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COMMUNICATION

Sodium silylsilanolate enables nickel-catalysed silylation of aryl chlorides.

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Structurally diverse aryl chlorides were silylated with sodium silylsilanolate reagents in the presence of a Ni(cod)$_2$ catalyst complexed with a phosphine ligand; PMe$_2$Ph for electron-rich substrates, and PCy$_2$Ph for electron-deficient ones. The mild reaction conditions allowed the silylation of various aryl chlorides including functionalised drug molecules.

Arylsilanes are fundamental synthetic units that are crucial to the expansion of the researches in medicinal chemistry[1] and materials science.[2] A number of coupling protocols have been developed for transition metal-catalysed silylation of aryl halides as a powerful method for the synthesis of arylsilanes.[3] In most cases, it is necessary to use relatively reactive aryl iodides and bromides, leaving aryl chlorides as challenging yet less explored substrates. Their low cost and wide availability surely render them even more attractive.[4] Previous efforts to develop transition metal-catalysed silylation conditions for aryl chlorides generally resorted to reagents such as hydrosilanes, disilanes, and silylboranes (Fig. 1a). The reactions with hydrosilanes have generally shown very low conversion rates against aryl chlorides[5] except for very recent results with catalytic Pd-Au alloy nano particles.[6] While disilanes generally showed higher yields, the reduced reactivity called for the harsher conditions that restricted the variations of substrates.[7] With silylboranes, silylation of aryl chlorides is limited to one example with a palladium catalyst[8] whereas an iron-catalysed method lately emerged with a relatively broad substrate scope.[9] These studies illustrate the difficulty of using an aryl chloride as a substrate for transition metal-catalysed silylation. Quite recently, we have proposed a sodium silylsilanolate as a new silylating reagent that could be employed for palladium-catalysed silylation of various aryl (pseudo)halides (Fig. 1b).[10]

We reported that our established conditions are much milder than those of conventional ones and were thus applicable to the silylation of highly functionalized substrates. However, these conditions were not applicable to electron-rich aryl chlorides such as *p*-chloroanisole, which remained unreacted even under the optimised conditions. We envisioned that the use of sodium silylsilanolate in combination with a nickel catalyst could address these issues, by leveraging the higher propensity of nickel metal for the oxidative addition of various aryl electrophiles.[11] Also, nickel catalysts have been employed in silylation reaction of various precursors such as benzoic acid derivatives via decarbonylation,[12] aryl ethers,[13] aryl esters,[14] triflates,[15] and fluorides[16] to name a few. Herein, we disclose the first nickel-catalysed silylation of aryl chlorides **1** (Fig. 1c). By implementing a crucial sodium silylsilanolate reagents **2**, arylsilanes **3** were efficiently synthesized under mild conditions.

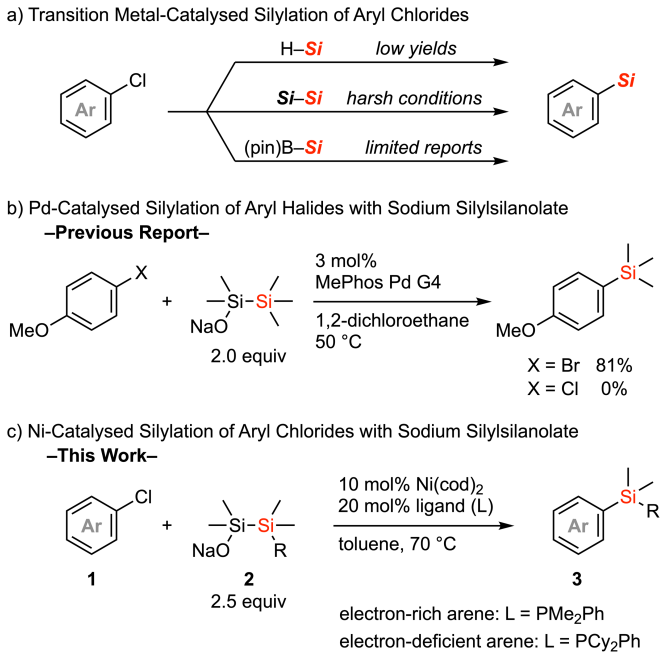

Fig. 1 Overview of the Current Study.

