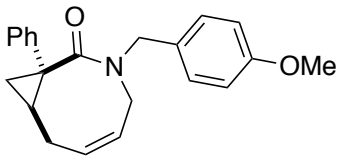
(1R*,8S*,9R*,Z)-3-Benzyl-9-methyl-1-phenyl-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6abb**). This compound was synthesized according to typical procedure **D** from *N*,2-diallyl-*N*-benzyl-3-methyl-1-phenylcyclopropane-1-carboxamide **3.5abb** (48 mg, 0.139 mmol). The product was isolated on column chromatography

eluting with hexane/EtOAc mixture (10:1) to give the title compound as colorless crystals, mp 112.1 - 113.8 °C, R_f 0.23. Yield 41 mg (0.13 mmol, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 7H), 7.17 – 7.11 (m, 3H), 5.90 (ddt, *J* = 11.5, 8.6, 3.0 Hz, 1H), 5.45 (ddt, *J* = 10.7, 6.9, 3.3 Hz, 1H), 5.12 (dd, *J* = 14.5, 1.4 Hz, 1H), 4.24 (dqd, *J* = 17.2, 3.3, 1.4 Hz, 1H), 3.93 (d, *J* = 14.5 Hz, 1H), 3.12 (dd, *J* = 17.2, 7.3 Hz, 1H), 2.47 (ddd, *J* = 16.8, 8.6, 3.0 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.78 (ddd, *J* = 12.0, 9.3, 3.0 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.15 (dq, *J* = 9.3, 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (+), 142. (+), 138.0 (+), 133.1 (+), 128.9 (+), 128.6 (+), 127.5 (+), 126.3 (+), 126.1 (+), 124.6 (+), 49.2 (–), 44.8 (–), 36.3 (+), 28.7 (+), 26.7 (+), 24.3 (–), 10.3 (+). FT IR (NaCl, cm^{-1}): 3022, 2917, 2750, 1634, 1470, 1428, 1265, 1163, 756, 707, 609. HRMS (TOF ES): found 340.1673, calculated for $C_{22}H_{23}NONa$ $(M+Na)^+$ 340.1677 (1.2 ppm).

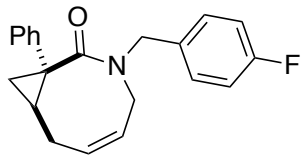


(1R*,7R*)-3-Benzyl-1-phenyl-3-azabicyclo[5.1.0]oct-5-en-2-one (**3.6abc**). This compound was synthesized according to typical procedure **D** from *N*-allyl-*N*-benzyl-1-phenyl-2-vinylcyclopropane-1-carboxamide **3.5abc** (50 mg, 0.16 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1) to give the title compound as a colorless oil, R_f 0.31. Yield 39 mg (0.13 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.37 – 7.22 (m, 6H), 7.22 – 7.17 (m, 2H), 6.01 (dt, *J* = 9.1, 2.0 Hz, 1H), 5.88 (dtd, *J* = 9.2, 6.7, 2.3 Hz, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 4.58 (d, *J* = 14.7 Hz, 1H), 4.47 (ddt, *J* = 14.9, 6.3, 1.8 Hz, 1H), 3.22 – 3.13 (m, 1H), 2.09 – 2.01 (m, 1H), 1.47 (dd, *J* = 9.8, 4.7 Hz, 1H), 1.02 (dd, *J* = 7.0, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9 (+), 141.5 (+), 137.4 (+), 132.9 (+), 130.7 (+), 128.8 (+), 128.7 (+), 128.5 (+), 127.6 (+), 127.5 (+), 127.1 (+), 51.1 (–), 43.4 (–), 35.5 (+), 25.3 (+), 18.5 (–). FT IR (NaCl, cm^{-1}): 3029, 2923, 1639, 1471, 1424, 1355, 1270, 1179,

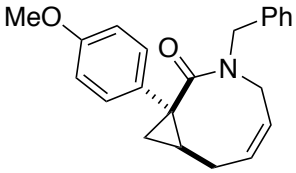
748, 698. HRMS (TOF ES): found 312.1370, calculated for $C_{20}H_{19}NONa$ $(M+Na)^+$ 312.1364 (1.9 ppm).



(1R*,8S*,Z)-3-(4-Methoxybenzyl)-1-phenyl-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6aca**). This compound was synthesized according to typical procedure D from *N*,2-diallyl-*N*-(4-methoxybenzyl)-1-phenylcyclopropane-1-carboxamide **3.5aca** (50 mg, 0.14 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1) to give the title compound as colorless solid, mp 94.8 - 95.7 °C, R_f = 0.23. Yield 38 mg (0.11 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.13 (m, 7H), 6.88 – 6.80 (m, 2H), 5.85 (ddt, *J* = 11.5, 8.6, 3.0 Hz, 1H), 5.50 (ddt, *J* = 10.8, 7.0, 3.2 Hz, 1H), 5.11 (dd, *J* = 14.4, 1.3 Hz, 1H), 4.37 – 4.27 (m, 1H), 3.94 (d, *J* = 14.4 Hz, 1H), 3.18 (dd, *J* = 17.2, 7.3 Hz, 1H), 2.74 (ddd, *J* = 16.8, 8.7, 3.0 Hz, 1H), 1.86 (dddd, *J* = 11.4, 8.5, 5.8, 3.0 Hz, 1H), 1.73 (dddd, *J* = 18.0, 11.4, 6.6, 3.3 Hz, 1H), 1.33 (t, *J* = 5.4 Hz, 1H), 0.96 (dd, *J* = 8.3, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5 (+), 159.0 (+), 140.9 (+), 132.8 (+), 129.8 (+), 128.8 (+), 126.8 (+), 126.4 (+), 124.5 (+), 113.9 (+), 55.3 (+), 48.8 (–), 44.5 (–), 35.5 (+), 29.7 (–), 24.1 (+), 22.8 (–). FT IR (NaCl, cm^{-1}): 3023, 2917, 2836, 1641, 1512, 1467, 1433, 1247, 1174, 1034, 812, 698. HRMS (TOF ES): found 356.1635, calculated for $C_{22}H_{23}NO_2Na$ $(M+Na)^+$ 356.1626 (2.5 ppm).

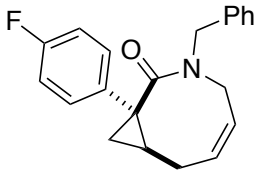


(1R*,8S*,Z)-3-(4-fluorobenzyl)-1-phenyl-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6ada**). This compound was synthesized according to typical procedure **D** from *N*,2-diallyl-*N*-(4-fluorobenzyl)-1-phenylcyclopropane-1-carboxamide **3.5ada** (50 mg, 0.14 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1) to give the title compound as colorless crystals, mp 149.2 - 150.0 °C, R_f 0.23. Yield 39 mg (0.122 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 4H), 7.23 – 7.14 (m, 3H), 7.02 – 6.96 (m, 2H), 5.85 (ddt, *J* = 11.6, 8.7, 3.0 Hz, 1H), 5.51 (ddt, *J* = 10.7, 6.9, 3.3 Hz, 1H), 5.07 (d, *J* = 14.5 Hz, 1H), 4.38 (dqd, *J* = 17.2, 3.3, 1.3 Hz, 1H), 4.02 (d, *J* = 14.5 Hz, 1H), 3.17 (dd, *J* = 17.2, 7.3 Hz, 1H), 2.75 (ddd, *J* = 16.9, 8.7, 3.1 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.77 – 1.65 (m, 1H), 1.32 (t, *J* = 5.4 Hz, 1H), 0.95 (dd, *J* = 8.4, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 172.6 (+), 163.2 (+), 161.3 (+), 140.7 (+), 133.5 (+), 133.5 (+), 132.9 (+), 130.1 (+), 130.0 (+), 128.8 (+), 126.6 (+), 126.5 (+), 124.5 (+), 115.4 (+), 115.3 (+), 48.9 (–), 44.8 (–), 35.4 (+), 29.7 (–), 23.9 (–), 22.8 (+). FT IR (NaCl, cm^{-1}): 3020, 2929, 2855, 1639, 1508, 1472, 1261, 1221, 1154, 777, 701. HRMS (TOF ES): found 344.1418, calculated for $C_{21}H_{20}FNONa$ $(M+Na)^+$ 344.1427 (2.6 ppm).



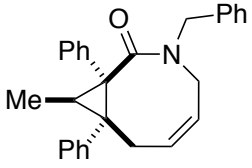
(1R*,8S*, Z)-3-Benzyl-1-(4-methoxyphenyl)-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6bba**). This compound was synthesized according to typical procedure **D** from *N*,2-diallyl-*N*-benzyl-1-(4-methoxyphenyl)cyclopropane-1-carboxamide **3.5bba** (50 mg, 0.14 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1) to give the title compound as a colorless solid mp 103.2 - 104.0 °C, R_f 0.21. Yield 39 mg (0.118 mmol, 85%). ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 5H), 7.18 – 7.09 (m, 2H), 6.87 – 6.79 (m, 2H), 5.86 (ddt, *J* = 11.5, 8.5, 3.0 Hz, 1H), 5.51 (ddt, *J* = 10.8, 7.2, 3.2 Hz, 1H), 5.26 – 5.15 (m, 1H), 4.45 – 4.36 (m, 1H), 3.95 (d, *J* = 14.6 Hz, 1H), 3.78 (s, 3H), 3.17 (dd, *J* = 17.2, 7.3 Hz, 1H), 2.74 (ddd, *J* = 16.7, 8.7, 2.9 Hz, 1H), 1.82 (dddd, *J* = 11.2, 8.3, 5.6, 2.9 Hz, 1H), 1.72 (dddd, *J* = 18.1, 11.5, 6.5, 3.3 Hz, 1H), 1.28 (t, *J* = 5.3 Hz, 1H), 0.88 (dd, *J* = 8.3, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9 (+), 158.2 (+), 137.7 (+), 132.7 (+), 128.3 (+), 127.3 (+), 126.7 (+), 125.9 (+), 114.2 (+), 55.3 (+), 49.3 (–), 44.5 (–), 34.9 (+), 29.7 (–), 23.4 (+), 22.3 (–). FT IR (NaCl, cm^{-1}): 3024, 2917, 2836, 1642, 1514, 1467, 1428, 1247, 1182, 1034, 829, 751, 700, 642. HRMS (TOF ES): found 356.1626, calculated for $C_{22}H_{23}NO_2Na$ $(M+Na)^+$ 356.1626 (0.0 ppm).

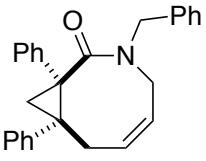


(1R*,8S*,Z)-3-Benzyl-1-(4-fluorophenyl)-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6cba**). This compound was synthesized according to typical procedure **D** from *N*,2-diallyl-*N*-benzyl-1-(4-fluorophenyl)cyclopropane-1-carboxamide (**3.5cba**) (49 mg, 0.14 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1) to give the title compound as colorless crystals (mp 164.2 - 165.2 °C), R_f 0.24. Yield 40 mg (0.125 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 7.23 – 7.15 (m, 2H), 7.06 – 6.95 (m, 2H), 5.89 (ddt, *J* = 11.5, 8.7, 3.0 Hz, 1H), 5.55 (ddt, *J* = 10.8, 7.3, 3.3 Hz, 1H), 5.22 (dd, *J* = 14.6, 1.4 Hz, 1H), 4.35 (dqd, *J* = 17.2, 3.3, 1.5 Hz, 1H), 3.98 (d, *J* = 14.6 Hz, 1H), 3.22 (dd, *J* = 17.2, 7.3 Hz, 1H), 2.78 (ddd, *J* = 16.7, 8.6, 2.9 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.81 – 1.70 (m, 1H), 1.34 (t, *J* = 5.4 Hz, 1H), 0.93 (dd, *J* = 8.3, 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4 (+), 162.5 (+), 160.5 (+), 137.5 (+), 136.5 (+), 136.5 (+), 132.9 (+), 128.6 (+), 128.3 (+), 127.5 (+), 126.6 (+), 126.3 (+), 126.2 (+), 115.7 (+), 115.6 (+), 49.4 (–), 44.5 (–), 35.0 (+), 29.7

(–), 23.8 (+), 22.6 (–). FT IR (NaCl, cm^{-1}): 3024, 2998, 2926, 2851, 1633, 1512, 1429, 1227, 1166, 835, 749,706, 646. HRMS (TOF ES): found 344.1429, calculated for $C_{21}H_{20}FNONa$ $(M+Na)^+$ 344.1427 (0.6 ppm).

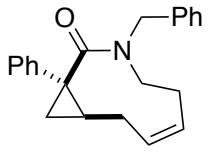


(1S*,8S*,9R*,Z)-3-Benzyl-9-methyl-1,8-diphenyl-3-azabicyclo-[6.1.0]non-5-en-2-one (**3.6ddb**). This compound was synthesized according to typical procedure **D** from *N*,2-diallyl-*N*-benzyl-3-methyl-1,2-diphenyl-cyclopropane-1-carboxamide (**3.5ddb**) (50 mg, 0.12 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (10:1) to give the title compound as colorless crystals (mp 113.8 - 114.2 °C), R_f 0.15. Yield 35 mg (0.089 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.42 – 7.36 (m, 2H), 7.36 – 7.31 (m, 1H), 7.19 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.05 – 6.94 (m, 5H), 6.57 (dd, *J* = 7.7, 1.7 Hz, 2H), 5.75 – 5.50 (m, 2H), 5.26 (dd, *J* = 14.1, 1.3 Hz, 1H), 4.69 – 4.56 (m, 1H), 4.11 (d, *J* = 14.1 Hz, 1H), 3.60 (dd, *J* = 17.1, 6.9 Hz, 1H), 2.63 – 2.53 (m, 2H), 1.89 (q, *J* = 6.6 Hz, 1H), 1.59 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4 (+), 141.3 (+), 138.4 (+), 137.8 (+), 132.3 (+), 130.3 (+), 129.2 (+), 128.6 (+), 127.9 (+), 127.7 (+), 127.6 (+), 126.6 (+), 125.7 (+), 49.6 (–), 45.5 (–), 41.6 (+), 39.6 (+), 33.3 (+), 33.1 (–), 11.1 (+). FT IR (NaCl, cm^{-1}): 3057, 3025, 2922, 1641, 1495, 1421, 1247, 738, 699, 644. HRMS (TOF ES): found 416.1991, calculated for $C_{28}H_{27}NONa$ $(M+Na)^+$ 416.1990 (0.2 ppm).



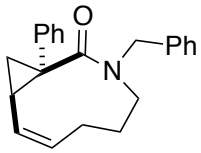
(1S*,8S*,9R*,Z)-3-Benzyl-1,9-diphenyl-3-azabicyclo[6.1.0]non-5-en-2-one (**3.6dba**). This compound was synthesized according to typical procedure **D** from *N*,2-diallyl-*N*-benzyl-1,3-diphenylcyclopropane-1-carboxamide

(**3.5dba**) (50 mg, 0.12 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1) to give the title compound as colorless crystals, mp 154.0 - 154.9 °C, R_f 0.21. Yield 38 mg (0.10 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.1 Hz, 2H), 7.43 – 7.37 (m, 2H), 7.36 – 7.32 (m, 1H), 7.19 (dd, *J* = 5.1, 1.8 Hz, 3H), 7.09 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.06 – 6.95 (m, 3H), 6.61 (dd, *J* = 7.7, 1.7 Hz, 2H), 5.69 – 5.58 (m, 2H), 5.34 (d, *J* = 14.2 Hz, 1H), 4.73 (dt, *J* = 17.5, 2.2 Hz, 1H), 4.08 (d, *J* = 14.2 Hz, 1H), 3.68 – 3.57 (m, 1H), 2.97 – 2.83 (m, 1H), 2.31 – 2.21 (m, 1H), 1.89 (d, *J* = 5.3 Hz, 1H), 1.65 (d, J = 5.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (+), 139.6 (+), 137.6 (+), 137.3 (+), 132.4 (+), 130.5 (+), 129.0 (+), 128.7 (+), 128.0 (+), 127.7 (+), 127.6 (+), 126.8 (+), 126.6 (+), 126.5 (+), 125.9 (+), 49.9 (–), 45.4 (–), 40.9 (+), 39.1 (–), 38.3 (+), 29.0 (–). FT IR (NaCl, cm^{-1}): 3057, 3026, 2917, 2848, 1641, 1495, 1453, 1247, 738, 699, 640. HRMS (TOF ES): found 402.1835, calculated for $C_{27}H_{25}NONa$ $(M+Na)^+$ 402.1834 (0.2 ppm).

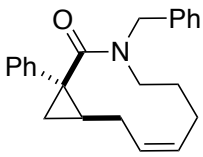


(1R*,9S*,Z)-3-Benzyl-1-phenyl-3-azabicyclo[7.1.0]dec-6-en-2-one (**3.6aea**). This compound was synthesized according to typical procedure **D** from 2-allyl-*N*-benzyl-*N*-(but-3-en-1-yl)-1-phenylcyclopropane-1-carboxamide (**3.5aea**) (50 mg, 14 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1) to give the title compound as colorless viscous oil, R_f 0.23. Yield 34 mg (0.11 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 10H), 5.80 (ddt, *J* = 12.5, 6.9, 3.4 Hz, 1H), 5.67 (ddd, *J* = 11.0, 8.6, 6.6 Hz, 1H), 5.35 (d, *J* = 14.7 Hz, 1H), 3.92 (d, *J* = 14.7 Hz, 1H), 3.55 (dt, *J* = 15.0, 5.0 Hz, 1H), 3.01 (ddd, *J* = 14.7, 9.2, 3.8 Hz, 1H), 2.72 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.49 (dtd, *J* = 15.0, 8.8, 4.5 Hz, 1H), 2.09 (dq, *J* = 15.7, 5.3 Hz, 1H), 2.04 – 1.86 (m, 2H), 1.53 (dd, *J* = 6.4, 4.7 Hz, 1H), 0.99 (dd, *J* = 8.6, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7 (+), 141.3 (+), 137.4 (+), 131.3 (+),

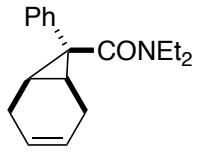
128.9 (+), 128.6 (+), 128.4 (+), 128.4 (+), 127.3 (+), 126.4 (+), 125.8 (+), 49.1 (–), 47.6 (–), 36.5 (+), 29.6 (–), 26.2 (–), 25.9 (+), 22.1 (–). FT IR (NaCl, cm^{-1}): 3060, 3022, 2925, 1634, 1496, 1425, 1187, 698. HRMS (TOF ES): found 340.1677, calculated for $C_{22}H_{23}NONa$ $(M+Na)^+$ 340.1677 (0.0 ppm).



(1R*,9R*,Z)-3-Benzyl-1-phenyl-3-azabicyclo[7.1.0]dec-7-en-2-one (**3.6afc**). This compound was synthesized according to typical procedure **D** from *N*-benzyl-*N*-(pent-4-en-1-yl)-1-phenyl-2-vinylcyclopropane-1-carboxamide (**3.5afc**) (40 mg, 0.12 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (7.5:1, R_f = 0.23) to give the title compound as colorless crystals (mp 134.9 - 136.1 °C). Yield 25 mg (0.079 mmol, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 7H), 7.22 – 7.10 (m, 3H), 5.88 (tdd, *J* = 10.1, 6.7, 2.2 Hz, 1H), 5.37 (dd, *J* = 10.1, 4.5 Hz, 1H), 5.25 (dd, *J* = 14.7, 1.4 Hz, 1H), 3.95 (d, *J* = 14.6 Hz, 1H), 3.72 – 3.60 (m, 1H), 2.86 (ddt, *J* = 15.3, 5.3, 1.4 Hz, 1H), 2.74 (dddd, *J* = 9.0, 6.7, 4.3, 1.9 Hz, 1H), 2.47 (tdd, *J* = 12.7, 10.1, 2.2 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.90 (dd, *J* = 6.4, 4.7 Hz, 1H), 1.65 (dddt, *J* = 14.8, 13.1, 11.5, 1.8 Hz, 1H), 1.44 – 1.36 (m, 1H), 1.07 (dd, *J* = 9.0, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8 (+), 141.5 (+), 138.0 (+), 136.5 (+), 129.2 (+), 128.9 (+), 128.5 (+), 128.4 (+), 127.3 (+), 126.1 (+), 124.7 (+), 49.3 (–), 48.5 (–), 37.8 (+), 29.3 (–), 26.0 (–), 25.9 (–), 22.5 (+). FT IR (NaCl, cm^{-1}): 3021, 2922, 2849, 1632, 1495, 1425, 1267, 1184, 757, 737, 699. HRMS (TOF ES): found 340.1679, calculated for $C_{22}H_{23}NONa$ (M+Na) 340.1677 (0.6 ppm).



(1R*,10S*,Z)-3-Benzyl-1-phenyl-3-azabicyclo[8.1.0]undec-7-en-2-one (**3.6afa**). This compound was synthesized according to typical procedure **D** from 2-allyl-*N*-benzyl-*N*-(pent-4-en-1-yl)-1-phenylcyclopropane-1-carboxamide (**3.5afa**) (50 mg, 0.14 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (10:1) to give the title compound as colorless crystals (mp 129 - 130.3 °C), R_f 0.19. Yield 36 mg (0.11 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.16 (m, 10H), 5.92 (td, *J* = 10.7, 5.5 Hz, 1H), 5.57 (d, *J* = 14.8 Hz, 1H), 5.51 (td, *J* = 10.9, 5.9 Hz, 1H), 3.99 (d, *J* = 14.8 Hz, 1H), 3.83 (td, *J* = 13.6, 3.1 Hz, 1H), 2.52 (dd, *J* = 12.5, 5.1 Hz, 2H), 2.12 (q, *J* = 12.3 Hz, 1H), 2.06 – 1.88 (m, 4H), 1.77 (dd, *J* = 6.4, 4.6 Hz, 1H), 1.08 (tt, *J* = 15.5, 2.5 Hz, 1H), 0.99 (dd, *J* = 8.8, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2 (+), 141.1 (+), 137.0 (+), 131.0 (+), 128.4 (+), 128.4 (+), 128.1 (+), 127.2 (+), 126.8 (+), 126.3 (+), 45.5 (–), 42.2 (–), 37.5 (+), 26.9 (–), 24.7 (+), 24.4 (–), 21.3 (–), 21.1 (–). FT IR (NaCl, cm^{-1}): 3060, 3004, 941, 2862, 1642, 1495, 1420, 1267, 1186, 721, 699, 584. HRMS (TOF ES): found 354.1835, calculated for $C_{23}H_{25}NONa$ $(M+Na)^+$ 354.1834 (0.3 ppm).



(1R*,6S*,Z)-N,N-Diethyl-7-phenylbicyclo[4.1.0]hept-3-ene-7-carboxamide (**3.10**). This compound was synthesized according to typical procedure **D** from 2,3-diallyl-*N*,*N*-diethyl-1-phenylcyclopropane-1-carboxamide (**3.9**) (42 mg, 0.14 mmol). The product was isolated on column chromatography eluting with hexane/EtOAc mixture (5:1, R_f = 0.28) to give the title compound as colorless crystals (mp 70.4 - 71.0 °C). Yield 31 mg (0.12 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 4H), 7.21 – 7.14 (m, 1H), 5.51 (m, 2H), 3.43 (q, *J* = 7.0 Hz, 2H), 3.35 – 3.30 (m, 2H), 2.70 (d, *J* = 18.0 Hz, 2H), 2.47 (dd, *J* = 16.5, 5.2 Hz, 2H), 1.70 (br, 2H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.66 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

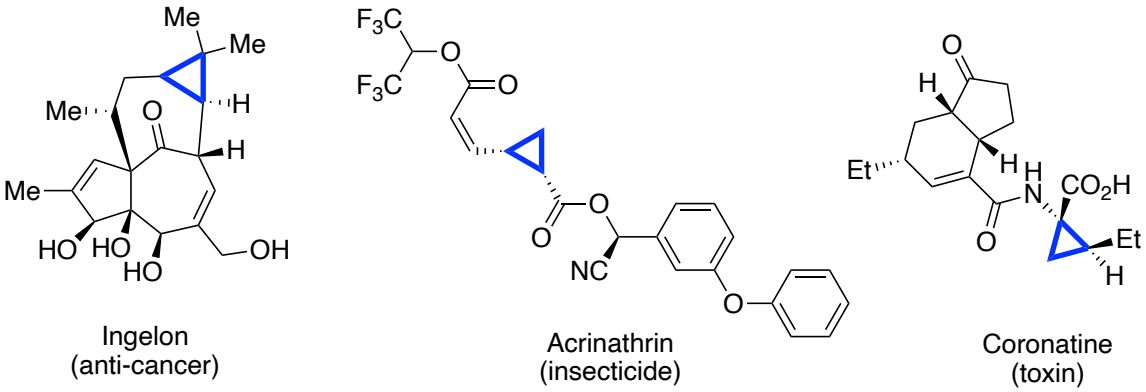
168.9 (+), 142.2 (+), 128.5 (+), 126.0 (+), 126.0 (+), 123.9 (+), 41.4 (–), 37.9 (–), 33.3 (+), 24.0 (+), 21.4 (–), 13.2 (+), 12.4 (+). FT IR (NaCl, cm-1): 3026, 2971, 2931, 2875, 1622, 1446, 1421, 1221, 1088, 699, 658. HRMS (TOF ES): found 292.1679, calculated for $C_{18}H_{23}NONa$ $(M+Na)^+$ 292.1677 (0.7 ppm).

