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Auxiliary-Enabled Pd-Catalyzed Direct Arylation of Methylene C(sp^3)–H Bond of Cyclopropanes: Highly Diastereoselective Assembling of Di- and Trisubstituted Cyclopropanecarboxamides

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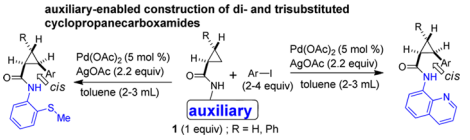
ABSTRACT



An auxiliary-enabled and $Pd(OAc)_2$-catalyzed direct arylation of C(sp^3)–H bonds of cyclopropanes and production of di- and trisubstituted cyclopropanecarboxamides having contiguous stereocenters are reported. The installation of aryl groups on cyclopropanecarboxamides led to the assembling of novel mono- and di- aryl-*N*-(quinolin-8-yl)cyclopropanecarboxamide scaffolds and mono- and di- aryl-*N*-(2-(methylthio)-phenyl)cyclopropanecarboxamides. The stereochemistry of products was unequivocally assigned from the X-ray structures of key compounds.

Cyclopropane, the smallest carbocyclic ring, is one of the privileged structural motifs, present as a core unit in numerous natural products, biologically active and prospective drug molecules, and synthetic intermediates.[1,2] Incorporation of cyclopropane rings in the molecular frameworks is considered an important molecular tool to constrain the conformation and study the reaction pathways.[3] Along this line, various arylcyclopropane-carboxylic acid derivatives have been reported to exhibit promising biological activities and used as molecular tools in the field of chemical biology.[3,4] Among the available methods,[1,2,5] cyclopropanation of olefins is one of the cornerstone protocols for producing cyclopropanes. Generally, the

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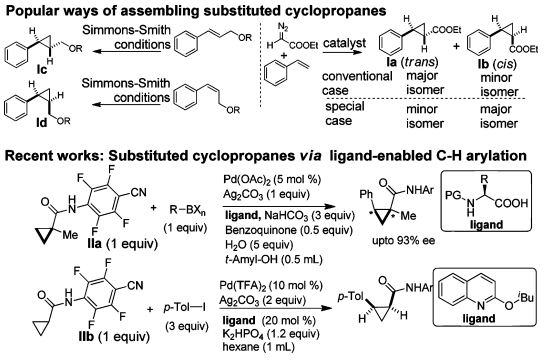
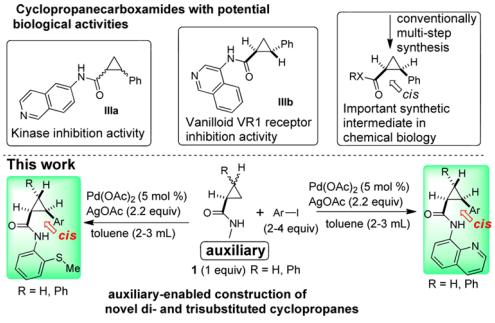
production of substituted cyclopropanes with the *trans* stereochemistry is a popular protocol. For example, the metal-catalyzed reaction of a diazo compound with styrene results in the cyclopropane **Ia** with *trans* stereochemistry as the major isomer (Scheme 1).[1b,c] The *cis*/*trans* substituted cyclopropanes **Ic/Id** can also be obtained under Simmons–Smith reaction conditions.[5a–c] Noticeably, the production of substituted cyclopropanes with *cis* stereochemistry is a challenging task.[1h,k] For example, the cyclopropane **Ia** can be obtained only by employing special efforts.[1h] When compared to the field dealing with the construction of cyclopropanes,[1–5] the direct functionalization of cyclopropanes is an underexplored research area. This is because the cyclopropane ring is known to have a strained structure and unique reactivity patterns due to the steric and electronic factors.[1,2]

