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C−H Functionalization of Cyclopropanes: A Practical Approach Employing a Picolinamide Auxiliary

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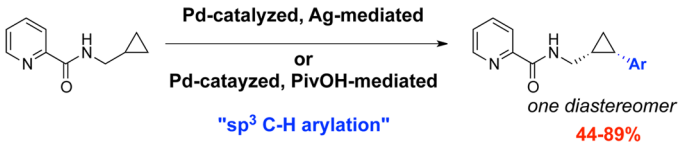
ABSTRACT



A Pd-catalyzed, picolinamide-enabled, and efficient C−H arylation of cyclopropanes is described. The reaction can be promoted by either a silver additive or catalytic pivalic acid in the presence of a carbonate base. Various aryl iodides can be employed as coupling partners, providing exclusively *cis*-substituted cyclopropylpicolinamides.

The catalytic transformation of C(sp^3)−H bonds is a continuously growing field in organic synthesis due to the ubiquity of C−H bonds in nature. As such, a plethora of powerful methods have already been developed, most of them employing a transition-metal catalyst.[1] One significant challenge is the regioselectivity of the reaction, and that has been overcome by the use of directing groups or auxiliaries.[2] Most notably, the picoline and aminoquinoline carboxamide auxiliaries introduced by Daugulis have proven to be valuable tools for the synthesis of C−C bonds at the γ-position of the amide nitrogen (Scheme 1).[3] These auxiliaries have also been exploited in the formation of C−N, C−O, and C−F bonds through the employment of different metal catalysts.[4]

Our group has had a long-standing interest in both the synthesis and functionalization of cyclopropanes[5] due to their versatility in medicinal chemistry, in natural product synthesis, and as scaffolds for other chemical transformations.[6] The rigidity of the cyclopropyl ring and orbital hybridization leads to a more sp^2-like character

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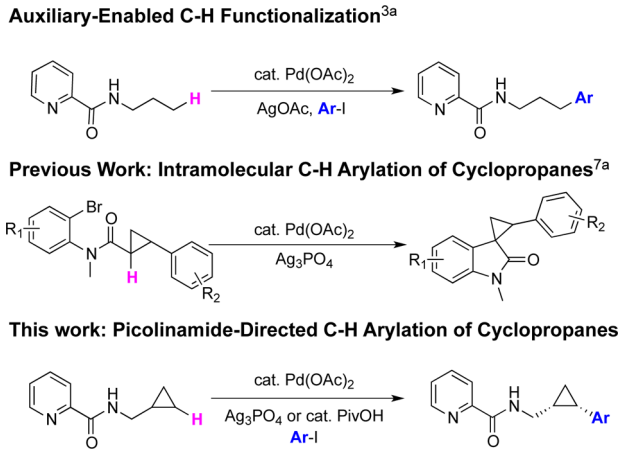
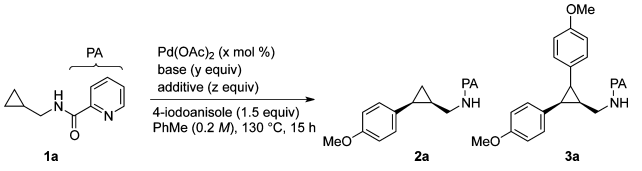
for its carbon atoms, which should facilitate C−H functionalization processes. To this end, our group has recently disclosed an intramolecular palladium-catalyzed direct C−H arylation reaction of cyclopropanes leading to the synthesis of biologically relevant spirooxindole scaffolds (Scheme 1).[7] We further expanded this methodology to the synthesis of seven-membered benzazepine rings through cyclopropyl C−H activation followed by ring-opening.[8] We next sought to develop a corresponding intermolecular process, as reports for these transformations are scarce in the literature.[9] The group of Yu has recently disclosed an enantioselective arylation of cyclopropanes employing boronic esters as coupling partners and an electron-poor, highly substituted arylamide as the auxiliary.[10] We were interested in developing a complementary methodology that would be robust, efficient and scalable. Furthermore, we sought to use an inexpensive and easy to cleave auxiliary. We were also encouraged by the fact that many of the resulting cyclopropyl carboxylic acids or amines possess interesting pharmacological properties.[11] To address these issues, we developed herein, a Pd-catalyzed, picolinamide-enabled C−H activation of cyclopropanes employing aryl iodides as coupling partners. Preliminary investigations into the reaction mechanism are also disclosed.

