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Development of a Palladium-Catalyzed α-Arylation of Cyclopropyl Nitriles

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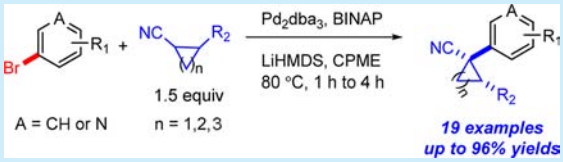
Supporting Information

ABSTRACT: 1,1-Disubstituted aryl cyclopropyl nitriles are useful moieties in biologically active compounds and provide access to a range of cyclopropyl derivatives. Herein, we describe the development of a palladium-catalyzed α-arylation of cyclopropyl, cyclobutyl, and cyclopentyl nitriles that affords these functional groups in one step from a variety of aryl bromides in good to excellent yields. Furthermore, we demonstrate the transformation of aryl cyclopropyl nitriles into aryl trifluoromethyl cyclopropanes.



Cyclopropanes are structural motifs found in many natural products and biologically active molecules.[1] The unique steric, electronic and conformational properties of cyclopropanes render them attractive and privileged pharmacophores for medicinal chemistry.[2] The appeal of 1,1-disubstituted cyclopropanes is the enhanced ability to lock two geminal or vicinal substituents conformationally into a bioactive conformation, often providing increased potency (Figure 1).[3] Another potential benefit, especially in the case of arylcyclopropanes, is the ability to block/divert metabolism at metabolically labile benzylic positions.[4]

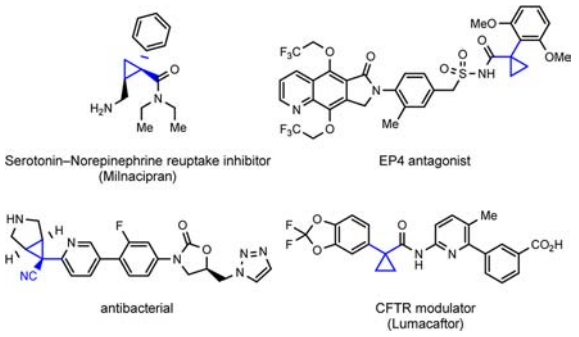


Figure 1. Bioactive 1,1-disubstituted cyclopropanes.

The utility of cyclopropane motifs has prompted intense research directed at discovering efficient and high-yielding methods for their preparation.[3,5] In the context of a drug discovery effort, we became interested in the preparation of 1,1-disubstituted aryl cyclopropanes of general **Type 1** (section A, Scheme 1). Traditional synthetic methods to access compounds of **Type 1** require construction of the cyclopropane ring, often via double alkylation of 1,2-dihaloethanes[6] or the Corey–Chaykovsky reaction.[7] Direct access via a single step transformation[8] would be enormously valuable when studying structure–activity relationships in medicinal chemistry because fragment coupling of this useful synthon would speed drug discovery efforts.[3a] Inspired by the recent advances in palladium-catalyzed α-arylation of esters[9] and nitriles,[10] we investigated the direct α-arylation of cyclopropyl nitrile (**2a**) and cyclopropyl ester (**2b**) for the preparation of 1,1-disubstituted aryl cyclopropanes.[11] Herein, we report the development of an effective protocol for the direct α-arylation of cyclopropyl nitriles with aryl bromides to afford 1,1-aryl cyclopropyl nitriles and their subsequent conversion to 1,1-aryl trifluoromethyl cyclopropanes.

