Strain-Release Activation of α,β-Unsaturated Amides Towards Conjugate Addition of N, O and S – Nucleophiles

BY

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Strain-Release Activation of α,β-Unsaturated Amides Towards Conjugate Addition of N, O and S – Nucleophiles

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Abstract

This thesis encompasses a novel methodology enabling the diastereoselective addition of heteroatom-centered nucleophiles to the conjugated double bond of *in situ*-generated α,β – unsaturated cyclopropenyl amides. The methodology is presented as a means of activating the relatively poorly electrophilic double bond of conjugated amides via release of the ring strain which is inherent to cyclopropenes. Through strain-release activation it was demonstrated that oxygen, sulfur and nitrogen-centered nucleophilic adducts of cyclopropylcarboxamides can be efficiently synthesized. The thesis is divided into three chapters which discuss not only the development and elaboration of our chemistry, but also other methods of activating α,β – unsaturated amides and why our method will benefit the synthetic community.

Chapter one is a review of activation methods which are commonly employed to facilitate nucleophilic addition to α,β – unsaturated amides. The utility of directly functionalizing conjugated amides through nucleophilic addition is discussed, as well as why activation is necessary. The discussion is organized as a comparison of the reactivity of unactivated systems to that of activated systems; meanwhile providing an overview of what the synthetic community has done to develop this area of chemistry.

Chapter two focuses on the development of the strain-release activation method and addresses the problems and solutions associated with using inherently unstable cyclopropenes. Elaboration of the methodology to include addition of alkoxide, phenoxide and thiolate nucleophiles, both inter- and intramolecularly, to *in situ* generated, conjugated cyclopropenylcarboxamides is then presented and discussed. Chapter three follows up with discussion of the benefits of nitrogen-centered nucleophilic addition and the challenges we faced

Abstract (Continued)

in accomplishing this task. Utilization of anilines, carboxamides and sulfonamides as nucleophilic amine-surrogates are presented as a viable means facilitating the addition of nitrogen-centered nucleophiles to conjugated cyclopropenes, thereby accessing biologically interesting β-aminocyclopropanecarboxylic acid derivatives.

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Chapter 1. Activation methods for conjugate addition to α,β-unsaturated amides.

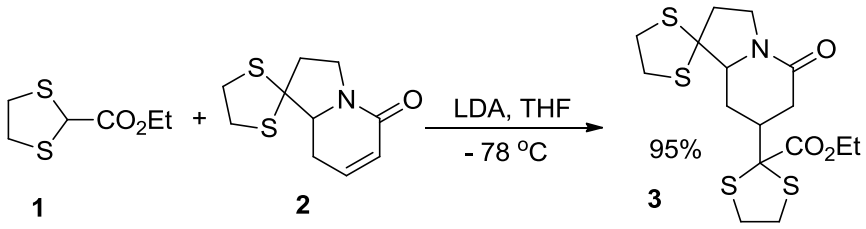
1.1. Introduction

The conjugate addition reaction has been known for over a century and has received vast attention from the synthetic community.[1a,2] The overwhelming majority of publications on the subject have focused on nucleophilic addition to α,β-unsaturated aldehyde, ketone and ester derivatives. Early in the 20th century, it was demonstrated that α,β-unsaturated amides could also undergo conjugate addition[1b-d], however, it was quickly recognized that this class of molecule suffers from poor electrophilicity as compared to analogous aldehydes, ketones or esters.[3,4] Despite having relatively poor reactivity, conjugate addition to unsaturated amides has received a great deal of attention over the past several decades, granting synthetic access to a number of valuable products including alkaloids, [5] polyamines,[6] β-peptides[7] and biologically interesting heterocycles.[8] Efforts leading to this development will be discussed in this review, which is organized into three sections based on the class of nucleophile; with each section being subdivided into two groups: unactivated amides, and activated amides.

1.2. Carbon nucleophiles and unactivated systems

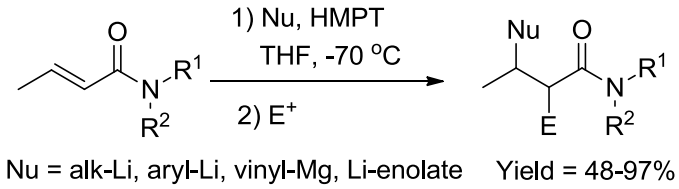
Many classes of carbon-based nucleophiles have been demonstrated as viable candidates for addition to α,β–unsaturated amides which have no activating groups. For example in 1973, Schlessinger demonstrated that the enolate anion generated from **1** is a viable nucleophile for conjugate addition to lactam **2**, *en route* to the total synthesis of vincamine (**Scheme 1**).[9]

Scheme 1



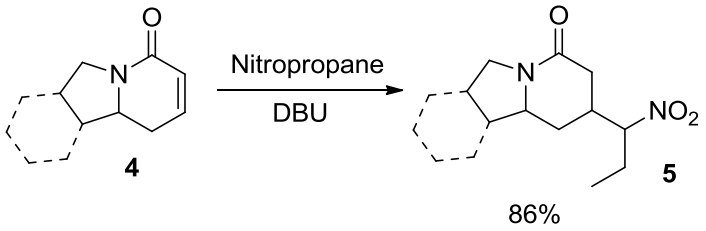
Interestingly, it was found that when a sterically hindered acyclic version of thioacetal **1**, bearing S-ethyl substituents, was employed under similar conditions; the reaction did not occur. In 1980, Baldwin demonstrated that alkyl and phenyl lithium reagents could be added to secondary amides, in a 1,4-fashion.[10] Concurrently Snieckus published that alkyl and aryl Grignards, alkyl, aryl and vinyl lithium reagents as well as cyclic and acyclic lithium enolates can be successfully added in a 1,4 fashion to unsaturated tertiary amides. He further demonstrated that many of the anionic conjugate addition intermediates can be trapped with carbon-based electrophiles (**Scheme 2**). [11]

Scheme 2



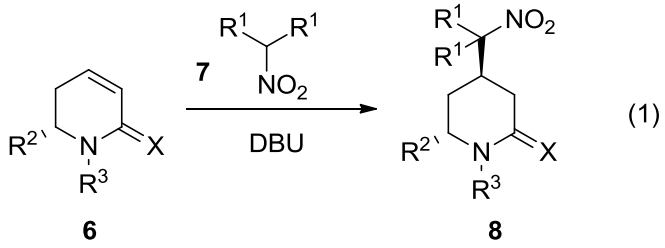
Nitroalkanes also react with unactivated amides as carbon nucleophiles. It was demonstrated that bicyclic lactam **4** in the presence of DBU and nitropropane as solvent, readily forms 1,4-adduct **5** (**Scheme 3**).[5]

Scheme 3



It is noteworthy that in the case of sterically demanding substrates such as substituted lactam **6** (Table 1, eq 1, entry 1) bearing a butyl group at the δ-position, reaction with nitromethane in the presence of DBU results in poor yields. [12] Steric factors play a defining role in this reaction as evidenced by the fact that the only nitroalkane adducts that were formed, were products of relatively unhindered nitromethane (entry 1) in contrast to nitropropane (entry 3) where only trace ammounts of products were observed. Also the substituents on unsaturated lactam **6** play a pivotal role. The best yields were obtained when the δ-substituent was hydrogen (entry 7), in which case, a more bulky nitro-cyclopentane was added in 37% yield. In contrast, the complementary thiolactam **6**, bearing various substituents at the δ-position, was found to be more reactive and accepts a variety of different alkyl-nitro nucleophiles under identical conditions to form thiolactam derivatives **8** in excellent yields (Table 1, entries 2, 4, 6 and 8).

Table 1

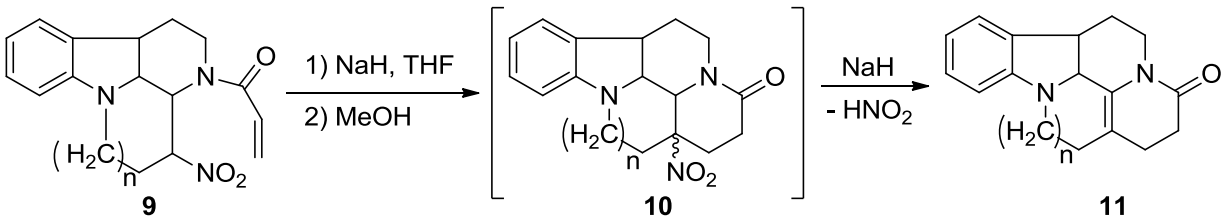


(1)

Entry	X	R^1	R^3	R^2	yield (%)	dr
1	O	H	H	*n*-Bu	17	-
2	S	H	H	*n*-Bu	88	>99:1
3	O	Me	H	*n*-Bu	trace	-
4	S	Me	H	*n*-Bu	88	>99:1
5	O	Me	Bn	Allyl	trace	-
6	S	Me	Bn	Allyl	90	>99:1
7	O	$(CH_2)_5$	Ph	H	37	na
8	S	$(CH_2)_5$	Ph	H	72	na

One other example of 1,4-addition of nitroalkanes to an unsaturated lactam was published in 2006 and demonstrates the viability of an intramolecular approach (Scheme 4).[13] It was demonstrated that pentacyclic lactam **11** can be synthesized through 6-endo-trig cyclization of unsaturated amide **9**.

Scheme 4



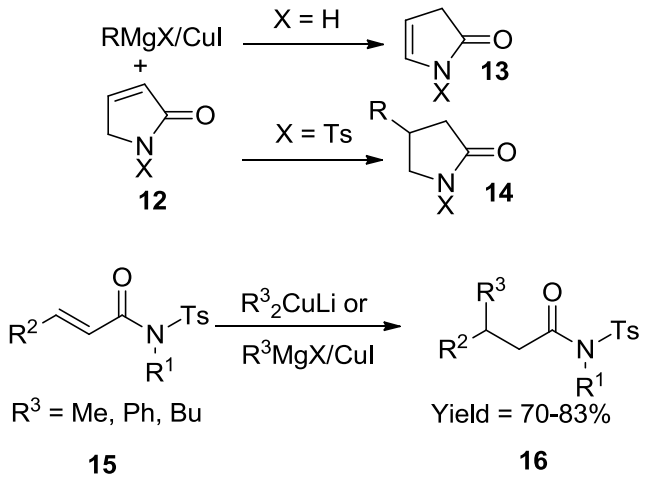
With the exception of the above examples (Scheme 3) which gave only poor yields of nitroalkane adducts, nitroalkane-substituted amides, synthesized by intermolecular nucleophilic addition, are formed by addition to the more reactive thiolactam followed by subsequent transformation into lactams.[4]

1.3. Carbon nucleophiles and activated systems

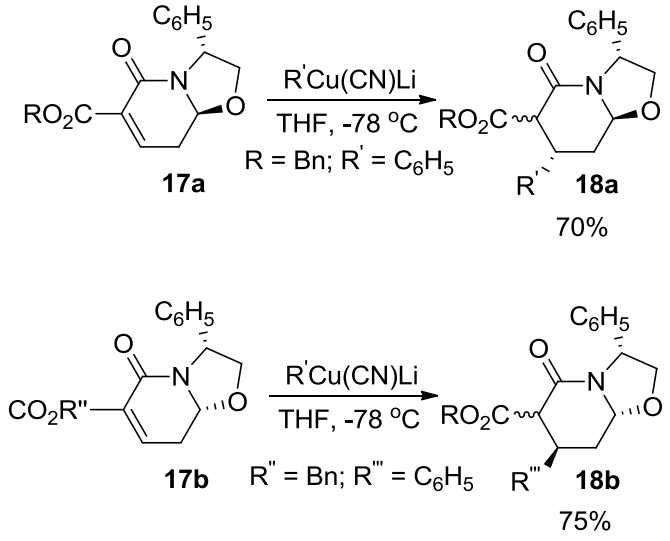
While Grignard, organolithium and stabilized enolate-type reagents are viable nucleophiles for unactivated systems, organocuprates are not well tolerated.[10,11] These less reactive nucleophiles necessitate activation of the olefin by various methods. It was shown that the addition of a tosyl group to the amide nitrogen of lactam **12** can enhance selectivity towards conjugate addition and grant access to products like β-substituted lactam **14**. The tosyl-group effectively diminishes the electron donating ability of the nitrogen, and subsequently enhances the electrophilicity of the conjugated olefin; enabling weaker nucleophiles to add.

In the absence of this activating substituent, deprotonation of the γ-carbon is favored and β,γ-unsaturated lactam **13** is formed (Scheme 5).[14] This activation-method was also demonstrated to work on acyclic systems allowing access to amides **16**.

Scheme 5



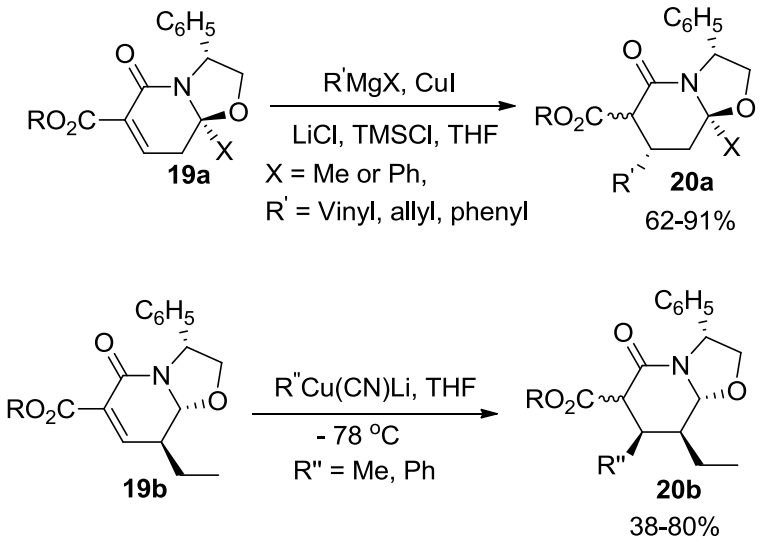
Scheme 6



In the case of five and six membered-lactams bearing a tertiary nitrogen, it was found that substitution of the α-carbon with an alkoxycarbonyl group activates the molecule towards addition of organocuprates.[15,16] Bosch and coworkers have shown that an ester substituent on the α–carbon activates bicyclic α,β-unsaturated amides **17** towards addition of alkyl and aryl-

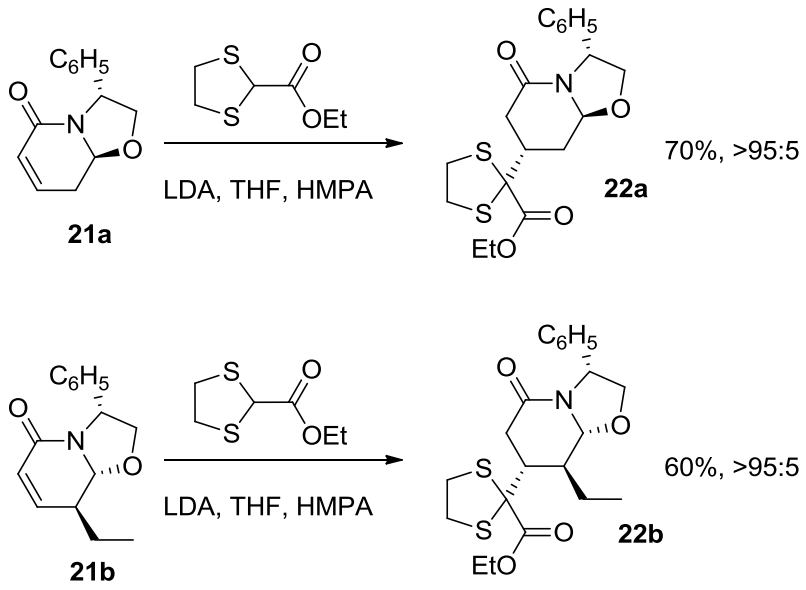
cuprates (Scheme 6). It was established that the angular position of the C-O bond at the δ-position determines the facial selectivity of the incoming nucleophile.

Scheme 7



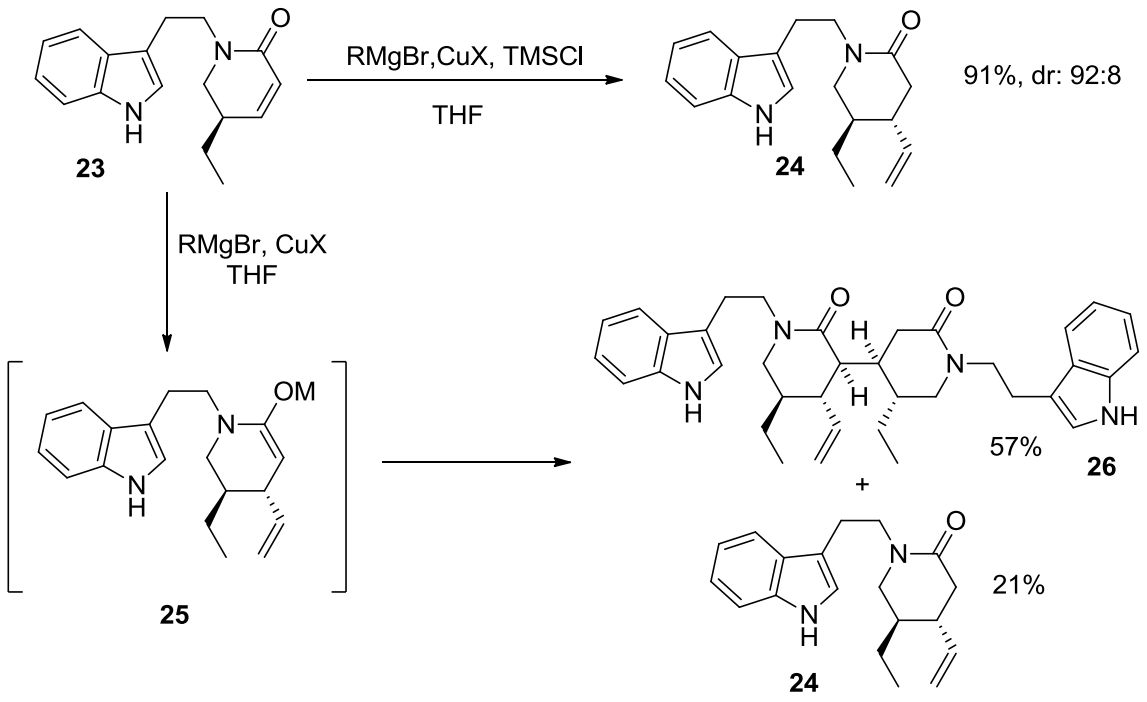
Utilizing a similar α-carbon activated system, investigations into the effects of γ and δ substituents on the lactam ring on the facial selectivity of cuprate addition were conducted (Scheme 7)[17,18,19,20] and it was determined that neither γ-(**19b**)[21] nor δ-(**19a**) substituents influence facial selectivity under kinetic control.

Scheme 8



Under thermodynamic control however (Scheme 8),[22,6] a stabilized enolate could be added to either isomer of **21** and it was found that the γ-substituent could influence the stereochemical outcome of the reaction. It is thought that enolate addition is reversible and in the case of **21b** the ethyl group likely forces the appended ester into a cis configuration with respect to the δ-CO bond as a result of thermodynamic equilibration.

Scheme 9

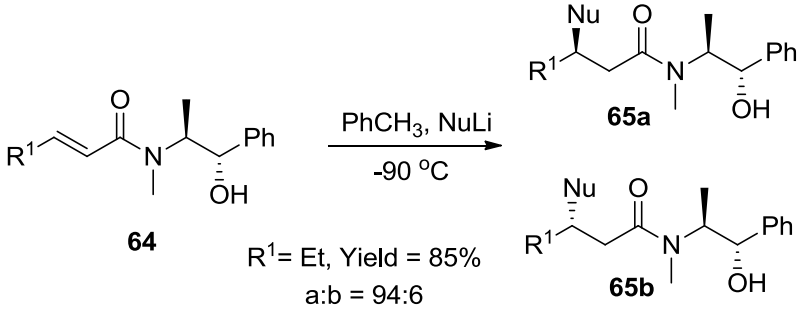


Aside from olefin isomerization, adding organocuprates to unsaturated lactams can have other chemoselectivity issues.[23,24,25] It was that demonstrated chemoselectivity can be enhanced by the addition of TMSCl, which traps the enolate ion until acidic workup, thereby affording vinyl adduct **24** in good yield (Scheme 9). In the absence of TMSCl, lactam **23** undergoes cuprate addition, but also significant dimerization via intermediate **25** reacting with **23** to form mixtures of dimerized adduct **26** as the major product**.** It is likely that TMSCl also enhances the electrophilicity of the double bond through interaction with the carbonyl-oxygen of the unsaturated lactam.

1.4. Nitrogen-centered nucleophiles and unactivated systems

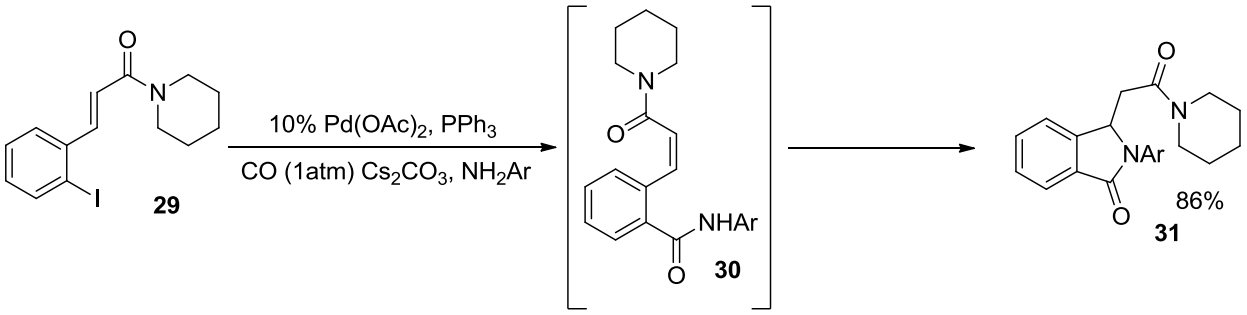
Unactivated α,β-unsaturated amides have been shown to react with several classes of nitrogen-based nucleophiles. Similar to carbon-based nucleophiles, stronger nitrogen-based nucleophiles readily add to unactivated amides while activation is often employed for weaker nucleophiles.

Scheme 10



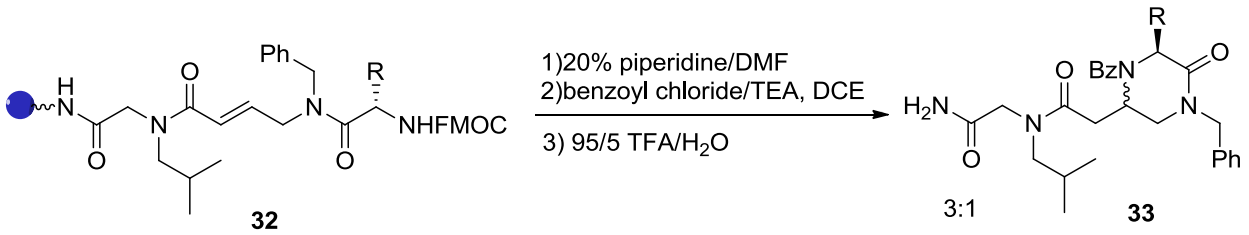
For example, acyclic unsaturated amides can react with secondary lithium amide nucleophiles with good to high yields (Scheme 10).[26,27,28] This example also demonstrates that the chiral auxiliary on **64** can lead to a high degree of enantio-induction.

Scheme 11



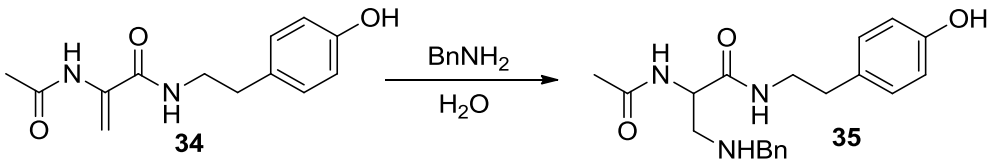
Intramolecular cyclization reactions between amine-derivatives and conjugated amides can also be realized for several substrates.[29,30,31] An intramolecular 5-exo-trig cyclization between weakly nucleophilic amide-derivative **30** and its appended β-carbon has been demonstrated as part of a Heck-Michael cascade reaction (Scheme 11).[30]

Scheme 12



Similarly, Scheme 12 highlights a reaction sequence beginning with removal of the FMOC group from silica-supported amide **32,** initiating 6-exo-trig cyclization, followed by *N*-acylation with benzoyl chloride and subsequent cleavage from the silica support with TFA/H_2O to yield **33** as a 3:1 mixture of diastereomers. HPLC was utilized for determination of diastereomeric ratio and products were isolated by semi-preparative HPLC. However, NMR resonances of **33** were broad and therefore assignments of major/minor diastereomeric products were not reported.[31]

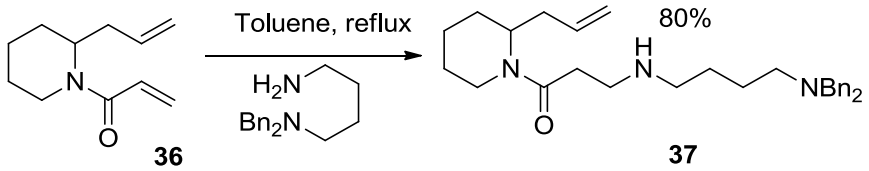
Scheme 13



Dehydroalanine derivatives are an attractive candidates for 1,4-addition despite being notoriously poor Michael acceptors.[32] This is likely due to the deactivation of the β-carbon by

both the amide nitrogen of the conjugated amide, and further deactivation by the amide nitrogen attached to the α-carbon. Despite these drawbacks, several papers have been published showing that through optimization of reaction conditions (solvent, temperature, etc…), several nitrogen-based nucleophiles can be added to this class of molecule. For example, dehydroalanine derivative **34** can accept benzyl amine to yield functionalized alanine **35** (Scheme 13).[33] It should be noted that reactions require protic solvents (water, methanol), have reaction times on the order of days and require a 5-20 fold excess of amine.

Scheme 14



36 **37**

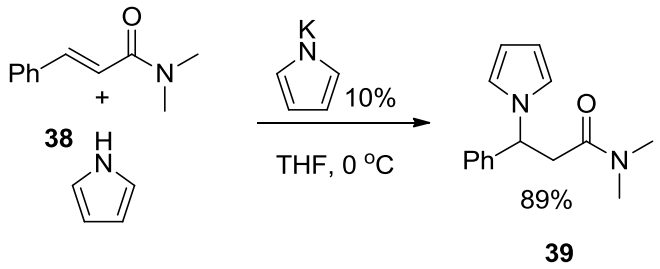
Given the observation that poor Michael acceptors like dehydroalanine can react with amines, it is no surprise that simple α,β-unsaturated amides like **36** can readily react with similar amine substrates (Scheme 14).[34] However, this reaction required refluxing toluene for 32 hours to complete. A similar system used ethanol as a solvent and required 24 hours to achieve a modest 60% yield.[35] Even large aza-crown ethers have been demonstrated to react with unsaturated amides, but require similar reaction times and a large excess of substrate.[36]

1.5. Nitrogen-centered nucleophiles and activated systems

The poor elecrophilicity of α,β-unsaturated amides further manifests itself when less reactive nitrogen nucleophiles are employed. A single example demonstrating addition of

pyrrole was present in the literature (Scheme 15).[37] Although pyrrole adds to **38** in high yield, it takes three days for the reaction to complete, compared to stronger Michael acceptors such as α,β-unsaturated esters and nitriles which take only 18 hours to achieve comparable yields under

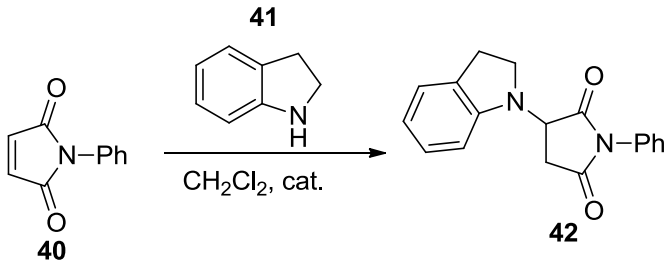
Scheme 15



identical reaction conditions. However, using various modes of activation, the addition of several amine derivatives, including aromatic amines, can be achieved for a variety of substrates under comparatively mild conditions and shorter reaction times.

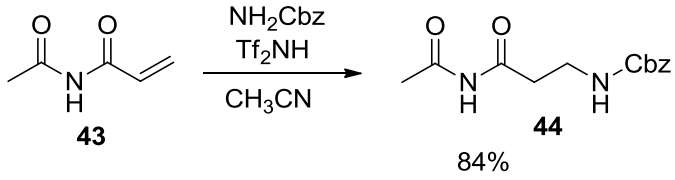
N-acyl activation is a viable approach for promoting the addition of nitrogen-based nucleophiles to unsaturated amides.[38,39,40,41] For example N-phenylmaleimide **40**, which can be viewed as an unsaturated amide with an N-carbonyl activating group, readily accepts aromatic heterocyclic nucleophile **41**; forming succinimide-derivative **42** (Scheme 16).[42]

Scheme 16



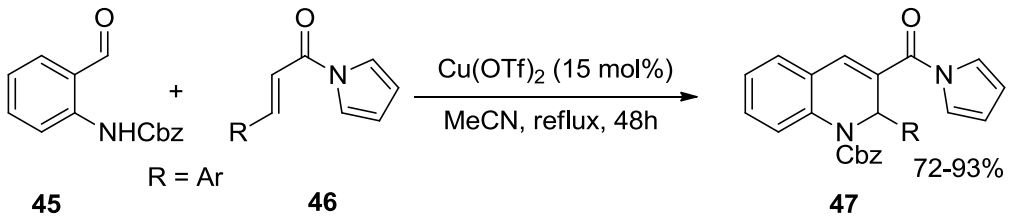
The utility of *N*-carbonyl activation is further showcased in Scheme 17, which illustrates the reaction of weakly nucleophilic Cbz-protected amine with activated amide **43** to yield glycine derivative **44** in good yield.[43]

Scheme 17

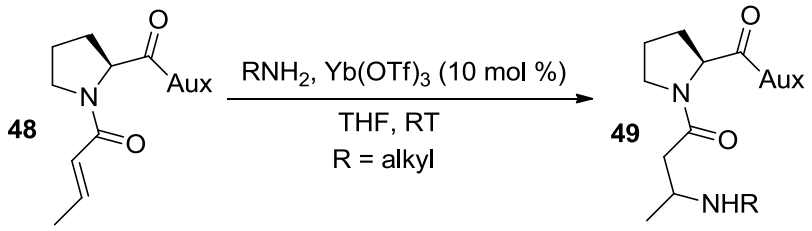


Lewis acids are sufficient activators for nucleophilic addition of weak nitrogen nucleophiles. Utilizing $Cu(OTf)_2$ as a Lewis acid catalyst enables highly deactivated Cbz-protected aromatic amine **45** to react cleanly with amide **46** to form adduct **47** in good to excellent yield (Scheme 18).[44]

Scheme 18



Scheme 19



Similarly, the above system utilizes catalytic ytterbium(III) triflate to enhance the reaction rate[7] of unsaturated amide **48** with alkyl amines. While examples involving unactivated amides (Scheme 13, Scheme 14, Scheme 15) sometimes require days of reaction time, 5-22 fold excess of amine, and/or harsh conditions, this particular case utilizes only a 1:1 ratio of starting materials, is performed in an aprotic solvent and requires only 12 hours to complete at room temperature yielding amine derivative **49** (Scheme 19).

Scheme 20

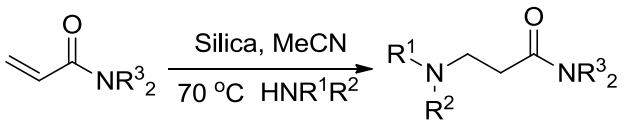


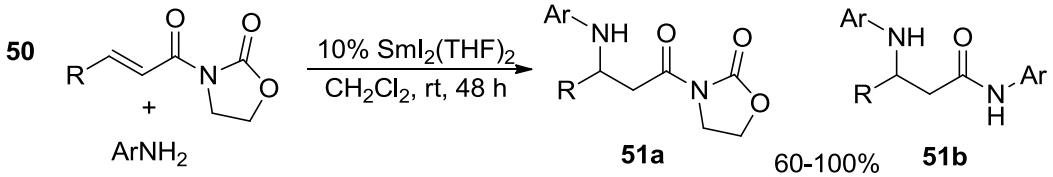
Table 2: Addition of amines to silica-activated unsaturated amides

Entry	R^3	R^1,R^2	Time (h)	yield (%)
1	H	*n*-Bu, H	3	92
2	H	R^1=R^2= CH_2CH_3	5	89
3	H	R^1=R^2= $(CH_2)_5$	5	93
4	H	R^1=R^2= $(CH_2CH_2)_2O$	5	92
5	CH_2CH_3	*n*-Bu, H	5	94
6	CH_2CH_3	R^1=R^2= CH_2CH_3	10	88
7	CH_2CH_3	R^1=R^2= $(CH_2)_5$	10	72
8	CH_2CH_3	R^1=R^2= $(CH_2CH_2)_2O$	10	84
9	CH_2CH_3	Ph, H	24	62

A weak Lewis acid like silica[45] and even alumina[46] can be used to promote amine addition to unsaturated amides (Table 2, entries 1-8) in aprotic MeCN on the timescale of several hours (Scheme 20); even allowing access to an adduct of weakly nucleophilic aniline within a reasonable amount of time and in good yield (Table 2, entry 9).

Collin demonstrated the effectiveness of SmI_2, in conjunction with an N-acyl group, at activating amide **50** towards 1,4-addition of a variety of aromatic amines in good to excellent yields under base-free conditions (Scheme 21).[47]

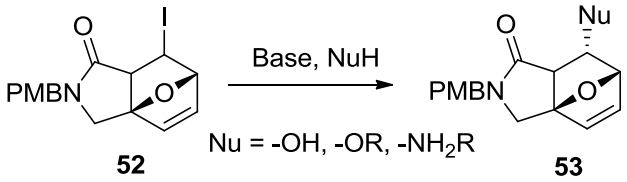
Scheme 21



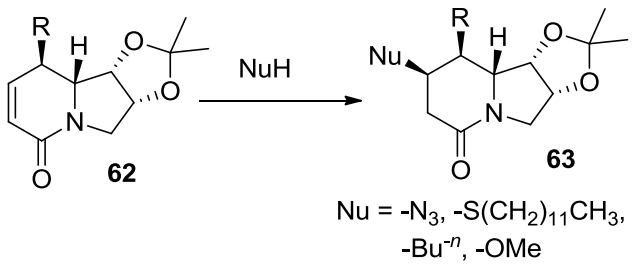
1.6. Oxygen-centered nucleophiles and unactivated systems

The literature provides scarce examples of oxygen-based conjugate addition to unactivated amides. One example demonstrates an elimination-addition pathway to add hydroxyl, alkoxyl and amino substituents to bicyclic amide **52** (Scheme 22).[48]

Scheme 22



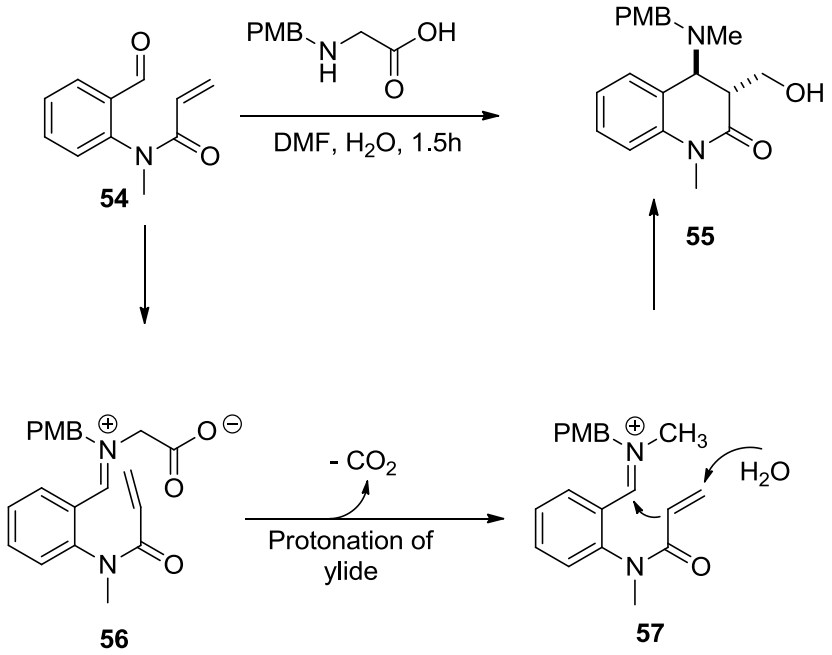
Scheme 23



Paolucci demonstrated that unsaturated lactam **62** is capable of accepting methoxide as a nucleophile without activation (Scheme 23).[49] This paper also demonstrates that azides,[50] as well as sulfur-based nucleophiles can be added to this system. Other similar reports confirm that alkoxides are indeed viable nucleophiles for these unactivated amide systems.[51]

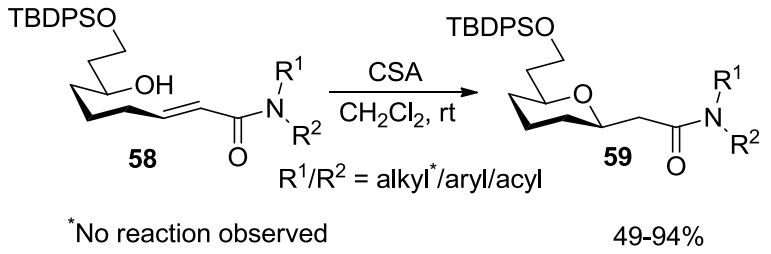
1.7. Oxygen-centered nucleophiles and activated systems

Scheme 24



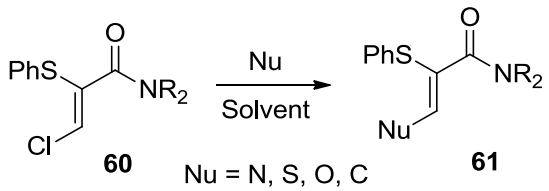
However when activated with an electron-withdrawing group on the amide-nitrogen,[52] oxygen-based nucleophiles add under relatively mild conditions, (Scheme 24).[53] In this example, PMB-protected glycine is added to aldehyde **54** to form iminium-adduct **56** which undergoes decarboxylation to form an azomethine ylide which is protonated in the presence of water to form iminium intermediate **57**. This imminium is in conjugation with the amide nitrogen, activating the olefin towards nucleophilic addition of water. This is the start of a Michael-Mannich cascade which produces product **55** in 90% yield.

Scheme 25



In another example, the amide nitrogen of **58** is substituted with either an aryl or acyl group to allow access to 6-membered cycle **59** under mild conditions (Scheme 25).[8] Note that when amide **58** has an alkyl substituent, no reaction occurs.

Scheme 26



Conjugated olefins can be activated towards nucleophilic addition by electron withdrawing groups on the β-carbon.[54,55,56] Nitrogen, sulfur, oxygen and carbon nucleophiles were successfully added to acrylamide-derivative **60**, accompanied by reformation of the double bond via chlorine elimination, yielding conjugated amide **61** (Scheme 26).[57]

1.8. Conclusions

α,β-unsaturated amides can readily react with carbon and nitrogen-based nucleophiles given that the nucleophile is sufficiently strong or that the reaction conditions are relatively harsh. Through various methods of activation including Lewis acidic catalysis, installation of electron withdrawing groups on the amide nitrogen, or installation of electron withdrawing groups on the α or β position of the appended olefin; the scope of nucleophilic addition to unsaturated amides can be greatly enhanced to encompass weaker organocuprates, deactivated amine-derivatives as well as oxygen-based nucleophiles. Work done in this area has allowed conjugate addition into unsaturated amides to grow into a valuable synthetic tool allowing access to a large number of valuable molecules.

Chapter 2. Strain-Release activation of unsaturated amides and oxygen-centered nucleophiles

2.1. Introduction

An alternative approach to activating α,β-unsaturated amides could be accessed through ring-strain release. It is known that cyclopropene is accompanied by large amounts of strain energy because of the fact that it contains sp^2 bonds which are locked at 60^o bond angles. This has several implications including instability but also that cyclopropene can serve as an effective energy reserve for driving otherwise unfavorable reactions.[58,59] We envisioned utilizing the strain-energy inherent to conjugated cyclopropenyl carboxamides as a means of both activating the amide and accessing a variety of interesting and useful cyclopropanecarboxamide derivatives (Figure 1).

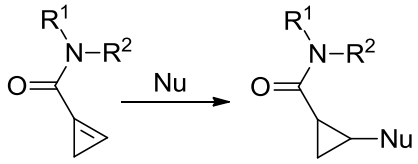


Figure 1: Strain-release activation of unsaturated amides.

Indeed the products of these reactions belong to the general class of molecules called donor-acceptor cyclopropanes (DAC's). DAC's have found widespread application in organic synthesis as equivalents of C3-electrophiles or all-carbon 1,3-dipoles.[60] A number of useful protocols employing DACs have been developed, including various nucleophilic additions,[61] [3 + 2],[62] [3 + 3],[63] and [3 + 4] cycloaddition reactions.[64] Synthesis of DAC's typically proceeds via catalytic cycloropanation of enol ethers with carbenoids generated from diazoacetates[65] or through reacting Fisher carbenes with electron-deficient olefins.[66] In contrast, our approach

enables the direct functionalization of cyclopropene with a variety of donor groups, or nucleophiles.

Direct functionalization of α,β-unsaturated cyclopropenyl carboxamides involves several unique challenges that had to be addressed in order to make this methodology viable. The first and perhaps, biggest challenge, stems from the instability of these highly reactive molecules, which readily decompose via polymerization and ene-reactions.[67] To circumvent the inherent lack of shelf-life, monosubstituted carbonyl-conjugated cyclopropenes have to be generated and used *in situ*.[68] Precedence for this pattern of reactivity has been sporadically observed in the literature, however elaboration of a general methodology has only recently seen development within the past five years by this research group.[67,69]

2.2. *In situ* generation and trapping of cyclopropene with alkoxide nucleophiles

Rubin and coworkers has demonstrated that while cyclopropene **65** can be synthesized, isolated and stored under nitrogen at low temperatures for several months[70a] to even several years; **65** can be used as an electrophile in the addition of oxygen-based nucleophiles, forgoing the isolation step.[70b] This was accomplished via bromocyclopropane **64**, which can undergo dehydrohalogenation in the presence of *t*-BuOK and catalytic 18-crown-6 to form **65** followed by subsequent trapping by base, or by a competing pronucleophile, to form cyclopropanol derivatives **66** (Scheme 27).

Scheme 27

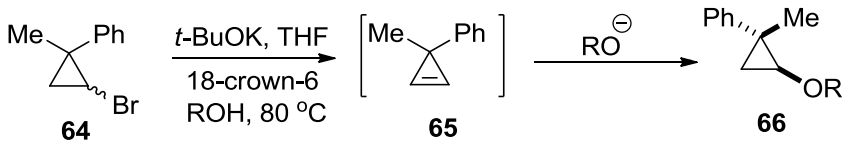


Table 3: Addition of alkoxides to steric controlled system

Entry	No.	R	Yield (%)	dr
1	**66a**	*t*-BuO	93	>25:1
2	**66b**	*i*-PrO	96	18:1
3	**66c**	*n*-PrO	99	16:1
4	**66d**	$PhCH_2O$	75	>25:1
5	**66e**	$Me_2NCH_2CH_2O$	83	11:1

The diastereoselectivity for this particular system is governed by steric factors, allowing nucleophiles to react at the least hindered face of the cyclopropene. It was demonstrated that a variety of functionally diverse (Table 3, entries 4, 5) and sterically demanding (entries 1 and 2) cyclopropanol-derivatives can be synthesized in this fashion, all giving good yields and a high diastereoselectivity.

Similarly, bromocyclopropanes **67** bearing a carboxamide or carboxylate moiety underwent dehydrohalogenation, followed by nucleophilic addition to form cyclopropanol derivatives **69** in good to excellent isolated yields (Scheme 28).[70b]

Scheme 28

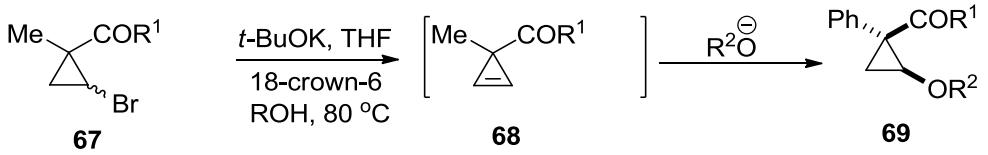


Table 4: Addition of alkoxides to cyclopropenes bearing directing groups

Entry	SM	R^1	R^2	No.	Yield (%)	dr
1	**67a**	NEt_2	*t*-BuO	**69a**	87	20:1
2	**67d**	NHBu-*t*	*t*-BuO	**69g**	92	>25:1
3	**67a**	NEt_2	*n-PrO*	**69b**	94	14:1
4	**67b**	$N(CH_2CH_2)_2$	CH_2=$CH(CH_2)_3O$	**69c**	92	20:1
5	**67c**	OK	*t*-BuO[a]	**69d**	79	>25:1
6	**67c**	OK	*t*-BuO[b]	**69e**	81	>25:1
7	**67c**	OK	*n*-PrO[a]	**69f**	83	>25:1

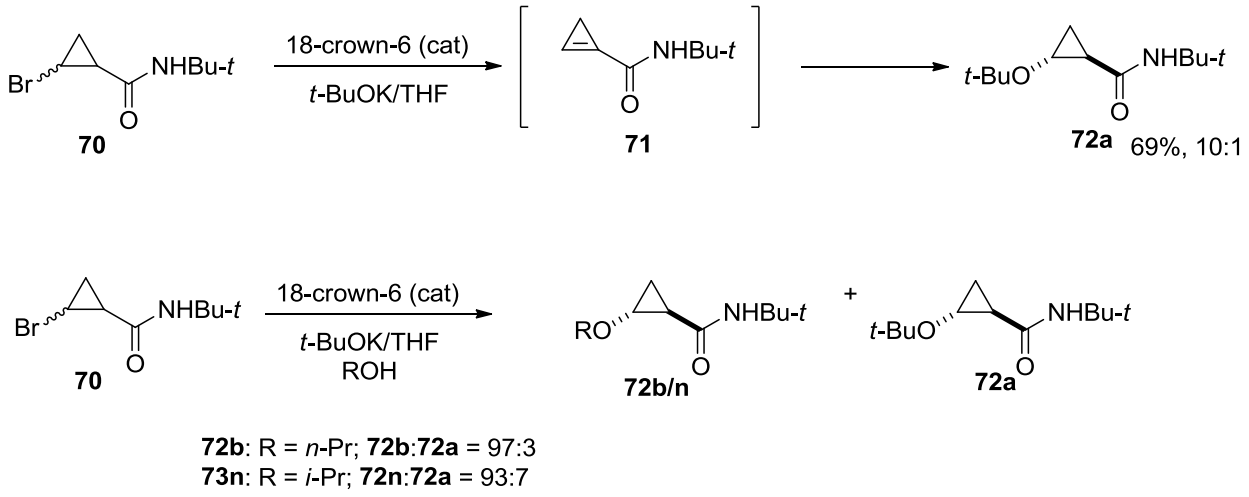
[a] Quenched with MeI prior to isolation. [b] Quenched with allyl bromide prior to isolation.

In this system, diastereoselectivity is controlled by the carbonyl group which coordinates to a potassium ion, thereby directing the negatively charged nucleophile to the carbonyl face of the cyclopropene. It was demonstrated that secondary (Table 4, entry 2) and tertiary amides (entries 1, 3, 5), as well as carboxylate moieties (entries 5-7) are effective directing groups.

Having met success with *in situ* trapping of relatively stable cyclopropene intermediates **65** and **68**, we then set out to apply our methodology to the unstable conjugated cyclopropene

intermediate **71** (Scheme 29).[70,71,72] Lacking any reasonable shelf life, *in situ* generation and trapping of intermediate **71** is not a synthetic shortcut, but is in fact a necessity.[68,69]

Scheme 29



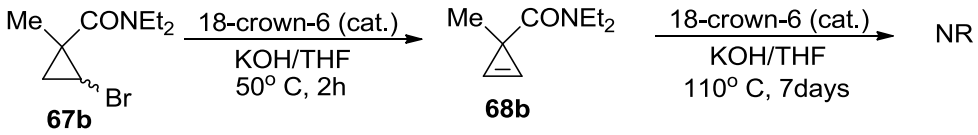
72b: R = *n*-Pr; **72b**:**72a** = 97:3
73n: R = *i*-Pr; **72n**:**72a** = 93:7

Initial experiments demonstrate that bromocyclopropane **70** undergoes 1,2-dehydrobromination in the presence of *t*-BuOK and catalytic 18-crown-6 to form **71**, which is subsequently trapped by base to form *tert*-butyl ether adduct **72** in good yield. Unlike cyclopropene intermediates **68** bearing an amide function and yielding diastereomeric ratios indicitave of directing control, the adduct of cyclopropene **71** yields predominately a *trans*-diastereomer. Given the fact that **71** is flat, achiral and has no possibility for a facially selective nucleophilic attack; the selectivity is thought to arise from a thermodynamically-driven epimerization of the C-H bond in the α-position to the carbonyl group after the addition step has occurred. This was an especially exciting result for several reasons. Not only did it provide a proof of concept that strain release energy could be used to drive nucleophilic addition to an α,β-unsaturated amide, [73] but it also

opened up the possibility for exploiting a new mode of selectivity control in our evolving methodology.

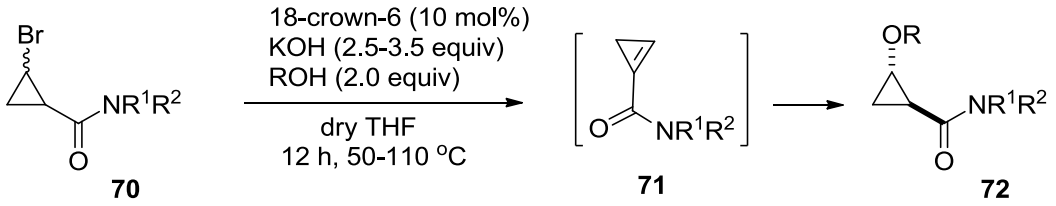
However, the next step involving the implementation of competing pronucleophiles revealed yet another challenge. It was observed that cyclopropene intermediate **71** is so reactive, that ^{t}BuOK can compete with isopropoxide, and even to some extent *n*-propoxide, for the electrophilic β-carbon (Scheme 29). To remedy this, we first had to take into account two observations. First, the fact that the carbonyl group on bromocyclopropane **70** renders the α-CH bond relatively acidic suggests that a potentially weaker base could be utilized for dehydrobromination. Secondly, during optimization of a preparative synthesis of cyclopropene intermediates **68**, it was found that KOH can affect 1,2-elimination and even after prolonged heating at 110 ^{o}C , cyclopropene **68b**[70,72] generated from bromocyclopropane **67b** in the presence of KOH and 18-crown-6, did not show any traces of addition or decomposition (Scheme 30).

Scheme 30



Fortunately, utilization of KOH was indeed a solution which allowed for combining the 1,2-elimination reaction with the addition of an alkoxide, generated *in situ* from an appropriate alcohol pronucleophile, in a sequential chemoselective transformation (Table 5, eq. 2).

Table 5: Addition of alkoxides to conjugated cyclopropenyl carboxamides



no.	R^1, R^2	RO	product	yield, %[b]	dr[c]	dr upgraded[d]
1	*t*-Bu, H (**70a**)	*n*-PrO	**72b**	71	9:1	39:1 (100)
2	*t*-Bu, H (**70a**)	$MeOCH_2CH_2O$	**72c**	97	8:1	19:1 (97)
3	Et, Et (**70b**)	$MeOCH_2CH_2O$	**72d**	87	16:1	
4	*t*-Bu, H (**70a**)	$CH_2=CH(CH_2)_3O$	**72e**	85	7:1	19:1 (95)
5	morph[e] (**70c**)	$CH_2=CH(CH_2)_3O$	**72f**	84	12:1	
6	*t*-Bu, H (**70a**)	*m*-$NO_2C_6H_4CH_2O$	**72g**	81	8:1	24:1 (98)
7	Et, Et (**70b**)	*m*-$NO_2C_6H_4CH_2O$	**72h**	93	7:1	22:1 (97)
8	Et, Et (**70b**)	$PhCH_2O$	**72i**	87[f]	6:1	>50:1 (100)
9	*t*-Bu, H (**70a**)	*c*-$HexNH(CH_2)_3O$	**72j**	78	14:1	
10	piper[g] (**70d**)	$CH_2=CHCH_2O$	**72k**	95[h]	15:1	

Table 5 (continued)

no.	R^1, R^2	RO	product	yield, %[b]	dr[c]	dr upgraded[d]
11	piper[g] (**70d**)	$PhCH{=}CHCH_2O$	**72l**	81	19:1	
12	*t*-Bu, H (**70a**)	$HC{\equiv}C\text{-}CH_2O$	**72m**	78[h]	10:1	
13	*t*-Bu, H (**70a**)	*i*-PrO	**72n**	71	8:1	16:1 (96)
14	*t*-Bu, H (**70a**)	$HC{\equiv}C\text{-}CMe_2O$	**72o**	59	10:1	
15	*t*-Bu, H (**70a**)	Ph_3CO	**72p**	50	25:1	
16	Me, MeO	$PhCH_2O$	**72q**	44[j]	>25:1	

[a] Reactions performed in 0.3-0.5 mmol scale unless specified otherwise. [b] Isolated yields of diastereomeric mixtures. [c] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures prior to the diastereoselectivity upgrade. [d] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures after the diastereoselectivity upgrade, material balance (%) is given in parentheses. [e] morph = morpholine derivative, $R^1R^2 = (CH_2CH_2)_2O$. [f] Reaction performed in 8 mmol scale. [g] piper = piperidine derivative, $R^1R^2 = (CH_2)_5$. [h] Reaction carried out at 50 °C. [i] Reaction mixture was stirred for 3 hrs at 60 °C. [j] t-BuOK (2.5 equiv) was employed as base, the reaction was performed at r. t.

Having a chemoselective method for the addition of pronucleophiles, the scope of this transformation was investigated with respect to the *N*-substituents on cyclopropanes **70** as well as the compatibility of functional groups and steric factors associated with the nucleophile. Thus, the reaction of bromocyclopropane **70a** with KOH in the presence of *n*-propanol and catalytic amounts of 18-crown-6 proceeded smoothly affording *trans*-*n*-propoxide adduct **72b** in good yield and high diastereoselectivity. Functional group compatibility was demonstrated through addition of other primary alkoxides possessing functional groups, such as a methyl ether or an isolated C=C double bond which added very efficiently without subsequent olefin isomerization or other chemoselectivity issues; providing cyclopropanol ethers **72c**, **72d**, **72e**, and **72f** in high yields (entries 2-5). Formal substitution with alkoxides generated from allyl and cinnamyl alcohols[72] also proceeded smoothly, affording the corresponding ethers **72k** and **72l**

(entries 10 and 11). Similarly, a reaction carried out in the presence of propargyl alcohol readily afforded propargyl ether **72m** (entry 12). It should be mentioned that the latter reaction must be performed at temperatures <60 ^{o}C and monitored closely to prevent a base-assisted 1,3-prototropic rearrangement of allyl and propargyl ether moieties into enol and allenyl ether functions, respectively.

After demonstrating that *m*-nitrobenzyl and benzyl-protected alcohols could be added (entries 6-7 and 16) we set out to investigate scalability. Utilizing benzyl alcohol as a nucleophile, we were able to isolate benzyl-protected cyclopropanol **72i** (entry 8) on 8 mmole scale via vacuum distillation in 87% yield. It is also noteworthy that cyclopropanes bearing both secondary and tertiary amides readily undergo nucleophilic addition. In the case of secondary amides, the relatively acidic N-H bond can undergo deprotonation by KOH to form equilibrium species **71aii** (Figure 2). As a consequence of charge delocalization, the electrophilicity of **71aii** should be much less than electronically neutral **71ai**. That being said, cyclopropanes bearing secondary amides readily undergo nucleophilic addition (Table 5, entries 1-2, 4, 6, 9, 12-15), indicating that either **71aii** is not present in significant quantities, or that **71aii** is still sufficiently reactive despite being highly deactivated. In the case of tertiary amides such as **71b**, potentially negative steric interactions did not seem to effect reaction efficacy (Table 5, entries 3, 5, 7-8, 10-11), yielding cyclopropanol derivatives bearing a tertiary carboxamide in good to excellent yields.

