Fluoride-mediated rearrangement of phenylfluorosilanes
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Abstract: Combining Ph₃SiF and fluoride ion under conditions used for the Hiyama coupling causes rapid formation of the expected [Ph₃SiF₂]⁻; however, real-time electrospray mass spectrometric analysis reveals that phenyl-fluoride exchange occurs concomitantly, also producing substantial quantities of [Ph₃SiF₃⁻]⁻ (n = 0−2). The exchange process is verified using ¹⁹F NMR spectroscopy. This observation may have implications for Hiyama reaction protocols, which use transmetallation from triaryldifluorosilicates as a key step in cross-coupling.

Key words: mass spectrometry, electrospray ionization, fluorine NMR, fluoride, silane/silicate, exchange.

Résumé : La combinaison du Ph₃SiF et de l’ion fluorure en conditions de couplage d’Hiyama a provoqué la formation rapide et inattendue de l’ion [Ph₃SiF₂]⁻, mais l’analyse par spectrométrie de masse à ionisation par électroséparation en temps réel révèle qu’un échange phényl-fluorure se produit concurremment, ce qui donne lieu également à des quantités substantielles de l’ion [Ph₃SiF₃⁻]⁻ (n = 0−2). Nous avons vérifié le processus d’échange par spectroscopie RMN ¹⁹F. Cette observation pourrait avoir des implications pour les protocoles du couplage d’Hiyama, dont l’étape clé du couplage croisé est une transmétallation de triaryldifluorosilicates. [Traduit par la Rédaction]

Mots-clés: spectrométrie de masse, ionisation par électroséparation, RMN du fluor, fluorure, silane/silicate, échange.

Introduction

The palladium-catalyzed cross-coupling reaction of organosilicon reagents with organohalides, also known as the Hiyama coupling reaction, is a useful synthetic tool for the formation of carbon–carbon bonds. Relative to other organometallic compounds used in cross-coupling reactions (e.g. SnR₃, Stille–Migita–Kosugi; B(OR)₃, Suzuki–Miyaura; Zn(R)(X), Negishi), organosilicon compounds are weak nucleophiles as a result of the low polarizability of the Si–C bond. The markedly inert character of these compounds is advantageous in synthesis, as they tolerate a wide variety of functional groups; however, their chemical stability makes them poor cross-coupling partners. Early work by Hatanaka and Hiyama showed that activation of organosilicon reagents can be achieved through use of a fluoride salt such as NBu₄F (tetrabutylammonium fluoride, TBAF) or [(Me₂N)₃S]+[F₂SiMe₃]⁻ (tris(dimethylamino)sulfonium difluorotrimethylsilicate, TASF), resulting in a competent coupling reagent.¹ Hiyama and colleagues proposed that fluoride activation of the organosilicon reagent allows for the in situ formation of a pentavalent organosilicon anion whose labile Si–C bond is essential for the facilitation of transmetalation in the catalytic cycle (Fig. 1).² ³ Four following this discovery, an abundance of diversely functionalized organosilicon reagents have been developed and reaction conditions have been modified to drastically increase the scope and efficiency of the reaction.⁵ ⁶

Although the mechanism of more well-established palladium-catalysed cross-coupling reactions (e.g., Suzuki, Stille, etc.) have been extensively studied, there have only been a few detailed studies on the mechanism of the Hiyama reaction.⁷–⁹ The absence of experimentally supported information about the details of the Hiyama coupling mechanism, especially regarding the transmetalation step and the pentacoordinate silicon intermediates, leaves many important questions unanswered. Elucidation of the mechanism through use of experimental techniques is difficult due to short-lived intermediates which are difficult to detect. Previous studies demonstrate the complexity of transmetalation, indicating that rates of coupling are dictated by substituents, catalyst, and (or) ligand.¹¹ We have developed methodologies — in particular, real-time monitoring of reactions via pressurized sample infusion (PSI)¹² coupled with electrospray ionization mass spectrometry (ESI-MS)¹³–¹⁵ — that allow mechanistic studies on difficult problems, and we attempted to apply these methods to the Hiyama cross-coupling reaction of organosilicon reagents with aryl halides. Initially, our attention was attracted by the presence of anionic pentacoordinate silicon as the reactive species in transmetalation, because charged species are easy to detect and measure using ESI-MS. This manuscript deals with just one component of the overall reaction: an examination of the reactivity between the fluoride source and the neutral triphenylfluorosilane. It proved to be considerably more complicated than anticipated, and the results are very much a cautionary tale.

Methods

All manipulations were performed under an inert atmosphere (N₂), using oven-dried glassware where appropriate. ACS grade DMF (Caledon) was dried and stored over 4 A molecular sieves and sparged with nitrogen for 15 min before use. Commercially obtained Ph₃SiF (TCI Chemicals, >97.0%) and [CH₃(CH₂)₂]₄NF·3H₂O (Sigma-Aldrich, >97.0%) were used without further purification and stored under nitrogen.

