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Formal Substitution of Bromocyclopropanes with Nitrogen Nucleophiles

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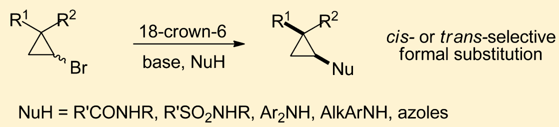
Supporting Information

ABSTRACT: A highly chemo- and diastereoselective protocol toward amino-substituted donor−acceptor cyclopropanes via the formal nucleophilic displacement in bromocyclopropanes is described. A wide range of *N*-nucleophiles, including carboxamides, sulfonamides, azoles, and anilines, can be efficiently employed in this transformation, providing expeditious access to stereochemically defined and densely functionalized cyclopropylamine derivatives.



■ INTRODUCTION

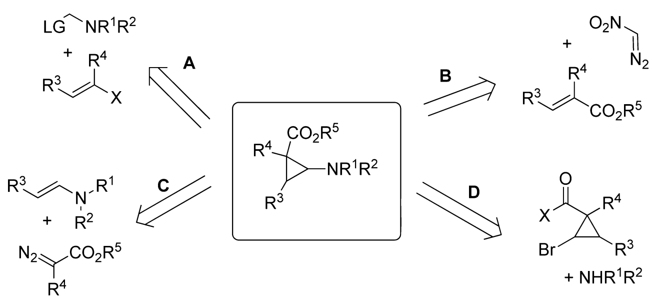
β-Aminocyclopropanecarboxylic acid derivatives (*β*-ACCs)[1] are important members of a versatile and synthetically challenging family of donor−acceptor cyclopropanes (DAC).[2] *β*-ACCs have been recognized for their ability to produce surprisingly stable secondary structures even in short peptides,[3−5] and served as useful tools for conformational analysis.[4a,6] They have also been used as key elements in natural products,[7] organocatalysts,[8] and prospective drug candidates,[6,9] including potent antiviral,[10] antitumor,[11] and antihypertensive agents.[12] In contrast to a plethora of natural and synthetic analogues of *α*-aminocyclopropanecarboxylic acid (*α*-ACC), which have been extensively exploited in medicinal, chemical, and agricultural research,[13] synthesis of many *β*-ACC analogues faces a number of difficulties and limitations. The problem associated with stability of the three-membered ring in heteroatom-substituted "push−pull" cyclopropanes,[14] narrows the access to these structural motifs and limits their further use in the assembly of complex architectures.[15] As a result, substituted aminocyclopropane carboxylic acids possessing an additional stabilizing carboxylic group in the three-membered unit have been commonly used as more available *β*-ACC surrogates.[3−15]

We have recently communicated a convergent synthesis of racemic *trans*-*β*-ACC diamides[16] and *N*-cyclopropylheteroaryls[17] via a formal nucleophilic substitution of bromocyclopropanes. Herein, we wish to report a full account of this methodology that has evolved into a general approach to a broad spectrum of *N*-cyclopropyl derivatives including carboxamides, heterocycles, sulfonamides, and anilines. Factors affecting the reactivity of the nucleophilic components and modes for controlling the stereoselectivity of the addition are discussed.

■ RESULTS AND DISCUSSION

Carboxamides as *N*-Based Nucleophiles. The *β*-ACC core is usually assembled via the following routes (**A**−**C**, Scheme 1): Michael-initiated ring closure reactions (route **A**),[18]

Scheme 1



[2 + 1]-cyclopropanation of acrylates with *α*-nitrodiazo compounds (route **B**),[19] and more rarely, diazo transfer onto enamines (route **C**).[20] Approaches that allow direct and efficient installation of an amine function in a pre-existing three-membered ring remain scarce;[21] most earlier attempts on the addition of *N*-nucleophiles to cyclopropenes resulted in cleavage of the small ring.[22] Prior to our studies, a few examples of formal nucleophilic substitution of halocyclopropanes with *N*-based nucleophiles have been reported (route **D**), which proceeded readily only with unsubstituted cyclopropyl halides, or in the presence of vicinal electron-withdrawing groups.[21d,23,24]

Recently, we reported a method for direct addition of oxygen and sulfur-based nucleophiles to cyclopropenes generated in situ via 1,2-dehydrobromination of bromocyclopropanes.[25,26] To access *β*-ACC derivatives through this methodology, we tested a series of different amines as *N*-pronucleophiles; however, our initial attempts to induce addition of ammonia, as well as primary and secondary amines, were unsuccessful. Moreover, we discovered that amino alcohols and amino thiols can be employed as *O*- and *S*-nucleophiles, respectively, in highly chemo- and diastereoselective reactions with bromocyclopropanes **1a**,**b** and **4a** (Schemes 2 and 3).[26b]

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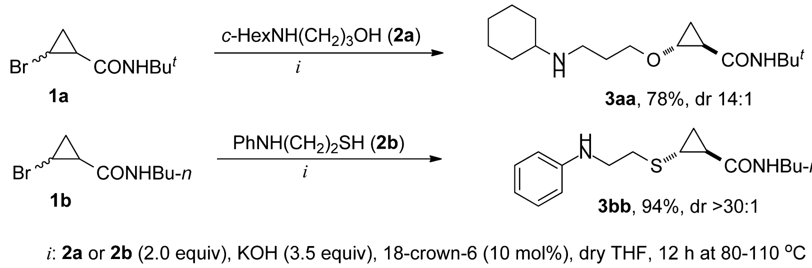
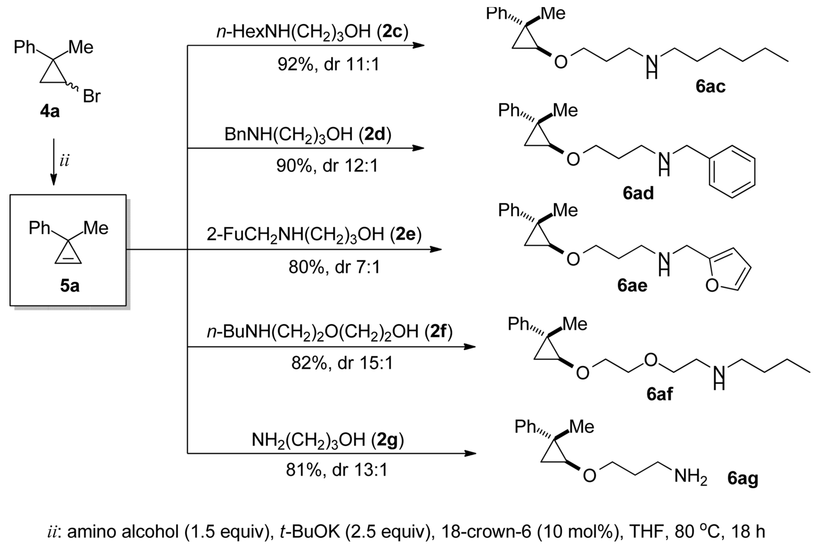
Scheme 2



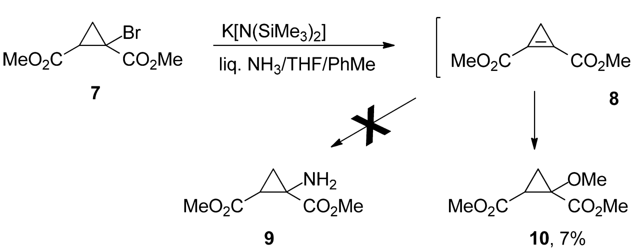
Scheme 3



Such high chemoselectivity was attributed to selective deprotonation of the more acidic alcohol or thiol functions in the presence of a relatively weak base, which rendered these moieties more nucleophilic as compared to less acidic 1° or 2° amines.[27] As we have demonstrated previously,[26] success in the formal substitution reaction is strongly dependent on a fine balance between basicity and nucleophilicity of the reactive species, which creates certain limitations. Thus, soft nucleophiles with decreased basicity, like phenolates and thiolates, can produce a buffer with the base, inhibiting the dehydrohalogenation reaction. On the other hand, generation of a nucleophilic species via deprotonation of less acidic pronucleophiles, such as amines, is suppressed, which explains the observed lack of reactivity.