Scheme 1. Cyclopropane Functionalization



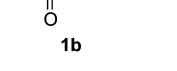
We initiated our screen by looking at different picolinamide (PA) and aminoquinoline derived auxiliaries (**1a**−**c**). We identified **1a** as a promising lead and performed further optimization studies (Table 1). Employing our previously reported conditions[7a,8a] with Ag_3PO_4, K_2CO_3, $Pd(OAc)_2$ and $P(t\text{-}Bu)_3 \cdot HBF_4$ as the ligand, 59% of monoarylated product **2a** was observed, along with 10% diarylation **3a** (entry 1). It should be noted that **2a** was determined to be one diastereomer with a *cis* substitution pattern, while diaryl **3a** was a mixture of *cis* and *trans*.[12] Replacing the base with Na_2CO_3 improved the yield of **2a** (entry 2, 75%), while removing the carbonate base and increasing the amount of silver additive had a detrimental effect on the yield (entries 3 and 4). We soon realized that the reaction did not require the addition of a phosphine ligand (entry 5) and that the amounts of catalyst and base could be decreased to 5 mol % and 0.3 equiv to give >90% conversion (entry 5, conditions A).[13] Cognizant of the use of pivalic acid in C−H activation chemistry,[14,8b] we also tested this additive and observed comparable yields to the silver conditions (entry 7, conditions B).[15] Changing the base from K_2CO_3 to Na_2CO_3 (entry 8) provided little conversion and no product formation. Applying both optimized conditions to other picoline and aminoquinoline auxiliaries **1b** and **1c**, we observed little or no product formation.

Table 1. Reaction Optimization

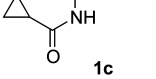


entry	Pd (x)	base (y), additive (z)	yield[a] (%) 1a	2a	3a
1[b]	$Pd(OAc)_2$ (10)	K_2CO_3 (2), Ag_3PO_4 (0.33)	13	59	10
2[b]	$Pd(OAc)_2$ (10)	Na_2CO_3 (2), Ag_3PO_4 (0.33)	15	75	10
3[b]	$Pd(OAc)_2$ (10)	−, Ag_3PO_4 (0.5)	54	20	1
4[b]	$Pd(OAc)_2$ (10)	−, Ag_2CO_3 (1.25)	16	51	9
5[c]	**$Pd(OAc)_2$ (5)**	**Na_2CO_3 (0.3), Ag_3PO_4 (0.5)**	**8**	**78**	**5**
6	$Pd(OAc)_2$ (5)	K_2CO_3(2), −	78	<5	1
7[d]	**$Pd(OAc)_2$ (5)**	**K_2CO_3 (2), PivOH (0.3)**	**6**	**76**	**15**
8	$Pd(OAc)_2$ (5)	Na_2CO_3 (2), PivOH (0.3)	82	1	−
9	$Pd(OAc)_2$ (5)	K_2CO_3 (2), PivOH (0.5)	74	20	1

[a] ^1H NMR yield using trimethoxybenzene as internal standard. [b] $P\text{-}t\text{-}Bu_3 \cdot HBF_4$ (10 mol %) was used in the reaction. [c] Conditions A. [d] Conditions B.



A: 33% (mono), 5% (di)
B: 20% (mono), <1% (di)



A: <1% (mono)
B: <1% (mono)

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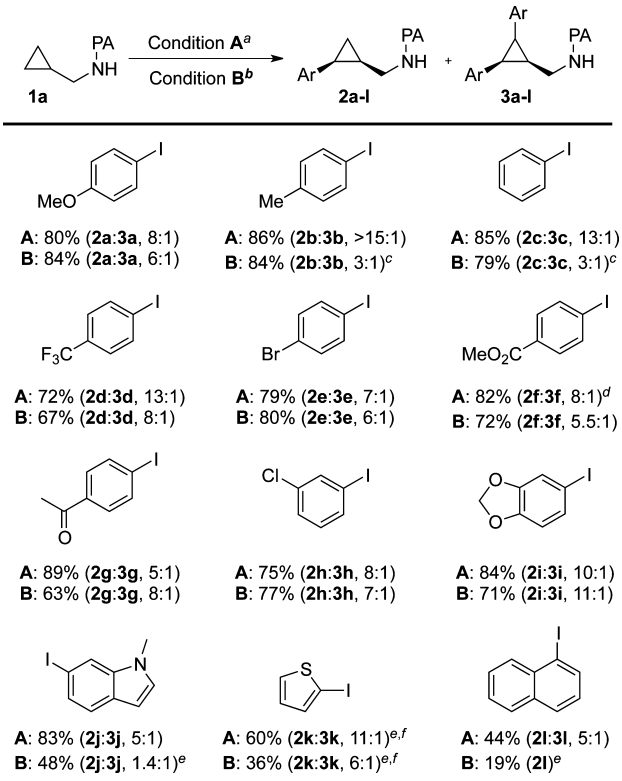
(12) See the Supporting Information.