Our investigations began by probing the cross-coupling between cyclopropyl nitrile **2a** and ester **2b** with aryl bromide **1**.[12] Attempts to apply Verkade's[10] conditions for the α-arylation of nitriles [NaHMDS, $Pd(OAc)_2$, and $P(i\text{-}BuNCH_2CH_2)_3N$] or Hartwig's[13] conditions for the α-arylation of esters [Cy_2NLi and $\{[P(t\text{-}Bu)_3]PdBr\}_2$] or [base, Zn*, Pd source and Q-Phos/$\{[P(t\text{-}Bu)_3]PdBr\}_2$] to form quaternary centers were unsuccessful. To identify a desirable starting point for reaction development, we employed high-throughput experimentation (HTE)[14] to interrogate a large array of reaction parameters simultaneously. Our initial screen employing 1-(benzyloxy)-4-bromobenzene (**1a**) yielded no product formation with ester **2b**;[15] however, when Josiphos catalyst **SL-J009-1** was used, a low yield (<5%) of aryl nitrile **3a** was observed. Using these conditions as a starting point, we were able to improve the efficiency of the catalytic system by optimizing the base, solvent, and reaction temperature.

Lithium hexamethyldisilazide (LiHMDS) and cyclopentyl methyl ether (CPME) at 80 °C provided the cleanest conversion of bromide **1a** to **3a** as assessed by HPLC analysis; however, only 15% yields were obtained upon scale-up. Finally, rescreening of palladium source and ligands, employing the optimal base, solvent, and temperature, revealed BINAP as the ideal ligand for this reaction (section C, Scheme 1), which are similar conditions

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Scheme 1. Development of the Direct Palladium-Catalyzed α-Arylation of Cyclopropyl Nitrile 2a

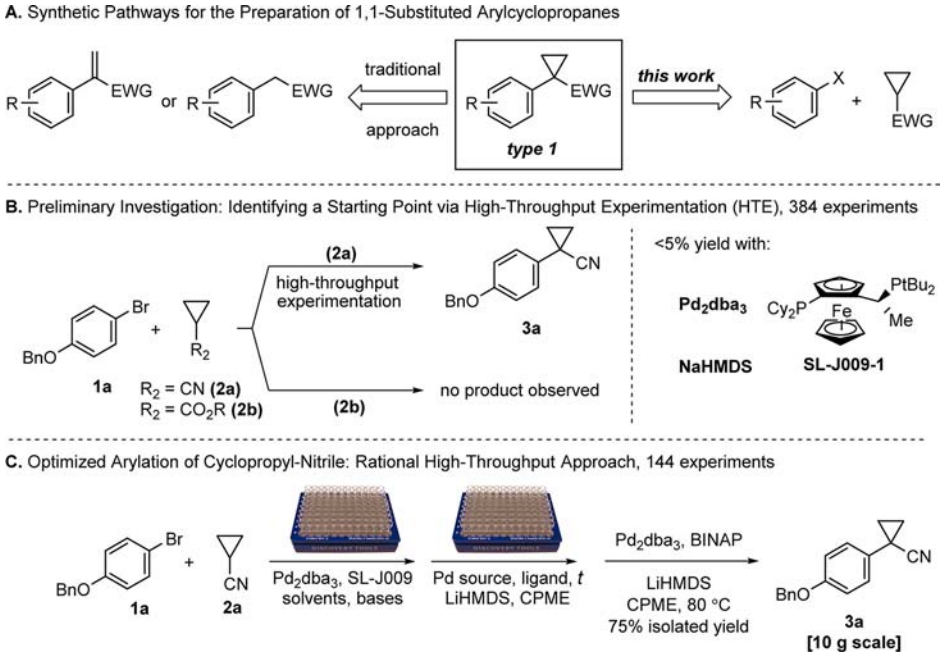
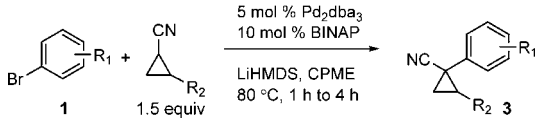