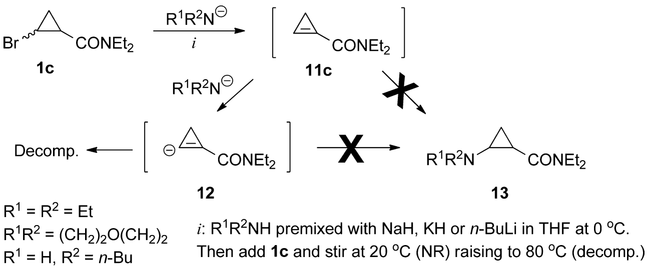
Since the inertness of *N*-nucleophiles was apparently related to their insufficient acidity, the following solutions to circumvent this problem were put forth: (a) use of stronger bases or (b) installation of electron-withdrawing activating groups to enhance N−H deprotonation or employment of other acidic amine surrogates. The first idea was previously evaluated by Taylor,[23d] who attempted synthesis of amino acid derivative **9** via dehydrobromination of bromocyclopropane **7** in the presence of $K[N(SiMe_3)_2]$, followed by trapping of intermediate cyclopropene **8** with ammonia (Scheme 4). This approach proved inefficient, leading to the formation of methoxycyclopropane **10** in low yields as the only isolable product. The methoxide nucleophile in this case was generated in the reaction mixture via a base-assisted hydrolysis of the methyl ester function.[23d]

Scheme 4



We have previously demonstrated that conversion of bromocyclopropylcarboxylic acid precursors into carboxamides helped alleviate problems associated with intolerance of sensitive ester functionalities toward strong bases at higher temperatures, often required for generation of cyclopropenes via 1,2-elimination.[26b,28] Nonetheless, our initial attempts to react cyclopropylcarboxamide **1c** with various alkali dialkylamides, generated from 1° or 2°, amines proved unsuccessful (Scheme 5). In all cases the consumption of the starting material was very sluggish and, when forced by heating, substrates decomposed, providing no isolable products. We believe that such outcome can be rationalized as follows. Intermediate **11c** possessing an acidic $C(sp^2)$−H bond reacts with basic amide species as an acid rather than electrophile.[29] As a result, deprotonation leads to the formation of anionic species **12** as a resting state, in which the double bond has reduced electrophilicity, rendering the subsequent reaction with a nucleophile impossible. Thus, the reaction poses two contradicting requirements: a weaker base must be employed

Scheme 5

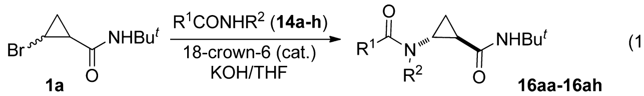


to avoid inhibition of the electrophilic species, while a stronger base is needed for *N*-nucleophile activation. To overcome this problem, we turned to an alternative method for activating the reaction by employing more acidic *N*-pronucleophiles bearing electron-withdrawing substituents. First, we probed the reaction in the presence of *N*-methylacetamide (NMA, **14aa**).

Gratifyingly, nucleophilic attack by NMA at the double bond of the generated in situ cyclopropene (**5a**)[28,30] afforded *trans*-cyclopropylamine derivative **15aaa** in good yield and high diastereoselectivity, which was controlled by sterics (Scheme 6). Encouraged by these results, we tested the reactivity of NMA toward unstable conjugated cyclopropene **11a**,[31] generated via 1,2-elimination of bromocyclopropane **1a** (Scheme 6) under conditions previously employed for reactions with *O*-nucleophiles.[26] To our delight, trapping of **11a** with NMA proceeded efficiently affording a high yield of *trans*-diamide **16aaa**, with diastereoselectivity controlled by thermodynamically driven epimerization of the α-CH center.[26a]

Next, we investigated the formal nucleophilic substitution reaction with carboxamides **14ba**−**14ed** possessing substituents with variable steric demands. It was found that increased steric hindrance at the *N*- or *C*-termini of the pronucleophile had a profound adverse effect on the reaction course. Thus, amides bearing secondary alkyl substituents significantly decreased the reaction's efficacy (entries 3, 4), while substrates with tertiary alkyl groups at either terminus did not undergo the addition at all (entries 5, 6). We reasoned that the effective nucleophilicity of the sterically hindered amide species (which in this process correlates with N−H acidity) can be enhanced by tuning their electronic properties. To test this idea, we substituted an alkyl group at the *C*-terminus of the pronucleophile with a more electron-deficient phenyl ring. Along with our expectations, the reaction between bromocyclopropane **1a** and benzamides **14fa** and **14fd** afforded the corresponding diamides **16afa** and **16afd** with high yields and excellent diastereoselectivities (Table 1, entries 7, 8). To further unveil the important role of electronic factors, we tested **1a** against a series of differently substituted

Table 1. Steric Effect in the Formal Substitution of Bromocyclopropane 1a with Secondary Amides



no.	R^1	R^2	NuH	product[a]	yield,[b] %	dr[c]
1	Me	Me	**14aa**	**16aaa**	88	11:1
2	*n*-Pr	*n*-Bu	**14bd**	**16abd**	51	25:1
3	*n*-Pr	*i*-Pr	**14bc**	**16abc**	28[d]	25:1
4	*i*-Pr	*n*-Bu	**14 cd**	**16acd**	31[d]	17:1
5	*n*-Bu	^{t}Bu	**14de**	**16ade**	nr[e]	
6	^{t}Bu	*n*-Bu	**14ed**	**16aed**	nr	
7	Ph	Me	**14fa**	**16afa**	75	>25:1
8	Ph	*n*-Bu	**14fd**	**16afd**	72	>25:1

[a]Reactions performed in 0.5 mmol scale. [b]Isolated yields of diastereomeric mixtures unless specified otherwise. [c]Diastereomeric ratio (trans:cis) determined by GC or ^{1}H NMR analyses of crude reaction mixtures. [d]NMR yields determined by analyses of crude reaction mixtures. Bromocyclopropane **1a** was consumed completely. [e]No reaction.

N-butylbenzamides **14gd**−**md** (Table 2). Remarkably, introduction of an electron-donating *p*-MeO group resulted in no reaction (Table 2, entry 2); however, 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- (**16ald**, entry 7) and 3,5-bis(CF_3)$_2$-substituted aryl groups (**16amd**, entry 8). It should be mentioned that no diamide product **17** was obtained in the reaction with primary amide *p*-$CF_3C_6H_4CONH_2$ (**20**) despite complete consumption of the bromocyclopropane **1a**. We failed to detect any cyclopropane-containing products in this reaction; instead, a complete conversion of starting material into aldehyde **21** was observed in GC/MS analysis of the crude reaction mixture. We propose the following rationale to account for the distinct reactivity of primary carboxamides (Scheme 7). Addition of primary amide pronucleophile **20** to cyclopropene **11a** produces secondary diamide **17**, the high N−H acidity of which is additionally enhanced by the adjacent electron-deficient aromatic ring. As a result, it undergoes facile base-assisted deprotonation under our typical reaction conditions to give an activated DAC species **18** with relatively high electron density on the nitrogen atom. Subsequent facile cleavage of the small ring gives rise to linear acylimine **19**, which after hydrolysis affords aldehyde **21** and regenerates primary amide **20**. In contrast, adducts of secondary amide

Scheme 6

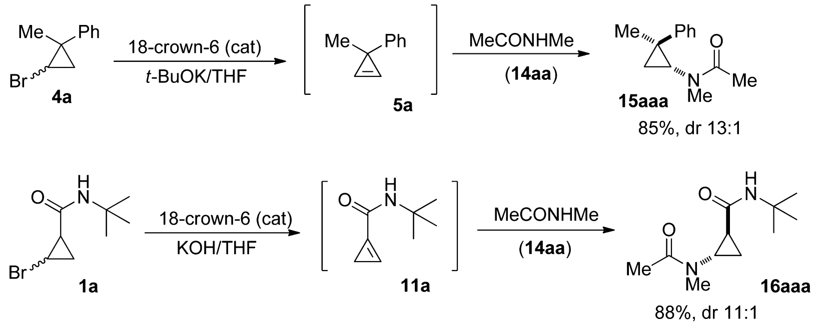


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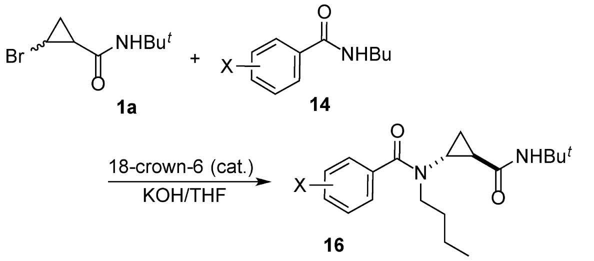
Table 2. Electronic Effect in the Formal Substitution of Bromocyclopropane 1a with Secondary Benzamides



(2)

no.	X–C_6H_4–	NuH	product[a]	yield,[b] %	dr[c]
1	Ph	**14fd**	**16afd**	72	>25:1
2	*p*-$MeOC_6H_4$	**14gd**	**16agd**	nr[d]	
3	*o*-ClC_6H_4	**14hd**	**16ahd**	80[e]	>25:1
4	*p*-ClC_6H_4	**14id**	**16aid**	81	>25:1
5	*p*-CNC_6H_4	**14jd**	**16ajd**	80	>25:1
6	*p*-$NO_2C_6H_4$	**14kd**	**16akd**	80	>25:1
7	*p*-$CF_3C_6H_4$	**14ld**	**16ald**	85	>25:1[f]
8	3,5-$(CF_3)_2C_6H_3$	**14md**	**16amd**	87	>25:1[f]

[a]Typical reaction conditions: bromocyclopopane **1a** (0.5 mmol), amide **14** (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]Diastereomeric ratio (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]No reaction. [e]NMR yields determined by analysis of a crude reaction mixture. [f]Diastereomeric ratio (trans:cis) determined by ^{19}F NMR analysis of crude reaction mixtures.

pronucleophiles **16** do not possess acidic N–H bond and therefore are stable toward ring-opening.

