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Direct Bis-Arylation of Cyclobutanecarboxamide via Double C−H Activation: An Auxiliary-Aided Diastereoselective Pd-Catalyzed Access to Trisubstituted Cyclobutane Scaffolds Having Three Contiguous Stereocenters and an All-*cis* Stereochemistry

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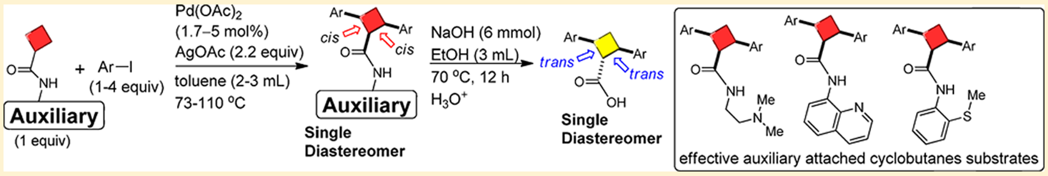
Supporting Information



ABSTRACT: An auxiliary-aided Pd-catalyzed highly diastereoselective double C−H activation and direct bis-arylation of methylene C(sp^3)−H bonds of cyclobutanecarboxamides and the syntheses of several novel trisubstituted cyclobutanecarboxamide scaffolds having an all-*cis* stereochemistry are reported. Extensive screening of various auxiliaries and reaction conditions was performed to firmly establish the optimized reaction conditions required for effecting the mono- or double C−H arylation of cyclobutanecarboxamides. The auxiliary-attached cyclobutanecarboxamides **15a**, **15g**, and **15h**, prepared from the auxiliaries such as, 8-aminoquinoline, 2-(methylthio)aniline, and *N*′,*N*′-dimethylethane-1,2-diamine were found to undergo an efficient direct bis-arylation. The Pd-catalyzed arylation reaction of *N*-(quinolin-8-yl)cyclobutanecarboxamide **15a** with one equivalent or more of aryl iodides, afforded the corresponding bis-arylated cyclobutanecarboxamides **16a−y**. Nevertheless, the Pd-catalyzed arylation of **15a** with just 0.5 equiv of the aryl iodides **13a**, **13b**, **13e**, and **13m**, selectively gave the corresponding monoarylated cyclobutanecarboxamides **17a−17d**. The Pd-catalyzed arylation of **15g** or **15h** with one equivalent or more of aryl iodides afforded the bis-arylated cyclobutanecarboxamides **19a−19c** and **21a−21m**, respectively. However, the Pd-catalyzed arylations of compounds **15g** or **15h** with just 0.5 equiv of aryl iodides were ineffective. The stereochemistry of compounds obtained in this work was unambiguously assigned from the X-ray structures of representative products.

■ INTRODUCTION

Cyclobutane is the second smallest, strained four-membered carbocyclic ring in the family of smallest rings (as the first member in the family is cyclopropane ring) and presents as a core unit of natural products (Figure 1), pharmaceutical agents, and synthetic compounds.[1−3] Several cyclobutane natural products, especially, monoarylated and bis-arylated cyclobutanecarboxamides exhibit a variety of biological activities and medicinal properties.[1−17] For example, incarvillateine has been traditionally used in treating rheumatism and relieving pain as an ancient Chinese crude medicine named as “Jiaohao”.[4] Biyouyanagin[5] is exhibiting substantial activity against HIV and inhibiting cytokine production. Littoralisone[6] is an active agent for increased NGF-induced neurite outgrowth in PC12D cells. Furthermore, cyclobutanes isolated from *Piper nigram* and *Piper chaba* are known to exhibit broad pharmacological activities.[7,8] Various research groups have elegantly completed the total synthesis of several cyclobutane-based natural products by using different routes.[8−17]

It is believed that in Nature the cyclobutane natural products are constructed via the direct coupling of the parent monomeric olefins with a very high degree of stereo- and regiocontrol. On the other hand, in laboratories, the direct [2 + 2] photocycloaddition reaction involving two similar olefins or heterodimerizations of two distinct olefins has been one of the most desirable routes for assembling cyclobutanes (Figure 2).[18,19] However, the experimental synthetic method has limitations such as the head-to-head or head-to-tail type additions, homodimerization and *E*/*Z* isomerization of olefins, thereby leading to the uncontrolled production of a complex mixture of stereoisomers without the stereo- and regiocontrol.[20] Fortunately, the crystal engineering tactic and solid-state photochemistry experiments lead to the assembly of a set of stereochemically defined cyclobutanes.[18,19] Apart from these techniques, there exist only rare examples of direct heterodimerizations of two different olefins leading to the formation of cyclobutanes with a high regio- and stereocontrol.[21,22] Hence, the construction of substituted, especially the monoarylated or bis-arylated, cyclobutanecarboxamides with a high degree of regio- and stereocontrol is a demanding task in organic chemistry

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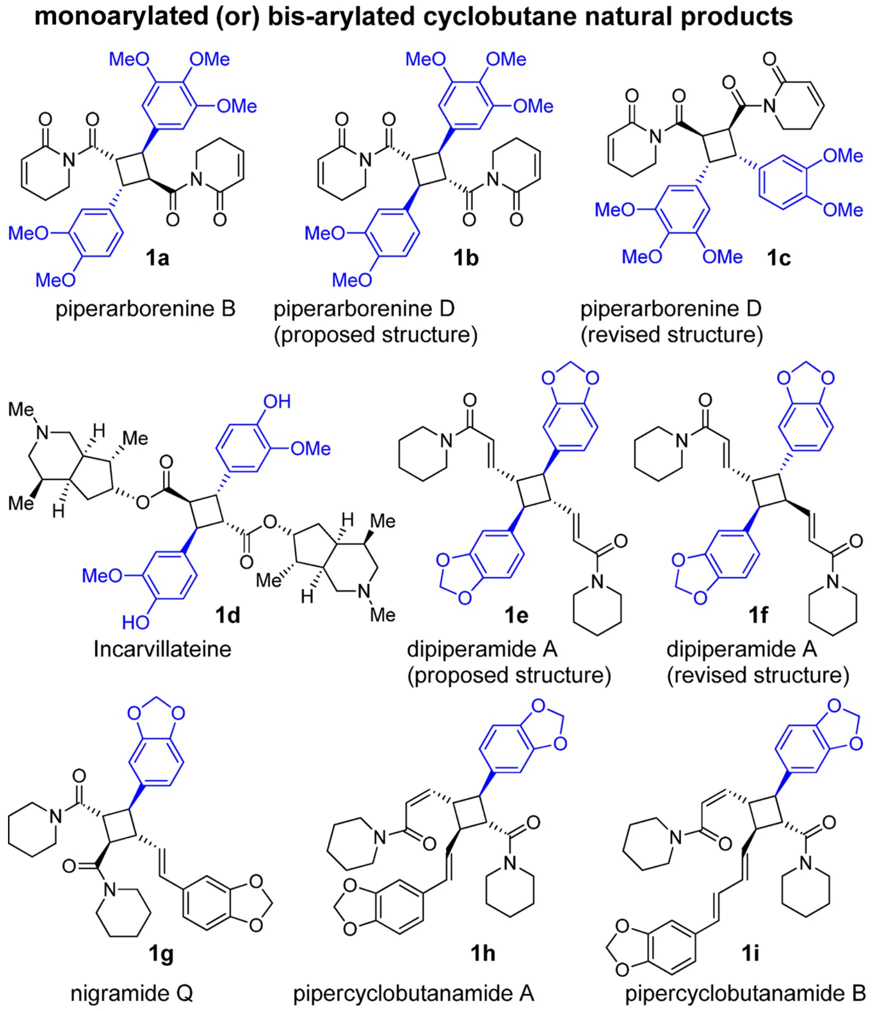


Figure 1. Representative cyclobutane natural products.

due to the fact that many of the bioactive cyclobutane natural products contain an aryl group as one of the substituents.

An efficient and commanding route for the construction of stereodefined, arylated cyclobutanecarboxamides would be the direct metal-catalyzed C−H arylation of the C(sp^3)−H bond of cyclobutanes. However, when compared to the field dealing with the [2 + 2] photocycloaddition-based dimerization of olefins leading to substituted cyclobutanes with an unpredictable stereocontrol, the direct C−H functionalization of cyclobutanes is an underexplored topic of research. To the best of our knowledge there exist only two exceptional reports in this regard,[16,17] nevertheless the C−H activation reactions, especially, the Pd-catalyzed C−H activation/functionalization of C(sp^3)−H bond is one of the potential topics of the present and future research since the direct C−H functionalization reactions are considered to be the attractive methods in terms of simplicity and atom economy.[23−34]

Employing the pioneering Pd-catalyzed C−H arylation strategy developed by Daugulis et al., recently, Baran's group[16,17] reported the synthesis of piperarborenines and pipercyclobutanamide A. Baran's group elegantly established and optimized the reaction condition for an effective monoarylation of **6a** and **7a**, which was a crucial step during the synthesis of cyclobutane natural products (Scheme 1).[16,17] In this regard, Baran' group reported that the Pd-catalyzed C−H arylation of the substrates **6a** and **7a** gave the corresponding monoarylated products **6c** (52%) and **7c** (54%).[16,17] In contrast to these results, during an attempt to synthesize pipercyclobutanamide A via the mono C−H vinylation of **7a**, Baran's group obtained the bis(olefinated)cyclobutane **8b** (50%) instead of the mono-olefinated product **8c**.[17] Notably, this is the only example available on the "double C−H functionalization of cyclobutane" using a vinyl iodide as the coupling partner. Baran's group has stated that "the reason for the direct bis(olefination) is unclear, but it may be that the vinyl iodide **8a** is smaller than the aryl iodides, thereby leading to a more facile second reaction".[17]

It is noteworthy to mention that Yu's group has obtained the bis-arylated product **11b** along with the monoarylated product **11a** from the Pd-catalyzed C−H arylation of the smallest carbocyclic ring, cyclopropanecarboxamide **9**.[27c] Daugulis's group has showed the occurrence of the bis-arylation of cyclohexane ring and monoarylation of cyclopentane ring in their groundbreaking report on an auxiliary-directed, palladium-catalyzed arylation of C(sp^3)−H bonds of various carboxylic acids.[26b]

Recently, we reported[35a] an auxiliary-enabled and Pd-catalyzed C−H arylation reaction of methylene C(sp^3)−H bond of the cyclopropanecarboxamide **12** using four equivalents of 1-iodo-4-methoxybenzene (**13a**) in toluene, which exclusively gave the monoarylated cyclopropanecarboxamide **14**[35b] as the single isomer via the C−H activation (Scheme 2). During our previous work,[35b] by using the similar experimental conditions

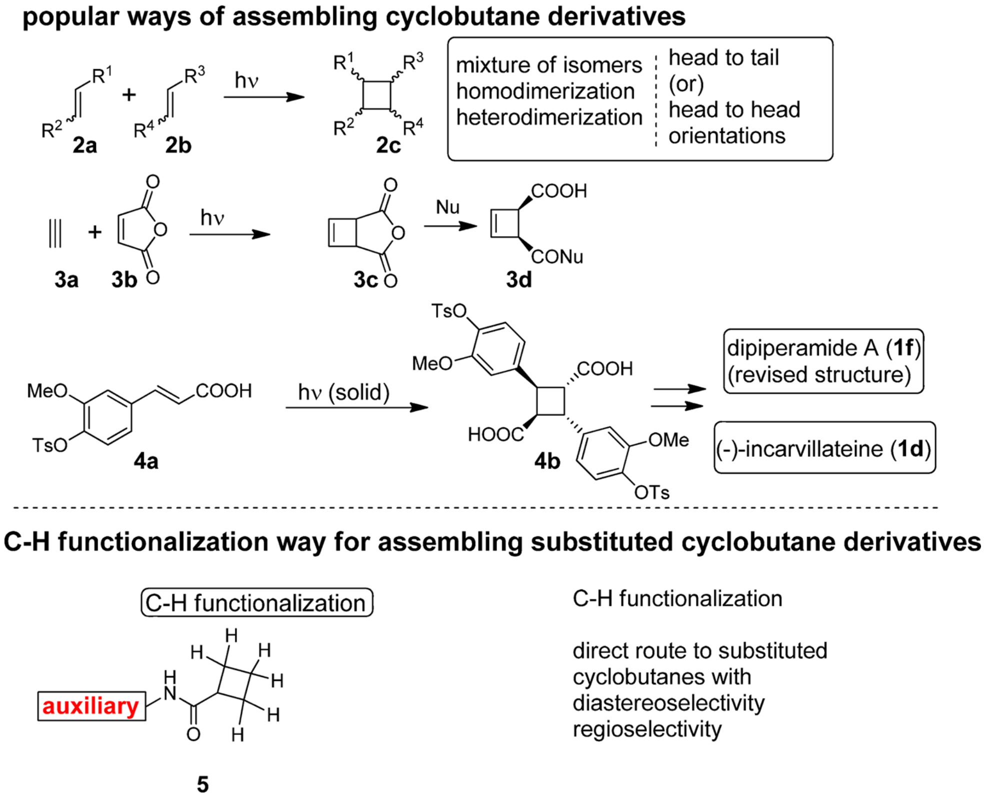
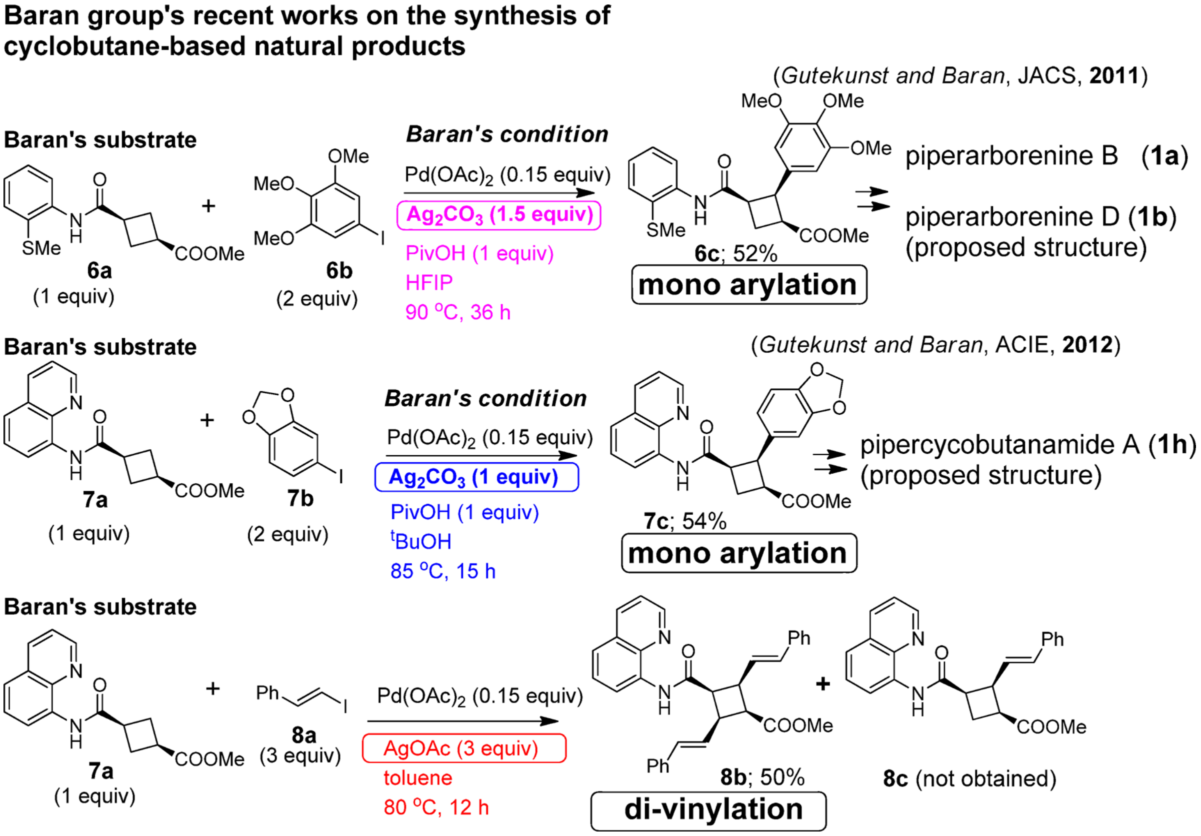


Figure 2. Methods for assembling substituted cyclobutane derivatives.

Scheme 1. Existing Examples Dealing with C−H Activation of Cyclobutane



adopted for the cyclopropanecarboxamide **12**, curiously, we attempted the Pd-catalyzed, C−H activation reaction of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**15a**) with 1-iodo-4-methoxybenzene (**13a**) in toluene. Surprisingly, in contrast to

Scheme 2. Theme of This Work: Double C−H Activation and Direct Bis-Arylation of Cyclobutanecarboxamides

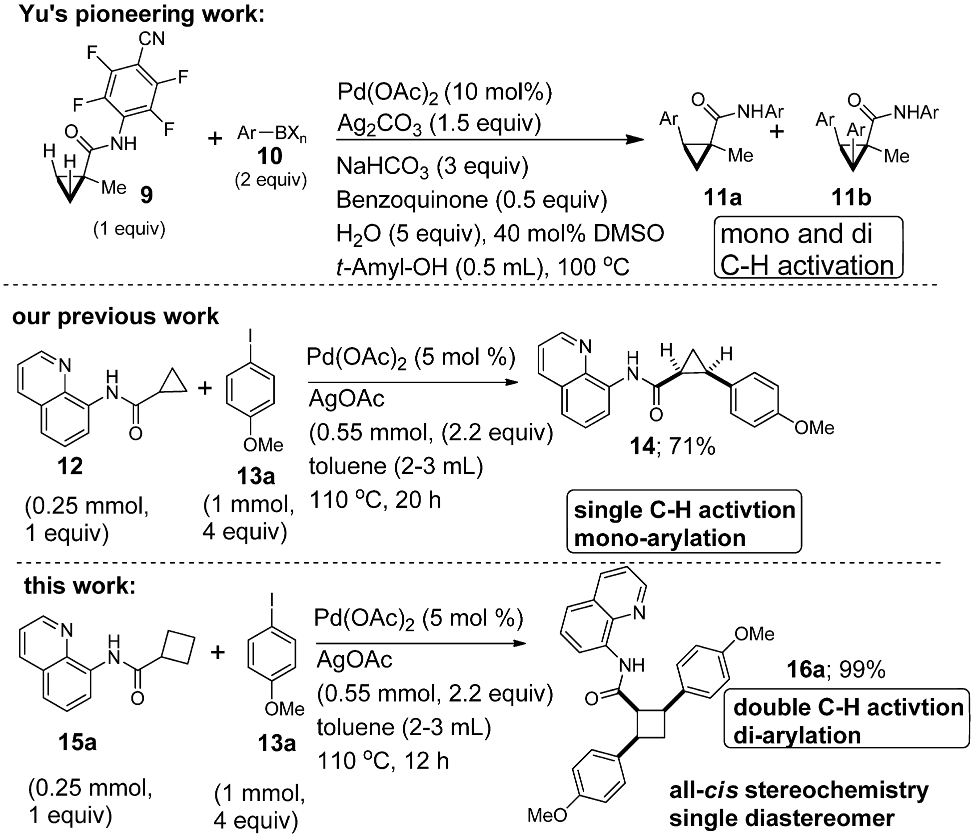
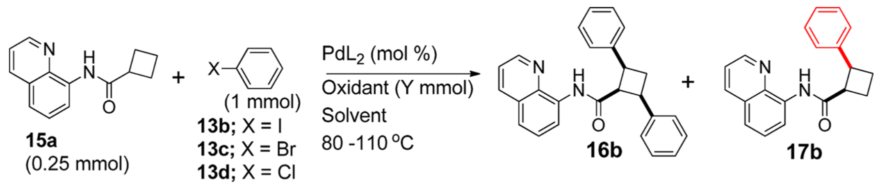


Table 1. Optimization of the Reaction Conditions for the C−H Arylation of 15a

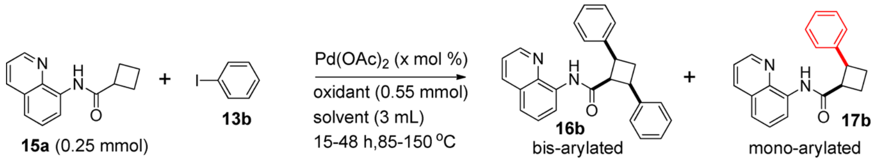


entry	catalyst (mol %)	oxidant (Y mmol)	solvent (mL)	temp (°C)	time (h)	16b: yield (%)[a]	17b: yield (%)
1	nil	AgOAc (1.0)	toluene	110	24	0	N. D.
2	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,2-DCE	80	15	68	N. D.
3	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,4-Dioxane	100	15	63	N. D.
4	$Pd(OAc)_2$ (5)	AgOAc (0.55)	CH_3CN	80	15	37	N. D.
5	$Pd(OAc)_2$(5)	AgOAc (0.55)	toluene	110	20	94	N. D.
6	$Pd(PPh_3)_4$ (5)	AgOAc (0.55)	toluene	110	15	0	N. D.
7	$PdCl_2$ (5)	AgOAc (0.55)	toluene	110	15	73	N. D.
8	$Pd(TFA)_2$ (5)	AgOAc (0.55)	toluene	110	15	70	N. D.
9	$Pd(AcAc)_2$ (5)	AgOAc (0.55)	toluene	110	15	69	N. D.
10	$Pd(CH_3CN)_2Cl_2$ (5)	AgOAc (0.55)	toluene	110	15	72	N. D.
11	$Pd(OAc)_2$(5)	$PhI(OAc)_2$ (0.55)	toluene	110	24	5	N. D.
12	$Pd(OAc)_2$(5)	KOAc (0.55)	toluene	110	20	20	N. D.
13	$Pd(OAc)_2$(5)	$Cu(OAc)_2$ (0.55)	toluene	110	24	0	N. D.
14	$Pd(OAc)_2$(5)	Ag_2CO_3 (0.55)	toluene	110	24	68	N. D.
15[b]	$Pd(OAc)_2$(5)	Ag_2CO_3 (0.55)	toluene	110	24	0	N. D.