Scheme 1. Assembling of Substituted Cyclopropanes



A simple and an alternative route for the production of the *cis* substituted cyclopropanes especially is the direct metal-catalyzed functionalization of the C(sp^3)–H bond of cyclopropanes. However, only a few exceptional reports[6–8] exist in this regard, while the activation of the methylene C(sp^3)–H bond still remains a challenging and potential topic of current and future research.[9] In a primary work, Yu's group showed an example related to the arylation of the C(sp^3)–H bond of 1-methyl cyclopropanecarboxylic acid using an arylboronic acid as the coupling partner, which resulted in the corresponding arylated product in 20% yield. Then, in 2011, the same group reported the ligand-enabled Pd-catalyzed stereoselective arylation of *N*-aryl cyclopropanecarboxamide (**IIa**) using a boronic acid derivative (Scheme 1). While we were engaged in investigating the 'auxiliary-enabled $Pd(OAc)_2$-catalyzed C–H arylation of cyclopropanecarboxamides', in late 2012, Yu's group revealed an example related to the arylation of *N*-aryl cyclopropanecarboxamide (**IIb**) *via* 'the ligand-enabled $Pd(TFA)_2$-catalyzed C–H activation in the presence of K_2HPO_4'. Successively, Cramer,[8b] Rousseaux,[8d] and Charette[8e] have reported the Pd-catalyzed intramolecular arylation of cyclopropanecarboxamides using an appropriate ligand and additive and the synthesis of tetrahydroquinoline- and spirooxindole scaffolds, possessing a cyclopropyl unit.

Scheme 2. Theme of This Work



Taking impetus from the recent progress in C–H activation reactions, particularly, the directing group enabled Pd-catalyzed C(sp^3)–H bond activation reactions reported by the Daugulis, Chen, and Baran groups,[9a–f] we envisaged examining the construction of mono- and diaryl-*N*-(quinolin-8-yl)cyclopropanecarboxamide scaffolds. Nevertheless, it is important to mention that the 2-aryl *N*-(isoquinolinyl)cyclopropanecarboxamide scaffolds (**IIIa** and **IIIb**, Scheme 2), which are analogous to the present investigation, are known to exhibit kinase and vanilloid VR1 receptor inhibition activities.[4] Herein, we report an efficient, auxiliary-enabled, and $Pd(OAc)_2$-catalyzed direct functionalization of methylene bonds of cyclopropanecarboxamides (**1**) and diastereoselective production of novel mono- and diaryl-*N*-(quinolin-8-yl)cyclopropanecarboxamides and mono- and diaryl-*N*-(2-(methylthio)-phenyl)cyclopropanecarboxamides.

At the outset, several reactions were carried out to find the best reaction conditions and solvents. Table 1 shows the reaction scheme, which comprises the Pd-catalyzed arylation of *N*-(quinolin-8-yl)cyclopropane-carboxamide (**1a**), prepared from cyclopropanecarbonyl chloride and an auxiliary, e.g. 8-aminoquinoline, with 1-iodo-4-methoxybenzene (**2a**).

The C–H functionalization reaction of *N*-(quinolin-8-yl)-cyclopropanecarboxamide (**1a**) with 1-iodo-4-methoxybenzene (**2a**) in the absence of a Pd catalyst did not afford any

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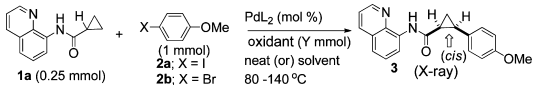
Table 1. Optimization of C−H Activation Reaction Conditions