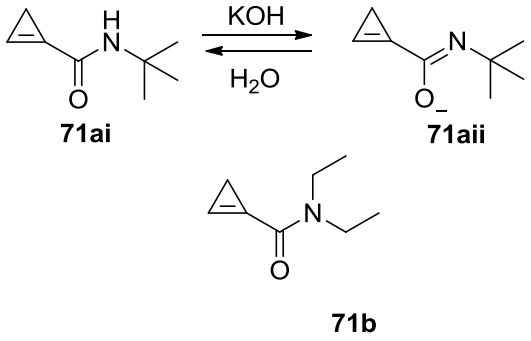


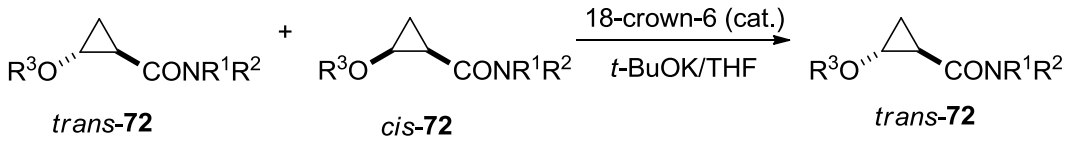
Figure 2: Potential electronic and steric challenges to nucleophilic addition.

When bifunctional 3-cyclohexylaminopropanol pronucleophile bearing an N- and O-terminus was reacted with bromocyclopropane **71a**, the reaction was chemoselective for the O-terminus yielding exclusively cyclopropyl ether **72j** in good yield (entry 9). Initially, it was rationalized that chemoselectivity was a result of selective deprotonation of more acidic O-H bond, however further investigations that will be discussed in following sections revealed that nitrogen nucleophiles require an activating group in order to add to conjugated cyclopropene intermediates.

Finally the impact of the steric environment about the alkoxide nucleophile was investigated. While primary alkyl and benzyl as well as secondary alkoxide nucleophiles add with good to excellent yield[74] (71-97% yield; Table 5, representative entries 1, 3, 7 and 13); it was found that tertiary alcohols were viable, but suffered from diminished yields as steric bulk increased. For example, tertiary propargyl alcohol added to form propargyl ether **72o** in 59% yield (entry 14). When extremely bulky trityl alcohol was used, only 50% of the corresponding ether **72p** was isolated.

Regardless of the nucleophile source, all of these additions provided *trans*-cyclopropylethers as major products. However, in some cases, the relatively low basicity of hydroxide led to incomplete epimerization and less than ideal diastereoselectivity was achieved (Table 5, entries 1-2, 4, 6-8, 13). Initial attempts at improving selectivity via increasing base loading, reaction temperature or reaction time had no effect. However it was found that after removing solvent, crude mixtures could be treated with fresh THF and *t*-BuOK, which significantly improved diastereomeric ratios without notable decomposition (Table 6).

Table 6: Epimerization protocol



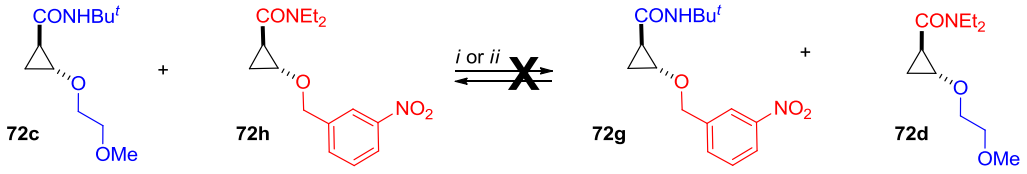
trans-**72** *cis*-**72** *trans*-**72**

	dr before treatment	dr after treatment	material balance, %
72b	9:1	39:1	100
72c	8:1	19:1	97
72e	7:1	19:1	95
72i	6:1	>50:1	100
72n	8:1	16:1	96

We also questioned whether the thermodynamic control of the diastereoselectivity is realized via an epimerization of the tertiary carbon atom adjacent to the amide functionality, or via a reversible addition of a nucleophilic species. To clarify the mechanism, we performed a crossover experiment employing a pair of 2-alkoxycyclopropane carboxamides **72c** and **72h**, bearing different alkoxide and amide groups. A mixture of **72c** and **72h** was subjected to the typical reaction conditions in the presence of either KOH or t-BuOK as a base. In both cases no

formation of crossover products **72g** and **72d** was detected by GC analysis of the crude reaction mixtures (Scheme 31). These results strongly support irreversibility of the nucleophilic addition which, in turn, suggests that thermodynamic control of the diastereoselectivity in this reaction is realized solely via a base-assisted epimerization of the α-CH group.

Scheme 31. Test on Reversibility of the Nucleophilic Addition of Alkoxide Species

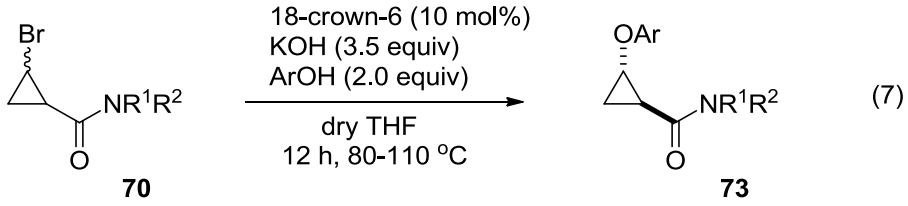


Conditions *i*: **72c** (50 µmol), **72h** (50 µmol), 18-crown-6 ((5 µmol), KOH (175 µmol), THF (500 µL), 85 °C , 48 h. Conditions *ii*: Same as above, but using *t*-BuOK (175 µmol) in place of KOH.

2.3. Phenoxide addition

While there has been interest in β-phenoxy substituted amides as antitumor agents,[75] protein modulators[75b] and Alzheimer's therapeutics,[76] these compounds are accessed via addition to epoxide-substituted amides or through substitution of a β-bromomethylene group; resulting in a non-stereogenic center. Reports of efficient, diastereoselective methods to add aryloxy moieties to the β-carbon of amides are non-existent in literature. Conjugate addition to an unsaturated amide would be an attractive method to achieve this goal.[77] With an established protocol for the addition of alkoxides to unsaturated cyclopropenyl amides, we ventured to extend this methodology to the addition of aryloxide species.[78] To our delight, reactions between cyclopropyl bromide and phenol provided phenyl ether in good isolated yield and high diastereoselectivity (Table 7, eq. 7).[72]

Table 7: Phenoxide addition



(7)

no.	R^1, R^2	ArO	product	yield, %[b]	dr[c]	dr upgraded[d]
1	*t*-Bu, H (**70a**)	PhO	**73a**	79	6:1	>50:1 (96)
2	*t*-Bu, H (**70a**)	*p*-$MeOC_6H_4O$	**73b**	75	7:1	>50:1 (97)
3	*t*-Bu, H (**70a**)	*p*-BrC_6H_4O	**73c**	86	8:1	46:1 (100)
4	*t*-Bu, H (**70a**)	*p*-IC_6H_4O	**73d**	80	10:1	
5	*t*-Bu, H (**70a**)	*p*-$PhCOC_6H_4O$	**73e**	90	10:1	
6	*t*-Bu, H (**70a**)	*p*-NCC_6H_4O	**73f**	74	10:1	42:1 (96)
7	*t*-Bu, H (**70a**)	*o*-FC_6H_4O	**73g**	89	12:1	
8	*t*-Bu, H (**70a**)	*o*-$CF_3OC_6H_4O$	**73h**	84	15:1	
9	Et, Et (**70b**)	*o*-FC_6H_4O	**73i**	82	12:1	
10	*t*-Bu, H (**70a**)	3,5-$(CH_3)_2C_6H_3O$	**73j**	95	13:1	
11	morph[e] (**70c**)	3,5-$(CH_3)_2C_6H_3O$	**73k**	87	20:1	
12	*t*-Bu, H (**70a**)	3,5-$(CF_3)_2C_6H_3O$	**73l**	85	17:1	
13	*t*-Bu, H (**70a**)	2,4-(*t*-Bu)$_2C_6H_3O$	**73m**	95	15:1	
14	morph[e] (**70c**)	2,6-$(CH_3)_2C_6H_3O$	**73n**	83	25:1	
15	piper[f] (**70d**)	quinolin-8-olate	**73o**	97	single	

[a] Reactions performed in 0.3-0.5 mmol scale unless specified otherwise. [b] Isolated yields of diastereomeric mixtures. [c] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures. [d] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures after diastereoselectivity upgrade, material balance (%) is given in parentheses. [e] morph = morpholine derivative, $R^1R^2 = (CH_2CH_2)_2O$. [f] piper = piperidine derivative, $R^1R^2 = (CH_2)_5$.

Electronically diverse para-substituted aryloxides also reacted smoothly producing the corresponding aryl cyclopropyl ethers **73b, 73c, 73d, 73e, 73f** in high yields (entries 2-6). Similarly, excellent reactivity was demonstrated in the addition of ortho-substituted phenoxides (entries 7-9). Both electron-rich and electron-poor 3,5-disubstituted phenoxides reacted smoothly to produce aryloxycyclopropanes **73j**, **73k**, and **73l** (entries 10-12). Remarkably, highly sterically encumbered phenoxides derived from 2,4-di-tertbutylphenol, 2,6-dimethylphenol, and 8-hydroxyquinoline provided the corresponding adducts **73m**, **73n**, and **73o** in high yields and excellent diastereoselectivities (entries 13-15).

It also deserves noting that formal substitution with phenoxides proceeded much slower and required higher temperatures to achieve complete conversion, as compared to analogous reactions with alkoxides. This difference can be explained in terms of increased acidity of phenols, which readily produce phenoxides and water by a stoichiometric reaction with KOH. Although small amounts of moisture do not adversely affect this transformation, formation of the hydroxide-phenoxide "buffer" lowers the effective basicity of the system. This, in turn, results in significant inhibition of the dehydrobromination step. The latter process is a rate-determining step in this reaction, which was confirmed by the fact that the overall kinetic rate of the transformation did not depend on electronic properties of the phenoxide species. The Swain-Lupton LFER parameters obtained from a series of competing parallel reactions reveal a profound negative F-value, indicating the diminution of the negative charge in the anionic phenoxide reagent as a result of addition to an electrophilic double bond (Figure 3).

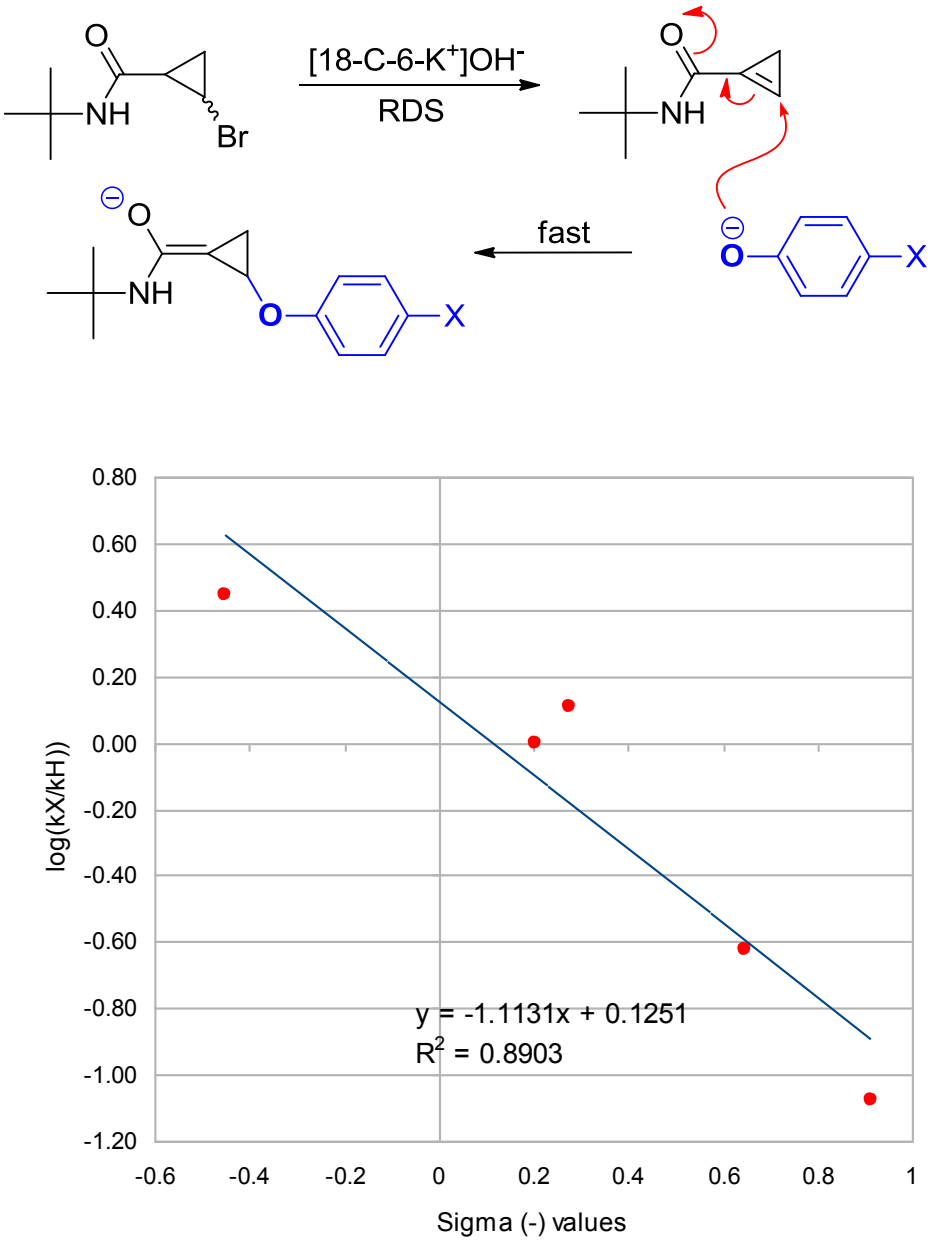
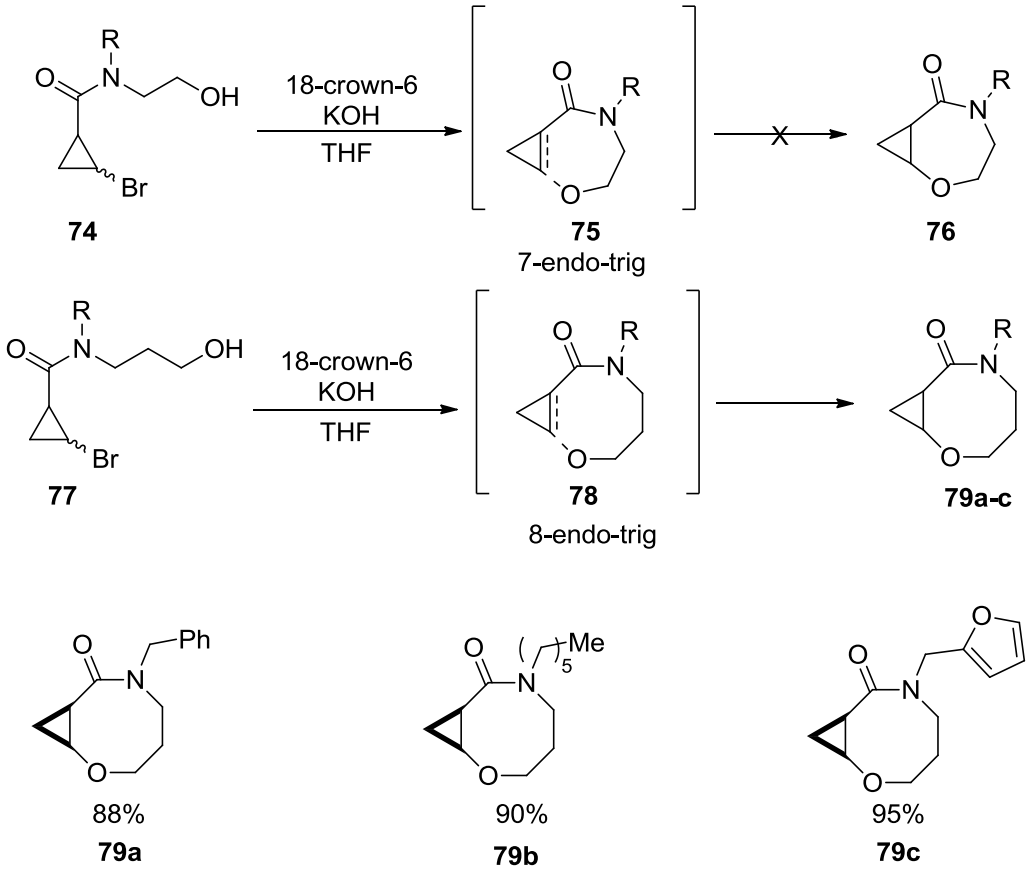


Figure 3. Swain-Lupton LFER studies of the formal nucleophilic substitution of bromocyclopropane 70a with aryloxides.[79]

With a well-elaborated protocol for intermolecular addition of oxygen–based nucleophiles in hand, we began investigating intramolecular cyclization reactions. Initial

attempts involved 7-*endo*-trig cyclization of bromocyclopropane **74** which did not yield any observable quantity of **76**. It is thought that intermediate **75** is too strained for intramolecular addition and instead prefers intermolecular addition to another equivalent of **75**, resulting in polymeric products. 8-*endo*-trig cyclization of alkoxy-tethered cyclopropane **77** on the other hand, proceeds smoothly yielding 8-membered heterocyclic adducts **79a-c** in excellent yield (Scheme 32).

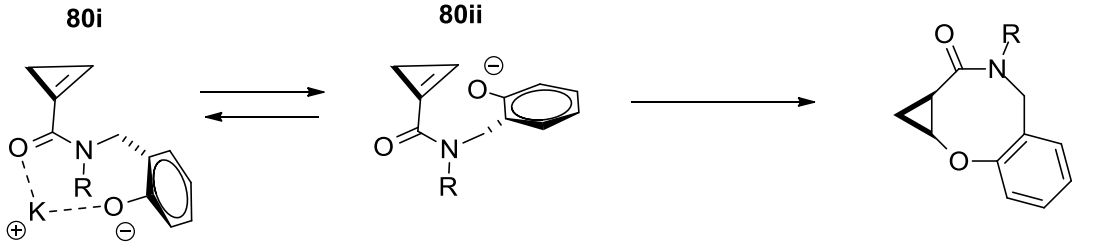
Scheme 32



When attempting 8-*endo*-trig cyclization of phenoxide-tethered cyclopropane **80**, it was found that increasing steric bulk of the amide substituent has a positive effect on the efficacy of the reaction (Scheme 33).

Experimentally, it was observed that cyclizations of *N*-hexyl (**80a**) and *N*-cyclohexyl (**80b**) derivatives proceeded sluggishly to give 40-50% conversion, and after a laborious purification benzoxacinones **81a** and **81b** were isolated in ~30% yield only. In contrast, *N*-*tert*-butyl amide **80c** reacted cleanly affording cyclization product **81c** in high yield (Scheme 33). To explzin this observation, we rationalized that upon forming cyclopropene intermediate **80i**, the phenoxide anion is coordinated with potassium, which in turn is also coordinated with the carbonyl oxygen. This coordination would cause the phenoxide anion to rotate away from the electrophilic β-carbon leaving the molecule in a non-reactive conformation. If the amide substituent is sufficiently bulky, de-coordination is favored allowing the phenoxide anion to rotate into reactive conformation **80ii** for nucleophilic attack on the olefin.

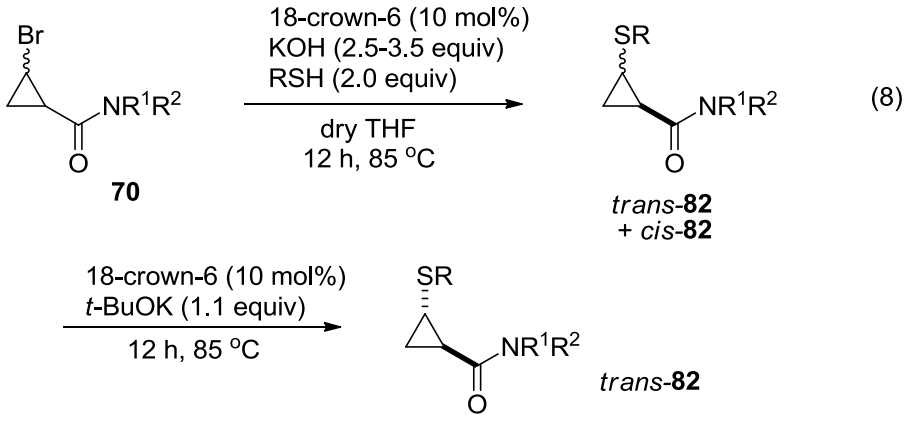
Scheme 33



2.4. Thiolate addition

Given our success with the addition of relatively soft phenoxide nucleophiles, we began exploring the addition of thiolates to bromocyclopropanes **70** (Table 8, eq 8). These reactions were carried out under conditions identical to those used for phenoxide addition, in the presence of alkylthiol pronucleophiles to afford the corresponding cyclopropylsulfides **82a**, **82b**, **82c** in high yields but with only marginal diastereoselectivity. The selectivity was substantially improved, however, upon treatment of the crude products with a stronger base (entries 1-3). The chemoselectivity in the reaction with bifunctional nucleophiles 2-mercaptoethanol and 2-(benzylamino)ethanethiol was investigated (entries 4-6). Expectedly, the less reactive alkoxide and the 2^{o} amine moieties were completely outcompeted by the much more nucleophilic thiolate species, leading to the exclusive formation of cyclopropyl sulfides **82d**, **82d**, and **82e** (entries 4-6). Interestingly, the reactions with 2-mercaptoethanol were sufficiently stereoselective for preparative purpose, therefore no further diastereoselectivity upgrade was necessary (entries 4-5). Finally, the reaction with thiophenol provided the corresponding adduct **82f** in high yield and poor diastereoselectivity, which was routinely upgraded after treatment of the crude reaction mixture with potassium *tert*-butoxide (Table 8, entry 7).

Table 8. Formal nucleophilic substitution of bromocyclopropanes with thiolates and thiophenols[a]



(8)

no.	R^1, R^2	RS	product	yield, %[b]	dr[c]	dr upgraded[d]
1	Bu, H (**70f**)	*n*-$C_{12}H_{25}S$	**82a**	95	1:1	16:1
2	morph[e] (**70c**)	$PhCH_2S$	**82b**	92	2:1	>30:1
3	$PhCH_2$, H (**70g**)	$PhCH_2S(CH_2)_3S$	**82c**	87	2:1	>30:1
4	*t*-Bu, H (**70a**)	$HOCH_2CH_2S$	**82d**	97	10:1	
5	Ph, H (**70h**)	$HOCH_2CH_2S$	**82d**	85	>30:1	
6	Bu, H (**70f**)	$PhNHCH_2CH_2S$	**82e**	94	2:1	>30:1
7	Bu, H (**70f**)	PhS	**82f**	98	2:1	>30:1

[a] Reactions performed in 0.5 mmol scale unless specified otherwise. [b] Isolated yields of diastereomeric mixtures after the diastereoselectivity upgrade. [c] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures prior to the upgrade. [d] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures after the diastereoselectivity upgrade. [e] morph = morpholine derivative, $R^1R^2 = (CH_2CH_2)_2O$.

2.5. Conclusions

In situ generation and trapping of cyclopropene has been demonstrated as a viable approach to accessing a variety of sterically and functionally diverse cyclopropanol and

cyclopropyl thiol derivatives, even when the generated cyclopropene has no shelf life. We demonstrated that diastereoselectivity can be controlled by steric factors, directing groups or thermodynamic epimerization of the nucleophilic adduct, granting access to stereodefined DAC's from diastereomeric mixtures of starting material. Through this methodology, we have demonstrated a new activation pathway for oxa- and thio- Michael additions, showing unprecedented reactivity towards alkoxide and aryloxide nucleophiles.

2.6. Experimental

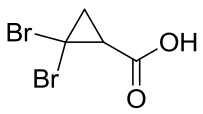
2.6.1. General Information

NMR spectra were recorded on a Bruker Avance DPX-400 instrument, equipped with a quadruple-band gradient probe (H/C/P/F QNP) or a Bruker Avance DRX-500 with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broad-band decoupling. The (+) and (-) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. Column chromatography was carried out employing silica gel (Selecto Scientific, 63-200 μm). Pre-coated silica gel plates (Merck Kieselgel 60 F-254) were used for thin-layer chromatography. GC/MS analyses were performed on a Shimadzu GC-2010 gas chromatograph interfaced to a Shimadzu GCMS 2010S mass selective detector, and equipped with an AOC-20i auto-injector and an AOC-20S auto-sampler tray (150 vials). 30 m × 0.25 mm × 0.25 □m capillary column, SHR5XLB, polydimethylsiloxane, 5% Ph was employed. Helium (99.96%), additionally purified by passing consecutively through a CRS oxygen/ moisture/hydrocarbon trap (#202839) and VICI oxygen/moisture trap (P100-1), was used as a carrier gas. High resolution mass-spectra were obtained using a LCT Premier

(Micromass Technologies) instrument using electrospray ionization and time of flight detection techniques. IR spectra were recorded on a Shimadzu FT-IR 8400S instrument.

Glassware employed in moisture-free syntheses was flame-dried in vacuum prior to use. Water was purified by dual stage deionization, followed by dual stage reverse osmosis. Anhydrous THF was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent consecutively through two columns filled with activated alumina (Innovative Technology). Anhydrous Et_3N was obtained by distillation of ACS-grade commercially available materials over calcium hydride in a nitrogen atmosphere. 3-Benzylamino-1-propanol was purchased from TCI America and used as received. All other commercially available reagents were purchased from Sigma-Aldrich or Acros Organics. Synthesis, physical properties and spectral data of all new compounds obtained in a frame of these studies are described below. All manipulations with *t*-BuOK and 18-crown-6 ether were conducted under inert atmosphere (<8 ppm residual oxygen and moisture) using a combination of glovebox and standard Schlenk techniques. After quench the reaction mixtures and compounds were treated on air. All the obtained materials were moisture and oxygen stable at ambient temperatures.

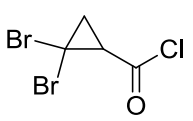
2.6.2. Synthesis of 2,2-Dibromocyclopropanecarboxylic acid derivatives



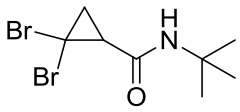
2,2-Dibromocyclopropanecarboxylic acid (**83**): A three neck round-bottom 2000 mL flask was equipped with an overhead mechanical stirrer, dropping funnel and Dewar condenser (filled with a dry ice-acetone mixture) connected to a cylinder with 1,3-butadiene. The flask was filled with dry nitrogen and charged with *t*-BuOK (123 g, 1.10

mol) and 450 mL of anhydrous hexane, then cooled down to -50 ^{o}C, and 1,3-butadiene (76 g, 117 mL, 1.40 mol) was condensed. The formed suspension was vigorously stirred at -50 ^{o}C , while a solution of bromoform (270 g, 95 mL, 1.07 mmol) in dry hexane (200 mL) was added dropwise over 2 hrs. After the addition was complete the reaction mixture was stirred for 1 hr at -50 ^{o}C, and then warmed up to room temperature. To destroy unreacted bromoform an additional portion of *t*-BuOK was added (11 g, 0.10 mol), the mixture was stirred for 2 hrs, and then quenched with water (500 mL). The organic layer was separated; the aqueous phase was extracted with hexane (3 x 100 mL). Combined organic phases were dried with $MgSO_4$, filtered and concentrated in vacuum. The oily residue was distilled in vacuum to afford 2,2-dibromo-1-vinylcyclopropane as a colorless oil. Yield 162 g (716 mmol, 67%). This material was oxidized to the corresponding carboxylic acid by $KMnO_4$ under PTC-conditions. A 4000 mL Erlenmeier flask equipped with overhead stirrer, and thermometer was charged with water (1200 mL), glacial acetic acid (25 mL), a solution of H_2SO_4 (75 mL) in water (100 mL), a solution of 2,2-dibromo-1-vinylcyclopropane (90.4 g, 0.40 mmol) in CH_2Cl_2 (1200 mL), and cetrimide (2.9 g, 8 mmol). The mixture was vigorously stirred at 5 ^{o}C (cooled in rock salt-ice bath), and $KMnO_4$ (213 g, 1.35 mmol) was added by portions over 2 hrs. The mixture was warmed to room temperature, and stirred for additional 2 hrs. Then a solution of H_2SO_4 (54 mL) in water (500 mL) was added, followed by powdered Na_2SO_3 (179 g, 1.42 mol), which was put in by small portions maintaining the temperature in the interval of 15-20 ^{o}C until the brown precipitate of MnO_2 dissolved completely. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 500 mL). Combined organic solutions were concentrated to the total volume of 500 mL and extracted with 1M aqueous NaOH (400 mL, 100 mL). Combined aqueous extracts were acidified with 5M aqueous H_2SO_4 (60 mL) and extracted with $CHCl_3$ (300

mL, 3 x 200 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuum. A similar reaction was performed with a second batch of vinylcyclopropane (71.6 g, 31.7 mmol). Combined crude acid from both batches was purified by recrystallization from hexane-benzene (3:2) to obtain pure **83** as colorless crystals, identical to the material previously described in literature.2 Yield 85.37 g (0.35 mmol, 49%).



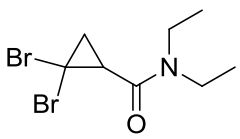
2,2-Dibromocyclopropanecarbonyl chloride (**84**): A mixture of carboxylic acid **83** (26.9 g, 110 mmol) and thionyl chloride (20.0 mL, 276 mmol) was stirred overnight at room temperature under an atmosphere of dry nitrogen. The excess thionyl chloride was distilled out at ambient pressure, and the residue was distilled in vacuum (bp 82-84 ^{o}C /4 torr) to afford acyl chloride **84** as colorless oil, identical to the material previously described in literature.3 Yield 26.3 g (100 mmol, 91%).



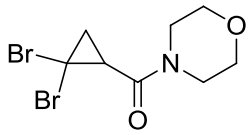
2,2-Dibromo-*N*-*tert*-butylcyclopropanecarboxamide (**85a**):

Typical procedure. To a stirred solution of acyl chloride **84** (6.00 g, 22.9 mmol) in dry THF (40 mL) was added *tert*-butylamine (3.90 mL, 2.74 g, 45.8 mmol). The mixture was stirred at room temperature overnight, then partitioned between water (100 mL) and EtOAc (50 mL). The organic layer was separated; the aqueous phase was extracted with EtOAc (2 x 50 mL). Combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by vacuum distillation on Kugelröhr (oven temp. 120 ^{o}C at 0.4 torr) to afford a colorless crystalline material, mp 107-109 ^{o}C (from hexane). Yield 6.60 g (22.2 mmol, 97%). ^{1}H NMR (500.19 MHz, $CDCl_3$) δ 5.76 (br.s, 1H), 2.36 (dd, *J* = 9.7 Hz, 7.5 Hz, 1H), 2.18 (t, *J* = 7.5 Hz, 1H), 1.91 (dd, *J* = 9.7 Hz, 7.5 Hz, 1H),

1.42 (s, 9H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 164.2, 52.3, 35.6, 28.8 (3C), 26.1, 21.3; IR (film, cm^{-1}): 3308, 3078, 2968, 2967, 1657, 1551, 1454, 1414, 1366, 1271, 1225, 1205, 1103; HRMS (TOF ES): found 297.9443, calculated for $C_8H_{14}Br_2NO$ (M+H) 297.9442 (0.3 ppm).



2,2-Dibromo-*N*,*N*-diethylcyclopropanecarboxamide (**85b**): Was obtained according to the typical procedure from acyl chloride **84** (3.00 g, 11.4 mmol) and diethylamine (2.38 mL, 1.67 g, 22.9 mmol). Kugelrohr distillation (oven temperature 115 ^{o}C at 0.4 torr) afforded a title compound as a colorless oil. Yield 3.286 g (10.99 mmol, 96%). ^{1}H NMR (500.19 MHz, $CDCl_3$) δ 3.70 (dq, *J* = 14.3 Hz, 7.3 Hz, 1H), 3.62 (dq, *J* = 14.3 Hz, 7.3 Hz, 1H), 3.49 (dq, *J* = 14.3 Hz, 7.3 Hz, 1H), 3.28 (dq, *J* = 14.3 Hz, 7.3 Hz, 1H), 2.57 (dd, *J* = 9.7 Hz, 7.7 Hz, 1H), 2.28 (t, *J* = 7.7 Hz, 1H), 1.95 (dd, *J* = 9.7 Hz, 7.7 Hz, 1H), 1.34 (t, *J* = 7.3 Hz, 3H), 1.16 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 164.8, 42.0 (-), 40.6 (-), 34.0 (+), 26.2 (-), 21.8, 14.1 (+), 12.9 (+); IR (film, cm^{-1}): 2974, 2934, 2874, 1651, 1477, 1447, 1381, 1346, 1263, 1221, 1144, 1107; HRMS (TOF ES):found 224.0657, calculated for $C_8H_{19}BrNO$ (M-Br) 224.0650 (3.1 ppm).

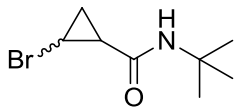


(2,2-Dibromocyclopropyl)(morpholin-4-yl)methanone (**85c**): Was obtained according to the typical procedure from acyl chloride **84** (3.71 g, 14.1 mmol) and morpholine (4.0 mL, 3.7 g, 424 mmol). After aqueous work up and extraction, crude crystalline solid was re-crystallized from hexane-dichloromethane mixture to colorless glassy solid. Yield 2.06 g (6.65 mmol, 47%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.96-3.66 (m, 7H), 3.50 (ddd, *J* = 13.4 Hz, 7.7 Hz, 3.4 Hz, 1H), 2.56 (dd, *J* = 10.0 Hz, 7.7 Hz, 1H), 2.29 (t, *J* = 7.7 Hz, 1H), 2.02 (dd, *J* = 10.0 Hz, 7.7 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 163.8, 66.20

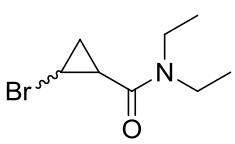
(-), 66.17 (-), 45.5 (-), 42.2 (-), 33.7 (+), 25.7 (-), 20.8; IR (film, cm^{-1}): 2974, 2934, 1653, 1483, 1460, 1448, 1435, 1381, 1362, 1265, 1221, 1142; HRMS (TOF ES): found 234.0127, calculated for $C_8H_{13}BrNO_2$ (M-Br+H) 234.0130 (1.3 ppm).

2.6.3. Synthesis of 2-bromocyclopropanecarboxamide derivatives

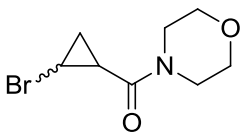
Nonselective Grignard reduction:



2-Bromo-*N*-*tert*-butylcyclopropanecarboxamide (**70a**): Typical procedure. To a stirred at -50 ^oC solution of dibromocyclopropane **85a** (3.20 g, 10.7 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise a solution of *i*-PrMgBr (2.0M in Et2O, 8.0 mL, 16 mmol). The mixture was stirred at -50 ^oC for 15 min, then quenched with saturated aqueous NH4Cl (10 mL), followed by 5% aqueous HCl (20 mL) to dissolve inorganic precipitate. Organic layer was separated; aqueous phase was extracted with EtOAc (3 x 20 mL). Combined organic solutions were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by Kugelrohr distillation (oven temp. 100 ^oC at 0.4 torr) to afford a mixture of diastereomeric bromocyclopropanes **70a** (2.13:1) as colorless solid, mp 87-89 ^oC . Yield 1.72 g (7.85 mmol, 73%). ^1H NMR (500.19 MHz, $CDCl_3$) δ [5.82 (br.s) & 5.87 (br.s), Σ1H], [3.17 (ddd, *J* = 7.7 Hz, 4.0 Hz, 3.2 Hz) & 3.08 (td, *J* = 7.7 Hz, 5.5 Hz), Σ1H], 1.81-1.72 (m, 1H), 1.58-1.51 (m, 1H), [1.38 (s) & 1.35 (s), Σ9H], [1.34-1.29 (m) & 1.24-1.20 (m), Σ1H]; ^{13}C NMR (125.76 MHz, $CDCl_3$) δ major: 169.1, 51.6, 28.8 (+, 3C), 26.2 (+), 18.9 (+), 17.2 (-); minor: 169.4, 51.8, 28.9 (+, 3C), 22.5 (+), 19.2 (+), 13.1 (-); IR (film, cm^{-1}): 3315, 3080, 2966,2932, 1641, 1555, 1454, 1391, 1364, 1277, 1225; HRMS (TOF ES): found 220.0340, calculated for $C_8H_{15}BrNO$ (M+H) 220.0337 (1.4 ppm).

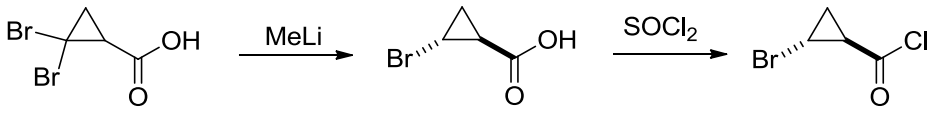


2-Bromo-*N*,*N*-diethylcyclopropanecarboxamide (**75b**): Was obtained according to a typical procedure from dibromocyclopropane **85b** (3.24 g, 10.82 mmol). Kugelrohr distillation (oven temp. 70 ^{o}C at 0.3 torr) afforded a title compound (mixture of diastereomers 7:1) as a colorless oil. Yield 2.09 g (9.50 mmol, 88%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ major: 3.49 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 3.23 (ddd, *J* = 7.6 Hz, 4.6 Hz, 3.2 Hz, 1H), 2.12 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.0 Hz, 1H), 1.67 (dt, *J* = 7.5 Hz, 5.8 Hz, 1H), 1.31 (ddd, *J* = 9.4 Hz, 5.8 Hz, 4.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ major: 169.0, 42.2 (-), 40.9 (-), 22.6 (+), 19.9 (+), 17.7 (-), 14.9 (+), 13.1 (+); IR (film, cm^{-1}): 2964, 2918, 2856, 1653, 1460, 1437, 1362, 1273, 1234, 1115; GC 8.28 min (minor), 8.42 min (major); HRMS (TOF ES): found 220.0333, calculated for $C_8H_{15}BrNO$ (M+H) 220.0337 (1.8 ppm).



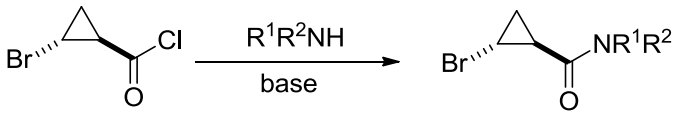
(2-Bromocyclopropyl)(morpholin-4-yl)methanone (**70c**): Was obtained according to a typical procedure from dibromocyclopropane **85c** (2.06 g, 6.65 mmol). Flash column chromatography on silica gel (eluent hexane-EtOAc 3:1) afforded a title compound (single diastereomer) as colorless crystalline solid, mp. 74-77 ^{o}C . Yield 1.34 g (5.74 mmol, 86%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.74-3.50 (m, 8H), 3.25 (ddd, *J* = 7.6 Hz, 4.7 Hz, 3.2 Hz, 1H), 2.13 (ddd, *J* = 9.2 Hz, 6.0 Hz, 3.3 Hz, 1H), 1.77-1.59 (m, 1H), 1.36 (ddd, *J* = 9.2 Hz, 5.8 Hz, 4.7 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 168.5, 66.5 (-, 2C), 45.8 (-), 42.4 (-), 22.1 (+), 19.3 (+), 17.7 (-); IR (film, cm^{-1}): 2968, 2920, 2999, 2856, 1632, 1441,1364, 1274, 1242, 1115, 1043; HRMS (TOF ES): found 177.0771, calculated for $C_8H_{12}NO_2Na$ (M-Br+Na) 177.0766 (2.8 ppm).

Alternative selective reduction:



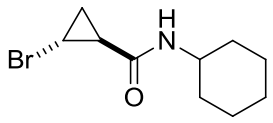
(1*S,2*R**)-2-Bromocyclopropanecarbonyl chloride (87)**: Flame-dried 3000 mL three neck round bottom flask was charged with solution of 2,2-dibromocyclopropanecarboxylic acid (**83**) (27.0 g, 111 mmol) in anhydrous ether (1300 mL) under nitrogen atmosphere. The mixture was vigorously stirred (500-650 rpm) at -20 ^{o}C, and methyl lithium solution (1.6M in ether, 95 mL, 152 mmol, 1.37 equiv) was added dropwise. For safety reasons it is essential to add methyl lithium directly to a solution rather than draining along the flask wall to minimize the amount of solid precipitate, which might ignite during the following work up. An aliquot of solution (1 mL) was withdrawn from the flask with a syringe, quenched consecutively with brine (2-3 drops) and 5% aqueous HCl (2-3 drops) in 10 mL test tube. The aqueous layer was saturated with NaCl, and extracted with EtOAc (3 x 0.5 mL). The combined organic phases collected with Pasteur pipet were dried with $MgSO_4$ and concentrated. The conversion was measured based on ^{1}H NMR analysis of this probe, and additional amount of MeLi necessary to complete the transformation was assessed (35 mL, 56 mmol). The mixture was quenched at -20 ^{o}C by adding brine (100 mL) and 5% aqueous HCl (100 mL). (It is essential to perform the quenching at low temperature and to maintain inert atmosphere to avoid ignition of the mixture). The mixture was allowed to warm up to rt, then aqueous layer was saturated with NaCl. Ethereal layer was separated, and then aqueous phase was extracted with EtOAc (6 x 100 mL). Combined organic

phases were dried with $MgSO_4$, filtered and concentrated. The oily residue was distilled in vacuum (bp 71 ^oC at 3 torr) to provide (1*S**,2*R**)-2-bromocyclopropanecarboxylic acid (**86**) as a colorless oil, which solidified upon standing. Yield 8.79 g (53.3 mmol, 48%). This material was charged into a 25 mL round bottomed flask equipped and thionyl chloride (11.5 g, 110 mmol) was added. The mixture was stirred at room temperature overnight, then an excess of thionyl chloride was distilled off, and the residue was fractionated in vacuum to obtain the title compound as clear oil, bp 56 ^oC at 15 torr. Yield 9.19 g (50.1 mmol, 94%).



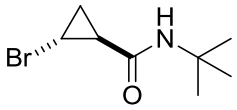
87

70a: R^1 = *t*-Bu, R^2 = H
70b: R^1 R^2 = -$(CH_2)_2O(CH_2)_2$-
70c: R^1 R^2 = -$(CH_2)_5$-
70d: R^1 = Cy, R^2 = H
70e: R^1 = Me, R^2 = OMe
70f: R^1 = H, R^2 = *n*-Bu
70g: R^1 = H, R^2 = Bn
70h: R^1 = H, R^2 = Ph

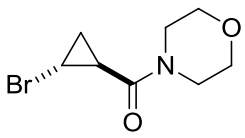


(1*S,2*R**)-2-bromo-*N*-cyclohexylcyclopropanecarboxamide (70d)** (typical procedure): To a stirred solution of cyclohexylamine (1.87 mL, 1.62 g, 16.4 mmol, 3 equiv.) in dry THF (30 mL) was added *trans*-2-bromocyclopropanecarbonyl chloride **87** (1.0 g, 5.5 mmol). The mixture was stirred for 1 hr at room temperature, and then the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). The organic layer was separated and washed consecutively with 10% aqueous HCl (3 x 20 mL) and 4N aqueous NaOH (5 mL), dried with $MgSO_4$, filtered and concentrated. The obtained colorless crystalline material (mp 102-105 ^oC) was pure enough to be used for the following transformations without additional purification.

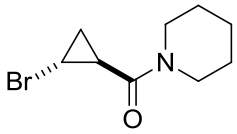
Yield 1.26 g (5.12 mmol, 94%). ^{1}H NMR (500.13 MHz, CD3OD) δ ppm 3.62 (tt, *J* = 10.7 Hz, 3.7 Hz, 1H), 3.14 (ddd, *J* = 7.9 Hz, 4.7 Hz, 3.2 Hz, 1H), 1.99 (ddd, *J* = 9.1 Hz, 6.0 Hz, 3.2 Hz, 1H), 1.90-1.80 (m, 2H), 1.79-1.72 (m, 2H), 1.67-1.61 (m, 1H), 1.49 (dt, *J* = 7.6 Hz, 6.0 Hz, 1H), 1.40-1.30 (m, 2H), 1.28-1.16 (m, 4H); ^{13}C NMR (125.76 MHz, CD3OD) δ ppm 171.7, 50.2 (+), 34.0 (-), 33.9 (-), 26.8 (-), 26.24 (-, 2C), 26.18 (+), 19.3 (+), 17.8 (-); FTIR (NaCl, film, cm^{-1}): 3292, 2932, 2854, 1634, 1553, 1450, 1393, 1211, 1024, 945, 981, 843; HRMS (TOF ES): found 246.0483, calculated for C10H17BrNO (M+H) 246.0494 (4.5 ppm).



(1*S,2*R**)-2-Bromo-*N*-tert-butylcyclopropanecarboxamide** (**70a**): The reaction was performed according to the typical procedure, employing acyl chloride **87** (1.0 g, 5.5 mmol) and *tert*-butylamine (1.72 mL, 1.20 g, 16.4 mmol) to produce the title compound as a colorless solid, yield 1.13 g (5.12 mmol, 93%). The physical and spectral properties of this material were identical to those reported above.

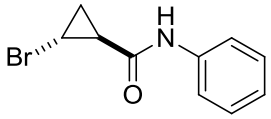


((1*S,2*R**)-2-Bromocyclopropyl)(morpholino)methanone** (**70b**): The reaction was performed according to the typical procedure, employing acyl chloride **87** (1.0 g, 5.5 mmol) and morpholine (1.42 mL, 1.43 g, 16.4 mmol) to produce the title compound as a colorless solid, yield 1.16 g (4.95 mmol, 90%). The physical and spectral properties of this material were identical to those reported above.

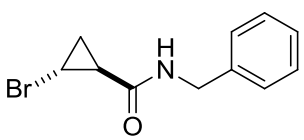


((1*S,2*R**)-2-Bromocyclopropyl)(piperidin-1-yl)methanone** (**70c**): The reaction was performed according to the typical procedure, employing acyl chloride **87** (1.0 g, 5.5 mmol) and piperdine (1.64 mL, 1.40 g , 16.4 mmol) to produce the title

compound as a colorless oil, yield 1.20 g (5.18 mmol, 95%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 3.63-3.59 (m, 2H), 3.57-3.53 (m, 2H), 3.22 (ddd, *J* = 9.5 Hz, 6.0 Hz, 3.2 Hz, 1H), 1.70-1.61 (m, 5H), 1.57-1.52 (m, 2H), 2.18 (ddd, *J* = 7.6 Hz, 4.7 Hz, 3.2 Hz, 1H), 1.31 (ddd, *J* = 9.5 Hz, 6.0 Hz, 4.7 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.1, 46.8 (-), 43.4 (-), 26.6 (-), 25.4 (-), 24.5 (-), 22.6 (+), 19.6 (+), 17.5 (-); FTIR (NaCl, film, cm^{-1}): 2935, 2854, 1634, 1445, 1367, 1354, 1254, 1223, 1138, 1024, 955, 926, 852; HRMS (TOF ES): found 232.0327, calculated for C9H15BrNO (M+H) 232.0337 (4.3 ppm).

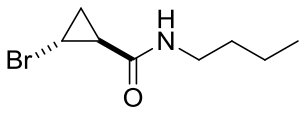


2-Bromo-N-phenylcyclopropanecarboxamide (**70h**): The reaction was performed according to the typical procedure, employing aniline (930 mg, 10 mmol, 2.5 equiv.) and 2-bromocyclopropanecarbonyl chloride (730 mg, 4.0 mmol). Yield 874 mg (3.64 mmol, 91%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.66 (br. s., 1H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 3.34 (ddd, *J* = 7.7 Hz, 4.9 Hz, 3.2 Hz, 1H), 1.98 (ddd, *J* = 8.9 Hz, 5.8 Hz, 3.0 Hz, 1H), 1.77 (dt, *J* = 7.6 Hz, 6.0 Hz, 1H), 1.43 (dt, *J* = 9.0 Hz, 5.4 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 168.4, 137.6, 129.1 (+, 2C), 124.6 (+), 119.9 (+, 2C), 26.6 (+), 19.3 (+), 18.2 (-); FT IR (NaCl, film, cm^{-1}): 3300, 3063, 2932, 1657, 1547, 1447, 1385, 1186, 1024, 756; HRMS (TOF ES): found 261.9844, calculated for $C_{10}H_{10}BrNONa$ (M+Na) 261.9843 (0.4 ppm).

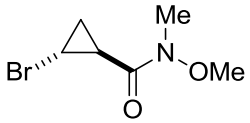


N-Benzyl-2-bromocyclopropanecarboxamide (**70g**): The reaction was performed according to the typical procedure, employing benzylamine (1.10 g, 10.0 mmol, 2.50 equiv.) and 2-bromocyclopropanecarbonyl chloride (730 mg, 4.0 mmol). Yield 910 mg (3.57 mmol, 89%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.37-7.23 (m, 5H), 6.89 (br. s., 1H), 4.42-4.31 (m, 2H), 3.18 (ddd, *J* = 7.6 Hz, 4.7 Hz, 3.0 Hz, 1H), 1.91 (ddd,

J = 9.2 Hz, 5.9 Hz, 3.0 Hz, 1H), 1.58 (dt, J = 7.6 Hz, 5.9 Hz, 1H), 1.27 (dt, J = 9.2 Hz, 5.4 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.2, 137.7, 128.6 (+, 2C), 127.6 (+, 2C), 127.5 (+), 43.8 (-), 25.3 (+), 19.0 (+), 17.5 (-); FT IR (NaCl, film, cm^{-1}): 3296, 3088, 3063, 2930, 1634, 1553, 1454, 1213, 1034, 746, 696, 515; HRMS (TOF ES): found 254.0176, calculated for $C_{11}H_{13}BrNO$ (M+H) 254.0181 (2.0 ppm).



2-Bromo-N-butylcyclopropanecarboxamide (**70f**): The reaction was performed according to the typical procedure, employing butylamine (0.73 g, 10.0 mmol, 2.50 equiv.) and 2-bromocyclopropanecarbonyl chloride (730 mg, 4.0 mmol). Yield 809 mg (3.68 mmol, 92%). ^{1}H NMR (500.13 MHz, CD_3OD) δ 3.19 (t, J = 6.9 Hz, 2H), 3.16 (td, J = 7.6 Hz, 4.7 Hz, 3.2 Hz, 1H), 2.01 (ddd, J = 9.2 Hz, 5.9 Hz, 3.2 Hz, 1H), 1.55-1.46 (m, 3H), 1.38 (sxt, J = 7.4 Hz, 2H), 1.32-1.25 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ 172.7, 40.6 (-), 32.7 (-), 26.1 (+), 21.2 (-), 19.2 (+), 17.8 (-), 14.2 (+); FT IR (NaCl, film, cm^{-1}): 3302, 3092, 3065, 2959, 2932, 2872, 2419, 1634, 1462, 1223, 1020, 953, 800, 696; HRMS (TOF ES): found 220.0337, calculated for $C_8H_{15}BrNO$ (M+H) 220.0337 (0.0 ppm).

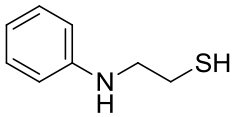


(1*S,2*R**)-2-Bromo-*N*-methoxy-*N*-methylcyclopropanecarboxamide** (**70e**): To a solution of carboxylic acid **86** (3.27 g, 19.82 mmol) in dry CH_2Cl_2 (60 mL) was added 1,1-carbonyldiimidazole (3.86 g, 23.8 mmol, 1.20 equiv) at 0 ^{o}C, and the resulting mixture was stirred for 30 min. Then *N*,*O*-dimethylhydroxylamine hydrochloride (4.50 g, 46.5 mmol, 2.35 equiv) was added; the resulting suspension was stirred for 24 hrs at room temperature, then filtered. The filter cake was washed with DCM. The filtrate was washed

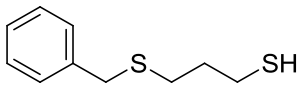
with water, brine, dried with $MgSO_4$, filtered, and concentrated in vacuum to give 3.41 g (16.4 mmol, 83%) of Weinreb amide **70e** as an yellow oil. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 3.80 (s, 3H), 3.24 (ddd, *J* = 7.6 Hz, 4.7 Hz, 3.2 Hz, 1H), 3.22 (s, 3H), 2.59 (br. s, 1H), 1.65 (dt, *J* = 7.6 Hz, 6.0 Hz, 1H), 1.39 (ddd, *J* = 9.5 Hz, 5.7 Hz, 4.7 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 171.1, 61.9 (+), 32.5 (+), 21.2 (+), 19.9 (+), 18.0 (-); FTIR (teflon, film, cm^{-1}): 3501, 3082, 3069, 3003, 2966, 2937, 2901, 1655, 1475, 1462, 1421, 1391, 1327, 1207, 1177, 1153, 1105, 1016, 997, 943, 760, 727, 609, 582, 507, 440; HRMS (TOF ES): found 207.9974, calculated for C6H11BrNO2 (M+H) 207.9973 (0.5 ppm).

2.6.4. Preparation of Nucleophiles

Thiols

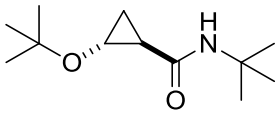


2-(Phenylamino)ethanethiol:[80] An oven dried 250 mL round bottom flask equipped with a reflux condenser was charged with 2-(phenylamino)ethanol (686 mg, 5.00 mmol), 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, 1.01 g, 2.50 mmol) and dry toluene (150 mL). The mixture was stirred at reflux for 1 hr, and then filtered through a frit funnel. The filtrate was concentrated, and the crude residual oil was distilled in vacuum. (Kugelrohr oven temperature 250 ^{o}C, at 2.5 torr) to yield colorless oil (475 mg, 3.10 mmol, 62% yield). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.22 (app. t, *J* = 8.2 Hz, 7.3 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 3.39 (t, *J* = 6.3 Hz, 2H), 2.81 (q, *J* = 6.6 Hz, 2H), 1.44 (t, *J* = 6.9 Hz, 1H, 1H, suppressed after treatment with D_2O); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 147.7, 129.4 (+, 2C), 117.9 (+), 113.2 (+, 2C), 42.4 (-), 32.8 (-).



