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# Nickel-Catalyzed Monofluoroalkylation of Arylsilanes via Hiyama Cross-Coupling

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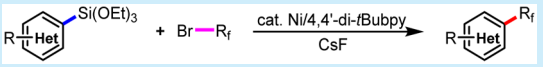
Supporting Information

**ABSTRACT:** The first example of nickel-catalyzed monofluoroalkylation of arylsilanes has been developed with readily available fluoroalkyl halides. This novel transformation has demonstrated high reactivity, broad substrate scope, excellent functional group tolerance, and mild reaction conditions. The selective activation of a relatively inert C−Si bond for slow release of aryl carbanion is the key reason for reducing the amount of arylmetal species, which makes this method more promising for fluorine-containing modification of complex bioactive molecules. Mechanistic investigations indicate that a free fluoroalkyl radical is involved in this catalytic cycle.

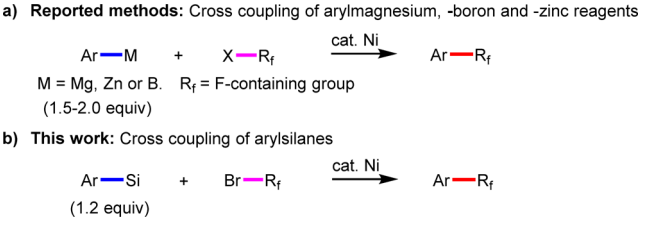



The selective incorporation of fluorine or fluorine-containing groups into organic molecules has emerged as a general and effective strategy in drug design and screening because the fluorinated compounds can often drastically enhance the metabolic stability, lipophilicity, and bioavailability of their parent molecules.[1] Among all intriguing fluoroalkylated moieties, the monofluoromethyl group ($CH_2F$) and its functionalized derivatives are widely found in many biologically active molecules as the essential motif[2] because the exchange of hydrogen by fluorine prevents the metabolic oxidation owing to the electron-withdrawing effect of fluorine and the strength of the C−F bond.[3] While a great number of methods for trifluoromethylation[4] and difluoroalkylation[5] of arenes have been well developed in recent decades, there are still few examples of transition-metal-promoted monofluoroalkylation.[6]

As recent research on catalysis in organic synthesis tends to move away from precious-metal catalysts, nickel has attracted increasing attention very recently as a more abundant and lower cost metal.[7] Accordingly, nickel-catalyzed fluoroalkylation of aryl- or alkylmetal species has recently been developed as a powerful tool to synthesize fluorine-containing compounds (Scheme 1). The coupling nucleophiles to construct fluorinated arenes were limited to arylmagnesium,[8] -boron,[9] or -zinc[10] species. However, the amount of such metal species needed as high as 1.5−2.0 equiv, probably because of the simultaneous aryl−aryl homocoupling side reactions. Thus, it hampered their practical use in organic synthesis, especially for the fluoroalkylation of complex molecules. Meanwhile, nickel-[11] palladium-[12] or copper-catalyzed[13] cross coupling of arylsilanes with organic halides, known as Hiyama coupling, has already been well developed as a highly efficient method to build C−C bonds selectively. As one part of our continuous efforts to develop transition-metal-catalyzed fluoroalkylations,[14] we envisioned that the selective activation of the much less polarized and relatively inert C−Si bond in arylsilanes will greatly inhibit the Ar−Ar homocoupling, thus allowing a reduction in the amount of arylmetal species that can broaden its potential applications on modification of complex bioactive molecules. Herein, we report the first example of nickel-catalyzed monofluoroalkylation of arylsilanes with readily available fluoroalkyl halides, in which high reactivity and broad substrate scope have been demonstrated. Meanwhile, to the best of our knowledge, there was still no report on fluoroalkylation via transition-metal-catalyzed Hiyama coupling.

Inspired by our previous research on nickel-catalyzed monofluoromethylation of arylboronic acids with activated fluoroalkylating reagents,[9g] we commenced our study with phenylsilyl ether **1a** as the pilot substrate and $EtO_2CFHBr$ **2** as the fluoroalkyl coupling partner in the presence of a catalytic amount of $Ni(dme)Cl_2$ (10 mol %) and 1,10-phenanthroline (**L1**, 12 mol %) in dioxane at 80 °C. Considering the key role of fluoride ion for activation of the inert C−Si bond, several fluorides have been used to start this coupling reaction via the attack on organosilicon compounds to form pentacoordinate species.[12] The desired monofluoroalkylated product **3a** was obtained smoothly in 22% yield when 2.0 equiv of CsF was used as the activator, while other fluorides gave almost none of the

