C–H Activation

International Edition: DOI: 10.1002/anie.201508181
German Edition: DOI: 10.1002/ange.201508181

Catalytic Electrophilic C–H Silylation of Pyridines Enabled by Temporary Dearomatization

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Abstract: *A C–H silylation of pyridines that seemingly proceeds through electrophilic aromatic substitution (S_EAr) is reported. Reactions of 2- and 3-substituted pyridines with hydrosilanes in the presence of a catalyst that splits the Si–H bond into a hydride and a silicon electrophile yield the corresponding 5-silylated pyridines. This formal silylation of an aromatic C–H bond is the result of a three-step sequence, consisting of a pyridine hydrosilylation, a dehydrogenative C–H silylation of the intermediate enamine, and a 1,4-dihydropyridine retro-hydrosilylation. The key intermediates were detected by ^{1}H NMR spectroscopy and prepared through the individual steps. This complex interplay of electrophilic silylation, hydride transfer, and proton abstraction is promoted by a single catalyst.*

Catalytic processes that employ hydrosilanes to transform an unactivated C–H bond into a synthetically valuable C–Si bond are presently garnering tremendous attention.[1] The current state of the art includes broadly applicable transition-metal-catalyzed C–H silylations[2] and a rather unorthodox C–Si bond formation promoted by KO*t*Bu,[3] as well as Friedel–Crafts-type approaches.[4] Something that these and other methods, except for a few recent examples,[5] share is that pyridines do not participate readily. Instead, the pyridin-2-yl donor in **1** usually acts as a robust directing group in transition-metal-catalyzed C–H silylation (Figure 1, left).[6] We disclose herein a counterintuitive solution to the problem of pyridine C–H silylation that even leaves the phenyl group in **1** intact (Figure 1, right).

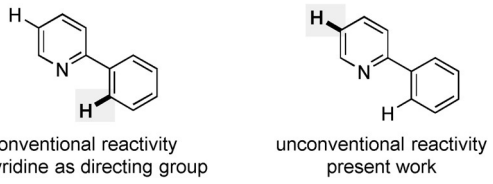

Figure 1. C–H bonds in 2-phenylpyridine (**1**) addressed by conventional (left) and unconventional (right) C–H silylation.

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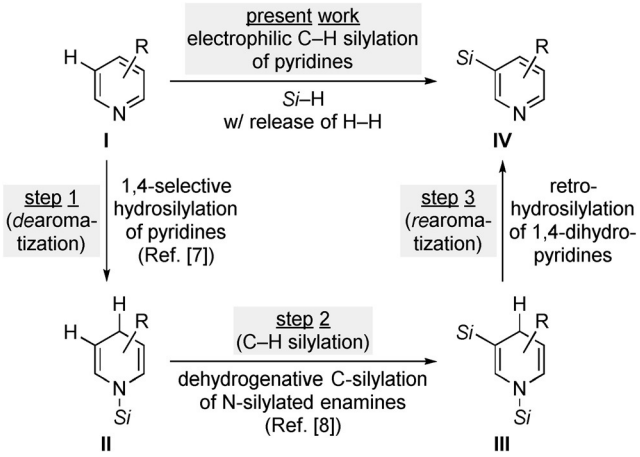
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201508181.

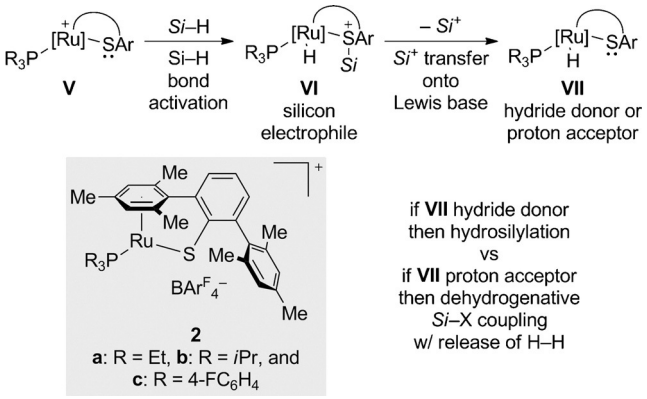
Our strategy merges 1,4-hydrosilylation of pyridines[7] (**I**→**II**), dehydrogenative C-silylation of N-silylated enamines[8,9] (**II**→**III**), and retro-hydrosilylation of 1,4-dihydropyridines[10] (**III**→**IV**) into a one-pot procedure (Scheme 1). A simplified description of this three-step sequence is that the



Scheme 1. Strategy for an electrophilic C–H silylation of pyridines that does not follow an S_EAr reaction at the pyridine nucleus. *Si* = triorganosilyl.

