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Diastereoselective Pd(II)-Catalyzed sp^3 C−H Arylation Followed by Ring Opening of Cyclopropanecarboxamides: Construction of *anti* *β*-Acyloxy Carboxamide Derivatives

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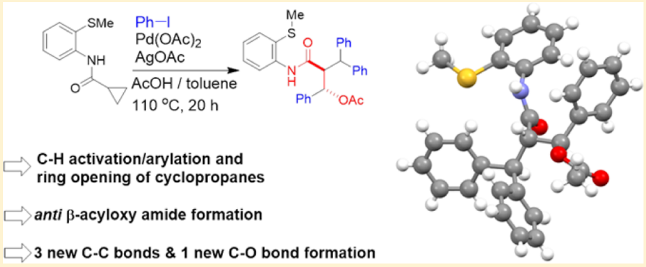
S Supporting Information

ABSTRACT: The diastereoselective Pd(OAc)$_2$-catalyzed, bidentate ligand-directed sp^3 C−H activation/arylation followed by ring opening of cyclopropanecarboxamides, which were assembled from cyclopropanecarbonyl chlorides and bidentate ligands (e.g., 8-aminoquinoline and 2-(methylthio)aniline), has been investigated. The treatment of various cyclopropanecarboxamides with excess amounts of aryl iodides in the presence of the Pd(OAc)$_2$ catalyst, AgOAc and AcOH directly afforded the corresponding multiple *β*-C−H arylated open-chain carboxamides (*anti* *β*-acyloxy amides). This method has led to the construction of several *anti* *β*-acyloxy amides that possess vicinal stereocenters with a high degree of stereocontrol with the formation of a new C−O bond and three new C−C bonds. A plausible mechanism for the formation of multiple *β*-C−H arylated open-chain carboxamides from the Pd-catalyzed, bidentate ligand-directed *β*-C−H arylation and the ring opening of cyclopropanecarboxamides is proposed based on several control experiments. The observed diastereoselectivity and *anti* stereochemistry of the *β*-acyloxy amides were ascertained based on X-ray structural analysis of representative *β*-acyloxy amides.



INTRODUCTION

Cyclopropane is the smallest ring in the cycloalkane family and is regularly encountered in the core of numerous natural products and medicinally/biologically active molecules.[1,2] The chemistry of cyclopropanes is well understood, and cyclopropanes are one of the most versatile building blocks in organic synthesis.[2−5] In addition, the release of the inherent ring strain associated with the ring opening of the cyclopropane system has led to the discovery of numerous tandem transformations. In general, the ring-opening reaction pathways depend on the electronic nature of the functional groups or substituents that are present in the cyclopropane systems.[1−5]

Cyclopropenes,[2a] methylenecyclopropanes,[3] alkylidenecyclopropanes,[3] donor−acceptor cyclopropanes[4] and cyclopropyl ketones[6a,b] are the most important classes of compounds in the cyclopropane family. In general, cyclopropane systems readily undergo a wide range of transformations including cyclodimerizations, cycloadditions, rearrangements, and ring-opening (C−C cleavage) reactions under the influence of a variety of chemical reagents and suitable catalysts.[1−5] The chemistry, usefulness and different modes of ring cleavage of these individual classes of cyclopropane systems have been well documented and summarized in various reviews.[1−5]

Although several types of cyclopropane ring-opening reactions are popularly known, the transition metal-catalyzed/promoted activation of the C−C bond and cleavage of the cyclopropane ring has received unique attention.[2,3,5] The relevant reviews by Cramer,[5c] Rubin/Gevorgyan,[2a] Pellissier,[3a,b] Brandi,[3c] Shi[3d,e] and Marek[3f] provide an overview of transition metal-catalyzed/promoted activation and modes of cleavage of the C−C bonds of substituted cyclopropanes, cyclopropenes, methylenecyclopropanes and alkylidenecyclopropanes, leading to ring-opening reactions. For the reactions involving cyclopropanes, “the strain-driven oxidative addition of the C−C bond of cyclopropanes to a transition-metal leads to the formation of metallacyclobutane, which was shown to open the way to different reaction”.[5c] For the reactions involving cyclopropenes, methylenecyclopropanes and alkylidenecyclopropanes, “an unsaturated tether facilitates the activation of the cyclopropane and directs the metal toward the cleavable C−C bond and can also participate in the post-activation transformation”.[5c] Representative transition metal-catalyzed/promoted reactions consisting of activation and cleavage of the C−C bonds of cyclopropane, methylenecyclopropane and alkylidenecyclopropane are shown in Figure 1.[6−9] Some of the transition metal-catalyzed/promoted reactions for donor−acceptor cyclopropane systems (activated cyclopropanes) are also shown in Figure 1.

Transition metal-catalyzed C−H activation/functionalization reactions have received significant attention in recent years, and in general, C−H functionalization-based cross-coupling reac-

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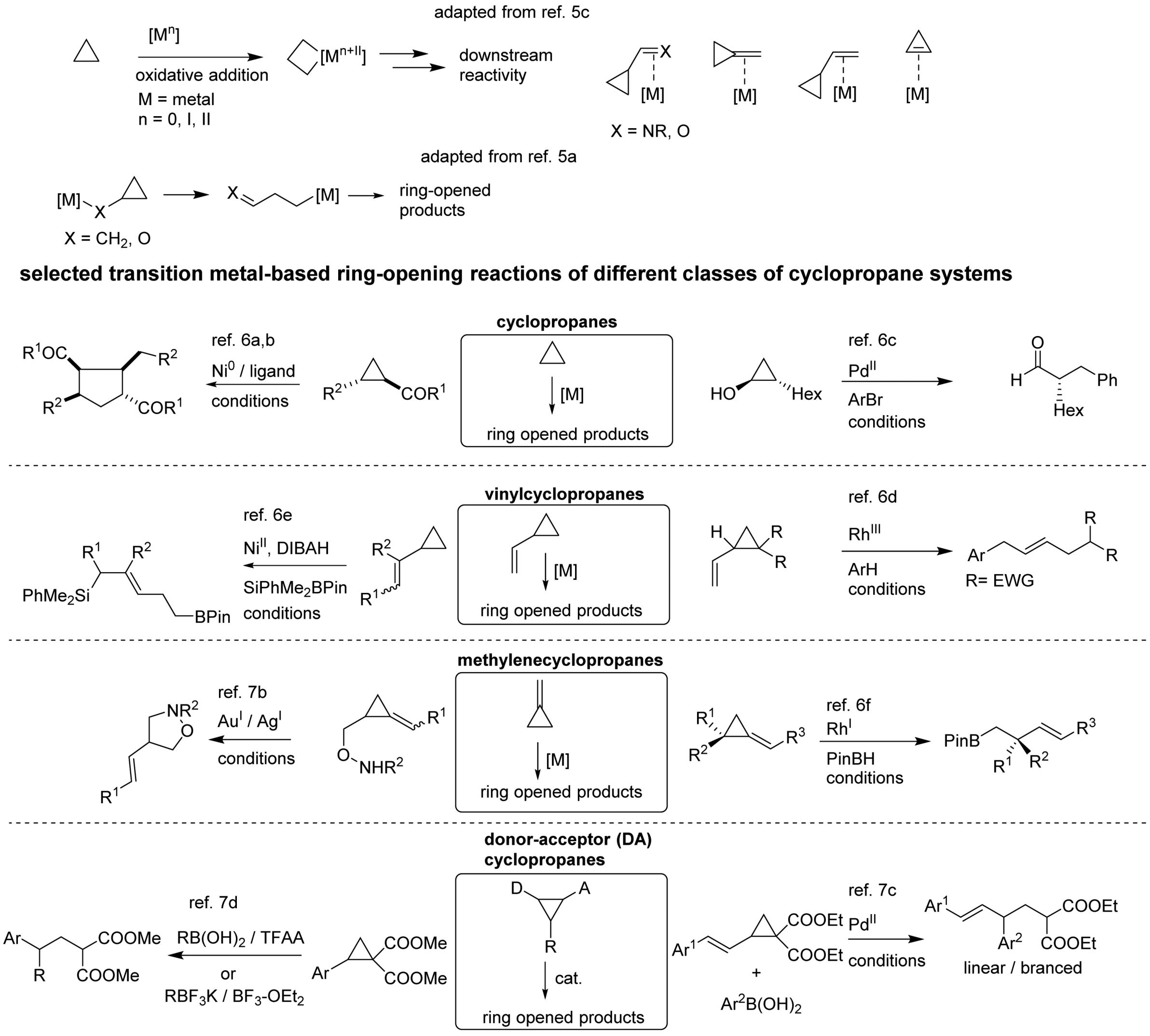
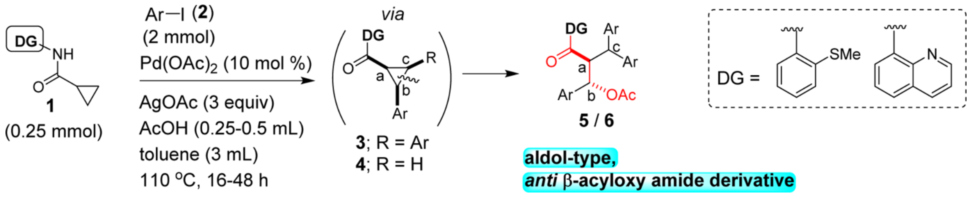


Figure 1. Representative metal-catalyzed/promoted ring opening reactions of cyclopropane systems.

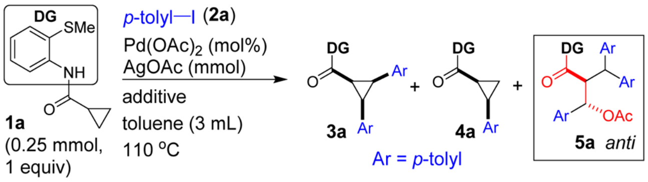
Scheme 1. Diastereoselective Pd(II)-Catalyzed C–H Arylation Followed by Ring Opening of Cyclopropanecarboxamides 1



tions are considered to be step-economical organic transformations.[10−14] Among the transition metal catalysts, the Pd(II) catalysts are frequently employed to perform sp^2 and sp^3 C–H activation/functionalization reactions.[10−14] Although the directing group-assisted or directing group-free sp^2 C–H activation/functionalization reactions have been extensively studied, the sp^3 C–H activation/functionalization reactions have received much attention after the seminal reports by Daugulis,[12a,13a] Yu[11b,13b,c] and other distinguished research groups.[10−14] Therefore, in recent years, the research area pertaining to the directing group-aided sp^3 C–H activation/functionalization of aliphatic/alicyclic carboxamides remains active.[10−16] Although sp^3 C–H activation/functionalization was investigated using a variety of aliphatic/alicyclic substrates, it is important to note that cyclopropane, which is the smallest carbocyclic ring, was also successfully subjected to the Pd(II)-catalyzed C–H activation/functionalization.[15] In this regard, our group recently reported the diastereoselective Pd(II)-catalyzed, bidentate ligand-directed *β*-C–H arylation of cyclopropanecarboxamide derivatives.[16g]

Inspired by the transition metal-catalyzed ring opening of cyclopropanes including the C–H/C-C bond activation strategy[2a,3,5−9] as well as our previous work,[16g] we envisioned a one-pot method involving Pd(II)-catalyzed, bidentate directing group-aided *β*-C–H arylation followed by ring opening of cyclopropanecarboxamide derivatives. Accordingly, the reaction of unsubstituted cyclopropanecarboxamide **1** with excess amounts of aryl iodide **2** in the presence of $Pd(OAc)_2$ as a catalyst, AgOAc and AcOH as the additive afforded the open-chain carboxamide derivatives **5**/**6** with a high degree of

Table 1. Optimization Reactions: Pd(II)-Catalyzed C−H Arylation/Ring Opening of Cyclopropanecarboxamide **1a**



entry	**2a** (mmol)	AgOAc (mmol)	$Pd(OAc)_2$ (mol %)	additive (equiv)/mL	*t* (h)	yield (%) **3a**	yield (%) **4a**	yield (%) **5a**
1	1.5	0.55	5	nil	24	0	15	7
2	2	0.55	5	nil	16	37	40	7
3	1.5	0.55	10	nil	16	8	35	11
4	1.5	0.55	10	nil	7	29	38	7
5	1.5	0.55	5	nil	15	23	13	7
6	1.5	0.55	20	nil	15	0	13	15
7	1.5	0.75	5	nil	19	12	13	20
8	1.5	0.38	10	Na_2SO_4 (0.5)	12	12	12	7
9	1.5	0.38	5	NaOAc (0.5)	19	5	38	28
10	1.5	0.25	10	NaOAc (2.5)	16	5	47	0
11	1.5	0.25	10	KOAc (2.5)	16	7	30	0
12	1.5	0.55	30	KOAc (2.5)	16	6	30	20
13	1.5	0.55	10	PivOH (2)	16	0	19	5
14	1.5	0.55	10	TfOH (0.5 mL)	16	0	0	0
15	1.5	0.55	10	AcOH (0.5 mL)	16	0	0	47
16	2	0.75	10	AcOH (0.5 mL)	24	0	0	62
17	2.5	1.0	10	AcOH (0.5 mL)	24	0	0	60
18	2	0.75	10	AcOH (0.5 mL)	20	0	0	64
19	2	0.75	10	AcOH (0.25 mL)	20	0	0	86

stereocontrol (Scheme 1). Herein, the results from our investigations including a plausible mechanism for the formation of the open-chain carboxamide derivatives **5**/**6** from the Pd(II)-catalyzed C−H arylation followed by ring opening of cyclopropanecarboxamides **1** are reported.

