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Copper-mediated Fluorination of Aryl Trisiloxanes with Nucleophilic Fluoride

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Abstract

A method for the nucleophilic fluorination of heptamethyl aryl trisiloxanes to form fluoroarenes is reported. The reaction proceeds in the presence of $Cu(OTf)_2$ and KHF_2 as the fluoride source under mild conditions for a broad range of heptamethyltrisiloxyarenes with high functional group tolerance. The combination of this method with the silylation of aryl C–H bonds enables the regioselective fluorination of non-activated arenes controlled by steric effects following a two-step protocol.

Graphical Abstract

Keywords

fluorination; aryl silanes; copper; nucleophilic fluoride; fluoroarenes

The distinctive properties of aryl fluorides, which lead to applications in pharmaceuticals,[1] agrochemicals,[2] and positron emission tomography (PET) agents,[3] have prompted the development of synthetic methodologies for the formation of C_{sp2}–F bonds over the last decade.[4] While classical methods for the formation of bonds between an aryl group and fluorine involve the reaction of highly electron-deficient aryl halides or aryl diazonium reagents with fluoride salts,[5] the use of transition metals has recently enabled the development of more general alternatives to these methods starting from prefunctionalized substrates, such as aryl halides,[6] aryl triflates,[7[diaryl iodonium salts,[8] and phenols.[9] The regioselective direct fluorination of aryl C–H bonds has also been accomplished in the

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presence of transition metal complexes.[10] However, methods based on the functionalization of C-H bonds are typically limited to the preparation of *ortho*-fluorination products by coordination of the catalyst to a directing group. The undirected, electrophilic fluorination of aromatic C–H bonds has been realized with a palladium catalyst recently, but mixtures of constitutional isomers are often obtained.[11]

The direct fluorination of main group organometallic species, such as aryl stannanes, has been described with both electrophilic,[12] and nucleophilic fluorinating agents.[13] Nonetheless, the toxicity of the required organotin reagents limits the general applicability of these methods. The fluorination of boronic acid derivatives also has been developed with electrophilic fluorinating reagents in the presence of palladium,[14] silver,[15] and copper complexes,[16] and with nucleophilic fluorinating reagents in the presence of copper(II).[17] Arylsilanes represent an attractive alternative to arylboronic acid derivatives because they are derived from inexpensive reagents, are nontoxic, and are more stable than their organoboron counterparts. However, the direct fluorination of arylsilanes is less developed. The first examples of fluorination of arylsilanes were reported by Jolly in 1984 and Angelini in 1985, both with elemental fluorine for the labeling of arenes with ^{18}F.[18] In 2011, the fluorination of triethoxysilanes was described in the presence of silver(I) (Scheme 1),[19] and the fluorination of simple aryltrimethylsilanes was reported to occur, albeit with narrow scope, with XeF_2.[20]

Our group has developed Rh- and Ir-catalyzed silylations of aromatic C–H bonds with the arene as limiting reagent,[21] and developed methods for the trifluoromethylation[22] and amination[23] of the resulting arylsilanes. If the fluorination of the type of arylsilane that forms by the silylation of C-H bonds, with common nucleophilic fluoride sources could be developed, then a process for the fluorination of aryl C-H bonds via silylarenes would result. Herein, we report a method for the fluorination of stable aryl heptamethyl trisiloxanes, which are readily accessible by C–H silylation. These $Cu(OTf)_2$-mediated fluorinations occur with KHF_2 as the fluorine source under mild conditions (65 °C, 16 h) and with a broad scope of aryl groups on the silane. When combined with C–H bond silylation, this protocol gives access to fluoroarenes directly from non-activated arenes in a regioselective fashion.

