Site-Selective Electrochemical C–H Silylations of Pyridines Enabled by Temporary Reductive Dearomatization

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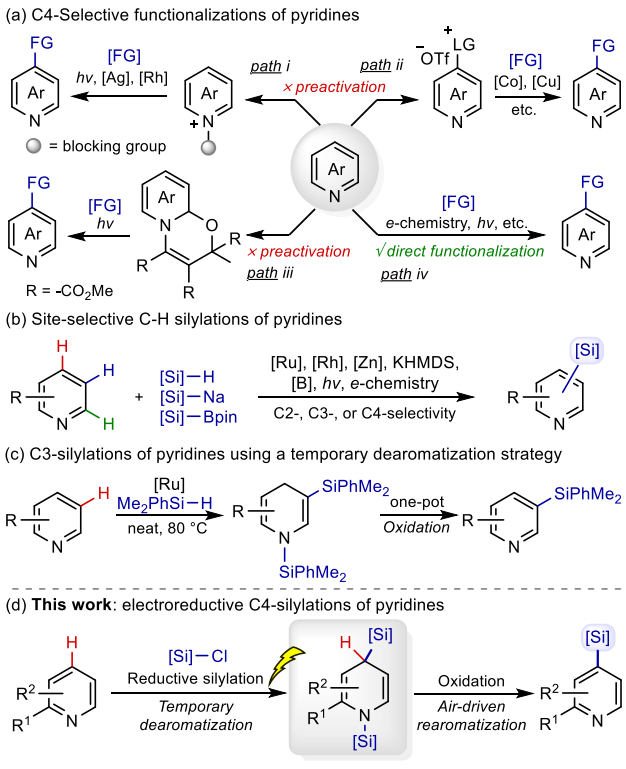
Abstract: Site-selective pyridine C–H silylation chemistry is of significant value but remains underdeveloped. In this study, we demonstrated that electron-deficient pyridines are highly selectively reductively silylated at the C4-position under electrochemical reduction conditions. A diverse array of C4-silylated pyridines was synthesized in good-to-excellent yields using common chlorosilanes as activating agents. Additionally, the use of bulky chlorotriisopropylsilane led to the formation of the C5-silylated products, albeit in moderate yields. This method is noteworthy due to its mild reaction conditions, simplicity, and excellent site selectivity for a diverse range of pyridines. Mechanistic studies revealed that the reaction involves temporary dearomatization to yield a 1,4-disilylated compound, which is quickly converted into the final C4-silylated pyridine through hydrolysis and air-driven rearomatization.

Introduction

N-Heteroarenes, particularly pyridines, play widespread roles in biologically active molecules,[1] ligands,[2] catalysts,[3] and materials.[4] Owing to the prevalence of *para*-substituted pyridines in medicinal agents, including milrinone,[5] tropicamide,[6] brequinar,[7] and others,[8] direct C–H functionalization at the C4 position of the pyridine ring has gained significant academic and industrial attention.[9] Recent significant advances in the synthesis of C4-functionalized pyridines include Minisci-type reactions using pyridinium compounds as substrates (Scheme 1a, *path i*),[10] strategies that employ C4-prefunctionalization or *in-situ*-generated phosphonium or *N*-(4-pyridyl)-DABCO salts (Scheme 1a, *path ii*),[11] and photo-induced C4-functionalization chemistry involving oxazino pyridine derivatives (Scheme 1a, *path iii*).[12] Although these seminal studies are generally useful, they still exhibit some deficiencies, including the requirement for specialized prefunctionalized starting materials, relatively narrow substrate scopes, low-to-moderate efficiencies, or the need for harsh temperatures. Consequently, strategies for C–H functionalizing pyridine derivatives that do not require substrate preactivation remain highly sought after (Scheme 1a, *path iv*).[13] For instance, Yu and Lin reported the direct electrochemical C4-carboxylations of pyridines using carbon dioxide, with selectivity switching to the C5-position as the electrochemical cell was changed from an undivided one to a divided one.[13b] We previously investigated the coupling behavior of pyridine-derived molecules under reducing conditions;[14] these recent elegant tactics have rekindled our interests in pyridine functionalization.