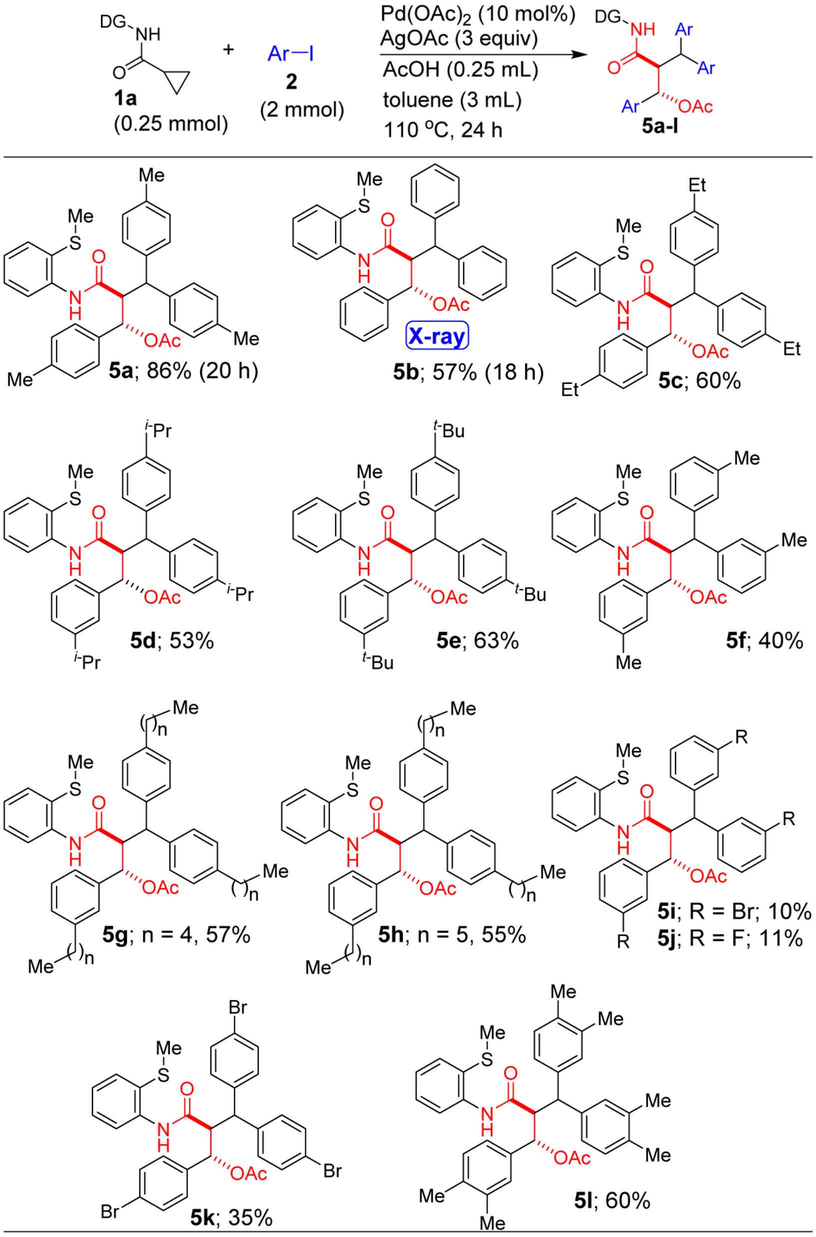
■ RESULTS AND DISCUSSION

To initially explore the Pd(II)-catalyzed C−H arylation followed by ring opening of cyclopropanecarboxamides, we performed optimization reactions using unsubstituted cyclopropanecarboxamide **1a**, which was prepared from the 2-aminothioanisole bidentate ligand. Table 1 shows the results for the $Pd(OAc)_2$-catalyzed reaction of **1a** with excess amounts of *p*-tolyl iodide in the presence of various additives. Upon treatment of cyclopropanecarboxamide **1a** with excess amounts of *p*-tolyl iodide in the presence of the $Pd(OAc)_2$ catalyst and AgOAc, we expected that compound **1a** would undergo mono/bis C−H arylation followed by ring opening to afford the corresponding open-chain carboxamide derivatives. Accordingly, the reaction of **1a** (0.25 mmol) with excess amounts of *p*-tolyl iodide (0.38−2.0 mmol) in the presence of the $Pd(OAc)_2$ catalyst and AgOAc afforded bis-arylated cyclopropanecarboxamide **3a** (yields up to 37%) and monoarylated cyclopropanecarboxamide **4a** (yields up to 40%) along with anticipated ring-opened product **5a** (yields up to 20%, entries 1−7, Table 1).

To obtain ring-opened product **5a** as the major compound in satisfactory yield, we performed the Pd(II)-catalyzed reaction of **1a** with **2a** in the presence of additional additives (e.g., Na_2SO_4, NaOAc and KOAc). These reactions also afforded the corresponding three products (**3a**, **4a** and **5a**) without much selectivity (entries 8−12, Table 1). Next, we performed the Pd(II)-catalyzed reaction of **1a** with **2a** in the presence of PivOH or TfOH, which was also ineffective (entries 13 and 14, Table 1). Fortunately, the $Pd(OAc)_2$/AgOAc catalytic system-based reaction of **1a** with excess amounts of aryl iodide **2a** in the presence of AcOH directly afforded multiple β-C−H arylated open-chain carboxamide (*anti* β-acyloxy amide[17a,b]) **5a** in 47−86% yields (entries 15−19, Table 1). It is important to note that this process, which consists of the $Pd(OAc)_2$/AgOAc-catalytic system-based reaction of **1a** with excess amounts of aryl iodide **2a** in the presence of AcOH, has led to the construction of *anti* β-acyloxy amide **5a**,[18] possessing vicinal stereocenters with a high degree of stereocontrol with the formation of a new C−O bond and three new C−C bonds.

After determining the suitable reaction conditions for obtaining multiple β-C−H arylated open-chain carboxamide **5a** from **1a**, we investigated the generality of this protocol and performed the diastereoselective C−H arylation followed by ring opening of substrate **1a** using various aryl iodides (Table 2). Using the optimized reaction conditions (entry 19, Table 1), we performed the $Pd(OAc)_2$/AgOAc catalytic system-based diastereoselective C−H arylation followed by ring opening of substrate **1a** with different aryl iodides, which furnished the corresponding multiple β-C−H arylated open-chain carboxamides (*anti* β-acyloxy amides) **5a**−**l** in 10−86% yields (Table 2). We observed that the C−H arylation followed by ring opening of substrate **1a** proceeded smoothly and afforded products **5a**−**h** and **5l** when the Pd(II)-catalyzed reaction of substrate **1a** was performed with aryl iodides that possessed electron-donating alkyl groups (e.g., Me, Et and ^{i}Pr) at the *para* or *meta* position of the aryl ring in the aryl iodides. However, we experienced some difficulty when the Pd(II)-catalyzed C−H arylation reaction of substrate **1a** was performed with aryl

Table 2. Pd(II)-Catalyzed C−H Arylation Followed by Ring Opening of Cyclopropanecarboxamide 1a[18]



iodides that possessed electron-withdrawing groups (i.e., Br, F and NO_2) at the *para* or *meta* position of the aryl ring in the aryl iodides. Therefore, the $Pd(OAc)_2$/AgOAc catalytic system-based reaction of substrate **1a** with aryl iodides possessing electron-withdrawing groups afforded corresponding products **5i−k** in low yields. Although a clear reason is not known at this stage, we assume that the aryl iodides that possess electron-withdrawing groups may be less reactive than aryl iodides containing alkyl groups under our experimental conditions.

Next, we investigated diastereoselective C−H arylation followed by ring opening of cyclopropanecarboxamide using cyclopropanecarboxamide **1b**, which was assembled from 8-aminoquinoline bidentate ligand (Table 3). The $Pd(OAc)_2$/AgOAc catalytic system-based diastereoselective C−H arylation followed by ring opening of cyclopropanecarboxamide **1b** with different aryl iodides in AcOH afforded the corresponding multiple β-C−H arylated open-chain carboxamides **6a−e** (*anti* β-acyloxy amides possessing vicinal stereocenters) in 20−75% yields (Table 3). In these studies, we have revealed the concept of Pd(II)-catalyzed C−H arylation followed by ring opening of cyclopropanecarboxamides using unsubstituted cyclopropanecarboxamides **1a** and **1b** as the substrates. Next, we examined the Pd(II)-catalyzed C−H arylation followed by ring opening of cyclopropanecarboxamides using various monoarylated cyclopropanecarboxamides **4a**/**8**/**9**/**13**/**14**/**15b** (*cis* isomers) and **15a** (*trans* isomer) as the substrates (Scheme 2).

The Pd(II)-catalyzed C−H arylation followed by ring opening of *cis* cyclopropanecarboxamides **8** and **9** with aryl iodides **2c**/**2b** furnished the corresponding multiple β-C−H arylated open-chain carboxamides **5c** (61%) and **5b** (39%, Scheme 2). It is important to note that the substituents present at the *para* positions of the respective aryl iodides (**2c**/**2b**) and the substituents present at the *para* positions of the aryl rings of the respective substrates (**8**/**9**) were identical. Therefore, the Pd(II)-catalyzed C−H arylation followed by ring opening of **8**/**9** with **2c**/**2b** furnished corresponding products **5c** and **5b**, in

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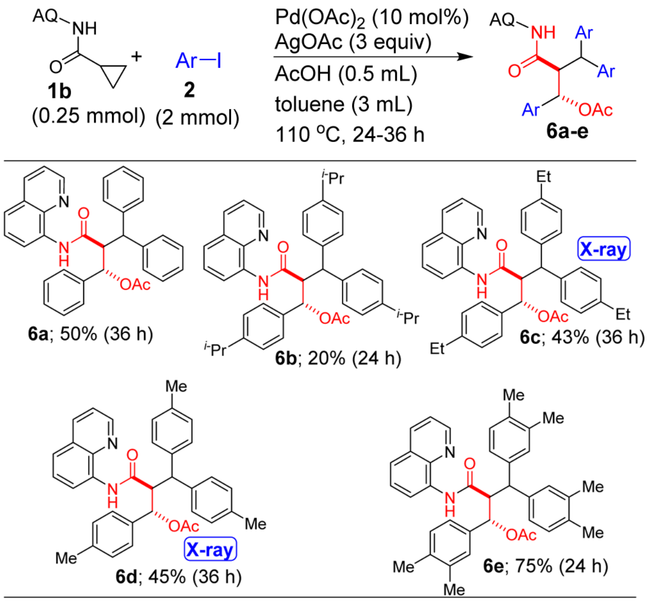
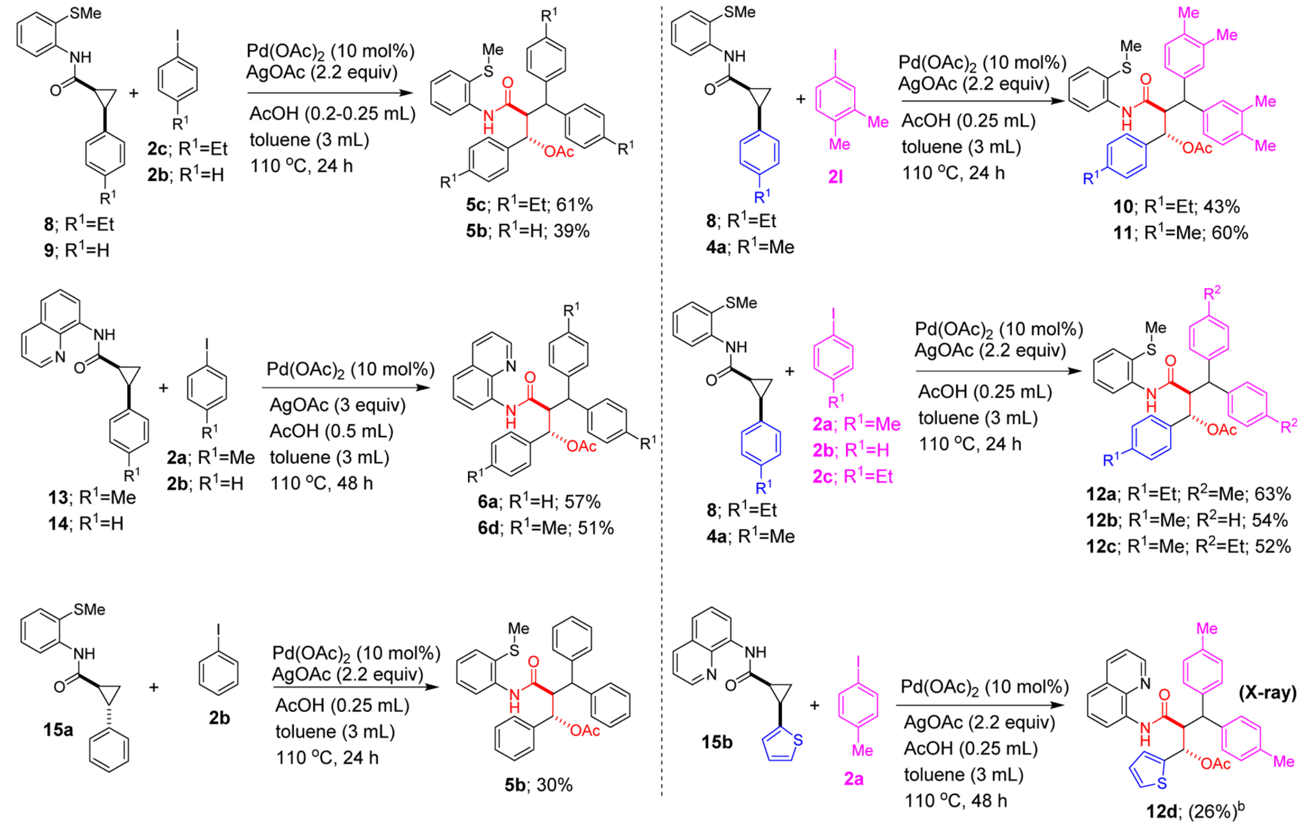
Table 3. Pd(II)-Catalyzed C−H Arylation Followed by Ring Opening of Cyclopropanecarboxamide 1b[18]



which the corresponding aryl rings had identical substituents at the *para/meta* positions. Similar to the reactions involving substrates **8** and **9**, the Pd(II)-catalyzed C−H arylation followed by ring opening of the *cis* cyclopropanecarboxamides **13** and **14** with *para*-substituted aryl iodides **2a** and **2b** afforded the corresponding multiple β-C−H arylated open-chain carboxamides **6d** (51%) and **6a** (57%, Scheme 2). Additionally, the Pd(II)-catalyzed C−H arylation followed by ring opening of the *trans* cyclopropanecarboxamide **15a** with iodobenzene also furnished multiple β-C−H arylated open-chain carboxamides **5b** in 30% yield (Scheme 2).[18c]

The Pd(II)-catalyzed C−H arylation followed by ring opening of *cis* cyclopropanecarboxamides **4a** and **8** with the corresponding aryl iodides **2a−c** and **2l** furnished the respective multiple β-C−H arylated open-chain carboxamides **10**,**11** (43−60%) and **12a−c** (52−63%, Scheme 2).[18] It is important to note that the substituents present at the *para/meta* positions of the respective aryl iodides **2a−c** and **2l** and the substituents present at the *para* positions of the aryl rings of the respective substrates **4a** and **8** were not identical. Therefore, the Pd(II)-catalyzed C−H arylation followed by ring opening of **4a** and **8** with **2a−c** and **2l** furnished corresponding products **10**,**11** and **12a−c**, in which the corresponding aryl rings did not contain identical substituents at the *para* positions.[18] Along this line, the Pd(II)-catalyzed C−H arylation followed by ring opening of *cis* cyclopropanecarboxamide **15b** with **2a** furnished the respective multiple β-C−H arylated open-chain carboxamide **12d** in 26% yield (Scheme 2). The structure and stereochemistry of compound **12d** were unambiguously established based on X-ray structure analysis (see SI for the X-ray structure of the compound **12d**).

Scheme 2. Pd(II)-Catalyzed C−H Arylation Followed by Ring Opening of Cyclopropanecarboxamides 4a, 8, 9, 13, 14 and 15a,b[a,18]



[a]The reactions were performed using the corresponding carboxamide (0.25 mmol) and ArI (1.2 mmol). [b]This reaction was performed using carboxamide **15b** (0.25 mmol) and ArI (2 mmol).