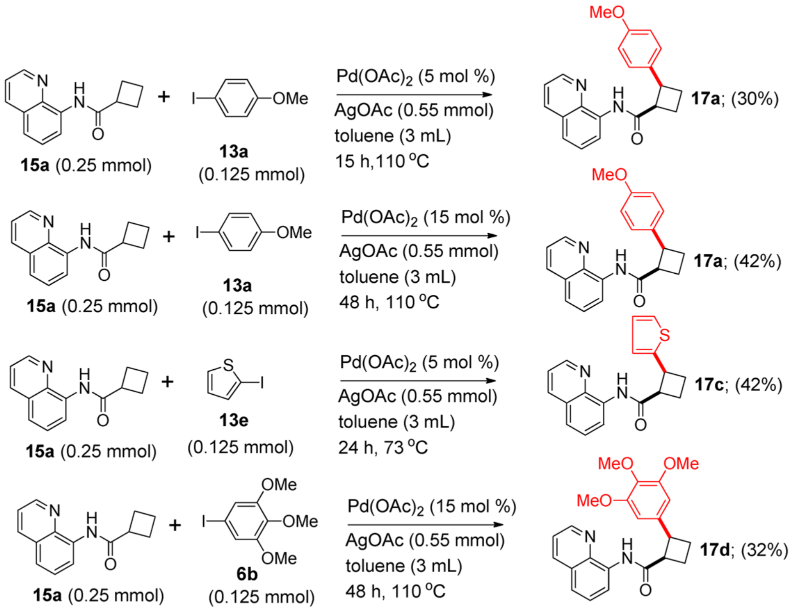
[a] All the reactions were done using phenyl iodide (**13b**) and solvent (3 mL) under nitrogen atmosphere. The yields denoted here were calculated on the basis of the starting compound **15a**. [b] In this case, bromobenzene (**13c**) or chlorobenzene (**13d**) was used instead of iodobenzene (**13b**).

the Baran's substrate,[16,17] we observed the formation of only the bis-arylated product **16a** as the single diastereomer in 99% yield. Encouraged by this outcome and in continuation of our interest on the construction of contiguous stereocenters of small carbocyclic rings using C−H activation route,[35] we envisaged capitalizing on this result to accomplish the diastereoselective direct bis-arylation of cyclobutanes. In this regard, to the best of our knowledge there exist no reports dealing with the one-pot bis-arylation of the cyclobutane ring by directly using aryl iodides as the coupling partners.[16,17,23−34]

Table 2. Ratio of Aryl Iodide Leading to the Formation of Monoarylated or Bis-Arylated Cyclobutanecarboxamide[a]



entry	phenyl iodide **13b** (mmol)	ratio of **15a** : **13b**	Pd(OAc)$_2$ (x mol %)	oxidant	solvent	temp (°C)	time (h)	**16b**: yield (%)[a]	**17b**: yield (%)[a]
1	1.5	1 : 6	5	AgOAc	toluene	110	15	98	0
2	1.0	1 : 4	5	AgOAc	toluene	110	15	94	0
3	0.75	1 : 3	5	AgOAc	toluene	110	15	78	0
4	0.5	1 : 2	5	AgOAc	toluene	110	15	63	0
5	0.25	1 : 1	5	AgOAc	toluene	110	15	49	traces
6	0.187	1 : 0.75	5	AgOAc	toluene	110	15	11	33
7	0.125	1 : 0.5	5	AgOAc	toluene	110	15	traces	20
8	0.125	1 : 0.5	5	AgOAc	toluene	110	48	0	22
9	0.125	1 : 0.5	15	AgOAc	toluene	110	48	0	35
10	0.125	1 : 0.5	15	AgOAc	*p*-xylene	140	48	0	18
11	0.125	1 : 0.5	15	AgOAc	mesitylene	150	48	0	20
12	0.125	1 : 0.5	15	Ag_2CO_3	toluene	110	48	0	19
13	0.125	1 : 0.5	15	Ag_2CO_3	^{t}BuOH	85	48	0	10



[a] All the reactions were done under nitrogen atmosphere. The yields denoted here were calculated based on the starting compound **15a**.

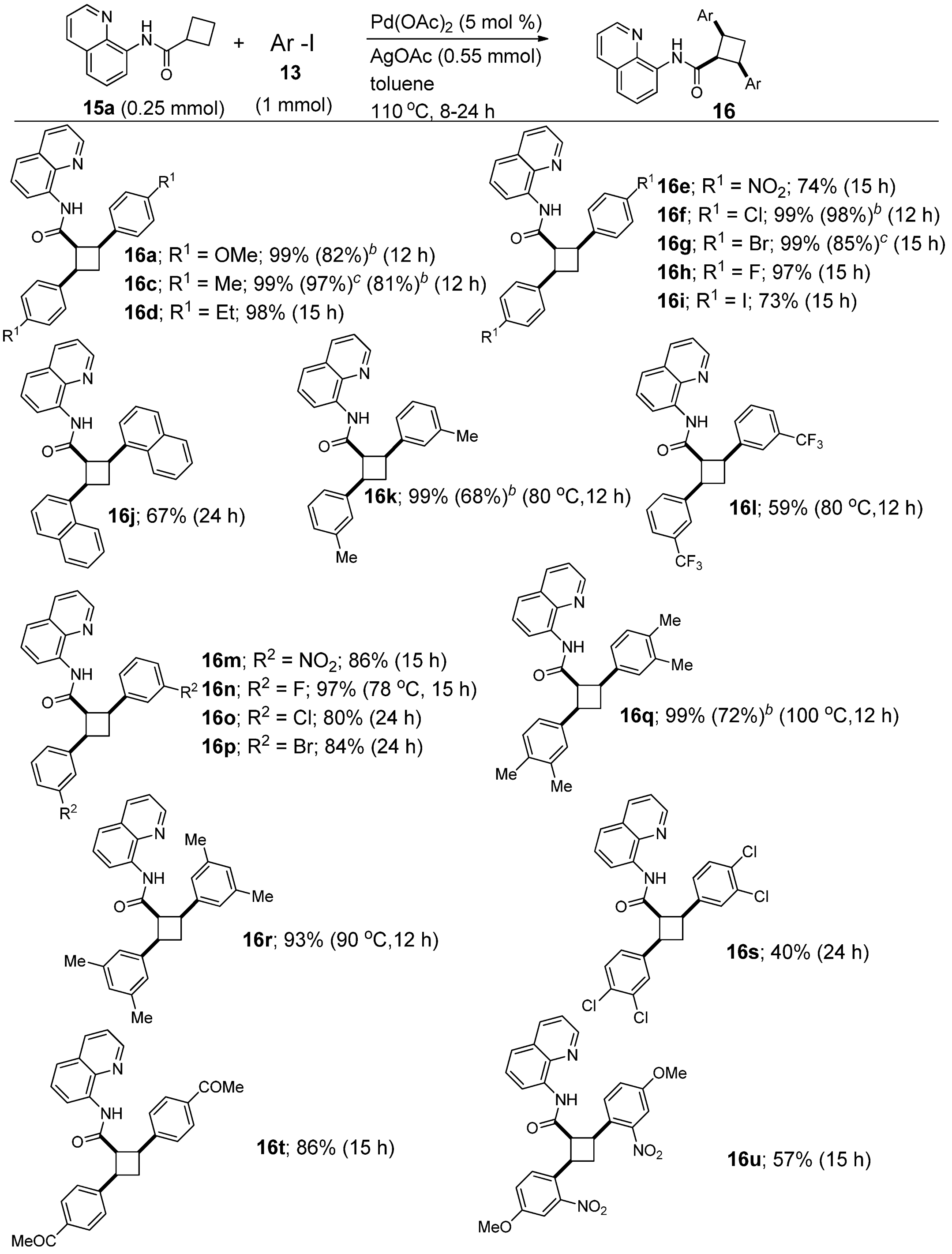
Inspired by the latest developments on the Pd-catalyzed C−H activation reactions, we envisaged examining a direct protocol for the production of novel bis-arylated cyclobutanecarboxamide scaffolds under the 'auxiliary-aided and Pd(OAc)$_2$-catalyzed C−H activation method'.[26b] We herein, report an auxiliary-aided Pd-catalyzed highly diastereoselective "double C−H activation and direct bis-arylation of methylene C(sp^3)−H bonds of cyclobutanecarboxamides" and an efficient access to novel 1,2-*cis*, 1,3-*cis*, and 2,3-*cis* trisubstituted cyclobutane scaffolds having three contiguous stereocenters with a high degree of stereo- and regiocontrol.

■ RESULTS AND DISCUSSION

We commenced our study to find the optimized reaction conditions and solvents. Table 1 reveals the Pd- catalyzed arylation reaction of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**15a**), obtained from cyclobutanecarbonyl chloride and an auxiliary, 8-aminoquinoline, with iodobenzene (**13b**). The reaction of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**15a**) with iodobenzene (**13b**) in the absence of a palladium catalyst failed to afford any product (entry 1, Table 1). The C−H arylation of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**15a**) in the presence of Pd(OAc)$_2$ catalyst and AgOAc in 1,2-DCE gave the bis-arylated product **16b** in 68% yield (entry 2, Table 1). Usage of other solvents such as 1,4-dioxane or MeCN did not improve the yield of the product **16b** (entries 3 and 4, Table 1).

The C−H arylation of cyclobutane **15a** in the presence of Pd(OAc)$_2$ and AgOAc went smoothly in toluene at 110 °C and afforded the bis-arylated product **16b** in 94% yield as a single diastereomer (entry 5, Table 1). Employing Pd(PPh$_3$)$_4$ as a catalyst failed to furnish the product **16b** (entry 6, Table 1), and usage of other Pd catalysts instead of Pd(OAc)$_2$ also gave the product **16b** in 69−73% yields (entries 7−10, Table 1). The Pd-

Scheme 3. Double C−H Activation Route to Trisubstituted Cyclobutane Scaffolds Having Contiguous Stereocenters with an All-*cis* Stereochemistry[a,b,c]

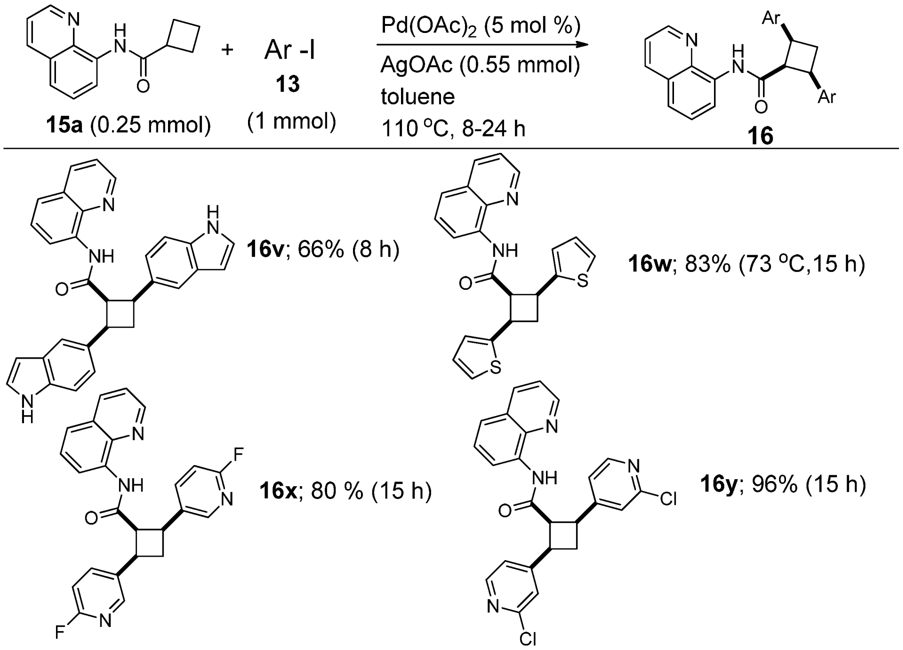


[a] All the reaction were done under nitrogen atmosphere. The yields denoted here were calculated based on the starting compound **15a**. [b] The reaction was performed using 1.7 mol % (1 mg) of $Pd(OAc)_2$. [c] The reaction was performed using 3 mol % (1.7 mg) of $Pd(OAc)_2$.

catalyzed arylation reaction of **15a** with **13b** in the presence of other oxidants/additives such as $PhI(OAc)_2$, KOAc, and $Cu(OAc)_2$ furnished the product **16b** in significantly low yields or traces (entries 11−13, Table 1). The arylation of **15a** with **13b** in the presence of Ag_2CO_3 instead of AgOAc gave the bis-arylated product **16b** in 68% yield (entry 14, Table 1). Employing bromobenzene (**13c**) or chlorobenzene (**13d**) instead of iodobenzene (**13b**) did not afford the product **16b** (entry 15, Table 1).

In order to obtain products with very good yields and to have an efficient the C−H functionalization on the molecules, typically, more than one equivalent of aryl iodide (1−4 equiv) has been employed in the $C(sp^3)$−H arylation strategy.[23−35] However, though we have used the same experimental conditions and reagent amounts which were used for the C−H arylation of cyclopropanecarboxamides which gave only the monoarylated products, in this work, the C−H arylation of the cyclobutane **15a** (1 equiv) with 1-iodo-4-methoxybenzene **13a**

Scheme 4. Double C–H Activation Route to Trisubstituted Cyclobutane Scaffolds Having Contiguous Stereocenters with an All-*cis* Stereochemistry[a]



[a]All the reaction were done under nitrogen atmosphere. The yields denoted here were calculated based on the starting compound **15a**.

(4 equiv) in the presence of Pd(OAc)$_2$ and AgOAc afforded only the bis-arylated product **16b** as a single diastereomer (Scheme 2).

Further, the Baran's group also reported that the Pd-catalyzed C–H arylation of **6a** and **7a** with excess of aryl iodides (**6b** and **7b**, 2 equiv) gave only the corresponding monoarylated products **6c** and **7c** (Scheme 1).[16,17] In order to have a clear insight regarding equivalents of phenyl iodides required for producing the monoarylated cyclobutane product **17** or the bis-arylated cyclobutane product **16**, we investigated the C–H arylation of cyclobutane **15a** by varying the amount of the aryl iodide **13b** (Table 2). Usage of one equivalent or more of iodobenzene (**13b**) in the Pd-catalyzed C–H arylation of **15a** gave only the bis-arylated product **16b** (entries 1–5, Table 2). The Pd-catalyzed C–H arylation of **15a** with 0.75 equiv of iodobenzene (**13b**) gave both the bis-arylated cyclobutane **16b** (11%) and the monoarylated cyclobutane **17b** (33%) (entry 6, Table 2). Notably, the Pd-catalyzed C–H arylation reaction of **15a** with just 0.5 equiv of iodobenzene (**13b**) in toluene (refluxed for 15 h) selectively gave the monoarylated cyclobutane **17b** in 20% yield (entry 7, Table 2). Increasing the reaction period from 15 to 48 h did not improve the reaction yield (entry 8, Table 2).