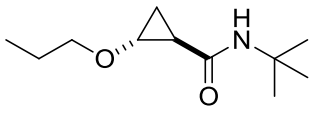
3-(Benzylthio)propane-1-thiol:[81] An oven dried 250 mL round bottom flask was charged with 1,3-propanedithiol (2.16 g, 20 mmol, 1.1 equiv) and tetrabutylammonium iodide (150 mg, 0.40 mmol, 2.2 mol%) in dry THF (100 mL). The mixture was stirred at room temperature and sodium hydride (60% suspension in mineral oil, 0.80 g, 20 mmol, 1.1 equiv.) was added by portions. The resulting mixture was stirred for 30 minutes, then benzyl bromide (2.1 mL, 3.1 g, 18 mmol) was added dropwise. The solution was stirred for 1 hr at room temperature, then filtered on a frit funnel and concentrated in vacuum. The resulting crude oil was distilled in vacuum to afford the title compound as colorless oil, bp 135-136 ^{o}C (1.0 torr). Yield 1.82 g (9.19 mmol, 51%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.30-7.25 (m, 1H), 3.74 (s, 2H), 2.62 (dt, *J* = 7.9 Hz, 6.9 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 1.87 (quin, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 8.0 Hz, 1H, suppressed after treatment with D_2O); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 138.3, 128.8 (+, 2C), 128.4 (+, 2C), 126.9 (+), 36.2 (-), 32.9 (-), 29.5 (-), 23.3 (-); HRMS (TOF ES): found 199.0613, calculated for $C_{10}H_{15}S_2$ (M+H) 199.0615 (1.0 ppm);

2.6.5. Alkoxide adducts



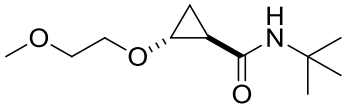
(1*R,2*R**)-2-*tert*-butoxy-*N*-(*tert*-butyl)cyclopropanecarboxamide** (**72a**): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (219 mg, 1.00 mmol), 18-crown-6 (26.4 mg, 0.10 mmol, 10 mol%), *t*-BuOK (281 mg, 2.50 mmol, 2.5 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 20 ^{o}C for 1 hr, when GC analysis showed full consumption of starting material and formation of two diastereomeric adducts in a ratio ~1:1. Further stirring at 80 ^{o}C

for 12 hrs caused *cis*- to *trans*-isomerization, achieving the final diastereomeric ratio ~10:1. The mixture was partitioned between water (50 mL) and EtOAc (15 mL). Organic layer was separated; aqueous phase was extracted with EtOAc (2 x 15 mL). Combined organic phases were washed with brine (20 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (eluent hexane/EtOAc 3:1, R*f* 0.45) to afford the title compound as crystalline white solid, mp. 98-99 ^oC Yield 148 mg (0.69 mmol, 69%) ^1H NMR (500.19 MHz, $CDCl_3$) δ 5.46 (br.s, 1H), 3.48 (ddd, *J* = 6.6 Hz, 4.4 Hz, 2.2 Hz, 1H), 1.37-1.33 (m, 1H), 1.35 (s, 9H), 1.25 (s, 9H), 1.22 (ddd, *J* = 6.6 Hz, 5.7 Hz, 5.4 Hz, 1H), 0.97 (ddd, *J* = 9.5 Hz, 5.4 Hz, 4.4 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.8, 75.4, 53.1 (+), 51.2, 28.9 (+, 3C), 28.1 (+, 3C), 24.1 (+), 14.3 (-); IR (film, cm^{-1}): 3317, 2974, 2934, 1643, 1549, 1456, 1435, 1393, 1366, 1258, 1227, 1196, 1099, 945, 930, 908, 866; HRMS (TOF ES): found 236.1627, calculated for $C_{12}H_{23}NO_2Na$ (M+Na) 236.1626 (0.4 ppm).

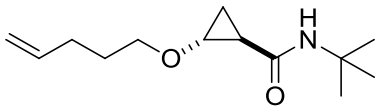


(1*R,2*R**)-*N*-(*tert*-butyl)-2-propoxycyclopropanecarboxamide** (**72b**): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (220 mg, 1.00 mmol), 18-crown- 6 (16.4 mg, 0.10 mmol, 10 mol%), powdered KOH (112 mg, 2.00 mmol, 2.00 equiv.), 1- propanol (180 mg, 3.00 mmol, 3.00 equiv.), and anhydrous THF (10 mL). The mixture was stirred at 85 ^oC for 12 hrs, then filtered through a fritted funnel and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (eluent hexane:EtOAc 4:1; R*f* 0.30) to afford the title compound as colorless solid, mp 61-63 ^oC . Yield 143 mg (0.72 mmol, 72%), d.r. 9:1 (GC). ^1H NMR (500.19 MHz, $CDCl_3$) δ 5.49 (br.s, 1H), 3.55 (ddd, *J* = 6.3 Hz, 4.1 Hz, 2.2 Hz, 1H), 3.51-3.44

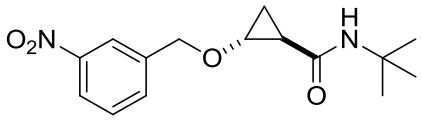
(m, 2H), 1.59 (sextet, J = 7.3 Hz, 2H), 1.44 (ddd, J = 9.5 Hz, 5.7 Hz, 2.2 Hz, 1H), 1.35 (s, 9H), 1.20 (ddd, J = Hz, 1H), 1.03 (ddd, J = 9.5 Hz, 5.4 Hz, 4.1 Hz, 1H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.5, 72.6 (-), 59.3 (+), 51.2, 28.9 (+, 3C), 23.6 (+), 22.7 (-), 14.1 (-), 10.5 (+); IR (film, cm^{-1}): 3315, 2966, 2934, 1641, 1549, 1456, 1443, 1391, 1364, 1255, 1224, 1200, 1177, 1099, 974; HRMS (TOF ES): found 222.1479, calculated for $C_{11}H_{21}NO_2Na$ (M+Na) 222.1470 (4.1 ppm).



(1*R,2*R**)-*N*-*tert*-Butyl-2-(2-methoxyethoxy)cyclopropanecarboxamide** (**72c**): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 2-methoxyethanol (79 μL, 76.1 mg, 1.00 mmol, 2 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 2:1) to afford the title compound as a colorless oil. Yield 104 mg (0.49 mmol, 97%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.47 (br.s., 1H), 3.62-3.73 (m, 2H), 3.58 (ddd, J = 5.3 Hz, 3.5 Hz, 2.2 Hz, 1H), 3.52 (t, J = 4.4 Hz, 2H), 3.37 (s, 3H), 1.49 (ddd, J = 9.5 Hz, 6.0 Hz, 2.2 Hz, 1H), 1.33 (s, 9H), 1.20 (ddd, J = 6.3 Hz, 6.0 Hz, 5.3 Hz, 1H), 1.07 (ddd, J = 9.5 Hz, 6.3 Hz, 3.5 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.3, 71.4 (-), 69.9 (-), 59.7 (+), 58.9 (+), 51.2, 28.8 (+, 3C), 23.5 (+), 14.0 (-); IR (KBr, cm^{-1}): 3321, 2966, 2928, 2881, 1645, 1549, 1456, 1393, 1366, 1331, 1256, 1227, 1202, 1173, 1128, 1099, 1030, 962, 928, 908, 878, 865; HRMS (TOF ES): found 216.1599, calculated for $C_{11}H_{22}NO_3$ (M+H) 216.1600 (0.5 ppm).

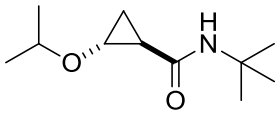


(1*R,2*R**)-*N*-*tert*-Butyl-2-(pent-4-en-1-yloxy)cyclopropanecarboxamide** (**72e**): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 4- penten-1-ol (103 μL, 86.1 mg, 1.00 mmol, 2.0 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 10:1) to afford the title compound as a colorless oil. Yield 96 mg (0.43 mmol, 85%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.0 Hz, 10.3 Hz, 6.6 Hz, 1H), 5.46 (br. s., 1H), 5.04 (ddt, *J* = 17.0 Hz, 1.8 Hz, 1.5 Hz, 1H), 4.99 (ddt, *J* = 10.4 Hz, 2.0 Hz, 1.0 Hz, 1H), 3.60-3.47 (m, 3H), 2.17-2.05 (m, 2H), 1.79-1.55 (m, 4H), 1.44 (ddd, *J* = 9.3 Hz, 5.8 Hz, 2.0 Hz, 1H), 1.36 (s, 9H), 1.20 (q, *J* = 6.1 Hz, 1H), 1.04 (ddd, *J* = 9.4 Hz, 5.3 Hz, 4.0 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.5, 138.0 (+), 114.9 (-), 70.2 (-), 59.4 (+), 51.3, 30.2 (-), 28.9 (+, 3C), 28.6 (-), 23.6 (+), 14.1 (-); IR (KBr, cm^{-1}): 3317, 3078, 2964, 2928, 2868, 1643, 1549, 1456, 1441, 1391, 1381, 1364, 1256, 1225, 1200, 1169, 1101, 1076, 1043, 995, 962, 910, 881; HRMS (TOF ES): found 226.1811, calculated for $C_{13}H_{24}NO_2$ (M+H) 226.1807 (1.8 ppm).



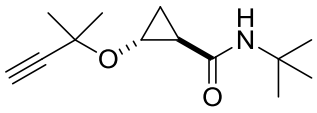
(1*R,2*R**)-*N*-*tert*-Butyl-2-(3-nitrobenzyloxy)cyclopropanecarboxamide** (**72g**): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 3-nitrobenzyl alcohol (153 mg, 1.00 mmol, 2 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then filtered through a fritted funnel and concentrated. The

residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 10:1) to afford the title compound as a colorless oil. Yield 96 mg (0.41 mmol, 81%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 8.20 (t, *J* = 2.2 Hz, 1H), 8.16 (dd, *J* = 8.2 Hz, 2.2 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 5.45 (br. s., 1H), 4.69 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 12.3 Hz, 1H), 3.67 (ddd, *J* = 6.4 Hz, 4.0 Hz, 1.9 Hz, 1H), 1.52 (ddd, *J* = 9.7 Hz, 5.9 Hz, 2.0 Hz, 1H), 1.34 (s, 9 H), 1.25 (ddd, *J* = 6.4 Hz, 5.9 Hz, 5.6 Hz, 1H), 1.12 (ddd, *J* = 9.5 Hz, 5.6 Hz, 4.1 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.0, 148.3, 139.8, 133.5 (+), 129.3 (+), 122.7 (+), 122.4 (+), 71.6 (-), 59.6 (+), 51.3, 28.8 (+, 3C), 23.6 (+), 14.1 (-); IR (KBr, cm^{-1}): 3304, 2968, 2928, 1639, 1531, 1456, 1350, 1254, 1225, 1202, 1165, 1099, 810, 731, 671; HRMS (TOF ES): found 293.1506, calculated for $C_{15}H_{21}N_2O_4$ (M-H) 293.1501 (1.7 ppm).

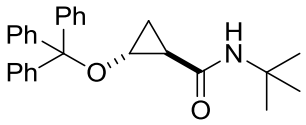


(1*R,2*R**)-*N*-(*tert*-butyl)-2-isopropoxycyclopropanecarboxamide** (**72n**): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (220 mg, 1.00 mmol), 18-crown-6 (16.4 mg, 0.10 mmol, 10%), powdered KOH (112 mg, 2.00 mmol, 2.00 equiv.), 2- propanol (180 mg, 3.00 mmol, 3.00 equiv.), and anhydrous THF (10 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane:EtOAc 4:1; R*f* 0.29) to afford the title compound as a white needles, mp. 84-86 ^{o}C . Yield 141 mg (0.71 mmol, 71%), d.r. 9:1 (GC). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.49 (br.s, 1H), 3.75 (septet, *J* = 6.1 Hz, 1H), 3.54 (ddd, *J* = 6.3 Hz, 4.0 Hz, 2.0 Hz, 1H), 1.43 (ddd, *J* = 9.3 Hz, 5.8 Hz, 2.0 Hz, 1H), 1.34 (s, 9H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.21 (m, 1H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.01 (ddd, *J* = 9.3 Hz, 5.3 Hz, 4.0 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 170.6, 72.3 (+), 57.3 (+), 51.2, 28.9 (+, 3C), 23.8 (+), 22.3 (+), 22.1 (+), 14.1 (-);

IR (film, cm^{-1}): 3315, 2972, 2931, 1641, 1549, 1456, 1436, 1394, 1364, 1258, 1225, 1200, 1182, 1097, 957, 889; HRMS (TOF ES): found 200.1644, calculated for $C_{11}H_{22}NO_2$ (M+H) 200.1651 (3.5 ppm).

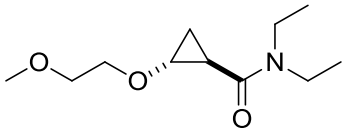


(1*R,2*R**)-*N*-*tert*-Butyl-2-(2-methylbut-3-yn-2-yloxy)cyclopropanecarboxamide** (**72o**): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 2-methyl-3-butyn-2-ol (97 μL, 84.1 mg, 1.00 mmol, 2 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 10:1) to afford the title compound as a white needle-like solid, mp. 56-58 ^{o}C . Yield 66 mg (0.30 mmol, 59%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.48 (br. s, 1H), 3.74 (ddd, *J* = 6.9 Hz, 4.1 Hz, 2.2 Hz, 1H), 2.49 (s, 1H), 1.53 (s, 3H), 1.52 (m, 1H), 1.51 (s, 3H), 1.36 (s, 9H), 1.27 (m, 1H), 1.08 (ddd, *J* = 9.5 Hz, 5.7 Hz, 4.1 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.5, 86.2, 72.6 (+), 71.3, 54.9 (+), 51.2, 29.3 (+), 28.9 (+, 3C), 28.7 (+), 23.9 (+), 13.4 (-); IR (KBr, cm^{-1}): 3310, 2970, 2934, 1643, 1549, 1456, 1435, 1394, 1381, 1364, 1258, 1227, 1194, 1148, 1097, 955, 908, 864, 654, 632, 444, 432; HRMS (TOF ES): found 246.1481, calculated for $C_{13}H_{21}NO_2Na$ (M+Na) 246.1470 (4.5 ppm).



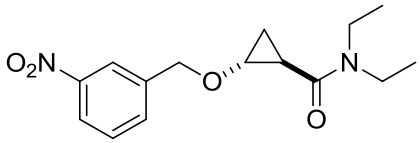
(1*R,2*R**)-*N*-*tert*-Butyl-2-(trityloxy)cyclopropanecarboxamide** (**72p**): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%),

powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), triphenylmethanol (260 mg, 1.00 mmol, 2 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs. then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 10:1) to afford the title compound as a white solid, mp. 176-184 ^{o}C (dec). Yield 90 mg (0.23 mmol, 45%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.43-7.51 (m, 6H), 7.30-7.36 (m, 6H), 7.24-7.30 (m, 3H), 4.52 (br.s, 1H), 3.53 (ddd, *J* = 7.1 Hz, 3.9 Hz, 1.9 Hz, 1H), 1.23 (s, 9H), 1.18 (ddd, *J* = 7.1 Hz, 5.9 Hz, 5.3 Hz, 1H), 1.04 (ddd, *J* = 9.2 Hz, 5.3 Hz, 4.1 Hz, 1H), 0.75 (ddd, *J* = 9.1 Hz, 5.9 Hz, 2.0 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.0, 144.1 (3C), 128.7 (+, 6C), 127.9 (+, 6C), 127.0 (+, 3C), 87.6, 54.9 (+), 50.9, 28.8 (+, 3C), 25.0 (+), 12.3 (-); IR (film, cm^{-1}): 3085, 3057, 2996, 2358, 1660, 1643, 1590, 1448, 1391, 1151; HRMS (TOF ES): found 422.2092, calculated for $C_{27}H_{29}NO_2Na$ (M+Na) 222.2096 (0.9 ppm).

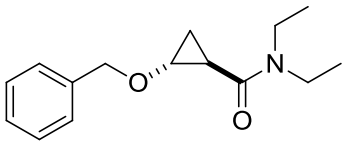


(1*R,2*R**)-*N*,*N*-Diethyl-2-(2-methoxyethoxy)cyclopropanecarboxamide** (**72d**): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70b** (110 mg, 0.50 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.50 equiv.), 2-methoxyethanol (76 mg, 1.00 mmol, 2.00 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 80 ^{o}C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 2:1, R*f* 0.13) to afford the title compound as a colorless oil. Yield 93 mg (0.43 mmol, 87%), dr 6:1 (GC). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.76-3.63 (m, 3H), 3.53 (t, *J* = 4.6 Hz, 2H), 3.47 (dq, *J* = 11.7 Hz, 7.4 Hz, 2H), 3.41-3.33 (m, 2H), 3.38 (s, 3H), 1.94 (ddd, *J* = 9.5 Hz, 5.9 Hz, 2.3 Hz, 1H), 1.31-1.22 (m, 4H), 1.17 (ddd, *J* = 9.4 Hz, 5.2 Hz, 3.8 Hz, 1H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125.76

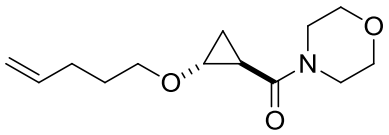
MHz, $CDCl_3$) δ ppm 170.4, 71.4 (-), 70.0 (-), 60.8 (+), 59.0 (+), 42.1 (-), 40.6 (-), 19.5 (+), 15.3 (+), 14.8 (-), 13.1 (+); IR (film, cm^{-1}): 2976, 2932, 2876, 1632, 1483, 1462, 1452, 1379, 1360, 1256, 1208, 1130, 1097, 1032, 957; GC: 9.71 min (major); 9.75 min (minor). HRMS (TOF ES): found 222.1682 calculated for $C_{11}H_{21}NO_3Li$ (M+Li) 222.1681 (0.5 ppm)



(1*R,2*R**)-*N*,*N*-Diethyl-2-[(3-nitrobenzyl)oxy]cyclopropanecarboxamide** (**72h**): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70b** (110 mg, 0.50 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.50 equiv.), 3-nitrobenzyl alcohol (153 mg, 1.00 mmol, 2.00 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 80 ^oC for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 3:1, R*f* 0.19) to afford the title compound as a white solid, mp. 83-85 ^oC . Yield 136 mg (0.46 mmol, 92%) dr 7:1 (GC). ^1H NMR (500.13 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 4.70 (d, *J* = 12.3 Hz, 1H), 4.65 (d, *J* = 12.3 Hz, 1H), 3.76 (ddd, *J* = 6.3 Hz, 4.1 Hz, 2.2 Hz, 1H), 3.46 (q, *J* = 7.3 Hz, 2H), 3.38 (q, *J* = 7.0 Hz, 2H), 1.97 (ddd, *J* = 9.8 Hz, 6.0 Hz, 2.2 Hz, 1H), 1.32 (ddd, *J* = 6.3 Hz, 6.0 Hz, 5.3 Hz, 1H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.21 (ddd, *J* = 9.5 Hz, 5.3 Hz, 3.8 Hz, 1H), 1.11 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.1, 148.4, 139.8, 133.5 (+), 129.4 (+), 122.8 (+), 122.4 (+), 71.7 (-), 60.6 (+), 42.2 (-), 40.7 (-), 19.7 (+), 15.3 (+), 14.9 (-), 13.2 (+); IR (KBr, cm^{-1}): 3450, 2976, 2932, 1632, 1585, 1529, 1483, 1462, 1427, 1379, 1350, 1321, 1256, 1209, 1171, 1138, 1095, 10559, 1022, 960, 891, 808, 733, 689, 673, 420, 411; GC: 13.86 min (major); 13.99 min (minor). HRMS (TOF ES): found 293.1500, calculated for $C_{15}H_{21}N_2O_4$ (M+H) 293.1501 (0.3 ppm).

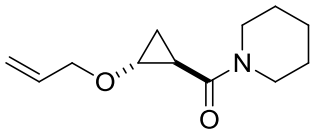


(1*R,2*R**)-2-(benzyloxy)-*N*,*N*-diethylcyclopropanecarboxamide** (**72i**): An oven-dried 100 mL pressure tube was charged with bromocyclopropane **70b** (1.80 g, 8.18 mmol), 18-crown-6 (216 mg, 0.82 mmol, 10 mol%), powdered KOH (1.60 g, 28.6 mmol, 3.50 equiv.), benzyl alcohol (1.67 g, 15.6 mmol, 2.00 equiv.), and anhydrous THF (80 mL). The mixture was stirred at 80 ^{o}C for 12 hrs, then filtered through a silica gel plug eluting with DCM to remove 18-crown-6 and concentrated. Te residue was purified by short path distillation (60 ^{o}C, 0.008 torr) to afford the title compound as clear oil. Yield 1.75 g (7.09 mmol, 87%), dr 6:1 (GC). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 3.73 (ddd, *J* = 6.4 Hz, 4.0 Hz, 2.2 Hz, 1H), 3.46-3.31 (m, 4H), 1.91 (ddd, *J* = 9.5 Hz, 5.8 Hz, 2.0 Hz, 1H), 1.31 (ddd, *J* = 6.4 Hz, 5.8 Hz, 5.4 Hz, 1H), 1.24 (t, *J* = 7.3 Hz, 3H), 1.19 (ddd, *J* = 9.1 Hz, 5.4 Hz, 4.1 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.4, 137.6, 128.4 (+, 2C), 128.0 (+, 2C), 127.8 (+), 73.2 (-), 60.5 (+), 42.1 (-), 40.6 (-), 19.8 (+), 15.1 (-), 14.8 (+), 13.2 (+); IR (film, cm^{-1}): 3030, 2974, 2931, 1632, 1483, 1454, 1379, 1362, 1321, 1254, 1209, 1167, 1138, 1095, 1053, 955, 739, 698; GC: 11.73 min (major); 11.83 min (minor); HRMS (TOF ES): found 248.1665 calculated for $C_{15}H_{22}NO_2$ (M+H) 248.1651 (5.6 ppm).



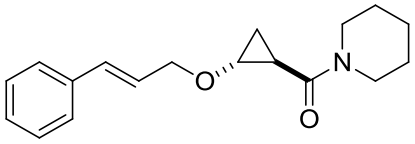
4-Morpholino((1*R,2*R**)-2-(pent-4-enyloxy)cyclopropyl)-methanone** (**72f**): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70c** (117 mg, 0.50 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.50 equiv.), 4-pentene-1-ol (86 mg, 1.00 mmol, 2.00 equiv), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 13 hrs. The

solvent was removed in vacuum, and the residue was purified by flash column chromatography on silica gel (eluent hexane/EtOAc 5:1, R*f*: 4-pentene-1-ol 0.3, major 0.15 minor 0.04). After seperation of 4-pentene-1-ol the eluent polarity was increased (hexane/EtOAc 1:1; R*f*: major 0.38 minor 0.15) to afford the title compound as clear oil. Yield 100 mg (0.42 mmol, 84%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.1 Hz, 10.3 Hz, 6.6 Hz, 1H), 5.01 (dq, *J* = 17.0 Hz, 1.6 Hz, 1H), 4.97 (dq, *J* = 10.4 Hz, 1.6 Hz, 1H), 3.70-3.60 (br. m., 8H), 3.59 (ddd, *J* = 6.3 Hz, 4.4 Hz, 2.5 Hz, 1H), 3.54 (dt, *J* = 9.5 Hz, 6.5 Hz, 1H), 3.48 (dt, *J* = 9.5 Hz, 6.6 Hz, 1H), 2.09 (q, *J* = 7.0 Hz, 2H), 1.86 (ddd, *J* = 9.4 Hz, 5.9 Hz, 2.1 Hz, 1H), 1.66 (quin, *J* = 7.0 Hz, 2H), 1.30 (ddd, *J* = 6.3 Hz, 5.9 Hz, 5.0 Hz, 1H), 1.14 (dt, *J* = 9.4 Hz, 5.0 Hz, 4.4 Hz, 1 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.2, 137.9 (+), 114.9 (-), 70.3 (-), 66.7 (-, 2C), 60.5 (+), 46.0 (-), 42.3 (-), 30.1 (-), 28.5 (-), 19.1 (+), 15.2 (-); GC: 11.33 min (major), 11.38 min (minor); IR (film, cm^{-1}): 2959, 2922, 2897, 2856, 1639, 1462, 1445, 1429, 1364, 1300, 1271, 1234, 1205, 1167, 1117, 1099, 1068, 1041, 995, 953, 914, 872, 847, 571; HRMS (TOF ES): found 262.1425, calculated for $C_{13}H_{21}NO_3Na$ (M+Na) 262.1419 (2.3 ppm).

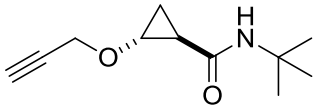


((1R,2R)-2-(Allyloxy)cyclopropyl)(piperidin-1-yl)methanone (**72k**): Was prepared according to Typical Procedure I, employing (2-bromocyclopropyl)(piperidin-1-yl)methanone (**70d**) (70 mg, 0.3 mmol, 1.0 equiv) and allylic alcohol (19.9 mg, 0.36 mmol, 1.2 equiv). The reaction was carried out at 50 ^{o}C for 12 hrs. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane/EtOAc 2:1). Yield 59 mg (0.29 mmol, 95%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 17.3 Hz, 10.4 Hz, 5.8 Hz, 1H), 5.28 (dq, *J* = 17.3 Hz, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.4 Hz, 1.3 Hz, 1H), 4.07 (ddt, *J* = 12.6 Hz, 5.6 Hz, 1.3 Hz, 1H), 4.02 (m, *J* = 12.6

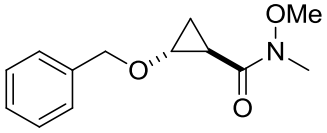
Hz, 5.8 Hz, 1.5 Hz, 1H), 3.63 (ddd, *J* = 6.3 Hz, 3.8 Hz, 2.3 Hz, 1H), 3.62-3.52 (m, 4H), 1.97 (ddd, *J* = 9.5 Hz, 5.9 Hz, 2.0 Hz, 1H), 1.71-1.58 (m, 4H), 1.58-1.49 (m, 2H), 1.29 (td, *J* = 6.3 Hz, 5.9 Hz, 5.3 Hz, 1H), 1.14 (ddd, *J* = 9.5 Hz, 5.3 Hz, 3.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ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



((1R*,2R*)-2-(Cinnamyloxy)cyclopropyl)(piperidin-1-yl)methanone (**72l**): Was prepared according to Typical Procedure I, employing (2-bromocyclopropyl)(piperidin-1-yl)methanone (**70d**) (62 mg, 0.30 mmol, 1.0 equiv) and cinnamyl alcohol (44 mg, 0.36 mmol, 1.2 equiv). The reaction was carried out at 60 ^{o}C for 12 hrs. Preparative column chromatography of a residue on silica gel afforded the title compound as a colorless oil, R_f 0.40 (hexane/EtOAc 2:3). Yield 69 mg (0.24 mmol, 81%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.43-7.37 (m, 2H), 7.37-7.30 (m, 2H), 7.30-7.23 (m, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.9 Hz, 6.2 Hz, 1H), 4.27 (ddd, *J* = 12.5 Hz, 5.9 Hz, 1.3 Hz, 1H), 4.20 (ddd, *J* = 12.4 Hz, 6.4 Hz, 1.4 Hz, 1H), 3.71 (ddd, *J* = 6.4 Hz, 4.0 Hz, 2.0 Hz, 1H), 3.66-3.47 (m, 4H), 2.02 (ddd, *J* = 9.6 Hz, 5.9 Hz, 2.1 Hz, 1H), 1.70-1.49 (m, 6H), 1.33 (ddd, *J* = 6.4 Hz, 5.9 Hz, 5.3 Hz, 1H), 1.19 (ddd, *J* = 9.5 Hz, 5.3 Hz, 3.9 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.5, 136.4, 132.9 (+), 128.5 (+, 2C), 127.8 (+), 126.5 (+, 2C), 125.2 (+), 71.6 (-), 60.3 (+), 46.7 (-), 43.1 (-), 26.6 (-), 25.5 (-), 24.6 (-), 19.5 (+), 14.9 (-); FT IR (KBr, cm^{-1}): 3059, 3024, 2935, 2855, 1634, 1446, 1225; HRMS (TOF ES): found 286.1801, calculated for $C_{18}H_{24}NO_2$ (M+H) 286.1807 (2.1 ppm).

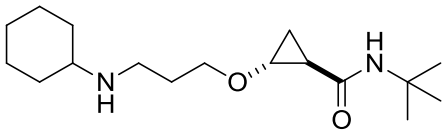


(1R*,2R*)-N-(tert-Butyl)-2-(prop-2-yn-1-yloxy)cyclopropanecarboxamide (**72m**): Was prepared according to Typical Procedure I, employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**70a**) (66 mg, 0.30 mmol, 1.0 equiv) and propargyl alcohol (21 mg, 0.32 mmol, 1.2 equiv). The reaction was carried out at 60 ^{o}C for 3 hrs. Preparative column chromatography of a residual oil on silica gel afforded the title compound as a colorles oil, R_f 0.30 (hexane/EtOAc, 4:1). Yield 46 mg (0.23 mmol, 78%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.46 (br. s., 1 H), 4.24-4.19 (m, 1H), 4.19-4.14 (m, 1H), 3.71 (ddd, *J* = 6.4 Hz, 4.0 Hz, 2.2 Hz, 1H), 2.46 (t, *J* = 2.5 Hz, 1H), 1.55 (ddd, *J* = 9.6 Hz, 6.0 Hz, 2.0 Hz, 1H), 1.35 (s, 9H), 1.24 (q, *J* = 6.0 Hz, 1H), 1.10 (ddd, *J* = 9.5 Hz, 5.6 Hz, 4.1 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.0, 79.3, 74.7 (+), 59.4 (+), 58.2 (-), 51.3, 28.9 (+, 3C), 23.5 (+), 13.6 (-); FT IR (NaCl, cm^{-1}): 3308, 3078, 2968, 2930, 2870, 1724, 1643, 1549, 1537, 1479, 1454, 1394, 1364, 1331, 1256, 1227, 1202, 1153, 1097, 1061, 1043, 1026, 995, 986, 955, 926, 910, 893, 878, 764, 737, 665, 635; HRMS (TOF ES): found 196.1341, calculated for $C_{11}H_{18}NO_2$ (M+H) 196.1338 (1.5 ppm).



(1R,2R)-2-(Benzyloxy)-N-methoxy-N-methylcyclopropanecarboxamide (**72q**): An oven dried 5 mL Wheaton vial was charged with *t*-BuOK (135 mg, 1.20 mmol, 2.5 equiv.), 18-crown-6 (13 mg, 50 μmol, 10 mol%), benzyl alcohol (124 mL, 130 mg, 1.20 mmol, 2.50 equiv), and anhydrous THF (3 mL). The mixture was stirred at room temperature and bromocyclopropane **70e** (100 mg, 0.48 mmol) was injected via syringe. The resulting dark-brown mixture was stirred at room temperature for 1 hr, then the formed precipitate of KBr was filtered off using a short plug of

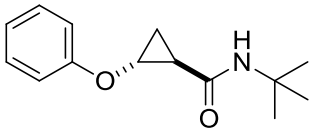
celite, and the filtrate was concentrated in vacuum. Flash column chromatography of a residual dark crude oil silica gel afforded the title compound as colorless oil, R_f 0.33 (hexane/EtOAc 1:1). Yield 50 mg (0.21 mmol, 44%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 3.73 (s, 3H), 3.70 (ddd, *J* = 6.5 Hz, 4.3 Hz, 1.9 Hz, 1H), 3.19 (s, 3H), 2.36 (br. s., 1H), 1.35-1.24 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 172.6, 137.3, 128.4 (+, 2C), 127.9 (+, 2C), 127.8 (+), 73.2 (-), 61.5 (+), 60.7 (+), 32.4 (+), 18.6 (+), 15.4 (-); FT IR (film, cm^{-1}): 3030, 3005, 2964, 2935, 2897, 2866, 1661, 1643, 1495, 1454, 1445, 1418, 1385, 1350, 1211, 1175, 1155, 1113, 1086, 1047, 1028, 1005, 972, 951, 897, 872, 741, 698, 611, 440; HRMS (TOF ES): found 258.1117, calculated for $C_{13}H_{17}NO_3Na$ (M+Na) 258.1106 (4.3 ppm).



(1R*,2R*)-N-(tert-Butyl)-2-(3-(cyclohexylamino)propoxy)cyclopropanecarboxamide (**72j**) (Typical Procedure I): An oven-dried 10 mL Weaton vial was charged with 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**70a**) (110 mg, 0.5 mmol), 18-crown-6 (13 mg, 50 μmol, 10 mol%), powdered KOH (62 mg, 1.1 mmol, 2.2 equiv.), *N*-cyclohexylaminopropanol (157 mg, 1.0 mmol, 2.0 equiv), and anhydrous THF (5 mL). The mixture was stirred at 85 °^{o}C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel, eluting with a mixture EtOAc/triethylamine 95:5. The title compound was isolated as an amorphous yellow solid, R_f 0.26. Yield 116 mg (0.39 mmol, 78%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.68 (br. s., 1H), 3.53 (t, *J* = 6.1 Hz, 2H), 3.44 (ddd, *J* = 6.5 Hz, 4.1 Hz, 2.0 Hz, 1H), 2.73-2.62 (m, 2H), 2.43 (tt, *J* = 10.6 Hz, 3.6 Hz, 1H), 1.91-1.82 (m, 2H), 1.82-1.63 (m, 4H), 1.56 (dt, *J* = 12.5 Hz, 3.2 Hz, 1H), 1.43 (ddd, *J* = 9.6 Hz, 5.8 Hz, 1.9 Hz, 1H), 1.27 (s, 9H), 1.24-1.01 (m, 7H), 0.94 (ddd, *J* = 9.5

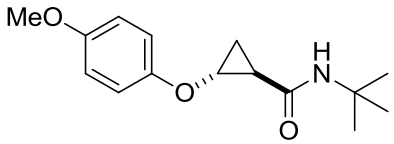
Hz, 5.4 Hz, 4.1 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.5, 69.2 (-), 59.5 (+), 57.0 (+), 51.2, 43.7 (-), 32.71 (-), 32.65 (-), 29.4 (-), 28.9 (+, 3C), 25.9 (-), 24.9 (-, 2C), 23.5 (+), 13.9 (-); FTIR (NaCl, film, cm[1]): 3300, 2928, 2854, 1643, 1549, 1454, 1391, 1381, 1364, 1333, 1258, 1225, 1200, 1169, 1099, 1078, 1047, 1034, 964, 889, 802, 764, 748, 702, 405; HRMS (TOF ES): found 319.2362, calculated for $C_{17}H_{32}N_2O_2Na$ (M+Na) 319.2361 (0.3 ppm).

2.6.6. Phenoxide adducts



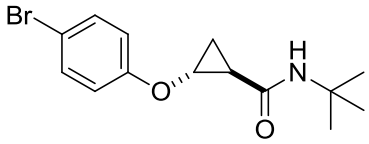
(1*R,2*R**)-*N*-(*tert*-butyl)-2-phenoxycyclopropanecarboxamide (73a)**: An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (220 mg, 1.00 mmol), 18-crown- 6 (26.4 mg, 0.10 mmol, 10 mol%), powdered KOH (196 mg, 3.50 mmol, 3.5 equiv.), phenol (188.2 mg, 2.00 mmol, 2 equiv.), and anhydrous THF (7 mL). The mixture was stirred at 80 ^{o}C for 14 hrs. The mixture was partitioned between 3N aqueous NaOH (20 mL) and EtOAc (10 mL). Organic layer was separated and washed with NaOH solution (2 x 10 mL). Combined aqueous phases were extracted with EtOAc (3 x 10 mL). Combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (eluent hexane/EtOAc 6:1; R*f*: 0.45) to afford the title compound as colorless solid, mp. 73-74 ^{o}C . Yield 185 mg (0.79 mmol, 79%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.03-6.99 (m, 3H), 5.57 (br.s, 1H), 4.04 (ddd, *J* = 6.0 Hz, 3.8 Hz, 2.2 Hz, 1H), 1.60 (ddd, *J* = 9.5 Hz, 6.0 Hz, 2.2 Hz, 1H), 1.51 (ps.-q, *J* = 6.3 Hz, 6.0 Hz, 1H), 1.41 (s, 9H), 1.30-1.26 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.8, 158.2, 129.5 (+, 2C),

121.4 (+), 114.8 (+, 2C), 56.5 (+), 51.5, 28.9 (+, 3C), 24.0 (+), 14.3 (-); IR (KBr, cm^{-1}): 3319, 3083, 2966, 2930, 2870, 2856, 1641, 1601, 1560, 1497, 1458, 1437, 1396, 1364, 1242, 1221, 978, 752; GC: 10.86 min (major), 10.96 min (minor). HRMS (TOF ES): found 234.1502, calculated for $C_{14}H_{20}NO_2$ (M+H) 234.1494 (3.4 ppm).



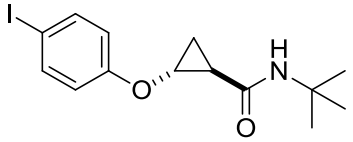
***N*-(*tert*-butyl)-2-(4-methoxyphenoxy)cyclopropanecarboxamide (73b):** An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (220 mg, 1.00 mmol), 18-crown-6 (26.4 mg, 0.10 mmol, 10 mol%), powdered KOH (280 mg, 5.00 mmol, 5 equiv.), *p*-methoxyphenol (372.4 mg, 3.00 mmol, 3 equiv), and anhydrous THF (7 mL). The mixture was stirred at 60 ^oC for 14 hrs. The mixture was partitioned between between 3N aqueous NaOH (20 mL) and EtOAc (10 mL). Further work up was performed in the same way as described in protocol for the preparation of compound **73a**. The residue was purified by flash column chromatography on silica gel (eluent hexane/EtOAc 5:1) to afford the title compound as white crystalline solid, mp. 93-94 ^oC . Yield 196 mg (0.75 mmol, 75%). (**1*R**,2*R**-73b**), major: ^1H NMR (500.13 MHz, $CDCl_3$) δ 6.92 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 5.55 (br.s, 1H), 4.00 (ddd, *J* = 6.6 Hz, 3.8 Hz, 2.2 Hz, 1H), 3.80 (s, 3H), 1.58 (ddd, *J* = 9.5 Hz, 6.0 Hz, 2.2 Hz, 1H), 1.48 (ps.-q, *J* = 6.0 Hz, 1H), 1.40 (s, 9H), 1.25 (ddd, *J* = 9.5 Hz, 5.4 Hz, 3.8 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.8, 154.3, 152.2, 115.5 (+, 2C), 114.7 (+, 2C), 56.9 (+), 55.7 (+), 51.5, 28.9 (+, 3C), 24.0 (+), 14.4 (-); IR (KBr, cm^{-1}): 3329, 2997, 2970, 2935, 2908, 1659, 1639, 1553, 1506, 1460, 1433, 1394, 1366, 1232, 1215, 1177, 1034, 1026, 966, 827; GC: R*t* 12.18 min; HRMS (TOF ES): found 264.1606, calculated for $C_{15}H_{22}NO_3$ (M+) 264.1600 (2.3 ppm).

(**1*R**,2*S**-73b**), minor: ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.99 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 5.60 (br.s, 1H), 3.89 (td, *J* = 6.3 Hz, 4.4 Hz, 1H), 3.79 (s, 3H), 1.78 (dt, *J* = 9.8 Hz, 6.8 Hz, 1H), 1.42 (td, *J* = 6.9 Hz, 4.1 Hz, 1H), 1.31 (dt, *J* = 10.1 Hz, 6.3 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 168.2, 154.6, 151.9, 115.6 (+, 2C), 114.7 (+, 2C), 55.7 (+), 55.1 (+), 50.9, 28.5 (+, 3C), 23.5 (+), 12.7 (-); GC: R*t* 12.23 min.

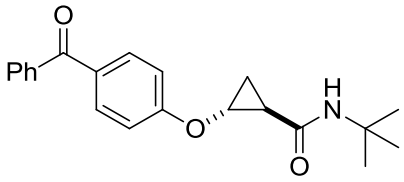


(1*R,2*R**)-2-(4-bromophenoxy)-*N*-*tert*-butylcyclopropanecarboxamide** (**73c**): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.50 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 4-bromophenol (173 mg, 1.00 mmol, 2.00 equiv) and anhydrous THF (5 mL). The mixture was stirred at 80 ^{o}C for 13hrs. The solvent was removed in vacuum, and the mixture was partitioned between base (5 N NaOH, 5 mL) and diethyl ether (15 mL). Combined organic phases were washed consecutively with aqueous NaOH (3N, 3 x 5 mL) and brine (10 mL), and then dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent hexane/EtOAc 6:1 R*f* major 0.32 minor 0.02) to afford the title compound as clear crystalline solid, mp. 122-125 ^{o}C . Yield 135 mg (0.43 mmol, 86%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 9.1 Hz, 2H), 5.58 (br.s., 1H), 4.01 (ddd, *J* = 6.4 Hz, 4.0 Hz, 2.2 Hz, 1H), 1.59 (ddd, *J* = 9.6 Hz, 6.1 Hz, 2.2 Hz, 1H), 1.50 (ddd, *J* = 6.4 Hz, 6.1 Hz, 5.7 Hz, 1H), 1.40 (s, 9H), 1.25 (ddd, *J* = 9.8 Hz, 5.7 Hz, 4.1 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.5, 157.4, 132.3 (+, 2C), 116.6 (+, 2C), 113.7, 56.7 (+), 51.6, 28.9 (+, 3C), 23.8 (+), 14.3 (-); IR (KBr, cm^{-1}): 3315, 3074, 3067, 2962, 2924, 2852, 1643, 1549, 1485, 1433,

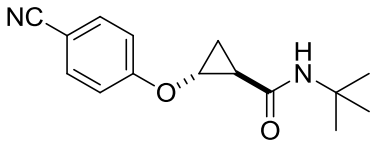
1394, 1364, 1283, 1238, 1070, 821; GC: 12.38 min (major), 12.49 min (minor); HRMS (TOF ES): found 312.0605, calculated for $C_{14}H_{19}BrNO_2$ (M+H) 312.0599 (1.9 ppm).



(1*R,2*R**)-*N*-*tert*-butyl-2-(4-iodophenoxy)cyclopropanecarboxamide** (**73d**): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 4-iodophenol (220 mg, 1.0 mmol, 2 equiv), and anhydrous THF (5 mL). The mixture was stirred at 105 ^{o}C for 8 hrs. The solvent was evaporated, then the mixture was partitioned between aqueous NaOH (3N, 10 mL) and diethyl ether (10 mL). Organic layer was washed consecutively with 3N NaOH (3 x 4 mL) and brine (5 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel, eluting first with mixture hexane/EtOAc 6:1 to separate the major diastereomer (R*f* 0.30), then with mixture hexane/EtOAc 1:1 to obtain the minor diastereomer (R*f* 0.32). The title compound was afforded as clear crystalline solid, mp. 101-102 ^{o}C . Yield 144 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 5.57 (br. s., 1H), 3.99 (ddd, *J* = 6.5 Hz, 3.9 Hz, 2.2 Hz, 1H), 1.57 (ddd, *J* = 9.8 Hz, 6.3 Hz, 2.2 Hz, 1H), 1.47 (ddd, *J* = 6.5 Hz, 6.3 Hz, 5.7 Hz, 1H), 1.38 (s, 9H), 1.23 (ddd, *J* = 9.6 Hz, 5.7 Hz, 3.9 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.5, 158.1, 138.3 (+, 2C), 117.2 (+, 2C), 83.6, 56.6 (+), 51.6, 28.9 (+, 3 ^{o}C), 23.8 (+), 14.3 (-); IR (KBr, cm^{-1}): 3306, 2961, 2918, 1637, 1551, 1485, 1429, 1393, 1335, 1281, 1261, 1236, 1217, 1171, 1028, 1001, 978, 845, 792; GC: 12.96 min (major), 13.05 min (minor); HRMS (TOF ES): found 360.0565, calculated for $C_{14}H_{19}INO_2$ (M+H) 360.0461 (1.1 ppm).

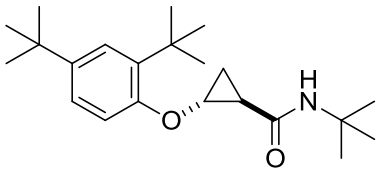


(1*R,2*R**)-*N*-*tert*-Butyl-2-[4-(phenylcarbonyl)-phenoxy]cyclopropanecarboxamide** (**73e**): Anoven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 4-hydroxy-benzophenone (198 mg, 1.0 mmol, 2 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 105 ^{o}C for 14 hrs. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography on silica gel elueting first with mixture hexane/EtOAc 5:1. After seperation of the major diasteromer (R*f* 0.19), 4-hydroxy-benzophenone the minor diasteromer were flushed out with EtOAc. The title compound was afforded as white crystalline solid, mp. 72-74 ^{o}C .. Yield 152 mg (0.45 mmol, 90%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.79-7.85 (m, 2H), 7.74-7.78 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.01-7.07 (m, 2H), 5.63 (br. s, 1H), 4.11 (ddd, *J* = 6.4 Hz, 4.0 Hz, 2.2 Hz, 1H), 1.64 (ddd, *J* = 9.6 Hz, 6.1 Hz, 2.2 Hz, 1H), 1.53 (ps.-q, *J* = 6.4 Hz, 6.1 Hz, 5.8 Hz, 1H), 1.39 (s, 9H), 1.28 (ddd, *J* = 9.7 Hz, 5.8 Hz, 3.8 Hz, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 195.5, 169.4, 161.9, 138.1, 132.4 (+, 2C), 132.0 (+), 130.9, 129.7 (+, 2C), 128.2 (+, 2C), 114.5 (+, 2C), 56.8 (+), 51.6, 28.9 (+, 3C), 23.9 (+), 14.3 (-); IR (KBr, cm^{-1}): 3331, 2964, 2924, 2856, 1647, 1601, 1576, 1541, 1504, 1420, 1394, 1364, 1310, 1281, 1263, 1244, 1227, 1171, 1151, 1088, 1028, 974, 922, 891, 845, 793, 741, 700, 619; GC: 17.05 min (major), 17.35 min (minor); HRMS (TOF ES): found 344.1842, calculated for $C_{21}H_{23}NO_3Li$ (M+Li) 344.1838 (1.2 ppm).



(1*R,2*R**)-*N*-*tert*-butyl-2-(4-cyanophenoxy)cyclopropanecarboxamide** (**73f**): An oven-dried

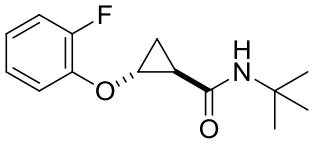
5 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), *p*-cyanophenol (119 mg, 1.00 mmol, 2 equiv) and anhydrous THF (3 mL). The mixture was stirred at 110 ^{o}C for 12 hrs. The mixture was partitioned between water (10 mL) and EtOAc (10 mL). Aqueous layer was extracted with EtOAc (3 x 10 mL). Combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (eluent hexane/EtOAc 1:1) to afford the title compound as white fluffy crystalline solid, mp. 106-108 ^{o}C . Yield 96 mg (0.37 mmol, 74%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.91 (br.s, 1H), 4.02 (ddd, *J* = 6.6 Hz, 4.4 Hz, 2.2 Hz, 1H), 1.68 (ddd, *J* = 9.8 Hz, 6.0 Hz, 2.2 Hz, 1H), 1.47 (ps.-q, *J* = 6.6 Hz, 6.3 Hz, 6.0 Hz, 1H), 1.36 (s, 9H), 1.22 (ddd, *J* = 9.8 Hz, 6.3 Hz, 4.4 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.2, 161.6, 133.8 (+, 2C), 118.8, 115.6 (+, 2C), 104.5, 56.7 (+), 51.4, 28.7 (+, 3C), 23.4 (+), 14.0 (-); IR (KBr, cm^{-1}): 3304, 3094, 2976, 2961, 2932, 2228, 1645, 1605, 1560, 1504, 1454, 1435, 1393, 1362, 1337, 1269, 1248, 1225, 1171, 1086, 837; GC: R*t* 12.65 min (major), 12.82 min (minor); HRMS (TOF ES): found 258.1363, calculated for $C_{15}H_{18}N_2O_2$ (M+) 258.1368 (1.9 ppm).



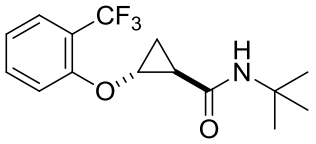
(1*R,2*R**)-*N*-*(tert-butyl)*-2-*(2,4-di-tert-butylphenoxy)cyclopropanecarboxamide* (**73m**) (Typical Procedure II): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), powdered KOH (98 mg, 1.75 mmol, 3.5 equiv.), 2,4-di-*tert*-butylphenol (206 mg, 1.00 mmol, 2 equiv), and anhydrous THF (3 mL). The mixture was stirred at 80 ^{o}C for 14 hrs. The mixture

was partitioned between water (10 mL) and EtOAc (10 mL). Aqueous layer was extracted with EtOAc (3 × 10 mL). Combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel eluting first with a mixture hexane/EtOAc 10:1 until separation of 2,4-di-*tert*-butylphenol. Then polarity of the eluent was increased (hexane/EtOAc 4:1) and two fractions of diastereomeric products were collected, R_f 0.50 (155 mg); 0.38 (10 mg). Both compounds were white crystalline solids. Combined yield 165 mg (0.48 mmol, 95%). **73m** (major): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.35 (d, *J* = 2.5 Hz, 1H), 7.21 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 5.69 (br.s, 1H), 4.06 (ddd, *J* = 6.3 Hz, 4.1 Hz, 2.2 Hz, 1H), 1.61 (ddd, *J* = 9.5 Hz, 6.0 Hz, 2.2 Hz, 1H), 1.54 (ps.-q, *J* = 6.3 Hz, 6.0 Hz, 1H), 1.42 (s, 9H), 1.37 (s, 9H), 1.34 (s, 9H), 1.33-1.30 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.1, 154.6, 143.2, 136.9, 123.9 (+), 123.3 (+), 112.1 (+), 56.2 (+), 51.5, 34.9, 34.3, 31.6 (+, 3C), 29.8 (+, 3C), 28.9 (+, 3C), 24.2 (+), 14.5 (-); IR (KBr, cm^{-1}): 3298, 3090, 2964, 2907, 2868, 1641, 1560, 1495, 1485, 1454, 1433, 1394, 1360, 1234, 1204, 1165, 1095; GC: R_t 13.01 min; HRMS (TOF ES): found 345.2661, calculated for $C_{22}H_{35}NO_2$ (M^+) 345.2668 (2.0 ppm). *cis*-**73m** (minor): ^{1}H NMR (500.19 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.2 Hz, 1H), 7.19 (dd, *J* = 8.5 Hz, 2.2 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 5.50 (br.s, 1H), 3.82 (td, *J* = 6.6 Hz, 4.4 Hz, 1H), 1.82 (dt, *J* = 9.5 Hz, 6.9 Hz, 1H), 1.58 (td, *J* = 6.3 Hz, 4.4 Hz, 1H), 1.38 (s, 9H), 1.32 (s, 9H), 1.25 (dt, 9.5 Hz, 6.3 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 167.2, 154.6, 143.6, 137.3, 123.9 (+), 123.1 (+), 112.6 (+), 55.2 (+), 51.1, 35.0, 34.3, 31.6 (+, 3C), 30.0 (+, 3C), 28.6 (+, 3C), 23.6 (+), 11.6 (-); GC: R_t 13.10 min; IR (KBr, cm^{-1}): 3277, 3074, 2959, 2926, 2866, 1651, ,1556, 1489, 1456, 1435, 1392, 1362, 1339, 1265, 1234, 1205, 1161, 1142, 1126, 1092, 1026, 1007, 970, 932, 889, 841, 806, 787, 748,

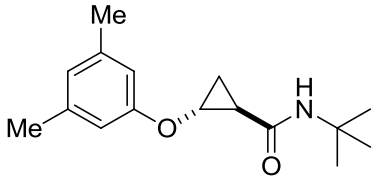
721, 704, 644; GC: R_t 13.10 min; HRMS (TOF ES): found 346.2754, calculated for $C_{22}H_{36}NO_2$ (M+H) 346.2746 (2.3 ppm).



(1R*,2R*)-N-tert-butyl-2-(2-fluorophenoxy)cyclopropanecarboxamide (**73g**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70a** (110 mg, 0.5 mmol) and 2-flurophenol (112 mg, 1.0 mmol, 2 equiv). The reaction was carried out at 110 ^oC for 13 hrs. Flash column chromatography on silica gel, eluting first with mixture hexane/EtOAc 12:1 to separate 2-flurophenol (R_f 0.34), then with mixture hexane/EtOAc 3:1 (R_f 0.36 (major), 0.10 (minor)) afforded the title compound as white crystalline solid. Yield 111 mg (0.44 mmol, 89%). ^1H NMR (500.13 MHz, $CDCl_3$) δ 7.13-7.20 (m, 1H), 7.03-7.10 (m, 2H), 6.90-6.96 (m, 1H), 5.70 (br. s., 1H), 4.08 (ddd, J = 6.3 Hz, 3.9 Hz, 2.0 Hz, 1H), 1.70 (ddd, J = 9.7 Hz, 6.2 Hz, 2.0 Hz, 1H), 1.49 (ddd, J = 6.3 Hz, 6.2 Hz, 5.8 Hz, 1H), 1.37 (s, 9H), 1.28 (ddd, J = 9.7 Hz, 5.8 Hz, 3.8 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.6, 152.1 (d, $^1J_{CF}$ = 245.6 Hz), 146.2 (d, $^2J_{CF}$ = 10.1 Hz), 124.3 (d, $^3J_{CF}$ = 3.8 Hz, +), 121.6 (d, $^3J_{CF}$ = 6.8 Hz, +), 116.1 (d, $^2J_{CF}$ = 18.3 Hz, +), 115.0 (+), 57.3 (+), 51.5, 28.8 (+, 3C), 23.7 (+), 14.2 (-); ^{19}F NMR (376.50 MHz, $CDCl_3$) δ -135.2; IR (KBr, cm^{-1}): 3294, 3090, 3074, 2993, 2962, 1638, 1560, 1502, 1400, 1340, 1279, 1254, 1205, 1111, 1080, 974, 928, 912, 773, 739; GC: 10.86 min (major), 11.00 min (minor); HRMS (TOF ES): found 258.1490, calculated for $C_{14}H_{18}FNO_2Li$ (M+Li) 258.1481 (3.5 ppm).

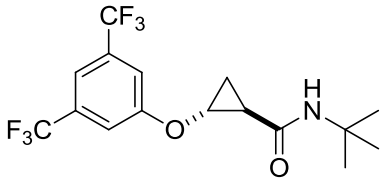


(1R*,2R*)-N-tert-butyl-2-((2-trifluoromethoxy)phenoxy)cyclopropanecarboxamide (**73h**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70a** (110 mg, 0.5 mmol) and 2-(trifluoromethoxy)phenol (178 mg, 1.0 mmol, 2 equiv). The reaction was carried out at 105 ^{o}C for 4 hrs. Flash column chromatography on silica gel eluting with hexane/EtOAc 1:1 (R_f 0.49 (major), 0.30 (minor)) afforded the title compound as white crystalline solid. Yield 133 mg (0.42 mmol, 84%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.28 (ddd, *J* = 8.5 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.21-7.25 (m, 2 H), 6.99 (ddd, *J* = 7.9 Hz, 7.6 Hz, 1.6 Hz, 1H), 5.69 (br.s., 1H), 4.11 (ddd, *J* = 6.3 Hz, 3.9 Hz, 2.0 Hz, 1H), 1.69 (ddd, *J* = 9.7 Hz, 6.2 Hz, 2.0 Hz, 1H), 1.50 (ddd, *J* = 6.3 Hz, 6.2 Hz, 5.8 Hz, 1H), 1.39 (s, 9H), 1.26 (ddd, *J* = 9.7 Hz, 5.8 Hz, 3.8 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.5, 150.8, 137.8, 127.9 (+), 123.0 (+), 121.4 (+), 120.6 (q, $^{1}J_{CF}$ = 257.5 Hz), 114.7 (+), 57.1 (+), 51.5, 28.8 (+, 3C), 23.8 (+), 14.4 (-); ^{19}F NMR (376.50 MHz, $CDCl_3$) δ -58.3; IR (KBr, cm^{-1}): 3300, 3092, 2968, 2930, 2908, 2872, 1639, 1607, 1564, 1501, 1456, 1435, 1396, 1362, 1339, 1302, 1285, 1269, 1225, 1196, 1161, 1150, 1115, 978, 750, 403; GC: 10.49 min (major), 10.68 min (minor); HRMS (TOF ES): found 340.1127, calculated for $C_{15}H_{18}F_3NO_3Na$ (M+Na) 340.1136 (2.6 ppm).



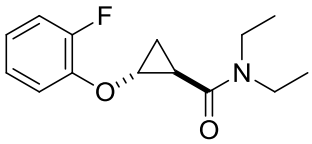
(1R*,2R*)-N-tert-butyl-2-(3,5-dimethylphenoxy)cyclopropanecarboxamide (**73j**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70a** (110 mg, 0.5 mmol) and 3,5-dimethylphenol (122 mg, 1.00 mmol, 2 equiv). The reaction was carried out at 100 ^{o}C for 13 hrs. Flash column chromatography on silica gel (eluent hexane/EtOAc 3:1, R_f 0.56 (major), 0.13 (minor)) afforded the title compound

as colorless crystalline solid. Yield 124 mg (0.47 mmol, 95%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.63 (s, 2H), 5.56 (br.s, 1H), 4.00-3.98 (m, 1H), 2.31 (s, 6H), 1.56-1.50 (m, 2H), 1.41 (s, 9H), 1.30-1.26 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.9, 158.3, 139.3 (2C), 123.1 (+), 112.5 (+, 2C), 56.6 (+), 51.5, 28.9 (+, 3C), 24.2 (+), 21.4 (+), 14.2 (-); IR (KBr, cm^{-1}): 3300, 3207, 3092, 2966, 2918, 2870, 1641, 1614, 1595, 1564, 1474, 1458, 1433, 1396, 1364, 1342, 1317, 1296, 1261, 1231, 1205, 1167, 1144, 1097, 982, 891, 831; GC: R_t 11.66 min (major), 11.83 min (minor); HRMS (TOF ES): found 262.1805, calculated for $C_{16}H_{24}NO_2$ (M+H) 262.1807 (0.8 ppm).