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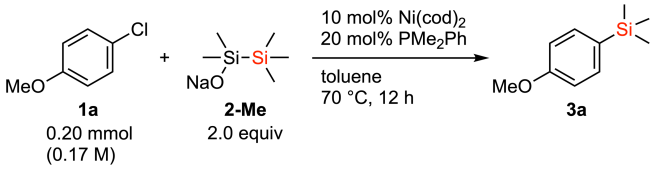
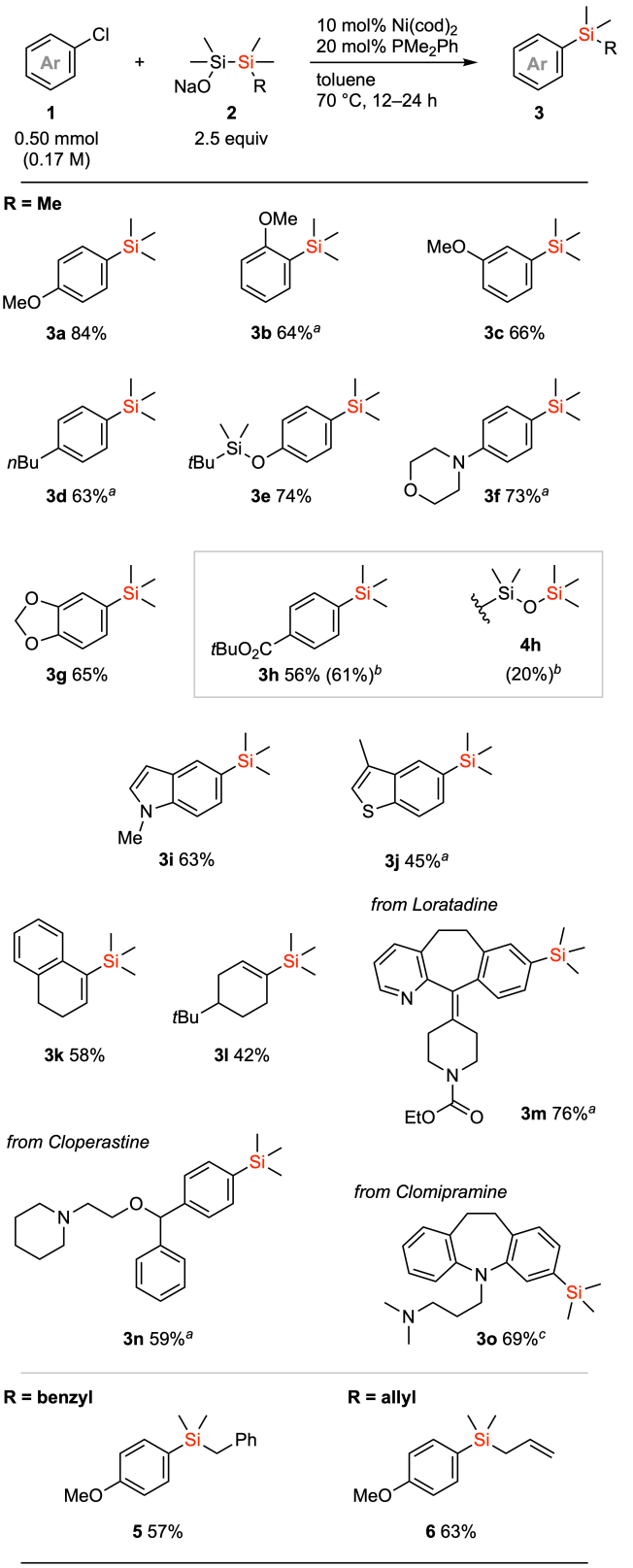
The reaction was initially examined with 2.0 equiv of sodium trimethylsilyldimethylsilanolate (**2-Me**) in the presence of 10 mol% $Ni(cod)_2$ and 20 mol% PMe_2Ph at 70 °C for 12 h, using *p*-chloroanisole (**1a**) as a substrate. Aryltrimethylsilane **3a** was obtained in 71% yield, in concomitant with 5% of remaining **1a** (Table 1, entry 1). Lowering the amount of the catalyst to 5.0 mol% led to the slower reaction (entry 2). When PCy_3 was used as a ligand instead of PMe_2Ph, a lower yield (47%) was observed (entry 3). We confirmed that the use of the preformed complex $NiCl_2(PCy_3)_2$ gave the same yield as that of the *in situ*-formed complex (entry 4). The reaction with $NiCl_2(PPh_3)_2$ was slow and gave only 28% yield (entry 5). An NHC complex with IPr ligand did not improve the efficiency of the reaction (entry 6). In the case of bidentate ligands such as dcype and 2,2'-bipyridine, the reaction was markedly decelerated (entries 7, 8). Bulky monodentate phosphine ligands P*t*Bu_3 (37%) and PCy_2Ph (47%) did not improve the yields (entries 9, 10). A slight decrease in yield (65%) was observed when PEt_2Ph was used (entry 11). The above results indicate the superiority of PMe_2Ph as the ligand for this reaction. An investigation on the solvents showed that THF and hexane gave **3a** in moderate yields (entries 12, 13), whereas the reaction almost stopped in MeCN (entry 14). Finally, we attempted a full conversion of **1a**. The longer reaction time (18 h) or slightly higher temperature (80 °C) was not sufficient for completing the reaction (entries 15, 16). When an increased amount of **2-Me** (2.5 equiv) was used, **1a** was fully consumed, and **3a** was obtained in 82% NMR yield (entry 17). The optimised conditions "2.5 equiv **2**, 10 mol% $Ni(cod)_2$, 20 mol% PMe_2Ph, 12 h, 70 °C in toluene" were employed as the standard conditions in this study.[17]