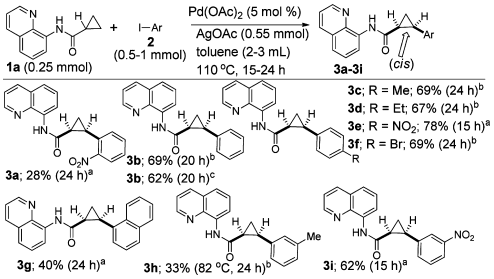
entry	catalyst (mol %)	oxidant (Y mmol)	solvent (mL)	t (°C)	time (h)	**3**: yield (%)[a]
1	nil	AgOAc (1.5)	neat	110	36	0
2[b]	$Pd(OAc)_2$ (5)	nil	neat	110	36	28
3	$Pd(OAc)_2$ (5)	AgOAc (0.27)	neat	110	10	35
4	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,2-DCE	80	20	32
5	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,4-Dioxane	100	20	15
6	$Pd(OAc)_2$ (5)	AgOAc (0.55)	CH_3CN	80	20	5
7	$Pd(OAc)_2$ (5)	AgOAc (0.55)	DMF	130	20	0
8	$Pd(OAc)_2$ (5)	AgOAc (0.55)	AcOH	110	20	10
9	**$Pd(OAc)_2$ (5)**	**AgOAc (0.55)**	**toluene**	**110**	**20**	**71** (39)[c] (51)[d]
10	$PdCl_2$ (5)	AgOAc (0.55)	toluene	110	20	37
11	$Pd(PPh_3)_4$ (5)	AgOAc (0.55)	toluene	110	20	0
12	$Pd(TFA)_2$ (5)	AgOAc (0.55)	toluene	110	20	10
13	$Pd(AcAc)_2$ (5)	AgOAc (0.55)	toluene	110	20	26
14	$Pd(CH_3CN)Cl_2$ (5)	AgOAc (0.55)	toluene	110	20	33
15	$Ni(AcAc)_2$ (5)	AgOAc (0.55)	toluene	110	20	0
16[e]	$Pd(OAc)_2$(5)	AgOAc (0.55)	toluene	110	20	50
17	$Pd(OAc)_2$(5)	$PhI(OAc)_2$ (0.55)	toluene	110	20	0
18	$Pd(OAc)_2$(5)	KOAc (0.55)	toluene	110	20	6
19	$Pd(OAc)_2$(5)	$Cu(OAc)_2$ (0.55)	toluene	110	20	6
20	$Pd(OAc)_2$(5)	Benzophenone	toluene	110	20	15
21	$Pd(OAc)_2$(5)	Oxone (0.55)	toluene	110	20	0
22	$Pd(OAc)_2$(5)	O_2	toluene	110	20	10
23	$Pd(OAc)_2$ (5)	K_2CO_3 (0.55)	toluene	110	20	0
24[f]	$Pd(OAc)_2$ (5)	AgOAc (0.55)	toluene	110	24	0
25[g]	$Pd(OAc)_2$ (5)	AgOAc (0.55)	toluene	110	24	0
26[h]	$Pd(OAc)_2$ (10)	AgOAc (2.2)	toluene	110	36	37
27[h]	$Pd(OAc)_2$ (10)	AgOAc (2.2)	xylene	140	36	48

[a] All the reactions were done using 1-iodo-4-methoxybenzene (**2a**) under a nitrogen atmosphere. Isolated yields are given. [b] 1.2 mmol of **2a** was used. [c] In this case, 0.5 mmol of **2a** was used. [d] In this case, 0.75 mmol of **2a** was used. [e] The reaction was done under an open atmosphere. [f] In this case, 1-bromo-4-methoxybenzene (**2b**) was used instead of **2a**. [g] In this case, 1-chlorobenzene (**2c**) was used instead of **2a**. [h] In this case, 0.26 mmol of **2a** was used.

product under neat conditions (entry 1, Table 1). The arylated product **3** was obtained in 28% yield in the presence of a $Pd(OAc)_2$ catalyst without any oxidant under neat conditions (entry 2). The arylation of **1a** with **2a** in the presence of a $Pd(OAc)_2$ catalyst and AgOAc under neat conditions gave **3** in only 35% yield (entry 3). Usage of different solvents such as 1,2-DCE, 1,4-dioxane, MeCN, DMF, and AcOH for the arylation of **1a** did not improve the yield of **3** (entries 4−8). The arylation of **1a** in the presence of $Pd(OAc)_2$ and AgOAc proceeded smoothly in toluene at 110 °C and furnished **3** having *cis* stereochemistry in 71% yield as a single diastereomer (entry 9). Employing other Pd- and Ni-based catalysts failed to furnish **3** with improved yields (entries 10−15). The arylation of **1a** with **2a** in the presence of $Pd(OAc)_2$ and AgOAc under an open or nitrogen atmosphere and further trials using a variety of oxidants did not significantly improve the yield of **3** (entries 16−21). The Pd-catalyzed arylation of **1a** with **2a** without AgOAc under an open atmosphere gave **3** in 10% yield (entry 22). This reaction indicates that perhaps AgOAc helps in the catalyst regeneration *via* a ligand exchange process, producing AgI and $Pd(OAc)_2$.[9] The arylation of **1a** with **2a** in the presence of K_2CO_3 instead of AgOAc was not effective (entry 23). Employing 1-bromo-4-methoxybenzene (**2b**) or chlorobenzene (**2c**) instead of **2a** was not effective (entries 24, 25). Using just 0.26 mmol of **2a** instead of 1 mmol gave **3** only in 37% yield (entry 26).