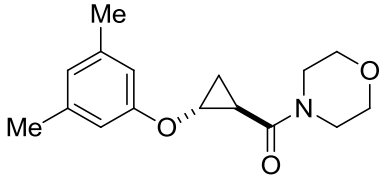


(1R*,2R*)-2-(3,5-bis(trifluoromethyl)phenoxy)-N-tert-butylcyclopropanecarboxamide (**73l**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70a** (110 mg, 0.5 mmol), and 3,5-bis(trifluromethyl)phenol (230 mg, 1.0 mmol, 2 equiv). The reaction was carried out at 100 ^{o}C for 6.5 hrs. Flash column chromatography on silica gel, eluting first with hexane/EtOAc mixture 10:1, then after separation of the residual phenol (R_f 0.25) with hexane/EtOAc mixture 3:1 (R_f 0.43 (major), 0.40 (minor)) afforded the title compound as white crystalline solid. Yield 157 mg (0.43 mmol, 85%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.42 (s, 2H), 5.62 (br.s, 1H), 4.11-4.07 (m, 1H), 1.64-1.58 (m, 2H), 1.41 (s, 9H), 1.37-1.34 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 168.9, 159.0, 133.0 (q, $^{2}J_{CF}$ = 33.0 Hz, 2C), 123.1 (q, $^{1}J_{CF}$ = 272.2 Hz, 2C), 115.3 (q, $^{3}J_{CF}$ = 3.7 Hz, 2C), 115.0 (septet, $^{3}J_{CF}$ = 4.1 Hz), 57.4 (+), 51.8, 28.8 (+, 3C), 23.9 (+), 14.1 (-); ^{19}F NMR (376.50 MHz, $CDCl_3$) δ -63.1; IR (KBr, cm^{-1}): 3306, 3097, 2989, 2974, 2939, 1637, 1560, 1464, 1400, 1377, 1342, 1321, 1277, 1231, 1188,

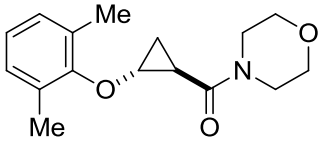
1128, 1092, 959; GC: 10.03 min (major), 9.99 min (minor); HRMS (TOF ES): found 392.1055, calculated for $C_{16}H_{17}F_6NO_2Na$ (M+Na) 392.1061 (1.5 ppm).



(1R*,2R*)-N,N-Diethyl-2-(2-fluorophenoxy)cyclopropanecarboxamide (**73i**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70b** (110 mg, 0.50 mmol) and 2-flurophenol (112 mg, 1.00 mmol, 2.00 equiv). The reaction was carried out at 110 ^oC for 14 hrs. Flash column chromatography on silica gel (eluent hexane/EtOAc 12:1, R_f 2-flurophenol 0.34, major 0.11, minor 0.03) after elution of 2-flurophenol the eluent polarity was increased (hexane/EtOAc 3:1, R_f 0.19 (major), 0.06 (minor)) afforded the title compound as colorless oil. Yield 103 mg (0.41 mmol, 82%). ^1H NMR (500.13 MHz, $CDCl_3$) δ 7.18 (td, J = 8.1 Hz, 1.4 Hz, 1H), 7.07 (t, J = 9.1 Hz, 2H), 6.96 - 6.90 (m, 1H), 4.20 (ddd, J = 6.4 Hz, 3.9 Hz, 2.0 Hz, 1H), 3.50 - 3.39 (m, 4H), 2.09 (ddd, J = 9.7 Hz, 6.2 Hz, 2.0 Hz, 1H), 1.53 (ddd, J = 6.4 Hz, 6.2 Hz, 5.8 Hz, 1H), 1.40 (ddd, J = 9.7 Hz, 5.8 Hz, 3.8 Hz, 1H), 1.21 (t, J = 7.3 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.6, 152.3 (d, $^1J_{CF}$ = 245.6 Hz), 146.3 (d, $^2J_{CF}$ = 11.0 Hz), 124.3 (d, J_{CF} = 4.6 Hz, +), 121.7 (d, J_{CF} = 7.3 Hz, +), 116.2 (d, $^3J_{CF}$ = 17.4 Hz, +), 115.4 (+), 58.3 (+), 42.2 (-), 40.8 (-), 19.9 (+), 15.5 (-), 14.8 (+), 13.2 (+); GC: 11.18 min (major), 11.34 min (minor); FTIR (NaCl, film, cm^{-1}): 2976, 2934, 1634, 1504, 1458, 1265, 1254, 1209, 1136, 748; HRMS (TOF ES): found 252.1398, calculated for $C_{14}H_{19}FNO_2$ (M+H) 252.1400 (0.8 ppm).

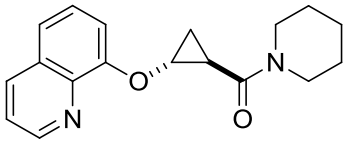


((1R*,2R*)-2-(3,5-Dimethylphenoxy)cyclopropyl)(4-morpholino)methanone (**73k**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70c** (117 mg, 0.50 mmol) and 3,5-dimethyl-phenol (122 mg, 1.00 mmol, 2.00 equiv), and anhydrous THF (5 mL). The reaction was carried out at 100 ^{o}C for 13 hrs. Flash column chromatography on a silica gel (eluent hexane/EtOAc 3:1, R_f 0.16) afforded the title compound as colorless crystalline solid. Yield 120 mg (0.44 mmol, 87%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.62 (s, 2H), 4.08 (ddd, *J* = 6.5 Hz, 3.9 Hz, 2.2 Hz, 1H), 3.82-3.58 (m, 8H), 2.32 (s, 6H), 2.02 (ddd, *J* = 9.5 Hz, 6.2 Hz, 2.2 Hz, 1H), 1.61 (ddd, *J* = 6.5 Hz, 6.2 Hz, 5.4 Hz, 1H), 1.38 (ddd, *J* = 9.5 Hz, 5.4 Hz, 3.9 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.5, 158.2, 139.3 (2C), 123.3 (+), 112.5 (+, 2C), 66.9 (-), 66.8 (-), 57.4 (+), 46.1 (-), 42.5 (-), 21.4 (+), 19.6 (+), 15.4 (-); GC: 13.27 min (major), 13.42 min (minor); FTIR (NaCl, film, cm^{1}) 2961, 2918, 2854, 1639, 1443, 1319, 1294, 1117, 1032, 835, 689; HRMS (TOF ES): found 276.1612, calculated for $C_{16}H_{22}NO_3$ (M+H) 276.1600 (4.3 ppm).



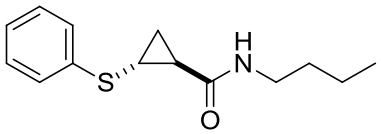
((1R*,2R*)-2-(2,6-Dimethylphenoxy)cyclopropyl)(morpholino)methanone (**73n**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70c** (117 mg, 0.50 mmol), and 2,6-dimethylphenol (122 mg, 1.00 mmol, 2.0 equiv). The reaction was carried out at 90 ^{o}C for 14 hrs. Flash column chromatography on silica gel afforded a title compound as a colorless oil, R_f 0.17 (eluent hexane/EtOAc 3:1), Yield 114 mg (0.42 mmol, 83%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 6.94 (d, *J* = 7.6 Hz, 2H), 6.86 (dd, *J* = 8.2 Hz, 6.6 Hz, 1H), 3.99 (ddd, *J* = 6.5 Hz, 3.9 Hz, 2.2 Hz, 1H), 3.66-3.49 (m, 4H), 3.48-3.30 (m, 4H), 2.20 (s, 6H), 2.02 (ddd, *J* =

9.6 Hz, 6.1 Hz, 2.2 Hz, 1H), 1.40 (ddd, *J* = 6.5 Hz, 6.2 Hz, 5.6 Hz, 1H), 1.31 (ddd, *J* = 9.5 Hz, 5.6 Hz, 4.1 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.4, 155.0, 130.3 (2C), 128.9 (+, 2C), 124.1 (+), 66.7 (-), 66.6 (-), 62.1 (+), 45.9 (-), 42.3 (-), 19.4 (+), 17.0 (+, 2C), 15.1 (-); FTIR (NaCl, film, cm[1]): 2961, 2920, 2854, 1643, 1443, 1371, 1265, 1236, 1211, 1188, 1117, 932, 851; HRMS (TOF ES): found 275.1524, calculated for $C_{16}H_{21}NO_3$ (M^+) 275.1521 (1.1 ppm).

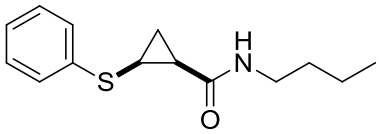


Piperidin-1-yl((1R*,2R*)-2-(quinolin-8-yloxy)cyclopropyl)methanone (**73o**): Was prepared according to Typical Procedure II, employing bromocyclopropane **70d** (116 mg, 0.50 mmol) and 8-hydroxy-quinoline (145 mg, 1.00 mmol, 2.00 equiv). Flash column chromatography on silica gel (eluent EtOAc, R_f 0.73 (8-hydroxyquinoline), 0.23 (title product)) afforded a colorless amorphous solid. Yield 144 mg (0.49 mmol, 97%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.95 (dd, *J* = 4.0 Hz, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.2 Hz, 1.6 Hz, 1H), 7.53-7.41 (m, 4H), 4.37 (ddd, *J* = 6.3 Hz, 4.6 Hz, 2.3 Hz, 1H), 3.75-3.55 (m, 4H), 2.34 (ddd, *J* = 9.3 Hz, 6.9 Hz, 2.3 Hz, 1H), 1.79-1.56 (m, 8H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 168.9, 154.2, 149.4 (+), 139.7, 135.9 (+), 129.3, 126.6 (+), 121.6 (+), 120.3 (+), 110.1 (+), 58.0 (+), 46.8 (-), 43.1 (-), 26.5 (-), 25.5 (-), 24.5 (-), 19.6 (+), 15.5 (-); FT IR (NaCl, film, cm^{-1}): 3007, 2935, 2854, 1628, 150, 1470, 1375, 1247, 1209, 1184, 1103, 1022, 825, 792; HRMS (TOF ES): found 297.1603, calculated for $C_{18}H_{21}N_2O_2$ (M+H) 297.1603 (0.0 ppm).

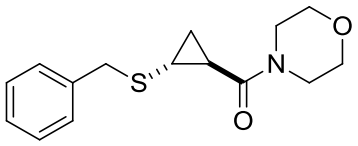
2.6.7. Thiolate Adducts



(1S*,2R*)-N-Butyl-2-(phenylthio)cyclopropanecarboxamide (**82g**) (Typical Procedure III): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70f** (110 mg, 0.5 mmol, 1 equiv), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), KOH (98 mg, 1.75 mmol, 3.5 equiv.), thiophenol (110 mg, 1 mmol, 2 equiv), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs. The crude mixture was filtered through a fritted funnel and the filtrate was concentrated in vacuum. The residual crude material, containing a mixture of diastereomeric cyclopropylsulfides (*trans*:*cis* = 2:1) was combined potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 eq) in 10 mL Weaton vial, the mixture was dissolved in dry THF (total volume of 8 mL) and heated at 85 ^{o}C for 6 hr. The resulting mixture was filtered through a fritted funnel into an evaporating flask, and the filtrate was concentrated in vacuum. The residue was purified by flash column chromatography on silica gel to obtain the individual *trans*-isomer fo a title compound as white solid, mp 95-97 ^{o}C , R_f : 0.29 (eluent hexane/EtOAc 3:1). Yield 121 mg (0.483 mmol, 97%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.33-7.27 (m, 4H), 7.21-7.15 (m, 1H), 5.82 (br. s., 1H), 3.42-3.21 (m, 2H), 2.76 (ddd, *J* = 8.2 Hz, 5.4 Hz, 3.5 Hz, 1H), 1.70 (dt, *J* = 8.2 Hz, 5.0 Hz, 1H), 1.59 (ddd, *J* = 8.5 Hz, 5.2 Hz, 3.6 Hz, 1H), 1.57-1.47 (m, 2H), 1.39 (dq, *J* = 14.9 Hz, 7.4 Hz, 2H), 1.16 (ddd, *J* = 8.5 Hz, 5.4 Hz, 4.7 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.6, 137.5, 128.8 (+, 2C), 126.6 (+, 2C), 125.3 (+), 39.6 (-), 31.7 (-), 26.2 (+), 20.7 (+), 20.0 (-), 16.3 (-), 13.7 (+); IR (NaCl, cm^{-1}): 3296, 3223, 3202, 3196, 3084, 3055, 2955, 2922, 2851, 2826, 1636, 1583, 1558, 1479, 1466, 1456, 1439, 1423, 1396; HRMS (TOF ES): found 250.1268, calculated for $C_{14}H_{20}NOS$ (M+H) 250.1266 (0.8 ppm).

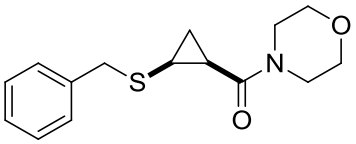


(1S*,2S*)-N-Butyl-2-(phenylthio)cyclopropanecarboxamide (*cis*-**82g**) was isolated as a reference sample in a separate experiment by column chromatography of the crude reaction micture prior to re-equilibration with *t*-BuOK, Rf 0.15 (eluent hexane/ EtOAc 3:1). Yield 37 mg (0.15 mmol, 30%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 2H), 7.32-7.27 (m, 2H), 7.20-7.15 (m, 1H), 5.81 (br. s., 1H), 3.24-3.16 (m, 2H), 2.64 (td, *J* = 8.0 Hz, 6.3 Hz, 1H), 2.09 (td, *J* = 8.0 Hz, 6.6 Hz, 1H), 1.47 (td, *J* = 8.4 Hz, 5.4 Hz, 1H), 1.40 (q, *J* = 6.3 Hz, 1H), 1.35-1.27 (m, 2H), 1.26-1.17 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.5, 137.2, 128.8 (+, 2C), 127.3 (+, 2C), 125.6 (+), 39.5 (-), 31.5 (-), 23.5 (+), 20.7 (+), 19.9 (-), 13.7 (+), 12.9 (-);

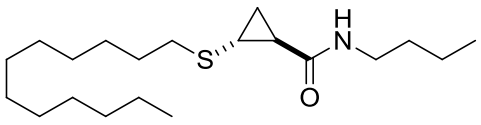


((1S*,2R*)-2-(Benzylthio)cyclopropyl)(morpholino)methanone (**82b**): The reaction was performed according to Typical Procedure III, employing bromocyclopropane **70c** (117 mg, 0.50 mmol) and benzylmercaptan (124 mg, 1.00 mmol) to produce the title compound as a yellow oil, R_f 0.28 (eluent hexane/EtOAc 1:1, yield 128 mg (0.46 mmol, 92%). Initial dr 2:1, after equilibration was upgraded to >30:1. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.33-7.30 (m, 4H), 7.29-7.24 (m, 1H), 3.82 (d, *J* = 13.6 Hz, 1H), 3.77 (d, *J* = 13.6 Hz, 1H), 3.72-3.58 (m, 5H), 3.56-3.34 (m, 3H), 2.44 (ddd, *J* = 8.4 Hz, 5.3 Hz, 3.6 Hz, 1H), 1.66 (ddd, *J* = 8.7 Hz, 5.2 Hz, 3.5 Hz, 1H), 1.43 (dt, *J* = 8.2 Hz, 5.2 Hz, 4.5 Hz, 1H), 0.97 (ddd, *J* = 8.4 Hz, 5.3 Hz, 4.8 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.8, 138.5, 128.7 (+, 2C), 128.4 (+, 2C), 126.9 (+), 66.7 (-), 66.5 (-), 45.7 (-), 42.3 (-), 37.9 (-), 22.1 (+), 22.0 (+), 16.2 (-); IR (NaCl, cm^{-1}): 3001, 2961, 2918, 2899, 2854, 1637, 1603, 1495, 1454, 1439, 1389, 1362, 1329, 1300, 1273, 1231, 1194, 1115, 1070, 1041,

1026, 966, 918, 868, 845, 771, 744, 702, 667, 642, 567, 440, 419; HRMS (TOF ES): found 300.1033, calculated for $C_{15}H_{19}NO_2SNa$ (M+Na) 300.1034 (0.3 ppm).

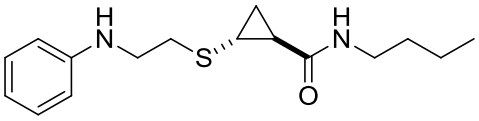


((1S*,2S*)-2-(Benzylthio)cyclopropyl)(morpholino)methanone (*cis*-**82b**), was isolated as a reference sample in a separate experiment by column chromatography of the crude reaction micture prior to re-equilibration with *t*-BuOK, Rf 0.15 (eluent hexane/ EtOAc 1:1). Yield 42 mg (0.15 mmol, 30%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.30-7.25 (m, 1H), 3.86 (ddd, *J* = 13.2 Hz, 5.4 Hz, 3.2 Hz, 1H), 3.77 (s, 2H), 3.76-3.62 (m, 5H), 3.58 (ddd, *J* = 13.2 Hz, 6.9 Hz, 3.8 Hz, 1H), 3.52 (ddd, *J* = 13.4 Hz, 7.4 Hz, 3.2 Hz, 1H), 2.20 (td, *J* = 8.0 Hz, 6.0 Hz, 1H), 2.02 (td, *J* = 8.3 Hz, 6.1 Hz, 1H), 1.45 (q, *J* = 5.8 Hz, 1H), 1.25 (td, *J* = 8.0 Hz, 5.2 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 167.1, 138.2, 128.8 (+, 2C), 128.5 (+, 2C), 127.0 (+), 66.9 (-), 66.8 (-), 45.9 (-), 42.5 (-), 37.8 (-), 21.8 (+), 19.8 (+), 13.1 (-); HRMS (TOF ES): found 278.1219, calculated for $C_{15}H_{20}NO_2S$ (M+H) 278.1215 (1.4 ppm).



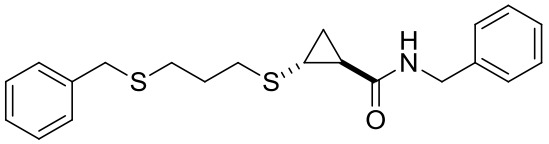
(1S*,2R*)-N-Butyl-2-(dodecylthio)cyclopropanecarboxamide (**82a**): The reaction was performed according to Typical Procedure III, employing bromocyclopropane **70f** (110 mg, 0.50 mmol) and dodecanethiol (202 mg, 1.00 mmol) to produce the title compound as a white solid (mp 50-52 ^{o}C), R_f 0.23 (eluent hexane/EtOAc 3:1). Yield 162 mg (0.48 mmol, 95%). Initial dr 1:1, after equilibration was upgraded to 16:1. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.84 (br. s., 1H), 3.32-3.22 (m, 2H), 2.64-2.52 (m, 2H), 2.45-2.36 (m, 1H), 1.69-1.56 (m, 2H), 1.55-1.44 (m, 4H), 1.42-1.33 (m, 4H), 1.44-1.20 (m, 16H), 1.02-0.96 (m, 1H), 0.94 (t, *J* = 7.4

Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 171.1, 39.5 (-), 33.4 (-), 31.9 (-), 31.7 (-), 29.62 (-), 29.60 (-), 29.58 (-), 29.57 (-), 29.5 (-), 29.3 (-), 29.2 (-), 28.8 (-), 25.9 (+), 22.6 (-), 21.4 (+), 20.0 (-), 16.3 (-), 14.1 (+), 13.7 (+); IR (KBr, cm^{-1}): 3271, 2955, 2918, 2849, 1636, 1558, 1456, 1277, 1232, 746, 719, 658, 501, 403; HRMS (TOF ES): found 342.2833, calculated for $C_{20}H_{40}NOS$ (M+H) 342.2831 (0.6 ppm).

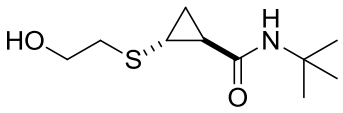


(1S*,2R*)-N-Butyl-2-((2-(phenylamino)ethyl)thio)cyclopropanecarboxamide (**82f**): This compound was prepared according to Typical Procedure III starting from bromo-cyclopropane **70f** (55 mg, 0.25 mmol) and 2-anilinoethanthiol (78 mg, 0.50 mmol, 2.0 equiv). The product was isolated by column chromatography on silica gel (eluent hexane/EtOAc 3:1, gradually changed to 1:1) as yiellowish oil, Rf 0.28 (hexane/EtOAc, 1:1). Yield 128 mg (0.46 mmol, 92%). Initial dr 2:1, after equilibration was upgraded to >30:1. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.23 (t, *J* = 7.9 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 5.40 (br. s., 1H), 4.12 (br. s., 1H), 3.40 (t, *J* = 6.3 Hz, 2H), 3.25 (dq, *J* = 13.4 Hz, 6.8 Hz, 1H), 3.15 (dq, *J* = 12.6 Hz, 6.9 Hz, 1H), 2.95 (dt, *J* = 13.6 Hz, 6.0 Hz, 1H), 2.85 (dt, *J* = 13.6 Hz, 6.6 Hz, 1H), 2.39 (ddd, *J* = 8.4 Hz, 5.3 Hz, 3.6 Hz, 1H), 1.49 (dt, *J* = 8.2 Hz, 4.7 Hz, 1H), 1.44 (dq, *J* = 15.4 Hz, 6.9 Hz, 2H), 1.40 (ddd, *J* = 8.5 Hz, 5.0 Hz, 3.5 Hz, 1H), 1.33 (dq, *J* = 14.9 Hz, 7.2 Hz, 2H), 0.99 (dt, *J* = 8.4 Hz, 5.0 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.6, 147.7, 129.4 (+, 2C), 117.8 (+), 113.1 (+, 2C), 42.3 (-), 39.5 (-), 32.8 (-), 31.7 (-), 26.4 (+), 20.9 (+), 20.0 (-), 15.6 (-), 13.7 (+); IR (KBr, cm^{-1}): 3304, 2957, 2930, 1641, 1603, 1556, 1506, 1466, 1433, 1394, 1373, 1323, 1288, 1261, 1225, 1196, 1180, 1153, 1113, 1095, 1072,

1030, 989, 962, 920, 868, 852, 804, 748, 692, 652, 617, 554, 538, 511; HRMS (TOF ES): found 293.1685, calculated for $C_{16}H_{25}N_2OS$ (M+H) 293.1688 (1.0 ppm).

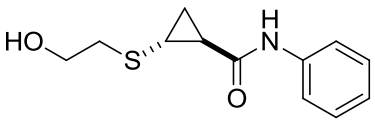


(1S*,2R*)-N-Benzyl-2-((3-(benzylthio)propyl)thio)cyclopropanecarboxamide (**82c**): The reaction was performed according to Typical Procedure III employing bromocyclopropane **70g** (127 mg, 0.50 mmol) and 3-(benzylthio)propane-1-thiol (198 mg, 1.00 mmol, 2.0 equiv) to produce the title compound as a white solid, mp 78-80 ^{o}C , R_f 0.40 (hexane/EtOAc, 3:1). Yield 107 mg (0.44 mmol, 87%). Initial dr 2:1, after equilibration was upgraded to >30:1. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.40-7.24 (m, 10H), 6.00 (br. s., 1H), 4.52-4.41 (m, 2H), 3.71 (s, 2H), 2.74-2.61 (m, 2H), 2.60-2.49 (m, 2H), 2.43 (ddd, *J* = 8.2 Hz, 5.7 Hz, 3.8 Hz, 1H), 1.94-1.85 (m, 2H), 1.55 (dt, *J* = 8.2 Hz, 4.7 Hz, 1H), 1.47 (ddd, *J* = 8.5 Hz, 5.0 Hz, 3.5 Hz, 1H), 1.02 (ddd, *J* = 8.5 Hz, 5.7 Hz, 4.4 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 170.9, 138.3, 138.0, 128.8 (+, 2C), 128.7 (+, 2C), 128.5 (+, 2C), 127.8 (+, 2C), 127.5 (+), 127.0 (+), 43.9 (-), 36.2 (-), 32.2 (-), 29.9 (-), 28.6 (-), 25.9 (+), 21.5 (+), 16.2 (-); FT IR (NaCl, film, cm^{-1}): 3290, 3061, 3028, 2918, 1641, 1603, 1551, 1495, 1452, 1423, 1394, 1356, 1298, 1273, 1227, 1196, 1157, 1109, 1082, 1070, 1040, 1028, 1003, 966, 918, 860, 841, 802, 768, 731, 698, 656, 621, 600, 565, 538, 509, 474, 447, 432; HRMS (TOF ES): found 371.1374, calculated for $C_{21}H_{25}NOS_2$ (M^+) 371.1374 (1.1 ppm);



(1S*,2R*)-N-tert-Butyl-2-(2-hydroxyethylthio)cyclopropanecarboxamide (**82d**) (Typical Procedure IV): An oven-dried 5 mL Weaton vial was charged with bromocyclopropane **70a**

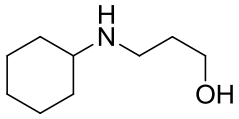
(110 mg, 0.50 mmol), 18-crown-6 (13 mg, 0.05 mmol, 10%), powdered KOH (140 mg, 2.5 mmol, 5.0 equiv.), 2-mercaptoethanol (70 μL, 78 mg, 1.00 mmol, 2.0 equiv.), and anhydrous THF (5 mL). The mixture was stirred at 85 °°C for 12 hrs, then filtered through a fritted funnel and concentrated. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 1:1) to afford the title compound as a colorless oil, R_f 0.40 (hexane/EtOAc 1:3). Yield 108 mg (0.49 mmol, 97%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 5.59 (br. s., 1H), 3.82 (t, *J* = 6.0 Hz, 2H), 2.89-2.75 (m, 2H), 2.43-2.33 (m, 1H), 2.22 (br. s., 1H), 1.50 - 1.43 (m, 2H), 1.37 (s, 9H), 1.03-0.93 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 170.0, 60.4 (-), 51.5, 36.4 (-), 28.8 (+, 3C), 26.5 (+), 20.4 (+), 16.1 (-); IR (KBr, cm^{-1}): 3315, 2966, 2928, 1651, 1553, 1456, 1425, 1393, 1364, 1283, 1244, 1225, 1196, 1047, 1016; HRMS (TOF ES): found 240.1031, calculated for $C_{10}H_{19}NO_2SNa$ (M+Na) 240.1034 (1.2 ppm).



(1S*,2R*)-2-((2-hydroxyethyl)thio)-N-phenylcyclopropanecarboxamide (**82e**): Was prepared according to Typical Procedure IV, employing bromocyclopropane **70h** (120 mg, 0.50 mmol). The reaction was carried out at 60 °C for 14 hrs. Flash column chromatography on silica gel afforded a title compound as colorless crystals, mp 87-88 °C , R_f 0.38 (hexane/EtOAc 1:3). Yield 101 mg (0.43 mmol, 85%). ^{1}H NMR (400.13 MHz, CD_3CN) δ 8.78 (br. s., 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 3.72 (q, *J* = 6.3 Hz, 2H), 3.10 (t, *J* = 5.7 Hz, 1H), 2.77 (t, *J* = 6.6 Hz, 2H), 2.44 (ddd, *J* = 8.3 Hz, 5.3 Hz, 3.5 Hz, 1H), 1.84 (ddd, *J* = 8.5 Hz, 5.2 Hz, 3.5 Hz, 1H), 1.47 (dt, *J* = 8.3 Hz, 4.8 Hz, 1H), 1.08 (ddd, *J* = 8.6 Hz, 5.6 Hz, 4.6 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.4, 137.8, 129.0 (+, 2C), 124.3 (+), 119.8 (+, 2C), 60.5 (-), 36.5 (-), 27.1 (+), 21.8 (+), 16.8 (-); FT IR (NaCl, film, cm^{-1}): 3286,

2922, 2872, 1655, 1601, 1549, 1447, 1393, 1313, 1190, 1036, 756, 692; HRMS (TOF ES): found 260.0714, calculated for $C_{12}H_{15}NO_2SNa$ (M+Na) 260.0721 (2.7 ppm).

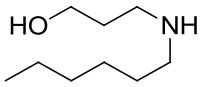
2.6.8. Cyclization precursors



3-Cyclohexylamino-1-propanol[82]: Three neck round bottom flask (250 mL) equipped with a reflux condenser, a thermometer, and addition funnel (100 mL) was charged with $LiAlH_4$ (1.30 g, 38.4 mmol, 1.50 eq) and anhydrous THF (30 mL). The resulting suspension was stirred at 0 ^oC and a solution of methyl 3-(cyclo-hexylamino)propanoate[83] (4.40 g, 23.2 mmol, 1.00 equiv) in dry THF (50 mL) was added drop wise over 30 min. Once addition was complete the mixture was stirred at reflux overnight, then quenched at 0 ^oC consecutively with water (20 mL) and a concentrated aqueous solution of NaOH (5.0 g in 5 mL of water). The resulting suspension was diluted with water (30 mL) and THF (50 mL) and filtered through a fritted funnel. The filter cake was washed with THF (3 x 20 ml), and the washing liquids were combined with the filtrate. The resulting solution was saturated with NaCl and extracted with THF (3 x 20 ml). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by vacuum distillation (bp 60 ^oC at 15 torr) to afford the titled compound as colorless oil, solidifying upon standing. Yield 2.4 g (15.1 mmol, 65%).

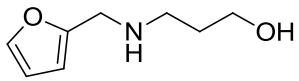
^1H NMR (400.13 MHz, $CDCl_3$) δ 3.80 (t, J = 5.2 Hz, 2H), 2.89 (t, J = 5.7 Hz, 2H), 2.41 (tt, J = 10.3 Hz, 3.6 Hz, 1H), 2.05 (br. s, 2H), 1.97-1.79 (m, 2 H), 1.77-1.52 (m, 5H), 1.31-1.13 (m, 3H),

1.11-0.99 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 64.5 (-), 56.6 (+), 46.9 (-), 33.4 (-, 2C), 31.2 (-), 26.0 (-), 24.9 (-, 2C);



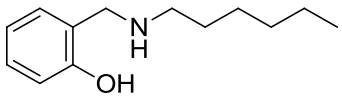
3-(Hexylamino)propan-1-ol[83]: Three neck round bottom flask (250 mL) equipped with a reflux condenser, a thermometer, and addition funnel (100 ml) was charged with $LiAlH_4$ (1.50 g, 38.4 mmol, 1.5 equiv) and anhydrous THF (30 mL). The resulting suspension was stirred at 0 ^{o}C, a solution of methyl 3-(hexylamino)propanoate[84] (4.80 g, 25.6 mmol, 1.00 equiv) in dry THF (50 mL) and was added dropwise over 30 min. Once addition was complete the mixture was stirred at reflux overnight, and then quenched consecutively with water (20 mL) and a concentrated solution of NaOH (5.00 g in 5 ml of water) at 0 ^{o}C. The mixture was diluted with THF (50 mL) and of water (30 mL) and the resulting suspension was filtered through a fritted funnel. The filter cake was washed with THF (3 x 20 mL), and the washing liquid was combined with the filtrate. The resulting filtrate was saturated with NaCl and extracted with THF (3 x 20 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated. The resulting yellowish oil was purified by vacuum distillation to afford the titled compound as colorless oil. Yield 2.80 g (15.9 mmol, 62%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.77 (t, J = 5.6 Hz, 2H), 2.84 (t, J = 5.8 Hz, 2H), 2.57 (t, J = 7.1 Hz, 2H), 1.67 (quin, J = 5.6 Hz, 2H), 1.44 (quin, J = 7.1 Hz, 2H), 1.35-1.19 (m, 6H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 64.1 (-), 49.9 (-), 49.8 (-), 31.6 (-), 30.7 (-), 29.8 (-), 26.9 (-), 22.5 (-), 13.9 (+);



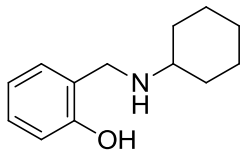
3-((Furan-2-ylmethyl)amino)propan-1-ol[85]: To a stirred solution of furfural (5.00 g, 52.0 mmol, 1.00 equiv) in MeOH (30 mL) was added 3-aminopropan-1-ol (4.00 g, 53.3 mmol, 1.00 equiv), and the mixture was stirred for 30 min at room temperature, then cooled to 0 ^{o}C and $NaBH_4$ (2.90 g, 76.6 mmol, 1.50 equiv) was added by small portions over 10 min. The suspension was stirred for 4 hrs at room temperature and the solvent was removed in vacuum. An aqueous solution of KOH (5.00 g, 47.8 mmol, 1.7 equiv in 20 mL of water) was added and the solution was partitioned between EtOAC and brine. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The resulting crude oil was distilled (130 ^{o}C) to afford the title compound as a colorless viscous oil. Yield 7.50 g (48.4 mmol, 93%).

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



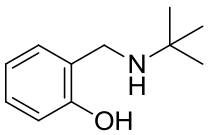
2-((*n*-Hexylamino)methyl)phenol: A solution of salicyl aldehyde (1.22 g, 10.0 mmol, 1.0 equiv.) and *n*-hexylamine (2.02 g, 20.0 mmol, 2.0 equiv.) was stirred in dry MeOH (40.0 mL) for 1 hour. $NaBH_4$ (600 mg, 16.0 mmol, 1.6 equiv.) was added causing a color change from yellow to clear over the course of 10 minutes, after which the reaction was quenched with 5% aqueous HCl (15 mL). The resulting mixture was then partitioned between Et_2O (25 mL) and brine (25 mL). The aqueous layer was extracted

with ether (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated affording 2-((hexylamino)methyl)phenol as a light-brown viscous oil. Yield 1.53 g (7.40 mmol, 74%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 4.00 (s, 2H), 2.69 (t, *J* = 7.1 Hz, 2H), 1.56 (p, *J* = 6.9 Hz, 2H), 1.42 – 1.26 (m, 6H), 0.91 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 158.4, 128.7 (+), 128.4 (+), 122.5, 118.9 (+), 116.4 (+), 52.6 (-), 48.7 (-), 31.6 (-), 29.4 (-), 26.8 (-), 22.6 (-), 14.1 (+); FT IR (NaCl, film, cm^{-1}): 3292, 3008, 2954, 2927, 2856, 1589, 1458, 1515, 1257, 754; HRMS (TOF ES): found 208.1703, calculated for $C_{13}H_{22}NO$ (M+H) 208.1701 (0.1 ppm).

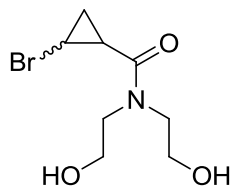


2-((*c*-Hexylamino)methyl)phenol: A solution of salicyl aldehyde (1.22 g, 10.0 mmol, 1.0 equiv.) and cyclohexylamine (1.98 g, 20.0 mmol, 2.0 equiv.) was stirred in dry MeOH (40.0 mL) for 1 hour. $NaBH_4$ (600 mg, 16.0 mmol, 1.6 equiv.) was added causing a color change from yellow to clear over the course of 10 minutes, after which the reaction was quenched with 5% aqueous HCl (15 mL). The resulting mixture was then partitioned between Et_2O (25 mL) and brine (25 mL). The aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated affording 2-((cyclohexylamino)methyl)phenol as a crystalline solid (mp 28-30 ^{o}C). Yield 1.30 g (6.34 mmol, 63%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 4.04 (s, 2H), 2.56 (tt, *J* = 10.2, 3.8 Hz, 1H), 2.00 (m, 2H), 1.77 (m, 2H), 1.65 (ddd, *J* = 12.1, 4.9, 3.2 Hz, 1H), 1.39 – 1.07 (m, 5H). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 158.52, 128.57 (+), 128.07 (+),

123.08, 118.87 (+), 116.45 (+), 55.60 (+), 49.67 (-), 33.02 (-, 2C), 25.91 (-, 2C), 24.83 (-, 2C). FT IR (NaCl, film, cm^{-1}): 3265, 2930, 2899, 1591, 1497, 1444, 1421, 1267, 754; HRMS (TOF ES): found 206.1549, calculated for $C_{13}H_{20}NO$ (M+H) 206.1545 (0.2 ppm).

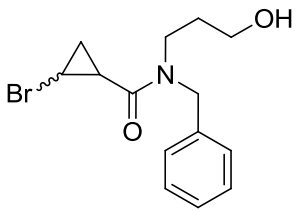


2-((*tert*-Butylamino)methyl)phenol[86]: A solution of salicyl aldehyde (1.22 g, 10.0 mmol, 1.00 equiv.) and *tert*-butyl amine (1.46 g, 20.0 mmol, 2.00 equiv.) was stirred in dry MeOH (40 mL) for 1 hr. $NaBH_4$ (600 mg, 16.0 mmol, 1.60 equiv.) was added causing a color change from yellow to clear over the course of 10 min, after which the reaction was quenched with 5% aqueous HCl (15 mL). The resulting mixture was then partitioned between Et_2O (25 mL) and brine (25 mL). The aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The obtained crystalline material was pure enough to be used for the following transformations without additional purification. Yield 1.45 g (8.01 mmol, 81%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.17 (td, *J* = 8.0 Hz, 1.8 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.84 (dd, *J* = 8.1 Hz, 1.0 Hz, 1H), 6.79 (td, *J* = 7.4 Hz, 1.1 Hz, 1H), 3.92 (s, 2H), 1.23 (s, 9H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 158.3, 128.2 (+), 127.7 (+), 123.4, 118.6 (+), 116.2 (+), 50.8, 45.8 (-), 28.3 (+); HRMS (TOF ES): found 180.1383, calculated for $C_{11}H_{18}NO$ (M+H) 180.1388 (2.8 ppm).



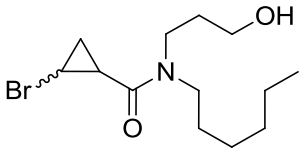
2-Bromo-N,N-bis(2-hydroxyethyl)cyclopropanecarboxamide (**74**): To a 50 mL round bottom flask containing 15 mL of dry THF was added

diethanolamine (252 mg, 2.4 mmol) and triethylamine (242 mg, 2.4 mmol). To this stirring mixture was added via syringe 5 mL of a THF solution containing 2-bromocyclopropanecarbonyl chloride (200 mg, 1.2 mmol). The resulting mixture was stirred at RT for 1h, then filtered through a glass filter to remove salts. The THF was removed in vacuum and resulting oil was partitioned between dilute aqueous acid (10 mL, 5% HCl) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x10 mL). The organic layer was dried with $MgSO_4$ and volatiles were removed to yield 263 mg (1.04 mmol, 87%) of colorless oil used without further purification. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.90 (s, 2H), 3.84 (t, *J* = 4.9 Hz, 2H), 3.79 – 3.66 (m, 2H), 3.65 – 3.52 (m, 4H), 3.25 (ddd, *J* = 7.8, 4.7, 3.1 Hz, 1H), 2.29 (ddd, *J* = 9.2, 6.0, 3.2 Hz, 1H), 1.69 (ddd, *J* = 7.6, 5.9 Hz, 1H), 1.39 (ddd, *J* = 9.1, 5.3 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 172.22, 61.36 (-), 61.30 (-), 52.32 (-), 51.36 (-), 23.16 (+), 19.97 (+), 18.24 (-); FT IR (NaCl, film, cm^{-1}): 3328, 2983, 2974, 1646, 1488, 1460,1437, 1379, 1343, 1275, 1228, 1130. HRMS (TOF ES): found 250.0079, calculated for $C_8H_{13}BrNO_3$ (M-H) 250.0081 (1.3 ppm).



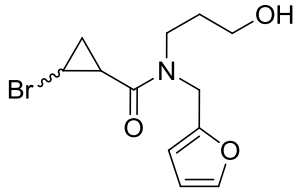
N-Benzyl-2-bromo-N-(3-hydroxypropyl)cyclopropanecarboxamide (**77a**): To a stirred solution of (3-benzylamino)propane-1-ol (550 mg, 3.3 mmol, 1.1 equiv) and triethylamine (610 mg, 6 mmol, 2 equiv) in dry THF (30 mL) was added 2-bromocyclopropanecarbonyl chloride (550 mg, 3.0 mmol). The mixture was stirred for 1 hr at room temperature, then the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). The organic layer was separated and washed consecutively with 10% aqueous HCl (3 x 10 mL) and 4N

aqueous NaOH (5 mL), dried with $MgSO_4$, filtered, and concentrated. The title compound was obtained as colorless oil, mixture of diastereomers, 2:1. This material was pure enough to be used for the following transformations without additional purification. Yield 690 mg (2.22 mmol, 74%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm [7.48-7.36 (m) & 7.36-7.27 (m) & 7.26-7.19 (m), 5H], [4.74 (d, *J* = 17.2 Hz) & 4.65 (d, *J* = 14.9 Hz), 1H], [4.66 (d, *J* = 17.4 Hz) & 4.54 (d, *J* = 14.9 Hz), 1H], 3.88 (br. s., 1 H), 3.71-3.42 (m, 4H), [3.30 (ddd, *J* = 7.6 Hz, 4.6 Hz, 3.0 Hz) & 3.27 (ddd, *J* = 7.8 Hz, 4.8 Hz, 3.0 Hz), 1H], [2.37 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.0 Hz) & 2.17 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.2 Hz), 1H], [1.83 (tt, *J* = 7.1 Hz, 6.1 Hz) & (1.78-1.64 (m), 3H], [1.37 (ddd, *J* = 9.4 Hz, 5.6 Hz, 4.8 Hz) & 1.33 (ddd, *J* = 9.1 Hz, 5.6 Hz, 4.8 Hz), 1H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 171.9, 136.0, 128.9 (+, 2C), 127.8 (+), 126.2 (+, 2C), 58.2 (-), 51.0 (-), 42.8 (-), 29.8 (-), 22.6 (+), 19.9 (+), 18.3 (-), minor: 170.4, 137.3, 128.4 (+, 2C), 127.9 (+, 2C), 127.3 (+), 58.9 (-), 49.0 (-), 43.9 (-), 31.5 (-), 22.3 (+), 20.2 (+), 18.1 (-); FTIR (NaCl, film, cm[1]) 3387, 2930, 2874, 1620, 1450, 1215, 1055, 731, 698, 581; HRMS (TOF ES): found 334.0217, calculated for $C_{14}H_{18}NO_2BrNa$ (M+Na) 334.0419 (0.6 ppm);



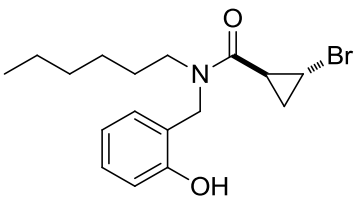
2-Bromo-N-hexyl-N-(3-hydroxypropyl)cyclopropanecarboxamide (**77b**): mixture of diastereomers, 5:1. To a solution of (3-hexylamino)propan-1-ol (350 mg, 2.2 mmol, 1.1 equiv) and triethylamine (410 g, 4.0 mmol, 2.0 equiv) in dry THF (15 mL) stirred at 0 ^{o}C was added a solution of 2-bromocyclopropanecarbonyl chloride (370 mg, 2.0 mmol, 1.0 equiv.) in dry THF (15 mL). The mixture was stirred for 5 hr at RT, then the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). The organic

layer was separated and washed consecutively with 10% aqueous HCl (3 x 10 mL) and 4N aqueous NaOH (5 mL), dried with $MgSO_4$, filtered, and concentrated. The title compound was obtained as colorless oil, mixture of diastereomers, 5:1. This material was pure enough to be used for the following transformations without additional purification. Yield 527 mg (1.72 mmol, 86%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.90 (br. s., 2H), [3.68 (t, *J* = 5.7 Hz) & 3.56 (sxt, *J* = 6.8 Hz) & 3.49 (td, *J* = 6.1 Hz, 2.3 Hz) & 3.44 (t, *J* = 5.3 Hz) & 3.41-3.34 (m) & 3.34-3.23 (m) & 3.20 (ddd, *J* = 7.8 Hz, 4.7 Hz, 3.2 Hz), 7H], [2.26 (ddd, *J* = 9.2 Hz, 5.9 Hz, 3.0 Hz) & 2.12 (ddd, *J* = 9.2 Hz, 6.0 Hz, 3.0 Hz), 1H], [1.85 (quin, *J* = 6.3 Hz) & 1.77-1.56 (m) & 1.56-1.43 (m), 5H], 1.43-1.19 (m, 7H), [0.89 (t, *J* = 7.1 Hz) & 0.86 (t, *J* = 6.8 Hz), 3H]; ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 171.2, 58.0 (-), 48.2 (-), 42.6 (-), 31.3 (-), 30.2 (-), 29.4 (-), 26.4 (-), 22.5 (+), 22.4 (-), 19.9 (+), 18.1 (-), 13.9 (+); minor: 169.7, 59.0 (-), 46.7 (-), 44.7 (-), 32.0 (-), 31.5 (-), 27.6 (-), 26.5 (-), 22.4 (+), 22.3 (-), 20.2 (+), 17.8 (-), 13.9 (+); FT IR (NaCl, film, cm^1) 3408, 2955, 2930, 2858, 1620 1462, 1377, 1229, 1190, 1057, 725, 588; HRMS (TOF ES): found 328.0887, calculated for $C_{13}H_{24}BrNO_2Na$ (M+Na) 328.0888 (0.3 ppm);



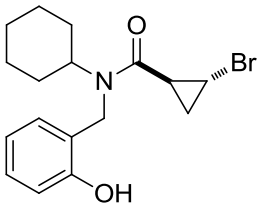
2-Bromo-N-(furan-2-ylmethyl)-N-(3-hydroxypropyl)cyclopropanecarboxamide (**79c**): To a stirred solution of 3-((furan-2-ylmethyl)amino)propan-1-ol (282 mg, 1.81 mmol, 1.10 equiv) and triethylamine (686 µL, 500 mg, 4.95 mmol, 3.00 equiv) in dry THF (5 mL) a solution of 2-bromo-1-methylcyclopropanecarbonyl chloride (300 mg, 1.65 mmol, 1.00 equiv) in dry THF (5 mL) was added dropwise over 10 min. The resulting suspension was stirred for 30 min at room temperature, and then filtered through a fritted funnel. The filter cake was washed with EtOAc

(3 x 10 ml). Combined organic solution was concentrated in vacuum. Preparative column chromatography of a crude residue on silica gel afforded the title compound as a colorless oil, R_f 0.50 (DCM-EtOAc, 3:1). Yield 310 mg (1.02 mmol, 62%), mixture of two diastereomers, 2:1. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ [7.36 (s) & 7.29 (s), 1H], [6.35-6.28 (m) & 6.25 (d, *J* = 3.0 Hz) & 6.19 (d, *J* = 3.0 Hz), 2H], [4.59 (d, *J* = 16.9 Hz) & 4.53 (d, *J* = 15.4 Hz) & 4.53 (d, *J* = 16.9 Hz) & 4.48 (d, *J* = 15.4 Hz), 2H], [3.63-3.53 (m) & 3.54-3.44 (m) & 3.40 (t, *J* = 5.6 Hz) & 3.20 (ddd, *J* = 7.5 Hz, 4.7 Hz, 2.9 Hz), 4H], [2.35 (ddd, *J* = 9.1 Hz, 5.9 Hz, 3.2 Hz) & 2.28 (ddd, *J* = 9.1 Hz, 5.9 Hz, 3.2 Hz), 1H), [1.76 (quin, *J* = 6.5 Hz) & 1.69-1.55 (m), 3H], [1.34 (dt, *J* = 9.1 Hz, 5.6 Hz, 1H) & 1.29 (dt, *J* = 9.1 Hz, 5.3 Hz), 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ major: 171.5, 149.5, 142.6 (+), 110.3 (+), 108.2 (+), 58.0 (-), 44.7 (-), 42.8 (-), 29.8 (-), 22.6 (+), 19.7 (+), 18.1 (-); minor: 170.1, 150.6, 141.9 (+), 110.2 (+), 108.4 (+), 58.6 (-), 44.3 (-), 42.1 (-), 31.4 (-), 22.1 (+), 20.1 (+), 18.0 (-); FT IR (NaCl, film, cm^1): 3414, 3117, 2932, 2876, 2341, 1626, 1504, 1477, 1454, 1373, 1356, 1229, 1188, 1072, 1055, 1013, 922, 741, 598, 586; HRMS (TOF ES): found 302.0391, calculated for $C_{12}H_{17}NO_3Br$ (M+H) 302.0392 (0.3 ppm);



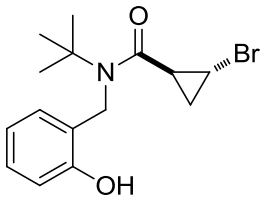
2-Bromo-N-(n-hexyl)-N-(2-hydroxybenzyl)cyclopropanecarboxamide (**80a**): A solution of Me_3SiCl (21.5 mg, 0.197 mmol, 1.20 equiv), NEt_3 (28 mg, 80 mL, 0.57 mmol, 3.5 equiv), and 2-((*n*-hexylamino)methyl)phenol (37.3 mg, 0.18 mmol, 1.10 equiv) was stirred in dry THF (4 mL) overnight under a nitrogen atmosphere. Then 2-bromocyclopropanecarbonyl chloride (30 mg, 0.16 mmol, 1.0 equiv) was added and allowed to stir for 3 hours. The solvent was removed by rotary evaporation and then partitioned between 10 mL 5% HCl & 10 mL EtOAc. The organic

layer was washed with 5% HCl (3 x 15 mL) then dried with $MgSO_4$, filtered, and concentrated which afforded 2-bromo-N-*n*-hexyl-*N*-(2-hydroxybenzyl)cyclopropanecarboxamide (**80a**) as a viscous oil. The obtained material was pure enough for the following transformation with no additional purification. Yield 23 mg (0.065 mmol, 40%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.84 (t, *J* = 7.4 Hz, 1H), 4.47 (s, 2H), 3.49 (t, *J* = 7.9 Hz, 2H), 3.30 (ddd, *J* = 7.7, 4.8, 3.1 Hz, 1H), 2.14 (ddd, *J* = 9.0, 5.8, 3.1 Hz, 1H), 1.79 – 1.69 (m, 3H), 1.44 – 1.35 (m, 7H), 0.97 – 0.93 (m, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 172.2, 156.3, 131.4 (+), 130.4 (+), 122.1, 119.3 (+), 117.6 (+), 48.0 (-), 47.4 (-), 31.5 (-), 28.8 (-), 26.5 (-), 22.7 (+), 22.6 (-), 20.2 (+), 18.7 (-), 14.0 (+); FT IR (NaCl, film, cm^{-1}): 3321, 2954, 2925, 1633, 1589, 1454, 1446, 1352, 1215, 1108, 1070, 754; HRMS (TOF ES): found 353.0994, calculated for $C_{17}H_{24}BrNO_2$ (M+) 353.0990 (1.1 ppm).



2-Bromo-N-(c-hexyl)-N-(2-hydroxybenzyl)cyclopropanecarboxamide (**80b**): A solution of Me_3SiCl (65 mg, 0.60 mmol, 1.20 equiv), NEt_3 (177 mg, 243μL, 1.75 mmol, 3.50 equiv), and 2-((cyclohexyl-amino)methyl)phenol (113 mg, 0.55 mmol, 1.10 equiv) was stirred in dry THF (30 mL) overnight under a nitrogen atmosph ere. Then 2-bromocyclopropanecarbonyl chloride (91 mg, 0.50 mmol, 1.0 equiv) was added and allowed to stir for 3 hours. The solvent was removed by rotary evaporation and then partitioned between 10 mL 5% HCl & 10 mL EtOAc. The organic layer was washed with 5% HCl (3 x 15 mL) then dried with $MgSO_4$, filtered, and concentrated which afforded 2-bromo-N-cyclohexyl-N-(2-hydroxybenzyl)-cyclopropanecarboxamide (**80b**) as a viscous oil. The obtained material was pure enough for

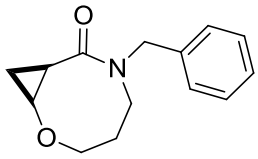
the following transformation with no additional purification. Yield 75 mg (0.21 mmol, 42%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 6.93 – 6.87 (m, 1H), 6.86 – 6.79 (m, 1H), 4.51 (d, *J* = 6.1 Hz, 2H), 4.02 – 3.89 (m, 1H), 3.32 (ddd, *J* = 7.8, 4.9, 3.1 Hz, 1H), 2.24 (ddd, *J* = 9.1, 6.0, 3.1 Hz, 1H), 2.00 – 1.63 (m, 8H), 1.56 – 1.06 (m, 4H). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 172.6, 156.4, 131.6 (+), 129.9 (+), 123.1, 119.2 (+), 117.7 (+), 77.3 (+), 59.2 (+), 32.7 (-), 32.5 (-), 26.2 (-), 26.0 (-), 25.3 (-), 23.5 (+), 20.13 (+), 18.5 (-, 2C); FTIR (NaCl, film, cm^{-1}): 3258, 2932, 1614, 1593, 1456, 1444, 1375, 1261, 1231, 1095, 1043, 754; HRMS (TOF ES): found 352.0906, calculated for $C_{17}H_{23}BrNO_2$ (M+H) 352.0912 (1.7 ppm).



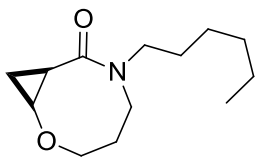
2-Bromo-N-(tert-butyl)-N-(2-hydroxybenzyl)cyclopropanecarboxamide (**80c**) A solution of Me_3SiCl (261 mg, 2.40 mmol, 1.20 equiv), NEt_3 (708 mg, 975 μL, 7.00 mmol, 3.50 equiv), and 2-((*tert*-butylamino)-methyl)phenol (394 mg, 2.20 mmol, 1.10 equiv) was stirred in dry THF (30 mL) overnight under a nitrogen atmosphere. Then 2-bromocyclopropanecarbonyl chloride (367 mg, 2 mmol, 1 equiv) was added and allowed to stir for 3 hours. The solvent was removed by rotary evaporation and then partitioned between 10 mL 5% HCl & 10 mL EtOAc. The organic layer was washed with 5% HCl (3 x 15 mL) then dried with $MgSO_4$, filtered, and concentrated. The obtained crystalline material (mp 165-168 ^{o}C) was pure enough for the following transformation with no additional purification. Yield 583 mg (1.78 mmol, 89%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.04 (d, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.67 (d, *J* = 19.2 Hz, 1H), 4.62 (d, *J* = 19.2 Hz, 1H), 3.04 (ddd, *J* = 7.6 Hz, 4.4 Hz, 3.2 Hz, 1H), 1.88 (ddd, *J* = 9.0 Hz, 6.0 Hz, 3.0 Hz, 1H), 1.41 (ddd, *J* = 7.6 Hz, 6.0 Hz, 5.0 Hz, 1H), 1.29 (s, 9H),

1.09 (dt, J = 9.5 Hz, 5.0 Hz, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 174.0, 155.4, 129.2 (+), 127.7 (+), 126.6, 120.8 (+), 116.0 (+), 59.3, 45.4 (-), 28.8 (+, 3C), 26.6 (+), 20.4 (+), 18.6 (-); FT IR (NaCl, film, cm^1): 3300, 2964, 2930, 1622, 1595, 1456, 1427, 1364, 1227, 1192, 754; HRMS (TOF ES): found 325.0670, calculated for $C_{15}H_{20}BrNO_2$ (M^+) 325.0677 (2.2 ppm).