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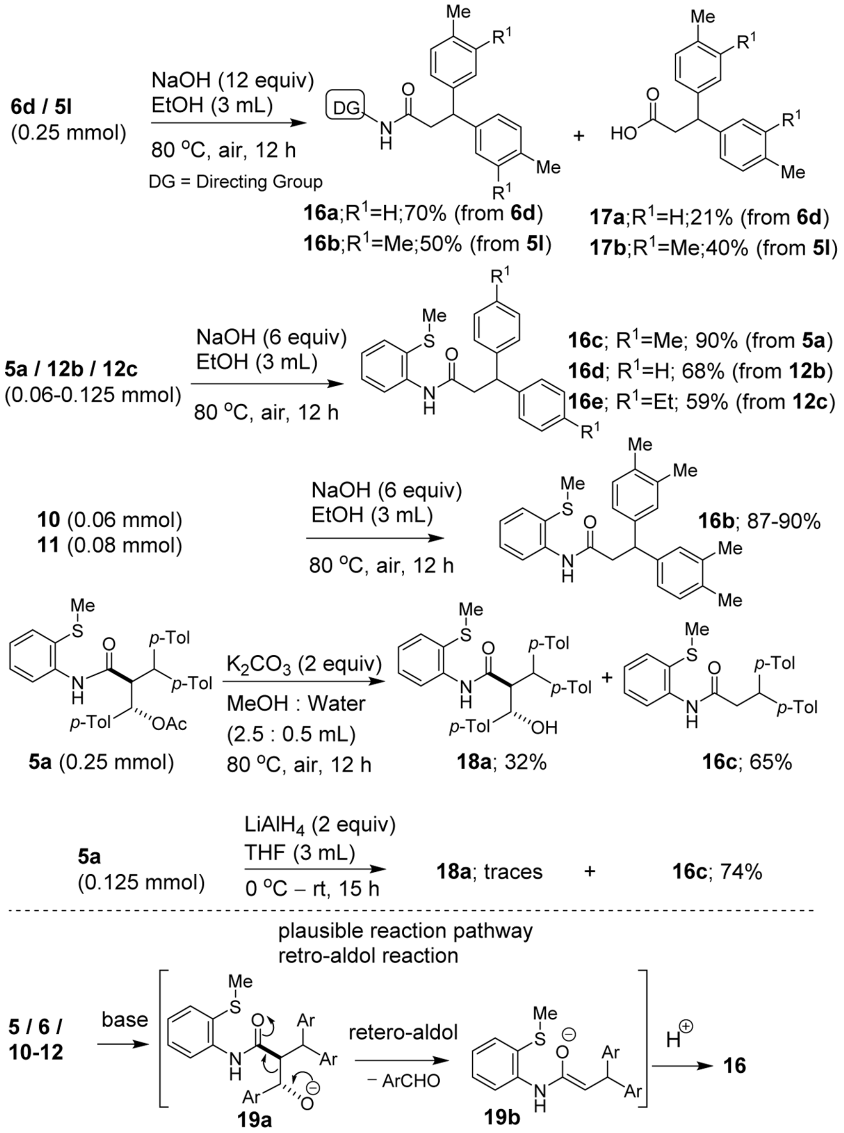
Scheme 3. Representative Synthetic Transformations



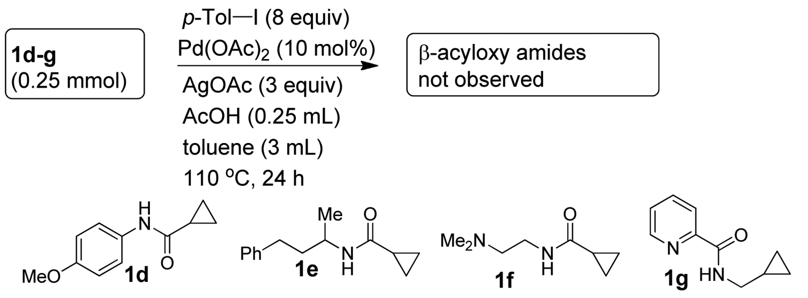
We also performed synthetic transformations to remove the directing groups from the representative multiple β-C–H arylated open-chain carboxamides that were obtained from the Pd(II)-catalyzed C–H arylation followed by ring opening of cyclopropanecarboxamide. Initially, we attempted the amide hydrolysis reaction of *anti* β-acyloxy amide **6d** with 12 equiv of NaOH in EtOH, and this reaction afforded carboxamide **16a**, which contain the directing group, and carboxylic acid **17a** (formed from carboxamide **16a**, Scheme 3). Similarly, the amide hydrolysis reaction of *anti* β-acyloxy amide **5l** with 12 equiv of NaOH in EtOH afforded carboxamide **16b** and carboxylic acid **17b** (formed from carboxamide **16b**, Scheme 3). Then, the treatment of *anti* β-acyloxy amide **5a** with less NaOH (6 equiv) in EtOH only furnished carboxamide **16c**, and in this case, the corresponding carboxylic acid was not detected. In addition, we reacted carboxamides **10**, **11** and **12b,c** possessing different aryl groups at the 1,3-positions with less NaOH (6 equiv) to afford corresponding carboxamides **16b,d,e** (Scheme 3).

Next, the amide hydrolysis reaction was investigated under mild reaction conditions. We performed the amide hydrolysis of *anti* β-acyloxy amide **5a** in the presence of K_2CO_3 in MeOH, and this reaction afforded β-hydroxy amide **18a** and carboxamide **16c**.[17c] In addition, the reaction of *anti* β-acyloxy amide **5a** in the presence of $LiAlH_4$ afforded carboxamide **16c**. We also attempted the amide hydrolysis and removal of the directing groups (i.e., 8-aminoquinoline and 2-(methylthio)-aniline) under acidic conditions. However, these trials were not fruitful at this stage (see the SI for further trials in this regard). In the base-mediated amide hydrolysis reactions of the substrates investigated in Scheme 3, we expected the removal of the directing groups (i.e., 8-aminoquinoline and 2-(methylthio)aniline) as well as the deprotection of the OAc group present in the corresponding substrates. However, because the products (**5**/**6**/**10**–**12**) obtained from the Pd(II)-catalyzed C–H arylation followed by ring opening of cyclopropanecarboxamides were aldol-type derivatives, these compounds readily underwent retro-aldol type reactions[17b,c] even under mild or strongly basic conditions and furnished corresponding products **16** under the experimental conditions.[17e]

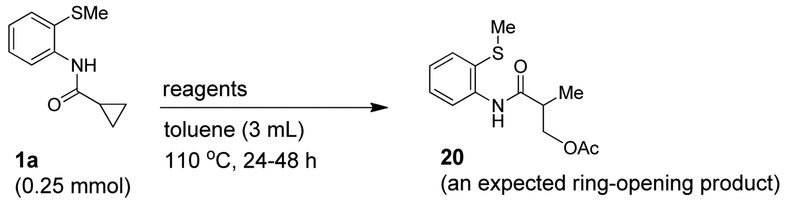
Because the Pd-catalyzed reaction of cyclopropanecarboxamides with aryl iodides in AcOH affords the corresponding open-chain carboxamides **5**/**6**/**10**–**12**, control experiments

Scheme 4. Screening of Other Ligands and Control Experiments Performed Using Substrate 1a[a]

other directing groups screened



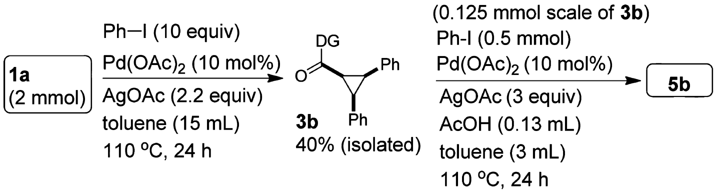
control experiments by using **1a**

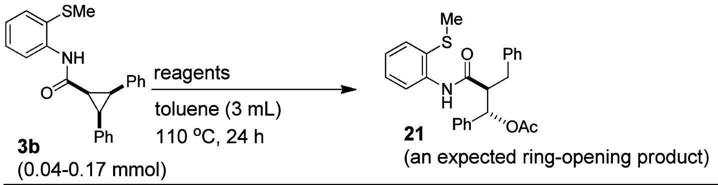


entry	ArI	$Pd(OAc)_2$ (10 mol%)	AgOAc (0.75 mmol)	AcOH (1 mL)	observation
1	✗	✓	✓	✓	no ring-opening product
2	✗	✗	✓	✓	no ring-opening product
3	✗	✗	✗	✓	no ring-opening product

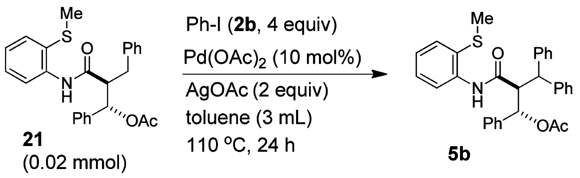
[a] See the SI for the crude NMR spectra of the reactions of compound **1a**.

Scheme 5. Control Experiments Performed Using Substrates 3b and 21 to Elucidate the Proposed Mechanism[a]



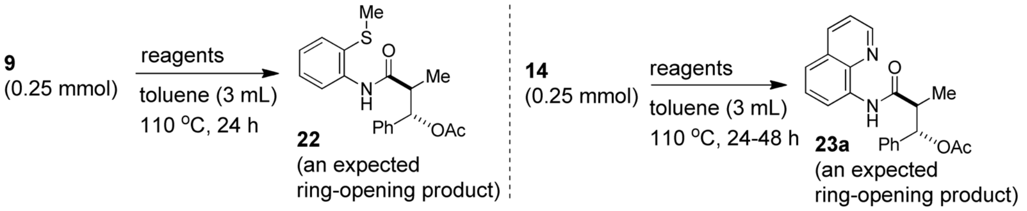


entry	ArI	$Pd(OAc)_2$ (10 mol%)	AgOAc (3 equiv)	AcOH (0.1-1 mL)	observation
1[b]	✗	✓	✓	✓	**21**; yield = 25%
2[c]	✗	✗	✓	✓	no ring-opening product
3[d]	✗	✗	✓	✗	no ring-opening product
4[e]	✗	✗	✗	✓	no ring-opening product

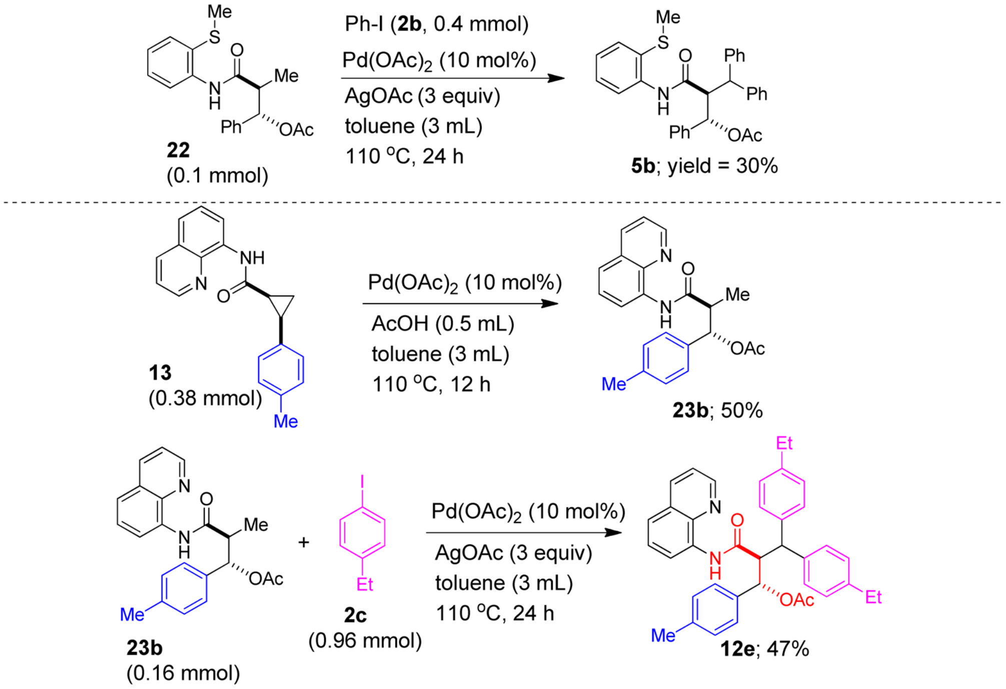


[a] See the SI for the crude NMR spectra of the reactions of compounds **3b** and **21**. [b] 0.17 mmol of **3b** and 0.2 mL of AcOH were used. [c] 0.08 mmol of **3b**, 0.1 mL of AcOH and 2 mL of toluene were used. [d] 0.04 mmol of **3b** was used. [e] 0.125 mmol of **3b** and 1 mL of AcOH were used.

Scheme 6. Control Experiments Performed Using Substrates 9, 13, 14 and 22 to Elucidate the Proposed Mechanism[a]



entry	substrate	ArI	$Pd(OAc)_2$ (10 mol%)	AgOAc (0.75 mmol)	AcOH (0.5 mL)	observation
1	**9**	✗	✓	✓	✓	**22**; yield = 33%
2	**14**[b]	✗	✓	✓	✓	**23a**; yield = 43%
3	**9** (or) **14**[b]	✗	✗	✓	✓	no ring-opening product
4	**9** (or) **14**	✗	✗	✓	✗	no ring-opening product
5	**9**	✗	✗	✗	✓	no ring-opening product
6[c]	**4a**	✗	✗	✗	✓	no ring-opening product
7	**9** (or) **14**	✗	✓	✓	✗	no ring-opening product
8	**14**[b]	✗	✓	✗	✓	**23a**; yield = 47%



[a] See the SI for the crude NMR spectra of the reactions of compounds **4a**, **9**, **13**, **14** and **22**. [b] The reaction time was 48 h. [c] This reaction was performed using **4a** (0.125 mmol) rather than **9** and 1 mL of AcOH.

were performed to determine a plausible mechanism for the formation of products **5**/**6**/**10**−**12** from their corresponding cyclopropanecarboxamide substrates shown in Tables 1−3 and Scheme 2. Initially, we attempted the Pd(II)-catalyzed C−H arylation followed by ring opening of cyclopropanecarboxamides **1d** and **1e**, which contain no directing groups, and cyclopropanecarboxamides **1f** and **1g**, which were prepared using other bidentate ligands. The Pd(II)-catalyzed C−H arylation followed by ring opening of substrates **1d**−**g** failed to yield the corresponding *β*-acyloxy amides (Scheme 4). These reactions revealed that 8-aminoquinoline and 2-(methylthio)-aniline were efficient bidentate ligands and essential for accomplishing the Pd(II)-catalyzed C−H arylation followed by ring opening of the respective cyclopropanecarboxamides shown in Tables 1−3 and Scheme 2.

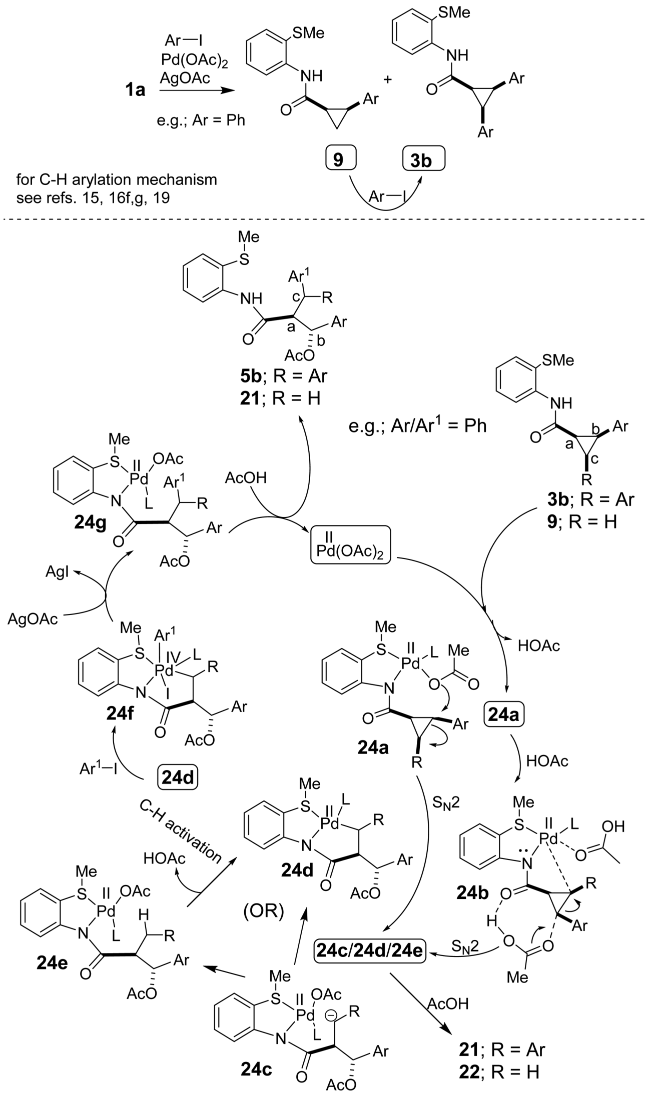
Then, we performed control experiments to understand at what stage the C−C cleavage of the corresponding cyclopropanecarboxamides occurs and how the open-chain carboxamides **5**/**6**/**10**−**12** are formed with a high degree of stereocontrol. Initially, we performed the control experiments using unsubstituted cyclopropanecarboxamide **1a**. The reaction of **1a** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH did not yield β-acyloxy amide **20** (i.e., the expected open-chain compound, entry 1, Scheme 4). The treatment of **1a** with only AgOAc and AcOH did not yield compound **20** (entry 2, Scheme 4). In addition, the reaction of **1a** with only AcOH did not yield expected compound **20** (entry 3, Scheme 4, see the SI for the crude NMR spectra of the reactions of compound **1a**).

