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Formal Nucleophilic Silyl Substitution of Aryl Halides with Silyllithium Reagents via Halogenophilic Attack of Silyl Nucleophiles

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Abstract A new reaction has been developed for the formal nucleophilic silyl substitution of aryl halides with silyllithium or silylpotassium reagents. Dimethylphenylsilyllithium reacted with various aryl halides to form the corresponding arylsilanes in moderate to good yields with concomitant formation of the disilanes under the optimized reaction conditions. Mechanistic studies indicated that this silyl substitution reaction progresses through polar halogenophilic attack of silyl nucleophiles.

Key words halogenophilic attack, silyl nucleophiles, silyl substitution, organohalides, organosilanes

Arylsilane is used as a versatile synthetic intermediate in medicinal chemistry and materials science.² Among the many methods available for the synthesis of organosilanes, the nucleophilic substitution of silicon electrophiles with aryl lithium or aryl Grignard reagents is one of the most reliable reactions for the preparation of arylsilanes.^{3,4} Chemists have devoted considerable effort to the development of transition-metal-catalyzed methods for the silvlation of aryl halides with silvl nucleophile surrogates such as disilane and silvlborane.⁵ Although these methods represent attractive alternative routes to arylsilanes, they require costly transition-metal catalysts and silvlation reagents, thereby limiting their application. In contrast, the direct silylation of aryl halides with silvllithium reagents is counterintuitive, but possible. This reaction represents an inexpensive and attractive alternative to the synthesis of arylsilanes. In the absence of a transition-metal catalyst, the substitution of a C(sp²)-X (X=halogen) bond with organometallic nucleophiles is generally difficult.

In 2011, Strohmann et al. reported their work towards the reactions of chiral silyllithium compounds from the perspective of the stereochemistry of the silicon center in the product. During the course of their research, Strohmann's group found that a silyllithium reagent underwent a silyl substitution reaction with aryl halides in the absence of a transition-metal catalyst (Scheme 1a).⁶ Based on a series of density functional theory (DFT) calculations, Strohmann's group proposed that the nucleophilic silyl substitution reaction proceeded through halogenophilic attack of the silyl nucleophile on the halogen atom of the aryl halide substrate,^{6a,7} and the possibility of a radical mechanism was also proposed as a minor reaction pathway. Furthermore, Strohmann's group only conducted this study to rationalize the mechanism of their chiral silylation reactions and did not, therefore, conduct a detailed exploration of the scope of this reaction.

In 2012, we reported a transition-metal-free boryl substitution of aryl halides with PhMe₂Si-B(pin) and KOMe.^{8a} In terms of its mechanism, the silyl nucleophile in the silylborate complex, which was prepared by the reaction of PhMe₂Si-B(pin) with KOMe, attacked the halogen group of the aryl halide to produce the corresponding aryl anion species. The subsequent reaction of the aryl anion with the boryl group gave an organoboron compound with concomitant formation of a small amount of the silylation product (Scheme 1b).^{8b,8c,9} A mechanistic investigation was conducted involving the reaction of dimethylphenylsilyllithium with aryl bromide to confirm whether the halogenophilic attack of a silyl nucleophile was capable of forming an aryl anion.^{8b} The results revealed that the silyl substitution product was obtained in moderate yield, as we expected.

We envisaged that this interesting formal silyl substitution reaction could be used as an inexpensive method for the rapid construction of various arylsilanes, avoiding the requirement for transition-metal catalysts or the preparation of aryl lithium or aryl Grignard reagents. However, none of these studies have advanced beyond the mechanistic investigation stage and very little is currently known about the scope of silyllithium reagents, aryl halides, and optimum reaction conditions. Herein, we report the results of our recent study towards the formal nucleophilic silyl substitution of aryl halides with silyllithium reagents. In this study, we have focused on the optimization of reaction conditions, substrate scopes of the aryl halides and silyl nucleophiles, and the elucidation of the reaction mechanism (Scheme 1).