Chapter 4 Stereoselective hydrogenation of cyclopropenes

4.1 Introduction

The stereo-defined cyclopropane motif is a common structural feature of many biologically active natural products, synthetic industrially-produced pesticides, as well as commercially available drugs and drug candidates.[120–122] These compounds demonstrate a wide variety of biological properties such as antibacterial, antifungal, anticancer, plant growth and fruit ripening control.[11]

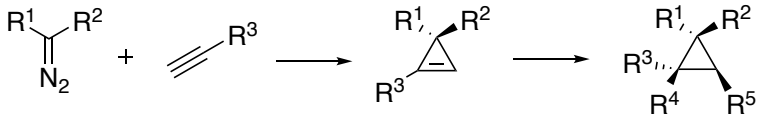
Figure 4. 1



The approaches for asymmetric synthesis of substituted cyclopropanes are well established and documented in a number of reviews published in recent years.[123–125] Among the most commonly utilized methods are the Simmons-Smith reaction involving the use of iodomethylzinc carbenoids, TM-catalyzed decomposition of diazo compounds, and Johnnson-Corey-Chaykovsky cyclopropanation reaction employing sulfur ylides. Asymmetric versions of these transformations allow for preparation of substituted cyclopropanes with high enantiomeric ratios from a wide variety of substrates.[126–129]

Methods of cyclopropanation simultaneously enabling both diastereo- and enantio-control of the reaction are rare and still present a challenge to this date. A prominent example is the Kulinkovich reaction - the titanium catalyzed cyclopropanation of esters using Grignard reagents for synthesis of chiral cyclopropanols.[130] Another important example enabling excellent levels of both diastereo- and enantioselectivity is cobalt-based metalloradical catalysis for cyclopropanation of olefins using α-ketodiazoacetates reported by Zhang.[131] Such transformations, however, are often substrate-dependent and involve complex custom-tailored chiral catalysts, which limits their broad synthetic application. Taking into account recent developments in asymmetric cyclopropenation of acetylenes,[8] which can be strategically combined with subsequent stereocontrolled reactions of chiral cyclopropene products, a stepwise approach for synthesis of the stereodefined smallest carbocycles in many situations appears more practical (**Scheme 4.1**).

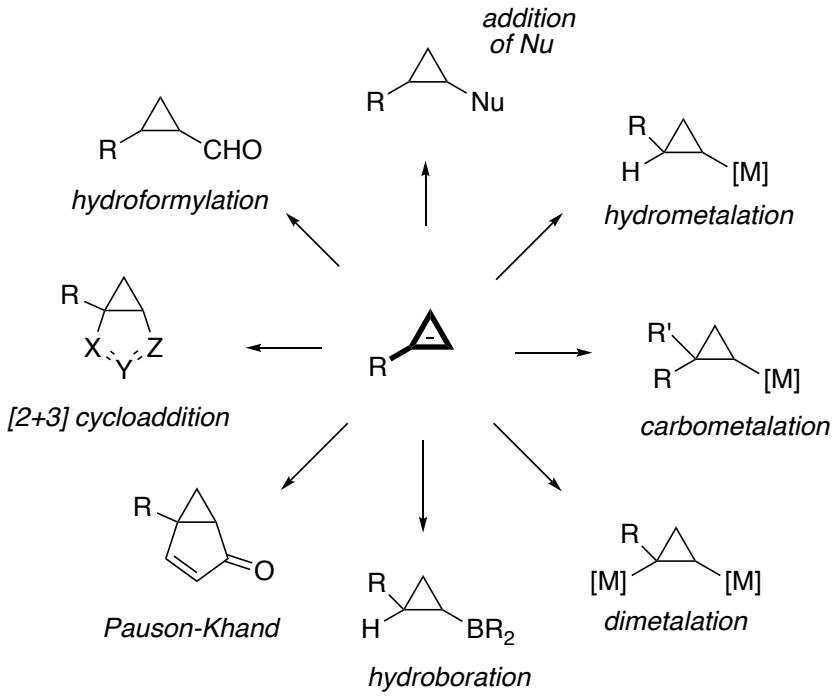
Scheme 4. 1



The rich chemistry of cyclopropenes was summarized in a selection of excellent reviews,[4,5,7,10,63,65,132] which was comprehensively amended[8,9,133] in recent years to keep the topic updated. A versatile reactivity of cyclopropenes includes but not limited to such transformations as non-catalyzed and metal-templated nucleophilic addition, TM-catalyzed metalations and related reactions, hydroformylation, and [2+3]-cycloadditon (**Scheme 4.2**), while

stereoselectivity of these reactions is controlled termodinamically, sterically or *via* directing effect (see above).

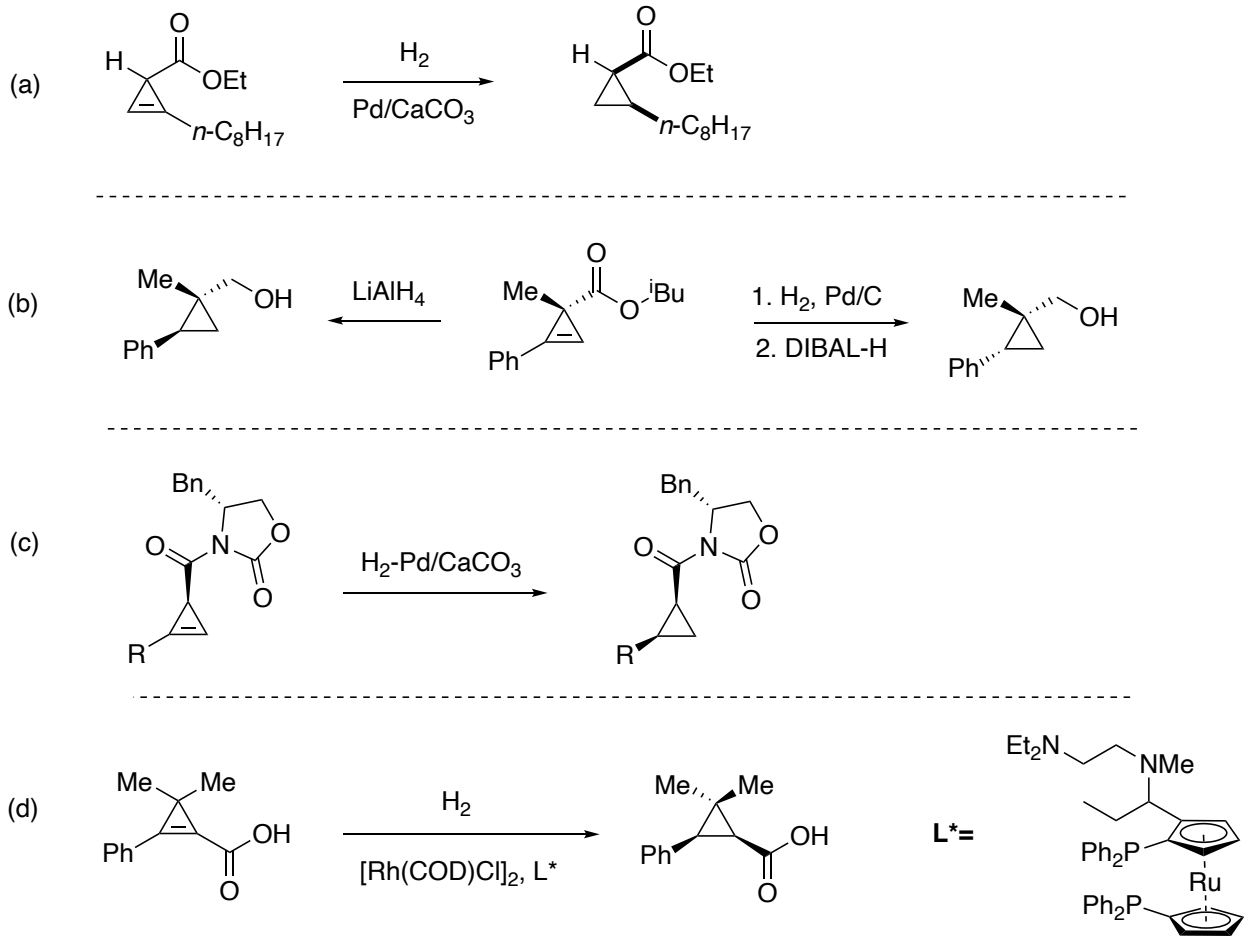
Scheme 4. 2



Despite such rich reactivity of cyclopropenes and facile stereocontrol of their reactions, examples of stereoselective hydrogenation of their double bonds are very limited. Corey[63] reported diastereoselective reduction of cyclopropenes with hydrogen in the presence of $Pd/CaCO_3$ catalyst (**Scheme 4.3, a**). The facial selectivity of this reaction was shown to be entirely controlled by steric factors. Hashimoto[134] utilized this approach for the synthesis of (*cis*-2-phenylcyclopropyl)methanol while the *trans*-diastereomer could be readily obtained *via* reduction using $LiAlH_4$ (**Scheme 4.3, b**). The analogous Pd-catalyzed hydrogenation was implemented in the total synthesis of *cis*-cyclopropane fatty acids reported by Williams (**Scheme 4.3, c**).[135] While the main product of the catalytic hydrogenation was reported as *cis*-isomer, the

authors also detected up to 10% of *trans*-cyclopropane forming as a main side product. The formation of the *trans*-product was attributed to inherent imperfection of facial selectivity of the reduction. To the best of our knowledge, directed hydrogenation of cyclopropenes employing heterogeneous catalysis to afford *trans*- substituted cyclopropanes remains unprecedented to this day.

Scheme 4. 3

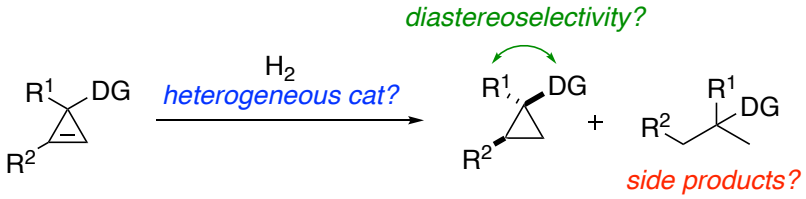


A single example of the highly efficient catalytic enantioselective hydrogenation of prochiral cyclopropene was shown by Kawamura. This transformation was catalyzed by a

homogenous Rh(I) complex bearing an elaborated non-commercially available ruthenocene-based chiral diphosphine ligand and was strictly limited to tetrasubstituted cyclopropenes bearing a carboxylic group at the double bond (**Scheme 4.3, d**).[133]

Having previous success with amide-directed diastereoselective reactions of cyclopropenes, we were interested to evaluate the directing effect of the amide function in hydrogenation of cyclopropene. The possibility to conduct this reaction in a diastereoselective fashion in the presence of a heterogeneous catalyst seemed especially intriguing (**Scheme 4.4**). In this chapter we disclose stereoselective hydrogenation of cyclopropyl carboxamides in the presence of heterogeneous platinum catalyst.

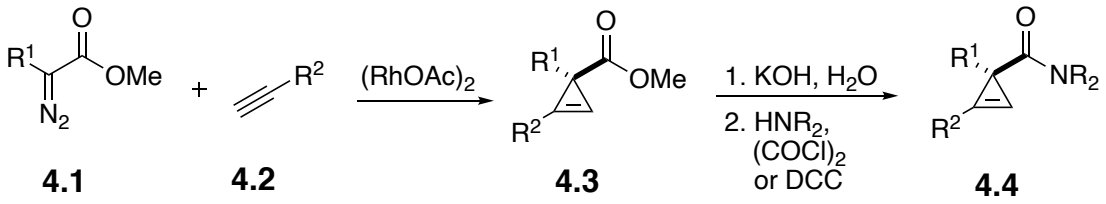
Scheme 4. 4



4.2 Initial results and reaction optimization

As it was previously demonstrated[136] in our laboratory, C-2 substituted carboxamides **4.4** can be conveniently prepared through the sequence of Rh-catalyzed cyclopropenation of corresponding acetylenes followed by hydrolysis and subsequent amidation of intermediate **4.3** (**Scheme 4.5**). We hypothesized that a presence of a strong chelating group such as amide function could provide sufficient directing effect for diastereoselective reduction of the double bond to afford trans-diastereomeric product.

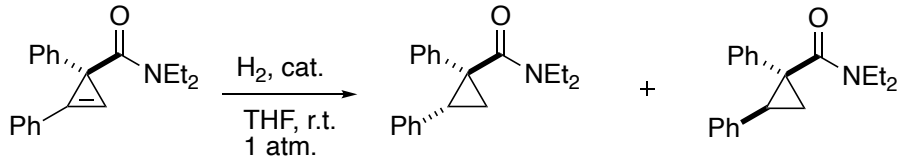
Scheme 4. 5



4.1 **4.2** **4.3** **4.4**

To test the viability of directed reduction of cyclopropenes we first examined hydrogenation of *N*,*N*-diethyl-1,2-diphenylcycloprop-2-ene-1-carboxamide **4.4a** with hydrogen in a presence of 10% Pd on carbon (**Table 4.1**, entry 1). After 3 hours at room temperature and ambient pressure, when conversion reached 100%, a 60:40 mixture of diastereomers was formed. Even though the reaction demonstrated poor diastereoselectivity, this result was reassuring as the *trans*- isomer (**4.5a**) was afforded as the main product. We then tested other transition metals commonly used in hydrogenation reactions. To our delight both Ru/C and Rh/C provided significant increase in diastereoselectivity yielding 75:25 mixtures of diastereomers (entries 2 and 3). However, in both cases the reaction proceeded much slower, reaching only 10% conversion after 3 hours. Even greater facial selectivity was achieved when Pt on carbon was used (entry 4). This reaction afforded 93% of the *trans*- product **4.5a** while full conversion was observed within 3 hours. A two-fold reduction of the catalyst load had no effect on neither diastereoselectivity nor the rate of the reaction (entry 5). We also tested metal oxides as an alternative to carbon supported catalysts (entries 6,7,8). While the former demonstrated comparable results to entries 2, 3 and 4 respectively, the use of the latter seemed more practical as it proved more convenient in terms of reaction loading and subsequent isolation of the product. Notably, none of the tested conditions produced any side products, such as commonly observed in previous reports product of three membered ring opening.[133,135]

Table 4. 1

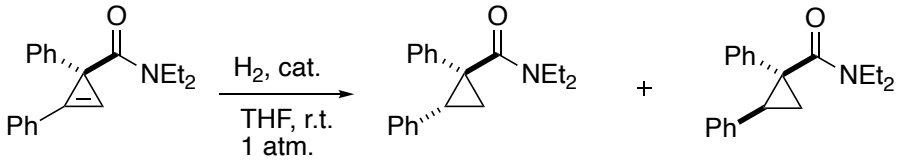


4.4a **4.5a** **4.6**

Entry	Catalyst	TM wt%	dr (by GC) *trans*- : *cis*-	Conversion after 3h
1	10%Pd/C	0.5	60:40	100%
2	5%Ru/C	0.5	75:25	10%
3	5%Rh/C	1	75:25	10%
4	**3%Pt/C**	**0.3**	**93:7**	**100%**
5	**3%Pt/C**	**0.15**	**93:7**	**100%**
6	RuO_2	1.71	82:16	35%
7	RhO_2	1.65	87:13	26%
8	PtO_2	2.49	90:10	100%

Next, we evaluated the effect of a solvent on the reaction. It was found that the use of ethanol slightly reduced the diastereoselectivity of the process while it had no effect on the rate of the reaction (**Table 4.2**, entry 1). Reactions in dichloromethane and benzene produced nearly identical results (**Table 4.2**, entries 2 and 3) producing high levels of diastereomeric ratios, matching that of reactions in THF (**Table 4.2**, entry 4).

Table 4. 2



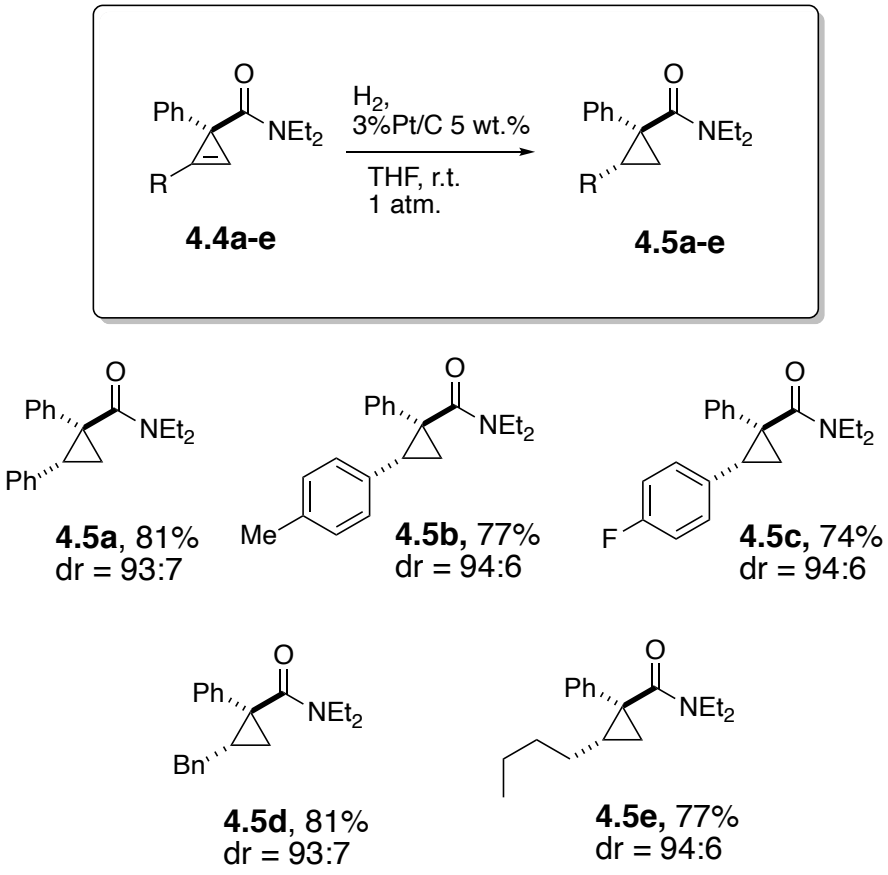
4.4a **4.5a** **4.6**

Entry	Catalyst	Solvent	dr (by GC) *trans*- : *cis*-	Conversion after 3h
1	3%Pt/C	EtOH	81:19	100%
2	3%Pt/C	DCM	93:7	100%
3	3%Pt/C	PhH	94:6	100%
4	**3%Pt/C**	**THF**	**93:7**	**100%**

4.3 Diastereoselective hydrogenation of cyclopropenes

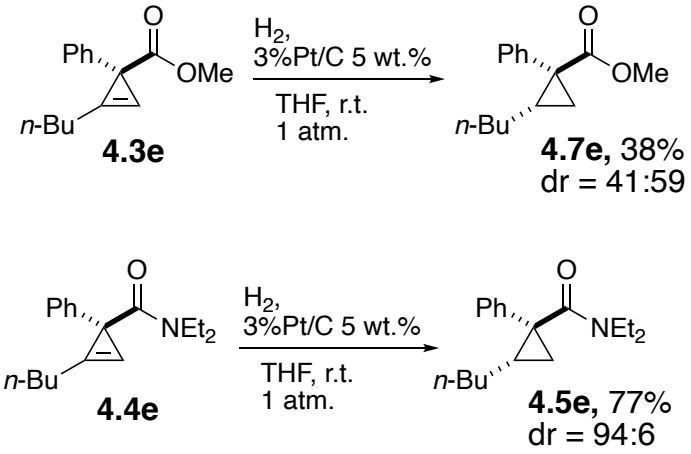
With the optimized conditions in hand, we first evaluated the effect of substituent at C-2 position. it was found that a presence of EDG or EWG at *para*-position of a phenyl substituent did not have any effect on the facial selectivity of the reaction as both **4.5b** and **4.5c** were obtained with identical ratios of diastereomers (**Scheme 4.6**). Benzyl- substituted and *n*-butyl-substituted cyclopropenes were also synthesized with nearly the same dr. This result suggests that the identity of the substituent at the double bond of compound **4.4** has a negligible effect on the facial selectivity of the reduction.

Scheme 4. 6



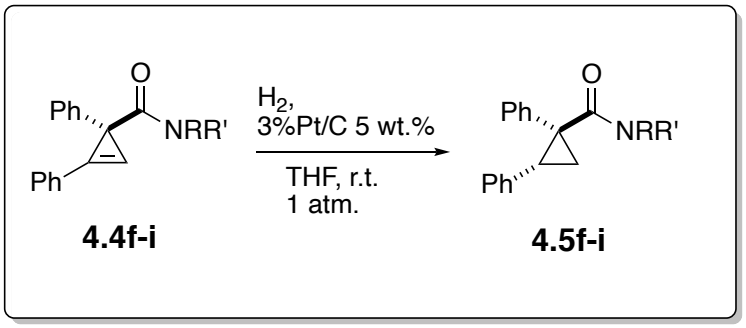
To confirm that the observed directing effect indeed originates due to the chelating ability of carboxamide function we compared reactions of 2-butyl-*N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide **4.4e** and analogous methyl carboxylate **4.3e** (**Scheme 4.7**). Since the reductions of carboxylates were previously reported to be governed by steric factors, we reasoned that the reaction of **4.3e** is likely to have much lower level of facial selectivity with carboxylate and phenyl groups being comparable in size. Expectedly, the *trans*- diastereomer **4.7e** was obtained as a minor product of the reaction with *trans*-:*cis*- ratio of 41:59. In contrast, hydrogenation of a corresponding carboxamide **4.4e** afforded **4.5e** in 77% yield and excellent dr, clearly indicating the effect of the directing group.

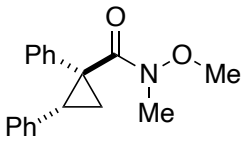
Scheme 4. 7



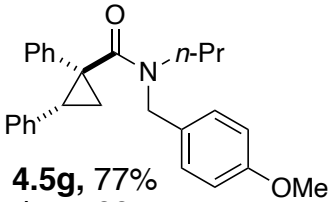
We have also explored whether the identity of the amide function itself affects the level of stereoselectivity. To this end, a series of 1,2-diphenyl substituted cyclopropenes with divergent carboxamide groups was subjected to the reduction (**Scheme 4.8**). Reactions of Wienreb amide and a *N*-propyl-*N*-benzyl amide afforded products **4.5f** and **4.5g** respectively with excellent levels of diastereomeric ratios. However, a bulky *N*,*N*-dibenzyl carboxamide demonstrated only a moderate selectivity, producing *trans*- product **4.5h** with only 80:20 dr. A significantly impaired facial selectivity was observed in reaction of a secondary amide yielding *trans*-*N*-benzyl-1,2-diphenylcyclopropane-1-carboxamide **4.5i** with only 50% excess.