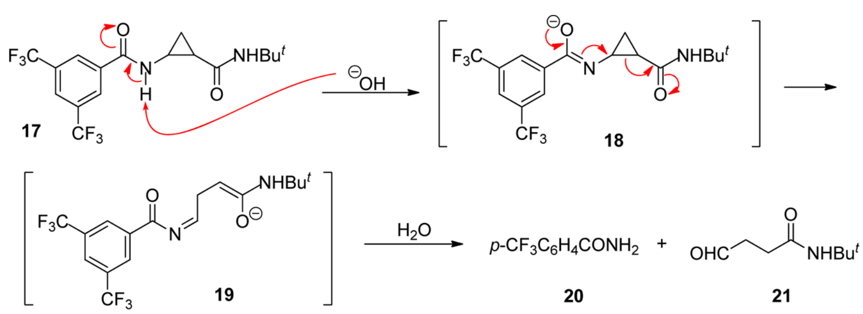
The described methodology can potentially serve as a convenient route for convergent synthesis of a large number of conformationally constrained *trans*-cyclopropyl amino acid derivatives (Scheme 8). A variety of fragments can be introduced with the possibility for a three-dimensional diversification. The readily available acyl chloride **22** can be converted into an array of amides **1** by varying primary or secondary amines **23**. At the same time, a variety of pronucleophiles **14** can be obtained from primary amines **25** and different carboxylic acids **24**. As shown above, amides **14** derived from linear aliphatic and electron-deficient benzoic acids **19** provide the highest yields in this transformation (Tables 1 and 2). Installation of the CF_3 groups in the benzamide derivatives **14ld** and **14md** improved solubility in organic solvents and significantly facilitated isolation and purification of the corresponding products **16ald** and **16amd**. Another benefit of the presence of fluorine is the possibility to use ^{19}F NMR to assess stereoselectivity in the product mixtures, since ^{1}H NMR was inapplicable due to severe line broadening resulting from slow conformational rotation. Accordingly, CF_3-substituted benzamides were chosen for more detailed investigation of the scope and limitations of this reaction. It was found that *p*-CF_3-substituted benzamides possessing primary *N*-alkyl groups undergo efficient nucleophilic addition to give *n*-octyl- (**16ale**), benzyl- (**16alf**), and 2-phenethyl benzamides (**16alg**) in high yields and perfect diastereoselectivities (Table 3, entries 1–3). At the same time, nucleophilic addition of a more sterically hindered *N*-cyclohexyl 4-(trifluoromethyl)benzamide (**14lh**) proceeded sluggishly, resulting in marginal yield of the corresponding diamide **16alh** (Table 3, entry 4). In contrast, amides **14mc** and **14mg–mi** derived from 3,5-bis(trifluoromethyl)benzoic acid reacted with bromocyclopropane **1a** much more readily. Improved product yields were obtained not only for the less sterically hindered derivative **16amg** (Table 3, entry 8) but also for more challenging bulky products **16amh**, **16amc**, and **16ami** (entries 5–7), bearing secondary *N*-alkyl substituents. However, very bulky *N*-*tert*-butylamide **14me** did not provide any product in the reaction with **1a** (entry 9).

The scope of the cyclopropylcarboxamides **1** was also investigated. Bromocyclopropylcarboxamide derivatives of piperidine (**1d**), morpholine (**1e**), and cyclohexylamine (**1f**) afforded diamides **16dmg**, **16dmf**, **16emg**, and **16fmh** in good to high yields (Table 3, entries 10–13). Weinreb amide **1g** was also tested in this reaction; however, the corresponding product **16gmf** was obtained in 31% yield only, presumably due to a decreased stability of the intermediate cyclopropene species (Table 3, entry 14). Derivatives of 4-nitro- (**14kf**, **14kj**) and 4-cyanobenzoic (**14jf**, **14jk**) acids were also successfully employed for activation of benzylamine and hetarylmethylamines (Table 3, entries 15–18).

Similarly to the previously reported formal nucleophilic substitution reaction with alkoxides and phenoxides,[26] the trans stereoselectivity in the described transformation was a result of a base-assisted epimerization of the α-carbon. However, additional treatment of the reaction mixture with ^{t}BuOK was not required in this case,[26] as the thermodynamically more favored *trans*-diastereomer was produced exclusively under the standard reaction conditions. Trans configuration of diamide **16emg** was unambiguously assigned by X-ray crystallography .[32]

Sulfonamides as *N*-Based Nucleophiles. Sulfonamides are broadly employed as N–H acidic surrogates of amines in various C–N bond forming processes, such as classical nucleophilic displacement reactions[33] (including Mitsunobu

Scheme 7



Scheme 8

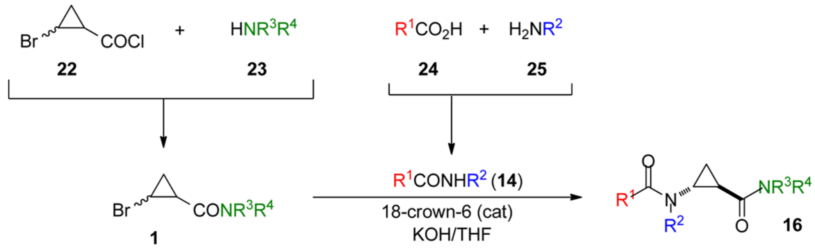


Table 3. Convergent Approach to Conformationally Constrained *trans*-Cyclopropyl Amino Acid Derivatives via Formal Substitution of Bromocyclopropanes with Nucleophilic Carboxamides

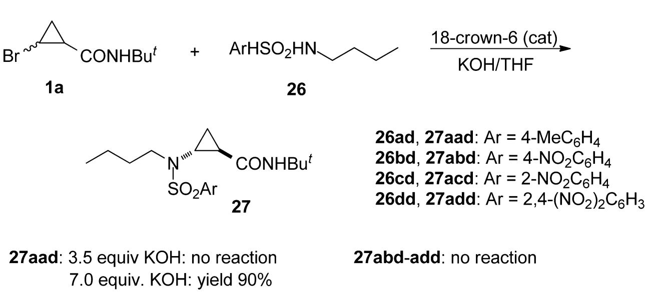
	R^3, R^4 (**1**)	R^1	R^2	14	16	yield,[a] %
1	^{t}Bu, H (**1a**)	p-$CF_3C_6H_4$	n-Oct	**14le**	**16ale**	85
2	^{t}Bu, H (**1a**)	p-$CF_3C_6H_4$	$PhCH_2$	**14lf**	**16alf**	80
3	^{t}Bu, H (**1a**)	p-$CF_3C_6H_4$	$Ph(CH_2)_2$	**14lg**	**16alg**	82
4	^{t}Bu, H (**1a**)	p-$CF_3C_6H_4$	c-Hex	**14lh**	**16alh**	45
5	^{t}Bu, H (**1a**)	3,5-$(CF_3)_2C_6H_3$	c-Hex	**14mh**	**16amh**	83
6	^{t}Bu, H (**1a**)	3,5-$(CF_3)_2C_6H_3$	i-Pr	**14mc**	**16amc**	61
7	^{t}Bu, H (**1a**)	3,5-$(CF_3)_2C_6H_3$	c-Pr	**14 mi**	**16ami**	59
8	^{t}Bu, H (**1a**)	3,5-$(CF_3)_2C_6H_3$	$Ph(CH_2)_2$	**14 mg**	**16amg**	94
9	^{t}Bu, H (**1a**)	3,5-$(CF_3)_2C_6H_3$	^{t}Bu	**14me**	**16ame**	
10	$-(CH_2)_5-$ (**1d**)	3,5-$(CF_3)_2C_6H_3$	$Ph(CH_2)_2$	**14mg**	**16dmg**	76
11	$-(CH_2)_2O(CH_2)-$ (**1e**)	3,5-$(CF_3)_2C_6H_3$	$Ph(CH_2)_2$	**14mg**	**16emg**	76
12	c-Hex, H (**1f**)	3,5-$(CF_3)_2C_6H_3$	c-Hex	**14mh**	**16fmh**	66
13	$-(CH_2)_5-$ (**1d**)	3,5-$(CF_3)_2C_6H_3$	$PhCH_2$	**14mf**	**16dmf**	68
14	Me, OMe (**1g**)	3,5-$(CF_3)_2C_6H_3$	$PhCH_2$	**14mf**	**16gmf**	31
15	^{t}Bu, H (**1a**)	4-$NO_2-C_6H_4$	$PhCH_2$	**14kf**	**16akf**	63
16	^{t}Bu, H (**1a**)	4-$NO_2-C_6H_4$	$ThCH_2$[b]	**14kj**	**16akj**	52
17	^{t}Bu, H (**1a**)	4-CN-C_6H_4	$PhCH_2$	**14jf**	**16ajf**	47
18	^{t}Bu, H (**1a**)	4-CN-C_6H_4	$FuCH_2$[c]	**14jk**	**16ajk**	81

[a]Isolated yields. In all cases diastereomeric ratio (trans:cis) > 25:1 was obtained. [b]Th = 2-thienyl. [c]Fu = 2-furyl.

coupling),[33,34] conjugate addition,[35] and transition metal catalyzed coupling involving both C−Hal[36] and C−H bond activation.[37] Having met success with reaction of carboxamides, we focused on extending this methodology to the synthesis of β-ACC sulfonamide derivatives via a formal substitution of bromocyclopropanes with nucleophilic sulfonamide species. Initial attempts to employ sulfonamide nucleophile **26ad** under the reaction conditions previously optimized for addition of carboxamides resulted in recovery of bromocyclopropane **1a** (Scheme 9). We rationalized the lack of reactivity by increased acidity of sulfonamides as compared to other nucleophiles, that could decrease the effective concentration of the base in the reaction mixture. This phenomenon was previously observed in the reactions of relatively acidic pronucleophiles (such as phenols and thiols), when overall basicity of the medium was too low to achieve the base-assisted epimerization into thermodynamically more stable trans products, calling for a requisite additional treatment of crude product mixtures with a stronger base. However, in the reaction with sulfonamides, the basicity appears to be insufficient even for the initial dehydrobromination step.