2.6.9. Cyclization products

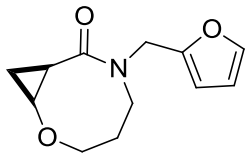


(1S*,8R*)-6-Benzyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**79a**): An oven-dried 50 mL round bottom flask was charged with bromocyclopropane **77a** (140 mg, 0.45 mmol, 1.0 equiv), 18-crown-6 (11.8 mg, 0.045 mmol, 10 mol%), KOH (88 mg, 1.57 mmol, 3.5 equiv) and anhydrous THF (10 mL). The mixture was stirred at RT for 2.25 hrs. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography on silica gel (R_f 0.28, eluent EtOAc) to obtain a title compound as a colorless crystalline solid, mp 51-55 ^{o}C. Yield 91 mg (0.40 mmol, 88%) ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.29-7.23 (m, 2H), 7.23-7.17 (m, 3H), 5.24 (d, *J* = 14.8 Hz, 1H), 3.85 (d, *J* = 15.1 Hz, 1H), 3.60 (td, *J* = 12.8 Hz, 3.2 Hz, 1H), 3.45 (ddd, *J* = 6.9 Hz, 6.1 Hz, 4.1 Hz, 1H), 3.17 (dd, *J* = 15.4 Hz, 6.9 Hz, 1H), 1.96 - 1.80 (m, 1H), 1.63 (dt, *J* = 10.2 Hz, 6.5 Hz, 1H), 1.53 (ddd, *J* = 15.2 Hz, 7.2 Hz, 3.2 Hz, 1H), 1.17 (td, *J* = 6.9 Hz, 3.9 Hz, 1H), 1.03 (dt, *J* = 10.2 Hz, 7.1 Hz, 1H); ^{13}C NMR (125.76 MHz, CD_3Cl) δ 169.7, 137.5, 128.5 (+, 2C), 128.1 (+, 2C), 127.3 (+), 72.8 (-), 61.0 (+), 48.6 (-), 46.0 (-), 30.1 (-), 22.7 (+), 10.5 (-); FTIR (NaCl, film, cm^{1}) 2928, 2870, 1634, 1481, 1439, 1229, 1080, 735, 698; HRMS (TOF ES): found 232.1332, calculated for $C_{14}H_{18}NO_2$ (M+H) 232.1338 (2.6 ppm).



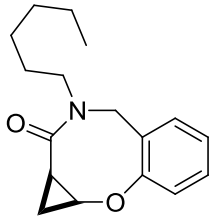
(1S*,8R*)-6-Hexyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**79b**): An oven-dried 50 mL round bottom flask was charged with bromocyclopropane **77b** (165 mg, 0.53 mmol, 1.0 equiv), 18-crown-6 (14 mg, 0.053 mmol, 10 mol%), KOH (74 mg, 1.33 mmol, 2.5 equiv.) and anhydrous THF (10 mL).

The mixture was stirred at RT for 2.25 hrs. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography on silica gel, eluting first with mixture EtOAc/hexane 3:1, and then with mixture EtOAc/MeOH 3:1, to obtain a title compound as a colorless amorphous solid, R_f 0.83 (EtOAc/MeOH 3:1). Yield 107 mg (90%, 0.48 mmol). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 4.22-4.06 (m, 2H), 3.88 (dddd, *J* = 13.4 Hz, 8.1 Hz, 6.6 Hz, 1.0 Hz, 1H), 3.66 (td, *J* = 12.7 Hz, 3.2 Hz, 1H), 3.48 (td, *J* = 6.7 Hz, 4.0 Hz, 1H), 3.28 (dd, *J* = 15.3 Hz, 6.9 Hz, 1H), 2.76 (ddd, *J* = 13.9 Hz, 8.8 Hz, 5.6 Hz, 1H), 2.02-1.86 (m, 1H), 1.71-1.43 (m, 4H), 1.13-1.21 (m, 6H), 1.15 (td, *J* = 6.8 Hz, 3.8 Hz, 1H), 1.03 (dt, *J* = 10.2 Hz, 7.0 Hz, 1H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.1, 72.8 (-), 61.0 (+), 46.8 (-), 45.9 (-), 31.6 (-), 30.7 (-), 27.6 (-), 26.6 (-), 22.9 (+), 22.6 (-), 14.0 (+), 10.3 (-); FTIR (NaCl, film, cm^1) 2955, 2930, 2858, 1626, 1485, 1462, 1373, 1225, 1095, 725; HRMS (TOF ES): found 226.1807, calculated for $C_{13}H_{24}NO_2$ (M+H) 226.1807 (0.0 ppm).

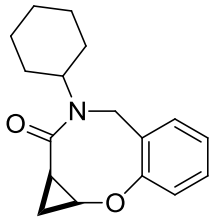


(1S*,8R*)-6-(Furan-2-ylmethyl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**79c**): To a stirred suspension of powdered KOH (46 mg, 0.83 mmol, 2.5 equiv) and 18-crown-6 ether (8.7 mg, 0.033 mmol, 10 mol%) in dry THF (3 mL) was added bromocyclopropane **77c** (100 mg, 0.33 mmol, 1.0 equiv). The mixture was vigorously stirred at 25 ^{o}C for 3 hrs. The KBr precipitate was filtered off on a fritted funnel and the filtrate was concentrated in vacuum. Preparative column chromatography of a residual oil on silica gel afforded the title compound as a crystalline solid, R_f 0.30 (CH_2Cl_2-EtOAc, 3:1). Yield 69 mg (0.31 mmol, 95%).

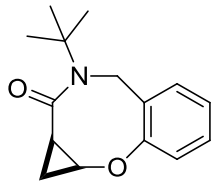
^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.37 (d, *J* = 1.0 Hz, 1H), 6.37-6.31 (m, 1H), 6.29 (d, *J* = 3.3 Hz, 1H), 5.06 (d, *J* = 15.4 Hz, 1H), 4.22-4.08 (m, 2H), 3.68 (td, *J* = 12.6 Hz, 3.3 Hz, 1H), 3.55-3.48 (m, 1H), 3.41 (dd, *J* = 15.4 Hz, 6.8 Hz, 1H), 1.95-1.80 (m, 1H), 1.74-1.59 (m, 3H), 1.22 (td,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



(1aR*,9aS*)-3-hexyl-1,3,4,9a-tetrahydrobenzo[b]cyclopropa[g][1,5]ox-azocin-2(1aH)-one (**81a**): To a stirred solution of 2-bromo-*N*-hexyl-*N*-(2-hydroxybenzyl)cyclopropanecarboxamide (**80a**) (70 mg, 0.20 mmol) and 18-crown-6 (5.6 mg, 0.019 mmol, 0.1 equiv) in dry tetrahydrofuran (4.0 mL) was added potassium hydroxide (33 mg, 0.60 mmol, 3.0 equiv). The mixture was stirred for 3.5 hours at 50^{o}C, filtered through a Pasteur pipette with a cotton plug, and then the solvent was removed in vacuum. Column chromatography on basic alumina oxide (eluent hexan-EtOAc 3:1) afforded the titled compound as an amorphous colorless solid. Yield 16 mg (0.058 mmol, 29%). FTIR (NaCl, film, cm^{-1}): 2954, 2925, 1643, 1604, 1591, 1469, 1454, 1229, 1190, 1107, 756; HRMS (TOF ES): found 273.1729, calculated for $C_{17}H_{23}NO_2$ (M+) 273.1729 (0.0 ppm).



(1aR*,9aS*)-3-cyclohexyl-1,3,4,9a-tetrahydrobenzo[b]cyclopropa[g][1,5]-oxazocin-2(1aH)-one (**81b**): To a stirred solution of 2-bromo-*N*-cyclohexyl-*N*-(2-hydroxybenzyl)cyclopropanecarboxamide **80b** (67 mg, 0.190 mmol) and 18-crown-6 (5.0 mg, 0.019 mmol, 0.1 equiv) in dry tetrahydrofuran (4.0 mL) was added potassium hydroxide (32 mg, 0.57 mmol, 3.0 equiv). The mixture was stirred for 3.5 hours at 50°C, filtered through a Pasteur pipette with a cotton plug, and then the solvent was removed in vacuum. Column chromatography on basic alumina oxide (eluent hexane-EtOAc 3:1) afforded the titled compound as a white solid. Yield 16 mg (0.059 mmol, 31%). FTIR (NaCl, film, cm^{-1}): 2926, 2856, 1643, 1605, 1578, 1487, 1454, 1429, 1227, 1111, 756; HRMS (TOF ES): found 271.1563, calculated for $C_{17}H_{21}NO_2$ (M+) 271.1572 (3.3 ppm).



(1aR*,9aS*)-3-(tert-Butyl)-1,3,4,9a-tetrahydrobenzo[b]cyclopropa[g]-[1,5]oxazocin-2(1aH)-one (**81c**): An oven-dried 50 mL round bottom flask was charged with bromocyclopropane **81c** (184mg, 0.56 mmol, 1 equiv), 18-crown-6 (14.9 mg, 0.056 mmol, 10 mol%), KOH (78.6 mg, 1.4 mmol, 2.5 equiv.) and anhydrous THF (15 mL). The mixture was stirred at 50 °C for 12 hrs. The solvent was removed by rotary evaporation. The residue was absorbed onto silica gel and then purified by flash column chromatography on silica gel being flushed (eluent EtOAc/hexane 1:2 R_f:.3 product). Yield 129 mg (93%, 0.52 mmol) clear crystalline solid, mp 115-116 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.24 (td, *J* = 7.6 Hz, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.6 Hz, 1.5 Hz, 1H), 7.09-7.03 (m, 2H), 5.59 (d, *J* = 17.2 Hz, 1H), 4.35 (d, *J* = 16.9 Hz, 1H), 3.79 (td, *J* = 6.2 Hz, 3.0 Hz, 1H), 2.22 (dt, *J* = 10.1 Hz, 6.3 Hz, 1H), 1.41 (td, *J* = 6.9 Hz, 3.2 Hz, 1H), 1.35 (s, 9H), 1.15 (dt, *J* = 10.1 Hz, 6.7 Hz,

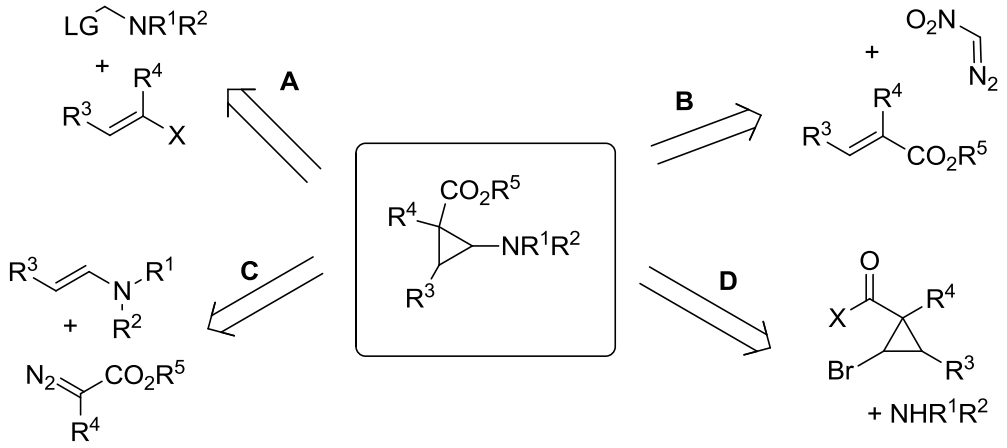
1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.9, 157.5, 130.8 (+), 128.9 (+), 128.7, 123.6 (+), 121.8 (+), 57.7, 56.9 (+), 48.9 (-), 28.5 (+, 3C), 26.6 (+), 10.4 (-); FT IR (NaCl, film, cm^1): 3456, 2993, 2966, 2924, 1651, 1489, 1408, 1358, 1225, 1194, 1111, 754; HRMS (TOF ES): found 268.1311, calculated for $C_{15}H_{19}NO_2Na$ (M+Na) 268.1313 (0.7 ppm).

Chapter 3. Nitrogen-centered nucleophile

3.1. Introduction

Having successfully demonstrated that strain-release activation can be utilized to activate α,β-unsaturated amides, enabling the addition of a variety of oxygen and sulfur based nucleophiles; we directed our focus towards expanding the methodology to include nitrogen-based nucleophiles. The rationale for this objective stems from the fact that the aza-Michael reaction is a heavily explored and extremely useful synthetic tool,[87] and nitrogen-substituted cyclopropane derivatives constitute a variety of useful molecules. For example, natural and synthetic analogs of α-aminocyclopropanecarboxylic acid (α-ACC) are ubiquitous; they have been extensively explored and find a widespread application in medicinal, chemical and agricultural research.[88] β-ACC derivatives are emerging as important tools for investigation of conformational preferences in peptides, [89] key elements of multiple natural products,[90] organocatalysts[91] and prospective drug candidates.[89,92] This is also evidenced by the incorporation of this key structural element into the structure of potent antiviral,[93] antitumor,[94] and antihypertensive agents.[95]

Scheme 34



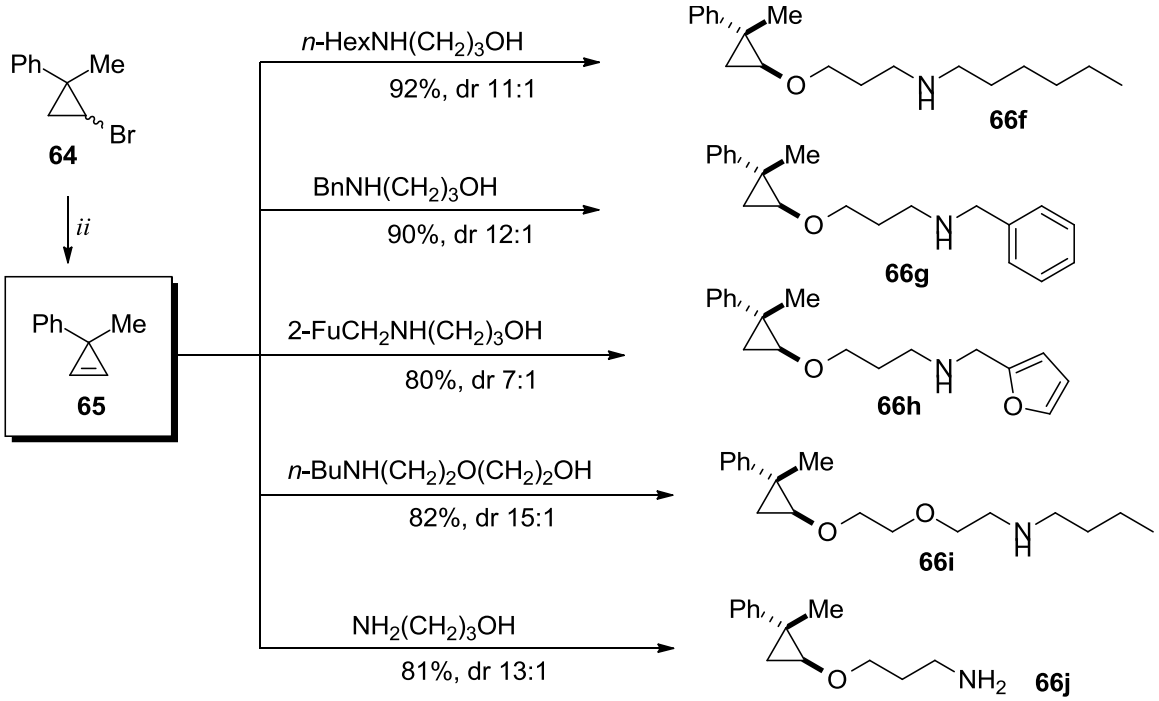
Cyclopropylamine derivatives, including β-ACC scaffolds are traditionally accessed by Michael-initiated ring closure reactions (Scheme 34, route **A**),[96] [2 + 1]-cyclopropanation of acrylates with α-nitrodiazocompounds (route **B**),[97] and to a much lesser extent, diazo transfer onto enamines (route **C**).[101] At the same time, approaches that allow direct and efficient installation of an amine function in a pre-existing three-membered ring (route **D**) remain scarce and typically involve the installation of an achiral cyclopropane ring.[98,99] Several previously reported attempts on the addition of such nucleophiles to cyclopropenes resulted in cleavage of the small ring and[100] the direct diastereoselective synthesis of this moiety remains a challenge.[101]

3.2. Carbonyl activation of nitrogen nucleophiles.

Our first insight into the behavior of nitrogen-based nucleophiles was gathered from bifunctional oxygen and sulfur-based nucleophiles bearing a 2^{o} amino group. It was observed that in both cases the addition occured through the O (Table 5, entry 9), or S (Table 8, entry 6)

terminus with perfect chemoselectivity over the N terminus (Scheme 36). This observation was rationalized to be a result of the disparity between N-H acidity and O-H or S-H acidity, resulting in selective deprotonation of the more acidic heteroatom followed by addition of the more reactive thiolate or alkoxide species.

Scheme 35

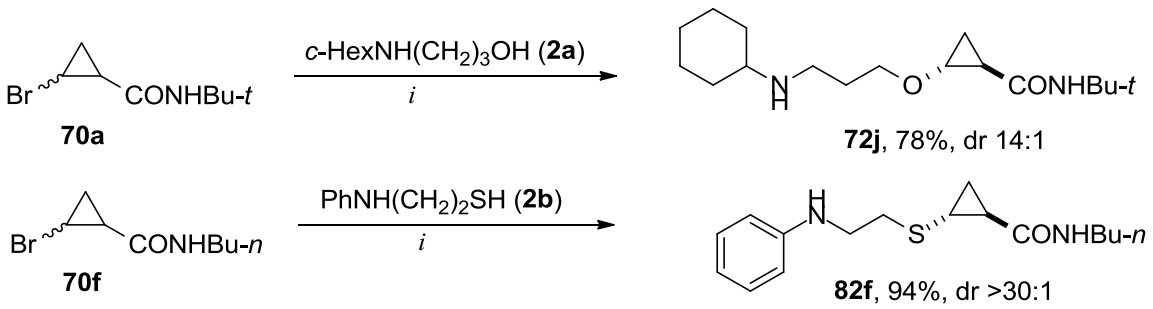


ii: aminoalcohol (1.5 equiv), *t*-BuOK (2.5 equiv), 18-crown-6 (10 mol%), THF, 80 ^{o}C, 18 h

A similar reactivity pattern was observed when isolable cyclopropene **65** was used, exclusively forming alkoxy-ether adducts **66f-66gg** when reacted with bifunctional amino alcohol nucleophiles (Scheme 35).

Unfortunately, when the possibility of a competing reaction was eliminated by employing ammonia as well as 1° or 2° alkylamines, cyclopropane starting material was consumed but no amine adducts were observed (Scheme 36).

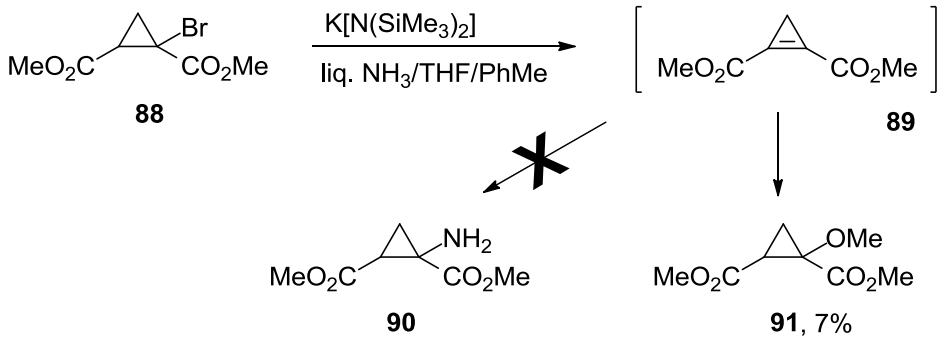
Scheme 36



i: **70a** or **70f** (2.0 equiv), KOH (3.5 equiv), 18-crown-6 (10 mol%), dry THF, 12 h at 80-110 °C

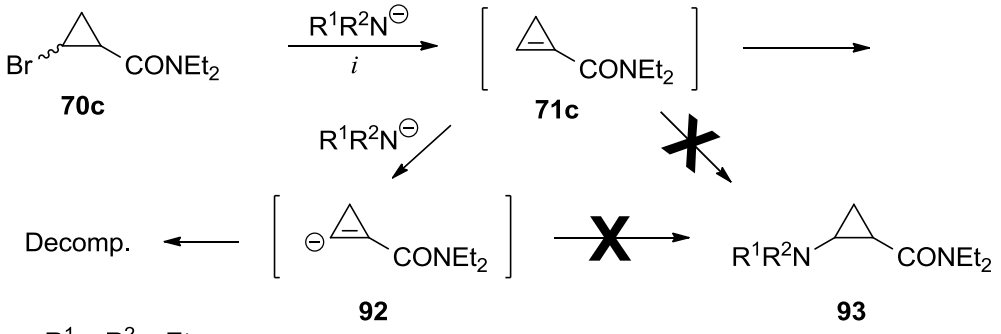
Again, lack of acidity could be blamed for the apparent low reactivity of nitrogen nucleophiles leading to the postulation of two possible solutions: (a) employing stronger base, or (b) installing electron-withdrawing activating groups enhancing the N-H acidity. The first idea was evaluated previously by Taylor,[102] who attempted synthesis of amino acid derivative **90** via dehydrobromination of bromocyclopropane **88** in the presence of $K[N(SiMe_3)_2]$ followed by trapping of intermediate cyclopropene **89** with ammonia (Scheme 37). This approach proved totally inefficient, leading to the formation in low yields of metoxycyclopropane **91** as the only isolable product, with the methoxide nucleophile originating from base-assisted cleavage of the cyclopropyl ester function.[102]

Scheme 37



Despite the fact that α,β-unsaturated ester **89** has a higher degree of activation towards conjugate addition as compared to unsaturated cyclopropenecarboxamides, we rationalized that the amide may be a viable candidate for the addition of 1° or 2° alkyl amides due to the fact that the carboxamide function should be less prone to hydrolysis. To test this hypothesis, bromocyclopropane **70c** was added to premixed solutions of metal hydride or alkyl lithium and 1° or 2° alkyl amines (Scheme 38). Initially we observed the formation of cycloropene **71c** to be sluggish, and upon heating; starting material was consumed but aminocyclopropane **93** was not observed.

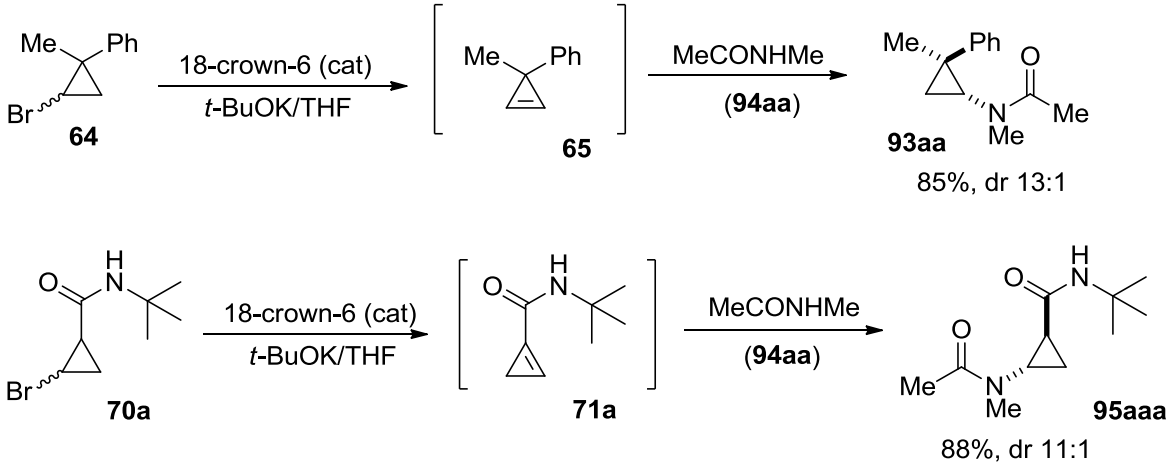
Scheme 38



This outcome may be explained as deprotonation of the relatively acidic C(sp^2)-H bond of cyclopropene **70c** resulting in cyclopropenyl anion **92** which has severely diminished aptitude towards conjugate addition. Therefore a nucleophile was unable to add and the unstable intermediate decomposed.

The implication of these findings is that we must activate nitrogen nucleophiles with electron withdrawing groups in order to modulate the N-H acidity into a range that is appropriate for our standard reaction conditions.

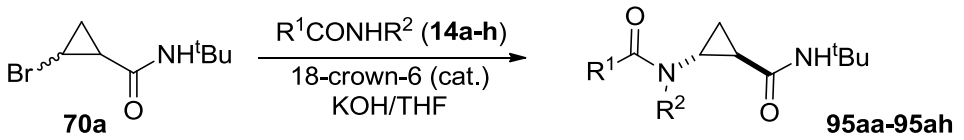
Scheme 39



Initial tests employed carbonyl activated N-methylacetamide (NMA, **94aa**) in the reaction with arylcyclopropene **65** using *t*-BuOK as base to affect dehydrobromination of bromocyclopropane **64** in the presence of catalytic 18-crown-6. We were pleased to find that these conditions lead to amide adduct **93aa** in high yield and excellent diastereoselectivity (Scheme 39). In persuit of β-

ACC derivatives, we also tested these same conditions with carboxamide cyclopropane **70a** yielding *trans*-diamide **95aaa** in equally high yield and good diastereoselectivity.

Table 9. Steric effect in the formal substitution of bromocyclopropane 70a with secondary amides



(1)

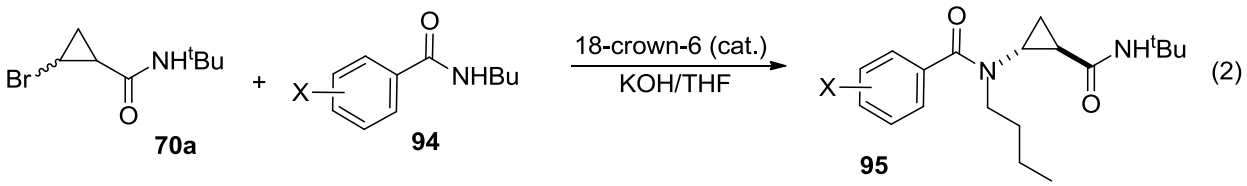
no.	R^1	R^2	NuH	product[a]	yield, %[b]	dr[c]
1	Me	Me	**94aa**	**95aaa**	88	11:1
2	*n*-Pr	*n*-Bu	**94bd**	**95abd**	51	25:1
3	*n*-Pr	*i*-Pr	**94bc**	**95abc**	28[d]	25:1
4	*i*-Pr	*n*-Bu	**94cd**	**95acd**	31[d]	17:1
5	*n*-Bu	*t*-Bu	**94de**	**95ade**	NR	-
6	*t*-Bu	*n*-Bu	**94ed**	**95aed**	NR	-
7	Ph	Me	**94fa**	**95afa**	75	>25:1
8	Ph	*n*-Bu	**94fd**	**95afd**	72	>25:1

a) Reactions performed in 0.5 mmol scale. b) Isolated yields of diastereomeric mixtures unless specified otherwise. c) dr (*trans*:*cis*) determined by GC or 1H NMR analyses of crude reaction mixtures. d) NMR yields determined by analyses of crude reaction mixtures. Bromocyclopropane 1a was consumed completely.

To further understand the role of sterics in carboxamide addition, we probed the reaction with carboxamides **94ba**-**94ed**, carrying substituents with variable steric demands. It was found that increased steric hindrance at the *N*- or *C*- terminus of the pronucleophile resulted in an adverse effect on reaction efficacy. Indeed, installation of primary alkyl substituents to both termini diminished the yield of product **95abd** to 51% (Table 9, entry 2) while secondary alkyl substituents on either terminus result in poor yields (entries 3, 4). Installation of a tertiary alkyl substituent to either terminus completely inhibited the nucleophilic additions (entries 5, 6).

We rationalized that the effective nucleophilicity (which for this process has the same trend as N-H acidity) of the sterically hindered amide species can be enhanced by adjusting their electronic properties. To test this idea, we substituted an alkyl group at the *C*-terminus of the pronucleophile with a phenyl ring. Gratifyingly, the reaction between bromocyclopropane **70a** and benzamides **94fa** and **94fd** afforded the corresponding diamides **94afa** and **94afd** with high yields and excellent diastereoselectivities (Table 9, entries 7, 8). Next, we tested **70a** in reactions with a series of differently substituted N-butylbenzamides **94gd**-**md** to further explore the effect of electronic factors on reactivity (Table 10). Interestingly, introduction of an electron donating *p*-MeO group completely shut down the reaction with **94gd** (Table 10, entry 2).

Table 10. Electronic effect in the formal substitution of bromocyclopropane 1a with secondary benzamides



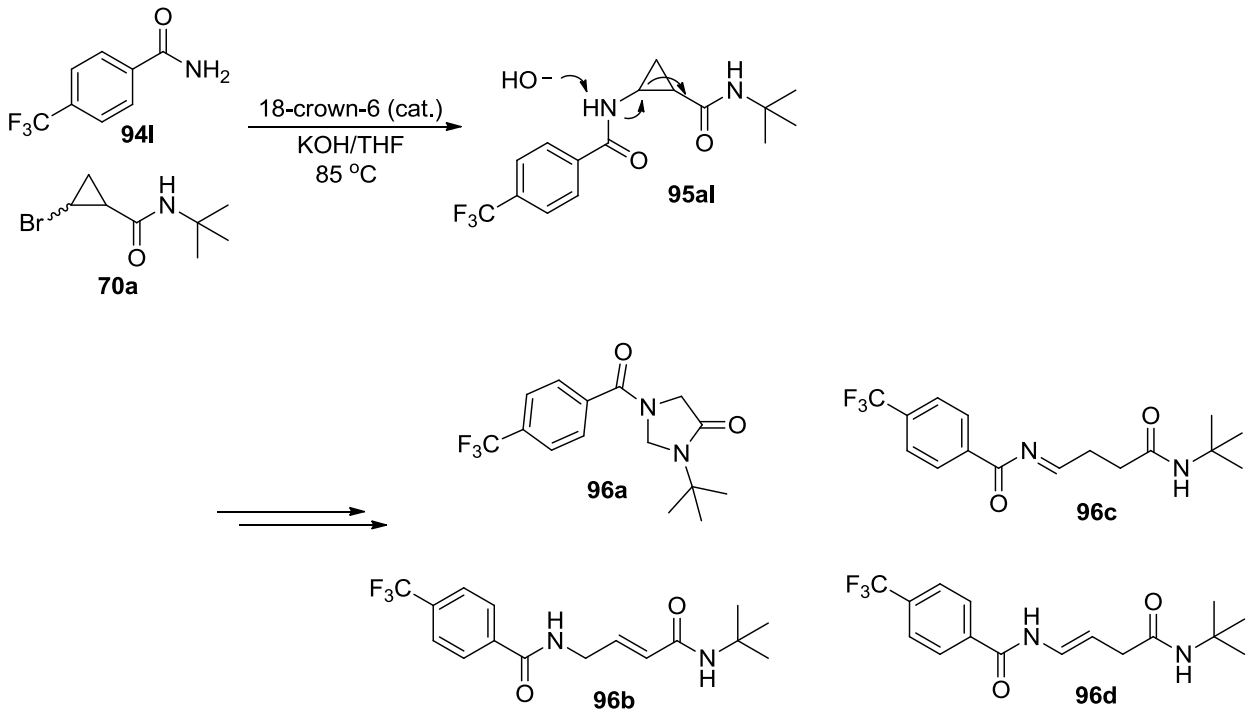
no.	X-C_6H_4-	NuH	Product[a]	yield, %[b]	dr[c]
1	Ph	**94fd**	**95afd**	72	>25:1
2	*p*-$MeOC_6H_4$	**94gd**	**95agd**	NR	-
3	*o*-ClC_6H_4	**94hd**	**95ahd**	80[d]	>25:1
4	*p*-ClC_6H_4	**94id**	**95aid**	81	>25:1
5	*p*-CNC_6H_4	**94jd**	**95ajd**	80	>25:1
6	*p*-$NO_2C_6H_4$	**94kd**	**95akd**	80	>25:1
7	*p*-$CF_3C_6H_4$	**94ld**	**95ald**	85	>25:1[e]
8	3,5-$(CF_3)_2C_6H_3$	**94md**	**95amd**	87	>25:1[e]

a) Typical reaction conditions: bromocyclopopane **70a** (0.5 mmol), amide **94** (1.0 mmol), powdered KOH (1.75 mmol), 18-crown-6 (0.05 mmol), THF (5 mL) - stirred at 85 °C for 12 h. b) Isolated yields of *trans*-diamide. c) dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures. The notation >25:1 is used when no minor diastereomer was detected. d) NMR yields determined by analysis of a crude reaction mixture. e) dr (trans:cis) determined by ^{19}F NMR analysis of crude reaction mixtures.

On the other hand, incorporation of electron-withdrawing groups in the *ortho*- (entry 3) or *para*- (entries 4-7) positions of the aromatic ring in the benzamide pronucleophile allowed for improved reactivity. The best results were achieved with *p*-CF_3- (**95ald**, entry 7) and 3,5-bis$(CF_3)_2$-substituted aryl groups (**95amd**, entry 8). It should be mentioned that no diamide product was observed in the reaction with primary amide (**94l**) despite complete consumption of

the bromocyclopropane **70a**.[103] This outcome could potentially result from addition of the primary amide, followed by subsequent deprotonation of secondary amide adduct **95al** resulting in ring-opening to form several possible products. Initial ring opening would result in imine **96c** which could isomerize to olefinic products **96b** or **96d** (Scheme 40). Cyclization could also occur between electrophilic imine and secondary *tert*-butyl amide to form aminal **96a**. ^{1}H NMR shows evidence for all of these as possible outcomes (Figure 4, peaks in olefinic region from 5.33-6.22 ppm), but was inconclusive as to which outcome(s) predominated.

Scheme 40



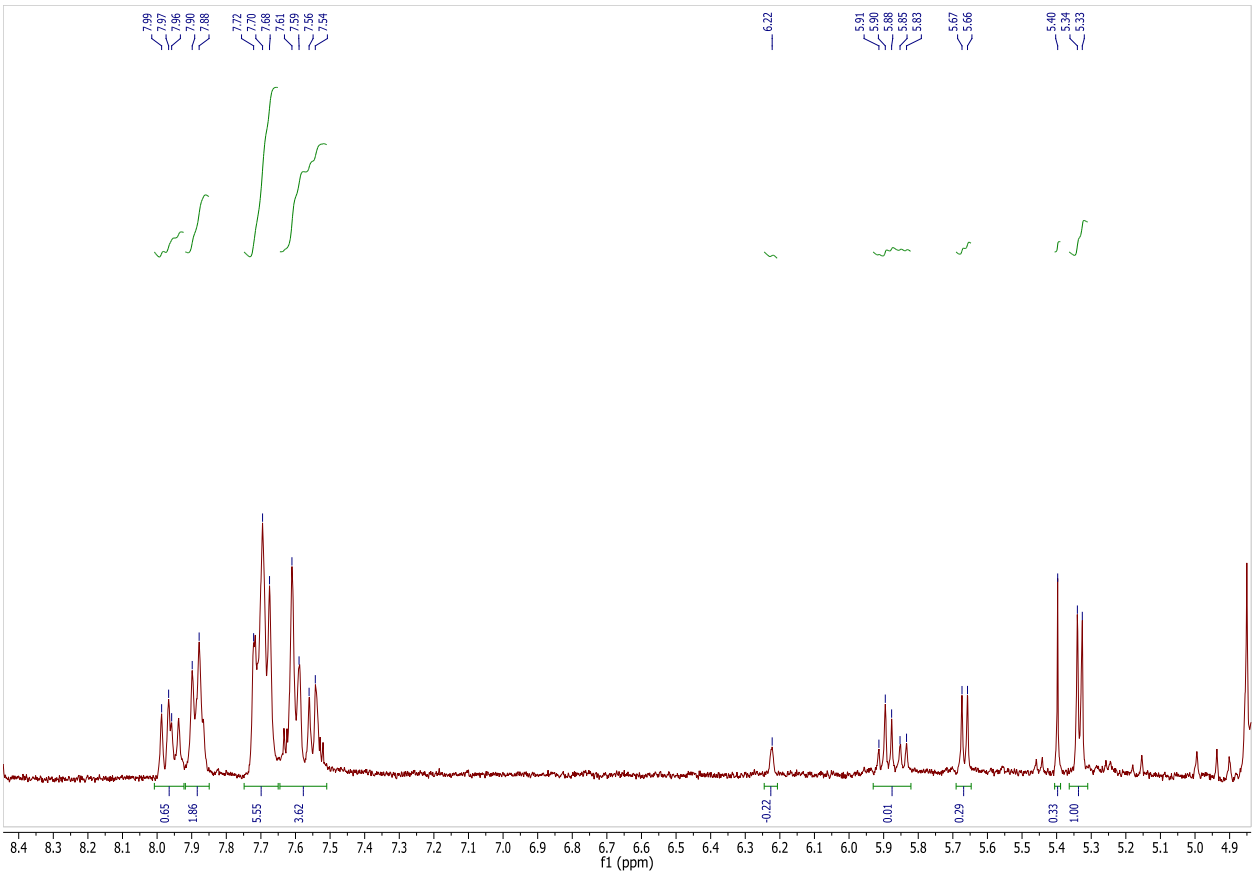


Figure 4: ^{1}H NMR showing evidence for product mixture potentially containing **96a-d**.

We envisioned that the described methodology, utilizing secondary amides as nucleophiles, could be efficiently applied toward convergent synthesis of conformationaly constrained *trans*-cyclopropyl amino acid derivatives, with the possibility for a three-dimensional diversification (Scheme 41). Thus, readily available acyl chlorides can be converted into an array of amides **70** by varying the primary or secondary amines. At the same time, a variety of pronucleophiles **94** can be obtained from primary amines and different carboxylic acids. As shown above, amides **94** derived from linear aliphatic and electron-defficient benzoic acids usually provide the highest yields in this transformation (Tables 1 and 2). Notably,

installation of the CF_3-groups in the benzamide derivatives **94ld**, **94md** significantly facilitated isolation and purification of the corresponding products **95ald** and **95amd** due to their improved solubility in organic solvents compared to other *N*-butyl benzamide derivatives (**95ahd-95akd**, Table 10). The presence of fluorine-containing groups also allowed for accurate assessment of the selectivity by ^{19}F NMR, as severe line broadening in proton spectra resulting from slow conformational rotation made ^{1}H NMR data inapplicable for the analysis. Accordingly, CF_3-substituted benzamides were used for more detailed investigations of the scope and limitation of this reaction. It was found that p-CF_3-substituted benzamides possessing primary *N*-alkyl groups rendered efficient nucleophilic addition to give *n*-octyl- (**95ale**), benzyl- (**95alf**), and 2-phenethyl benzamides (**95alg**) in high yields and perfect diastereoselectivites (Table 11, entries 1-3). At the same time, nucleophilic addition of a more sterically hindered *N*-cyclohexyl 4-(trifluoro-methyl)benzamide (**94lh**) proceeded sluggishly, resulting in marginal yield of the corresponding diamide **95alh** (Table 11, entry 4). In contrast, amides **94mc**, **94mg-mi** derived from 3,5-bis(trifluoromethyl)benzoic acid reacted with bromocyclopropane **70a** much more readily. Improved product yields were obtained not only for the less sterically hindered derivative **95amg** (Table 11, entry 8), but also for more challenging bulky products **95amh**, **95amc**, **95ami** (entries 5-7), bearing secondary *N*-alkyl substituents. However, very bulky *N*-*tert*-butylamide **94me** did not provide any product in the reaction with **70a** (entry 9).

Scheme 41

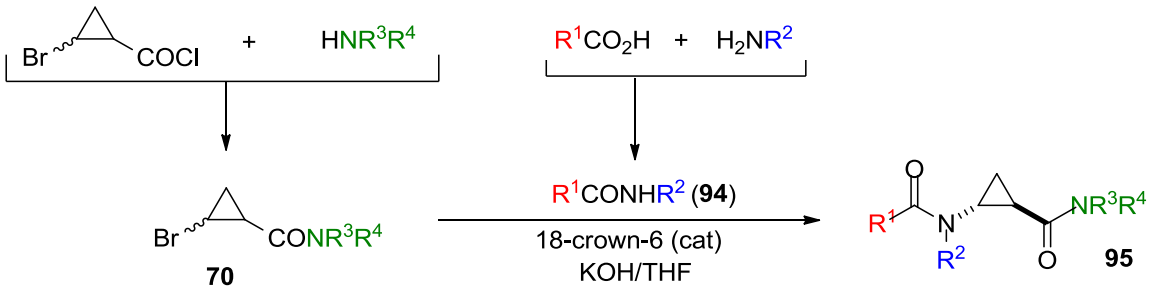


Table 11. Convergent approach to conformationally constrained *trans*-cyclopropyl amino acid derivatives via formal substitution of bromocyclopropanes with nucleophilic carboxamides

	R^3,R^4 (**70**)	R^1	R^2	(**94**)	(**95**)	yield, %[a]
1	^{t}Bu, H (**70a**)	*p*-$CF_3C_6H_4$	*n*-Oct	**94le**	**95ale**	85
2	^{t}Bu, H (**70a**)	*p*-$CF_3C_6H_4$	$PhCH_2$	**94lf**	**95alf**	80
3	^{t}Bu, H (**70a**)	*p*-$CF_3C_6H_4$	$Ph(CH_2)_2$	**94lg**	**95alg**	82
4	^{t}Bu, H (**70a**)	*p*-$CF_3C_6H_4$	*c*-Hex	**94lh**	**95alh**	45
5	^{t}Bu, H (**70a**)	3,5-$(CF_3)_2C_6H_3$	*c*-Hex	**94mh**	**95amh**	83
6	^{t}Bu, H (**70a**)	3,5-$(CF_3)_2C_6H_3$	*i*-Pr	**94mc**	**95amc**	61
7	^{t}Bu, H (**70a**)	3,5-$(CF_3)_2C_6H_3$	*c*-Pr	**94mi**	**95ami**	59
8	^{t}Bu, H (**70a**)	3,5-$(CF_3)_2C_6H_3$	$Ph(CH_2)_2$	**94mg**	**95amg**	94
9	^{t}Bu, H (**70a**)	3,5-$(CF_3)_2C_6H_3$	*t*-Bu	**94me**	**95ame**	-
10	-$(CH_2)_5$- (**70c**)	3,5-$(CF_3)_2C_6H_3$	$Ph(CH_2)_2$	**94mg**	**95cmg**	76
11	-$(CH_2)_2O(CH_2)$-(**70b**)	3,5-$(CF_3)_2C_6H_3$	$Ph(CH_2)_2$	**94mg**	**95bmg**	76
12	*c*-Hex, H (**70d**)	3,5-$(CF_3)_2C_6H_3$	*c*-Hex	**94mh**	**95dmh**	66

Table 11 (Continued)

	R^3,R^4 (**70**)	R^1	R^2	(**94**)	(**95**)	yield, %[a]
13	-$(CH_2)_5$- (**70c**)	3,5-$(CF_3)_2C_6H_3$	$PhCH_2$	**94mf**	**95cmf**	68
14	Me, OMe (**70e**)	3,5-$(CF_3)_2C_6H_3$	$PhCH_2$	**94mf**	**95emf**	31
15	^{t}Bu, H (**70a**)	4-NO_2-C_6H_4	$PhCH_2$	**94kf**	**95akf**	63
16	^{t}Bu, H (**70a**)	4-NO_2-C_6H_4	$ThCH_2$[b]	**94kj**	**95akj**	52
17	^{t}Bu, H (**70a**)	4-CN-C_6H_4	$PhCH_2$	**94jf**	**95ajf**	47
18	^{t}Bu, H (**70a**)	4-CN-C_6H_4	$FuCH_2$[c]	**94jk**	**95ajk**	81

a) Isolated yields. In all cases dr > 25:1 was obtained. b) Th = 2-thienyl. C) Fu = 2-furyl.

The scope of the cyclopropylcarboxamides **70** was also investigated. Bromocyclopropylcarboxamide derivatives of piperidine (**70c**), morpholine (**70b**), and cyclohexylamine (**70d**), afforded diamides **95cmg**, **95cmf**, **95bmg**, and **95dmh** in good to high yields (Table 11, entries 10-13). Weinreb amide **70e** was also tested in this reaction; however, the corresponding product **95emf** was obtained in 31% yield only, presumably, due to a decreased stability of the intermediate cyclopropene species (Table 11, entry 14). As discussed above, efficient activation of the nitrogen atom for nucleophilic attack is possible by almost any electron-withdrawing group (Table 10). Thus, derivatives of 4-nitro- (**94kf**, **94kj**) and 4-cyanobenzoic (**94jf**, **94jk**) acids were successfully employed for activation of benzylamine and hetarylmethylamines (Table 11, entries 15-18).

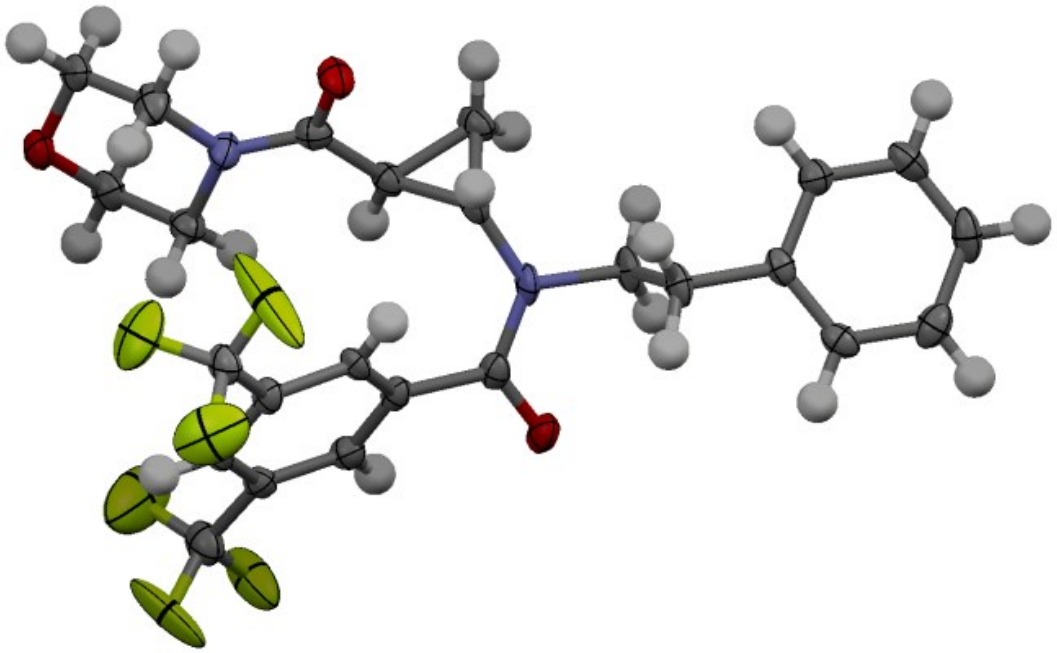


Figure 5. ORTEP drawing of diamide **95bmg** showing 50% probability amplitude displacement ellipsoids.

Similarly to the formal nucleophilic substitution reaction with alkoxides and phenoxides, the diastereoselectivity in the described transformation was governed by a base-assisted epimerization. However, additional treatment of the reaction mixture with t-BuOK was unnecessary in this case, as the thermodynamically more favored *trans*-diastereomer was produced exclusively under the standard reaction conditions. It should be mentioned that accurate assignment of the product configuration by ^{1}H NMR based on the analysis of $^{3}J_{HH}$ coupling constants of the cyclopropyl proton signals was impeded by severe broadening of the corresponding resonance lines. Careful optimization of the sample temperature provided acceptable resolution for measuring the coupling constants in **95aba** in DMSO-d_6. As additional

evidence, *trans*-configuration of diamide **95bmg** was unambiguously assigned by X-ray crystallography (Figure 5). These data were used to assign the structures of all other products by analogy.

3.3. Sulfonyl activation of nitrogen nucleophiles.

Despite having found success with addition of carboxamide nucleophiles, carbonyl activation was found to have several drawbacks. The two largest being the necessity of strong withdrawing groups such as a trifluoromethyl or nitro substituted aryl ring on the C-terminus as well as the severe line broadening in the ^{1}H NMR. These hindrances, coupled with the growing literature precedence for bioactive cyclopropyl sulfonamides,[95,104] lead us to pursue N-sulfonyl activation for nucleophilic addition to conjugated cyclopropanes. Indeed, sulfonamides are broadly employed as N-H acidic surrogates of amines in various C-N bond forming processes, for example, classical nucleophilic displacements[105] (including Mitsunobu coupling),[105,106] conjugate addition reactions,[107] and transition metal catalyzed couplings involving both C-Hal[108] and C-H bond activation.[109] Initially we attempted to employ sulfonamide nucleophile **97ad** under reaction conditions previously optimized for addition of alkoxides. This reaction, however, did not proceed at all, allowing for recovery of unreacted bromocyclopropane **70a** (Scheme 42). We rationalized the lack of reactivity by insufficient amount of base as an effect of the increased acidity of sulfonamides as compared to alcohol-based nuclephiles. This type of behavior was previously observed in reactions of relatively acidic pronucleophiles (such as phenols and thiols). The overall basicity of the media was not sufficient to achieve the base-assisted epimerizations into thermodynamically more stable *trans*-products, calling for a requisite additional treatment of crude products with stronger base. For the reactions with

sulfonamides, the basicity seems to be insufficient to ensure the initial dehydrobromination step. Accordingly, in attempt to

Scheme 42

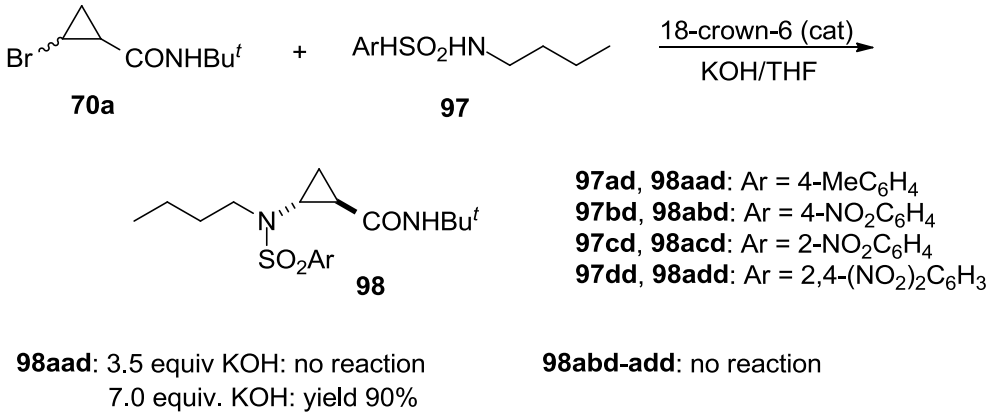
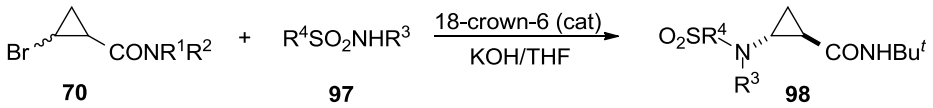


Table 12. Convergent approach to conformationally constrained *trans*-cyclopropyl amino acid derivatives via formal substitution of bromocyclopropanes with nucleophilic sulfonamides



	R^1,R^2	**70**	R^3,R^4	**97**	**98**	Yield (%)	dr
1	*t*-Bu, H	**70a**	4-MeC$_6$H$_4$, *n*-Bu	**97ad**	**98aad**	90	16:1
2	*t*-Bu, H	**70a**	4-MeOC$_6$H$_4$, *n*-Bu	**97ed**	**98aed**	95	11:1
3	*t*Bu, H	**70a**	4-MeC$_6$H$_4$, Bn	**97af**	**98aaf**	75	11:1
4	*c*-Hex, H	**70d**	4-MeC$_6$H$_4$, *n*-Bu	**97ad**	**98dad**	89	15:1

Table 12 (Continued)

	R^1,R^2	**70**	R^3,R^4	**97**	**98**	Yield (%)	dr
5	*t*Bu, H	**70a**	4-MeC_6H_4, Furfuryl	**97ak**	**98aak**	84	25:1
6	*t*-Bu, H	**70a**	Ph, *n*-Bu	**97fd**	**98afd**	73	10:1
7	*t*-Bu, H	**70a**	□-$C_{10}H_8$, *n*-Bu	**97gd**	**98agd**	78	10:1
8	*c*-Hex, H	**70d**	□-$C_{10}H_8$, *n*-Bu	**97gd**	**98dgd**	94	25:1
9	*t*Bu, H	**70a**	Me, *n*-Hex	**97he**	**98ahe**	90	9:1
10	*t*Bu, H	**70a**	Me, Bn	**97hf**	**98ahf**	83	15:1
11	*t*Bu, H	**70a**	Me, *c*-Hex	**97hh**	**98ahh**	67	11:1
12	*t*Bu, H	**70a**	4-FC_6H_4, *n*-Bu	**97id**	**98aid**	96	19:1
13	*c*-Hex, H	**70d**	4-FC_6H_4, *n*-Bu	**97id**	**98did**	97	10:1
14	-$(CH_2)_2O(CH_2)$-	**70b**	4-FC_6H_4, *n*-Bu	**97id**	**98bid**	71	11:1
15	*t*Bu, H	**70a**	4-FC_6H_4, Furfuryl	**97ik**	**98aik**	93	si
16	*t*Bu, H	**70a**	4-ClC_6H_4, *n*-Bu	**97jd**	**98ajd**	94	11:1
17	*t*Bu, H	**70a**	4-ClC_6H_4, Bn	**97jf**	**98ajf**	72	25:1
18	*t*Bu, H	**70a**	4-BrC_6H_4, *n*-Bu	**97kd**	**98akd**	91	11:1

force the reaction to completion we increased the base load to 7.0 equiv in the reaction with tosylamide **97ad**, to obtain the desired product **98aad** in excellent yield and high

diastereoselectivity (Scheme 42, Table 12, entry 1). Encouraged by the promising reactivity of tosylamide **97ad**, we set out to explore electronic influence on the efficacy of this reaction. Interestingly, in contrast to carboxamides, which require strong electron withdrawing groups, sulfonamides bearing an electron donating *p*-anisyl (**97ed**, Table 12, entry 2) and p-tolyl groups (**97af**, **97ad**, **97ak**, entries 3-5), as well as an electron-neutral phenyl (**97fd**) and □-naphthyl substituent (**97gd**) added smoothly, affording the corresponding cyclopropylamine sulfonates in high yield (Table 12, entries 6-8). The necessity of an aryl group was also probed and it was found that mesylamides **97he**, **97hf**, **97hh** also added with good to excellent yield to provide the corresponding products **98ahe**, **98ahf**, and **98ahh** (Table 12, entries 9-11). Sulfonamides bearing mild inductively electron withdrawing groups, such as p-FC_6H_4 (**97id**, **97ik**), p-ClC_6H_4 (**97jd**, **97jf**), and p-BrC_6H_4 (**97kd**) also proved viable in this reaction (Table 12, entries 12-18). At the same time, we failed to persuade the reaction of **70a** with highly acidic 4-nitro- (**97bd**), 2-nitro- (**97cd**), and 2,4-dinitro- (**97dd**) -benzenesulfonates of *n*-butylamine (Scheme 42). When base equivalencies were increased to above 15 equivalents, the dehydrobromination occurs but the nucleophilicity of the nosylates does not seem sufficient to produce any observable quantity of adducts.

3.4. Aromatic activation of nitrogen nucleophiles.

Removal of the nitrogen activating group would allow us to further functionalize the generated secondary amine of our β-ACC derivatives. Therefore the inability to utilize nosylates as nucleophilic amine surrogates was disappointing given their relative ease of deprotection under mild conditions. However, we rationalized that the enhanced N-H acidity of anilines compared to alkylamines could allow them to be used to install pre-functionalized amines

without carbonyl or sulfonyl activators. For this reason, we decided to investigate the possibility to employ them in the formal substitution reaction as N-based nucleophiles. In our initial experiments, reaction in the presence of *N*-methylaniline (**99a**) resulted in formation of aldehyde **103**. This compound can be viewed as product of formal addition of water to cyclopropene **71a**, accompanied by a base-assisted cleavage of the intermediate cyclopropanol **101**. On the other hand, formation of **103** was never observed in the absence of secondary aniline, thus suggesting a crucial role of this promoter. We believe the reaction begins with normal base-assisted conjugate addition of aniline species **99a** across the C=C bond of cyclopropene **71a**. Then, due to the strong donating ability of the nitrogen substituent, ring cleavage of the donor-acceptor cyclopropane **100aa** takes place, leading to the formation of iminium intermediate **102aa**, undergoing further base-assisted hydrolysis into aldehyde **103** (Scheme 43).