Scheme 4. 8

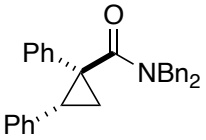




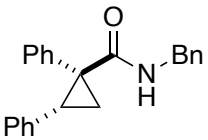
4.5f, 76%
dr = <99:1



4.5g, 77%
dr = <99:1



4.5h, 74%
dr = 80:20

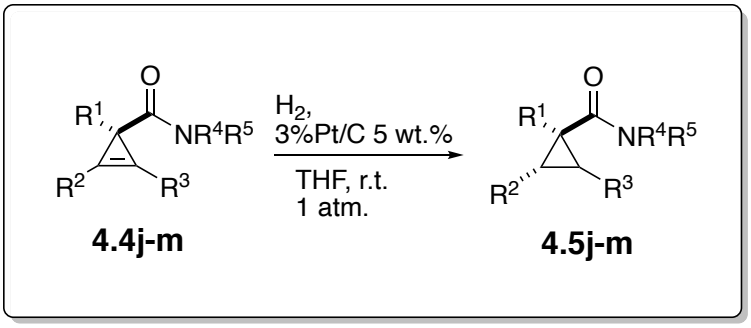


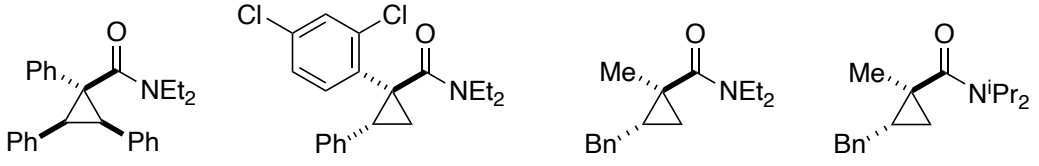
4.5i, 48%
dr = 67:34

We then conducted a series of experiments to further investigate the substrate dependence of the diastereoselective hydrogenation of cyclopropenes. We found that the replacement of a phenyl substituent at C-1 for a methyl group also resulted in highly selective reduction. Thus, cyclopropane **4.5l** was obtained with identical diastereomeric ratio as its 1-phenyl counterpart **4.5d**, while 2-benzyl-*N*,*N*-diisopropyl-1-methylcyclopropane-1-carboxamide **4.5m** was obtained exclusively in *trans*- configuration. It should be noted that bulkier substituents at the nitrogen atom of the directing group seem to increase facial selectivity of the reduction as formation of *cis*-diastereomers of **4.5g** and **4.5m** was not observed in the reaction mixtures. We reasoned that such high level of diastereoselectivity may originate from a favorable conformation of the amide function caused by the large substituents, pre-organizing the group for directed hydrogenation.

It is worth mentioning that 1-(2,4-dichlorophenyl)-*N*,*N*-diethyl-2-phenylcyclopropane-1-carboxamide **4.5k** was obtained with somewhat lower facial selectivity. It is possible that a presence of a halogen in *ortho*- position of the aromatic ring at C-1 provides a complimentary coordination of the substrate to the Pt catalyst, analogous to the effect previously described by Rubin in Rh-catalyzed hydroboration reactions.[32] We also found that facial selectivity does not translate on tetra-substituted substrates as compound **5.5j (Scheme 4.9)** was obtained exclusively as *cis*-diastereomer. The rate of this reaction was notably slower, taking approximately 18 hours to reach full conversion. Apparently, thermodynamic effect is this case overweighs the directing effect of the amide function as the formation of a product featuring three phenyl groups on the same face of cyclopropane would proceed through a transition state of very high energy.

Scheme 4. 9





4.5j, 72%
dr = <99:1

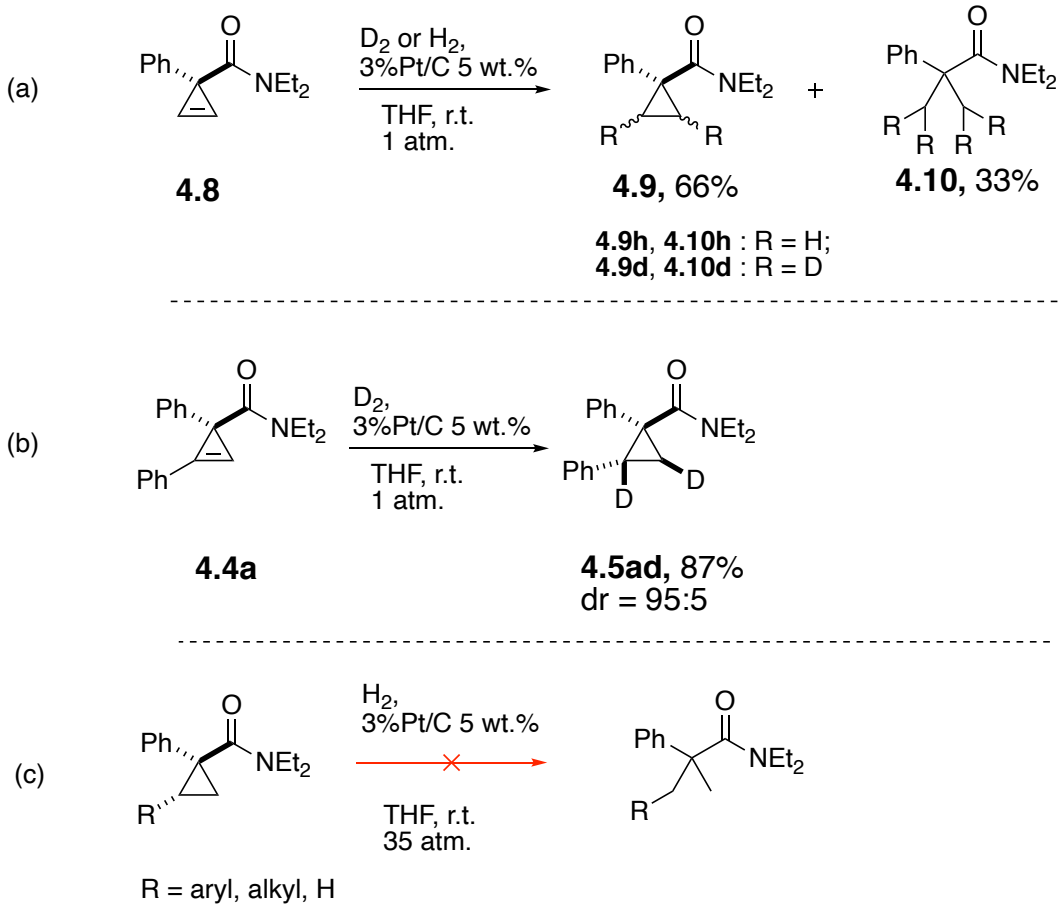
4.5k, 68%
dr = 78:22

4.5l, 73%
dr = 93:7

4.5m, 85%
dr = <99:1

We next investigated reductions of 2,3-non-substituted cyclopropenes employing deuterium instead of hydrogen (**Scheme 4.10**). Deuterium gas was generated in reaction of deuterated water with aluminum amalgamized with catalytic amount of mercury. To our great surprise, the reduction of **4.8** produced both deuterated *trans*- and *cis*- diastereomers of **4.9d** in equal amounts (**Scheme 4.10, equation a**), while the control deuteration of **4.4a** afforded product **4.5ad** (**Scheme 4.10, equation b**) with diastereomeric ratio nearly identical to the hydrogenation reaction of **4.4a** (see scheme 4.6). Perhaps even more importantly, we observed a C2–C3 distal bond cleavage of **4.8** yielding 33% of a product of hydrogenolysis **4.10d**. Hydrogenation of **4.8** resulted in formation of the same 33% amount of **4.10h**.

Scheme 4. 10



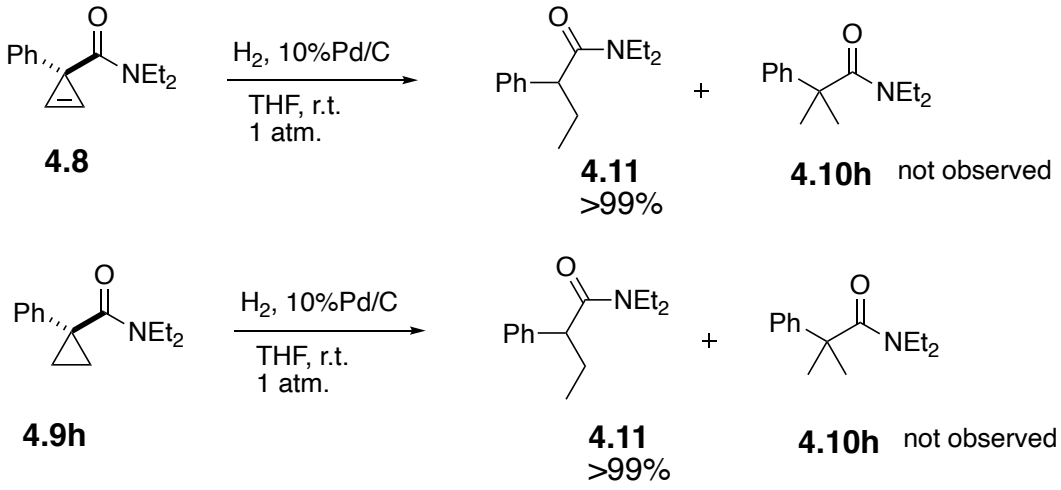
It should be mentioned that products of C2–C3 distal bond cleavage were observed with up to 10% yield in aforementioned reductions of tri-substituted cyclopropenes **4.4a-m** as well. However, our attempts to conduct ring opening reactions from cyclopropanes **4.5a-m**, as well as from a disubstituted cyclopropene **4.8**, using the same reaction conditions were unsuccessful (**Scheme 4.10, equation c**) even under increased pressure (550 psi).

4.4 Hydrogenolysis of cyclopropanes

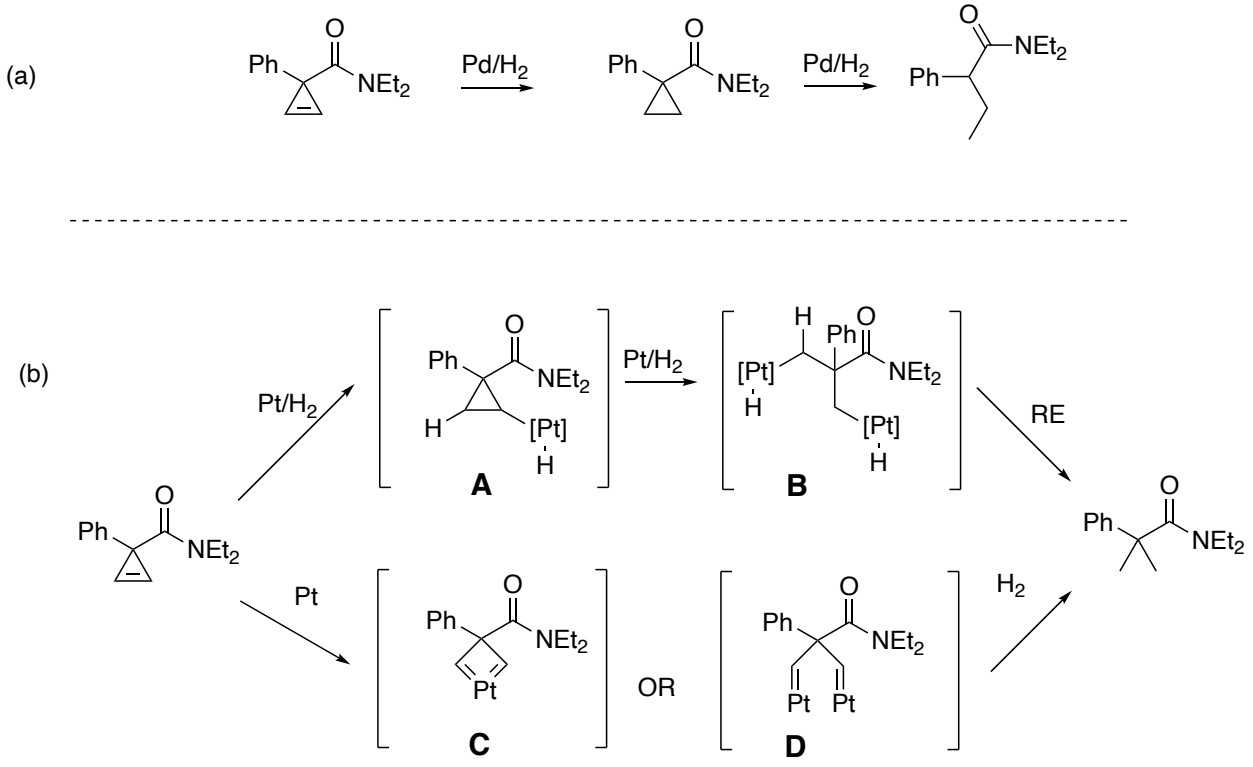
The products of over-reduction in hydrogenation of cyclopropenes were previously reported[135,137] with palladium on carbon used as a catalyst. We, therefore, switched the catalyst to 10% palladium on carbon in an attempt to maximize the yield of the ring opening product. Our first attempt to reduce cyclopropene **4.8** using 10 weight % catalyst load resulted in formation of product of hydrogenolysis **4.11** in nearly quantitative yield (**Scheme 4.11**). Remarkably, a reaction of cyclopropane **4.9h** produced identical result. In contrast to Pt catalyzed processes, reactions in presence of Pd resulted in C1–C2 proximal bond cleavage, while formation of product **4.10h** was observed in neither reaction. Such drastic difference in reactivity clearly indicates that Pt and Pd catalyzed reactions are operating via different mechanisms. We hypothesized that while palladium catalyzed reactions most probably proceed in a stepwise fashion where hydrogenation of cyclopropene is followed by hydrogenolysis step cleaving the more strained proximal bond (**Scheme 4.12, equation a**), the Pt catalyzed reaction presumably occur in a single step, since cyclopropane proved to be unreactive in presence of platinum. We reasoned, that under Pt/C reaction conditions a hydrometallated cyclopropane species **A** could undergo a second C-C insertion event to form intermediate **B**, which then undergoes reductive elimination to afford

the product. Alternately, this reaction could proceed through formation of Pt dicarbene species **C** or **D,** which would explain a site selectivity of the hydrogenolysis. (**Scheme 4.12, equation b**).

Scheme 4. 11



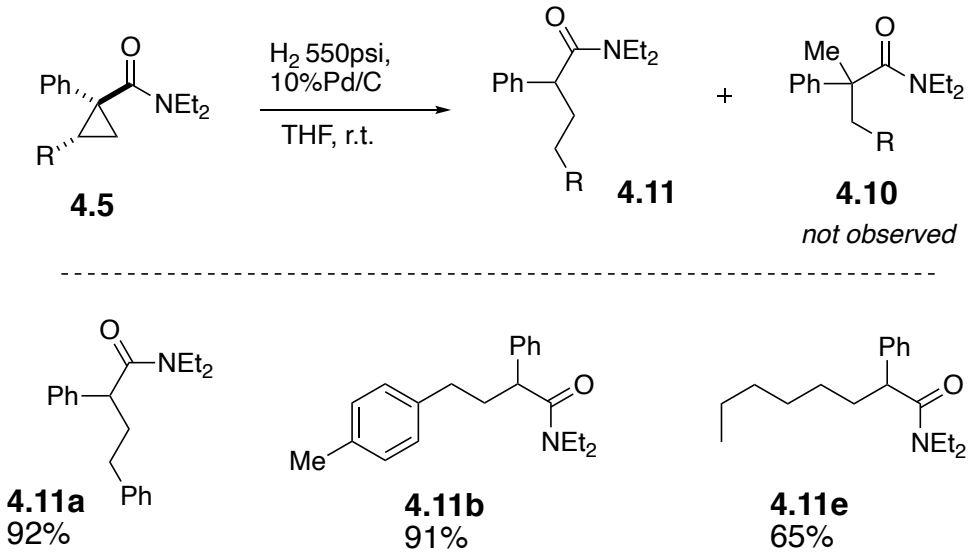
Scheme 4. 12



Our further investigation showed that Pd-catalyst is capable of opening the three-membered ring in hydrogenolysis reactions of 2-substituted cyclopropanes as well. While compounds **4.5a**, **b**, and **e** were unreactive under standard reaction conditions, the increase of hydrogen pressure to 550 psi forced the ring opening. Analogous to the Pd-catalyzed reaction of **4.9h**, we observed products of the proximal bond cleavage exclusively (**4.11a, 4.11b, 4.11c**) (**Scheme 4.13**), while products of the distant C2–C3 bond cleavage were not observed in the reaction mixture. Unlike **4.9h**, the cyclopropanes **4.5** feature two non-equivalent proximal bonds. We expected the most strained (the most substituted) of the two bonds to be cleaved, which was supported by the experiment.

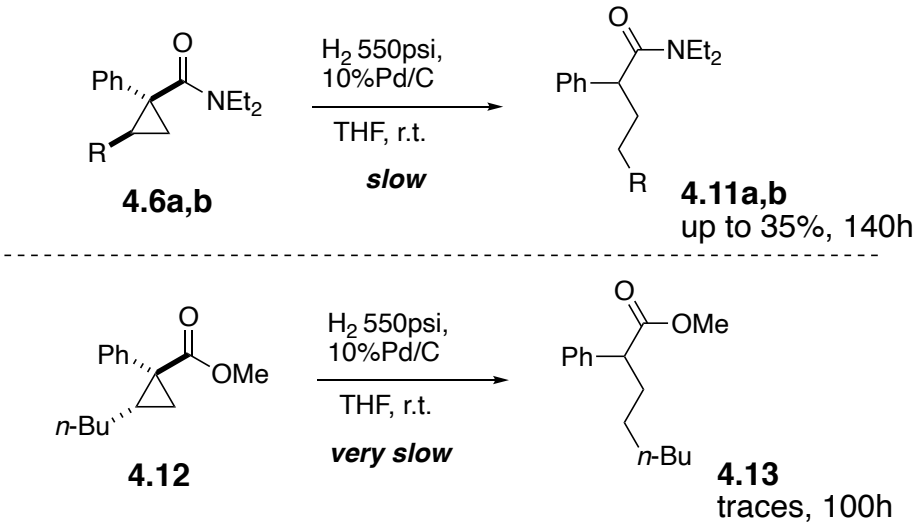
Hydrogenolysis of 2-arylsubstituted cyclopropylcarboxamides **4.5a** and **4.5b** require 24 to 48 hours to reach conversion above 90%, while reaction of 2-alkyl substituted **4.5e** was much slower and reached only 65% conversion after 48 h. Our attempts to increase the rate of this reaction by the increase of reaction temperature to 50 °C as well as the increase of the catalyst load up to 50 weight % did not have a significant effect.

Scheme 4. 13



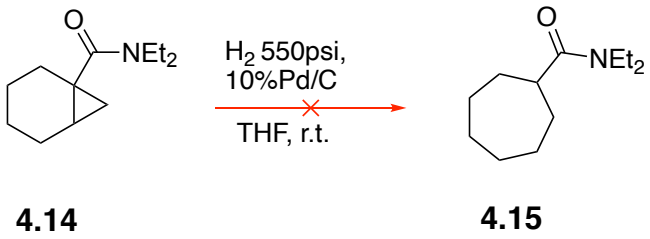
The *cis*-substituted substrates reacted even slower. We were able to hydrogenate 2-aryl substituted cyclopropanes **4.6a** and **4.6b** into **4.11a** and **4.11b** in 148 and 96 hours respectively using 30 mass% of 10%Pd/C catalyst. We also compared reaction rates of cyclopropylcarboxamide **4.5e** and respective methyl carboxylate **4.12**, and found the latter almost unreactive, providing only 10% conversion after 1 week of reaction time. Such significant difference in reaction rates between *cis*- and *trans*- diastereomers as well as between carboxamides and carboxylates suggests that the ring opening hydrogenation is likely a directed reaction where the directing amide group coordinating on a metal center brings in into a close proximity to C1–C2 bond for its subsequent cleavage.

Scheme 4. 14



In context of our previously published study on assembly of medium-sized rings (See chapter 3) we were curious if we could employ the aforementioned hydrogenolysis reactions for ring expansion of [n.1.0] bicyclic systems to afford medium cycles. We assembled a bicyclo[4.1.0]heptane bearing a diethylcarboxamide group in at C1 position according to previously described methodology.[138] It was reasoned, that analogous to hydrogenolysis of **4.5**, the C1–C6 bridge bond should be a primary target for cleavage. Unfortunately, we did not observe any reaction even under hydrogen pressure of 550 psi and catalyst load as high as 50% by weight (**Scheme 4.15**).

Scheme 4. 15



4.5 Conclusion

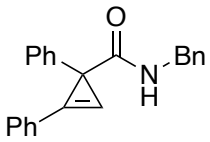
Directed stereoselective hydrogenation of cyclopropenes in the presence of heterogeneous catalysts was reported for the first time. The facial selectivity of the reaction is governed by the strong chelating effect of the carboxamide function to afford *cis*-hydrogenation. Additionally, directed site-selective hydrogenolysis of the three-membered ring of cyclopropanes was demonstrated. It was shown that platinum-based catalyst selectively cleaves distant C2–C3 bond, while palladium-based catalyst affects proximal C1–C2 bond only.

4.6 Experimental

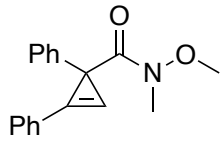
4.6.1 General Information

NMR spectra were recorded on a Bruker Avance DRX-500 with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (–) designations represent positive and negative intensities of signals in ^{13}C DEPT experiments. IR spectra were recorded on a ThermoFisher Nicolet™ iS™ 5 FT-IR Spectrometer. HRMS was carried out on LCT Premier (Micromass Technologies) instrument; ESI TOF detection techniques were used. Glassware employed in moisture-free syntheses was oven-dried prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40-63 mm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous dichloromethane and THF were obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent consecutively through two columns filled with activated alumina and stored over molecular sieves under argon. Deuterium gas was synthesized from MNR grade deuterium oxide in reaction with aluminum amalgamized with catalytic (0.1 mol%) amount of mercury chloride. Water was purified by dual stage deionization followed by dual stage reverse osmosis. All reagents, unless otherwise specified were used in their commercially-available forms and purities.

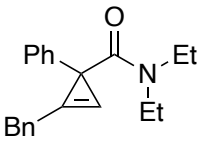
5.6.2 Synthesis of carboxamide precursors



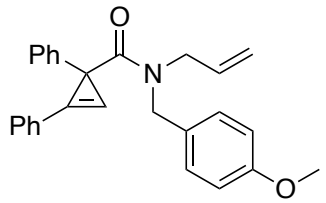
Typical procedure A. ***N*-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide 4.4i**: An oven dried 25 mL round bottom flask was charged with anhydrous THF (10 mL) and then triethylamine (354 µL, 3 Eq, 2.54 mmol), 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (200 mg, 846 µmol), DCC (192 mg, 1.1 Eq, 931 µmol), and HOBt (114 mg, 1 Eq, 846 µmol) were added. The reaction mixture was stirred at room temperature for 1 hour and then phenylmethanamine (181 mg, 1.69 mmol) was added. The reaction mixture was stirred at 45 °C overnight. After the reaction was complete (control by TLC) the formed precipitate was filtered off, the mother liquor was concentrated under reduced pressure, dissolved in 15 mL of DCM. The solution was washed with 5 mL of 1M HCl solution three times, then organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and fractioned on silica gel eluting with Hexane:EtOAc mixture (3:1) to afford the title compound as a colorless oil; R_f 0.18 in Hexane:EtOAc (3:1); Yield 167 mg (513 µmol, 61 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.60 (m, 2H), 7.43 – 7.31 (m, 5H), 7.29 – 7.23 (m, 4H), 7.22 (s, 1H), 7.21 – 7.17 (m, 4H), 5.98 (t, *J* = 6.0 Hz, 1H), 4.50 (dd, *J* = 15.0, 5.9 Hz, 1H), 4.43 (dd, *J* = 15.0, 5.8 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.4, 141.3, 138.8 (+), 130.1 (+), 130.1 (+), 129.0 (+), 128.9 (+), 128.7 (+), 128.7 (+), 127.7 (+), 127.4 (+), 127.1 (+), 125.9 (+), 119.1 (+), 101.6 (+), 44.1 (–), 35.6 (+); FT IR (NaCl, cm-1): 3296, 3059, 3030, 1645, 1515, 1453, 1495, 1267, 736, 699; HRMS (TOF ES): found 348.1352, calculated for $C_{23}H_{19}NONa$ (M+Na) 348.1364 (3.4ppm).