The scope of this auxiliary-enabled Pd-catalyzed intermolecular direct arylation of the methylene C(sp^3)−H bond of cyclopropanecarboxamides was tested using a variety of electron-withdrawing and -donating groups containing aryl iodides (Scheme 3). The arylation of the methylene C−H bond of **1a** with various substituted aryl iodides proceeded smoothly and gave the corresponding products **3a**−**3f** in 28−78% yields. The arylation of **1a** with 1-iodonaphthalene and 1-iodo-3-methylbenzene gave **3g** and **3h** in only 40 and 33% yields, respectively. The arylation of **1a** with 1-iodo-3-nitrobenzene gave **3i** in 62% yield. All these reactions were highly stereoselective and gave cyclopropanes with *cis* stereochemistry.[10a]

Scheme 3. Diastereoselective C−H Arylation of **1a**



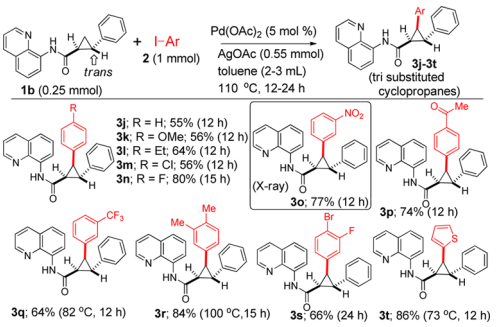
[a] In this case, 1 mmol of aryl iodide was used. [b] In this case, 0.5 mmol of aryl iodide was used. [c] The reaction was done using **1a** (1.06 g, 5 mmol), **2a** (1.02 g, 10 mmol), AgOAc (1.83 g, 11 mmol), and toluene (15 mL).

Subsequently, we extended the scope of this protocol by producing a wide range of novel trisubstituted cyclopropanes *via* the Pd-catalyzed direct arylation of the C−H bond of (1*S**,2*S**)-2-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (**1b**) (Scheme 4).[10b] The arylation of cyclopropanecarboxamide (**1b**) with phenyl iodide and other aryl iodides having electron-donating or -withdrawing groups at the *para*-position gave the corresponding trisubstituted cyclopropanes (**3j**−**3n**) as single diastereomers in 55−80% yields. Similarly, the trisubstituted cyclopropanes **3o** (77%), **3p** (74%), and **3q** (64%) were obtained using various aryl iodides having different substituents (e.g., NO_2, acetyl, and CF_3) on the aromatic ring. Further,

(10) (a) The stereochemistry of the products **3a**−**i** was assigned based on the X-ray structure of **3** and the similarity in the ^{1}H NMR spectral pattern of **3** and **3a**−**i**. (b) The stereochemistry of the products **3j**−**t** was assigned based on the X-ray structure of **3o** and the similarity in the ^{1}H NMR spectral pattern of **3j**−**t**. (c) The stereochemistry of the products **4a**−**c** was assigned based on the X-ray structure of **4b** and the similarity in the ^{1}H NMR spectral pattern of **4a**−**c**. (d) The stereochemistry of the products **4d**−**j** was assigned based on the X-ray structure of **4d** and the similarity in the ^{1}H NMR spectral pattern of **4d**−**j**. (e) The stereochemistry of the products **5a**−**d** was assigned based on the X-ray structure of **5a** and the similarity in the ^{1}H NMR spectral pattern of **5a**−**d**. (f) Crystallographic data of X-ray structures (**3**: CCDC 936504; **3o**: CCDC 936506; **4b**: CCDC 936505; **4d**: CCDC 936623; and **5a**: CCDC 936503) of this work have been deposited at the Cambridge Crystallographic Data Centre. (g) All the reactions gave only a single diastereomer under the present experimental conditions (if the aryl iodide is used in <4 equiv), and along with products the corresponding unreacted starting materials **1a**−**d** were recovered. In some cases, we also obtained a mixture of mono- and diarylated compounds when we used the aryl iodide in excess (6−8 equiv). We are unable to represent the results at this stage, as the optimization work and establishment of the stereochemistry of the mono- and diarylated compounds is incomplete.

the arylated products **3r** (84%) and **3s** (66%) were obtained by using the respective disubstituted aryl iodides (Scheme 4). Heterocyclic substitution on the cyclopropane **1b** *via* the C−H functionalization using 2-iodothiophene successfully gave **3t** (86%). The Pd-catalyzed arylation of **1b** led to the stereoselective installation of various second aryl groups at the methylene group of **1b** and the synthesis of novel trisubstituted cyclopropane-carboxamides **3j**−**3t** having contiguous stereocenters.

