Cross-Coupling

Deutsche Ausgabe: DOI: 10.1002/ange.201601163
Internationale Ausgabe: DOI: 10.1002/anie.201601163

Trifluoromethylation of Arylsilanes with [(phen)$CuCF_3$]

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Abstract: *A method for the trifluoromethylation of arylsilanes is reported. The reaction proceeds with [(phen)$CuCF_3$] as the CF_3 source under mild, oxidative conditions with high functional-group compatibility. This transformation complements prior trifluoromethylation of arenes in several ways. Most important, this method converts arylsilanes formed by the silylation of aryl C–H bonds to trifluoromethylarenes, thereby allowing the conversion of arenes to trifluoromethylarenes. The unique capabilities of the reported method are demonstrated by the conversion of a C–H bond into a C–CF_3 bond in active pharmaceutical ingredients which do not undergo this overall transformation by alternative functionalization processes, including a combination of borylation and trifluoromethylation.*

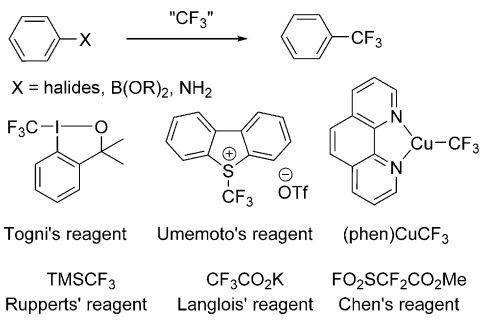
Fluoroalkyl substituents modulate physicochemical properties, metabolic stability, and protein–ligand interactions.[1] For this reason, approximately 30% of the most recently approved drugs contain fluorine, and nearly half of these fluorinated molecules contain a trifluoromethyl group.[2] Yet, most commercial syntheses of trifluoromethylarenes still rely on Swarts reactions[3] of benzotrichlorides with HF and SF_5 under harsh conditions, and are unsuitable for transformations of molecules containing most functional groups. Most commercial syntheses of trifluoromethyl heteroarenes are conducted by condensation reactions of trifluoroacetic acid derivatives.[4] Although milder than the Swarts reactions, these methods limit the position on the heteroarene at which a trifluoromethyl group can be installed. In both cases, these methods require that the trifluoromethyl group be installed early in a synthetic sequence.

More recently, arylboron reagents have been shown to undergo copper-mediated, oxidative trifluoromethylation reactions.[5–11] The ability to form trifluoromethylarenes from arylboronates is important because the arylboronates can be formed by metal-catalyzed borylation of aryl C–H bonds, which occurs with regioselectivities that are controlled by the steric environment at the aryl C–H bonds.[12,13]

Yet, organosilanes would be attractive alternatives to arylboronates as precursors to trifluoromethylarenes because silanes are inexpensive[14] and because arylsilanes and heteroarylsilanes are more stable than their boronate counterparts.[15] Recent advances in the regioselective, catalytic silylation of C–H bonds in unactivated arenes and heteroarenes have greatly expanded the accessibility of arylsilanes.[16–19] The silylation of C–H bonds forms arylsilanes with regioselectivities that are enhanced or distinct from those of the borylation of C–H bonds.[17,20] The greater selectivity and stability enables the late-stage functionalization of arenes and heteroarenes in complex molecules to form arylsilane intermediates when the arylboronate analogues are unstable. Thus, if a method to convert arylsilanes into trifluoromethyl arenes could be developed, a method to prepare trifluoromethylarenes from a wide range of arenes and heteroarenes, via the products of C–H bond silylation, would result.

We report the trifluoromethylation of readily accessible, stable arylsilanes. These reactions occur with [(phen)$CuCF_3$] as the CF_3 source and air as the oxidant. The reactions occur with a broad scope of arenes, heteroarenes, and active pharmaceutical ingredients and, when combined with C–H bond silylation, provide access to trifluoromethylarenes directly from both simple and complex arenes.