Next, we performed control experiments using bis-arylated cyclopropanecarboxamide **3b**. We assembled compound **3b**, which was subjected to a Pd(II)-catalyzed C−H arylation reaction with iodobenzene in the presence of AcOH (Scheme 5). This reaction resulted in the formation of product **5b**, which was directly obtained from **1a** (Table 2). The reaction of **3b** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH afforded expected open-chain compound **21**, which was isolated in 25% yield and characterized (entry 1, Scheme 5). The treatment of **3b** with only AgOAc and AcOH did not yield compound **21** (entry 2, Scheme 5). Similarly, the reaction of **3b** with only AgOAc or AcOH also did not yield compound **21** (entries 3 and 4, Scheme 5). Next, we performed a control experiment involving the C−H arylation reaction of **21** with PhI in the presence of the $Pd(OAc)_2$ catalyst and AgOAc, which resulted in the formation of **5b** (Scheme 5, see the SI for the crude NMR spectra for the reactions of compounds **3b** and **21**).

Although we performed the control reactions using unsubstituted cyclopropanecarboxamide **1a** and bis-arylated cyclopropanecarboxamide **3b**, based on the results shown in Scheme 2, we envisioned that the ring opening can also occur after the monoarylation of **1a** (or before the bis-arylation of **1a**). To validate this hypothesis, control experiments were performed using monoarylated cyclopropanecarboxamides **9** and **14** (Scheme 6). The reaction of substrates **9** and **14** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH yielded the corresponding open-chain compounds (i.e., **22** (33%) and **23a** (43%)), which were isolated and characterized (entries 1 and 2, Scheme 6). Then, a control experiment involving the C−H arylation reaction of **22** with PhI in the presence of the $Pd(OAc)_2$ catalyst and AgOAc resulted in the formation of **5b**, which was obtained directly from **1a** (Table 2). Then, additional control experiments were performed using substrates **9**/**14** by varying the control reagents (entries 3−7, Scheme 6). However, none of these reactions afforded the corresponding compounds **22** and **23a**. A control experiment involving the reaction of **14** with only the $Pd(OAc)_2$ catalyst and AcOH afforded open-chain compound **23a** (entry 8, Scheme 6). In addition, the reaction of **13** with only the $Pd(OAc)_2$ catalyst and AcOH afforded open-chain compound **23b** (Scheme 6). Then, the C−H arylation reaction of **23b** with **2c** in the presence of the $Pd(OAc)_2$ catalyst and AgOAc afforded compound **12e** (47%, Scheme 6). It is important to note that the substituent present at the *para* position of **2c** and the substituent present at the *para* position of the aryl ring of **23b** were not the same.

The formation of compounds **22**/**23a** from the reactions of respective substrates **9**/**14** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH indicated that monoarylated cyclopropanecarboxamides **9**/**14** and ring-opened carboxamides **22**/**23a** were possible intermediates in the reaction of **1a**/**1b** with PhI in the presence of the $Pd(OAc)_2$ catalyst, AgOAc and AcOH. This hypothesis was further validated from the $Pd(OAc)_2$-catalyzed double C−H arylation reaction of the methyl group of **22** with PhI, which yielded compound **5b** (see the SI for the crude NMR spectra for the reactions of compounds **4a**, **9**, **13**, **14**, **22** and **23b**). On the basis of the results from the control reactions (Schemes 4−6) as well as observed products **5**/**6**/**10**−**12** (*anti* β-acyloxy amides), we propose a plausible mechanism for the diastereoselective Pd(II)-catalyzed C−H arylation followed by ring opening of cyclopropanecarboxamides in Scheme 7. The mechanism is proposed on the basis of the generally accepted Pd(II/IV) catalytic cycle mechanism[19] involving bidentate ligand-aided C−H arylation. Based on the control experiments (Schemes 4−6), we have elucidated a possible mechanism for the formation of *anti* β-acyloxy amide **5b** from the Pd(II)-catalyzed reaction of **1a** with PhI in the presence of AgOAc and AcOH. The C−C cleavage of the cyclopropane ring is predicted to only occur after the formation of monoarylation product **9** as well as bis-arylation product **3b.** For the C−C bond cleavage process, both the $Pd(OAc)_2$ catalyst and AcOH are essential. However, AgOAc is not essential for the C−C bond cleavage process, and AgOAc simply helps to regenerate the $Pd(OAc)_2$ catalyst in the C−H arylation process involved in the Pd(II/IV) catalytic cycle mechanism.[19]

Scheme 7. Plausible Mechanism for the Diastereoselective Pd(II)-Catalyzed C−H Arylation Followed by Ring Opening of Cyclopropanecarboxamides[19]



Under the current experimental conditions, compound **3b** or **9** is also expected to be present as **24a**. Then, due to the ring strain, the mono or bis C–H arylated cyclopropanecarboxamide system **24a** undergoes C–C cleavage through (a) a S_N2 type internal attack by the OAc group of the Pd(II) species **24a** or (b) an AcOH-influenced Pd-based C–C activation/C–C bond cleavage[15a] involving a S_N2 type attack by the OAc group of AcOH (as shown in species **24b**). Both of these possibilities could form any one of the plausible intermediates **24c**/**24d**/**24e** with a high degree of stereocontrol. It is important to note that the stereochemistry of the OAc and CONH groups were determined to be *anti* in the X-ray structures (e.g., **5b**, **6c** and **6d**). Notably, the C–H arylation of cyclopropanecarboxamides has been reported to be a stereoselective process,[16g,19] and in the current study, the ring opening of the cyclopropanecarboxamides was determined to be a stereoselective process.

The formation of compounds **21** (entry 1, Scheme 5) and **22** (entry 1, Scheme 6) from **3b** or **9** confirmed the involvement of the plausible ring-opened intermediates **24c**/**24d**/**24e** in the proposed mechanism. If intermediates **24c**–**e** were not quenched by AcOH, a further C–H arylation of intermediates **24c**/**24d**/**24e** (R = H/Ph) affords product **5b**.[19,20] However, starting from **9** (R = H), if compound **22** was formed after the ring opening and before any further C–H arylation due to the AcOH-mediated quenching of **24c**/**24d**/**24e** (when R = H), the double C–H arylation of the methyl group of **22** would afford compound **5b** (based on the control reaction shown in Scheme 6). Similarly, starting from **3b** (R = Ph), if compound **21** was formed after the ring opening and before any further C–H arylation due to the AcOH-mediated quenching of **24c**/**24d**/**24e** (when R = Ph), the C–H arylation of the methylene group of **21** would afford compound **5b** (based on the control reaction shown in Scheme 5). Moreover, the second arylation of **9** may be a slow reaction due to the formation of the corresponding sterically crowded trisubstituted cyclopropanecarboxamide **3b**. Therefore, the ring opening of **9** may occur before the C–H arylation to afford **5b** via **24a**–**e** (based on the control reaction shown in Scheme 6). Furthermore, starting from **1a**, product **5b** may have been directly formed from **9** rather than **3b**.

Finally, based on these discussions and the formation of ring-opened carboxamide **23b** from the reaction of **13** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH (Scheme 6) as well as the subsequent formation of **12e** from the $Pd(OAc)_2$-catalyzed double C–H arylation of the methyl group of **23b** with **2c** indicated the following conclusions. First, the proposed structures of compounds **10**, **11**, **12a**–**d** (Scheme 2) have been confirmed. Second, the arylation of **8**/**4a**/**15b** with the respective aryl iodides **2a**–**c**,**l** may involve the corresponding ring-opened product similar to **23b** as the potential predominantly formed intermediates. In addition, because the second arylation of **8**/**4a**/**15b** may be a slow reaction due to the formation of the corresponding sterically crowded trisubstituted cyclopropanecarboxamide (e.g., compound type **3b**), we believe that the ring opening of **8**/**4a**/**15b** may occur prior to the C–H arylation of **8**/**4a**/**15b**. Therefore, although the respective reactions of **8**/**4a**/**15b** with **2a**–**c** and **2l** are expected to afford more than one isomer, the respective arylation reactions of **8**/**4a**/**15b** with **2a**–**c** and **2l** yielded the respective compounds **10**–**12** (Scheme 2) as the predominant compounds.

■ CONCLUSION

Our studies have demonstrated $Pd(OAc)_2$-catalyzed, bidentate ligand-directed sp^3 C–H activation/arylation followed by ring opening of cyclopropanecarboxamides. The treatment of various cyclopropanecarboxamides with excess amounts of aryl iodides in the presence of the $Pd(OAc)_2$ catalyst, AgOAc and AcOH directly afforded the corresponding multiple β-C–H arylated open-chain carboxamides (*anti* β-acyloxy amides). This method has led to the construction of several *anti* β-acyloxy amides that possess vicinal stereocenters with a high degree of stereocontrol with the formation of a new C–O bond and three new C–C bonds. On the basis of various control experiments, a plausible mechanism has been proposed for the formation of multiple β-C–H arylated open-chain carboxamides from the diastereoselective Pd-catalyzed, bidentate ligand-directed β-C–H arylation and ring opening of cyclopropanecarboxamides. The observed diastereoselectivity and *anti* stereochemistry of the obtained products were confirmed by X-ray structure analysis of representative β-acyloxy amides.

■ EXPERIMENTAL SECTION

General Methods. The melting points of the compounds were uncorrected, and the IR spectra of the products were recorded as thin films or KBr pellets. The ^1H and $^{13}C\{^1H\}$ NMR spectra of all of the compounds were recorded on 400 and 100 MHz spectrometers, respectively, using TMS as an internal standard. The HRMS measurements of the samples were obtained from QTOF mass analyzer using the electrospray ionization (ESI) method. Column chromatography was performed using neutral alumina (in some cases, silica gel 100–200 mesh was used). The cyclopropanecarboxamides that were employed in the Pd(II)-catalyzed C–H arylation reactions were prepared from their corresponding acid chlorides and amines using standard literature procedures. The reactions were performed in anhydrous solvents, which were prepared using standard procedures, under a nitrogen atmosphere. The isolated yields of all of the compounds are reported, and the yields were not optimized. In most cases, the purification of the crude reaction mixtures yielded only the major diastereomer in pure form and did not afford any other characterizable compounds. Compounds **1a**,[16g] **1b**,[16g] **1d**,[21a] **1g**,[15c] **3b**,[16g] **15a**/**15b**,[16g] **13**,[16g] **14**,[16g] **16d**,[19b] and **17a**[21b] have been previously reported in the literature.

General Procedure for the Preparation of 1a,b/1d–g/15a. To a dry round-bottom (RB) flask, an appropriate ligand/amine (1 mmol), triethyl amine (1.1 mmol) and DCM (6 mL) were added under a nitrogen atmosphere. To this solution, the corresponding acid chloride (1 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 20 h. After the reaction period, the mixture was diluted with DCM (2 × 10 mL) and transferred to a separatory funnel, and the DCM solution was washed with water followed by an aq. $NaHCO_3$ solution (2–5 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum, and purification of the crude reaction mixture by column chromatography (EtOAc/hexane) furnished products **1a,b**/**1d–g**/**15a**.

General Procedure for the Pd(II)-Catalyzed C–H Arylation/Ring Opening of 1a/1b and the Preparation of 5a–l/6a–e. To an oven-dried RB flask, an appropriate cyclopropanecarboxamide (0.25 mmol, 1 equiv), the corresponding aryl iodide (2 mmol, 8 equiv), $Pd(OAc)_2$ (5.6 mg, 10 mol %, 0.1 equiv), AgOAc (125 mg, 0.75 mmol, 3 equiv), AcOH (0.25–0.5 mL) and anhydrous toluene (2–3 mL) were added, and the reaction mixture was refluxed at 110 °C for 16–36 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc (15–20 mL), transferred to a separatory funnel and washed with a dilute aq. $NaHCO_3$ solution (2–5 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum, and purification of the reaction crude mixture by column chromatography on neutral alumina furnished the corresponding multiple C–H arylated aliphatic carboxamides **5a**–**l**/

6a−e (β-acyloxy amide derivatives) (see the corresponding Tables/Schemes for specific examples).

General Procedure for the Pd(II)-Catalyzed Mono C−H Arylation of 1a/1b and the Preparation of 4a/8/9/13/14/15b.[16g] To an oven-dried RB flask, an appropriate cyclopropanecarboxamide (1.0 mmol, 1 equiv), the corresponding aryl iodide (4 mmol, 4 equiv), Pd(OAc)$_2$ (11.2 mg, 5 mol %, 0.05 equiv), AgOAc (367 mg, 2.2 mmol, 2.2 equiv) and anhydrous toluene (6−8 mL) were added, and the reaction mixture was refluxed at 110 °C for 15 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated under vacuum, and purification of the resulting reaction mixture by column chromatography on neutral alumina furnished the corresponding carboxamides **4a**/**8**/**9**/**13**/**14**/**15b**.

General Procedure for the Pd(II)-Catalyzed bis C−H Arylation of 1a and the Preparation of 3b.[16g] To an oven-dried RB flask, cyclopropanecarboxamide **1a** (1.0 mmol, 1 equiv), iodobenzene (10 mmol, 10 equiv), Pd(OAc)$_2$ (22.4 mg, 10 mol %, 0.1 equiv), AgOAc (367 mg, 2.2 mmol, 2.2 equiv) and anhydrous toluene (6−8 mL) were added, and the reaction mixture was refluxed at 120 °C for 20−24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated under vacuum, and purification of the resulting reaction mixture by column chromatography on neutral alumina furnished the corresponding carboxamide **3b** (careful repetitive purification was performed to obtain the pure compound **3b**).

General Procedure for the Pd(II)-Catalyzed C−H Arylation/Ring-Opening of 4a/8/9/13−15 and the Preparation of 5c,b/6a,d/10/11/12a−d. To an oven-dried RB flask, an appropriate cyclopropanecarboxamide (0.25 mmol, 1 equiv), the corresponding aryl iodide (1.2−1.5 mmol, 4.8−6 equiv), Pd(OAc)$_2$ (5.6 mg, 10 mol %, 0.1 equiv), AgOAc (92 mg, 0.55 mmol, 2.2 equiv), AcOH (0.25 mL) and anhydrous toluene (2−3 mL) were added, and the reaction mixture was refluxed at 110 °C for 24−48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc (15−20 mL), transferred to a separatory funnel and washed with a dilute aq. NaHCO$_3$ solution (2−5 mL). The organic layer was separated, dried over Na$_2$SO$_4$ and concentrated under vacuum, and purification of the reaction crude mixture by column chromatography on neutral alumina furnished the corresponding multiple C−H arylated aliphatic carboxamides **5c**,**b**/**6a**,**d**/**10**/**11**/**12a**−**d** (β-acyloxy amide derivatives).

General Procedure for the K$_2$CO$_3$-Mediated Hydrolysis Carboxamide 5a and the Preparation of 18a/16c. To a RB flask (with a capacity of 25 mL) fitted with a condenser, a solution of carboxamide **5a** (0.25 mmol) dissolved in a mixture of methanol (2.5 mL), water (0.5 mL) and K$_2$CO$_3$ (69 mg, 2 equiv) were sequentially added. The reaction mixture was heated at 80 °C for 12 h in an open atmosphere. Then, the reaction mixture was transferred to a separatory funnel with the aid of a syringe. The reaction mixture was diluted with ethyl acetate and washed with a dilute aq. Na$_2$CO$_3$ solution (5−10 mL). The combined organic layers were separated and concentrated under vacuum, and purification of the reaction mixture on neutral alumina furnished products **18a**/**16c**.

