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Research Article

Design, Synthesis, and Implementation of Sodium Silylsilanolates as Silyl Transfer Reagents

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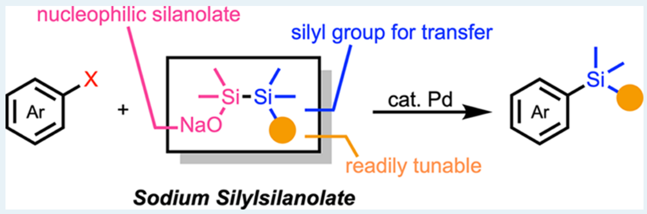
ABSTRACT: There is an increasing demand for facile delivery of silyl groups onto organic bioactive molecules. One of the common methods of silylation via a transition-metal-catalyzed coupling reaction employs hydrosilane, disilane, and silylborane as major silicon sources. However, the labile nature of the reagents or harsh reaction conditions sometimes render them inadequate for the purpose. Thus, a more versatile alternative source of silyl groups has been desired. We hereby report a design, synthesis, and implementation of storable sodium silylsilanolates that can be used for the silylation of aryl halides and pseudohalides in the presence of a palladium catalyst. The developed method allows a late-stage functionalization of polyfunctionalized compounds with a variety of silyl groups. Mechanistic studies indicate that (1) a nucleophilic silanolate attacks a palladium center to afford a silylsilanolate-coordinated arylpalladium intermediate and (2) a polymeric cluster of silanolate species assists in the intramolecular migration of silyl groups, which would promote an efficient transmetalation.



KEYWORDS: *silylsilanolate, silanolate salts, silylation, palladium, DFT calculation*

INTRODUCTION

Silicon typically adopts four covalent, tetrahedrally disposed bonds in molecular architectures, so that it resembles one of the most fundamental elements of life, carbon. The major difference between these two group 14 elements lies in electronegativity and the bond length to the adjacent atoms. Thus, in the realm of silicon-containing drugs and bioactive molecules,[1] a carbon atom could be exchanged to a silicon atom as a bioisostere to modify the physical and biological characteristics. Through these strategies known as "silicon switch",[1a] silicon-containing bioactive molecules have been successfully devised (Figure 1). Retinoid X receptor (RXR)-selective retinoid antagonist, bexarotene, has been redesigned to disila-bexarotene by exchanging two carbon atoms with silicon atoms without any detrimental effect on bioactivity.[2] The silicon switch strategy has also effectively proposed potent sila-analogs of acaricide cyflumetofen[3] and p38 MAP kinase inhibitor doramapimod[4] (BIRB 796). As illustrated in these examples, the substitution of a *tert*-butyl group with a bioisosteric trimethylsilyl group is an intriguing tactic for changing physicochemical properties such as human microsomal stability without lowering the biological activities.

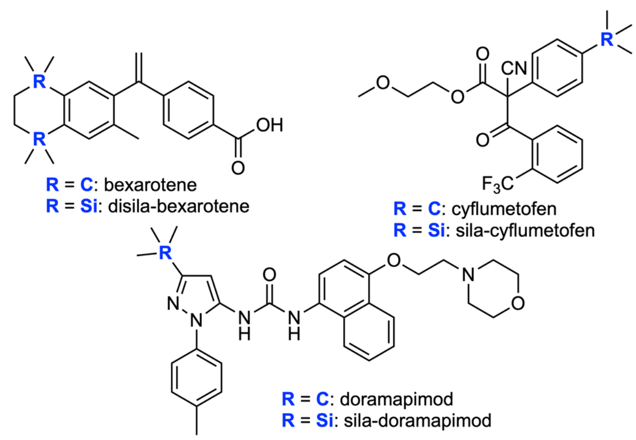


Figure 1. Sila-analogs developed via a carbon/silicon switch strategy.

Despite this successful implementation of the silicon switch strategy, synthetic approaches to complex silicon-containing molecules have been restricted. Selective deprotonation and subsequent trapping with silicon electrophiles, such as trimethylsilyl cyanide,[5] constitute a viable strategy only if the substrate allows strongly basic conditions. Thus, we hypothesized that the synthetic difficulty would be due to the scarcity of an appropriate reagent that is amenable even to the late-stage functionalization of complex molecules through transition-metal-catalyzed silylation of aryl halides or C−H silylation[6] of arenes (Figure 2A). Commonly used reagents for those silylation can be mainly classified into three silicon