To initiate our search for reagents and conditions which lead to the trifluoromethylation of arylsilanes, we investigated reaction conditions reported for the trifluoromethylation of arylboranates.[5–11] We tested this reaction with $PhSiMe(OSiMe_3)_2$ (Ph-HMTS for phenyl heptamethyltrisiloxane) because Ar–HMTS compounds can be formed by the silylation of aryl and heteroaryl C–H bonds. A range of common trifluoromethylation reagents, including both electrophilic CF_3 sources (Togni's reagent[21] and Umemoto's reagent[22]) and nucleophilic CF_3 sources (Ruppert's reagent,[23] Langlois' reagent,[24] Chen's reagent,[25] and [(phen)$CuCF_3$][26]; Scheme 1) were tested as the source of the CF_3 group. We conducted reactions with a series of fluoride sources to activate the arylsilane by forming a hypervalent silicon species. The identity of the source of fluoride is likely to be crucial for the activation of the silane. The fluoride must be sufficiently nucleophilic to add to the silicon, but it must not trigger rapid cleavage of the carbon–silicon bond. Most combinations of the sources of trifluoromethyl groups and fluoride we tested yielded either trace amounts or



Scheme 1. Common reagents for the trifluoromethylation of prefunctionalized arenes. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

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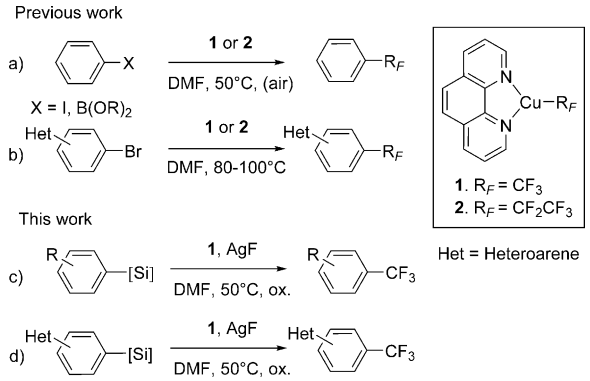
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201601163.

no desired product (see the Supporting Information for a list of these reaction conditions).

However, reactions of Ph–HMTS with [(phen)$CuCF_3$] (**1**) and KF in air formed the trifluoromethylarene product in a measurable yield (20%).[27] The [(phen)$CuCF_3$] is commercially available and is a free-flowing solid, which can be stored indefinitely under nitrogen and weighed in air. Our group previously reported the trifluoromethylation of aryl iodides,[26] aryl boronates,[27] and heteroaryl bromides[28] with **1** (Scheme 2 a,b). Thus, a convenient method to convert arylsilanes into trifluoromethylarenes would be created if the yields of this initial reaction could be improved.

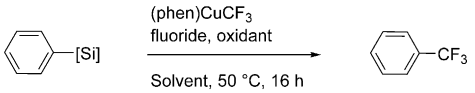


Scheme 2. Copper-mediated trifluoromethylation of arylsilanes. DMF = *N*,*N*-dimethylformamide.

Further studies showed that the trifluoromethylation of Ph–HMTS (Table 1) can occur in high yields with the proper fluoride source and solvent. The reactions with AgF under air occurred in higher yields than those with either KF, KHF_2, or TBAF. Interestingly, reactions in the presence of benzoquinone formed trifluoromethylbenzene in a higher yield (71%) than with air as an oxidant alone (62% yield). The same reaction with benzoquinone under nitrogen gave the product in 42% yield, thus suggesting that oxygen serves as the oxidant in this system.[29] Finally, an evaluation of these reaction conditions with a series of arylsilanes, including phenyl trimethylsilane, triphenyl silanol, and both dimethoxymethyl and trimethoxy phenylsilane (see the Supporting Information) showed that the yield of trifluoromethylbenzene was highest from the reaction of phenyl hepatmethyltrisiloxane.