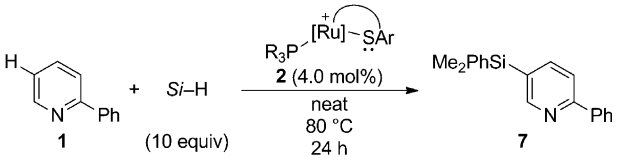
reversible 1,4-hydrosilylation[10] is the tool to break (step 1) and reestablish (step 3) the aromaticity of the pyridine **I**.[11,14,15] The actual C–H silylation event (step 2) happens at the stage of the dearomatized pyridine, i.e., the 1,4-dihydropyridine **II**. All steps are mediated by the same catalyst, the tethered Ru–S complex **V**[16] (**2**; Scheme 2). The Ru–S bond in **V** cleaves the Si–H bond of hydrosilanes into a metal hydride and a sulfur-stabilized silicon cation (**V**→**VI**).[17] Lewis-basic substrates such as pyridines **I**[7] or enamines **II**[8] abstract the silicon electrophile from **VI** to form the Ru–H complex **VII** (**VI**→**VII**). The dichotomous reactivity of **VII** is critical for the success of the present undertaking: it reacts either as a hydride donor or a proton acceptor, thereby enabling both hydrosilylations (as step 1; Scheme 1) and dehydrogenative couplings (as step 2; Scheme 1). When these components all act in concert, the one-pot transformation of pyridines **I** into 5-silylated pyridines **IV** outlined in Scheme 1 will be achievable.

The individual reactions[7,8] proceed at room temperature but the desired sequence then stops at the stage of the 1,4-dihydropyridine. We therefore tested pyridine (**3**) as well as selected 3-[7] and 2-substituted congeners (**4**–**6** and **1**; Figure 2)



Scheme 2. Cooperative Si–H bond activation and silicon cation transfer (counteranion $BAr^F{}_4^-$ omitted for clarity, top), and the tethered Ru–S complexes **2** tested as catalysts (bottom). Ar^F = 3,5-bis(trifluoromethyl)phenyl.

Table 1: Catalyst and hydrosilane identification.[a]



Entry	Catalyst	Hydrosilane	Conv. [%][b]
1	**2a** (R = Et)	Me_2PhSiH	33
2	**2b** (R = *i*Pr)	Me_2PhSiH	82
3	**2c** (R = 4-FC_6H_4)	Me_2PhSiH	47
4	**2b** (R = *i*Pr)	$EtMe_2SiH$	3[c]
5	**2b** (R = *i*Pr)	$MePh_2SiH$	no reaction
6	**2b** (R = *i*Pr)	Et_3SiH	no reaction

[a] Reactions were performed on a 0.14 mmol scale. [b] Determined by GLC analysis with reference to the starting material. [c] Desired pyridine not detected by GLC–MS analysis.