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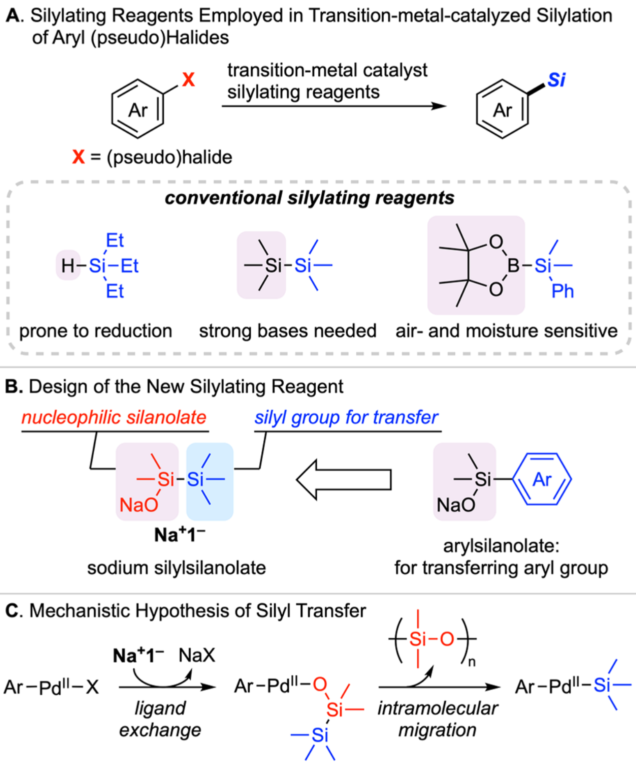
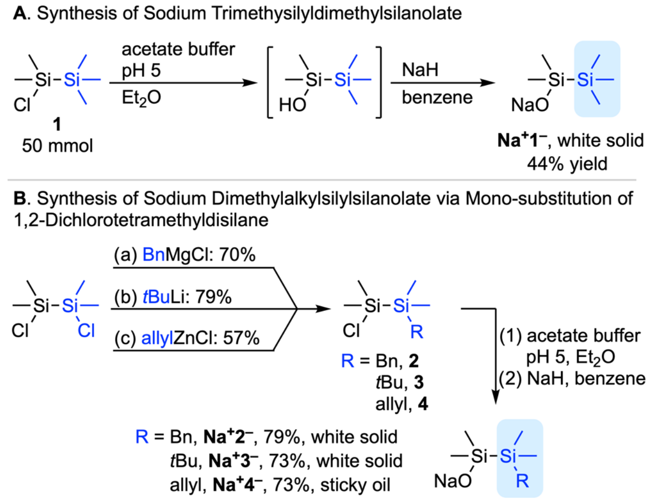


Figure 2. Blueprint for development of sodium silylsilanolate.

Scheme 1. Synthesis of Sodium Silylsilanolates[a,b,c]



[a]1.05 equiv of 1,2-dichlorotetramethyldisilane, 1.0 equiv of BnMgCl, tetrahydrofuran (THF), 0−50 °C, 4 h. [b]1.03 equiv of 1,2-dichlorotetramethyldisilane, 1.0 equiv of *t*BuLi, hexane, reflux, 13 h. [c]1.0 equiv of 1,2-dichlorotetramethyldisilane, 1.0 equiv of allylZnCl, THF, 0 °C to r.t., 4 h.

species: hydrosilanes, disilanes, and silylboranes. Hydrosilanes often provide reduced products during a transition-metal-catalyzed silylation reaction, which often complicates the reaction consequences.[7] Particularly, trimethylhydrosilane is a gaseous and pyrophoric reagent that is impractical to use in the laboratory. Disilanes are less likely to cause transmetalation so that relatively high temperatures (>100 °C) and strong bases are often necessary for the activation.[8] In most cases, hexamethyldisilane is employed as a reagent, and a judicious choice of ligands is often necessary for each substrate. Thus, the use of disilanes leads to the reduced variation of the silyl group and functional group tolerance. Silylboranes[9] are silylation reagents that are now frequently used in transition-metal-catalyzed silylation of aryl (pseudo)halides.[9b,10] While silylboranes bearing bulky silyl groups are reported to be stable,[11] typical silylborane $Me_2PhSi{-}Bpin$ is known to be air- and moisture-sensitive.[9b] $Me_3Si{-}Bpin$ has long been considered fairly labile, so that it is hydrolyzed during purification.[12] As the synthetic preparation of $Me_3Si{-}Bpin$ was reported to be possible only quite recently,[13] the utility of silylboranes as the source of trimethylsilyl groups is currently yet to be revealed. In terms of nucleophilic silylation reactions, the simplest trialkylsilyl group, trimethylsilyl, is definitely not a trivial one. By probing these three reagents, it is now evident that the development of a novel practical nucleophilic silylating reagent is necessary for more efficient silylation under mild conditions.

Herein, we propose sodium trimethylsilyldimethylsilanolate (**Na**$^+$**1**$^-$) as a new silylating reagent that works in the presence of palladium catalyst (Figure 2B). The design of this reagent was inspired by analogy to arylsilanolates that have been known as reagents for transferring aryl groups in palladium-catalyzed cross-coupling reactions.[14] The molecular structure of **Na**$^+$**1**$^-$ contains one Si−Si bond that connects a trimethylsilyl group to be delivered and a nucleophilic silanolate as a catapult. We hypothesized the mode of migration of a silyl group from silylsilanolate, as shown in Figure 2C, based on a similar system for arylsilanolate proposed by Denmark.[14g] In contrast to the ordinary disilanes, an anionic silylsilanolate can act as a nucleophile that attacks the palladium(II) center to form a silylsilanolate-coordinated intermediate. This proximity effect would facilitate an intramolecular delivery of the terminal silyl group to the palladium center, with concomitant formation of a waste polysiloxane.

