Base-Free Hiyama Coupling Reaction via a Group 10 Metal Fluoride Intermediate Generated by C−F Bond Activation

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Ⓢ Supporting Information

ABSTRACT: A Pd(0)-catalyzed Hiyama coupling reaction of tetrafluoroethylene (TFE) proceeded without the use of a base to give α,β,β-trifluorostyrene derivatives. A Ni(0)-catalyzed Hiyama coupling reaction of perfluoroarenes also occurred without a base. The key intermediate in these reactions would be a transition-metal fluoride complex that is generated in situ by the oxidative addition of a C−F bond.
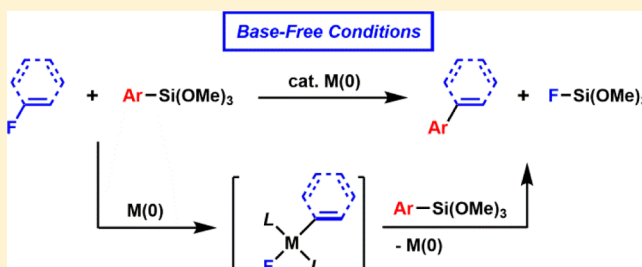
Among the transition-metal-catalyzed C−C bond formation reactions, the Hiyama coupling reaction of organic halides with organosilicon reagents has garnered a great deal of interest in recent years, due to the ease of preparation, stability, and environmentally benign nature of organosilicon reagents. Since the pioneering works accomplished by Hiyama, several groups have reported various modifications with functionalized organosilicon reagents.[1] These reactions generally require an activator to enhance the reactivity of an organosilicon reagent, which is achieved by the addition of a fluoride anion source such as TBAF. Recent developments have made this reaction possible with the aid of a Brønsted base instead of the fluoride anion.[1e,g,2] These methods are called "fluoride-free" Hiyama coupling reactions and have attracted much attention for decades. However, little is known about "base-free" Hiyama coupling reactions. To the best of our knowledge, base-free coupling reactions of organosilicon reagents have been achieved only while using allylic carbonate or vinyl oxirane as a substrate.[3] These reactions would proceed via (η^3-allyl)-palladium alkoxide intermediates, which are considered to be an activator for neutral organosilicon reagents. However, base-free reactions using alkenyl or aryl halides as substrates have not been reported, except for those using preliminarily activated organosilicon reagents.[4]

Our group has recently developed novel transformation reactions via C−F bond activation.[5] In 2013, we disclosed a base-free Suzuki−Miyaura coupling reaction using either fluoroalkenes or fluoroarenes.[5b] Although the Suzuki−Miyaura coupling reaction also generally requires some base as an activator, our reactions proceeded smoothly in the absence of any base. This is because the transition-metal fluoride key intermediate [L$_n$Tm-F], which is generated by the oxidative addition of a C−F bond, is reactive enough to undergo the transmetalation with neutral organoboron compounds. Also, transition-metal fluoride complexes are considered to have high

reactivity toward organosilicon reagents. In fact, the trans-metalation of a transition-metal fluoride complex with an organosilicon reagent [XSiR$_3$] (X = H, Cl, CF$_3$, etc.) is a well-established method for the synthesis of various kinds of transition-metal complexes [L$_n$Tm-X].[6] Although aryl group transfer (X = Ar) has remained less developed due to the relatively inert Si−C bond, Ball demonstrated the reaction of (IPr)CuF with ArSi(OMe)$_3$ for the synthesis of the corresponding organocopper reagents.[6d] Against the aforementioned research backgrounds, we assumed that the Hiyama coupling reaction via C−F bond activation could also proceed without the use of a base, because the transition-metal fluoride intermediate generated by the oxidative addition of a C−F bond would be sufficiently reactive toward neutral organosilicon reagents (Scheme 1).