Table 1 Optimisation of reaction conditions



Entry	Deviation from the standard conditions	**3a**[a] [%]	**1a**[a] [%]
1	none	71	5
2	5.0 mol% $Ni(cod)_2$, 10 mol% PMe_2Ph	50	24
3	PCy_3 instead of PMe_2Ph	47	10
4	10 mol% $NiCl_2(PCy_3)_2$	47	9
5	10 mol% $NiCl_2(PPh_3)_2$	28	49
6	10 mol% $NiCl_2(PPh_3)$(IPr)	24	14
7	10 mol% $NiCl_2$(dcype)	14	55
8	10 mol% $NiCl_2$(bpy)	5	62
9	P*t*Bu_3 instead of PMe_2Ph	37	15
10	PCy_2Ph instead of PMe_2Ph	47	21
11	PEt_2Ph instead of PMe_2Ph	65	2
12	THF instead of toluene	52	10
13	hexane instead of toluene	56	10
14	MeCN instead of toluene	3	77
15	18 h	77	2
16	80 °C	71	6
17	2.5 equiv **2-Me**	82	0

[a]Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.



Scheme 1 Scope of silylation with respect to aryl groups [a]3.5 equiv **2-Me**, 20 mol% $Ni(cod)_2$, 40 mol% PMe_2Ph were used. [b]Determined by ^1H NMR analysis using mesitylene as an internal standard. [c]4.0 equiv **2-Me**, 20 mol% $Ni(cod)_2$, 40 mol% PMe_2Ph were used.

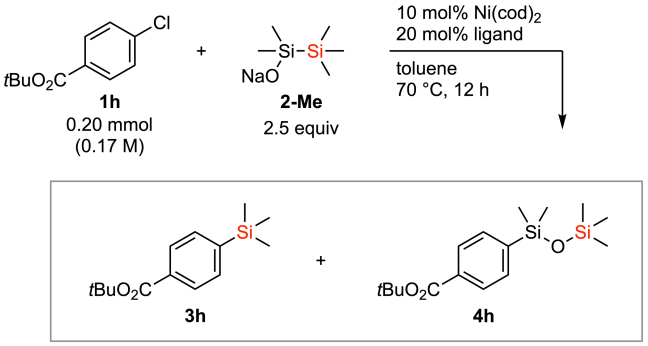
The conditions thus developed for silylation were applied to a series of substrates (Scheme 1). Arylsilanes bearing *o*-, *m*-, and