With these reaction conditions in hand, we explored the scope of the trifluoromethylation of arylsilanes bearing the HMTS group (Table 2). The reaction of arylsilanes with

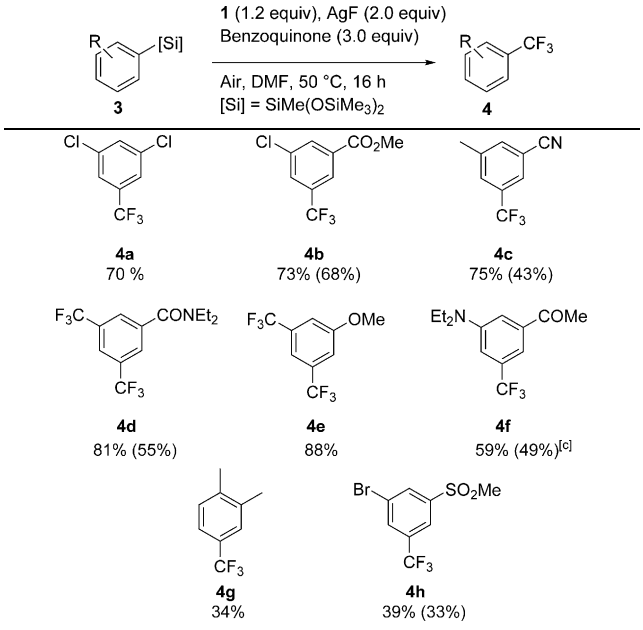
Table 1: Optimization of trifluoromethylation of $PhSiMe(OSiMe_3)_2$.[a]



Entry	Oxidant	Additive	Fluoride (2.0 equiv)	Solvent	Yield [%][b]
1	air	–	KF	DMF	20
2	air	–	KHF_2	DMF	38
3	air	–	AgF	DMF	62
4	air	–	TBAF	DMF	17
5	air	KOTMS (2.0 equiv)	–	DMF	–
6	–	–	KHF_2	DMF	8
7	air	–	AgF	DMSO	58
8	air	BQ (3.0 equiv)	AgF	DMF	71
9	–	BQ (3.0 equiv)	AgF	DMF	42

[a] Reactions run on a 0.1 mmol scale. [b] Determined by ^{19}F NMR spectroscopy with 4-trifluoromethoxyanisole as the internal standard. BQ = *p*-benzoquinone, TBAF = tetra-*n*-butylammonium fluoride.

Table 2: Trifluoromethylation of arylsilanes.[a,b]

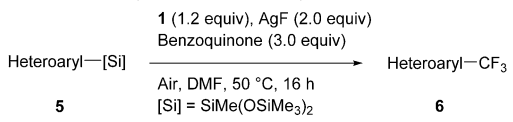


[a] Reactions run on a 0.1 mmol scale to determine yields by ^{19}F NMR spectroscopy and run on a 0.3 mmol scale to obtain yields of the isolated products. Yields determined by ^{19}F NMR spectroscopy are listed first followed by yields of isolated products within parentheses. [b] Determined by ^{19}F NMR spectroscopy with 4-trifluoromethoxyanisole as the internal standard. [c] Reaction run without benzoquinone.

1 tolerates a wide range of functional groups. Substrates bearing a chloride, ether, ketone, ester, amide, nitrile, or trifluoromethyl functionality (**3a–f**) gave the trifluoromethylarene in good yields. In general, the reactions of more electron-deficient arenes (**3a–e**) formed the trifluoromethylarene products in higher yields than did reaction with electron-rich arenes (**3g**). More specifically, the 3,4-dimethylphenylsilane gave the corresponding trifluoromethylxylene in a yield (34%) which was lower than that of most other examples. Reaction of a substrate containing a bromide substituent (**3h**) also gave the product in a moderate yield (39%), most likely because of competing trifluoromethylation at the aryl bromide.[30]

