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Palladium-Catalyzed Arylation of Cyclopropanes via Directing Group-Mediated C(sp^3)–H Bond Activation To Construct Quaternary Carbon Centers: Synthesis of *cis*- and *trans*-1,1,2-Trisubstituted Chiral Cyclopropanes

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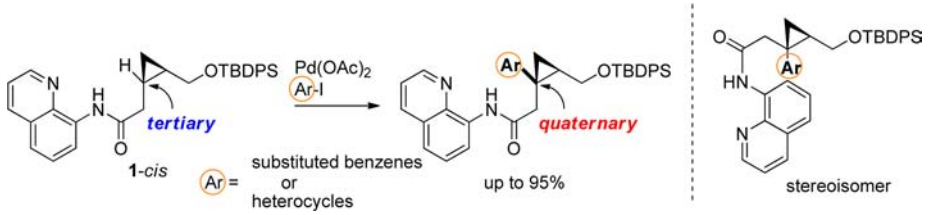
ABSTRACT



Pd(II)-catalyzed tertiary C(sp^3)–H arylation of cyclopropanes via directing group-mediated C–H activation for the construction of a chiral quaternary carbon center on cyclopropanes using aryl iodides as a coupling partner is reported. The arylation had a wide substrate scope and good functional group tolerance, including heteroaryl iodides, to provide various chiral arylcyclopropanes with the *cis*- and *trans*-1,1,2-trisubstituted structures.

Cyclopropane motifs are efficient conformational restricting units in medicinal chemistry due to their characteristic small and rigid structural features, and therefore, synthetic methods of cyclopropanes have been extensively investigated.[1] In cyclopropane chemistry, cyclopropanes bearing an aryl or heteroaryl moiety constitutes a unique and specific scaffold due to their significant biological activity (Figure 1).[2]

For example, milnacipran, having a phenylcylopropane structure, is a clinically useful antidepressant.[3] Thus, various arylcyclopropanes have been designed and synthesized extensively to investigate their biological activity.[4]

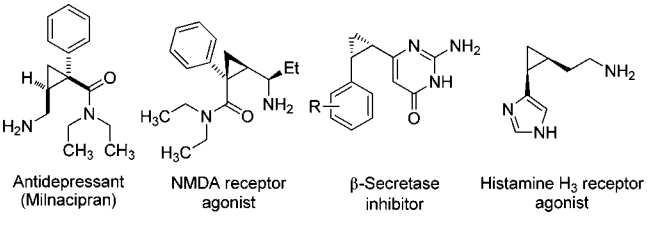


Figure 1. Biologically active arylcyclopropanes.

In our continuous studies using cyclopropanes as key conformational restriction units, we needed to prepare a variety of chiral 1,1,2-trisubstituted arylcyclopropane structures (**A**, *ent*-**A**, **B**, and *ent*-**B**) with a quaternary carbon center bearing an aromatic ring (Figure 2). To construct such chiral 1,1,2-trisubstituted arylcyclopropane

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(1) (a) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Shi, M.; Lu, J. M.; Wei, Y.; Shao, L. X. *Acc. Chem. Res.* **2012**, *45*, 641.
(2) (a) Rubin, M.; Rubina, M.; Gevorgyam, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Gagnon, A.; Duplessis, M.; Fader, L. *Org. Prep. Proc. Int.* **2010**, *42*, 1.
(3) (a) Briley, M. *Drugs Future* **1986**, *11*, 21. (b) Moret, C.; Charveron, M.; Finberg, J. P. M.; Cozinier, J. M.; Briley, M. *Neuropharmacology* **1985**, *24*, 1211.

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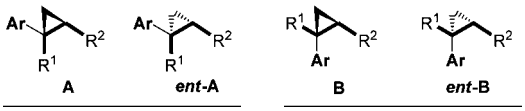
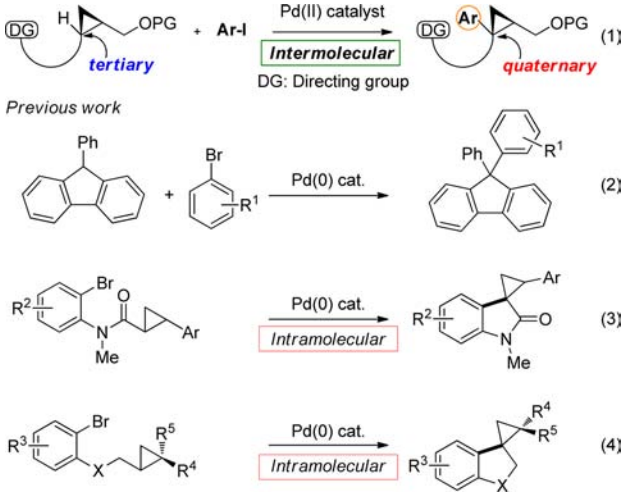


Figure 2. Chiral 1,1,2-trisubstituted arylcyclopropanes having a quaternary carbon center.