Organosilicon compounds play crucial roles in materials science owing to their distinctive physical and chemical properties,[15] and because they are highly versatile and applicable to various organic transformations.[16] Recently, considerable attention has been directed toward site-selective C–H silylations of pyridines to yield valuable silylated compounds (Scheme 1b).[17] For instance, in 2015, the Oestreich group reported ruthenium-catalyzed electrophilic pyridine C–H silylation chemistry that involved a temporary dearomatization strategy, to afford C3-selective silylated products in good yields (Scheme 1c).[17a] In 2019, Martin developed potassium-bis(trimethylsilyl)amide-mediated pyridine C–H silylation chemistry in which C2- or C4-selectivity can be adjusted through choice of solvent.[17b] These silylation reactions use a variety of silanes, predominantly hydrosilanes or specialized silanes such as silylborane and sodium trimethylsiliconide that require prior synthesis.



Scheme 1. C4-selective functionalizations of pyridines and site-selective silylations of heteroarenes: Research background.

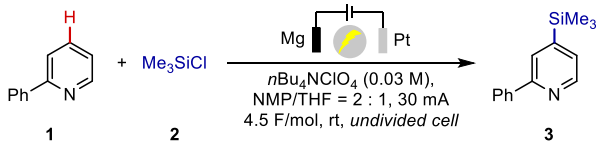
We previously developed a series of reductive silylation reactions involving electron-deficient heteroarenes and aromatic-

conjugated substrates that use chlorosilanes under magnesium- or calcium-promoted reduction conditions.[14a][18] To the best of our knowledge, C–H silylation chemistry that uses inexpensive and commercially available chlorosilanes under electroreduction conditions, targets pyridine derivatives without directing groups, and does not require substrate preactivation, has not been reported. With our sustained interest in the synthesis of valuable organosilicon compounds, we now present our endeavors toward a method that uses a temporary dearomatization strategy for site-selectively silylating pyridines under very mild electroreduction conditions (Scheme 1d).[19][20]

Results and Discussion

Our investigation began by assessing the direct electroreductive silylation of 2-phenylpyridine (**1**) with chlorotrimethylsilane (**2**) (Table 1). The optimal conditions for this reaction include the use of a magnesium plate as the sacrificial anode, platinum plate as the cathode, nBu$_4$NClO$_4$ (0.03 M) as the supporting electrolyte in a mixture of NMP and THF as the solvent in an undivided cell. These conditions yielded C4-silylated product **3** in 87% yield at a constant current of 30 mA (entry 1). Substituting the solvent for straight NMP or THF resulted in yields of 77% and 28%, respectively, for the C4-silylated product **3** (entries 2 and 3). Notably, a significantly enhanced yield was obtained (77% *vs* 28%) as the concentration of the electrolyte in THF was increased from 0.03 to 0.30 M (entry 4). The reaction was highly efficient even in the absence of an electrolyte, with **3** obtained in 81% yield (entry 5), which suggests that the anodically generated Mg^{2+} (from the sacrificial anode) and the Cl^- from chlorotrimethylsilane may facilitates electrical conduction (see Figure S1, Supporting Information for details). As expected, product **3** was not obtained without electrical input (entry 6). The study also revealed that a total charge of 4.5 F/mol is optimal (entry 7). When employing a divided electrochemical cell, C4-silylated product **3** was obtained in only 42% yield (entry 8). Additionally, we investigated factors such as the current, reagent equivalents, solvent, concentration, reaction temperature, electrolyte, and electrode to no avail, with no further improvement in yield observed (see Tables S1–S3 for details). In addition, the use of a stoichiometric reducing metal, such as calcium or magnesium (rather than electrochemical reduction) resulted in a slightly lower yield of 80% with calcium, and 41% with magnesium (entries 9 and 10, see Table S4 for details).