NMR spectra were acquired on a Bruker AV 360 MHz spectrometer in d₆-DMSO (³⁹F(H), ³²Si) or in DMF with a d₆-acetone coaxial insert (³⁹F) at room temperature. All chemical shifts (δ) are quoted...
in parts per million (ppm), and the coupling constants (J) are expressed in hertz (Hz).

ESI-MS spectra were collected using either a (i) Micromass Q-ToF micro hybrid quadrupole/time-of-flight mass spectrometer (QtoF) or a (ii) Waters Acquity triple quadrupole detector with a Z-spray ionization source (TQD) in the negative mode using pneumatically assisted electrospray ionization. Capillary voltage: 3000 V. Cone voltage: 15 V. Source temperature: 110 °C. Desolvation temperature: 220 °C. Cone gas flow: 200 L h−1. Desolvation gas flow: 200 L h−1. Collision energy: 2 V. MCP voltage (QToF): 2400 V. Phosphor detector gain (TQD): 470 V. MSMS experiments were performed with a collision energy between 2 and 30 V with an Argon collision gas flow rate of 0.1 mL hr−1.

The general reaction procedure for the PSI-ESI-MS experiments is as follows: a solution of tetrabutylammonium fluoride trihydrate (0.0158 g, 0.05 mmol) was dissolved in 4.5 mL N,N-dimethylformamide (DMF) in the specially designated PSI reaction flasks. The reaction mixture was heated to 110 °C (regulated using a thermocouple) and stirred for the course of the reaction. A solution of fluoro(triphenyl)silane (0.0070 g, 0.025 mmol) in 0.5 mL DMF was then added to the reaction flask via syringe.

Results and discussion

Electrospray ionization mass spectrometry

Before embarking on a full study of the Hiyama reaction, we needed to establish parameters for the conditions employed. Hiyama reactions are generally carried out at a high temperature (>100 °C) and in strongly coordinating solvents (e.g., DMF), and we had previously employed neither such forcing conditions, nor such a high boiling point solvent in PSI-ESI-MS studies. However, with appropriate source conditions (see Experimental), DMF proved to be a well-behaved solvent for electrospray ionization (befitting a polar albeit high-boiling point solvent), and the high temperature of the reaction flask is not an issue for the PSI analysis as the solvent is rapidly cooled on exit into the capillary tubing leading to the mass spectrometer.

The most commonly used fluoride activator for the Hiyama reaction is TBAF, which is only commercially available in hydrate form due to the instability of anhydrous tetraalkylammonium fluoride salts. Two equivalents with respect to the triarylfluoride (DMF) and we had previously employed neither such forcing conditions, nor such a high boiling point solvent in PSI-ESI-MS studies. However, with appropriate source conditions (see Experimental), DMF proved to be a well-behaved solvent for electrospray ionization (befitting a polar albeit high-boiling point solvent), and the high temperature of the reaction flask is not an issue for the PSI analysis as the solvent is rapidly cooled on exit into the capillary tubing leading to the mass spectrometer.

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When Ph₃SiF and two equivalents of [NBu₄]F are combined in room temperature DMF, the pentacoordinate silicate [Ph₃SiF₂]− immediately appears in the negative ion mode in the mass spectrum, and its intensity stays stable over an extended period. Its MS/MS product ion spectrum (Fig. 1) exhibits unimolecular decomposition at high collision voltages only, breaking down by rearomatization to eliminate benzene or by heterolytic bond cleavage of a Si–C bond.

However, the same experiment conducted at typical Hiyama reaction temperatures (110 °C) results in dramatically different behavior. Redistribution of the aryl groups is immediately initiated and the temporal evolution of the observed species is shown in Fig. 2. The most prominent signal shows the appearance and decay of m/z 297, readily assigned as [Ph₃SiF₂]−. The reaction between F− and Ph₃SiF is extremely fast (t½ < 45 s), given the near-vertical ascent of the line immediately following combination of reagents. The exchange reaction that consumes it is slower, with a half-life of approximately 5 min. Three other anionic pentavalent silicon species were observed as products: [Ph₂SiF₃]− (m/z 239), [PhSiF₄]− (m/z 181), and [SiF₅]− (m/z 123), whose identities were confirmed through the use of MS/MS experiments and isotope pattern analysis (Supplementary Figs. S1 and S2). A fifth prominent species immediately appears in the negative ion mode in the mass spectrumb, and its intensity stays stable over an extended period. Its MS/MS product ion spectrum (Fig. 1) exhibits unimolecular decomposition at high collision voltages only, breaking down by rearomatization to eliminate benzene or by heterolytic bond cleavage of a Si–C bond.