Scheme 1. Arylation of Cyclopropanes via C−H Activation for Constructing a Quaternary Carbon Center



structures,[5] the directing group mediated arylation via transition-metal-catalyzed direct C−H activation might be the most attractive strategy to employ because it regio- and stereoselectively provides a wide range of arylated compouds via a short synthetic route.[6] In this paper, we report a method of preparing chiral 1,1,2-trisubstituted arylcyclopropanes by directing group-mediated arylation via transition-metal-catalyzed tertiary C(sp^3)−H activation to construct quaternary carbon centers.[7−9]

To achieve this aim required "*intermolecular*" arylation of a tertiary carbon of cyclopropane rings via C(sp^3)−H activation (Scheme 1, eq 1). This type of arylation of tertiary C(sp^3) remains extremely elusive; however, there is only one notable report by Huang's group in which highly reactive triarylmethyl carbons were arylated via the C(sp^3)−H activation (Scheme 1, eq 2).[10]

In cyclopropane chemistry, two "*intramolecular*" versions of the Pd(0)-catalyzed direct arylation of the tertiary

Scheme 2. Synthesis of the Designed Chiral Substrates **1**-*cis* and **1**-*trans* from our Chiral Cyclopropane Units **2**-*cis* and **2**-*trans*

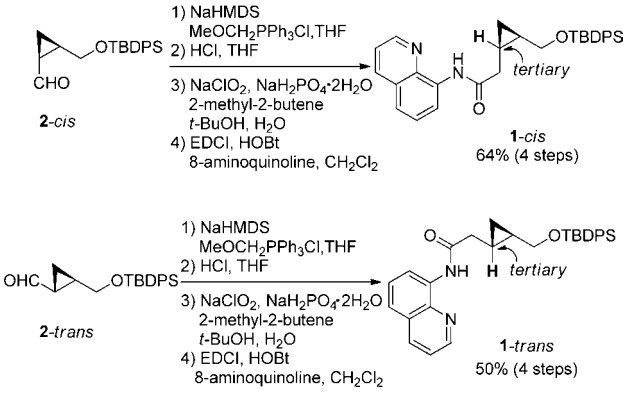
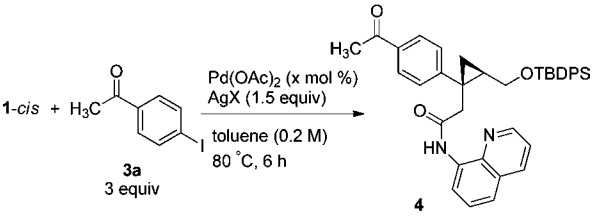


Table 1. Optimization of Reaction Conditions



entry	$Pd(OAc)_2$ (mol %)	AgX	yield[a,b] (%)
1	10	$Ag(OAc)_2$	95
2	5	$Ag(OAc)_2$	82
3	10	Ag_2CO_3	75
4	10	Ag_3PO_4	81

[a] These reactions were performed with 0.2 mmol (entry 1) or 0.05 mmol (entries 2−4) of **1**-*cis*. [b] Yields are isolated yield (entries 1 and 2) or determined by ^1H NMR spectra using benzyl alcohol as an internal standard (entries 3 and 4).