**Scheme 1. Nickel-Catalyzed Fluoroalkylation of Arylmetal Species**

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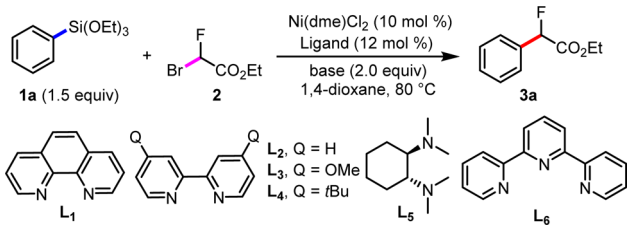
product (entry 1, Table 1). To improve the yield further, a variety of phosphine and diamine ligands were next examined. In

**Table 1. Optimization of Conditions**[a,b]



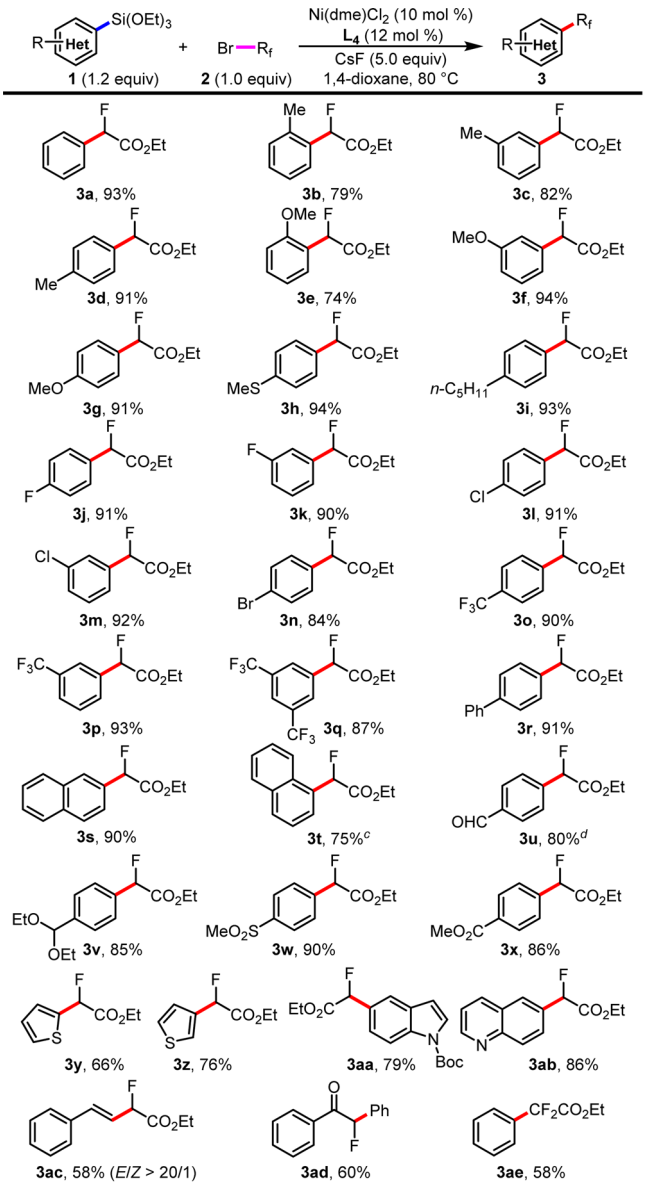

| entry | ligand | base | yield (%) |
|---|---|---|---|
| 1 | **L1** | CsF | 22 |
| 2 | **L2** | CsF | 26 |
| 3 | **L3** | CsF | 37 |
| 4 | **L4** | CsF | 45 |
| 5 | **L5** | CsF | 22 |
| 6 | TMEDA | CsF | 30 |
| 7 | **L6** | CsF | 0 |
| 8 | $PPh_3$ | CsF | 0 |
| 9 | dppp | CsF | 0 |
| 10 | **L4** | KF | 0 |
| 11 | **L4** | TBAF | 0 |
| 12 | **L4** | $K_2CO_3$ | 0 |
| 13 | **L4** | $Cs_2CO_3$ | 0 |
| 14 | **L4** | NaOH | 0 |
| 15[c] | **L4** | CsF | 37 |
| 16[d] | **L4** | CsF | 41 |
| 17[e] | **L4** | CsF | 30 |
| 18[f] | **L4** | CsF | 87 |
| 19[g] | **L4** | CsF | 90 |
| 20[h] | **L4** | CsF | 90 |
| 21[i] | **L4** | CsF | 96 (93)[j] |
| 22[k] | **L4** | CsF | 96 |
| 23[l] | **L4** | CsF | 96 (93)[j] |
| 24[m] | **L4** | CsF | 0 |
| 25[n] | **L4** | | 0 |
| 26[o] | | CsF | 0 |

