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Cross-Coupling of [2-Aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes with Aryl Halides

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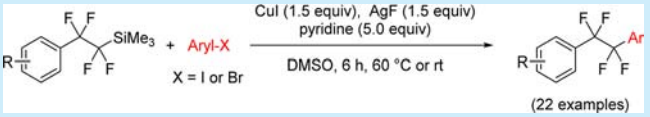
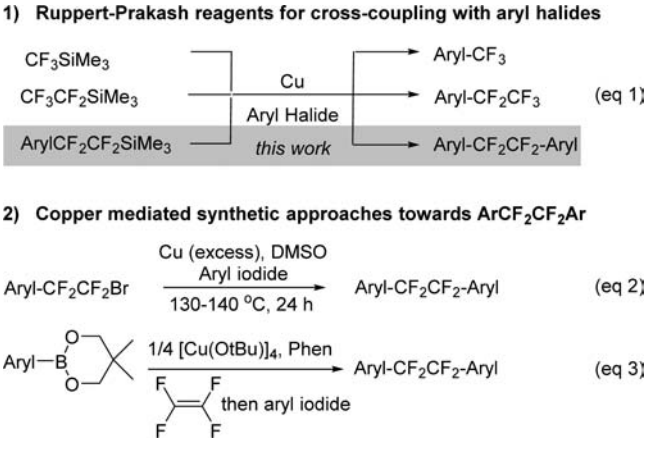
Supporting Information

ABSTRACT: The synthesis of arylCF$_2$CF$_2$SiMe$_3$ and their reactivity in cross-coupling reactions with aryl iodides and aryl bromides to afford a range of 1,1,2,2-tetrafluoro-1,2-arylethanes is reported. The use of pyridine as an alternative to phenanthroline, and the ability to carry out the reaction at 60 °C or room temperature are the key features of this Cu−Ag mediated cross-coupling methodology. The chemistry is compatible with (hetero)aryl halides, offering a platform to develop products of interest in material and medicinal chemistry.



The Ruppert−Prakash reagent (CF_3TMS) is a stable and easy to handle commercially available reagent widely employed for late stage trifluoromethylation.[1] Metal-mediated cross-coupling strategies with this reagent have been extensively studied,[2] more recently with a focus on copper-mediated processes with aryl halides.[3,4] The use of this class of reagents to install extended perfluoroalkyl chains is limited to (pentafluoroethyl)trimethylsilane (C_2F_5TMS) and some selected studies employing more functionalized perfluorinated trimethylsilane derivatives (Scheme 1).[4a,g−i] We noted a single example of a copper-mediated cross-coupling reaction of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silane (arylCF$_2$CF$_2$-TMS) with 1-iodo-4-nitrobenzene, a reaction affording 1-(1,1,2,2-tetrafluoro-2-(4-nitrophenyl)ethyl)-1*H*-pyrazole in 25% yield.[5] The product formed in this reaction belongs to a class of highly valuable 1,1,2,2-tetrafluoro-1,2-arylethane derivatives presenting with a CF$_2$CF$_2$ unit flanked by two aryl (or heteroaryl) groups; however, the low yield for this isolated reaction implies narrow applicability. The usefulness of these compounds to access novel perfluorinated materials such as liquid-crystalline compounds[6] has encouraged the development of a range of alternative methods for their synthesis, using precursors other than [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes. Strategies featuring late stage fluorination are known but suffer from harsh reaction conditions.[7] More recently, 2-bromo-1,1,2,2-tetrafluoroethylarenes were found to be suitable for cross-coupling reactions with aryl iodides in the presence of an excess of copper, but these couplings require temperatures higher than 130 °C and extended reaction times (Scheme 1, eq 2).[8] Ogoshi et al. disclosed an elegant alternative strategy based on the generation of 2-aryl-1,1,2,2-tetrafluoro-ethylcopper complexes from [CuO*t*Bu]$_4$, tetrafluoroethylene (TFE), and arylboronic esters (Scheme 1, eq 3). These complexes were successfully used in cross-coupling reactions with aryl iodides; the use of gaseous TFE is not ideal for common research laboratory settings, and the sensitivity of the [CuO*t*Bu]$_4$ precursor may be limiting as a glovebox is preferable for handling.[9] Our research program on Cu-mediated ^{18}F-radiochemistry for positron emission tomography applications is currently expanding with the development of new methodologies for the labeling of perfluorinated arenes.[10] This program led us to prepare [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes and develop an efficient protocol for the synthesis of 1,1,2,2-tetrafluoro-1,2-arylethanes via copper/silver-mediated cross-coupling with a range of aryl halides (Scheme 1). Herein, we disclose this operationally simple and mild reaction and exemplify its scope on a range of (hetero)aryl iodides and bromides.