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behaved very similarly, in that the $[\text{Ph}_3\text{SiF}_2]^{-}$ always formed very quickly and disappeared with a consistent half-life of about 5 ± 2 min; however, the relative abundance of the product species was considerably more variable. We attribute this variability from experiment to experiment rather than any inherent erratic behavior in the PSI-ESI-MS methodology, which regularly produces traces with high reproducibility in other contexts.21–23 One possible cause is the solvent, DMF, whose hydrolysis into dimethylamine and formic acid occurs without catalyst at room temperature.20 These decomposition products, even if present in only small amounts, may dramatically influence the rate and (or) success of the reaction, especially if the exchange reaction is acid catalyzed. Unfortunately, commercial TBAF cannot be obtained free of water; therefore, the presence of water cannot be completely eliminated from the reaction mixture.21 Nonetheless, the overall trend is clear in all experiments: within about 20 min, very little $[\text{Ph}_3\text{SiF}_2]^{-}$ remains in solution and the spectrum is dominated instead by fluorine rich silicate species. Note that no $[\text{Ph}_3\text{SiF}]^{-}$ or $[\text{Ph}_3\text{Si}]^{-}$ is observed, so the mass balance of Ph is not preserved. It is possible that formation of tetraphenyfluorosilicates is disfavored on steric grounds, given that reaction of PhLi with $\text{Ph}_2\text{SiF}$ produced a 4:3 mixture of $\text{Ph}_4\text{Si}$ and $[\text{Ph}_3\text{SiF}]^{-}$, rather than the intended $[\text{Ph}_3\text{SiF}]^{-}$.22 As such, we investigated whether neutral $\text{Ph}_4\text{Si}$ is the invisible (to ESI-MS) sink for the “missing” phenyl groups. An authentic sample of $\text{Ph}_4\text{Si}$ revealed rearrangement of the rapidly formed $[\text{Ph}_3\text{SiF}_2]^{-}$ ion to generate a range of more highly fluorinated silicate ions of the form $[\text{Ph}_{n}\text{SiF}_{6-n}]^{-}$ ($n = 0$–2) over a period of minutes. Confirmation of the rearrangement came from room temperature $^{19}\text{F}$ NMR studies. Neither of these techniques, nor $^{29}\text{Si}$ NMR, or $^1\text{H}$ NMR, or GC-MS were informative as far as the mass spectrometric observation of rapid formation of $[\text{Ph}_3\text{SiF}_2]^{-}$. The doublet at −143 ppm arises because the spectrum is not proton decoupled and so coupling to the H of $[\text{HF}_2]^{-}$ occurs. At room temperature, further change was slow (consistent with MS results at room temperature). A few small new peaks had grown in after 16 h, and after 72 h, they had become appreciable. This can be attributed to appearance of the $[\text{HF}_2]^{-}$- and replacement by F-, consistent with the growth of the signal at −105 ppm.

![Image](https://www.nrcresearchpress.com/9254/files/19F_NMR_of_Phi_SiF_2_Fig_4.png)

**Fig. 4.** $^{19}\text{F}$ NMR of $\text{Ph}_4\text{SiF} + 2$ equiv TBAF·$3\text{H}_2\text{O}$ in DMF acquired at 0, 16, and 72 h after mixing at room temperature.

Literature values for the chemical shifts of some anionic silicon fluoride species are available, albeit in different solvents. $[\text{Ph}_3\text{SiF}_2]^{-}$ has been reported at −95 ppm (close to our observed value),25 and $[\text{Ph}_3\text{Si}]^{-}$ appears at −127 ppm (a possible candidate for the peak at −125 ppm) and $[\text{SiF}_6]^{-}$ appears at −136 ppm26 (we observe no peaks in that region). The outstanding peaks at −112 and −119 ppm can be assigned to $[\text{Ph}_3\text{SiF}]^{-}$ and $[\text{Ph}_3\text{SiF}_2]^{-}$, respectively, based on literature values for the methyl analogues.27

**Conclusions**

The application of real-time ESI-MS to a high temperature reaction (<10 s) formed $[\text{Ph}_3\text{SiF}_2]^{-}$ ion to generate a range of more highly fluorinated silicate ions of the form $[\text{Ph}_{n}\text{SiF}_{6-n}]^{-}$ ($n = 0$–2) over a period of minutes. Confirmation of the rearrangement came from room temperature $^{19}\text{F}$ NMR studies. Neither of these techniques, nor $^{29}\text{Si}$ NMR, or $^1\text{H}$ NMR, or GC-MS were informative as far as the
fate of the “missing” phenyl groups was concerned. The observation of rearrangement itself is significant insofar as reactions that utilize [Ph₃SiF₂]− ions (most notably the Hiyama reaction) are concerned, because the rearrangement leads to lower availability of Ph for cross-coupling. Further elucidation of the details of the rearrangement will likely require the use of a triarylfluorosilane with a good ¹H NMR handle (e.g., the para-tolyl analogue).

Supplementary data

Acknowledgements
JSM thanks NSERC (Discovery and Discovery Accelerator Supplements) for operational funding and CFI, BCKDF, and the University of Victoria for infrastructural support. We also acknowledge Neil Burford, to whom this issue is dedicated, for his tremendous energy, support, and leadership over the years.

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