Scheme 4. Stereoselective C−H Functionalization of **1b**

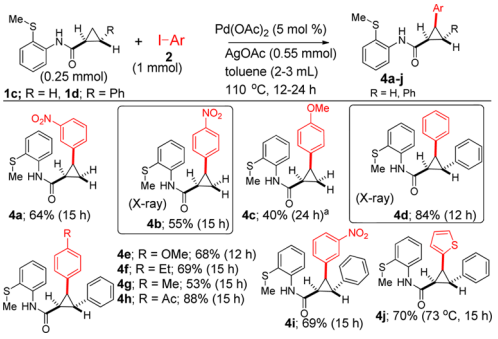


Furthermore, we were focused on establishing the arylation scope by using the cyclopropanecarboxamides prepared by using other auxiliaries. Toward this end, the Pd-catalyzed arylation of *N*-(2 (methylthio)phenyl)cyclopropanecarboxamides (**1c,1d**) with a variety of aryl iodides was studied (Scheme 5).[10c,d] The arylation of **1c** gave the products **4a**−**c** in 64, 55, and 40% yields as single diastereomers, respectively (Scheme 5). Next, the Pd-catalyzed C−H functionalization of (1*S**,2*S**)-*N*-(2-(methylthio)-phenyl)-2-phenylcyclopropanecarboxamide (**1d**) with different aryl iodides was explored for the production of trisubstituted cyclopropanecarboxamides. Along this line, various (1*R**,2*S**,3*S**)-2-(aryl)-*N*-(2-(methylthio)phenyl)-3-phenylcyclopropanecarboxamides (**4d**−**4j**) were obtained as single diastereomers from the installation of various second aryl groups at the methylene C−H bond of the cyclopropane **1d** (Scheme 5).

Additionally, the Pd-catalyzed arylation of **1a,1b** with excess iodobenzene or 1-iodo-4-methylbenzene furnished the respective diarylated cyclopropanes **5a**−**c** having the 1,2-*cis*/2,3-*cis*/1,3-*cis* stereochemistry[10e] (Scheme 6). Likewise, the Pd-catalyzed arylation of **4a** having the 1,2-*cis* stereochemistry with 1-iodo-4-ethylbenzene furnished the cyclopropanecarboxamide **5c** with the 1,2-*cis*/2,3-*cis*/1,3-*cis* stereochemistry. Then, to reveal the utility of this protocol, we performed the amide hydrolysis of **3j,3t**, which gave the corresponding substituted cyclopropanecarboxylic acids **6a,6b**. The reduction of the amide group of the representative compound **3b** afforded *N*-(((1*S**,2*R**)-2-phenylcyclopropyl)methyl)quinolin-8-amine (**7**).

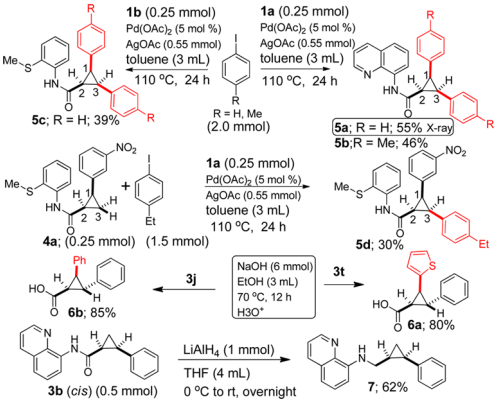
In summary, we have reported an auxiliary-enabled and $Pd(OAc)_2$-catalyzed highly diastereoselective direct arylation of the methylene C(sp^3)−H bond of cyclopropanes

Scheme 5. Diastereoselective C−H Activation of **1c,1d**



[a] In this case, 0.5 mmol of aryl iodide was used.

Scheme 6. Scope of This Work



and a facile access to novel mono- and diaryl-*N*-(quinolin-8-yl)-cyclopropanecarboxamide scaffolds and mono- and diaryl-*N*-(2-(methylthio)phenyl)cyclopropanecarboxamide scaffolds, having contiguous stereocenters. Further work is in progress to reveal the applications of these molecules.

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Supporting Information Available. Experimental procedures, X-ray structures, characterization data, and copy of ^1H, ^{13}C NMR charts of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.