p-methoxy groups (**3a**–**c**) were obtained in good to moderate yields. Silylated products substituted with *n*-butyl group **3d**, a siloxy group **3e**, or a morpholino group **3f** at the para-positions were obtained in good yields. Arylsilane with 1,3-benzodioxole skeleton **3g** was obtained in 65% yield. The substrate with an electron-withdrawing *t*-butoxycarbonyl substituent gave **3h** in 56% yield. Here, the siloxysilylated byproduct **4h** formed during the transformation, which lowered the yield of **3h** and encumbered the purification. *N*-methyl indole survived the conditions to give **3i** in 63% yield. Benzothiophene was not an optimal substrate, and **3j** was obtained in 45% yield. It is noteworthy that alkenyl chlorides could also be used for this reaction, which provided alkenyl silane **3k** in 58% yield and **3l** in 42% yield. Furthermore, the silylation of non-simple bioactive substances was investigated. Loratadine contains pyridyl and carbamate moieties and was employed as a substrate to provide the silylated product **3m** in 76% yield. Cloperastine and clomipramine with tertiary amine moieties also gave silylated products **3n** and **3o** in acceptable yields. We also examined the introduction of other silyl groups. Similar conditions using a silylsilanolate **2-Benzyl** or **2-Allyl** allowed the synthesis of the corresponding arylsilane **5** or **6** bearing a benzyldimethylsilyl or allyldimethylsilyl groups.[10]

As shown in the bordered entry in Scheme 1, **3h** was generated in concomitant with the siloxysilyl byproduct **4h**. This example indicates the difficulty of applying the current conditions to the electron-deficient substrates. Based on this result, ligands were re-investigated for the electron-deficient substrates in order to reduce the formation of siloxysilylated byproducts in comparison to PMe_2Ph (Table 2, entry 1). **1h** was employed as a representative substrate to screen ligands. Both small PMe_3 and very bulky $PtBu_3$ were ineffective, either giving rearranged **4h** or the reduced yield of **3h** (entries 2, 3). PPh_3 gave a better result with a higher yield of **3h** (67%) and the reduced amount (8%) of **4h** (entry 4). Finally, PCy_2Ph was found to suppress the formation of byproduct **4h** to a trace amount, and the yield of **3h** was greatly improved to 83% (entry 5). Although the effect of the ligand is not clear at this stage, it is unlikely that the steric factor is the only reason that affects the ratio between **3h** and **4h**. We thus employed PCy_2Ph as a ligand for electron-deficient substrates and investigated the substrate scope under the modified conditions (Scheme 2). Arylsilanes substituted at the *para*-position with cyano (**3p**) and acetyl group (**3q**) were obtained in good yields. The reaction allowed two electron-withdrawing substitutions (cyano and CF_3) at the *meta*-positions (**3r**). Relatively electron-poor 2-naphthylsilane **3s** could be synthesized in 80% yield. *p*-B(pin) substituent was also compatible although the product **3t** was obtained only in 37% yield, which would be due to a partial decomposition of the B(pin) group under the reaction conditions. In the case of a COX-1 inhibitor SC-560 bearing an electron-withdrawing pyrazole moiety, the desired silylated product **3u** was efficiently obtained in 73% yield.

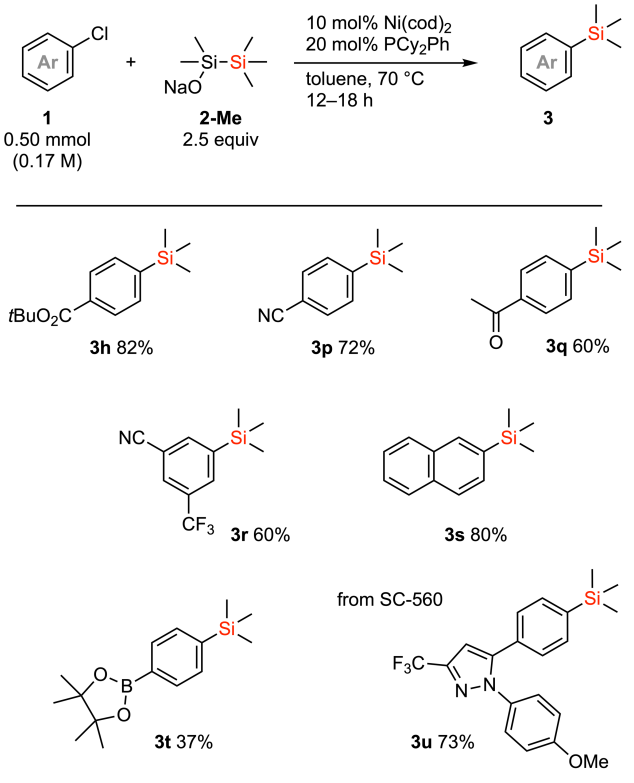
In Fig. 2, a plausible reaction mechanism is proposed by analogy to the palladium-catalysed mechanism that we recently reported.[10] As the nickel-catalysed reaction of aryl halides is known to proceed via a Ni(0)/Ni(II) cycle, we did not take