Accordingly, we increased the base load to 7.0 equiv in the reaction of tosylamide **26ad** and **1a** to obtain the desired product **27aad** in excellent yield and high diastereoselectivity (Scheme 9, Table 4, entry 1). Trans configuration of sulfonamide **27aad** was unambiguously assigned by X-ray crystallography.[32] Encouraged by the promising reactivity of tosylamide **26ad**, we set out to explore the efficacy of this reaction as a function of electronic factors. Interestingly, in contrast to carboxamides, which required activating electron-withdrawing groups, sulfonamides bearing electron-donating p-anisyl (**26ed**, Table 4, entry 2) and p-tolyl groups (**26af**, **26ad**, and **26ak**, entries 3−5), as well as electron-neutral phenyl (**26fd**) and β-naphthyl substituents (**26gd**) added smoothly, affording the corresponding cyclopropylamine sulfonates in high yield (Table 4, entries 6−8). Furthermore, mesylamides **26he**, **26hf**, and **26hh** also reacted efficiently providing the corresponding products **27ahe**, **27ahf**, and **27ahh** in good to excellent yield (Table 4, entries 9−11). Sulfonamides bearing relatively weak inductively electron-withdrawing groups, such as p-FC_6H_4 (**26id**, **26ik**), p-ClC_6H_4 (**26jd**, **26jf**), and p-BrC_6H_4

Scheme 9



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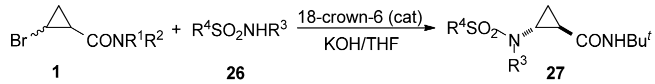


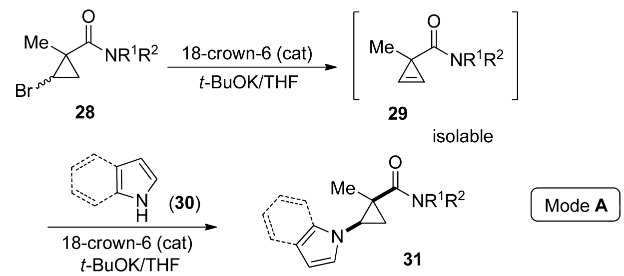
	R^1, R^2	1	R^3, R^4	26	27	yield,[a] %	dr[b]
1	^{t}Bu, H	**1a**	4-MeC_6H_4, *n*-Bu	**26ad**	**27aad**	90	16:1
2	^{t}Bu, H	**1a**	4-$MeOC_6H_4$, *n*-Bu	**26ed**	**27aed**	95	11:1
3	^{t}Bu, H	**1a**	4-MeC_6H_4, Bn	**26af**	**27aaf**	75	11:1
4	c-Hex, H	**1f**	4-MeC_6H_4, *n*-Bu	**26ad**	**27fad**	89	15:1
5	^{t}Bu, H	**1a**	4-MeC_6H_4, Furfuryl	**26ak**	**27aak**	84	25:1
6	^{t}Bu, H	**1a**	Ph, *n*-Bu	**26fd**	**27afd**	73	10:1
7	^{t}Bu, H	**1a**	β-$C_{10}H_8$, *n*-Bu	**26gd**	**27agd**	78	10:1
8	c-Hex, H	**1f**	β-$C_{10}H_8$, *n*-Bu	**26gd**	**27fgd**	94	25:1
9	^{t}Bu, H	**1a**	Me, *n*-Hex	**26he**	**27ahe**	90	9:1
10	^{t}Bu, H	**1a**	Me, Bn	**26hf**	**27ahf**	83	15:1
11	^{t}Bu, H	**1a**	Me, c-Hex	**26hh**	**27ahh**	67	11:1
12	^{t}Bu, H	**1a**	4-FC_6H_4, *n*-Bu	**26id**	**27aid**	96	19:1
13	c-Hex, H	**1f**	4-FC_6H_4, *n*-Bu	**26id**	**27fid**	97	10:1
14	$-(CH_2)_2O(CH_2)-$	**1e**	4-FC_6H_4, *n*-Bu	**26id**	**27eid**	71	11:1
15	^{t}Bu, H	**1a**	4-FC_6H_4, Furfuryl	**26ik**	**27aik**	93	25:1
16	^{t}Bu, H	**1a**	4-ClC_6H_4, *n*-Bu	**26jd**	**27ajd**	94	11:1
17	^{t}Bu, H	**1a**	4-ClC_6H_4, Bn	**26jf**	**27ajf**	72	25:1
18	^{t}Bu, H	**1a**	4-BrC_6H_4, *n*-Bu	**26kd**	**27akd**	91	11:1

[a]Isolated yields. [b]Diastereomeric ratio (trans:cis) determined by GC or ^{1}H NMR analysis of crude reaction mixtures.

(**26kd**), also proved efficient in this reaction (Table 4, entries 12–18). At the same time, highly acidic 4-nitro- (**26bd**), 2-nitro- (**26cd**), and 2,4-dinitrobenzenesulfonates (**26dd**) of *n*-butylamine failed to react with **1a** (Scheme 9). When the amount of base was increased to 15 equiv, dehydrobromination took place to give the cyclopropene intermediate; however, the nucleophilicity of nosylates was still insufficient to produce observable quantities of adducts. Reaction with $TsNH_2$ did not yield cyclopropylamine sulfonate, but led to complete cleavage of the small cycle to afford aldehyde **21**, apparently, via the same mechanistic pathway realized in the case of carboxamides (Scheme 7).

Azoles as *N*-Based Nucleophiles. Efficient overlap of the cyclopropane's Walsh orbitals with the π-system of the adjacent aromatic substituent endows cyclopropyl(het)arenes with unique conformational features. It has been demonstrated that arylcyclopropanes can efficiently mimic active conformations of the bis-aryl[38] or benzylaryl moieties,[39] producing remarkable pharmacological effects. Successful employment of cyclopropyl(het)arenes as bioisosteres is evidenced by a growing number of aryl- and hetarylcyclopropanes with impressive biological profiles, including antimalarial,[40] anticancer,[41] anti-HIV,[42] antidepressant,[43] immunemodulatory,[39] antibiotic,[44] and analgesic[45] activity. Assembly of hetarylcyclopropanes possessing a cyclopropyl–N_{HetAr} bond is a challenging task and thus far has been achieved only via Cu-catalyzed coupling of azoles to cyclopropylboronic acids[46] and cyclopropylbismuth reagents,[47] and the reaction of magnesium cyclopropylidene with *N*-lithioarylamines.[48] The N–H bond acidity of azoles (whose pK_a fall in the same range as values for carboxamides and sulfonamides) makes them good candidates for the title reaction. The lack of success in previous attempts on *N*-alkylation of azoles via the formal nucleophilic substitution of bromocyclopropane by other groups[21c,49] can be attributed to the unstable, electron-rich intermediate—unsubstituted cyclopropene—which undergoes rapid concurrent polymerization. Indeed, we have previously shown that analogous transformation proceeding via a stable, isolable cyclopropene **29h**[28,29] produced *N*-pyrrolyl cyclopropane **31ha** in good yield (Table 5, entry 1).[25] Nucleophilic attack of

Table 5. Convergent Approach to Conformationally Constrained *cis*-Cyclopropyl Amino Acid Derivatives via the Formal Substitution of Bromocyclopropanes with Nucleophilic Azoles: Mode A, Directed Addition of Nucleophiles



	R^1, R^2 (28)	30	31	yield,[a] %	dr[b]
1	$-(CH_2)_4-$ (**28h**)	pyrrole (**30a**)	**31ha**	85	14:1
2	$-(CH_2)_2NMe(CH_2)_2-$ (**28i**)	pyrrole (**30a**)	**31ia**	54	9:1
3	$-(CH_2)_2NMe(CH_2)_2-$ (**28i**)	indole (**30b**)	**31ib**	45	10:1
4	$-(CH_2)_2O(CH_2)_2-$ (**28e**)	pyrrole (**30a**)	**31ea**	61	19:1
5	$-(CH_2)_2O(CH_2)_2-$ (**28e**)	indole (**30b**)	**31eb**	41	11:1
6	^{t}Bu, H (**28a**)	pyrrole (**30a**)	**31aa**	67	3:1

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

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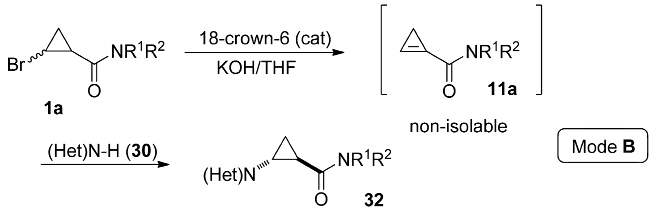
pyrrole (**30a**) in this case was efficiently directed by the carboxamide function affording predominantly cis diastereomer. Likewise, trans products were obtained selectively, albeit in slightly lower yields, in the reactions of pyrrole (**30a**) or indole (**30b**) with tertiary cyclopropylamides—derivatives of *N*-methylpiperazine (**28i**) and morpholine (**28e**) (Table 5, entries 2–5). In contrast, cyclopropyl bromide **28a** bearing a secondary carboxamide moiety provided adduct **31aa** with poor diastereoselectivity (entry 6). This result was rather surprising as we previously demonstrated that the secondary carboxamide function served as superior directing group in reactions with *O*-based nucleophiles.[26]