Thus, the reactivity of trans-(PCy$_3$)$_2$Pd(F)(CF$_2$=CF) (1) toward organosilicon reagents was examined. We previously

Scheme 1. Base-Free Hiyama Coupling Reaction via a Transition-Metal Fluoride Key Intermediate
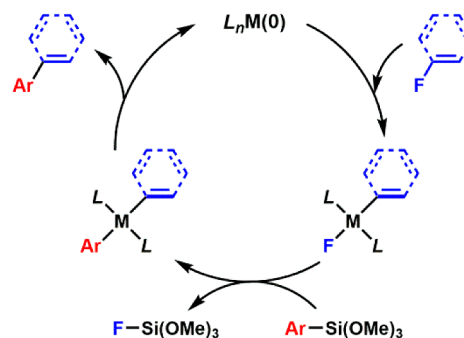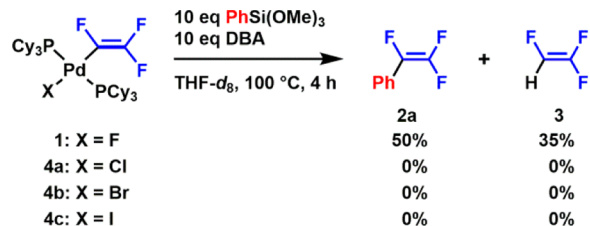
reported that **1** was generated by the oxidative addition of a C−F bond of tetrafluoroethylene (TFE) by heating at 100 °C.[5b] In the presence of dibenzylideneacetone (DBA), the reaction of **1** with an excess amount of PhSi(OMe)$_3$ occurred at 100 °C to give α,β,β-trifluorostyrene (**2a**) in 50% yield (Scheme 2). It

Scheme 2. Reactivity of 1 toward PhSi(OMe)$_3$

	2a	**3**
1: X = F	50%	35%
4a: X = Cl	0%	0%
4b: X = Br	0%	0%
4c: X = I	0%	0%

would be the result of transmetalation of PhSi(OMe)$_3$ with **1**, followed by reductive elimination. Undesired trifluoroethylene (**3**) was also observed in 35% yield, which would be generated via methoxy group transfer, followed by β-hydride elimination and reductive elimination.[7,8] In contrast, the corresponding palladium chloride (**4a**), bromide (**4b**), and iodide (**4c**) did not react with PhSi(OMe)$_3$ at all under the same reaction conditions. These results indicated that the fluoropalladium complex is reactive enough toward neutral organosilicon compounds, and that a fluorine atom bound to palladium plays an essential role in this transmetalation reaction.

Encouraged by the results of the stoichiometric reactions, we developed a Pd(0)-catalyzed base-free coupling reaction of TFE with PhSi(OMe)$_3$ (Table 1).[9,10] Reactions were conducted in a

Table 1. Pd(0)-Catalyzed Coupling Reaction of TFE[a]

run	ligand (amt (mol %))	additive (amt)	time (h)	yield (%)
1	PCy$_3$ (10)	none	25	73
2	PCyp$_3$ (5)	none	4	76
3	PCyp$_3$ (5)	FSi(OEt)$_3$ (10 mol %)	6	91
4	PCyp$_3$ (5)	TBAF (1 equiv)	6	0
5	PCyp$_3$ (5)	LiI (1 equiv)	6	0

[a]Yields were determined by ^{19}F NMR with PhCF$_3$ as an internal standard.