(4) (a) Yonezawa, S.; Yamamoto, T.; Yamakawa, H.; Muto, C.; Hosono, M.; Hattori, K.; Higashino, K.; Yutsudo, T.; Iwamoto, H.; Kondo, Y.; Sakagami, M.; Togame, H.; Tanaka, Y.; Nakano, T.; Takemoto, H.; Arisawa, M.; Shuto, S. *J. Med. Chem.* **2012**, *55*, 8838. (b) Watanabe, M.; Kobayashi, T.; Hirokawa, T.; Yoshida, A.; Ito, Y.; Yamada, S.; Orimoto, N.; Yamasaki, Y.; Arisawa, M.; Shuto, S. *Org. Biomol. Chem.* **2012**, *10*, 736. (c) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2003**, *46*, 1980. (d) Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Biol. Chem.* **2011**, *9*, 1219. (e) Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669. (f) Shuto, S.; Ono, S.; Hase, Y.; Ueno, Y.; Noguchi, T.; Yoshii, K.; Matsuda, A. *J. Med. Chem.* **1996**, *39*, 4844.

(5) (a) Kazuta, Y.; Tsujita, R.; Yamashita, K.; Uchino, S.; Kohsaka, S.; Matsuda, A.; Shuto, S. *Bioorg. Med. Chem.* **2002**, *10*, 3829. (b) Shuto, S.; Ono, S.; Imoto, H.; Yoshii, K.; Matsuda, A. *J. Med. Chem.* **1998**, *41*, 3507.

(6) In C−H activation, the 8-aminoquinoline auxiliary developed by Daugulis was the most effective directing group. Other investigators have also applied this method to various C−H activation reactions. (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.

(7) Arylation of the secondary C(sp^3)−H of cyclopropane was reported by the Yu, Cramer, and Charette groups. (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (c) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. (d) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842. (e) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394.

(8) During the present study, the Babu group reported achiral cyclopropane "*secondary*" C(sp^3)−H arylation using the 8-aminoquinoline auxiliary as a directing group. Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238.

(9) Hydroarylation of biscylopropylidenes and methylenecyclopropanes by ruthenium catalyst giving arylcyclopropanes through C−H activations was recently reported. (a) Ackermann, L.; Kozhushkov, A. I.; Yufit, D. S. *Chem.—Eur. J.* **2012**, *18*, 12068. (b) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409.

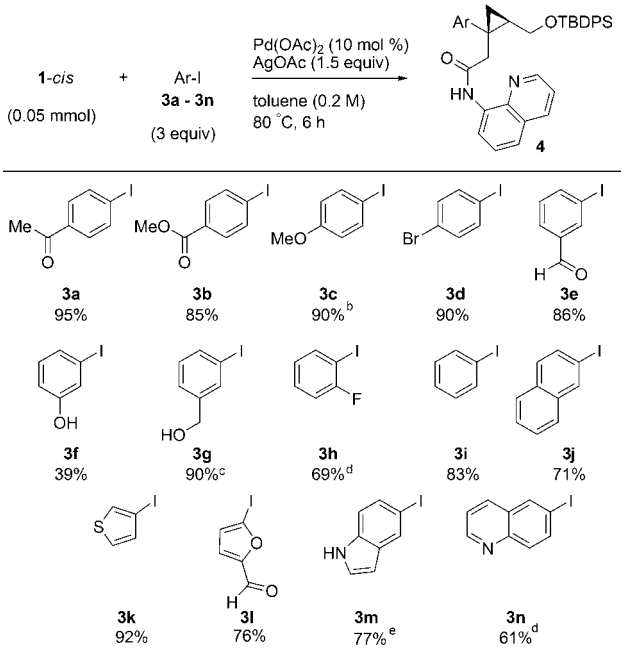
C(sp^3)−H of cyclopropane were reported by Charette's and Cramer's groups, respectively, by which spiro-cyclopropane compounds were effectively prepared (Scheme 1, eqs 3 and 4).[11,12] These results suggested that tertiary C(sp^3)−H activation of cyclopropane occurs more readily, especially in an intramolecular manner, than usual C(sp^3)−H activations, due to its sterically rigid and stereoelectronically sp^2-like properties.[13] Thus, we speculated that selective activation of the tertiary C(sp^3)−H of cyclopropanes and subsequent "*intermolecular*" arylation for constructing a quaternary carbon center on cyclopropanes might proceed. To this end, we planned to use of the directing group strategy with a chelating auxiliary to facilitate the access of the active metal species to the target tertiary C(sp^3)−H of cyclopropanes.

