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

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Supporting Information Placeholder

**ABSTRACT:** The synthesis of arylCF$_3$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$_3$TMS) is a stable and easy to handle commercially available reagent widely employed for late stage trifluoromethylation. Metal-mediated cross-coupling strategies with this reagent have been extensively studied, more recently with a focus on copper-mediated processes with aryl halides. The use of this class of reagents to install extended perfluoroalkyl chains is limited to (pentafluoroethyl)trimethylsilane (CF$_3$F:TMS) and some selected studies employing more functionalized perfluorinated trimethylsilane derivatives (Scheme 1a). We noted a single example of a copper-mediated cross-coupling reaction of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silane (arylCF$_3$CF$_2$TMS) with 1-iodo-4-nitrobenzene, a reaction affording 1-(1,1,2,2-tetrafluoro-2-(4-nitrophenylethyl)-1H-pyrazole in 25 % yield. 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$_3$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 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. 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 1b, eq 2). Ogoshi et al. disclosed an elegant alternative strategy based on the generation of 2-aryl-1,1,2,2-tetrafluoroethylcopper complexes from [CuO$_2$Bu$_4$], tetrafluoroethylene (TFE) and arylboronic esters (Scheme 1b, 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$_2$Bu$_4$] precursor may be limiting as a glove box is preferable for handling. Our research program on Cu-mediated $^{19}$F-radiochemistry for Positron Emission Tomography (PET) applications is currently expanding with the development of new methodologies for the labeling of perfluorinated arenes. 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.

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 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.\textsuperscript{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.\textsuperscript{12}

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

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

\[ \text{Scheme 3. Synthesis and X-ray structure of [2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl][trimethyl]silane 1a.} \]

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.\textsuperscript{a}

| entry | fluoride source | solvent | additive | NMR ratio\textsuperscript{b} |
|-------|----------------|---------|----------|-----------------------------|
| 1     | KF             | DMF     | -        | 3aa/4aa/5aa/6aa             |
| 2     | KF             | NMP     | -        | 1.25                        |
| 3     | KF             | DMSC    | -        | 26:35:31:8                  |
| 4     | KF             | DMSO    | -        | 31:38:18:13                 |
| 5     | CaF            | DMSO    | -        | 36:38:15:11                 |
| 6     | AgF            | DMSO    | -        | 0:100:0:0                   |
| 7     | AgF            | DMSO    | -        | 53:18:19:10                 |
| 8     | AgF            | DMSO    | -        | 8:3:2:18                    |
| 9     | AgF            | DMSO    | -        | 8:5:3:21                    |
| 10    | AgF            | DMSO    | B(OMe)   | 37:25:25:12                 |
| 11    | AgF            | DMSO    | TMEDA    | 2:9:24:2                    |
| 12    | AgF            | DMSO    | Phen     | 5:26:12:13                  |
| 13    | AgF            | DMSO    | Bipy     | 47:10:30:13                 |
| 14    | AgF            | DMSO    | Bu-Bipy  | 64:14:5:16                  |
| 15    | AgF            | DMSO    | Py       | 63:11:21:13                 |
| 16    | AgF            | DMSO    | Py       | 73:5:19:1                   |
| 17    | AgF            | DMSO    | Py       | 63:6:27:4                   |
| 18    | AgF            | DMSO    | Py       | 76:5:13:5                   |
| 19    | AgF            | DMSO    | Py       | 60:20:18:2                  |

\textsuperscript{a} Standard conditions: 1.0 equiv 1-iodo-2-methoxy-4-nitrobenzene, 1.2 equiv 1a, 1.5 equiv fluoride source, 1.5 equiv of CuI, 1.5 equiv additive (if applicable), 0.25 M in solvent, 60 °C, 16 h. TMEDA = N,N,N,N,N,N-tetramethyl-1,2-ethylenediamine; Phen = 1,10-phenanthroline; Bipy = 2,2'-bipyridine; Bu-Bipy = 4,4'-dister-butyl-2,2'-bipyridine; Py = pyridine.\textsuperscript{b} Determined by \textsuperscript{19}F NMR by integration of the product peak(s) using PhCF\textsubscript{3} as the internal standard. Reaction with CuCl. Reaction with CuBr. 20 mol % of CuI. 5.0 equiv of pyridine. \textit{rt} for 6 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 18% of alkene 6a. A similar product distribution was obtained using NMP, but the use of DMSO proved beneficial (Table 1, entries 2–3). AgF\textsubscript{w} 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\textsubscript{3}TMS has been reported for other systems by Weng and co-workers.\textsuperscript{4e} Alternative sources of Cu(I) such as CuBr or CuCl were less effective (Table 1, entries 7–8).\textsuperscript{14} The reaction did proceed with a catalytic amount of CuI, however a substantial amount of by-product formation was observed (entry 9). Several additives were considered next. With the Ruppert-Prahask reagent CF\textsubscript{3}SiMe\textsubscript{2}, B(OMe)\textsubscript{3} was shown to stop the CF\textsubscript{3} anion in copper mediated cross-coupling, thus minimizing the formation of protodesilylated by-product;\textsuperscript{9} 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. 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), 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 sub-stoichiometric 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 substitu-

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

\[
\begin{align*}
\text{Ph}_3\text{C}-\text{CH} &= \text{Ar}^+ \quad \text{CuI (1.5 equiv)} \quad \text{AgF (1.5 equiv)} \\
\text{DMSO, 60 °C, 6 h} &= \text{Pyridine (0.5 equiv)} \\
\end{align*}
\]

- 3aa (78%, 60%\(^a\))
- 3ab (71%, 77%\(^b\))
- 3ac (86%, 51%\(^b\))
- 3ad (68%)
- 3ae (70%)
- 3af (70%)
- 3ag (79%, 65%\(^b\))
- 3ah (68%)
- 3ai (68%)
- 3aj (85%, 27%\(^b\))
- 3ak (79%, 66%\(^b\))
- 3al (72%)
- 3am (65%)
- 3an (65%)
- 3ao (55%)
- 3ap (65%)
- 3aq (85%, 27%\(^b\))
- 3ar (85%, 27%\(^b\))
- 3as (91%, 68%\(^b\))
- 3at (74%, 69%\(^b\))
- 3au (74%, 69%\(^b\))
- 3av (74%, 69%\(^b\))
- 3aw (74%, 69%\(^b\))
- 3ax (74%, 69%\(^b\))
- 3ay (74%, 69%\(^b\))
- 3az (74%, 69%\(^b\))
- 3ba (77%)
- 3bb (83%)
- 3bc (34%)
- 3bd (82%)
- 3be (70%)

\(^a\) 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.

were performed using CuI (1.5 equiv), AgF (1.5 equiv), 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-arylethenes from the reaction of stable arylCF\(_3\)C\(_6\)H\(_4\)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.

![Image](image-url)
However, improved routes towards aryl(CF$_3$)$_2$SiMe$_3$ will be necessary to 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. 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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(13) 4-(1,2,2-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.
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