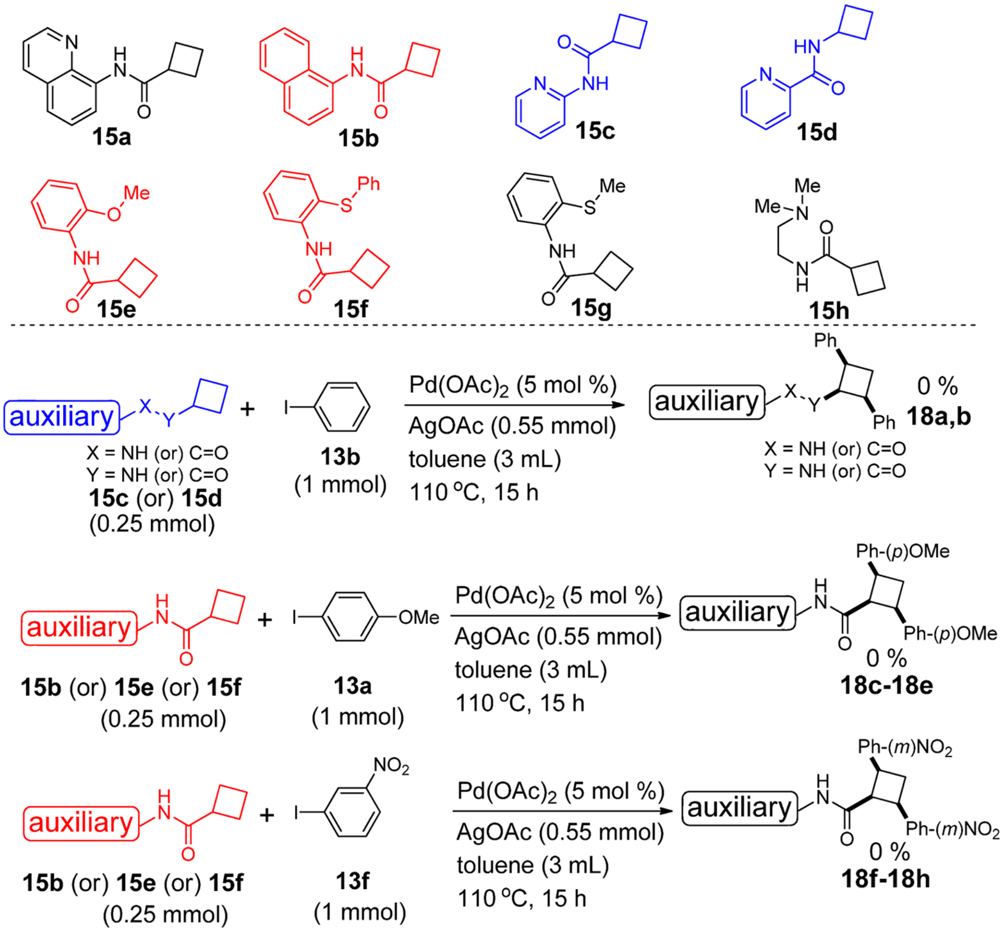
Next, we attempted the Pd-catalyzed C–H arylation reaction of **15a** with 0.5 equiv of iodobenzene by increasing the catalyst (Pd(OAc)$_2$) loading to 15 mol %. However, this reaction also afforded the monoarylated cyclobutane **17b** in 35% yield (entry 9, Table 2). Furthermore, we performed the Pd-catalyzed C–H arylation reaction of **15a** by changing the reaction conditions and however, our attempts to get the monoarylated cyclobutane **17b** in good yields were not fruitful (entries 10–13. Table 2). Using the best reaction conditions (entries 7 and 9) described in the Table 2, the other monoarylated cyclobutane derivatives **17a**, **17c** and **17d** were synthesized (Table 2).

Having the optimized reaction conditions in hand, the generality and scope of this auxiliary-aided Pd-catalyzed double C–H activation and bis-arylation of the methylene C(sp^3)–H bond of cyclobutanecarboxamides were investigated (Scheme 3). A variety of substituted aryl iodides having valuable functional groups was used as the coupling partner in the Pd-catalyzed double C–H activation and bis-arylation of methylene C(sp^3)–H bonds of cyclobutanecarboxamide **15a**, thus offering an ample opening and an efficient access to novel 1,2-*cis*, 1,3-*cis*, and 2,3-*cis* trisubstituted cyclobutane scaffolds having three contiguous stereocenters with a high degree of stereo- and regiocontrol (Scheme 3).

The arylation of methylene C–H bonds of **15a** with para-substituted aryl iodides having electron-withdrawing and -donating groups went smoothly and gave the corresponding cyclobutanes **16a**, **16c–16i** in 73–99% yields. The arylation of **15a** with 1-iodonaphthalene, 1-iodo-3-methylbenzene, and 1-iodo-3-(trifluoromethyl)benzene gave the corresponding cyclobutanes **16j–16l** in 59–99% yields. The arylation of **15a** with meta-substituted aryl iodides having electron-withdrawing groups furnished the respective products **16m–16p** in 80–97% yields. The bis-arylation of the cyclobutanecarboxamide **15a** with various disubstituted aryl iodides and 1-(4-iodophenyl)-ethanone afforded the cyclobutane scaffolds **16q–16u** in moderate to very good yields (Scheme 3). In some cases, we have performed the C–H arylation reaction of cyclobutane **15a** using 3 mol % of the catalyst Pd(OAc)$_2$, which gave the corresponding bis-arylated products **16c** and **16g** in 97 and 85% yields, respectively (Scheme 3). Furthermore, we have attempted to use only 1.7 mol % (1 mg) of the catalyst Pd(OAc)$_2$ for the double C–H arylation of the cyclobutane derivative **15a**. The C–H arylation of the cyclobutane **15a** in the presence of just 1.7 mol % of Pd(OAc)$_2$ gave the corresponding bis-arylated products **16a** (82%), **16c** (81%), **16f** (98%), **16k** (68%), and **16q** (72%) in good to moderate yields (Scheme 3).

Next, we aimed the auxiliary-aided Pd-catalyzed double C–H activation and bis-arylation of the methylene C(sp^3)–H bond of cyclobutanecarboxamides with various heteroaryl iodides (Scheme 4). The Pd-catalyzed double C–H functionalization

Scheme 5. Screening of Various Auxiliaries for the C−H Activation of Cyclobutane

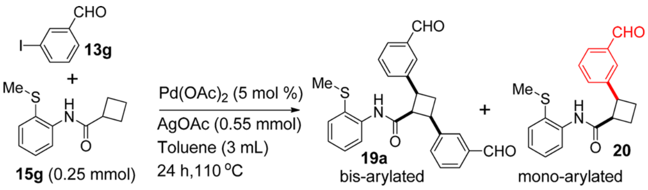


and heterocyclic substitution on the cyclobutanecarboxamide **15a** commendably gave the trisubstituted cyclobutanecarboxamide scaffolds **16v**−**16y** in good to excellent yields (66−96%) (Scheme 4). It is noteworthy to mention that all these reactions selectively gave the 1,2-*cis*, 1,3-*cis*, and 2,3-*cis* trisubstituted cyclobutanes having three contiguous stereocenters with a high degree of stereo- and regiocontrol, and the stereochemistries of the products **16a**−**16y** (Schemes 3 and 4) were assigned on the basis of analysis of the X-ray structures of the representative compounds **16c**, **16f**, **16g**, and **16m**.[36]

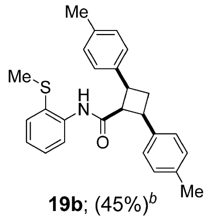
After the successful Pd-catalyzed bis-arylation reactions of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**15a**), we prepared a variety of cyclobutanecarboxamides **15b**−**15h** by linking cyclobutane carbonyl chloride with various auxiliaries, respectively (Scheme 5). The Pd-catalyzed C−H arylation of cyclobutanecarboxamides **15b**−**15f** did not afford the expected bis-arylated cyclobutanes **18a**−**18h**. The reason for this may be that the corresponding auxiliaries linked with the cyclobutane ring have not aided the C−H functionalization of the cyclobutane ring.

Along this line, next we carried out the Pd-catalyzed arylation of *N*-(2-(methylthio)phenyl)cyclobutanecarboxamide (**15g**, prepared from an auxiliary, 2-(methylthio)aniline with different aryl iodides. Initially, we investigated the C−H arylation of cyclobutane **15g** by varying the equivalents of 3-iodobenzaldehyde (**13g**, Table 3). Usage of one equivalent or more of 3-iodobenzaldehyde (**13g**) in the Pd-catalyzed C−H arylation of **15g** gave only the bis-arylated product **19a** (entries 1−3, Table 3). Similarly, subsequent examples of the bis-arylated cyclo-

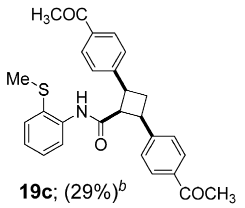
Table 3. C−H Arylation *N*-(2-(Methylthio)phenyl)cyclobutanecarboxamide 15g



entry	aryl iodide 13g (mmol)	ratio of 15g : 13g	19a: yield (%)[a]	20: yield (%)[a]
1	1.0	1 : 4	52	0
2	0.5	1 : 2	37	0
3	0.25	1 : 1	20	0
4	0.125	1 : 0.5	0	0



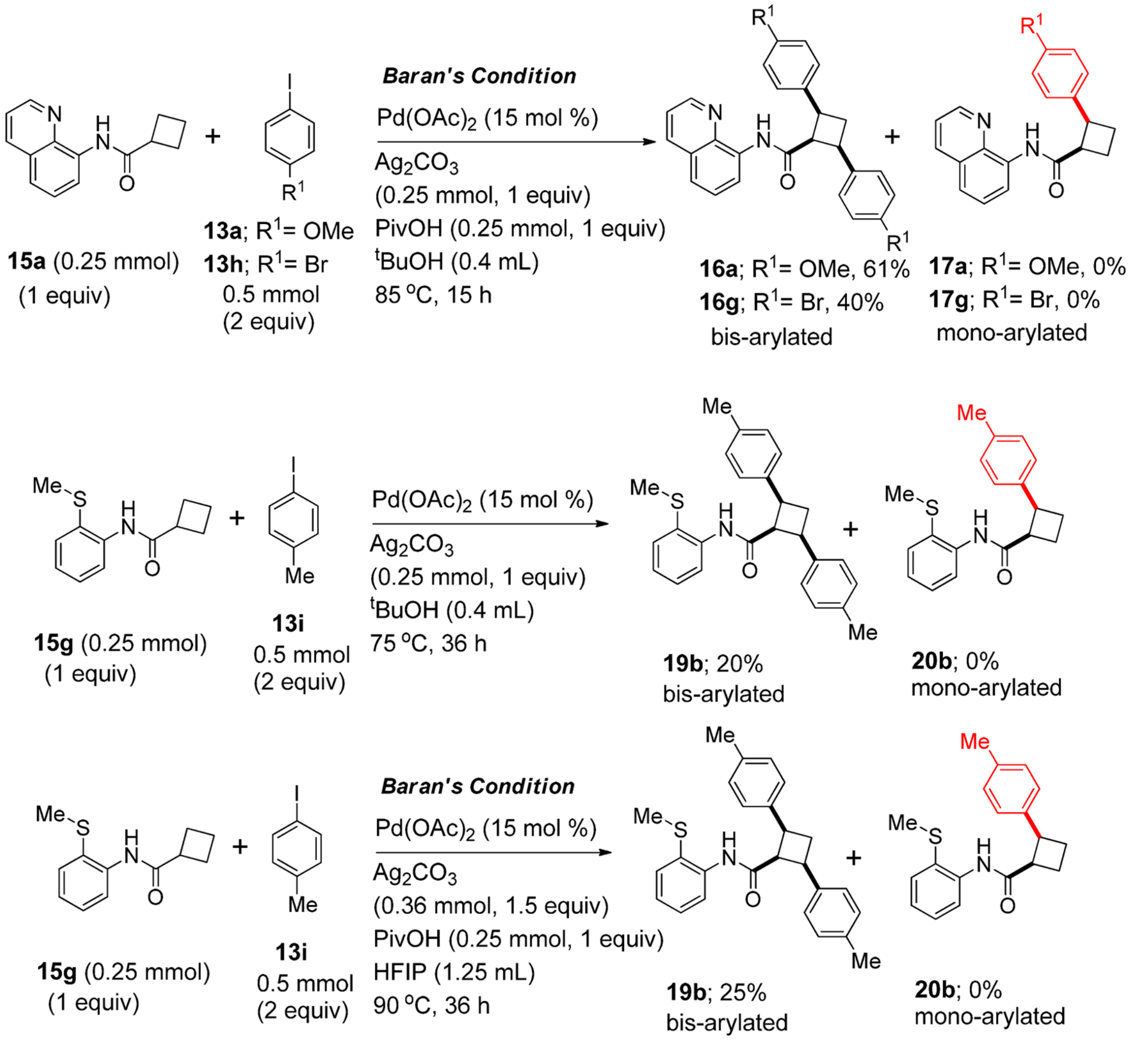
19b; (45%)[b]



19c; (29%)[b]

[a] All the reactions were done under nitrogen atmosphere. The yields denoted here were calculated based on the starting compound 15g. [b] The reaction was done using the reaction condition given for ’entry 1’.

Scheme 6. Trials Performed Aiming at the Monoarylation of 15a and 15g Using Baran's Reaction Condition[a] [16,17]



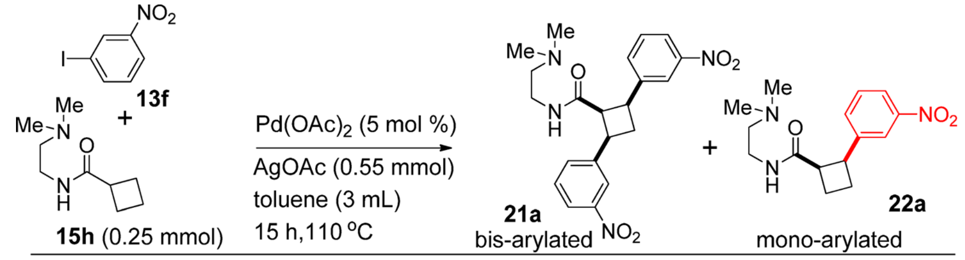
[a] The yields denoted here were calculated based on the starting compound **15a** or **15g**.

butanes **19b** and **19c** having the 1,2-*cis*, 1,3-*cis*, and 2,3-*cis* stereochemistry were obtained in 45 and 29% yields, respectively (Table 3).[37] When compared to the starting material **15a**, the C−H arylation of **15g** gave relatively low yields of the bis-arylated cyclobutanes **19a**−**19c**. However, unlike the substrate **15a**, the Pd-catalyzed C−H arylation of **15g** with just 0.5 equiv of 3-iodobenzaldehyde (**13g**) did not afford the monoarylated cyclobutane **20** (entry 4, Table 3).

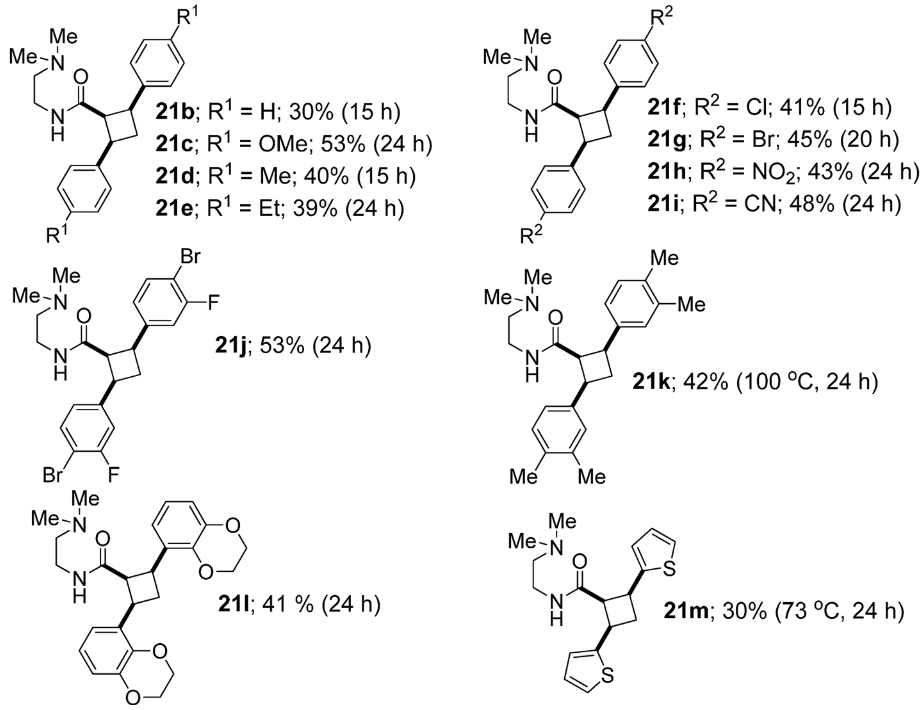
Baran's group used the cyclobutanecarboxamides **6a** and **7a** which were similar to the cyclobutanecarboxamides **15g** and **15a**, respectively.[16,17] When compared to this work, the Pd-catalyzed C−H arylation reaction conditions were different in the Baran's work. Baran's group performed the C−H arylation of **6c** and **7c** with 2 equiv of **6b** and **7b** and revealed the formation of monoarylated products **6c** and **7c**, respectively. Contrastingly, under the experimental conditions of this work, the Pd-catalyzed C−H arylation of the substrates **15g** or **15a** with even just one equivalent of an aryl iodide gave only the bis-arylated cyclobutanes as the major compounds. Consequently, we were also interested to test the fate of our substrates **15g** and **15a** under Baran's reaction condition.[16,17] Hence, we performed the C−H arylation reactions of the substrate **15a** and **15g** under the monoarylation reaction condition[16,17] established by Baran's group for the C−H arylation of **7a** (Baran's substrate). However, our attempts resulted in the formation of only the bis-arylated cyclobutanes **16a**, **16g**, and **19b** as the single isomers (Scheme 6) and we did not obtain the monoarylated cyclobutanes **17a**, **17g**, and **20b** (Scheme 6). The reason for formation of only the respective bis-arylated compounds **16a**, **16g**, and **19b** from **15a** and **15g** may be due to the substituent effect on the cyclobutane ring. Baran's substrates **6c** and **7c** have a substituent (carboxylic acid ester group) at the third position of cyclobutane ring, and hence the double arylation of **6c** and **7c** may not be a facile reaction due to the steric hindrance of aryl groups (if two aryl groups are introduced). However, the substrates investigated in this work, such as **15a**, **15g**, and **15h**, do not have any substituent at the third position of the cycobutane ring when compared to Baran's substrate. Hence, the double arylations of cyclobutanecarboxamides **15a**, **15g**, and **15h** occur in a facile manner.