Scheme 43

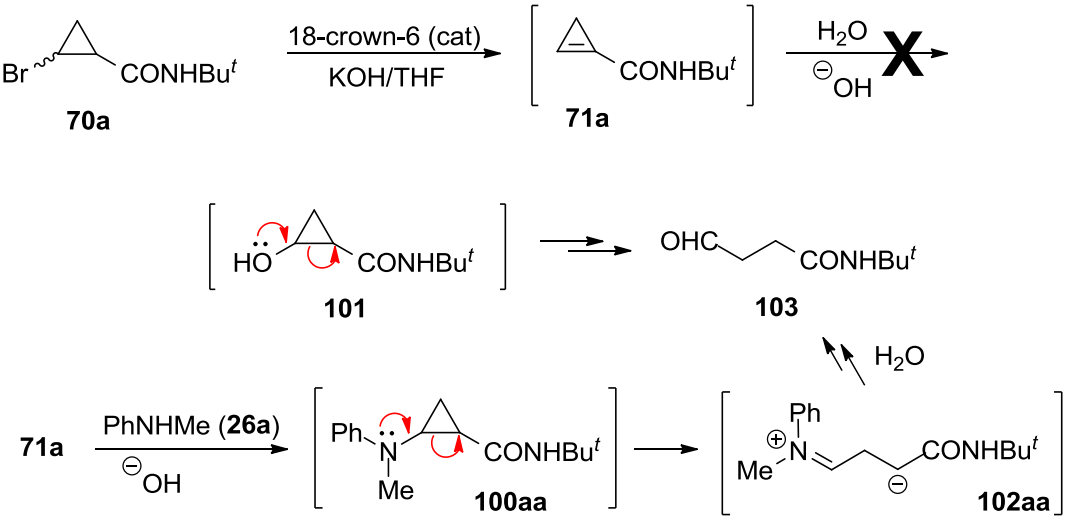
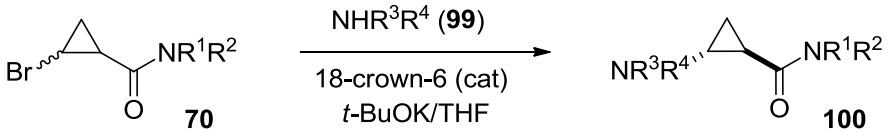


Table 13. Convergent approach to conformationally constrained *trans*-cyclopropyl amino acid derivatives via formal substitution of bromocyclopropanes with nucleophilic anilines.



	R^1,R^2 (**70**)	R^3,R^4 (**99**)	**100**	Yield (%)	dr
1	*t*-Bu, H (**70a**)	4-$NO_2C_6H_4$, Me (**99b**)	**100ab**	99	>25:1
2	*t*-Bu, H (**70a**)	4-NCC_6H_4, Bn (**99c**)	**100ac**	99	>25:1
3	*t*-Bu, H (**70a**)	4-$CF_3C_6H_4$, Bn (**99d**)	**100ad**	65	>25:1
4	-$(CH_2)_2O(CH_2)_2$- (**70b**)	4-$NO_2C_6H_4$, Bn (**99e**)	**100be**	75	>25:1
5	*t*-Bu, H (**70a**)	3-$NO_2C_6H_4$, Bn (**99f**)	**100af**	50	>25:1
6	*t*-Bu, H (**70a**)	Ph, Ph (**99g**)	**100ag**	96	>25:1
7	*t*-Bu, H (**70a**)	10*H*-phenothiazine (**99h**)	**100ah**	59	>25:1

We envisioned this aptitude to the ring cleavage could be dramatically diminished in cyclopropylamine intermediates with electron-deficient nitrogen. To this end we tested reactions with both KOH and t-BuOK in the presence of *p*-nitroaniline **100b** and catalytic 18-crown-6. To our delight the reaction with alkoxide base proceeded smoothly providing a single diastereomer of cyclopropylaniline **100ab** in nearly quantitative yield (Table 13). In a similar manner, several electron-deficient *N*-benzyl anilines, possessing cyano- (**99c**), trifluoromethyl-

(**99d**), and nitro- (**99e**) groups in *para*-positions were employed, having in mind a potential removal of the benzyl protecting group. All these nucleophiles added smoothly, affording the corresponding aminocyclopropanes **100ac**, **100ad**, and **10ee** in good to excellent yields and with perfect diastereoselectivities. *meta*-Nitroaniline **99f** possessing a less electron-deficient nitrogen atom provided the corresponding adduct **100af** in lower yield, yet the diastereoselectivity remained perfect (entry 5). Finally, diphenylamine (**99g**) and 10H-phenothiazine (**99h**) proved to be suitable pronucleophiles for the featured transformation. In this case electron-withdrawing substituents are not necessary, and the individual *trans*-diastereomers of the corresponding cyclopropylamine derivatives **100ag** and **100ah** could be optained in good to excellent yields (Table 13, entries 6-7).

3.4. Conclusions

In conclusion the work presented in this thesis is useful to the synthetic community as a general diastereoselective method for synthesizing functionally diverse and stereochemically defined cyclopropane derivatives via metal-free, inter- and intramolecular formal nucleophilic substitution reactions of readily available bromocyclopropanes **70** (Figure 6). The method hinges on the in-situ generation (path A) and trapping of unstable, conjugated cyclopropene **71** - which has no intrinsic shelf life - in a highly efficient elimination addition pathway.

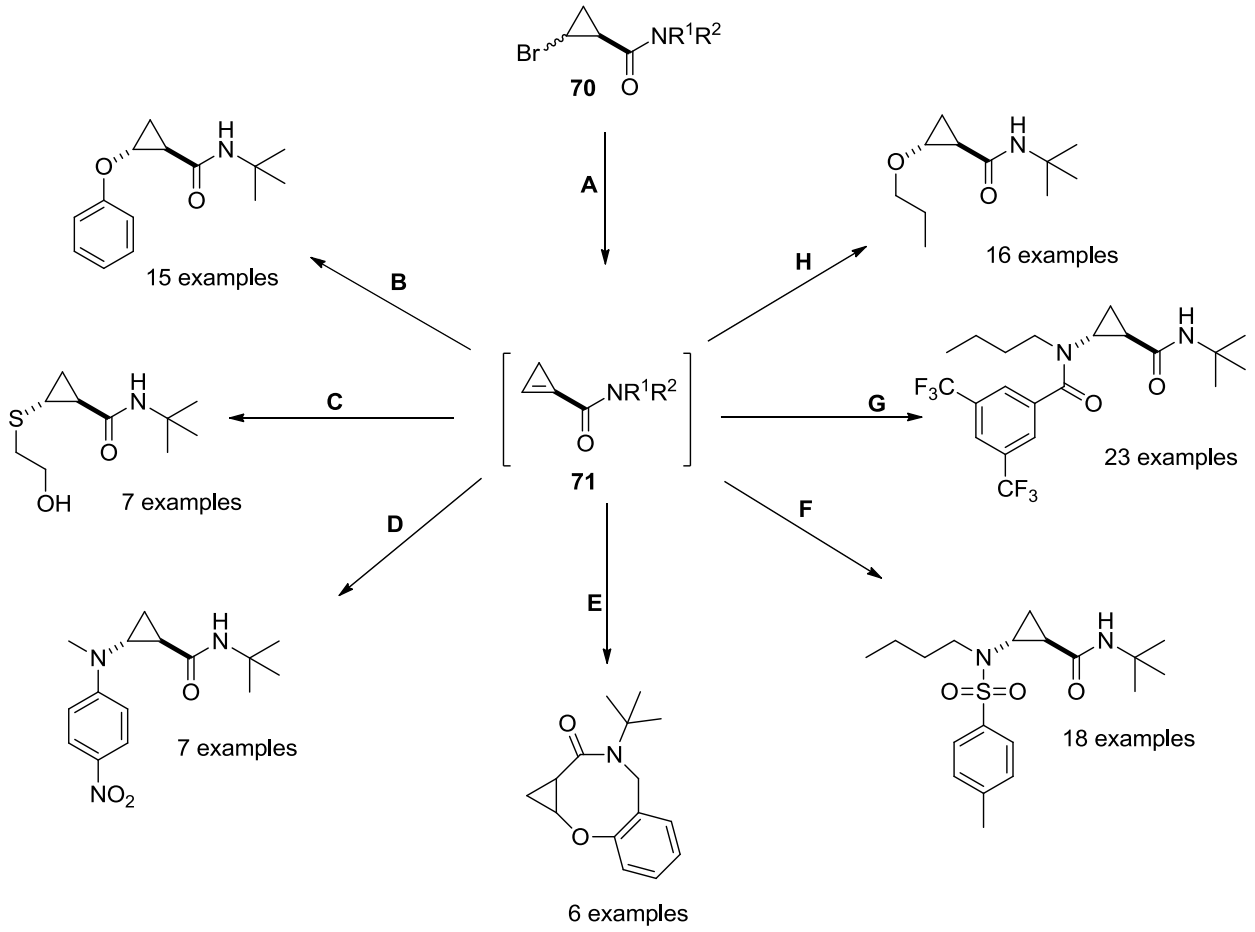


Figure 6

The formal substitution reactions exhibit a high degree of functional group tolerance, which allows for facile diversification leading to numerous derivatives bearing structural similarities to several biologically important classes of molecules. For example, the addition of nitrogen-based nucleophiles results in cyclopropyl amine derivatives, a class of molecules which encompass compounds such as tranylcypromine, β-ACC's [89, 91] and cyclopropyl suflonamides (Figure 7).[95, 104] Utilizing the method described in this thesis allows efficient access to β-ACC's

(Paths D, F and G), cyclopropyl sulfonamides (Path F) as well cyclopropanol derivatives (Paths B, E and H).

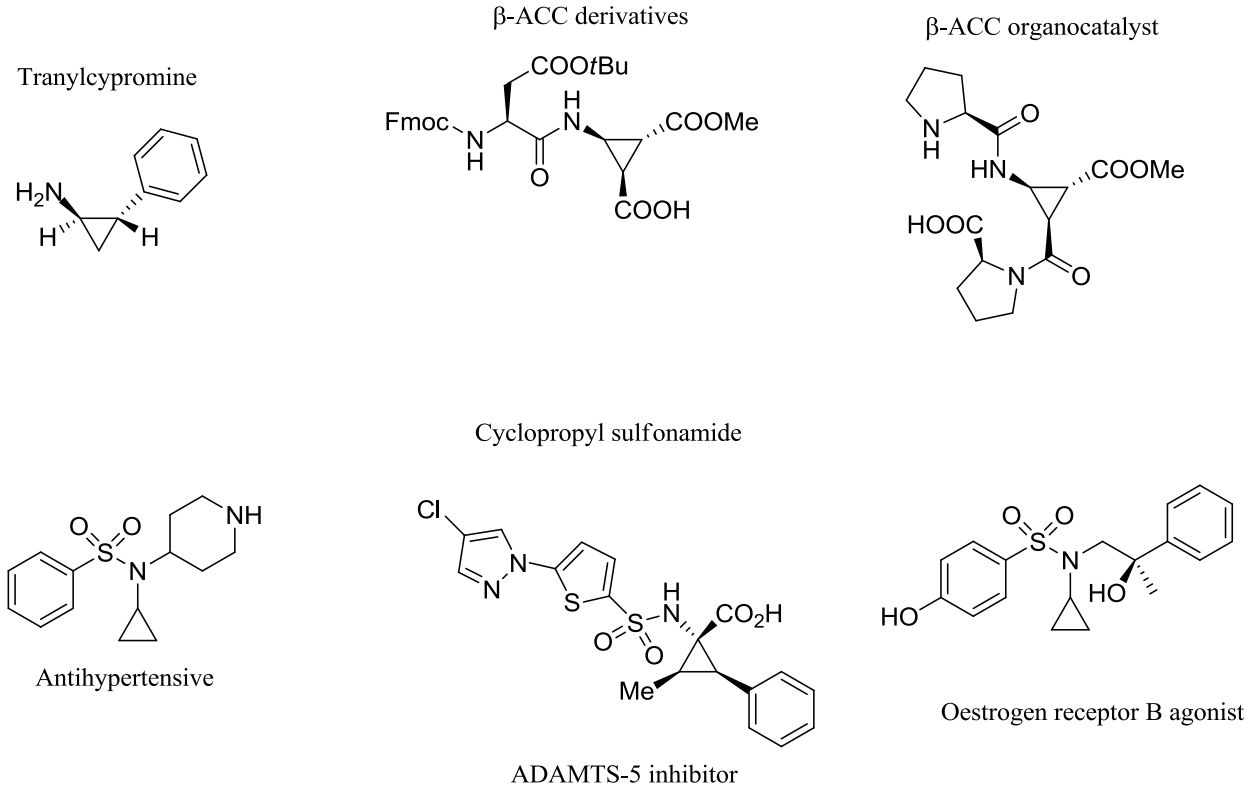


Figure 7

Along with a broad scope, the method benefits from generally high yields and is amenable to multi-gram scale. This coupled with simple and expedient isolation and purification of products via preparative silica chromatography suggests that rapid library synthesis to aid in early stage drug discovery can be accomplished by utilizing this method; especially if work were to be undertaken to develop automated reaction protocols. Given that the reaction is stereochemically oblative, the possibility exists for exploration into chiral catalysis and

diastereoselective additions with chiral nucleophiles or auxiliaries, potentially leading to enantiomerically enriched products such as β-ACC-based β-turns (Figure 8, eq. 1). Utilizing an intramolecular approach, it may also be possible to synthesize β-strand mimetics (eq. 2).

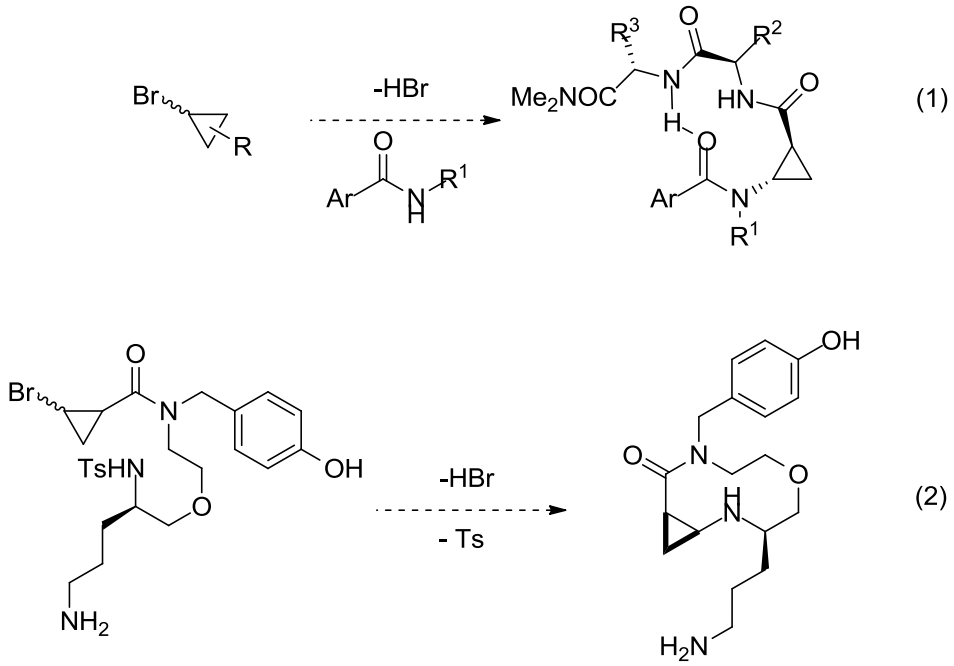


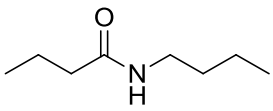
Figure 8: Potential Future directions

Further work will be aimed at expanding the scope of the reaction to include inter- and intramolecular carbon-based nucleophilic addition of enolates, nitroalkanes, nitriles and grignards, which would serve to greatly increase the structural diversity of the generated scaffolds. These explorations, in conjunction with collaborative biological screening of the final products have a high potential for the discovery of new drug-like molecules and molecular probes.

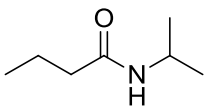
3.5. Experimentals

3.5.1. Synthesis of carbonyl-activated nucleophiles

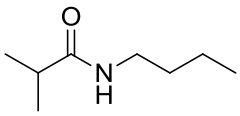
N-methylacetamide (**94aa**) and *N*-methylbenzamide (**94fa**) were commercially available and used as recieved.



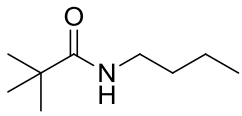
***N*-Butylbutyramide** (**94bd**) (typical procedure): To a stirred solution of *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) in 1M aqueous NaOH (50 mL, 50 mmol, 2.36 equiv) was added butyryl chloride (4.19 mL, 4.33 g, 40.6 mmol, 1.67 equiv). The mixture was stirred for 2 hrs at room temperature, then aqueous layer was saturated with brine and extracted with EtOAc (3 x 25 mL). Combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuum. The residue was distilled in vacuum employing Kugelröhr apparatus to afford the title compound as colorless amorphous solid. Yield 3.08 g (21.5 mmol, 88%). Physical and spectral properties of this material were identical to those previously reported in literature.[110]



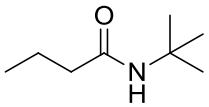
***N*-Isopropylbutyramide** (**94bc**): This compound was prepared according to a typical procedure starting from isopropylamine (2.09 mL, 1.44 g, 24.4 mmol) and butyryl chloride (4.19 mL, 4.33 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 2.52 g (19.5 mmol, 80%). Physical and spectral properties of this material were identical to those previously reported in literature.[111]



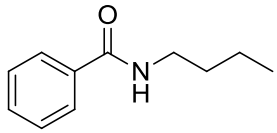
***N*-Butylisobutyramide** (**94cd**): This compound was prepared according to a typical procedure starting from *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) and isobutyryl chloride (4.26 mL, 4.33 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 2.65 g (20.5 mmol, 84%). Physical and spectral properties of this material were identical to those previously reported in literature.[112]



***N*-*tert*-Butylbutyramide** (**94ed**): This compound was prepared according to a typical procedure starting from *t*-butylamine (2.56 mL, 1.78 g, 24.4 mmol) and butyryl chloride (4.19 mL, 4.33 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 2.94 g (20.5 mmol, 84%). Physical and spectral properties of this material were identical to those previously reported in literature.[113]

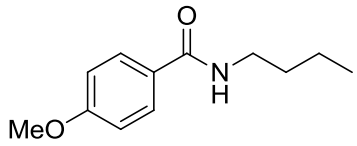


***N*-Butylpivalamide** (**94de**): This compound was prepared according to a typical procedure starting from *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) and pivaloyl chloride (5.00 mL, 4.90 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 3.23 g (20.5 mmol, 84%). Physical and spectral properties of this material were identical to those previously reported in literature.[112]

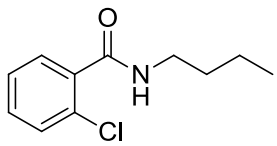


***N*-Butylbenzamide** (**94fd**): This compound was prepared according to a typical procedure starting from *n*-butylamine (2.42 mL, 1.78 g, 24.4 mmol) and benzoyl chloride (4.71 mL, 5.71 g, 40.6 mmol, 1.67 equiv). Kugelröhr distillation afforded the title compound as colorless oil. Yield 3.63 g (20.5 mmol,

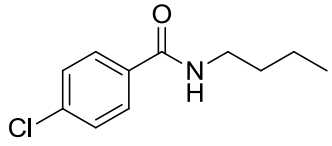
84%). Physical and spectral properties of this material were identical to those previously reported in literature.[114]



***N*-Butyl-4-methoxybenzamide** (**94gd**): To a stirred solution of dicyclohexyl carbodiimide (1.36 g, 6.57 mmol), DMAP (0.04 g, 0.33 mmol), and *p*-anisic acid (1.03 g, 6.57 mmol) in dry CH_2Cl_2 (15 mL) was added dry *n*-butylamine (0.82 mL, 600 mg, 8.21 mmol). The mixture was stirred for 36 hrs at 30 ^oC, then quenched with 5N aqueous NaOH (25 mL) and extracted with ether (4 x 15 mL). Combined organic phases were dried with $MgSO_4$, and concentrated. Flash column chromatography afforded the title compound as colorless solid. Yield 721 mg (3.48 mmol, 53%). Physical and spectral properties of this material were identical to those previously reported in literature.[115]

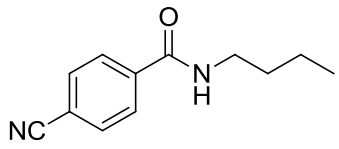


***N*-Butyl-2-chlorobenzamide** (**94hd**): was obtained from ochlorobenzoic acid (1.00 g, 6.57 mmol) according to a protocol, described for preparation of amide **94gd**. Yield 760 mg (3.61 mmol, 55%). Physical and spectral properties of this material were identical to those previously reported in literature.[116]

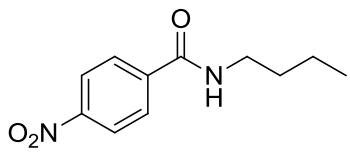


***N*-Butyl-4-chlorobenzamide** (**94id**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 4-chlorobenzoyl chloride (547 μL, 753 mg, 4.30 mmol) as colorless crystalline solid, mp 62-64 ^oC. Yield 865 mg (4.09 mmol, 95%); ^1H NMR (500.13 MHz, CD_3OD) δ ppm 7.79 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 3.37 (t, J = 7.3 Hz, 2H),

1.60 (quin, J = 7.3 Hz, 2H), 1.41 (sxt, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 169.3, 138.7, 134.7, 130.1 (+, 2C), 129.8 (+, 2C), 41.0 (-), 32.8 (-), 21.4 (-), 14.3 (+); FTIR (NaCl, film, cm-1): 3323, 2962, 2932, 2870, 2359, 2341, 1632, 1547, 1472, 843, 654; HRMS (TOF ES): found 229.1109, calculated for $C_{11}H_{14}ClN_2O$ (M+NH_4) 229.1108 (0.4 ppm).

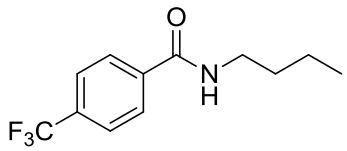


***N*-Butyl-4-cyanobenzamide** (**94jd**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 4-cyanobenzoyl chloride (712 mg, 4.30 mmol) as colorless crystalline solid, mp 45-50 ^{o}C. Yield 834 mg (4.13 mmol, 96%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.94 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 3.39 (t, J = 7.1 Hz, 2H), 1.61 (quin, J = 7.3 Hz, 2H), 1.41 (sxt, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.5, 140.2, 133.7 (+, 2C), 129.3 (+, 2C), 119.2, 116.1, 41.1 (-), 32.7 (-), 21.3 (-), 14.3 (+); FTIR (NaCl, film, cm-1): 3319, 2959, 2934, 2872, 2231, 1643, 1549, 1499, 1306, 858; HRMS (TOF ES): found 209.1274, calculated for $C_{12}H_{14}N_2OLi$ (M+Li) 209.1266 (3.8 ppm).

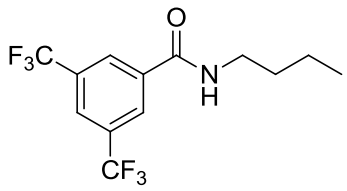


***N*-Butyl-4-nitrobenzamide** (**94kd**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 4-nitrobenzoyl chloride (522 μL, 798 mg, 4.30 mmol) as colorless crystalline solid, mp 135-140 ^{o}C. Yield 668 mg (3.01 mmol, 70%); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.30 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 6.14 (br. s, 1H),

3.50 (td, J = 7.3 Hz, 5.8 Hz, 2H), 1.68- 1.59 (m, 2H), 1.49-1.40 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{1}H NMR (125.76 MHz, CD_3OD) δ ppm 178.3, 151.1, 141.8, 129.8 (+, 2C), 124.8 (+, 2C), 41.1 (-), 32.7 (-), 21.3(-), 14.3 (+); FTIR (NaCl, film, cm-1): 3304, 2955, 2932, 1643, 1601, 1526, 1346, 868, 841, 719; HRMS (TOF ES): found 245.0901, calculated for $C_{11}H_{14}N_2O_3Na$ (M+Na) 245.0902 (0.4 ppm).

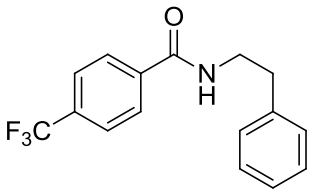


***N*-Butyl-4-(trifluoromethyl)benzamide** (**94ld**) To a solution of 4-(trifuluoromethyl)benzoic acid (2.89 g, 13.0 mmol) in dry CH_2Cl_2 (50 mL) was added 1,1-carbonyldiimidazole (2.53 g, 15.6 mmol, 1.20 equiv). The resulting suspension was stirred for 30 min at 0 ^oC, and then *n*-butylamine (3.03 mL, 2.23 g, 30.5 mmol, 2.35 equiv) was added dropwise. The mixture was stirred at room temperature overnight, then filtered. The filter cake was washed with CH_2Cl_2, the filtrate was washed consecutively with water and brine, dried with $MgSO_4$, filtered and concentrated. Crude material was filtered through a short plug of Silica gel, eluting with EtOAc to afford the title material as a colorless oil. Yield 3.00 g (12.2 mmol, 94%). This material was identical to the one previously described in literature.[117]

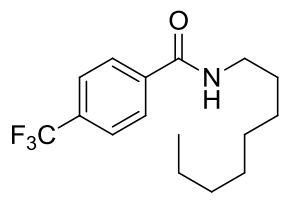


***N*-Butyl-3,5-bis(trifluoromethyl)benzamide** (**94md**): was obtained according to a typical procedure from *n*-butylamine (1.07 mL, 790 mg, 10.8 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 61- 63 ^oC. Yield 1.28 g (4.09 mmol, 95%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.42 (s, 2H), 8.15 (s, 1H), 3.42 (t, J = 6.8 Hz, 2H), 1.63 (qnt, J = 6.9 Hz, 2H), 1.43 (sxt, J = 7.3 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C

NMR (125.76 MHz, CD_3OD) δ ppm 166.7, 138.4, 133.2 (q, $^2J_{CF}$ =33.6 Hz, 2C), 129.1 (+, 2C), 126.0 (+), 124.7 (q, $^1J_{CF}$ =271.6 Hz, 2C), 41.2 (-), 32.6 (-), 21.4 (-), 14.3 (+); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm-1): 3319, 3092, 2964, 2937, 1649, 1556, 1381, 1335, 1182, 1134, 908, 845, 702, 681; HRMS (TOF ES): found 336.0809, calculated for $C_{13}H_{13}F_6NONa$ (M+Na) 336.0799 (3.0 ppm).

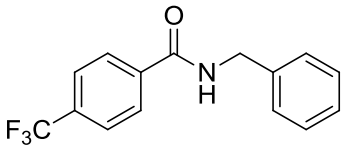


***N*-Phenethyl-4-(trifluoromethyl)benzamide** (**94lg**): was obtained according to a typical procedure from phenethylamine (1.36 mL, 1.31 g, 10.8 mmol, 2.5 equiv.) and and 4-(trifluoromethyl) benzoyl chloride (640 μL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 140-142 ^oC. Yield 1.15 g (3.91 mmol, 91%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.92 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.31-7.25 (m, 4H), 7.22-7.18 (m, 1H), 3.62 (t, *J* = 7.4 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.9, 140.7, 139.7, 134.1 (q, $^2J_{CF}$ =32.7 Hz), 130.1 (+, 2C), 129.7 (+, 2C), 129.1 (+, 2C), 127.6 (+), 126.7 (q, $^3J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^1J_{CF}$ =271.5 Hz), 42.9 (-), 36.6 (-); ^{19}FNMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 3F); FTIR (NaCl, film, cm-1): 3319, 1641, 1549, 1337, 1165, 1155, 1111, 1072, 858, 748, 700, 685; HRMS (TOF ES): found 316.0923, calculated for $C_{16}H_{14}F_3NONa$ (M+Na) 316.0925 (0.6 ppm).

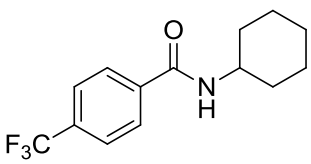


***N*-Octyl-4-(trifluoromethyl)benzamide** (**94le**): was obtained according to a typical procedure from *n*-octylamine (1.79 mL, 1.40 g, 10.8 mmol, 2.5 equiv.) and 4-(trifluoromethyl)benzoyl chloride (640 μL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 49-53 ^oC. Yield 1.24 g (4.13 mmol, 96%); ^{1}H

NMR (500.13 MHz, CD_3OD) δ ppm 7.97 (d, *J* = 7.9 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 3.38 (t, *J* = 7.2 Hz, 2H), 1.62 (quint, *J* = 7.3 Hz, 2H), 1.41-1.25 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.8, 139.7, 134.1 (q, $^2J_{CF}$ = 32.6 Hz), 129.2 (+, 2C), 126.6 (+, 2C), 125.4 (q, $^1J_{CF}$ = 271.3 Hz), 41.3 (-), 33.1 (-), 30.6 (-, 2C), 28.3 (-), 23.8 (-), 14.6 (-), 14.5 (+); FTIR (NaCl, film, cm-1): 3339, 2920, 2849, 2957, 1541, 1468, 1335, 1169, 1130, 1107, 1074, 1018, 860, 773; HRMS (TOF ES): found 308.1801, calculated for $C_{16}H_{22}F_3NOLi$ (M+Li) 308.1814 (4.2 ppm).

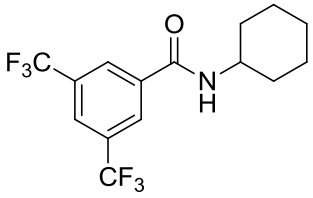


***N*-Benzyl-4-(trifluoromethyl)benzamide** (**94lf**): was obtained according to a typical procedure from benzylamine (1.18 mL, 1.16 g, 10.8 mmol) and and 4-(trifluoromethyl)benzoyl chloride (640 µL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 149-151 ^oC. Yield 1.12 g (4.00 mmol, 93%); ^1H NMR (500.13 MHz, CD_3OD) δ ppm 8.02 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.38-7.31 (m, 4H), 7.28-7.24 (m, 1H), 4.59 (s, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.7, 139.9, 139.4, 134.1 (q, $^2J_{CF}$ = 31.8 Hz), 129.6 (+, 2C), 129.1 (+, 2C), 128.6 (+, 2C), 128.3 (+), 126.6 (q, $^3J_{CF}$ = 3.6 Hz, +, 2C), 125.3 (q, $^1J_{CF}$ = 271.6 Hz), 44.7 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 3F); FTIR (NaCl, film, cm-1): 3329, 3053, 2986, 1643, 1547, 1421, 1265, 1167, 1157, 1124, 862, 739; HRMS (TOF ES): found 302.0783, calculated for $C_{15}H_{12}F_3NONa$ (M+Na) 302.0769 (4.6 ppm).

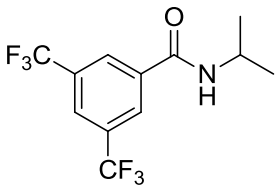


N-Cyclohexyl-4-(trifluoromethyl)benzamide (94lh): was obtained according to a typical procedure from cyclohexylamine (1.23 mL, 1.07

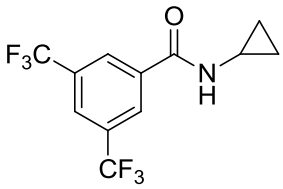
g, 10.8 mmol) and and 4-(trifluoromethyl) benzoyl chloride (640 *f*ÝL, 897 mg, 4.30 mmol) as colorless crystalline solid, mp 167-170 ^{o}C. Yield 1.10 g (4.04 mmol, 94%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.96 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 3.87 (tt, J = 11.0 Hz, 4.1 Hz, 1H), 1.99-1.94 (m, 2H), 1.85-1.80 (m, 2H), 1.72-1.67 (m, 1H), 1.47-1.32 (m, 4H), 1.28-1.18 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.1, 139.9, 133.9 (q, $^{2}J_{CF}$ = 32.7 Hz), 129.1 (+), 126.4 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 125.3 (q, $^{1}J_{CF}$ = 271.5 Hz), 50.8 (+), 33.7 (-, 2C), 26.6 (-), 26.4 (-, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 3F); FTIR (NaCl, film, cm-1): 3312, 2941, 2908, 1634, 1545, 1325, 1161, 1124, 1065, 856; HRMS (TOF ES): found 272.1269, calculated for $C_{14}H_{17}F_3NO$ (M+H) 272.1262 (2.6 ppm).



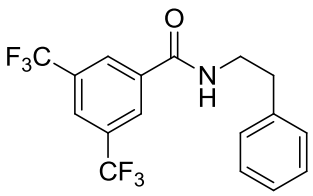
***N*-Cyclohexyl-3,5-bis(trifluoromethyl)benzamide (94mh)**: was obtained according to a typical procedure fromcyclohexylamine (1.23 mL, 1.07 g, 10.8 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (780 µL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 150-152 ^{o}C. Yield 1.37 g (4.04 mmol, 94%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.42 (s, 2H), 8.14 (s, 1H), 3.92-3.87 (m, 1H), 2.00-1.96 (m, 2H), 1.86-1.81 (m, 2H), 1.47-1.34 (m, 4H), 1.29-1.19 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 166.0, 138.6, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.2 (q, $^{3}J_{CF}$ =3.3 Hz, +, 2C), 125.9 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.8 (q, $^{1}J_{CF}$ = 272.5 Hz, 2C), 51.2 (+), 33.7 (-, 2C), 26.8 (-), 26.6 (-, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm-1): 3416, 2937, 2858, 1643, 1553, 1279, 1182, 1134, 908, 702, 681; HRMS (TOF ES): found 362.0958, calculated for $C_{15}H_{15}F_6NONa$ (M+Na) 362.0956 (0.6 ppm).



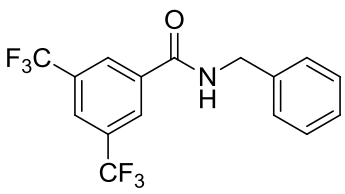
***N*-Isopropyl-3,5-bis(trifluoromethyl)benzamide** (**94mc**): was obtained according to a typical procedure from isopropylamine (924 μL, 638 mg, 10.8 mmol) and 3,5-bis(trifluoromethyl)- benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 108-111 ^{o}C. Yield 1.22 g (4.09 mmol, 95%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.43 (s, 2H), 8.14 (s, 1H), 4.24 (spt, J = 6.6 Hz, 1H), 1.28 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 165.9, 138.6, 133.2 (q, $^{2}J_{CF}$ = 33.5 Hz, 2C), 129.2 (q, $^{3}J_{CF}$ =3.6 Hz, +, 2C), 125.9 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.8 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 43.8 (+), 22.5 (+, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm-1): 3339, 2986, 1641, 1556, 1452, 1369, 1344, 1279, 1134, 910, 741, 700, 681; HRMS (TOF ES): found 322.0640, calculated for $C_{12}H_{11}F_6NONa$ (M+Na) 322.0643 (0.9 ppm).



***N*-Cyclopropyl-3,5-bis(trifluoromethyl)benzamide** (**94mi**): was obtained according to a typical procedure from cyclopropylamine (748 μL, 617 mg, 10.8 mmol) and 3,5-bis(trifluoromethyl)- benzoyl chloride (780 μL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 90-94 ^{o}C. Yield 1.12 g (3.78 mmol, 88%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.41 (s, 2H), 8.14 (s, 1H), 2.91 (tt, J = 7.4 Hz, 3.8 Hz, 1H), 0.87 - 0.80 (m, 2H), 0.72-0.66 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 168.2, 138.1, 133.2 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.1 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 126.1 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 24.4 (+), 6.6 (-, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.6 (s, 6F); FTIR (NaCl, film, cm-1): 3315, 3086, 3022, 2448, 1641, 1545, 1448, 1375, 1354, 1277, 1136, 908, 698, 681; HRMS (TOF ES): found 297.0589, calculated for $C_{12}H_9F_6NO$ (M+) 297.0588 (0.3 ppm).

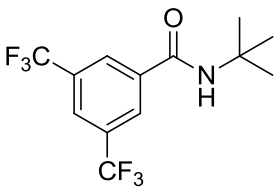


***N*-Phenethyl-3,5-bis(trifluoromethyl)benzamide** (**94mg**), (typical procedure): To a stirred solution of phenethylamine (1.36 mL, 1.31 g, 10.8 mmol, 2.5 equiv.) in dry THF (30 mL) was added 3,5-bis(trifluoromethyl)benzoyl chloride (780 µL, 1.19 g, 4.30 mmol). The mixture was stirred for 1 hr at room temperature, than the solvent was removed in vacuum. The residue was partitioned between 10% aqueous HCl (20 mL) and EtOAc (20 mL). Organic layer was separated and washed consecutively with 10% aqueous HCL (3 x 20 mL) and 4N aqueous NaOH (5 mL), dried with $MgSO_4$, filtered and concentrated. The obtained crystalline material (colorless crystalline solid, mp 44-47 ^oC) was pure enough to be used for the following transformation without additional purification. Yield 1.44 g (4.00 mmol, 93%). ^1H NMR (500.13 MHz, CD_3OD) δ ppm 8.35 (s, 2H), 8.15 (s, 1H), 7.31- 7.25 (m, 4H), 7.22-7.19 (m, 1H), 3.64 (t, J = 7.4 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H),; ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 166.8, 140.6, 138.4, 133.2 (q, $^2J_{CF}$ = 33.6 Hz, 2C), 130.1 (+, 2C), 129.7 (+, 2C), 129.1 (q, $^3J_{CF}$ = 2.7 Hz, +, 2C), 127.6 (+), 126.1 (spt, $^3J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^1J_{CF}$ = 272.5 Hz, 2C), 43.0 (-), 36.5 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.7 (s, 6F); FTIR (NaCl, film, cm-1): 3313, 3089, 1647, 1555, 1383, 1279, 1184, 1134, 908, 700, 681; HRMS (TOF ES): found 384.0793, calculated for $C_{17}H_{13}F_6NONa$ (M+Na) 313.0901 (1.6 ppm

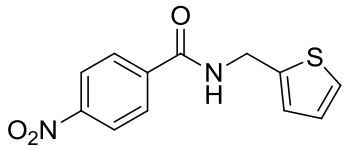


***N*-Benzyl-3,5-bis(trifluoromethyl)benzamide** (**94mf**): was obtained according to a typical procedure from benzylamine (1.18 mL, 1.16 g, 10.8 mmol) and 3,5-bis(trifluoromethyl)- benzoyl chloride (780 µL, 1.19 g, 4.30 mmol) as colorless crystalline solid, mp 92-95 ^oC. Yield 1.45 g

(4.17 mmol, 97%); ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.46 (s, 2H), 8.17 (s, 1H), 7.39-7.32 (m, 4H), 7.28-7.24 (m, 1H), 4.61 (s, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 166.7, 139.8, 138.2, 133.3 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.8 (+, 2C), 129.2 (q, $^{3}J_{CF}$ = 2.7 Hz, +, 2C), 128.9 (+, 2C), 128.5 (+), 126.2 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 45.0 (-); FTIR (NaCl, film, cm-1): 3292, 3090, 3069, 1647, 1553, 1454, 1381, 1279, 1184, 1136, 908, 698; HRMS (TOF ES): found 370.0645, calculated for $C_{16}H_{11}F_6NONa$ (M+Na) 370.0643 (0.5 ppm).

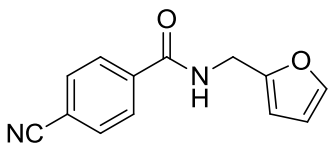


***N-tert*-Butyl-3,5-bis(trifluoromethyl)benzamide:** (**94me**): ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.34 (s, 2H), 8.11 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 166.9, 139.8, 133.0 (q, 2*J*CF = 33.6 Hz, 2C), 129.2 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 125.6 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.8 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 53.4, 28.9 (+, 3C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.6 (s, 6F); FTIR (NaCl, film, cm-1): 3317, 3072, 1645, 1547, 1448, 1364, 1302, 1275, 1144, 1130, 906, 845, 702; HRMS (TOF ES): found 313.0896, calculated for $C_{13}H_{23}F_6NO$ (M+) 313.0901 (1.6 ppm).



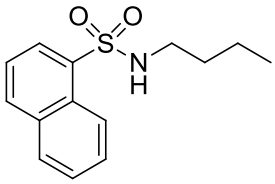
4-Nitro-N-(thiophen-2-ylmethyl)benzamide (**94kj**): To a stirred solution of 4-nitrobenzoyl chloride (930 mg, 5.0 mmol) in dry CH_2Cl_2 (50.0 mL) was added solution of 2-thiophenemethylamine (850 mg, 7.5 mmol) and triethylamine (510 mg, 5.0 mmol) in dry CH_2Cl_2 (8 mL). The mixture was stirred for 2 h at room temperature, then quencged with 10% aqueous HCl (20 mL). The organic phase was separated, washed consecutively with 10% NaOH and brine, then dried with and $MgSO_4$ and concentrated to provide the titled compound pure enough to use at the following step without additional purification. Yield 1.06 g (4.05 mmol, 81%). ^{1}H NMR (400.13 MHz,

$CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.35 – 7.24 (m, 1H), 7.08 (dd, *J* = 3.3, 1.2 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.69 (s, 1H), 4.85 (dd, *J* = 5.7, 0.8 Hz, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 165.20, 149.69, 139.79, 139.65, 128.27 (+, 2C), 127.14 (+), 126.72 (+), 125.77 (+), 123.88 (+, 2C), 39.10 (-). FTIR (NaCl, cm^{-1}): 3311, 3097, 3068, 1643, 1596, 1547, 1487, 1425, 1346, 1296, 1251, 1224, 1012, 870, 709 cm^{-1}; HRMS (TOF ES): found 269.0569, calculated for $C_{12}H_{10}N_2O_3SLi$ (M+Li) 269.0572 (1.1 ppm).

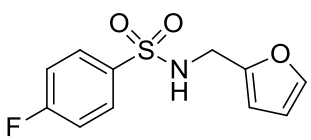


4-Cyano-N-(furan-2-ylmethyl)benzamide (**94jk**): Compound was prepared by adding furfurylamine (850 mg, 8.8 mmol) to a stirred solution of 4-cyanobenzoyl chloride (580 mg, 3.5 mmol) in dry DCM (15 mL). The mixture was stirred for 2h at room temperature, then worked up as described above for the synthesis of **94kj**. Yield 975 mg (4.3 mmol, 49%). ^1H NMR (500.13 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.40 (s, 1H), 6.64 (br, 1H), 6.37 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.33 (d, *J* = 3.4 Hz, 1H), 4.66 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 165.46, 150.46, 142.56 (+), 138.05, 132.46 (+, 2C), 127.78 (+, 2C), 117.95, 115.25, 110.63 (+), 108.14 (+), 77.30, 77.04, 76.79, 37.21 (-); FTIR (NaCl, cm^{-1}): 3292, 3089, 2995, 2972, 1639, 1608, 1546, 1499, 1418, 1350, 1301, 1143, 1072, 1023, 883, 729 cm^{-1}; HRMS (TOF ES): found 249.0637, calculated for $C_{13}H_{10}N_2O_2Li$ (M+Li) 249.06402 (1.2 ppm).

3.5.4: Synthesis of sulfonamide nucleophiles



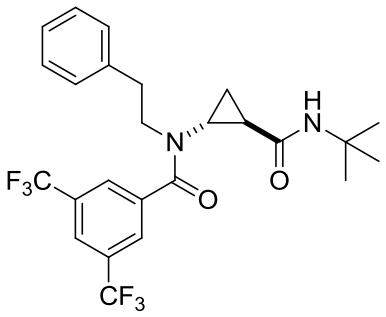
N-Butylnaphthalene-2-sulfonamide (**97gd**): Compound was prepared by adding *N*-butylamine (804 mg, 11 mmol) to a stirred solution of 2-naphthylenesulfonyl chloride (1.00 g, 4.41 mmol) in dry CH_2Cl_2 (40 mL). The mixture was stirred for 2h followed by quench with 10% aqueous HCl. The organic phase was washed consecutively with 10% NaOH and brine, dried with $MgSO_4$ and concentrated to provide the titled compound as white crystalline solid, mp 54-58 ^oC. Yield 1.06 g (4.01 mmol, 91%). ^1H NMR (400.13 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.99 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 7.7 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.70 – 7.60 (m, 2H), 4.71 (s, 1H) 3.00 (q, J = 6.9 Hz, 2H), 1.47 (p, J = 7.1 Hz, 2H), 1.30 (h, J = 14.3, 7.3 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 136.73, 134.79, 132.17, 129.51 (+), 129.24 (+), 128.76 (+), 128.46 (+), 127.92 (+), 127.56 (+), 122.35 (+), 43.02 (-), 31.63 (-), 19.69 (-), 13.53 (+); FTIR (NaCl, cm^{-1}): 3273, 3053, 2958, 2931, 1587, 1502, 1464, 1427, 1348, 1317, 1244, 1130, 1078, 953, 825, 744, 642 cm^{-1}; HRMS (TOF ES): found 286.0872, calculated for $C_{14}H_{17}NO_2SNa$ (M+Na) 286.0878 (2.1 ppm).



4-Fluoro-N-(furan-2-ylmethyl)benzenesulfonamide (**97ik**): Compound was prepared by adding furfural amine (1.3 g, 13 mmol) to a stirred solution of 4-fluorobenzenesulfonyl chloride (1.0 g, 5.3 mmol) in dry CH_2Cl_2 (25 mL) and. The mixture was stirred for 2h and then worked up as described above in the protocol for preparation of compound **97gd**. Yield 1.01 g (4.3 mmol,

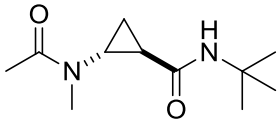
81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.9, 5.0 Hz, 2H), 7.23 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.16 (t, *J* = 8.6 Hz, 2H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.11 – 6.09 (m, 1H), 4.98 (s, 1H), 4.23 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-d) δ 169.25 , 165.25 (d, *J* = 255.3 Hz), 133.54 , 130.23 (d, *J* = 9.1 Hz, 2C), 116.46 (d, *J* = 22.5 Hz, 2C), 67.06 , 66.95 , 46.15 , 42.61 , 38.61 , 30.23 , 21.36 , 20.06 , 14.97 , 13.70 . ^{19}F NMR (376 MHz, Chloroform-d) δ -104.67 – -104.78 (m). . Ir (salt plate): ν= 3331, 3087, 2962, 2872, 1645, 1585, 1547, 1475, 1454, 1392, 1294, 1225, 1205, 1167, 1094 HRMS found $C_{18}H_{24}FN_2O_4S$ (-H) 383.1441, (0.5 ppm).

3.5.2. Synthesis of β-ACC derivatives

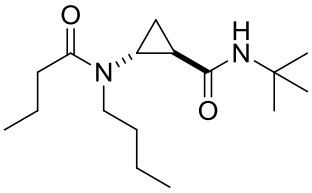


***N*-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*phenethyl- 3,5-bis(trifluoromethyl)benzamide (95amg)**: (Typical procedure) An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (110 mg, 0.5 mmol, 1.0 equiv), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), KOH (98 mg, 1.75 mmol, 3.5 equiv), *N*-Phenethyl- 3,5-bis(trifluoromethyl)benzamide (**94mg**) (290 mg, 1.0 mmol, 2.0 equiv), and anhydrous THF (5 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then the reaction mixture was filtered into a 100 mL round bottom flask, both the reaction vessel and filter were rinsed consecutively with DCM (15 mL) and EtOAc (15 mL), which were combined with filtrate. Silica gel (2.0 g) was added to a filtrate, and then the solvent was removed by rotary evaporation. The residue absorbed onto silica gel was loaded on the top of the column packed with silica gel, which was eluted with hexane/EtOAc 1:1 to obtain two fractions. The less polar fraction (R*f* 0.54) was identified as non-reacted benzamide **94mg**, and

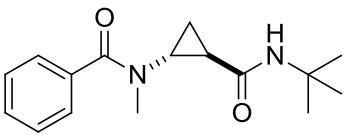
the more polar one (R*f* 0.23) as the title product, white amorphous solid. Yield 236 mg (94%, 0.47 mmol). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.02 (s, 1H), 7.64 (s, 2H), 7.38-7.32 (m, 4H), 7.28-7.25 (m, 1H), 4.11 (ddd, *J* = 13.7 Hz, 7.3 Hz, 6.0 Hz, 1H), 3.70 (ddd, *J* = 13.7 Hz, 6.9 Hz, 6.0 Hz, 1H), 3.10-3.07 (m, 2H), 2.84 (br. s, 1H), 1.61-1.55 (m, 1H), 1.12 (s, 9H), 1.06-1.01 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.9, 171.0, 141.2, 140.1, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 130.3 (+, 2C), 129.9 (+, 2C), 128.6 (q, $^{3}J_{CF}$ = 2.7 Hz, +, 2C), 128.0 (+), 124.5 (q, $^{1}J_{CF}$ = 272.5 Hz), 124.6 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 52.0, 48.4 (-), 39.3 (+), 34.6 (-), 28.9 (+, 3C), 28.4 (+), 17.1 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm-1): 3342, 3065, 3030, 2970, 2934, 1651, 1545, 1456, 1366, 1281, 1178, 1140, 905, 741, 702, 681; HRMS (TOF ES): found 501.1964, calculated for $C_{25}H_{27}F_6N_2O_2$ (M+H) 501.1977 (2.6 ppm).



(1*R,2*R**)-*N*-*tert*-butyl-2-(*N*-methylacetamido)cyclopropanecarboxamide** (**95aaa**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-methylacetamide (9**4aa**) (73.1 mg, 1.00 mmol). The excess of *N*-methylacetamide was distilled out in vacuum. Flash column chromatography on Silica gel afforded the title compound as a viscous oil, R*f* 0.31 (hexane-EtOAc 1:3). Yield 106 mg (0.44 mmol, 88%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 5.98 (br. s, 1H), 3.10 (br. s, 1H), 2.87 (s, 3H), 2.15 (s, 3H), 1.64 (br. s, 1H), 1.45 (br, sm 1H), 1.35 (s, 9H), 1.17-1.12 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 173.2, 169.2, 51.5, 38.9 (+), 33.5 (+), 28.8 (+, 3C), 26.2 (+), 22.3 (+), 16.0 (-); FTIR (NaCl, film, cm-1): 3299, 2964, 2930, 1645, 1556, 1454, 1253, 1111, 960; HRMS (TOF ES): found 213.1609, calculated for $C_{11}H_{21}N_2O_2$ (M+H) 213.1603 (2.8 ppm).

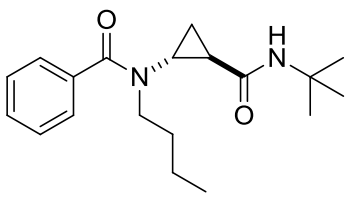


(1*R,2*R**)-*N*-*tert*-Butyl-2-(*N*-butylbutyramido)cyclopropanecarboxamide** (**95abd**): The reaction was performed according to the typical procedure, employing bromocyclopropane **5a** (110 mg, 0.50 mmol) and *N*-butylbutyramide (**94bd**) (143 mg, 1.00 mmol). The excess of *N*-butylbutyramide was distilled out in vacuum (Kugelrhor oven temperature 110 ^{o}C at 0.05 torr for 4 hrs) to afford to produce the title compound as a viscous oil, which did not require further purification. Yield 71 mg (0.25 mmol, 51%). ^{1}H NMR (500.13 MHz, DMSO-*d*6 at 370 K)δ ppm 7.85 (br. s, 1H), 3.36 (ddd, *J* = 13.9 Hz, 7.3 Hz, 6.6 Hz, 1H), 3.14 (ddd, *J* = 13.6 Hz, 7.9 Hz, 6.0 Hz, 1H), 2.74 (ddd, *J* = 7.6 Hz, 4.7 Hz, 2.8 Hz, 1H), 2.43 (ddd, *J* = 15.5 Hz, 8.5 Hz, 6.9 Hz, 1H), 2.30 (dt, J = 15.5 Hz, 7.8 Hz, 1H), 1.90 (ddd, *J* = 8.8 Hz, 6.0 Hz, 2.8 Hz, 1H), 1.54-1.47 (m, 2H), 1.41-1.34 (m, 2H), 1.26 (s, 9H), 1.24- 1.13 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, DMSO-*d*6 at 370 K) δ ppm 173.9, 169.1, 54.8 (-), 50.1, 44.0 (-), 36.1 (+), 35.4 (-), 29.6 (-), 28.5 (+), 25.5 (+), 19.5 (-), 17.9 (-), 14.3 (-), 13.7 (+), 13.6 (+); FTIR (NaCl, film, cm-1): 3323, 2962, 2932, 1639, 1549, 1456, 1402, 1259, 1094, 912; HRMS (TOF ES): found 370.0645, calculated for $C_{16}H_{11}F_6NONa$ (M+Na) 370.0643 (0.5 ppm).

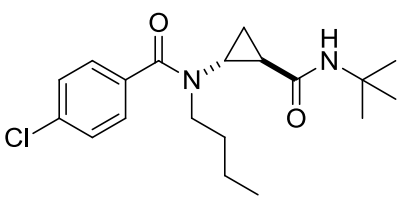


***N*-((1R*,2R*)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-N-methylbenzamide** (**95afa**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and N-methylbenzamide (**94fa**) (135 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar

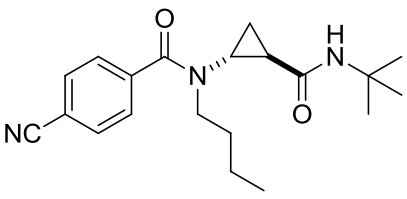
one (Rf 0.28) was identified as non-reacted Nmethylbenzamide, and the more polar one (Rf 0.14) as the title compound, colorless crystalline solid, mp 108-111 ^{o}C. Yield 103 mg (0.375 mmol, 75%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.52-7.40 (m, 5H), 4.57 (br. s, 1H), 3.11 (br. s, 3H), 1.63 (br. s, 1H), 1.34-1.25 (br. m, 2H), 1.20 (br. s, 9H), 0.92 (br. m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 172.3, 168.6, 137.4, 129.7 (+), 128.4 (+, 2C), 127.2 (+, 2C), 51.1, 39.4 (br, +), 35.0 (br, +), 28.7 (+, 3C), 27.6 (+), 15.0 (br, -); FTIR (NaCl, film, cm-1): 3325, 2966, 2928, 1632, 1547, 1447, 1389, 1074, 704; HRMS (TOF ES): found 275.1764, calculated for $C_{16}H_{23}N_2O_2$ (M+H) 275.1760 (1.5 ppm).



N-Butyl-N-((1R*,2R*)-2-(tert-Butylcarbamoyl)cyclopropyl) benzamide (95afd): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and N-butylbenzamide (**94fd**) (177 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (Rf 0.61) was identified as non-reacted N-butylbenzamide, and the more polar one (Rf 0.39) as the title compound, colorless crystalline solid, mp 95-97 ^{o}C. Yield 115 mg (0.365 mmol, 73%). ^{1}H NMR (500.13 MHz, DMSO-d6)δ ppm 7.44-7.36 (m, 5H), 7.27 (br. s, 1H), 3.50-3.36 (br. m, 2H), 2.89 (br. s, 1H), 1.69 (br. s, 1H), 1.61-1.54 (br. m, 2H), 1.40-1.29 (br. m, 2H), 1.15 (br. s, 9H), 0.95-0.79 (br. m, 5H); ^{13}C NMR (125.76 MHz, DMSO-d6) δ ppm 171.3, 168.6, 137.5, 129.1 (+), 128.0 (+, 2C), 126.7 (+, 2C), 49.9, 44.9 (br., -), 37.4 (br., +), 29.3 (-), 28.4 (+, 3C), 25.7 (br., +), 19.5 (-), 15.8 (br., -),13.6 (+); FTIR (NaCl, film, cm-1): 3325, 292, 2930, 2872, 1626, 1547, 1448, 1400, 1053, 791, 729, 702; HRMS (TOF ES): found 317.2245, calculated for $C_{19}H_{29}N_2O_2$ (M+H) 317.2229 (5.0 ppm).