Earlier reports on the reductive elimination from high valent Cu(III) species[6a,b,8a,12b,16,24] prompted our search for copper reagents and fluoride sources that would enable the fluorination of arylsilanes. For the development of such a reaction, we selected 3,5-substituted arylsilane **1a**, due to its high stability and ease of preparation on a multi-gram scale. A range of common fluoride sources were initially tested at 120 °C in the presence of an excess of $Cu(OTf)_2$. While the use of alkali metal fluorides led exclusively to the protodesilylation of **1a**, trace amounts of the fluorinated arene **2a** were observed in the presence of KHF_2 (Table 1, entry 1). Reactions at lower temperatures resulted in higher yields of **2a**, which reached a maximum at 65 °C (Table 1, entries 2–4). Reactions conducted with various copper(I) and copper(II) sources as well as additives including bases, oxidants, or nitrogen-containing ligands occurred in the same or lower yield,[25] and low yields of the aryl fluoride were obtained in any solvent other than acetonitrile. In sharp contrast, reactions with amounts of $Cu(OTf)_2$ and KHF_2 up to 6.0 equiv (Table 1, entries 6–7) gave higher yields of **2a** (74%). Reactions conducted with the same amount of other Cu(I) and Cu(II)

sources (Table 1, entry 8–9) or 6.0 equiv of other fluoride sources under the same reaction conditions gave lower yields of the aryl fluoride **2a** (Table 1, entries 10–11).[25] Like prior work on the fluorination of arylstannanes and boronates,[13, 17] superstoichiometric amounts of $Cu(OTf)_2$ and the fluoride source were necessary for the fluorination of arylsilanes to proceed in satisfactory yields, suggesting that a similar reaction mechanism is followed.[25]

The scope of arylsilanes that form the corresponding fluoroarenes under the developed reaction conditions is shown in Table 2. The process tolerates variation in the electronic properties of the arene; both electron-rich and electron-deficient arylsilanes reacted to give the fluoroarene in moderate to good yields. Substrates functionalized with halides (**2a,c,n**), esters (**2e**,**k,m,q**), ketones (**2f**), aldehydes (**2g**), ethers (**2h**), nitriles (**2j**), sulfones (**2l**), trifluoromethyl groups (**2i,o**) and imides (**2p**) converted to the corresponding fluoroarenes. In the case of non-volatile fluoroarenes (**2d-f**, **2j-l**, **2p**), these products were isolated in pure form in yields comparable to those calculated by NMR spectroscopy using an internal standard. Furthermore, reactions conducted at 0.10 and 1.00 mmol scale provided comparable yields of the fluorinated arenes as illustrated for **2n**. Unfortunately, the fluorination of heteroaromatic substrates did not occur.

With a procedure identified to convert aryl disiloxymethylsilanes to aryl fluorides, we considered that a tandem silylation-fluorination sequence could enable the overall fluorination of C–H bonds. To illustrate the potential of this two-step protocol, the fluorination of the natural product *O*-methylmellenine (**3**) was conducted. The reaction of this arene with heptamethyl trisiloxane in the presence of the recently reported[26] iridium catalyst containing 2,9-dimethyl phenanthroline in an open system for the silylation of more electron-rich arenes gave the silylarene intermediate, and treatment with KHF_2 and $Cu(OTf)_2$ formed the previously unreported fluorinated derivative **2q** (Scheme 2a).[27] No purification of the arylsilane was required in this sequence. A similar two-step protocol for the fluorination of dimethyl naphthalene-2,3-dicarboxylate (**1k**), but with the first-generation iridium catalyst, gave the fluoroarene **2k** in a yield over two steps that was comparable to that obtained for the individual steps combined (Scheme 2b). This sequence therefore represents a simple strategy for a sequential *meta*-selective fluorination of aryl C–H bonds.

In summary, we have developed an operationally simple and direct method for the copper-mediated fluorination of arylsilanes to fluoroarenes with KHF_2. This reaction occurs with readily available reagents under mild conditions. Electron-rich, electron-deficient and diversely functionalized arylsilanes undergo fluorination in moderate to good yield. A sequential process allows the regioselective fluorination of aryl C–H bonds via the arylsilane with exquisite regioselectivity, which we also showed in the context of natural product derivatization. Methods for a related fluorination of heteroaryl silanes will be part of future studies.