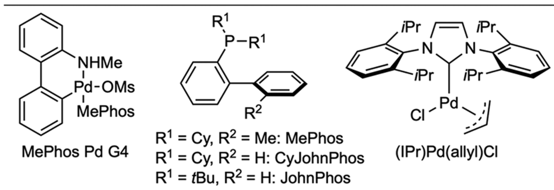
RESULTS AND DISCUSSION

Na$^+$**1**$^-$ was easily synthesized from commercially available chloropentamethyldisilane **1** over two steps (Scheme 1A): hydrolysis of a chlorosilane in an acetate buffer to afford a silanol and the subsequent deprotonation with NaH. The reagent was obtained as an analytically pure, mildly hygroscopic, and thermally stable white powder that can be easily handled in a dry atmosphere. Sodium silylsilanolates other than **Na**$^+$**1**$^-$ were synthesized, as shown in Scheme 1B. Commercially available 1,2-dichlorotetramethyldisilane was treated with nucleophilic organometallic species (BnMgBr, *t*BuLi, allylZnCl) to mediate monosubstitutions to give the corresponding chlorodisilanes **2**, **3**, and **4**.[15] Hydrolysis of **2**−**4** followed by deprotonation with NaH provided the corresponding sodium silylsilanolates **Na**$^+$**2**$^-$−**Na**$^+$**4**$^-$ in good yields. **Na**$^+$**2**$^-$ and **Na**$^+$**3**$^-$ were obtained as white solids, and **Na**$^+$**4**$^-$ was isolated as a sticky oil.

To evaluate the synthetic utility of sodium silylsilanolate, we studied the silylation of aryl bromide **5** in the presence of a palladium catalyst with **Na**$^+$**1**$^-$ (Table 1). Under our optimized standard conditions, treatment of ethyl 4-bromobenzoate (**5**) with preformed MePhos Pd G4 (3 mol %)[16] and **Na**$^+$**1**$^-$ (2.0 equiv) in 1,2-dichloroethane (DCE) as the solvent at 50 °C for 2 h provided the silylated product **6** in 89% NMR yield (88% isolated yield) (entry 1). The yield of **6** was competitive (83%) with the use of the catalyst generated in situ from Pd_2dba_3 and MePhos (entry 2). The influence of ligands on the efficiency of

Table 1. Optimization of the Reaction Conditions[a,b]

Entry	Deviations from standard conditions	Yield (%)[a]
1	none	89 (88)[b]
2	1.5 mol % Pd_2dba_3 + 3 mol % MePhos	83
3	1.5 mol % Pd_2dba_3 + 3 mol % PCy_3	80
4	1.5 mol % Pd_2dba_3 + 3 mol % CyJohnPhos	75
5	1.5 mol % Pd_2dba_3 + 3 mol % JohnPhos	51
6	3 mol % (IPr)Pd(allyl)Cl	72
7	1.5 mol % Pd_2dba_3 + 3 mol % dppe	7
8	$\mathbf{Li^{+}1^{-}}$	2
9	$\mathbf{K^{+}1^{-}}$	31
10	toluene	74
11	THF	25
12	CH_3CN	14
13	without MePhos Pd G4	0



[a]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield (0.50 mmol scale).

the reaction was examined first. Monodentate ligands, PCy_3, CyJohnPhos, and JohnPhos afforded **6** in competitive yet lower yields (51−81%) (entries 3−5).