Scheme 1. Synthesis of 1,1,2,2-Tetrafluoro-1,2-arylethanes



This study began with the synthesis of the model [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silane **1a**, which was prepared from the parent aryl bromide following a three-step procedure (Scheme 2). First, the Schlosser Grignard reagent derived from 4-bromo-1,1′-biphenyl was reacted with methyl chlorodifluoroacetate at −40 °C in THF. Treatment of the resulting ketone with DAST at 60 °C afforded 4-(2-chloro-1,1,2,2-tetrafluoroethyl)-1,1′-biphenyl in 65% overall yield after

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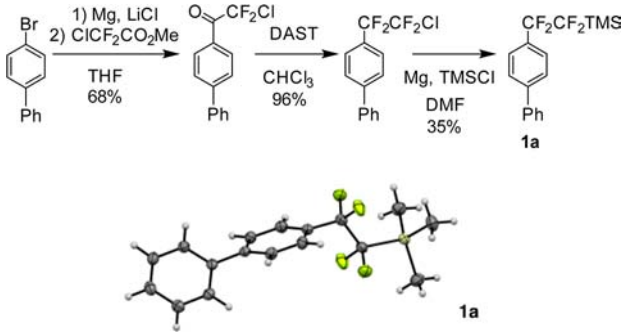
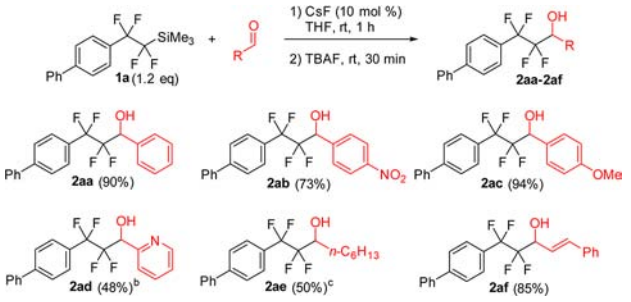
Scheme 2. Synthesis and X-ray Structure of [2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane 1a



two steps. The subsequent reaction, a magnesium-mediated trimethylsilylation, was less efficient, but this process was readily scalable, delivering more than two grams of [2-(biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane **1a**; this compound is a white crystalline solid found suitable for single crystal X-ray diffraction analysis.[11,12] The additional [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes **1b** and **1c** used in this study were prepared following a similar reaction sequence. For **1c**, lithium halogen exchange was preferable to Grignard formation for the trimethylsilylation step.[12]

In the first instance, the reactivity of **1a** was probed with a benchmark reaction, a fluoride-mediated addition to enolizable and nonenolizable aldehydes (Scheme 3).

Scheme 3. Reactivity of [2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane 1a with Aldehydes[a]

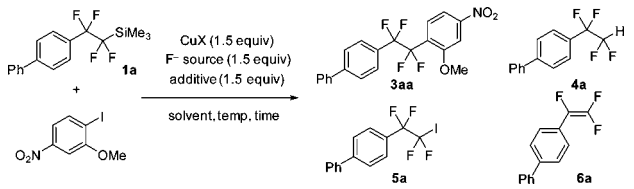


[a]1.2 equiv of **1a** and 1.0 equiv of aldehyde; yields of isolated product. [b]4-(1,1,2,2-Tetrafluoroethyl)-1,1′-biphenyl was formed as side-product (40%). [c]4-(1,1,2,2-Tetrafluoroethyl)-1,1′-biphenyl (30%) and 4-(1,2,2,2-tetrafluoroethyl)-1,1′-biphenyl (20%) were formed as side-products.