Scheme 1 Formal nucleophilic silyl substitution of aryl halides with silyl nucleophiles

We initially investigated the silyl substitution reaction of 4-bromoanisole (**1a**) with PhMe₂SiLi (**2a**) (0.8 M in THF, 1.0 equiv) in THF at 30 °C for one hour, which gave the corresponding arylsilane **3aa** in low yield, along with PhMe₂Si-SiMe₂Ph (**4**) (Table 1, entry 1, **3aa**: 27%, **4**: 21% respectively). The use of a small excess of **2a** (1.5 equiv) led to an improvement in the yield of **3aa** (57%; entry 2). Although the use of a 0.4 M solution of PhMe₂SiLi resulted in a lower yield than that obtained using a 0.8 M solution, the best results were obtained when 2 equivalents of 0.4 M PhMe₂SiLi solution were used (47 and 68%, respectively; entries 3 and 4). Notably, the use of a 0.2 M PhMe₂SiLi solution instead of the 0.4 M solution led to a reduction in the yield to 51% (entry 5). The reaction was performed at different temperatures (50 and 0 °C), but provided the desired arylsilane **3aa** in similar yields of 48 and 50% yield, respectively (entries 6 and 7). We also investigated the effect of the leaving group on the yield of the reaction. The use of 4-iodoanisole as a substrate afforded a similar yield of arylsilane **3aa** to that of 4-bromoanisole (61%; entry 8), whereas the reactions of 4-chloro- and 4-fluoroanisole resulted in much lower yield (31 and 24%, respectively; entries 9 and 10).



MeO [^]	B	r PhMe ₂ SiLi 2a (conc., equiv) THF, temp, 1 h	MeO	Si Ph	Ph-Si-S	Si-Ph
	1a			3aa	byprodu	ict
Entry	Temp	PhMe ₂ SiLi 2a		Conv. (%) ^b	Yield (%) ^b	
	(°C)	Conc. (M)	Equiv	1a	3aa	4
1	30	0.8	1.0	78	27	21
2	30	0.8	1.5	>99	57	22
3	30	0.4	1.5	>99	47	23
4	30	0.4	2.0	>99	68	30
5	30	0.2	2.0	98	51	33
6	50	0.4	2.0	>99	48	19
7	0	0.4	2.0	92	50	26
8 ^c	30	0.4	2.0	94	61	30
9 ^d	30	0.4	2.0	>99	31	33
10 ^e	30	0.4	2.0	81	24	23

^a Reaction conditions: **1a** (0.5 mmol) was added to a solution of PhMe₂SiLi in THF, and the resulting mixture was stirred for 1 h.

^b Conversion and yields were determined by GC analysis.

^c 4-lodoanisole was used as a substrate.

^d 4-Chloroanisole was used instead of **1a**.

^e 4-Fluoroanisole was used instead of **1a**.

With the optimized conditions in hand, we proceeded to investigate the substrate scope of the aryl bromide electrophile (Scheme 2). Substrates bearing a simple aliphatic group afforded the corresponding arylsilanes in good yields (**3ba**: 69%, **3ca**: 62%, **3da**: 76%, **3ea**: 59%). However, the sterically hindered substrates **1f** and **1g** failed to afford any of the desired products. Notably, the reaction of **1f** resulted in the formation of 2,4,6-triisopropyl benzene in 72% yield (based on NMR spectroscopic analysis) as opposed to the desired product **3ga**. The electron-rich and electron-deficient substrates **1h** and **1i** also reacted smoothly to afford the desired arylsilanes **3ha** and **3ia** in 67 and 41% yields, respectively. Aryl bromides **1j** and **1k**, bearing an ester or a 3-pyridyl group, were poorly tolerated under the present reaction conditions (**3ja**: 0%, **3ka**: 7%).

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Intrigued by the effects of the substituents on the silvl nucleophile, we proceeded to investigate the reaction of 4bromoanisole (1a) with several silvl nucleophiles 2 (Table 2). The reaction of aryl bromide **1a** with Ph₂MeSiLi (**2b**) gave **3ab** in 65% yield (entry 1). The use of the bulky silyl nucleophile Ph₃SiLi (2c) resulted in a much lower yield (**3ac**: 19%; entry 2). The use of (TMS)₃SiK (**2d**) afforded the corresponding arylsilane **3ad** in 14% yield, along with aryl trimethylsilane 3ad' in 26% yield (entry 3).