Experimental Section

Inside a glovebox filled with N_2, a 4 mL vial was charged with anhydrous KHF_2 (46.9 mg, 0.600 mmol, 6.00 equiv), anhydrous MeCN (1.0 mL), arylsilane (0.1 mmol, 1 equiv), and anhydrous $Cu(OTf)_2$ (217 mg, 0.600 mmol, 6.00 equiv). The vial was sealed with a Teflon-

lined cap, and the suspension was heated at 65 °C for 16 h. The resulting mixture was allowed to cool to room temperature. 1-Fluoro-3-nitrobenzene was added as internal standard, and the reaction was analyzed by ^{19}F NMR spectroscopy. For volatile products, the identity was confirmed by GC-MS. The reaction mixture of non-volatile products was diluted with Et_2O (2 mL) and washed with a saturated solution of NH_4OH (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 mL), and the combined organic layers were dried over Na_2SO_4. The organic layers were filtered through a short pad of SiO_2, the SiO_2 was flushed with CH_2Cl_2, and the resulting solution was concentrated under reduced pressure. The product was purified by preparative thin layer chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

[1]. a)Purser S, Moore PR, Swallow S, Gouverneur V, Chem. Soc. Rev 2008, 37, 320–330. [PubMed: 18197348] b)Hagmann WK, J. Med. Chem 2008, 51, 4359–4369. [PubMed: 18570365]

[2]. Jeschke P, ChemBioChem 2004, 5, 570–589.

[3]. Ametamey SM, Honer M, Schubiger PA, Chem. Rev 2008, 108, 1501–1516. [PubMed: 18426240]

[4]. Selected Reviews:a)O'Hagan D, Chem. Soc. Rev 2008, 37, 308–319. [PubMed: 18197347] b)Campbell MG, Ritter T, Chem. Rev 2015, 115, 612–633. [PubMed: 25474722] c)Champagne PA, Desroches J, Hamel JD, Vandamme M, Paquin JF, Chem. Rev 2015, 115, 9073–9174. [PubMed: 25854146] d)Furuya T, Klein JEMN, Ritter T, Synthesis. 2010, 10, 1804–1821.e)Liang T, Neumann CN, Ritter T, Angew. Chem. Int. Ed 2013, 52, 8214–8264.f)Brown JM, Gouverneur V, Angew. Chem. Int. Ed 2009, 48, 8610–8614.g)Furuya T, Kamlet AS, Ritter T, Nature 2011, 473, 470–477. [PubMed: 21614074] h)Hollingworth C, Gouverneur V, Chem. Commun 2012, 48, 2929–2942.

[5]. a)Adams DJ, Clark JH, Chem. Soc. Rev 1999, 28, 225–231.b)Swain CG, Rogers RJ, J. Am. Chem. Soc 1975, 97, 799–800.

[6]. a)Lee E, Hooker JM, Ritter T, J. Am. Chem. Soc 2012, 134, 17456–17458. [PubMed: 23061667] b)Casitas A, Canta M, Solà M, Costas M, Ribas X, J. Am. Chem. Soc 2011, 133, 19386–19392. [PubMed: 22026511] c)Fier PS, Hartwig JF, J. Am. Chem. Soc 2012, 134, 10795–10798. [PubMed: 22709145] d)Lee HG, Milner PJ, Buchwald SL, J. Am. Chem. Soc 2014, 136, 3792–3795. [PubMed: 24559304]

[7]. a)Watson DA, Su M, Teverovskiy G, Zhang Y, Garcia-Fortanet J, Kinzel T, Buchwald SL, Science 2009, 325, 1661–1664. [PubMed: 19679769] b)Maimone TJ, Milner PJ, Kinzel T, Zhang Y, Takase MK, Buchwald SL, J. Am. Chem. Soc 2011, 133, 18106–18109. [PubMed: 21999801] c)Noël T, Maimone TJ, Buchwald SL, Angew. Chem. Int. Ed 2011, 50, 8900–8903.

[8]. a)Ichiishi N, Canty AJ, Yates BF, Sanford MS, Org. Lett 2013, 15, 5134–5137. [PubMed: 24063629] b)Wang B, Qin L, Neumann KD, Uppaluri S, Cerny RL, DiMagno SG, Org. Lett 2010, 12, 3352–3355. [PubMed: 20617820]

[9]. a)Tang P, Wang W, Ritter T, J. Am. Chem. Soc 2011, 133, 11482–11484. [PubMed: 21736304] b)Fujimoto T, Ritter T, Org. Lett 2015, 17, 544–547. [PubMed: 25619627]

[10]. a)Hull KL, Anani WQ, Sanford MS, J. Am. Chem. Soc 2006, 128, 7134–7135. [PubMed: 16734446] b)Wang X, Mei TS, Yu JQ, J. Am. Chem. Soc 2009, 131, 7520–7521. [PubMed:

19435367] c)Chan KSL, Wasa M, Wang X, Yu JQ, Angew. Chem. Int. Ed 2011, 50, 9081–9084.d)Lou SJ, Xu DQ, Xu ZY, Angew. Chem. Int. Ed 2014, 53, 10330–10335.e)Testa C, Gigot É, Genc S, Decréau R, Roger J, Hierso JC, Angew. Chem. Int. Ed 2016, 55, 5555–5559.f)Truong T, Klimovica K, Daugulis O, J. Am. Chem. Soc 2013, 135, 9342–9345. [PubMed: 23758609]

[11]. Yamamoto K, Li J, Garber JAO, Rolfes JD, Boursalian GB, Borghs JC, Genicot C, Jacq J, Van Gastel M, Neese F, Ritter T, Nature 2018, 554, 511–514. [PubMed: 29469096]

[12]. a)Tang P, Furuya T, Ritter T, J. Am. Chem. Soc 2010, 132, 12150–12154. [PubMed: 20695434] (b)Ye Y, Sanford MS, J. Am. Chem. Soc 2013, 135, 4648–4651. [PubMed: 23485148]

[13]. a)Gamache RF, Waldmann C, Murphy JM, Org. Lett 2016, 18, 4522–4525. [PubMed: 27571319] b)Makaravage KJ, Brooks AF, Mossine AV, Sanford MS, Scott PJH, Org. Lett 2016, 18, 5440–5443. [PubMed: 27718581]

[14]. a)Furuya T, Ritter T, J. Am. Chem. Soc 2008, 130, 10060–10061. [PubMed: 18616246] b)Furuya T, Kaiser HM, Ritter T, Angew. Chem. Int. Ed 2008, 47, 5993–5996.c)Mazzotti AR, Campbell MG, Tang P, Murphy JM, Ritter T, J. Am. Chem. Soc 2013, 135, 14012–14015. [PubMed: 24040932]

[15]. Furuya T, Ritter T, Org. Lett 2009, 11, 2860–2863. [PubMed: 19507870]

[16]. Fier PS, Luo J, Hartwig JF, J. Am. Chem. Soc 2013, 135, 2552–2559. [PubMed: 23384209]

[17]. Ye Y, Schimler SD, Hanley PS, Sanford MS, J. Am. Chem. Soc 2013, 135, 16292–16295. [PubMed: 24160267]

[18]. a)Di Raddo P, Diksic M, Jolly D, J. Chem. Soc. Chem. Commun 1984, 159–160.b)Speranza M, Shiue CY, Wolf AP, Wilbur DS, Angelini G, G. J. Fluorine Chem 1985, 30, 97–107.

[19]. Tang P, Ritter T, Tetrahedron 2011, 67, 4449–4454. [PubMed: 21691436]

[20]. Lothian AP, Ramsden CA, Shaw MM, Smith RG, Tetrahedron 2011, 67, 2788–2793.

[21]. a)Chen C, Hartwig JF, Science 2014, 343, 853–857. [PubMed: 24558154] b)Cheng C, Hartwig JF, J. Am. Chem. Soc 2014, 136, 12064–12072. [PubMed: 25082802] c)Cheng C, Hartwig JF, J. Am. Chem. Soc 2015, 137, 592–595. [PubMed: 25514197]

[22]. Morstein J, Hou H, Cheng C, Hartwig JF, Angew. Chem. Int. Ed 2016, 55, 8054–8057.