pressure-tight NMR tube and were monitored by ^{19}F NMR analysis. In the presence of 2.5 mol % of Pd$_2$(dba)$_3$(C$_6$H$_6$) and 10 mol % of PCy$_3$, the reaction of PhSi(OMe)$_3$ with TFE proceeded at 100 °C to afford **2a** in 73% yield without the use of either a fluoride anion or a Brønsted base (run 1). After a series of surveys of the reaction conditions, we found that a reaction using 5 mol % of PCyp$_3$ (Cyp = c-C$_5$H$_9$) as a ligand was faster than that using PCy$_3$ (run 2; see also the Supporting Information). In these catalytic reactions, only a small amount (~10%) of trifluoroethylene **3** was observed, unlike the case for the stoichiometric reaction shown in Scheme 2. The time−product yield curve of this catalytic reaction resembled that observed for an autocatalytic reaction (Figure 1A). The generation rate of **2a** was slow at the early stage of the reaction and then increased sharply at some point. We assumed the increase was caused by the fluorosilanes that were generated
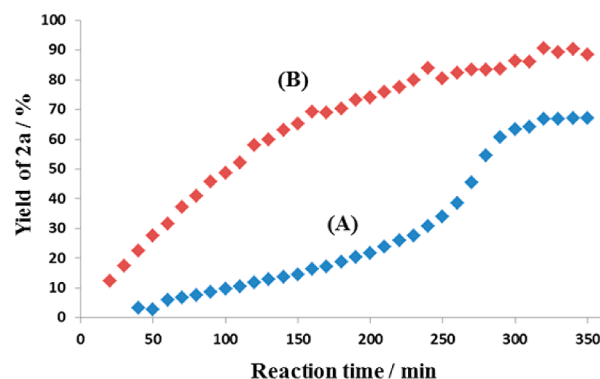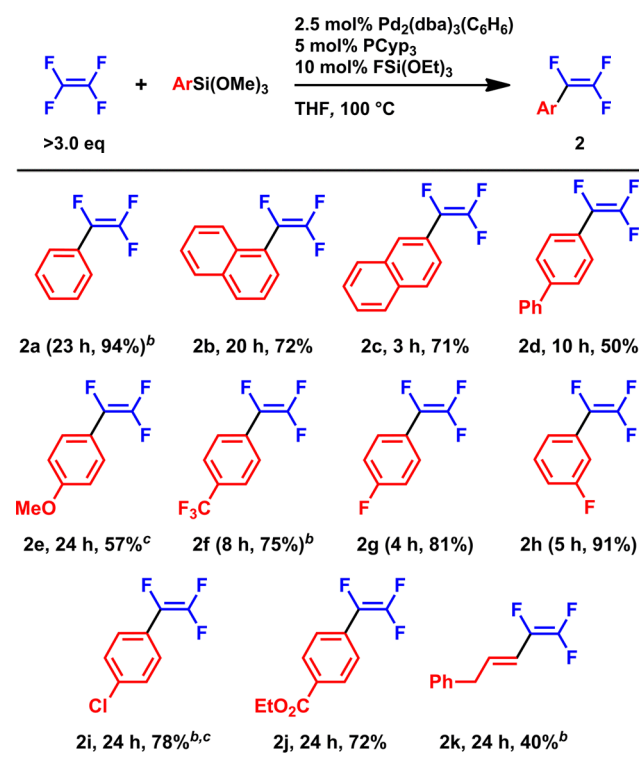
Figure 1. Comparison between the reaction rates in the absence (A, blue) and presence (B, red) of 10 mol % of FSi(OEt)$_3$. The reactions were monitored by means of ^{19}F NMR spectroscopy. Conditions: PhSi(OMe)$_3$ (0.10 mmol), TFE (3.5 atm, >3.0 equiv), Pd$_2$(dba)$_3$(C$_6$H$_6$) (0.0025 mmol), PCyp$_3$ (0.005 mmol), THF-d_8 (0.6 mL) at 100 °C.

in situ as the coupling reaction proceeded. By using 10 mol % of FSi(OEt)$_3$ as an additive, the reaction was obviously accelerated (Figure 1B), and the yield of **2a** was increased to 91% (Table 1, run 3).[11] We attempted to uncover the acceleration mechanism, but it remains unclear. In contrast, when TBAF was used as an additive, the coupling reaction did not proceed at all (run 4). In this case, pentafluoroethane was obtained as a result of the addition reaction of a fluoride anion toward TFE.[12] This compound was not observed when the base-free coupling proceeded successfully (for example, runs 1−3). These results indicated that free fluoride anion would not be involved in the base-free coupling reaction. The catalytic reaction also did not proceed when lithium iodide (LiI) was used as an additive, because the fluorine atom cleaved from TFE formed stable and insoluble lithium fluoride (run 5).[5a,e]