The addition of **1a** (1.2 equiv) to benzaldehyde (1.0 equiv) was accomplished at room temperature in THF in the presence of 10 mol % CsF. The resulting silylated alcohol was subjected to deprotection using TBAF. The desired compound was isolated in 90% yield. Electron poor and electron rich benzaldehydes are tolerated, but the reaction proved less efficient with pyridine 2-carboxaldehyde and hexanal, affording **2ad** and **2ae** in 48% and 50% yields, respectively. For reactions giving the desired products in yields inferior to 70%, protodesilylation of **1a** leading to 4-(1,1,2,2-tetrafluoroethyl)-1,1′-biphenyl was observed as a competitive side reaction, and an additional product identified as 4-(1,2,2,2-tetrafluoroethyl)-1,1′-biphenyl was formed when using hexanal.[13] Only traces of 4-(1,2,2-trifluorovinyl)-1,1′-biphenyl resulting from elimination were detectable in the crude reaction mixtures.

We focused next on the Cu-mediated cross-coupling of **1a** with 1-iodo-2-methoxy-4-nitrobenzene (Table 1).

Table 1. Optimization Studies for the Cross-Coupling of 1a with 1-Iodo-2-methoxy-4-nitrobenzene[a]



entry	fluoride source	solvent	additive	NMR ratio[b] 3aa/4a/5a/6a
1	KF	DMF		26:35:31:8
2	KF	NMP		16:33:28:22
3	KF	DMSO		31:38:18:13
4	CsF	DMSO		36:38:15:11
5	TBAF	DMSO		0:100:0:0
6	AgF	DMSO		53:18:19:10
7[c]	AgF	DMSO		8:53:21:14
8[d]	AgF	DMSO		48:16:26:11
9[e]	AgF	DMSO		44:24:21:11
10	AgF	DMSO	$B(OMe)_3$	37:25:25:12
11	AgF	DMSO	TMEDA	2:92:4:2
12	AgF	DMSO	Phen	50:26:12:13
13	AgF	DMSO	Bipy	47:10:30:13
14	AgF	DMSO	tBu$_2$-Bipy	64:14:5:16
15	AgF	DMSO	Py	63:11:21:3
16	AgF	DMSO	Py[f]	73:5:19:1
17[g]	AgF	DMSO	Py[f]	63:6:27:4
18[h]	AgF	DMSO	Py[f]	76:5:13:5
19[e]	AgF	DMSO	Py[f]	60:20:18:2

[a]Standard conditions: 1.0 equiv of 1-iodo-2-methoxy-4-nitrobenzene, 1.2 equiv of **1a**, 1.5 equiv of fluoride source, 1.5 equiv of CuI, 1.5 equiv of additive (if applicable), 0.25 M in solvent, 60 °C, 16 h. TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine; Phen = 1,10-phenanthroline; Bipy = 2,2′-bipyridine; tBu$_2$-Bipy = 4,4′-di-*tert*-butyl-2,2′-bipyridine; Py = pyridine. [b]Determined by ^{19}F NMR by integration of the product peak(s) using $PhCF_3$ as the internal standard. [c]Reaction with CuCl. [d]Reaction with CuBr. [e]20 mol % of CuI. [f]5.0 equiv of pyridine. [g]rt for 6 h. [h]6 h reaction time.

Our investigation began with the coupling of **1a** and our model aryl iodide in DMF with 1.5 equiv of KF and CuI at 60 °C for 16 h (Table1, entry 1). These conditions led to the desired product **3aa** in 26% yield along with 35% of 4-(1,1,2,2-tetrafluoroethyl)-1,1′-biphenyl **4a** resulting from competitive protodesilylation. The two additional side products observed in the crude reaction mixture were the iodo derivative **5a** formed in 31% yield along with 8% of alkene **6a**. A similar product distribution was obtained using NMP, but the use of DMSO proved beneficial (Table 1, entries 2−3). AgF was the most efficient activator affording the desired coupling product in 53% yield (Table 1, entry 6). The cooperative effect of silver in the Cu-catalyzed trifluoromethylation of aryl iodides with CF_3TMS has been reported for other systems by Weng and co-workers.[4e] Alternative sources of Cu(I) such as CuBr or CuCl were less effective (Table 1, entries 7−8).[14] The reaction did proceed with a catalytic amount of CuI; however, a substantial amount of byproduct formation was observed (Table 1, entry 9). Several additives were considered next. With the Ruppert−Prakash reagent CF_3SiMe_3, $B(OMe)_3$ was shown to stabilize the CF_3 anion in copper mediated cross-coupling, thus minimizing the formation of protodesilylated