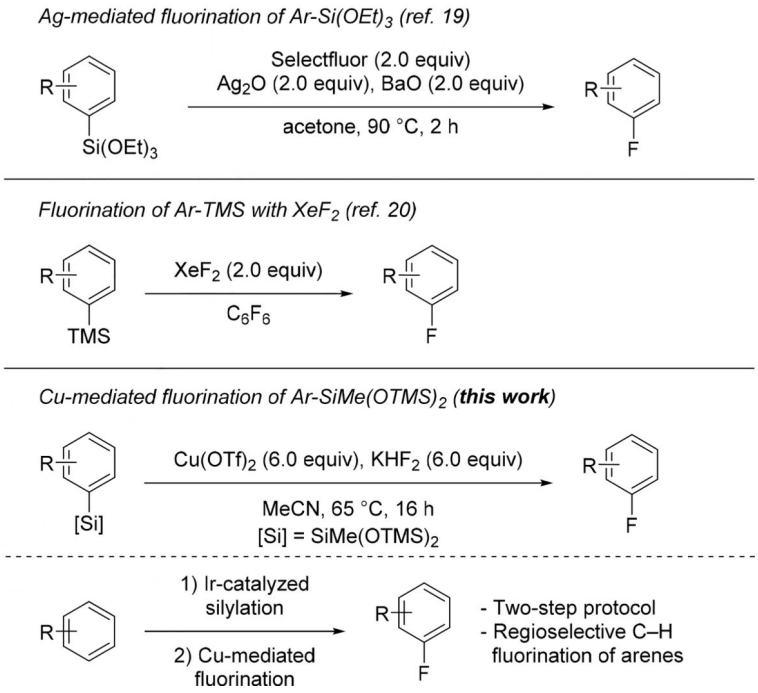
[23]. Morstein J, Kalkman ED, Cheng C, Hartwig JF, Org. Lett 2016, 18, 5244–5247. [PubMed: 27689746]

[24]. a)Casitas A, Ribas X, Chem. Sci 2013, 4, 2301–2318.b)Hickman AJ, Sanford MS, Nature 2012, 484, 177–185. [PubMed: 22498623]

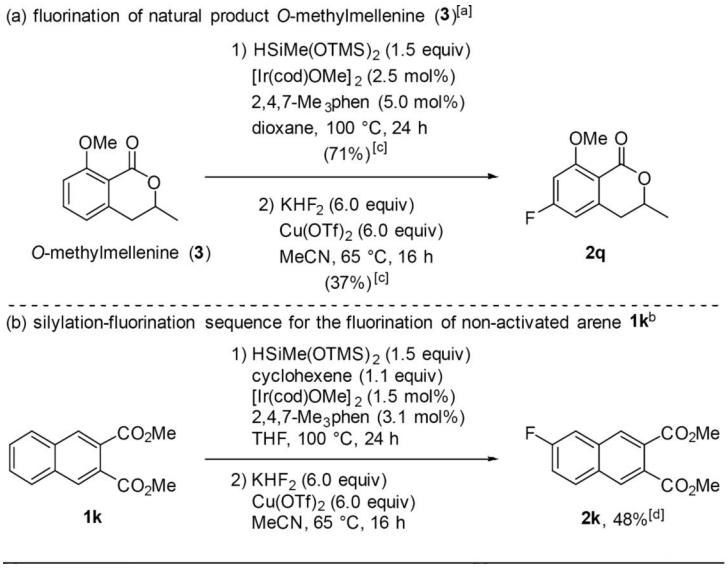
[25]. See Supporting Information for details.

[26]. Karmel C, Chen Z, Hartwig JF, J. Am. Chem. Soc 2019, 141, 7063–7072. [PubMed: 30971087]

[27]. Trita AS, Biafora A, Pichette Drapeau M, Weber P, Gooßen LJ, Angew. Chem. Int. Ed 2018, 57, 14580–14584.



Scheme 1.
Fluorination of Arylsilanes.



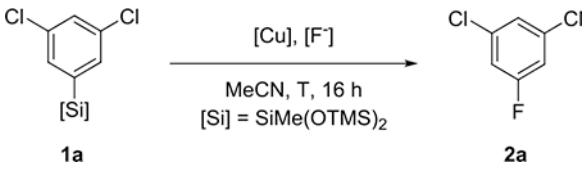
Scheme 2.

Fluorination of C-H bonds by a combination of iridium-catalyzed arene silylation and fluorination of the arylsilane.

[a]Reaction was performed with 0.1 mmol of **1q**. [b] Reaction sequence was performed with 0.3 mmol of dimethyl naphthalene-2,3-dicarboxylate. [c] Isolated yield in parentheses. [d] yields determined by ^{19}F NMR spectroscopy with fluorobenzene as an internal standard.

Table 1.