Then, we scrutinized the scope of the Pd-catalyzed C−H activation and mono- or bis-arylation by using the *N*-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (**15h**, prepared from an aliphatic auxiliary, *N′*,*N′*-dimethylethane-1,2-diamine and cyclobutanecarbonyl chloride). At the outset, we examined the Pd-catalyzed C−H arylation of *N*-(2-(dimethylamino)-ethyl)-cyclobutanecarboxamide (**15h**) by varying the equivalents

Scheme 7. Investigation of the Pd-Catalyzed C−H Arylation of *N*-(2-(Dimethylamino)ethyl)-cyclobutanecarboxamide.[a,b]



entry	aryl iodide **13f** (mmol)	ratio of **15h** : **13f**	**21a**: yield (%)[a]	**22a**: yield (%)[a]
1	1.5	1 : 6	56	0
2	1.0	1 : 4	45	0
3	0.75	1 : 3	34	0
4	0.5	1 : 2	24	0
5	0.25	1 : 1	10	0
6	0.125	1 : 0.5	0	0



21b; R^1 = H; 30% (15 h)
21c; R^1 = OMe; 53% (24 h)
21d; R^1 = Me; 40% (15 h)
21e; R^1 = Et; 39% (24 h)

21f; R^2 = Cl; 41% (15 h)
21g; R^2 = Br; 45% (20 h)
21h; R^2 = NO$_2$; 43% (24 h)
21i; R^2 = CN; 48% (24 h)

21j; 53% (24 h)

21k; 42% (100 °C, 24 h)

21l; 41 % (24 h)

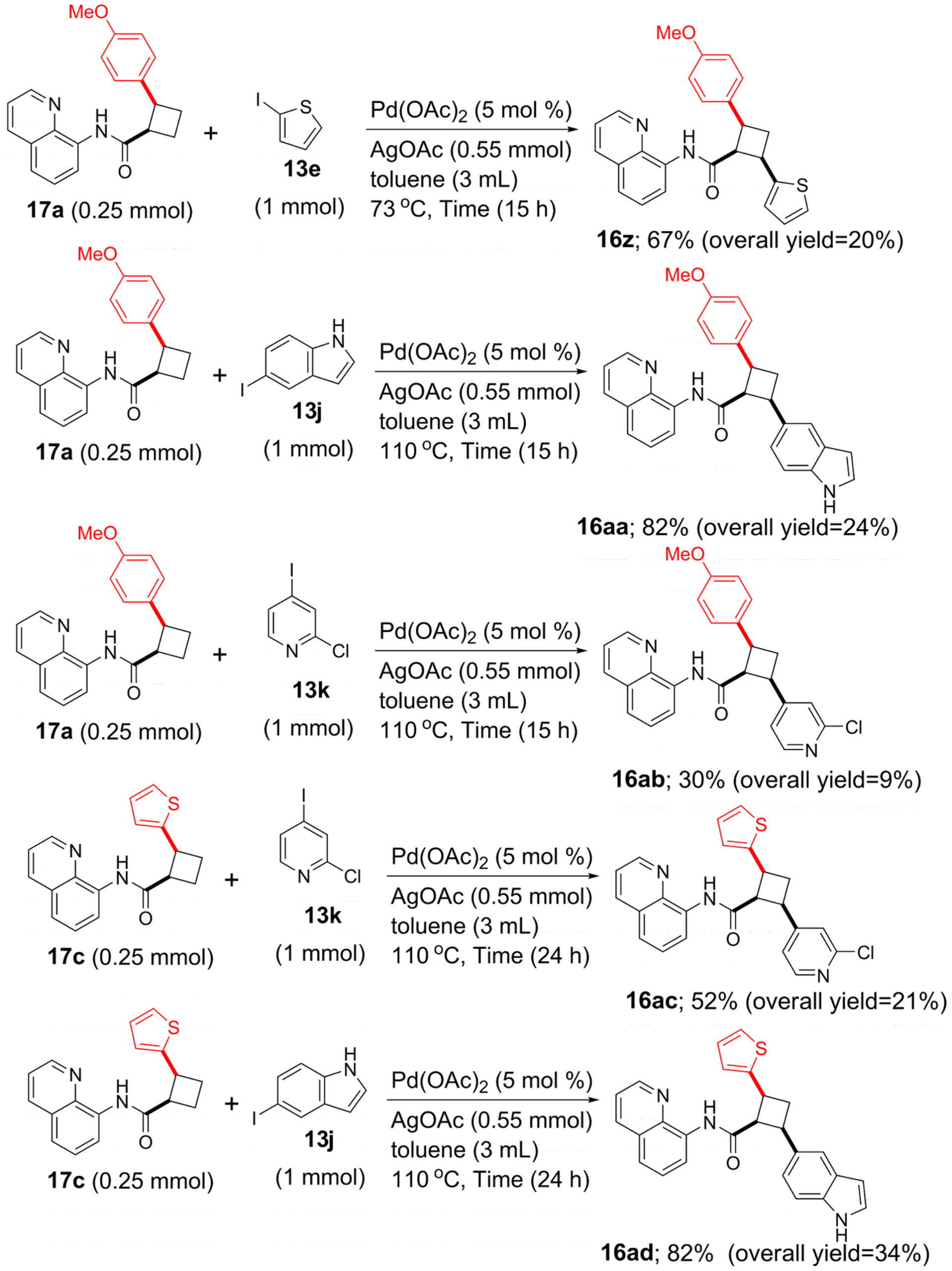
21m; 30% (73 °C, 24 h)

[a] All the reactions were done under nitrogen atmosphere. The yields denoted here were calculated on the basis of the starting compound **15h**. [b] The preparation of the compounds **21b**−**21m** was carried out using the reaction condition given for 'entry 2'.

of 1-iodo-3-nitrobenzene (**13f**) (Scheme 7). The Pd-catalyzed C−H arylation of *N*-(2-(dimethylamino)ethyl)-cyclobutanecarboxamide (**15h**) by using either one equivalent or more of 1-iodo-3-nitrobenzene (**13f**) selectively afforded the bis-arylated cyclobutanecarboxamide **21a** (entries 1−5, Scheme 7). These reactions did not afford any traces of the monoarylated cyclobutanecarboxamide **22a** (entries 1−5, Scheme 7). However, unlike the substrate **15a**, the Pd-catalyzed C−H arylation of **15h** with just 0.5 equiv of iodo-3-nitrobenzene (**13f**) did not afford the monoarylated cyclobutane **22a** (entry 6, Scheme 7). Further, several substituted aryl iodides and hetereoaryl iodides were used as the coupling partners in the Pd-catalyzed C−H activation and bis-arylation of methylene C(sp^3)−H bonds of cyclobutanecarboxamide **15h**, which led to the assembling of various 1,2-*cis*, 1,3-*cis*, and 2,3-*cis* trisubstituted cyclobutanecarboxamides **21a**−**21m** (Scheme 7). Noticeably, all these reactions selectively gave the 1,2-*cis*, 1,3-*cis*, and 2,3-*cis* trisubstituted cyclobutanes having three contiguous stereocenters with a high degree of stereo- and regiocontrol and the stereochemistry of the products **21a**−**21m** (Scheme 7) was assigned on the basis of the X-ray structure analysis of the representative compounds **21a** and **21f**.[36]

Furthermore, we extended the scope this protocol by producing a wide range of novel trisubstituted cyclobutanecarboxamides **16z** and **16aa**−**16ad** having an all-*cis* stereochemistry by performing a second C−H activation/arylation on the corresponding monoarylated cyclobutanecarboxamides **17a** and **17c** (Scheme 8). The C−H functionalization reaction of the monoarylated cyclobutanecarboxamides **17a** and **17c** with a variety of hetereoaryl iodides **13e**, **13j**, and **13k** in the presence of

Scheme 8. Scope and Investigation of Second Arylation of Mono-Arylated Cyclobutanes Using Heteroaryl Iodides.[a]



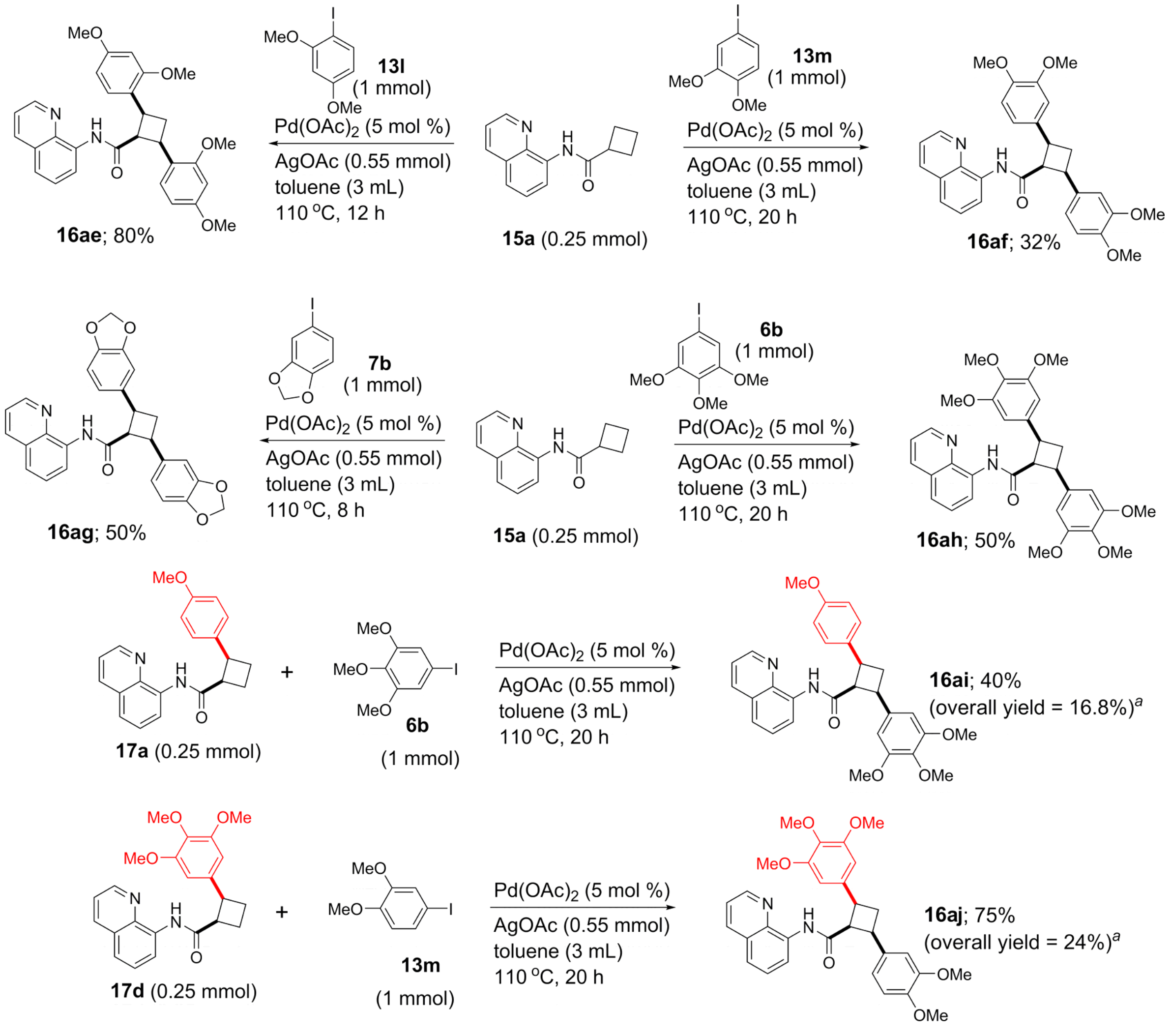
[a]The overall yields were calculated for the reaction of the starting material **15a** converting in to the corresponding bis-arylated products.

Pd(OAc)$_2$ catalyst and AgOAc gave the corresponding trisubstituted cyclobutanecarboxamides **16z** and **16aa**−**16ad** in 30−82% yields, having two different aryl groups. The stereochemistry of the products **16z** and **16aa**−**16ad** (Scheme 8) was assigned on the basis of the X-ray structure analysis of the representative compounds **16c**, **16f**, **16g**, and **16m** and the similarity in the ^{1}H NMR pattern.

Next, we planned to construct a variety of trisubstituted cyclobutanecarboxamide frameworks analogous to the naturally occurring cyclobutanecarboxamide molecules shown in the Figure 1 (Scheme 9). In this line, initially, we performed the Pd-catalyzed C−H arylation reaction of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**15a**) by using more than one equivalent of the aryl iodides **13l**, **13m**, **7b** and **6b**, which selectively afforded the corresponding bis-arylated cyclobutanecarboxamide frameworks **16ae**, **16af**, **16ag**, and **16ah** having an all *cis*-stereochemistry (Scheme 9).[37] Along this line, the C−H functionalization reaction of the monoarylated cyclobutanecarboxamides **17a** and **17d** with the aryl iodides **6b** and **13m** in the presence of the catalyst Pd(OAc)$_2$ and the AgOAc gave the corresponding trisubstituted cyclobutanecarboxamide derivatives **16ai** (40%) and **16aj** (75%), which are structurally equivalent to some of the naturally occurring cyclobutanecarboxamide molecules with respect to the arene units (Scheme 9 and Figure 1).

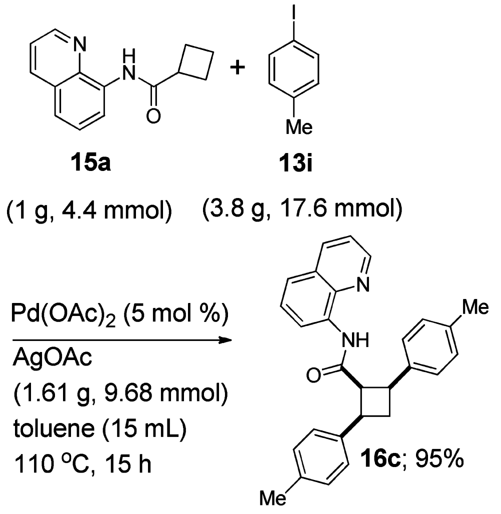
Consequently, to reveal the synthetic value of this protocol, the Pd-catalyzed direct bis-arylation of the C−H bonds of the cyclobutanecarboxamide **15a** was carried out in a gram scale, which afforded the product **16c** in an excellent yield (95%) (Scheme 10). Additionally, we also tried to elaborate the Pd-catalyzed C−H activation of **15a** by using different alkyl iodides

Scheme 9. Scope and Synthesis of Cyclobutane Derivatives Analogous to Cyclobutane Natural Products.[a]



[a]The overall yields were calculated for the reaction of the starting material **15a** converting in to the corresponding bis-arylated products.

Scheme 10. Gram Scale Double C−H Arylation of 15a

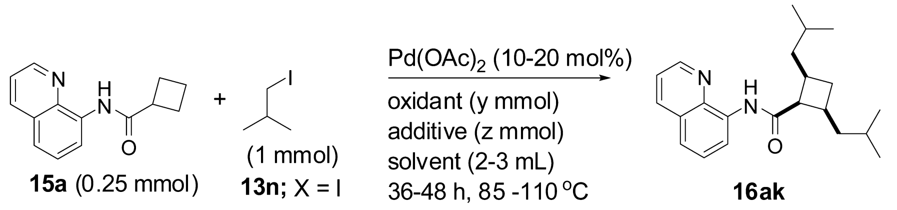


as the coupling partners. We performed the Pd-catalyzed C−H activation of **15a** by using different alkyl iodides (**13n**−**p**) under several reaction conditions, however, all our attempts failed to give the expected mono- or bis-alkylated compounds, such as **16ak**, **16al**, **16am**, and **16an** (Scheme 11).

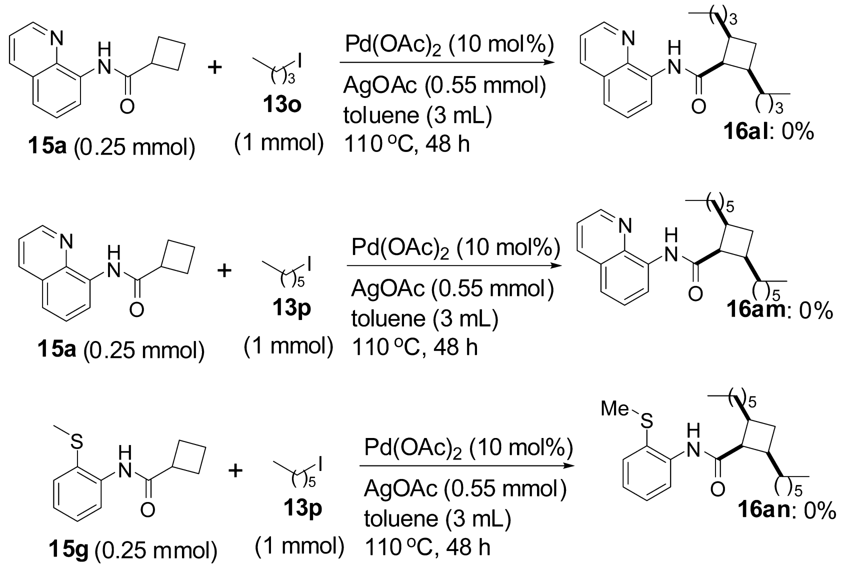
In line with the pioneering studies carried out by Daugulis,[26b] Chen[28a] and a recent work by Charette,[24r] a plausible mechanism for the auxiliary-aided Pd(OAc)$_2$-catalyzed, AgOAc-promoted double C−H activation and direct bis-arylation of methylene C(sp^3)−H bonds of cyclobutanecarboxamides leading to the formation of monoarylated and bis-arylated cyclobutanecarboxamide is shown in the Scheme 12.

Additionally, to explore the synthetic utility we carried out the LiAlH$_4$-mediated reduction of the amide group of a representative compound **16g**, which furnished *N*-(((1*S**,2*R**,4*S**)-2,4-bis(4-bromophenyl)cyclobutyl)methyl)quinolin-8-amine (**23**). Further, the base-mediated amide hydrolysis of the representative compounds **16c**, **16f**, and **16g** successfully gave the corresponding substituted bis-arylated cyclobutanecarboxylic acids **24**−**26** in very good yields, respectively (Scheme 13). The stereochemistry of the compounds **24**−**26** was unambiguously established based on the X-ray structure analysis of a representative compound **25**,[36,38] which revealed the occurrence of complete epimerization at the carbonyl group containing stereocenter of the cyclobutanes **16c**, **16f** and **16g** during the formation of the corresponding carboxylic acids **24**−**26** from the

Scheme 11. Trials on the Alkylation of Cyclobutanecarboxamide 15a[a,b,c]



entry	$Pd(OAc)_2$ (mol%)	oxidant (y mmol)	additive (z mmol)	solvent (mL)	temp (°C)	time (h)	**16ak**: yield (%)[a]
1	$Pd(OAc)_2$ (10)	AgOAc (0.55)	none	toluene	110	48	0
2	$Pd(OAc)_2$ (15)	AgOAc (0.55)	none	toluene	110	36	0
3	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	none	toluene	110	36	0
4	$Pd(OAc)_2$ (15)	AgOAc (0.55)	PivOH (0.25)	toluene	110	36	0
5	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	PivOH (0.25)	toluene	110	48	traces
6	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	PivOH (0.25)	t-BuOH	85	48	0
7	$Pd(OAc)_2$ (20)	Ag_2CO_3 (0.25)	PivOH (0.25)	t-BuOH	85	48	0
8	$Pd(OAc)_2$ (20)	Ag_2CO_3 (0.25)	Ag_3PO_4 (0.25)	t-BuOH	85	48	0
9	$Pd(OAc)_2$ (20)	Ag_2CO_3 (0.25)	Ag_3PO_4 (0.25)	toluene	110	48	0
10[b]	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	PivOH (0.25)	toluene	110	48	0
11[c]	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	PivOH (0.25)	toluene	110	48	0



[a] All the reaction were done under nitrogen atmosphere. [b] In this case, 1.5 mmol of **13r** was used. [c] The reaction was carried out in the open atmosphere.

base-mediated hydrolysis of the amides **16c**, **16f** and **16g**. Treatment of the compound **16g** with NaH followed by MeI gave the *N*-methylated cyclobutanamide derivative **27**, having a *cis*-sterochemistry similar to the starting material **16g**, and we did not observe epimerization in this reaction (Scheme 13). The stereochemistry of the product **27** was unambiguously assigned on the basis of the single-crystal X-ray structure analysis.[36]

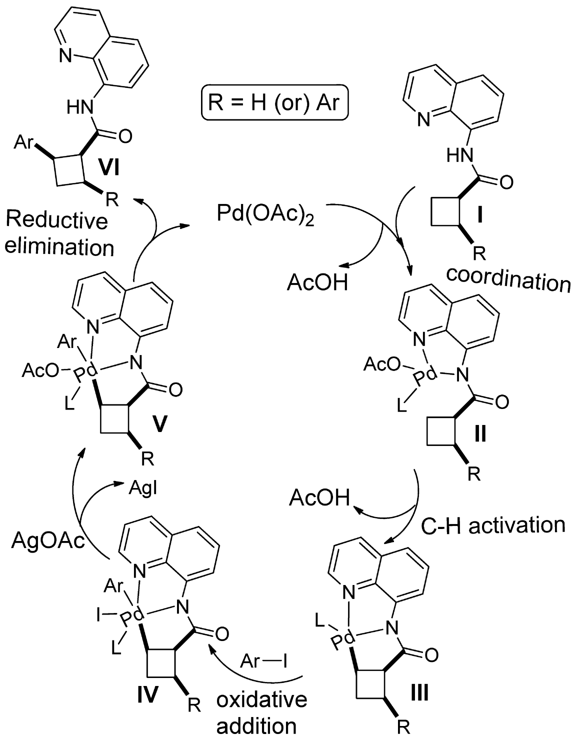
■ CONCLUSION

In summary, we have reported an auxiliary-aided Pd-catalyzed highly diastereoselective, double C−H activation and unprecedented direct bis-arylation of methylene C(sp^3)−H bonds of cyclobutanecarboxamides. Extensive screening of several auxiliaries and reaction conditions was performed to firmly establish the regiocontrol and the exact reaction condition required for effecting the mono- or double C−H arylation of cyclobutanecarboxamides. The direct double C−H activation of cyclobutanecarboxamide led to the installation of two aryl groups on cyclobutanecarboxamide and a facile synthesis of several novel 1,2-*cis*, 1,3-*cis* and 2,3-*cis* trisubstituted cyclobutanecarboxamide frameworks having three contiguous stereocenters,[39] which are relatively difficult to prepare via the existing, popular direct [2 + 2] photocycloaddition method with a high degree of regio- and stereocontrol.