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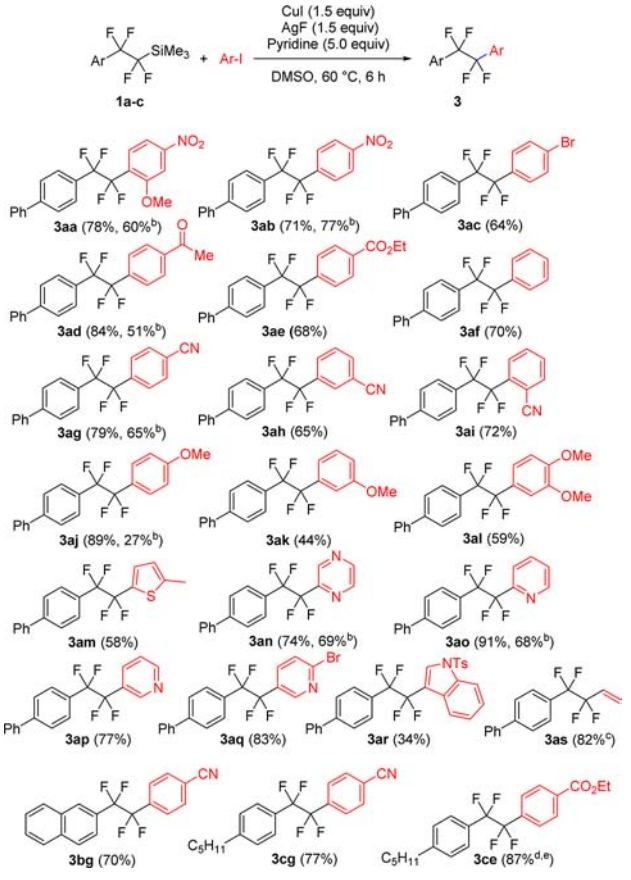
byproduct;[4j] no beneficial effect was observed with **1a** (Table 1, entry 10). As anticipated, we found that 1,10-phenanthroline and bipyridine were superior to TMEDA, but these ligands afforded product **3aa** in only low to moderate conversion (Table 1, entries 11−13); the more electron rich 4,4′-di-*tert*-butyl-2,2′-bipyridine ligand gave **3aa** in 64% (Table 1, entry 14) and pyridine afforded **3aa** in 63% (Table 1, entry 15). Cost-effective pyridine was identified as the best additive for cross-coupling (Table 1, entries 15−16). The use of pyridine as a preferential ligand for copper-mediated cross-coupling methodologies for perfluoroalkylation is not common, but its advantage over other ligands has been documented in the context of flow chemistry.[15] Monitoring the reaction by NMR indicated that the starting material was consumed after 6 h (Table 1, entry 17). Applying our best conditions consisting of CuI (1.5 equiv), AgF (1.5 equiv), and pyridine (5.0 equiv) in DMSO at 60 °C for 6 h, **3aa** was isolated in 78% yield (Table 1, entry 18). Similar conditions using 20 mol % of CuI instead of 1.5 equiv led to inferior results, so these conditions using substoichiometric amount of CuI were not retained to study the scope of this cross-coupling reaction (Table 1, entry 19).

The substrate scope was investigated next (Scheme 4). Numerous functionalized aryl iodides underwent cross-coupling with **1a**. Ketone, nitro, cyano, ether, ester, and bromo substituents are well tolerated with good conversions obtained for both electron-donating and electron-withdrawing substituents. This methodology can be extended to a vinyl iodide as well as a range of heteroaryl iodides including thiophene, pyrazine, indole, and pyridine derivatives. The reaction also proceeds with alternative 2-substituted trimethyl(1,1,2,2-tetrafluoroethyl)-silanes, as exemplified by the synthesis of **3bg**, **3cg**, and **3ce**. Compound **3ce** is an advanced precursor for the synthesis of a liquid crystalline compound.[6c] We noted that this protocol allowed for the coupling of CF_3CF_2TMS with 1-iodo-2-methoxy-4-nitrobenzene and HCF_2TMS with 1-*tert*-butyl-4-iodobenzene affording the desired products in 82% (yield of isolated product) and 59% (^{19}F NMR yield), respectively. This is an improvement over current methods reported in the literature because of the mildness of our reaction conditions.[4h,16] The cross-coupling of **1a** with aryl iodides could also be performed at room temperature, but the yields of the isolated products were generally lower under these conditions (Scheme 4). The diaryl derivatives **3ac**, **3aq**, and **3as** stand out as candidates for further derivatization via cross-coupling or metathesis.