Table 1. Optimizing the reaction conditions.[a]



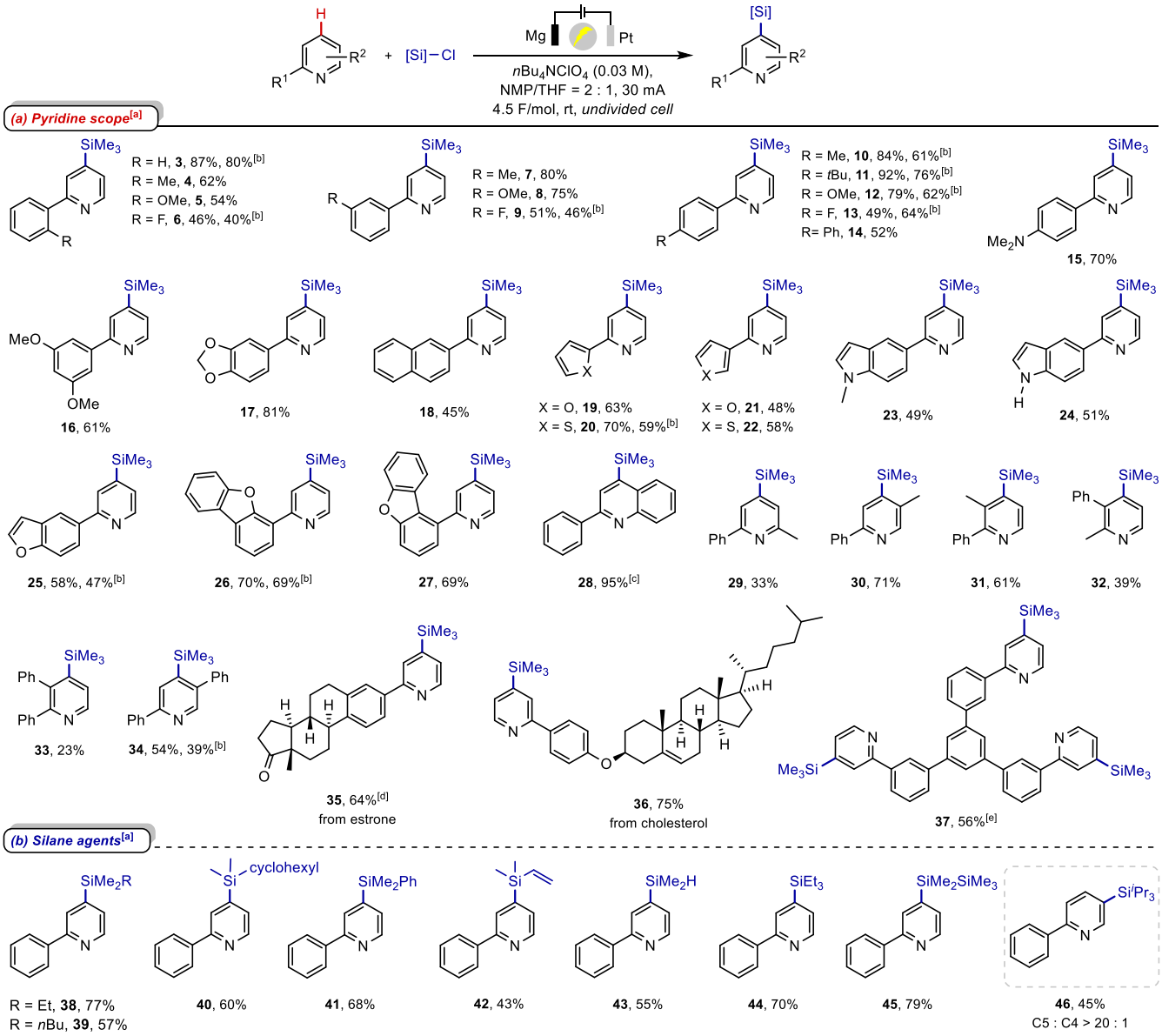
1 **2** **3**

Entry	Variations from standard conditions	Yield of **3** [%][b]
1	None	87
2	NMP as solvent; nBu$_4$NClO$_4$ (0.03 M)	77
3	THF as solvent; nBu$_4$NClO$_4$ (0.03 M)	28
4	THF as solvent; nBu$_4$NClO$_4$ (0.30 M)	77
5	No supporting electrolyte	81
6	No electricity	0
7	4.0 F/mol; 5.0 F/mol	77; 87
8[c]	Divided cell; nBu$_4$NClO$_4$ (0.30 M)	42
9[d]	Ca instead of electroreductive silylation	80
10[d]	Mg instead of electroreductive silylation	41

[a] Reaction conditions of entry 1: 2-phenylpyridine (**1**, 0.5 mmol, 1 equiv.), chlorotrimethylsilane (**2**, 5 equiv.), Mg (+) / Pt (−), nBu$_4$NClO$_4$ (0.03 M), NMP/THF = 2:1 (*v*/*v*) (0.1 M, 5 mL), under Ar; electrolysis at rt at a constant current of 30 mA (current density = 9.7 mA/cm^2) until 4.5 F/mol of total charge had passed. [b] C4-silylated product **3** was identified as a single regioisomer by GC and GC-MS; reported yields are isolated yields obtained after flash column chromatography. [c] 2-Phenylpyridine (**1**) on a 1 mmol scale. [d] Reactions using calcium granules or magnesium turnings instead of electrochemical reduction: 2-phenylpyridine (**1**, 0.5 mmol, 1 equiv.), chlorotrimethylsilane (**2**, 6 equiv.), and Ca or Mg (3 equiv.) in NMP (0.1 M, 5 mL) under Ar, rt, 18 h.

We systematically studied the substrate scope of our protocol under the optimal conditions (Scheme 2) by initially scrutinizing the effects of various substituents, which revealed that a diverse array of substituents are compatible. Specifically, 2-arylpyridines with electron-donating groups, such as methyl, *tert*-butyl, or methoxy, at the *ortho*-, *meta*-, and *para*-positions of the aryl ring were well tolerated, to afford C4-silylated products **4**, **5**, **7**, **8**, **10**–**12** in yields of between 54% and 92%. Substrates featuring fluorine atoms were also tolerated, with desired products **6**, **9**, and **13** obtained in moderate yields. Additionally, substrates