Based on the above-mentioned considerations and examination of various directing groups, we reached the two chiral cyclopropane substrates **1**-*cis* and **1**-*trans* having an 8-aminoquinoline auxiliary as a directing group for the intermolecular arylations to prepare the desired chiral arylcyclopropanes with both *cis*- and *trans*-1,1,2-substituted structures (Scheme 2). The substrates **1**-*cis* and **1**-*trans* were effectively prepared from the chiral *cis*- and *trans*-cyclopropane units **2**-*cis* and **2**-*trans*, which we previously developed (Scheme 2).[4e]

With the chiral cyclopropane substrates **1**-*cis* and **1**-*trans* in hand, we investigated the reaction using **1**-*cis* and 4-iodoacetophenone **3a** (Table 1). Thus, when the reaction was performed under the conditions with $Pd(OAc)_2$ (10 mol %) and AgOAc (1.5 equiv) in toluene at 80 °C, the tertiary C(sp^3)−H bond activation of **1**-*cis* occurred effectively to afford the desired arylation product **5a** with the 1,1,2-trisubstituted cyclopropane structure in 95% isolated yield (entry 1).[14] The reaction proceeded under lower catalyst loading conditions with 5 mol % of $Pd(OAc)_2$, giving **5a** in 82% yield (entry 2). Use of Ag_2CO_3 or Ag_3PO_4 instead of AgOAc did not improve the yield of **5a** (entries 3 and 4). Therefore, the optimized conditions were confirmed to be 10 mol % of $Pd(OAc)_2$, 1.5 equiv of AgOAc in toluene at 80 °C for 6 h.[15]

We next examined the scope of the arylation by using various aryl iodides (**3a**−**n**) under the optimized conditions (Scheme 3).[16] Most of the aryl iodides examined reacted smoothly with **1**-*cis* under the conditions to afford the corresponding arylation products in good yields. Substitution with an electron-withdrawing or electron-donating group at the *para*- (**3a**−**d**) or *meta*-position (**3e**−**g**) of aryl iodides was well-tolerated to give the coupling products in high yields.

Scheme 3. Scope of Arylation of **1**-*cis*[a]



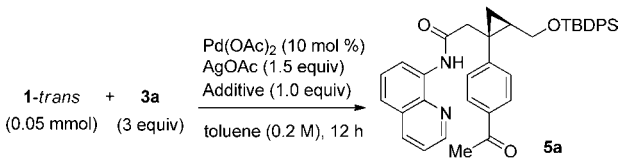
[a] Yields are isolated yields. [b] The yield on a 0.2 mmol scale was 82%. [c] The reaction was run for 12 h. [d] The reaction was carried out at 100 °C for 12 h. [e] $Pd(OAc)_2$ (20 mol %) was used.

For an *ortho*-substituted aryl iodide (**3h**), a higher reaction temperature was required to provide the product in 69% yield. Nonsubstituted phenyl iodide (**3i**) and 2-iodonaphthalene (**3j**) were also good coupling partners to afford the corresponding products in 83% and 71% yields, respectively. In the arylation, functional groups, ketone (**3a**), ester (**3b**), aldehyde (**3e**), phenolic alcohol (**3f**), aliphatic alcohol (**3g**), and bromide (**3d**) were tolerated. Fortunately, the reactions with various aromatic heterocyclic iodides gave the corresponding arylation products in synthetically useful yields: 3-iodothiophene (**3k**, 92%) and 5-substituted 1-iodofuran (**3l**, 76%), unprotected 5-iodoindole (**3m**, 77%), and 5-iodoquinoline (**3n**, 61%), respectively.

We next investigated the arylation of **1**-*trans* to obtain chiral arylcyclopropanes with the stereoisomeric 1,1,2-substituted structures, which would be more challenging than that of the **1**-*cis*, because both the C−H abstraction and the subsequent arylation might be impeded by the steric effects of the adjacent bulky $TBDPSOCH_2$ moiety. The arylation of **1**-*trans* was optimized with 4-iodoacetophenone **3a** (Table 2). The reaction under the conditions optimized for **1**-*cis* described above successfully produced the desired coupling product **4a**, but the yield was rather low (entry 1).[17] A higher temperature (110 °C) did not improve the yield (49%, entry 2), and addition of CsOPiv