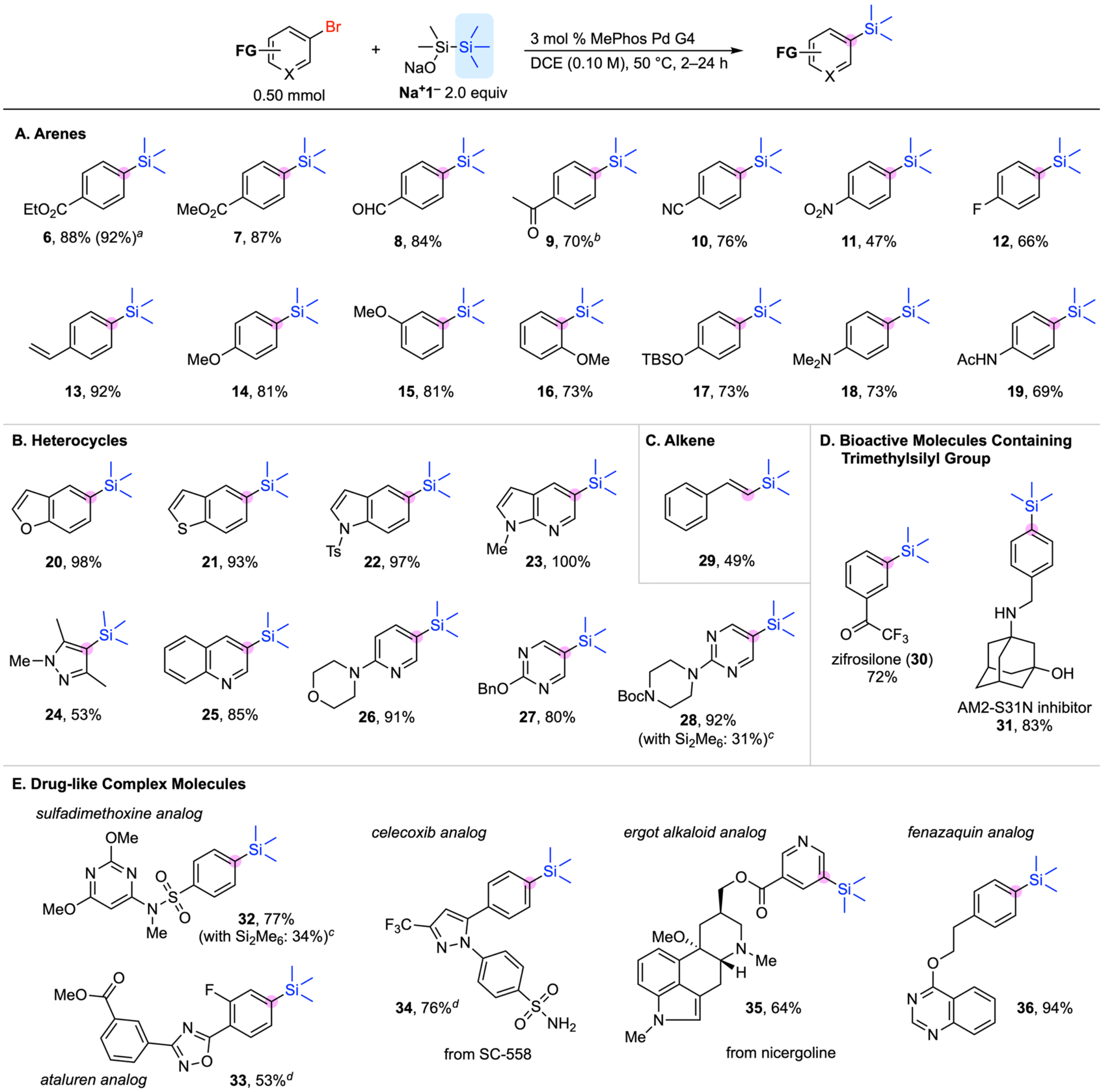
An acceptable result was also obtained with *N*-heterocyclic carbene complex (IPr)Pd(allyl)Cl as a catalyst (73%) (entry 6). A bidentate phosphine ligand, dppe, was ineffective (7%) in the current reaction system (entry 7). Use of lithium silylsilanolate $\mathbf{Li^{+}1^{-}}$ or potassium silylsilanolate $\mathbf{K^{+}1^{-}}$ showed lower efficiency (entries 8 and 9), which underscored the importance of the choice of the countercation for efficient silylation. The reaction in toluene was similarly efficient (74%), while low yields were observed in THF and CH_3CN with the recovery of most of the substrates (entries 10−12) in concomitant with the formation of the reduced product (<20%). No conversion of **5** was observed in the absence of a palladium catalyst (entry 13).

Next, we explored the reaction scope with respect to aryl bromides (Table 2A). Silylation of **5** could be run even on a 5.0 mmol scale to afford **6** in excellent yield (92%). The reaction could tolerate various electronic and steric properties of substituents (**6**−**11**). Esters in **6** and **7** survived the silylation conditions. This outcome is intriguing given that trimethylsilanolates are generally used for the hydrolysis of esters.[17] The substrate with a formyl or acetyl group could be transformed in good yield into **8** or **9**. In the case of **9**, the reaction was performed at 25 °C to suppress the formation of an α-arylated byproduct. Cyano and nitro groups could poison a palladium catalyst. While a substrate with a cyano group was converted into arylsilane **10** in good yield, arylsilane **11** with a nitro group was obtained only in moderate yield. Fluoro and vinyl substituents were also confirmed to be compatible (**12**, **13**). Substrates with electron-rich substituents, such as methoxy (*p*-, *m*-, and *o*-OMe)-, silyloxy-, amino-, and amido-substituted aryls, were generally transformed into arylsilanes (**14**−**19**). A wide range of heteroaryl trimethylsilanes could also be synthesized under our silylation reaction (Table 2B). Electron-rich heteroarenes, such as benzofuran **20**, benzothiophene **21**, *N*-(*p*-toluenesulfonyl)indole **22**, and *N*-methylpyrrolopyridine **23**, were obtained in excellent yields. A sterically hindered pyrazole was converted to the silylated product **24**, albeit in moderate yield (53%). Electron-deficient heteroarenes were also compatible. The conditions were amenable to the syntheses of quinoline **25**, as well as pyridine **26** and pyrimidines **27** and **28**. As an entry to alkenes, β-bromostyrene could be transformed into the trimethylsilylated derivative **29** (Table 2C). The reaction was also applicable to the synthesis of known biologically relevant compounds (Table 2D). Acetylcholinesterase inhibitor zifrosilone[18] (**30**) was synthesized from the commercially available 3′-bromo-2,2,2-trifluoromethylacetophenone in good yield. A potent inhibitor of the drug-resistant S31N mutant of the M2 ion channel of influenza A virus **31**[19] was synthesized from the corresponding aryl bromide even in the presence of a free hydroxy and a secondary amino group.