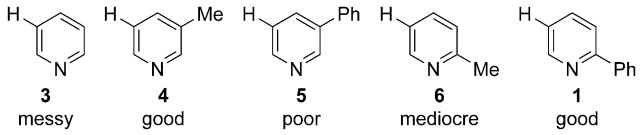
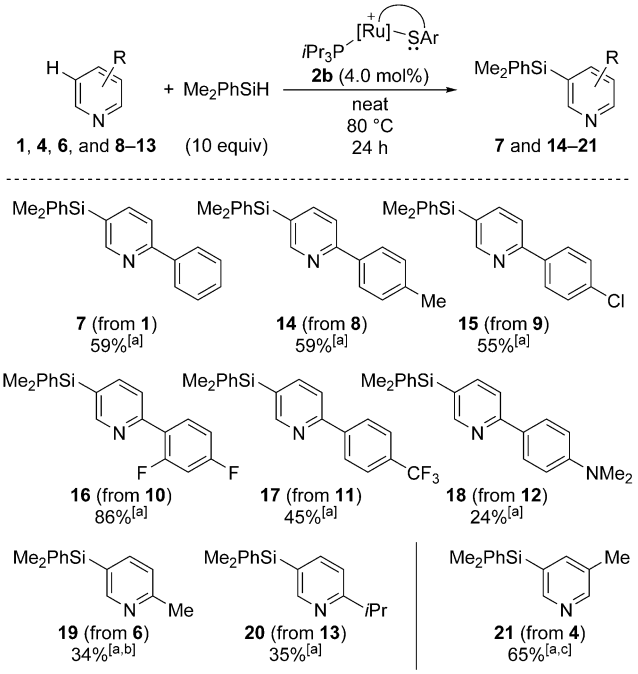


Figure 2. Performance of model compounds tested in the initial screening.

at 80 °C with catalysts **2a**[7] and **2b**.[8] The reaction of 4-substituted pyridines was messy (data not shown). It must be noted that 2-substituted pyridines **6** and **1** had not been amenable to room-temperature hydrosilylation.[7] A broad screening of reaction parameters applied to those pyridines revealed that parent **3** yields complex mixtures while the other model compounds showed formation of the desired 5-silylated pyridine derivative (Figure 2). The reactions of pyridine **1** with a phenyl group at C2 were fairly clean, and we continued with **1** to further optimize the method. Also, unlike the work of Chang, Park, and co-workers,[9] quinoline yielded an intractable mixture.

Another result of this preliminary screening was that the use of any solvent, typically non-donating solvents such as (chlorinated) hydrocarbons, thwarts conversion. As a consequence, reactions were run in excess hydrosilane (10 equiv). Under these boundary conditions, we tested catalysts **2a–c** in the C–H silylation of **1** with Me_2PhSiH (**1**→**7**; Table 1, entries 1–3). Complex **2b**, which was previously used in enamine dehydrogenative coupling,[8] was superior to **2a** from the pyridine hydrosilylation;[7] **2c**,[18] which has an electron-deficient phosphine ligand, was also less effective. Other triorganosilanes such as $EtMe_2SiH$, $MePh_2SiH$, and Et_3SiH did not participate in this multistep sequence (Table 1, entries 4–6).

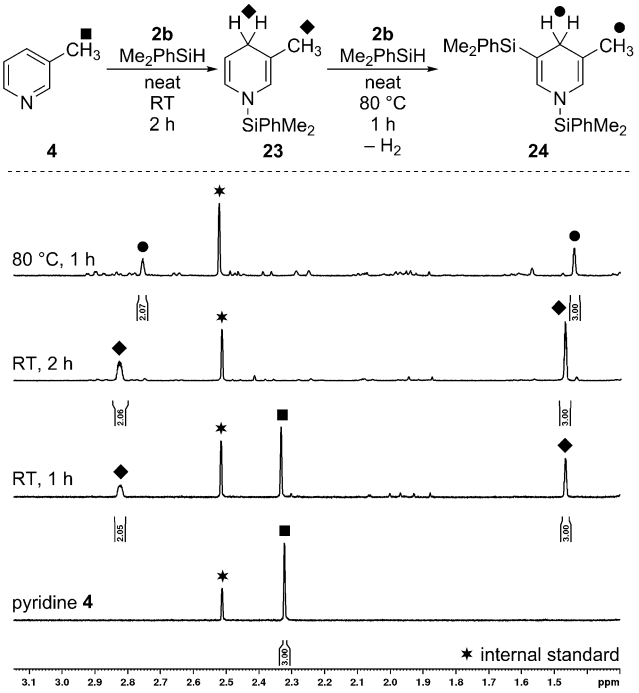
The optimized reaction setup afforded the 5-silylated 2-phenylpyridine **7** in 59% yield of isolated product. We consider this a decent result, keeping in mind that the reaction passes through several reactive intermediates. Despite the moderate yields in this and subsequent reactions, we were not able to identify any major byproducts. We next probed the scope with respect to pyridines substituted with electronically different aryl groups in the 2-position (**8**–**12**; Scheme 3). Both electron-donating and electron-withdrawing groups were tolerated. Compound **10**, which has a difluorinated aryl group, afforded an excellent 86% yield, but a dimethylamino group in the 4-position of the aryl group led to a diminished