We subsequently explored the scope of the trifluoromethylation of heteroarylsilanes (Table 3). The reaction occurs with five-membered ring heteroarylsilanes, including benzofused examples, such as silylindoles. The reaction also occurs

Table 3: Trifluoromethylation of heteroarylsilanes.[a,b]



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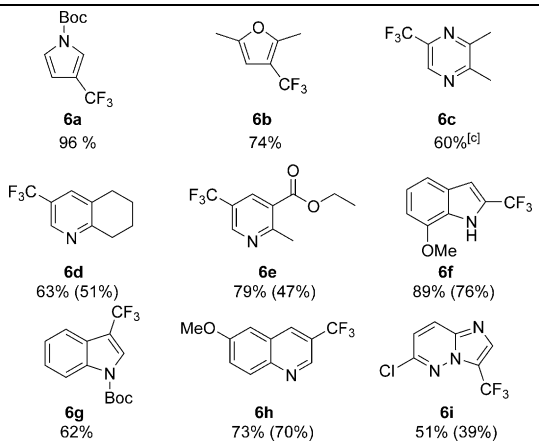
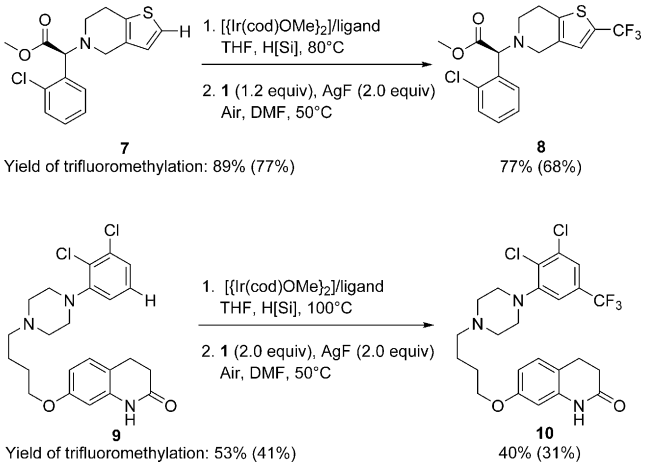


6a 96 % **6b** 74% **6c** 60%[c]
6d 63% (51%) **6e** 79% (47%) **6f** 89% (76%)
6g 62% **6h** 73% (70%) **6i** 51% (39%)

[a] Reactions run on a 0.1 mmol scale to determine yields by ^{19}F NMR spectroscopy and run on a 0.3 mmol scale to obtain yields of the isolated products. Yields determined by ^{19}F NMR spectroscopy are listed first followed by yields of isolated products within parentheses. [b] Determined by ^{19}F NMR spectroscopy with 4-trifluoromethoxyanisole as an internal standard. [c] Reaction run at 80 °C. Boc = *tert*-butoxycarbonyl.



7 Yield of trifluoromethylation: 89% (77%) **8** 77% (68%)

9 Yield of trifluoromethylation: 53% (41%) **10** 40% (31%)

Scheme 3. Late-stage trifluoromethylation of pharmaceutically active molecules. Yields determined by ^{19}F NMR spectroscopy (using 4-trifluoromethoxyanisole as an internal standard) are listed first followed by yields of isolated products given within parentheses. cod = 1,5-cyclootadiene.

with six-membered ring heteroarylsilanes, including those derived from pyridines, pyrazines, and quinolines. The ability to conduct the reaction with both electron-rich and electron-poor heteroarenes demonstrates the exceptionally broad scope of the reaction conditions we developed.