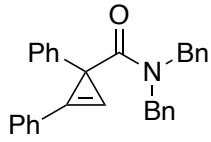
Typical procedure B. ***N*-methoxy-*N*-methyl-1,2-diphenylcycloprop-2-ene-1-carboxamide 4.4f**: A flame-dried round bottom flask was charged with anhydrous dichloromethane (5 mL), 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (200 mg, 846 µmol), and 3 drops of freshly distilled DMF under argon atmosphere and the reaction mixture was cooled on ice bath. Oxalyl dichloride (161 mg, 109 µL, 1.5 Eq, 1.27 mmol) was then added dropwise and the mixture stirred for 15 min at 0°C and then allowed to room temperature for 2 h. The solution was then concentrated under reduced pressure to provide a solid chloro-anhydride residue, which was dissolved in anhydrous dichloromethane (2.0 mL) and added dropwise to a solution of N,O-dimethylhydroxylamine hydrochloride (91 mg, 1.1 Eq, 931 µmol) and triethylamine (257 mg, 354 µL, 3 Eq, 2.54 mmol) in anhydrous dichloromethane (3.0 mL). The reaction mixture was stirred for 2 hours at RT and then partitioned between water and dichloromethane. The aqueous phase was acidified with 1M HCl. The organic phase was then washed with water (3 x 10 mL). The combined aqueous layers were back-extracted once with dichloromethane, which was combined with other organic phases, washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The product was fractioned on Silica gel eluting with a Hexane:EtOAc mixture (5:1) to afford the title compound as a pale yellow oil. R_f 0.3 in Hexane:EtOAc (5:1); Yield 157 mg (562 µmol, 66 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.73 – 7.72 (m, 1H), 7.71 (br. s, 1H), 7.38 – 7.30 (m, 3H), 7.29 – 7.22 (m, 5H), 7.18 – 7.13 (m, 1H), 3.27 (br. s, 3H), 3.17 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 130.2 (+), 129.8 (+), 128.8 (+), 128.4 (+), 126.8 (+), 126.6 (+), 126.4 (+), 120.5 (+), 60.7 (+), 35.4 (+); FT IR (NaCl, cm-1): 3056, 3026, 2916, 2849, 1759, 1651, 1445, 1378, 764, 735, 700; HRMS (TOF ES): found 302.1156, calculated for $C_{18}H_{17}NO_2Na$ (M+Na) 302.1157 (0.3ppm).



Typical procedure C. 2-benzyl-*N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide 4.4d: An oven-dried 50 mL round-bottomed flask was charged with 5 mL of anhydrous THF and lithium bis(trimethylsilyl)amide (311 mg, 1.86 mL of 1M solution in THF, 2 Eq, 1.86 mmol). The mixture was stirred at -30C, and cold solution of *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (200 mg, 929 µmol) in anhydrous THF (5 mL) was added dropwise to obtain a bright orange-red solution. The mixture was stirred for 5 min at -30C before (bromomethyl)benzene (167 mg, 116 µL, 1.05 Eq, 975 µmol) was added via syringe. Then the mixture was stirred for 2h at -30C. When the reaction was complete (control by GC) 10 mL of brine and 10 mL of ethyl acetate were added, organic layer was separated, and aqueous phase was extracted with ethyl acetate (2x10 mL). Combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The dry residue was fractioned on Silica gel eluting with a Hexane:EtOAc mixture (5:1) to afford the title compound as colorless crystals; m.p. = 94.7-98.1 °C; R_f 0.23 in Hexane:EtOAc (5:1); Yield 197 mg (645 µmol, 69 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 – 7.55 (m, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.28 – 7.23 (m, 5H), 7.22 – 7.18 (m, 1H), 6.96 (t, *J* = 2.6 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.39 – 3.29 (m, 2H), 2.62 (dd, *J* = 9.8, 2.5 Hz, 1H), 1.66 (dd, *J* = 9.8, 2.5 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.8 (+), 140.8 (+), 136.9 (+), 128.9 (+), 128.8 (+), 127.8 (+), 127.2 (+), 127.1 (+), 126.9 (+), 126.1 (+), 120.1 (+), 42.1 (–), 39.7 (–), 32.5 (+), 21.7 (–), 13.2 (+), 12.6 (+); FT IR (NaCl, cm-1): 3083, 3058, 3026, 2973, 2934, 1636, 1453, 1445, 1276, 754, 695; HRMS (TOF ES): found 305.1788, calculated for $C_{21}H_{23}NO$ (M+) 305.1780 (2.6 ppm).

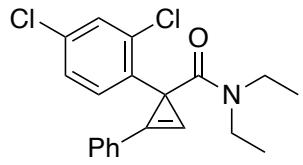


***N*-allyl-*N*-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide 4.4g**. This product was synthesized according to **typical procedure A** from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (200 mg, 846 µmol) using *N*-(4-methoxybenzyl)prop-2-en-1-amine (165 mg, 931 µmol). The product was purified on Silica gel to afford the title compound as a colorless oil. R_f 0.38 Hexane : EtOAc (3:1); Yield 225 mg (569 µmol, 67 %). NMR spectra were taken at 100 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.77 – 7.71 (m, 2H), 7.63 – 7.51 (m, 1H), 7.35 – 7.25 (m, 4H), 7.21 (td, *J* = 7.1, 1.7 Hz, 1H), 7.16 – 7.02 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 5.63 (br. s, 1H), 5.13 – 5.00 (m, 2H), 4.62 (d, *J* = 15.0 Hz, 1H), 4.38 (d, *J* = 14.9 Hz, 1H), 4.01 (dd, *J* = 15.9, 5.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.4, 158.2, 142.0, 133.0, 129.3, 129.1, 128.5 (br. s), 128.1, 127.8, 125.9, 125.6, 125.5, 121.9, 116.8 (br. s), 113.6, 99.8, 54.7, 34.4.; FT IR (NaCl, cm-1): 3058, 2932, 2836, 1683, 1627, 1512, 1492, 1248, 734, 700; HRMS (TOF ES): found 396.1974, calculated for $C_{27}H_{26}NO_2$ (M+H) 396.1964 (2.5ppm).

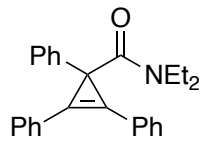


***N*,*N*-dibenzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide 4.4h**. This product was synthesized according to **typical procedure A** from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (200 mg, 846 µmol) using dibenzylamine (334 mg, 2 Eq, 1.69 mmol). The product was purified on Silica gel to afford the title compound as a colorless oil. R_f 0.38 Hexane:EtOAc (5:1); Yield 277 mg (667 µmol, 79 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.38 – 7.21 (m, 15H), 7.20 – 7.14 (m, 1H), 6.99 (d, *J* = 7.2 Hz, 2H), 6.82 (s, 1H), 5.16 (d, *J* = 14.6 Hz, 1H), 4.78 (d, *J* = 16.4 Hz, 1H), 4.20 (d, *J* = 16.4 Hz, 1H), 3.95 (d, *J* = 14.5 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.5, 142.2, 137.5,

136.9, 130.6 (+), 129.9 (+), 128.9 (+), 128.8 (+), 128.7 (+), 128.7 (+), 128.7 (+), 127.6 (+), 127.5 (+), 127.2 (+), 126.6 (+), 126.2 (+), 126.2 (+), 122.9 (+), 98.5 (+), 50.4 (–), 47.2 (–), 35.3 (+); FT IR (NaCl, cm-1): 3054, 3031, 2926, 1633, 1445, 1422, 1266, 739, 702.; HRMS (TOF ES): found 416.2028, calculated for $C_{30}H_{26}NO$ (M+H) 416.2014 (3.4ppm).

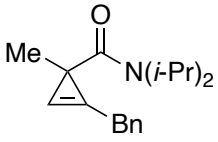


***N*,*N*-dibenzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide 4.4k**. This product was synthesized according to **typical procedure A** from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (200 mg, 846 µmol) using diethylamine (96 mg, 2 Eq, 1.31 mmol). The product was purified on Silica gel to afford the title compound as a colorless oil. R_f 0.44 Hexane:EtOAc (1:1); Yield 262 mg (727 µmol, 86 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 – 7.76 (m, 2H), 7.41 – 7.32 (m, 5H), 7.23 (s, 1H), 7.18 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.36 (dtt, *J* = 35.1, 13.7, 7.0 Hz, 4H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.9 (+), 139.2 (+), 134.7 (+), 133.1 (+), 131.5 (+), 130.2 (+), 130.1 (+), 130.0 (+), 128.8 (+), 127.5 (+), 126.3 (+), 122.7 (+), 100.4 (+), 42.2 (–), 40.2 (–), 35.6 (+), 13.3 (+), 12.7 (+); FT IR (NaCl, cm-1): 3081, 2973, 2934, 1631, 1470, 1278, 701; HRMS (TOF ES): found 360.0945, calculated for $C_{20}H_{20}Cl_2NO$ (M+H) 360.0922 (6.4 ppm).



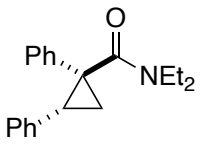
***N*,*N*-diethyl-1,2,3-triphenylcycloprop-2-ene-1-carboxamide 4.4j**. This product was synthesized according to **typical procedure B** from 1,2,3-triphenylcycloprop-2-ene-1-carboxylic acid (240 mg, 768 µmol) using diethylamine (84 mg, 1.5 Eq, 1.15 mmol). The product was purified on Silica gel to afford the title compound as a colorless oil; R_f 0.31 Hexane:EtOAc (3:1); Yield 175 mg (476 µmol, 62 %). ^{1}H NMR

(500 MHz, Chloroform-*d*) δ 7.81 – 7.72 (m, 4H), 7.39 (t, *J* = 7.5 Hz, 4H), 7.35 – 7.28 (m, 4H), 7.25 (s, 1H), 7.23 (s, 1H), 7.19 – 7.12 (m, 1H), 3.55 (q, *J* = 7.1 Hz, 2H), 3.43 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.9 (+), 142.2 (+), 131.2 (+), 129.7 (+), 129.1 (+), 128.9 (+), 128.7 (+), 128.0 (+), 126.3 (+), 113.5 (+), 42.8 (–), 39.5 (+), 38.9 (–), 13.9 (+), 12.8 (+); FT IR (NaCl, cm-1): 3081, 3057, 3022, 2973, 2934, 2873, 1626, 1494, 1444, 1427, 1274, 801, 756, 734; HRMS (TOF ES): found 390.1832, calculated for $C_{26}H_{25}NONa$ (M+Na) 390.1834 (0.5 ppm).

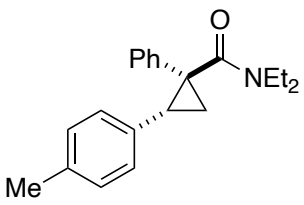


2-benzyl-*N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide 4.4m. This product was synthesized according to **typical procedure C** from N,N-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (285 mg, 1.57 mmol). The product was purified on Silica gel to afford the title compound as a colorless oil. R_f 0.23 Hexane:EtOAc (3:1); Yield 301 mg (1.57 mmol, 70 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.20 (m, 1H), 6.75 (t, *J* = 2.5 Hz, 1H), 4.56 – 4.48 (m, 1H), 3.37 – 3.28 (m, 1H), 2.03 (dd, *J* = 9.7, 2.5 Hz, 1H), 1.46 (s, 3H), 1.44 – 1.22 (m, 13H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.1 (+), 137.5 (+), 130.0 (+), 128.7 (+), 127.4 (+), 126.9 (+), 117.6 (+), 49.1 (+), 46.0 (+), 24.5 (+), 21.9 (+), 21.2 (+), 20.9 (+), 20.7 (+), 20.3 (+), 17.2 (–); FT IR (NaCl, cm-1): 2969, 2932, 1718, 1624, 1370, 1037, 697; HRMS (TOF ES): found 294.1823, calculated for $C_{18}H_{25}NONa$ (M+Na) 294.1834 (3.7 ppm).

4.6.3 Directed stereoselective reduction of cyclopenes

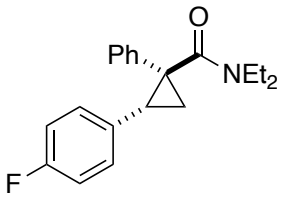


Typical procedure D. *N*,*N*-diethyl-1,2-diphenylcyclopropane-1-carboxamide 4.5a: A round-bottom flask was charged with anhydrous THF (10mL), *N*,*N*-diethyl-1,2-diphenylcycloprop-2-ene-1-carboxamide (300 mg, 1.03 mmol), and 3% Pt on carbon (15 mg, 5 wt.%). The flask was sealed with a septum and purged with hydrogen three times by subjecting the flask to vacuum and then refiling it with hydrogen. Then the flask was fitted with a balloon filled with hydrogen and the reaction mixture was vigorously stirred for 3 hours at room temperature. When the reaction was complete (control by GC) the solid catalyst was filtered off, the solvent was removed on rotary evaporator and the dry residue was purified on Silica gel to afford the title compound as a colorless oil; dr = 93:7; R_f 0.31 Hexane:EtOAc (5:1); Yield 243 mg (0.83 mmol, 81 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.12 – 7.06 (m, 4H), 7.06 – 6.96 (m, 6H), 3.49 (p, *J* = 7.1 Hz, 1H), 3.40 – 3.28 (m, 3H), 3.25 (dd, *J* = 9.1, 7.0 Hz, 1H), 2.05 (dd, *J* = 6.9, 5.5 Hz, 1H), 1.56 (dd, *J* = 9.2, 5.5 Hz, 1H), 1.10 (br. s, 3H), 0.66 (br. s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.7 (+), 137.2 (+), 136.3 (+), 128.8 (+), 128.6 (+), 128.1 (+), 127.7 (+), 126.5 (+), 125.9 (+), 41.6 (–), 39.9 (–), 38.6 (+), 29.9 (+), 15.5 (–), 12.9 (+), 12.5 (+); FT IR (NaCl, cm-1): 3059, 3027, 2974, 2935, 1630, 14,57, 1426, 1275, 1133, 699; HRMS (TOF ES): found 294.1848, calculated for $C_{20}H_{24}NO$ (M+H) 294.1858 (3.4 ppm)

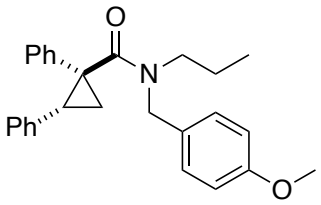


***N*,*N*-diethyl-1-phenyl-2-(*p*-tolyl)cyclopropane-1-carboxamide (YPM-4.5b**. This product was synthesized according to **typical procedure D** from *N*,*N*-diethyl-1-phenyl-2-(*p*-tolyl)cycloprop-2-ene-1-carboxamide (50 mg, 0.15 mmol) using 2.5 mg of 3% Pt on carbon. The product was purified on Silica gel to

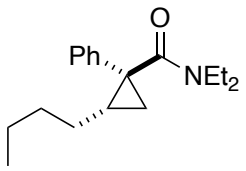
afford the title compound as colorless crystals; dr = 94:6; m.p. = 127.6-128.3 °C; R_f 0.24 Hexane:EtOAc (3:1); Yield 39 mg (0.13 mmol, 77 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.13 – 7.07 (m, 4H), 7.06 – 7.01 (m, 1H), 6.91 – 6.82 (m, 4H), 3.49 (p, *J* = 7.4 Hz, 1H), 3.33 (s, 3H), 3.19 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.17 (s, 3H), 1.99 (dd, *J* = 7.0, 5.5 Hz, 1H), 1.54 (dd, *J* = 9.2, 5.4 Hz, 1H), 1.10 (br. s, 3H), 0.66 (br. s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 136.5 (+), 135.4 (+), 134.0 (+), 128.7 (+), 128.6 (+), 128.4 (+), 128.1 (+), 126.4 (+), 41.5 (–), 39.9 (–), 38.5 (+), 29.7 (+), 21.1 (+), 15.7 (–), 12.9 (+), 12.5 (+); FT IR (NaCl, cm-1): 3061, 2973, 2934, 1630,1456, 1275, 700; HRMS (TOF ES): found 330.1835, calculated for $C_{21}H_{25}NONa$ (M+Na) 330.1834 (0.3 ppm).



***N*,*N*-diethyl-2-(4-fluorophenyl)-1-phenylcyclopropane-1-carboxamide 4.5c**. This product was synthesized according to **typical procedure D** from *N*,*N*-diethyl-2-(4-fluorophenyl)-1-phenylcycloprop-2-ene-1-carboxamide (50 mg, 0.16 mmol) using 2.5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as colorless crystals; dr = 94:6; m.p. = 85.7-86.0 °C; R_f 0.29 Hexane:EtOAc (5:1); Yield 37 mg (0.12 mmol, 74 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.14 – 7.01 (m, 5H), 6.94 (dd, *J* = 8.3, 5.4 Hz, 2H), 6.72 (t, *J* = 8.6 Hz, 2H), 3.53 – 3.41 (m, 1H), 3.40 – 3.25 (m, 3H), 3.26 – 3.20 (m, 1H), 2.00 (t, *J* = 6.3 Hz, 1H), 1.54 (dd, *J* = 9.2, 5.6 Hz, 1H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.65 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.4 (+), 161.2 (d, *J* = 243.7 Hz, +), 136.0 (+), 132.8 (d, *J* = 3.3 Hz, +), 130.1 (d, *J* = 8.1 Hz, +), 128.3 (+), 128.1 (+), 126.5 (+), 114.4 (d, *J* = 21.0 Hz, +), 41.4 (–), 39.8 (–), 38.3 (+), 29.0 (+), 15.4 (–), 12.8 (+), 12.4 (+); FT IR (NaCl, cm-1): 3066, 2975, 2936, 1629, 1513, 1457, 1429, 1223, 879, 700; HRMS (TOF ES): found 334.1581, calculated for $C_{20}H_{22}FNONa$ (M+Na) 334.1583 (0.6 ppm).

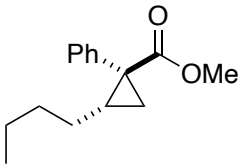


***N*-benzyl-1,2-diphenyl-*N*-propylcyclopropane-1-carboxamide 4.5g**. This product was synthesized according to **typical procedure D** from *N*-allyl-*N*-(4-methoxybenzyl)-1,2-diphenylcycloprop-2-ene-1-carboxamide (50 mg, 0.13 mmol) using 2.5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as a colorless oil; dr = <99:1; R_f 0.4 Hexane:EtOAc (3:1); Yield 42 mg (0.11 mmol, 83 %). NMR spectra were taken at 100 °C: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 – 7.21 (m, 1H), 7.19 – 7.14 (m, 2H), 7.14 – 7.08 (m, 2H), 7.07 – 7.01 (m, 3H), 7.00 – 6.94 (m, 4H), 6.84 – 6.79 (m, 2H), 4.49 (s, 2H), 3.73 (s, 3H), 3.19 – 3.07 (m, 3H), 2.24 (t, *J* = 6.5 Hz, 1H), 1.58 (dd, *J* = 9.1, 5.8 Hz, 1H), 1.35 (dq, *J* = 15.1, 7.7 Hz, 1H), 1.05 (br. s, 1H), 0.64 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.1, 158.1, 136.6, 135.7, 128.1, 128.0, 127.8, 127.3, 126.9, 125.8, 125.1, 113.5, 54.7, 38.1, 29.2, 19.3, 14.7, 10.2; FT IR (NaCl, cm-1): 3059, 3028, 2961, 2933,2873, 1632, 1512, 1247, 1175, 1031, 698.; HRMS (TOF ES): found 422.2094, calculated for $C_{27}H_{29}NO_2Na$ (M+Na) 422.2096 (0.5 ppm).

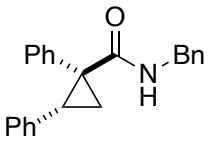


2-butyl-*N*,*N*-diethyl-1-phenylcyclopropane-1-carboxamide 4.5e. This product was synthesized according to **typical procedure D** from 2-butyl-*N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (70 mg, 0.26 mmol) using 3.5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as a colorless oil; dr = 94:6; R_f 0.32 Hexane:EtOAc (5:1); Yield 59 mg (0.22 mmol, 84 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.24 (m, 4H), 7.23 – 7.18 (m, 1H), 3.54 – 3.39 (m, 1H), 3.28 (s, 2H), 3.24 – 3.11 (m, 1H), 1.87 (tt, *J* = 8.6, 6.3 Hz, 1H), 1.34 – 1.12 (m, 5H), 1.12 – 1.00

(m, 5H), 0.79 – 0.65 (m, 4H), 0.57 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.5, 137.8, 128.6 (+), 128.3 (+), 126.5 (+), 41.4 (–), 39.8 (–), 35.4 (+), 31.1 (–), 28.6 (–), 24.7 (+), 22.4 (–), 16.1 (–), 14.1 (+), 12.8 (+), 12.5 (+); FT IR (NaCl, cm-1): 2959, 2931, 2872, 1634, 1457, 1426, 1274, 1141, 701.; HRMS (TOF ES): found 296.1988, calculated for $C_{18}H_{27}NONa$ (M+Na) 296.199 (0.7 ppm).

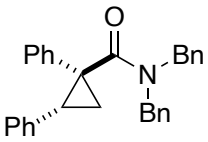


methyl 2-butyl-1-phenylcyclopropane-1-carboxylate 4.7e. This product was synthesized according to **typical procedure D** from methyl 2-butyl-1-phenylcycloprop-2-ene-1-carboxylate (100 mg, 0.434 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as a colorless oil; dr = 41:59; R_f 0.46 Hexane:EtOAc (20:1); Yield 38 mg (0.16 mmol, 38 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 3H), 3.59 (s, 2H), 1.86 – 1.78 (m, 1H), 1.68 (dd, *J* = 9.0, 4.1 Hz, 1H), 1.40 – 1.30 (m, 3H), 1.27 – 1.18 (m, 2H), 1.08 (dd, *J* = 6.8, 4.1 Hz, 1H), 0.80 (t, *J* = 7.3 Hz, 3H), 0.55 – 0.45 (m, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 175.4, 136.5, 131.5 (+), 128.0 (+), 127.1 (+), 52.4 (+), 33.7 (+), 31.4 (–), 30.1 (–), 28.9 (+), 22.5 (–), 21.8 (–), 14.1 (+); FT IR (NaCl, cm-1): 3060, 3032, 2954, 2859, 1731, 1433, 1312, 1196, 1172, 699; HRMS (TOF ES): found 255.1367, calculated for $C_{15}H_{20}O_2Na$ (M+Na) 255.1361 (2.4 ppm).



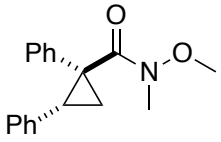
***N*-benzyl-1,2-diphenylcyclopropane-1-carboxamide 4.5i**. This product was synthesized according to **typical procedure D** from *N*-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide (95 mg, 0.29 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as a colorless

oil; dr = 67:34 (inseparable mixture of diastereomers); R_f 0.25 Hexane:EtOAc (5:1); Yield 46 mg (0.14 mmol, 48 % by NMR). NMR data indicates the presence of both diastereomers. Major diastereomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.52 (m, 1H), 7.44 – 7.01 (m, 12H), 6.79 – 6.76 (m, 2H), 5.69 (s, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 3.26 (dd, *J* = 9.2, 7.1 Hz, 1H), 2.15 (dd, *J* = 9.2, 4.5 Hz, 1H), 1.75 (dd, *J* = 7.1, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.2 (+), 138.5 (+), 137.5 (+), 135.2 (+), 132.4 (+), 129.3 (+), 128.8 (+), 128.7 (+), 128.2 (+), 128.1 (+), 127.8 (+), 127.4 (+), 127.2 (+), 44.1 (–), 39.1 (+), 31.5 (+), 20.5 (–); Minor diastereomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.01 (m, 13H), 6.75 (dd, *J* = 6.7, 2.8 Hz, 2H), 5.60 (s, 1H), 4.38 (d, *J* = 7.0 Hz, 1H), 3.95 (dd, *J* = 15.2, 5.1 Hz, 1H), 2.90 (dd, *J* = 9.0, 7.6 Hz, 1H), 2.53 (dd, *J* = 7.5, 4.7 Hz, 1H), 1.48 (dd, *J* = 9.1, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.5 (+), 141.2 (+), 138.5 (+), 136.7 (+), 130.2 (+), 129.3 (+), 129.2 (+), 128.5 (+), 128.0 (+), 128.0 (+), 127.1 (+), 126.8 (+), 126.1 (+), 43.7 (–), 39.9 (+), 32.3 (+), 18.2 (–). FT IR (NaCl, cm-1): 3429, 3085, 3059, 3028, 1660, 1509, 1470, 1264, 730, 698; HRMS (TOF ES): found 350.1521, calculated for $C_{23}H_{21}NONa$ (M+Na) 350.1521 (0 ppm).