In an attempt to demonstrate the applicability of our method to the late-stage silylation, we tested several drugs and drug-like molecules containing aryl bromides (Table 2E). Trimethylsilylated analogs of sulfadimethoxine **32** and ataluren **33** were synthesized in 77% and 53% respective yields from the corresponding aryl bromides. The bromide moiety of SC-558 was similarly converted to a trimethylsilyl group to give a celecoxib analog **34** in 76% yield. Nicergoline was also trimethylsilylated to give an ergot alkaloid analog **35** in 64% yield. An increased amount of the catalyst and silylsilanolate was required for ataluren and celecoxib analogs, whose oxadiazole and sulfonamide moieties might work inhibitively to the catalyst. Thus, in the case of the ataluren analog, the slower rate of the coupling reaction seemed to result in partial hydrolysis of the ester moiety in **33**. The sila-analog of fenazaquin **36**,[20] in which a *tert*-butyl group is replaced with a trimethylsilyl group, was analogously synthesized from the corresponding aryl bromide in excellent yield. Just to compare the functional group tolerance, the known palladium-catalyzed silylation conditions[8h] using hexamethyldisilane were applied for the syntheses of relatively functionalized **28** and **32**, which resulted in 31 and 34% respective yields. The reaction proceeded in concomitant with the formation of the reduced products both in ca. 30% yields with about 30% recovery of the starting material (see the Supporting Information (SI)). These results indicate that the new silylation strategy using sodium silylsilanolate is suitable for the highly versatile syntheses of sila-analogs of bioactive molecules.

We applied the optimized silylation conditions to other aryl halides and pseudohalides (Table 3). For electron-deficient arenes, iodide, triflate, and chloride were silylated to provide **6** in high yields. Iodide could be transformed even at 25 °C. For

Table 2. Scope of Silylation of Aryl Bromides[a,b,c,d]

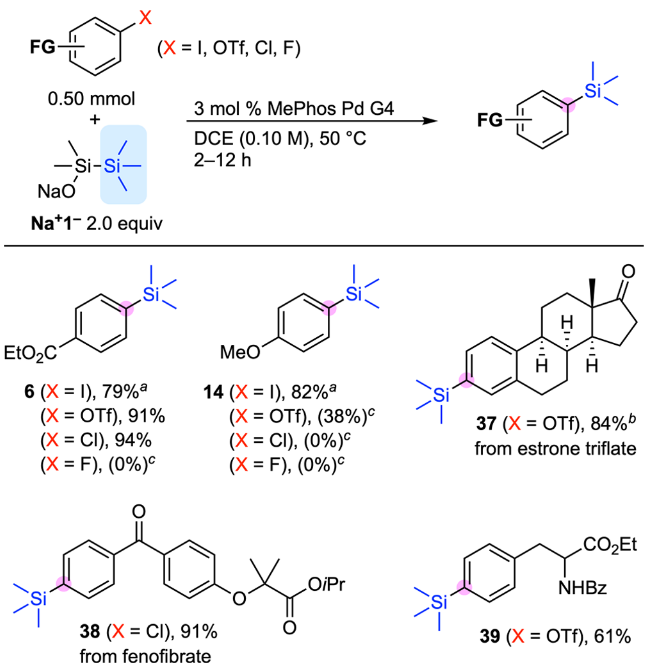


^{a}5.0 mmol scale. ^{b}Temperature: 25 °C. ^{c}NMR yield. Reaction conditions: 1.2 equiv of hexamethyldisilane, 1.5 mol % Pd_2dba_3, 9 mol % JohnPhos, 5.0 equiv of KF, 2.0 equiv of H_2O, DMPU (0.90 mL), 100 °C, 12 h. ^{d}6 mol % MePhos Pd G4 and 3.0 equiv of **Na$^+$1$^-$** were used.

an electron-rich series, aryl iodide was also converted to the corresponding product **14** in high yield, while triflate and chloride showed low or no conversion even under the optimized conditions. In the case of aryl fluoride, both electron-withdrawing and electron-donating substrates remained intact throughout the reaction conditions.[9b,21] Silylation of aryl triflate and chloride on more functionalized molecules was also achieved. The silylated products **37** and **38** were obtained from the estrone derivative (X = OTf) or fenofibrate (X = Cl), respectively, in high yields. In the case of a protected L-tyrosine derivative (X = OTf), the silylated product **39** was obtained in good yield, albeit in an almost racemized form. In terms of transition-metal-catalyzed silylation, the reaction developed in this study is exceptional in that most of the electron-rich/deficient aryl halides and pseudohalides could be silylated under identical catalytic reaction conditions.