[a]Unless otherwise noted, the reaction conditions were as follows: $EtO_2CCFHBr$ (0.2 mmol, 1.0 equiv), **1** (1.5 equiv), $Ni(dme)Cl_2$ (10 mol %), ligands (12 mol %), CsF (2.0 equiv), 1,4-dioxane, 80 °C, 24 h. [b]Yields determined by $^{19}F$ NMR using $CF_3Ph$ as an internal standard. [c]DCM was used as solvent. [d]THF was used as solvent. [e]DMF was used as solvent. [f]CsF (4.0 equiv). [g]CsF (5.0 equiv). [h]CsF (6.0 equiv). [i]1,4-Dioxane (2.5 mL). [j]Isolated yield. [k]1,4-Dioxane (3.0 mL). [l]**1a** (1.2 equiv) and 1,4-dioxane (2.5 mL). [m]Without $Ni(dme)Cl_2$. [n]Without CsF. [o]Without ligand. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

contrast to our previous report on nickel-catalyzed fluoroalkylation of arylboronic acids, in which phosphine ligands are the most effective,[9g] diamine ligands, including 1,10-phenanthroline, bipyridine and their derivatives, and TMEDA, afforded **3a** in up to 45% yield (entries 2−6), while di- and monophosphines and tpy ($L_6$) showed no catalytic activity at all (entries 7−9). Unfortunately, the replacement of CsF with other bases quenched the reaction completely. Furthermore, a careful survey of solvents (Table S3) was then performed, which showed dioxane was still the best choice. Notably, an increase of the amount of CsF to 5.0 equiv improved the yield greatly, and up to 93% yield was finally obtained when the reaction concentration was adjusted, and no reduction was observed even if the amount of arylsilane **1a** was decreased to 1.2 equiv (entry 23). Lastly, a control experiment indicated that none of the monofluoroalkylated product was obtained without the addition of nickel catalyst (entry 24).

With the optimized reaction conditions in hand, we next investigated the substrate scope of this nickel-catalyzed monofluoroalkylation of arylsilanes to provide a practical method for modification of complex bioactive molecules. As shown in Scheme 2, aryl silyl ethers with *para-*, *meta-*, and *ortho*-substituents are all compatible coupling partners, affording the corresponding monofluoroalkylated arenes in good to excellent yields. Arylsilanes installed with electron-donating groups were monofluoroalkylated smoothly to give the desired products with good yields (**3b−i**). A range of halogenated silyl ethers were also

**Scheme 2. Scope of Arylsilane Substrates**[a,b]




[a]Unless otherwise noted, the reaction conditions were as follows: $BrR_f$ (0.2 mmol, 1.0 equiv), **1** (1.2 equiv), $Ni(dme)Cl_2$ (10 mol %), **L4** (12 mol %), CsF (5.0 equiv), 1,4-dioxane (2.5 mL), 80 °C, 24 h. [b]Isolated yield. [c]2.0 equiv of **1t** was used, and the temperature was 100 °C. [d]2.0 equiv of **1u** was used.



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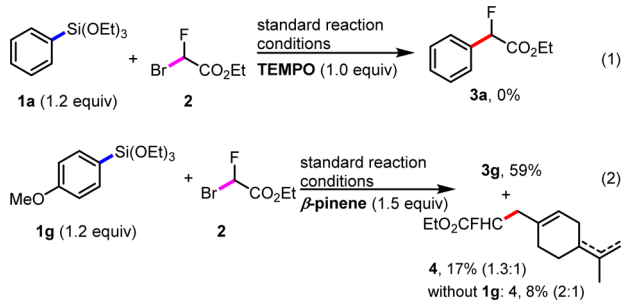
well-tolerated by this method (**3j**−**n**). The presence of halogen substituents in the products offered the synthetic potential for further elaboration via transition-metal-catalyzed coupling reactions. In particular, aryl silyl ethers containing electron-withdrawing groups, such as trifluoromethyl (**3o**−**q**), aldehyde (**3u**), sulfone (**3w**), and ester (**3x**), were fluoroalkylated successfully with pretty good yields in this catalytic system. In contrast, our previously reported nickel-catalyzed monofluoroalkylations using arylboronic acids as the coupling partners required higher catalyst and ligand loadings and batch addition of catalyst and substrates.[9g] Additionally, aryl silyl ethers derived from heteroarenes, including thiophene, indole, and even quinoline, were also monofluoroalkylated successfully, leading to **3y**, **3z**, **3aa**, and **3ab**, respectively, all in satisfactory yields under the standard reaction conditions. Notably, a styryl silane was also well tolerated in this transformation, giving the fluoroalkyl alkene **3ac** in moderate yield and excellent *E*/*Z* selectivity (>20/1). Most remarkably, some other available fluoroalkyl halides, such as *α*-bromo-*α*-fluoroacetophenone and bromodifluoroacetate, were also applicable to the reaction (**3ad**−**ae**).