Table 2 Optimisation of ligands for electron-deficient aryl chloride



Entry	Ligand	**3h** [%][a]	**4h** [%][a]
1[b]	PMe_2Ph	61 (56[c])	20
2	PMe_3	58	33
3	$PtBu_3$	20	13
4	PPh_3	67	8
5	PCy_2Ph	83	1

[a]Determined by ^1H NMR analysis using mesitylene as an internal standard. [b]0.50 mmol scale. [c]Isolated yield.



Scheme 2 Scope of silylation with respect to more electron-deficient aryl groups

a Ni(I)/Ni(III) cycle for this reaction.[18] Oxidative addition of ArCl to Ni(0) would provide a Ni(II) species **A**, which then participates in ligand exchange with sodium silylsilanolate **2** to form a silylsilanolate-coordinated divalent nickel species **B**. Similarly to the mechanism for the palladium-catalysed reaction, the terminal silyl group would be rearranged to the Ni centre to give the silylnickel species **C**. The concomitant energetically-

favoured formation of a polysiloxane from the intermediate silanone species would compensate for the energy required for transferring silyl group to the nickel centre. Reductive elimination from **C** would lead to the formation of an arylsilane **3** with simultaneous regeneration of the Ni(0) species, thus completing the catalytic cycle. Byproduct **4** would form through the siloxysilylated nickel intermediate **D**, which would be generated via 1,2-anion migration that resembles [1,2]-Brook rearrangement.[19]

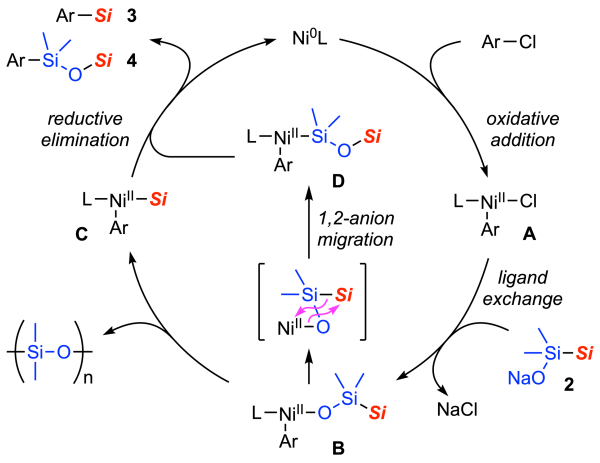


Fig. 2 Plausible catalytic reaction mechanism.

In conclusion, sodium silylsilanolate that we have developed was applied to the silylation of aryl chlorides using a nickel catalyst. We have shown that a catalytic system using $Ni(cod)_2$ and PMe_2Ph is optimal for the silylation of electron-rich aryl chlorides, which was not possible under the previously reported conditions based on palladium catalysts. The current method can also be applied to the aryl chloride moiety of highly functionalized drugs, demonstrating the high degree of functional group compatibility. In addition to the TMS groups, the silyl groups substituted with benzyl or allyl groups can be introduced by applying the corresponding silylsilanolates. In the case of electron-deficient substrates, a siloxysilylated byproduct was observed in concomitant with a desired silylated product. We have found that the use of PCy_2Ph as a ligand suppresses this side reaction and enables the selective synthesis of the desired silylated product from electron-deficient substrates. The reaction of silylsilanolate species in combination with other transition metal species will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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