With the optimized reaction conditions established, we explored the scope of the reaction with respect to arylsiloxanes (Table 2). In the presence of 2.5 mol % of Pd$_2$(dba)$_3$(C$_6$H$_6$), 5 mol % of PCyp$_3$, and 10 mol % of FSi(OEt)$_3$, the coupling reaction of TFE with PhSi(OMe)$_3$ occurred at 80 °C to give **2a** in 94% yield, although an attempt to isolate **2a** failed due to its high volatility. The reaction using sterically hindered trimethoxy(naphthalen-1-yl)silane also proceeded, and the corresponding coupling product (**2b**) was isolated in 72% yield. Trimethoxy(naphthalen-2-yl)silane and (1,1′-biphenyl-4-yl)trimethoxysilane were converted into the corresponding trifluorostyrene derivatives (**2c,d**) in 71% and 50% yields, respectively. The reaction using electron-rich trimethoxy(4-methoxyphenyl)silane required high catalyst loading to furnish **2e** in 57% yield. Electron-deficient trimethoxy(4-(trifluoromethyl)phenyl)silane was smoothly converted into **2f** in 75% yield. The reactions using arylsiloxanes bearing a C−F bond on the aromatic ring gave the corresponding coupling products in high yields (**2g,h**). C−Cl bonds on the aromatic ring and ester group were tolerated in the reaction (**2i,j**). An alkenylsiloxane was also applicable to this coupling reaction (**2k**).

Furthermore, we expanded this base-free method to the coupling reaction of fluoroarenes. Our previous study showed that the Suzuki−Miyaura coupling reaction of fluoroarenes proceeded under base-free conditions using the NHC-coordinated Ni(0) complex [Ni$_2$(^{i}Pr$_2$Im)$_4$(COD)] that was developed by Radius.[5b,13] They reported the efficient oxidative

Table 2. Scope of the Reaction Involving TFE[a]

$$\text{(F}_2\text{C=CF}_2\text{)} + \text{ArSi(OMe)}_3 \xrightarrow[\text{THF, 100 °C}]{\substack{2.5\ \text{mol\% Pd}_2(\text{dba})_3(\text{C}_6\text{H}_6) \\ 5\ \text{mol\% PCyp}_3 \\ 10\ \text{mol\% FSi(OEt)}_3}} \mathbf{2}$$

>3.0 eq   2

2a (23 h, 94%)[b]   2b, 20 h, 72%   2c, 3 h, 71%   2d, 10 h, 50%

2e, 24 h, 57%[c]   2f (8 h, 75%)[b]   2g (4 h, 81%)   2h (5 h, 91%)

2i, 24 h, 78%[b,c]   2j, 24 h, 72%   2k, 24 h, 40%[b]

[a]Isolated yields. The yields in parentheses are NMR yields determined by ^{19}F NMR with PhCF₃ as an internal standard. [b]Heated to 80 °C. [c]Conducted with 5 mol % of Pd₂(dba)₃(C₆H₆), 10 mol % of PCyp₃, and 20 mol % of FSi(OEt)₃.

addition of an Ar−F bond when using this complex to form $[(i\text{Pr}^2\text{Im})_2\text{Ni(F)(Ar)}]$.[13b,d] This type of fluoronickel complex would be a key intermediate in our base-free Suzuki−Miyaura coupling reaction and would be expected to play the same role in the base-free Hiyama coupling reaction.