To gain some insight into the mechanism of this transformation, a series of control experiments were then performed. First, the reaction was completely quenched when 1.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known free radical inhibitor, was added into the standard conditions (eq 1, Scheme 3). This observation is consistent with the reports that

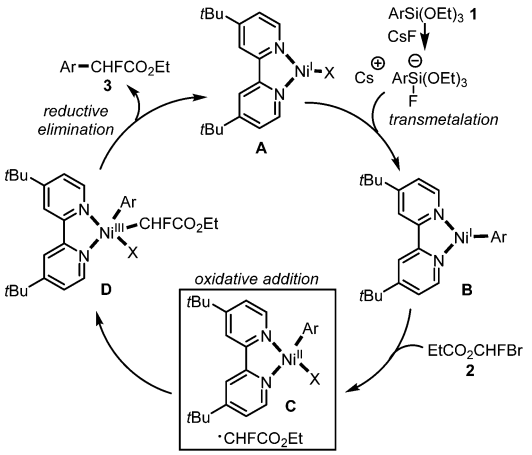
**Scheme 3. Radical-Trapping Experiments**




the oxidative addition step in the catalytic cycle of nickel-catalyzed cross-couplings proceeds via a radical pathway.[15] Meanwhile, the $EtCO_2CHF^{\bullet}$ radical was trapped successfully with *β*-pinene used as a radical scavenger under the standard conditions, affording the ring-opened diene **4** as an isomeric mixture (eq 2, Scheme 3) along with the desired fluoroalkylated product **3g**, which further implicated the generation of the monofluoroalkyl radical in the catalytic cycle.

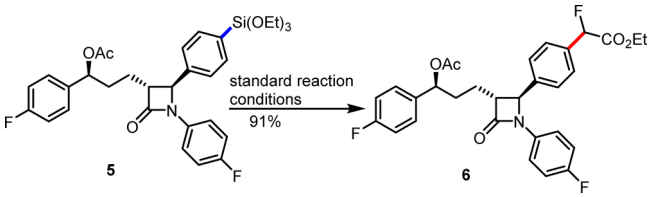
Although the definite mechanism of this transformation is still unclear at this stage, on the basis of our preliminary results and previous reports,[16] a plausible mechanism involving a Ni(I)/Ni(III) catalytic cycle is proposed as shown in Scheme 4. The Ni(I)−Ar species **B** can be generated via transmetalation between the initial Ni(I) species **A** with the arylsilane under the activation of CsF. Subsequently, Ni(I) species **B** activates $EtO_2CFHBr$ **2** via single-electron transfer (SET) to afford Ni(II) intermediate **C** and the fluoroalkyl radical, and Ni(III) species **D** is generated through the following oxidative radical addition of monofluoroalkyl radical to intermediate **C**. The final monofluoroalkylated product **3** is obtained after the reductive elimination from Ni(III) species **D**, and Ni(I) catalyst **A** is regenerated to complete the catalytic cycle.[17]

**Scheme 4. Plausible Mechanism**




To demonstrate both the functional group tolerance and the application prospect of this method, this novel transformation has also been attempted in the late-stage fluoroalkylation of a complex bioactive molecule. As shown in Scheme 5, the

**Scheme 5. Monofluoroalkylation of Ezetimibe Derivative**




arylsilane **5** derived from ezetimibe, a drug known to inhibit cholesterol absorption,[18] underwent fluoroalkylation to yield the monofluoroalkylated ezetimibe **6** smoothly in excellent yield (91%). This type of fluorine-containing modification shows great promise for drug discovery and development as a powerful tactic for fluorinated analogue synthesis.

In summary, we have developed the first example of monofluoroalkylation reaction of arylsilanes catalyzed by in situ generated nickel/4,4′-di*t*Bu-bpy complex. Both electron-rich and electron-deficient arylsilanes are found to be compatible with this new transformation under mild conditions. The reduction in the amount of arylmetal reagent makes this method promising for future applications in fluorine-containing modification of complex bioactive molecules. Mechanistic investigations indicate that a monofluoroalkyl radical is involved in the catalytic cycle. Further exploration of the mechanistic details of this transformation and the application of this novel tactic to the late-stage modification of complex molecules are ongoing in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02803.

Experimental procedure and characterization of all new compounds (PDF)



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### Notes

The authors declare no competing financial interest.

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