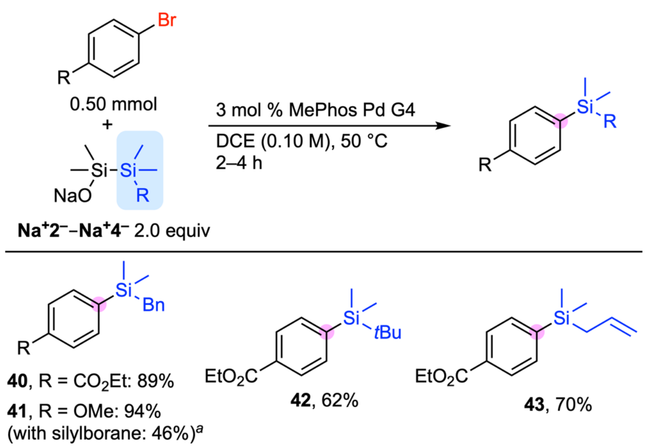
With **Na$^+$2$^-$–Na$^+$4$^-$**, introduction of other silyl groups was also possible in the current strategy (Table 4). Delivery of a benzyldimethylsilyl group has been known to be inefficient with a disilane[8m] or silylborane[22] as a precursor. Under the optimized conditions with **Na$^+$2$^-$**, a benzyldimethylsilyl group could be introduced to afford both electron-deficient and -donating arenes **40** and **41** in high yields. In the case of *p*-

Table 3. Scope of Silylation of Aryl Halides and Pseudohalides[a,b,c]



[a]Temperature: 25 °C. [b]6 mol % MePhos Pd G4 was used. [c]NMR yield.

Table 4. Scope of Silyl Groups[a]



[a]Reported yield in Ref 18.

bromoanisole, the yield of **41** under the current conditions (94%) is higher than the one in the known result with silylborane-based conditions.[22] While no coupling reaction with *tert*-butyldimethylsilyl and allyldimethylsilyl groups has so far been reported under transition-metal-catalyzed conditions with conventional silylating reagents, our silylation method with silylsilanolates $\mathbf{Na^+3^-}$ and $\mathbf{Na^+4^-}$ enabled an easy access to the *tert*-butyldimethylsilyl arene **42** (62%) and allylsilylated arene **43** (70%). These results indicate that the core structure of silylsilanolate would be generally more viable for the transmetalation of various silyl groups than the known silylating reagents.

To gain mechanistic insights into the silylation with silylsilanolates, we conducted ^{31}P and ^{19}F NMR experiments (Figure 3 and S1). T-shape complex SPhosPdBr(4-FC_6H_4)

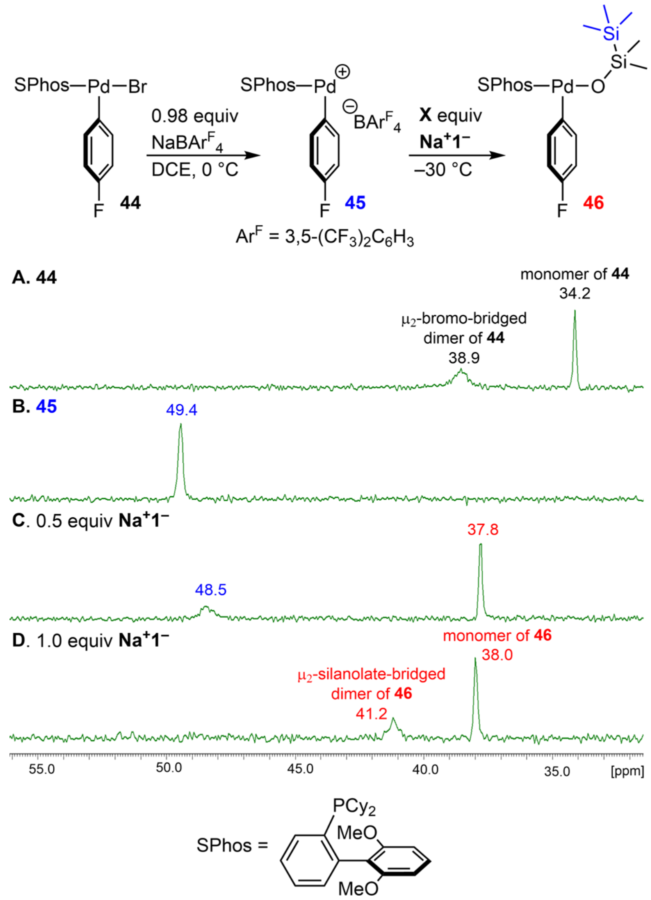


Figure 3. Sequential ^{31}P NMR spectra on the ligand exchange of **44** with sodium silylsilanolate: (A) **44** in DCE at r.t., (B) **45** generated in situ by the reaction of **44** with $NaBAr_4^F$ at 0 °C, (C) **45** with 0.5 equiv of $\mathbf{Na^+1^-}$ at −30 °C, and (D) **45** with total 1.0 equiv of $\mathbf{Na^+1^-}$ at −30 °C in DCE.