We examined the reaction conditions in the model reaction of octafluorotoluene (**5**) with PhSi(OMe)₃ (Table 3). The

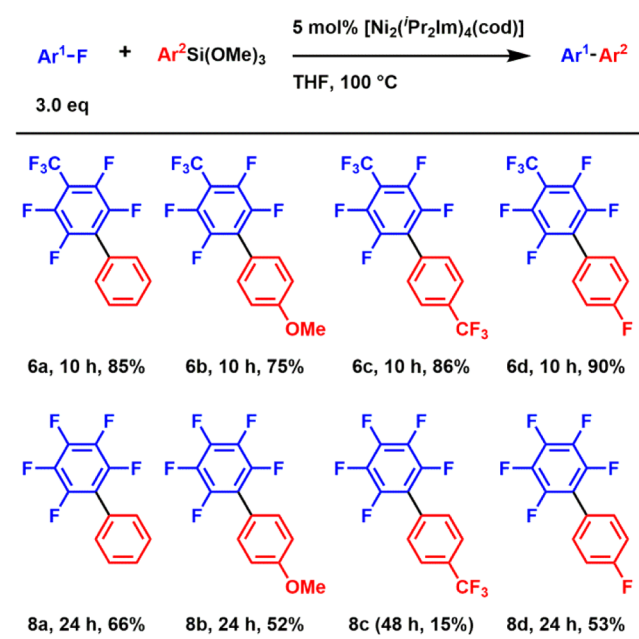## Table 3. Ni(0)-Catalyzed Hiyama Coupling Reaction of 5[a]

run	catalyst (amt (mol %))	additive (amt (mol %))	yield (%)
1	Pd₂(dba)₃(C₆H₆) (2.5), PCyp₃ (5)	FSi(OEt)₃ (10)	0
2	[Ni₂(iPr₂lm)₄(COD)] (5)	none	99
3	[Ni₂(iPr₂lm)4(COD)] (5)	FSi(OEt)₃ (10)	95

[a]Yields were determined by ^{19}F NMR with PhCF₃ as an internal standard.

Pd(0)/PCyp₃ catalyst did not work at all in the reaction (run 1), since the oxidative addition of a C−F bond to Pd(0) did not occur.[5d,14] On the other hand, in the presence of 5 mol % of [Ni₂(iPr₂Im)₄(COD)], the base-free reaction proceeded to afford 4-phenylheptafluorotoluene (**6a**) in excellent yield (run 2). Unlike the case of the reaction using TFE as a substrate, neither the reaction rate nor the yield of **6a** was improved by the addition of FSi(OEt)₃ (run 3). In this reaction, undesired 4-

methoxyheptafluorotoluene was also observed as a side-reaction product, as a result of the methoxy group transfer.[15]

Next we investigated the scope of the Ni(0)-catalyzed base-free Hiyama coupling reaction (Table 4). The reaction of **5**

Table 4. Scope of the Reaction Involving Fluoroarenes[a]

$$\text{Ar}^1\text{-F} + \text{Ar}^2\text{Si(OMe)}_3 \xrightarrow[\text{THF, 100 °C}]{5\ \text{mol\% [Ni}_2(i\text{Pr}_2\text{Im})_4(\text{cod})]} \text{Ar}^1\text{-Ar}^2$$

3.0 eq

6a, 10 h, 85%   6b, 10 h, 75%   6c, 10 h, 86%   6d, 10 h, 90%

8a, 24 h, 66%   8b, 24 h, 52%   8c (48 h, 15%)   8d, 24 h, 53%

[a]Isolated yields. The yield in parentheses is the NMR yield determined by ^{19}F NMR with PhCF₃ as an internal standard.

with trimethoxy(4-methoxyphenyl)silane gave the coupling product **6b** in 74% isolated yield. Moreover, electron-deficient arylsiloxanes bearing a trifluoromethyl or fluorine group were converted into the corresponding biaryls in excellent yields (**6c,d**). In these reactions, the formation of 4-methoxyhepta-fluorotoluene could not be avoided, but it could be easily separated by means of silica gel column chromatography. In addition, the coupling reaction of hexafluorobenzene (**7**) with arylsiloxanes also proceeded in the absence of any base to give the corresponding biaryls in moderate yields (**8a,b,d**). The reaction using trimethoxy(4-(trifluoromethyl)phenyl)silane afforded **8c** in only 15% yield, and substantial amounts of unreacted starting materials were recovered.