We have shown earlier that conjugation of the strained C═C bond with an electron-withdrawing functionality can enhance the affinity of the cyclopropene intermediate toward soft nucleophiles, such as phenoxides and thiolates.[26] However, the corresponding rather acidic pronucleophiles reduce the overall basicity of the media leading, to inefficient epimerization at the α-carbon and, consequently, lower diastereoselectivities. Along these lines, 1,2-dehydrobromination of bromocyclopropane **1a** in the presence of pyrrole (**30a**) (mode B) afforded the corresponding cyclopropyl pyrrole **32aa** in high yield but poor diastereomeric ratio (dr), which was addressed by our standard postreaction treatment of a crude mixture with a stronger base[26] (Table 6, entry 1) to give a 98:2 trans selectivity with perfect material balance (Table 6, entry 1). Likewise, reaction of **1a** with 2-cyanopyrrole (**30c**), followed by base-assisted epimerization, afforded the corresponding trans adduct **32ac** in high yield and excellent diastereoselectivity (Table 6, entry 2). Indoles reacted uneventfully, in spite of their susceptibility to Friedel–Crafts alkylation, dimerization, and polymerization.[50] As expected, skatole (**30d**), possessing a substituent at the vulnerable C3 position, provided the best yield in the series (entry 3–7). When imidazole **30g** was used as a nucleophilic component, we stumbled upon the isolation issue. Although the corresponding adduct **32ag** was produced in reasonable yield (50% as judged by ^{1}H NMR analysis of crude reaction mixture), chromatographic purification of the product proved inefficient due to its partial decomposition on silica gel (27% isolated yield, entry 8). In contrast, reactions in the presence of its fused analogues benzimidazoles **30h**, **30i**, and **30j** proceeded cleanly to afford the corresponding trans products in high yields and excellent diastereoselectivities (entries 8–10). Similarly, pyrazole (**30k**) was engaged in a very efficient transformation with cyclopropyl bromides **1a** and **1j**, providing good yields of *N*-cyclopropylpyrazoles **32ak** and **32jk**, respectively (entries 12 and 13). The trans configuration of the carboxamide and azole substituents was unambiguously confirmed by X-ray analysis of **32jk**.[32] It should be mentioned that the scope of this reaction is generally limited to poorly acidic azoles with pK_a ~ 16–23. Nonetheless, a more acidic *N*-heterocycle benzotriazole (**30l**, pK_a 11.9) was also reactive, producing two regioisomers, **32al** and **33al** resulting from two tautomeric forms[51,52] (Scheme 10). Attempts on addition of tetrazoles **30m** and **30n** (pK_a ~ 8.2) were unsuccessful (Scheme 10), which was expected for such poor aza-Michael donors.[53]

Anilines as *N*-Based Nucleophiles. The higher N–H acidity of anilines as compared to alkylamines makes them attractive N-based nucleophiles for the formal substitution reaction. However, our initial test using anilines as nucleophiles proved unsuccessful: reaction of *N*-methylaniline (**35a**) with **1a** produced aldehyde **21** as the only isolable compound. Formation of the latter can be envisioned via a formal addition

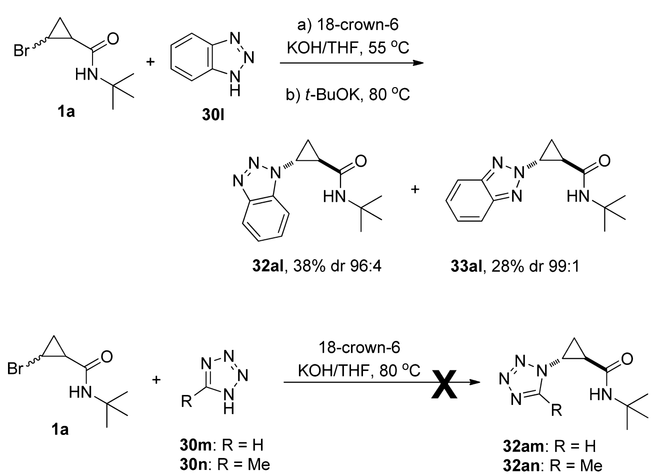
Table 6. Convergent Approach to Conformationally Constrained *trans*-Cyclopropyl Amino Acid Derivatives via the Formal Substitution of Bromocyclopropanes with Nucleophilic Azoles: Mode B, Nucleophilic Addition Followed by Thermodynamically Driven Base-Assisted Epimerization



	R^1, R^2 (1)	heterocycle (30)	32	crude dr[b]	yield,[a] % (dr after upgrade)[b]
1	^{t}Bu, H (1a)	pyrrole (**30a**)	**32aa**	72:28	66 (98:2)
2	^{t}Bu, H (1a)	2-cyanopyrrole (**30c**)	**32ac**	85:15	82 (95:5)
3	^{t}Bu, H (1a)	indole (**30b**)	**32ab**	73:27	66 (97:3)
4	Bn, H (1j)	indole (**30b**)	**32jb**	75:25	48 (97:3)
5	^{t}Bu, H (1a)	3-methyl-1*H*-indole (**30d**)	**32ad**	75:25	73 (99:1)
6	^{t}Bu, H (1a)	5-methoxy-1*H*-indole (**30e**)	**32ae**	75:25	61 (97:3)
7	^{t}Bu, H (1a)	5-bromo-1*H*-indole (**30f**)	**32af**	58:42	48 (97:3)
8	^{t}Bu, H (1a)	imidazole (**30g**)	**32ag**	87:13	50 (100:0)[c]
9	^{t}Bu, H (1a)	1*H*-benzo[*d*]imidazole (**30h**)	**32ah**	87:13	66 (100:1)
10	^{t}Bu, H (1a)	2-methyl-1*H*-benzo[d] imidazole (**30i**)	**32ai**	93:7	84 (95:5)
11	^{t}Bu, H (1a)	5,6-dimethyl-1*H*-benzo[*d*]imidazole (**30j**)	**32aj**	95:5	72 (97:3)
12	^{t}Bu, H (1a)	pyrazole (**30k**)	**32ak**	86:14	85 (99:1)
13	Bn, H (1j)	pyrazole (**30k**)	**32jk**	88:12	73 (97:3)

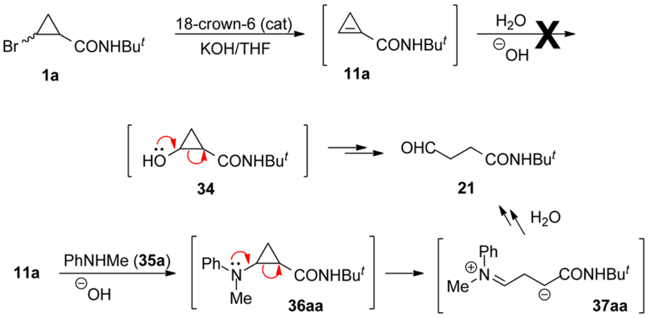
[a]Isolated yields, unless specified otherwise. [b]Diastereomeric ratio (trans:cis) determined by GC or ^{1}H NMR analyses of crude reaction mixtures. [c]NMR yield.

Scheme 10



of water to cyclopropene **11a**, followed by a base-assisted cleavage of the intermediate cyclopropanol **34**; yet product **21** was never observed in our reactions in the absence of the secondary aniline, suggesting an alternative mechanism. We believe the reaction begins with a base-assisted conjugate addition of aniline species **35a** across the C=C bond of cyclopropene **11a**. The resulting donor−acceptor cyclopropane **36aa** undergoes ring-opening to give the iminium intermediate **37aa**, which upon base-assisted hydrolysis produces aldehyde **21** (Scheme 11). It should be emphasized that, mechanistically,

Scheme 11



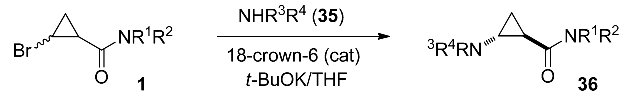
this ring-opening process is related to the small cycle cleavage observed in the attempted additions of primary carboxamides and sulfonamides discussed above (Scheme 7). The propensity of the donor−acceptor cyclopropane toward ring-opening depends on the extent of polarization of the C−C bond between the electron-donating (EDG) and electron-withdrawing groups (EWG). Polarization is commonly achieved through installation of strong EWGs, typically two ester functions, additionally activated by a Lewis acid ("pull" strategy).[2] In our case polarization is realized through installation of an EDG with increased electron density, such as anionic *N*-moiety or a neutral *N*-group bearing an electron-donating substituents ("push" strategy).[54]

Accordingly, the aptitude toward small ring cleavage was significantly reduced in cyclopropylanilines possessing electron-deficient nitrogen. Thus, reaction of *p*-nitroaniline **35b** with **1a** in the presence of ^{t}BuOK and 18-crown-6 proceeded smoothly providing a single diastereomer of cyclopropylaniline **36ab** in nearly quantitative yield (Table 7). Several other electron-deficient *N*-benzyl protected anilines, possessing cyano- (**35c**), trifluoromethyl- (**35d**), and nitro- (**35e**) groups in para positions, reacted in a similar manner, affording the corresponding aminocyclopropanes **36ac**, **36ad**, and **36ee** in good to excellent yields. *m*-Nitroaniline **35f** possessing a less electron-deficient nitrogen atom provided the corresponding adduct **36af** in lower yield (entry 5). Regardless of the yield, the diastereoselectivity of addition was perfect in all these examples (Table 7). It should be also mentioned that diphenylamine (**35g**) and 10*H*-phenothiazine (**35h**) did not require electron-withdrawing substituents to furnish *trans*-diastereomers of the corresponding cyclopropylamine derivatives **36ag** and **36ah** (Table 7, entries 6 and 7).