Table 1. Scope of the Direct α-Arylation of Cyclopropyl Nitrile



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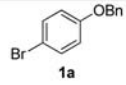
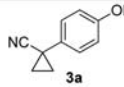
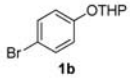
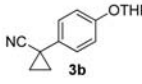
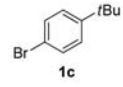
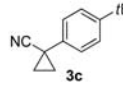
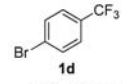
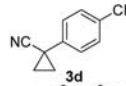
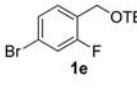
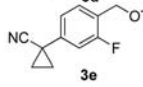
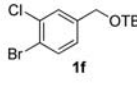
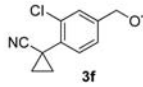
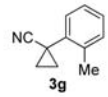
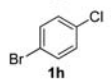
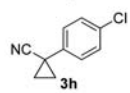
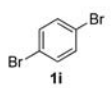
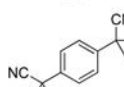
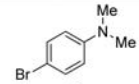
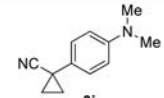
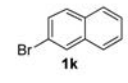
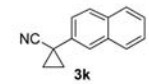
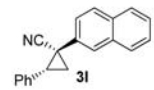
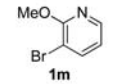
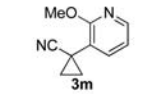
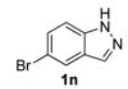
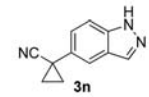
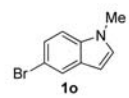
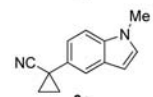
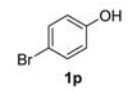
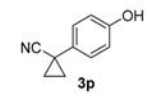
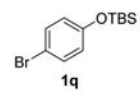
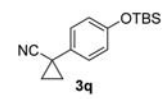
1	 1a	H	 3a	75
2	 1b	H	 3b	54
3	 1c	H	 3c	75
4	 1d	H	 3d	64
5	 1e	H	 3e	55
6	 1f	H	 3f	76
7	 1g	H	 3g	71
8	 1h	H	 3h	79
9	 1i	H	 3i	64
10	 1j	H	 3j	59
11	 1k	H	 3k	88
12	1k	Ph	 3l	65[b]
13	 1m	H	 3m	43[c]
14	 1n	H	 3n	50
15	 1o	H	 3o	31
16	 1p	H	 3p	n.r.
17	 1q	H	 3q	0[d]

[a]Percent isolated yields reported. [b]Single diastereomer isolated. [c]Product co-eluted with ligand during chromatography, leading to material loss. [d]Complete TBS group cleavage was observed via HPLC yielding **1p**.

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previously developed by Hartwig and Culkin for the coupling acyclic nitriles with aryl bromides.[16] In the final optimized protocol, a mixture of bromide **1a** and cyclopropyl nitrile **2a** in CPME was first treated with a preactivated mixture of Pd_2dba_3 and BINAP in THF[17] followed by LiHMDS. This solution was then heated to 80 °C until complete consumption of starting material was observed. This robust protocol was performed on 10 g scale to produce adduct **3a** in 75% yield.

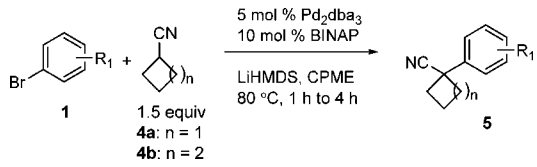
Having successfully demonstrated the application of our protocol to 4-(benzyloxy)bromobenzene (**1a**), the scope of the aryl bromide component was evaluated. Many substrates showed good reactivity under the standard reaction conditions (Table 1). As seen with the benzyloxy case (entry 1, Table 1), a THP-protected phenol was well-tolerated under the reaction conditions (entry 2). Conversely, base-labile silyl-protected phenols were cleaved to the corresponding 4-bromophenol with no reaction (entry 17). Reaction of 4-bromophenol failed to provide any of the desired product, and the starting material was recovered intact (entry 16). However, silyl-protected benzyl alcohols were tolerated[18] (entries 5 and 6) along with *ortho*-substitution on the aromatic ring (entries 6 and 7). Aryl bromides containing electron-donating groups and electron-withdrawing groups underwent α-arylation, providing moderate to high yields (59−79%) of coupled products (entries 1−4, 8, and 10). The products obtained by reacting bromochloroarenes **1f** or **1h** afforded selective coupling at the bromide, leaving the chloride intact as a useful handle for further functionalization (entries 6 and 8). Reaction of 1,4-dibromobenzene (**1i**) in the presence of an excess of base and nitrile **2a** provided the bis-aryl cyclopropyl product **3i**, thus demonstrating the feasibility of dicyclopropanations. Heterocyclic aryl bromides provided substituted pyridines, imidazoles, and indoles (entries 13, 14, and 15). Lastly, reaction of 2-phenylcyclopropanecarbonitrile with 2-bromonaphthalene (**1l**) provided the desired product **3l** as a single diastereomer (entry 12).