■ EXPERIMENTAL SECTION

General. Melting points are uncorrected. IR spectra were recorded as thin films or KBr pellets. ^1H and ^{13}C NMR spectra

Scheme 12. Plausible Mechanism for the Double C−H Arylation of Cyclobutanecarboxamide[24r,26b,28a]

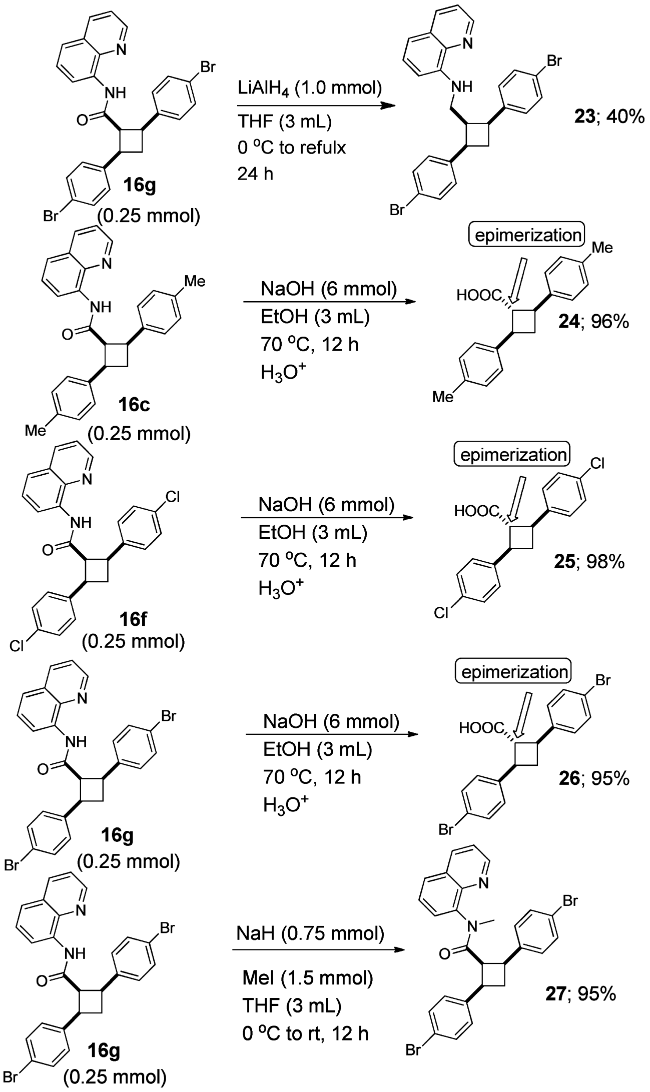


were recorded on 400 and 100 MHz spectrometers respectively using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. HRMS measurements reported in this work were obtained from TOF and quadrupole mass analyzers. Column chromatography was carried out on silica gel (100−200 mesh). Reactions were carried out in anhydrous solvent under nitrogen atmosphere. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under iodine. Yields of products were not optimized. In all the reactions, the column chromatographic purification of the reaction mixture afforded only the bis-arylated cyclobutanecarboxamides as the major diastereomer in pure form. However, in special cases, monoarylated cyclobutanecarboxamides were obtained when the experimental condition was changed.

General Procedure for the Synthesis of Cyclobutanecarboxamides 15a−15c and 15e−15h. A dry flask containing the corresponding amine (auxiliary) (1 mmol), Et_3N (1.1 mmol) was stirred for 5−10 min under a nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (4 mL) was added followed by dropwise addition of cyclobutanecarbonyl chloride (1 mmol). The resulting mixture was stirred for 10 min at rt. Then, the reaction mixture was refluxed for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and twice with saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh, EtOAc/hexanes =20:80) furnished the corresponding cyclobutanecarboxamides **15a**−**15c** and **15e**−**15h**.

Procedure for Synthesis of Cyclobutanecarboxamide 15d. 2-Picolinic acid (1.5 mmol) was dissolved in $SOCl_2$ (4 mmol) and stirred for 24 h at rt under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under nitrogen atmosphere. Then, the DCM solution containing 2-picolinoyl chloride was added to a separate flask containing cyclobutanamine (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). Then, reaction mixture was stirred at rt for 10 min. Next, the reaction mixture was refluxed for 12 h. Then, the reaction mixture was further diluted with dichloromethane (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (EtOAc/hexanes =20:80) furnished the cyclobutanecarboxamide **15d**.

Scheme 13. Synthetic Transformation and Observation of Epimerization



General Procedure for the Preparation of Bis-arylated Cyclobutanecarboxamides 16a−16aj/19a−19c/21a−21m. A solution of cyclobutanecarboxamide **15** (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol (5 mol %)), aryl iodide (1 mmol) AgOAc (91.8 mg, 0.55 mmol) in anhydrous toluene (2−3 mL) was heated at an appropriate temperature (73−110 °C, see the corresponding Tables/Schemes for specific examples) for an appropriate time (8−24 h, see the corresponding Tables/

Schemes for specific examples) under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh) furnished the corresponding bis-arylated cyclobutanecarboxamides **16a-16aj/19a-19c/21a-21m** (see the corresponding Tables/Schemes for specific examples).

General Procedure for the Preparation of Monoarylated Cyclobutanecarboxamides 17a−17d. A solution of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**15a**, 56 mg, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol (5 mol %)), aryl iodide (0.125 mmol) AgOAc (91.8 mg, 0.55 mmol) in anhydrous toluene (2−3 mL) was heated at an appropriate temperature (73−110 °C, see the corresponding Tables/Schemes for specific examples) for an appropriate time (15−24 h, see the corresponding Tables/Schemes for specific examples) under nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh) furnished the corresponding monoarylated cyclobutanecarboxamides **17a−17d** (see the corresponding Tables/Schemes for specific examples).

Procedure for the Preparation 23 from 16g. To dry flask was added anhydrous THF (4 mL) and (1*S**,2*R**,4*S**)-2,4-bis(4-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (**16g**, 0.25 mmol) and the reaction flask was cooled to 0 °C under a nitrogen atmosphere. To this solution was added $LiAlH_4$ (1 mmol) in portions and was refluxed overnight. Then EtOAc (3 mL) and water (1−2 mL) were added sequentially. The resulting solution was extracted with EtOAc (2 × 15 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed by rotary evaporation; product was purified by column chromatography on silica gel (EtOAc/hexane, 10:90), which afforded the product **24**.

Procedure for the Hydrolysis of the Bis-arylated Cyclobutanecarboxamides 16c, 16f, and 16g. The corresponding bis-arylated cyclobutanecarboxamides **16c** or **16f** or **16g** (0.25 mmol) and NaOH (6 mmol) in ethanol (3 mL) were heated at 80 °C for overnight. After this period, the reaction mixture was diluted with water and extracted with ether (2 × 10 mL), and then acidified with 1 N HCl to get a pH ≈ 2. Extraction with ether (2 × 10 mL) and drying of the combined organic layers over Na_2SO_4 was followed by evaporation of the solvent in vacuum and gave the corresponding carboxylic acids **24−26**.

Procedure for *N*-Methylation of 16g. To a dry flask was added a suspension of NaH in oil (0.75 mmol) and washed with hexane (2 × 2 mL). Then, to this reaction flask, anhydrous THF (3 mL) and (1*S**,2*R**,4*S**)-2,4-bis(4-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (**16g**, 0.25 mmol) were added, and the reaction flask was cooled to 0 °C and allowed to stir for 15 min under a nitrogen atmosphere. To this solution was added MeI (1.5 mmol) in dropwise and the reaction mixture was stirred at rt for 12 h. Then, EtOAc (3 mL) and water (1−2 mL) were added sequentially. The resulting solution was extracted with EtOAc (2 × 10 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed by under vacuum, and the crude reaction mixture was purified by column chromatography on silica gel (EtOAc/hexane 15:85), which afforded the product **27**.

***N*-(Quinolin-8-yl)cyclobutanecarboxamide (15a).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown color solid; 221 mg, 98% yield; mp 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (br s, 1H), 8.79 (d, 1H, *J* = 8.0 Hz), 8.70 (d, 1H, *J* = 4.0 Hz), 8.02 (d, 1H, *J* = 8.0 Hz), 7.47−7.30 (m, 3H), 3.37−3.29 (m, 1H), 2.50−2.41 (m, 2H), 2.30−2.23 (m, 2H), 2.22−1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 148.0, 138.2, 136.2, 134.4, 127.8, 127.2, 121.5, 121.3, 116.2, 41.3, 25.4, 18.1; FT-IR (KBr): 2988, 1698, 1598, 1351, 778 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$: 227.1184; found 227.1189.

***N*-(Naphthalen-1-yl)cyclobutanecarboxamide (15b).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; red color liquid; 164 mg, 73%yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95−7.92 (m, 2H), 7.64 (br s, 1H), 7.56−7.51 (m, 3H), 7.29 (q, 1H, *J* = 8.0 Hz), 3.55−3.48 (m, 2H), 2.41−2.33 (m, 1H), 2.08 (q, 1H, *J* = 8.0 Hz), 1.89−1.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 134.8, 134.4, 131.0, 129.4, 128.7, 127.5, 127.2, 126.6, 125.4, 121.8, 41.5, 26.2, 25.0, 17.6 ; FT-IR (DCM): 2940, 1611, 1511, 1432, 810 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}NO$: 226.1231; found 226.1226.

***N*-(Pyridin-2-yl)cyclobutanecarboxamide (15c).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white color liquid; 132 mg, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (br s, 1H), 8.15−8.06 (m, 2H), 7.51 (q, 1H, *J* = 8.0 Hz), 6.85−6.82 (m, 1H), 3.07 (q, 1H, *J* = 8.0 Hz), 2.24−2.16 (m, 2H), 1.94 (t, 2H, *J* = 4.0 Hz), 1.74−1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 152.0, 147.0, 138.4, 119.3, 114.6, 40.4, 24.9, 18.0; FT-IR (DCM): 2850, 1601, 1530, 1421, 801 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$: 177.1027; found 177.1029.

***N*-Cyclobutylpicolinamide (15d).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.60; red color liquid; 140 mg, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (br s, 1H), 8.22 (d, 2H, *J* = 8.0 Hz),7.67 (t, 1H, *J* = 8.0 Hz), 7.44−7.41 (m, 1H), 4.62 (q, 1H, *J* = 8.0 Hz), 2.46−2.39 (m, 2H), 2.10−2.01 (m, 2H), 1.82−1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 149.8, 147.8, 137.5, 126.1, 122.3, 44.6, 31.2, 15.2; FT-IR (DCM): 2953, 1523, 1510, 1435, 798 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$: 177.1027; found 177.1029.

***N*-(2-Methoxyphenyl)cyclobutanecarboxamide (15e).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown color liquid; 164 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (q, 1H, *J* = 8.0 Hz), 7.73 (br s, 1H), 6.95−6.84 (m, 2H), 6.83−6.75 (m, 1H), 3.74 (s, 3H), 3.14 (q, 1H, *J* = 8.0 Hz), 2.37−2.27 (m, 2H), 2.18−2.10 (m, 2H), 1.95−1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 147.8, 127.7, 123.4, 120.8, 119.6, 109.8, 55.5, 41.0, 25.2, 18.0; FT-IR (DCM): 2990, 1672, 1588, 1393, 810 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$: 206.1181; found 206.1189.

***N*-(2-(Phenylthio)phenyl)cyclobutanecarboxamide (15f).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow color liquid; 240 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, *J* = 8.0 Hz), 8.20 (br s, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.46 (q, 1H, *J* = 8.0 Hz), 7.27−7.18 (m, 2H), 7.17−7.07 (m, 4H), 3.09−3.04 (m, 1H), 2.16−2.08 (m, 4H), 1.94−1.89 (m, 1H), 1.80−1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 139.9, 136.9, 135.6, 131.1, 129.3, 126.9, 126.2, 124.1, 120.7, 119.5, 41.0, 25.1, 17.8; FT-IR (DCM): 2965, 1578, 1559, 1401, 815 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{18}NOS$: 284.1109; found 284.1104.

***N*-(2-Methylthio)phenyl)cyclobutanecarboxamide (15g).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; White color solid; 194 mg, 88% yield; mp 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, *J* = 8.0 Hz),8.27 (br s, 1H), 7.47−7.45 (d, 1H, *J* = 8.0 Hz), 7.29 (q, 1H, *J* = 4.0 Hz), 7.06

(t, 1H, J = 8.0 Hz), 3.27 (q, 1H, J = 8.0 Hz), 2.45−2.36 (m, 2H), 2.35 (s, 3H), 2.35−2.26 (m, 2H), 2.06−1.91 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.3, 138.4, 132.9, 128.9, 125.1, 124.1, 120.4, 41.1, 25.4, 18.8, 18.2; FT-IR (KBr): 3322, 1621, 1532, 1413, 807 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{16}NOS$: 222.0952; found 222.0943.

***N*-(2-(Dimethylamino)ethyl)cyclobutanecarboxamide (15h).** Analytical TLC on silica gel, 2.5:2.5 methanol/ethyl acetate R_f = 0.50; light-yellow color liquid; 136 mg, 80% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.43 (q, 2H, J = 4.0 Hz), 3.01 (q, 1H, J = 4.0 Hz), 2.61 (t, 2H, J = 8.0 Hz), 2.36 (s, 6H), 2.30−2.25 (m, 2H), 2.14−2.12 (m, 2H), 2.03−1.93 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 175.4, 57.7, 44.4, 39.8, 36.0, 25.3, 18.2; FT-IR (DCM): 3290, 1603, 1557, 1485, 861 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{19}N_2O$: 171.1497; found 171.1499.

(1*S,2*R**,4*S**)-2,4-Bis(4-methoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16a).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.60; yellow color solid; 108 mg, 99% yield; mp 146−149 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.43 (br s, 1H), 8.65 (q, 1H, J = 4.0 Hz), 8.30 (q, 1H, J = 4.0 Hz), 7.95 (q, 1H, J_1 = 8.0 Hz), 7.29−7.20 (m, 7H), 6.72−6.69 (m, 4H), 4.02−3.97 (m, 1H), 3.95−3.90 (m, 2H), 3.61 (s, 6H), 3.44 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz) 2.65−2.61 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.2, 157.9, 147.8, 138.2, 136.1, 134.3, 132.7, 128.2, 127.7, 127.2, 121.3, 120.9, 116.4, 113.5, 55.1, 54.8, 38.5, 30.5; FT-IR (KBr): 2936, 1689, 1612, 1519, 825 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{28}H_{27}N_2O_3$: 439.2021; found 439.2019.

(1*S,2*R**,4*S**)-2,4-Diphenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16b).**[39] Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.70; brown color solid; 89 mg, 94% yield; mp 145−147 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.47 (br s, 1H), 8.67 (q, 1H, J = 4.0 Hz), 8.25 (q, 1H, J = 4.0 Hz), 7.97 (q, 1H, J = 4.0 Hz), 7.32−7.15 (m, 11H), 7.06−7.02 (m, 2H), 4.13−4.10 (m, 1H), 4.06−3.99 (m, 2H), 3.53 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.71−2.68 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.9, 147.8, 140.6, 138.2, 136.1, 134.2, 128.1, 127.7, 127.2, 127.0, 126.1, 121.3, 120.9, 116.4, 54.6, 39.1, 29.9; FT-IR (KBr): 3342, 1669, 1521, 1484, 993 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{23}N_2O$: 379.1810; found 379.1824.

(1*S,2*R**,4*S**)-*N*-(Quinolin-8-yl)-2,4-di-*p*-tolylcyclobutanecarboxamide (16c).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.70; light-yellow color solid; 100 mg, 99% yield; mp 156−160 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.45 (br s, 1H), 8.65 (q, 1H, J = 4.0 Hz), 8.32 (q, 1H, J = 4.0 Hz), 7.94 (q, 1H, J = 8.0 Hz), 7.29−7.20 (m, 7H), 6.98 (d, 4H, J = 8.0 Hz), 4.09−4.04 (m, 1H), 4.0−3.93 (m, 2H), 3.51 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.67−2.64 (m, 1H), 2.15 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.1, 147.5, 138.2, 137.5, 136.1, 135.4, 134.3, 128.9, 127.6, 127.3, 126.9, 121.2, 120.8, 116.4, 54.6, 38.9, 30.2, 21.0; FT-IR (KBr): 3359, 1689, 1595, 1484, 791 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{28}H_{27}N_2O$: 407.2123; found 407.2117.

(1*S,2*R**,4*S**)-2,4-Bis(4-ethylphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16d).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.70; white color solid; 106 mg, 98% yield; mp 136−138 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.43 (br s, 1H), 8.68 (q, 1H, J = 4.0 Hz), 8.30 (q, 1H, J = 4.0 Hz), 7.98 (q, 1H, J = 4.0 Hz), 7.32−7.22 (m, 7H), 7.02 (d, 4H, J = 8.0 Hz), 4.11−4.08 (m, 1H), 4.04−3.97 (m, 2H), 3.53 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz) 2.70−2.66 (m, 1H), 2.50 (q, 4H, J = 8.0 Hz), 1.08 (t, 6H, J = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.2, 147.7, 141.8, 138.2, 137.8, 136.1, 134.3, 127.6, 127.5, 127.2, 127.0, 121.3, 120.8, 116.4, 54.7, 39.0, 30.2, 28.5, 15.5; FT-IR (KBr): 3358, 1519, 1462, 1378, 825 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{31}N_2O$: 435.2436; found 435.2436.

(1*S,2*R**,4*S**)-2,4-Bis(4-nitrophenyl)-*N*-(quinolin-8-yl)-cyclobutanecarboxamide (16e).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.50; brown color solid; 86 mg, 74% yield; mp 182−184 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.65 (br s, 1H), 8.73 (q, 1H, J = 4.0), 8.19 (q, 1H, J = 8.0), 8.08−8.03 (m, 5H), 7.46−7.36 (m, 6H), 7.28 (q, 1H, J = 4.0 Hz), 4.35−4.30 (m, 1H), 4.20−4.13 (m, 2H), 3.60 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.89−2.83 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.8, 148.2, 148.1, 146.4, 138.0, 136.5, 133.3, 127.8, 127.6, 127.1, 123.4, 121.9, 121.7, 116.4, 54.5, 38.6, 30.0; FT-IR (KBr): 3344, 1682, 1596, 1391, 840 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1511; found 469.1500.