bearing functionalities such as phenyl, tertiary amino, and multiple substituents were also successfully transformed into **14**–**17**, respectively. The reaction was also found to be compatible with the naphthyl moiety (to form **18**) and common heterocyclic moieties, including furyl (to form **19** and **21**), thienyl (to form **20** and **22**), indolyl (to form **23** and **24**), benzofuranyl (to form **25**), and benzobifuranyl (to form **26** and **27**). Additionally, 2-phenylquinoline was compatible with our electroreductive silylation protocol to afford the corresponding product **28** in satisfactory yield. Furthermore, we discovered that disubstituted pyridines are also competent substrates, with C4-silylated products **29**–**34** exclusively obtained in yields of between 23% and 71%. On the other hand, the use of calcium as the reductant delivered **6**, **9**, **10**, **11**, **12**, **13**, **20**, **25**, **26**, and **34**, albeit in lower yields of 39–76%. This reaction is also applicable to bioactive molecules and functional materials; noteworthy examples include the successful conversion of estrone into **35** in 64% yield, cholesterol into **36** in 75% yield, and 1,3,5-tri(*m*-pyridin-2-ylphenyl)benzene into **37** in 56% yield.

We finally explored the scope of low-to-moderately sterically hindered silanes, including common chlorotrialkylsilanes, chlorodimethylvinylsilane, chlorodimethylsilane, and chloropentamethyldisilane, with the aim of generating a variety significantly synthetically useful C4-silylated pyridines **38**–**45** in satisfactory yields (Scheme 2b). Surprisingly, bulky chlorotriisopropylsilane underwent electroreductive C5-silylation, to afford the C5-silylated product **46** in 45% yield and excellent site-selectivity. Unfortunately, attempts to enhance the yield of **46**, including screening the current, varying the equivalents of chlorosilane, exploring various additives, and using a divided electrochemical cell, were unsuccessful.