(**44**) was synthesized from 4-FC_6H_4Br, $Pd(cod)(CH_2SiMe_3)_2$, and SPhos.[23] As reported by Hii, Pd complexes with SPhos such as **44** were known to show two signals corresponding to the monomer of **44** and its μ_2-halo-bridged dimer (Figure 3A).[24] Cationic Pd(II) species **45** was prepared in situ by the reaction of **44** with $NaBAr_4^F$ at 0 °C (Ar^F = 3,5-$(CF_3)_2C_6H_3$),[25] which showed a downfield shift of the ^{31}P NMR signal[26] at 49.4 ppm (Figure 3B). Upon treatment of **45** with 0.5 equiv of $\mathbf{Na^+1^-}$ at −30 °C, a new ^{31}P NMR signal appeared (37.8 ppm), in addition to the broadened signal for the remaining **45** (Figure 3C). After the addition of an additional 0.5 equiv of $\mathbf{Na^+1^-}$ to the solution at −30 °C, **45** was fully consumed, leaving the species that shows the sharp signal at 38.0 ppm with a broadened signal at 41.2 ppm (Figure 3D). The stoichiometry obtained in these experiments revealed that the attack of $\mathbf{Na^+1^-}$ on **45** rapidly occurred and resulted in the formation of a Pd species **46** bearing a silylsilanolate substituent.[14g] We attributed the slight shift of the broadened signal of **45** in Figure 3C to the fast equilibrium between the free cationic **45** and a complex of **45** and **46**. By analogy to Figure 3A, the sharp signal at 38.0 ppm and the broad peak at 41.2 ppm in Figure 3D could be respectively assigned as the monomeric species of **46** and its silanolate-bridged dimer. A ^{19}F NMR study was separately conducted for the same time courses (see the SI). The product that formed in the reaction was confirmed to be the coupled product 4-fluorotrimethylsi-

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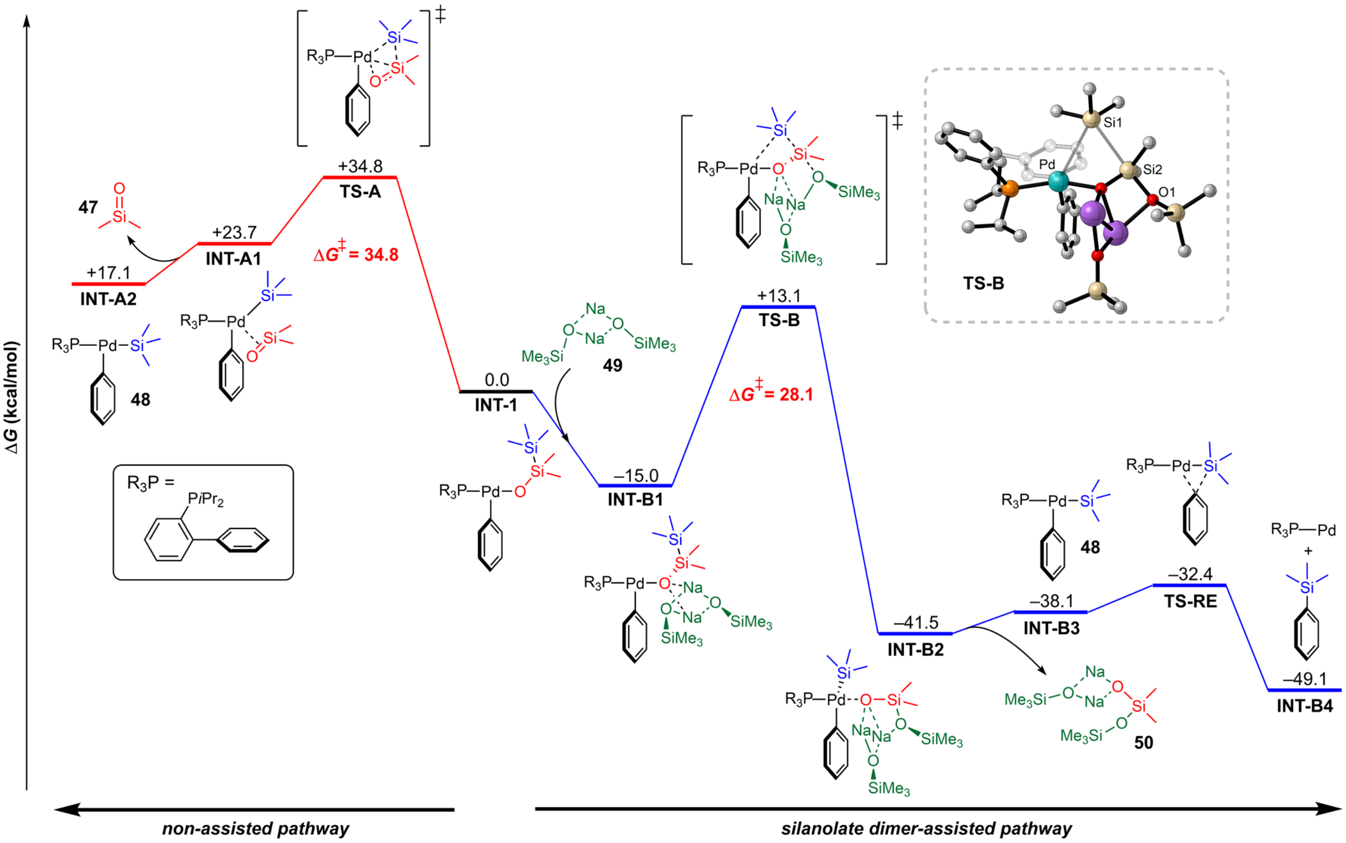

Figure 4. Energy profile for migration of the silyl group of silylsilanolate to the palladium atom at the ωB97X-D/def2-TZVP/SMD (DCE)//ωB97X-D/def2-SVP level of theory at 323.15 K.

lylbenzene from the ^{19}F NMR spectrum. Also, after the solution of **46** was warmed to room temperature, the ^{19}F NMR signal showed the disappearance of **46**. These NMR experiments corroborated the hypothesis that silylsilanolate-coordinated species **46** was a viable intermediate for the palladium-catalyzed silylation.