Although the mechanistic details of the base-free Hiyama coupling reaction have not been fully revealed at this time, on the basis of the stoichiometric reaction shown in Scheme 2, there is no doubt that metal fluoride complexes play a crucial role. We ruled out the mechanism involving free fluoride anion, because the coupling reaction of TFE did not proceed at all when TBAF was added. Fluorosilanes accelerated the Pd(0)-catalyzed Hiyama coupling reaction of TFE, but it would not be necessary for the base-free mechanism. We considered the possibility that fluorosilanes would facilitate the oxidative addition of a C−F bond of TFE toward Pd(0), which seems to be an inefficient step in the absence of a Lewis acidic species.[14] This is consistent with the fact that fluorosilanes did not affect the Ni(0)-catalyzed Hiyama coupling reaction of fluoroarenes, because [Ni₂(iPr₂Im)₄(COD)] is highly efficient in the oxidative addition of a C−F bond on fluoroarenes without the aid of a Lewis acidic additive.[13]

In summary, we developed a novel base-free Hiyama coupling reaction of either TFE or fluoroarenes via C−F bond activation. In the reaction involving TFE, fluorosilanes accelerated the catalytic reaction. Metal fluoride complexes generated in situ by the oxidative addition of a C−F bond played an essential role in the base-free reaction. Further investigation into the mechanistic details is now ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving detailed experimental procedures and analytical and spectral 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.

■ ACKNOWLEDGMENTS

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(7) When using PhSi(OEt)₃ instead of PhSi(OMe)₃, we detected acetaldehyde by means of ¹H NMR. It indicated that β-hydrogen elimination took place.

(8) Alkoxy group transfer from RSi(OMe)₃ has been reported in some papers; see: (a) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (b) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138. (c) Milton, E. J.; Fuentes, J. A.; Clarke, M. L. *Org. Biomol. Chem.* **2009**, *7*, 2645. (d) Wang, T.; Love, J. A. *Synthesis* **2007**, *15*, 2237. (e) Buckley, H. L.; Wang, T.; Tran, O.; Love, J. A. *Organometallics* **2009**, *28*, 2356. (f) Keyes, L.; Sun, A. D.; Love, J. A. *Eur. J. Org. Chem.* **2011**, 3985. (g) Bhadra, S.; Dzik, W. I.; Goossen, L. J. *J. Am. Chem. Soc.* **2012**, *134*, 9938.

(9) See the Supporting Information for details of the optimization of the reaction conditions.

(10) We assumed that the oligomerization of trifluorostyrene might occur, although no practical evidence was obtained. We did not detect a significant amount of potential further reaction products, including difluorodiphenylethyrene, difluorostyrene, and 1,2,3,3,4,4-hexafluoro-1,2-diphenylcyclobutane.

(11) We did not use FSi(OMe)₃ but rather FSi(OEt)₃, because the latter is commercially available.

(12) The hydrogen source is residual water in the solvent or in the solution of TBAF (1.0 M in THF). This kind of addition reaction is found to occur even in the absence of palladium and/or organosilicon reagent, due to the highly nucleophilic nature of TFE.

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(14) It is generally known that the oxidative addition of an Ar−F bond to Pd(0) is hard to carry out. Grushin reported that the reaction of C₆F₆ with Pd(PCy₃)₂ in THF at 70 °C afforded [(PCy₃)₂Pd(F)(C₆F₅)] in only 3% yield; see: Macgregor, S. A.; Roe, D. C.; Marshall, W. J.; Bloch, K. M.; Bakhmutov, V. I.; Grushin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 15304 See also Ref⁵ᵉ.

(15) A possible pathway for the methoxy group transfer is SNAr type substitution on [LₙNi(F)(C₇F₇)] by activated ArSi(OMe)₃ via a five-membered intermediate.