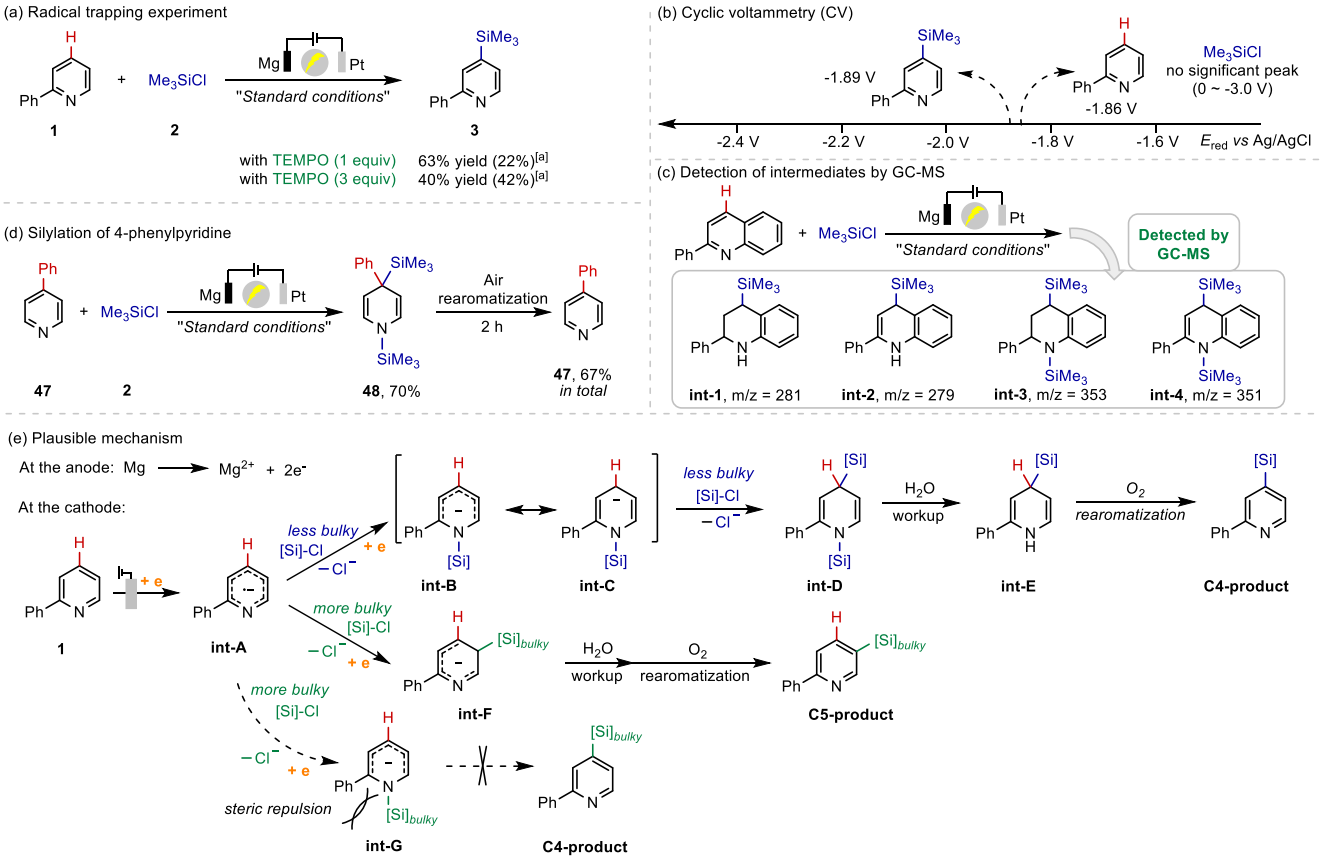


Scheme 2. Pyridine and silane substrate scope. Isolated yields are reported after flash column chromatography. Unless otherwise noted, the C4-silylated product is the main (>20:1) regioisomer. [a] Standard conditions: pyridine derivative (0.5 mmol, 1 equiv.) and chlorosilane (5 equiv.), Mg (+) / Pt (−), nBu$_4$NClO$_4$ (0.03 M), constant current at 30 mA, 4.5 F/mol, NMP/THF = 2:1 (*v*/*v*, 0.1 M, 5 mL) under Ar, rt. [b] Reactions using calcium granules instead of electrochemical reductive silylation: pyridine derivative (0.5 mmol, 1 equiv.), chlorosilane (6 equiv.) and calcium granules (3 equiv.) in NMP (0.1 M, 5 mL) under Ar, rt, 18 h. [c] Constant current of 10 mA. [d] The crude products obtained from the first step were subjected to DDQ-driven oxidation: DDQ (0.5 equiv.), DCM (1 mL), rt, 6 h. [e] Chlorotrimethylsilane (15 equiv.) was used.

Unfortunately, our protocol was found to be incompatible with 2-methylpyridine, 2-methylquinoline, 2,6-diphenylpyridine, and bipyridines, including 2,2'-bipyridine and 2,3'-bipyridine, with either no reaction observed or a complex mixture of silylated products obtained (see Scheme S1 for a comprehensive overview).

Radical-trapping experiments were used to gain insight into the possible reaction mechanism (Scheme 3a). The reaction was not completely inhibited when one or three equivalents of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), a radical scavenger, was included under the standard conditions; desired product **3** was obtained in yields of 63% and 40%, respectively, with the starting materials recovered in yields of 22% and 