General Procedure for the LiAlH$_4$-Mediated Reduction of Carboxamide 5a and the Preparation of 16c. To a dry RB flask containing carboxamide **5a** (0.125 mmol, 1 equiv) in THF (3 mL), LiAlH$_4$ (10 mg, 0.25 mmol, 2 equiv) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for a total period of 15 h. After this period, the THF was evaporated, and the reaction mixture was diluted with EtOAc and water. Then, the reaction mixture was transferred to a separatory funnel, and the layers were separated. The organic layer was concentrated under vacuum, and purification of the reaction mixture on neutral alumina furnished products **16c**.

General Procedure for the NaOH-Mediated Hydrolysis of Carboxamides 5a,l/6d/10/11/12b,c. To a RB flask (with a capacity of 25 mL) fitted with a condenser, a solution of an appropriate carboxamide (0.25 mmol) dissolved in ethanol (3 mL) and NaOH (6 or 12 equiv) were sequentially added. The reaction mixture was heated at 80 °C for 12 h in an open atmosphere. Then, EtOH was removed under vacuum, and the reaction mixture was diluted with ethyl acetate (10−15 mL) and washed with aq. 1 N NaOH (5 mL × 2). The organic layer was concentrated under vacuum, and purification of the reaction mixture on a neutral alumina column furnished the corresponding products **16a**−**e**. Then, the combined aqueous layers were acidified with 1 N HCl (15 mL × 2) to achieve a pH of ∼2. The aqueous layers were extracted using ethyl acetate (10 mL × 2), and the combined organic layers were dried over anhydrous Na$_2$SO$_4$ and evaporation under vacuum to afford the corresponding carboxylic acids **17a**,**b**.

*N-(2-(Methylthio)phenyl)cyclopropanecarboxamide (**1a**).*[16g] Following the general procedure, **1a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as a colorless solid; mp 69−71 °C; Yield: 45% (93 mg); IR (KBr) 3264, 3005, 2916, 1651, 1578 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.53 (br. s, 1H), 8.27 (d, 1H, J = 6.0 Hz), 7.44 (d, 1H, J = 7.7 Hz), 7.26−7.21 (m, 1H), 7.03 (t, 1H, J = 7.4 Hz), 2.36 (s, 3H), 1.63−1.58 (m, 1H), 1.10−1.06 (m, 2H), 0.87−0.82 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 172.0, 138.5, 132.7, 128.7, 125.2, 125.2, 124.2, 120.8, 18.9, 16.0, 8.2; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{11}$H$_{14}$NOS: 208.0796, found 208.0793.

*N-(Quinolin-8-yl)cyclopropanecarboxamide (**1b**).*[16g] Following the general procedure, **1b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colorless solid; mp 81−83 °C; Yield: 83% (176 mg); IR (KBr) 3242, 3351, 1676, 1525, 1487 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.05 (br. s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.76 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.56−7.49 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 1.87−1.81 (m, 1H), 1.20−1.16 (m, 2H), 0.96−0.91 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 172.3, 148.1, 138.2, 136.4, 134.7, 128.0, 127.5, 121.6, 121.2, 116.4, 16.3, 8.2; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{13}$H$_{13}$N$_2$O: 213.1028, found 213.1035.

(1S,2S*)-N-(2-(Methylthio)phenyl)-2-phenylcyclopropanecarboxamide (**15a**).*[16g] Following the general procedure, **15a** (*trans* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 10:90) as a colorless solid; mp 119−121 °C; Yield: 78% (220 mg); IR (KBr) 3434, 3242, 3098, 1649, 1593 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.61 (br. s, 1H), 8.41 (d, 1H, J = 7.8 Hz), 7.51 (d, 1H, J = 7.6 Hz), 7.36−7.24 (m, 4H), 7.19 (d, 2H, J = 7.3 Hz), 7.10 (t, 1H, J = 7.3 Hz), 2.69−2.64 (m, 1H), 2.41 (s, 3H), 1.90−1.86 (m, 1H), 1.80−1.76 (m, 1H), 1.46−1.41 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 170.3, 140.5, 138.6, 133.2, 129.1, 128.6, 126.5, 126.2, 124.7, 124.2, 120.4, 28.0, 26.1, 19.2, 16.7; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{17}$H$_{18}$NOS: 284.1109, found 284.1090.

*N-(4-Methoxyphenyl)cyclopropanecarboxamide (**1d**).*[21a] Following the general procedure, **1d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a pink colored solid; mp 134−136 °C; Yield: 68% (130 mg); IR (KBr) 3283, 3095, 2822, 1648, 1555 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 (br. s, 1H), 7.41 (d, 2H, J = 8.9 Hz), 6.83 (d, 2H, J = 8.9 Hz), 3.79 (s, 3H), 1.53−1.49 (m, 1H), 1.07−1.03 (m, 2H), 0.82−0.77 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 172.1, 156.2, 131.4, 121.8, 114.0, 55.5, 15.4, 7.7; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{11}$H$_{14}$NO$_2$: 192.1025, found 192.1020.

*N-(4-Phenylbutan-2-yl)cyclopropanecarboxamide (**1e**).* Following the general procedure, **1e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colorless solid; mp 109−111 °C; Yield: 92% (199 mg); IR (KBr) 3270, 3094, 2967, 1638, 1550 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31−7.28 (m, 2H), 7.21−7.18 (m, 3H), 6.01 (br. s, 1H), 4.13- 4.05 (m, 1H), 2.67 (t, 2H, J = 8.4 Hz), 1.84−1.73 (m, 2H), 1.38−1.34 (m, 1H), 1.19 (d, 3H, J = 6.6 Hz), 0.99−0.94 (m, 2H), 0.74−0.69 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 173.0, 141.9, 128.4, 128.4, 125.9, 45.2, 38.8, 32.6, 21.1, 14.8, 7.0, 6.9; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{14}$H$_{20}$NO: 218.1545, found 218.1538.

*N-(2-(Dimethylamino)ethyl)cyclopropanecarboxamide (**1f**).* Following the general procedure, **1f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colorless liquid ; Yield: 8% (13 mg); IR (DCM) 3241, 3189, 3096, 1592, 1561 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (dd, 1H, J_1 = 11.5 Hz, J_2 = 5.6 Hz), 2.85 (br. s, 1H), 2.41 (t, 2H, J = 6.0), 2.23 (s, 6H), 1.42−1.35 (m, 1H), 0.96−0.91 (m, 2H), 0.73−0.68 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.7, 58.0, 45.1, 36.9, 14.6, 7.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_8H_{17}N_2O$: 157.1341, found 157.1338.

*N-(Cyclopropylmethyl)picolinamide (**1g**).*[15c] Following the general procedure, **1g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless liquid ; Yield: 63% (111 mg); IR (DCM) 3241, 3186, 3092, 1667, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57−8.56 (m, 1H), 8.21 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 8.16 (br. s, 1H), 7.85 (dt, 1H, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 7.44−7.41 (m, 1H,), 3.34 (dd, 2H, J_1 = 7.0 Hz, J_2 = 6.0 Hz), 1.13−1.08 (m, 1H), 0.58−0.54 (m, 2H), 0.32−0.28 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.1, 150.1, 148.0, 137.3, 126.1, 122.2, 44.2, 10.8, 3.5; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{10}H_{13}N_2O$: 177.1028, found 177.1024.

(1S,2R*,3S*)-N-(2-(Methylthio)phenyl)-2,3-di-p-tolylcyclopropanecarboxamide (**3a**).* Following the general procedure, **3a** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 2:98) as a colorless semisolid; Yield: 35% (28 mg); IR (KBr) 3241, 3094, 1692, 1578, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (br. s, 1H), 8.26 (d, 1H, J = 8.0 Hz), 7.40 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.23−7.19 (m, 1H), 7.14 (d, 4H, J = 8.1 Hz), 7.02 (d, 4H, J = 8.1 Hz), 7.03−6.98 (m, 1H), 2.96 (d, 2H, J = 9.4 Hz), 2.60 (t, 1H, J = 9.4 Hz), 2.30 (s, 6H), 2.11 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.0, 138.6, 135.9, 133.1, 131.2, 130.9, 128.8, 128.8, 128.4, 123.9, 120.6, 29.7, 29.2, 28.2, 21.1, 18.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{25}NNaOS$: 410.1555, found 410.1540.

(1R,2S*)-N-(2-(Methylthio)phenyl)-2-(p-tolyl)cyclopropanecarboxamide (**4a**).* Following the general procedure, **4a** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless solid; mp 77−79 °C; Yield: 56% (166 mg); IR (KBr) 3234, 3014, 2919, 1681, 1652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (br. s, 1H), 8.10 (d, 1H, J = 7.4 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.23−7.21 (m, 3H), 7.08 (d, 2H, J = 7.9 Hz), 7.01 (t, 1H, J = 7.4 Hz), 2.60 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.6 Hz), 2.31 (s, 3H), 2.30 (s, 3H), 2.18−2.13 (m, 1H), 1.87−1.83 (m, 1H), 1.43−1.38 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.9, 138.6, 138.6, 136.1, 133.4, 133.1, 133.0, 128.9, 124.6, 123.9, 120.6, 25.4, 25.1, 21.1, 18.9, 10.8; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{19}NNaOS$: 320.1085, found 320.1105.

(1S,2R*,3S*)-N-(2-(Methylthio)phenyl)-2,3-diphenylcyclopropanecarboxamide (**3b**).*[16g] Following the general procedure, **3b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 2:98) as a colorless solid; mp 92−94 °C; Yield: 40% (144 mg); IR (KBr) 3337, 3091, 1692, 1578, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br. s, 1H), 8.23 (d, 1H, J = 8.0 Hz), 7.40 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.25−7.16 (m, 11H), 7.0 (t, 1H, J = 7.5 Hz), 3.02 (d, 2H, J = 9.4 Hz), 2.67 (t, 1H, J = 9.4 Hz), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 138.5, 134.3, 133.1, 131.0, 128.8, 127.6, 126.4, 124.9, 124.0, 120.5, 29.4, 28.5, 19.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{22}NOS$: 360.1422, found 360.1404.

(1S,2S*)-2-(Di-p-tolylmethyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(p-tolyl)propyl acetate (**5a**).* Following the general procedure, **5a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colorless solid; mp 123−125 °C; Yield: 86% (115 mg); IR (KBr) 3241, 3264, 2921, 1739, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br. s, 1H), 7.95 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.43−7.39 (m, 3H), 7.27 (d, 2H, J = 8.1 Hz), 7.22−7.15 (m, 5H), 7.09 (d, 2H, J = 8.1 Hz), 7.04−6.98 (m, 3H), 6.12 (d, 1H, J = 6.3 Hz), 4.29 (d, 1H, J = 11.6 Hz), 3.94 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.3 Hz), 2.36 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 1.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.3, 140.0, 139.1, 138.1, 138.0, 136.2, 135.9, 134.0, 132.7, 129.6, 129.3, 128.8, 128.7, 128.1, 127.5, 125.0, 124.2, 120.6, 76.0, 57.4, 51.3, 21.3, 21.1, 21.0, 20.9, 19.0; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{34}H_{35}NNaO_3S$: 560.2235, found 560.2249.

(1S,2S*)-2-Benzhydryl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-phenylpropyl acetate (**5b**).* Following the general procedure, **5b** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 170−172 °C; Yield: 57% (71 mg); IR (KBr) 3228, 3025, 2920, 1735, 1657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br. s, 1H), 7.80 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.51 (d, 2H, J = 7.3 Hz), 7.40−7.35 (m, 5H), 7.26−7.11 (m, 9H), 7.05 (t, 1H, J = 7.4 Hz), 6.98 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 6.16 (d, 1H, J = 7.0 Hz), 4.40 (d, 1H, J = 11.5 Hz), 3.93 (dd, 1H, J_1 = 11.5 Hz, J_2 = 7.0 Hz), 2.19 (s, 3H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.2, 142.6, 141.9, 137.6, 137.3, 132.5, 128.9, 128.6, 128.6, 128.5, 128.3, 128.2, 127.8, 127.5, 126.8, 126.6, 125.1, 124.4, 120.6, 76.1, 57.6, 52.6, 20.8, 19.0; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{31}H_{29}NNaO_3S$: 518.1766, found 518.1779.

(1S,2S*)-2-(Bis(4-ethylphenyl)methyl)-1-(4-ethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5c**).* Following the general procedure, **5c** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow solid; mp 68−70 °C; Yield: 60% (87 mg); IR (KBr) 3542, 3427, 3024, 2918, 1708, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br. s, 1H), 7.80 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.41 (d, 2H, J = 8.1 Hz), 7.36 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28 (d, 2H, J = 8.2 Hz), 7.22−7.18 (m, 4H), 7.14 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.09 (d, 2H, J = 8.2 Hz), 7.01−6.96 (m, 3H), 6.12 (d, 1H, J = 6.9 Hz), 4.33 (d, 1H, J = 11.5 Hz), 3.90 (dd, 1H, J_1 = 6.9 Hz, J_2 = 11.5 Hz), 2.64 (q, 2H, J = 7.6 Hz), 2.58 (q, 2H, J = 7.6 Hz), 2.47 (q, 2H, J = 7.6 Hz), 2.17 (s, 3H), 1.75 (s, 3H), 1.24 (t, 3H, J = 7.6 Hz), 1.16 (t, 3H, J = 7.6 Hz), 1.07 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.5, 144.3, 142.4, 142.2, 140.2, 139.4, 137.9, 134.6, 132.6, 128.6, 128.3, 128.2, 128.1, 127.6, 127.5, 125.1, 124.2, 120.6, 76.1, 57.8, 51.8, 28.5, 28.4, 28.3, 20.8, 18.9, 15.5, 15.3, 15.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{37}H_{41}NNaO_3S$: 602.2705, found 602.2721.

(1S,2S*)-2-(Bis(4-isopropylphenyl)methyl)-1-(4-isopropylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5d**).* Following the general procedure, **5d** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 109−111 °C; Yield: 53% (82 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br. s, 1H), 7.63 (d, 1H, J = 8.0 Hz), 7.41 (d, 2H, J = 8.1 Hz), 7.33−7.29 (m, 4H), 7.21 (d, 4H, J = 8.2 Hz), 7.11−7.07 (m, 2H), 7.01 (d, 2H, J = 8.1 Hz), 6.94 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 6.14 (d, 1H, J = 7.6 Hz), 4.37 (d, 1H, J = 11.4 Hz), 3.84 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.6 Hz), 2.95−2.87 (m, 1H), 2.85−2.77 (m, 1H), 2.74−2.66 (m, 1H), 2.11 (s, 3H), 1.63 (s, 3H), 1.25 (d, 3H, J = 6.9 Hz), 1.25 (d, 3H, J = 6.9 Hz), 1.15 (d, 6H, J = 6.9 Hz), 1.07 (d, 6H, J = 6.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.7, 148.8, 146.9, 146.8, 140.2, 139.6, 137.7, 135.1, 132.4, 128.5, 128.2, 127.7, 127.4, 126.8, 126.6, 126.3, 125.3, 124.2, 120.7, 76.3, 58.3, 52.4, 33.8, 33.7, 33.5, 24.0, 23.9, 23.8, 23.8, 23.8, 20.7, 18.7; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{40}H_{47}NNaO_3S$: 644.3174, found 644.3190.