Scheme 2. Aryl Iodide Scope[a]

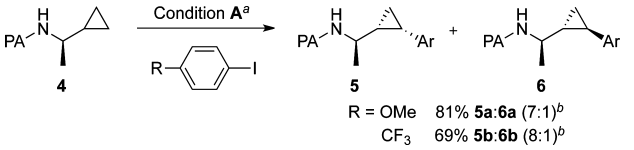


[a] Conditions A: **1a** (0.5 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %), Na_2CO_3 (0.3 equiv), Ag_3PO_4 (0.5 equiv), aryl iodide (1.5 equiv), PhMe (0.2 M), 130 °C, 15 h. [b] Conditions B: **1a** (0.5 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (2 equiv), PivOH (0.3 equiv), aryl iodide (1.5 equiv), PhMe (0.2 M), 130 °C, 15 h. [c] The reaction was run for 45 h. [d] 0.4 equiv Ag_3PO_4. [e] Reported as ^1H NMR yield using an internal standard. [f] 10 mol % of $Pd(OAc)_2$.

With the optimized conditions in hand, the scope of the reaction was explored (Scheme 2). Substitution at the *para* position was well-tolerated, with electron-donating (**2a**) and electron-neutral (**2b**, **2c**) aryl iodides giving great yields. A variety of electron-withdrawing groups were also well tolerated in the reaction, including trifluoromethyl (**2d**), ester (**2f**), and ketone (**2g**). Bromo- (**2e**) and chloro-substituted (**2h**) aryl iodides were also great coupling partners (80% and 77%, respectively), thus allowing for further functionalization of the products through cross-coupling methods. The reaction also tolerated heterocycles, with a protected indole reacting in 83% yield under conditions A (**2j**). 2-Iodothiophene was also reactive, with 60% yield (**2k**). The reaction proved to be slightly sensitive to sterics, as only a modest yield of 44% was isolated for 1-iodonaphthalene (**2l**:**3l**, 5:1) under conditions A, while conditions B resulted in poor conversion. In general, the yields and ratios between the monoarylated and diarylated products were better under conditions A. In all cases, the monoarylated product **2** was exclusively the *cis* diastereomer, thus providing a robust method for the synthesis of aryl and heteroaryl *cis*-substituted cyclopropanes.[16] The diarylation product **3** had a predominant *cis* stereochemistry, with the exception of **3a**, **3j**, and **3l** which provided *trans*, while **3f** and **3g** gave a mixture of both.[17]

To further demonstrate the applicability of the reaction, a picolinamide derivative **4** containing a methyl α to the cyclopropane was synthesized via Ellman's chiral auxiliary[18] and submitted to conditions A (Scheme 3).[19] For *p*-OMe and *p*-CF_3, two diastereomers were obtained in 81% and 69% yield, respectively, with good dr (7:1 and 8:1, respectively).[20]

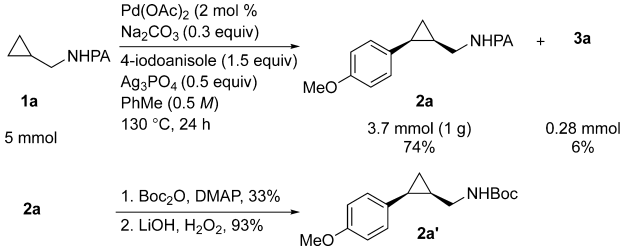
Scheme 3. Diastereoselective C−H Activation of Cyclopropanes[a]



[a] Conditions A: **1a** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %), Na_2CO_3 (0.3 equiv), Ag_3PO_4 (0.5 equiv), aryl iodide (1.5 equiv), PhMe (0.2 M), 130 °C, 15 h. [b] Traces of diarylation < 3% also observed.

To prove the practicality and robustness of the methodology, the reaction was carried out on a 5 mmol scale to provide 1.05 g (74%) of desired product **2a** employing only 2 mol % of $Pd(OAc)_2$ (Scheme 4). Moreover, the auxiliary could be removed in good yield to provide the Boc-protected amine **2a′** (Scheme 4).