(1*S,2*R**,4*S**)-2,4-Bis(4-chlorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16f).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.60; light-yellow color solid; 110 mg, 99% yield; mp 171−174 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.48 (br s, 1H), 8.69 (q, 1H, J = 4.0 Hz), 8.27 (q, 1H, J = 4.0 Hz), 8.03 (q, 1H, J = 4.0 Hz), 7.36−7.27 (m, 3H), 7.25−7.20 (m, 4H), 7.20−7.11 (m, 4H), 4.10−4.05 (m, 1H), 3.99−3.97 (m, 2H), 3.42 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.70−2.63 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.5, 147.9, 138.9, 138.1, 136.3, 133.8, 131.9, 128.4, 128.2, 127.7, 127.2, 121.5, 121.4, 116.5, 54.3, 38.4, 30.1; FT-IR (KBr): 2988, 1698, 1598, 1351, 778 cm^{-1}; FT-IR (KBr): 3350, 1683, 1596, 1486, 790 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}Cl_2N_2O$: 447.1030; found 447.1010.

(1*S,2*R**,4*S**)-2,4-Bis(4-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16g).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; light-yellow color solid; 131 mg, 99% yield; mp 158−160 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.49 (br s, 1H), 8.69 (q, 1H, J = 4.0 Hz), 8.27 (q, 1H, J = 4.0 Hz), 8.03 (q, 1H, J = 4.0 Hz), 7.37−7.29 (m, 7H), 7.28−7.15 (m, 4H) 4.10−4.05 (m, 1H), 3.96−3.90 (m, 2H), 3.42 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.70−2.64 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.5, 147.9, 139.5, 138.1, 136.3, 133.9, 131.1, 128.8, 127.7, 127.2, 121.5, 121.4, 120.1, 116.5, 54.2, 38.5, 30.1; FT-IR (KBr): 3349, 1687, 1524, 1323, 824 cm$^{-1;}$ HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}Br_2N_2O$: 535.0020; found 534.9999.

(1*S,2*R**,4*S**)-2,4-Bis(4-fluorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16h).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; pale-yellow color solid; 100 mg, 97% yield; mp 137−139 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.48 (br s, 1H), 8.69 (q, 1H, J = 4.0 Hz), 8.28 (q, 1H, J = 4.0 Hz), 8.02 (q, 1H, J = 8.0 Hz), 7.36−7.23 (m, 7H), 6.90−6.89 (m, 4H), 4.10−4.05 (m, 1H), 4.00 (dd, 2H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 3.48 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.71−2.67 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.7, 161.5 (d, J_{C-F} = 242 Hz), 147.9, 138.2, 136.3, 136.2 (d, J_{C-F} = 3 Hz), 134.0, 128.5 (d, J_{C-F} = 8.0 Hz), 127.7, 127.2, 121.4, 121.3, 116.4, 115.1 (d, J_{C-F} = 21.1 Hz), 54.5, 38.3, 30.3; FT-IR (KBr): 3349, 1605, 1599, 1392, 737 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}F_2N_2O$: 415.1621; found 415.1611.

(1*S,2*R**,4*S**)-2,4-Bis(4-iodophenyl)-*N*-(quinolin-8-yl)-cyclobutanecarboxamide (16i).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; brown color solid; 114 mg,73% yield; mp 169−171 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.48 (br s, 1H), 8.70 (q, 1H, J = 4.0 Hz), 8.28 (q, 1H, J = 4.0 Hz), 8.06 (q, 1H, J = 4.0 Hz), 7.50−7.46 (m, 4H), 7.39−7.24 (m, 3H), 7.04 (d, 4H, J = 8.0 Hz), 4.11–4.06 (m, 1H), 3.97–3.90 (m, 2H), 3.42 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.70–2.63 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.4, 147.9, 140.2, 138.1, 137.1, 136.3, 133.9, 129.0, 127.7, 127.2, 121.5, 121.4, 116.5, 91.6, 54.2, 38.6, 29.9; FT-IR (KBr): 3346, 1681, 1520, 1485, 808 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}I_2N_2O$: 630.9743; found 630.9737.

(1*S,2*R**,4*S**)-2,4-Di(naphthalen-1-yl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16j).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; brown color solid; 112 mg, 94% yield; mp 225–227 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.03 (br s, 1H), 8.43 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz), 8.23 (d, 2H, J = 8.0 Hz), 7.85 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz), 7.77 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz), 7.70–7.64 (m, 4H), 7.58–7.50 (m, 4H), 7.48–7.38 (m, 2H), 7.35–7.31 (m, 2H), 7.16 (q, 1H, J = 4.0 Hz), 7.03–6.94 (m, 2H), 4.77–4.72 (m, 3H), 4.08 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.91–2.84 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.1, 147.2, 137.7, 135.8, 135.7, 133.7, 133.5, 131.8, 128.8, 127.1, 126.9, 126.7, 126.0, 125.4, 125.2, 125.0, 123.5, 120.8, 120.4, 115.7, 56.6, 37.9, 28.1; FT-IR (KBr): 3351, 1683, 1523, 1485, 780 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{34}H_{27}N_2O$: 479.2123; found 479.2115.

(1*S,2*R**,4*S**)-*N*-(Quinolin-8-yl)-2,4-di-*m*-tolylcyclobutanecarboxamide (16k).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; light-yellow color solid; 100 mg, 99% yield; mp 98–100 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.46 (br s, 1H), 8.70 (q, 1H, J = 4.0 Hz), 8.28 (q, 1H, J = 8.0 Hz), 8.0 (q, 1H, J_1 = 8.0 Hz), 7.35–7.23 (m, 3H), 7.23–7.04 (m, 6H), 6.85 (d, 2H, J = 8.0 Hz), 4.14–4.10 (m, 1H), 4.04–3.97 (m, 2H), 3.52 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.71–2.67 (m, 6H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.1, 147.8, 140.6, 138.2, 137.5, 136.2, 134.3, 127.9, 127.7, 127.5, 127.2, 126.8, 124.0, 121.3, 120.9, 116.4, 54.6, 39.1, 30.0, 21.4; FT-IR (KBr): 3400, 1596, 1389, 1360, 1047 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{28}H_{27}N_2O$: 407.2123; found 407.2123.

(1*S,2*R**,4*S**)-*N*-(Quinolin-8-yl)-2,4-bis(3-(trifluoromethyl)phenyl)cyclobutanecarboxamide (16l).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown color solid; 75 mg, 59% yield; mp 114–116 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.46 (br s, 1H), 8.65 (q, 1H, J = 4.0), 8.14 (q, 1H, J = 4.0 Hz), 7.99 (q, 1H, J = 4.0 Hz), 7.50 (s, 2H), 7.44 (q, 2H, J = 8.0 Hz), 7.32–7.18 (m, 7H), 4.17–4.12 (m, 1H), 4.06–3.99 (m, 2H), 3.51 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.77–2.69 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.2, 148.0, 141.3, 138.0, 136.2, 133.6, 130.3 (q, J_{C-F} = 32 Hz), 130.3, 128.5, 127.6, 127.1, 126.8 (q, J_{C-F} = 271 Hz), 123.7 (q, J_{C-F} = 4 Hz), 123.1 (q, J_{C-F} = 4 Hz), 121.4, 121.4, 116.3, 54.2, 38.7, 29.9; FT-IR (KBr): 3445, 1519, 1321, 1313, 989 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{28}H_{21}F_6N_2O$: 515.1558; found 515.1536.

(1*S,2*R**,4*S**)-2,4-Bis(3-nitrophenyl)-*N*-(quinolin-8-yl)-cyclobutanecarboxamide (16m).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.50; brown color solid; 100 mg, 86% yield; mp 183–185 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.57 (br s, 1H), 8.67 (q, 1H, J = 4.0 Hz), 8.16 (s, 2H), 8.16 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz), 8.01 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz), 7.88 (q, 2H, J = 4.0 Hz), 7.63 (d, 2H, J = 8.0 Hz), 7.36–7.28 (m, 4H) 7.23 (q, 1H, J = 4.0 Hz), 4.29–4.24 (m, 1H), 4.17–4.10 (m, 2H), 3.60 (q, 1H, J = 12.0 Hz), 2.84–2.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.9, 148.2, 148.1, 142.4, 138.0, 136.3, 133.4, 133.1, 129.0, 127.7, 127.0, 122.0, 121.7, 121.6, 121.4, 116.3, 54.2, 38.3, 29.7; FT-IR (KBr): 3344, 1682, 1579, 1485, 792 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1511; found 469.1512.

(1*S,2*R**,4*S**)-2,4-Bis(3-fluorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16n).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; pale-yellow color solid; 100 mg, 97% yield; mp 132–134 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.49 (br s, 1H), 8.68 (q, 1H, J = 4.0 Hz), 8.25 (q, 1H, J = 4.0 Hz), 7.99 (q, 1H, J = 8.0 Hz), 7.33–7.20 (m, 3H), 7.12–6.98 (m, 6H), 6.73–6.69 (m, 2H), 4.12–4.07 (m, 1H), 4.01–3.93 (m, 2H), 3.45 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.70–2.63 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.4, 164.0 (d, J_{C-F} = 244 Hz) 147.9, 143.1 (d, J_{C-F} = 8.0 Hz), 138.1, 136.2, 133.9, 129.5 (d, J_{C-F} = 9.0 Hz), 127.7, 127.2, 122.5 (d, J_{C-F} = 3 Hz), 121.4, 121.3, 116.4, 114.1 (d, J_{C-F} = 21.5 Hz), 113.1 (d, J_{C-F} = 20.9 Hz); FT-IR (KBr): 3435, 1655, 1528, 1481, 793 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}F_2N_2O$: 415.1621; found 415.1609.

(1*S,2*R**,4*S**)-2,4-Bis(3-chlorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16o).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white color solid; 89 mg, 80% yield; mp 130–132 °C;^{1}H NMR (400 MHz, CDCl$_3$): δ 9.52 (br s, 1H), 8.79 (q, 1H, J = 4.0 Hz), 8.30 (q, 1H, J = 4.0 Hz,), 8.10 (q, 1H, J = 4.0 Hz,), 7.44–7.11 (m, 5H), 7.07–7.04 (m, 6H), 4.19–4.14 (m, 1H), 4.06–4.0 (m, 2H), 3.50 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.77–2.70 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.3, 148.0, 142.5, 138.2, 136.2, 134.0, 133.8, 129.3, 127.7, 127.3, 127.2, 126.4, 125.1, 121.4, 121.3, 116.5, 54.3, 38.6, 29.8; FT-IR (KBr): 3434, 1601, 1525, 1323, 890 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}NCl_2O$: 447.1030; found 447.1018.

(1*S,2*R**,4*S**)-2,4-Bis(3-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16p).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; yellow color liquid; 106 mg, 80% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.55 (br s, 1H), 8.78 (q, 1H, J = 4.0 Hz), 8.33 (q, 1H, J = 4.0 Hz), 8.06 (q, 1H, J = 4.0 Hz), 8.50 (s, 2H), 7.40–7.21 (m, 7H), 7.08 (t, 2H, J = 8.0 Hz), 4.17–4.12 (m, 2H), 4.05–4.0 (m, 2H), 3.50 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.74–2.71 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.3, 148.0, 142.8, 138.1, 136.2, 133.8, 130.1, 129.7, 129.3, 127.7, 127.2, 126.4, 125.6, 122.4, 121.4, 121.3, 116.5, 54.3, 38.5, 29.9; FT-IR (DCM): 3332, 1592, 1423, 1361, 889 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{21}Br_2N_2O$: 535.0020; found 535.0024.

(1*S,2*R**,4*S**)-2,4-Bis(3,4-dimethylphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16q).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; light-yellow color solid; 107 mg, 99% yield; mp 99–102 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.42 (br s, 1H), 8.64 (q, 1H, J = 4.0 Hz), 8.32–8.30 (m, 1H), 7.92 (d, 1H, J = 8.0 Hz), 7.28–7.17 (m, 3H), 7.08 (t, 4H, J = 8.0 Hz), 6.92 (d, 2H, J = 8.0 Hz) 4.07–4.03 (m, 1H), 3.92 (q, 2H, J = 8.0 Hz), 3.48 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.66–2.63 (m, 1H), 2.05 (s, 12H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.4, 147.7, 138.2, 138.1, 136.1, 136.0, 134.4, 134.1, 129.4, 128.4, 127.6, 127.2, 124.5, 121.2, 120.8, 116.4, 54.7, 39.0, 30.3, 19.8, 19.4; FT-IR (KBr): 3435, 1575, 1365, 1291, 1047 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{31}N_2O$: 435.2423; found 435.2419.

(1*S,2*R**,4*S**)-2,4-Bis(3,5-dimethylphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16r).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; pale-yellow color liquid; 100 mg, 93% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.40 (br s, 1H), 8.69 (q, 1H, J = 4.0 Hz), 8.28 (q, 1H, J = 4.0 Hz), 7.98 (q, 1H, J = 4.0 Hz), 7.32–7.19 (m, 3H), 6.90 (s, 4H), 6.62 (s, 2H), 4.09–4.04 (m, 1H), 3.96–3.90 (m, 2H), 3.45 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.67–2.62 (m, 1H), 2.09 (s, 12H); ^{13}C

NMR (100 MHz, CDCl$_3$): δ 169.3, 147.7, 140.5, 138.3, 137.3, 136.1, 134.4, 127.8, 127.7, 127.2, 124.8, 121.2, 120.7, 116.4, 54.6, 39.0, 30.0, 21.3; FT-IR (DCM): 3358, 1690, 1520, 1387, 791 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{30}$H$_{31}$N$_2$O: 435.2436; found 435.2423.

(1S*,2R*,4S*)-2,4-Bis(3,4-dichlorophenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (16s). Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.60; white color solid; 51 mg, 40% yield; mp 140−145 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.64 (br s, 1H), 8.81 (q, 1H, J = 4.0 Hz), 8.19 (q, 1H, J = 8.0 Hz), 8.09 (q, 1H, J = 4.0 Hz), 7.44−7.30 (m, 4H), 7.29−7.18 (m, 5H), 4.58−4.53 (m, 1H), 4.19−4.12 (m, 2H), 3.60 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.66−2.60 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.3, 148.0, 138.2, 136.3, 136.1, 134.0, 133.9, 132.6, 129.7, 128.8, 127.7, 127.1, 126.8, 121.4, 121.3, 116.2, 53.6, 37.4, 27.5; FT-IR (KBr): 3341, 1631, 1587, 1332, 804 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{26}$H$_{19}$Cl$_4$N$_2$O: 515.0251; found 515.0249.

(1S*,2R*,4S*)-2,4-Bis(4-acetylphenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (16t). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow color solid; 99 mg, 86% yield; mp181−183 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.60 (br s, 1H), 8.75 (q, 1H, J = 4.0 Hz), 8.25 (q, 1H, J = 4.0 Hz), 8.06 (q, 1H, J = 8.0 Hz), 7.81−7.79 (m, 4H), 7.42−7.24 (m, 7H), 4.28 (q, 1H, J = 4.0 Hz), 4.16−4.09 (m, 2H), 3.59 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.83 (t, 1H, J = 4.0 Hz), 2.47 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 197.9, 168.4, 148.0, 146.3, 138.1, 136.3, 135.1, 133.8, 128.3, 127.7, 127.1, 127.0, 121.5, 121.4, 116.4, 54.4, 38.9, 29.8, 26.5; FT-IR (KBr): 3345, 1605, 1524, 1391, 793 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{30}$H$_{27}$N$_2$O$_3$: 463.2021; found 463.2012.

(1S*,2R*,4S*)-2,4-Bis(4-methoxy-2-nitrophenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (16u). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow color solid; 75 mg, 57% yield; mp145−147 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.53 (br s, 1H), 8.74 (q, 1H, J = 4.0 Hz), 8.12 (q, 1H, J = 8.0 Hz), 8.01 (q, 1H, J = 8.0 Hz), 7.57 (d, 2H, J = 8.0 Hz), 7.37−7.34 (m, 1H), 7.30−7.29 (m, 3H), 7.28−7.29 (m, 1H), 7.09−7.07 (m, 2H), 4.65 (q, 1H, J = 4.0 Hz), 4.34−4.27 (m, 2H), 3.70 (s, 6H), 3.52 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.61 (q, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.9, 158.2, 148.9, 148.2, 138.2, 135.8, 133.9, 130.8, 127.5, 126.7, 121.4, 121.2, 119.5, 116.1, 109.3, 55.6, 55.2, 35.9, 28.1; FT-IR (KBr): 3430, 1555, 1521, 1493, 819 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{28}$H$_{25}$N$_4$O$_7$: 529.1723; found 529.1728.

(1S*,2R*,4S*)-2,4-Di(1H-indol-5-yl)-N-(quinolin-8-yl)cyclobutanecarboxamide (16v). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow color semisolid; 75 mg, 66% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.53 (br s, 1H), 8.95 (br s, 2H), 8.45 (d, 1H, J = 4.0 Hz), 8.13 (d, 1H, J = 8.0 Hz), 7.90−7.78 (m, 1H), 7.66−7.39 (m, 2H), 7.22 (q, 1H, J = 4.0 Hz), 7.20−6.75 (m, 8H), 6.32 (s, 2H), 4.16 (t, 3H, J = 8.0 Hz), 3.58 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.79 (t, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 147.8, 138.1, 135.9, 134.6, 134.2, 131.5, 127.8, 127.5, 126.9, 124.3, 121.2, 120.7, 118.7, 116.2, 110.8, 101.8, 55.2, 39.7, 30.9; FT-IR (KBr): 3440, 1616, 1528, 1412, 710 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{30}$H$_{25}$N$_4$O: 457.2028; found 457.2035.

(1S*,2R*,4S*)-N-(Quinolin-8-yl)-2-(thiophen-2-yl)-4-(thiophen-3-yl)cyclobutanecarboxamide (16w). Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow color solid; 81 mg, 83% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.61 (br s, 1H), 8.75 (q, 1H, J = 4.0 Hz), 8.56 (t, 1H, J = 4.0 Hz), 8.08 (q, 1H, J = 4.0 Hz), 7.40−7.37 (m, 3H), 7.10−7.06 (m, 4H), 6.92 (q, 2H, J = 4.0 Hz), 4.22−4.16 (m, 2H), 4.06−4.01 (m, 1H), 3.57 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.95−2.88 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.1, 147.9, 143.4, 138.2, 136.2, 134.3, 127.7, 127.3, 126.7, 125.2, 123.9, 121.4, 121.2, 116.6, 55.9, 35.7, 35.5; FT-IR (DCM): 3313, 1612, 1554, 1302, 801 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{22}$H$_{19}$N$_2$OS$_2$: 391.0938; found 391.0936.

(1S*,2R*,4S*)-2,4-Bis(6-fluoropyridin-3-yl)-N-(quinolin-8-yl)cyclobutanecarboxamide (16x). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow color solid; 83 mg, 80% yield; mp187−189 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.70 (br s, 1H), 8.76 (q, 1H, J = 4.0 Hz), 8.23−8.17 (m, 4H), 7.86−7.81 (m, 2H), 7.48 (t, 2H, J = 4.0 Hz), 7.46−7.28 (m, 1H), 6.80 (q, 2H, J = 8.0 Hz), 4.20−4.05 (m, 3H), 3.56 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.79 (q, 1H, J = 4.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.3, 162.4 (d, $J_{\mathrm{C-F}}$ = 236 Hz), 147.6, 146.2 (d, $J_{\mathrm{C-F}}$ = 14.5 Hz), 140.1 (d, $J_{\mathrm{C-F}}$ = 8 Hz), 137.8, 137.2, 133.1, 132.8, 128.0, 127.5, 122.3, 121.5, 118.2, 108.9 (d, $J_{\mathrm{C-F}}$ = 37.1 Hz), 54.1, 36.1, 30.0; FT-IR (KBr): 3430, 1624, 1554, 1341, 798 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{24}$H$_{19}$F$_2$N$_4$O: 417.1526; found 417.1526.