■ CONCLUSIONS

An efficient diastereoselective synthesis of *β*-aminocyclopropylcarboxylic acid derivatives via the formal nucleophilic substitution of bromocyclopropanes with *N*-based nucleophiles has been developed. This transformation proceeds via

Table 7. Conformationally Constrained *trans*-Cyclopropyl Amino Acid Derivatives via the Formal Substitution of Bromocyclopropanes with Nucleophilic Anilines



	R^1, R^2 (**1**)	R^3, R^4 (**35**)	**36**	yield,[a] %	dr[b]
1	^{t}Bu, H (**1a**)	4-$NO_2C_6H_4$, Me (**35b**)	**36ab**	99	>25:1
2	^{t}Bu, H (**1a**)	4-NCC_6H_4, Bn (**35c**)	**36ac**	99	>25:1
3	^{t}Bu, H (**1a**)	4-$CF_3C_6H_4$, Bn (**35d**)	**36ad**	65	>25:1
4	−$(CH_2)_2O(CH_2)_2$− (**1e**)	4-$NO_2C_6H_4$, Bn (**35e**)	**36ee**	75	>25:1
5	^{t}Bu, H (**1a**)	3-$NO_2C_6H_4$, Bn (**35f**)	**36af**	50	>25:1
6	^{t}Bu, H (**1a**)	Ph, Ph (**35g**)	**36ag**	96	>25:1
7	^{t}Bu, H (**1a**)	10*H*-phenothiazine (**35h**)	**36ah**	59	>25:1

[a]Isolated yields. [b]Diastereomeric ratio (trans:cis) determined by GC or ^{1}H NMR analysis of crude reaction mixtures.

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

■ EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on a 400 MHz instrument, equipped with a quadruple-band gradient probe (H/C/P/F QNP) or a 500 MHz instrument 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. GC/MS analyses were performed using a 30 m × 0.25 mm × 0.25 *μ*m capillary column (polydimethylsiloxane, 5% Ph). Helium (99.96%), additionally purified by passing consecutively through an oxygen/moisture/hydrocarbon trap and an oxygen/moisture trap, was used as a carrier gas. High resolution mass spectra were obtained using electrospray ionization and time-of-flight detection techniques. 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. Anhydrous triethylamine was obtained by distillation of ACS-grade commercially available materials over calcium hydride in a nitrogen atmosphere. All other commercially available reagents were used as received. Bromocyclopropanes **1a**−**g**,[16] **1j**[17] **4a**,[30] **28a**,[25] **28e**,[28] **28h**,[25] and **28i**[28] were prepared according to the previously published procedures. Preparative procedures and characterization data for carboxamide adducts **15aaa**[25] (**16aaa**, **16abd**, **16abc**, **16acd**, **16afa**, **16afd**, **16agd**, **16ahd**, **16aid**, **16ajd**, **16akd**, **16ald**, **16amd**, **16ale**, **16alf**, **16alg**, **16alh**, **16amh**, **16amc**, **16ami**, **16amg**, **16dmg**, **16emg**, **16fmh**, **16dmf**, **16gmf**)[16] and azole adducts **31ha**[25] (**32aa**, **32ac**, **32ab**, **32jb**, **32ad**, **32ae**, **32ag**, **32ah**, **32ai**, **32aj**, **32ak**, **32jk**, **32al**, **32al**)[17] are described in the Supporting Information files of the corresponding preliminary communications. Synthesis, physical properties, and spectral data of all new compounds obtained in the frame of these studies are described below. Accurate assignment of the product configuration by ^{1}H NMR based on the analysis of $^3J_{HH}$ 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 **16aba** in DMSO-d_6. Trans configurations of products **16emg**, **27aad**, and **32jk** were unambiguously assigned by X-ray crystallography. Cis configuration of compound **31aa** was assigned based on 1D NOE experiments. These data were used to assign the structures of all other products by analogy.

Preparation of Starting Materials. *4-Nitro-N-(thiophen-2-ylmethyl)benzamide (**14kj**).* To a stirred solution of 4-nitrobenzoyl chloride (930 mg, 5.0 mmol) in dry CH_2Cl_2 (50.0 mL) was added a 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 and then quenched with 10% aqueous HCl (20 mL). The organic phase was separated, washed consecutively with 10% NaOH and brine, then dried with $MgSO_4$, and concentrated to provide the title compound as yellowish solid (mp 147−149 °C) 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 165.2, 149.7, 139.8, 139.7, 128.3 (+, 2C), 127.1 (+), 126.7 (+), 125.8 (+), 123.9 (+, 2C), 39.1 (−). 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 (**14jk**).* 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 2 h at room temperature and then worked up as described above for the synthesis of **14kj**. Yield: 975 mg (4.3 mmol, 49%), colorless solid, mp 150−151 °C. ^{1}H 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 165.5, 150.5, 142.6 (+), 138.1, 132.5 (+, 2C), 127.8 (+, 2C), 118.0, 115.3, 110.6 (+), 108.1 (+), 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) 249.0640 (1.2 ppm).

*N-Butylnaphthalene-2-sulfonamide (**26gd**).* 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 2 h 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 title compound as white crystalline solid, mp 54−58 °C. Yield: 1.06 g (4.01 mmol, 91%). ^{1}H 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 136.7, 134.8, 132.2, 129.5 (+), 129.2 (+), 128.8 (+), 128.5 (+), 127.9 (+), 127.6 (+), 122.4 (+), 43.0 (−), 31.6 (−), 19.7 (−), 13.5 (+). 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 (**26ik**).* 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). The mixture was stirred for 2 h and then worked up as described above in the protocol for preparation of compound **26gd**. Yield: 1.01 g (4.3 mmol, 81%), colorless solid, mp 92−93 °C. ^{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 169.3, 165.3 (d, J = 255.3 Hz), 133.5, 130.2 (d, J = 9.1 Hz, 2C), 116.5 (d, J = 22.5 Hz, 2C), 67.1, 67.0, 46.2, 42.6, 38.6, 30.2, 21.4, 20.1, 15.0, 13.7. ^{19}F NMR (376 MHz, chloroform-d): δ −104.67 to −104.78 (m). Ir (salt plate): 3331, 3087, 2962, 2872, 1645, 1585, 1547, 1475, 1454, 1392, 1294, 1225, 1205, 1167, 1094. HRMS: found 255.0363, calculated for $C_{11}H_{10}FNO_3S$ (M^+) 255.0365, (0.7 ppm).

Adducts Resulting from Nucleophilic Attack by Carboxamides. *N-Benzyl-N-((1R*,2R*)-2-(tert-butylcarbamoyl)-cyclopropyl)-4-nitrobenzamide (**16akf**). Typical Procedure I.* An oven-dried 10 mL Wheaton vial was charged with 2-bromo-N-($tert$-butyl)cyclopropanecarboxamide **1a** (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 (**14kf**)[55] (256 mg, 1.0 mmol, 2.0 equiv), and anhydrous THF (5 mL). The mixture was stirred at 85 °C for 12 h, then the reaction mixture was filtered into a 100 mL round-bottom flask, and 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 171.3, 169.7, 148.4, 143.0, 137.0, 128. Six (+, 2C), 128.4 (+) 127.9 (+), 127.7 (+), 127.4 (+), 123.6 (+), 50.5, 49.7 (−), 38.0 (+), 27.5 (+, 3C), 26.9 (+), 15.4 (−). 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 (**16ajf**).* This compound was synthesized according to typical procedure I employing 2-bromo-N-($tert$-butyl)-cyclopropanecarboxamide (**1a**) (110 mg, 0.5 mmol), N-benzyl-4-cyanobenzamide (**14jf**)[56] (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 °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 171.5, 169.7, 141.2, 137.0, 132.3 (+), 128.5 (+), 128.5 (+), 127.7 (+), 127.5 (+), 127.4 (+), 117.8, 113.3, 50.5, 49.7 (−), 37.9 (+), 27.5 (+, 3C), 26.7 (+), 15.4 (−). 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 (**16akj**).* This compound was synthesized according to typical procedure I employing 2-bromo-N-($tert$-butyl)cyclopropanecarboxamide (**1a**) (110 mg, 0.50 mmol), 4-nitro-N-(thiophen-2-ylmethyl)benzamide (**14kj**) (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 a DCM:MeOH mixture (24:1) as a yellow solid (R_f 0.27, mp 150−152 °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 171.0, 169.7, 148.5, 142.8, 139.3, 127.8 (+, 2C), 126.8 (+), 126.5 (+), 125.5 (+), 123.6 (+, 2C), 50.4, 44.7 (−), 37.8 (+), 27.5 (+, 3C), 27.0 (+), 15.3 (−). 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 (**16ajk**).* This compound was synthesized according to typical procedure I employing 2-bromo-N-(*tert*-butyl)cyclopropanecarboxamide (**1a**) (110 mg, 0.5 mmol), 4-cyano-N-(furan-2-ylmethyl)benzamide (**14jk**) (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 °C, R_f 0.17. Yield: 149 mg (0.41 mmol, 81%). ^1H 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 171.4, 169.7, 150.3, 142.5, 141.0 (+), 132.3 (+, 2C), 127.6 (+), 117.8, 113.3, 110.2 (+), 108.5 (+), 50.5, 42.7 (−), 37.9 (+), 27.6 (+, 3S), 26.8 (+), 15.5 (−). 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).