The trifluoromethylation of heteroarylsilanes is particularly valuable because heteroarylsilanes are less prone to oxidation and protodemetalation than are heteroarylboronates. For example, trifluoromethyl pyrazines (**6c**) cannot be prepared from an isolated heteroarylboronate because of rapid protodeborylation.[31] Moreover, the combination of C–H bond silylation and trifluoromethylation of the heteroarylsilane provides isomers which complement those generated from direct trifluoromethylation. For example, the reaction of **5a** gave 3-trifluoromethylpyrrole in an excellent yield (96 %), whereas direct trifluoromethylation with common trifluoromethylation reagents, such as Togni's reagent,[32] trifluoromethyliodide,[33] and Umemoto's reagent,[34] form the product from reaction at the 2′ position of pyrrole. Although the borylation of the Boc-protected pyrrole occurs at the 3′ position, the yields of trifluoromethyl pyrroles from the corresponding heteroarylboronates are below 50 %.[35]

Encouraged by the high functional-group tolerance and broad substrate scope of the trifluoromethylation of arylsilanes, we evaluated the applicability of our conditions to the late-stage trifluoromethylation of pharmaceutically active molecules (Scheme 3). We prepared analogues of clopidogrel (antiaggregant) and aripiprazole (antipsychotic) containing HMTS groups under the reaction conditions we reported previously.[18] Most striking, the trifluoromethylation of the silylated clopidogrel gave the corresponding trifluoromethylthiophene in good yield (89 %), tolerating all four functional groups present, with only minor epimerization of the stereocenter (3.8 % of **7** epimerized). The overall yield of **8** for the two-step sequence comprising silylation and trifluoromethylation was 77 % (68 % isolated, 95.1 % *ee*). Likewise, reaction of the silylated aripiprazole gave the corresponding trifluoromethylarene in 53 % yield (41 % isolated). The compounds **8** and **10** are not accessible by an analogous sequence comprising borylation and trifluoromethylation. The borylation of clopidogrel gave a mixture of constitutional isomers, as determined by GC and ^{11}B NMR spectroscopy. The borylated aripiprazole is unstable; this arylboronate decomposed during purification on silica gel.

In conclusion, we report the first method for the trifluoromethylation of arylsilanes. Trifluoromethylation of the arylsilanes with **1** proceeds with high functional-group compatibility, broad scope of arenes and heteroarenes, and is suitable for the functionalization of pharmaceutically active molecules. Furthermore, the trifluoromethylation of arylsilanes gives access to complex, trifluoromethylated molecules which are inaccessible by the sequence of borylation and trifluoromethylation.

Experimental Section

General procedure for the synthesis of trifluoromethyl arenes from arylsilanes with **1**: To an oven-dried 20 mL vial was added **1** (0.36 mmol, 1.2 equiv), anhydrous DMF (3.0 mL, stored under nitrogen), AgF (0.60 mmol, 2.0 equiv), *p*-benzoquinone (0.90 mmol, 3.0 equiv), and arylsilane (0.30 mmol, 1.0 equiv) under air. The suspension was purged with dry air for 30 seconds, and the vial was sealed with a Teflon-lined cap and heated at 50 °C for 16 h under vigorous stirring. The suspension was allowed to cool to room temperature. Water was added to the reaction mixture (5 mL), and the aqueous layer was extracted with diethylether (3 × 5 mL). The organic layers were combined, washed with a saturated NaCl solution (1 × 2 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography or preparative

thin layer chromatography. See the Supporting Information for detailed procedures.

Acknowledgments

We thank the NIH (GM-115812) for support of this work. J.M. thanks the German National Academic Foundation (Studienstiftung) for supporting his research in the Hartwig lab. We thank Michael Mormino for a sample of (phen)-$CuCF_3$, Jeff Pelton (UC Berkeley NMR facility) for expert technical assistance, and Johnson-Matthey for a gift of $[\{Ir(cod)Cl\}_2]$.

Keywords: arenes · copper · cross-coupling · fluorine · silanes

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8054–8057
Angew. Chem. **2016**, *128*, 8186–8189

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Received: February 1, 2016
Revised: April 10, 2016
Published online: May 23, 2016