(1S,2S*)-2-(Bis(4-(tert-butyl)phenyl)methyl)-1-(4-(tert-butyl)phenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5e**).* Following the general procedure, **5e** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow solid; mp 227−229 °C; Yield: 63% (104 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br. s, 1H), 7.56 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.45 (d, 2H, J = 8.4 Hz), 7.39 (d, 2H, J = 8.4 Hz), 7.34−7.26 (m, 7H), 7.18 (d, 2H, J = 8.4 Hz), 7.07 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 6.94 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 6.17 (d, 1H, J = 7.8 Hz), 4.41 (d, 1H, J = 11.3 Hz), 3.84 (dd, 1H, J_1 = 11.3 Hz, J_2 = 7.8 Hz), 2.09 (s, 3H), 1.58 (s, 3H), 1.32 (s, 9H), 1.22 (s, 9H), 1.15 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.8, 151.0, 149.1, 149.0, 139.8, 139.2, 137.6, 134.9, 132.3, 128.4, 128.0, 127.5, 127.2, 125.6, 125.5, 125.4, 125.2, 124.3, 120.8, 76.3, 58.5, 52.4, 34.5, 34.4, 34.2, 31.4, 31.2, 31.2, 20.6, 18.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{43}H_{53}NNaO_3S$: 686.3644, found 686.3635.

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(1S*,2S*)-2-(Di-m-tolylmethyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(m-tolyl)propyl acetate (**5f**). Following the general procedure, **5f** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 105−107 °C; Yield: 40% (54 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br. s, 1H), 7.90 (dd,1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.38 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.34−7.26 (m, 4H) 7.21−6.97 (m, 9H), 6.86 (d, 1H, J = 7.5 Hz), 6.10 (d, 1H, J = 6.7 Hz), 4.29 (d, 1H, J = 11.6 Hz), 3.92 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 2.40 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.3, 142.7, 141.9, 138.3, 138.0, 137.9, 137.6, 137.2, 132.7, 129.3, 129.2, 128.7, 128.7, 128.5, 128.3, 128.0, 127.5, 127.4, 125.3, 124.9, 124.5, 124.5, 124.2, 120.4, 76.1, 57.6, 52.3, 21.6, 21.5, 21.4, 20.9, 18.9; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{34}H_{35}NNaO_3S$: 560.2235, found 560.2247.

(1S*,2S*)-2-(Bis(4-pentylphenyl)methyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(4-pentylphenyl)propyl acetate (**5g**). Following the general procedure, **5g** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow solid; mp 60−62 °C; Yield: 57% (100 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br. s, 1H), 7.78 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.35 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28 (d, 2H, J = 8.2 Hz), 7.29−7.17 (m, 4H), 7.13 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.07 (d, 2H, J = 8.2 Hz), 6.99−6.95 (m, 3H), 6.15 (d, 1H, J = 7.2 Hz), 4.34 (d, 1H, J = 11.4 Hz), 3.88 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.2 Hz), 2.59 (t, 2H, J = 7.9 Hz), 2.52 (t, 2H, J = 7.9 Hz), 2.42 (t, 2H, J = 7.9 Hz), 2.16 (s, 3H), 1.72 (s, 3H), 1.66−1.15 (m, 18H), 0.92 (t, 3H, J = 7.0 Hz), 0.87 (t, 3H, J = 7.0 Hz), 0.83 (t, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.6, 143.0, 141.1, 140.9, 140.1, 139.4, 137.8, 134.7, 132.6, 128.8, 128.6, 128.6, 128.2, 128.2, 127.7, 127.5, 125.1, 124.2, 120.6, 76.2, 58.0, 52.1, 35.6, 35.5, 35.4, 31.6, 31.5, 31.4, 31.2, 31.0, 30.9, 22.6, 22.5, 22.5, 20.8, 18.9, 14.1, 14.0, 14.0; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{46}H_{59}NNaO_3S$: 728.4113, found 728.4096.

(1S*,2S*)-2-(Bis(4-hexylphenyl)methyl)-1-(4-hexylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5h**). Following the general procedure, **5h** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as pale yellow solid; mp 68−70 °C; Yield: 55% (102 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br. s, 1H), 7.78 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.39 (d, 2H, J = 8.1 Hz), 7.35 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.20−7.17 (m, 4H), 7.12 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.06 (d, 2H, J = 8.2 Hz), 6.98−6.95 (m, 3H), 6.14 (d, 1H, J = 7.2 Hz), 4.34 (d, 1H, J = 11.4 Hz), 3.86 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.2 Hz), 2.59 (t, 2H, J = 7.9 Hz), 2.52 (t, 2H, J = 7.9 Hz), 2.41 (t, 2H, J = 7.9 Hz), 2.16 (s, 3H), 1.71 (s, 3H), 1.65−1.19 (m, 24H), 0.91 (t, 3H, J = 6.9 Hz), 0.91 (t, 3H, J = 6.9 Hz), 0.85 (t, 3H, J = 6.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.6, 143.1, 141.1, 140.9, 140.1, 139.4, 137.8, 134.7, 132.6, 128.8, 128.6, 128.6, 128.2, 128.2, 127.6, 127.5, 125.1, 124.2, 120.6, 76.2, 58.0, 52.0, 35.7, 35.6, 35.4, 31.8, 31.7, 31.7, 31.5, 31.3, 31.2, 29.1, 29.0, 28.9, 22.6, 22.6, 22.5, 20.8, 18.9, 14.1, 14.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{49}H_{65}NNaO_3S$: 770.4583, found 770.4565.

(1S*,2S*)-2-(Bis(3-bromophenyl)methyl)-1-(3-bromophenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5i**). Following the general procedure, **5i** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown colored solid; mp 161−163 °C; Yield: 10% (73 mg); IR (KBr) 3322, 3064, 2925, 1744, 1676, 1572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br. s, 1H), 7.78 (d, 1H, J = 8.1 Hz), 7.60 (s, 1H), 7.50 (s, 1H), 7.43−7.38 (m, 5H), 7.31−7.02 (m, 8H), 6.04 (d, 1H, J = 7.0 Hz), 4.33 (d, 1H, J = 11.4 Hz), 3.78 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.0 Hz), 2.27 (s, 3H), 1.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.5, 167.3, 143.9, 143.2, 139.2, 137.0, 132.2, 131.8, 131.4, 130.7, 130.6, 130.4, 130.4, 130.2, 129.9, 128.6, 127.0, 126.6, 126.3, 125.8, 124.9, 123.1, 122.8, 122.4, 120.8, 75.1, 57.2, 51.8, 20.7, 18.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{31}H_{27}Br_3NO_3S$: 729.9262, found 729.9246.

(1S*,2S*)-2-(Bis(3-fluorophenyl)methyl)-1-(3-fluorophenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5j**). Following the general procedure, **5j** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown solid; mp 176−178 °C; Yield: 11% (15 mg); IR (KBr) 3314 3067, 2930, 1743, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br. s, 1H), 7.79 (d, 1H, J = 8.1 Hz), 7.41−7.35 (m, 2H), 7.28−6.94 (m, 12H), 6.79 (t, 1H, J = 7.2 Hz), 6.10 (d, 1H, J = 6.9 Hz), 4.42 (d, 1H, J = 11.4 Hz), 3.81 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.0 Hz), 2.25 (s, 3H), 1.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.5, 167.4, 163.1 (d, J_{C-F} = 245 Hz), 162.8 (d, J_{C-F} = 245 Hz), 162.6 (d, J_{C-F} = 245 Hz), 144.3 (d, J_{C-F} = 6.9 Hz), 143.7 (d, J_{C-F} = 6.9 Hz), 139.5 (d, J_{C-F} = 6.9 Hz), 137.1, 132.3, 130.6 (d, J_{C-F} = 8.4 Hz), 130.3 (d, J_{C-F} = 8.3 Hz), 129.8 (d, J_{C-F} = 8.3 Hz), 128.6, 125.6, 124.8, 124.0 (d, J_{C-F} = 2.8 Hz), 123.6 (d, J_{C-F} = 2.5 Hz), 123.2 (d, J_{C-F} = 2.8 Hz), 120.7, 115.6 (d, J_{C-F} = 20.8 Hz), 115.2 (d, J_{C-F} = 21.5 Hz), 114.7 (d, J_{C-F} = 21.7 Hz), 114.3 (d, J_{C-F} = 22.3 Hz), 114.1 (d, J_{C-F} = 20.8 Hz), 114.0 (d, J_{C-F} = 21.0 Hz). 75.2 (d, J_{C-F} = 1.5 Hz), 57.3, 51.8, 20.7, 18.8; HRMS (ESI) m/z [M - H]$^+$ calcd for $C_{31}H_{25}F_3NO_3S$: 548.1507, found 548.1522.

(1S*,2S*)-2-(Bis(4-bromophenyl)methyl)-1-(4-bromophenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5k**). Following the general procedure, **5k** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 187−189 °C; Yield: 35% (64 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (br. s, 1H), 7.77 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.42−7.38 (m, 3H), 7.32 (d, 4H, J = 8.3 Hz), 7.21−7.16 (m, 3H), 7.09−7.04 (m, 3H), 6.03 (d, 1H, J = 6.6 Hz), 4.23 (d, 1H, J = 11.5 Hz), 3.80 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.6 Hz), 2.27 (s, 3H), 1.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.6, 167.4, 140.8, 140.0, 136.9, 135.6, 132.2, 132.0, 131.9, 131.4, 129.9, 129.4, 129.3, 128.5, 125.7, 125.0, 122.9, 121.1, 120.9, 120.8, 75.1, 56.7, 51.0, 20.9, 18.7; HRMS (ESI) m/z [M - H] calcd for $C_{31}H_{25}Br_3NO_3S$: 727.9105, found 727.9108.

(1S*,2S*)-2-(Bis(3,4-dimethylphenyl)methyl)-1-(3,4-dimethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (**5l**). Following the general procedure, **5l** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown colored semisolid; Yield: 60% (87 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br. s, 1H), 8.03 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.43 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28−7.12 (m, 6H), 7.06−6.93 (m, 5H), 6.04 (d, 1H, J = 6.0 Hz), 4.19 (d, 1H, J = 11.6 Hz), 3.94 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.0 Hz), 2.32 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 1.89 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 168.5, 140.6, 139.6, 138.3, 136.9, 136.7, 136.5, 136.0, 134.8, 134.5, 134.4, 132.9, 130.1, 129.8, 129.7, 129.4, 129.1, 128.8, 128.8, 125.5, 124.8, 124.7, 124.5, 124.0, 120.4, 75.9, 57.3, 51.1, 21.1, 20.0, 19.9, 19.8, 19.6, 19.4, 19.3, 19.0; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{37}H_{41}NO_3SNa$: 602.2705, found 602.2708.

(1S*,2S*)-2-Benzhydryl-3-oxo-1-phenyl-3-(quinolin-8-ylamino)propyl acetate (**6a**). Following the general procedure, **6a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 171−173 °C; Yield: 50% (63 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.48 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.54 (d, 2H, J = 7.4 Hz), 7.48−7.38 (m, 7H), 7.27−7.14 (m, 6H), 7.13 (t, 2H, J = 7.7 Hz), 6.99 (t, 1H, J = 7.4 Hz), 6.16 (d, 1H, J = 5.8 Hz), 4.39 (d, 1H, J = 11.7 Hz), 4.22 (dd, 1H, J_1 = 11.7 Hz, J_2 = 5.8 Hz), 1.94 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.9, 168.0, 147.9, 143.1, 142.0, 138.3, 136.6, 136.3, 134.1, 129.0, 128.5, 128.4, 128.0, 127.8, 127.6, 127.6, 127.4, 126.8, 126.3, 121.6, 121.3 116.4, 75.8, 56.8, 51.6, 21.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{33}H_{28}N_2O_3$: 501.2178, found 501.2172.

(1S,2S*)-2-(Bis(4-isopropylphenyl)methyl)-1-(4-isopropylphenyl)-3-oxo-3-(quinolin-8-ylamino)propyl acetate* ***(6b)***. Following the general procedure, **6b** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 201−203 °C; Yield: 20% (31 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.44 (dd, 1H, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.46−7.41 (m, 5H), 7.31 (d, 2H, J = 8.2 Hz), 7.23 (d, 2H, J = 8.2 Hz), 7.15 (d, 2H, J = 8.2 Hz), 7.01 (d, 2H, J = 8.2 Hz), 6.94 (dd, 2H, J = 8.2 Hz), 6.15 (d, 1H, J = 6.6 Hz), 4.36 (d, 1H, J = 11.6 Hz), 4.11 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.6 Hz), 2.93−2.87 (m, 1H), 2.76−2.59 (m, 2H), 1.80 (s, 3H), 1.26 (d, 3H, J = 6.9 Hz), 1.25 (d, 3H, J = 6.9 Hz), 1.06 (d, 3H, J = 6.9 Hz), 1.05 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.9 Hz), 0.97 (d, 3H, J = 6.9 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 168.6, 148.6, 147.8, 146.8, 146.3, 140.6, 139.7, 138.2, 136.2, 134.5, 134.2, 128.3, 127.8, 127.4, 127.4, 127.3, 126.8, 126.5, 126.1, 121.4, 121.1, 116.2, 76.1, 57.5, 51.4, 33.7, 33.7, 33.4, 24.0, 23.7, 23.7, 20.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{42}H_{47}N_2O_3$: 627.3587, found 627.3610.

(1S,2S*)-2-(Bis(4-ethylphenyl)methyl)-1-(4-ethylphenyl)-3-oxo-3-(quinolin-8-ylamino)propyl acetate* ***(6c)***. Following the general procedure, **6c** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 160−162 °C; Yield: 43% (63 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.50 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.6 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.48−7.41 (m, 5H), 7.30 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.0 Hz), 7.01 (d, 2H, J = 8.0 Hz), 6.93 (d, 2H, J = 8.0 Hz), 6.12 (d, 1H, J = 5.8 Hz), 4.32 (d, 1H, J = 11.7 Hz), 4.16 (dd, 1H, J_1 = 11.8 Hz, J_2 = 6.0 Hz), 2.65 (q, 2H, J = 7.6 Hz), 2.51 (q, 2H, J = 7.6 Hz), 2.40 (q, 2H, J = 7.6 Hz), 1.91 (s, 3H), 1.25 (t, 3H, J = 7.6 Hz), 1.08 (t, 3H, J = 7.6 Hz), 1.0 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 168.4, 147.9, 144.2, 142.4, 141.8, 140.6, 139.5, 138.2, 136.2, 134.3, 134.0, 128.4, 128.3, 128.0, 127.8, 127.5, 127.5, 127.4, 127.4, 121.5, 121.2, 116.3, 75.9, 57.0, 50.8, 28.5, 28.4, 28.2, 21.1, 15.5, 15.2, 15.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{39}H_{41}N_2O_3$: 585.3117, found 585.3134.

(1S,2S*)-2-(Di-p-tolylmethyl)-3-oxo-3-(quinolin-8-ylamino)-1-(p-tolyl)propyl acetate* ***(6d)***. Following the general procedure, **6d** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 174−176 °C; Yield: 45% (61 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (br. s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.55 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.6 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.49−7.43 (m, 3H), 7.41 (d, 2H, J = 7.9 Hz), 7.27 (d, 2H, J = 8.7 Hz), 7.21 (d, 2H, J = 7.9 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.02 (d, 2H, J = 8.0 Hz), 6.93 (d, 2H, J = 8.0 Hz), 6.10 (d, 1H, J = 5.2 Hz), 4.27 (d, 1H, J = 11.8 Hz), 4.19 (dd, 1H, J_1 = 11.8 Hz, J_2 = 5.2 Hz), 2.35 (s, 3H), 2.25 (s, 3H), 2.12 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 168.2, 147.9, 140.5, 139.2, 138.3, 138.1, 136.3, 136.2, 135.5, 134.4, 133.5, 129.7, 129.2, 128.7, 128.2, 127.8, 127.5, 127.5, 127.3, 121.5, 121.2, 116.4, 75.7, 56.6, 50.4, 21.2, 21.2, 21.1, 20.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{36}H_{35}N_2O_3$: 543.2648, found 543.2659.