Cyclohexyl nitrile is the smallest reported monocyclic nitrile reported to undergo successful direct Pd-catalyzed α-arylation.[10a,c] Given our success with cyclopropyl nitrile **2a**, we postulated that other smaller ring nitriles would also be reactive under our conditions. We were gratified to find that this was the case, and both aryl and heteroaryl bromides coupled with cyclobutyl nitrile **4a** and cyclopentyl nitrile **4b** in high yields (Table 2).

With a method in hand to generate 1,1-disubstituted aryl cyclopropyl nitriles, we elected to demonstrate their synthetic utility in the synthesis of trifluoromethylcyclopropanes.[10a,b] While the nitrile functional group of 1,1-disubstituted aryl cyclopropyl nitriles had been transformed to an aldehyde, acid, alcohol, difluoromethyl, and an amide,[19] the conversion of 1,1-disubstituted aryl cyclopropyl nitriles to a 1,1-disubstituted aryl trifluoromethyl cyclopropane had not been demonstrated. This is particularly relevant since the cyclopropyltrifluoromethyl group has recently been identified as an attractive *tert*-butyl replacement in medicinal chemistry owing to its increased metabolic stability.[20] The conventional method to synthesize 1,1-disubstituted aryl trifluoromethyl cyclopropanes employs diazomethane, which raises safety concerns, especially on a large scale.[20,21]

We chose to demonstrate the conversion of the nitrile group on substrates **1h** and **7** to a cyclopropyltrifluoromethyl group, since these substrates provide handles for further functionalization. Hydrolysis of cyclopropyl nitrile **1h** and **7** with LiOH in MeOH provided the desired cyclopropyl acid (Scheme 2). Treatment of the crude cyclopropyl carboxylic acids with Fluolead (3 equiv) at 60 °C provided the desired 1,1-disubstituted aryl trifluoromethyl cyclopropanes **6** and **8** in 92% and 87% yields, respectively.[22] To our knowledge, this is the first example of the synthesis of a 1,1-disubstituted aryl trifluoromethyl cyclopropane starting from a cyclopropyl nitrile (via a cyclopropyl acid) and provides a general method to cyclopropyltrifluoromethyl arenes. Further scope and limitations of this transformation are being explored and will be the subject of a separate publication.

Table 2. Scope of Direct α-Arylation of Cyclobutyl- and Cyclopentyl Nitrile



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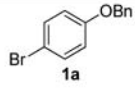
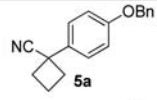
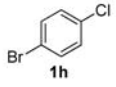
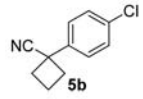
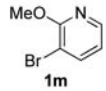
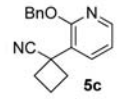
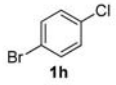
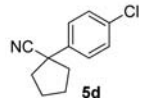
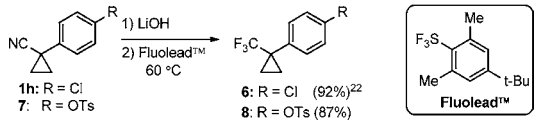
1	 1a	1	 5a	80
2	 1h	1	 5b	96
3	 1m	1	 5c	71
4	 1h	2	 5d	71

[a]Isolated yields reported.