Adducts Resulting from Nucleophilic Attack by Sulfonamides. *(1R*,2R*)-N-(tert-Butyl)-2-(N-butyl-4-fluorophenylsulfonamido)cyclopropanecarboxamide (**27aid**). Typical Procedure II.* An oven-dried 10 mL Wheaton vial was charged with bromocyclopropane **1a** (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 (**26id**)[36b] (31 mg, 0.13 mmol, 1.0 equiv), and anhydrous THF (8 mL). The mixture was stirred at 85 °C for 12 h and 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. ^1H 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 (**27aad**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26ad**)[57] (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%). ^1H 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 366.1980, calculated for $C_{19}H_{30}N_2O_3S$ (M^+) 366.1977 (0.8 ppm).

(1R,2R*)-N-(tert-Butyl)-2-(N-butyl-4-methoxyphenylsulfonamido)cyclopropanecarboxamide (**27aed**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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-*p*-methoxybenzenesulfonamide (**26ed**)[58] (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%). ^1H 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 (**27aaf**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26af**)[59] (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%). ^1H 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 (**27fad**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1f** (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 (**26ad**)[57] (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%). ^1H 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 (**27aak**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26ak**)[60] (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 °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 $C_{20}H_{26}N_2NaO_4S$ (M + Na) 413.1511 (1.2 ppm).

(1R,2R*)-N-(tert-Butyl)-2-(N-butylphenylsulfonamido)-cyclopropanecarboxamide (**27afd**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26fd**)[61] (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 (**27agd**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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*-butylnaphthalenesulfonamide (**26gd**) (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-cyclohexyl-cyclopropanecarboxamide (**27fgd**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1f** (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*-butylnaphthylsulfonamide (**26gd**) (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 (**27ahe**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (44 mg, 0.2 mmol, 1.5 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol %), KOH (52 mg, 0.93 mmol, 7.0 equiv), and *N*-hexylmethanesulfonamide (**26he**)[62] (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 (1*R**,2*S**)-diastereomer.

(1R,2R*)-2-(N-Benzylmethylsulfonamido)-N-(tert-butyl)-cyclopropanecarboxamide (**27ahf**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (46 mg, 0.21 mmol, 1.5 equiv), 18-crown-6 (3.5 mg, 0.013 mmol, 10 mol %), KOH (52 mg, 0.93 mmol, 7.0 equiv), and *N*-benzylmethanesulfonamide (**26hf**)[63] (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 (**27ahh**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26hh**)[64] (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 (**27fid**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1f** (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-fluorobenzenesulfonamide (**26id**)[36b] (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 (**27eid**).* The reaction was performed according to typical procedure II, employing (2-bromocyclopropyl)(morpholino)methanone (**1e**) (37 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-fluorobenzenesulfonamide (**26id**)[36b] (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 169.3, 165.3 (d, *J* = 255.3 Hz), 133.5, 130.2 (d, *J* = 9.1 Hz, 2C), 116.5 (d, *J* = 22.5 Hz, 2C), 67.1, 67.0, 46.2, 42.6, 38.6, 30.2, 21.4, 20.1, 15.0, 13.7. ^{19}F NMR (376.46 MHz, $CDCl_3$): δ −104.67 to −104.78 (m). FT IR (NaCl, cm^{-1}): 3331, 3087, 2962, 2872, 1645, 1585, 1547, 1475, 1454, 1392, 1294, 1225, 1205, 1167, 1094. HRMS (TOF ES): found 383.1441, calculated for $C_{18}H_{24}FN_2O_4S$ $(M - H)^+$ 383.1435 (1.6 ppm).

(1R,2R*)-N-(tert-Butyl)-2-(4-fluoro-N-(furan-2-ylmethyl)-phenylsulfonamido)cyclopropanecarboxamide (**27aik**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26ik**) (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 °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, 165.2 (d, *J* = 259.40 Hz, 1C), 148.9, 142.5 (+), 133.0 (d, *J* = 2.93 Hz, 1C), 130.5 (+, d, *J* = 8.78 Hz, 1C), 116.2 (+, 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 $C_{19}H_{23}FLiN_2O_4S$ (M + Li) 401.1523 (3.0 ppm).

(1R,2R*)-N-(tert-Butyl)-2-(N-butyl-4-chlorophenylsulfonamido)-cyclopropanecarboxamide (**27ajd**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26jd**)[65] (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 (**27ajf**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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 (**26jf**)[66] (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 (**27akd**).* The reaction was performed according to typical procedure II, employing bromocyclopropane **1a** (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-bromobenzenesulfonamide (**26kd**)[65] (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).

Adducts Resulting from Nucleophilic Attack by Azoles. *(1R*,2R*)-2-(5-Bromo-1H-indol-1-yl)-N-(tert-butyl)-cyclopropanecarboxamide (**32af**).* To a 10 mL Wheaton vial equipped with a magnetic stir bar, under N_2, were added THF (5 mL), powdered KOH (56 mg, 1.0 mmol), 5-bromo-1*H*-indole (**30f**) (147 mg, 0.75 mmol), 18-crown-6 (6.0 mg, 0.025 mmol), and 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**1a**) (55 mg, 0.25 mmol). This solution was stirred at 55 °C for 12 h, and then filtered through a fritted funnel. The filtrate was concentrated to yield a crude mixture of diastereomeric products with dr 42:58. This mixture was subjection to the epimerization procedure, involving treatment with

^{t}BuOK (84 mg, 0.75 mmol, 3.0 equiv) in dry THF (5 mL) at 80 °C for 18 h. After this treatment the diastereomeric ratio was improved to 97:3. The product was purified by flash column chromatography on silica gel eluting with hexane/EtOAc 6:1 to afford the title compound as amber oil, R_f 0.39. Yield: 40 mg (0.12 mmol, 48%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 7.74 (dd, J = 1.7, 0.8 Hz, 1H), 7.34−7.32 (m, 2H), 7.09 (d, J = 3.3 Hz, 1H), 6.39 (dd, J = 3.2, 0.7 Hz, 1H), 5.68 (s, 1H), 3.84−3.73 (m, 1H), 1.79−1.68 (m, 2H), 1.56−1.48 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ ppm 169.3, 135.8, 130.3, 128.2 (+), 124.8 (+), 123.6 (+), 113.3, 111.3 (+), 101.2 (+), 51.8, 34.3 (+), 29.0 (+, 3C), 24.4 (+), 13.9 (−). FT IR (KBr, cm^{-1}): 3325, 2966, 2934, 2874, 1647, 1549, 1508, 1462, 1225, 795. HRMS (TOF ES): found 357.0570, calculated for $C_{16}H_{19}BrN_2ONa$ (M + Na) 357.0578 (2.2 ppm).

((1R,2S*)-2-(1H-Indol-1-yl)-1-methylcyclopropyl)(morpholino)-methanone (**31eb**). Typical Procedure III.* An oven-dried 10 mL Wheaton vial equipped with a magnetic stir bar was loaded under N_2 with potassium *tert*-butoxide (168 mg, 1.5 mmol), 18-crown-6 (13 mg, 0.05 mmol), (2-bromo-1-methylcyclopropyl)(morpholino)methanone (**28e**) (124 mg, 0.50 mmol), indole (**30b**) (117 mg, 1.00 mmol), and THF (5 mL). The mixture was stirred at 80 °C for 12 h, then filtered through a fritted funnel, and concentrated. Preparative column chromatography on silica gel afforded the title compound as an amber oil, R_f 0.46 (CH_2Cl_2:MeOH 20:1). Yield: 58 mg (0.25 mmol, 50%, dr >25:1). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 7.63 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.23 (dd, J = 8.2, 7.0 Hz, 1H), 7.14 (dd, J = 8.0, 7.0 Hz, 1H), 6.95 (d, J = 3.4 Hz, 1H), 6.45 (d, J = 3.3 Hz, 1H), 3.84 (dd, J = 8.8, 5.4 Hz, 1H), 3.79−3.69 (br s, 1H), 3.61−3.44 (br s, 2H), 3.19 (br s, 2H), 2.97 (m, 3H), 2.22 (dd, J = 6.9, 5.4 Hz, 1H), 1.49 (s, 3H), 1.29 (dd, J = 8.7, 6.8 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ ppm 168.8, 137.2, 129.1, 123.8 (+), 121.8 (+), 121.4 (+), 120.0 (+), 108.6 (+), 101.5 (+), 46.1 (−), 42.4(−), 41.0 (+), 28.8, 21.0 (+), 16.1 (−). FT IR (KBr, cm^{-1}): 2962, 2921, 2856, 1635, 1512, 1464, 1223, 847. HRMS (TOF ES): found 284.1530, calculated for $C_{17}H_{20}N_2O_2$ (M^+) 284.1525 (1.8 ppm).