(1S,2S*)-2-(Bis(3,4-dimethylphenyl)methyl)-1-(3,4-dimethylphenyl)-3-oxo-3-(quinolin-8-ylamino)propyl acetate* ***(6e)***. Following the general procedure, **6e** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 134−136 °C; Yield: 75% (109 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (br. s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.59 (t, 1H, J = 4.5 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.49−7.46 (m, 3H), 7.31−7.28 (m, 2H), 7.20−7.17 (m, 3H), 6.99−6.90 (m, 4H), 6.09 (d, 1H, 1H, J = 4.5 Hz), 4.23−4.21 (m, 2H), 2.34 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.10 (s, 6H), 2.03 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 168.5, 147.9, 141.0, 139.8, 138.3, 136.9, 136.6, 136.4, 136.3, 135.9, 134.8, 134.5, 134.2, 134.0, 130.2, 129.8, 129.8, 129.3, 129.1, 129.0, 127.8, 127.5, 125.6, 124.9, 124.3, 121.5, 121.2, 116.4, 75.8, 56.7, 50.4, 21.2, 20.0, 19.9, 19.7, 19.5, 19.4, 19.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{39}H_{41}N_2O_3$: 585.3117, found 585.3105.

(1R,2S*)-2-(4-Ethylphenyl)-N-(2-(methylthio)phenyl)cyclopropanecarboxamide* ***(8)***. Following the general procedure, **8** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 10:90) as pale brown color solid; mp 95−97 °C; Yield: 51% (159 mg); IR (KBr) 3252, 2999, 2961, 2919, 1659, 1585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (br. s, 1H), 8.09 (d, 1H, J = 4.8 Hz), 7.45 (d, 1H, J = 7.6 Hz), 7.28−7.19 (m, 3H), 7.11 (d, 1H, J = 7.6 Hz), 7.03−6.99 (m, 1H), 2.60 (dd, 1H, J_1 = 15.4 Hz, J_2 = 7.6 Hz), 2.60 (q, 2H, J = 7.6 Hz), 2.29 (s, 3H), 2.19−2.13 (m, 1H), 1.87−1.83 (m, 1H), 1.43−1.38 (m, 1H), 1.21 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 142.5, 138.6, 133.7, 133.1, 128.9, 127.7, 124.6, 124.6, 124.0, 120.6, 28.5, 25.5, 25.2, 18.9, 15.5, 10.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{21}NNaOS$: 334.1242, found 334.1243.

(1R,2S*)-N-(2-(Methylthio)phenyl)-2-phenylcyclopropanecarboxamide* ***(9)***. Following the general procedure, **9** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless solid; mp 112−114 °C; Yield: 62% (176 mg); IR (KBr) 3231, 3019, 2917, 1652, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (br. s, 1H), 8.07 (d, 1H, J = 7.5 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.34 (d, 2H, J = 7.2 Hz), 7.30−7.25 (m, 2H), 7.22−7.17 (m, 2H), 7.01 (t, 1H, J = 7.3 Hz), 2.63 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.6 Hz), 2.31 (s, 3H), 2.21−2.16 (m, 1H), 1.90−1.86 (m, 1H), 1.45−1.40 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.7, 138.5, 136.5, 133.0, 129.0, 128.1, 126.7, 124.7, 124.6, 124.0, 120.7, 25.7, 25.2, 18.9, 10.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{17}NNaOS$: 306.0929, found 306.0925.

(1S,2S*)-2-(Bis(3,4-dimethylphenyl)methyl)-1-(4-ethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate* ***(10)***. Following the general procedure, **10** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 118−120 °C; Yield: 43% (62 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br. s, 1H), 7.96 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.41 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.26−7.09 (m, 10H), 7.0 (dt, 1H, J_1 = 7.3 Hz, J_2 = 1.3 Hz), 6.94 (d, 1H, J = 8.3 Hz), 6.10 (d, 1H, J = 6.2 Hz), 4.22 (d, 1H, J = 11.7 Hz), 3.93 (dd, 1H, J_1 = 11.7 Hz, J_2 = 6.2 Hz), 2.60 (q, 2H, J = 7.6 Hz), 2.31 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 1.85 (s, 3H), 1.19 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 168.5, 144.3, 140.5, 139.6, 138.1, 136.8, 136.5, 134.8, 134.5, 134.3, 132.8, 130.1, 129.8, 129.6, 129.1, 128.7, 127.6, 127.5, 125.5, 124.9, 124.6, 124.1, 120.5, 76.0, 57.4, 51.3, 28.6, 20.9, 20.0, 19.9, 19.4, 19.3, 19.0, 15.3; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{37}H_{41}NNaO_3S$: 602.2705, found 602.2706.

(1S,2S*)-2-(Bis(3,4-dimethylphenyl)methyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(p-tolyl)propyl acetate* ***(11)***. Following the general procedure, **11** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 121−123 °C; Yield: 60% (85 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (br. s, 1H), 7.98 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.42 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.28−7.07 (m, 10H), 7.01 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 6.93 (d, 1H, J = 8.3 Hz), 6.09 (d, 1H, J = 6.1 Hz), 4.20 (d, 1H, J = 11.7 Hz), 3.94 (dd, 1H, J_1 = 11.7 Hz, J_2 = 6.1 Hz), 2.31 (s, 6H), 2.25 (s, 6H), 2.13 (s, 3H), 2.08 (s, 3H), 1.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 168.4, 140.5, 139.5, 138.1, 138.1, 136.9, 136.5, 134.8, 134.5, 134.0, 132.7, 130.1, 129.8, 129.6, 129.6, 129.1, 128.7, 127.5, 125.5, 124.9, 124.6, 124.1, 120.5, 75.9, 57.3, 51.1, 21.2, 21.0, 20.0, 19.9, 19.4, 19.3, 19.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{36}H_{39}NNaO_3S$: 588.2548, found 588.2553.

(1S,2S*)-2-(Di-p-tolylmethyl)-1-(4-ethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate* ***(12a)***. Following the general procedure, **12a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 99−101 °C; Yield: 63% (89 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (br. s, 1H), 7.90 (d, 1H, J = 7.8 Hz),

7.40−7.37 (m, 3H), 7.25 (d, 2H, J = 8.0 Hz), 7.19−7.14 (m, 5H), 7.09 (d, 1H, J = 7.9 Hz), 7.01−6.97 (m, 3H), 6.10 (d, 1H, J = 6.4 Hz), 4.29 (d, 1H, J = 11.6 Hz), 3.91 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.5 Hz), 2.59 (q, 2H, J = 7.6 Hz), 2.34 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 1.83 (s, 3H), 1.17 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.8, 168.4, 144.3, 140.0, 139.2, 138.0, 136.2, 135.9, 134.3, 132.7, 129.6, 129.3, 128.7, 128.1, 127.6, 127.5, 127.5, 125.0, 124.2, 120.5, 76.0, 57.5, 51.4, 28.5, 21.0, 20.9, 20.9, 19.0, 15.3; HRMS (ESI) *m*/*z* $[\mathrm{M + H}]^+$ calcd for $\mathrm{C_{35}H_{37}NNaO_3S}$: 574.2392, found 574.2392.

(1S,2S*)-2-Benzhydryl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(p-tolyl)propyl acetate* (**12b**). Following the general procedure, **12b** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 146−148 °C; Yield: 54% (69 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 8.06 (br. s, 1H), 7.84 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.51 (d, 2H, J = 7.4 Hz), 7.41−7.37 (m, 5H), 7.25 (t, 1H, J = 7.4 Hz), 7.19−7.13 (m, 5H), 7.09−7.03 (m, 3H), 6.99 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 6.12 (d, 1H, J = 6.8 Hz), 4.37 (d, 1H, J = 11.5 Hz), 3.94 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.8 Hz), 2.29 (s, 3H), 2.20 (s, 3H), 1.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.8, 168.2, 142.7, 141.9, 138.2, 137.7, 134.1, 132.5, 128.9, 128.7, 128.6, 128.4, 127.8, 127.5, 126.8, 126.5, 125.1, 124.3, 120.6, 76.0, 57.5, 52.4, 21.2, 20.9, 18.9; HRMS (ESI) *m*/*z* $[\mathrm{M + H}]^+$ calcd for $\mathrm{C_{32}H_{31}NNaO_3S}$: 532.1922, found 532.1940.

(1S,2S*)-2-(Bis(4-ethylphenyl)methyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(p-tolyl)propyl acetate* (**12c**). Following the general procedure, **12c** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; mp 79−81 °C; Yield: 52% (73 mg); IR (KBr) 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 8.02 (br. s, 1H), 7.83 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.41 (d, 2H, J = 8.1 Hz), 7.38 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.28 (d, 2H, J = 7.2 Hz), 7.21 (d, 2H, J = 8.1 Hz), 7.16 (d, 2H, J = 8.0 Hz), 7.16−7.13 (m, 1H), 7.07 (d, 2H, J = 8.0 Hz), 7.01−6.97 (m, 3H), 6.11 (d, 1H, J = 6.7 Hz), 4.31 (d, 1H, J = 11.5 Hz), 3.90 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 2.64 (q, 2H, J = 7.6 Hz), 2.24 (q, 2H, J = 7.6 Hz), 2.29 (s, 3H), 2.19 (s, 3H), 1.78 (s, 3H), 1.24 (t, 3H, J = 7.6 Hz), 1.07 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.8, 168.4, 142.4, 142.1, 140.1, 139.3, 138.1, 137.9, 134.3, 132.6, 128.8, 128.6, 128.3, 128.2, 128.0, 127.6, 127.5, 125.1, 124.2, 120.7, 76.1, 57.7, 51.7, 28.4, 28.3, 21.2, 20.9, 18.9, 15.5, 15.3; HRMS (ESI) *m*/*z* $[\mathrm{M + Na}]^+$ calcd for $\mathrm{C_{36}H_{39}NNaO_3S}$: 588.2548, found 588.2549.

(1S,2S*)-2-(Di-p-tolylmethyl)-3-oxo-3-(quinolin-8-ylamino)-1-(thiophen-2-yl)propyl acetate* (**12d**). Following the general procedure, the compound **12d** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a pale yellow color solid; mp 114−116 °C; Yield: 26% (35 mg); IR (KBr) 3240, 3094, 1687, 1591, 1527 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 10.0 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.59 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.7 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.49−7.46 (m, 3H), 7.35 (d, 2H, J = 7.9 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.20 (d, 1H, J = 5.0 Hz), 7.17 (d, 2H, J = 7.8 Hz), 6.95−6.93 (m, 3H), 6.87 (dd, 1H, J_1 = 4.9 Hz, J_2 = 3.8 Hz), 6.39 (d, 1H, J = 5.6 Hz), 4.40 (d, 1H, J = 11.7 Hz), 4.16 (dd, 1H, J_1 = 11.7 Hz, J_2 = 5.7 Hz), 2.33 (s, 3H), 2.11 (s, 3H), 2.0 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.7, 168.2, 147.9, 140.2, 138.8, 138.6, 138.3, 136.3, 135.7, 134.3, 129.6, 129.3, 128.2, 127.8, 127.5, 127.4, 127.3, 126.3, 126.0, 121.5, 121.3, 116.6, 116.4, 71.9, 56.5, 50.6, 21.1, 21.0, 20.9; HRMS (ESI) *m*/*z* $[\mathrm{M + H}]^+$ calcd for $\mathrm{C_{33}H_{31}N_2O_3S}$: 535.2055, found 535.2035.

(1S,2S*)-2-(Bis(4-ethylphenyl)methyl)-3-oxo-3-(quinolin-8-ylamino)-1-(p-tolyl)propyl acetate* (**12e**). Following the general procedure, **12e** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a colorless liquid; Yield: 47% (43 mg); IR (DCM) 3241, 2963, 1741, 1690, 1527 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 9.87 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.51 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.5 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.49−7.42 (m, 5H), 7.29 (d, 2H, J = 7.3 Hz), 7.22 (d, 2H, J = 7.9 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.01 (d, 2H, J = 8.0 Hz), 6.93 (d, 2H, J = 8.0 Hz), 6.12 (d, 1H, J = 5.6 Hz), 4.30 (d, 1H, J = 11.8 Hz), 4.17 (dd, 1H, J_1 = 11.8 Hz, J_2 = 5.6 Hz), 2.65 (q, 2H, J = 7.6 Hz), 2.40 (q, 2H, J = 7.6 Hz), 2.24 (s, 3H), 1.95 (s, 3H), 1.25 (2.65 (t, 3H, J = 7.6 Hz), 0.99 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.9, 168.3, 147.9, 142.4, 141.8, 140.6, 139.5, 138.3, 138.0, 136.3, 134.3, 133.7, 128.7, 128.4, 128.3, 128.0, 127.8, 127.5, 127.4, 127.4, 121.5, 121.2, 116.4, 75.8, 56.9, 50.7, 28.4, 28.2, 21.2, 21.1, 15.5, 15.1; HRMS (ESI) *m*/*z* $[\mathrm{M + H}]^+$ calcd for $\mathrm{C_{38}H_{39}N_2O_3}$: 571.2961, found 571.2943.

(1S,2R*)-N-(Quinolin-8-yl)-2-(thiophen-2-yl)cyclopropanecarboxamide* (**15b**). Following the general procedure, **15b** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 2:98) as a brown color liquid; Yield: 41% (121 mg); IR (DCM) 3241, 3191, 3095, 1684, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 9.99 (br. s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65−8.61 (m, 1H), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.50−7.45 (m, 3H), 7.09 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 6.99−6.98 (m, 1H), 6.89 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 2.72 (dd, 1H, J_1 = 16.6 Hz, J_2 = 8.3 Hz), 2.39−2.33 (m, 1H), 1.96−1.92 (m, 1H), 1.57−1.52 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 167.4, 148.0, 140.4, 138.2, 136.4, 134.6, 127.9, 127.5, 126.7, 126.3, 124.1, 121.6, 121.2, 116.4, 25.9, 20.2, 12.8; HRMS (ESI) *m*/*z* $[\mathrm{M + H}]^+$ calcd for $\mathrm{C_{17}H_{15}N_2OS}$: 295.0905, found 295.0893.

N-(Quinolin-8-yl)-3,3-di-p-tolylpropanamide (**16a**). Following the general procedure, **16a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as an orange colored solid; mp 110−112 °C; Yield: 70% (67 mg); IR (KBr) 3353, 3242, 1685, 1524, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 9.79 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.75 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.53−7.46 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.26 (d, 4H, J = 8.0 Hz), 7.12 (d, 4H, J = 8.0 Hz), 4.75 (t, 1H, J = 7.8 Hz), 3.32 (d, 2H, J = 7.8 Hz), 2.30 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.8, 148.0, 141.0, 138.3, 136.3, 135.9, 134.4, 129.3, 127.9, 127.6, 127.4, 121.5, 121.4, 116.5, 46.4, 44.6, 21.0; HRMS (ESI) *m*/*z* $[\mathrm{M + H}]^+$ calcd for $\mathrm{C_{26}H_{25}N_2O}$: 381.1967, found 381.1983.

3,3-Bis(3,4-dimethylphenyl)-N-(2-(methylthio)phenyl)propanamide (**16b**). Following the general procedure, **16b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as a pale yellow solid; mp 111−113 °C; Yield: 50% (50 mg); IR (KBr) 3242, 2919, 1676, 1578, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 8.30 (d, 1H, J = 8.2 Hz), 8.25 (br. s, 1H), 7.45 (d, 1H, J = 7.0 Hz), 7.30−7.26 (m, 1H), 7.09−7.02 (m, 7H), 4.57 (t, 1H, J = 7.8 Hz), 3.15 (d, 2H, J = 7.8 Hz), 2.23 (s, 6H), 2.21 (s, 6H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.7, 141.3, 138.5, 136.8, 134.7, 133.3, 129.9, 129.0, 124.9, 124.8, 124.2, 120.6, 116.4, 46.8, 44.8, 19.9, 19.4, 18.9; HRMS (ESI) *m*/*z* $[\mathrm{M + Na}]^+$ calcd for $\mathrm{C_{26}H_{29}NNaOS}$: 426.1868, found 426.1856.