The difference in availability and price of (hetero)aryl iodides and bromides prompted us to study the coupling of representative (hetero)aryl bromides (Scheme 5). These reactions were performed using CuI (1.5 equiv), AgF (1.5 equiv), and pyridine (5.0 equiv) in DMSO at 60 °C for 6 h. We found that this reaction does not proceed for electron rich cross-coupling partners such as 1-bromo-4-methoxybenzene. For electron deficient aryl bromides, cross-coupling proceeded under the reaction conditions applied to aryl iodides with yields of isolated products reaching up to 68%. 2-Bromopyridine was more reactive than 3-bromopyridine, a reactivity order allowing for the exclusive formation of product **3aq** from 2,3-dibromopyridine.

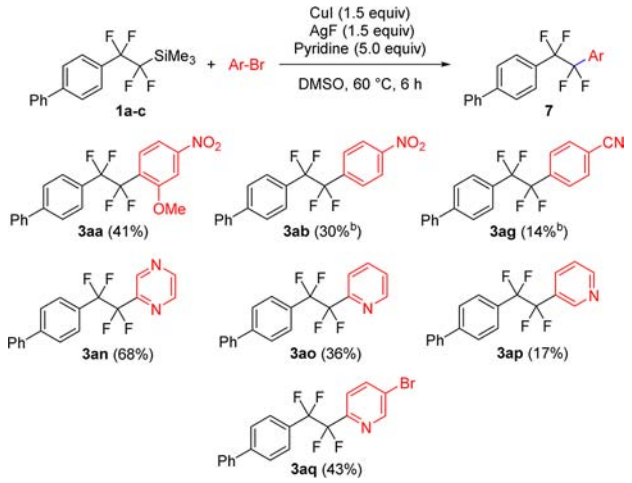
In summary, we have developed a simple synthetic procedure for the generation of 1,1,2,2-tetrafluoro-1,2-arylethanes from the reaction of stable $arylCF_2CF_2SiMe_3$ Ruppert−Prakash type reagents with (hetero)aryl iodides or bromides. These reactions are an improvement over current fluoroalkylation reactions due to the mildness of the reaction conditions applied. However, improved routes toward $arylCF_2CF_2SiMe_3$ will be necessary to

Scheme 4. Copper-Mediated Cross Coupling of 1a with (Hetero)aryl Iodides[a]



[a]1.2 equiv of **1** and 1.0 equiv of aryl iodide (0.2 mmol scale); All yields are for isolated products. [b]Reaction performed at room temperature for 6 h. [c]Chemical purity 91%. [d]0.5 mmol scale. [e]Chemical purity 90%.

Scheme 5. Copper-Mediated Cross Coupling of 1a with (Hetero)aryl Bromides[a]



[a]1.2 equiv of **1a** and 1.0 equiv of aryl iodide (0.2 mmol scale); yields of isolated products unless stated otherwise. [b]^{19}F NMR yields, determined by integration of the product peak(s) using $PhCF_3$ as the internal standard.

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progress this methodology from research to process. The use of pyridine as an alternative to phenanthroline and the ability to carry out the reaction at 60 °C or room temperature for aryl iodides are the key features of this cross-coupling methodology. An additional characteristic is the range of (hetero)aryl halides amenable to cross-coupling under such mild reaction conditions. We anticipate that this process will facilitate research programs focusing on the discovery of high performance materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01510.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (b) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683 and references therein. .

(2) (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. and references therein. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. - Asian J.* **2012**, *7*, 1744 and references therein. .

(3) Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012**, *2012*, 6679.