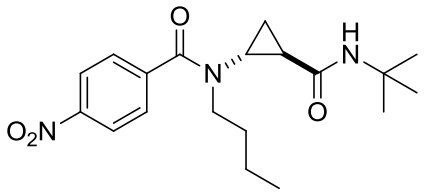


***N*-Butyl-N-((1*R*,2*R*)-2-(*tert*-butylcarbamoyl)cyclopropyl)- 4-chlorobenzamide** (**95aid**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*butyl- 4-chlorobenzamide (**94id**) (212 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (R*f* 0.44) was identified as non-reacted benzamide, and the more polar one (R*f* 0.20) as the title compound, a colorless crystalline solid, mp 162-164 ^{o}C. Yield 142 mg (0.41 mmol, 81%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 7.44 (s, 4H), 3.85 (br. s, 1H), 3.27 (ddd, *J* = 13.7 Hz, 7.7 Hz, 5.7 Hz, 1H), 3.11 (br. s, 1H), 1.76-1.66 (m, 2H), 1.53 (br. s, 1H), 1.48-1.42 (m, 2H), 1.20 (s, 9H), 1.14 (br. s, 1H), 1.07 (br. s, 1H), 1.01 (br. s, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.9, 171.5, 137.3, 136.9, 130.1 (+, 2C), 129.9 (+, 2C), 52.0, 47.4 (-), 39.5 (+), 31.0 (-), 28.9 (+, 3C), 21.3 (-), 16.6 (-), 14.3 (+); FTIR (NaCl, film, cm-1): 3333, 3065, 3053, 2966, 2932, 1668, 1630, 1553, 1435, 1418, 1315, 1256, 1225, 1209, 1090, 843, 756, 636; HRMS (TOF ES): found 373.1644, calculated for $C_{19}H_{27}ClN_2O_2Na$ (M+Na) 373.1659 (4.0 ppm).



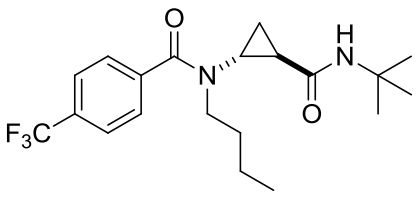
***N*-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-cyanobenzamide** (**95ajd**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-butyl-4-cyanobenzamide (**94jd**) (202 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:2) afforded two fractions. The less polar one (R*f* 0.73) was identified as non-reacted benzamide, and the

more polar one (R*f* 0.47) as the title compound, a colorless crystalline solid, mp 136-140 ^{o}C. yield 136 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 7.81 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.23 (br. s, 1H), 3.86-3.79 (m, 1H), 3.34-3.28 (m, 1H), 3.09 (br. s, 1H), 1.78-1.66 (m, 2H), 1.53 (br. s, 1H), 1.49-1.42 (m, 2H), 1.19 (s, 9H), 1.14-1.04 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.0, 171.4, 143.2, 133.8 (+, 2C), 129.0 (+, 2C), 119.4, 114.7, 52.1, 47.4 (-), 39.3 (+), 30.9 (-), 29.0 (+, 3C), 28.7 (+), 21.3 (-), 16.7 (-), 14.3 (+); FTIR (NaCl, film, cm-1): 3339, 2962, 2932, 2230, 1634, 1547, 1418, 1398, 1310, 1258, 1275, 1225, 1207, 1107, 849, 764, 737; HRMS (TOF ES): found 342.2169, calculated for $C_{20}H_{28}N_3O_2$ (M+H) 342.2182 (3.8 ppm).

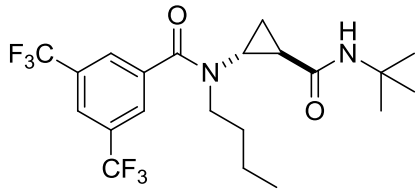


***N*-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-nitrobenzamide (95akd)**: The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-butyl-4-nitrobenzamide (**94kd**) (222 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluenthexane/EtOAc 1:2) afforded two fractions. The less polar one (Rf 0.77) was identified as non-reacted benzamide, and the more polar one (Rf 0.36) as the title compound, yellowish crystalline solid, mp 143-145 ^{o}C. Yield 145 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.32 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 4.61 (br. s, 1H), 3.86 (ddd, J = 14.2 Hz, 7.6 Hz, 6.6 Hz, 1H), 3.10 (br. s, 1H), 1.78-1.70 (m, 2H), 1.54 (br. s, 1H), 1.50-1.44 (m, 2H), 1.35-1.25 (m, 3H), 1.10 (s, 9H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 172.8, 171.3, 149.9, 144.9, 129.4 (+, 2C), 125.1 (+, 2C), 51.9, 47.4 (-), 39.3 (+), 30.9 (-), 29.1 (+), 28.9 (+, 3C), 21.3 (-), 16.6 (-), 14.3 (+); FTIR (NaCl, film, cm-1): 3335, 2961, 2928,

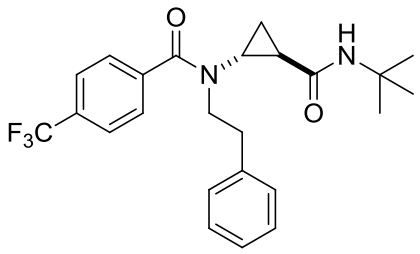
1634, 1524, 1456, 1348, 1312, 1259, 1105, 864, 735; HRMS (TOF ES): found 362.2068, calculated for $C_{19}H_{28}N_3O_4$ (M+H) 362.2080 (3.3 ppm).



***N*-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-(trifluoromethyl)benzamide** (**94ald**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70aa** (110 mg, 0.50 mmol) and *N*-butyl(*p*-triflouromethyl)benzamide (**94ld**) (245 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar one (R*f* 0.60) was identified as non-reacted benzamide, and the more polar one (R*f* 0.22) as the title compound, colorless crystalline solid, mp 158-161 ^{o}C. Yield 163.5 mg (0.425 mmol, 85%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 7.74 (d, *J* = 7.9 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 2H), 4.04 (br. s, 1H), 3.06 (br. s, 1H), 1.96-1.84 (m, 4H), 1.75-1.70 (m, 2H), 1.60 (br. s, 1H), 1.44-1.29 (m, 3H), 1.19 (s, 9H), 1.07-1.02 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.5, 171.9, 143.0, 132.6 (q, $^{2}J_{CF}$ = 32.1 Hz), 129.1 (+, 2C), 126.7 (q, $^{3}J_{CF}$ = 3.7 Hz, +, 2C), 125.5 (q, $^{1}J_{CF}$ = 271.3 Hz), 52.1, 52.0 (-), 32.5 (+), 32.2 (-), 28.9 (+, 3C), 27.44 (+), 27.38 (-), 27.0 (-), 17.5 (br, +); ^{19}F NMR (376.50 MHz, $CDCl_3$) δ ppm -62.6 (s, 3F); FTIR (NaCl, film, cm-1): 3335, 2928, 2854, 1628, 1549, 1323, 1167, 1130, 1067, 854, 737, 652, 592; HRMS (TOF ES): found 407.1941, calculated for $C_{20}H_{27}F_3N_2O_2Na$ (M+Na) 407.1922 (4.7 ppm).

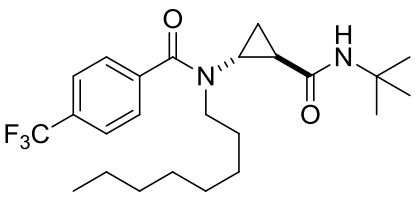


***N*-Butyl-*N*-((1*R**,2*R**)-2-(*tert*-butylcarbamoyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzamide** (**95amd**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-butyl-3,5-bis(triflouromethyl)benzamide (**94md**) (313 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:2) afforded two fractions. The less polar one (R*f* 0.75) was identified as non-reacted benzamide, and the more polar one (R*f* 0.38) as the title compound, a colorless amorphous solid. Yield 180 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.08 (s, 1H), 8.05 (s, 2H), 3.76-3.69 (m, 1H), 3.46-3.39 (m, 1H), 3.18 (br. s, 1H), 1.80-1.68 (m, 2H), 1.62 (br. s, 1H), 1.50-1.42 (m, 2H), 1.14 (s, 9H), 1.11-1.05 (m, 2H), 1.05-0.99 (m, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.6, 171.2, 141.4, 133.2 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 128.8 (+, 2C), 124.6 (+), 124.6 (q, $^{1}J_{CF}$ =272.5 Hz), 52.0, 47.6 (-), 39.2 (+), 30.9 (-), 28.9 (+, 3C), 28.4 (+), 21.4 (-), 17.3 (-), 14.3 (+); ^{19}F NMR(376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm-1): 3344, 2966, 2933, 2876, 1643, 1545, 1456, 1427, 1398, 1366, 1279, 1171, 1140, 903, 681; HRMS (TOF ES): found 475.1818, calculated for $C_{21}H_{26}F_6N_2O_2Na$ (M+Na) 475.1796 (4.6 ppm).



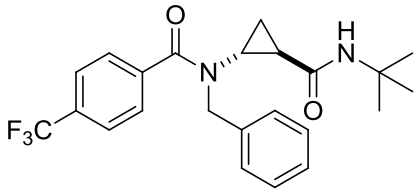
***N*-((1*R**,2R*)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*phenethyl-4-(trifluoromethyl)benzamide** (**95alg**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-phenethyl-(*p*-triflouromethyl)-benzamide (**94lg**) (293 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The less polar

one (R*f* 0.68) was identified as non-reacted benzamide, and the more polar one (R*f* 0.36) as the title compound, a colorless crystalline solid, mp 146-147 ^{o}C. Yield 178 mg (0.41 mmol, 82%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 7.70 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.37-7.33 (m, 3H) 7.28-7.24 (m, 2H), 4.10 (ddd, *J* = 13.3 Hz, 7.3 Hz, 6.6 Hz, 1H), 3.65 (ddd, *J* = 13.3 Hz, 6.6 Hz, 6.3 Hz, 1H), 3.10-3.03 (m, 2H), 2.91 (br. s, 1H), 1.56 (br. s, 1H), 1.15 (s, 9H), 1.08-0.96 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.5, 171.3, 142.3, 140.2, 132.6 (q, $^{2}J_{CF}$ = 31.8 Hz), 130.2 (+, 2C), 129.8 (+, 2C), 128.8 (+, 2C), 127.9 (+), 126.7 (+, 2C), 125.4 (q, $^{1}J_{CF}$ = 271.6 Hz), 51.9, 49.2 (-), 39.5 (+), 34.8 (-), 28.9 (+, 3C), 28.5 (+), 16.8 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm - 65.2 (s, 3F); FTIR (NaCl, film, cm-1): 3337, 2970, 1639, 1547, 1454, 1420, 1325, 1167, 1130, 1067, 851, 741, 700; HRMS (TOF ES): found 433.2113, calculated for $C_{24}H_{28}F_3N_2O_2$ (M+H) 433.2103 (2.3 ppm).

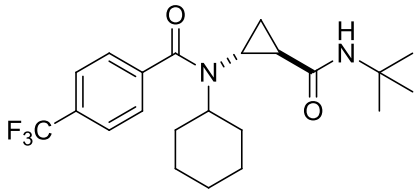


***N*-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-octyl-4-(trifluoromethyl)benzamide** (**95ale**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-octyl-4-(triflouromethyl)benzamide (**94le**) (301 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 3:1) afforded two fractions. The less polar one (R*f* 0.57) was identified as non-reacted benzamide, and the more polar one (R*f* 0.15) as the title compound, a colorless amorphous solid. Yield 187 mg (0.43 mmol, 85%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 7.75 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.31 (br. s, 1H), 3.83-3.77 (m, 1H), 3.38-3.32 (m, 1H), 3.14 (br. s, 1H), 1.79-1.69 (m, 2H), 1.60 (br. s, 1H), 1.45-1.29 (m, 10H), 1.16 (s, 9H), 1.12-1.04 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.3, 171.5, 142.5, 132.6 (q, $^{2}J_{CF}$ = 32.7

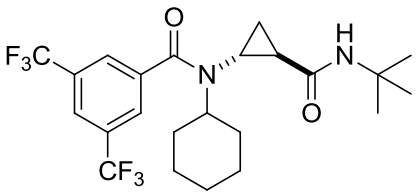
Hz), 128.9 (+, 2C), 126.8 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^{1}J_{CF}$ = 271.6 Hz), 52.1, 47.7 (-), 39.2 (+), 33.2 (-), 30.5 (-, 2C), 28.9 (+, 3C), 28.8 (-), 28.5 (+), 28.2 (-), 23.9 (-), 16.9 (-), 14.6 (+); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.2 (s, 3F); FTIR (NaCl, film, cm-1): 3337, 2961, 2930, 2856, 1632, 1547, 1456, 1421, 1402, 1325, 1258, 1227, 1167, 1130, 851, 613; HRMS (TOF ES): found 463.2533, calculated for $C_{24}H_{35}F_3N_2O_2Na$ (M+Na) 463.2548 (3.2 ppm).



***N*-Benzyl-*N*-((1R*,2R*)-2-(*tert*-butylcarbamoyl)cyclopropyl)-4-(trifluoromethyl)benzamide** (**95alf**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and N-benzyl-4-(triflouromethyl)benzamide (**94lf**) (279 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 3:1) afforded two fractions. The less polar one (Rf 0.40) was identified as non-reacted benzamide, and the more polar one (Rf 0.13) as the title compound, a colorless crystalline solid, mp 163-167 ^{o}C. Yield 168 mg (0.40 mmol, 80%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 7.77 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.42-7.36 (m, 4H), 7.34-7.30 (m, 1H), 4.88 (d, J = 14.2 Hz, 1H), 4.73 (d, J = 14.2 Hz, 1H), 2.96 (br. s, 1H), 1.67 (br. s, 1H), 1.15 (s, 9H), 1.02 (br. s, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.4, 171.4, 142.1, 138.6, 132.8 (q, $^{2}J_{CF}$ = 32.7 Hz), 130.1 (+, 2C), 129.3 (+, 2C), 128.9 (+, 2C), 128.9 (+), 126.8 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^{1}J_{CF}$ = 271.6 Hz), 52.0, 51.3 (-), 39.4 (+), 28.9 (+, 3C), 28.1 (+), 17.1 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.3 (s, 3F); FTIR (NaCl, film, cm-1): 2979, 2934, 1636, 1454, 1418, 1325, 1169, 1130, 1067, 851, 702; HRMS (TOF ES): found 419.1926, calculated for $C_{23}H_{26}F_3N_2O_2$ (M+H) 419.1946 (4.8 ppm).

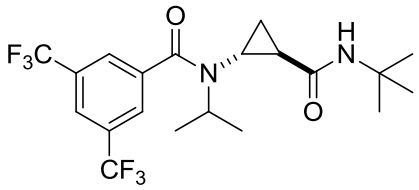


***N*-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*cyclohexyl-4-(trifluoromethyl)benzamide** (**95alh**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and N-cyclohexyl-4-(triflouromethyl)benzamide (**94lh**) (271 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/EtOAc 3:1) afforded two fractions. The less polar one (R*f* 0.58) was identified as non-reacted benzamide, and the more polar one (R*f* 0.21) as the title compound, a colorless crystalline solid, mp 160-163 ^{o}C. Yield 92 mg (0.225 mmol, 45%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 7.74 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 4.06 (br. s, 1H), 3.07 (br. s, 1H), 1.99- 1.83 (m, 6H), 1.78-1.69 (m, 2H), 1.60 (br. s, 1H), 1.46-1.36 (m, 2H), 1.18 (s, 9H), 1.10- 1.00 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.4, 171.9, 142.9, 132.6 (q, $^{2}J_{CF}$ = 31.8 Hz), 129.1 (+, 2C), 126.7 (q, $^{3}J_{CF}$ = 3.6 Hz, +, 2C), 125.5 (q, $^{1}J_{CF}$ = 271.6 Hz), 60.6 (+), 52.0, 37.2 (+), 32.5 (-), 32.1 (-), 28.9 (+, 3C), 27.7 (+), 27.44 (-), 27.38 (-), 27.0 (-), 17.5 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.3 (s, 3F); FTIR (NaCl, film, cm-1): 3337, 2934, 2858, 1628, 1547, 1454, 1418, 1323, 1167, 1130, 1067, 854, 735; HRMS (TOF ES): found 417.2343, calculated for $C_{22}H_{29}F_3N_2O_2Li$ (M+Li) 417.2341 (0.5 ppm).



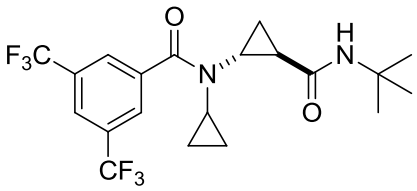
***N*-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-cyclohexyl- 3,5-bis(trifluoromethyl)benzamide** (**95amh**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-cyclohexyl-3.5-bis(triflouromethyl)- benzamide (**94mh**) (339 mg, 1.00 mmol). Flash columnchromatography on

Silica gel (eluent hexane/EtOAc 5:1) afforded two fractions. The less polar one (R*f* 0.58) was identified as non-reacted benzamide, and the more polar one (R*f* 0.19) as the title compound, a colorless crystalline solid, mp 140-141 ^{o}C. Yield 198 mg (0.42 mmol, 83%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.07 (s, 3H), 4.02 (br. s, 1H), 3.09 (br. s, 1H), 2.03-1.98 (m, 2H), 1.94-1.84 (m, 3H), 1.76-1.70 (m, 2H), 1.66 (br. s, 1H), 1.18 (s, 9H), 1.06-0.99 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ ppm 171.7, 171.5, 141.8, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.0 (q, $^{3}J_{CF}$ = 2.7 Hz, +, 2C), 124.5 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 272.5 Hz), 60.9 (+), 52.1, 37.2 (+), 32.3 (-), 32.1 (-), 29.0 (+), 28.0 (+), 27.39 (-), 27.36 (-), 27.0 (-), 17.7 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm-1): 3337, 2935, 2856, 1630, 1547, 1356, 1281, 1184, 1138, 905, 683; HRMS (TOF ES): found 479.2122, calculated for $C_{23}H_{29}F_6N_2O_2$ (M+H) 479.2133 (2.3 ppm).

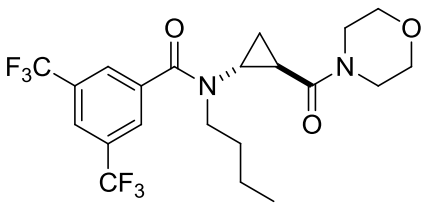


***N*-((1*R**,2*R**)-2-(tert-butylcarbamoyl)cyclopropyl)-*N*-isopropyl- 3,5-bis(trifluoromethyl)benzamide** (**95amc**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-isopropyl-3,5-bis(triflouromethyl)benzamide (**94mc**) (299 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/ EtOAc 3:1) afforded two fractions. The less polar one (R*f* 0.58) was identified as non-reacted benzamide, and the more polar one (R*f* 0.19) as the title compound, a colorless amorphous solid. Yield 134 mg (0.31 mmol, 61%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.09 (s, 2H), 8.07 (s, 1H), 4.38 (br. s, 1H), 3.10 (br. s, 1H), 1.70-1.65 (m, 1H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 9H), 1.06-1.02 (m, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.8, 171.5, 141.8, 133.1 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.0 (q, $^{3}J_{CF}$ = 2.7 Hz, +,

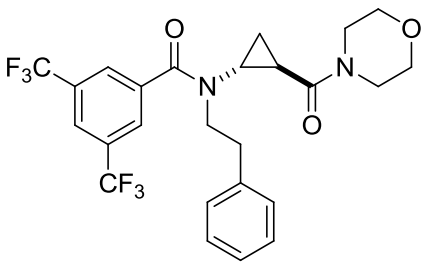
2C), 124.6 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 52.4 (+), 52.1, 37.1 (+), 29.0 (+, 3C), 27.7 (+), 21.3 (+), 21.0 (+), 17.4 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm-1): 3342, 2976, 2937, 2494, 1634, 1427, 1346, 1281, 1184, 1140, 905, 681; HRMS (TOF ES): found 461.1618, calculated for $C_{20}H_{24}F_6N_2O_2Na$ (M+Na) 461.1640 (4.8 ppm).



***N*-((1*R**,2*R**)-2-(*tert*-Butylcarbamoyl)cyclopropyl)-*N*-cyclopropyl- 3,5-bis(trifluoromethyl)benzamide (95ami)**: The reaction was performed according to the typical procedure, employing bromocyclopropane **70a** (110 mg, 0.50 mmol) and *N*-cyclopropyl-3.5-bis(triflouromethyl)- benzamide (**94mi**) (297 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/ EtOAc 1:1) afforded two fractions. The less polar one (R*f* 0.51) was identified as non-reacted benzamide, and the more polar one (R*f* 0.21) as the title compound, a colorless crystalline solid, mp 148-151 ^{o}C. Yield 129 mg (0.30 mmol, 59%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.14 (s, 2H), 8.09 (s, 1H), 7.42 (br. s, 1H), 3.10 (br. s, 1H), 2.79 (br. s, 1H), 1.78 (br. s, 1H), 1.45-1.04 (m, 11H), 0.96-0.62 (m, 4H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 173.1, 171.8, 140.8, 132.9 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 129.3 (+, 2C), 124.8 (+), 124.5 (q, $^{1}J_{CF}$ = 272.5 Hz, 2C), 52.0, 51.9 (+), 39.4 (br. s, +), 31.4 (br. s, +),28.9 (+, 3C), 16.7 (br. s, -), 9.3 (br. s, -, 2C); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); FTIR (NaCl, film, cm-1): 3340, 2966, 2933, 1651, 1545, 1458, 1424, 1364, 1281, 1173, 1140, 905, 681; HRMS (TOF ES): found 437.1661, calculated for $C_{20}H_{23}F_6N_2O_2$ (M+H) 437.1664 (0.7 ppm).

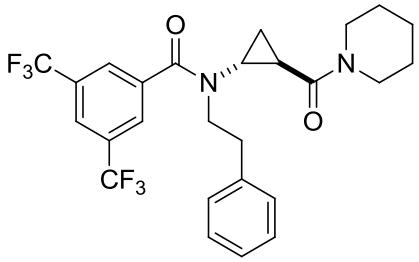


***N*-Butyl-*N*-((1R*,2R*)-2-(morpholine-4-carbonyl)cyclopropyl)- 3,5-bis(trifluoromethyl)benzamide (95emd):** The reaction was performed according to the typical procedure, employing bromocyclopropane **70b** (117 mg, 0.50 mmol) and N-butyl-3,5-bis(triflouromethyl)- benzamide (**94md**) (313 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (Rf 0.72) was identified as non-reacted benzamide, and the more polar one (Rf 0.13) as the title compound, a white solid mp 69-71 ^{o}C. Yield 171.7 mg (0.37 mmol, 74%); ^{1}H NMR (400.13 MHz, CD_3OD) δ ppm 8.14 (s, 1H) 8.10 (s, 2H), 3.84 (br. s, 1H), 3.56-3.33 (m, 8H), 3.15 (br. s, 1H), 3.04 (br. s, 1H), 2.08 (br. s, 1H), 1.83-1.68 (m, 2H), 1.53-1.14 (5H), 1.05-0.98 (m, 3H), 0.80 (br. s, 1H); ^{13}C NMR (100.67 MHz, CD_3OD) δ ppm 170.7, 170.6, 141.0, 133.0 (q, $^{2}J_{CF}$ = 32.3 Hz, 2C), 129.2 (+, 2C), 124.7 (spt, $^{3}J_{CF}$ = 3.7 Hz, +), 124.6 (q, $^{1}J_{CF}$ = 272.2 Hz, 2C), 67.7 (-), 67.6 (-), 48.1 (-), 47.0 (-), 43.7 (-), 40.5 (+), 30.9 (-), 24.4 (+), 21.4 (-), 18.8 (-), 14.3 (+); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm-1): 2962, 2932, 2862, 1645, 1464, 1448, 1425, 1362, 1281, 1184, 1171, 1136, 1119, 905, 849, 757, 704, 681; HRMS (TOF ES): found 466.1698, calculated for $C_{21}H_{24}F_6N_2O_3$ (M+) 466.1691 (1.5 ppm).



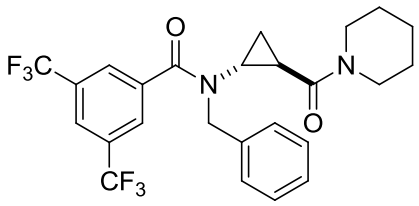
***N*-((1*R**,2*R**)-2-(Morpholine-4-carbonyl)cyclopropyl)- *N*-phenethyl-3,5-bis(trifluoromethyl)benzamide (95bmg)**: The reaction was performed according to the typical procedure, employing bromocyclopropane **70b** (117 mg, 0.50 mmol) and *N*-phenethyl-3,5-bis(triflouromethyl)- benzamide (**94mg**) (313 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less

polar one (R*f* 0.69) was identified as non-reacted benzamide, and the more polar one (R*f* 0.10) as the title compound, a colorless viscous oil. Yield 195 mg (0.38 mmol, 76%); ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.10 (s, 1H), 7.79 (s, 2H), 7.39- 7.32 (m, 4H), 7.28-7.23 (m, 1H), 4.15 (dt, *J* = 13.2 Hz, 6.6 Hz, 1H), 3.73-3.63 (m, 3H), 3.53-3.41 (m, 5H), 3.16-3.01 (m, 4H), 2.02 (br. s, 1H), 1.20-1.15 (m, 1H), 1.13-1.08 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.1, 170.5, 140.9, 140.2, 133.0 (q, $^{2}J_{CF}$ = 33.6 Hz), 130.4 (+, 2C), 129.9 (+, 2C), 129.1 (+, 2C), 128.0 (+), 124.7 (+, 2C), 124.6 (q, $^{1}J_{CF}$ = 271.6 Hz), 67.8 (-), 67.6 (-), 49.3 (-), 47.0 (-), 43.7 (-), 40.8 (+), 34.6 (-), 24.4 (+), 18.9 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); FTIR (NaCl, film, cm-1): 2924, 2890, 1645, 1456, 1423, 1366, 1280, 1236, 1177, 1136, 905, 752, 702; HRMS (TOF ES): found 515.1765, calculated for $C_{25}H_{25}F_6N_2O_3$ (M+H) 515.1769 (0.8 ppm);

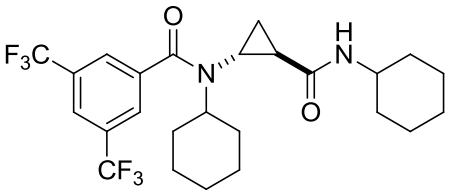


***N*-Phenethyl-*N*-((1*R**,2*R**)-2-(piperidine-1-carbonyl)-cyclopropyl)-3,5-bis(trifluoromethyl)benzamide** (**95cmg**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70c** (115 mg, 0.50 mmol) and *N*-phenethyl-3,5-bis(triflouromethyl)- benzamide (**94mg**) (313 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (R*f* 0.69) was identified as non-reacted benzamide, and the more polar one (R*f* 0.21) as the title compound, a colorless viscous oil. Yield 195 mg (0.38 mmol, 76%); ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.07 (s, 1H), 7.80 (s, 2H), 7.40- 7.33 (m, 4H), 7.29-7.24 (m, 1H), 4.16 (ddd, *J* = 12.9 Hz, 6.6 Hz, 6.3 Hz, 1H), 3.72-3.64 (m, 1H), 3.56-3.49 (m, 1H), 3.16-2.98 (m, 4H), 2.06-2.00 (m, 1H), 1.75-1.50 (m, 4H), 1.44-1.33 (m, 4H), 1.18-1.12 (m, 1H), 1.10-1.05 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.2, 169.8, 140.9, 140.2, 132.9 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C),

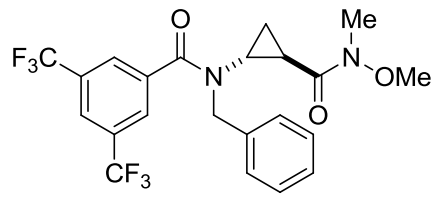
130.3 (+, 2C), 129.8 (+, 2C), 129.0 (+, 2C), 128.0 (+), 124.6 (+), 124.6 (q, $^{1}J_{CF}$ = 272.5 Hz, 2C), 49.3 (-), 47.7 (-), 44.5 (-), 40.6 (+), 34.6 (-), 27.8 (-), 26.6 (-), 25.5 (-), 24.5 (+), 18.6 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); HRMS (TOF ES): found 519.2058, calculated for $C_{26}H_{26}F_6N_2O_2Li$ (M+Li) 519.2059 (0.2 ppm);



***N*-Benzyl-*N*-((1*R**,2*R**)-2-(piperidine-1-carbonyl)cyclopropyl)- 3,5-bis(trifluoromethyl)benzamide** (**95cmf**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70c** (116 mg, 0.50 mmol) and *N*-benzyl-3,5-bis(triflouromethyl)benzamide (**94mf**) (347 mg, 1.00 mmol). Flash column chromatography on Silica gel (eluent hexane/ EtOAc 1:1) afforded two fractions. The less polar one (R*f* 0.61) was identified as non-reacted benzamide, and the more polar one (R*f* 0.21) as the title compound, a colorless viscous oil. Yield 170 mg (0.34 mmol, 68%). ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.12 (s, 3H), 7.44-7.35 (m, 4H), 7.35-7.29 (m, 1H), 5.06 (d, *J* = 14.5 Hz, 1H), 4.58 (d, *J* = 14.5 Hz, 1H), 3.49 (dt, J = 13.2 Hz, 5.0 Hz, 1H), 3.22 (br. s, 1H), 3.07 (br. s, 1H), 2.93 (br. s, 1H), 2.07 (br. s, 1H), 1.63- 1.49 (m, 3H), 1.40-1.27 (m, 4H), 1.14 (br. s, 1H), 1.03 (br. s, 1H); ^{13}C NMR (126 MHz, MeOD) δ ppm 171.1, 169.9, 140.6, 138.6, 133.0 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 130.1 (+, 4C), 129.2 (+, 2C), 128.9 (+), 124.8 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.6 (q, $^{1}J_{CF}$ = 272.5 Hz, 2C), 52.0 (-), 47.6 (-), 44.5 (-), 40.6 (+), 27.8 (-), 26.6 (-), 25.5 (-), 24.1 (+), 18.5 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.4 (s, 6F); FTIR (NaCl, film, cm-1): 3088, 3064, 3032, 3009, 2941, 2858, 1643, 1452, 1364, 1281, 1184,1138, 905, 849, 700, 681; HRMS (TOF ES): found 499.1817, calculated for $C_{25}H_{25}F_6N_2O_2$ (M+H) 499.1820 (0.6 ppm).

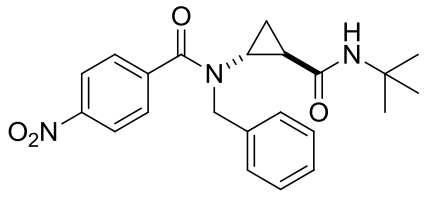


***N*-Cyclohexyl-*N*-((1*R**,2*R**)-2-(cyclohexylcarbamoyl) cyclopropyl)-3,5-bis(trifluoromethyl)benzamide** (**95dmh**): The reaction was performed according to the typical procedure, employing bromocyclopropane **70d** (123 mg, 0.50 mmol) and *N*-cyclohexyl-3,5- bis(triflouromethyl)-benzamide (**94mh**) (339 mg, 1.00 mmol). Flash chromatography on silica gel (eluent hexane/EtOAc 2:1) afforded two fractions. The less polar one (R*f* 0.78) was identified as non-reacted benzamide, and the more polar one (R*f* 0.31) as the title compound, a colorless viscous oil. Yield 166 mg (0.33 mmol, 66%); ^{1}H NMR (500.13 MHz, CD_3OD)δ ppm 8.09 (s, 2H), 8.06 (s, 1H), 4.06 (br. s, 1H), 3.48- 3.41 (m, 1H), 3.19 (br. s, 1H), 2.04-1.97 (m, 1H), 1.93-1.84 (m, 3H), 1.76-1.58 (m, 9H), 1.46-1.00 (m, 11H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.4 (2C), 141.5, 133.0 (q, $^{2}J_{CF}$ = 34.5 Hz, 2C), 129.2 (s, +, 2C), 124.7 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.7 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 60.8 (+), 49.9 (+), 37.3 (+), 33.93 (-), 33.85 (-), 32.4 (-), 32.1 (-), 27.5 (br. s., +), 27.39 (-), 27.36 (-), 27.0 (-), 26.7 (-), 26.2 (-), 26.1 (-), 18.0 (-); ^{19}F NMR (376.50 MHz, CD_3OD) δ ppm -65.5 (s, 6F); FTIR (NaCl, film, cm-1): 3302, 2933, 2856, 1632, 1547, 1454, 1427, 1352, 1278, 1182, 1138, 905, 681; HRMS (TOF ES): found 505.2287, calculated for $C_{25}H_{31}F_6N_2O_2$ (M+H) 505.2290 (0.6 ppm).



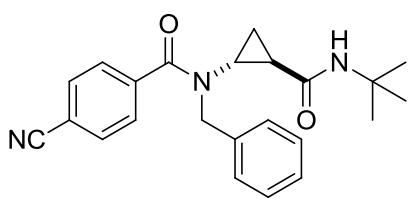
***N*-Benzyl-*N*-((1R*,2R*)-2-(methoxy(methyl)carbamoyl) cyclopropyl)-3,5-bis(trifluoromethyl)benzamide (95emf):** The reaction was performed according to the typical procedure, employing bromocyclopropane **70e** (104 mg, 0.50 mmol) and N-benzyl-3,5-bis(trifluoromethyl) benzamide (**94mf**) (347 mg, 1.00 mmol). Flash column chromatography on

Silica gel (eluent hexane/ EtOAc 2:1) afforded two fractions. The less polar one (Rf 0.61) was identified as non-reacted benzamide, and the more polar one (Rf 0.31) as the title compound, a yelowish viscous oil. ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.09 (s, 3H), 7.45-7.38 (m, 4H), 7.35-7.31 (m, 1H), 5.03 (d, J = 14.5 Hz, 1H), 4.63 (d, J = 14.5 Hz, 1H), 3.45 (br. s, 3H), 3.17 (br. s, 1H), 2.93 (br. s, 3H), 2.26 (br. s, 1H), 1.28-1.21 (m, 1H), 1.11 (br. s, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 172.1, 171.3, 140.6, 138.5, 133.2 (q, $^{2}J_{CF}$ = 33.6 Hz, 2C), 130.1 (+, 2C), 129.3 (+, 2C), 129.0 (q, $^{3}J_{CF}$ = 2.7 Hz, +, 2C), 129.0 (+), 124.8 (spt, $^{3}J_{CF}$ = 3.6 Hz, +), 124.6 (q, $^{1}J_{CF}$ = 271.6 Hz, 2C), 62.2 (+), 51.9 (-), 40.8 (+), 32.4 (+), 23.6 (+), 18.3 (-); FTIR (teflon, film, cm-1): 2939, 1651, 1620, 1441, 1418, 1364, 1279, 1207, 1184, 1150, 1138, 1109, 1003, 905, 756, 700, 681; HRMS (TOF ES): found 475.1457, calculated for $C_{22}H_{21}F_6N_2O_3$ (M+H) 475.1456 (0.2 ppm);

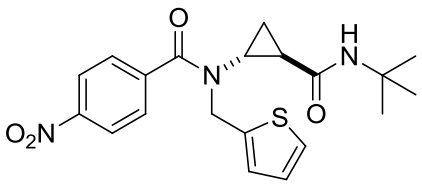


N-Benzyl-N-((1R*,2R*)-2-(tert-butylcarbamoyl)cyclopropyl)-4-nitrobenzamide (**95akf**): **Typical Procedure I**: An oven-dried 10 mL Weaton vial was charged with 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide **70a** (110 mg, 0.5 mmol, 1.0 equiv), 18-crown-6 (13.2 mg, 0.05 mmol, 10 mol%), KOH (98 mg, 1.75 mmol, 3.5 equiv), *N*-benzyl-4-nitrobenzamide (**94kf**)[118] (256 mg, 1.0 mmol, 2.0 equiv), and anhydrous THF (5 mL). The mixture was stirred at 85 °C for 12 hrs, then the reaction mixture was filtered into a 100 mL round bottom flask, both the reaction vessel and filter were rinsed consecutively with DCM (15 mL) and EtOAc (15 mL), which were combined with filtrate. The product was isolated by column chromatography in 24:1 DCM:MeOH as a white solid (R_f 0.17, mp 146-150 °C). Yield 124.0 mg (0.32 mmol, 63%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.37 – 8.23 (m, 2H), 7.75 – 7.64 (m, 2H), 7.39 (d, *J* = 5.6 Hz, 4H), 7.32 (d, *J* = 4.3 Hz, 1H), 7.19 (s, 1H), 4.90 (d, *J* = 14.6

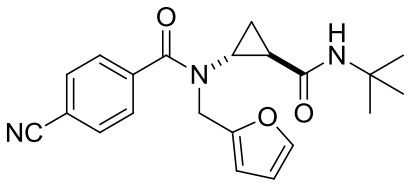
Hz, 1H), 4.67 (d, *J* = 14.6 Hz, 1H), 3.01 – 2.86 (m, 1H), 1.33 (d, *J* = 4.1 Hz, 2H), 1.10 (s, 10H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.28, 169.70, 148.43, 142.98, 136.96, 128.56 (+, 2C), 128.42 (+) 127.90 (+), 127.72 (+), 127.42 (+), 123.56 (+), 50.51, 49.70 (-), 37.99 (+), 27.45 (+, 3C), 26.92 (+), 15.41 (-); FTIR (NaCl, cm^{-1}): 3336, 2968, 2931, 1643, 1523, 1454, 1396, 1348, 1267, 1155, 846, 702; HRMS (TOF ES): found 394.1763, calculated for $C_{22}H_{24}N_3O_4$ (M-H) 394.1767 (1.0 ppm).



N-benzyl-N-((1R*,2R*)-2-(tert-butylcarbamoyl)cyclopropyl)-4-cyanobenzamide (**95ajf**): This compound was synthesized according to Typical Procedure I employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**70a**) (110 mg, 0.5 mmol), *N*-benzyl-4-cyanobenzamide (**94jf**)[119] (236 mg, 1.0 mmol), 18-crown-6 (13.2 mg, 0.05 mmol) and KOH (56 mg, 1.75 mmol). The product was isolated by column chromatography (eluting with a ternary mixture Hexanes/Acetone/DCM 3:1:1) as a tan solid, (R_f 0.37, mp 79-82 ^{o}C). Yield 177.0 mg (0.24 mmol, 47%). ^{1}H NMR (400.13 MHz, CD_3OD) δ ppm 7.85 – 7.79 (m, 2H), 7.66 – 7.59 (m, 2H), 7.39 (d, *J* = 4.5 Hz, 3H), 7.32 (q, *J* = 4.2 Hz, 1H), 7.26 (s, 1H), 4.88 (d, *J* = 14.6 Hz, 1H), 4.67 (d, *J* = 14.6 Hz, 1H), 2.91 (ddd, *J* = 7.4, 4.2, 4.2 Hz, 1H), 1.62 (m, *J* = 8.5 Hz, 1H), 1.37 – 1.30 (m, 1H), 1.18 (s, 9H), 1.02 (m, 1H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.54, 169.70, 141.22, 136.96, 132.31 (+), 128.51 (+), 128.47 (+), 127.69 (+), 127.52 (+), 127.38 (+), 117.77, 113.28, 50.50, 49.69 (-), 37.90 (+), 27.49 (+, 3C), 26.72 (+), 15.42 (-); FTIR (NaCl, cm^{-1}): 3339, 2966, 2929, 2230, 1643, 1544, 1497, 1396, 1336, 1267, 1153, 849, 734; HRMS (TOF ES): found 374.1867, calculated for $C_{23}H_{24}N_3O_2$ (M-H) 374.1869 (0.5 ppm).



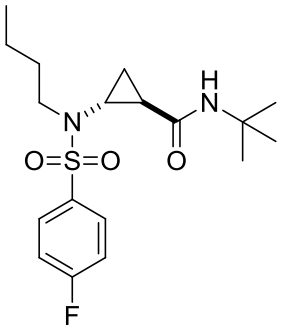
N-((1R*,2R*)-2-(tert-butylcarbamoyl)cyclopropyl)-4-nitro-N-(thiophen-2-ylmethyl)benzamide (**95akj**): This compound was synthesized according to Typical Procedure I employing 2-bromo-*N*-(tert-butyl)cyclopropanecarboxamide (**70a**) (110 mg, 0.50 mmol), 4-nitro-N-(thiophen-2-ylmethyl)benzamide (**94kj**) (262 mg, 1.00 mmol), 18-crown-6 (13.2 mg, 0.05 mmol) and KOH (56 mg, 1.75 mmol). The product was isolated by column chromatography eluting with DCM:MeOH mixture (24:1) as a yellow solid (R_f 0.27, mp 150-152 ^{o}C). Yield 104 mg (0.26 mmol, 52%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 8.31 (dd, *J* = 8.9, 2.2 Hz, 2H), 7.66 (dd, *J* = 9.0, 2.3 Hz, 2H), 7.39 (d, *J* = 4.8 Hz, 1H), 7.21 (s, 1H), 7.13 (s, 1H), 7.01 (dd, *J* = 5.2, 3.3 Hz, 1H), 5.08 (d, *J* = 15.0 Hz, 1H), 4.86 – 4.79 (d, *J* = 15.0, 1H), 3.04 – 2.97 (m, 1H), 1.68 – 1.53 (m, 1H), 1.34 (s, 1H), 1.12 (s, 9H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 170.96, 169.67, 148.45, 142.78, 139.26, 127.83 (+, 2C), 126.83 (+), 126.53 (+), 125.53 (+), 123.59 (+, 2C), 50.43, 44.69 (-), 37.78 (+), 27.47 (+, 3C), 26.98 (+), 15.29 (-); FTIR (NaCl, cm^{-1}): 3348, 2968, 2930, 1637, 1524, 1439, 1418, 1346, 1261, 856, 717; HRMS (TOF ES): found 401.1411, calculated for $C_{22}H_{24}N_3O_4$ (M+) 401.1409 (0.5 ppm).



N-((1R*,2R*)-2-(tert-butylcarbamoyl)cyclopropyl)-4-cyano-N-(furan-2-ylmethyl)benzamide (**95ajk**): This compound was synthesized according to Typical Procedure I employing 2-bromo-N-(tert-butyl)cyclopropanecarboxamide (**70a**) (110 mg, 0.5 mmol), 4-cyano-N-(furan-2-ylmethyl)benzamide (**94jk**) (226 mg, 1.0 mmol), 18-crown-6 (13.2 mg, 0.05 mmol) and KOH

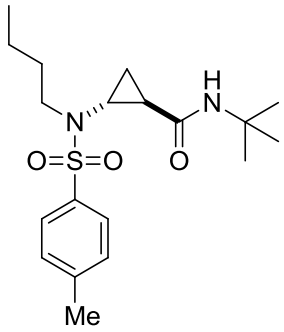
(56 mg, 1.75 mmol). The product was isolated by column chromatography on silica gel eluting with ternary mixture hexane/DCM/acetone 3:1:1 as a yellow solid, mp 126-130 ^{o}C, R_f 0.17. Yield 149 mg (0.41 mmol, 81%). ^{1}H NMR (500.13 MHz, CD_3OD) δ ppm 7.82 (s, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.52 (s, 1H), 7.21 (s, 1H), 6.42 (s, 2H), 4.87 (d, *J* = 12.8 Hz, 1H), 4.66 (d, *J* = 14.2 Hz, 1H), 2.99 (s, 1H), 1.60 (s, 1H), 1.22 (s, 9H), 1.11 (s, 2H); ^{13}C NMR (125.76 MHz, CD_3OD) δ ppm 171.41, 169.72, 150.26, 142.48, 141.02 (+), 132.33 (+, 2C), 127.58 (+), 117.82, 113.31, 110.21 (+), 108.48 (+), 50.51, 42.72 (-), 37.89 (+), 27.55 (+, 3S), 26.84 (+), 15.51 (-); FTIR (NaCl, cm^{-1}): 3325, 2966, 2925, 2331, 1645, 1524, 1456, 1396, 1346, 1261, 1178, 862, 700; HRMS (TOF ES): found 365.1740, calculated for $C_{21}H_{23}N_3O_3$ (M+) 365.1739 (0.3 ppm).

3.5.5. Adducts Resulting from Nucleophilic Attack by Sulfonamides.



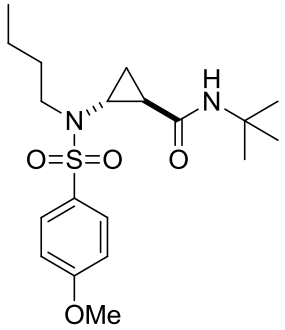
(1R*,2R*)-N-(tert-Butyl)-2-(N-butyl-4-fluorophenylsulfonamido)cyclopropanecarboxamide (**98aid**) (Typical Procedure II): An oven-dried 10 mL Weaton vial was charged with bromocyclopropane **70a** (44 mg, 0.20 mmol, 1.5 equiv), 18-crown-6 (3.5 mg, 13 μmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv), *N*-butyl-4-fluorobenzenesulfonamide (**97jd**)[120] (31 mg, 0.13 mmol, 1.0 equiv), and anhydrous THF (8 mL). The mixture was stirred at 85 ^{o}C for 12 hrs, then filtered through a sintered funnel into a 100 mL round bottom flask. Both the reaction vessel and the filter were rinsed consecutively with EtOAc (15 mL), which was combined with filtrate. Silica gel (2.0 g) was added to a filtrate, and then the solvent was removed by rotary evaporation. The residue absorbed onto

silica gel was loaded on the top of the column packed with silica gel, which was eluted with hexane/EtOAc 3:1 to afford two fractions. The major fraction (R_f = 0.30) contained the title product as a colorless solid, mp 112-113°C. Yield 47 mg (96%, 0.127 mmol). A second fraction (R_f = 0.07) contained minute amounts of (1R*,2S*)-isomer. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.76 - 7.83 (m, 2H), 7.19 (t, *J* = 8.5 Hz, 2H), 5.87 (s, 1H), 3.19 (ddd, *J* = 13.6, 9.6, 6.1 Hz, 1H), 3.02 (ddd, *J* = 13.6, 9.6, 5.6 Hz, 1H), 2.15 (ddd, *J* = 7.3, 4.3, 2.9 Hz, 1H), 1.99 (ddd, *J* = 9.2, 6.3, 2.8 Hz, 1H), 1.47 - 1.57 (m, 2H), 1.39 (s, 9H), 1.23 - 1.32 (m, 3H), 1.19 (dt, *J* = 9.3, 4.9 Hz, 1H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.4, 165.2 (d, *J* = 255.4 Hz), 133.3 (d, *J* = 2.9 Hz), 130.3 (+, d, *J* = 9.5 Hz, 2C), 116.4 (+, d, *J* = 22.7 Hz, 2C), 51.5, 51.1 (-), 37.3 (+), 30.1 (-), 28.8 (+, 3C), 25.7 (+), 20.0 (-), 13.7 (+), 13.4 (-); ^{19}F NMR (376.31 MHz, $CDCl_3$) δ ppm -104.81 (tt, *J* = 8.1, 5.7 Hz, 1 F); FT IR (KBr, cm^{-1}): 3325, 2964, 2934, 2874, 1651, 1593, 1493, 1456, 1229, 839; HRMS (TOF ES): found 393.1621, calculated for $C_{18}H_{27}N_2O_3SFNa$ (M+Na) 393.1624 (0.8 ppm).



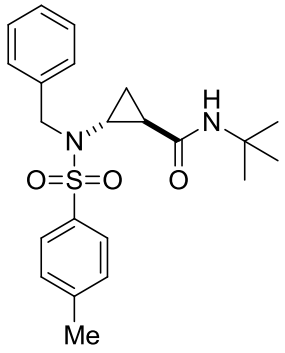
(1R*,2R*)-N-(tert-Butyl)-2-(N-butyl-4-methylphenylsulfonamido)cyclopropanecarboxamide (**98aad**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (176 mg, 0.8 mmol, 1.2 equiv), 18-crown-6 (18 mg, 0.067 mmol, 10 mol%), KOH (263 mg, 4.7 mmol, 7.0 equiv) and *N*-butyl-4-methylbenzenesulfonamide (**97ad**)[121] (151.4 mg, 0.67 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 16:1), mp 115-117°C R_f 0.26 (eluent hexane/EtOAc 3:1). Yield 216 mg (0.60 mmol, 90%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.67 (m, *J* = 8.5 Hz, 2H), 7.30 (m, *J*=8.2 Hz, 2H), 5.83 (s, 1H), 3.20 (ddd, *J* = 13.9, 9.8, 6.0 Hz, 1H), 3.00 (ddd, *J* = 13.6, 9.8,

5.7 Hz, 1H), 2.43 (s, 3H), 2.13 (ddd, *J* = 7.4, 4.6, 2.8 Hz, 1H), 1.99 (ddd, *J* = 9.1, 6.3, 2.8 Hz, 1H), 1.43 - 1.58 (m, 2H), 1.41 (s, 9H), 1.22 - 1.33 (m, 3H), 1.16 (dt, *J* = 9.2, 4.7 Hz, 1H), 0.89 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 169.5, 143.7, 134.3, 129.6 (+, 2C), 127.6 (+, 2C), 51.5, 51.1 (-), 37.4 (+), 30.3 (-), 28.9 (+, 3C), 25.8 (+), 21.5 (+), 20.1 (-), 13.7 (+), 13.1 (-); FT IR (KBr, cm^{-1}): 3334, 2962, 2931, 1647, 1545, 1456, 1205, 1045, 816; HRMS (TOF ES): found 366.1977, calculated for $C_{19}H_{30}N_2O_3S$ (M^+) 366.1977 (0.0 ppm).

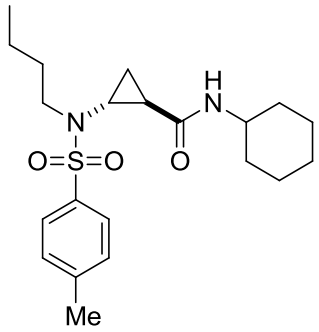


(1R*,2R*)-N-(tert-Butyl)-2-(N-butyl-4-methoxyphenylsulfonamido)cyclopropanecarboxamide (**98aed**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butyl-*p*-methoxybenzenesulfonamide (**97ed**)[122] (32 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 11:1), mp 97-100°C, R_f 0.18 (eluent hexane/EtOAc 3:1). Yield 51 mg (0.126 mmol, 95%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.72 (m, 2H), 6.97 (m, *J* = 8.8 Hz, 2H), 5.85 (s, 1H), 3.87 (s, 3H), 3.19 (ddd, *J* = 13.6, 9.6, 6.1 Hz, 1H), 3.00 (ddd, *J* = 13.9, 9.6, 5.6 Hz, 1H), 2.13 (ddd, *J* = 7.4, 4.5, 2.8 Hz, 1H), 1.98 (ddd, *J* = 9.1, 6.2, 2.9 Hz, 1H), 1.43 - 1.58 (m, 2H), 1.41 (s, 9H), 1.23 - 1.32 (m, 3H), 1.17 (dt, *J* = 9.0, 4.7 Hz, 1H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.6, 163.0, 129.6 (+, 2C), 128.7, 114.1 (+, 2C), 55.5 (+), 51.4, 51.0 (-), 37.3 (+), 30.1 (-), 28.8 (+, 3C), 25.6 (+), 20.0 (-), 13.6 (+), 13.2 (-); FT IR

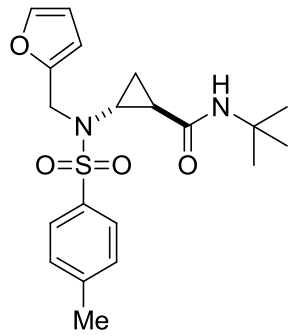
(KBr, cm^{-1}): 3325, 2962, 2934, 2872, 1653, 1541, 1443, 1259, 1092, 835; HRMS (TOF ES): found 405.1834, calculated for $C_{19}H_{30}N_2O_4SNa$ (M+Na) 405.1824 (2.5 ppm).



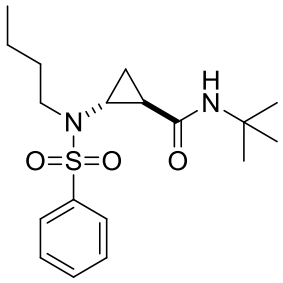
(1R*,2R*)-2-(N-Benzyl-4-methylphenylsulfonamido)-N-(tert-butyl)cyclopropanecarboxamide (**98aaf**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-benzyl-4-methylbenzenesulfonamide (**97ff**)[123] (35 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a yellow oil (diastereomeric mixture 11:1), R_f 0.65 (eluent hexane/EtOAc 3:1). Yield 40 mg (0.10 mmol, 75%). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.71 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.34 - 7.36 (m, 5H), 5.16 (s, 1H), 4.42 (d, *J* = 13.9 Hz, 1H), 4.04 (d, *J* = 13.6 Hz, 1H), 2.45 (s, 3H), 2.09 (ddd, *J* = 7.4, 4.6, 2.8 Hz, 1H), 1.32 - 1.37 (m, 1H), 1.30 (s, 9H), 1.08 - 1.19 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 169.5, 143.9, 136.7, 133.8, 129.8 (+, 2C), 129.1 (+, 2C), 128.5 (+, 2C), 127.8 (+), 127.7 (+, 2C), 55.4 (-), 51.3, 38.0 (+), 28.8 (+, 3C), 25.1 (+), 21.5 (+), 13.5 (-); FT IR (KBr, cm^{-1}): 3334, 2966, 1651, 1599, 1537, 1456, 1256, 1028, 849; HRMS (TOF ES): found 423.1717, calculated for $C_{22}H_{28}N_2O_3SNa$ (M+Na) 423.1718 (0.2 ppm).



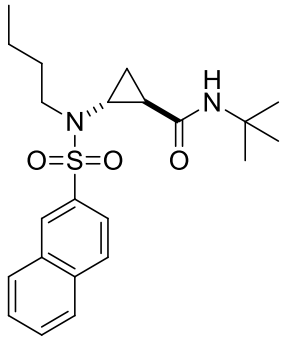
(1R*,2R*)-2-(N-Butyl-4-methylphenylsulfonamido)-N-cyclohexylcyclopropanecarboxamide (**98dad**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70d** (39 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butyl-4-methylbenzenesulfonamide (**97ad**)[121] (30 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 15:1) mp 118-120 °C; R_f 0.24 (eluent hexane/EtOAc 3:1). Yield 46 mg (0.118 mmol, 89%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.66 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.89 (d, *J* = 8.1 Hz, 1H), 3.74 - 3.86 (m, 1H), 3.20 (ddd, *J* = 13.9, 9.9, 6.1 Hz, 1H), 3.01 (ddd, *J* = 13.9, 9.9, 5.6 Hz, 1H), 2.43 (s, 3H), 2.17 (ddd, *J* = 7.2, 4.0, 2.9 Hz, 1H), 1.95 - 2.06 (m, 2H), 1.91 (d, *J* = 12.4 Hz, 1H), 1.68 - 1.81 (m, 2H), 1.60 - 1.66 (m, 1H), 1.51 - 1.57 (m, 1H), 1.31 - 1.49 (m, 4H), 1.16 - 1.30 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.3, 143.7, 134.2, 129.7 (+, 2C), 127.6 (+, 2C), 51.1 (-), 48.5 (+), 37.5 (+), 33.4 (-), 33.0 (-), 30.2 (-), 25.5 (-), 25.2 (+), 24.9 (-, 2C), 21.5 (+), 20.0 (-), 13.7 (+), 13.4 (-); FT IR (KBr, cm^{-1}): 3296, 2932, 2854, 1639, 1599, 1548, 1450, 1346, 1165, 1090, 816; HRMS (TOF ES): found 392.2143, calculated for $C_{21}H_{32}N_2O_3S$ (M^+) 392.2134 (2.3 ppm).