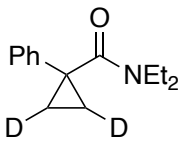
***N,N*-dibenzyl-1,2-diphenylcyclopropane-1-carboxamide 4.5h**. This product was synthesized according to **typical procedure D** from N,N-dibenzyl-1,2-diphenylcycloprop-2-ene-1-carboxamide (95 mg, 0.23 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as colorless crystals; dr = 4:1; m.p. = 91.9-93.1 °C; R_f 0.21 Hexane:EtOAc (10:1); Yield 84 mg (0.2 mmol, 88 %). NMR data indicates presence of two diastereomers. Major diastereomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.26 – 6.85 (m, 18H), 6.73 – 6.66 (m, 2H), 4.59 – 4.32 (m, 4H), 3.24 (dd, *J* = 9.2,

7.0 Hz, 1H), 1.96 (dd, *J* = 7.0, 5.8 Hz, 1H), 1.60 (dd, *J* = 9.2, 5.7 Hz, 1H).; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.8 (+), 137.2 (+), 136.8 (+), 136.2 (+), 135.6 (+), 128.9 (+), 128.6 (+), 128.5 (+), 128.2 (+), 128.2 (+), 127.6 (+), 127.2 (+), 126.8 (+), 125.9 (+), 49.9 (–), 47.4 (–), 38.6 (+), 29.8 (+), 15.5 (–); Minor diasereomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.34 (m, 2H), 7.26 – 6.85 (m, 14H), 6.55 (d, *J* = 6.9 Hz, 2H), 6.08 – 6.01 (m, 2H), 4.59 – 4.32 (m, 2H), 3.79 (d, *J* = 14.8 Hz, 1H), 3.68 (d, *J* = 15.4 Hz, 1H), 3.11 (dd, *J* = 9.1, 7.0 Hz, 1H), 2.37 (dd, *J* = 7.0, 5.3 Hz, 1H), 1.26 (dd, *J* = 9.2, 5.3 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.1 (+), 141.1 (+), 137.0 (+), 136.4 (+), 135.3 (+), 128.9 (+), 128.7 (+), 128.4 (+), 128.1 (+), 128.1 (+), 127.7 (+), 127.7 (+), 127.4 (+), 127.1 (+), 127.0 (+), 126.8 (+), 126.7 (+), 50.0 (–), 46.8 (–), 40.8 (+), 28.9 (+), 21.2 (–). FT IR (NaCl, cm-1): 3061, 3028, 2922, 1636, 1495, 1451, 1418, 781, 697.; HRMS (TOF ES): found 440.1985, calculated for $C_{30}H_{27}NONa$ (M+Na) 440.199 (1.1 ppm).

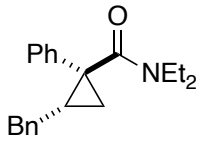


***N*-methoxy-N-methyl-1,2-diphenylcyclopropane-1-carboxamide 4.5 f**. This product was synthesized according to **typical procedure D** from *N*-methoxy-*N*-methyl-1,2-diphenylcycloprop-2-ene-1-carboxamide (100 mg, 0.358 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as colorless crystals; dr = 1:0 (by NMR); m.p. = 112.4-113.0 °C; R_f 0.29 Hexane:EtOAc (5:1); Yield 77 mg (0.328 mmol, 76 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.14 – 7.07 (m, 4H), 7.07 – 6.97 (m, 4H), 6.95 – 6.90 (m, 2H), 3.27 (dd, *J* = 9.2, 7.0 Hz, 1H), 3.14 (s, 3H), 3.12 (s, 3H), 1.99 (dd, *J* = 7.1, 5.5 Hz, 1H), 1.66 (dd, *J* = 9.2, 5.6 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 137.0, 136.2, 130.0 (+), 128.6 (+), 127.9 (+), 127.7 (+), 126.6 (+), 126.0 (+), 60.2 (+), 38.4 (+), 33.9 (+), 28.9 (+), 16.4 (–); FT IR (NaCl, cm-1): 3059, 3026, 3003, 2971, 2935, 2850, 1651, 1457, 1369,

1004, 698.; HRMS (TOF ES): found 304.1314, calculated for $C_{18}H_{19}NO_2Na$ (M+Na) 304.1313 (0.3 ppm).

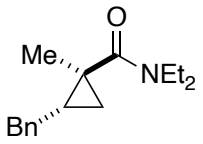


***N*,*N*-diethyl-1-phenylcyclopropane-1-carboxamide-2,3-*d*$_2$ 4.9d**. This product was synthesized according to **typical procedure D** from *N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (100 mg, 0.464 mmol) using 5 mg of 3% Pt on carbon and deuterium instead of hydrogen. The product was purified on Silica gel to afford the title compound as a colorless oil; dr = 1:1 (by NMR); R_f 0.33 Hexane:EtOAc (5:1); Yield 55 mg (0.25 mmol, 55); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.35 – 7.26 (m, 2H), 7.24 – 7.10 (m, 3H), 3.26 (q, *J* = 7.0 Hz, 4H), 1.22 (s, 0.45H), 1.11 (s, 0.45H), 1.02 (t, *J* = 7.0 Hz, 3H), 0.70 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.8 (+), 141.2 (+), 128.8 (+), 126.3 (+), 125.7 (+), 41.7 (–), 39.6 (–), 29.9 (+), 29.8 (+), 15.0 – 14.3 (m) (+), 12.9 (+), 12.5 (+); FT IR (NaCl, cm-1): 2973, 2935, 2874, 1633, 1459, 1427, 1380, 1277, 1220, 1130, 699.; HRMS (TOF ES): found , calculated for () (ppm).

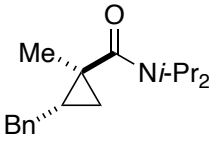


2-benzyl-*N*,*N*-diethyl-1-phenylcyclopropane-1-carboxamide 4.5d. This product was synthesized according to **typical procedure D** from 2-benzyl-*N*,*N*-diethyl-1-phenylcycloprop-2-ene-1-carboxamide (100 mg, 0.372 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as a colorless oil; dr = 82:18; R_f 0.18 Hexane:EtOAc (5:1); Yield 66 mg (0.21 mmol, 66 %). NMR spectra indicates presence of two diastereomers: Major diastereomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.11 (m, 10H), 3.59 – 3.43 (m, 1H), 3.34 – 3.26 (m, 2H), 3.26 – 3.16 (m, 1H), 2.47 (dd, *J* = 15.3, 6.2 Hz, 1H), 2.28 (tt, *J* = 8.6, 6.9 Hz, 1H), 2.02 (dd, *J* = 15.3, 8.5 Hz, 1H), 1.47 (t, *J* = 5.8 Hz,

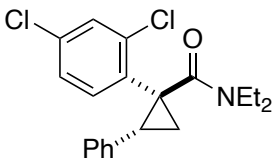
1H), 1.20 (dd, *J* = 9.0, 5.2 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.58 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 141.0, 137.2, 128.5, 128.4, 128.3, 128.1, 126.7, 125.7, 41.3, 39.7, 35.7, 34.6, 24.7, 16.0, 12.7, 12.4; Minor diastereomer ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.11 (m, 10H), 3.59 – 3.43 (m, 1H), 3.26 – 3.16 (m, 2H), 3.03 – 2.90 (m, 2H), 2.38 (dd, *J* = 14.5, 9.9 Hz, 1H), 2.18 – 2.08 (m, 1H), 1.66 (t, *J* = 5.5 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.99 (dd, *J* = 8.7, 4.7 Hz, 1H), 0.52 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.2, 141.5, 141.0, 128.6, 128.5, 128.4, 126.3, 126.3, 126.2, 41.6, 39.4, 35.8, 35.5, 25.4, 22.6, 12.5, 12.5; FT IR (NaCl, cm-1): 3060, 3025, 2973, 2934, 1631, 1454, 1275, 737, 701.; HRMS (TOF ES): found 308.2014, calculated for $C_{21}H_{26}NO$ (M+H) 308.2014 (0 ppm).



2-benzyl-*N*,*N*-diethyl-1-methylcyclopropane-1-carboxamide 4.5l. This product was synthesized according to **typical procedure D** from 2-benzyl-*N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide (100 mg, 0.411 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as a colorless oil; dr = 93:7; R_f 0.23 Hexane:EtOAc (3:1); Yield 74 mg (0.3 mmol, 73 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.79 (dq, *J* = 14.3, 7.1 Hz, 1H), 3.51 (dq, *J* = 14.1, 7.1 Hz, 1H), 3.36 – 3.20 (m, 2H), 3.00 (dd, *J* = 14.6, 4.2 Hz, 1H), 2.01 (dd, *J* = 14.6, 10.4 Hz, 1H), 1.32 (s, 3H), 1.28 – 1.16 (m, 4H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 5.3 Hz, 1H), 0.71 (dd, *J* = 8.3, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 141.5, 128.5, 128.4, 126.1, 41.3 (–), 39.0 (–), 36.6 (–), 27.4 (+), 26.2 (+), 23.0,(+) 19.6 (–), 14.3 (+), 12.7 (+); FT IR (NaCl, cm-1): 3061, 3026, 2972, 2933, 2874, 1715, 1631, 1495, 1479, 1122, 743, 700; HRMS (TOF ES): found 268.1676, calculated for $C_{16}H_{23}NONa$ (M+Na) 268.1677 (0.4 ppm).

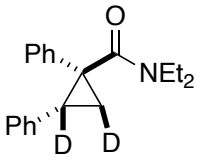


2-benzyl-*N*,*N*-diisopropyl-1-methylcyclopropane-1-carboxamide 4.5m. This product was synthesized according to **typical procedure D** from 2-benzyl-*N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (50 mg, 0.18 mmol) using 2.5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as colorless chrystals; dr = <99:1; m.p. = 79.4-79.5 °C; R_f 0.25 Hexane:EtOAc (5:1); Yield 43 mg (0.16 mmol, 85 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.20 (m, 4H), 7.19 – 7.15 (m, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H), 3.32 (hept, *J* = 6.9 Hz, 1H), 3.20 (dd, *J* = 14.5, 3.7 Hz, 1H), 1.93 (dd, *J* = 14.5, 11.1 Hz, 1H), 1.40 (dd, *J* = 16.5, 6.7 Hz, 6H), 1.30 (s, 3H), 1.24 (dd, *J* = 9.5, 6.7 Hz, 6H), 1.17 (ddt, *J* = 9.1, 5.4, 3.1 Hz, 1H), 0.96 (t, *J* = 5.4 Hz, 1H), 0.67 (dd, *J* = 8.4, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.0 (+), 141.7 (+), 126.1 (+), 126.1 (+), 48.7 (+), 46.1 (+), 37.1 (–), 27.8 (+), 27.5 (+), 23.2 (+), 21.9 (+), 21.2 (+), 20.9 (+), 20.4 (+), 19.8 (–); FT IR (NaCl, cm-1): 3061, 3026, 2998, 2965, 2931, 1631, 1453, 1436, 1368, 1344, 1214, 1039, 715, 699; HRMS (TOF ES): found 274.2159, calculated for $C_{18}H_{28}NO$ (M+H) 274.2171 (4.4 ppm).

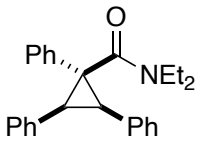


1-(2,4-dichlorophenyl)-*N*,*N*-diethyl-2-phenylcyclopropane-1-carboxamide 4.5k. This product was synthesized according to **typical procedure D** from 1-(2,4-dichlorophenyl)-*N*,*N*-diethyl-2-phenylcycloprop-2-ene-1-carboxamide (100 mg, 0.278 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as colorless crystals; dr = 78:22; m.p. = 137.4-137.9 °C; R_f 0.14 Hexane:EtOAc (5:1); Yield 68 mg (0.19 mmol, 68 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 – 7.10 (m, 2H), 7.08 – 6.98 (m, 6H), 3.71 (dd, *J* = 9.1, 7.0 Hz, 1H), 3.59

– 2.94 (m, 4H), 2.09 (dd, *J* = 7.0, 5.6 Hz, 1H), 1.60 (dd, *J* = 9.2, 5.6 Hz, 1H), 1.11 (s, 3H), 0.59 – 0.43 (m, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.4 (+), 137.8 (+), 135.9 (+), 134.2 (+), 133.2 (+), 132.1 (+), 129.8 (+), 128.4 (+), 127.7 (+), 126.6 (+), 126.3 (+), 42.2 (–), 41.6 (–), 37.8 (+), 29.9 (+), 17.0 (–), 12.8 (+); FT IR (NaCl, cm-1): 3060, 3033, 2973, 2934, 2873, 1632, 1473, 1456, 1275, 1135,718; HRMS (TOF ES): found 384.0897, calculated for $C_{20}H_{21}Cl_2NONa$ (M+Na) 384.0898 (0.3 ppm).



***N*,*N*-diethyl-1,2-diphenylcyclopropane-1-carboxamide-2,3-d_2 4.5ad**. This product was synthesized according to **typical procedure D** from *N*,*N*-diethyl-1,2-diphenylcycloprop-2-ene-1-carboxamide (100 mg, 0.343 mmol) using 5 mg of 3% Pt on carbon and using deuterium instead of hydrogen. The product was purified on Silica gel to afford the title compound as colorless crystals; dr = 96:4; m.p. = 94.4-94.6 °C; R_f 0.26 Hexane:EtOAc (5:1); Yield 83 mg (0.31 mmol, 82 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.11 – 6.96 (m, 10H), 3.50 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.32 (dp, *J* = 21.4, 6.8 Hz, 3H), 3.25 (dd, *J* = 8.7, 7.0 Hz, 0.7H), 2.08 – 2.01 (m, 1H), 1.59 – 1.53 (m, 0.7H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.66 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.7, 137.1, 136.3, 128.8 (+), 128.6 (+), 128.1 (+), 127.7 (+), 126.5 (+), 125.9 (+), 41.6 (–), 39.9 (–), 38.7 – 38.5 (m) (+), 29.8 (+), 15.4 (+), 13.0 (+), 12.5 (+); FT IR (NaCl, cm-1): 3059, 3027, 2973, 2934, 2874, 1628, 1472, 1447, 1272, 1131, 698.; HRMS (TOF ES): found 318.1798, calculated for $C_{20}H_{21}D_2NONa$ (M+Na) 318.1803 (1.6 ppm).



***N*,*N*-diethyl-1,2,3-triphenylcyclopropane-1-carboxamide 4.5j**. This product was synthesized according to **typical procedure D** from *N*,*N*-diethyl-1,2,3-triphenylcycloprop-2-ene-1-carboxamide (100 mg, 0.272 mmol) using 5 mg of 3% Pt on carbon. The product was purified on Silica gel to afford the title compound as colorless crystals; dr = <99:1; m.p. = 121.9-122.0 °C; R_f 0.23 Hexane:EtOAc (5:1); Yield 72 mg (0.19 mmol, 72 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.21 (m, 2H), 7.11 (qdd, *J* = 8.6, 5.7, 2.7 Hz, 9H), 7.00 – 6.94 (m, 4H), 3.64 (q, *J* = 7.1 Hz, 2H), 3.35 (q, *J* = 7.1 Hz, 2H), 3.30 (s, 2H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.6 (+), 135.6 (+), 134.6 (+), 131.2 (+), 128.0 (+), 127.6 (+), 126.9 (+), 126.3 (+), 42.2 (–), 41.5 (+), 40.0 (–), 33.6 (+), 13.2 (+), 12.5 (+); FT IR (NaCl, cm-1): 3056, 3026, 2972, 2933, 1632, 1496, 1444, 1270, 766, 730, 700; HRMS (TOF ES): found 392.1995, calculated for $C_{26}H_{27}NONa$ (M+Na) 392.1990 (1.3 ppm).

Appendix

A-1. X-Ray data for 2.20db

Figure A 1

ORTEP drawing of **2.20db** showing atom numbering labels and 50% probability amplitude displacement ellipsoids

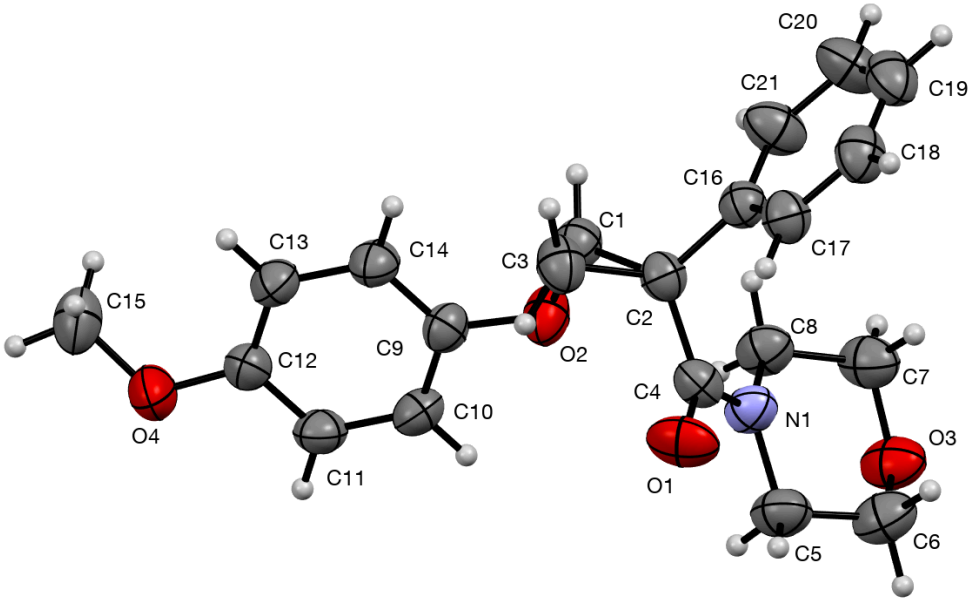


Figure A 2

Packing of 2.20db molecules in crystalline lattice

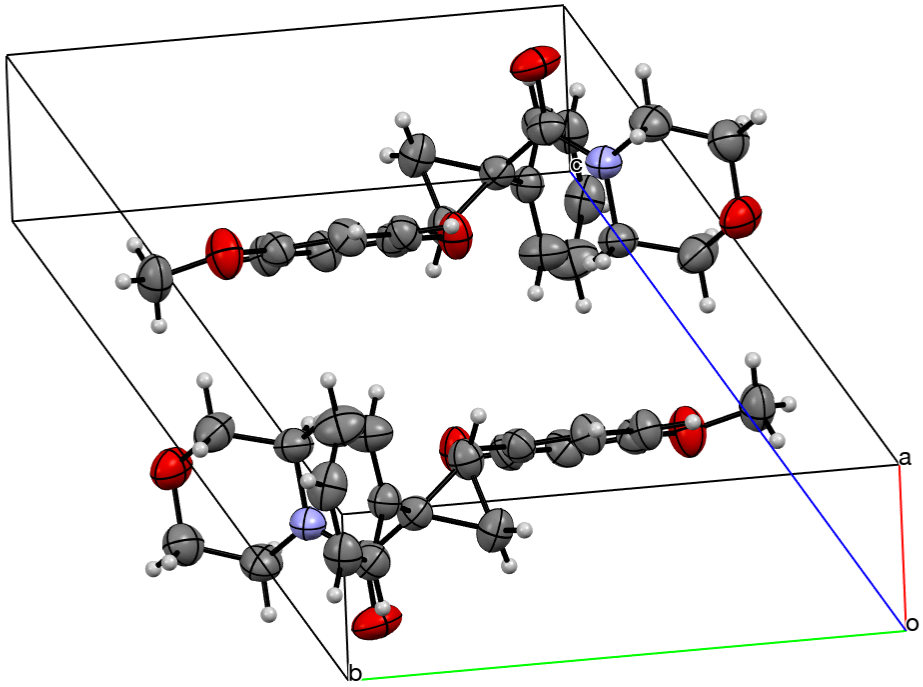


Table A 1

Crystal data and structure refinement for ***cis*-2.20db**

Identification code	ANNA_23082017_YPM29_1
Empirical formula	$C_{21}H_{23}NO_4$
Formula weight	353.40
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	9.4667(5)
b/Å	10.5554(6)
c/Å	10.6002(6)
α/°	62.334(6)
β/°	83.248(5)
γ/°	79.062(5)
Volume/Å^3	920.55(10)
Z	2
ρ_{calc}g/cm^3	1.275
μ/mm^{-1}	0.715
F(000)	376.0
Crystal size/mm^3	0.562 × 0.3 × 0.247
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.426 to 136.45
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -12 ≤ l ≤ 9
Reflections collected	8033
Independent reflections	3369 [R_{int} = 0.0172, R_{sigma} = 0.0176]
Data/restraints/parameters	3369/0/237
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0401, wR_2 = 0.1119
Final R indexes [all data]	R_1 = 0.0448, wR_2 = 0.1163
Largest diff. peak/hole / e Å^{-3}	0.26/-0.16

Table A 2

Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for ***cis*-2.20db**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor

Atom	***x***	***y***	***z***	**U(eq)**
O2	5071.9(11)	3706.6(11)	7169.7(13)	57.0(3)
O3	5981.5(14)	-1147.9(13)	6711.2(12)	66.9(3)
O4	618.9(12)	6952.8(13)	8734.5(14)	65.8(3)
O1	7352.6(14)	683.0(14)	9756.8(11)	67.8(4)
N1	6605.9(15)	596.5(13)	7871.7(12)	50.1(3)
C4	7161.9(15)	1257.4(16)	8475.0(14)	45.0(3)
C9	4042.1(15)	4605.0(14)	7542.2(15)	44.6(3)
C10	2757.2(16)	4083.3(15)	8095.8(15)	47.9(3)
C16	9051.9(15)	2634.6(15)	6726.5(15)	43.9(3)
C12	1801.1(16)	6233.5(15)	8329.8(15)	46.8(3)
C2	7629.8(15)	2722.3(15)	7506.8(15)	44.4(3)
C17	10272.3(16)	1908.6(16)	7520.9(16)	50.1(4)
C13	3079.9(16)	6759.3(15)	7777.2(16)	49.5(4)
C11	1650.6(16)	4882.2(16)	8495.8(16)	50.5(4)
C14	4207.0(16)	5943.0(15)	7382.2(16)	49.7(4)
C1	6486.2(16)	4027.6(16)	6888.6(17)	51.1(4)
C8	6181.5(19)	1234.3(17)	6395.1(15)	54.4(4)
C21	9190.3(18)	3218(2)	5263.0(17)	62.3(4)
C18	11600.4(17)	1775.4(18)	6861.7(19)	57.2(4)
C3	7307.9(17)	3796.9(18)	8113.1(18)	55.9(4)
C19	11725.3(18)	2367.8(19)	5400.4(19)	61.8(4)
C7	6590(2)	134.1(19)	5844.4(17)	62.8(4)
C5	6064(2)	-776.5(18)	8770.2(17)	62.6(4)
C15	628(2)	8432.4(19)	8357(2)	67.7(5)
C6	6481(2)	-1789.4(19)	8121.2(19)	66.5(5)
C20	10525(2)	3082(2)	4605.1(19)	71.1(5)