Scheme 2. Synthesis of Cyclopropyltrifluoromethyl Compounds



In conclusion, we discovered conditions for a single-step route to 1,1-disubstituted aryl cyclopropyl nitriles via high-throughput experimentation. Under optimized conditions, the reaction was effective on a variety of aryl and heteroaryl bromides to afford adducts in high yield. Furthermore, cyclobutyl nitrile **4a** and cyclopentyl nitrile **4b** were also effective substrates in the coupling reaction. Lastly, we expanded the utility of aryl cyclopropyl nitriles by transforming them into cyclopropyl trifluoromethyl arenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental data and characterization of all new compounds. 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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■ REFERENCES

(1) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631.

(2) de Meijere, A.; Hadjiarapoglou, L. P.; Iwasawa, N.; Khlebnikov, A. F.; Kozhushkov, S. I.; Narasaka, K.; Salaün, J. Small Ring Compounds in Organic Synthesis VI. In *Topics in Current Chemistry*; de Meijere, A., Ed.; Springer-Verlag: Berlin, 2000; Vol. *207*, p 3.

(3) For a review and leading references, see: (a) Gagnon, A.; Duplessis, M.; Fader, L. *Org. Prep. Proced. Int.* **2010**, *42*, 1. (b) Nowak, G.; Pomierny-Chamioło, L.; Siwek, A.; Niedzielska, E.; Pomierny, B.; Pałucha-Poniewiera, A.; Pilc, A. *Neuropharmacology* **2014**, *84*, 46. (c) Burch, J. D.; Belley, M.; Fortin, R.; Deschênes, D.; Girard, M.; Colucci, J.; Farand, J.; Therien, A. G.; Mathieu, M.-C.; Denis, D.; Vigneault, E.; Lévesque, J.-F.; Gagné, S.; Wrona, M.; Xu, D.; Clark, P.; Rowland, S.; Han, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2048. (d) Komine, T.; Kojima, A.; Asahina, Y.; Saito, T.; Takano, H.; Shibue, T.; Fukuda, Y. *J. Med. Chem.* **2008**, *51*, 6558. (e) Hadida-Ruah, S.; Hamilton, M.; Miller, M.; Grootenhuis, P. D. J.; Bear, B.; McCartney, J.; Zhou, J.; van Goor, F. Modulators of ATP-Binding Cassette Transporters. U.S. Pat. Appl. Publ. 20080019915, 2008.

(4) (a) Yan, L.; Huo, P.; Hale, J. J.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G.-J.; Chrebet, G.; Bergstrom, J.; Card, D.; Mandala, S. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 828. (b) Gagnon, A.; Amad, M. H.; Bonneau, P. R.; Coulombe, R.; DeRoy, P. L.; Doyon, L.; Duan, J.; Garneau, M.; Guse, I.; Jakalian, A.; Jolicoeur, E.; Landry, S.; Malenfant, E.; Simoneau, B.; Yoakim, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4437.

(5) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(6) (a) Papahatjis, D. P.; Nikas, S.; Tsotinis, A.; Vlachou, M.; Makriyannis, A. *Chem. Lett.* **2001**, *3*, 192. (b) Arava, V. R.; Siripalli, U. B. R.; Dubey, P. K. *Tetrahedron Lett.* **2005**, *46*, 7247. (c) Barbasiewicz, M.; Marciniak, K.; Fedoryński, M. *Tetrahedron Lett.* **2006**, *47*, 3871.

(7) (a) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (b) Clemens, J. J.; Asgian, J. L.; Busch, B. B.; Coon, T.; Ernst, J.; Kaljevic, L.; Krenitsky, P. J.; Neubert, T. D.; Schweiger, E. J.; Termin, A.; Stamos, D. *J. Org. Chem.* **2013**, *78*, 780. (c) For a review, see: Gololobov, Y. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609.