(4) (a) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 91. (b) Dubinina, G. G.; Furutachi, H.; Vicic, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 8600. (c) Dubinina, G. G.; Ogikubo, J.; Vicic, D. A. *Organometallics* **2008**, *27*, 6233. (d) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909. (e) Weng, Z.; Lee, R.; Jia, W.; Yuan, Y.; Wang, W.; Feng, X.; Huang, K. *Organometallics* **2011**, *30*, 3229. (f) Tomashenko, O. A.; Escudero-Adán, E. C.; Martínez Belmonte, M.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 7655. (g) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3793. (h) Hafner, A.; Bräse, S. *Adv. Synth. Catal.* **2013**, *355*, 996. (i) Mormino, M. G.; Fier, P. S.; Hartwig, J. F. *Org. Lett.* **2014**, *16*, 1744. (j) Gonda, Z.; Kovács, S.; Wéber, C.; Gáti, T.; Mészáros, A.; Kotschy, A.; Novák, Z. *Org. Lett.* **2014**, *16*, 4268.

(5) Petko, K. I.; Kot, S. Y.; Yagupolskii, L. M. *J. Fluorine Chem.* **2008**, *129*, 301.

(6) (a) Kirsch, P.; Bremer, M.; Huber, F.; Lannert, H.; Ruhl, A.; Lieb, M.; Wallmichrath, T. *J. Am. Chem. Soc.* **2001**, *123*, 5414. (b) Kirsch, P.; Huber, F.; Lenges, M.; Taugerbeck, A. *J. Fluorine Chem.* **2001**, *112*, 69. (c) Kirsch, P.; Huber, F.; Krause, J.; Heckmeier, M.; Pauluth, D. U.S. Patent 20030230737 A1, December 2003. (d) Kirsch, P.; Bremer, M. *ChemPhysChem* **2010**, *11*, 357.

(7) (a) Zupan, M.; Pollak, A. *J. Org. Chem.* **1974**, *39*, 2646. (b) York, C.; Prakash, G. K. S.; Olah, G. a. *J. Org. Chem.* **1994**, *59*, 6493. (c) Singh, R. P.; Majumder, U.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 6263. (d) Chang, Y.; Tewari, A.; Adi, A.-I.; Bae, C. *Tetrahedron* **2008**, *64*, 9837. (e) Gatenyo, J.; Rozen, S. *J. Fluorine Chem.* **2009**, *130*, 332.

(8) (a) Zhu, J.; Ni, C.; Gao, B.; Hu, J. *J. Fluorine Chem.* **2015**, *171*, 139. (b) Watanabe, Y.; Konno, T. *J. Fluorine Chem.* **2015**, *174*, 102.

(9) Saijo, H.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2014**, *136*, 15158.

(10) (a) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chem.* **2013**, *5*, 941. (b) Tredwell, M.; Preshlock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2014**, *53*, 7751. (c) Emer, E.; Twilton, J.; Tredwell, M.; Calderwood, S.; Collier, L. T.; Liégault, B.; Taillefer, M.; Gouverneur, V. *Org. Lett.* **2014**, *16*, 6004.

(11) CCDC 1401715. (a) Cosier, J.; Glazer, A. M. *J. Appl. Crystallogr.* **1986**, *19*, 105. (b) Otwinowski, Z.; Minor, W. *Macromolecular Crystallography Part A*; Carter, C. W., Jr.; Sweets, R. M., Eds.; Methods in Enzymology; Academic Press: New York, 1997; Vol. *276*, p 307. (c) Palatinus, L.; Chapuis, G. *J. Appl. Crystallogr.* **2007**, *40*, 786. (d) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487. (d) Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, *43*, 1100. (e) Parois, P.; Cooper, R. I.; Thompson, A. L. *Chem. Cent. J.* **2015**, *9*, 30. (f) Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2011**, *44*, 1017.

(12) For details, see the Electronic Supporting Information.

(13) 4-(1,2,2,2-Tetrafluoro-ethyl)-1,1′-biphenyl is likely formed by regioselective addition of fluoride onto 4-(1,2,2-trifluorovinyl)-1,1′-biphenyl, a product resulting from competitive elimination.

(14) The formation of side-product **5a** for these reactions performed in the absence of copper iodide indicates that the substrate can serve as the source of iodine.

(15) Chen, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 11628.

(16) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524.

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Org. Lett. 2015, 17, 3466−3469