Table A 3

Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for ***cis*-2.20db**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O2	41.4(5)	53.9(6)	85.7(8)	-41.3(6)	-3.7(5)	-2.5(4)
O3	85.4(9)	65.5(7)	59.5(7)	-28.7(6)	-1.3(6)	-33.5(6)
O4	56.7(7)	60.0(7)	84.2(8)	-39.8(6)	17.7(6)	-9.7(5)
O1	79.7(8)	85.4(8)	37.9(6)	-19.9(5)	-2.7(5)	-33.1(7)
N1	65.4(8)	44.0(6)	38.8(6)	-16.0(5)	-3.6(5)	-9.9(6)
C4	38.9(7)	54.5(8)	39.6(7)	-20.7(6)	-0.1(5)	-4.9(6)
C9	42.7(7)	40.5(7)	48.2(7)	-18.9(6)	-6.9(6)	-1.1(6)
C10	51.4(8)	35.8(7)	52.9(8)	-15.2(6)	-5.8(6)	-9.4(6)
C16	43.2(7)	43.8(7)	47.3(7)	-22.5(6)	-0.7(6)	-8.2(6)
C12	47.8(8)	44.6(7)	44.8(7)	-18.7(6)	2.1(6)	-6.2(6)
C2	40.7(7)	48.8(8)	45.5(7)	-23.3(6)	-2.5(6)	-4.9(6)
C17	47.2(8)	53.5(8)	51.3(8)	-25.9(7)	-3.2(6)	-5.1(6)
C13	52.1(8)	40.1(7)	57.2(8)	-22.2(6)	1.2(7)	-10.4(6)
C11	47.8(8)	46.4(8)	51.6(8)	-15.9(6)	4.4(6)	-15.1(6)
C14	44.2(8)	45.2(7)	59.3(9)	-22.5(7)	2.7(6)	-12.4(6)
C1	44.4(8)	48.2(8)	61.8(9)	-26.5(7)	-1.3(6)	-5.3(6)
C8	64.1(10)	52.7(8)	43.7(8)	-17.6(7)	-8.3(7)	-10.5(7)
C21	50.9(9)	78.1(11)	48.2(8)	-20.7(8)	-2.2(7)	-9.0(8)
C18	42.6(8)	60.8(9)	73.7(10)	-36.1(8)	-3.3(7)	-4.8(7)
C3	48.3(8)	63.6(9)	68.9(10)	-41.5(8)	0.6(7)	-8.6(7)
C19	48.1(9)	71.8(10)	76.7(11)	-43.6(9)	13.8(8)	-17.5(8)
C7	77.9(11)	68.3(10)	50.6(9)	-29.2(8)	3.5(8)	-27.9(9)
C5	79.4(12)	56.9(9)	46.0(8)	-15.9(7)	3.0(8)	-21.2(8)
C15	61.2(10)	62.9(10)	91.2(13)	-48.5(10)	-7.1(9)	2.5(8)
C6	78.6(12)	53.8(9)	65.9(10)	-21.3(8)	-7.0(9)	-20.9(8)
C20	63.2(11)	94.4(14)	51.6(9)	-29.9(9)	12.0(8)	-20.4(10)

Table A 4

Bond Lengths for ***cis*-2.20db**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O2	C9	1.3827(17)	C16	C17	1.387(2)
O2	C1	1.4073(18)	C16	C21	1.378(2)
O3	C7	1.4227(19)	C12	C13	1.380(2)
O3	C6	1.422(2)	C12	C11	1.387(2)
O4	C12	1.3712(18)	C2	C1	1.504(2)
O4	C15	1.422(2)	C2	C3	1.514(2)
O1	C4	1.2238(17)	C17	C18	1.381(2)
N1	C4	1.3436(19)	C13	C14	1.392(2)
N1	C8	1.4599(18)	C1	C3	1.490(2)
N1	C5	1.468(2)	C8	C7	1.498(2)
C4	C2	1.523(2)	C21	C20	1.385(2)
C9	C10	1.383(2)	C18	C19	1.375(2)
C9	C14	1.379(2)	C19	C20	1.371(3)
C10	C11	1.371(2)	C5	C6	1.494(2)
C16	C2	1.5056(19)			

Table A 5

Bond Angles for ***cis*-2.20db**

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C9	O2	C1	117.42(11)	C1	C2	C4	118.44(12)
C6	O3	C7	110.00(12)	C1	C2	C16	121.15(12)
C12	O4	C15	117.38(13)	C1	C2	C3	59.18(10)
C4	N1	C8	126.36(12)	C3	C2	C4	114.50(12)
C4	N1	C5	119.98(12)	C18	C17	C16	120.82(14)
C8	N1	C5	112.35(13)	C12	C13	C14	120.22(13)
O1	C4	N1	121.62(14)	C10	C11	C12	120.27(13)
O1	C4	C2	120.16(13)	C9	C14	C13	119.81(13)
N1	C4	C2	118.14(12)	O2	C1	C2	114.15(12)
O2	C9	C10	115.13(12)	O2	C1	C3	117.71(14)
C14	C9	O2	125.14(13)	C3	C1	C2	60.74(10)
C14	C9	C10	119.73(13)	N1	C8	C7	109.56(13)
C11	C10	C9	120.47(13)	C16	C21	C20	120.39(16)
C17	C16	C2	118.38(12)	C19	C18	C17	119.99(15)
C21	C16	C2	122.98(13)	C1	C3	C2	60.07(10)
C21	C16	C17	118.63(14)	C20	C19	C18	119.67(15)
O4	C12	C13	125.04(13)	O3	C7	C8	111.83(13)
O4	C12	C11	115.47(13)	N1	C5	C6	110.37(13)
C13	C12	C11	119.48(13)	O3	C6	C5	110.94(14)
C16	C2	C4	114.04(12)	C19	C20	C21	120.50(16)
C16	C2	C3	118.38(12)				

Table A 6

Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for ***cis*-2.20db**

Atom	***x***	***y***	***z***	**U(eq)**
H10	2642.9	3184.41	8197.44	57
H17	10194.92	1506.54	8509.79	60
H13	3189.3	7662.29	7668.18	59
H11	795.68	4516.45	8879.96	61
H14	5068.86	6298.63	7011.35	60
H1	6698.57	4808.52	5952.89	61
H8A	6657.62	2069.58	5814.8	65
H8B	5149.96	1553.7	6340.59	65
H21	8383.21	3705.45	4713.57	75
H18	12410.3	1284.9	7406.14	69
H3A	6810.24	3499.29	9036.47	67
H3B	8009.9	4429.18	7926.55	67
H19	12619.58	2284.92	4953.39	74
H7A	6262.93	547.09	4879.72	75
H7B	7630.22	-109.05	5814.51	75
H5A	5024.03	-594.48	8873.09	75
H5B	6458.32	-1214.77	9710.74	75
H15A	756.08	8964.75	7341.66	102
H15B	1403.64	8506.62	8814.17	102
H15C	-269.74	8824.42	8658.62	102
H6A	7520.44	-2042.82	8102.84	80
H6B	6074.87	-2671.5	8700.04	80
H20	10606.75	3477.48	3616.78	85

A-2. X-Ray data for 2.20cb

Figure A 3

ORTEP drawing of **2.20cb** showing atom numbering labels and 50% probability amplitude displacement ellipsoids

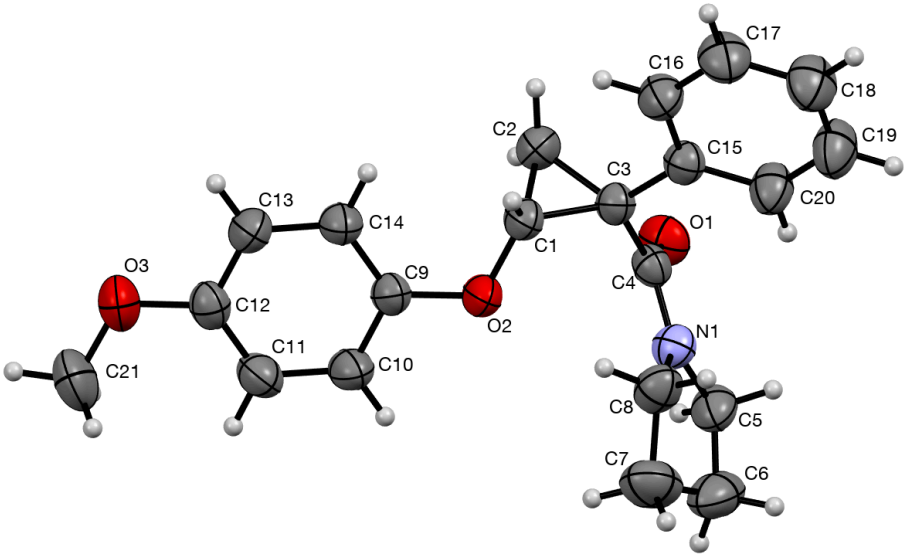


Figure A 4

Packing of 2.20cb molecules in crystalline lattice

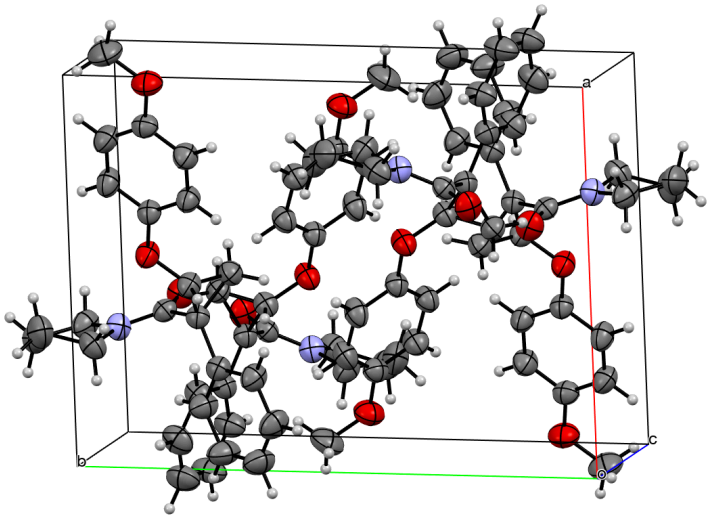


Table A 7

Crystal data and structure refinement for **2.20cb**

Identification code	ANNA_23082017_YPM30_3
Empirical formula	$C_{21}H_{23}NO_3$
Formula weight	337.40
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.9367(4)
b/Å	14.2449(4)
c/Å	11.4918(3)
α/°	90
β/°	112.287(4)
γ/°	90
Volume/Å^3	1808.07(10)
Z	4
ρ_{calc}g/cm^3	1.239
μ/mm^{-1}	0.661
F(000)	720.0
Crystal size/mm^3	0.44 × 0.32 × 0.23
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.004 to 136.496
Index ranges	-14 ≤ h ≤ 13, -17 ≤ k ≤ 17, -13 ≤ l ≤ 11
Reflections collected	11506
Independent reflections	3304 [R_{int} = 0.0411, R_{sigma} = 0.0263]
Data/restraints/parameters	3304/0/215
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0592, wR_2 = 0.1653
Final R indexes [all data]	R_1 = 0.0632, wR_2 = 0.1717
Largest diff. peak/hole / e Å^{-3}	0.30/-0.32

Table A 8

Fractional atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2×10^3) for **2.20cb**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor

Atom	***x***	***y***	***z***	**U(eq)**
O2	5261.1(11)	4281.3(9)	7193.1(10)	54.1(3)
O1	5933.0(12)	3340.0(9)	10384.0(12)	57.8(3)
O3	1294.6(12)	4619.5(11)	2721.2(13)	66.1(4)
N1	6863.1(13)	4606(1)	10022.8(12)	49.1(4)
C4	6440.8(13)	3728.2(11)	9764.9(13)	42.5(4)
C3	6680.3(14)	3202.1(11)	8733.9(14)	42.6(4)
C9	4283.8(14)	4332.5(11)	6050.8(14)	44.8(4)
C15	7950.9(8)	2802.9(8)	9124(1)	45.2(4)
C16	8237.1(9)	2213.1(9)	8313.2(8)	56.8(4)
C17	9386.9(11)	1821.5(10)	8687.5(11)	67.0(5)
C18	10250.5(9)	2019.6(11)	9872.5(12)	71.1(6)
C19	9964.3(9)	2609.3(12)	10683.4(10)	72.7(6)
C20	8814.5(10)	3000.9(9)	10309.1(9)	59.8(5)
C1	5990.1(15)	3482.1(12)	7379.2(14)	46.3(4)
C12	2280.8(14)	4577.0(12)	3849.7(16)	49.2(4)
C14	4017.5(16)	3667.9(12)	5109.7(16)	51.7(4)
C2	5623.5(15)	2624.5(12)	7866.6(16)	51.3(4)
C5	6722.5(18)	5134.5(14)	11056.9(17)	60.1(5)
C11	2552.2(17)	5239.9(13)	4784.0(18)	57.8(5)
C13	3015.0(17)	3800.7(13)	4007.3(17)	55.7(4)
C8	7413.7(18)	5186.0(14)	9327.8(18)	58.7(5)
C10	3557.7(18)	5113.1(13)	5888.9(17)	57.2(5)
C6	7133(2)	6120.7(16)	10911(3)	78.0(7)
C7	7081(2)	6163.0(16)	9582(3)	83.2(7)
C21	558(2)	5425(2)	2498(3)	86.8(8)

Table A 9

Anisotropic displacement parameters ($Å^2 \times 10^3$) for **2.20cb**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O2	63.4(7)	48.6(7)	39.4(6)	-4.7(5)	7.4(5)	9.6(5)
O1	69.6(8)	60.5(8)	52.4(7)	8.8(5)	33.5(6)	1.1(6)
O3	54.4(7)	76.3(9)	53.6(7)	5.4(6)	4.8(6)	5.9(6)
N1	57.5(8)	50.2(8)	41.2(7)	-3.0(6)	20.5(6)	0.8(6)
C4	44.7(7)	45.5(8)	36.3(7)	5.7(6)	14.2(6)	5.3(6)
C3	46.5(8)	43.3(8)	36.9(7)	0.9(6)	14.5(6)	0.9(6)
C9	51.7(8)	43.1(8)	37.1(8)	2.2(6)	14.0(6)	1.8(6)
C15	48.5(8)	47.0(8)	40.3(8)	1.2(6)	17.0(6)	1.2(6)
C16	62.1(10)	59.4(10)	47.1(9)	-5.8(8)	18.5(8)	8.7(8)
C17	69.4(11)	73.0(13)	62.7(11)	-6.9(9)	29.7(9)	17.1(10)
C18	52.3(10)	87.1(15)	72.4(13)	-7.0(11)	22.0(9)	14(1)
C19	50.2(10)	95.3(16)	62.1(11)	-12.8(11)	9.5(8)	11.9(10)
C20	53.0(9)	74.7(12)	47.5(9)	-10.5(8)	14.3(7)	9.0(8)
C1	53.4(8)	46.8(8)	36.0(7)	-1.7(6)	13.7(6)	5.8(7)
C12	46.6(8)	54.6(9)	44.3(8)	9.0(7)	14.9(7)	0.6(7)
C14	57.7(9)	45.9(9)	46.6(9)	-3.0(7)	14.0(7)	7.8(7)
C2	51.2(8)	47.6(9)	50.1(9)	-5.1(7)	13.5(7)	-1.8(7)
C5	64.8(10)	63.2(11)	48.1(9)	-11.9(8)	16.9(8)	12.0(8)
C11	62.9(10)	50.9(9)	56.4(10)	6.5(8)	19.0(8)	14.0(8)
C13	60.7(10)	53.7(10)	45.5(9)	-6.0(7)	11.8(7)	2.8(8)
C8	63.3(10)	57.4(10)	54.9(10)	-1.2(8)	21.9(8)	-12.5(8)
C10	73.3(11)	45.9(9)	47.1(9)	-4.0(7)	16.9(8)	9.4(8)
C6	68.5(12)	62.1(12)	97.1(17)	-26.6(12)	24.1(11)	2.3(9)
C7	86.5(15)	53.3(12)	108.2(19)	4.5(12)	35.2(14)	-6.4(10)
C21	65.3(12)	90.6(17)	81.0(15)	15.9(13)	1.3(11)	19.9(12)

Table A 10

Bond lengths for **2.20cb.**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O2	C9	1.3884(19)	C15	C16	1.3900
O2	C1	1.399(2)	C15	C20	1.3900
O1	C4	1.2273(19)	C16	C17	1.3900
O3	C12	1.383(2)	C17	C18	1.3900
O3	C21	1.409(3)	C18	C19	1.3900
N1	C4	1.339(2)	C19	C20	1.3900
N1	C5	1.469(2)	C1	C2	1.478(2)
N1	C8	1.466(2)	C12	C11	1.373(3)
C4	C3	1.518(2)	C12	C13	1.380(3)
C3	C15	1.5196(16)	C14	C13	1.387(2)
C3	C1	1.513(2)	C5	C6	1.518(3)
C3	C2	1.519(2)	C11	C10	1.389(3)
C9	C14	1.381(2)	C8	C7	1.506(3)
C9	C10	1.378(2)	C6	C7	1.506(4)

Table A 11

Bond angles for **2.20cb**

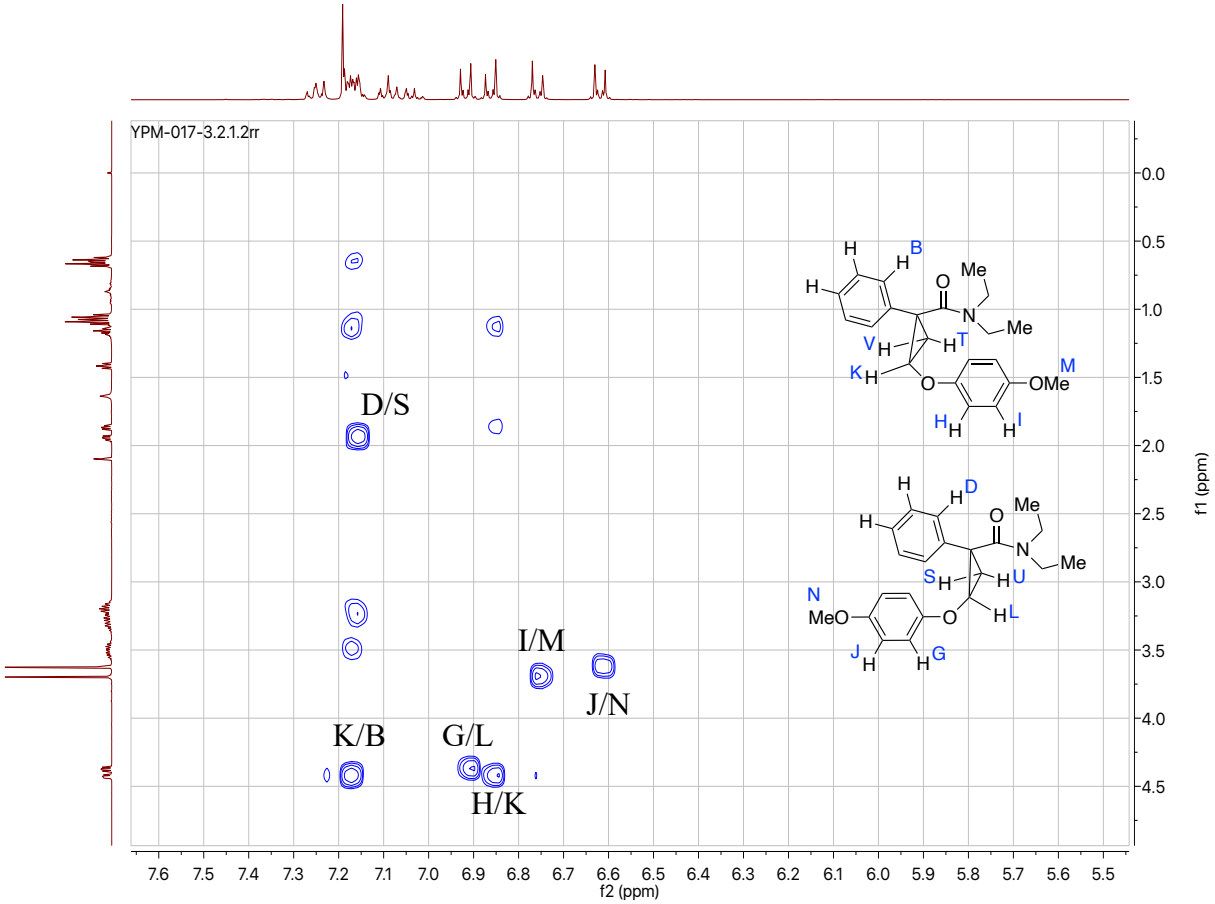
Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C9	O2	C1	115.98(12)	C17	C16	C15	120.0
C12	O3	C21	117.18(17)	C16	C17	C18	120.0
C4	N1	C5	120.58(15)	C17	C18	C19	120.0
C4	N1	C8	127.93(14)	C20	C19	C18	120.0
C8	N1	C5	111.35(15)	C19	C20	C15	120.0
O1	C4	N1	121.32(15)	O2	C1	C3	115.86(13)
O1	C4	C3	120.70(14)	O2	C1	C2	118.30(15)
N1	C4	C3	117.86(13)	C2	C1	C3	61.05(10)
C4	C3	C15	114.64(11)	C11	C12	O3	124.58(16)
C4	C3	C2	115.10(13)	C11	C12	C13	119.92(16)
C1	C3	C4	118.87(13)	C13	C12	O3	115.51(16)
C1	C3	C15	119.69(12)	C9	C14	C13	118.99(16)
C1	C3	C2	58.33(11)	C1	C2	C3	60.62(10)
C2	C3	C15	118.58(13)	N1	C5	C6	104.12(17)
C14	C9	O2	124.46(14)	C12	C11	C10	119.42(16)
C10	C9	O2	115.46(14)	C12	C13	C14	120.96(16)
C10	C9	C14	120.09(15)	N1	C8	C7	102.10(17)
C16	C15	C3	120.00(8)	C9	C10	C11	120.62(16)
C16	C15	C20	120.0	C7	C6	C5	104.96(17)
C20	C15	C3	119.96(8)	C8	C7	C6	104.29(19)

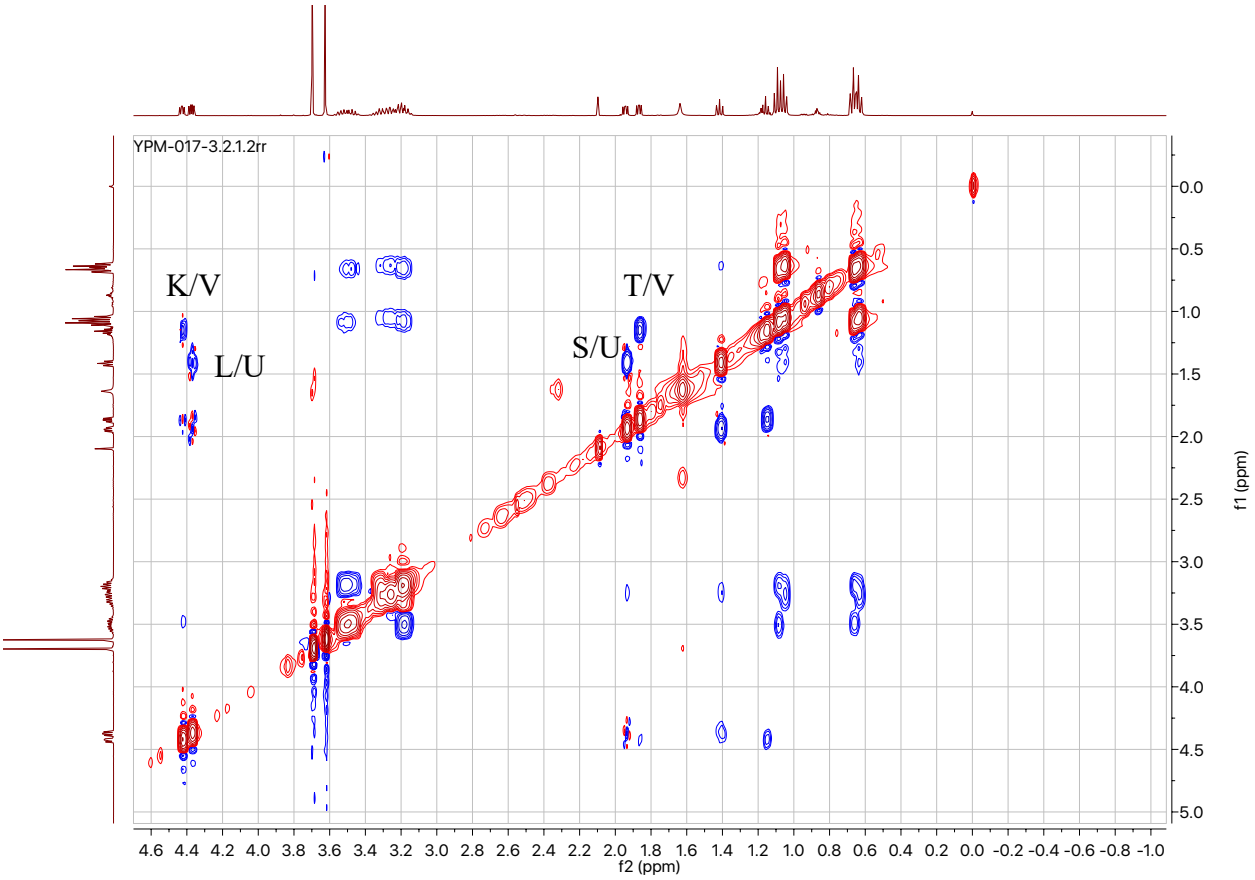
Table A 12

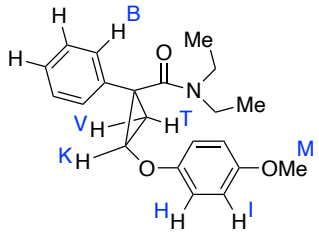
Hydrogen atom coordinates (Å×10^4) and isotropic displacement parameters (Å^2×10^3) for **2.20cb.**