(1S*,2R*,4S*)-2,4-Bis(2-chloropyridin-4-yl)-N-(quinolin-8-yl)cyclobutanecarboxamide (16y). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow color liquid; 107 mg, 96% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.70 (br s, 1H), 8.75 (q, 1H, J = 4.0 Hz), 8.22−8.15 (m, 3H), 8.10 (q, 1H, J = 8.0 Hz), 7.43−7.39 (m, 2H), 7.34−7.26 (m, 3H), 7.13−7.11 (m, 2H), 4.28−4.23 (m, 1H), 4.03−3.96 (m, 2H), 3.45 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.78−2.73 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.3, 152.7, 151.5, 149.8, 148.3, 138.1, 136.5, 133.6, 127.8, 127.1, 122.7, 122.1, 121.7, 120.9, 116.7, 53.6, 37.7, 28.9; FT-IR (DCM): 3350, 1624, 1510, 1491, 810 cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{24}$H$_{19}$Cl$_2$N$_4$O: 449.0935; found 449.0936.

(1S*,2S*,4R*)-2-(4-Methoxyphenyl)-N-(quinolin-8-yl)-4-(thiophen-2-yl)cyclobutanecarboxamide (16z). Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow color liquid; 69 mg, 67% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.55 (br s, 1H), 8.75 (q, 1H, J = 4.0 Hz), 8.46 (q, 1H, J = 4.0 Hz), 8.09 (q, 1H, J = 4.0 Hz), 7.41−7.27 (m, 5H), 7.07−7.03 (m, 2H), 6.88−6.81 (m, 1H), 6.80−6.78 (m, 2H), 4.22−4.17 (m, 1H), 4.09−4.0 (m, 2H), 3.98 (s, 3H), 3.55 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.83−2.71 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.6, 157.9, 147.8, 143.8, 138.2, 136.2, 134.3, 132.4, 128.1, 127.7, 127.3, 126.6, 125.0, 123.8, 121.3, 121.0, 116.5, 113.5, 55.3, 55.1, 38.7, 35.2, 33.2; FT-IR (KBr): 3439, 1602, 1534, 1423, 990 cm^{-1}; HRMS(ESI): m/z [M + H]$^+$ calcd for C$_{25}$H$_{23}$N$_2$O$_2$S: 415.1480; found 415.1488.

(1S*,2R*,4S*)-2-(1H-Indol-5-yl)-4-(4-methoxyphenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (16aa). Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; yellow color liquid; 91 mg, 82% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.60 (br s, 1H), 8.60 (q, 1H, J = 4.0 Hz), 8.32 (q, 1H, J = 4.0 Hz), 8.21 (br s, 1H), 7.96−7.94 (m, 1H), 7.67 (d, 1H, J = 4.0 Hz), 7.32−7.05 (m, 8H), 6.98−6.75 (m, 2H), 6.42−6.41 (m, 1H), 4.20−4.15 (m, 2H), 4.06 (t, 1H, J = 4.0 Hz), 3.68 (s, 3H), 3.59 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.80−2.72 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.7, 157.8, 147.7, 138.2, 136.0, 134.6, 134.2, 132.9, 131.6, 128.2, 127.8, 127.6, 127.1, 124.2, 121.3, 121.2, 120.9, 118.8, 116.4, 113.5, 110.8, 102.1, 55.1, 55.0, 39.3, 38.7, 30.7; FT-IR (KBr): 3430, 1623, 1515, 1421, 890 cm^{-1};

HRMS(ESI): *m/z* [M + H]$^+$ calcd for $C_{29}H_{26}N_3O_2$: 448.2025; found 448.2034.

(1*S,2*R**,4*S**)-2-(2-Chloropyridin-4-yl)-4-(4-methoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16ab).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; light-yellow color liquid; 33 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 8.70 (m, 1H), 8.22−8.04 (q, 1H, *J* = 4.0 Hz), 7.40−7.09 (m, 8H), 6.65 (q, 2H, *J* = 8.0 Hz), 4.24−3.87 (m, 3H), 3.59 (s, 3H), 3.40 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.68−2.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 158.1, 154.2, 151.4, 149.0, 148.0, 147.9, 144.3, 138.1, 136.3, 133.7, 131.3, 128.2, 127.7, 127.1, 122.6, 121.5, 120.9, 116.5, 113.5, 55.1, 54.2, 39.0, 37.3, 31.9; FT-IR (KBr): 3423, 1566, 1513, 1448, 810 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{26}H_{23}ClN_3O_2$: 444.1478; found 444.1483.

(1*S,2*S**,4*R**)-2-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)-4-(thiophen-2-yl)cyclobutanecarboxamide (16ac).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; yellow color solid; 54 mg, 52% yield; mp 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (br s, 1H), 8.77 (q, 1H, *J* = 4.0 Hz), 8.40 (q, 1H, *J* = 4.0 Hz), 8.24 (q, 1H, *J* = 4.0 Hz), 8.10 (q, 1H, *J* = 8.0 Hz), 7.44−7.35 (m, 3H), 7.28 (d, 1H, *J* = 8.0 Hz), 7.14 (q, 1H, *J* = 4.0 Hz), 7.03−7.02 (m, 2H), 6.82 (q, 1H, *J* = 8.0 Hz), 4.31−4.24 (m, 1H), 4.18−4.13 (m, 1H), 3.94−3.80 (m, 1H), 3.50 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.89−2.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 153.9, 151.5, 149.2, 148.0, 142.3, 138.2, 136.3, 133.8, 127.8, 127.3, 126.7, 125.4, 124.3, 122.5, 121.6, 121.5, 120.8, 116.6, 54.9, 37.5, 35.5, 32.5; FT-IR (KBr): 3530, 1654, 1529, 1409, 990 cm^{-1}; HRMS(ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}ClN_3OS$: 420.0937; found 420.0943.

(1*S,2*S**,4*R**)-2-(1*H*-Indol-5-yl)-*N*-(quinolin-8-yl)-4-(thiophen-2-yl)cyclobutanecarboxamide (16ad).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; red color liquid; 54 mg, 51% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (br s, 1H), 8.60 (q, 1H, *J* = 4.0 Hz), 8.40 (q, 1H, *J* = 4.0 Hz), 8.16 (br s, 1H), 8.01 (q, 1H, *J* = 8.0 Hz), 7.99 (d, 1H, *J* = 4.0 Hz), 7.65−7.23 (m, 3H), 7.13−7.04 (m, 5H), 6.88 (q, 1H, *J* = 4.0 Hz), 6.45 (q, 1H, *J* = 8.0 Hz), 4.29−4.10 (m, 3H), 3.62 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.92−2.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 147.8, 144.0, 138.2, 136.0, 134.6, 134.3, 131.3, 127.9, 127.6, 127.2, 126.6, 125.0, 124.2, 123.8, 121.3, 121.2, 121.0, 118.7, 116.5, 110.8, 102.3, 55.6, 39.4, 35.5, 33.4; FT-IR (KBr): 3400, 1613, 1531, 1454, 910 cm^{-1}; HRMS(ESI): *m/z* [M + H]$^+$ calcd for $C_{26}H_{22}N_3OS$: 424.1483; found 424.1492.

(1*S,2*R**,4*S**)-2,4-Bis(2,4-dimethoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16ae).** Analytical TLC on silica gel, 4:1 ethyl acetate/hexanes R_f = 0.60 red color liquid; 100 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (br s, 1H), 8.80 (q, 1H, *J* = 4.0 Hz), 8.36 (q, 1H, *J* = 4.0 Hz), 8.07 (q, 1H, *J* = 4.0 Hz), 7.40 (q, 1H, *J* = 4.0 Hz), 7.31−7.24 (m, 4H), 6.48 (q, 2H, *J* = 4.0 Hz), 6.25 (d, 2H, *J* = 4.0 Hz), 4.27−4.24 (m, 1H), 4.09−4.02 (m, 2H), 3.75 (s, 6H), 3.71 (s, 6H), 3.40 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.64−2.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 159.1, 158.0, 147.6, 138.2, 136.2, 134.8, 128.1, 127.7, 127.4, 122.1, 121.2, 120.2, 115.9, 103.5, 97.5, 55.3, 55.2, 53.8, 35.4; FT-IR (DCM): 2881, 1643, 1511, 1423, 811 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{31}N_2O_5$: 499.2333; found 499.2227.

(1*S,2*R**,4*S**)-2,4-Bis(3,4-dimethoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16af).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexanes R_f = 0.30; pale-yellow color solid; 40 mg, 32% yield; mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (br s, 1H), 8.72 (q, 1H, *J* = 4.0 Hz), 8.43 (q, 1H, *J* = 4.0 Hz), 8.10 (q, 1H, *J* = 4.0 Hz), 7.42−7.28 (m, 3H), 6.90−6.87 (m, 4H), 6.76 (t, 1H, *J* = 8.0 Hz), 4.17−4.10 (m, 1H), 4.04−3.98 (m, 2H), 3.73 (s, 6H), 3.73 (s, 6H), 3.72 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.75−2.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 148.5, 147.7, 147.2, 138.2, 136.3, 134.2, 133.3, 127.7, 127.3, 121.3, 121.1, 119.1, 116.4, 110.8, 110.1, 50.7, 55.6, 54.6, 38.8, 31.1; FT-IR (KBr): 2922, 1601, 1545, 1434, 821 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{31}N_2O_5$: 499.2233; found 499.2245.

(1*S,2*R**,4*S**)-2,4-Bis(benzo-[*d*][1,3]-dioxol-5-yl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (16ag).** Analytical TLC on silica gel, 4:1 ethyl acetate/hexanes R_f = 0.70 yellow color liquid; 58 mg, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51(br s, 1H), 8.76 (q, 1H, *J* = 4.0 Hz), 8.41 (q, 1H, *J* = 4.0 Hz), 8.09 (q, 1H, *J* = 4.0 Hz), 7.44−7.33 (m, 3H), 6.85−6.79 (m, 4H), 6.68 (q, 2H, *J* = 4.0 Hz), 5.82 (d, 4H, *J* = 4.0 Hz),4.09−4.04 (m, 1H), 3.98−3.91 (m, 2H), 3.42 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.70−2.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 147.8, 147.4, 145.8, 138.2, 136.2, 134.4, 134.2, 127.7, 127.7, 127.3, 121.3, 121.0, 120.0, 116.4, 107.9, 107.7, 100.7, 54.7, 38.8, 30.6; FT-IR (DCM): 3041, 1723, 1487, 1421, 991 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{28}H_{23}N_2O_5$: 467.1607; found 467.1608.

(1*S,2*R**,4*S**)-*N*-(Quinolin-8-yl)-2,4-bis(3,4,5-trimethoxyphenyl)cyclobutanecarboxamide (16ah).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexanes R_f = 0.30 light-yellow color liquid; 70 mg, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (br s, 1H), 8.73 (q, 1H, *J* = 4.0 Hz), 8.46 (q, 1H, *J* = 4.0 Hz), 8.12 (q, 1H, *J* = 4.0 Hz), 7.44−7.34 (m, 3H), 6.53 (s, 4H), 4.16 (q, 1H, *J* = 4.0 Hz), 4.03−3.91 (m, 2H), 3.73 (s, 12H), 3.67 (s, 6H), 3.40 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.80−2.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 152.9, 147.8, 138.1, 136.5, 136.3, 136.2, 134.2, 127.8, 127.3, 121.5, 121.3, 116.4, 103.7, 60.7, 55.9, 54.4, 39.2, 31.2; FT-IR (DCM): 3120, 1611, 1436, 1346, 771 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{32}H_{35}N_2O_7$: 559.2444; found 559.2455.

(1*S,2*S**,4*R**)-2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-4-(3,4,5-trimethoxyphenyl)cyclobutanecarboxamide (16ai).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexanes R_f = 0.40 red color liquid; 50 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (br s, 1H), 8.73 (q, 1H, *J* = 4.0 Hz), 8.42 (q, 1H, *J* = 8.0 Hz), 8.10 (q, 1H, *J* = 4.0 Hz), 7.42−7.26 (m, 5H), 6.82 (q, 2H, *J* = 4.0 Hz), 6.50 (d, 2H, *J* = 8.0 Hz), 6.55 (t, 2H, *J* = 4.0 Hz), 4.15−4.10 (m, 1H), 4.02−3.97 (m, 2H), 3.73 (s, 3H), 3.71 (s, 6H), 3.61 (s, 3H), 3.44 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.25−2.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 157.8, 152.8, 147.8, 138.1, 136.4, 136.3, 136.2, 134.2, 132.7, 127.8, 127.7, 127.3, 121.4, 121.1116.4, 113.6, 103.8, 60.6, 55.8, 55.2, 54.6, 30.7, 38.1, 30.8; FT-IR (DCM): 2921, 1523, 1476, 1444, 749 cm^{-1};HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{31}N_2O_5$: 499.2233; found 499.2234.

(1*R,2*R**,4*S**)-2-(3,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)-4-(3,4,5-trimethoxyphenyl)cyclobutanecarboxamide (16aj).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexanes R_f = 0.30 light-brown color liquid; 99 mg, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (br s, 1H), 8.72 (q, 1H, *J* = 4.0 Hz), 8.44 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz), 8.10 (q, 1H, *J* = 4.0 Hz), 7.41−7.32 (m, 3H), 6.90 (q, 1H, *J* = 4.0 Hz), 6.77 (t, 1H, *J* = 8.0 Hz), 6.55 (t, 2H, *J* = 4.0 Hz), 4.14−4.11 (m, 1H), 4.02−3.98 (m, 2H), 3.78 (s, 6H), 3.74 (s, 3H), 3.72 (s, 6H), 3.65 (s, 3H), 3.43 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.77−2.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 152.9, 148.6, 147.8, 147.3, 138.1, 136.6, 136.3, 136.1, 134.2, 133.3, 127.7, 127.3, 121.4, 121.2, 119.0, 116.4, 110.8, 110.4, 103.8, 60.7, 55.9, 55.6, 54.5, 39.4, 38.6, 31.3; FT-IR (DCM): 2811, 1535, 1476, 1423, 981 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{33}N_2O_6$: 529.2338; found 529.2343.

(1*R,2*S**)-2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-cyclobutanecarboxamide (17a).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown color liquid; 25 mg, 30% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.36 (br s, 1H), 8.73 (q, 1H, J = 8.0 Hz), 8.54 (q, 1H, J = 8.0 Hz), 8.11 (q, 1H, J = 8.0 Hz), 7.47−7.39 (m, 3H), 7.25−7.23 (m, 2H), 6.65 (q, 2H, J = 4.0 Hz), 4.08 (dd, 1H, J_1 = 20.0 Hz, J_2 = 8.0 Hz), 3.75 (q, 1H, J = 4.0 Hz), 3.57 (s, 3H), 2.69−2.63 (m, 2H), 2.12−2.33 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.4, 158.0, 147.8, 138.2, 136.1, 134.4, 132.8, 128.4, 127.7, 127.3, 121.3, 120.9, 116.1, 113.5, 55.0, 47.8, 42.8, 25.4, 20.4, ; FT-IR (DCM): 3231, 1610, 1494, 1321, 710 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2$: 333.1603; found 333.1599.

(1*R,2*S**)-2-Phenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (17b).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown color liquid; 15 mg, 20% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.40 (br s, 1H), 8.73 (t, 1H, J = 8.0 Hz), 8.54 (q, 1H, J = 8.0 Hz), 8.10 (q, 1H, J = 8.0 Hz), 7.46−7.36 (m, 2H), 7.34−7.32 (m, 2H), 7.32−7.28 (m, 1H), 7.24−7.09 (m, 2H), 6.98−6.94 (m, 1H), 4.12 (dd, 1H, J_1 = 20.0 Hz, J_2 = 8.0 Hz), 3.80 (q, 1H, J = 4.0 Hz), 2.75−2.64 (m, 2H), 2.45−2.36 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.3, 147.8, 140.7, 138.2, 136.1, 134.3, 128.0, 127.4, 127.3, 126.9, 126.3, 121.3, 121.1, 116.1, 47.7, 43.4, 25.1, 20.6; FT-IR (DCM): 3355, 1650, 1534, 1475, 890 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1504.

(1*R,2*S**)-*N*-(Quinolin-8-yl)-2-(thiophen-2-yl)cyclobutanecarboxamide (17c).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow color liquid; 32 mg, 42% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.51 (br s, 1H), 8.76 (q, 1H, J = 8.0 Hz), 8.65 (q, 1H, J = 4.0 Hz), 8.12 (q, 1H, J = 8.0 Hz), 7.49−7.40 (m, 3H), 6.98−6.93 (m, 2H), 6.76 (q, 1H, J = 4.0 Hz), 4.35−4.35 (dd, 1H, J_1 = 20.0 Hz, J_2 = 8.0 Hz), 3.79 (q, 1H, J_2 = 4.0 Hz), 2.71−2.53 (m, 3H), 2.36−2.30 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.8, 147.9, 144.2, 138.3, 136.2, 134.4, 127.8, 127.4, 126.7, 124.7, 123.7, 121.4, 121.1, 116.2, 48.2, 38.7, 27.8, 20.6; FT-IR (KBr): 3335, 1641, 1510, 1431, 790 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2OS$: 309.1061; found 309.1071.

(1*R,2*S**)-*N*-(Quinolin-8-yl)-2-(3,4,5-trimethoxyphenyl)cyclobutanecarboxamide (17d).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexanes R_f = 0.40; white solid 31 mg, 32% yield; mp 125−127 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.26 (br s, 1H), 8.67−8.62 (m, 2H), 8.08 (q, 1H, J = 8.0 Hz), 7.46−7.39 (m, 3H), 6.50 (s, 2H), 4.08−4.05 (m, 1H), 4.04−3.71 (m, 1H), 3.67 (s, 6H), 3.67 (s, 6H), 3.30 (s, 3H), 2.70−2.60 (m, 2H), 2.38−2.28 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.4, 152.8, 147.7, 138.1, 136.4, 136.3, 136.2, 134.5, 127.8, 127.2, 121.4, 121.1, 115.8, 104.3, 60.3, 55.8, 48.2, 43.9, 25.5, 19.9; FT-IR (KBr): 2830, 1599, 1502, 1391, 881 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{25}N_2O_4$: 393.1814; found 393.1808.

(1*S,2*R**,4*S**)-2,4-Bis(3-formylphenyl)-*N*-(2-(methylthio)phenyl)cyclobutanecarboxamide (19a).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.30; brown color solid; 56 mg, 52% yield; mp 100−102 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.1 (s, 2H), 7.95 (br s, 1H), 7.84 (s, 2H), 7.69 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.0 Hz), 7.50−7.44 (m, 1H), 7.29 (q, 2H, J = 4.0 Hz), 7.02 (q, 1H, J = 8.0 Hz), 6.98−6.90 (m, 2H), 4.17−4.04 (m, 3H), 3.64 (dd, 1H, J_1 = 20.0 Hz, J_2 = 8.0 Hz), 2.82−2.79 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 192.5, 168.0, 141.4, 137.1, 136.3, 133.1, 132.1, 128.9, 128.3, 125.6, 124.5, 121.0, 54.1, 38.5, 29.5, 18.5; FT- IR (KBr): 3351, 1668, 1582, 1398, 810 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{24}NO_3S$: 430.1476; found 430.1482.