(10) Cao, X.; Yang, W.; Liu, C.; Wei, F.; Wu, K.; Sun, W.; Song, J.; Xie, L.; Huang, W. *Org. Lett.* **2013**, *15*, 3102.
(11) Ladd, C. L.; Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 1350.
(12) Saget, T.; Perez, D.; Cramer, N. *Org. Lett.* **2013**, *15*, 1354.
(13) (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-Y.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165. (b) *Small Ring Compounds in Organic Synthesis VI. Topics in Current Chemistry 207*; de Meijere, A., Ed.; Springer: Berlin, 1999.
(14) For the structure determination of **4a**, see the Supporting Information.
(15) When 2 equiv of **3a** was used, the reaction was not completed.
(16) Diarylation or arylation of the secondary carbon center or epimerization of stereogenic center was not observed in all of the entries.
(17) For the structure determination of **5a**, see the Supporting Information.
(18) Metal acetates are known to promote the C−H activation. (a) Mousseau, J. J.; Vallée, F.; Lorion, M. M.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 14412. (b) Lapoint, D.; Fangnou, K. *Chem. Lett.* **2010**, *39*, 1118.

Table 2. Reaction Optimization of Arylation of **1**-*trans*



entry	temp (°C)	additive	conv[a] (%)	yield[a,b] (%)
1	80	none	49	41
2	110	none	89	49
3	80	CsOPiv	39	30
4	80	LiOAc	58	51
5	80	NaOAc	51	43
6	80	KOAc	99	67
7	80	CsOAc	59	59
8	80	K_2CO_3	65	56
9	80	K_3PO_4	87	75

[a] Yields are isolated yield (entries 1, 2, and 9) or determined by ^{1}H NMR spectra using benzyl alcohol as an internal standard (entries 3–8). [b] Any epimerization of the stereogenic center was not observed in all of the entries. A trace of diaryl product (less than 5% yield) was obtained (entries 2, 6, 8, and 9).

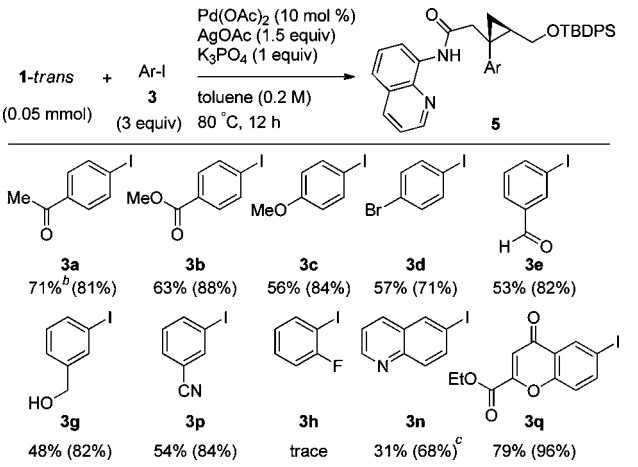
was also ineffective (entry 3). We then tested various acetates as additives[18](entries 4–7), and KOAc improved the yield of **5a** (67%, entry 6). Furthermore, we examined effect of the counteranion and found that K_3PO_4 improved the yield of **5a** (75%, entry 8).

Using the optimized conditions, the arylation of **1**-*trans* with a variety of substituted aryl iodides was tested (Scheme 4). Aryl iodides with a substituent at the *para*- or *meta*-position furnished the desired coupling products in 71% to 48% yields (**3a**–**e**,**g**,**p**), while the *ortho*-substituted aryl iodide **3e** was ineffective under these conditions. The arylation of **1**-*trans* showed excellent functional group tolerance, and heterocyclic aryl iodides (**3n**,**q**) were also tolerated in the reaction to provide the corresponding coupling products. The 8-aminoquinoline auxiliary was effectively removed and provided the corresponding carboxylic acid in high yield.[19]

In conclusion, we have successfully developed a methodology of Pd(II)-catalyzed intermolecular directing group-mediated arylation of cyclopropanes via the tertiary

(19) For details, see the Supporting Information.

Scheme 4. Scope of Arylation of **1**-*trans*[a]



[a] All yields are isolated yields, and the numbers in parentheses are conversion yields. [b] The yield on a 0.2 mmol scale was 70%. [c] The reaction was performed at 100 °C for 24 h.

C(sp^3)–H activation for constructing a chiral quaternary carbon center on cyclopropanes. The arylation had a wide substrate scope as well as good functional group tolerance including heterocyclic substrates to provide a variety of chiral arylcyclopropanes with both the *cis*- and *trans*-1,1,2-trisubstituted structures.

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Supporting Information Available. Experimental details; spectral and analytical data for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.