((1R,2S*)-N-(tert-Butyl)-1-methyl-2-(1H-pyrrol-1-yl)-cyclopropanecarboxamide (**31aa**).* This compound was synthesized according to typical procedure III, employing 2-bromo-*N*-(*tert*-butyl)-1-methylcyclopropanecarboxamide (**28a**) (214 mg, 0.91 mmol), pyrrole (**30a**) (112 mg, 1.82 mmol), potassium *tert*-butoxide (307 mg, 2.74 mmol), and 18-crown-6 (24 mg, 0.09 mmol) to afford after purification the title compound as a light brown solid, mp 80 °C, R_f 0.34 (hexane/EtOAc 1:1), 133 mg (0.61 mmol, 67%, dr 3:1). ^{1}H NMR (400.13 MHz, chloroform-*d*): δ 6.70 (t, J = 2.1 Hz, 2H), 6.14 (t, J = 2.1 Hz, 2H), 4.78 (s, 1H), 3.45 (dd, J = 7.9, 5.0 Hz, 1H), 1.86 (dd, J = 6.0, 5.3 Hz, 1H), 1.41 (s, 3H), 1.23 (dd, J = 7.8, 6.4 Hz, 1H), 1.12 (s, 9H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 169.4, 121.4 (+, 2C), 109.0 (+, 2C), 50.9, 42.6 (+), 28.3 (+, 3C), 20.8 (+), 19.3 (−). FT IR (NaCl, cm^{-1}): 3393, 2966, 2929, 1653, 1526, 1495, 1456, 1392, 1364, 1258, 1238, 1221, 725. HRMS (TOF ES): found 220.1577, calculated for $C_{13}H_{20}N_2O$ (M^+) 220.1576 (0.5 ppm).

((1R,2S*)-2-(1H-Pyrrol-1-yl)-1-methylcyclopropyl)(morpholino)-methanone (**31ea**).* This compound was synthesized according to typical procedure III, employing (2-bromo-1-methylcyclopropyl)-(morpholino)methanone (**28e**) (124 mg, 0.50 mmol), pyrrole (**30a**) (60 mg, 1.00 mmol), potassium *tert*-butoxide (168 mg, 1.50 mmol), and 18-crown-6 (13 mg, 0.05 mmol) to afford after purification the title compound as yellow oil, R_f 0.34 (hexane/EtOAc 1:1), 72 mg (0.31 mmol, 61%, dr >25:1). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 6.59 (t, J = 2.1 Hz, 2H), 6.11 (t, J = 2.1 Hz, 2H), 3.81 (br s, 1H), 3.58 (br s, 2H), 3.49 (dd, J = 8.6, 5.4 Hz, 1H), 3.36 (br s, 1H), 3.46 (br s, 1H), 3.27 (br s, 2H), 3.15 (br s, 1H), 2.59 (br s, 1H), 1.93 (dd, J = 6.9, 5.5 Hz, 1H), 1.39 (s, 3H), 1.15 (dd, J = 8.6, 7.0 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ ppm 168.9, 119.1 (+), 108.7 (+), 66.1 (−, 2C), 46.0 (−), 44.5 (+), 42.4 (−), 28.7, 21.3 (+), 16.7 (−). FT IR (KBr, cm^{-1}): 2962, 2925, 2901, 2856, 1634, 1494, 1464, 1230, 851. HRMS (TOF ES): found 235.1448, calculated for $C_{13}H_{19}N_2O_2$ (M^+) 235.1447 (0.4 ppm).

((1R,2R*)-2-(1H-Pyrrol-1-yl)-1-methylcyclopropyl)(4-methylpi-perazin-1-yl)methanone (**31ia**).* This compound was synthesized according to typical procedure III, employing (2-bromo-1-methylcyclopropyl)(4-methylpiperazin-1-yl)methanone (**28i**) (78 mg, 0.30 mmol), pyrrole (**30a**) (40 mg, 0.60 mmol), potassium *tert*-butoxide (101 mg, 0.90 mmol), and 18-crown-6 (8 mg, 0.03 mmol) affording after purification the title compound as yellow oil, R_f = 0.23 (CH_2Cl_2/MeOH 20:1). Yield: 39 mg (0.16 mmol, 52%, dr 10:1). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ ppm 6.58 (t, J = 2.1 Hz, 2H), 6.08 (t, J = 2.2 Hz, 2H), 3.73 (br s, 1H), 3.51−3.46 (dd, J = 7.8, 5.3 Hz, 1H), 3.40 (br s, 1H), 3.27 (br s, 2H), 2.33 (br s, 1H), 2.23 (br s, 2H), 2.15 (s, 1H), 2.01 (br s, 1H), 1.90 (dd, J = 6.9, 5.4 Hz, 1H), 1.39 (s, 3H), 1.14 (dd, J = 8.6, 6.9 Hz, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ ppm 168.8, 119.2 (+, 2C), 108.6 (+, 2C), 54.0 (−, 2C), 45.6 (+), 44.5 (+), 41.8 (−, 2C), 28.8, 21.6 (+), 16.9 (−). FT IR (KBr, cm^{-1}): 2935, 2856, 1630, 1492, 1437, 1227, 827. HRMS (TOF ES): found 247.1690, calculated for $C_{14}H_{21}N_3O$ (M^+) 247.1685 (2.0 ppm).

((1R,2S*)-2-(1H-Indol-1-yl)-1-methylcyclopropyl)(4-methylpiper-azin-1-yl)methanone (**31ib**).* This compound was synthesized according to typical procedure III, employing (2-bromo-1-methylcyclopropyl)(4-methylpiperazin-1-yl)methanone (**28i**) (78 mg, 0.30 mmol), indole (**30b**) (70 mg, 0.60 mmol), potassium *tert*-butoxide (101 mg, 0.90 mmol), and 18-crown-6 (10 mg, 0.03 mmol) affording after purification the title compound as yellow oil, R_f 0.23 (CH_2Cl_2:MeOH 20:1). Yield: 46 mg (0.15 mmol, 52%, dr >25:1). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ ppm 7.61 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.23 (dd, J = 8.0, 7.7 Hz, 1H), 7.13 (dd, J = 8.1, 7.9 Hz, 1H), 6.96 (d, J = 3.4 Hz, 1H), 6.43 (d, J = 3.3 Hz, 1H), 3.84 (dd, J = 8.7, 5.4 Hz, 1H), 3.70 (br, 1H), 3.16 (br, 3H), 2.50−2.26 (m, 1H), 2.25−2.16 (dd, 7.3, 5.4, Hz, 1H), 1.95 (s, 3H), 1.85 (br, 3H), 1.51 (s, 3H), 1.30 (dd, J = 10.5, 5.1 Hz, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 168.7, 137.4, 129.2, 123.9 (+), 121.7 (+), 121.2 (+), 119.9 (+), 108.8 (+), 101.5 (+), 54.0 (−), 45.5 (+), 41.9 (−), 41.0 (+), 28.8, 21.4 (+), 16.4 (−). FT IR (KBr, cm^{-1}): 3325, 2966, 2934, 2874, 1647, 1549, 1508, 1462, 1225, 795. HRMS (TOF ES): found 297.1840, calculated for $C_{18}H_{23}N_3O$ (M^+) 297.1841 (0.3 ppm).

Adducts Resulting from Nucleophilic Attack by Anilines. *(1R*,2R*)-N-(tert-Butyl)-2-(methyl(4-nitrophenyl)amino)-cyclopropanecarboxamide (**36ab**), Typical Procedure IV.* A 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 (**35b**) (228 mg, 1.50 mmol), 18-crown-6 (13 mg, 0.050 mmol), and 2-bromo-*N*-(*tert*-butyl)-cyclopropanecarboxamide (**1a**) (110 mg, 0.50 mmol). This solution was stirred at 55 °C for 12 h, 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 (**36ac**).* This compound was synthesized according to the typical procedure employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**1a**) (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 (**35c**)[67] (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 (**36ad**).* This compound was synthesized according to the typical procedure employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**1a**) (22 mg, 0.1 mmol), KOH (22 mg, 0.40 mmol), 18-crown-6 (2.6 mg, 0.01 mmol), THF (1 mL), and *N*-benzyl-4-trifluoroaniline (**35d**)[67] (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 °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, ^3J = 3.9 Hz, 2C), 126.2 (2C), 124.9 (q, ^1J = 270.3 Hz), 119.6 (q, ^2J = 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 (**36ee**).* This compound was synthesized according to the typical procedure employing (2-bromocyclopropyl)-(morpholino)methanone (**1e**) (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 (**35e**)[68] (68 mg, 0.30 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 (**36af**).* This compound was synthesized according to the typical procedure employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**1a**) (22 mg, 0.10 mmol), KOH (22 mg, 0.40 mmol), 18-crown-6 (2.6 mg, 0.01 mmol), THF (1 mL), and *N*-benzyl-3-nitroaniline (**35e**)[69] (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 (**36ag**).* This compound was synthesized according to the typical procedure employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**1a**) (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 (**35g**) (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 °C for 12 h, to improve the dr to 25:1. Flash column chromatography on silica gel afforded the title compound as white solid, mp 111.3 °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 (**36ah**).* This compound was prepared according to the typical procedure employing 2-bromo-*N*-(*tert*-butyl)cyclopropanecarboxamide (**1a**) (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 (**35h**) (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 °C for 12 h to improve the 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 °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, 122.9, 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).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectral charts for new compounds, X-ray crystallography information, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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