Scheme 4. Large Scale and Auxiliary Cleavage



(13) Unreacted aryl iodide is still present at the end of the reaction, as determined by GC−MS analysis. No significant biaryl formation was observed.

(14) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

(15) Aryl bromides were unreactive under both reaction conditions.

(16) Cyclopropanation methods often provide a hard-to-separate mixture of *cis* and *trans* diastereomers; for example, Cu-catalyzed addition of diazo compounds to styrenes: Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. See also ref 11c.

(17) See the Supporting Information for characterization details. Attempts at performing a mixed diarylation to a *cis* substrate **2** resulted in low yields (< 30%), even after longer reaction times.

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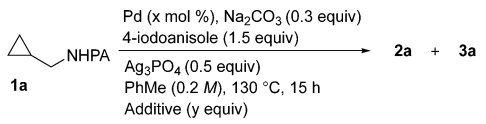
(19) Conditions B led to lower yields (45%).

(20) The stereochemistry of the major diastereomer was determined via 1D NOE analysis.

Table 2. Screen of Pd Sources and Additives

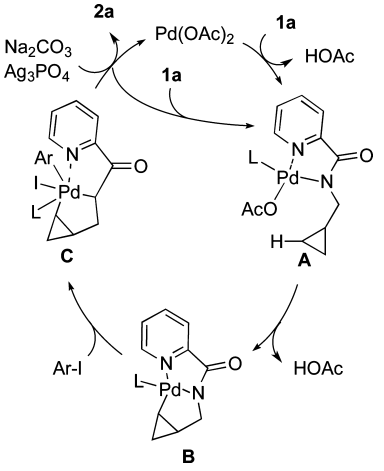


			yield[a] (%)	
entry	Pd (x)	additive (y)	**1a**	**2a/3a**
1	Pd_2dba_3 (2.5)	none	53	43/–
2	Pd_2dba_3 (2.5)	KOAc (10)	8	76/14
3	$PdBr_2$ (5)	none	56	28/–
4	$PdBr_2$ (5)	KOAc (10)	5	63/3

[a] ^{1}H NMR yield using trimethoxybenzene as internal standard.

The mechanism proposed by Daugulis[3b] for the picolinamide auxiliary involves a Pd(II)/Pd(IV)[21] catalytic cycle.[22] In our case, it is hypothesized that an initial five-membered metallocycle species **A** is formed, where Pd is stabilized through coordination to the pyridine nitrogen as well as the highly acidic secondary amide moiety (Scheme 5). C−H palladation mediated by acetate provides intermediate **B**,[23] followed by oxidative addition of the aryl iodide to give **C**. Reductive elimination provides the final product and the palladium amide **A** is regenerated. When our reaction was performed in presence of a Pd(0) source, Pd_2dba_3, 43% desired product **2a** was observed (Table 2, entry 1), while a different Pd(II) source, $PdBr_2$, provided 28% **2a** (entry 3). Interestingly, upon addition of a catalytic amount of acetate in the reaction, the reactivity is restored (entries 2 and 4), clearly demonstrating the necessity of acetate in the concerted metalation deprotonation step as a ligand for Pd.[24] Also, the *cis* C−H bonds of the cyclopropane of **1a** could be deuterated in 75% upon stirring the starting material and $Pd(OAc)_2$ in AcOD, suggesting that activation of the C−H bond occurs in absence of the aryl iodide. No deuteration was observed when Pd_2dba_3 was employed as the catalyst.[25]

Scheme 5. Proposed Mechanism



In conclusion, a highly diastereoselective C−H arylation of cyclopropanes employing a practical and versatile picolinamide auxiliary was developed.[26] The transformation tolerates a variety of aryl iodides as coupling partners, it is scalable, and the auxiliary can be easily removed. Both Pd(0) and Pd(II) sources catalyze the reaction, but the presence of catalytic acetate is required for high conversions. More detailed mechanistic studies are underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) A Pd(II)/Pd(III) mechanism cannot be excluded: Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050.

(23) Attempts to isolate the putative palladacycle in our case have been unsuccessful thus far.

(24) A similar effect has been previously reported: Mousseau, J. J.; Vallée, F.; Lorion, M. M.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 14412. See also ref 8a.

(25) This suggests that in the presence of Ar−I, Pd(0) will form Pd(II)I_2 and Ar−Ar. We observed traces amount of biaryl by GC−MS. Alternatively, Ag^+ may be involved in oxidizing Pd(0) to Pd(II).

(26) During the preparation of this manuscript, a related report appeared: Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238.

The authors declare no competing financial interest.