(1*S,2*R**,4*S**)-*N*-(2-(Methylthio)phenyl)-2,4-di-*p*-tolylcyclobutanecarboxamide (19b).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white color solid; 45 mg, 45% yield; mp 98−100 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95 (br s, 1H),7.74 (d, 1H, J = 8.0 Hz), 7.34 (q, 1H, J = 8.0 Hz), 7.29−7.21 (m, 4H), 7.09−7.05 (m, 5H), 6.94−6.91 (m, 1H), 4.01−3.94 (m, 3H), 3.48 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.70−2.67 (m, 1H), 2.28 (s, 6H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.8, 138.2, 137.3, 135.6, 132.8, 129.0, 128.9, 128.6, 126.8, 123.8, 121.0, 54.5, 38.7, 30.0, 21.1, 18.8; FT-IR (KBr): 3324, 1622, 1534, 1491, 810 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}NOS$: 402.1891; found 402.1896.

(1*S,2*R**,4*S**)-2,4-Bis(4-acetylphenyl)-*N*-(2-(methylthio)phenyl)cyclobutanecarboxamide (19c).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; white color solid; 33 mg, 29% yield; mp 189−191 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.99 (br s, 1H),7.94 (q, 4H, J = 8.0 Hz), 7.61 (q, 1H, J = 8.0 Hz), 7.39 (q, 4H, J = 8.0 Hz), 7.33−7.28 (m, 1H), 7.05−7.03 (m, 1H), 7.01−6.93 (m, 1H), 4.11−4.06 (m, 3H), 3.57 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.0 Hz), 2.77−2.67 (m, 1H), 2.56 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 197.9, 168.0, 146.0, 137.3, 135.3, 134.9, 132.3, 128.5, 128.4, 128.3, 127.0, 125.3, 124.4, 120.9, 54.3, 38.9, 29.7, 26.6, 18.3; FT-IR (KBr): 3350, 1620, 1551, 1441, 710 cm^{-1}; HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{27}NO_3SNa$: 480.1609; found 480.1604.

(1*S,2*R**,4*S**)-*N*-(2-(Dimethylamino)ethyl)-2,4-bis(3-nitrophenyl)cyclobutanecarboxamide (21a).** Analytical TLC on silica gel, 2:3.methanol/ethyl acetate R_f = 0.40; black color solid; 46 mg, 45% yield; mp 130−132 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.07−8.01 (m, 4H), 7.60 (d, 2H, J = 12.0 Hz), 7.46 (t, 2H, J = 8.0 Hz), 6.34 (br s, 1H), 4.03−3.89 (m, 2H), 3.87 (q, 1H, J = 4.0 Hz), 3.51 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.83−2.72 (m, 3H), 2.01 (s, 6H), 1.96 (t, 2H, J = 4.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.0, 148.0, 143.0, 133.2, 129.0, 121.9, 121.3, 57.4, 52.5, 44.7, 37.9, 36.0, 29.7; FT-IR (KBr): 2876, 2325, 1618, 1532, 817 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_4O_5$: 413.1824; found 413.1813.

(1*S,2*R**,4*S**)-*N*-(2-(Dimethylamino)ethyl)-2,4-diphenylcyclobutanecarboxamide (21b).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; red color liquid; 24 mg, 30% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33−7.17 (m, 10H), 5.78 (br s, 1H), 3.96−3.89 (m, 2H), 3.78 (q, 1H, J = 4.0 Hz), 3.41 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.83−2.78 (q, 2H, J = 4.0 Hz), 2.65−2.61(q, 1H, J = 4.0 Hz), 2.0 (s, 6H), 1.86 (t, 2H, J = 4.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 140.9, 127.9, 127.1, 126.1, 57.4, 53.3, 44.8, 38.6, 35.9, 29.5; FT-IR (DCM): 2912, 2324, 1612, 1543, 809 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{27}N_2O$: 323.2123; found 323.2113.

(1*S,2*R**,4*S**)-*N*-(2-(Dimethylamino)ethyl)-2,4-bis(4-methoxyphenyl)cyclobutanecarboxamide (21c).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; pale-yellow color liquid; 51 mg, 53% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.26−7.17 (m, 4H), 6.84−6.80 (m, 4H), 5.67 (br s, 1H), 3.84−3.79 (m, 2H), 3.75 (s, 6H), 3.66−3.63 (m, 1H),3.26 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.84−2.79 (m, 2H), 2.56−2.52 (m, 1H), 1.98 (s, 6H), 1.85 (t, 2H, J = 4.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.2, 157.9, 132.9, 128.2, 113.4, 57.6, 55.2, 53.5, 44.8, 38.0, 36.0, 30.1; FT-IR (DCM,): 2948, 2213, 1623, 1534, 812 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{31}N_2O_3$: 383.2335; found 383.2352.

(1S*,2R*,4S*)-N-(2-(Dimethylamino)ethyl)-2,4-di-p-tolylcyclobutanecarboxamide (21d). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; brown color liquid; 35 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19−7.11 (m, 8H), 5.70 (br s, 1H), 3.89−3.84 (m, 2H), 3.72 (q, 1H, *J* = 4.0 Hz), 3.32 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.86−2.82 (m, 2H), 2.61 (q, 1H, *J* = 4.0 Hz), 2.33 (s, 6H), 2.01 (s, 6H), 1.85 (t, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 137.8, 135.4, 128.6, 127.2, 57.5, 53.4, 44.8, 38.4, 36.0, 29.7, 21.1; FT-IR (DCM): 2900, 2316, 1627, 1553, 737 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{31}N_2O$: 351.2436; found 351.2429.

(1S*,2R*,4S*)-N-(2-(Dimethylamino)ethyl)-2,4-bis(4-ethylphenyl)cyclobutanecarboxamide (21e). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; brown color solid; 37 mg, 39% yield; mp 185−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.12 (m, 8H), 6.50 (br s, 1H), 3.88 (q, 2H, *J* = 4.0 Hz), 3.73 (q, 1H, *J* = 4.0 Hz), 3.33 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.91−2.87 (m, 3H), 2.61 (q, 4H, *J* = 4.0 Hz), 2.05 (s, 6H), 1.94 (t, 2H, *J* = 4.0 Hz), 1.24 (t, 6H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 141.8, 138.1, 127.4, 127.1, 57.4, 53.2, 44.1, 38.4, 35.6, 29.7, 28.5, 15.7; FT-IR (DCM): 3240, 1634, 1494, 1344, 710 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{35}N_2O$: 379.2749; found 3792746.

(1S*,2R*,4S*)-2,4-Bis(4-chlorophenyl)-N-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (21f). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; white color solid; 40 mg, 41% yield; mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.18 (m, 8H), 5.71 (br s, 1H), 3.88−3.81 (m, 2H), 3.70−3.65 (m, 1H), 3.36 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.86−2.82 (m, 2H), 2.62−2.55 (m, 1H), 1.90 (s, 6H), 1.89 (t, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 139.1, 131.9, 128.5, 128.1, 57.5, 53.2, 44.9, 38.1, 36.0, 29.7; FT-IR (KBr): 2912, 2323, 1618, 1512, 812 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{25}Cl_2N_2O$: 391.1343; found 391.1340.

(1S*,2R*,4S*)-2,4-Bis(4-bromophenyl)-N-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (21g). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; brown color liquid; 54 mg, 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.38 (m, 4H), 7.14 (d, 4H, *J* = 8.0 Hz), 6.50 (br s, 1H), 3.82−3.77 (m, 2H), 3.70 (q, 1H, *J* = 4.0 Hz), 3.33 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.92−2.82 (m, 2H), 2.57 (t, 1H, *J* = 4.0 Hz), 2.09 (s, 6H), 2.0 (t, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 139.8, 130.9, 129.1, 119.9, 57.5, 52.9, 44.4, 38.1, 35.5, 29.5; FT-IR (KBr): 2912, 2316, 1637, 1544, 917 cm^{-1} HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{25}Br_2N_2O$: 479.0333; found 479.0316.

(1S*,2R*,4S*)-N-(2-(Dimethylamino)ethyl)-2,4-bis(4-nitrophenyl)cyclobutanecarboxamide (21h). Analytical TLC on silica gel, 2.5:2.5. methanol/ethyl acetate R_f = 0.40; yellow color liquid; 44 mg, 43% yield; ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO-d_6): δ 8.08 (d, 4H, *J* = 8.0 Hz), 7.36−7.28 (m, 4H), 6.56 (br s, 1H), 3.96−3.91 (m, 2H), 3.86 (q, 1H, *J* = 4.0 Hz), 3.42 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.81−2.77 (m, 2H), 2.68 (q, 2H, *J* = 4.0 Hz), 2.0 (s, 6H), 1.92 (t, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 169.0, 148.8, 146.3, 127.7, 123.2, 57.6, 53.0, 44.7, 38.2, 35.9, 29.5; FT-IR (KBr): 3243, 1632, 1521, 1494, 810 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{25}N_4O_5$: 413.1824; found 413.1823.

(1S*,2R*,4S*)-2,4-Bis(4-cyanophenyl)-N-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (21i). Analytical TLC on silica gel, 2.5:2.5. methanol/ethyl acetate R_f = 0.40; black color solid; 45 mg, 48% yield; mp 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.55 (m, 4H), 7.35−7.28 (m, 2H), 6.13 (br s, 1H), 3.97−3.90 (m, 2H), 3.82 (q, 1H, *J* = 4.0 Hz), 3.45 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.83 (q, 2H, *J* = 4.0 Hz), 2.66−2.63 (m, 1H), 2.03 (s, 6H), 1.94 (t, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 146.4, 131.8, 127.8, 119.1, 109.8, 57.5, 53.0, 45.1, 44.8, 38.4, 35.9, 29.2; FT- IR (KBr): 2945, 2226, 1607, 1506, 827 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{25}N_4O$: 373.2028; found 373.2026.

(1S*,2R*,4S*)-2,4-Bis(4-bromo-3-fluorophenyl)-N-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (21j). Analytical TLC on silica gel, 2.5:2.5. methanol/ethyl acetate R_f = 0.40; red color liquid; 68 mg, 53% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.42 (m, 2H), 7.03 (q, 2H, *J* = 4.0 Hz), 6.92 (q, 2H, *J* = 8.0 Hz), 6.45 (br s, 1H), 3.82−3.71 (m, 2H), 3.70 (q, 1H, *J* = 4.0 Hz), 3.23 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.94−2.90 (m, 2H), 2.61−2.58 (m, 1H), 2.10 (s, 6H), 2.03 (t, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 160.1, 157.5 (d, J_{C-F} = 246 Hz), 142.6 (d, J_{C-F} = 7.0 Hz), 132.9, 123.9 (d, J_{C-F} = 3.0 Hz), 115.2 (d, J_{C-F} = 22.0 Hz), 106.3 (d, J_{C-F} = 20.0 Hz), 57.6, 52.8, 44.8, 37.8, 36.0, 29.7; FT-IR (DCM): 3252, 1601, 1511, 1468, 710 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{23}Br_2F_2N_2O$: 515.0145; found 515.0101.

(1S*,2R*,4S*)-N-(2-(Dimethylamino)ethyl)-2,4-bis(3,4-dimethylphenyl)cyclobutanecarboxamide (21k). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40 black color solid; 40 mg, 42% yield; mp 220−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08−7.01 (m, 6H), 6.08 (br s, 1H), 3.85−3.81 (m, 2H), 3.71 (t, 1H, *J* = 4.0 Hz), 3.32 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.92−2.88 (m, 2H), 2.58−2.56 (m, 1H), 2.27 (s, 6H), 2.24 (s, 6H), 2.04 (s, 6H), 1.91 (t, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 138.3, 135.9, 134.0, 129.3, 128.4, 124.5, 57.5, 53.2, 44.5, 38.4, 35.8, 29.7, 19.9, 19.4; FT-IR (KBr): 2937, 2316, 1567, 1516, 918 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{35}N_2O$: 379.2749; found 379.2748.

(1S*,2R*,4S*)-2,4-Bis(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-N-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (21l). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40 brown color solid; 45 mg, 41% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77−6.70 (m, 6H), 6.11 (br s, 1H), 4.21 (q, 8H, *J* = 4.0 Hz), 3.77−3.70 (m, 2H), 3.64 (q, 1H, *J* = 4.0 Hz), 3.15 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 2.94 (q, 2H, *J* = 4.0 Hz), 2.52−2.49 (m, 1H), 2.09 (s, 6H), 2.10 (t, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 143.0, 141.8, 134.3, 120.0, 116.7, 115.9, 64.3, 57.6, 52.9, 44.8, 44.7, 37.8, 35.9, 30.0; FT-IR (DCM): 3303, 1651, 1588, 1425, 890 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{31}N_2O_5$: 439.2223; found 439.2233.

(1S*,2R*,4S*)-N-(2-(Dimethylamino)ethyl)-2,4-di(thiophen-2-yl)cyclobutanecarboxamide (21m). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40 black color liquid; 25 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (q, 2H, *J* = 4.0 Hz), 6.99−6.94 (m, 4H), 6.05 (br s, 1H), 4.03−3.98 (m, 2H), 3.61(q, 1H, *J* = 4.0 Hz), 3.35 (dd, 1H, J_1 = 20.0 Hz, J_2 = 12.0 Hz), 3.02 (q, 2H, *J* = 4.0 Hz), 2.80 (q, 1H, *J* = 4.0 Hz), 2.07 (s, 6H), 2.03 (t, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 143.7, 126.7, 125.1, 123.8, 57.6, 54.7, 48.1, 36.1, 35.4, 35.0; FT-IR (DCM): 2800, 2312, 1621, 1512, 800 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{23}N_2OS_2$: 335.1251; found 335.1245.

N-(((1S*,2R*,4S*)-2,4-Bis(4-bromophenyl)cyclobutyl)methyl)quinolin-8-amine (23). Analytical TLC on silica gel, 1:4 ethyl acetate/hexanes R_f . = 0.70 brown color liquid; 51 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (q, 1H, J = 4.0 Hz), 8.07 (q, 1H, J = 4.0 Hz), 7.50−7.17 (m, 10H), 7.07−7.04 (m, 1H), 6.62−6.59 (m, 1H), 3.59 (q, 2H, J = 4.0 Hz), 3.38−3.26 (m, 2H), 2.77−2.74 (m, 2H), 2.22−2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 142.6, 138.1, 135.9, 131.5, 131.4, 128.5, 127.6, 127.5, 126.9, 120.1, 114.0, 104.7, 51.0, 46.8, 40.3, 34.0; FT-IR (DCM): 3234, 1644, 1412, 1382, 819 cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{23}Br_2N_2$: 521.0228; found 521.0229.

(1R*,2R*,4S*)-2,4-Di-p-tolylcyclobutanecarboxylic acid (24). Following the general procedure described above, **24** was obtained as a brown color liquid (crude material was almost pure); 67 mg, 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.17 (m, 8H), 3.79 (q, 2H, J = 8.0 Hz), 3.30 (t, 1H, J = 12.0 Hz), 2.79−2.76 (m, 1H), 2.38 (s, 6H), 2.37−2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 139.7, 136.3, 129.2, 126.5, 52.6, 39.2, 32.9, 21.1; FT-IR (DCM): 2833, 1515, 1485, 1354, 806 cm^{-1}; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{19}H_{19}O_2$: 279.1385; found 279.1389.

(1R*,2R*,4S*)-2,4-Bis(4-chlorophenyl)cyclobutanecarboxylic acid (25). Following the general procedure described above, **25** was obtained as a white color liquid (crude material was almost pure); 78 mg, 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.32 (m, 8H), 3.80 (q, 2H, J = 8.0 Hz), 3.27 (t, 1H, J = 12.0 Hz), 2.84−2.78 (m, 1H), 2.31 (q, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 140.8, 132.6, 128.6, 128.0, 52.3, 38.8, 32.5; FT-IR (DCM): 2966, 1565, 1432, 1331, 800 cm^{-1}; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{17}H_{13}Cl_2O_2$: 319.0292; found 319.0298.

(1R*,2R*,4S*)-2,4-Bis(4-bromophenyl)cyclobutanecarboxylic acid (26). Following the general procedure described above, **26** was obtained as a brown color solid (crude material was almost pure); 97 mg, 95% yield; mp131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.46 (m, 4H), 7.21−7.19 (m, 4H), 3.79(q, 2H, J = 8.0 Hz), 3.27 (t, 1H, J = 12.0 Hz), 2.84−2.77 (m, 1H), 2.30−2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5, 141.3, 131.6, 128.3, 120.6, 52.2, 38.8, 32.3; FT-IR (KBr): 2922, 1698, 1516, 1425, 806 cm^{-1}; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{14}Br_2O_2Na$: 430.9258; found 430.9281.

(1S*,2R*,4S*)-2,4-Bis(4-bromophenyl)-N-methyl-N-(quinolin-8-yl)cyclobutanecarboxamide (27). Analytical TLC on silica gel, 1:4 ethyl acetate/hexanes R_f = 0.70 light-yellow color liquid; 130 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (q, 1H, J = 4.0 Hz), 8.26 (q, 1H, J = 4.0 Hz), 7.85 (q, 1H, J = 8.0 Hz), 7.54−7.46 (m, 6H), 7.26−7.23 (m, 4H), 6.72 (q, 1H, J = 4.0 Hz), 3.54−3.36 (m, 4H), 2.98 (s, 3H), 2.48 (q, 1H, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 151.0, 144.2, 141.4, 141.3, 139.2, 136.3, 131.0, 130.8, 130.4, 129.4, 128.8, 128.9, 128.1, 126.4, 122.1, 120.8, 119.2, 50.0, 39.7, 37.7, 37.1; FT-IR (DCM): 2941, 1613, 1523, 1468, 791 cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{23}Br_2N_2O$: 549.0177; found 549.0175.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra of all compounds and X-ray structures (ORTEP diagrams of the compounds **16c**, **16f**, **16g**, **16m**, **21a**, **21f**, **25** and **27**) and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(35) (a) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238. (b) We also observed the formation of bis-arylated cyclopropanecarboxamide only when the Pd-catalyzed reaction of an

auxiliary-attached cyclopropanecarboxamide (1 equiv) was carried out by using an aryl iodide in excess amount (8 equiv), see ref 35a.

(36) See SI for the X-ray structures.

(37) The stereochemistry of the products was assigned on the basis of the X-ray structures of **16c**, **16f**, **16g**, and **16m** as well as the similarity in the NMR pattern of the cyclobutane ring.

(38) The stereochemistry of the products **24** and **26** was assigned on the basis of the X-ray structure of **25** as well as the similarity in the NMR pattern of the cyclobutane ring.

(39) A day before the submission of this article, an article containing an example of the formation of the 2,4-diphenyl-*N*-(quinolin-8-yl) cyclobutanecarboxamide (**16b**, the compound number refers to the numbering with respect to our work) using a diarylhyperiodonium salt as the arylating agent was reported by Shi Z.-J. et al., see: Pan, F.; Shen, P.-X.; Zhang, L.-S.; Wang, X.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 4758. Shi Z.-J. et al., it is mentioned that the stereochemistry of 2,4-diphenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide was assigned based on the report by the Daugulis's group.[26b] To the best of our knowledge, the compound 2,4-diphenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide was not reported by Daugulis's group (ref 26b).