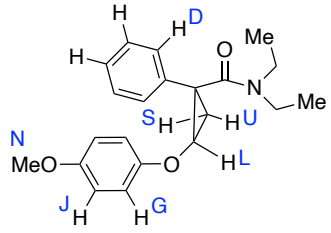
Atom	*x*	*y*	*z*	U(eq)
H16	7659.37	2080.60	7520.31	68
H17	9578.39	1426.92	8144.95	80
H18	11019.73	1757.51	10122.93	85
H19	10542.07	2741.80	11476.27	87
H20	8623.05	3395.49	10851.65	72
H1	6404.91	3391.48	6797.13	56
H14	4503.17	3139.27	5213.48	62
H2A	5803.39	2023.73	7579.71	62
H2B	4872.40	2644.03	8007.55	62
H5A	7223.82	4870.18	11865.04	72
H5B	5885.32	5133.15	10982.14	72
H11	2067.07	5769.01	4678.00	69
H13	2834.89	3360.01	3364.95	67
H8A	7075.47	5042.98	8436.05	70
H8B	8284.93	5102.82	9645.56	70
H10	3742.81	5559.15	6525.42	69
H6A	6598.69	6584.94	11042.63	94
H6B	7951.10	6232.47	11507.73	94
H7A	6274.03	6328.02	9000.30	100
H7B	7652.39	6619.78	9506.64	100
H21A	-71.10	5386.13	1675.93	130
H21B	1040.27	5973.82	2548.83	130
H21C	201.49	5463.22	3118.67	130

A-3. ^{1}H – ^{1}H NOESY spectrum of 2.20ab (mixture of *cis*- and *trans*- isomers 1:1)




YPM-017-3.2.1.2rr
K/V
L/U
T/V
S/U
f2 (ppm)
f1 (ppm)

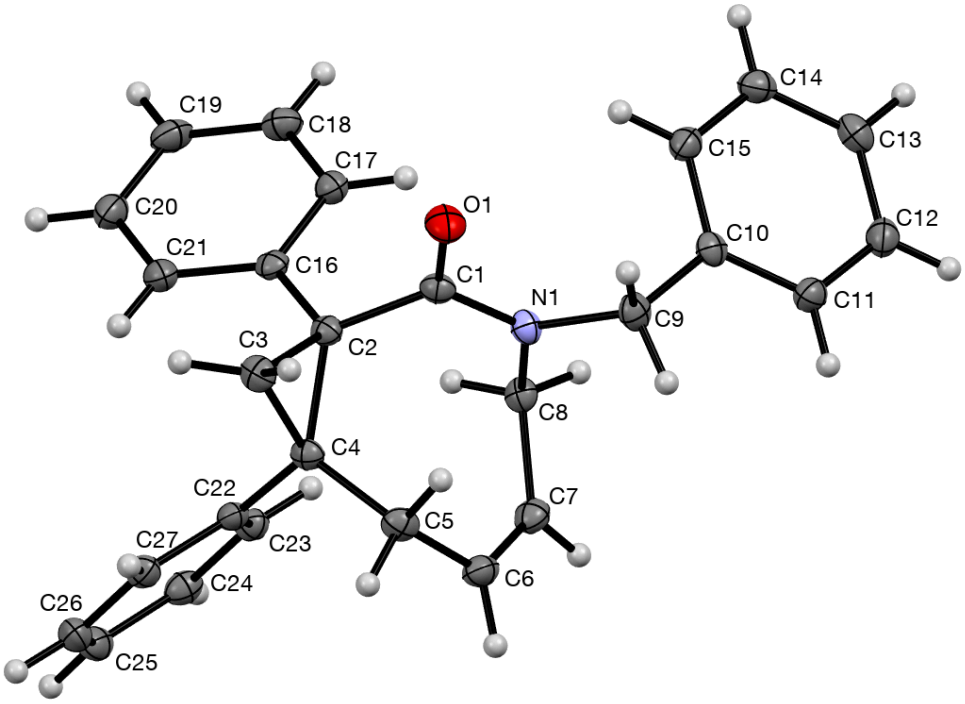

H
B
H
H
Me
O
N
Me
V
H
H
T
K
H
O
OMe
M
H
H
H
I


H
H
D
H
Me
O
N
Me
S
H
H
U
N
MeO
O
H
L
J
H
H
G

A-4. X-Ray data for 3.3dba

Figure A 5

ORTEP drawing of crystal structure of compound **3.3dba** showing atom-labeling scheme and 50% probability thermal ellipsoids (left); and micro-photography of the single crystal used for X-Ray diffraction (right).



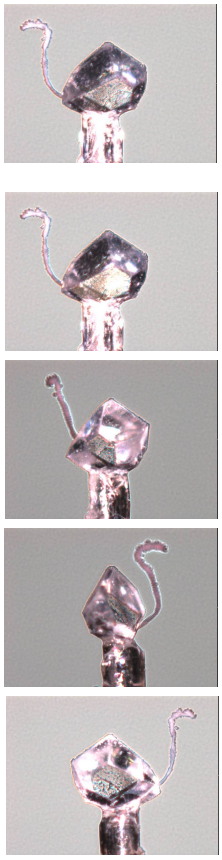


Table A 13

Crystal data and structure refinement for **3.3dba**

Identification code	ANNA12012018_MRUBIN_2
Empirical formula	$C_{27}H_{25}NO$
Formula weight	379.48
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.56975(18)
b/Å	10.85621(18)
c/Å	17.7073(3)
α/°	90
β/°	98.3009(15)
γ/°	90
Volume/Å^3	2010.58(6)
Z	4
ρ_{calc}g/cm^3	1.254
μ/mm^{-1}	0.581
F(000)	808.0
Crystal size/mm^3	0.52 × 0.401 × 0.247
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.2 to 152.568
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -20 ≤ l ≤ 22
Reflections collected	29282
Independent reflections	4192 [R_{int} = 0.0273, R_{sigma} = 0.0129]
Data/restraints/parameters	4192/0/262
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0390, wR_2 = 0.0973
Final R indexes [all data]	R_1 = 0.0399, wR_2 = 0.0982
Largest diff. peak/hole / e Å^{-3}	0.20/-0.27

Table A 14

Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **3.3dba**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	2081.5(8)	3209.8(7)	3246.1(5)	24.59(18)
N1	2503.9(8)	5202.2(8)	3573.7(5)	16.42(18)
C22	5778.7(9)	5202.7(9)	2383.6(5)	15.7(2)
C16	2893(1)	4699.4(9)	1775.1(6)	16.0(2)
C1	2627.7(9)	4183.1(9)	3148.0(6)	16.8(2)
C2	3516.2(9)	4276.0(9)	2547.4(6)	15.6(2)
C4	4938.5(9)	4512.0(9)	2852.2(6)	15.9(2)
C10	757.4(10)	5874.2(10)	4279.3(6)	17.1(2)
C23	5536.2(10)	6421.4(10)	2155.6(6)	17.4(2)
C17	1672.6(10)	5224.7(10)	1686.4(6)	18.9(2)
C8	3025(1)	6415.8(9)	3428.4(6)	16.8(2)
C3	4491.6(10)	3242.5(9)	2597.0(6)	19.2(2)
C21	3477(1)	4542.9(10)	1120.5(6)	20.2(2)
C15	-300.8(10)	5736.8(10)	3716.1(6)	19.6(2)
C11	707.7(10)	6737.1(10)	4852.3(6)	20.4(2)
C6	5278.8(10)	5937.7(10)	4035.6(6)	20.6(2)
C26	7717.9(10)	5251.7(11)	1799.5(6)	21.6(2)
C5	5339.4(10)	4652.6(10)	3717.0(6)	19.2(2)
C7	4289.4(10)	6701.6(10)	3909.0(6)	20.3(2)
C27	6873.7(10)	4626.1(10)	2196.2(6)	18.7(2)
C14	-1383.4(10)	6457.6(11)	3727.9(6)	21.9(2)
C24	6378.4(10)	7045.2(10)	1756.5(6)	20.1(2)
C25	7474.9(10)	6466.0(11)	1582.1(6)	22.1(2)
C13	-1419(1)	7319(1)	4305.6(6)	21.8(2)
C12	-377.1(11)	7456.4(10)	4871.4(6)	22.4(2)
C9	1932.4(10)	5086.9(10)	4275.7(6)	19.3(2)
C18	1068.4(11)	5598.8(11)	973.7(6)	22.9(2)
C19	1664.2(11)	5442.7(11)	331.2(6)	24.1(2)
C20	2867.9(11)	4908.4(11)	408.6(6)	23.7(2)

Table A 15

Anisotropic displacement parameters ($Å^2 \times 10^3$) for **3.3dba**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}
O1	26.3(4)	18.8(4)	30.0(4)	-1.1(3)	8.6(3)
N1	17.6(4)	15.5(4)	16.8(4)	1.6(3)	4.7(3)
C22	14.8(5)	17.3(5)	14.4(4)	-1.7(4)	-0.6(3)
C16	16.4(5)	13.4(4)	17.8(5)	-2.8(4)	0.9(4)
C1	15.1(5)	16.2(5)	18.5(5)	1.5(4)	0.8(4)
C2	15.3(5)	13.3(4)	18.0(5)	-1.2(4)	2.3(4)
C4	14.5(5)	14.7(5)	18.1(5)	0.5(4)	1.3(4)
C10	18.3(5)	18.3(5)	15.4(4)	3.1(4)	5.4(4)
C23	16.7(5)	18.1(5)	16.9(5)	-0.4(4)	0.4(4)
C17	17.8(5)	19.1(5)	19.4(5)	-2.6(4)	1.8(4)
C8	18.6(5)	13.8(5)	18.4(5)	0.6(4)	3.5(4)
C3	19.3(5)	13.7(5)	24.9(5)	0.3(4)	3.8(4)
C21	17.6(5)	21.9(5)	20.8(5)	-4.5(4)	2.4(4)
C15	21.7(5)	20.5(5)	16.8(5)	-1.7(4)	3.8(4)
C11	19.8(5)	24.9(5)	16.4(5)	-0.8(4)	2.2(4)
C6	19.4(5)	24.6(5)	16.9(5)	-0.7(4)	-0.2(4)
C26	16.7(5)	28.5(6)	19.8(5)	-3.6(4)	3.4(4)
C5	17.8(5)	20.5(5)	18.6(5)	3.9(4)	0.3(4)
C7	23.2(5)	18.0(5)	19.8(5)	-2.6(4)	3.3(4)
C27	17.7(5)	18.8(5)	19.1(5)	-1.3(4)	0.5(4)
C14	18.0(5)	26.4(6)	20.8(5)	2.2(4)	1.3(4)
C24	23.4(5)	18.8(5)	17.3(5)	1.6(4)	-0.2(4)
C25	20.6(5)	28.4(6)	17.6(5)	0.2(4)	3.9(4)
C13	19.3(5)	22.3(5)	25.0(5)	3.1(4)	7.8(4)
C12	25.0(5)	22.6(5)	21.0(5)	-3.4(4)	7.4(4)
C9	21.1(5)	22.1(5)	15.3(5)	3.3(4)	4.5(4)
C18	18.8(5)	23.9(5)	24.3(5)	-0.9(4)	-2.3(4)
C19	24.9(5)	27.6(6)	18.0(5)	0.7(4)	-3.5(4)
C20	24.6(5)	29.2(6)	17.6(5)	-3.9(4)	3.8(4)

Table A 16

Bond lengths for **3.3dba**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.2284(13)	C10	C9	1.5084(14)
N1	C1	1.3556(13)	C23	C24	1.3901(15)
N1	C8	1.4651(13)	C17	C18	1.3901(15)
N1	C9	1.4637(12)	C8	C7	1.5094(14)
C22	C4	1.5007(14)	C21	C20	1.3880(15)
C22	C23	1.3962(14)	C15	C14	1.3889(15)
C22	C27	1.3972(14)	C11	C12	1.3917(16)
C16	C2	1.5017(14)	C6	C5	1.5098(15)
C16	C17	1.3983(14)	C6	C7	1.3281(16)
C16	C21	1.4001(14)	C26	C27	1.3898(15)
C1	C2	1.5205(14)	C26	C25	1.3869(17)
C2	C4	1.5436(13)	C14	C13	1.3905(16)
C2	C3	1.5177(14)	C24	C25	1.3918(16)
C4	C3	1.5050(14)	C13	C12	1.3857(16)
C4	C5	1.5364(14)	C18	C19	1.3881(16)
C10	C15	1.3950(15)	C19	C20	1.3868(17)
C10	C11	1.3875(15)			

Table A 17

Bond angles for **3.3dba**

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C1	N1	C8	124.56(8)	C15	C10	C9	120.80(9)
C1	N1	C9	119.16(9)	C11	C10	C15	118.94(10)
C9	N1	C8	115.96(8)	C11	C10	C9	120.25(9)
C23	C22	C4	122.33(9)	C24	C23	C22	120.29(10)
C23	C22	C27	118.66(10)	C18	C17	C16	121.11(10)
C27	C22	C4	118.95(9)	N1	C8	C7	114.24(8)
C17	C16	C2	120.23(9)	C4	C3	C2	61.41(6)
C17	C16	C21	117.79(9)	C20	C21	C16	121.00(10)
C21	C16	C2	121.93(9)	C14	C15	C10	120.41(10)
O1	C1	N1	122.57(9)	C10	C11	C12	120.99(10)
O1	C1	C2	120.42(9)	C7	C6	C5	126.07(10)
N1	C1	C2	116.99(9)	C25	C26	C27	119.87(10)
C16	C2	C1	115.04(8)	C6	C5	C4	116.35(8)
C16	C2	C4	123.00(8)	C6	C7	C8	125.34(10)
C16	C2	C3	118.95(9)	C26	C27	C22	121.02(10)
C1	C2	C4	115.80(8)	C15	C14	C13	119.99(10)
C3	C2	C1	113.17(8)	C23	C24	C25	120.50(10)
C3	C2	C4	58.89(6)	C26	C25	C24	119.64(10)
C22	C4	C2	120.92(8)	C12	C13	C14	120.08(10)
C22	C4	C3	118.47(9)	C13	C12	C11	119.58(10)
C22	C4	C5	113.66(8)	N1	C9	C10	113.34(8)
C3	C4	C2	59.70(6)	C19	C18	C17	120.33(10)
C3	C4	C5	114.81(9)	C20	C19	C18	119.23(10)
C5	C4	C2	118.65(8)	C19	C20	C21	120.53(10)

Table A 18

Hydrogen atom coordinates (Å×10^4) and isotropic displacement parameters (Å^2×10^3) for **3.3dba**

Atom	*x*	*y*	*z*
H23	4807.9	6817.52	2271.25
H17	1258.21	5325.53	2111.21
H8A	2410.08	7040.51	3521.89
H8B	3131.4	6465.28	2894.19
H3A	4461.94	2621.22	2987.81
H3B	4731.72	2936.16	2123.05
H21	4285.35	4188.67	1163.24
H15	-281.3	5158.87	3330.24
H11	1409.87	6836.31	5229.27
H6	6001.63	6220.86	4349.77
H26	8444.27	4856.73	1680.13
H5A	4797.45	4123.21	3974.07
H5B	6209.21	4354.2	3843.23
H7	4383.29	7475.84	4134.9
H27	7040.15	3811.13	2339.03
H14	-2084.34	6364.21	3349.48
H24	6208.01	7855.76	1604.9
H25	8041.54	6890.95	1321.24
H13	-2142.91	7803.49	4312.28
H12	-402.53	8025.71	5261.39
H9A	2563.29	5316.71	4706.08
H9B	1705.96	4231.86	4342.1
H18	260.86	5955.44	927.24
H19	1260.96	5693.41	-145.66
H20	3270.05	4794.2	-19.88

A-5. X-Ray data for 3.3aaa

Figure A 6

ORTEP drawing of crystal structure of compound **3.3aaa** showing atom-labeling scheme and 50% probability thermal ellipsoids (left); and micro-photography of the single crystal used for X-Ray diffraction (right)

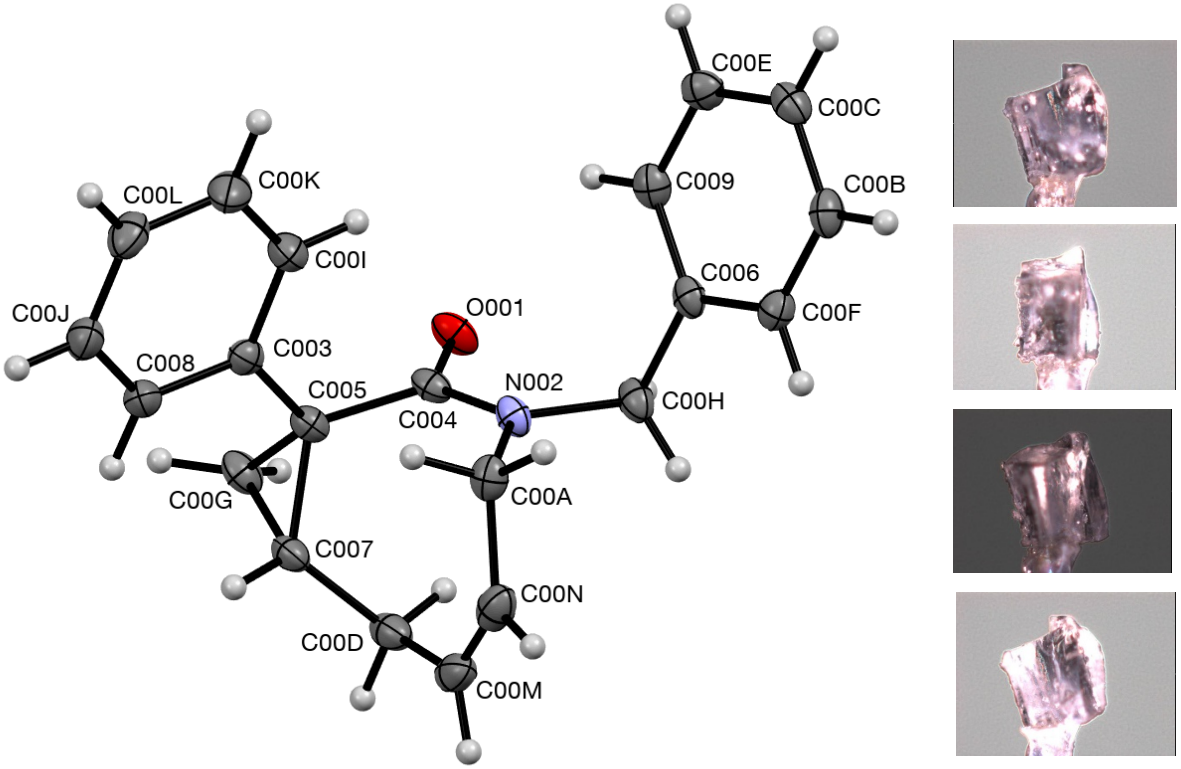


Table A 19

Crystal data and structure refinement for **3.3aaa**.

Identification code	ANNA__24102017_YPM82
Empirical formula	$C_{21}H_{21}NO$
Formula weight	303.39
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	6.87140(10)
b/Å	14.6838(3)
c/Å	16.0347(3)
α/°	90
β/°	93.506(2)
γ/°	90
Volume/Å^3	1614.85(5)
Z	4
ρ_{calc}g/cm^3	1.248
μ/mm^{-1}	0.589
F(000)	648.0
Crystal size/mm^3	0.577 × 0.505 × 0.401
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.172 to 152.258
Index ranges	-8 ≤ h ≤ 7, -18 ≤ k ≤ 15, -19 ≤ l ≤ 20
Reflections collected	9733
Independent reflections	3343 [R_{int} = 0.0156, R_{sigma} = 0.0148]
Data/restraints/parameters	3343/0/209
Goodness-of-fit on F^2	1.089
Final R indexes [I>=2σ (I)]	R_1 = 0.0354, wR_2 = 0.0872
Final R indexes [all data]	R_1 = 0.0395, wR_2 = 0.0892
Largest diff. peak/hole / e Å^{-3}	0.23/-0.18

Table A 20

Fractional atomic coordinates ($\times 10^4$) and equivalent Isotropic displacement parameters ($Å^2 \times 10^3$) for **3aaa**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***
O001	8064.5(11)	3347.9(5)	3670.1(5)
N002	6148.3(12)	2973.7(6)	2523.0(6)
C003	3809.7(15)	2254.3(7)	4066.7(6)
C008	1966.3(16)	2189.1(8)	4383.2(7)
C00J	1174.8(17)	1349.4(8)	4566.7(7)
C00L	2207.2(19)	555.8(8)	4448.3(7)
C00K	4049(2)	609.1(8)	4147.8(8)
C00I	4846.1(17)	1448.6(8)	3958.2(7)
C004	6442.9(15)	3156.8(7)	3345.8(7)
C005	4634.2(14)	3159.4(7)	3842.6(6)
C006	8675.3(14)	2213.3(7)	1719.7(7)
C009	9713.2(15)	1700.1(8)	2328.5(7)
C00E	10659.8(15)	906.8(8)	2116.4(7)
C00C	10566.7(15)	609.5(8)	1291.7(7)
C00B	9512.6(16)	1105.9(8)	685.0(7)
C00F	8569.0(16)	1906.0(8)	897.7(7)
C007	3287.4(15)	3970.5(7)	3652.8(7)
C00A	4244.6(15)	2743.8(8)	2115.9(7)
C00D	3754.8(16)	4641.8(8)	2976.5(8)
C00G	4513.7(16)	3939.5(8)	4458.5(7)
C00H	7736.4(16)	3099.0(7)	1961.1(7)
C00M	2918.9(16)	4358.0(9)	2124.1(8)
C00N	3106.4(16)	3551.8(9)	1762.9(7)

Table A 21

Anisotropic displacement parameters ($Å^2 \times 10^3$) for **3.3aaa**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}
O001	15.1(4)	27.1(4)	33.4(4)	-8.2(3)	-1.5(3)
N002	15.3(4)	20.5(4)	23.6(4)	-3.1(4)	3.9(3)
C003	19.9(5)	20.9(5)	15.6(5)	-1.0(4)	-0.9(4)
C008	22.3(5)	23.7(5)	20.2(5)	2.0(4)	2.2(4)
C00J	25.7(6)	30.3(6)	23.4(5)	5.6(5)	4.8(4)
C00L	42.2(7)	22.9(6)	26.4(6)	3.9(5)	7.5(5)
C00K	42.8(7)	21.6(6)	31.9(6)	2.6(5)	11.2(5)
C00I	26.3(6)	24.4(6)	27.6(6)	0.5(5)	7.1(4)
C004	15.9(5)	14.7(5)	26.7(5)	-3.0(4)	1.1(4)
C005	16.3(5)	19.1(5)	21.1(5)	-3.2(4)	0.4(4)
C006	15.3(5)	20.0(5)	23.3(5)	-1.5(4)	5.5(4)
C009	18.0(5)	27.0(5)	20.6(5)	-3.8(4)	1.0(4)
C00E	17.8(5)	26.2(5)	27.5(6)	1.3(4)	-1.5(4)
C00C	19.7(5)	20.9(5)	31.7(6)	-4.0(4)	6.6(4)
C00B	27.0(5)	26.6(6)	20.4(5)	-5.2(4)	6.3(4)
C00F	22.3(5)	23.8(5)	20.6(5)	2.0(4)	3.1(4)
C007	16.7(5)	19.5(5)	30.0(6)	-0.6(4)	5.4(4)
C00A	20.7(5)	26.0(5)	21.1(5)	-1.6(4)	1.0(4)
C00D	19.2(5)	20.3(5)	39.3(6)	3.7(5)	6.7(4)
C00G	22.9(5)	22.8(5)	28.8(6)	-8.6(4)	4.3(4)
C00H	21.4(5)	20.1(5)	28.4(6)	-1.6(4)	9.0(4)
C00M	20.6(5)	33.1(6)	34.7(6)	15.0(5)	4.6(5)
C00N	21.1(5)	39.9(7)	24.6(6)	8.1(5)	-0.2(4)