Effect of Reaction Parameters on the Fluorination of Arylsilanes.[a]



1a **2a**

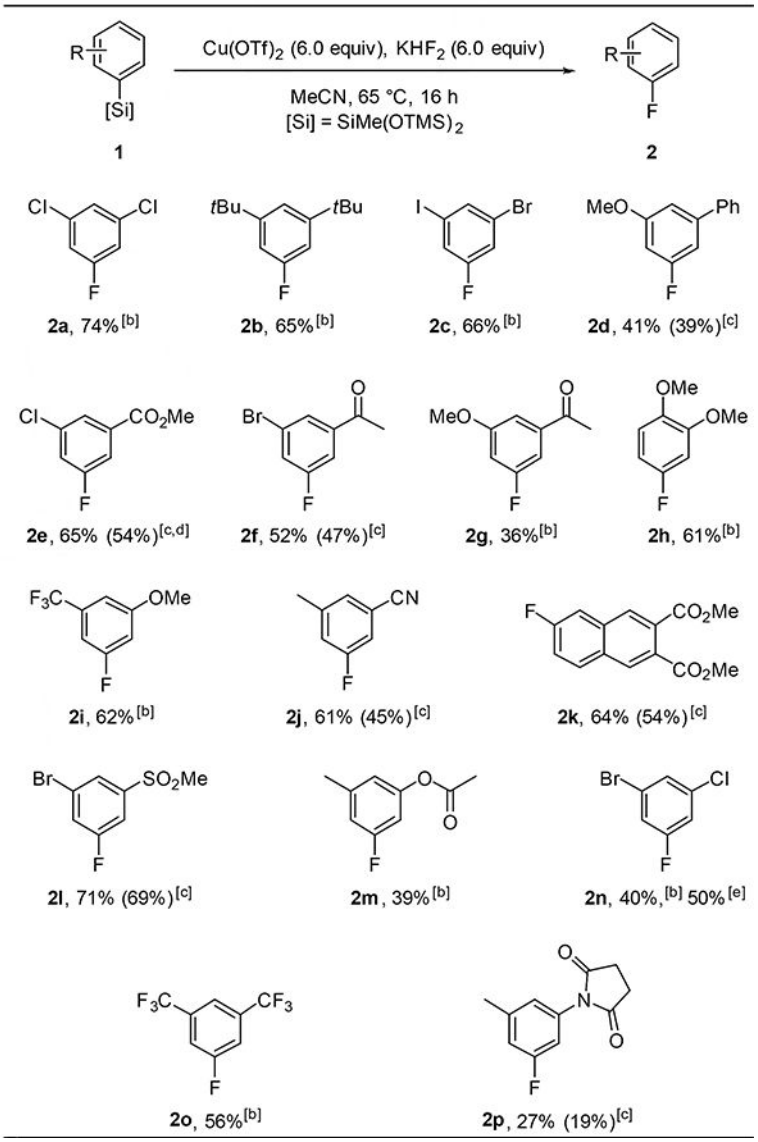
Entry	[Cu] (equiv)	[F⁻] (equiv)	T [°C]	Yield (%)[b]
1	$Cu(OTf)_2$ (3.0)	KHF_2 (4.0)	120	trace
2	$Cu(OTf)_2$ (3.0)	KHF_2 (4.0)	80	25
3	$Cu(OTf)_2$ (3.0)	KHF_2 (4.0)	65	40
4	$Cu(OTf)_2$ (3.0)	KHF_2 (4.0)	50	trace
5	$Cu(OTf)_2$ (2.0)	KHF_2 (4.0)	65	trace
6	$Cu(OTf)_2$ (6.0)	KHF_2 (4.0)	65	60
7	$Cu(OTf)_2$ (6.0)	KHF_2 (6.0)	65	74
8	CuF_2 (6.0)	KHF_2 (6.0)	65	0
9	(^{t}BuCN)CuOTf (6.0)	KHF_2 (6.0)	65	0
10	$Cu(OTf)_2$ (6.0)	AgF (6.0)	65	0
11	$Cu(OTf)_2$ (6.0)	CsF (6.0)	65	23

[a] Reactions run on a 0.05 mmol scale.

[b] Determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as internal standard.

Table 2.

Copper-mediated Fluorination of Arylsilanes.[a]



[a]Reactions were performed with 0.1 mmol of **1** to determine yields by ^{19}F NMR spectroscopy with fluorobenzene as an internal standard added after the reaction.

[b]Yield represents an average of two runs.

[c]Isolated yield in parentheses.

[d]Isolated with 4% of protodesilylated product.

[e]Reaction was performed on 1.00 mmol scale.