To figure out the mechanism of the migration of the silyl groups to the palladium atom of **46**, DFT calculations were carried out (Figure 4). Based on the results of the ^{31}P NMR experiments, silylsilanolate-coordinated arylpalladium **INT-1** was chosen as a reliable starting point of the calculated pathway. To simplify the calculations, the ligand was modeled as 2-(diisopropylphosphino)biphenyl. A pathway for the migration of the silyl group directly from **INT-1** (non-assisted pathway) was initially examined. The energy profile is summarized on the left side of Figure 4. The pathway for the direct elimination of dimethylsilanone (**47**) from **INT-1** to afford **INT-A2** via **TS-A** and **INT-A1** was found to be endergonic probably because of the thermodynamically unfavorable generation of a silanone. As the calculated activation energy from **INT-1** to **TS-A** is 34.8 kcal/mol, direct transfer of the silyl group to give **48** is not a likely pathway. We next hypothesized that sodium silylsilanolates that exist in large excess compared with the palladium species would promote the migration of a silyl group. Experimental observations revealed that non-polar solvents such as DCE and toluene were effective for the silylation, so we assumed that an aggregated cluster of sodium silylsilanolates may have an effect on the migration process. To simplify the calculation, an activator was modeled as sodium trimethylsilanolate dimer **49**. The energy profile with the aid of **49** is summarized on the right side of Figure 4 (silanolate dimer-assisted pathway). The complexation of **INT-1** with the sodium trimethylsilanolate dimer **49** proceeds exergonically to afford **INT-B1**. The intramolecular transfer of the trimethylsilyl group to the palladium atom requires a lower activation barrier ($\Delta G^{\ddagger}$ = 28.1 kcal/mol) via **TS-B** to afford **INT-B2** than that via **TS-A**. In the calculated structure of **TS-B** shown in Figure 4, the silicate moiety on the Si2 atom forms a trigonal bipyramidal structure, where Si1 and O1 atoms occupy the apical positions. NBO analysis revealed that the NPA charge of the trimethylsilyl unit of the silylsilanolate in **TS-B** ($-0.552e$) was significantly more negative than the one in **TS-A1** ($-0.110e$) (see the SI). Also, each of NPA charges of Si1 and Si2 atoms in **TS-B** is $+0.875e$ and $+2.081e$, which indicates that the Si1 atom is more negatively charged. Thus, through the formation of a silicate-like structure in **TS-B**, the trimethylsilyl unit containing the Si1 atom is rendered anionic to result in the smooth combination of the Si1 unit with the nearby palladium atom. Dissociation of a silanolate-bearing disiloxane moiety **50** from **INT-B2** affords **INT-B3**. Cluster **50** that goes off in the course of the reaction would again assist in the activation of the transfer of the silyl group. Of note, our simplified calculation model based on a sodium silanolate dimer does not exclude the possibility of the interference of a larger cluster of silanolates. From these results, we conclude that the transfer of the silyl group proceeds with the aid of a cluster of silanolates that would exist in the reaction mixture.[27] A calculation on the reductive elimination of **48** indicates that the final reductive elimination is a low-barrier process through **TS-RE** ($\Delta G^{\ddagger}$ = 5.7 kcal/mol) to exergonically afford **INT-B4**. This result is consistent with

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the fact that such a silylpalladium species was not observed either in the ^{31}P or ^{19}F NMR experiments.

■ CONCLUSIONS

We have developed a new class of practical silylating reagents, sodium silylsilanolates, and confirmed their efficiency for the delivery of silyl groups in the palladium-catalyzed silylation of aryl (pseudo)halides. The new silylation method with silylsilanolates allowed the introduction of a series of silyl groups including the ones that have been regarded to be laborious. A good functional group tolerance exhibited under the conditions proved an applicability to the late-stage silylation of drugs and complex molecules. Mechanistic studies with ^{31}P and ^{19}F NMR experiments and DFT calculations revealed a plausible reaction mechanism for the intramolecular transfer of the terminal silyl group on a silanolate to the palladium center, which was assisted by a cluster of silanolates. These results unveiled a broader potential versatility of sodium silylsilanolates as reagents for transferring broad silyl groups in a range of challenging silylating transformations. Development of other silylsilanolate species and further applications of alkali metal silylsilanolates in combination with other transition-metal catalysts will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02733.

Characterization of the products, experimental procedures, and details for NMR experiments and DFT calculations (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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