42%, respectively. These results suggest that the reaction is unlikely to proceed via a radical pathway. We next subjected 2-phenylpyridine and chlorotrimethylsilane to cyclic voltammetry (CV) (Scheme 3b and Figure S6), with a reduction peak observed at E_{red}= −1.86 V *vs* Ag/AgCl for the former, while the latter displayed no significant reduction peak in the 0 to −3.00 V range. Notably, the CV trace of the 2-phenyl-4-trimethylsilylpyridine product exhibited a reduction peak close to that of 2-phenylpyridine (E_{red}= −1.89 V *vs* Ag/AgCl), which suggests that **3** is not the final product of the electroreductive silylation reaction; rather it is produced during the post-treatment process. We then examined the electroreductive silylation of 2-phenylquinoline using GC-MS (Scheme 3c). After electrolysis, the reaction mixture was poured into a beaker containing saturated sodium bicarbonate and ethyl acetate, and the organic phase was directly subjected to GC-MS, which seemed to reveal the presence of mono- and disilylated intermediates **int-1**, **int-2**, **int-3**, and **int-4**. Unfortunately,

attempts to isolate these intermediates were unsuccessful due to instability issues.[21] We next electroreductively silylated 4-phenylpyridine (**47**) under standard reaction conditions (Scheme 3d). 1,4-Disilylated product **48** was obtained in 70% yield as a relatively stable intermediate, although it decomposed quickly and transformed into starting material **47** after 2 h of exposure to air.



Scheme 3. Mechanistic studies and a plausible mechanism. [a] Recoveries of the 2-phenylpyridine starting material is shown in parentheses.