N-(2-(Methylthio)phenyl)-3,3-di-p-tolylpropanamide (**16c**). Following the general procedure, **16c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as yellow solid; mp 89−91 °C; Yield: 65% (61 mg); IR (KBr) 3330, 2918, 1665, 1577, 1511 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 8.29 (d, 1H, J = 8.3 Hz), 8.26 (br. s, 1H), 7.46 (d, 1H, J = 7.7 Hz), 7.30−7.26 (m, 1H), 7.21 (d, 4H, J = 8.0 Hz), 7.11 (d, 4H, J = 8.0 Hz), 7.05 (t, 1H, J = 7.5 Hz), 4.64 (t, 1H, J = 7.8 Hz), 3.15 (d, 2H, J = 7.8 Hz), 2.31 (s, 6H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.6, 140.8, 138.4, 136.1, 133.3, 129.4, 129.0, 127.5, 125.0, 124.3, 120.6, 46.7, 44.8, 21.0, 19.0; HRMS (ESI) *m*/*z* $[\mathrm{M + Na}]^+$ calcd for $\mathrm{C_{24}H_{25}NNaOS}$: 398.1555, found 398.1565.

N-(2-(Methylthio)phenyl)-3,3-diphenylpropanamide (**16d**).[19b] Following the general procedure, **16d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as yellow solid; mp 87−89 °C; Yield: 68% (14 mg); IR (KBr) 3242, 3098, 1639, 1594, 1446 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ 8.27 (d, 1H, J = 8.4 Hz), 8.25 (br. s, 1H), 7.45 (d, 1H, J = 7.4 Hz), 7.32−7.23 (m, 9H), 7.22−7.19 (m, 2H), 7.05 (t, 1H, J = 7.5 Hz), 4.72 (t, 1H, J = 7.8 Hz), 3.19 (d, 2H, J = 7.8 Hz), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $\mathrm{CDCl_3}$) δ 169.4, 143.5, 138.3, 133.3, 129.0, 128.7, 127.8, 126.7, 125.0, 124.4, 120.6, 47.4, 44.6, 19.0; HRMS (ESI) *m*/*z* $[\mathrm{M + Na}]^+$ calcd for $\mathrm{C_{22}H_{21}NNaOS}$: 370.1242, found 370.1230.

3,3-Bis(4-ethylphenyl)-N-(2-(methylthio)phenyl)propanamide (16e). Following the general procedure, **16e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as a yellow solid; mp 67−69 °C; Yield: 59% (14 mg); IR (KBr) 3243, 3099, 1594, 1115, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, 1H, *J* = 8.3 Hz), 8.25 (br. s, 1H), 7.45 (d, 1H, *J* = 7.7 Hz), 7.27−7.20 (m, 1H), 7.23 (d, 4H, *J* = 8.1 Hz), 7.13 (d, 4H, *J* = 8.1 Hz), 7.04 (t, 1H, *J* = 7.4 Hz), 4.65 (t, 1H, *J* = 7.8 Hz), 3.16 (d, 2H, *J* = 7.8 Hz), 2.60 (q, 4H, *J* = 7.6 Hz), 2.16 (s, 3H), 1.21 (t, 6H, *J* = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.6, 142.4, 141.0, 133.4, 129.4, 129.1, 128.2, 127.6, 124.9, 124.2, 120.6, 46.7, 44.8, 28.4, 19.0, 15.5; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{29}NNaOS$: 426.1868, found 426.1855.

3,3-Di-p-tolylpropanoic acid (17a).[21b] Following the general procedure, **17a** was obtained after the work up as a pale brown semisolid (purity ~95%); Yield: 21% (13 mg); IR (KBr) 3242, 2923, 1704, 1261, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.21 (d, 4H, *J* = 8.0 Hz), 7.09 (d, 4H, *J* = 8.0 Hz), 4.46 (t, 1H, *J* = 7.9 Hz), 3.05 (d, 2H, *J* = 7.9 Hz), 2.26 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.1, 141.5, 135.5, 129.0, 127.5, 46.3, 39.8, 20.1; HRMS (ESI) *m*/*z* [M - H]$^+$ calcd for $C_{17}H_{17}O_2$: 253.1229, found 253.1220.

3,3-Bis(3,4-dimethylphenyl)propanoic acid (17b). Following the general procedure, **17b** was obtained after the work up as pale brown solid; mp 96−98 °C; Yield: 40% (28 mg); IR (KBr) 3242, 3098, 11702, 1593, 1445 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.09 (br. s, 2H), 7.06−7.03 (m, 4H), 4.39 (t, 1H, *J* = 8.0 Hz), 3.04 (d, 2H, *J* = 8.0 Hz), 2.20 (s, 6H), 2.18 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.2, 142.0, 136.1, 134.1, 129.5, 128.9, 124.8, 46.3, 39.8, 19.0, 18.4; HRMS (ESI) *m*/*z* [M - H]$^+$ calcd for $C_{19}H_{21}O_2$: 281.1542, found 281.1529. The carboxylic acid OH signal could not be detected in the ^{1}H NMR spectrum.

(2S*,3S*)-2-(Di-p-tolylmethyl)-3-hydroxy-N-(2-(methylthio)-phenyl)-3-(p-tolyl)propanamide (18a). Following the general procedure, **18a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colorless solid; mp 140−142 °C; Yield: 32% (40 mg); IR (KBr) 3341, 2920, 1677, 1578,1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (br. s, 1H), 8.05 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.43 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.1 Hz), 7.20 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.15 (d, 2H, *J* = 7.8 Hz), 7.11 (d, 2H, *J* = 8.1 Hz), 7.05 (d, 2H, *J* = 8.2 Hz), 7.02−6.99 (m, 3H), 5.01 (t, 1H, *J* = 3.5 Hz), 4.25 (d, 1H, *J* = 11.7 Hz), 3.91 (dd, 1H, J_1 = 11.7 Hz, J_2 = 4.5 Hz), 2.79 (d, 1H, *J* = 3.2 Hz), 2.33 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 140.3, 139.5, 138.3, 137.6, 137.5, 136.3, 135.8, 133.0, 129.8, 129.4, 128.8, 128.8, 128.0, 127.3, 126.6, 125.2, 124.1, 120.6, 74.2, 59.0, 50.0, 21.2, 21.0, 20.9, 19.0; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{34}NO_2S$: 496.2310, found 496.2305.

(1S*,2S*)-2-Benzyl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-phenylpropyl acetate (21).[22] Treatment of **3b** (0.17 mmol) with $Pd(OAc)_2$ (3.8 mg, 10 mol %), AgOAc (84 mg, 3 equiv) and AcOH (0.2 mL) in toluene (3 mL) at 110 °C for 24 h afforded the compound **21** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless semisolid; Yield: 25% (17 mg); IR (KBr) 3240, 3091, 1742, 1686, 1581 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.7 Hz), 7.74 (br. s, 1H), 7.44 (d, 2H, *J* = 7.2 Hz), 7.34−7.15 (m, 10H), 6.98 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 6.09 (d, 1H, *J* = 8.8 Hz), 3.22−3.11 (m, 2H), 3.08−3.02 (m, 1H), 2.17 (s, 3H), 1.91 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 169.3, 138.8, 138.5, 137.7, 133.0, 128.9, 128.8, 128.7, 128.6, 128.4, 126.9, 126.6, 125.3, 124.5, 120.7, 76.7, 57.9, 35.7, 21.3, 18.6; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{25}NNaO_3S$: 442.1453, found: 442.1435.

(1S*,2S*)-2-Methyl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-phenylpropyl acetate (22).[22] Treatment of **9** (0.25 mmol) with $Pd(OAc)_2$ (5.6 mg, 10 mol %), AgOAc (124 mg, 3 equiv) and AcOH (0.5 mL) in toluene (3 mL) at 110 °C for 24 h afforded the compound **22** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless solid; mp 117−119 °C; Yield: 33% (28 mg); IR (KBr) 3236, 3183, 3091, 1738, 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br. s, 1H), 8.22 (d, 1H, *J* = 8.2 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.39−7.24 (m, 6H), 7.06 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 6.04 (d, 1H, *J* = 7.4 Hz), 2.99−2.92 (m, 1H), 2.22 (s, 3H), 2.16 (s, 3H), 1.39 (d, 3H, *J* = 6.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.8, 169.8, 138.6, 138.0, 133.0, 129.0, 128.6, 128.3, 126.6, 125.1, 124.5, 120.6, 77.0, 49.1, 21.2, 18.9, 13.9; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO_3S$: 366.1140, found 366.1125.

(1S*,2S*)-2-Methyl-3-oxo-1-phenyl-3-(quinolin-8-ylamino)propyl acetate (23a).[22] Treatment of **14** (0.25 mmol) with $Pd(OAc)_2$ (5.6 mg, 10 mol %), AgOAc (124 mg, 3 equiv) and AcOH (0.5 mL) in toluene (3 mL) at 110 °C for 24 h afforded the compound **23a** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a colorless liquid; 43% (37 mg); IR (DCM) 3240, 3093, 1741, 1684, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.72 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.5 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55−7.50 (m, 2H), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.39 (d, 2H, *J* = 7.2 Hz), 7.31−7.27 (m, 2H), 7.22 (t, 1H, *J* = 7.3 Hz), 6.13 (d, 1H, *J* = 6.4 Hz), 3.20−3.13 (m, 1H), 2.23 (s, 3H), 1.42 (d, 3H, *J* = 7.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.0, 169.9, 148.1, 138.4, 138.3, 136.4, 134.3, 128.4, 128.2, 127.9, 127.4, 126.7, 121.6, 121.6, 116.6, 76.9, 48.5, 21.2, 13.5; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552, found 349.1536.

(1S*,2S*)-2-Methyl-3-oxo-3-(quinolin-8-ylamino)-1-(p-tolyl)-propyl acetate (23b). Treatment of **13** (0.38 mmol) with $Pd(OAc)_2$ (8.5 mg, 10 mol %) and AcOH (0.5 mL) in toluene (3 mL) at 110 °C for 12 h afforded the compound **23b** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a colorless liquid; Yield: 50% (68 mg); IR (DCM) 3241, 3094, 1742, 1687, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (br. s, 1H), 8.80−8.79 (m, 1H), 8.73 (d, 1H, *J* = 6.6 Hz), 8.17 (d, 1H, *J* = 8.2 Hz), 7.53−7.50 (m, 2H), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.09 (d, 2H, *J* = 7.7 Hz), 6.09 (d, 1H, *J* = 6.4 Hz), 3.19−3.12 (m, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 1.41 (d, 3H, *J* = 6.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.1, 169.9, 148.0, 138.4, 137.9, 136.4, 135.2, 134.4, 129.1, 127.9, 127.5, 126.6, 121.6, 121.5, 116.6, 76.9, 48.4, 21.3, 21.1, 13.6; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_3$: 363.1709, found 363.1695.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01635.

X-ray structure and brief X-ray structure data of the compounds **5b**, **6c**, **6d** and **12d**, copies of ^{1}H and ^{13}C NMR charts of isolated compounds and crude reaction mixtures related to proposed reaction mechanism (PDF)

X-ray structure data of the compound **5b** (CIF)

X-ray structure data of the compound **6c** (CIF)

X-ray structure data of the compound **6d** (CIF)

X-ray structure data of the compound **12d** (CIF)

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Notes

The authors declare no competing financial interest.

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(17) For a selected paper dealing on the synthesis of *β*-acyloxy amides via *β*-acetoxylation of amides, see: (a) Zhou, L.; Lu, W. *Org. Lett.* **2014**, *16*, 508. (b) For a selected recent paper dealing with retro-aldol reaction, see: Ganguly, B.; Kesharwani, M. K.; Matković, M.; Basarić, N.; Sing, A.; Mlinarić-Majerski, K. *J. Phys. Org. Chem.* **2011**, *24*, 578. (c) To support the proposed mechanism, we have recorded the crude NMR for the reaction mixture of the experiment involving amide hydrolysis of **5a** in the presence of K_2CO_3, which revealed the formation of *p*-tolualdehyde via the retro-aldol reaction (see the SI for the crude NMR). (d) On the basis of the literature reports regarding the ring opening reactions of cyclopropanes, during our revisiting of the C−H arylation of cyclopropanes we attained the C−H arylation/ring-opening of cyclopropanecarboxamides (e.g. **1a**), which successfully underwent with excess of aryl iodide in the presence of AcOH. Perhaps, in our previous work, ref 16g, we have missed the ring-opened product which is forming only in negligible quantity based on the optimization reaction Table 1. (e) A literature survey revealed that in general, the removal of bidentate ligands, such as, 8-aminoquinoline and 2-(methylthio)aniline) was successful only under harsh reaction conditions (e.g., see refs 12 and 16a).

(18) Stereochemistry of the compounds **5a−l**, **6a−e**, **10**, **11** and **12a−d**: (a) The *anti* stereochemistry of the compounds **5a−l**, **6a−e**, **10**, **11** and **12a−d** was assigned based on the X-ray structures of the compounds **5b**, **6c**, **6d** and **12d** and the similarity in their NMR spectral pattern. (b) The respective reactions of **4a**, **8**, **15b** with **2a−c** and **2l** are expected to give more than one isomer; however, the compounds **10**, **11** and **12a−d** were obtained as the predominant compounds from the column chromatography purification of the respective crude reaction mixtures and our trials to find out/obtain the formation of any other characterizable by-products were not fruitful. The structures of **10**, **11** and **12a−d** were assigned based on the retro-aldol reaction of **10**, **11**, and **12b**,**c**, which afforded the corresponding compounds **16b**,**d**,**e** (Scheme 3). Further the assignment of stereochemistry and structures of the compounds **10**, **11** and **12a−e** were supported by the single-crystal X-ray structure of the compound **12d**. Additionally, we have isolated the ring-opened carboxamide **23b** (Scheme 6) from **13**. Then, we have performed the $Pd(OAc)_2$-catalyzed double C−H arylation reaction of the methyl group of **23b** with **2c** to afford the compound **12e**. These sequences also supported the assigning of structures/stereochemistry of **10**, **11** and **12a−d**. (c) The reaction of **15a** with iodobenzene also gave the product **5b** (the NMR spectral pattern of **5b** obtained in this reaction was similar to the product **5b** obtained from **1a**).

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(20) (a) While the role of AgOAc is recognized that it helps in the ligand exchange step to regenerate the Pd(II) species (see ref 19), from the optimization reactions (Table 1) it is realized that the presence of AcOH perhaps eases the process of the C−H arylation/ring-opening of cyclopropanecarboxamides in the presence of $Pd(OAc)_2$/AgOAc-catalytic system to afford the multiple C−H arylated aliphatic carboxamides **5**/**6**/**10−12** (*β*-acyloxy amides having *anti* stereochemistry). (b) It is noteworthy that typically, the C−H arylation/ring-opening reactions of the cyclopropanecarboxamides **1a** (unsubstituted cyclopropanecarboxamide) or **9** (monoarylated cyclopropanecarboxamide) or **3b** (bis arylated cyclopropanecarboxamide) afforded the same product **5b**.

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(22) The *anti* stereochemistry of the compounds **21** and **22** was assigned based on their conversion into **5b** and by comparing the NMR of **5b** obtained from **21**/**22** as well as **1a**. In analogy to these reactions, the stereochemistry of **23a** was assigned. Similarly, the *anti* stereochemistry of the compounds **23b**/**12e** was assigned based on the X-ray structure of **12d** and the discussion given in ref 18.

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