Scheme 3. 5-Selective C–H silylation of 2- and 3-substituted pyridines. [a] Reactions were performed on a 0.14 mmol scale. Yields of isolated products after purification by flash chromatography on silica gel. [b] Isolated from a complex mixture, still containing impurities. [c] Reaction was performed on a 0.14 mmol scale with 5.0 equiv of the hydrosilane at 80 °C for 3 h.

yield of 24%. Alkylation at C2 of the pyridine was also accepted although yields were substantially lower (**6** and **13**; Scheme 3). Except for 3-picoline (**4**; Scheme 3), none of the 3-substituted pyridines[7] reacted cleanly, usually furnishing low yields (e.g., 15% for **5** to afford **22**, data not shown). The C–H silylation of **4** was successful, giving 65% yield of isolated product.

We were also able to detect the assumed key intermediates, 1,4-dihydropyridines **23** and **24** when monitoring the reaction of **4** and Me_2PhSiH by ^1H NMR spectroscopy (**4**→**23**→**24**; Scheme 4). In the presence of excess Me_2PhSiH,



Scheme 4. Monitoring the C–H silylation of 3-picoline (**4**) by ^1H NMR spectroscopy (400 MHz) in CD_2Cl_2: detection of key intermediates.

pyridine **4** fully converts into 1,4-dihydropyridine **23** within two hours at room temperature, and no further reaction is seen at this temperature. Heating at 80°C then initiates the C–H silylation of the N-silylated enamine motif in **23** to afford the 5-silylated 1,4-dihydropyridine **24** in one hour. No rearomatized **21** is detected after this time, thus indicating that the retro-hydrosilylation[10] is rate determining (**24**→**21**). We therefore prepared **23** according to the published procedure[7] at room temperature (**4**→**23**) and subjected it independently to the dehydrogenative enamine silylation method[8] with excess hydrosilane at 80°C (**23**→**24**). The desired 5-silylated 1,4-dihydropyridine **24** was formed, and the catalyst was removed by filtration through a small pad of Celite under inert atmosphere. This sample of **24** was then used for separate investigations of the retro-hydrosilylation, and it was shown that neither heating at 80°C nor exposure to air alone leads to rearomatization. The catalyst is thus required in the final step (**24**→**21**), which is consistent with earlier findings by Nikonov and co-workers.[10]

We present herein a one-pot transformation that is usually considered virtually impossible: a formal S_EAr of pyridines with electrophilic silicon. The trick is to temporarily break the aromaticity and exploit the nucleophilicity of the enamine intermediate.[11,14,15] The strategy hinges on the reversible 1,4-hydrosilylation of pyridines,[7,10] and we discovered that the same catalyst also promotes dehydrogenative silylation of the nucleophilic enamine carbon atom.[8] The net result of this three-step sequence is a *meta*-selective C–H silylation of mainly 2-substituted pyridines that would otherwise be difficult to achieve in a single synthetic operation.

Acknowledgements

This research was supported by the Deutsche Forschungsgemeinschaft (Oe 249/10-1). M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship. We thank Dr. Hendrik F. T. Klare (TU Berlin) for insightful discussions.

Keywords: C–H activation · electrophilic substitution · hydrosilylation · N-heterocycles · Si–H bond activation

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15876–15879
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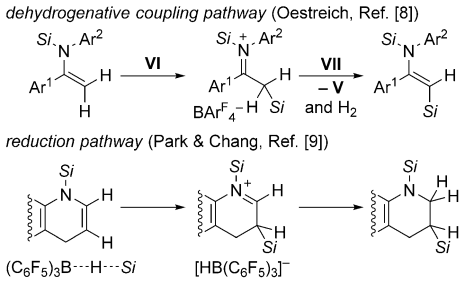

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Received: September 1, 2015
Revised: October 15, 2015
Published online: November 17, 2015