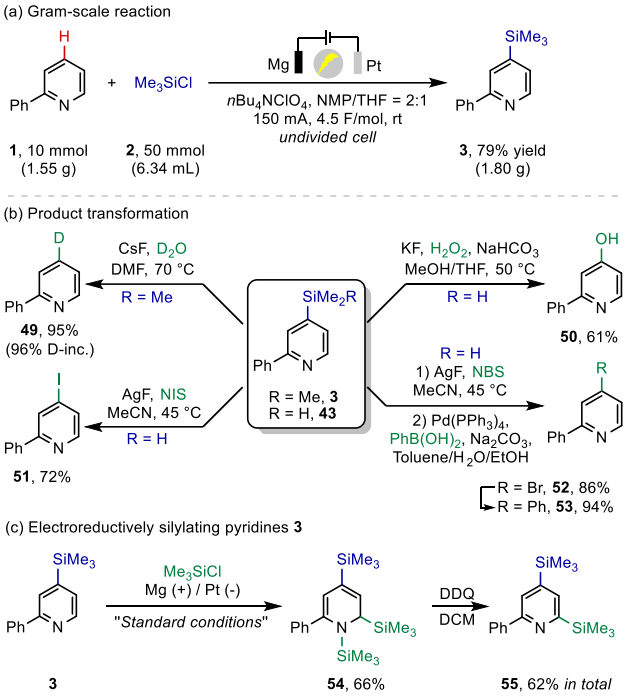
Based on the experimental data provided above and previous reports,[18][20][21] we propose a plausible mechanism for our electroreductive silylation chemistry (Scheme 3e). The initial one-electron reduction of 2-phenylpyridine forms radical anion **int-A**. In reactions with less bulky chlorosilanes, the nitrogen atom, which bears the highest electron population in the pyridine ring, attacks the chlorosilane to form an *N*-silylated intermediate. The *N*-silylated intermediate subsequently acquires a second electron to yield **int-B**, which is resonance stabilized by the benzene ring; this anion then preferentially reacts with another chlorosilane molecule at the C4 position to afford **int-D**, with hydrolysis and rearomatization affording C4-silylated **3** as a single product in a highly regioselective manner. On the other hand, steric repulsion between the aryl and bulky silyl groups prevents the formation of sterically disfavored **int-G** when a bulky chlorosilane, specifically chlorotriisopropylsilane, is used. Instead, silylation occurs at the C5 position, which is the most electron rich among the carbon atoms of the pyridine ring, leading to the formation of **int-F**, which is resonance stabilized by the benzene ring. Hydrolysis and rearomatization then affords the final C5-silylated product.

Finally, we focused on preparing the product on a gram scale and subsequently transforming silylated products (Scheme 4). As shown in Scheme 4a, we successfully synthesized C4-silylated product **3** on a 10 mmol scale with no significant decrease in yield (Scheme 4a). The product was subsequently derivatized to highlight its synthetic utility (Scheme 4b). The trimethylsilyl group was transformed into a deuterium atom in 95% yield in DMF with deuterium oxide and CsF. Moreover, the dimethylsilyl group underwent Tamao–Fleming oxidation to furnish 4-hydroxy-2-phenylpyridine (**50**) in 61% yield. Additionally, the dimethylsilyl group was converted into an iodide or bromide using NIS or NBS reagents. The resulting 4-bromo-2-phenylpyridine (**52**) underwent Suzuki coupling with phenylboronic acid to afford 2,4-diphenylpyridine (**53**) in 94% yield. We next explored electroreductively silylating the C4-silylated product **3** to investigate whether or not further silylation is possible (Scheme 4c). Interestingly, C4-silylated pyridine **3** underwent reductive 1,6-disilylation to furnish the dearomatized product **54** in 66% yield, which was subsequently subjected to DDQ-driven oxidation to yield the C4- and C6-disilylated pyridine **55** in 62% overall yield.

Conclusion

Herein, we described site-selective reductive silylation reactions of pyridines under electroreduction conditions. A diverse array of C4-silylated pyridines was synthesized under reducing conditions using various chlorosilanes. Mechanistic studies revealed that the reaction involves temporary dearomatization to yield a 1,4-disilylated product, which is then

quickly converted into the final product through hydrolysis and air-driven rearomatization. This method is notable because of its mild reaction conditions, simplicity, and excellent C4-selectivity for a diverse range of pyridines. Further studies are underway in our laboratory.



Scheme 4. Gram-scale reactions and product transformations.

Acknowledgements

The authors would like to thank Dr. Yifan Jin for fruitful suggestions. This work was financially supported by Scientific Research Start-up Grants of ZZU.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Electrochemistry • Reductive coupling • Silylation • Site-selective • Pyridine

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