This reaction could proceed through polar and radical mechanisms, as suggested by Strohmann's chiral silyl anion studies.⁶ We also observed the formation of biphenyl 5 when 1.5 equiv of 2a was used, which raised the possibility of a radical mechanism. However, this byproduct was not observed when the reaction was conducted under optimized conditions (Table 3, entries 1 and 2). To probe the possibility of a radical-mediated mechanism, we investigated the reaction of o-(3-butenvl)bromobenzene (11) under the silyl substitution conditions (Scheme 3a). It is noteworthy that the corresponding aryl radical has been reported to undergo a 5-exo-trig cyclization with a rate constant of 10⁸ s⁻¹ to form 1-methylindane following hydrogen atom abstraction.¹⁰ In practice, we observed the silvlated and protonated products 3la and 6l, but none of the cyclization product **7**. We also investigated the reaction of (*Z*)-alkenyl iodide (1m), which provided the desired product (Z)-3ma exclusively in 39% yield without any of the (E)-3ma isomer (Scheme 3b). These results therefore suggest that the polar mechanism is the most plausible mechanism for this reaction under the optimized conditions.

Based on these results, we proposed a plausible mechanism for this reaction involving a polar halogenophilic attack (Scheme 4). The halogen atom of the aryl halide would

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 Table 2
 Substrate Scope of Silvl Nucleophiles^a

^a Reaction conditions: **1a** (0.5 mmol) was added to a solution of R₃Si-M **2** in THE

(0.4 M, 2.0 equiv), and the resulting mixture was stirred for 1 h at 30 °C. ^b Yields were determined by GC analysis.









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undergo nucleophilic attack by the silyllithium reagent **2**, leading to the formation of the corresponding aryllithium and silyl halide species. The subsequent nucleophilic substitution reaction of the aryllithium species with the silyl halide electrophile would provide the arylsilane product with concomitant formation of LiBr.



Scheme 4 A plausible mechanism

In conclusion, we have explored the formal nucleophilic silyl substitution of aryl and alkenyl halides with silyl nucleophiles. In general, the reaction of aryl bromides with silyl nucleophiles gave the corresponding arylsilanes in moderate to good yields, along with the disilanes. However, sterically hindered aryl halides and substrates bearing an ester or 3-pyridyl group were not tolerated under the optimized reaction conditions. The scope of the silyl nucleophile was also investigated. Mechanistic studies indicated that this reaction most likely proceeds through a polar halogenophilic mechanism, as opposed to a radical-mediated mechanism.

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Supporting Information

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- (11) Typical Procedure for Silyl Substitution Reaction with Silyllithium Reagent

A vial with a screw cap and a silicon-coated rubber septum was connected to a vacuum/nitrogen manifold through a needle, and it was evacuated and refilled with nitrogen three times.

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Dimethylphenylsilyllithium (0.4 M in THF, 2.5 mL, 2.0 equiv) was added to the vial under nitrogen atmosphere. 1-Bromo-3,5dimethylbenzene (93.5 mg, 0.51 mmol) was added to the vial, then stirred at 30 °C. After 1 h, the reaction mixture was analyzed by GC to check completeness of the reaction. When the reaction was complete, H_2O was added and the mixture was extracted three times with Et_2O . The organic layer was washed with water and the combined organic layer was then dried over MgSO₄ followed by filtration and evaporation. The crude product was purified by silica-gel column chromatography with hexane eluent, then further purified by gel permeation chromatography to give **3da** in 63% isolated yield (76.5 mg, 0.318 mmol).

¹H NMR (392 MHz, CDCl₃): δ = 0.53 (s, 6 H), 2.30 (s, 6 H), 7.01 (s, 1 H), 7.13 (s, 2 H), 7.30–7.38 (m, 3 H), 7.49–7.55 (m, 2 H). ¹³C NMR (99 MHz, CDCl₃): δ = –2.3 (CH₃), 21.4 (C), 127.7 (CH), 129.0 (CH), 130.9 (CH), 131.9 (CH), 134.2 (CH), 137.1 (C), 137.9 (C), 138.5 (C). HRMS (EI): m/z [M]⁺ calcd for C₁₆H₂₀Si: 240.13343; found: 240.13281.