Table A 22

Bond lengths for **3.3aaa**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O001	C004	1.2328(13)	C005	C00G	1.5180(14)
N002	C004	1.3495(14)	C006	C009	1.3944(16)
N002	C00A	1.4652(13)	C006	C00F	1.3908(15)
N002	C00H	1.4686(13)	C006	C00H	1.5127(15)
C003	C008	1.3964(15)	C009	C00E	1.3866(16)
C003	C00I	1.3973(15)	C00E	C00C	1.3904(16)
C003	C005	1.4971(14)	C00C	C00B	1.3843(17)
C008	C00J	1.3864(16)	C00B	C00F	1.3943(16)
C00J	C00L	1.3834(17)	C007	C00D	1.5145(15)
C00L	C00K	1.3839(18)	C007	C00G	1.4993(16)
C00K	C00I	1.3899(17)	C00A	C00N	1.5119(17)
C004	C005	1.5167(14)	C00D	C00M	1.5086(18)
C005	C007	1.5274(14)	C00M	C00N	1.3275(19)

Table A 23

Bond angles for **3.3aaa**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C004	N002	C00A	123.92(9)	C00G	C005	C007	58.99(7)
C004	N002	C00H	120.14(9)	C009	C006	C00H	119.56(10)
C00A	N002	C00H	115.60(9)	C00F	C006	C009	118.89(10)
C008	C003	C00I	117.88(10)	C00F	C006	C00H	121.53(10)
C008	C003	C005	120.88(9)	C00E	C009	C006	120.64(10)
C00I	C003	C005	121.24(9)	C009	C00E	C00C	120.14(10)
C00J	C008	C003	120.96(10)	C00B	C00C	C00E	119.65(10)
C00L	C00J	C008	120.59(10)	C00C	C00B	C00F	120.20(10)
C00J	C00L	C00K	119.19(11)	C006	C00F	C00B	120.46(10)
C00L	C00K	C00I	120.48(11)	C00D	C007	C005	119.85(9)
C00K	C00I	C003	120.88(10)	C00G	C007	C005	60.20(7)
O001	C004	N002	122.37(10)	C00G	C007	C00D	120.27(10)
O001	C004	C005	121.76(10)	N002	C00A	C00N	114.41(9)
N002	C004	C005	115.80(9)	C00M	C00D	C007	112.54(9)
C003	C005	C004	117.26(8)	C007	C00G	C005	60.82(7)
C003	C005	C007	120.42(9)	N002	C00H	C006	113.19(9)
C003	C005	C00G	118.50(9)	C00N	C00M	C00D	126.85(11)
C004	C005	C007	113.79(9)	C00M	C00N	C00A	126.75(11)
C004	C005	C00G	115.01(9)				

Table A 24

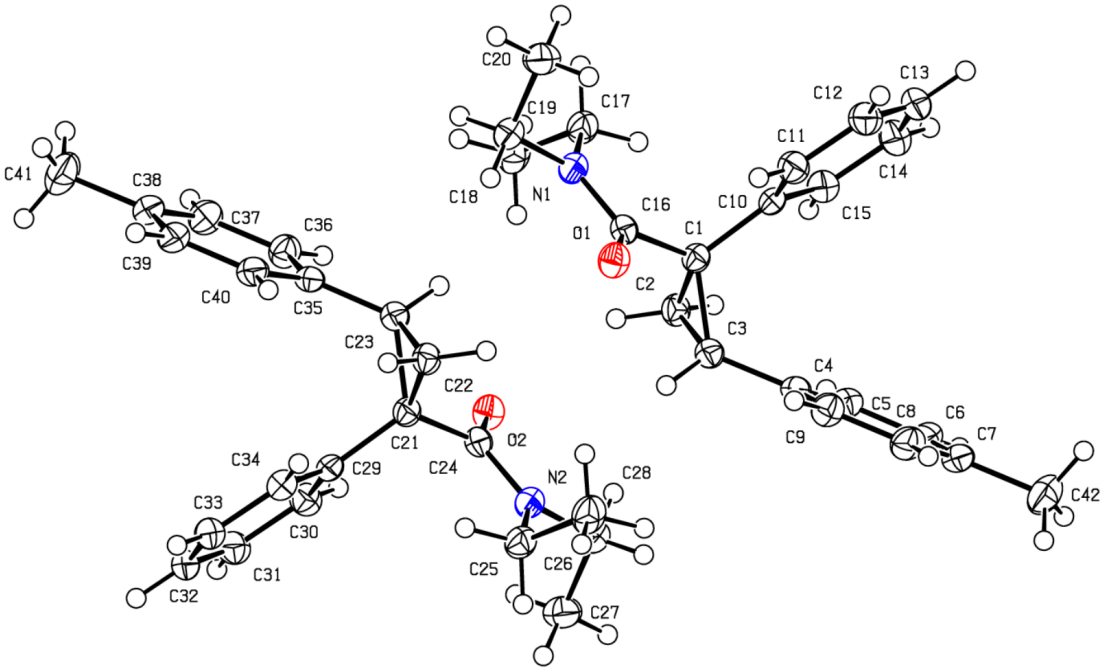
Hydrogen atom coordinates (Å×10^4) and isotropic displacement parameters (Å^2×10^3) for **3.3aaa**.

Atom	*x*	*y*	*z*	U(eq)
H008	1259.16	2716.57	4472.25	26
H00J	-61.29	1319.4	4771.16	32
H00L	1669.89	-6.74	4569.14	36
H00K	4759.29	79.41	4072.1	38
H00I	6085.42	1474.29	3756.58	31
H009	9771.12	1891.74	2882.28	26
H00E	11358.35	572.93	2526.61	29
H00C	11209.32	79.91	1148.37	29
H00B	9433.6	905.17	133.85	29
H00F	7863.67	2236.52	487.06	27
H007	1896.2	3849.9	3701.55	26
H00A	3472.15	2438.66	2518.35	27
H00D	4439.17	2317.53	1666.33	27
H00G	3238.29	5234.78	3112.24	31
H00H	5158.89	4698.46	2962.59	31
H00M	3858.42	3826.39	4967.34	30
H00N	5616.38	4351.49	4521.19	30
H00O	8723.73	3488.87	2232.21	28
H00P	7227.59	3406	1458.32	28
H00Q	2195.99	4793.7	1819.45	35
H00R	2471.78	3476.31	1238.45	34

A-6. Xray data for 4.5b

Figure A 7

ORTEP drawing of **4.5b** showing atom numbering labels and 50% probability amplitude displacement ellipsoids



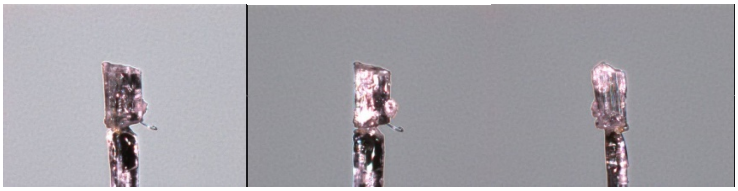


Table A 25

Crystal data and structure refinement for **4.5b**

Identification code	ANNA_YPM3016_5
Empirical formula	$C_{21}H_{25}NO$
Formula weight	307.42
Temperature/K	100.01(11)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	15.8590(3)
b/Å	6.64782(8)
c/Å	33.9589(4)
α/°	90
β/°	99.8838(14)
γ/°	90
Volume/Å^3	3527.08(9)
Z	8
ρ_{calc}g/cm^3	1.158
μ/mm^{-1}	0.540
F(000)	1328.0
Crystal size/mm^3	0.292 × 0.189 × 0.142
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.916 to 152.502
Index ranges	-19 ≤ h ≤ 19, -8 ≤ k ≤ 5, -42 ≤ l ≤ 42
Reflections collected	37411
Independent reflections	7330 [R_{int} = 0.0511, R_{sigma} = 0.0279]
Data/restraints/parameters	7330/0/397
Goodness-of-fit on F^2	1.020
Final R indexes [I>=2σ (I)]	R_1 = 0.0485, wR_2 = 0.1299
Final R indexes [all data]	R_1 = 0.0543, wR_2 = 0.1364
Largest diff. peak/hole / e Å^{-3}	0.48/-0.25

Table A 26

Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **4.5b**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O2	5010.8(6)	3429.9(14)	3514.1(3)	27.8(2)
O1	7453.2(6)	7306.3(14)	3988.1(3)	28.3(2)
N1	7697.8(7)	5557.3(17)	3447.3(3)	26.0(2)
N2	4785.3(7)	5203.9(17)	4054.3(3)	25.4(2)
C4	7314.9(8)	2846(2)	4780.6(4)	23.1(3)
C29	3859.2(4)	7525.1(12)	3253.5(2)	22.3(3)
C34	3583.6(5)	9513.2(10)	3231.9(2)	26.0(3)
C33	2742.8(5)	9969.5(10)	3064.9(3)	30.2(3)
C32	2177.6(4)	8437.9(13)	2919.5(3)	30.5(3)
C31	2453.2(5)	6449.8(11)	2941.1(3)	31.5(3)
C30	3294.0(5)	5993.4(9)	3108.1(3)	28.1(3)
C24	4873.3(7)	5059.8(19)	3665.5(4)	22.8(3)
C35	5186.8(8)	7752(2)	2713.6(4)	23.1(3)
C23	5445.8(8)	7132.4(19)	3137.9(4)	23.1(3)
C10	8630.3(4)	3243.3(12)	4240.9(2)	23.1(3)
C15	8909.6(5)	1260.2(11)	4281.0(3)	29.7(3)
C14	9753.0(5)	837.5(10)	4449.3(3)	36.6(3)
C13	10317.1(4)	2397.9(14)	4577.4(3)	36.1(3)
C12	10037.8(5)	4381.0(12)	4537.3(3)	33.1(3)
C11	9194.4(5)	4803.7(10)	4369.0(3)	28.6(3)
C16	7601.9(7)	5688(2)	3835.4(4)	23.0(3)
C3	7047.0(8)	3551.8(19)	4361.0(4)	23.3(3)
C1	7704.3(8)	3773.9(19)	4081.9(4)	22.2(3)
C7	7826.8(8)	1694(2)	5587.3(4)	28.3(3)
C5	7366.9(8)	828(2)	4888.5(4)	26.6(3)
C21	4782.2(8)	6961.5(19)	3415.3(3)	22.2(3)
C2	7007.3(8)	2202(2)	4002.8(4)	25.0(3)
C38	4666.8(8)	8702(2)	1897.0(4)	29.7(3)
C40	5036.6(8)	9739(2)	2591.3(4)	26.2(3)
C22	5482.3(8)	8525(2)	3489.2(4)	24.0(3)
C37	4817.8(9)	6722(2)	2019.5(4)	31.6(3)
C9	7525.6(9)	4280(2)	5081.2(4)	28.6(3)
C36	5075.5(9)	6251(2)	2421.0(4)	28.7(3)
C8	7781.5(9)	3712(2)	5477.6(4)	31.0(3)

C39	4779.7(8)	10193(2)	2188.1(4)	28.8(3)
C17	7892.4(9)	3702(2)	3247.8(4)	29.2(3)
C26	4798.0(9)	3345(2)	4288.8(4)	28.8(3)
C6	7615.7(9)	275(2)	5287.3(4)	28.7(3)
C25	4600.3(9)	7071(2)	4252.4(4)	29.2(3)
C19	7688.9(9)	7429(2)	3216.2(4)	29.4(3)
C28	5373.2(10)	7832(2)	4544.9(4)	34.8(3)
C18	7126.7(10)	2932(2)	2950.7(4)	34.9(3)
C20	8582.1(9)	8301(2)	3242.9(5)	35.1(3)
C27	3907.5(9)	2470(2)	4265.1(5)	34.4(3)
C42	8102.5(11)	1063(3)	6016.5(4)	39.8(4)
C41	4382.2(12)	9209(3)	1461.5(4)	44.0(4)

Table A 27

Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **4.5b**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O2	32.0(5)	25.0(5)	25.7(4)	-1.2(4)	2.8(4)	0.9(4)
O1	32.8(5)	26.0(5)	25.2(4)	-1.4(4)	2.6(4)	1.1(4)
N1	27.9(5)	28.5(6)	21.9(5)	2.6(4)	4.8(4)	2.4(4)
N2	27.0(5)	27.3(6)	22.0(5)	1.9(4)	4.6(4)	1.4(4)
C4	19.3(5)	28.9(6)	22.1(6)	-0.5(5)	6.3(4)	0.1(5)
C29	22.0(6)	29.9(6)	15.3(5)	-0.1(5)	4.3(4)	0.8(5)
C34	27.3(6)	28.5(6)	22.4(6)	2.3(5)	5.2(5)	0.2(5)
C33	27.9(7)	34.2(7)	29.5(6)	8.0(6)	7.5(5)	7.0(6)
C32	22.3(6)	46.4(8)	22.2(6)	5.0(6)	2.9(5)	4.5(6)
C31	25.2(6)	41.8(8)	26.6(6)	-5.1(6)	2.1(5)	-3.6(6)
C30	26.8(6)	30.0(7)	26.9(6)	-3.2(5)	3.0(5)	1.0(5)
C24	19.6(5)	26.0(6)	21.8(6)	-0.3(5)	0.9(4)	-0.7(5)
C35	18.9(5)	29.3(6)	21.9(6)	-0.2(5)	6.1(4)	0.4(5)
C23	21.5(6)	25.5(6)	22.2(6)	-0.1(5)	3.2(4)	0.4(5)
C10	23.0(6)	31.8(7)	14.8(5)	0.7(5)	4.3(4)	2.5(5)
C15	27.6(6)	32.4(7)	29.3(7)	3.6(5)	5.6(5)	1.9(5)
C14	30.7(7)	40.0(8)	39.2(8)	10.5(6)	6.2(6)	10.1(6)
C13	23.1(6)	57.4(10)	27.0(7)	5.5(6)	2.2(5)	6.5(6)
C12	25.8(6)	47.3(8)	25.3(6)	-5.1(6)	2.2(5)	-3.3(6)
C11	26.7(6)	34.5(7)	24.1(6)	-3.0(5)	2.9(5)	1.9(5)
C16	18.7(5)	27.6(6)	21.8(6)	0.0(5)	0.9(4)	-0.1(5)
C3	21.9(6)	25.3(6)	22.6(6)	-0.4(5)	3.3(4)	0.3(5)
C1	23.2(6)	24.5(6)	18.8(5)	-0.7(5)	2.8(4)	0.6(5)
C7	25.9(6)	37.1(7)	23.2(6)	1.5(5)	8.0(5)	-0.9(5)
C5	27.8(6)	28.0(7)	24.9(6)	-1.9(5)	6.9(5)	-2.3(5)
C21	22.9(6)	24.8(6)	18.4(5)	-1.5(5)	2.2(4)	0.5(5)
C2	24.5(6)	27.6(6)	21.6(6)	-1.2(5)	0.3(5)	-0.3(5)
C38	26.8(6)	40.4(8)	22.9(6)	2.9(5)	7.0(5)	1.2(6)
C40	25.5(6)	29.0(7)	25.1(6)	-0.5(5)	7.2(5)	0.1(5)
C22	23.7(6)	25.5(6)	21.6(6)	-0.8(5)	0.8(4)	-1.1(5)
C37	34.7(7)	35.5(7)	24.6(6)	-4.9(5)	5.3(5)	0.8(6)
C9	31.5(7)	27.3(7)	27.0(6)	-1.3(5)	5.2(5)	0.7(5)
C36	31.2(7)	28.5(7)	26.2(6)	-0.4(5)	4.7(5)	1.5(5)
C8	33.2(7)	35.5(7)	24.5(6)	-5.6(5)	5.8(5)	-1.9(6)

C39	28.5(6)	31.2(7)	28.0(7)	5.8(5)	8.3(5)	0.9(5)
C17	32.7(7)	32.8(7)	22.3(6)	-0.7(5)	5.6(5)	5.8(6)
C26	30.6(7)	31.2(7)	25.4(6)	5.5(5)	6.7(5)	1.7(5)
C6	31.0(7)	30.3(7)	26.3(6)	3.7(5)	8.8(5)	-0.8(5)
C25	32.5(7)	33.4(7)	22.3(6)	-0.7(5)	6.1(5)	4.1(6)
C19	30.6(7)	33.3(7)	25.0(6)	5.9(5)	6.4(5)	2.8(5)
C28	40.9(8)	38.6(8)	23.6(6)	-5.0(6)	2.0(6)	0.8(6)
C18	42.8(8)	37.3(8)	23.2(6)	-2.9(6)	1.3(6)	4.4(6)
C20	32.4(7)	38.2(8)	37.2(7)	4.4(6)	12.8(6)	1.4(6)
C27	33.6(7)	34.0(7)	38.2(8)	2.4(6)	13.7(6)	-0.3(6)
C42	48.4(9)	46.3(9)	24.1(7)	3.8(6)	5.0(6)	-3.7(7)
C41	56.1(10)	51.6(10)	23.7(7)	4.4(7)	4.8(6)	2.8(8)

Table A 28

Bond Lengths for **4.5b**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O2	C24	1.2345(16)	C10	C11	1.3900
O1	C16	1.2341(16)	C10	C1	1.5167(13)
N1	C16	1.3551(16)	C15	C14	1.3900
N1	C17	1.4656(17)	C14	C13	1.3900
N1	C19	1.4700(17)	C13	C12	1.3900
N2	C24	1.3549(16)	C12	C11	1.3900
N2	C26	1.4682(17)	C16	C1	1.5166(17)
N2	C25	1.4651(17)	C3	C1	1.5316(16)
C4	C3	1.4911(17)	C3	C2	1.5039(17)
C4	C5	1.3897(19)	C1	C2	1.5111(17)
C4	C9	1.3948(18)	C7	C8	1.391(2)
C29	C34	1.3900	C7	C6	1.386(2)
C29	C30	1.3900	C7	C42	1.5076(19)
C29	C21	1.5195(13)	C5	C6	1.3934(18)
C34	C33	1.3900	C21	C22	1.5102(17)
C33	C32	1.3900	C38	C37	1.389(2)
C32	C31	1.3900	C38	C39	1.390(2)
C31	C30	1.3900	C38	C41	1.5084(19)
C24	C21	1.5162(17)	C40	C39	1.3932(18)
C35	C23	1.4870(17)	C37	C36	1.3903(19)
C35	C40	1.3929(19)	C9	C8	1.3902(19)
C35	C36	1.3979(18)	C17	C18	1.5277(19)
C23	C21	1.5322(16)	C26	C27	1.5168(19)
C23	C22	1.5034(17)	C25	C28	1.5256(19)
C10	C15	1.3900	C19	C20	1.5188(19)

Table A 29

Bond Angles for **4.5b**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C16	N1	C17	124.85(11)	N1	C16	C1	117.62(11)
C16	N1	C19	118.19(11)	C4	C3	C1	120.61(10)
C17	N1	C19	116.69(10)	C4	C3	C2	123.42(11)
C24	N2	C26	118.36(11)	C2	C3	C1	59.70(8)
C24	N2	C25	124.73(11)	C10	C1	C3	118.53(9)
C25	N2	C26	116.68(10)	C16	C1	C10	113.39(9)
C5	C4	C3	123.37(12)	C16	C1	C3	113.75(10)
C5	C4	C9	118.11(12)	C2	C1	C10	122.45(10)
C9	C4	C3	118.52(12)	C2	C1	C16	118.44(10)
C34	C29	C30	120.0	C2	C1	C3	59.24(8)
C34	C29	C21	121.89(7)	C8	C7	C42	121.36(13)
C30	C29	C21	118.05(7)	C6	C7	C8	117.68(12)
C33	C34	C29	120.0	C6	C7	C42	120.97(13)
C32	C33	C34	120.0	C4	C5	C6	120.32(13)
C31	C32	C33	120.0	C29	C21	C23	118.69(9)
C32	C31	C30	120.0	C24	C21	C29	113.67(9)
C31	C30	C29	120.0	C24	C21	C23	113.38(10)
O2	C24	N2	121.52(12)	C22	C21	C29	121.70(10)
O2	C24	C21	120.35(11)	C22	C21	C24	118.96(10)
N2	C24	C21	118.12(11)	C22	C21	C23	59.22(8)
C40	C35	C23	123.78(12)	C3	C2	C1	61.06(8)
C40	C35	C36	118.08(12)	C37	C38	C39	117.95(12)
C36	C35	C23	118.13(12)	C37	C38	C41	120.83(14)
C35	C23	C21	120.77(10)	C39	C38	C41	121.22(14)
C35	C23	C22	124.40(11)	C35	C40	C39	120.33(13)
C22	C23	C21	59.66(8)	C23	C22	C21	61.12(8)
C15	C10	C11	120.0	C38	C37	C36	120.92(13)
C15	C10	C1	121.89(7)	C8	C9	C4	121.09(13)
C11	C10	C1	118.01(7)	C37	C36	C35	121.08(13)
C14	C15	C10	120.0	C9	C8	C7	120.98(13)
C15	C14	C13	120.0	C38	C39	C40	121.63(13)
C14	C13	C12	120.0	N1	C17	C18	112.37(11)
C11	C12	C13	120.0	N2	C26	C27	111.61(11)
C12	C11	C10	120.0	C7	C6	C5	121.82(13)
O1	C16	N1	121.73(12)	N2	C25	C28	112.22(11)
O1	C16	C1	120.64(11)	N1	C19	C20	111.60(11)

Table A 30

Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **4.5b**.

Atom	*x*	*y*	*z*	U(eq)
H34	3969.89	10560.02	3331.29	31
H33	2554.45	11328.29	3050.15	36
H32	1602.97	8749.79	2805.37	37
H31	2066.94	5403.01	2841.72	38
H30	3482.38	4634.7	3122.86	34
H23	5889.9	6049.55	3178.54	28
H15	8524.08	193.67	4193.44	36
H14	9943.9	-517.93	4476.67	44
H13	10893.53	2108.97	4692.37	43
H12	10423.35	5447.48	4624.85	40
H11	9003.53	6159.12	4341.61	34
H3	6600.15	4628.65	4329.13	28
H5	7232.13	-180.55	4689.34	32
H2A	6537.28	2427.42	3774.63	30
H2B	7175.26	777.52	4051.01	30
H40	5109.65	10788.99	2783.86	31
H22A	5318.32	9947.53	3433.77	29
H22B	5948.57	8319.12	3719.84	29
H37	4743.98	5674.9	1826.23	38
H9	7493.72	5668.53	5013.83	34
H36	5177.7	4886.04	2497.73	34
H8	7927.67	4716.65	5676.55	37
H39	4679.25	11556.8	2110.15	35
H17A	8072.71	2652.71	3451.89	35
H17B	8376.28	3951.95	3104.86	35
H26A	5041.86	3632.2	4571.49	35
H26B	5171.24	2345.15	4187.7	35
H6	7641.51	-1112.04	5355.6	34
H25A	4119.68	6835.95	4398.24	35
H25B	4419.44	8115.41	4047.57	35
H19A	7316.19	8425.88	3318.67	35
H19B	7446.37	7156.5	2932.82	35
H28A	5840.32	8139.8	4399.4	52
H28B	5560.39	6794.51	4745.93	52
H28C	5215.5	9051.58	4677.32	52

H18A	6951.02	3956.64	2745.6	52
H18B	6650.58	2647.16	3092.01	52
H18C	7287.2	1697.94	2824.03	52
H20A	8555.64	9519.93	3078.77	53
H20B	8954.67	7309.88	3145.4	53
H20C	8812.15	8637.37	3521.6	53
H27A	3674.87	2127.03	3986.98	52
H27B	3535.2	3461.6	4362.7	52
H27C	3937.06	1254.71	4430.34	52
H42A	8725.75	1182.57	6089.15	60
H42B	7932.73	-336.35	6049.07	60
H42C	7828.25	1932.98	6190.42	60
H41A	4632.26	8244.1	1296.12	66
H41B	4572.84	10570.33	1409.51	66
H41C	3756.46	9140.75	1395.95	66

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