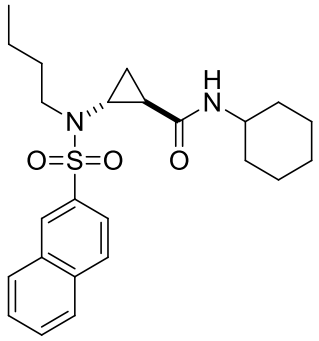
(1R*,2R*)-N-(tert-butyl)-2-(N-(furan-2-ylmethyl)-4-methylphenylsulfonamido)cyclopropanecarboxamide (**98aak**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and 4-methyl-*N*-(furan-2-ylmethyl)benzenesulfonamide (**97ak**)[124] (33 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 25:1) mp 108-110 ^{o}C, R_f 0.20 (eluent hexane/EtOAc 3:1). Yield 43 mg (0.112 mmol, 84%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.64 (d, *J* = 8.3 Hz, 2H), 7.26 - 7.30 (m, 3H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.20 (d, *J*=3.3 Hz, 1H), 5.62 (s, 1H), 4.46 (d, *J* = 14.9 Hz, 1H), 4.19 (d, *J* = 15.2 Hz, 1H), 2.42 (s, 3H), 2.17 (ddd, *J* = 7.3, 4.6, 2.8 Hz, 1H), 1.68 (ddd, *J* = 9.1, 6.3, 2.8 Hz, 1H), 1.37 (s, 9H), 1.25 - 1.30 (m, 1H), 1.16 (ddd, *J* = 9.3, 4.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.5, 149.3, 143.8, 142.4 (+), 133.7, 129.6 (+), 127.8 (+), 110.5 (+), 110.0 (+), 51.4, 47.1 (-), 37.0 (+), 28.9 (+), 25.6 (+), 21.5, 13.7 (-); FT IR (KBr, cm^{-1}): 3384, 2968, 2929, 2872, 1666, 1599, 1504, 1456, 1350, 1227, 885, 656; HRMS (TOF ES): found 413.1515, calculated for $C_{24}H_{32}N_2O_3S$ (M + Na) 413.1511 (1.2 ppm).



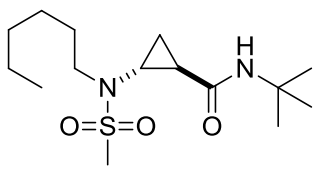
(1R*,2R*)-N-(tert-Butyl)-2-(N-butylphenylsulfonamido)cyclopropanecarboxamide (**98afd**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butylbenzenesulfonamide (**97fd**)[125] (28 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 10:1) mp 65-68 °C. R_f = 0.25 (eluent hexane/EtOAc 3:1). Yield 34.2 mg (0.097 mmol, 73%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 7.3 Hz, 2 H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 5.85 (s, 1H), 3.21 (ddd, *J* = 13.7, 9.7, 5.9 Hz, 1H), 2.98 - 3.08 (m, 1H), 2.15 (ddd, *J* = 7.3, 4.5, 2.8 Hz, 1H), 1.99 (ddd, *J* = 9.2, 6.3, 3.0 Hz, 1H), 1.43 - 1.57 (m, 2H), 1.40 (s, 9H), 1.22 - 1.36 (m, 3H), 1.18 (dt, *J* = 9.2, 4.7 Hz, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.5, 137.1, 132.8 (+), 129.0 (+, 2C), 127.5 (+, 2C), 51.5, 51.1 (-), 37.3 (+), 30.1 (-), 28.8 (+, 3C), 25.7 (+), 20.0 (-), 13.7 (+), 13.2 (-); FT IR (KBr, cm^{-1}): 3303, 2962, 2932, 2872, 1651, 1539, 1447, 1248, 1045, 887; HRMS (TOF ES): found 353.1907, calculated for $C_{18}H_{29}N_2O_3S$ (M+H) 353.1899 (2.3 ppm).



(1R*,2R*)-N-(tert-Butyl)-2-(N-butylnaphthalene-2-sulfonamido)cyclopropanecarboxamide (**98agd**): The reaction was performed according to the Typical Procedure II, employing bromo-cyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butylnaphthalenesulfonamide (**97gd**) (34 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 10:1) mp = 97-99 °C, R_f 0.38 (eluent hexane/EtOAc 3:1). Yield 44 mg (0.103 mmol, 78%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.36 (s, 1H), 7.90 - 7.99 (m, 3H), 7.78 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.59 - 7.69 (m, 2H), 5.81 (s, 1H), 3.26 (ddd, *J* = 13.7, 9.8, 6.1 Hz, 1H), 3.09 (ddd, *J* = 13.7, 9.7, 5.7 Hz, 1H), 2.27 (ddd, *J* = 7.4, 4.5, 2.8 Hz, 1H), 2.01 (ddd, *J* = 9.1, 6.3, 2.8 Hz, 1H), 1.45 - 1.58 (m, 2H), 1.43 (s, 9H), 1.25 - 1.37 (m, 3H), 1.18 - 1.24 (m, 1H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.5, 134.8, 134.4, 132.1, 129.2 (+, 2 C), 128.8 (+, 2 C), 127.9 (+), 127.6 (+), 122.8 (+), 51.5, 51.1 (-), 37.3 (+), 30.3 (-), 28.9 (+, 3 C), 25.9 (+), 20.0 (-), 13.7 (+), 13.2 (-); FT IR (KBr, cm^{-1}): 3377, 2961, 2930, 2870, 1649, 1589, 1541, 1456, 1259, 1132, 1020, 860; HRMS (TOF ES): found 403.2043, calculated for $C_{22}H_{31}N_2O_3S$ (M+H) 403.2055 (3.0 ppm).

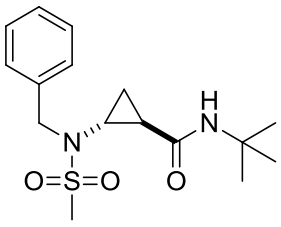


(1R*,2R*)-2-(N-Butylnaphthalene-2-sulfonamido)-N-cyclohexylcyclopropanecarboxamide (**98dgd**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70d** (39 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butylnaphthylsulfonamide (**97gd**) (35 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 11:1), mp 110-113 °C; R_f = 0.41 (eluent hexane/EtOAc 2:1). Yield 53 mg (0.125 mmol, 94%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.33 - 8.40 (m, 1H), 7.90 - 8.00 (m, 3H), 7.78 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.60 - 7.70 (m, 2H), 5.93 (d, *J* = 8.1 Hz, 1H), 3.77 - 3.89 (m, 1H), 3.27 (ddd, *J* = 13.7, 9.8, 6.1 Hz, 1H), 3.12 (ddd, *J* = 13.8, 9.7, 5.6 Hz, 1H), 2.33 (ddd, *J* = 7.3, 4.5, 2.8 Hz, 1H), 2.06 (tt, *J* = 6.1, 3.0 Hz, 2H), 1.89 - 1.97 (m, 1H), 1.70 - 1.84 (m, 2H), 1.53 - 1.68 (m, 2H), 1.36 - 1.51 (m, 4H), 1.18 - 1.34 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.3, 134.8, 134.4, 132.1, 129.3 (+), 129.2 (+), 128.8 (+, 2C), 127.9 (+), 127.6 (+), 122.8 (+), 51.0 (-), 48.5 (+), 37.4 (+), 33.4 (-), 33.0 (-), 30.2 (-), 25.5 (-), 25.3 (+), 24.8 (-, 2C), 20.0 (-), 13.7 (+), 13.5 (-); FT IR (KBr, cm^{-1}): 3321, 2932, 1637, 1541, 1535, 1450, 1269, 1116, 1020, 858; HRMS (TOF ES): found 428.2139, calculated for $C_{24}H_{32}N_2O_3S$ (M^+) 428.2134 (1.2 ppm).



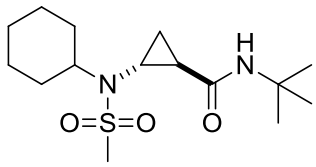
(1R*,2R*)-N-(tert-Butyl)-2-(N-hexylmethylsulfonamido)cyclopropanecarboxamide (**98ahe**): The reaction was performed according to the Typical Procedure II,

employing bromocyclopropane **70a** (44 mg, 0.2 mmol, 1.5 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-hexylmethanesulfonamide (**97he**)[126] (39 mg, 0.133 mmol, 1.0 equiv). Column chromatography on silica gel (eluent hexane/EtOAc 1:1) afforded two fractions. The major fraction contained a title compound as a white solid mp 62-64 °C, R_f 0.52. Yield 36.3 mg (0.114 mmol, 86%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 5.74 (br. s, 1H), 3.15 - 3.31 (m, 2H), 2.88 (s, 3H), 2.58 (ddd, *J* = 7.3, 4.4, 2.9 Hz, 1H), 1.90 (ddd, *J* = 9.2, 6.3, 2.9 Hz, 1H), 1.57 - 1.74 (m, 2H), 1.37 - 1.41 (m, 1H), 1.35 - 1.38 (m, 9H), 1.26 - 1.33 (m, 6H), 1.21 (dt, *J* = 9.4, 4.8 Hz, 1H), 0.87 - 0.94 (m, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.5, 51.4, 51.0 (-), 36.7 (+), 36.4 (+), 31.4 (-), 28.8 (+), 28.0 (+, 3C), 26.5 (-), 25.8 (+), 22.5 (-), 14.0 (+), 13.6 (-); FT IR (KBr, cm^{-1}): 3331, 2960, 2932, 2858, 1647, 1591, 1541, 1500, 1458, 1155, 883; HRMS (TOF ES): found 341.1871, calculated for $C_{15}H_{30}N_2O_3SNa$ (M+Na) 341.1875 (1.2 ppm). The minor fraction (R_f 0.31) contained minute amounts (3.7 mg) of (1R*,2S*)-diastereomer.

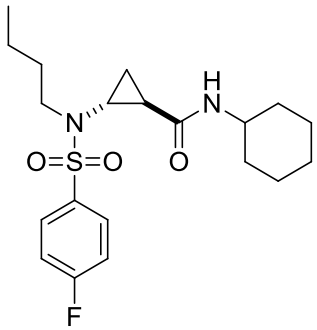


(1R*,2R*)-2-(N-Benzylmethylsulfonamido)-N-(tert-butyl)cyclopropanecarboxamide (**98ahf**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (46 mg, 0.21 mmol, 1.5 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-benzylmethanesulfonamide (**97hf**)[127] (26 mg, 0.14 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 15:1) mp 136-137 °C, R_f 0.28 (eluent hexane/EtOAc 3:2). Yield 37.8 mg (0.117 mmol, 83%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.31 - 7.42 (m, 5H),

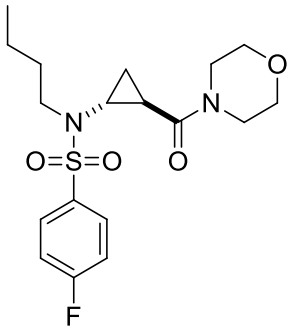
5.36 (br. s, 1H), 4.60 (d, J = 14.1 Hz, 1H), 4.21 (d, J = 14.1 Hz, 1H), 2.74 (s, 3H), 2.55 (ddd, J = 7.4, 4.5, 2.8 Hz, 1H), 1.54 (ddd, J = 9.2, 6.3, 2.8 Hz, 1H), 1.33 - 1.38 (m, 1H), 1.31 (s, 9H), 1.20 - 1.27 (m, 1H) ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.3, 135.5, 129.3 (+, 2C), 128.7 (+, 2C), 128.2 (+), 54.8 (-), 51.4, 36.9 (+), 36.5 (+), 28.7 (+, 3C), 25.8 (+), 14.0 (-); FT IR (KBr, cm^{-1}): , 2964, 2929, 2972, 1651, 1537, 1456, 1258, 1049, 841; HRMS (TOF ES): found 325.1588, calculated for $C_{16}H_{25}N_2O_3S$ (M+H) 325.1586 (0.6 ppm).



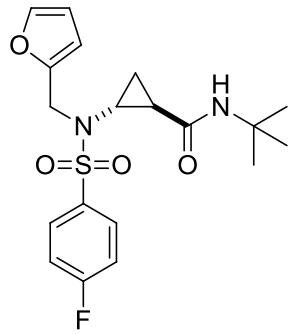
(1R*,2R*)-N-(tert-Butyl)-2-(N-cyclohexylmethylsulfonamido)cyclopropanecarboxamide (**98ahh**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-cyclohexylmethanesulfonamide (**97hh**)[128] (34 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a yellow oil (diastereomeric mixture 9:1) R_f 0.28 (eluent hexane/EtOAc 2:1). Yield 28 mg (0.089 mmol, 67%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 5.83 (br. s, 1H), 3.67 (tt, J = 12.1, 3.3 Hz, 1H), 2.87 (s, 3H), 2.49 (ddd, J = 7.4, 4.5, 3.0 Hz, 1H), 1.92 (ddd, J = 9.2, 6.3, 2.9 Hz, 1H), 1.75 - 1.87 (m, 4H), 1.49 - 1.74 (m, 3H), 1.36 - 1.41 (m, 1H), 1.35 (s, 9H), 1.24 - 1.32 (m, 3H), 1.00 - 1.15 (m, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.8, 60.2 (+), 51.4, 37.9 (+), 32.8 (+), 32.7 (-), 31.1 (-), 28.8 (+, 3C), 26.2 (-), 26.1 (-), 25.4 (-), 25.3 (+), 14.0 (-); FT IR (KBr, cm^{-1}): 3373, 2964, 2934, 2856, 1651, 1547, 1454, 1256, 1084, 893; HRMS (TOF ES): found 339.1721, calculated for $C_{15}H_{28}N_2O_3SNa$ (M+Na) 339.1718 (0.9 ppm).



(1R*,2R*)-2-(N-Butyl-4-fluorophenylsulfonamido)-N-cyclohexylcyclopropanecarboxamide (**98did**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70d** (39 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butyl-4-fluorobenzenesulfonamide (**97id**)[120] (31 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 10:1) mp 91-93 °C, R_f 0.29 (eluent hexane/EtOAc 3:1). Yield 51.3 mg (0.129 mmol, 97%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.75 - 7.84 (m, 2H), 7.20 (t, *J* = 8.6 Hz, 2H), 5.90 (d, *J* = 8.1 Hz, 1H), 3.73 - 3.86 (m, 1H), 3.19 (ddd, *J* = 13.7, 9.8, 5.8 Hz, 1H), 3.04 (ddd, *J* = 13.9, 9.9, 5.6 Hz, 1H), 2.21 (ddd, *J* = 7.3, 4.5, 2.8 Hz, 1H), 1.86 - 2.07 (m, 3H), 1.75 (td, *J* = 8.0, 3.8 Hz, 2H), 1.63 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.49 - 1.57 (m, 1H), 1.34 - 1.48 (m, 4H), 1.16 - 1.32 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.3, 165.2 (d, *J* = 255.4 Hz), 133.4 (d, *J* = 2.9 Hz), 130.3 (+, d, *J* = 8.8 Hz, 2C), 116.4 (+, d, *J* = 22.7 Hz, 2C), 51.1 (-), 48.6 (+), 37.4 (+), 33.5 (-), 33.0 (-), 30.2 (-), 25.5 (-), 25.3 (+), 24.89 (-), 24.88 (-), 20.1 (-), 13.7 (+), 13.6 (-); ^{19}F NMR (376.46 MHz, $CDCl_3$) δ ppm -104.8 (tt, *J* = 8.6, 4.7 Hz, 1F); FT IR (KBr, cm^{-1}): 3302, 2932, 2855, 1639, 1593, 1545, 1492, 1450, 1350, 1292, 1116, 1043, 872; HRMS (TOF ES): found 419.1799, calculated for $C_{20}H_{29}N_2O_3SFNa$ (M+Na) 419.1781 (4.3 ppm).

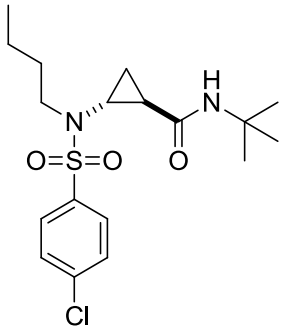


N-Butyl-4-fluoro-N-((1R*,2R*)-2-(morpholine-4-carbonyl)cyclopropyl)benzenesulfonamide (**98bid**): The reaction was performed according to the Typical Procedure II, employing (2-bromocyclopropyl)(morpholino)methanone (**70b**) (37 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butyl-4-fluorobenzenesulfonamide (**97id**)[120] (31 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a colorless oil (11:1 mixture of diastereomers), R_f = 0.25 (eluent EtOAc:Hexane 2:1). Yield 36 mg (0.11 mmol, 71%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.82 (ddd, *J* = 8.7, 5.0, 1.4 Hz, 2H), 7.23 (t, *J* = 8.5 Hz, 2H), 3.89 (m, 1H), 3.85 – 3.64 (m, 7H), 3.55 (ddd, *J* = 12.6, 7.1, 2.9 Hz, 1H), 3.21 – 3.02 (m, 2H), 2.51 – 2.41 (m, 2H), 1.64 – 1.49 (m, 1H), 1.50 – 1.19 (m, 5H), 0.95 – 0.84 (m, 3H). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 169.25 , 165.25 (d, *J* = 255.3 Hz), 133.54 , 130.23 (d, *J* = 9.1 Hz, 2C), 116.46 (d, *J* = 22.5 Hz, 2C), 67.06 , 66.95 , 46.15 , 42.61 , 38.61 , 30.23 , 21.36 , 20.06 , 14.97 , 13.70 . ^{19}F NMR (376.46 MHz, $CDCl_3$) δ -104.67 – -104.78 (m); FT IR (NaCl, cm^{-1}): 3331, 3087, 2962, 2872, 1645, 1585, 1547, 1475, 1454, 1392, 1294, 1225, 1205, 1167, 1094 HRMS found $C_{18}H_{24}FN_2O_4S$ $(M-H)^+$ 383.1441 (0.5 ppm).



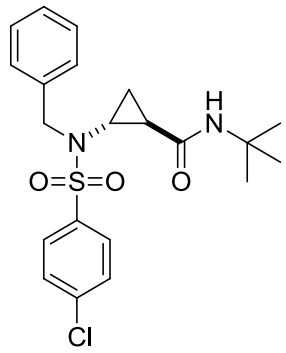
(1R*,2R*)-N-(tert-butyl)-2-(4-fluoro-N-(furan-2-ylmethyl)phenylsulfonamido)cyclopropanecarboxamide (**98aik**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0

equiv) and 4-fluoro-*N*-(furan-2-ylmethyl)benzenesulfonamide (**97ik**) (34 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 25:1) mp 121-124 ^{o}C, R_f 0.17 (eluent hexane/EtOAc 3:1). Yield 49 mg (0.123 mmol, 93%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.74 (dd, *J* = 5.1, 8.8 Hz, 2H), 7.25 (dd, *J* = 0.9, 1.9 Hz, 1H), 7.14 (dd, *J* = 8.6 Hz, 2H), 6.27 (dd, *J* = 1.9, 3.2 Hz, 1H), 6.21 (d, *J* = 3.0 Hz, 1H), 5.66 (s, 1H), 4.52 (d, *J* = 15.4 Hz, 1H), 4.20 (d, *J* = 15.4 Hz, 1H), 2.25 (ddd, *J* = 2.8, 4.5, 7.4 Hz, 1H), 1.74 - 1.78 (m, 1H), 1.38 (s, 9H), 1.31 - 1.35 (m, 1H), 1.20 (ddd, *J* = 4.8, 9.4 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.3, 165.20 (d, *J* = 259.40 Hz, 1C), 148.9, 142.5 (+) , 132.97 (d, *J* = 2.93 Hz, 1C), 130.45 (+, d, *J* = 8.78 Hz, 1C), 116.16 (+, d, *J* = 22.69 Hz, 1C), 110.5 (+), 110.2 (+), 51.5, 47.0 (-), 36.9 (+), 28.9 (+), 25.9 (+), 13.9 (-); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -104.73 (tt, *J* = 8.0, 5.7 Hz, 1F); FT IR (KBr, cm^{-1}): 3387, 3021, 2969, 2867, 1645, 1593, 1493, 1337, 1155, 885, 734; HRMS (TOF ES): found 401.1535, calculated for $C_{24}H_{32}N_2O_3S$ (M + Li) 401.1523 (3.0 ppm).



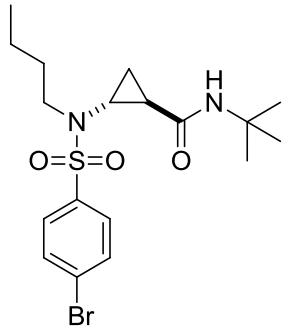
(1R*,2R*)-N-(tert-butyl)-2-(N-butyl-4-chlorophenylsulfonamido)cyclopropanecarboxamide (**98ajd**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butyl-4-chlorobenzenesulfonamide (**97jd**)[129] (33 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 11:1) mp 109-112 °C. Major: R_f 0.47 (major), 0.17 (minor), eluent

hexane/EtOAc 3:1. Yield 48 mg (0.126 mmol, 95%). ^{1}H NMR (400.13 MHz , $CDCl_3$) δ ppm 7.73 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 3.21 (ddd, *J* = 6.1, 9.6, 13.6 Hz, 1H), 3.04 (ddd, *J* = 5.6, 9.5, 13.7 Hz, 1H), 2.16 (ddd, *J* = 2.8, 4.5, 7.4 Hz, 1H), 2.00 (ddd, *J* = 2.8, 6.3, 9.2 Hz, 1H), 1.46 - 1.63 (m, 2H), 1.42 (s, 9H), 1.25 - 1.37 (m, 3H), 1.21 (ddd, *J* = 4.8, 9.4 Hz, 1H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.3, 139.7, 136.2, 129.5 (+, 2C), 129.1 (+, 2C), 128.6 (+, 2C), 128.0 (+. 2C), 55.4 (-), 51.4, 37.9 (+), 28.8 (+), 25.2 (+), 13.7; FT IR (KBr, cm^{-1}): 3386, 3087, 2962, 2871, 1645, 1547, 1475, 1352, 1259, 829, 739; HRMS (TOF ES): found 387.1506, calculated for $C_{24}H_{32}N_2O_3S$ (M + H) 387.1509 (0.8 ppm).



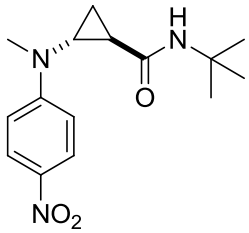
(1R*,2R*)-2-(N-benzyl-4-chlorophenylsulfonamido)-N-(tert-butyl)cyclopropanecarboxamide (**98ajf**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-benzyl-4-chlorobenzenesulfonamide (**97jf**)[130] (38 mg, 0.133 mmol, 1.0 equiv). Column chromatography on Silica gel afforded the title compound as a white solid (diastereomeric mixture 25:1) mp 88-92 °C, R_f = 0.17 (eluent hexane/EtOAc 3:1). Yield 41 mg (0.096 mmol, 72%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.30 - 7.37 (m, *J* = 2.5 Hz, 5H), 5.16 (s, 1H), 4.48 (d, *J* = 13.9 Hz, 1H), 4.05 (d, *J* = 13.9 Hz, 1H), 2.13 (ddd, *J* = 2.8, 4.7, 7.5 Hz, 1H), 1.36 - 1.40 (m, 1H), 1.32 (s, 9H), 1.14 - 1.24 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ ppm 169.4, 139.5, 135.7, 129.4 (+), 129.0 (+), 51.6,

51.2 (-), 37.3 (+), 30.2 (-), 28.9 (+), 25.7 (+), 20.1 (-), 13.7 (+), 13.4 (-); FT IR (KBr, cm^{-1}): 3332, 3031, 2966, 2867, 1645, 1546, 1496, 1336, 827, 739; HRMS (TOF ES): found 421.1341, calculated for $C_{24}H_{32}N_2O_3S$ (M + H) 421.1353 (2.8 ppm).

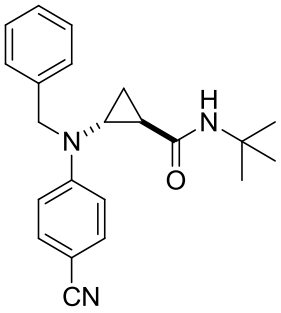


(1R*,2R*)-2-(4-Bromo-N-butylphenylsulfonamido)-N-(tert-butyl)cyclopropanecarboxamide (**98akd**): The reaction was performed according to the Typical Procedure II, employing bromocyclopropane **70a** (35 mg, 0.16 mmol, 1.2 equiv), 18-crown-6 (3.5 mg, 0.013mmol, 10 mol%), KOH (52 mg, 0.93 mmol, 7.0 equiv) and *N*-butyl-4-bromobenzenesulfonamide (**97kd**)[131] (39 mg, 0.13 mmol, 1.0 equiv). Column chromatography on Silica gel (eluent hexane/EtOAc 3:1) afforded two fractions. The major fraction (R_f 0.44) contained the title compound as a white solid, mp 101-103 °C. Yield 47.8 mg (0.11 mmol, 85%). Minor fraction (R_f 0.16) contained minute amounts (4.5 mg) of (1*R**,2*S**)-diastereomer. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.65 (s, 4 H), 5.82 (s, 1 H), 3.19 (ddd, *J* = 13.7, 9.8, 6.1 Hz, 1 H), 3.03 (ddd, *J* = 13.6, 9.6, 5.6 Hz, 1 H), 2.15 (ddd, *J* = 7.5, 4.5, 2.9 Hz, 1 H), 1.98 (ddd, *J* = 9.2, 6.3, 2.8 Hz, 1 H), 1.44 - 1.57 (m, 2 H), 1.40 (s, 9 H), 1.23 - 1.34 (m, 3 H), 1.15 - 1.23 (m, 1 H), 0.89 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ ppm 169.3, 136.1, 132.4 (+, 2C), 129.1 (+, 2C), 128.0, 51.5, 51.2 (-), 37.3 (+), 30.2 (-), 28.9 (+, 3C), 25.7 (+), 20.0 (-), 13.7 (+), 13.3 (-); FT IR (KBr, cm^{-1}): 3325, 2962, 2931, 2871, 1654, 1535, 1388, 1259, 1087, 821, 570; HRMS (TOF ES): found 453.0827, calculated for $C_{18}H_{27}N_2O_3SBrNa$ (M+Na) 453.0823 (0.9 ppm).

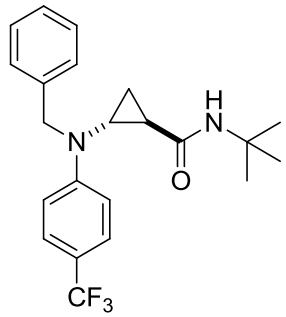
3.5.6. Aniline Adducts



(1R*,2R*)-N-(tert-Butyl)-2-(methyl(4-nitrophenyl)amino)cyclopropanecarboxamide (**100ab**), Typical Procedure IV: 10 mL Wheaton vial equipped with a magnetic stir bar, under dry nitrogen atmosphere was charged with THF (5 mL), powdered KOH (112 mg, 2.00 mmol), *N*-methyl-4-nitroaniline (**99b**) (228 mg, 1.50 mmol), 18-crown-6 (13 mg, 0.050 mmol) and 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**70a**) (110 mg, 0.50 mmol). This solution was stirred at 55 ^{o}C for 12h, then filtered through a fritted funnel and concentrated in vacuum. Purification by flash chromatography on silica gel (eluent hexane:EtOAc 3:1) afforded the title compound as yellow solid (R_f 0.18), yield 142 mg (0.49 mmol, 98%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.07 (d, *J* = 9.4 Hz, 2H), 6.76 (d, *J* = 9.4 Hz, 2H), 5.86 (s, 1H), 3.09 (s, 3H), 3.06 (ddd, *J* = 7.6, 4.8, 3.1 Hz, 1H), 1.56 (m, 2H), 1.44 (s, 9H), 1.22 (ddd, *J* = 4.4, 4.9, 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 169.5, 154.6, 138.1, 125.6 (+, 2C), 111.8 (+, 2C), 51.7, 40.6 (+), 38.0 (+), 29.0 (+, 3C), 27.1 (+), 16.3 (-); FT IR (NaCl, cm^{-1}): 3325, 2966, 2930, 2874, 1643, 1547, 1493, 1396, 1315, 1113, 831, 754; HRMS (TOF ES): found 290.1504, calculated for $C_{15}H_{20}N_3O_3$ (M-H) 290.1505 (0.3 ppm).

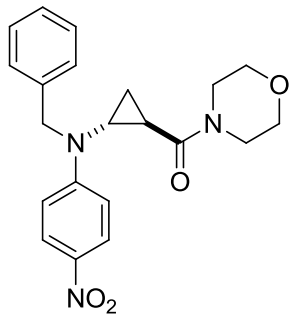


(1R*,2R*)-2-(Benzyl(4-cyanophenyl)amino)-N-(tert-butyl)cyclopropanecarboxamide (**100ac**): This compound was synthesized according to the typical procedure employing 2-bromo-*N*-(tert-butyl)cyclopropanecarboxamide (**70a**) (22 mg, 0.10 mmol), KOH (22 mg, 0.40 mmol), 18-crown-6 (2.6, 0.01 mmol), THF (1 mL), *N*-benzyl-4-cyanoaniline (**99c**)[132] (62 mg, 0.3 mmol). Column chromatography on silica gel eluting with hexane/EtOAc (3:1) afforded the title compound as pale yellow oil, R_f 0.28. Yield 32 mg (0.092 mmol, 92%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.43 (d, *J* = 9.0 Hz, 2H), 7.35 (m, 3H), 7.11 (d, *J* = 6.9 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 5.69 (s, 1H) 4.71 (d, *J* = 17.2 Hz, 1H) 4.62 (d, *J* = 17.2 Hz, 1H), 3.15 (ddd, *J* = 6.7, 4.8, 3.2 Hz, 1H), 1.55 (m, 2H), 1.41 (s, 9H), 1.20 (ddd, *J* = 8.7, 4.3, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ ppm 169.6, 152.2, 137.9, 133.3 (+, 2C), 128.9 (+, 2C), 127.4 (+), 126.0 (+, 2C), 113.7 (+, 2C), 99.7, 55.2 (-), 51.6, 40.3 (+), 29.0 (+, 3C), 26.9 (+), 16.0 (-). FT IR (NaCl, cm^{-1}): ν= 3338, 2964, 2927, 2871, 2216, 1644, 1605, 1546, 1435, 1383, 821, 737; HRMS (TOF ES): found 347.1993, calculated for $C_{22}H_{25}N_3O$ (M+H) 347.1998 (1.4 ppm).



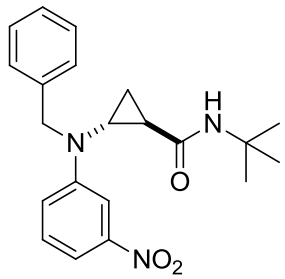
(1R*,2R*)-2-(benzyl(4-(trifluoromethyl)phenyl)amino)-N-(tert-butyl)cyclopropanecarboxamide (**100ad**): This compound was synthesized according to the typical procedure employing 2-bromo-*N*-(tert-butyl)cyclopropanecarboxamide (**70a**) (22 mg, 0.1 mmol), KOH (22 mg, 0.40 mmol), 18-crown-6 (2.6 mg, 0.01 mmol), THF (1 mL), *N*-benzyl-4-trifluoroaniline (**99d**)[132] (75 mg, 0.30 mmol). Column chromatography on silica gel

eluting with hexane/ EtOAc (3:1) afforded the title compound as white solid, mp 125-128 ^{o}C, R_f 0.45. Yield 25 mg (0.064 mmol, 65%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.46 (m, 2H), 7.33 (m, 2H), 7.29 (m, 1H), 7.16 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.54 (s, 1H), 4.72 (d, *J* = 17.1 Hz, 1H), 4.61 (d, *J* = 17.0 Hz, 1H), 3.14 (ddd, *J* = 7.7, 4.7, 3.1 Hz, 1H), 1.53 (m, 2H), 1.42 (s, 9H), 1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 169.8 , 151.6 , 138.6 , 130.9 , 128.8 (+, 2C), 127.2 (+), 126.3 (+, q, ^{3}J = 3.9 Hz, 2C), 126.2 (2C), 124.9 (q, ^{1}J = 270.3 Hz), 119.6 (q, ^{2}J = 32.5 Hz), 113.4 (+, 2C), 55.7 (-), 51.6 , 40.4 (+), 29.0 (+, 3C), 27.1 (+), 16.0 (-). FT IR (NaCl, cm^{-1}): 3315, 2964, 2929, 1730, 1643, 1556, 1454, 1393, 1325, 1226, 1111, 823, 725 cm; HRMS (TOF ES): found 391.2001, calculated for $C_{22}H_{26}N_2OF_3$ (M+H) 391.1997 (1.0 ppm).

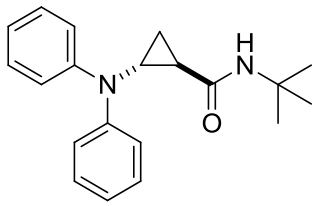


((1R*,2R*)-2-(benzyl(4-nitrophenyl)amino)cyclopropyl)(morpholino)methanone (**100be**): This compound was synthesized according to the typical procedure employing (2-bromocyclopropyl)(morpholino)methanone (**70b**) (23 mg, 0.10 mmol), KOH (22 mg, 0.40 mmol), 18-crown-6 (2.6, 0.01 mmol), THF (1 mL), and *N*-benzyl-4-nitroaniline (**99e**)[133] (68 mg, 0.3 mmol). Column chromatography on silica gel eluting with hexane/EtOAc (1:1) afforded the title compound as pale yellow oil, R_f 0.13. Yield 27 mg (0.071 mmol, 71%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 8.12 (d, *J* = 9.3 Hz, 2H), 7.36 (m, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 9.3 Hz, 2H), 4.81 (d, *J* = 17.3, 1H) 4.69 (d, *J* = 17.3, 1H), 3.78-3.63 (m, 6H), 3.53 (m, 2H), 3.37 (ddd, *J* = 2.9, 4.8, 7.6 Hz, 1H), 2.01 (ddd, *J* = 2.9, 5.8, 9.1 Hz, 1H), 1.65 (ddd, *J* = 5.39, 5.39, 7.20 1H), 1.35 (td, *J* = 5.0, 9.6 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ ppm

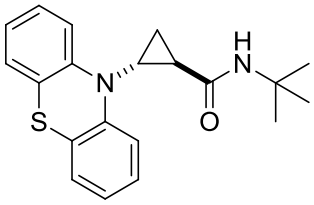
169.0, 154.1, 138.9, 137.6, 129.0 (+, 2C), 127.6 (+), 125.8 (+, 2C), 125.7 (+, 2C), 112.7 (+, 2C), 66.9 (-), 66.8 (-), 55.6 (-), 46.1 (-), 42.6 (-), 41.3 (+), 22.2 (+), 17.3 (-); HRMS (TOF ES): found 382.1784, calculated for $C_{21}H_{24}N_3O_4$ (M+H) 382.1767 (4.4 ppm).



(1R*,2R*)-2-(Benzyl(3-nitrophenyl)amino)-N-(tert-butyl)cyclopropanecarboxamide (**100af**): This compound was synthesized according to the typical procedure employing 2-bromo-N-(tert-butyl)cyclopropanecarboxamide (**70a**) (22 mg, 0.10 mmol), KOH (22 mg, 0.40 mmol), 18-crown-6 (2.6 mg, 0.01 mmol), THF (1 mL), *N*-benzyl-3-nitroaniline (**99e**)[134] (68 mg, 0.30 mmol). Column chromatography on silica gel eluting with hexane/EtOAc (3:1) afforded the title compound as yellow oil, R_f 0.26. Yield 18 mg (0.049 mmol, 50%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.79 (t, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.33 (m, 3H), 7.29 (m, 1H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.03 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.65 (s, 1H), 4.75 (d, *J* = 17.0 Hz, 1H), 4.62 (d, *J* = 17.1 Hz, 1H), 3.12 (m, 1H), 1.59 (m, 2H), 1.45 (s, 9H), 1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 169.3, 149.9, 138.0, 129.6 (+, 2C), 128.9 (+, 2C), 127.3 (+), 126.2 (+, 2C), 119.6 (+), 112.5 (+), 108.1 (+), 55.7 (-), 51.8, 40.4 (+), 29.0 (+, 3C), 27.4 (+), 15.7 (-); FT IR (KBr, cm^{-1}): 3336, 2964, 2929, 2869, 1642, 1605, 1549, 1447, 1381, 821, 736; HRMS (TOF ES): found 347.1993, calculated for $C_{22}H_{25}N_3O$ (M+) 347.1998 (1.4 ppm).



(1R*,2R*)-N-(tert-Butyl)-2-(diphenylamino)cyclopropanecarboxamide (**100ag**): This compound was synthesized according to the typical procedure employing 2-bromo-N-(tert-butyl)cyclopropanecarboxamide (**70a**) (55 mg, 0.25 mmol), powedered KOH (56 mg, 1.0 mmol), 18-crown-6 (6.6 mg, 0.025 mmol), THF (5 mL), and diphenyl amine (**99g**) (126 mg, 0.75 mmol). Crude mixture (dr 1.1:1) was concentrated in vacuum and treated with potassium *tert*-butoxide (112 mg, 1.0 mmol) in anhydrous THF (5 mL) at 80 ^{o}C for 12h, to improve the dr to 25:1. Flash column chromatography on silica gel afforded the title compound as white solid, mp 111.3 ^{o}C, R_f 0.27 (hexane/EtOAc 6:1). Yield 74 mg (0.24 mmol, 96%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.36 – 7.29 (m, 4H), 7.08 – 6.99 (m, 6H), 5.50 (s, 1H), 3.20 (ddd, *J* = 7.5, 4.8, 2.9 Hz, 1H), 1.04 (ddd, *J* = 8.6, 4.8 Hz, 1H), 1.43 – 1.39 (m, 9H), 1.53 (ddd, *J* = 7.2, 5.4 Hz, 1H), 1.50 – 1.46 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 170.1, 147.3, 129.2 (+, 4C), 122.3 (+, 2C), 121.4 (+, 4C), 51.5, 40.6 (+), 29.0 (+, 3C), 27.6 (+), 16.5 (-). FT IR (NaCl, cm^{-1}): 3325, 3057, 3044, 2966, 2930, 1647, 1591, 1500, 1456, 1394, 1364, 1313, 1248, 1224, 748; HRMS (TOF ES): found 308.1880, calculated for $C_{20}H_{24}N_2O$ (M+) 308.1889 (2.9 ppm).



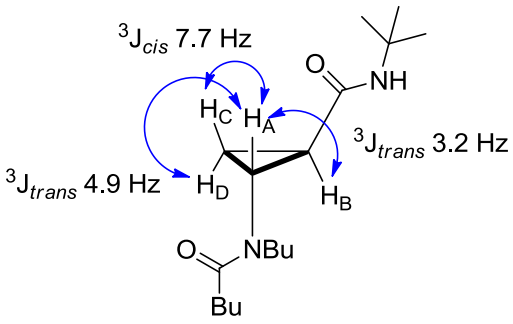
(1R*,2R*)-N-(tert-butyl)-2-(10H-phenothiazin-10-yl)cyclopropanecarboxamide (**100ah**): This compound was prepared according to the typical procedure employing 2-bromo-*N*-(tert-butyl)cyclopropanecarboxamide (**70a**) (55 mg, 0.25 mmol), powdered KOH (56 mg, 1.0 mmol), 18-crown-6 (6.6 mg, 0.025 mmol), THF (5 mL), and 10*H*-phenothiazine (**99h**) (149 mg, 0.75

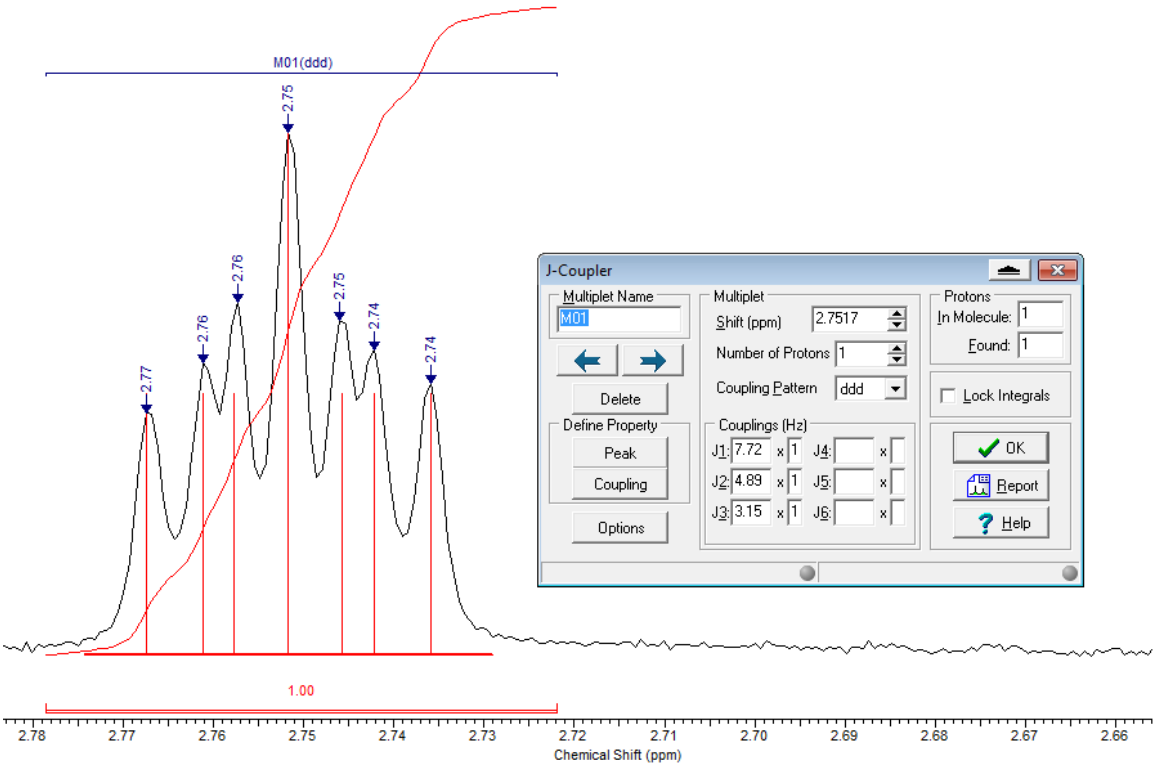
mmo l). Crude reaction mixture (dr 3.5:1) was concentrated in vacuum and treated with potassium *tert*-butoxide (112 mg, 1.00 mmol) in anhydrous THF (5 mL) at 80 ^{o}C for 12h to improve dr to 49:1. Purification by flash chromatography on silica gel (eluent hexane:EtOAc 8:1) afforded the title compound as white solid, mp 187-188 ^{o}C, R_f 0.52. Yield 50 mg (0.148 mmol, 59%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ ppm 7.24 – 7.12 (m, 4H), 6.98 (t, *J* = 8.0 Hz, 2H), 5.57 (s, 1H), 3.29 (ddd, *J* = 7.2, 4.7, 2.9 Hz, 1H), 1.83 (ddd, *J* = 6.7, 5.8, 4.9 Hz, 1H), 1.57 (ddd, *J* = 5.8, 2.9 Hz, 1H), 1.20 (ddd, *J* = 9.3, 4.8 Hz, 1H). ^{13}C NMR (100.61 MHz, CDCl3) δ ppm 169.8, 127.2, 127.1, 122.93, 51.6, 35.4, 29.0, 28.5, 18.1; FT IR (NaCl, cm^{-1}): 3358, 2992, 2961, 1649, 1542, 1461, 1374, 1367, 1250, 1129, 825, 750; HRMS (TOF ES): found 339.1528, calculated for $C_{20}H_{23}N_2OS$ (M+H) 339.1531 (0.9 ppm).

Appendix

A.1. Assignment of Relative Configurations by ^{1}H NMR

The relative configuration of compound **94abd** was assigned based on analysis of the coupling constants in the multiplet at 2.75 ppm. Albeit severe broadening of the resonance lines complicated the analysis, careful optimization of the sample temperature allowed for obtaining of an acceptable resolution in DMSO-d6 at 370 K (97 ^{o}C). Further improvement of the line resolution was achieved by applying Lorentzian-Gaussian Windows Function (LB = -1, GF = 0.5) prior to the Fourier Transform. Coupling constant values were determined by multiplete simulation using ACD/SpecManager 11.01. The observation of two *trans*-^{3}J coupling constants (3.15 Hz, 4.89 Hz) and only one *cis*-^{3}J coupling constant (7.72 Hz) allowed for unambiguous assignment of the *trans*-configuration to product **94abd**.


$^3J_{cis}$ 7.7 Hz
$^3J_{trans}$ 3.2 Hz
$^3J_{trans}$ 4.9 Hz
O
NH
H_C
H_A
H_D
H_B
O
NBu
Bu


M01(ddd)
2.75
2.77
2.76
2.76
2.75
2.74
2.74
1.00
2.78
2.77
2.76
2.75
2.74
2.73
2.72
2.71
2.70
2.69
2.68
2.67
2.66
Chemical Shift (ppm)
J-Coupler
Multiplet Name
M01
Delete
Define Property
Peak
Coupling
Options
Multiplet
Shift (ppm)
2.7517
Number of Protons
1
Coupling Pattern
ddd
Couplings (Hz)
J1: 7.72 x 1
J2: 4.89 x 1
J3: 3.15 x 1
J4:
J5:
J6:
Protons
In Molecule: 1
Found: 1
Lock Integrals
OK
Report
Help

A.2. Crystallographic Data

Colorless parallelepiped-shaped crystals of $C_{25}H_{24}F_6N_2O_3$ are, at 100(2) K, monoclinic, space group $P2_1/c - C_{2h}^5$ (No. 14)[135] with a = 15.679(9) Å, b = 16.496(10) Å, c = 8.969(5) Å, β = 95.185(11)°, V = 2310(2) $Å^3$ and Z = 4 molecules {dcalcd = 1.479 g/cm^3; μ_a(MoKα) = 0.130 mm^{-1}}. A full hemisphere of diffracted intensities (1850 10-second frames with a ω scan width of 0.30°) was measured for a 2-domain specimen using graphite-monochromated MoKα radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System.[136] The second domain accounted for 41% of the crystal volume and was rotated by 180° about the a axis of the unit cell for the major domain. X-rays were provided by a fine-focus sealed x-ray tube operated at 50 kV and 30 mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 3072 reflections. A total of 3875 unique integrated reflection intensities having 2θ((MoKα)< 50.00° and a coverage which was 95.1% complete were produced using the Bruker program SAINT;[137] 27.4% of the reflections had two twin components and the rest had just one. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.914 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package.[138] The final structural model took the 2-domain twinning into account and incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were included in the structural model as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atoms and C-H bond lengths of 0.95 – 1.00 Å). The isotropic

thermal parameters of all hydrogen atoms were fixed at values 1.2 times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded. A total of 326 parameters were refined using no restraints, 3875 data and weights of $w = 1/[\sigma^2(F^2) + (0.1314P)^2 + 1.8112P]$, where $P = [F_o^2 + 2F_c^2]/3$. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.089 for 2972 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 50.00°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.113 and wR_2(weighted, based on F^2) = 0.244 for 3875 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 50.00°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.85 and -0.61 $e^-/Å^3$, respectively.

Table 14 Atomic coordinates (Å) and equivalent isotopic factors ($Å^2$) for diamide **95bmg**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
F1	0.03357(15)	0.29620(15)	0.3107(5)	0.0911(12)
F2	0.1009(3)	0.30901(18)	0.1232(4)	0.1169(16)
F3	0.16018(15)	0.25784(14)	0.3149(4)	0.0724(9)
F4	0.00448(19)	0.60552(18)	0.1745(3)	0.0730(9)
F5	-0.0232(2)	0.60032(19)	0.3928(4)	0.0831(10)
F6	0.07646(18)	0.67539(14)	0.3336(6)	0.144(2)
O1	0.13519(14)	0.55382(14)	-0.2558(3)	0.0315(6)
O2	0.28798(15)	0.72017(13)	0.1247(3)	0.0357(6)
O3	0.35411(14)	0.44771(14)	0.6035(3)	0.0333(6)
N1	0.37900(16)	0.56393(16)	0.4826(3)	0.0264(6)
N2	0.22643(19)	0.61286(16)	0.0056(3)	0.0313(7)
C1	0.3620(2)	0.62182(19)	0.3643(4)	0.0270(7)
H1	0.3336	0.6733	0.3918	0.032
C2	0.4281(2)	0.6297(2)	0.2565(4)	0.0310(8)
H2A	0.4780	0.5928	0.2687	0.037
H2B	0.4407	0.6847	0.2203	0.037
C3	0.3419(2)	0.59320(19)	0.2052(4)	0.0260(7)
H3	0.3391	0.5335	0.1866	0.031
C4	0.2827(2)	0.64657(19)	0.1094(4)	0.0273(7)
C5	0.2018(2)	0.52773(19)	-0.0082(4)	0.0298(7)
H5A	0.1467	0.5193	0.0353	0.036
H5B	0.2457	0.4937	0.0479	0.036
C6	0.1930(2)	0.5029(2)	-0.1699(4)	0.0304(7)
H6A	0.2498	0.5054	-0.2098	0.036
H6B	0.1725	0.4462	-0.1782	0.036
C7	0.1646(2)	0.6352(2)	-0.2485(4)	0.0327(8)
H7A	0.1248	0.6698	-0.3124	0.039
H7B	0.2218	0.6383	-0.2870	0.039
C8	0.1702(2)	0.6655(2)	-0.0902(4)	0.0376(9)
H8A	0.1929	0.7215	-0.0861	0.045
H8B	0.1124	0.6663	-0.0541	0.045
C9	0.4561(2)	0.5791(2)	0.5853(4)	0.0306(8)
H9A	0.5004	0.6052	0.5295	0.037
H9B	0.4794	0.5267	0.6248	0.037
C10	0.4368(2)	0.6329(2)	0.7147(4)	0.0296(8)
H10A	0.4129	0.6852	0.6760	0.035
H10B	0.3937	0.6065	0.7727	0.035
C11	0.51772(19)	0.64782(18)	0.8143(3)	0.0234(7)
C12	0.5330(2)	0.60544(19)	0.9452(4)	0.0285(7)
H12	0.4911	0.5686	0.9746	0.034
C13	0.6087(2)	0.6156(2)	1.0351(4)	0.0351(8)
H13	0.6188	0.5859	1.1257	0.042
C14	0.6698(2)	0.6696(2)	0.9919(4)	0.0375(9)
H14	0.7224	0.6762	1.0521	0.045
C15	0.6545(2)	0.7131(2)	0.8635(4)	0.0347(8)
H15	0.6957	0.7510	0.8354	0.042
C16	0.5793(2)	0.7021(2)	0.7741(4)	0.0296(7)
H16	0.5694	0.7321	0.6838	0.036
C17	0.3309(2)	0.49846(19)	0.5094(3)	0.0249(7)
C18	0.24389(19)	0.48842(19)	0.4250(3)	0.0237(7)
C19	0.2176(2)	0.41142(19)	0.3843(4)	0.0268(7)
H19	0.2561	0.3672	0.4017	0.032
C20	0.1365(2)	0.39775(19)	0.3190(4)	0.0254(7)
C21	0.0784(2)	0.46126(19)	0.2954(3)	0.0263(7)
H21	0.0220	0.4516	0.2509	0.032
C22	0.10391(19)	0.5380(2)	0.3375(3)	0.0263(7)
C23	0.18691(19)	0.55252(19)	0.4007(3)	0.0240(7)
H23	0.2045	0.6061	0.4272	0.029
C24	0.1083(2)	0.3150(2)	0.2666(5)	0.0400(9)
C25	0.0431(2)	0.6063(2)	0.3113(4)	0.0326(8)

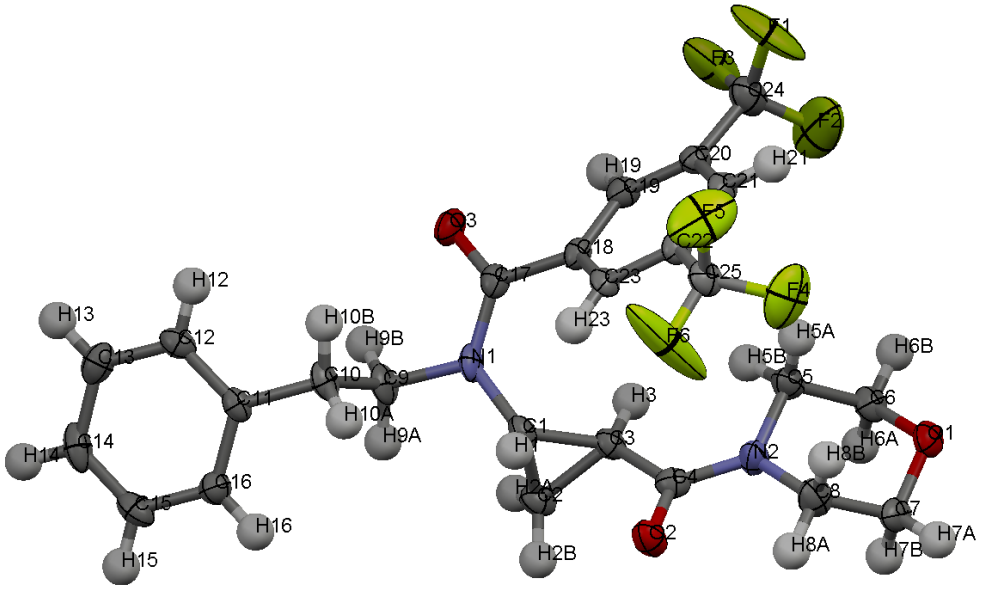


Figure 9. ORTEP drawing of diamide **95bmg** molecule, showing the atom numbering scheme; 50% probability amplitude displacement ellipsoids are shown.

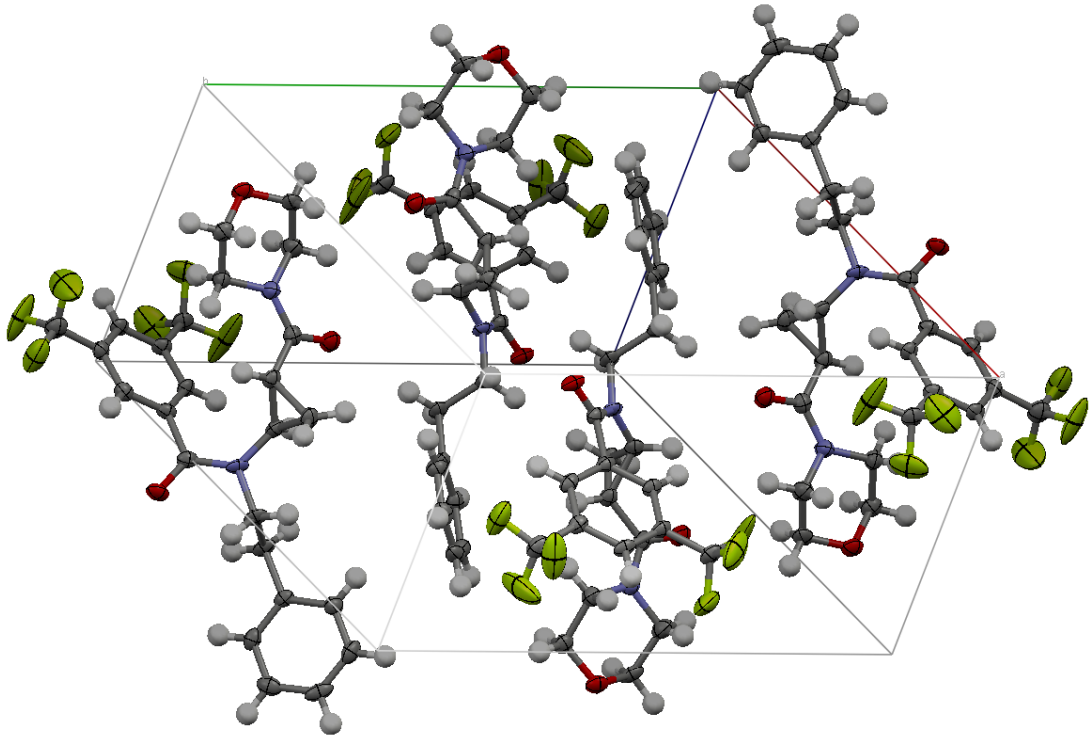


Figure 10. Packing of diamide **95bmg** molecules in the crystalline lattice cell.

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