(8) The direct coupling of 1,1-disubstituted aryl cyclopropanes via S_NAr is known. Typically, highly activated systems are required for good conversion. See: (a) Klapars, A.; Waldman, J. H.; Campos, K. R.; Jensen, M. S.; Mclaughlin, M.; Chung, J. Y. L.; Cvetovich, R. J.; Chen, C. *J. Org. Chem.* **2005**, *70*, 10186. (b) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712.

(9) For a recent review, see: Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676.

(10) (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (b) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003. (c) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. (d) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690. (e) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932.

(11) Cyclopropyl nitrile is found to have lower acidity and a unique carbanion structure and reactivity when compared to acyclic and larger ring cyclic nitriles. See: Juchnovski, I. N.; Tsenov, J. A.; Binev, I. G. *Spectrochim. Acta Part A* **1996**, *52*, 1145.

(12) To our knowledge, the direct Pd-catalyzed α-arylation of cyclopropyl-derived nitriles or cyclopropyl esters has not been reported. For a report on deprotonation kinetics of cyclopropanes, see: Van Wunen, W. Th.; Steinberg, H.; De Boer, TH. J. *Tetrahedron* **1972**, *28*, 5423.

(13) (a) Hama, T.; Ge, S.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8250. (b) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545.

(14) (a) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257. (b) Schultz, S. C.; Krska, S. W. *Acc. Chem. Res.* **2007**, *40*, 1320. (c) Schmink, J. R.; Bellomo, A.; Berritt, S. *Aldrichimica Acta* **2013**, *46*, 71.

(15) Unsuccessful reactions employing **2b** may be due to the instability of the deprotonated ester at elevated temperatures; see: Häner, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1655.

(16) This result is consistent with Hartwig's mechanistic analysis of the α-arylation of nitriles with various ligands, establishing that BINAP, as a ligand, provides an arylpalladium cyano complex that is C-bound and able to reductively eliminate providing the α-aryl nitriles. See ref 10c.

(17) Procedure for preactivated catalyst: a flask with BINAP (0.10 equiv) and Pd_2dba_3 (0.05 equiv) was evacuated and charged with N_2. Then degassed THF was added, and the suspension was stirred under N_2 for 20 min. THF was the optimal solvent for catalyst preactivation.

(18) Phenolic silyl ethers cleave more readily than alkyl silyl ethers under basic conditions; see: Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681.

(19) (a) Papahatjis, D. P.; Nahmias, V. R.; Nikas, S. P.; Andreou, T.; Alapafuja, S. O.; Tsotinis, A.; Guo, J.; Fan, P.; Makriyannis, A. *J. Med. Chem.* **2007**, *50*, 4048. (b) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (c) Sandanayaka, V.; Singh, J.; Gurney, M.; Mamat, B.; Yu, P.; Bedel, L.; Zhao, L. Biaryl substituted heterocycle inhibitors of LTA4H for treating inflammation. U.S. Pat. Appl. Publ. 20070066820, 2007. (d) Chin, E.; De Vicente Fidalgo, J.; Li, J.; Jui, A. S-T.; McCaleb, K. L.; Schoenfeld, R. C.; Talamas, F. X. Heterocyclic antiviral compound. WO2010149598, 2010.

(20) Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X.-H.; Amin, J.; Snodgrass, B.; Hatsis, P. *ACS Med. Chem. Lett.* **2013**, *4*, 514.

(21) During the preparation of this manuscript, a method for the direct installation of this functional group via a radical pathway was described; see: Gianatassio, R.; Kawamura, S.; Eprile, C. L.; Foo, K.; Ge, J.; Burns, A. C.; Collins, M. R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9851.

(22) The yield of 1,1-disubstituted aryl trifluoromethyl cyclopropane **6** is an NMR yield calculated by adding an internal standard (CH_2Cl_2) to the crude organic layer after treatment with pH 7 buffer and removal of the aqueous layer. This substrate was found to be volatile and provides a 45% isolated yield.